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Biodegradable Polymers: Drug Release Characteristics

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BIODEGRADABLE POLYMERS: DRUG RELEASE CHARACTERISTICS

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I do hereby certify that **Abu Mahmud, M. Sc.,** is the sole author of the thesis entitled **"BIODEGRADABLE POLYMERS: DRUG RELEASE CHARACTERISTICS"**. He has fulfilled all the requirements according to the rules of this University for the submission of a thesis for the Ph. D. (Engineering) degree. No part of this thesis has been published for any degree, diploma or prize.

I am forwarding the thesis to be examined for the degree of Ph. D. (Engineering) of Rajshahi University.

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ABSTRACT

Four polymers namely: i) maleic acid-butane-1,4-diol polyester (MBP), ii) maleic acid-adipic acid-propane-1,2-diol co-polyester (MAPC), iii) malic acid-adipic acid-butane-1,4-diol co-polyester (MABP) and iv) maleic acid-citric acid-propane-1,2-diol co-polyester (MCPC) from different composition and ratios of their corresponding monomers were synthesized and characterized. Their biodegradation and *in-vitro* drug release behavior in simulated physiological environments were also investigated.

All of these four polymers were synthesized using xylene as the reaction medium in Dean-Stark apparatus. The polycondensation temperature was varied from 130 to 145^{0}C for different polymers. The reaction time was about 5 hours followed by 1 hour post curing and anhydrous $FeCl_3$ (approximately 0.4% of the total weight) was used as catalyst. The synthesized co-polyesters were collected from the reaction vessel by dissolving them in acetone and re-precipitated using water as non-solvent. The purified co-polyesters were characterized by their solubility tests in common organic solvents, molecular weights, IR-spectra, elemental analyses, hydrolytic and soil degradation tests. Probable structures of the co-polyesters were also assigned. Molecular weight determination was carried out by end group analysis and viscosity method. Soil burial tests revealed that, all of these polyesters degraded biologically and normally mixed with soil imparting no natural imbalance. At room temperature, hydrolytic degradation study in solutions of different pH values showed that co-polyesters i), ii) and iii) remained almost intact in solutions of pH 0-3.0, slight degradation was observed in pH range 3.0-6.0 but they

gradually degraded in solutions of pH >6.0. Such pH responsive degradation nature of these polyesters led us to investigate their possible application as enteric coating material. Diclofenac sodium and naproxen core (uncoated) tablets were used as model drugs for this purpose. Simulated physiological environments and procedures according to British pharmacopoeia (BP) were followed to monitor the drug release pattern of polymer coated tablets and satisfactory results were obtained. However, hydrolytic degradation study of the co-polyester (iv) reveals that in acid medium the polymer sample swells insignificantly. But in alkaline medium it swells well and the ester linkage is hydrolyzed with respect to time. Because of such time dependent pH responsive nature, this polyester was tried as a drug carrier for extended release drug-polymer matrix tablets and pure dichlofenac sodium was used as the model drug. The drug was incorporated in the polymer matrix by melt granulation process keeping the drug polymer ratio as 1:2. The prepared granules were compressed in a single punch tablet machine to get them in tablet forms. *In-vitro* drug release from these matrix tablets were studied spectrophotometrically under physiological condition (phosphate buffer of pH 7.4 at 37^0C). The release pattern has shown a bit higher release in the first hour, then a nearly zero order release for 10-11 hours followed by declining release for the subsequent few hours.

CHAPTER-1

GENERAL INTRODUCTION

1.1 Biodegradable Polymers

1.1.1 Definition

Biodegradable polymers are those polymers that are degradable due to the enzymatic action of living organisms or because of the natural processes of the environment and thus ultimately are consumed by the living body or mix with the environment without creating any kind of adverse effects. Actually, in general, all of the natural polymers can be considered as biodegradable. So if the structural feature of a natural polymer that makes it biodegradable could be introduced in a synthetic polymer then it could possibly be turned into a biodegradable polymer. Generally, polymers containing hetero-linkage on their backbone are biodegradable[1].

Because of the inconveniences as well as environmental concerns that occur due to synthetic polymers, considerable interest is being focused on the development of biodegradable polymers, so that, they would mix themselves with soil after their applications being over. For ecological balance, the development of biodegradable polymers is one of the leading edges of research in polymer science for bio-medical, agricultural and domestic uses.

1.1.2 Factors of Biological Environment Responsible For Polymer Degradation

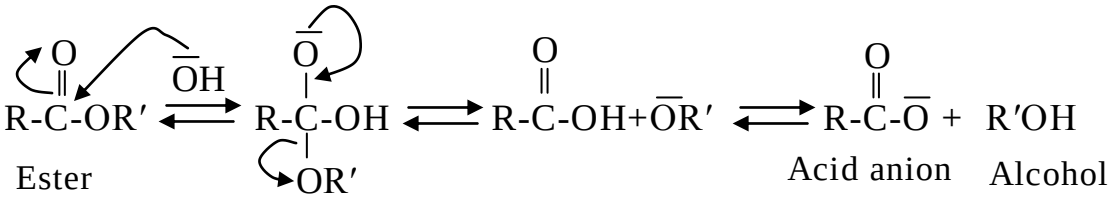
The degradation of the polymer implanted in an organism is brought about by a number of factors present in the bioprocess of the organism, namely, water, salts (cations and anions), pH and enzymes. It is pre-

requisite to the potential of each of these factors, which contribute, to the overall degradation process.

Water: Water dissolves well in hydrophilic polymers and therefore, may be an agent responsible for polymer degradation. Polymers that absorb water with adequately low diffusivity (hydrophobic and cross linked) degrade from the surface and indicate that water diffusion alone is not responsible for hydrolytic degradation of polymers.

Salt: The anions and cations in electrolytes as well as acidity and alkalinity may have an important effect on both hydrolytic and oxidative polymer degradation; salts solubility in polymers is related to water solubility. If a sufficiently large volume of water is absorbed, the concentration of salt in the polymer will also be rather high. Hydrophobic polymers do not absorb salts whereas hydrophilic polymers have a salt diffusivity close to that of water. Salts and pH of environment may produce a suitable catalytic effect on the hydrolysis of hetero-linkage, e.g. esters, amide etc. For carbon containing polymers, phosphate ions are especially effective as catalyst for hydrolytic degradation. Actually phosphate ion is available in sufficient concentration in plasma and cellular fluid.

In the alkaline environment ester hydrolysis takes place as follows:



In this case, degradation depends on water diffusivity and temperature of the reaction.

Enzyme: Enzymes markedly take part in polymer degradation in an organism. Due to the bulky molecular size they cannot normally get into a polymeric implant but attack it from the surface or in a surface of rough extensions, crack etc. On polymeric articles however they can be easily absorbed by macrophage and lysosome that swallow the polymers, foreign to the organism and later digest them as fragments inside the cells under the action of the enzymes. Lysosome enzymes, such as hydrolase and oxidase destroy polymers through either by phagocytosis or exocitosis. The pH (or acidity) of the environment appears to help the enzyme action. It is known that enzymes are the main active degrading agents in a bacterial environment along with various low molecular mass products that change the acidity of the environment[2].

pH: Some enzymes are active in acid medium others in alkaline medium, and yet others in neutral medium. The optimum pH of the enzyme changes with varying time, temperature and concentration of the substrate. Activity of the enzymes is believed to be controlled by isoelectric pH value of the system.

Finally, it can be said that water, certain ion, enzymes and pH of the system play the important role on the degradation of the polymeric materials.

1.1.3 Structural Feature for Polymer Degradation

In general, natural polymers are degradable and synthetic polymers are non-degradable. Degradation of polymers is dependent on the following structural factors.

A. Hydrophilic properties: All natural polymers are generally hydrophilic. So, synthetic polymers should have hydrophilic property. Because water dissolves well in hydrophilic polymer and therefore may be an agent responsible for polymer degradation.

B. Enzyme: From microbiological point of view, lack of specific enzyme attributes resistance to synthetic polymer. So, we should find out suitable enzyme for the degradation of synthetic polymer or we should synthesize a polymer in such a way that, the suitable enzymes are available almost everywhere.

C. Crosslinking: The more cross-links in a polymer, the more it becomes hydrophobic i.e. the penetration of water molecules is retarded. So, synthetic polymer should have low crosslinking.

D. Carbon chains length: Higher carbon chain length prolongs biodegradation. So, in synthetic polymers carbon chain length should be as shorter as possible.

E. Crystallinity: Higher regular configuration polymers have high crystallinity. The crystalline regions put up stiffer resistance to a penetrating molecule than the amorphous region. So, amorphous regions are more rapidly degraded than their crystalline counterparts.

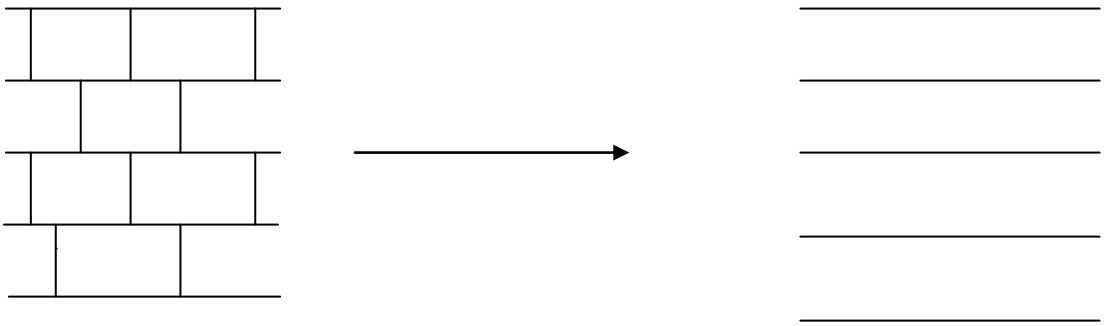
F. Hetero-linkage: Hetero-linkage polymers contain hydrolysable groups. So, degradable polymer must have hetero-linkage in their backbone.

Finally, if we want to get a new biodegradable polymer, the properties and structure of polymer should be as like as natural polymer. To achieve degradable polymer, condensation reaction is preferred to addition reaction.

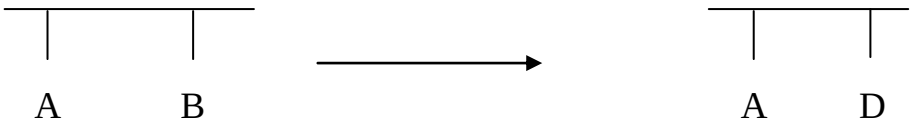
1.1.4 Mechanisms of Polymer Degradation

Degradation of the polymer induced by the aqueous environment takes place by one of the three distinct mechanisms as shown in the following figure:

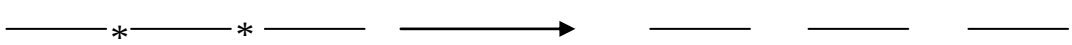
Mechanism 1: Degradation or solubilization by crosslink cleavage.



Mechanism 2: Solubilization by hydrolysis, ionization and protonization of pendant groups.



Mechanism 3: Solubilization by backbone cleavage.



A ⟶ Represents a hydrophobic substituent.

B & D ⟶ Represent hydrolysis, ionization or protonation.

* ⟶ Denotes a hydrolytically unstable bond.

Mechanism 1: In this system, water-soluble polymers are insoluble by means of hydrolytically unstable cross-links. Consequently, the matrix is highly hydrophilic and completely permeated by water, since active agent is in aqueous environment, its water solubility

becomes an important consideration and compounds with appreciable water solubility will be rapidly leached out, independent of matrix erosion.

There are two general applications in which erodable hydro-gels are useful in the controlled delivery of active agent. In the first, the active agent has extremely low water solubility and in the second, the active agent is a macromolecule that is entangled in the hydro-gel matrix and cannot escape until sufficient number of cross-links have been cleaved and matrix crosslink density has been reduced. For controlled release of active agent, there should be a balance between diffusion of active agent and erosion of polymer matrix.

Mechanism 2: System in this category included all polymers that are initially water insoluble but become water soluble as a consequence of hydrolysis, ionization or protonation of pendent groups, because no backbone cleavage takes place. The solubilization does not result in any significant change in molecular weight. Consequently, such polymers are not generally useful for systemic applications because of difficulty in the elimination of such molecules. The major emphasis in the development of these materials has been on enteric coatings.

Mechanism 3: In this category high molecular weight water insoluble polymers are converted to small water-soluble molecules by cleavage of labile bonds in the polymer backbone. These types of polymers are most useful in the systemic administration of therapeutic agents from subcutaneous, intramuscular or intraperitoneal implantation sites. It is essential that the degradation products of these polymers must be completely non-toxic. Examples of these polymers are polylactic acid, polyglycolic acid and lactic-glycolic copolymers.

1.1.5 Scope of Biodegradable Polymers

The development of biodegradable polymers is one of the brilliant aspects of polymer science and technology. For many biomedical, agricultural and ecological uses it is preferable to have a biodegradable polymer that will undergo degradation in the physiological environment or by the microbial action in the soil. This could lead to entirely new applications; especially it is desirable for medical uses. The principal medical uses of non-toxic biodegradable polymers are for controlled delivery of drugs, tissue adhesives, sutures, artificial organs and so on.

Biodegradable polymeric matrices can be used for the slow and controlled release of drugs. The value of these therapeutic systems lays the transformation of drug therapy into a continuously controlled process that can proceed unattended for a relatively longer period. These systems can eliminate the frequent dosing by patients by avoiding fluctuation and often-undesirable pharmacological effects that are inherent in these pulse entries of medication. Furthermore, the system permits the use of agents with narrow therapeutic indices or very short biological half-lives. Sustained delivery of drugs at controlled rates has been the objective of various publications in recent times[3].

The drug concentration of conventional dosage forms causes fluctuations in blood and tissues, which may result in adverse effect, decrease therapeutic action and create poor patient compliance. For optimizing drug effects, various oral dosage forms able to control the rate of delivery of the drug in the gastrointestinal tract (GIT) have been prepared and

studied. Other dosage forms such as parenteral dosage forms of this kind are also available, but we will give emphasis on oral dosage forms because this is our goal in this thesis. The simplest forms consist of a drug dispersed in a polymer which plays the role of a drug carrier[4-8].

1.1.6 pH Responsive Biodegradable Polymers for Drug Release

In the last few decades, the development of polymers which change their structures and properties in response to environmental stimuli such as pH, temperature and light, has attracted a great deal of attention[9-11]. Such polymers have been called ‘‘smart polymers,’’ ‘‘intelligent polymers,’’ ‘‘stimulus- sensitive polymers,’’ or ‘‘responsive polymers.’’ They have been used in many applications, ranging from bioactive agent delivery to separation[12, 13]. Various delivery systems based on the smart polymers have been proposed because of their unique potential in the modulation of drug release and targeting functionality[14-16]. A pH-sensitive polymer in drug delivery applications is different from other stimuli-responsive polymers that require external stimuli such as temperature and light. The pH sensitive polymers can take advantage of variations (whether they occur naturally or under pathological conditions) of pH in the body[17]. The pH-sensitive polymers containing acidic groups (e.g., carboxylic and sulfonic acids) or basic amino groups can accept or release protons in response to changes in environmental pH. If these polymers are cross-linked, they swell at this pH owing to ionization. On the other hand, polyanions, such as Poly (acrylic acid), swell at a high pH[18]. In general, the pH-sensitive polymers manifest their sensitivity to changes in pH, as soluble-insoluble phase transition, i.e., swelling-shrinking changes, or as conformational changes. These properties are dependent on the degree of the ionization of the ionizable groups in the polymers; this degree is

related to the pK values (pK_a or pK_b) of monomers and the environmental local pH. Thus, the selection of an ionizable monomer is a fundamental parameter for the control of pH-dependent properties; in the meantime, the sensitivity is further influenced by the nature of ionizable groups, the polymer composition, the ionic strength, and the hydrophobicity of the polymer backbone. Conformational changes were also induced by altering the pH[19, 20].

1.2 pH Distribution and Physiology of GIT

The most pronounced pH variation in the human body occurs in the gastrointestinal tract (GIT). The GIT is a continuous tube that runs from the mouth to the anus. The inter-digestive migration of a drug (or a dosage form) is governed by GI motility, wherein the drug is exposed to different pHs at different time periods, as summarized in Table 1. The stomach has an acidic environment (a pH of 1–2 in a fasting condition and pH-4 during digestion) induced by hydrochloric acid from the gastric mucosa. The acidic pH in the stomach increases up to a pH of 5.5 at the duodenum, in which the acidic chime mixes with the bicarbonate from pancreatic juices. The pH then increases progressively from the duodenum to the small intestines (a pH of 6–7) and reaches a pH of 7–8 in the distal ileum. After the ileocecal junction, the pH falls sharply to 5.6 owing to the presence of short-chain fatty acids and then climbs up to neutrality during transit through the colon (a pH of above 7–7.5) because of free fatty-acid absorption[21,22].

1.3 Controlled-Release Oral Dosage Forms

Compared to alternate routes, the oral route is the most natural, uncomplicated, convenient and safe for administering drugs. However,

Table 1.1: Physiological Parameters of the GIT Related to Drug Delivery[17].

GIT Segment	**Approx. Residence Time**	**Approx. pH of the Segment**	**Principal Catabolic Activities**
Oral cavity	Seconds to minutes	6.5	Polysaccharidases
Esophagus	Seconds	-	-
Stomach	0.2–2.0 Hours	1.0–2.0	Proteases, lipases
Duodenum	30–40 Minutes	4.0–5.5	Polysaccharidases; oligosaccharidases, proteases, peptidases, lipases
Jejunum	1.5–2.0 Hours	5.5–7.0	Oligosaccharidases
Ileum	—	7.0–8.0	Oligosaccharidases
Colon and rectum	13–68 Hours	7.0–7.5	Broad spectrum of bacterial enzymes (glycosidases, azoreductase, polysaccharidases)

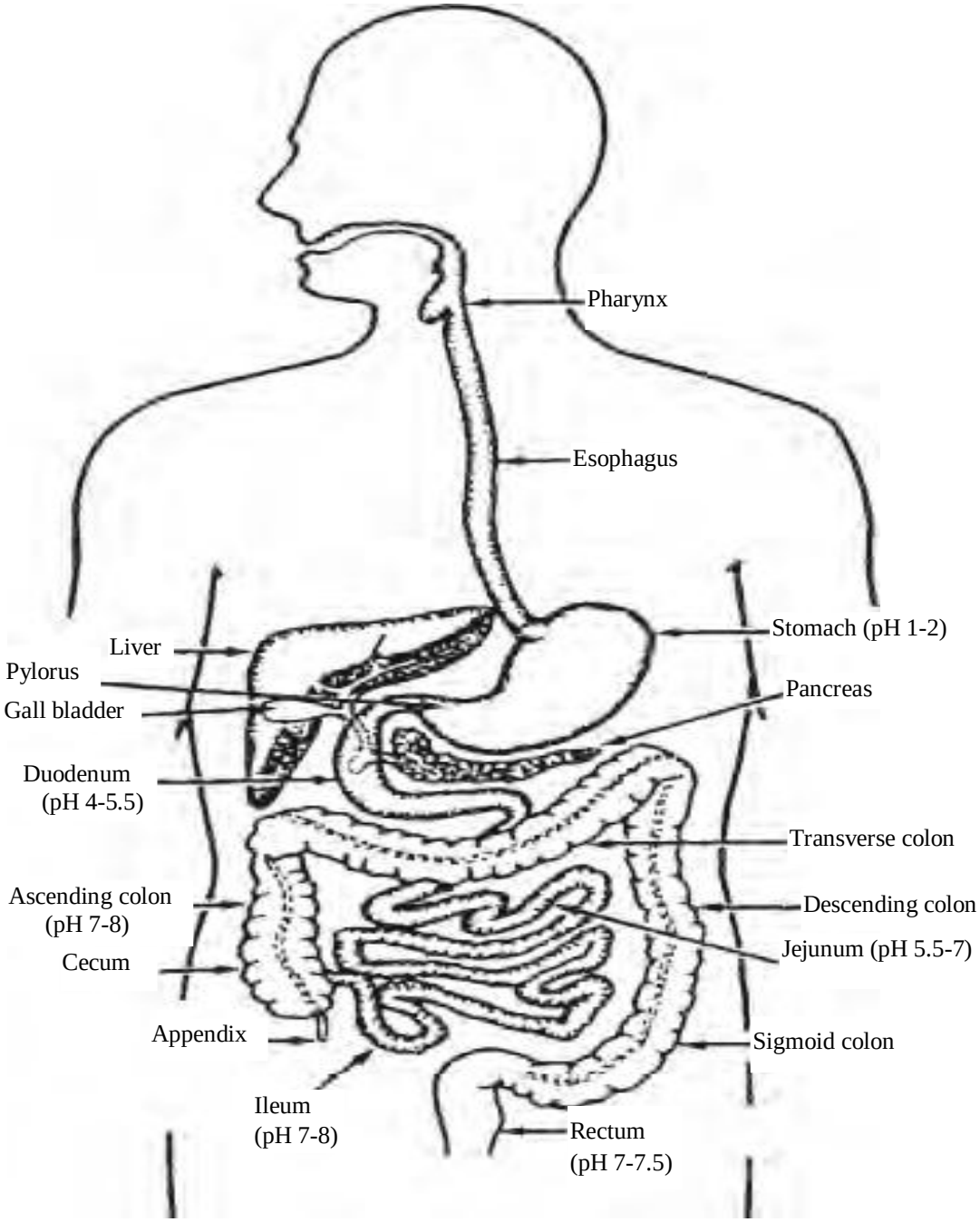


Fig. 1.1: pH Distribution and Physiology of GIT[23]

disadvantages include slow response (as compared to parenteral and sublingual dosage forms), chance of irregular absorption of drugs (depending upon such factors as constitutional gut make-up, the amount and/or type of food present at time of ingestion), and destruction of the drug by acid reaction in the stomach and/or by GI enzymes[22, 23]. Controlled release systems have been devised to enable superior control of drug exposure over time, to assist drug in crossing physiological barriers, to shield drug from premature elimination, and to shepherd drug to the desired site of action while minimizing drug exposure elsewhere in the body. Controlled release systems may also increase patient compliance by reducing frequency of administration[24, 25].

Controlled-release orally administrated drug delivery can either be

a) Time Specific (sustained and prolonged or zero order oral delivery) or b) Site Specific (oral delivery directed to the gut and colon).

However, a combination of both can also be possible.

1.3.1 Sustained and/or Zero Order Oral Delivery

Zero order or constant rate release of drug is desirable in order to minimize swings in drug concentration in the blood. Such excursions, which may lead to periods of underexposure or overexposure, are particularly likely to occur for drugs that are rapidly absorbed and rapidly eliminated. Figure 3 illustrates the plasma concentration profile over time for such drugs when administered from rapid-release dosage forms. A rapid increase in concentration is followed by a rapid decrease, and little time is spent inside the so-called therapeutic range, which is bounded below by a minimum effective concentration (MEC) and above by a minimum toxic concentration (MTC). Frequent repetitive dosing is required to maintain concentration within these limits and compliance

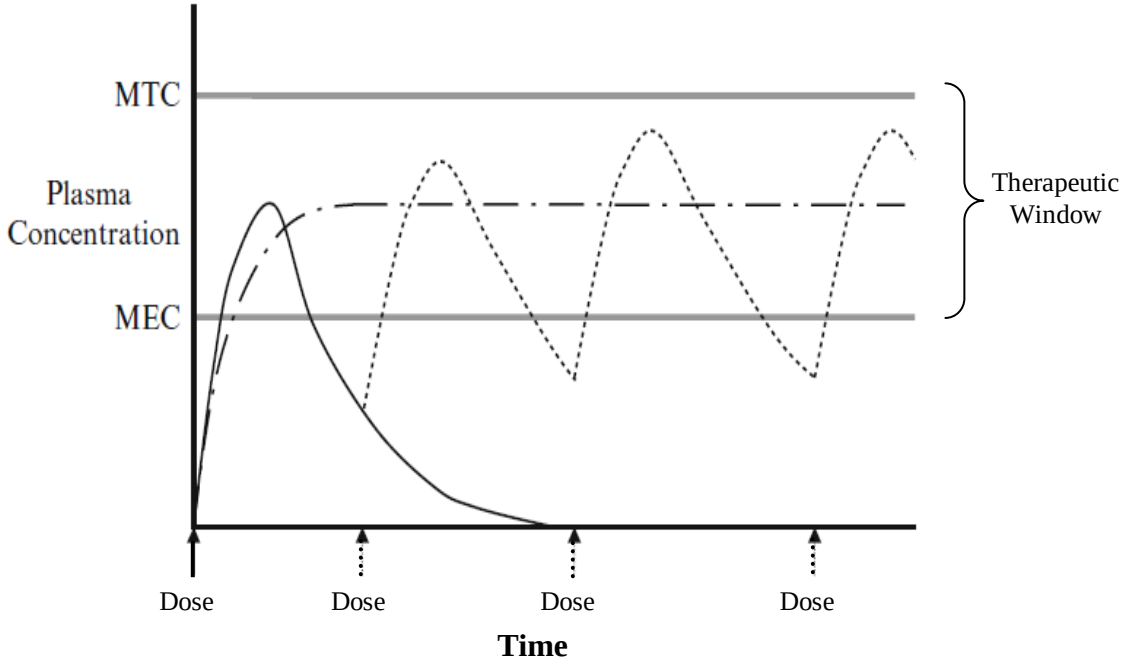


Fig. 1.2: Hypothetical Drug-Plasma Level: an efficacious, nontoxic therapy requires that drug concentration in plasma lies within the therapeutic range, which is bounded below by the minimum effective concentration (MEC) and above by the minimum toxic concentration (MTC). For rapidly absorbed, rapidly eliminated drugs, a single dose (solid arrow) leads to a rapid rise and fall in drug concentration (solid curve). Multiple dosing at regular intervals (solid arrow followed by dotted arrows) leads to oscillating drug concentrations (solid curve followed by dotted curve), which may fall outside the therapeutic range for significant time periods. Zero order release (dot–dash curve) leads, after an initial rise, to a constant concentration in plasma which, with proper dosing, lies between MEC and MTC[23].

and control are difficult. Dosage forms that prolong release can maintain drug concentration within the therapeutic range for extended periods and minimize episodes of underexposure or toxicity. A well designed system displays a narrow, predictable residence time distribution in the gastrointestinal (GI) tract, and releases drug by a controlled mechanism. As shown in Fig.1.2, zero order release leads, in principle, to the best control of plasma concentration. Such control leads to constant drug effect, provided the drug's pharmacokinetic and pharmaco-dynamic properties, including absorption, distribution, metabolism and excretion and its pharmacodynamic properties relating plasma concentration to drug effect, are stationary[23].

Controlled release or near zero-order release systems can be classified as following according to the mechanism of drug release:

1. Diffusion controlled systems
    A. Reservoirs or membranes
    B. Matrices or monoliths
2. Chemically controlled systems
    A. Erosion
    B. Pendant chain
3. Solvent activated systems
    A. Osmotic pressure
    B. Swelling

▪ **Diffusion controlled (reservoirs or membranes) systems:** These systems are the most widely used in medical applications. The diffusion of the drug takes place through the thin layer that separates the core of the drug from the biological environment. This layer remains intact along the complete gastrointestinal tract (GIT) and controls the release by diffusion of the drug through the layer.

▪ **Diffusion controlled (matrices or monoliths) systems:** In these systems the bioactive agent, either in dissolved or in dispersed form, is incorporated in the polymer phase. In the case where the drug is dissolved in the polymer, the release is controlled by the solubility of the drug in the polymer. When the drug is dispersed, the release is controlled by the dissolution of the drug in the site of release.

Almost all of the mechanisms of drug release by diffusion controlled systems can be explained by Fick's famous laws of diffusion.

▪ **Chemically controlled (erosion) systems:** Both reservoir and matrix devices can be employed for this purpose. The release from the reservoirs is dependent upon the permeability and thickness of the layer or membrane of reservoir itself. This layer erodes during action in a desired fashion and thus controls the drug release but release from matrices is controlled by a combination of erosion and diffusion of the drug at the targeted site.

▪ **Chemically controlled (pendant chain) systems:** This type of controlled release is not as extensively used as the cases described earlier. The drug is chemically bonded to the polymer and is released through the action of an enzyme or by hydrolysis.

▪ **Solvent activated (osmotic pressure) systems:** In these systems a core of drug is surrounded by a semi-permeable membrane or film equipped with an orifice for drug delivery. During contact with water or biological fluid, water is transported through the membrane toward the core resulting in release of equal volume of dissolved drug through the orifice. Release rate can be adjusted by varying the thickness of the semi-permeable membrane.

▪ **Solvent activated (swelling) systems:** In swelling controlled solvent activated systems, the drug is dissolved or dispersed in a polymer phase. The moment it comes in contact with the medium or biological fluid, the polymer swells, lowering its glass transition temperature and the polymer allows the drug to dissolve. There are two main interfaces during action. The first separates the glassy state from the rubbery state (swelling interface) moving inwards to the center of the core, and the other separates the rubbery state from the medium (polymer interface) moving outwards. Between glassy and rubbery state a macromolecular relaxation takes place. This relaxation affects the drug diffusion through the polymer, giving Fickian or non-Fickan diffusion[26]. The transport of the drug through the polymer can be controlled by the macromolecular relaxation or by the diffusion of the drug through the rubbery polymer.

1.3.2 Oral Drug Delivery Directed to the Gut and Colon

▪ Matrix Tablets

One of the least complicated approaches to manufacture both time and site controlled orally administrated solid drug release dosage form involves the direct compression of blends of drugs, retardant materials and additives to form a tablet in which drug is embedded in a matrix core

of the retardant. The matrix tablet, which incorporates the active ingredient in an inert material, has been well known to act as an effective sustained release medicament[26, 27]. Inert insoluble polymers have been used as a basis for many marketed formulations of this type. Tablets may be directly compressed from mixtures of drug and polymer where drug bio-availability depends on the drug-polymer ratio[27].

Release rate can be adjusted for low-milligram potency formulations by replacing a portion of the polymer with lactose. High drug-polymer ratios result in formulation from which drug release is controlled by attrition of the polymer. On contact with biological fluid, water soluble drugs are released by diffusion or by erosion, whereas poorly soluble drugs are released solely by erosion of the structure. Thus erosion of the matrix and diffusion of the drug play a predominant role for the rate of drug release. Generally, release rate modulation is achieved using different grades and types of biodegradable polymers[28], soluble fillers[29], or insoluble fillers[30].

- **Enteric Coatings**

Due to the pH variation in the GIT, pH-sensitive polymers have been historically utilized as an enteric coating material. Enteric-coated products include tablets, capsules, and pellets that are designed to keep an active substance intact in the stomach and then to release it in the neutral or slightly alkaline environment of the gut. The polymers used for enteric coatings remain unionised at low pH, and therefore remain insoluble. As the pH increases in the gastrointestinal tract the acidic functional groups are capable of ionisation, and the polymer swells or becomes soluble in the intestinal fluid. Thus, an enteric polymeric film coating allows the coated solid to pass intact through the stomach to the small intestine,

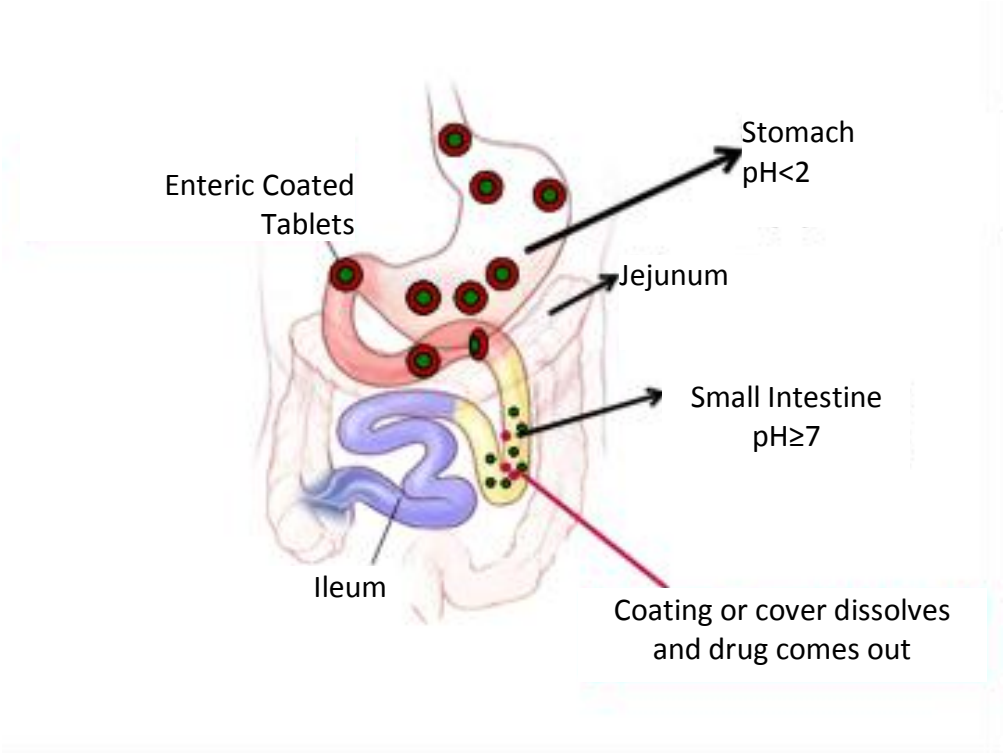
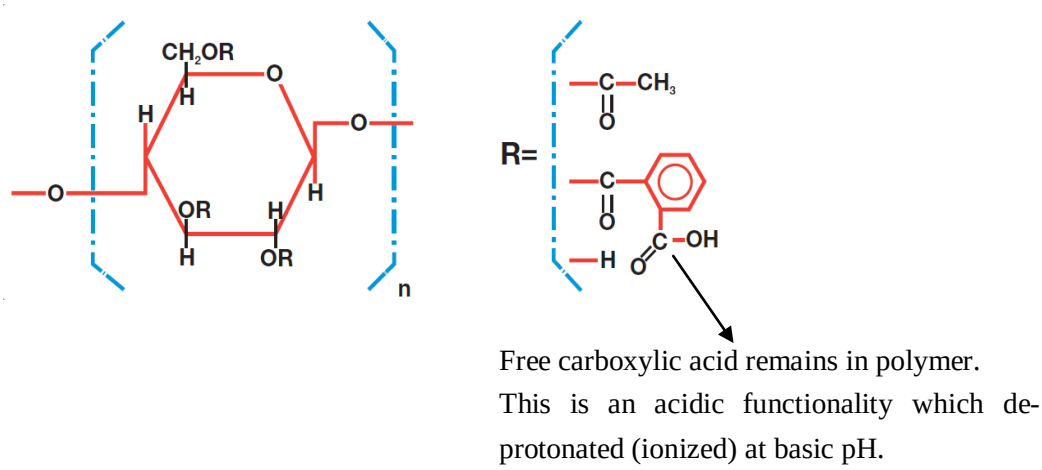


Fig. 1.3 (A): Function of Enteric Coatings



Free carboxylic acid remains in polymer. This is an acidic functionality which de-protonated (ionized) at basic pH.

Fig. 1.3 (B): Molecular structure and mechanism of action of a commonly used enteric coating material, cellulose acetate phthalate.

where the drug is then released for absorption through the intestinal mucosa into the human body to exert its pharmacologic effects.

In addition, the coat reduces the side effects such as foul taste and severe gastric irritation (in case of analgesics) or sometimes protects the drug to lose its activity (such as peptide drugs) or helps the drug to reach at its site of action (in case of anti-helminthics). Derivatives of acrylic acid (e.g., Eudragit) and cellulose-based polymers (e.g., cellulose acetate phthalate) are the commercially used enteric coating polymers[17]. During the passage of the dosage form from the stomach to the small intestine, the polymer will swell into a gel layer. Swelling and hydrolysis of the polymer coating and diffusion of drug particles simultaneously play an important role on the release behavior of the drug[31].

- **Colon-Targeted Drug Delivery**

Like enteric coating materials, but with different pH sensitivity, coating have been applied for colon-targeted drug delivery. This special pH sensitive coating is required due to a pH change in the ileocecal junction. Colon targeting is extremely beneficial when applied to the treatment of a variety of bowel diseases. In high local concentrations, colon-targeted drugs can remedy diseases such as Crohn's disease, ulcerative colitis, carcinomas and infections. In addition, site-specific absorption in the colonic regions offers excellent source of treatment. It targets maladies with diurnal rhythms such as asthma, arthritis and inflammation [17, 32-35].

Oral route is the most convenient and preferred route but other routes for colon specific drug delivery system may be used. Rectal administration offers the shortest route for targeting drugs to the colon.

However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal[36]. The polymers that are designed for colon targeting via oral route are able to withstand the low pH levels of the stomach and proximal part of the small intestine and then disintegrate at the neutral or slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction[21]. A process such as this distributes the drug throughout the large intestine and improves drug availability to the colon. In addition, the polymer can also be used for peptide/protein oral delivery systems. The pH-dependent solubility or swelling allows for the possibility that polymers can be engineered to conserve the stability of proteins at a low pH in the stomach and intestine and then release these proteins at a higher pH.

1.4 LITERATURE REVIEW

At present, polymer science and technology is enjoying a healthy period of modern science. Just as the use of polymers has proliferated in the past decade, so has its literature. The leading journals in this field are *Journal of polymer Science, Journal of Applied Polymer Science, European Polymer Journal, Polymer Science and Technology Journal, Journal of polymer materials,* etc. The chemical abstracts are serviced by the American Chemical Society.

D. Pramanik and T. T. Ray[37] (1990) studied synthesis and biodegradation of copolyester from citric acid and glycerol. They studied microbial degradation of the polymer sample in aqueous suspension, by using the fungus *asperagillus niger* and the bacterium *E. Coli*. All the polymer samples are degraded by

asperagillus niger and *E. Coli* and the more cross-linked products have been found to be degradable. The possible use of their cross-linked co-polyesters as matrices for controlled release of drugs has been also illustrated.

R. Jeyanthi and K. Panduranga Rao[38] (1990) used collegen-poly (HEMA) hydrogel matrices as carriers for the controlled release of anticancer drugs. Conventionally used anticancer drug such as 5-fluorouracil (5-FU), mitomycin C (MMC) and bleomycin A2 (BLM) were entrapped in the hydrogels and their in vitro release profiles from these matrices were studied.

D. Pramanick, T. T. Ray and M. A. Bakr[39] (1996) synthesized four samples of cross-linked co-polyesters of citric acid and 1,2,6-hexane triol using $FeCl_3$, as catalyst. These were characterized by IR spectra, elemental analysis, glass transition temperature (Tg) and equilibrium swelling in water, ethanol and ethylene carbonate and the drug release properties of the co-polyester was also evaluated.

M. A. Bakr, M. M. AIi and P. K. Sarker[40] (1997) synthesized co-polymers of saccinic acid, glycerol and P.E.G-200 using $FeCl_3$ as catalyst. These were characterized by IR spectra, glass transition temperatures, swelling behavior and elemental analysis and their soil, microbial and hydrolytic degradadtion study was performed.

K. E. Uhrich, S. M. Cannizzaro, R. S. Langer and K. M. Shakesheff (1999)[41] reviewed the chemical issues involved in the design of synthetic polymers used in the controlled release of drugs. Before considering the variety and the evolution of these polymeric structures, it is necessary to examine the motivation for achieving controlled release. This field of

pharmaceutical technology has grown and diversified rapidly in recent years. According to them, understanding the derivation of the methods of controlled release and the range of new polymers can be a barrier to involvement from the non-specialist.

M. A. Bakr, M. A. Islam, M. A. W. Sarker, M. Ahmed[42] (2000) synthesized co-polyester of malic acid and propane- l,2-diol following Dean-Stark method using xylene as the reaction medium. The co-polyesters were characterized by their IR spectra, molecular weight, elemental analysis, solubility behavior in common organic solvents and hydrolytic degradation. In-vitro release kinetics of drug polymer systems was also investigated.

B. Jeong, M. R. Kibbey, J. C. Birnbaum, Y. Y. Won, and A. Gutowska[43] (2000) studied to prepare a short-term system. Poly(ethylene glycol) grafted with poly(lactic acid-co-glycolic acid), where hydrophilic PEG is a backbone. This material is expected to show a different gelation and degradation behavior and, consequently, a different drug release profile as compared to PEG-PLGA-PEG or PLGA-g-PEG.

M. A. Bakr, M. A. Islam, M. A. Karim, G. Sadik, M. H. U. Biswas[44] (2002) synthesized co-polyesters of malic acid, phthalic acid, and propane-1,2-diol following Dean-Stark method using xylene as the reaction medium. The co-polyesters were characterized by their IR spectra, molecular weight, elemental analysis, solubility behavior in common organic solvents and hydrolytic degradation. In vitro release kinetics of drug polymer systems were also investigated.

R. Langer and N. A. Peppas (2003)[45] discussed recent advances in the fields of i) polymers as biomaterials; ii) materials in drug and protein delivery; iii) materials for tissue engineering; and iv) materials used in nanotechnology and micro-fabrication of medical devices. They analyzed scientific progress in these fields over the last ten years, and stressed the impact of chemical engineering thinking on developments in this field.

M. A. Bakr, S. Khatun, M. A. Islam and G. Sadik[46] **(2003)** synthesized co-polyesters of malic acid and butane-1,4-diol following Dean-Stark method using p-toluene sulphonic acid (approximately 0.4% of the total weight) as catalyst and xylene as the reaction medium.. The physiochemical properties of the copolyester remained unchanged in simulated gastric fluid (pH 1.20) but it gradually degraded in simulated intestinal fluid. It was then tried as an enteric coating material on diclofenac sodium as well as on naproxen core tablets and satisfactory result was observed.

M. Vert (2005) [47] tried to lay emphasis on aliphatic polyester-based polymeric structures as biodegradable polymers for biomedical applications because they are all more or less sensitive to hydrolytic degradation, a feature of interest when compared with the fact that living systems function in aqueous media. To be of practical interest, a degradable polymer must fulfill many requirements that depend very much on the targeted application, on the considered living system, and on living conditions. Their main characteristics are confronted to the specifications required by various potential sectors of applications, namely, surgery, pharmacology, and the environment.

L. Y. Qiu and Y. H. Bae (2006)[48] reviewed polymer architectures along with brief synthetic approaches and summarized the characteristic properties of each architecture useful for drug delivery applications, and cover recent advances in drug delivery relevant to polymer architecture. Polymers occupy a major portion of materials used for controlled release formulations and drug-targeting systems because this class of materials presents seemingly endless diversity in topology and chemistry. This is a crucial advantage over other classes of materials to meet the ever-increasing requirements of new designs of drug delivery formulations.

M. A. Bakr et al[49] (2006) Synthesized maleic acid-succinic acid-propane-1,2-diol co-polyester following Dean-Stark apparatus using p-toluene sulphonic acid as catalyst and xylene as the reaction medium at temperature 137-141^{0}c. The co-polyester was characterized by its molecular weight, IR-spectra, elemental analysis and solubility test in common organic solvents. At room temperature, the hydrolytic degradation study of the co-polyester in solutions of different pH values showed that it remained intact in solutions of pH values 1.5-6.0 but gradually degraded in solutions of pH values >6.0. It was then tried as an enteric coating material on diclofenac sodium core tablet and satisfactory result was observed.

D. Schmaljohann (2006)[50] reviewed Stimuli-responsive polymers that showed a sharp change in properties upon a small or modest change in environmental condition, e.g. temperature, light, salt concentration or pH. This behavior can be utilized for the preparation of so-called ‘smart’ drug delivery systems, which mimic biological response behavior to a certain extent. The possible environmental conditions to use for this purpose are limited due to the biomedical setting of drug delivery as application.

Different organs, tissues and cellular compartments may have large differences in pH, which makes the pH a suitable stimulus.

Yu-Kyoung Oh, P. D. Senter and Soo-Chang Song (2009)[51] discussed on "Smart polymers" and newer materials allow for controlled released of drugs under specific conditions. Advancements in material science has allowed for the production of solid supports for drug delivery in which imprinting technologies are used to produce novel scaffolds for drug attachment and controlled release. Several of the issues are being resolved including biocompatibility, scale-up, drug loading, and control of release kinetics. Other delivery systems of great interest include osmotically driven miniaturized implants, hydrogel capsules, polymeric drug derivatives, and inhalable formulations. While these technologies may offer significant advantages over current formulations, the regulatory, cost, and compliance issues are significant. Nanotechnology-based drug delivery systems were described that allow for both spatial and temporal control of drug release.

E. M. M. del Valle, M. A. Galan and R. G. Carbonell (2009)[52] reviewed the key issues to design an effective drug delivery system. The design and development of drug delivery systems involves many different sciences that underpin the research. There are three key and interrelated areas of research. (i) To achieve a greater understanding of the biological fate and the targeting of drugs, particularly biopharmaceuticals, macromolecules and macromolecular delivery systems, at the molecular, membrane, and cellular level. (ii) To provide a greater understanding of the physicochemical properties of biopharmaceuticals, macromolecules, and macromolecular delivery systems and how these are modified within a biological environment affecting their activity. (iii) To promote the

development of novel materials and delivery systems that will overcome these biological barriers.

S. Sudarshan, S. Sangeeta, N. R Sheth, P. Roshan and Y. V Ushir and R. Gendle (2009) [53] tried to explore the utility of coating technology for colonic targeting of single unit tablet systems. Ulcerative colitis is a disease of the intestine, explicitly the large intestine or colon that includes characteristic ulcers, or open sores, in the colon. For eradication of ulcerative colitis, there are various methods among the delivery of drugs to colon. Colon specific delivery can be achieved by using polymer, which will release the drug at specific pH, or by enzyme depended system, which will break the bond between drugs and polymer.

R. Bushra, M. H. Shoaib, N. Aslam, Z. Alam M. and D. Hashmat (2010) [54] studied to develop enteric coated ibuprofen tablets in order to avoid gastric mucosal irritation, diffusion of drug across mucosal lining and to let active ingredient be absorbed easily in small intestine. The formulation was developed and manufactured through the direct compression process, the simplest, easiest and most economical method of manufacturing. Enteric coating was done using an Opadry white sub-coating and an aqueous coating dispersion of Acryl-Eze. Their results reflect that ibuprofen can be successfully enteric coated in order to prevent its release in the stomach and facilitate rapid release of the drug in the duodenum, due to the presence of super disintegrant. Formulation of these enteric coated tablets could increase patient compliance by decreasing adverse drug reactions associated with Ibuprofen therapy.

H. Hosseinzadeh (2010)[55] investigated controlled release of diclofenac sodium from pH-sensitive carrageenan-g-poly (acrylic acid)

superabsorbent hydrogels. The hydrogels were prepared by graft copolymerization of acrylic acid onto kappa-carrageenan, using ammonium persulfate as a free radical initiator in the presence of methylene bisacrylamide as a cross-linker. The synthesized hydrogels were subjected to equilibrium swelling studies in simulated gastric and intestinal fluids. Hydrogels containing drug diclofenac sodium, at different drug-to-polymer ratios, were prepared by direct adsorption method. The loading yield was found to depend on both the impregnation time and the amount of encapsulated drug. In vitro drug-release studies in different buffer solutions showed that the most important parameter affecting the drug-release behavior of hydrogels is the pH of the solution.

A. K. Philip and B. Philip (2010)[56] reviewed on primary and novel approaches of colon targeted drug delivery systems. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. This review, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, and osmotic controlled drug delivery which are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process.

P. S. Salve (2011)[57] studied the formulation of sustained release tablet of ibuprofen for colon targeting. Tablets were prepared using combination of guar and xanthan gum. The drug excipient interaction studies were

carried out by FTIR and DSC. The prepared matrixes form enzyme controlled delivery systems with nearly 50 to 60% w/w of the tablet content being constituted by polysaccharides degradable by colonic microflora. In vitro drug release studies shows that guar and xanthan gum in 4:6 has optimum release in a controlled manner for 24 hour.

G. Vilar, J. T. Puche and F. Albericio (2012)[58] reviewed the relation between polymers and drug delivery systems. Polymeric systems of drug carriers are appropriate tool for time and distribution-controlled drug delivery. The mechanisms involved in controlled release require polymers with a variety of physicochemical properties. Thus, several types of polymers have been tested as potential drug delivery systems, including nano- and micro-particles, dendrimers, nano- and micro-spheres, capsosomes, and micelles. In all these systems, drugs can be encapsulated or conjugated in polymer matrices. These polymeric systems have been used for a range of treatments for anti-neoplastic activity, bacterial infections and inflammatory processes, in addition to vaccines.

A. Pandey, G. Kumar, P. Kothiyal and Y. Barshiliya (2012)[59] reviewed on current approaches in gastro retentive drug delivery system. Oral controlled release delivery systems are programmed to deliver the drug in predictable time frame that will increase the efficacy and minimize the adverse effects and increase the bioavailability of drugs. In fact the buoyant dosage unit enhances gastric residence time (GRT) without affecting the intrinsic rate of emptying. Unfortunately floating devices administered in a single unit form (Hydrodynamically balanced system) HBS are unreliable in prolonging the GRT owing to their ‘ all- or nothing’ emptying process and, thus they may causes high variability in

bioavailibity and local irritation due to large amount of drug delivered at a particular site of the gastrointestinal tract.

G. S. Weston, G. Kwame and Yeboah (2013)[60] said that successful targeting of therapeutic agents to any specific area of the GI tract requires both the exploration of a unique feature of the site and also the protection of the active agent until it reaches the target site. However, two scientific developments offer the potential promise of site-specific gastrointestinal drug delivery. The first is the discovery that *E. coli* microbes specifically adhere to the follicle-associated epithelium (FAE) that overlies the ileal Peyer's patches in the gastrointestinal tract. The second development that may allow for this new type of specifically targeted pharmaceutical administration is related to the continuing advances made in bio-adhesive drug formulation science. The process of bio-adhesion involves the formation of a bond between two surfaces, where both surfaces are biological in nature or one is biological and the other is synthetic. With regard to pharmaceutical agents, bio-adhesion may be used to increase residence time and, thus, increase drug absorption, at the target site.

1.5 OBJECTIVE OF THE PRESENT INVESTIGATION

Recently, considerable interest is being focused on the development of biodegradable polymers for specialized applications[37,61,62] such as controlled release formulations, insecticide and pesticide carriers as well as nontoxic surgical implant materials. Many of these polymers have a built-in self destruct mechanism by which they undergo slow hydrolytic and microbial degradation, releasing the impregnated materials at controlled rates.

One of the most encouraging applications of biodegradable polymers in pharmaceutics is enteric coating. The pH responsive coating materials dissolve very slowly over the gastric pH range (i.e. pH=1-3) but dissolve rapidly at the pH values associated with the small intestine (pH>7) and thus inhibit the drug release in the stomach but not in the intestine. All these polymers[63-65] such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polymers of acrylic acids (Eudragit) and polyvinyl acetate phthalate etc. are used as enteric coatings. Though cellulose acetate phthalate, the most popular enteric coating material, is generally regarded as a nontoxic material and free of side effects but has indicated a low toxicity for long term feeding in rats and dogs[66]. Moreover, many recent findings, have suggested that various phthalates and their metabolites could be responsible for the production of toxic effects in the reproductive system as well as liver tumors in humans[67,68]. On the other hand, enteric coating materials other than phthalic acid derivatives, show poor threshold pH for drug release[17]. Because of this, the search for a new, more effective and safe enteric coating material, is still going on.

Another interesting but least complicated approach to the manufacturer of sustained release dosage forms consists of a drug or biologically active agent dissolved or dispersed in a polymer, the polymer playing the role of a matrix or carrier (matrix tablets). The drug is then released to a local environment at a controlled rate either by erosion or chemical degradation of the polymer matrix. A number of polymers such as homo and copolymers of ∈-caprolactone and DL-lactic acid, glutamic acid/leucine copolymers, partial esters of methyl vinyl ether/maleic anhydride copolymers and polyanhydrides have been used as drug

delivery matrices[69-72]. However, the search for a new polymeric drug carrier aims to improve the effectiveness of drug therapy[73].

Biodegradable and bio-absorbable polymers from poly glycolic acid (PGA) and poly lactic acid (PLA) are the simplest linear polyesters, which are currently the most widely used synthetic, degradable polymers in human medicine[74,75]. Aliphatic polyesters produced by the condensation polymerization of aliphatic diols and aliphatic diacids are expected to be applicable as biodegradable polymer[76].

It is our interest to develop novel commercially viable polymers specifically designed to degrade under controlled biological conditions and thus help release the incorporated drug in the targeted site. In this connection, we have chalked out to synthesize four biodegradable aliphatic polyesters and their drug release characteristics in simulated biological environments will be investigated.

The present work can be divided into four parts:

1. Four polymers namely: i) maleic acid-butane 1,4-diol polyester (MBP), ii) maleic acid-adipic acid-propane-1,2-diol co-polyester (MAPC), iii) malic acid-adipic acid-butane-1,4-diol co-polyester (MABC) and iv) maleic acid-citric acid-propane-1,2-diol co-polyester (MCPC) from different composition and ratios of their corresponding monomers using anhydrous ferric chloride (approximately 0.4% of the total weight) as a catalyst will be synthesized.
2. The synthesized polyesters will then be characterized by their molecular weights, IR spectra, elemental analyses and solubility test in common organic solvents.

3. The degradation study of the polymers will be performed by hydrolytic test and soil degradation test.
4. Drug release study according to British Pharmacopoeia (BP) in simulated biological environments will be carried out with a view to evaluating their possible use as enteric coating materials or as carriers for sustained and controlled release of drugs.

An important consideration in designing polymers for any controlled release mechanism is the fate of the polymer after drug release. For oral applications in which the polymer passes through the gastrointestinal tract, it is desirable that after or during the drug release the polymer be biodegraded into smaller nontoxic products that are then bio-assimilated or excreted out [41]. All of the polymers we are going to investigate are aliphatic polyesters. Owing to their reputation as safe materials and their biodegradability, this kind of polyesters are primarily used as biocompatible and biodegradable carriers in many types of drug-delivery systems for both human and veterinary applications[77]. Hydrolysis of labile ester linkages along the polymer backbone converts these polyester materials into products that the human body can easily metabolize and eliminate them without adverse effects. However, a common prerequisite for designing a nontoxic polymeric material is to choose nontoxic monomers[78]. All of the monomers we have selected are being used as excipients in various formulations in the pharmaceutical industries[77].

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CHAPTER-2

EXPERIMENTAL

2.1 MATERIALS USED AND THEIR PURITY

All the chemicals employed in the present investigation are listed below with their sources and purities.

No.	Materials	Producers	Purity
1	Adipic acid	E. Merck, (India) Ltd. Worli, Mumbai	≥ 99%
2	Acetic acid	BDH-Chemical Ltd. Poole, England	98%
3	Acetone	E. Merck, (India) Ltd. Worli, Mumbai	≥ 99%
4	Anhydrous Ferric chloride	E. Merck, (India) Ltd. Worli, Mumbai	≥ 99%
5	Benzene	E. Merck, (India) Ltd. Worli, Mumbai	≥ 99%
6	Butane-1,4-diol	E. Merck, Darmstadt, Germany	99%
7	Carbon tetrachloride	E. Merck, Darmstadt, Germany	99%
8	Chloroform	BDH-Chemical Ltd. Poole, England	99%
9	Diclofenac sodium	Kemico Laboratories, Rajshahi, Bangladesh	A. R. grade
10	Di-potassium hydrogen orthophosphate	E. Merck, (India) Ltd. Worli, Mumbai.	≥ 99%
11	Di-sodium hydrogen orthophosphte	BDH-Chemical Ltd. Poole, England.	97.5%
12	Ethanol	E. Merck, Darmstadt, Germany.	100%
13	Ethyl acetate	E. Merck, (India) Ltd. Worli, Mumbai.	≥ 99%

14	Formic acid	P.P.H Polskic Odezynnikl Chemiczane, Gliwice, Poland.	85%
15	Glycerol	E. Merck, (India) Ltd. Worli, Mumbai.	98%
16	Hydrochloric acid	BDH-Chemical Ltd. Poole, England.	36-37%
17	Malic acid	E. Merck, (India) Ltd. Worli, Mumbai.	≥ 99%
18	Maleic acid	E. Merck, (India) Ltd. Worli, Mumbai.	≥ 99%
19	Methanol	E. Merck, Darmstadt, Germany.	99%
20	Naproxen	Beximco Pharmaceuticals Ltd., Dhaka, Bangladesh	A. R. grade
21	O-xylene	E. Merck, Darmstadt, Germany.	98%
22	Potassium-di-hydrogen orthophosphate	E. Merck, (India) Ltd. Worli, Mumbai.	≥ 99%
23	Potassium hydroxide	Riedel, de Hoen, Germany.	85%
24	Phenolphthalein	BDH-Chemical Ltd. Poole, England.	--------
25	Rectified Sprit (R.S)	Carew & Co. Ltd. Bangladesh.	75%
26	Sodium carbonate	E. Merck, (India) Ltd. Worli, Mumbai.	99.9%
27	Sodium chloride	BDH-Chemical Ltd. Poole, England.	99.9%
28	Succinic acid	BDH- Chemical Ltd. Poole, England.	99.9%
29	Sulfuric acid	E. Merck, (India) Ltd. Worli, Mumbai.	98%
30	Toluene	E. Merck, (India) Ltd. Worli, Mumbai.	≥ 99%

2.2 INSTRUMENTS & EQUIPMENTS

The following instruments & equipments were used in the investigation:

1. Dean-Stark apparatus.
2. Round bottom flask.
3. Condenser.
4. Burette, pipette, conical flask, thermometer, beaker.
5. Desiccator.
6. Heating mantle and regulator.
7. Vacuum pump.

   Type: Edward High Vacuum Crawly F-550 (England).
8. Electric balance.

   Type: H-51, Metter Instrument Co. (Switzerland).
9. IR- spectrophotometer.

   Type: SHIMADZU Model-500 (500-4000 cm^{-1} wave no.) made in Japan.
10. pH meter.

    Type: pHS-3C, made by Shanghai Rex Instrument Factory, China.
11. Water bath (thermostatic).

    Type: HH-S (Stainless steel), Made in India.
12. Vacuum oven.

    Type: Townson-Mercer, (England).
13. Tablet Dissolution Tester.

    Type: USP type-XXII, "ELECTROLAB TDT-01", made in USA.
14. UV-spectrophotometer.

    Type: UV-VIS Spectrophotometer (Model: U-1800), Made by HITACHI High Technologies Corporation, Tokyo, Japan.

2.3 SOLUTION PREPARATION

2.3.1 Alcoholic 0.1N KOH solution

5.611g of KOH pellets was taken in a 1000 ml volumetric flask and filled up to the mark by adding absolute ethyl alcohol. This solution was titrated with 0.1N standard succinic acid solution to obtain its accurate strength and was used for the molecular weight determination (end group analysis).

2.3.2 Standard 0.1N succinic acid solution

1.475g of succinic acid was taken in a 250 ml volumetric flask and filled up to the mark by adding distilled water. This solution was used to standardize alcoholic 0.1N KOH solution.

2.3.3 Phenolphthalein solution

0.25 g of powered phenolphthalein was dissolved in 25ml of ethyl alcohol and to it 25 ml of distilled water was added with constant stirring. The solution was filtered and used as indicator.

2.3.4 Hydrochloric acid solution

A requisite amount of conc. hydrochloric acid was taken in a beaker, diluted with dist. water to desired pH value and used for the acid hydrolytic test.

2.3.5 Sodium carbonate solution

A few gram of powdered sodium carbonate was taken in a beaker and dissolved in a few ml of distilled water to make concentrated solution. This solution was diluted to maintain different pH values in separate beakers. These solutions were used for the base hydrolytic test.

2.3.6 Simulated gastric fluid (pH-1.2)[1]

2 g of NaCI and 7ml of cone. HCl were dissolved in distilled water to make 1 litter solution and its pH was adjusted to 1.2. This solution was used as the simulated gastric fluid.

2.3.7 Simulated intestinal fluid (pH-7.4)[1]

4.35 of K_2HPO_4 and 3.42 gm of KH_2PO4 (dried for 2 hours at 110-130°C) were separately dissolved in CO_2 free distilled water. Then the two solutions were mixed at different ratios to maintain pH-7.4. This solution was used as the simulated intestinal fluid.

2.3.8 Diclofenac sodium and naproxen standard solution

A certain amount of pure diclofenac sodium or pure naproxen was dissolved in phosphate buffer medium to make 1000ml solution. These solutions were used for the preparation of the standard calibration curves of diclofenac sodium and naproxen in experimental buffer solution spectrophotometrically.

2.4 MATERIALS AND THEIR PURIFICATION

The various materials used in typical polymer synthesis were purified, since chemical purity is especially important to produce polymer of good quality.

2.4.1 Monomer and catalysts

Monomers were A. R. grade chemicals from E. Merck Ltd. and were used as such. Anhydrous $FeCl_3$ (A.R. grade chemical, E. Merck Ltd.), used as catalyst, was freshly sublimed before use.[2]

2.4.2 Solvents

Distilled water was redistilled form alkaline potassium permanganate solution by an 'all glass' distilling apparatus. The other solvents acetone, benzene, chloroform, toluene, etc. were A. R. grade chemicals and were used as such.

2.5 SYNTHESIS OF POLYMER

All of the four polymers were synthesized using Dean-Stark apparatus. Here the corresponding monomers of a polymer in desired composition and ratios were taken along with anhydrous $FeCl_3$ (approximately o.4% of the total weight) as catalyst in a 250ml round bottom flask and then 50-60ml xylene was added to it as the reaction medium. The flask was connected to a Dean-Stark apparatus for eliminating water (by-product of poly-condensation reaction) azeotropically with xylene. In all the cases, the reaction mixtures were heated at 130-140°C under nitrogen atmosphere for 5-6 hours. When elimination of water subsided, the reaction mixture was heated for additional one hour under the same condition to ensure the completion of reaction[3].The synthesized polymer was then collected from the vessel using a suitable solvent.

2.6 PURIFICATION OF POLYMER

Polymer formed will, however, be contaminated with the un-reacted monomer, catalyst, solvent and hence, need to be isolated and purified. The polymer was insoluble in water but soluble in common organic solvents. On the other hand, monomers and catalyst were soluble in water but insoluble in organic solvents such as acetone, ethanol, ethyl acetate, toluene etc.

The purification of a synthesized polymer was performed by precipitating it using a suitable non-solvent. Firstly, the polymer was dissolved in a suitable solvent and diluted to 2-5% concentration and then it was added as a thin stream to a large volume of water (non-solvent) under vigorous stirring. The non-solvent should be freely miscible both with the solvent and the monomers in all proportions. Polymer being precipitated from the solution with water was separated out as solid lump. Re-dissolving & re-precipitating of the polymer a couple of times, improved the purity of the polymer. After purification, the polymer sample was then vacuum dried at 60°C and finally stored in a vacuum desiccator.

2.7 CHARACTERIZATION OF THE POLYMER

2.7.1 Solubility Test

Solubility behavior of the synthesized polymer was studied in various solvents. The solvents were alcohol, acetone, acetic acid, formic acid, toluene, mixed solvent (Toluene: ethanol = 3:1), ethyl acetate, chloroform, xylene, rectified sprit (R. S), benzene, carbon tetrachloride and water.

2.7.2 Measurement of Swelling

In swelling experiments, the samples were cut into suitable slices and vacuum dried at 50^0C to constant weight. The slice was then placed in a suitable non-solvent in a beaker. After 6 hours intervals the slice was taken out of the solvent and its surface was dried by a piece of blotting paper and it was weighed till there was no more increase in weight. The final increase in weight gave the equilibrium swelling[2].

2.7.3 Fractionation of Polymer [4]

For fractionation, a dilute solution (1-2%) of the polymer in a poor solvent was taken in a sufficient large container with stirring provision and drop-wise addition of the non-solvent. The whole setup was in thermostatic condition so as to maintain a constant temperature. Since dissolution and precipitation are equilibrium processes and sensitive to temperature change, the whole process of fractional precipitation was carried out at a constant temperature for effective fractionation. As non-solvent was added drop-wise with continuous starring, turbidity appears, indicating the precipitation of the highest molecular weight species. When sufficient turbidity has been developed, the addition of the non-solvent was stopped and the content was slowly heated till the turbidity disappears. At that time, the precipitated polymer gets re-dissolved at slightly higher temperature. As this stage, the stirring was stopped and the set up was allowed to cool down slowly to the original precipitation temperature. Now the turbidity reappears. Finally, the gel like turbid substance was carefully separated by siphoning without disturbing the clear solution. Then non-solvent was added to the clear solution and the whole sequence of operations repeated again and again to separate the second, third and other fractions. Our experiment was carried out by using water as a non-solvent and ethanol as a solvent.

2.7.4 Determination of Molecular Weight

Molecular weight of polymer was determined following end group analysis and the viscosity method. End group analysis depends on the total number of molecules present in a system, hence the number average molecular weight was obtained. Then this number average molecular

weight was applied to find out the values of constants 'K' and 'a' (Mark-Houwink[5] constants) to determine the viscosity average molecular weight.

A. End group analysis

Apparatus: 1) Conical flask 2) Burette 3) Pipette 4) Electric balance.

Materials: Polyester (sample), suitable solvent, 0.1 (N) alcoholic potassium hydroxide solutions, phenolphthalein (indicator).

Procedure: A precisely weighed quantity (less than 1gm) of the polyester sample was dissolved in a suitable solvent. This was titrated against 0.1(N) alcoholic potassium hydroxide solution using phenolphthalein as indicator. The end point was the appearance of a slightly pink color.

Let,

The volume of KOH consumed = V ml

Normality of KOH solution = N

Weight of the sample = W g

Carboxyl value = $\frac{VN(56.1)}{W}$ g of KOH/gm

Carboxyl equivalent = $\frac{VN(56.1)}{W(1000)} \times \frac{100}{56.1} = \frac{VN}{10W}$

If the functionality was 1, then we get

$$\overline{M_n} = \frac{1 \times 1000 \times W}{V \times N}$$

B. Viscosity method

Different fractions of polymer sample were taken and for each fraction, the molecular weight was determined by end group analysis ($\overline{M_n}$). The intrinsic viscosity of each fraction was found out by the following method:

For each fraction, a number of solutions of different known concentrations (g/ml) of the polymer sample were made. Efflux times of the solvent and the solutions of different concentrations were measured using Ostwald viscometer. For each concentration, the corresponding reduced viscosity was calculated, graphed (reduced viscosity vs. concentration) and was extrapolated to zero concentration. The common ordinate intercept of these graphs gave the intrinsic viscosity.

Finally the logarithms of the intrinsic viscosities of these polymers were plotted against the logarithms of their molecular weights ($\overline{M_n}$) and a linear curve was obtained. The ordinate intercept and the slope of the curve gave the values of constants 'K' and 'a' respectively. The molecular weight ($\overline{M_v}$) of the polymer samples were calculated by putting the values of 'K' and 'a' in the Mark-Houwink equation,

$$[\eta] = K\left(\overline{M_v}\right)^a$$

2.7.5 Recording of IR Spectra

IR spectra of polymers were recorded using a SHIMADZU Model-470 IR-spectrophotometer (500-4000 cm^{-1} wave no.). For this purpose, the polymer sample was dissolved in a suitable volatile organic solvent (such as acetone in the case of maleic acid-butane 1,4-diol polyester) and a thin

film on KBr pellet surface was produced by putting a drop on it. After the solvent being evaporated its IR spectrum was recorded.

2.7.6 Elemental Analysis

The elemental analysis of the polymer was carried out for C and H. The results of the analysis were kindly supplied by the Central Drug Research Institute, Lucknow, India.

2.7.7 Soil Degradation Test

Soil degradation test was carried out according to the procedure used by Potts et al.[6] For this purpose a number of beakers (250ml) were taken and filled with gray color soil form the garden. The soil in the beakers were blended properly and a polymer sample weighing about 0.2gm was placed in the mid of each of the beakers at a depth of 2 inches. The soils in the beakers were kept constantly wet with water. The laboratory temperature was around 25^0C during the day time and 20^0C in the night time. The beakers were numbered for each of the samples to give its identity.

Then after regular intervals of 15 days one of the beakers was taken out and the polymer placed on it was found out, washed gently with water to remove soil adhered on its surface and then dried at 60° C under vacuum until constant weight was obtained. Weight loss of the polymer in the soil with respect to time was recorded as a mark of its degradation. Three sets were taken together and their average results were taken into account.

2.7.8 Hydrolytic Degradation Study[7]

1. In acid medium

Hydrochloric acid was used for this purpose. Polyester sample was cut into suitable slices and were placed in solutions of different pH values in separate conical flasks. Conical flasks were sealed with rubber corks. After a suitable time interval, its pH was measured up to 8 hours by a pH-meter at room temperature. Results were plotter in graph and compared with blank acid solutions.

2. In Basic medium

Sodium carbonate was used for this purpose. The solutions of different pH values of sodium carbonate were taken in separate conical flasks and closed with rubber corks. Suitable size of the polymer (about 1g in weight) was placed in each of the conical flasks containing 50ml of sodium carbonate solution at room temperature and pH values of these solutions were measured time to time and compared with blank sodium carbonate solution.

2.8 *IN-VITRO* DRUG RELEASE PROFILES OF THE POLYMERS

2.8.1 Coating of the Core (Uncoated) Tablets

Individually, three polymers (namely: MBP, MAPC and MABC), among four under investigation, were used as coating material. Each of the polyesters was dissolved in acetone separately to prepare its 40% solution, which was sprayed over the tablets (either diclofenac sodium or naproxen core tablets) in a small coating pan with continuous hot air flow. The coating pan was allowed to rotate until the solvent evaporated and the tablets dried.

2.8.2 Preparation of Drug-Polymer Matrix Tablets[8]

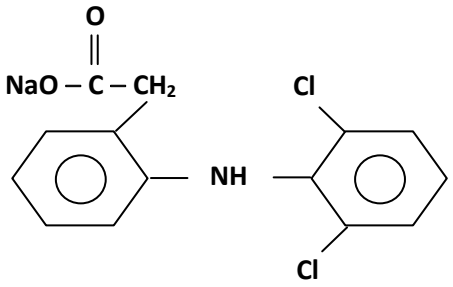
Maleic acid- citric acid-propane-1,2-diol co-polyester (MCPC) was used to prepare diclofenac sodium matrix tablets. For this, 100mg of the polyester sample was taken in a beaker, melted until it softened sufficiently and 50mg pure diclofenac sodium (drug: polymer=1:2) was gradually added with continuous stirring until uniformly mixed. The polyester-drug mixture was allowed to cool, solidify at room temperature and then passed through a sieve (mesh no. 25) followed by crushing in a mortar. The granules, thus made, were compressed in a single punched tablet machine to get them in a tablet form.

2.8.3 Preparation of Standard Calibration Curves for Drug Release Measurement

For the preparation of standard curves of the drugs for their quantitative determination in the subsequent experiments, phosphate buffer solution of pH 7.4 was used as the medium. Absorbances of some known solutions of the drug were measured at its λ_{max} on a UV-VIS (Model: U-1800) spectrophotometer. The standard curve was then constructed by plotting the absorbance of the drug against its concentration in the suitable region.

Diclofenac Sodium: Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) taken or applied to reduce inflammation. It has anti-pyretic properties and also used as an analgesic to reduce pain in certain conditions. It is the sodium salt of 2-(2, 6-dichloranilino) phenyl acetic acid. It was originally developed by Ciba-Geigy (now Novartis) in 1973 and came to market in 1979. Gastrointestinal disturbances are the major adverse effects associated with orally administrated diclofenac

therapy and because of this the drug is usually formulated as enteric coated tablets. Enteric coated dosage forms release drugs in the intestine and have been reported to decrease gastric irritation.

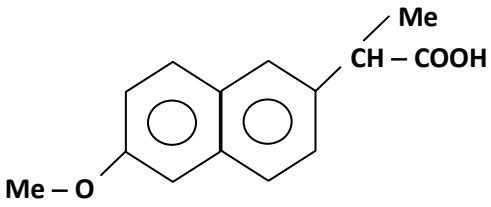


Molecular Structure of Diclofenac Sodium

Molecular weight of diclofenac sodium: 318

λ_{max} diclofenac sodium: 274nm

Naproxen: Naproxen is a non-steroidal, anti-inflammatory drug (NSAID) with potent analgesic and antipyretic properties. It is a propanoic acid derivative related to the aryl acetic acid. Its systematic IUPAC name is 2-(6-methoxynaphthalen-2-yl) propanoic acid.



Molecular Structure of Naproxen

Molecular weight of Naproxen: 230.3

λ_{max} of Naproxen: 332nm

2.8.4 Dissolution Studies

The dissolution of the core (uncoated) tablets, polymer coated tablets[9] and drug-polymer matrix tablets[10] were performed in order to evaluate the efficiency of the polymer(s) as an enteric coating material or as a drug carrier. A USP type-XXII tablet dissolution test apparatus (ELECTROLAB TDT-01) employing a paddle stirrer (paddle rotation speed of 50 rpm) was used for dissolution experiments. A solution of pH-1.2 was used as the simulated gastric fluid and a phosphate buffer solution of pH-7.4 was used as the simulated intestinal fluid. One liter of simulated gastric fluid heated at 37±0.5°C was used initially for the dissolution studies and this solution was replaced after 2 hours by one liter of simulated intestine fluid heated previously at 37°C. Samples (5ml) were withdrawn from the simulated gastric fluid at 30 minutes intervals for 2 hours and from simulated intestinal fluid at 15 minutes intervals for 1 hour and volumes of simulated fluids were immediately compensated with the same amount of fresh medium preheated at 37±0.5°C.

The amount of drug release was calculated by measuring the absorbance of the release medium after suitable dilution if necessary at 274 nm for diclofenac sodium and 332 nm for naproxen using a UV-VIS (Model: U-1800) spectrophotometer with the help of the corresponding calibration curve.

Table 2.1: Calibration of UV-spectrophotometer for diclofenac sodium.

Concentration of standard diclofenac sodium solution, (mgL^{-1})	Optical density at 274 nm
5	0.130
10	0.261
15	0.392
20	0.522
25	0.647
30	0.781
35	0.913
40	1.041
45	1.170
50	1.330

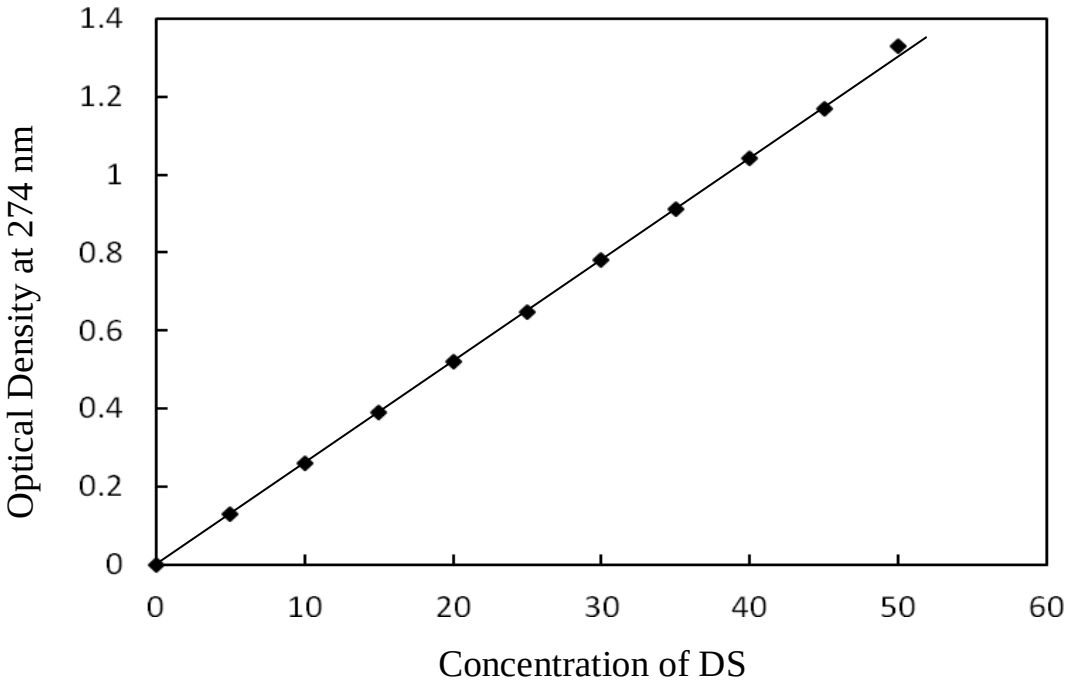


Fig. 2.1: Calibration curve for diclofenac sodium (DS).

Table 2.2: Calibration of UV-spectrophotometer for naproxen.

Concentration of standard naproxen solution, (mgL^{-1})	**Optical density at 332 nm**
50	0.033
100	0.065
150	0.098
200	0.130
250	0.160
300	0.194
350	0.222
400	0.253
450	0.286
500	0.320

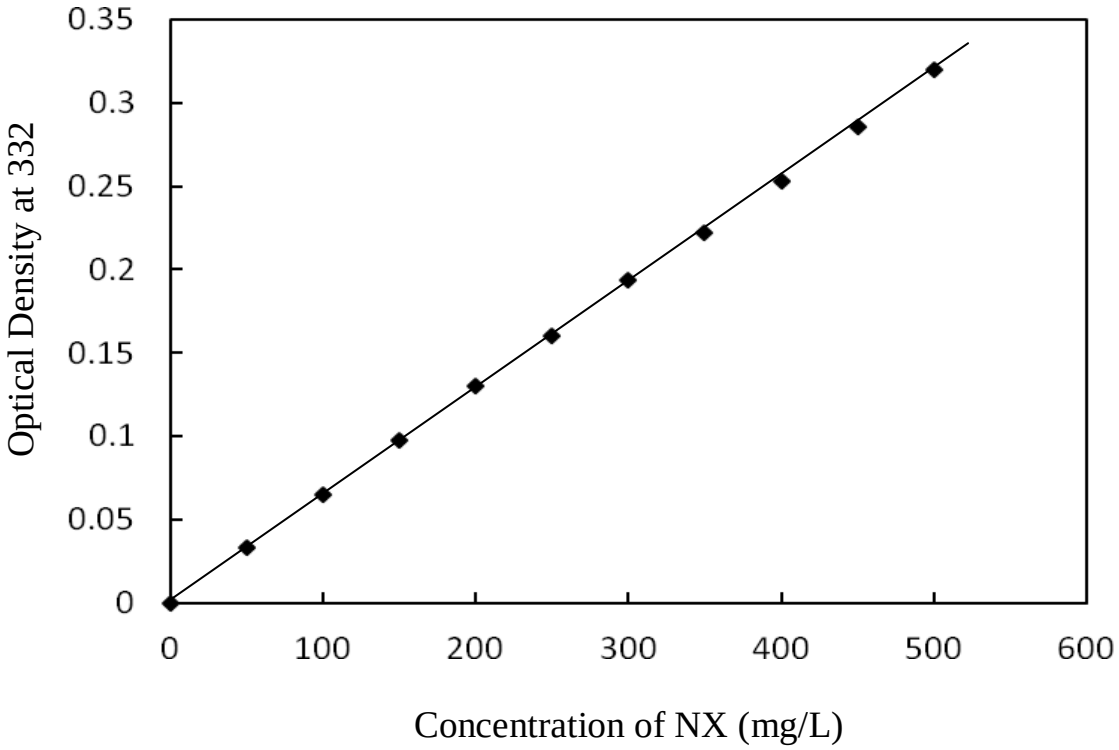


Fig. 2.2: Calibration curve for Naproxen (NX)

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CHAPTER-3

DRUG RELEASE PATTERN OF MALEIC ACID-BUTANE-1,4-DIOL POLYESTER

3.1 INTRODUCTION

For the last few decades, a brisk research activity is going on the development of biodegradable polymers for a variety of medical applications such as surgical sutures, orthopedic implants, scaffolds for tissue engineering as well as vehicles for controlled and sustained release of drugs[1-2]. Among these biodegradable polymers, the aliphatic polyesters such as polylactide (PLA), polyglycolide (PGA) and their copolymers are of great interest for applications in biological and biomedical areas due to their desirable properties of biodegradability, biocompatibility and permeability[3].

Our gastro-intestinal tract (GIT) consists of several different sections, each with a special anatomy (structure) and physiology (function)[4]. Thus the orally administered drug passes through several regions of different environments in the GIT. The successful targeting of therapeutic agents to any specific area of the GIT, via the oral route, requires both the exploration of a unique feature of the site and also the protection of the active agent until it reaches the target site[5]. Polymers, such as, cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HMP), polyvinyl acetate phthalate (PVAP), etc. have the property to remain intact in the acidic environment of the stomach but are susceptible in the basic pH of the intestinal fluid. Because of having such pH responsive characteristics, these polymers are being commercially used as enteric coatings in oral solid formulations for targeting the drug to release

in the small intestine where the pH is much higher than that in the stomach[6]. However, many recent *in-vivo* studies have suggested that various phthalates and their metabolites could be responsible to develop toxicity as well as liver tumors in mammals.[7-8]

Our research work is directed towards the synthesis and characterization of new biodegradable and flexible materials based on polyester but free of phthalates which can successfully be applicable for the controlled delivery of intestine targeted drugs. In this connection, we have chalked out to synthesize and investigate maleic acid-butane-1,4-diol polyester. Maleic acid is commonly used in the pharmaceutical industries as a drug intermediate to form the maleate salts of several categories of therapeutic agents, such as salts of antihistamines and other drug substances[9].The biomedical use of butane-1,4-diol derivatives have also been reported[10-11]. So, Hydrolysis of labile ester linkages along this polyester backbone could possibly convert it into products that the human body can easily metabolize and/or eliminate them without adverse effects after the delivery of the drugs being over.

In this chapter, we report synthesis, characterization, bio-degradation and intestine targeted *in-vitro* drug delivery profile of maleic acid-butane-1,4-diol polyester.

3.2 EXPERIMENTAL

3.2.1 Synthesis

Apparatus: 1) Dean-Stark apparatus 2) R. B. flask 3) Thermometer (range = 0-350^{0}C) 4) Heating mantle with regulator 5) condenser and 6) Vacuum desiccator.

Materials: All of the monomers were A. R. grade chemicals and all were used as such. p-toluene sulphonic acid (A.R. grade chemical), used as catalyst, was freshly sublimed before use.[12]

Procedure: Maleic acid-butane-1,4-diol polyester (MBP) was synthesized using Dean-Stark apparatus and xylene as the reaction medium. The corresponding monomers in desired ratio (maleic acid: butane-1,4-diol=1:1) together with p-toluene sulphonic acid (approximately o.4% of the total weight of the reactants) was heated at 135-140^{0}C until elimination of water subsided (about 5 hours) followed by one hour post curing under the same condition. After being cooled, the synthesized polymer was collected from the reaction vessel by dissolving it in acetone and purified by precipitating using water as non-solvent. This polymer was then vacuum dried at 60^{0}C and was stored in a desiccator. The details of synthesis and purification techniques have been described in **Chapter-2**.

3.2.2 Characterization

The polyester was characterized by its solubility in common organic solvents at the ambient temperature, molecular weight, IR spectrum, elemental analysis and degradation study in the soil. The polyester was insoluble in water but readily soluble in acetone and ethylacetate. Molecular weight determination was carried out by end group analysis and viscosity method. All tests were accomplished through the experimental procedures described in **Chapter-2**.

3.2.3 Hydrolytic Degradation Study

Hydrolytic degradation study was carried out to evaluate the pH responsive property of the polymer. If it can withstand in acidic media

but degraded in basic media then there is an indication of its possible use in intestine targeted drug delivery. This study was done in both acid and alkali solutions of various pH values. Hydrochloric acid and sodium carbonate were used to prepare solutions of different pH values. The change of pH of the polymer sample containing solutions with respect to time was considered as an indication of the degradation of the polyester. The detail of the study was described in **Chapter-2**.

3.2.4 Coating of the Core (Uncoated) Tablets

Maleic acid-butane-1,4-diol polyester (MBP) was used as coating material on uncoated diclofenac sodium (50 mg) and naproxen (500mg) tablets. The detail of the coating procedure is available in Chapter-2. Drug release from the coated tablet was tried as a function of weight gain of the core tablet by the coating material and 10-12% weight gain gave the best result.

3.2.5 Drug Dissolution Study

The dissolution studies for both the core and polymer coated tablets were performed with a view to evaluating the efficacy of the investigating polymer as a coating material on the release of the drug in the intestine but not in the stomach. A USP type-XXII dissolution apparatus 'ELECTROLAB TDT-O1' was used for dissolution experiments. The *in-vitro* drug release from the core and the polymer coated tablets in simulated physiological environments (simulated gastric and intestinal fluids) according to the guidelines of British Pharmacopoeia[13] was performed spectrophotometrically by recording the absorbance of the dissolution medium at the λ_{max} of the corresponding drug as a function of time. Five samples of each tablet (core and MBP coated) were tested in

this way and concentrations of the released drug were then averaged. This process has been described in **Chapter-2**.

3.3 RESULTS AND DISCUSSION

3.3.1 Synthesis

Since both of maleic acid and butane-1,4-diol are bi-functional monomers and their functional groups are positioned identically, their polycondensation with stoichiometric ratio in 1:1 should produce highest molecular weight. The expected structure of MBP would be as shown below:

$$[\text{-OC-CH=CH-CO.O-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-O-}]_n$$

The synthesized MBP samples were brown in color, sticky and slightly transparent at room temperature.

3.3.2 Characterization

Solubility

Solubility of this polyester in various organic solvents at the ambient temperature is presented in Table-3.1. This Table reveals that, acetone and ethylacetate are good solvents for MBP. But it is poorly soluble in toluene and mixed solvent (toluene: ethanol =3:1). However, benzene, xylene, chloroform, formic acid, phenol etc. and water are non-solvents for this polyester.

Fractionation

The synthesized polymer was fractionated at (20±1)°C by precipitation technique (described in **Chapter-2**) using acetone as solvent and water as

non-solvent. The results obtained from the experiments were given in Table-3.2.

Molecular Weight Determination

A. End group analysis

The number average molecular weight ($\overline{M}_n$) of each fraction of MBP was determined by end group analysis. The values of $\overline{M}_n$ for different fractions were found 26295, 25260, 21658, 17615 and 16422 respectively. The weight percentages (wt%) of the fractionated polymer in un-fractionated polymer sample are shown in Table-3.2 & Fig.- 3.1. The table and figure show that the fraction no.-iii of the sample (mol. wt. 21658) has highest in quantity in un-fractionated polymer sample.

B. Viscometry

For each fraction of MBP, a number of solutions of different known concentrations (g/ml) were made. The efflux time of each solution was measured using Ostwald viscometer and then relative viscosity, specific viscosity and reduced viscosity were calculated, which are presented in Tables-3.3-3.7. Reduced viscosity Vs concentration graph was plotted and extrapolated to zero concentration for each fraction as shown in Fig.-3.2. The common ordinate intercepts of these straight lines gave their intrinsic viscosities. The values of intrinsic viscosities and their corresponding molecular weights (obtained by End Group Analysis) of each fraction of the polyester sample are given in Table-3.8. The logarithms of the intrinsic viscosities of these polymer fractions were plotted against the logarithms of their molecular weights ($\overline{M_n}$) and a linear curve was obtained (Fig.-3.3) whose intercept and slope gave the values of Mark-Hauwink constants[14] 'K' and 'a' respectively.

According to Mark-Hauwink equation the relationship between viscosity average molecular weight ($\overline{M}_v$) and intrinsic viscosity can be expressed as:

$$[\eta] = K\left(\overline{M}_v\right)^a = 7.65\times10^{-3}\left(\overline{M}_v\right)^{0.7}$$

Table-3.8 also shows molecular weights of different fractions of this polymer sample obtained by viscosity method. It is observed that the molecular weight of the polymer sample found out by viscometry ($\overline{M}_v$) is greater than that of the same obtained by end group analysis ($\overline{M}_n$).

IR Spectra

The broad band representing the –OH group at the region 3100-3500cm^{-1} in the spectrum of the diol almost disappeared in the spectrum of the polyester (Fig.-3.4). The >C=O stretching frequency at the region 1700-1710cm^{-1} of the spectrum of maleic acid shifted to 1716-1730 cm^{-1} region (Fig.-3.4). A new band representing the ester linkage appeared at 1163cm^{-1} region in the spectrum of MBP (Fig.-3.4). All these indicate the reaction between –OH and –COOH groups and thereby ester linkage is formed in the sample [15,16].

Elemental Analysis

Calculated for expected structure: C = 46. 6% and H = 6.8 %

Found from the polyester sample: C = 46.1% and H = 7.1%.

It is seen that the percentage composition of the sample obtained by calculation nearly matches with the same obtained by analysis. The product is accordingly confirmed.

Soil Degradation Test

Table-3.9 and Fig.-3.5 show the gradual weight loss of the polymer sample buried in soil[17, 18]. MBP ultimately mixed with the soil after 42 days. This is an indication of the total soil degradation of the polyester sample.

3.3.3 Hydrolytic Degradation Study

From the hydrolytic degradation study (Table-3.10 & 3.11 and Fig.-3.6 & 3.7) it was found that the polyester sample remained almost intact in the acid medium (pH 1.2-6.0) but gradually degraded in basic medium (pH>7.0). In acid region the polymer sample swells insignificantly. But in alkaline region it swells and the ester linkage happens to be hydrolyzed resulting the meaningful decrease in the pH of the polymer sample containing solutions with respect to time. Such pH-responsive nature of this polyester has led us to figure out its possible use in intestine targeted drug delivery. In this connection, its *in-vitro* drug release behavior[13] needs to be investigated.

3.3.4 *In-vitro* Drug Release Characteristics (Drug Dissolution Study)

The aim of the intestinal targeted drug delivery is to deliver the drug in the nearly neutral or alkaline environment of the intestine rather than in the acidic environment of the stomach. To know whether our investigating polyester can be useful candidate for this purpose or not, *In-vitro* drug release study was performed and diclofenac sodium (un-coated 50mg tablets) and naproxen (un-coated 500mg tablets) were used as model drugs. These core tablets were separately coated by MBP and the study was carried out in both the simulated gastric fluid (pH 1.2) and in the simulated intestinal fluid (pH 7.4) consecutively. In this study, it was

found that the polyester did not degrade or swell in the gastric fluid for two hours when coated on a core tablet and less than 6% diclofenac sodium and naproxen released from MBP coated tablets, whereas around 42% of diclofenac sodium and 41% of naproxen released from the core tablets (uncoated tablets) in that time in the same media (Table-3.12 and Fig.-3.8 & 3.10). But in the simulated intestinal fluid the coating gradually degraded and drug release was observed from polyester coated tablets and more than 80% of diclofenac sodium and naproxen released within 45 minutes (Table-3.13 and Fig.-3.9 & 3.11). In acid region especially in pH-1.2 the ester linkages are resistant while in alkaline region especially in pH-7.4 they are susceptible and gradually get hydrolyzed. In pH-1.2 the coating remains intact i.e., negligible release of the drug happens. But in alkaline region i.e., in pH-7.4 the polyester swells and degrades resulting in the release of the drug. Therefore, the swelling and hydrolysis of the ester as well as diffusion of drug particles simultaneously play an important role on the release behavior of the drug.

The mean percent release of diclofenac sodium and naproxen from MBP coated tablets (Table-3.14 & Fig.-3.12) corresponds to the British Pharmacopoeia[13] drug release profile of enteric-coated solid oral dosage forms. So, maleic acid-butane-1,4-diol polyester could be usable for targeted drug release in the intestine. However, prior to clinical trial, toxicological and other pharmacological investigations of the polyester need to be performed.

TABLES OF EXPERIMENTAL DATA

Table 3.1: Solubility behavior of maleic acid-butane-1,4-diol polyester (MBP) at ambient temperature.

Solvent	Solubility
Acetone	++
Ethylacetate	++
Mixed Solvent (Toluene: Ethanol =3:1)	+
Toluene	+
Ethanol	-
Acetic acid	-
Benzene	-
Xylene	-
Chloroform	-
Formic acid	-
Phenol	-
Carbon tetrachloride	-
Rectified sprit (R.S)	-
Diethyl ether	-
Water	-

Here (+ +), (+) and (-) indicate high solubility, low solubility and no solubility respectively.

Table 3.2: Molecular weight distribution of fractionated maleic acid-butane-1,4-diol polyester in un-fractionated polymer.

Polymer fraction no.	Weight % of fraction	Mol. wt. by end group analysis ($\overline{M_n}$)
i	14.5	26295
ii	20.9	25260
iii	29.3	21658
iv	19.6	17615
v	15.7	16422

Table 3.3: Viscosity data for maleic acid-butane-1,4-diol polyester ($\overline{M_n}$=26295) in ethyl acetate at 26^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (ethyl acetate), t_0 = 152.3 sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.0040	161.7	1.0617	0.0617	15.43	9.83
0.0030	158.6	1.0414	0.0414	13.80	
0.0025	157.3	1.0328	0.0328	13.12	
0.0020	156.0	1.0243	0.0243	12.15	

Table 3.4: Viscosity data for maleic acid-butane-1,4-diol polyester ($\overline{M_n}$ =25260) in ethyl acetate at 26^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (ethyl acetate), t_0 = 152.3 sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.0046	163.1	1.0709	0.0709	15.41	9.64
0.0030	158.3	1.0394	0.0394	13.13	
0.0023	156.6	1.0282	0.0282	12.26	
0.0015	154.8	1.0164	0.0164	10.93	

Table 3.5: Viscosity data for maleic acid-butane-1,4-diol polyester ($\overline{M_n}$ =21658) in ethyl acetate at 26^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (ethyl acetate), t_0 = 152.3 sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.0050	163.0	1.0703	0.0703	14.06	8.43
0.0040	160.1	1.0512	0.0512	12.80	
0.0025	156.5	1.0276	0.0276	11.04	
0.0020	155.5	1.0210	0.0210	10.50	

Table 3.6: Viscosity data for maleic acid-butane-1,4-diol polyester ($\overline{M_n}$ =17615) in ethyl acetate at 26^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (ethyl acetate), t_0 = 152.3 sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.0060	164.4	1.0795	0.0795	13.25	7.40
0.0052	162.1	1.0643	0.0643	12.37	
0.0038	158.7	1.0420	0.0420	11.05	
0.0030	156.9	1.0302	0.0302	10.07	

Table 3.7: Viscosity data for maleic acid-butane-1,4-diol polyester ($\overline{M_n}$ =16422) in ethyl acetate at 26^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (ethyl acetate), t_0 = 152.3 sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.0064	164.8	1.0821	0.0821	12.83	7.06
0.0050	161.1	1.0578	0.0578	11.56	
0.0032	157.1	1.0315	0.0315	9.84	
0.0025	155.8	1.0230	0.0230	9.20	

Table 3.8: Comparison between molecular weights obtained by end group analysis and the same obtained by viscosity method.

Fraction no.	*Intrinsic* viscosity, $[\eta]$ ml/g (from graph)	$K \times 10^3$ (from graph)ml/g	a (from graph)	Molecular weight by	
				End group analysis($\overline{M}_n$)	Viscosity method($\overline{M}_v$)
i	9.83	7.65	0.7	26295	27623
ii	9.64			25260	26863
iii	8.43			21658	22481
iv	7.40			17615	18412
v	7.06			16422	17221

Table 3.9: Soil degradation of MBP at normal weathering condition.

Time (days)	**% of weight loss**
7	17.5
14	35.1
21	52.6
28	72.3
35	84.6
42	100

Table 3.10: pH-responsive characteristics (hydrolytic degradation study) of maleic acid-butane-1,4-diol polyester in acid media [HCl solution] at room temperature.

Reading	Time (hour)	Initial pH=1.24		Initial pH=2.68		Initial pH=4.19		Initial pH=5.33		Initial pH=6.42	
		pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)
1	0	1.24	1.24	2.68	2.68	4.19	4.19	5.33	5.33	6.42	6.42
2	1	1.24	1.24	2.68	2.68	4.19	4.19	5.33	5.33	6.42	6.42
3	2	1.23	1.23	2.67	2.66	4.19	4.18	5.32	5.31	6.42	6.37
4	3	1.23	1.22	2.67	2.65	4.18	4.18	5.32	5.31	6.42	6.34
5	4	1.22	1.22	2.66	2.65	4.18	4.17	5.31	5.30	6.40	6.30
6	5	1.22	1.22	2.66	2.64	4.18	4.17	5.31	5.30	6.40	6.28
7	6	1.22	1.21	2.66	2.64	4.17	4.16	5.31	5.30	6.39	6.25
8	7	1.21	1.21	2.65	2.63	4.16	4.15	5.30	5.29	6.39	6.20
9	8	1.21	1.21	2.65	2.63	4.16	4.15	5.30	5.29	6.38	6.12

Table 3.11: pH-responsive characteristics (hydrolytic degradation study) of maleic acid-butane-1,4-diol polyester in basic media [Na_2CO_3 solution] at room temperature.

Reading	Time (hour)	Initial pH=7.42		Initial pH=8.25		Initial pH=9.18		Initial pH=10.42	
		pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)
1	0	7.42	7.42	8.25	8.25	9.18	9.18	10.42	10.42
2	1	7.42	7.30	8.25	8.07	9.18	8.97	10.42	10.13
3	2	7.41	7.21	8.24	7.88	9.17	8.78	10.41	9.85
4	3	7.41	7.11	8.24	7.72	9.17	8.58	10.41	9.59
5	4	7.41	7.01	8.24	7.56	9.17	8.45	10.41	9.34
6	5	7.40	6.89	8.23	7.42	9.16	8.32	10.40	9.14
7	6	7.40	6.80	8.23	7.28	9.16	8.21	10.40	9.05
8	7	7.40	6.69	8.23	7.14	9.16	8.11	10.39	8.94
9	8	7.40	6.52	8.22	7.01	9.15	8.02	10.38	8.83

Table 3.12: In vitro drug release study of diclofenac sodium (DS) and Naproxen (NX) core tablets coated by maleic acid-butane-1,4-diol polyester in simulated gastric fluid (pH = 1.2).

Sample	% of drug release							
	Time (30 min.)		Time (60 min.)		Time (90 min.)		Time (120 min.)	
	DS	NX	DS	NX	DS	NX	DS	NX
Core	7.23	6.50	19.46	18.68	29.23	28.88	41.86	41.05
Tab-1	1.12	0.69	2.87	1.46	4.30	3.38	5.35	4.22
Tab-2	1.25	0.74	2.63	1.53	4.16	3.48	5.43	4.87
Tab-3	1.33	0.57	2.10	1.35	3.95	3.27	4.98	4.61
Tab-4	1.17	0.65	2.53	1.44	4.25	3.35	5.28	4.94
Tab-5	1.20	0.50	2.25	1.32	4.03	3.02	5.50	4.35

Table 3.13: In vitro drug release study of diclofenac sodium (DS) and Naproxen (NX) core tablets coated by maleic acid-butane-1,4-diol polyester in simulated intestinal fluid (pH =7.4).

Sample	% of drug release							
	Time (15min.)		Time (30min.)		Time (45min.)		Time (60min.)	
	DS	NX	DS	NX	DS	NX	DS	NX
Core	66.50	62.45	88.74	84.36	99.12	98.10	99.74	99.35
Tab-1	33.37	29.10	60.49	56.00	85.39	83.10	98.63	97.53
Tab-2	34.38	28.94	61.52	54.67	86.25	81.72	98.67	97.17
Tab-3	32.26	28.33	59.33	55.30	85.41	82.98	98.45	96.90
Tab-4	33.34	28.67	60.46	57.56	85.55	84.35	98.60	97.45
Tab-5	33.25	29.43	60.35	57.20	85.30	85.25	98.77	96.58

Table 3.14: Mean percent of drug release from diclofenac sodium (DS) and Naproxen (NX) core tablets coated by maleic acid-butane-1,4-diol polyester in simulated gastric fluid (pH = 1.2) and intestinal fluid (pH =7.4).

Mean % of drug release in simulated gastric fluid (pH=1.20)								Mean % of drug release in simulated intestinal fluid (pH = 7.40)							
30 min.		60 min.		90 min.		120 min.		135 min.		150 min.		165 min.		180 min.	
DS	NX	DS	NX	DS	NX	DS	NX	DS	NX	DS	NX	DS	NX	DS	NX
1.21	0.63	2.48	1.42	4.12	3.30	5.31	4.60	33.32	28.90	60.43	56.15	85.58	83.44	98.62	97.13

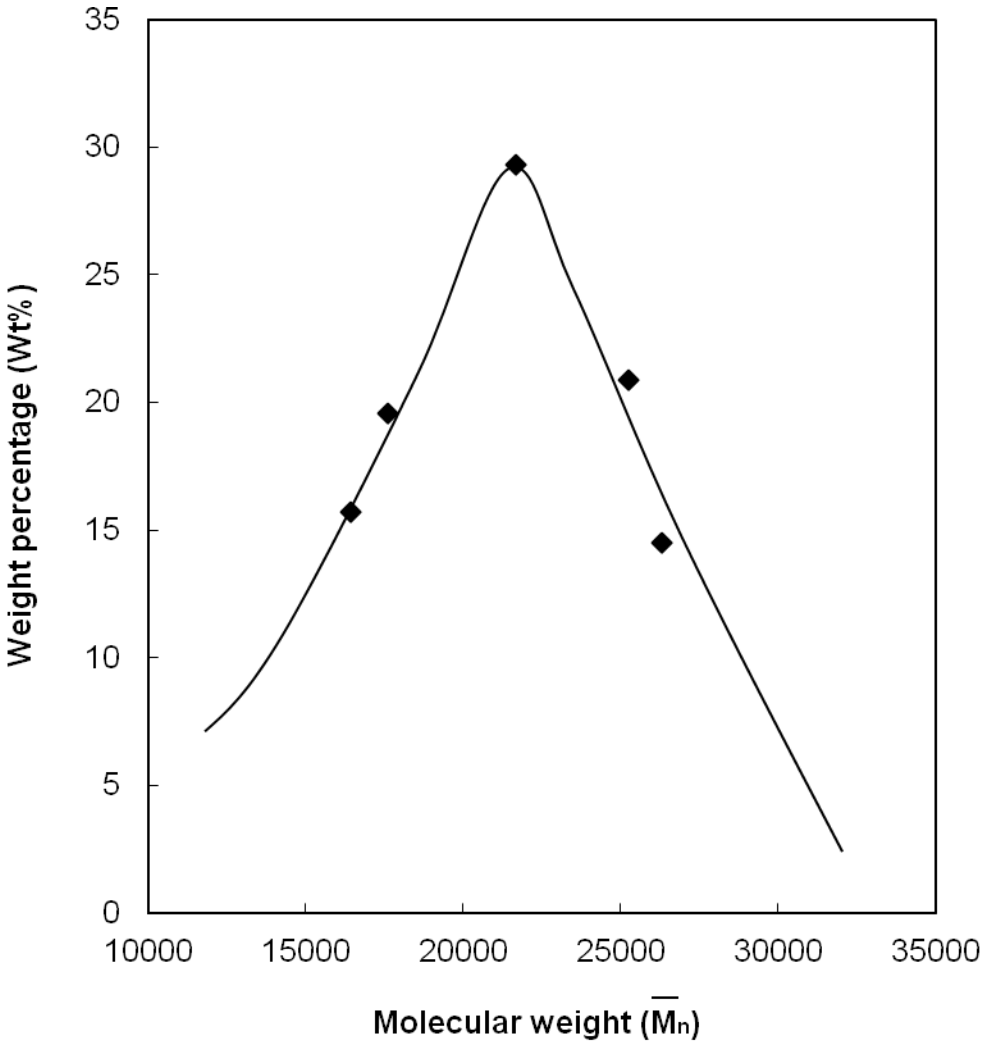

Fig. 3.1 : Molecular weight distribution curve of fractionated maleic acid-butane-1,4-diol polyester in unfractionated sample.

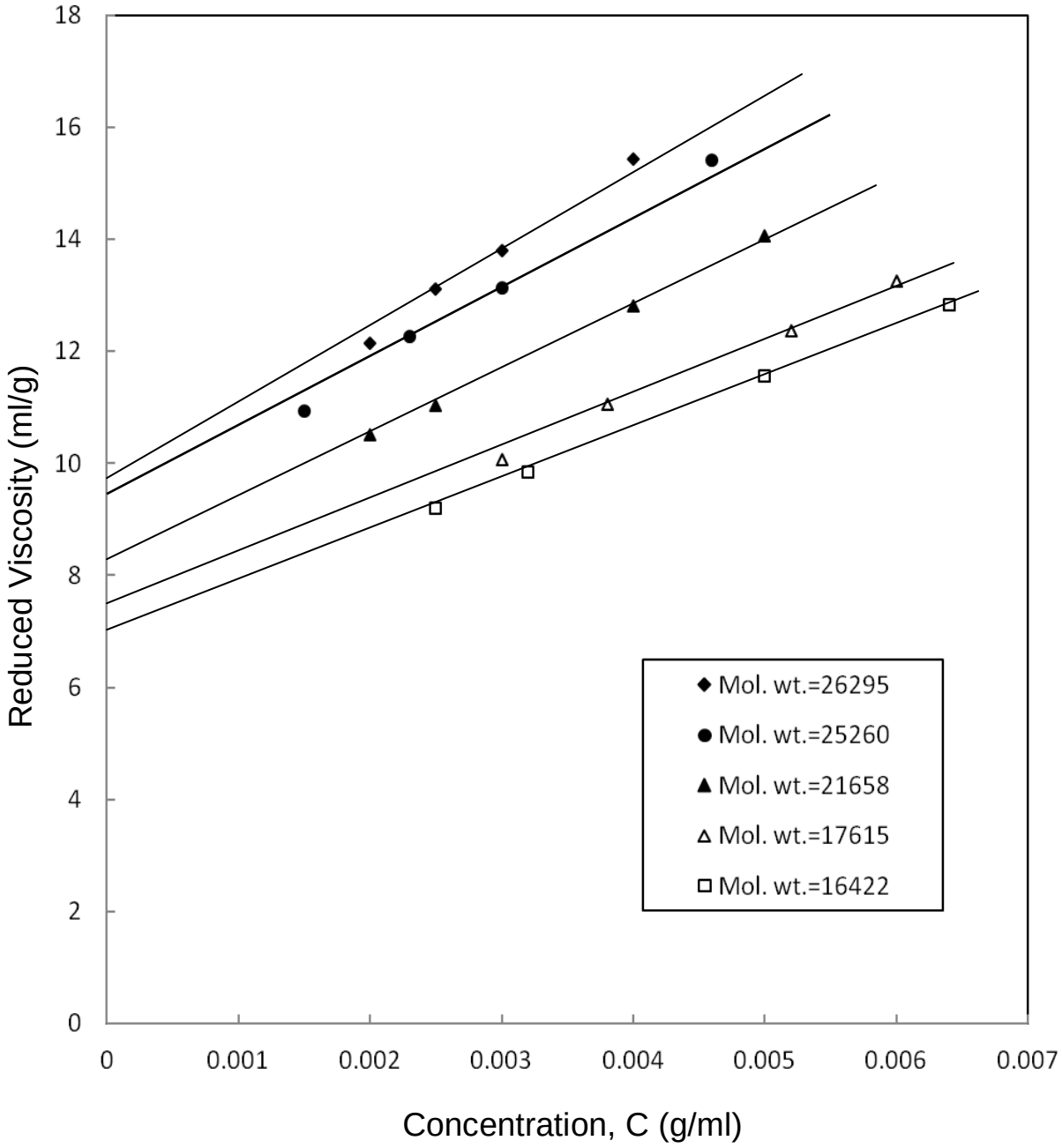

Fig. 3.2 : Plots of concentration Vs reduced viscosity for maleic acid-butane-1,4-diol polyester of different fractions in ethylacetate at 26^0C.

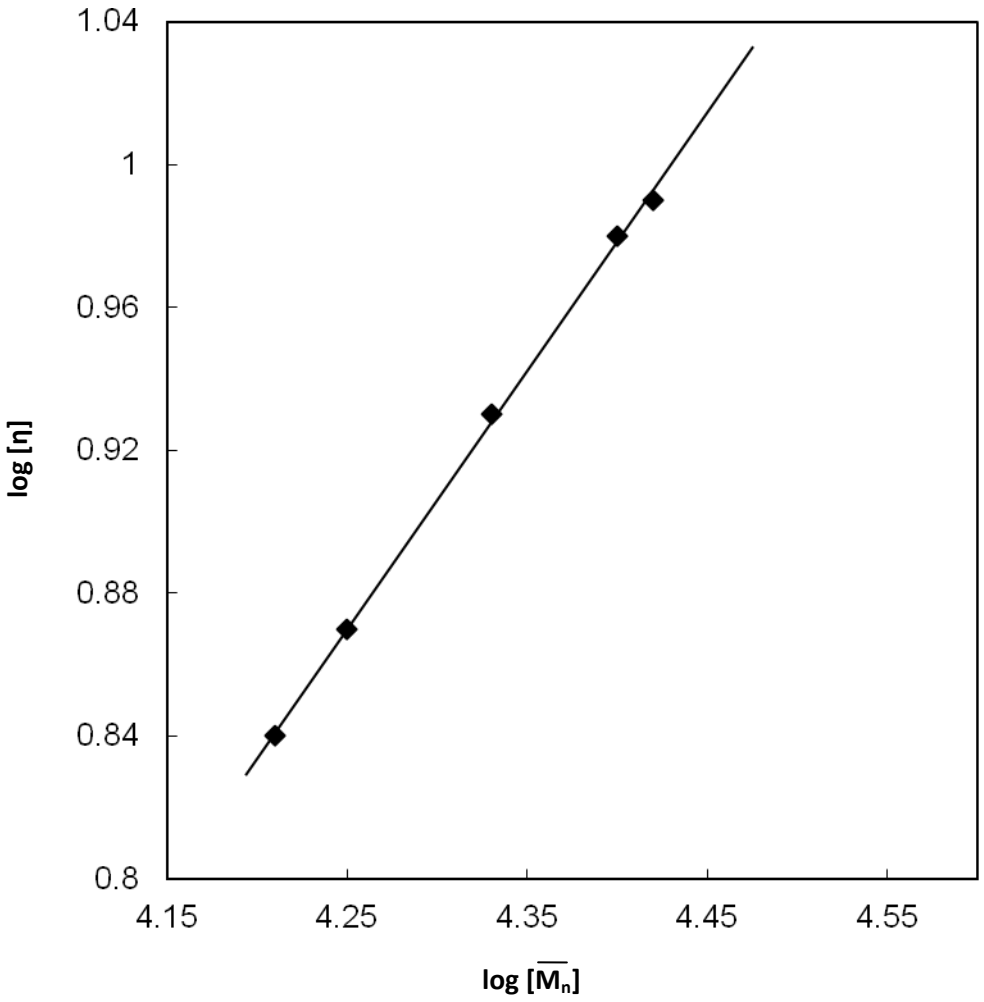

Fig. 3.3 : log of intrinsic viscosity Vs log of molecular weight relationship for maleic acid-butane-1,4-diol polyester in ethylacetate at 26°C.

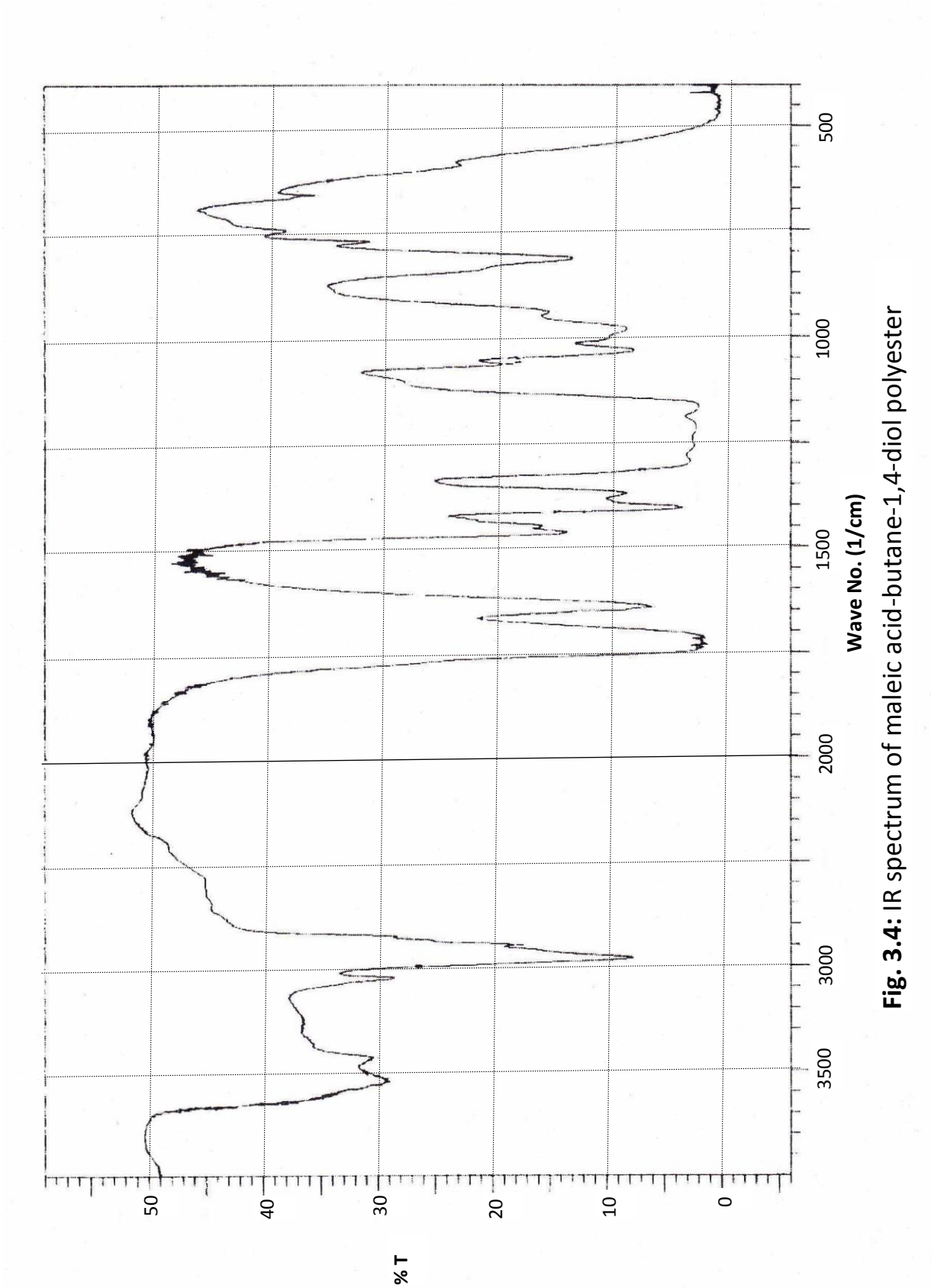

Fig. 3.4: IR spectrum of maleic acid-butane-1,4-diol polyester

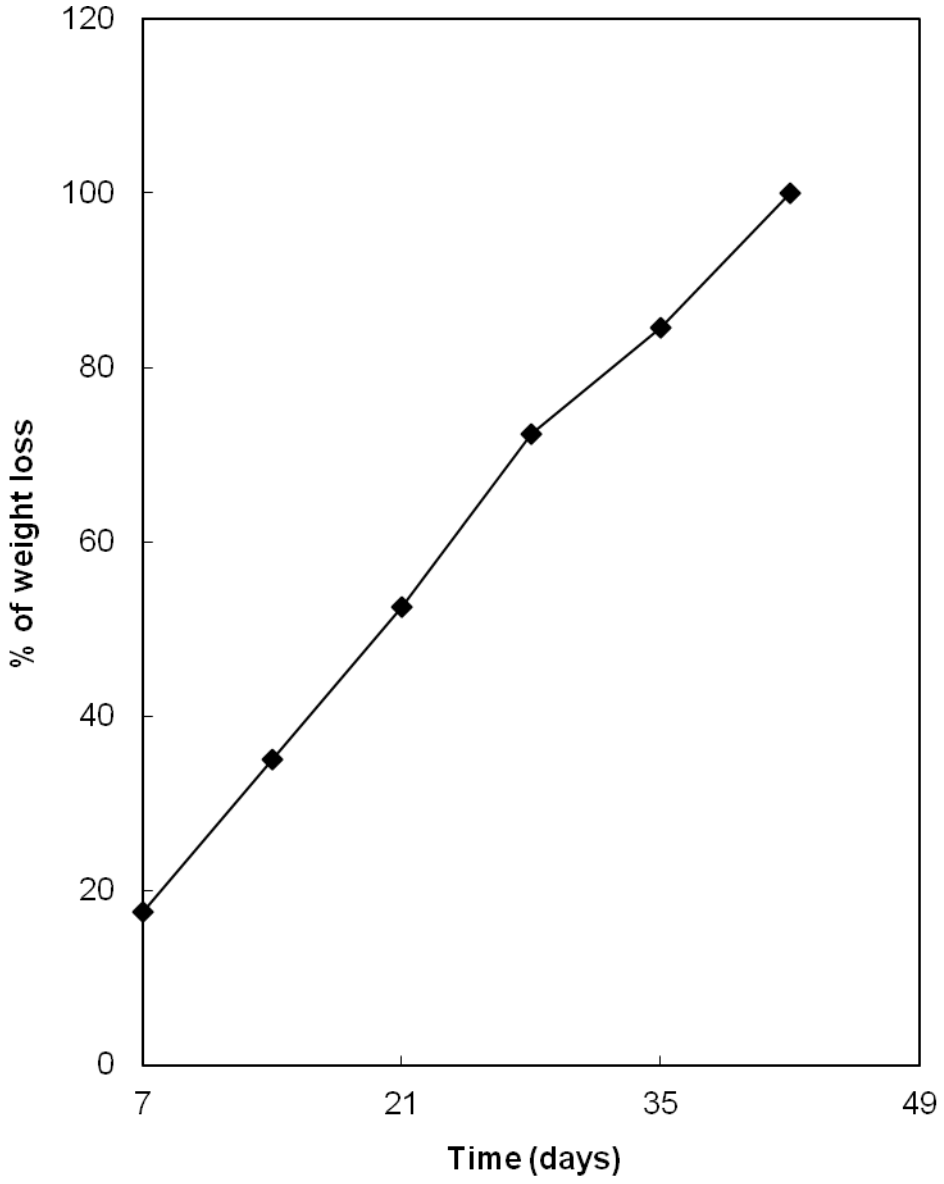

Fig. 3.5 : Soil degradation of maleic acid-butane-1,4-diol polyester at normal weathering condition.

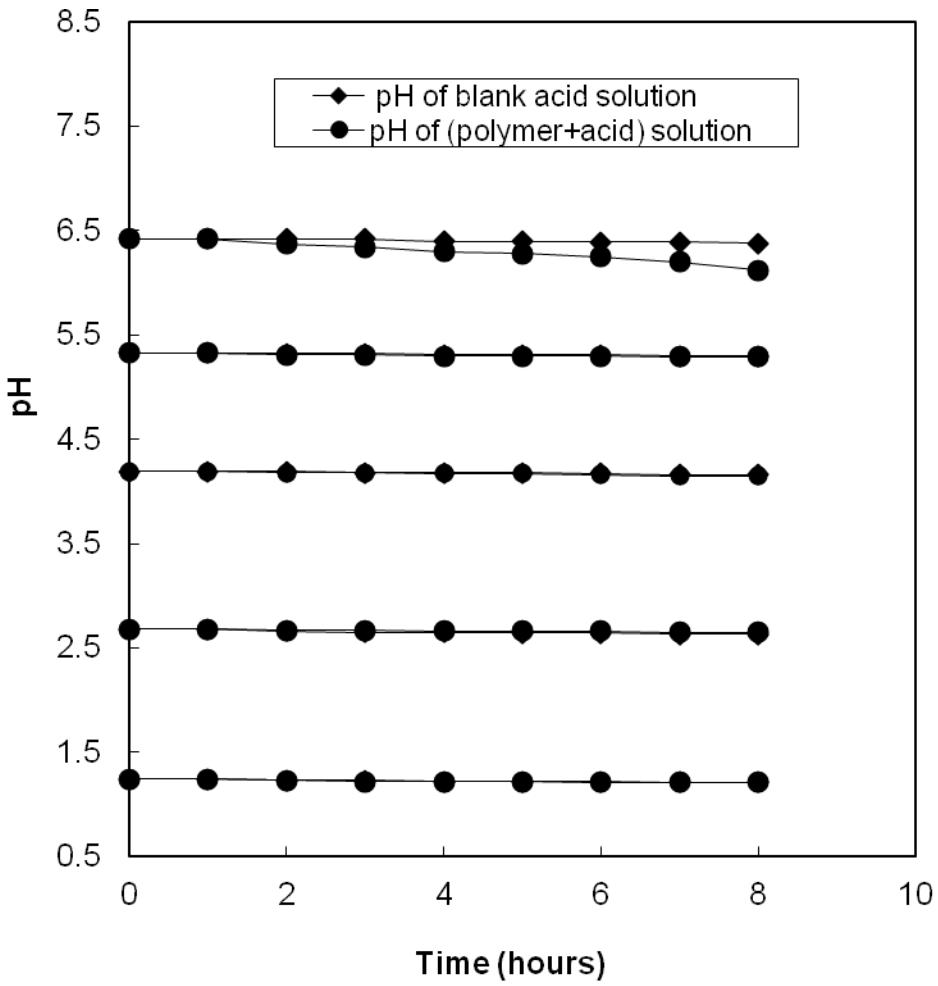

Fig. 3.6 : pH Vs time plots of maleic acid-butane-1,4-diol polyester in hydrochloric acid solution of different pH at room temperature.

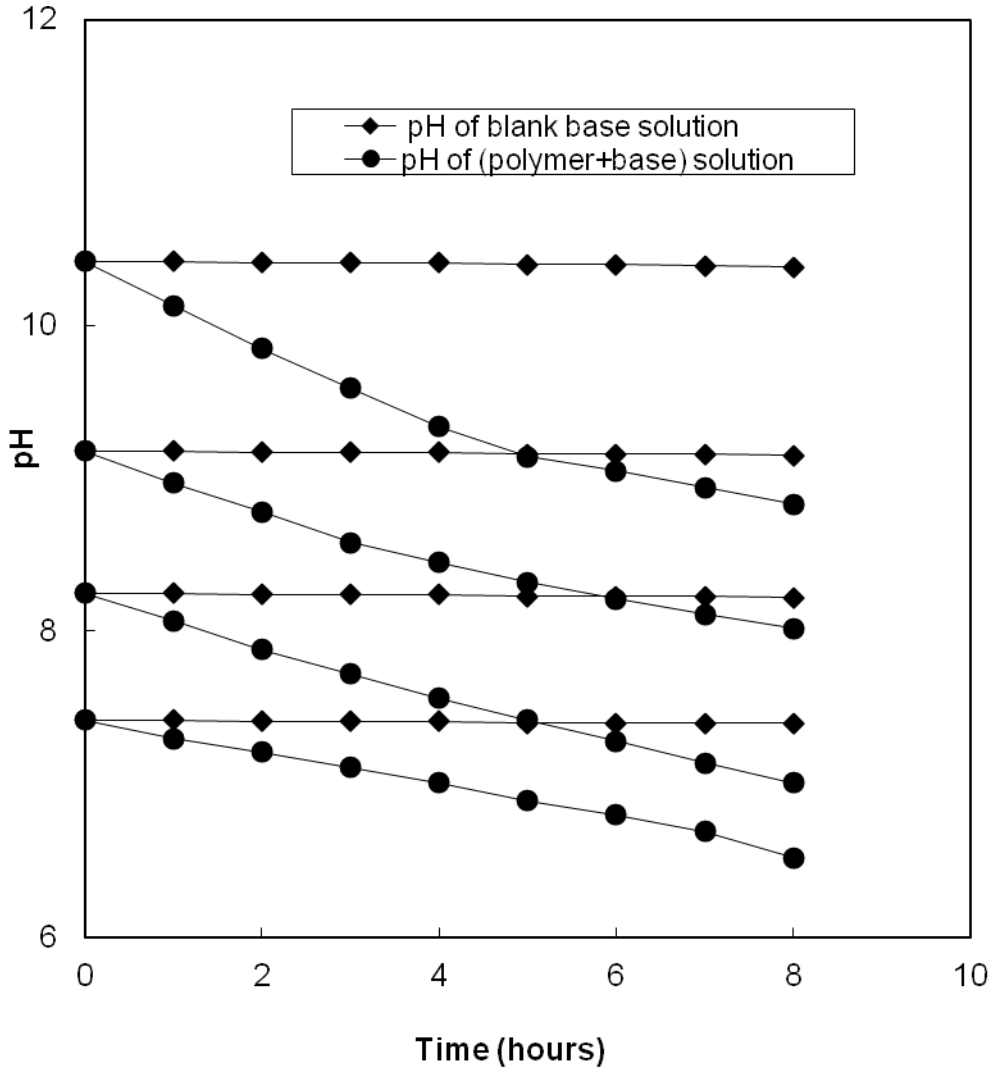

Fig. 3.7 : pH Vs time plots of maleic acid-butane-1,4-diol polyester in sodium carbonate solution of different pH at room temperature.

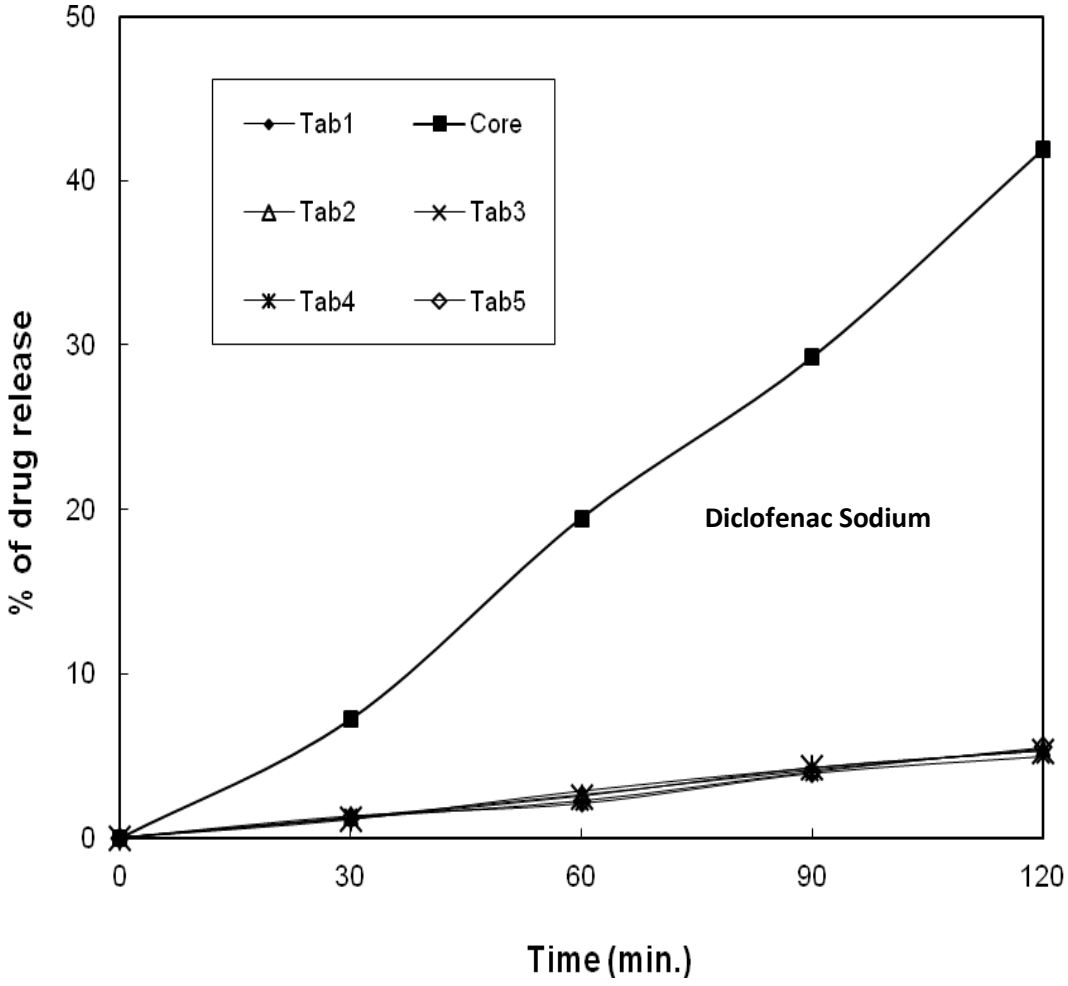

Fig. 3.8: Percent release of diclofenac sodium from core & coated tablets (coated by maleic acid-butane-1,4-diol polyester) in simulated gastric fluid (pH =1.2).

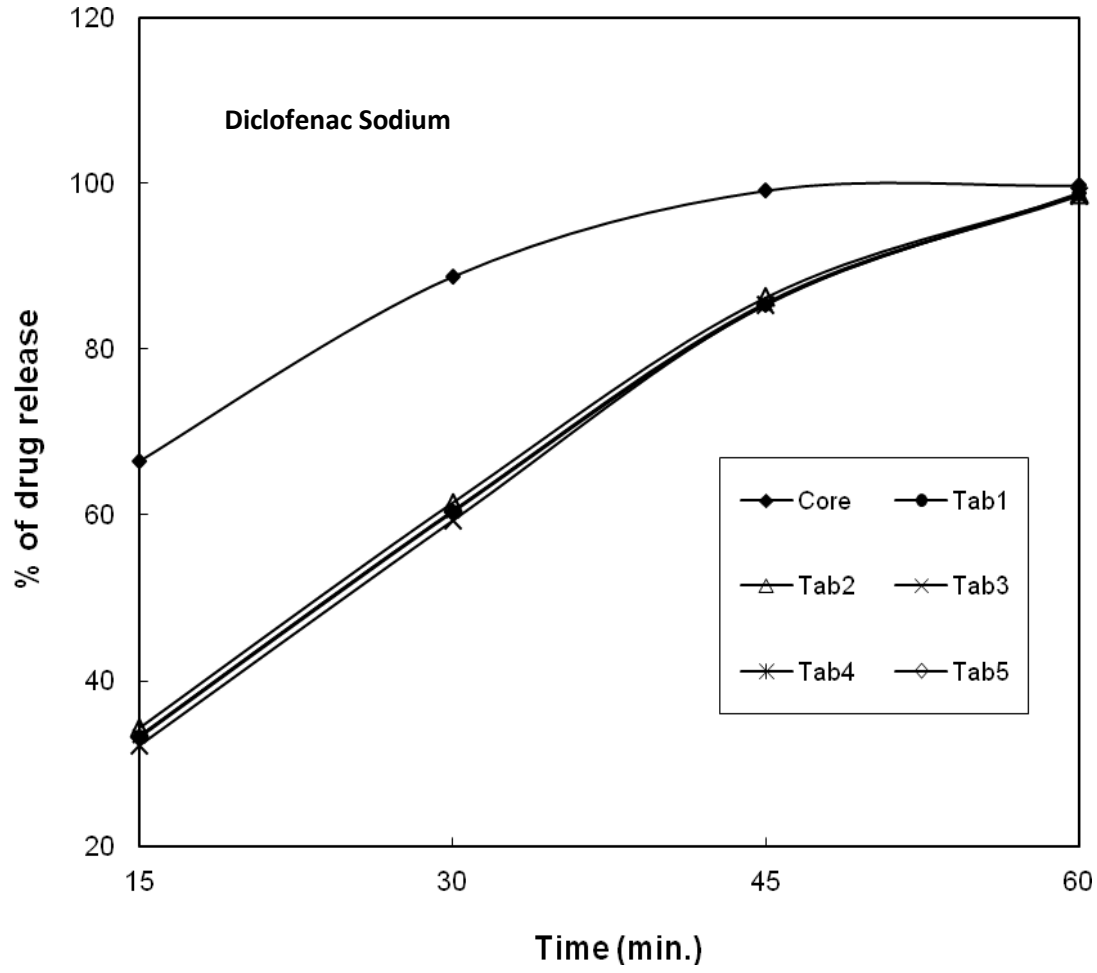

Fig. 3.9: Percent release of diclofenac sodium from core & coated tablets (coated by maleic acid-butane-1,4-diol polyester) in simulated intestinal fluid (pH =7.4).

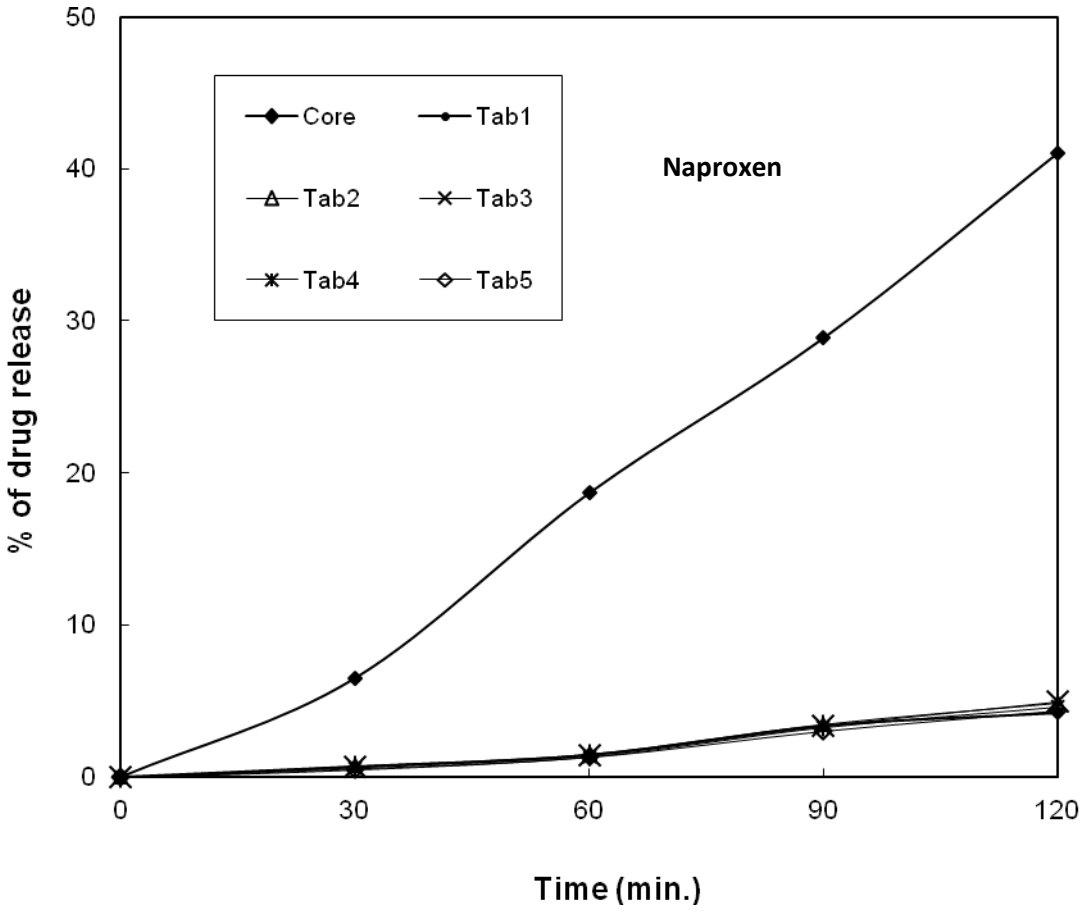

Fig. 3.10: Percent release of naproxen from core & coated tablets (coated by maleic acid-butane-1,4-diol polyester) in simulated gastric fluid (pH =1.2).

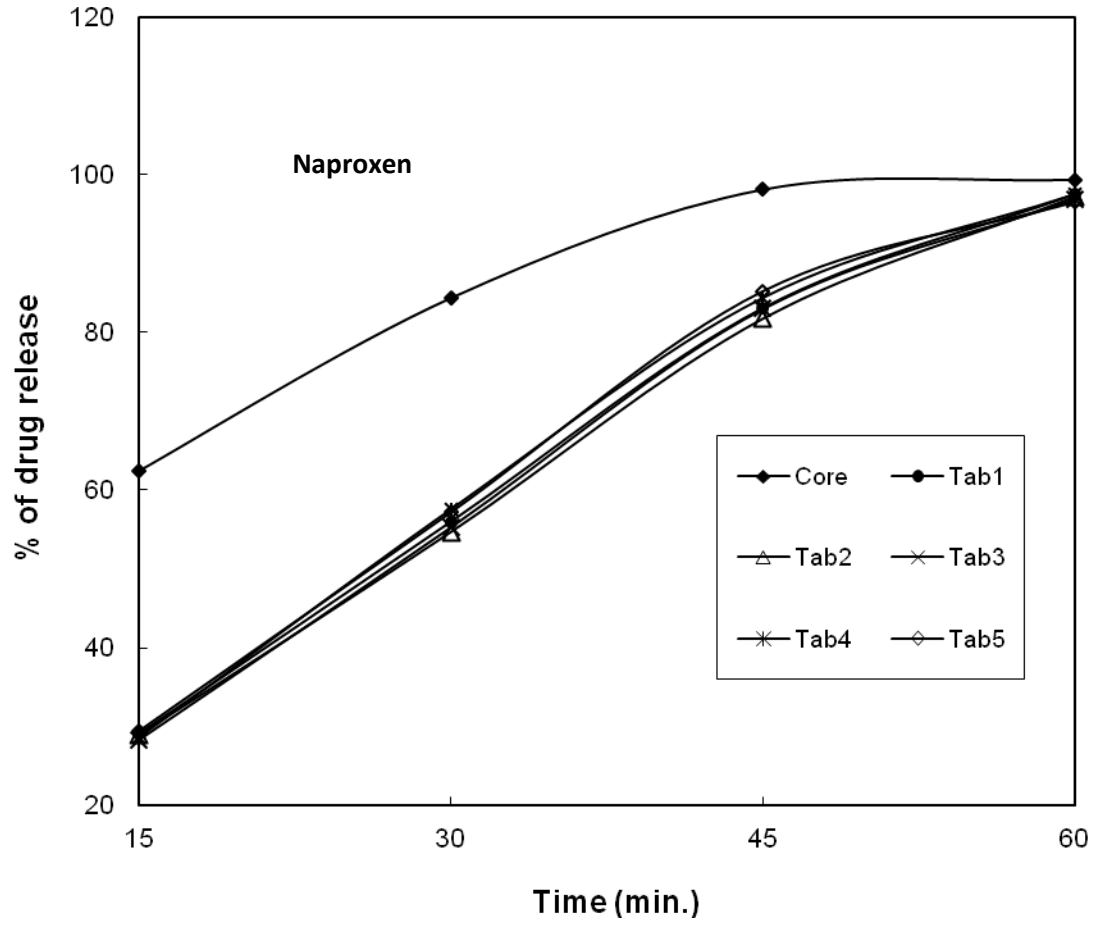

Fig. 3.11: Percent release of naproxen from core & coated tablets (coated by maleic acid-butane-1,4-diol polyester) in simulated intestinal fluid (pH =7.4).

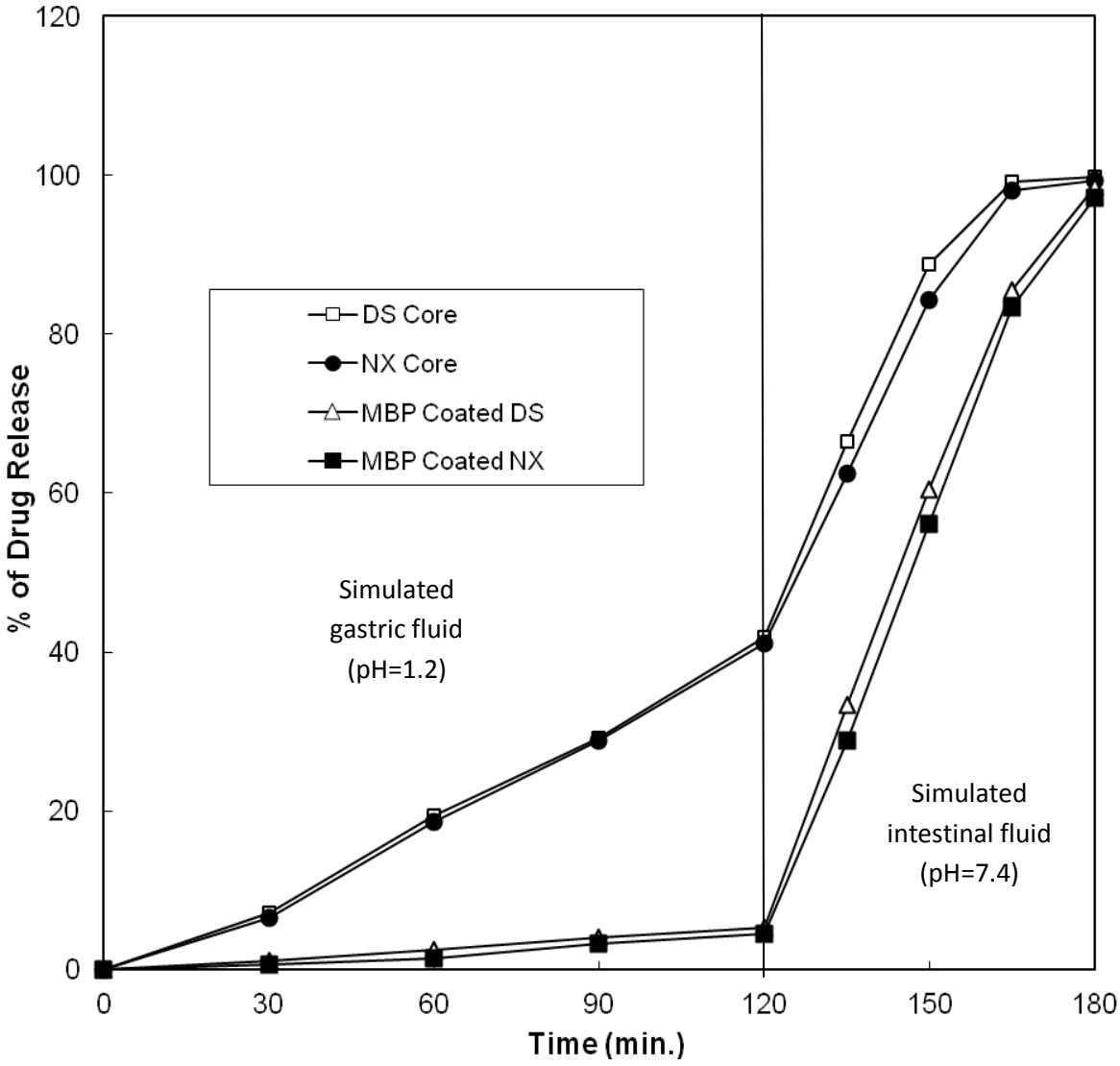

Fig. 3.12: Mean percent release of diclofenac sodium (DS) and naproxen (NX) from core & maleic acid-butane-1,4-diol polyester (MBP) coated tablets in simulated gastric fluid (pH=1.2) and in simulated intestinal fluid (pH =7.4).

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CHAPTER-4

DRUG DELIVERY PROFILE OF MALEIC ACID-ADIPIC ACID-PROPANE-1,2-DIOL CO-POLYESTER

4.1 INTRODUCTION

Recently, there have been many investigations of stimuli-responsive polymers, exhibiting sensitive swelling transitions dependent on various stimuli, e.g. pH[1-3], electric field[4], temperature[5], or other chemicals[6]. They have been considered to be useful in various bio-medical applications. Among these, pH sensitive orally administrated drug delivery systems are gaining importance as these systems can deliver the drug at the targeted site as per the physiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. The pH range of fluids in various segments of the gastrointestinal tract (GIT) may provide environmental stimuli for responsive drug release[7]. Poly (acrylic acid) and poly (methacrylic acid) based biodegradable polymers have been investigated for therapeutic use because of their ability of swelling with changes of pH[8].

A common prerequisite to develop medically applicable biodegradable polymer is that the monomers must be non-toxic, at least to some an extent, so that, there should be the possibility of the polymer to be non-toxic. The use of maleic acid in the pharmaceutical industries[9] has been discussed in the previous chapter. Pharmaceutical applications of adipic acid and propane-1,2-diol are also known [10-13].

Choosing these pharmaceutically safe monomers, we have attempted to synthesize maleic acid-adipic acid-propane-1,2-diol co-polyester (MAPC)

as pH- responsive aliphatic based biodegradable polymers that will be used as orally administrated drug carriers. In this chapter, we report synthesis, characterization, bio-degradation and *in-vitro* drug release behavior of this polyester.

4.2 EXPERIMENTAL

4.2.1 Synthesis

Apparatus: 1) Dean-Stark apparatus, 2) R. B. flask, 3) Thermometer (range = 0-350^{0}C), 4) Heating mantle with regulator, 5) Condenser and 6) Vacuum desiccator.

Materials: All of the monomers were A. R. grade chemicals and were used as such. Anhydrous $FeCl_3$ (A.R. grade chemical) was freshly sublimed[14] and then used as catalyst.

Procedure: Maleic acid-adipic acid-propane-1,2-diol co-polyester (MAPC) was synthesized taking the desired proportions of its corresponding monomers together with anhydrous $FeCl_3$ (approximately o.4% of the total weight) as catalyst. The reagents were taken in a 250 ml R. B. flask which was connected to a Dean-Stark apparatus for eliminating water (the by-product of the polycondensation reaction) azeotropically with xylene (the reaction medium). The reaction mixture was heated at 135-140^{0}C for about 5-6 hours. The synthesized polymer was then collected from the reaction vessel by dissolving it in acetone and purified by precipitating using water as non-solvent. This polymer was then vacuum dried at 60^{0}C and was stored in a desiccator. The details of synthesis and purification techniques have been described in **Chapter-2**.

4.2.2 Characterization

MAPC was characterized by its solubility in common organic solvents at the ambient temperature, molecular weight, IR spectrum and bio-degradation study in the soil. The polyester was insoluble in water but readily soluble in acetone. Molecular weight determination was carried out by end group analysis and viscosity method. All tests were accomplished through the experimental procedures described in **Chapter-2**.

4.2.3 Hydrolytic Degradation Study

Hydrolytic degradation study was carried out to evaluate the pH responsive character of the polymer. This study was performed in both acid and alkali solutions of various pH values. Hydrochloric acid and sodium carbonate were used to prepare solutions of different pH values. The change of pH of the polymer sample containing solutions with respect to time was considered as an indication of the degradation of the polyester. The detail of the study was described in **Chapter-2**.

4.2.4 Coating of the Core (Uncoated) Tablets

MAPC was used as coating material for the uncoated diclofenac sodium (50 mg) and naproxen (500mg) tablets. The detail of the coating procedure is available in **Chapter-2**. Drug release from the coated tablet was tried as a function of weight gain of the core tablet by the coating material and 8-10% weight gain gave best result.

4.2.5 Drug Dissolution Study

The dissolution studies for both the core and MAPC coated tablets were performed in order to evaluating the efficacy of the polymer as coating

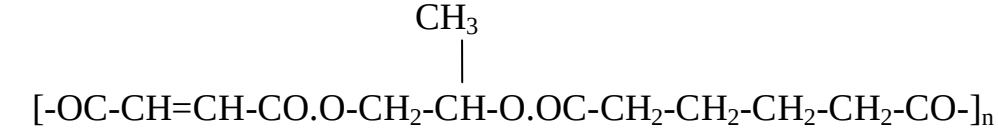
material on the release of the drug. A USP type-XXII dissolution apparatus 'ELECTROLAB TDT-O1' was used for dissolution experiments. The *in-vitro* drug release from the core and the polymer coated tablets in simulated physiological environments (simulated gastric and intestinal fluids) according to British Pharmacopoeia[15] was performed spectrophotometrically by recording the absorbance of the dissolution medium at the λ_{max} of the corresponding drug as a function of time. Five samples of each tablet (core and MAPC coated) were tested in this way and concentrations of the released drug were then averaged. This process has been described in **Chapter-2**.

4.3 RESULTS AND DISCUSSION

4.3.1 Synthesis

Since, both of maleic acid and adipic acid are dibasic acids and their carboxylic acid groups are positioned identically, the mole ratio of the monomers was kept as maleic acid: adipic acid: propane-1,2-diol= 1:1:2.

The expected structure of MAPC would be as shown below:



The synthesized MAPC was solid and brownish in color.

4.3.2 Characterization

Solubility

Solubility of this polyester in different organic solvents at the ambient temperature is presented in Table-4.1. This Table reveals that acetone, mixed solvent (toluene: ethanol =3:1) and ethylacetate are good solvents for MAPC. But it is poorly soluble in toluene and ethanol. However,

benzene, xylene, chloroform, formic acid, phenol etc. and water are common non-solvents for this polyester.

Fractionation

The polymer was fractionated at (20±1)°C by precipitation technique (described in **Chapter-2**) using acetone as solvent and water as non-solvent. The results obtained from the experiments were given in Table 4.2.

Molecular Weight Determination

A. End group analysis

The number average molecular weight ($\overline{M}_n$) of each fraction of the polymer sample was determined by end group analysis. The values of $\overline{M}_n$ for different fractions of this polymer were found as 21850, 19488, 17315, 15192 and 12390. The weight percentages (wt%) of the fractionated polymer in un-fractionated polymer samples are shown in Table-4.2 & Fig.-4.1. The table and figure show that the fraction no.-iii (mol. wt. 17315) is the highest in quantity in un-fractionated polymer samples.

B. Viscosity method

For each fraction of MAPC, a number of solutions of different known concentrations (g/ml) were made. The efflux time of each solution was measured using Ostwald viscometer and then relative viscosity, specific viscosity and reduced viscosity were calculated, which are presented in Tables-4.3-4.7. Reduced viscosity Vs concentration graph was plotted and extrapolated to zero concentration for each fraction as shown in Fig.-4.2. The common ordinate intercepts of these straight lines gave their intrinsic viscosities. The values of intrinsic viscosities and their corresponding molecular weights (obtained by End Group Analysis) of

each fraction of the polyester sample are given in Table-4.8. The logarithms of the intrinsic viscosities of these polymer fractions were plotted against the logarithms of their molecular weights ($\overline{M_n}$) and a linear curve was obtained (Fig.-4.3) whose intercept and slope gave the values of Mark-Hauwink constants[14] 'K' and 'a' respectively.

According to Mark-Hauwink equation the relationship between viscosity average molecular weight ($\overline{M}_v$) and intrinsic viscosity can be expressed as:

$$[\eta] = K\left(\overline{M}_v\right)^a = 14.2\times10^{-3}\left(\overline{M}_v\right)^{0.674}$$

Table-4.8 also shows molecular weights of different fractions of this polymer sample obtained by viscosity method. It is observed that the molecular weight of the polymer sample found out by viscometry ($\overline{M}_v$) is greater than that of the same obtained by end group analysis ($\overline{M}_n$).

IR Spectra

The >C=O stretching frequency at the region 1700-1710cm^{-1} of the spectrum of maleic acid shifted to 1716.7cm^{-1} and a new band due to −COOR appeared at 1161.2cm^{-1} in the spectrum of MAPC (Fig.-4.4). The broad band representing the –OH group at the region 3100-3500cm^{-1} in the spectrum of the diol almost disappeared in the spectrum of the polyester (Fig.-4.4). All these indicate the reaction between –OH and –COOH groups and thereby the formation of ester linkage in the sample[10,17].

Elemental Analysis

Calculated for expected structure: C = 55.46%, H = 4.20 %, and found for polyester sample: C = 55.23% and H = 4.47%. It is seen that the

percentage composition of the sample obtained by calculation matches with the same obtained by analysis. The product is accordingly confirmed.

Soil Degradation Test

Table-4.9 and Fig.-4.5 show the gradual weight loss of the polymer sample buried in soil[18, 19]. After 56 days MAPC ultimately mixed with the soil. This is an evidence of the total soil degradation of the polyester sample.

4.3.3 Hydrolytic Degradation Study

From the hydrolytic degradation study (Table: 4.10-4.11 and Fig.-4.6-4.7) it was found that the polyester sample remained almost intact in the acid medium (pH 1.2-6.0) but gradually degraded in basic medium (pH>7.0). In acid region the polymer samples swell insignificantly. But in alkaline region they swell and the ester linkage is hydrolyzed resulting the meaningful decrease in the pH of the polymer sample containing solutions with respect to time. Such pH-responsive nature of this polyester has led us to figure out its possible use as enteric coating material. In this connection, its *in-vitro* drug release behavior, according to the guidelines of pharmacopoeia[15], need to be investigated.

4.3.4 *In-vitro* Drug Release Characteristics (Drug Dissolution Study)

In-vitro drug release study was carried out for both MAPC coated diclofenac sodium (50mg) and naproxen (500mg) tablets in the simulated gastric fluid (pH 1.2) and in the simulated intestinal fluid (pH 7.4) consecutively. Dissolution of drug from its dosage form is dependent on many factors, which include not only the physicochemical properties of the drug, but also the formation of the dosage form and the process of

manufacture[20]. Such statement is also true for enteric-coated preparations. In this study, it was found that the co-polyester did not degrade or swell in the simulated gastric fluid for two hours when coated on a core tablet and less than 5% diclofenac sodium and naproxen released from MAPC coated tablets whereas 46.75% diclofenac sodium and 43.20% naproxen released from the core tablets (uncoated tablets) in that time in the same media (Table-4.12 and Fig.-4.8 & 4.10). But in the simulated intestinal fluid the polymer coating gradually degraded and more than 82% of diclofenac sodium and naproxen released within 45 minutes (Table-4.13 and Fig.-4.9 & 4.11).

The mean percent release of diclofenac sodium and naproxen from MAPC coated tablets (Table-4.14 & Fig.-4.12) corresponds to the British Pharmacopoeia[15] drug release profile of enteric-coated tablets. So, maleic acid-adipic acid-propane-1,2-diol co-polyester could possibly be used as an enteric coating material. One of the advantages of this coating material was that, no plasticizer was required to add to the formulation as the polymer itself had sticky property and hence could produce soft film on the tablet surface. However, prior to clinical trial, toxicological and other pharmacological tests of this polyester need to be performed.

TABLES OF EXPERIMENTAL DATA

Table 4.1: Solubility behavior of maleic acid-adipic acid-propane-1,2-diol polyester (MAPC) at ambient temperature.

Solvent	**Solubility**
Acetone	+ +
Mixed Solvent (Toluene: Ethanol =3:1)	+ +
Ethylacetate	++
Toluene	+
Ethanol	+
Acetic acid	-
Benzene	-
Xylene	-
Chloroform	-
Formic acid	-
Phenol	-
Carbon tetrachloride	-
Rectified sprit (R.S)	-
Diethyl ether	-
Water	-

Here (+ +), (+) and (-) indicate high solubility, low solubility and no solubility respectively.

Table 4.2: Molecular weight distribution of fractionated maleic acid-adipic acid-propane-1,2-diol polyester in un-fractionated polymer.

Polymer fraction no.	Weight % of fraction	Mol. wt. by end group analysis ($\overline{M_n}$)
i	10.1	21850
ii	21.1	19488
iii	33.2	17315
iv	23.4	15192
v	12.2	12390

Table 4.3: Viscosity data for maleic acid-adipic acid-propane-1,2-diol polyester ($\overline{M}_n$=21850) in acetone at 25^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (acetone), t_0 = 124.9sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00530	148.0	1.1849	0.1849	34.89	12.28
0.00440	141.7	1.1345	0.1345	30.57	
0.00265	132.5	1.0608	0.0608	22.94	
0.00220	130.9	1.0480	0.0480	21.82	

Table 4.4: Viscosity data for maleic acid-adipic acid-propane-1,2-diol polyester ($\overline{M_n}$ =19488) in acetone at 25^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (acetone), t_0 = 124.9sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00520	144.7	1.1585	0.1585	30.48	11.40
0.00400	137.7	1.1023	0.1023	25.58	
0.00260	131.6	1.0536	0.0536	20.62	
0.00200	129.5	1.0368	0.0368	18.40	

Table 4.5: Viscosity data for maleic acid-adipic acid-propane-1,2-diol polyester ($\overline{M}_n$ =17315) in acetone at 25^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (acetone), t_0 = 124.9sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00550	144.5	1.1569	0.1569	28.53	10.61
0.00450	139.0	1.1129	0.1129	25.09	
0.00275	131.6	1.0536	0.0536	19.49	
0.00225	129.8	1.0392	0.0392	17.42	

Table 4.6: Viscosity data for maleic acid-adipic acid-propane-1,2-diol polyester ($\overline{M_n}$ =15192) in acetone at 25^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (acetone), t_0 = 124.9 sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00500	140.5	1.1249	0.1249	24.98	9.89
0.00400	135.9	1.0881	0.0881	22.02	
0.00250	130.2	1.0424	0.0424	16.96	
0.00200	128.9	1.0320	0.0320	16.00	

Table 4.7: Viscosity data for maleic acid-adipic acid-propane-1,2-diol polyester ($\overline{M}_n$ =12390) in acetone at 25^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (acetone), t_0 = 124.9 sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00546	139.9	1.1201	0.1201	21.99	8.67
0.00460	136.7	1.0945	0.0945	20.54	
0.00273	130.2	1.0424	0.0424	15.53	
0.00230	129.1	1.0336	0.0336	14.61	

Table 4.8: Comparison between molecular weights obtained by end group analysis and the same obtained by viscosity method of maleic acid-adipic acid-propane-1,2-diol polyester.

Fraction no.	*Intrinsic* viscosity, $[\eta]$ ml/g (from graph)	$K \times 10^3$ (from graph)ml/g	a (from graph)	Molecular weight by	
				End group analysis($\overline{M}_n$)	Viscosity method($\overline{M}_v$)
i	12.28	14.20	0.674	21850	22773
ii	11.40			19488	20395
iii	10.61			17315	18333
iv	9.89			15192	16518
v	8.67			12390	13587

Table 4.9: Soil degradation of MAPC at normal weathering condition.

Time (days)	**% of weight loss**
7	19.2
14	33.1
21	48.8
28	60.9
35	74.4
42	89.6
49	93.4
56	100

Table 4.10: pH-responsive characteristics (hydrolytic degradation study) of maleic acid-adipic acid-propane-1,2-diol polyester in acid media [HCl solution] at room temperature.

Reading	Time (hour)	Initial pH=1.25		Initial pH=2.58		Initial pH=3.82		Initial pH=5.30		Initial pH=6.75	
		pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)
1	0	1.25	1.25	2.58	2.58	3.82	3.82	5.30	5.30	6.75	6.75
2	1	1.24	1.24	2.55	2.55	3.81	3.80	5.29	5.26	6.74	6.67
3	2	1.23	1.23	2.54	2.54	3.80	3.79	5.28	5.22	6.74	6.62
4	3	1.20	1.19	2.54	2.51	3.78	3.77	5.28	5.20	6.73	6.56
5	4	1.17	1.16	2.52	2.50	3.78	3.76	5.27	5.17	6.72	6.49
6	5	1.15	1.13	2.51	2.49	3.77	3.73	5.26	5.14	6.71	6.42
7	6	1.13	1.12	2.50	2.48	3.75	3.70	5.25	5.10	6.71	6.36
8	7	1.11	1.10	2.48	2.46	3.74	3.68	5.25	5.08	6.70	6.28
9	8	1.11	1.10	2.47	2.45	3.73	3.65	5.24	5.04	6.70	6.22

Table 4.11: pH-responsive characteristics (hydrolytic degradation study) of maleic acid-adipic acid-propane-1,2-diol polyester in basic media [Na_2CO_3 solution] at room temperature.

Reading	Time (hour)	Initial pH=7.45		Initial pH=8.50		Initial pH=9.83		Initial pH=10.65	
		pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)
1	0	7.45	7.45	8.50	8.50	9.83	9.83	10.65	10.65
2	1	7.45	7.34	8.49	8.35	9.82	9.63	10.65	10.37
3	2	7.44	7.23	8.49	8.22	9.82	9.42	10.65	10.06
4	3	7.43	7.14	8.47	8.08	9.82	9.24	10.63	9.71
5	4	7.43	7.03	8.47	7.90	9.81	9.02	10.63	9.46
6	5	7.43	6.94	8.47	7.67	9.80	8.83	10.62	9.22
7	6	7.42	6.80	8.46	7.48	9.80	8.58	10.62	8.99
8	7	7.42	6.74	8.45	7.23	9.79	8.41	10.61	8.81
9	8	7.42	6.62	8.45	7.05	9.79	8.15	10.60	8.65

Table 4.12: In vitro drug release study of diclofenac sodium (DS) and Naproxen (NX) core tablets coated by maleic acid-adipic acid-propane-1,2-diol polyester in simulated gastric fluid (pH = 1.2).

Sample	% of drug release							
	Time (30 min.)		Time (60 min.)		Time (90 min.)		Time (120 min.)	
	DS	NX	DS	NX	DS	NX	DS	NX
Core	9.95	6.10	23.85	18.64	34.43	29.30	46.75	43.20
Tab-1	0.87	0.62	1.67	1.36	3.73	2.47	4.90	3.83
Tab-2	0.83	0.76	1.55	1.23	3.16	2.88	4.68	4.00
Tab-3	0.95	0.68	1.89	1.20	3.77	2.12	4.67	3.46
Tab-4	0.88	0.77	1.91	1.38	3.28	2.84	4.82	3.58
Tab-5	0.96	0.70	2.24	1.42	3.65	2.76	4.97	3.97

Table 4.13: In vitro drug release study of diclofenac sodium (DS) and Naproxen (NX) core tablets coated by maleic acid-adipic acid-propane-1,2-diol polyester in simulated intestinal fluid (pH =7.4).

Sample	% of drug release							
	Time (15min.)		Time (30min.)		Time (45min.)		Time (60min.)	
	DS	NX	DS	NX	DS	NX	DS	NX
Core	65.30	63.50	87.66	82.74	98.45	97.12	99.65	99.14
Tab-1	36.68	32.25	65.55	61.02	84.89	82.67	98.25	97.90
Tab-2	35.93	33.41	65.87	62.57	86.33	82.22	98.54	97.15
Tab-3	35.30	33.20	66.43	63.21	84.64	82.43	98.89	97.42
Tab-4	38.41	34.81	67.22	63.42	85.35	83.90	98.30	98.00
Tab-5	36.64	34.10	65.57	64.54	84.58	83.24	98.10	97.50

Table 4.14: Mean percent of drug release from diclofenac sodium (DS) and Naproxen (NX) core tablets coated by maleic acid-adipic acid-propane-1,2-diol polyester in simulated gastric fluid (pH = 1.2) and intestinal fluid (pH =7.4).

Mean % of drug release in simulated gastric fluid (pH=1.20)								Mean % of drug release in simulated intestinal fluid (pH = 7.40)							
30 min.		60 min.		90 min.		120 min.		135 min.		150 min.		165 min.		180 min.	
DS	NX	DS	NX	DS	NX	DS	NX	DS	NX	DS	NX	DS	NX	DS	NX
0.90	0.71	1.85	1.32	3.52	2.61	4.81	3.77	36.59	33.55	66.13	62.95	85.16	82.89	98.42	97.59

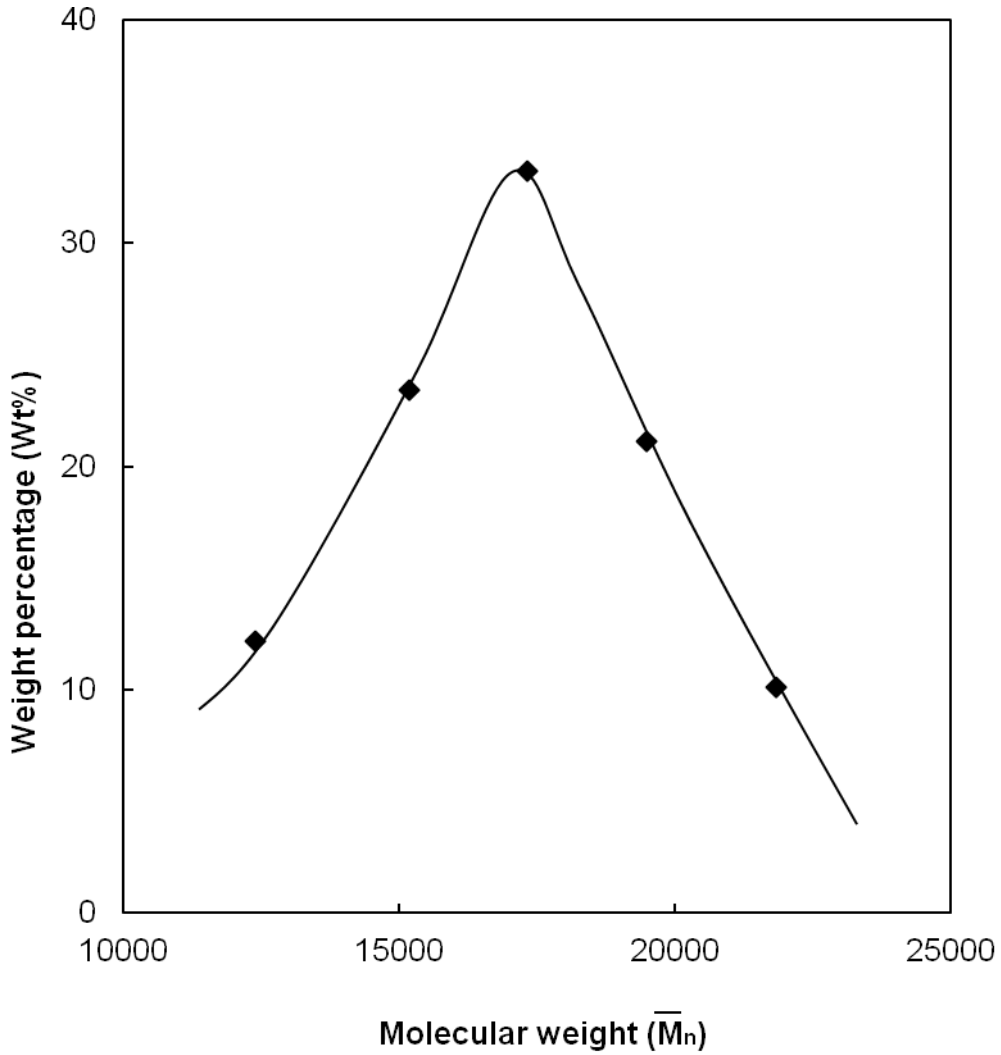


Fig. 4.1: Molecular weight distribution curve of fractionated maleic acid-adipic acid-propane-1,2-diol co-polyester in unfractionated sample.

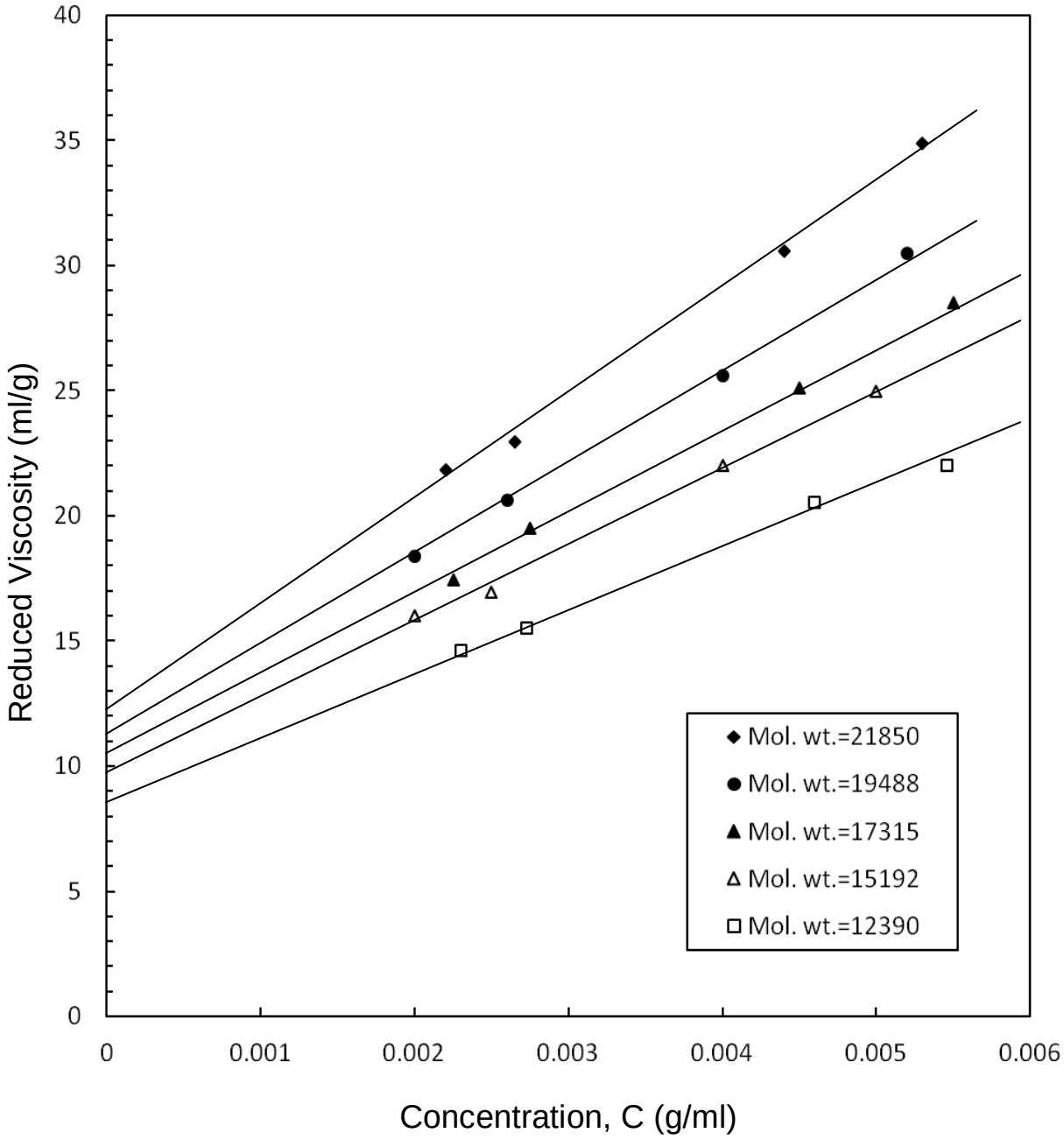


Fig. 4.2: Plots of concentration Vs reduced viscosity for maleic acid-adipic acid-propane-1,2-diol co-polyester of different fractions in acetone at 25^0C temperature.

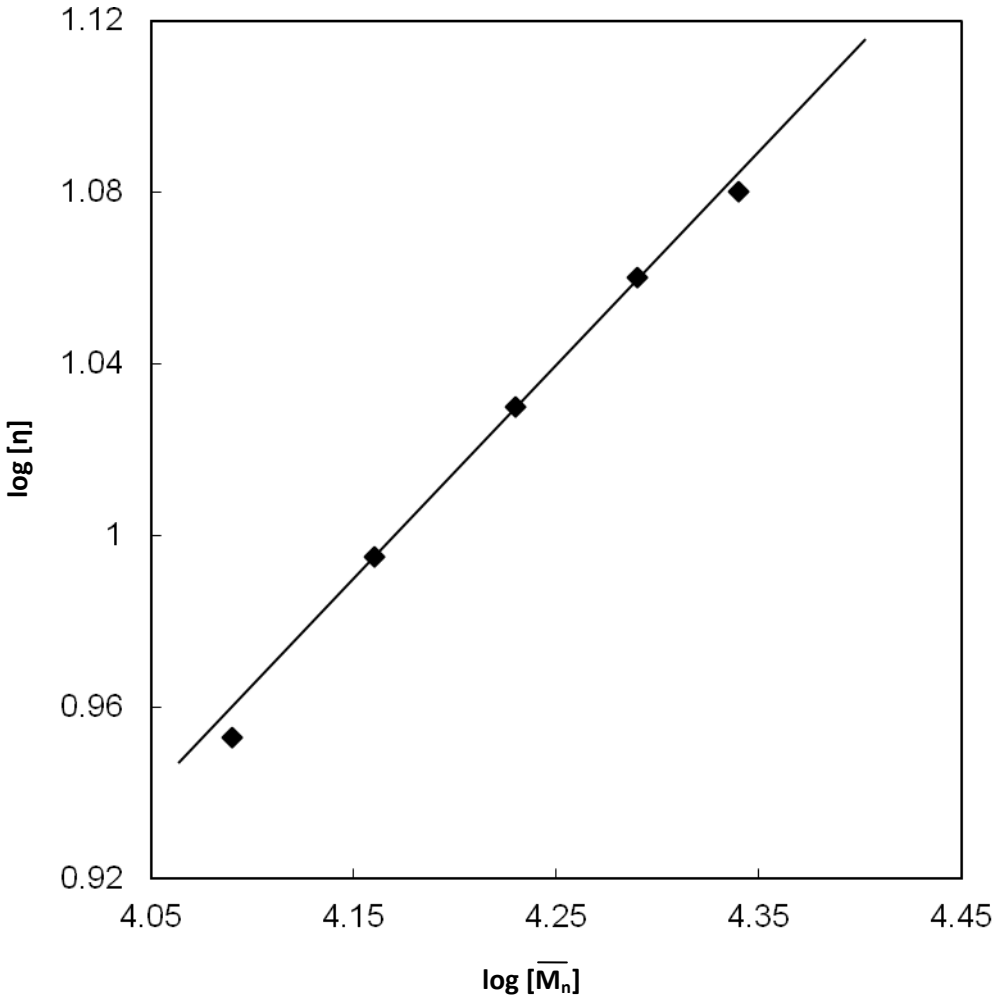


Fig. 4.3: log of intrinsic viscosity Vs log of molecular weight relationship for maleic acid-adipic acid-propane-1,2-diol co-polyester in acetone at 25°C.

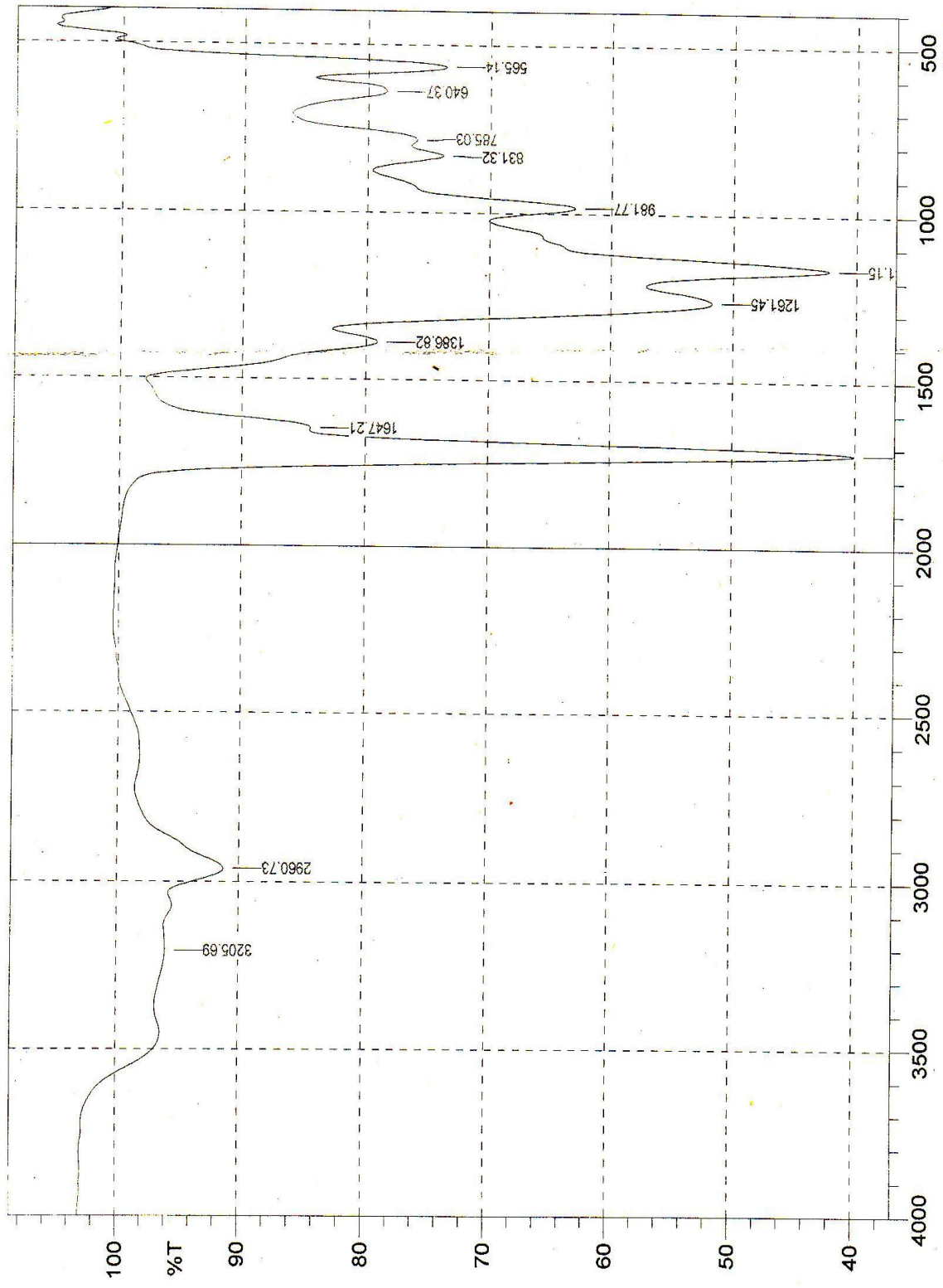


Fig 4.4: IR-spectrum of maleic acid-adipic acid-propane-1,2-diol co-polyester

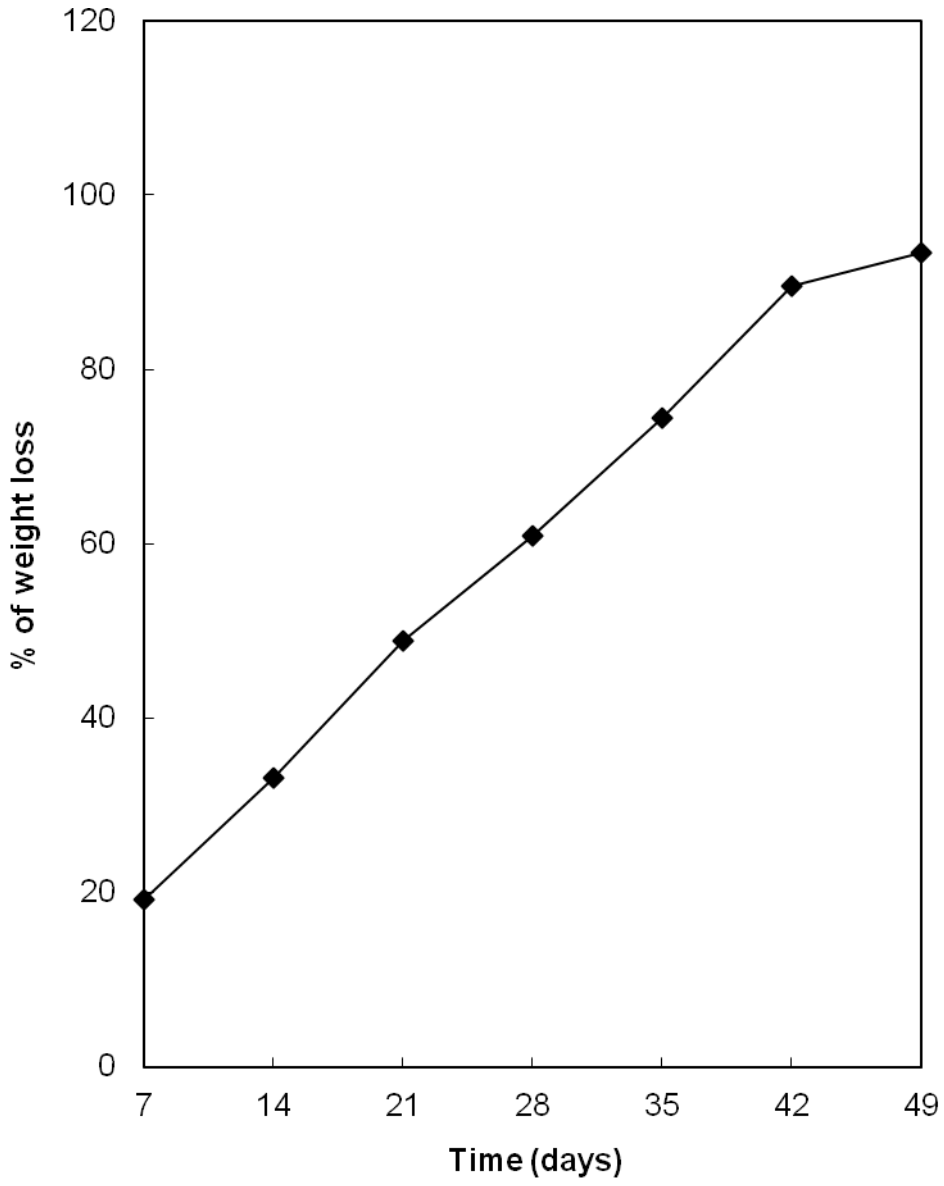


Fig. 4.5: Soil degradation of maleic acid-adipic acid-propane-1,2-diol co-polyester at normal weathering condition.

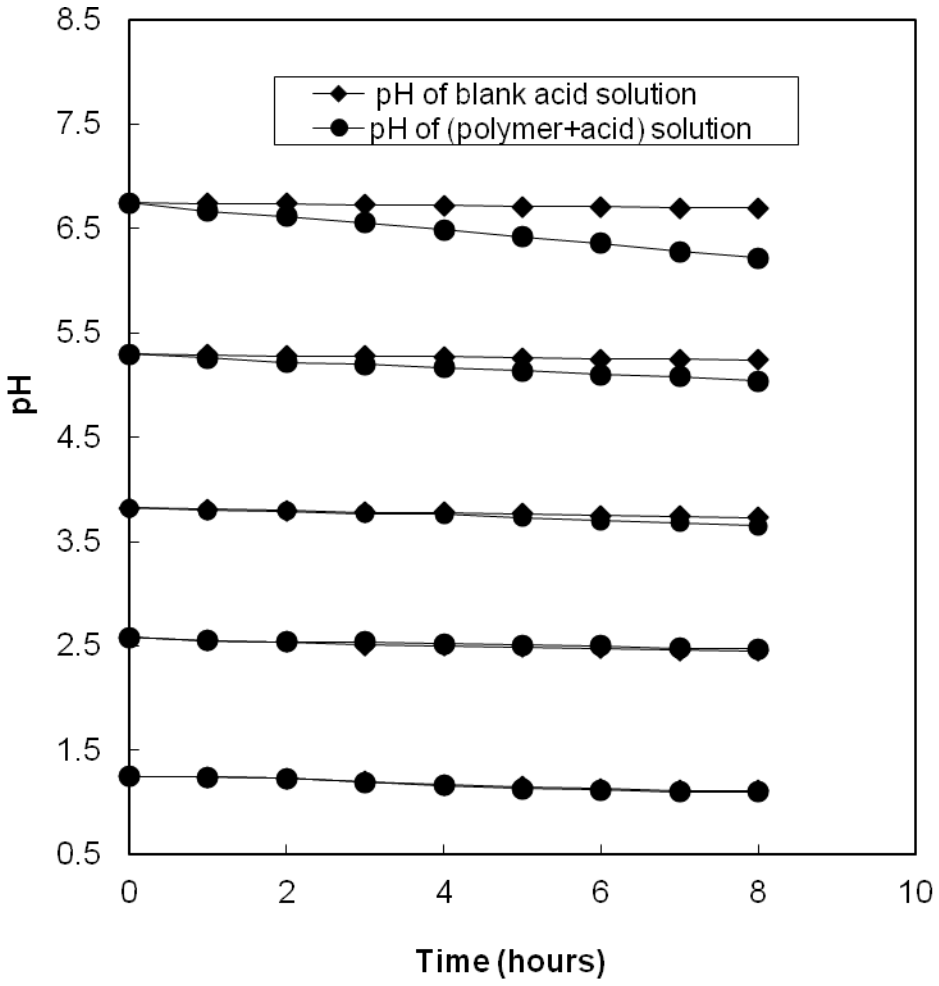


Fig. 4.6: pH Vs time plots of maleic acid-adipic acid-propane-1,2-diol co-polyester in hydrochloric acid solution of different pH at room temperature.

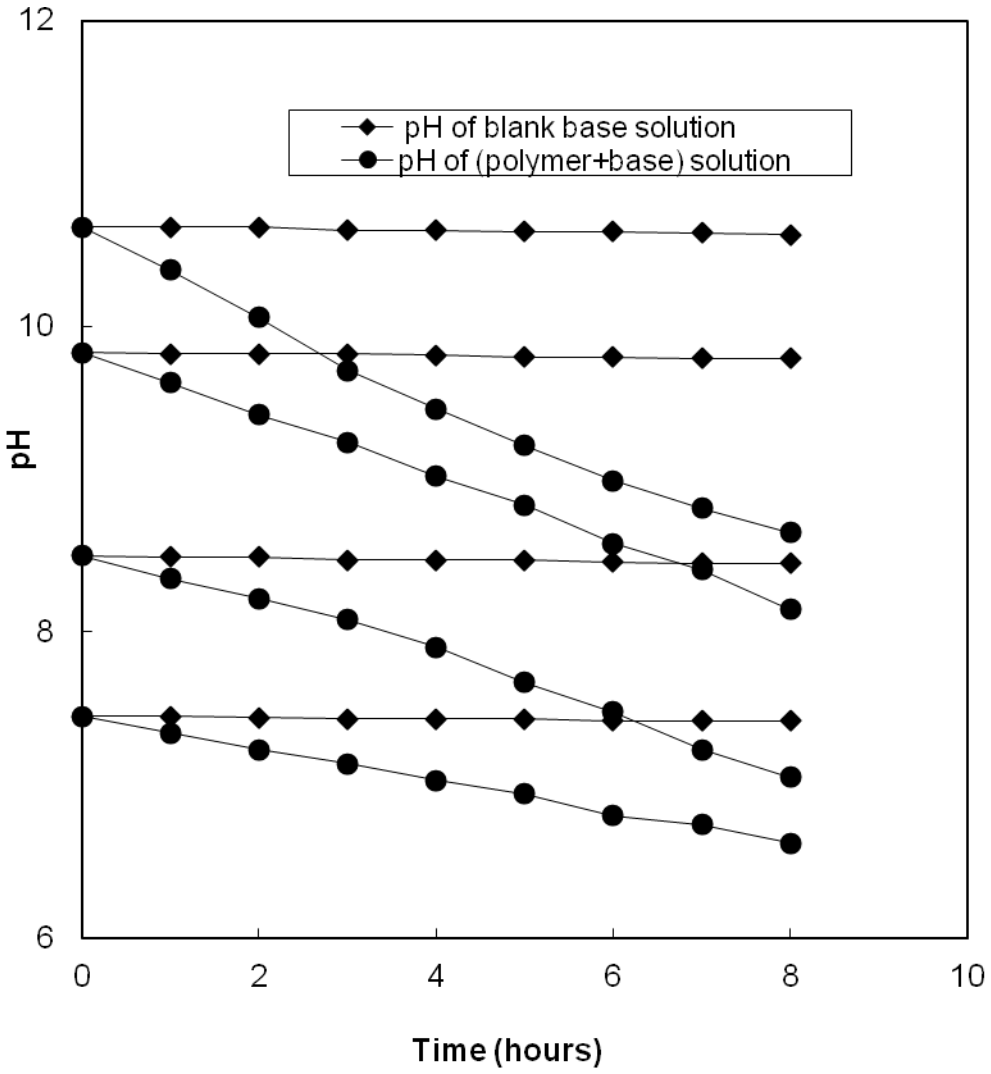


Fig. 4.7: pH Vs time plots of maleic acid-adipic acid-propane-1,2-diol co-polyester in sodium carbonate solution of different pH at room temperature.

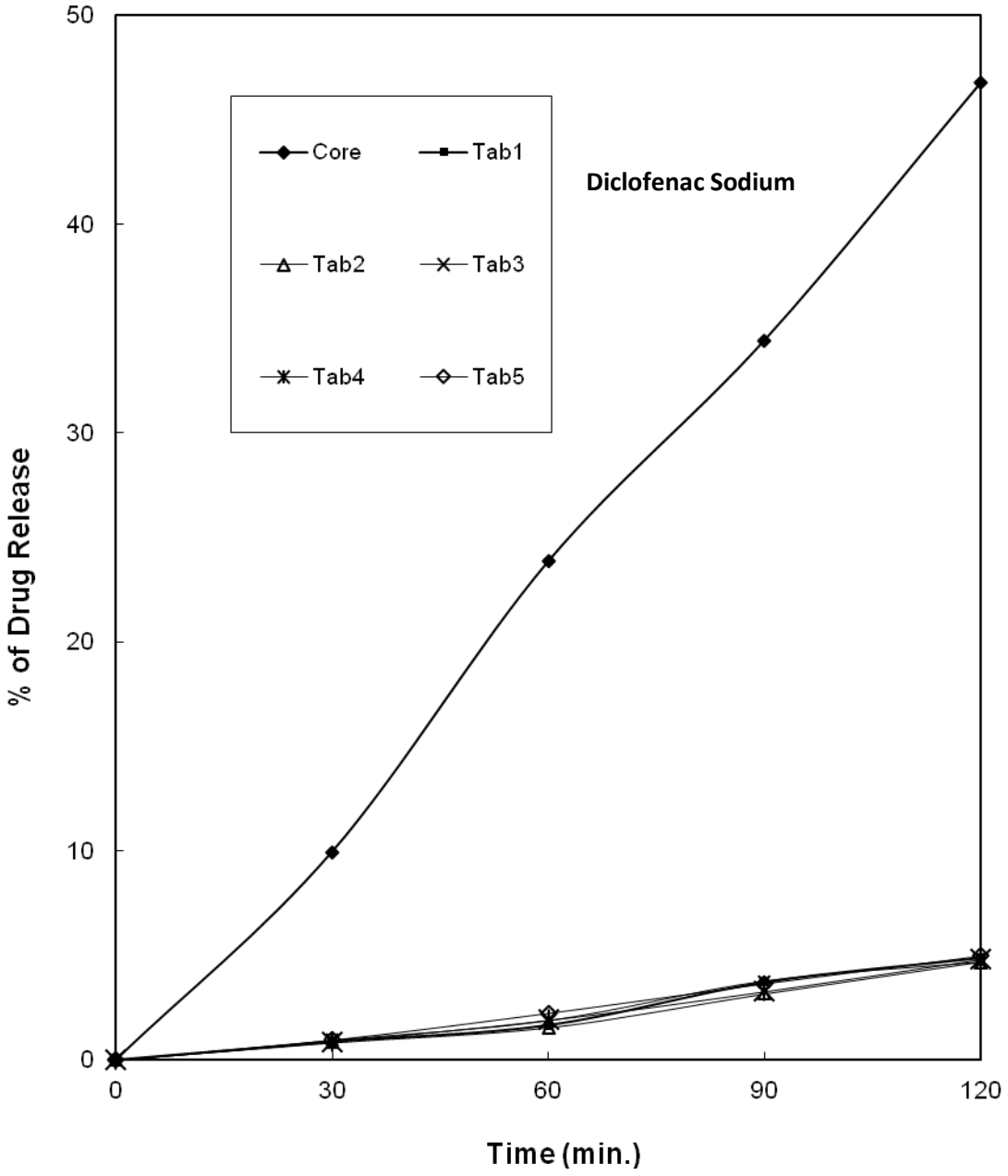


Fig. 4.8: Percent release of diclofenac sodium from core & coated tablets (coated by maleic acid-adipic acid-propane-1,2-diol co-polyester) in simulated gastric fluid (pH =1.2).

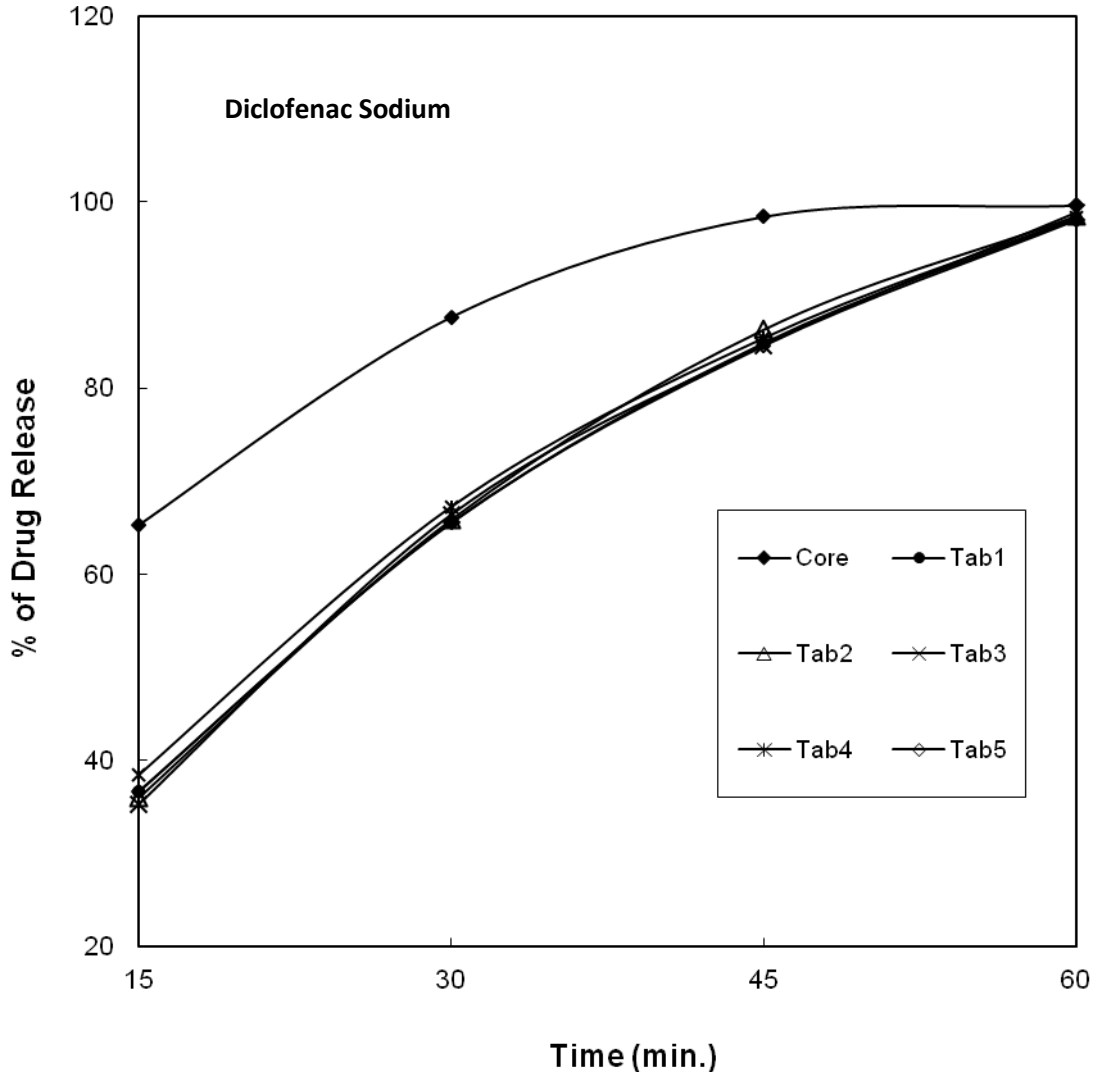


Fig. 4.9: Percent release of diclofenac sodium from core & coated tablets (coated by maleic acid-adipic acid-propane-1,2-diol co-polyester) in simulated intestinal fluid (pH =7.4).

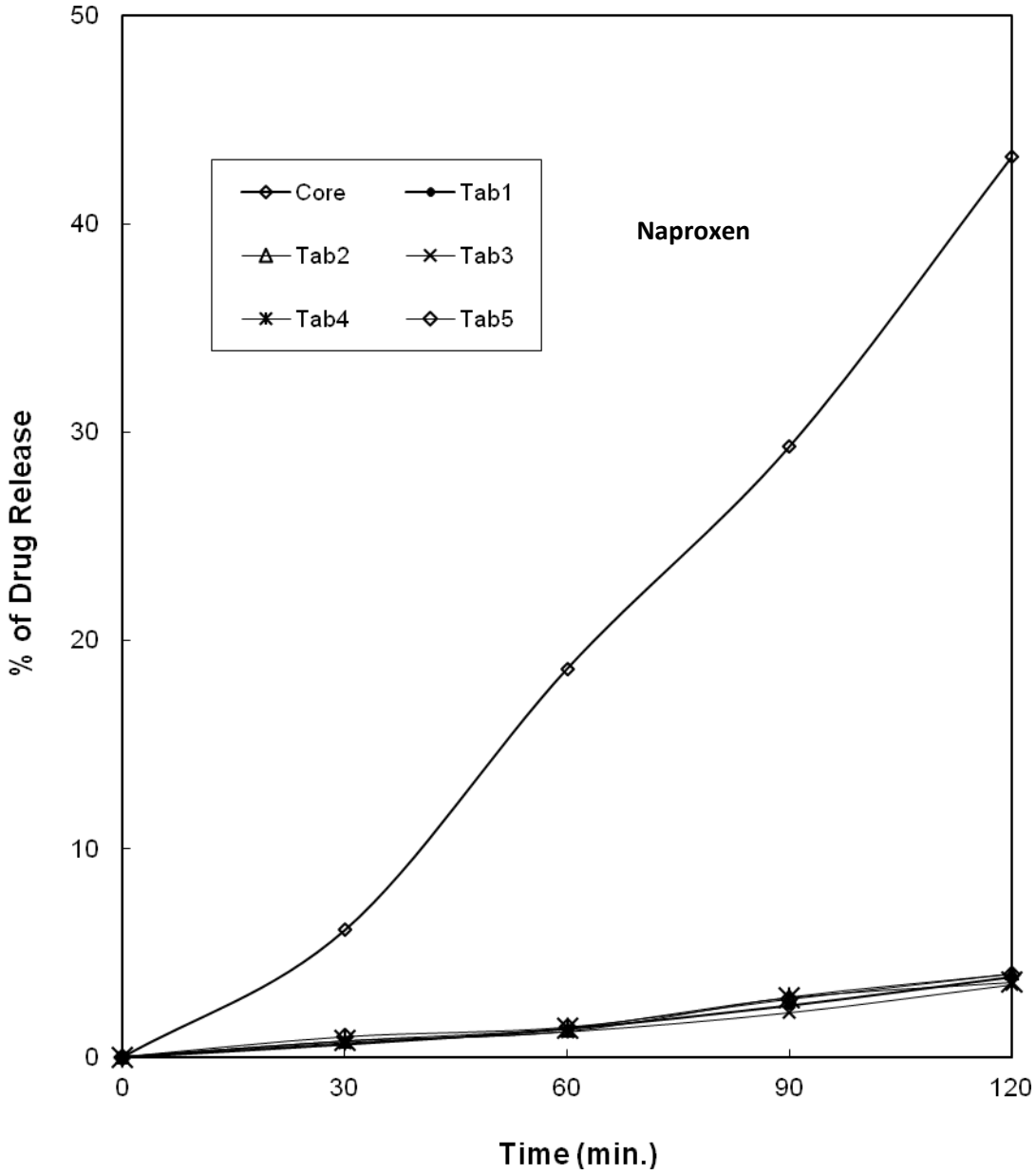


Fig. 4.10: Percent release of naproxen from core & coated tablets (coated by maleic acid-adipic acid-propane-1,2-diol co-polyester) in simulated gastric fluid (pH =1.2).

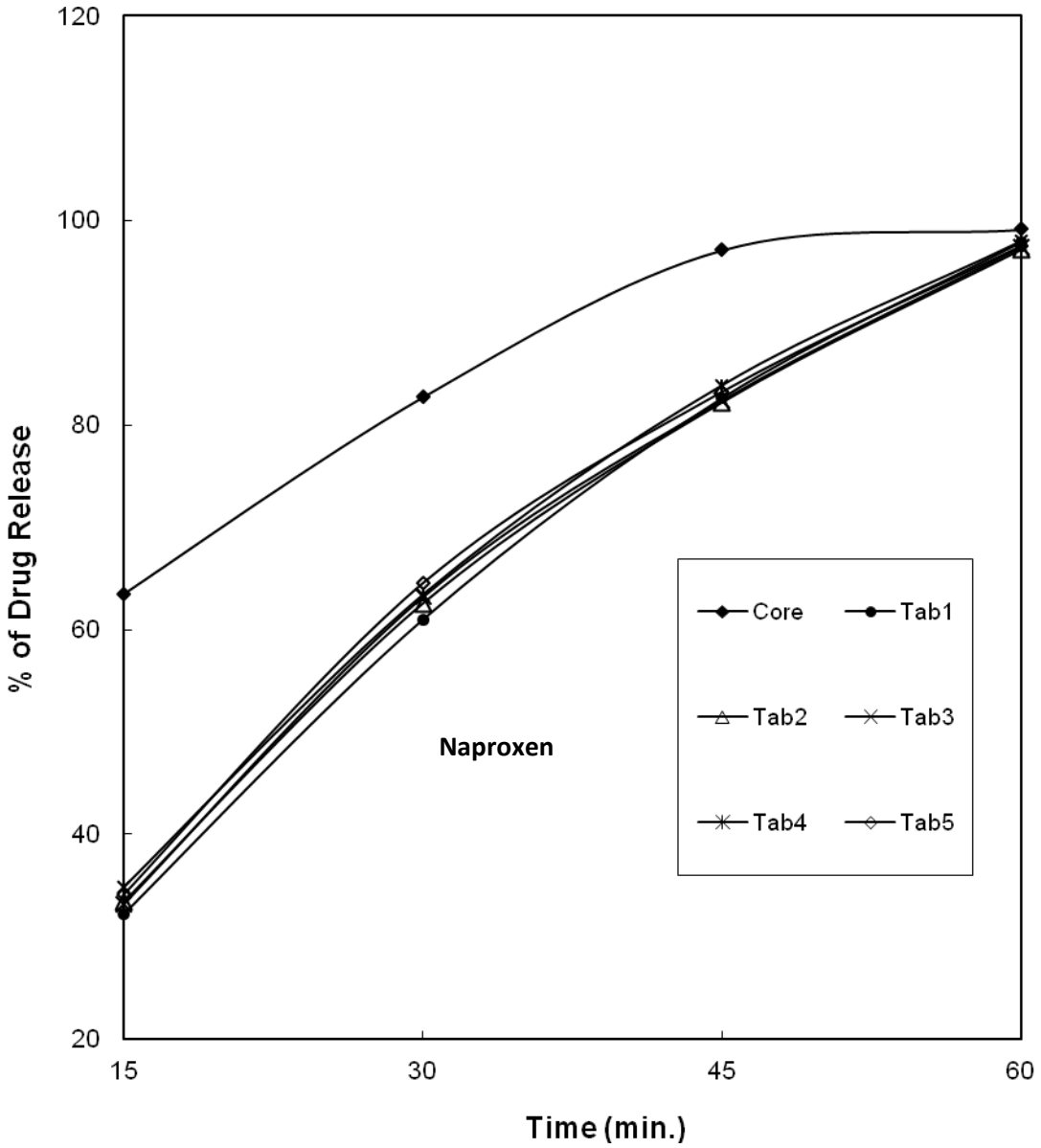


Fig. 4.11: Percent release of naproxen from core & coated tablets (coated by maleic acid-adipic acid-propane-1,2-diol co-polyester) in simulated intestinal fluid (pH =7.4).

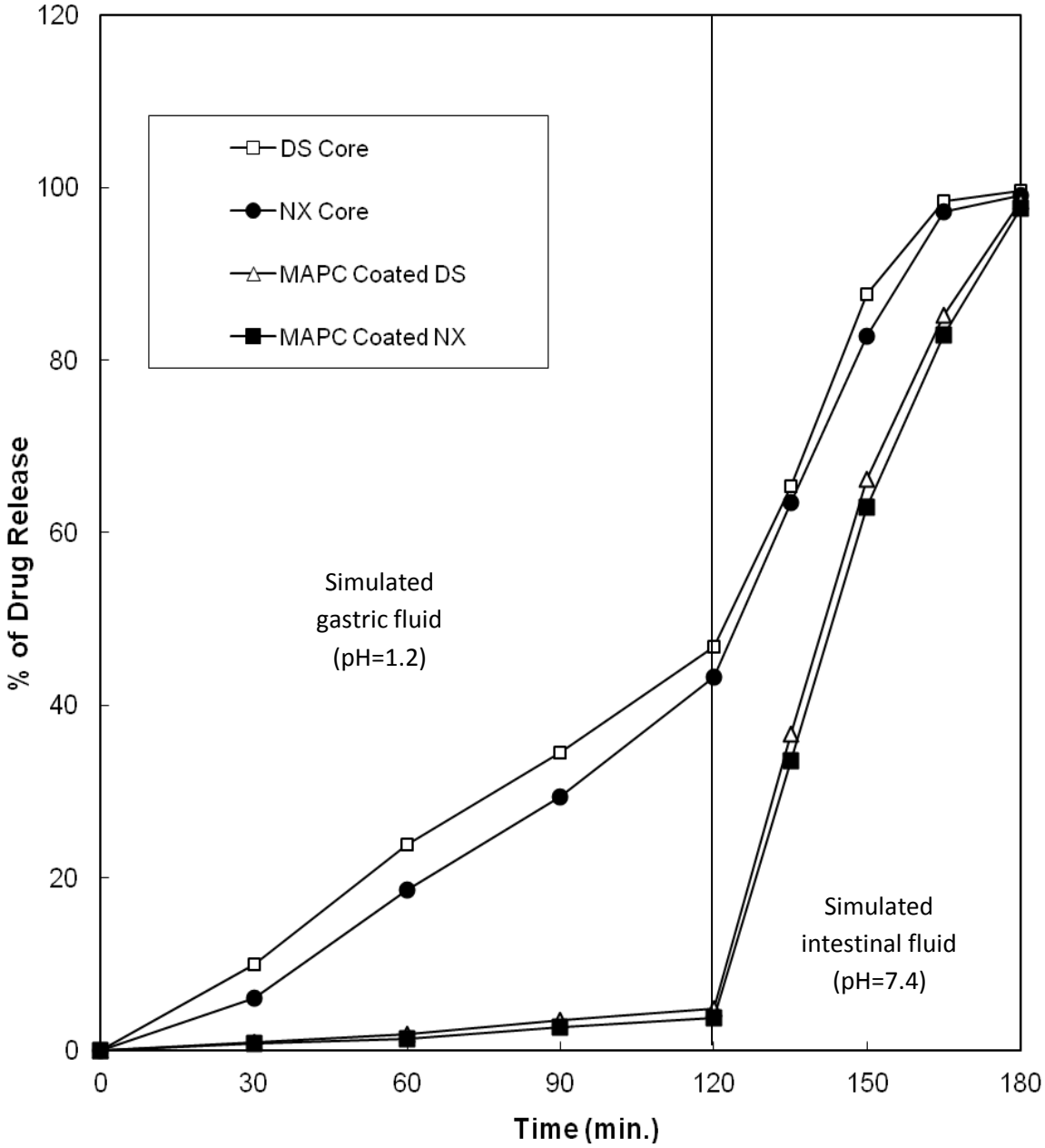


Fig. 4.12: Mean percent release of diclofenac sodium (DS) and naproxen (NX) from core & maleic acid-adipic acid-propane-1,2-diol co-polyester (MAPC) coated tablets in simulated gastric fluid (pH=1.2) and in simulated intestinal fluid (pH =7.4).

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CHAPTER-5

MALIC ACID-ADIPIC ACID-BUTANE-1,4-DIOL CO-POLYESTER FOR GASTRO-RESISTANT DRUG DELIVERY

5.1 INTRODUCTION

Despite tremendous advancements in drug delivery, the oral route is still the preferred way for the administration of therapeutic agents because of low cost and ease of administration[1]. Tablets and capsules are solid dosage forms while suspensions, solutions, elixirs, etc. are liquid. For manufacturing, handling, administration, stability and use, solid dosage forms posses various advantages. Tablets have advantage over capsule because there is no chance of adulteration after being marketed by manufacturer[2]. Gastro-resistant tablets are delayed-release, pH-sensitive formulations that are intended to resist the gastric fluid and to release their active substance(s) in the intestinal fluid. This can be achieved simply by covering the tablets with a suitable gastro-resistant polymer coating (enteric-coated tablets). In the GIT this approach utilizes the existence of the pH gradient that increases progressively from the stomach (pH 1.2-2.0) to the intestine (pH 6.0-7.4). The most commonly used pH-sensitive polymers are derivatives of acrylic acid and cellulose. Proton pump inhibitors, H_2 blockers, anthelmintics, some non-steroidal anti-inflammatory drugs (NSAIDs), etc. are suitable candidates for developing such type of dosage forms[3].

Among the monomers of our consideration in this chapter, malic acid (also known as fruit acid) naturally occurs in sour apples, barriers and in other fruits. The clinical uses of malic acid derivatives have also been

reported [4,5]. In the pharmaceutical industries, adipic acid is being used as a pH-controlling agent in various controlled-release formulations[6-8]. Pharmaceutical and clinical applications of butane-1,4-diol and its derivatives have been known [9,10].

Selecting these pharmaceutically applicable monomers, we have attempted to synthesize malic acid-adipic acid-butane-1,4-diol co-polyester (MABC) that will be used for orally administrated gastro-resistant drug delivery. In this chapter, we report its synthesis, characterization, bio-degradation and *in-vitro* drug delivery characteristics.

5.2 EXPERIMENTAL

5.2.1 Synthesis

Apparatus: 1) Dean-Stark apparatus, 2) R. B. flask, 3) Thermometer (range = 0-350^{0}C), 4) Heating mantle with regulator, 5) Condenser and 6) Vacuum desiccator.

Materials: All of the monomers were A. R. grade chemicals and all were used as such. Anhydrous $FeCl_3$ (A.R. grade chemical), used as catalyst, was freshly sublimed before use.[11]

Procedure: Malic acid-adipic acid-butane 1,4-diol co-polyester was synthesized using Dean-Stark apparatus and xylene as the reaction medium. The mole ratio of the reactants was malic acid: adipic acid: butane 1,4-diol= 1.2:1:2 (reasons to be discussed later). Anhydrous $FeCl_3$ (approximately o.4% of the total weight) was used as catalyst while the reaction temperature and time were 130-135^{0}C and about six hours respectively.

The details of synthesis and purification techniques have been described in **Chapter-2**.

5.2.2 Characterization

The co-polyester was characterized by its solubility in common organic solvents at the ambient temperature, molecular weight, IR spectrum, elemental analysis and degradation study in the soil. It was insoluble in water but readily soluble in acetone and ethylacetate. Molecular weight determination was carried out by end group analysis and viscosity method.

All the tests were accomplished following the experimental procedures described in **Chapter-2**.

5.2.3 Hydrolytic Degradation Study

Hydrolytic degradation study of the polyester was carried out with a view to investigate its degradation nature in different pH media and thus to have the conception of its probable application. This study was performed in both acid and alkali solutions of different pH values. Hydrochloric acid and sodium carbonate were used to prepare these solutions. The change of pH of the polymer sample containing solutions with respect to time was considered as an indication of the degradation of the polyester. The detail of the study was described in **Chapter-2**.

5.2.4 Coating of the Core (Uncoated) Tablets

Malic acid-adipic acid-butane-1,4-diol co-polyester (MABC) was used as coating material on diclofenac sodium tablets (uncoated 50 mg tablets). The detail of the coating procedure is available in **Chapter-2**. Drug

release from the coated tablet was tried as a function of weight gain of the core tablet by coating material and 7-9% weight gain gave the best result.

5.2.5 Drug Dissolution Study

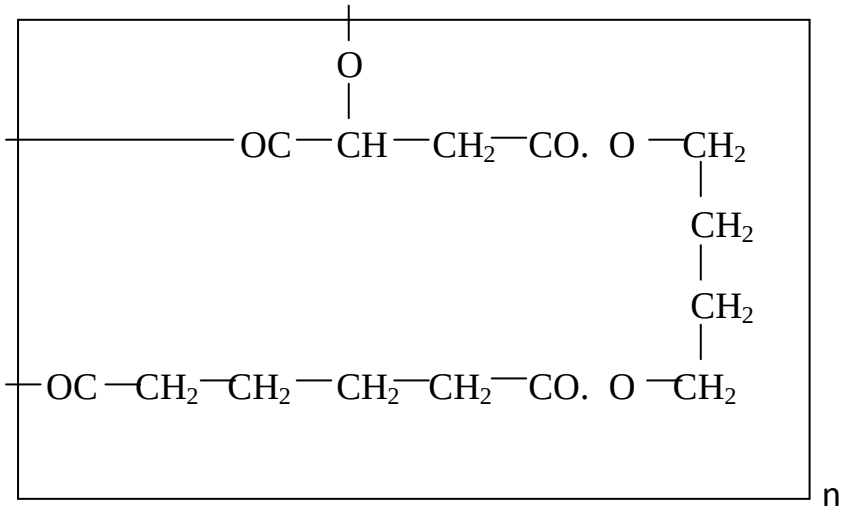
The dissolution studies for both the core and coated tablets were performed with a view to evaluating the efficacy of the polymer as a coating material on the release of the drug. A USP type-XXII dissolution apparatus 'ELECTROLAB TDT-O1' was used for dissolution experiments. The *in-vitro* drug release from the core and the polymer coated tablets in simulated physiological environments (simulated gastric and intestinal fluids) according to the guidelines of British Pharmacopoeia[12] was performed spectrophotometrically by recording the absorbance of the dissolution medium at the λ_{max} of the corresponding drug as a function of time. Five samples of each tablet (core and MABC coated) were tested in this way and concentrations of the released drug were then averaged. This process has been described in **Chapter-2**.

5.3 RESULTS AND DISCUSSION

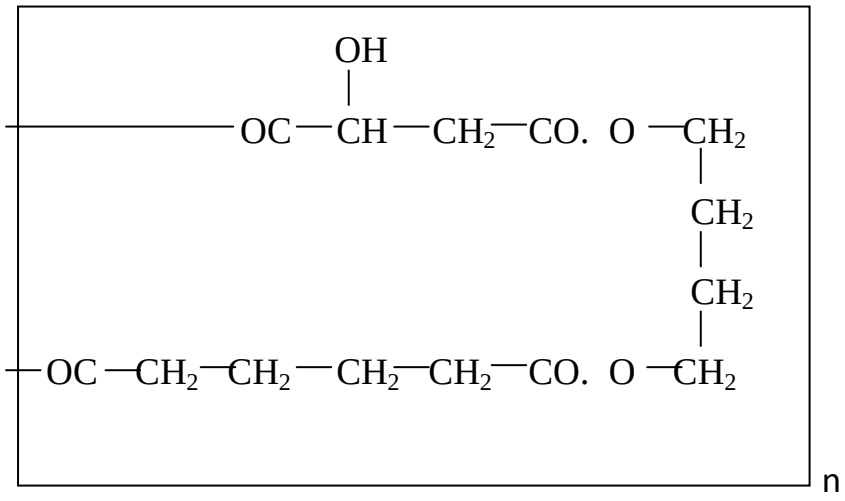
5.3.1 Synthesis

Malic acid possesses two carboxyl groups and one secondary hydroxyl group. Previous researchers from our laboratory have shown that under identical condition of poly-condensation, malic acid alone, in presence of anhydrous $FeCl_3$ catalyst, undergoes self-polycondensation in which around 20% of its carboxyl groups polycondense with its own hydroxyl groups[5,13]. Theoretically, 50% of the carboxyl groups should take part in the reaction, but it happens so probably due to steric effect. Considering this fact, the mole ratio of the monomers was kept as malic acid: adipic acid: butane 1,4-diol= 1.2:1:2.

Now, assuming the secondary hydroxyl group of malic acid to be totally reactive or totally non-reactive, the probable structure of MABC would be A or B as shown below:



Structure A



Structure B

The synthesized co-polyester was collected from the reaction vessel by dissolving it in acetone and purified by precipitating using water as a non-solvent. It was dried under vacuum at 60^0C and stored in a desiccator for subsequent experiments. Physically, it appears brownish in color, solid and sticky at room temperature.

5.3.2 Characterization

Solubility

Solubility of this polyester in different organic solvents at the ambient temperature is presented in Table-5.1. This Table reveals that, acetone, a mixture of toluene and ethanol (toluene: ethanol =3:1) and ethylacetate are good solvents for MABC. But it is poorly soluble in ethanol and chloroform. However, benzene, xylene, formic acid, phenol, etc. and water are common non-solvents for this polyester.

Fractionation

The synthesized polymer was fractionated at (20±1)°C by precipitation technique (described in **Chapter-2**) using acetone as a solvent and water as a non-solvent. The results obtained from the experiments were given in Table-5.2.

Molecular Weight Determination

A. End group analysis

The number average molecular weight ($\overline{M}_n$) of each fraction of MABC was determined by end group analysis. The values of $\overline{M}_n$ for different fractions were found 26440, 24595, 22340, 20950 and 18975 respectively. The weight percentages (wt%) of the fractionated polymer in un-fractionated polymer sample are shown in Table-5.2 & Fig.- 5.1. The table and figure show that the fraction no.-iii of the sample (mol. wt. 22340) is the highest in quantity in un-fractionated polymer sample.

B. By viscosity method

Intrinsic viscosities of each fraction of the polyester were determined. Tables-5.3-5.7 show the reduced viscosities of these fractions. Reduced viscosity Vs concentration graph was plotted and extrapolated to zero

concentration for each fraction as shown in Fig.-5.2. The common ordinate intercepts of these straight lines gave their intrinsic viscosities. The values of intrinsic viscosities and their corresponding molecular weights (obtained by End Group Analysis) of each fraction of the polyester sample are given in Table-5.8. Then the logarithms of the intrinsic viscosities of these polymer fractions were plotted against the logarithms of their molecular weights ($\overline{M_n}$) and a linear curve was obtained (Fig.-5.3) whose intercept and slope gave the values of Mark-Hauwink constants[14] 'K' and 'a' respectively.

According to Mark-Hauwink equation the relationship between viscosity average molecular weight ($\overline{M}_v$) and intrinsic viscosity can be expressed as:

$$[\eta] = K\left(\overline{M}_v\right)^a = 13.03\times10^{-3}\left(\overline{M}_v\right)^{0.71}$$

Table-5.8 also shows the molecular weights of different fractions of this polymer sample obtained by viscosity method. It is observed that the molecular weight of the polymer sample found out by viscometry ($\overline{M}_v$) is greater than that of the same obtained by end group analysis ($\overline{M}_n$).

IR Spectra

The broad band representing the –OH group at the region 3100-3500cm^{-1} in the spectrum of the diol almost disappeared in the spectrum of the MABC (Fig.-5.4). The >C=O stretching frequency at the region 1725-1735cm^{-1} of the spectrum of the malic acid shifted to 1720.5 cm^{-1} region (Fig.-5.4) and a new band representing the ester linkage appeared at the 1171cm^{-1} region in the spectrum of the polyester (Fig.-5.4). All these indicate the reaction between –OH and –COOH groups and thereby ester linkage is formed in the sample[5,15].

Elemental Analysis

Calculated for structure A: C = 53.14% and H = 5.54%

Calculated for structure B: C =52.94% and H = 5.88%

Found from the co-polyester sample: C =51.93% and H = 6.13%.

It is observed that the result of elemental analysis of the co-polyester is in-between structures A and B, but nearer to B than A. It may be concluded that the co-polyester is a mixture of structure A and structure B.

Soil Degradation Test

Table-5.9 and Fig.-5.5 show the gradual weight loss of the polymer buried in the soil[16, 17] and after nine weeks it ultimately mixed with the soil. This is an evidence of the total soil degradation of the polyester sample.

5.3.3 Hydrolytic Degradation Study

Table-5.10 & 5.11 and Fig.-5.6 & 5.7 reveal that, at room temperature, the co-polyester remained intact in solutions of pH=0-3.0, slight degradation happened in the pH range 3.0-6.0, but it gradually degraded in solutions of pH >6.0. Such pH responsive degradation behavior of this polyester led us to figure out its possible application in gastro-resistant drug delivery. In this connection, its *in-vitro* drug release charactreristics[12] needs to be investigated.

5.3.4 *In-vitro* Drug Release Characteristics (Drug Dissolution Study)

The task of the gastro-resistant material is to resist the release of the drug from the solid dosage forms in the gastric environment but assists drug release in the intestine. This study was carried out to evaluate the

performance of MABC as a gastro-resistant coating material on tablets and diclofenac sodium tablet (uncoated 50mg tablet) was used as a model drug. In this study, simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4) were used as the drug release media. According to the dissolution ANNEX of British Pharmacopoeia[12], within two hours, a solid gastro-resistant oral formulation should release the drug less than 10% in the simulated gastric fluid but in the simulated intestinal fluid it should release more than 80% of the drug within 45minutes.

In this study, it was found that the polyester did not degrade or swell in the gastric fluid for two hours when coated on a core tablet and less than 5% diclofenac sodium released from polymer coated tablets, whereas around 45% of diclofenac sodium released from the core tablets (uncoated tablets) in that time in the simulated gastric fluid (Table-5.12 and Fig.- 5.8). But in the simulated intestinal fluid the coating gradually degraded and more than 83% of diclofenac sodium released from co-polyester coated tablets within 45 minutes (Table-5.13 and Fig.-5.9). The mean percent release of diclofenac sodium from core and MABC coated tablets are presented in Table-5.14 & Fig.-5.10 which reveal that the drug release pattern of MABC corresponds to the British Pharmacopoeia[12] drug release profile of gastro-resistant drug formulations. So, malic acid-adipic acid-butane-1,4-diol co-polyester (MABC) could be a future candidate for gastro-resistant drug delivery. One of the advantages of this co-polyester was that, it had sticky property and hence could produce soft film on the tablet surface, no additional plasticizer was added to the formulation. However, prior to clinical trial, its toxicological and other necessary pharmacological investigations need to be performed.

TABLES OF EXPERIMENTAL DATA

Table 5.1: Solubility behavior of malic acid-adipic acid-butane-1,4-diol co-polyester (MABC) at ambient temperature.

Solvent	Solubility
Acetone	+ +
Mixed Solvent (Toluene: Ethanol =3:1)	+ +
Ethylacetate	++
Toluene	+
Chloroform	+
Acetic acid	-
Benzene	-
Xylene	-
Ethanol	-
Formic acid	-
Phenol	-
Carbon tetrachloride	-
Rectified sprit (R.S)	-
Diethyl ether	-
Water	-

Here (+ +), (+) and (-) indicate high solubility, low solubility and no solubility respectively.

Table 5.2: Molecular weight distribution of fractionated malic acid-adipic acid-butane-1,4-diol co-polyester in un-fractionated polymer.

Polymer fraction no.	Weight % of fraction	Mol. wt. by end group analysis ($\overline{M_n}$)
i	8.5	26440
ii	20.7	24595
iii	33.2	22340
iv	23.5	20950
v	14.1	18975

Table 5.3: Viscosity data for malic acid-adipic acid-butane-1,4-diol co-polyester ($\overline{M}_n$=26440) in acetone at 19^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (acetone), t_0 = 125.2 sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00400	142.0	1.1342	0.1342	33.55	18.62
0.00350	139.2	1.1118	0.1118	32.95	
0.00250	134.1	1.0710	0.0710	28.40	
0.00200	131.8	1.0527	0.0527	26.35	

Table 5.4: Viscosity data for malic acid-adipic acid-butane-1,4-diol co-polyester ($\overline{M_n}$ =24595) in acetone at 19^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (acetone), t_0 = 125.2 sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00450	143.5	1.1462	0.1462	32.48	17.58
0.00385	139.9	1.1174	0.1174	30.50	
0.00310	135.9	1.0855	0.0855	27.59	
0.00225	132.3	1.0567	0.0567	25.20	

Table 5.5: Viscosity data for malic acid-adipic acid-butane-1,4-diol co-polyester ($\overline{M}_n$ =22340) in acetone at 19^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (acetone), t_0 = 125.2sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00430	141.1	1.1270	0.1270	29.53	16.58
0.00350	137.0	1.0943	0.0943	26.95	
0.00285	134.3	1.0727	0.0727	25.51	
0.00200	130.8	1.0447	0.0447	22.35	

Table 5.6: Viscosity data for malic acid-adipic acid-butane-1,4-diol co-polyester ($\overline{M_n}$ =20950) in acetone at 19^0C.
Volume of the solution taken in viscometer = 10 ml
Efflux time for 10 ml solvent (acetone), t_0 = 125.2 sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00445	139.4	1.1134	0.1134	25.48	15.94
0.00350	135.8	1.0847	0.0847	24.20	
0.00300	133.6	1.0671	0.0671	22.37	
0.00210	132.9	1.0615	0.0615	20.50	

Table 5.7: Viscosity data for malic acid-adipic acid-butane-1,4-diol co-polyester ($\overline{M}_n$ =18975) in acetone at 19^0C.
Volume of the solution taken in viscometer = 10 ml
Efflux time for 10 ml solvent (acetone), t_0 = 125.2 sec.

Concentration **C (g/ml)**	**Efflux time t sec.**	**Relative viscosity** $t/t_0 = \eta_r$	*Specific* **viscosity** $\eta_r - 1 = \eta_{sp}$	**Reduced viscosity** η_{sp}/C **(ml/g)**	*Intrinsic* **viscosity,** $[\eta]$ **(ml/g)**
0.00500	140.1	1.1190	0.1190	23.80	14.65
0.00430	137.3	1.0966	0.0966	22.47	
0.00335	134.0	1.0703	0.0703	20.98	
0.00250	131.4	1.0495	0.0495	19.80	

Table 5.8: Comparison between molecular weights obtained by end group analysis and the same obtained by viscosity method of malic acid-adipic acid-butane-1,4-diol co-polyester.

Fraction no.	*Intrinsic* viscosity, $[\eta]$ ml/g (from graph)	$K \times 10^3$ (from graph)ml/g	a (from graph)	Molecular weight by	
				End group analysis($\overline{M}_n$)	Viscosity method($\overline{M}_v$)
i	18.62	13.03	0.71	26440	27779
ii	17.58			24595	25619
iii	16.58			22340	23590
iv	15.94			20950	22320
v	14.65			18975	19817

Table 5.9: Soil degradation of MABC at normal weathering condition.

Time (days)	% of weight loss
7	15.5
14	29.0
21	45.4
28	60.0
35	72.6
42	81.1
49	90.3
56	99.2
63	100

Table 5.10: pH-responsive characteristics (hydrolytic degradation study) of malic acid-adipic acid-butane-1,4-diol co-polyester in acid media [HCl solution] at room temperature.

Reading	Time (hour)	Initial pH=1.35		Initial pH=2.50		Initial pH=3.70		Initial pH=4.40		Initial pH=6.50	
		pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)
1	0	1.35	1.35	2.50	2.5	3.70	3.70	4.40	4.40	6.50	6.50
2	1	1.35	1.35	2.50	2.49	3.69	3.68	4.40	4.36	6.49	6.44
3	2	1.34	1.34	2.50	2.48	3.69	3.66	4.38	4.31	6.49	6.38
4	3	1.33	1.33	2.49	2.47	3.68	3.63	4.38	4.28	6.48	6.32
5	4	1.33	1.32	2.49	2.45	3.68	3.60	4.37	4.23	6.47	6.25
6	5	1.33	1.32	2.48	2.44	3.67	3.56	4.37	4.17	6.47	6.17
7	6	1.31	1.31	2.48	2.43	3.66	3.51	4.36	4.11	6.46	6.10
8	7	1.30	1.29	2.47	2.42	3.65	3.45	4.36	4.05	6.45	6.03
9	8	1.30	1.28	2.47	2.41	3.65	3.40	4.35	4.00	6.44	5.95

Table 5.11: pH-responsive characteristics (hydrolytic degradation study) of malic acid-adipic acid-butane-1,4-diol co-polyester in basic media [Na_2CO_3 solution] at room temperature.

Reading	Time (hour)	Initial pH=7.40		Initial pH=8.50		Initial pH=9.55		Initial pH=10.50	
		pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)
1	0	7.40	7.40	8.50	8.5	9.55	9.55	10.50	10.5
2	1	7.40	7.31	8.49	8.35	9.54	9.25	10.50	10.20
3	2	7.39	7.22	8.49	8.2	9.54	9.03	10.49	9.89
4	3	7.39	7.13	8.48	8.05	9.53	8.80	10.48	9.59
5	4	7.38	7.03	8.48	7.89	9.53	8.58	10.48	9.33
6	5	7.38	6.93	8.48	7.73	9.53	8.39	10.47	9.18
7	6	7.38	6.83	8.46	7.58	9.52	8.25	10.46	9.04
8	7	7.37	6.73	8.46	7.42	9.52	8.07	10.45	8.91
9	8	7.37	6.62	8.45	7.25	9.51	7.88	10.45	8.78

Table 5.12: In-vitro drug release study of diclofenac sodium (DS) core tablets coated by malic acid-adipic acid-butane-1,4-diol co-polyester in simulated gastric fluid (pH = 1.2).

Sample	% of drug release			
	Time (30 min.)	**Time (60 min.)**	**Time (90 min.)**	**Time (120 min.)**
Core	7.62	22.10	34.34	45.30
Tab-1	0.95	1.55	2.23	3.65
Tab-2	0.90	1.48	2.94	4.26
Tab-3	0.87	1.32	2.44	3.91
Tab-4	0.84	1.28	2.57	4.12
Tab-5	1.10	2.56	3.78	4.55

Table 5.13: In-vitro drug release study of diclofenac sodium (DS) core tablets coated by malic acid-adipic acid-butane-1,4-diol co-polyester in simulated intestinal fluid (pH =7.4).

Sample	% of drug release			
	Time (15min.)	**Time (30min.)**	**Time (45min.)**	**Time (60min.)**
Core	64.23	85.57	98.50	99.25
Tab-1	32.80	64.08	83.95	97.75
Tab-2	33.22	63.51	82.75	98.60
Tab-3	33.35	63.28	82.40	98.45
Tab-4	34.21	64.84	84.38	98.87
Tab-5	35.15	64.12	84.15	99.03

Table 5.14: Mean percent of drug release from diclofenac sodium (DS) core tablets coated by malic acid-adipic acid-butane-1,4-diol co-polyester (MABC) in simulated gastric fluid (pH = 1.2) and intestinal fluid (pH =7.4).

Mean % of drug release in simulated gastric fluid (pH=1.20)				**Mean % of drug release in simulated intestinal fluid (pH = 7.40)**			
30 min.	60 min.	90 min.	120 min.	135 min.	150 min.	165 min.	180 min.
0.93	1.64	2.79	4.10	33.75	63.97	83.53	98.54

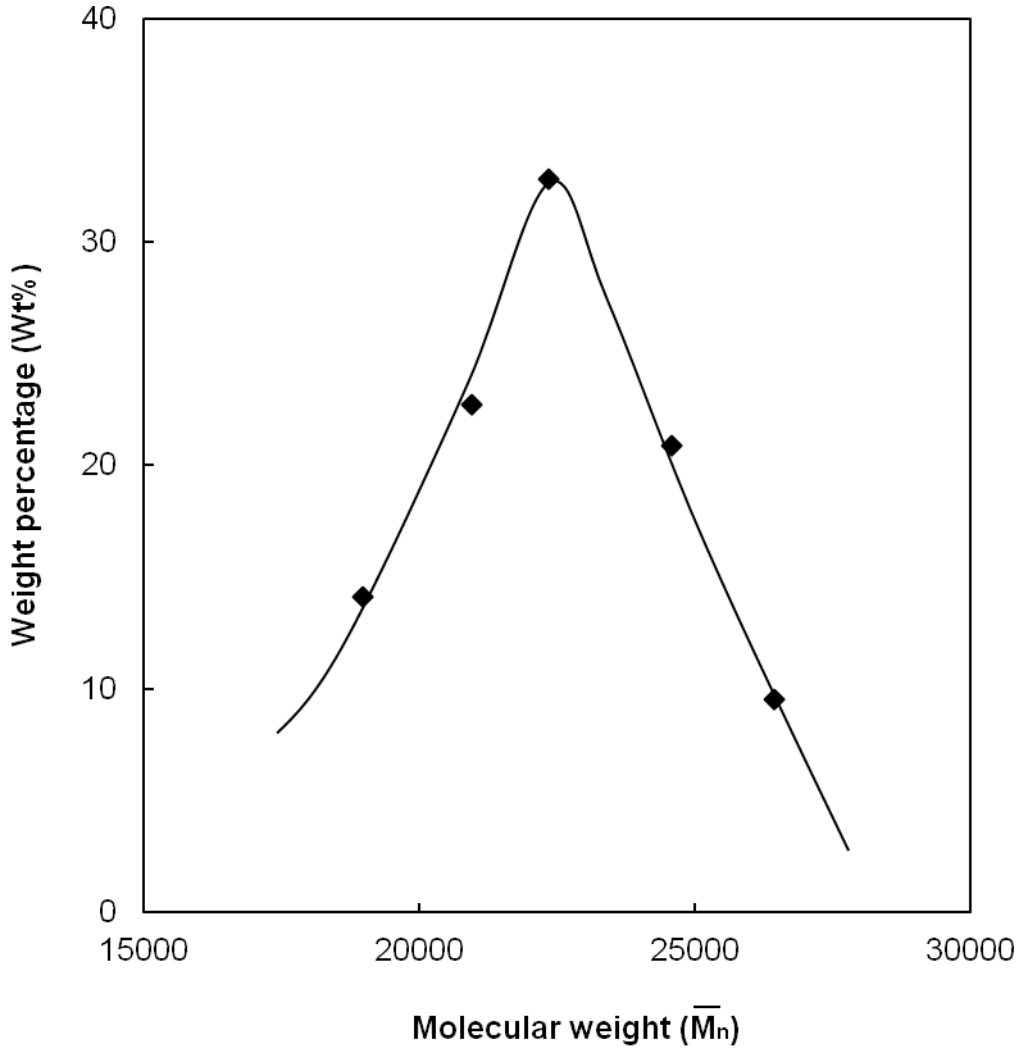


Fig. 5.1: Molecular weight distribution curve of fractionated malic acid-adipic acid-butane-1,4-diol co-polyester in unfractionated sample.

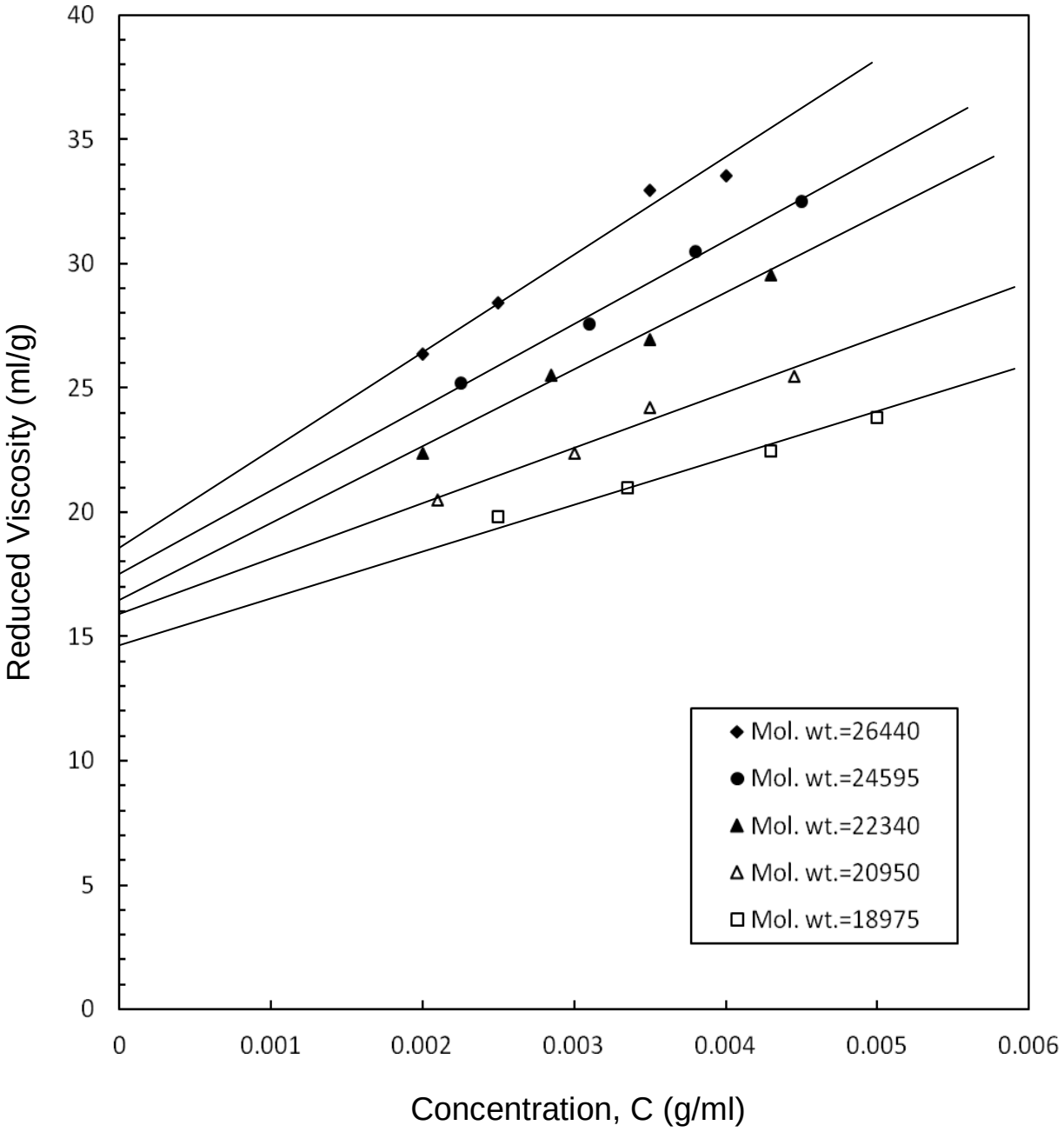


Fig. 5.2: Plots of concentration Vs reduced viscosity for malic acid-adipic acid-butane-1,4-diol co-polyester of different fractions in acetone at 19^0C.

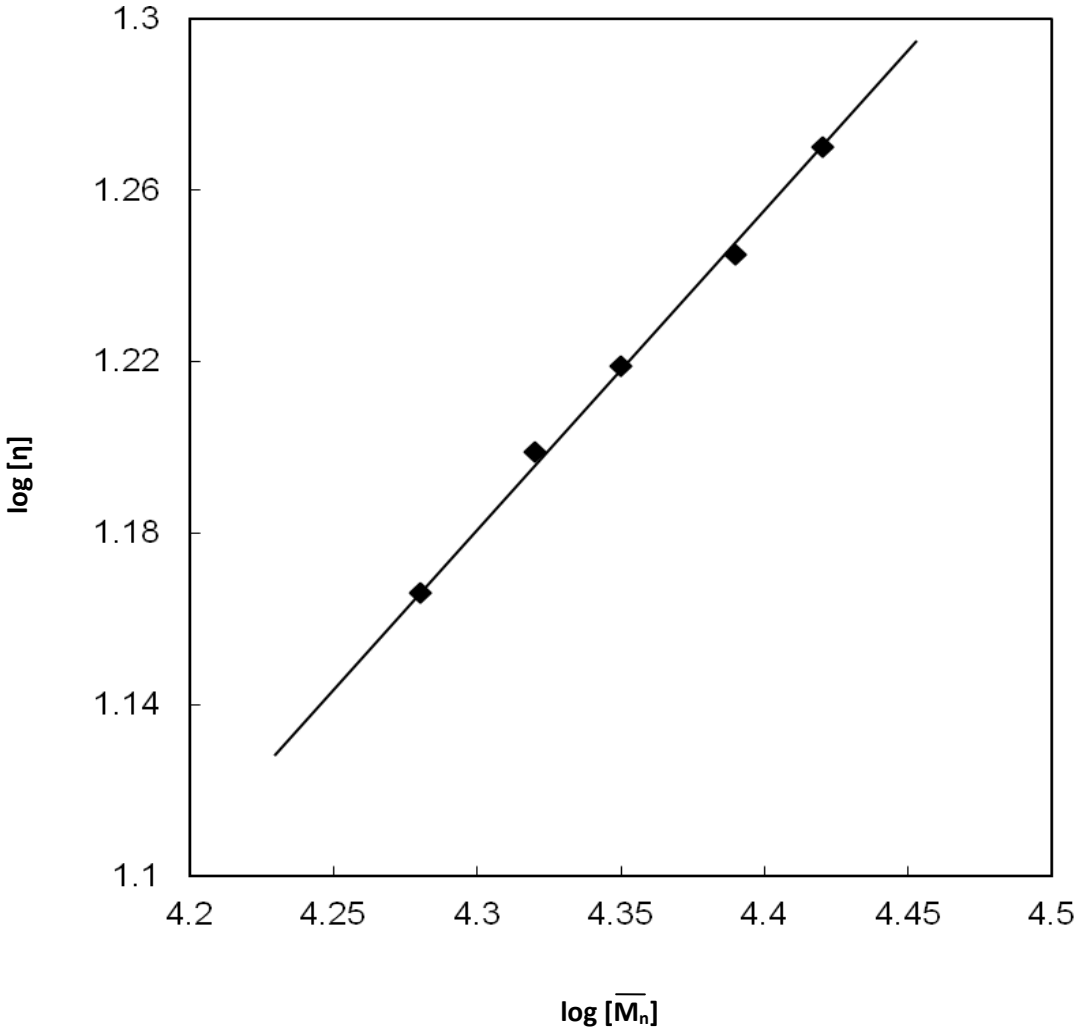


Fig. 5.3: log of intrinsic viscosity Vs log of molecular weight relationship for malic acid-adipic acid-butane-1,4-diol co-polyester in acetone at 19°C.

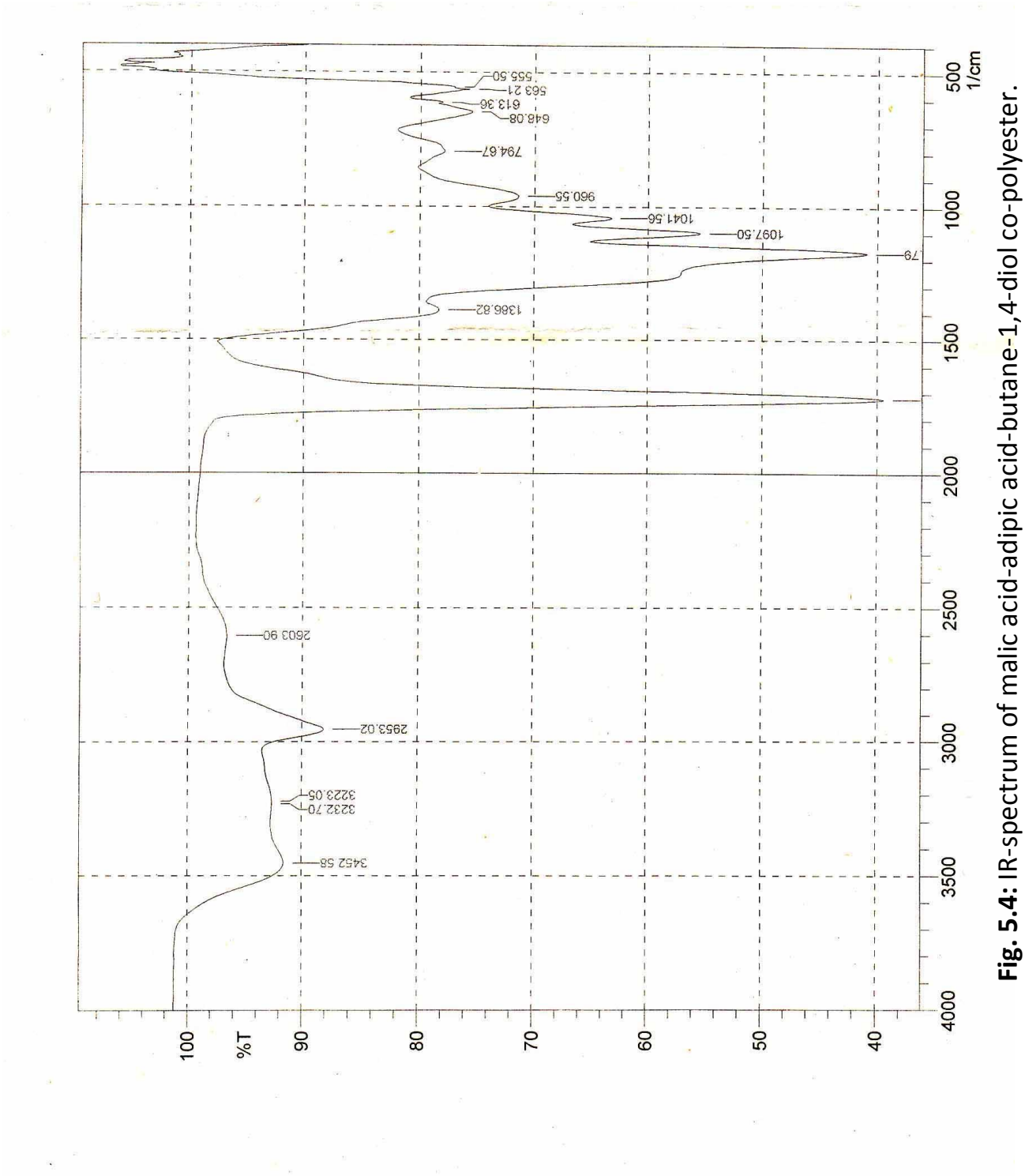


Fig. 5.4: IR-spectrum of malic acid-adipic acid-butane-1,4-diol co-polyester.

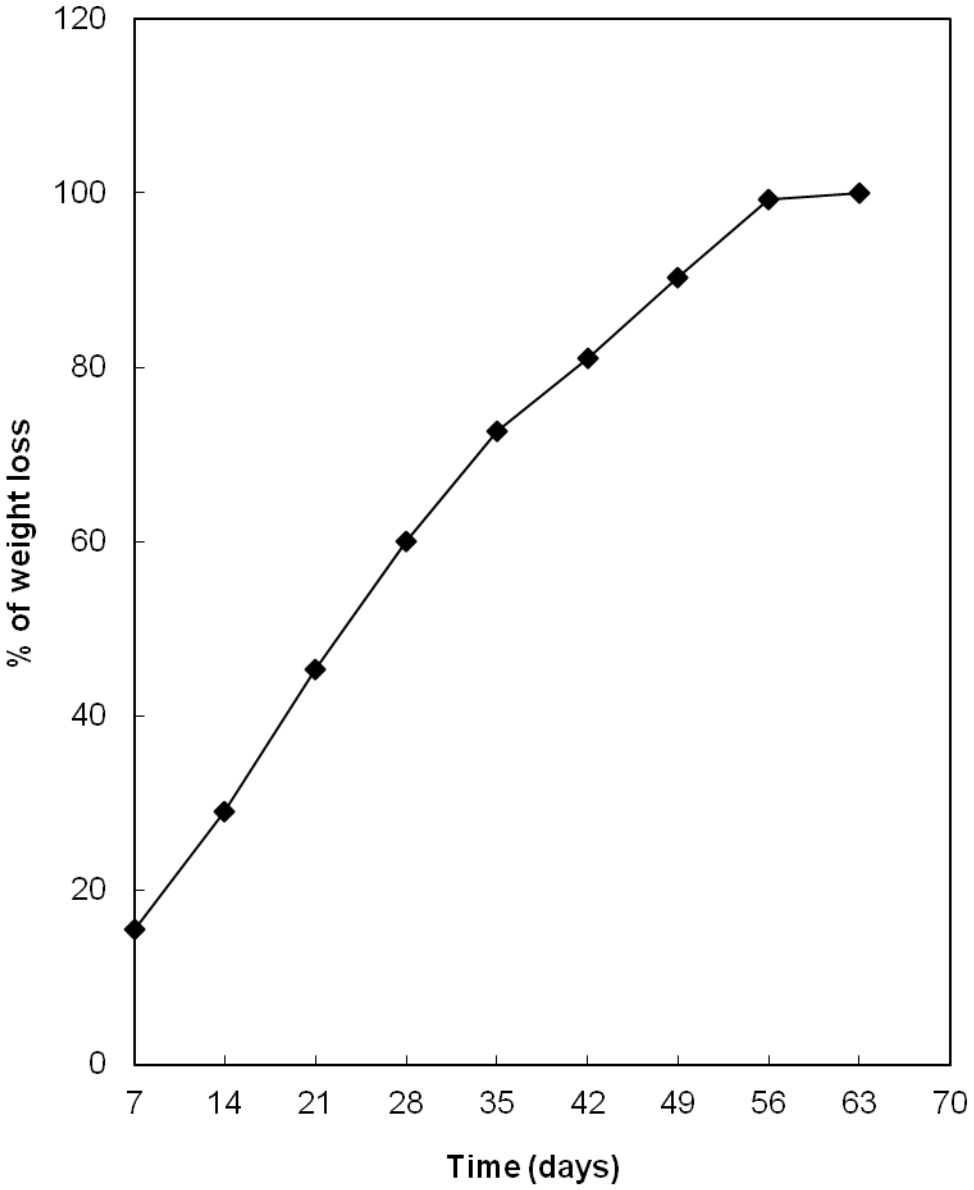


Fig. 5.5: Soil degradation of malic acid-adipic acid-butane-1,4-diol co-polyester at normal weathering condition.

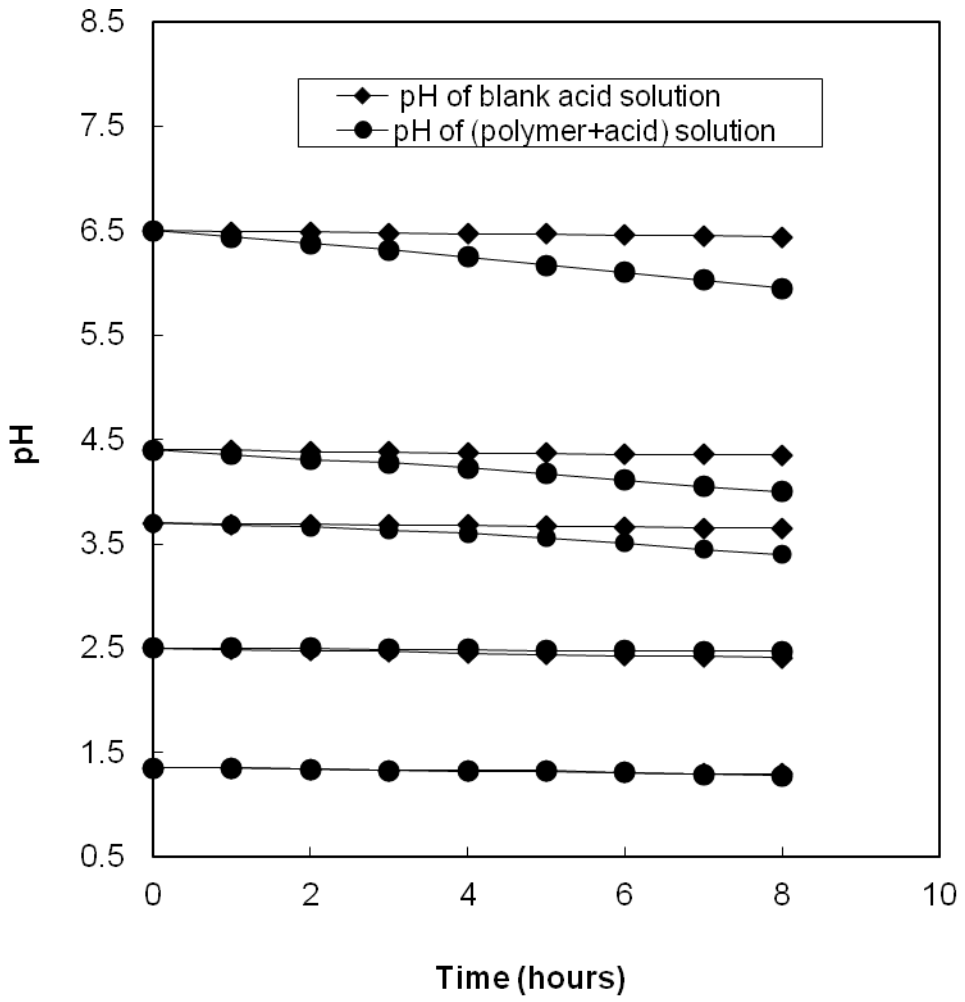


Fig. 5.6: pH Vs time plots for malic acid-adipic acid-butane-1,4-diol co-polyester in hydrochloric acid solution of different pH at room temperature.

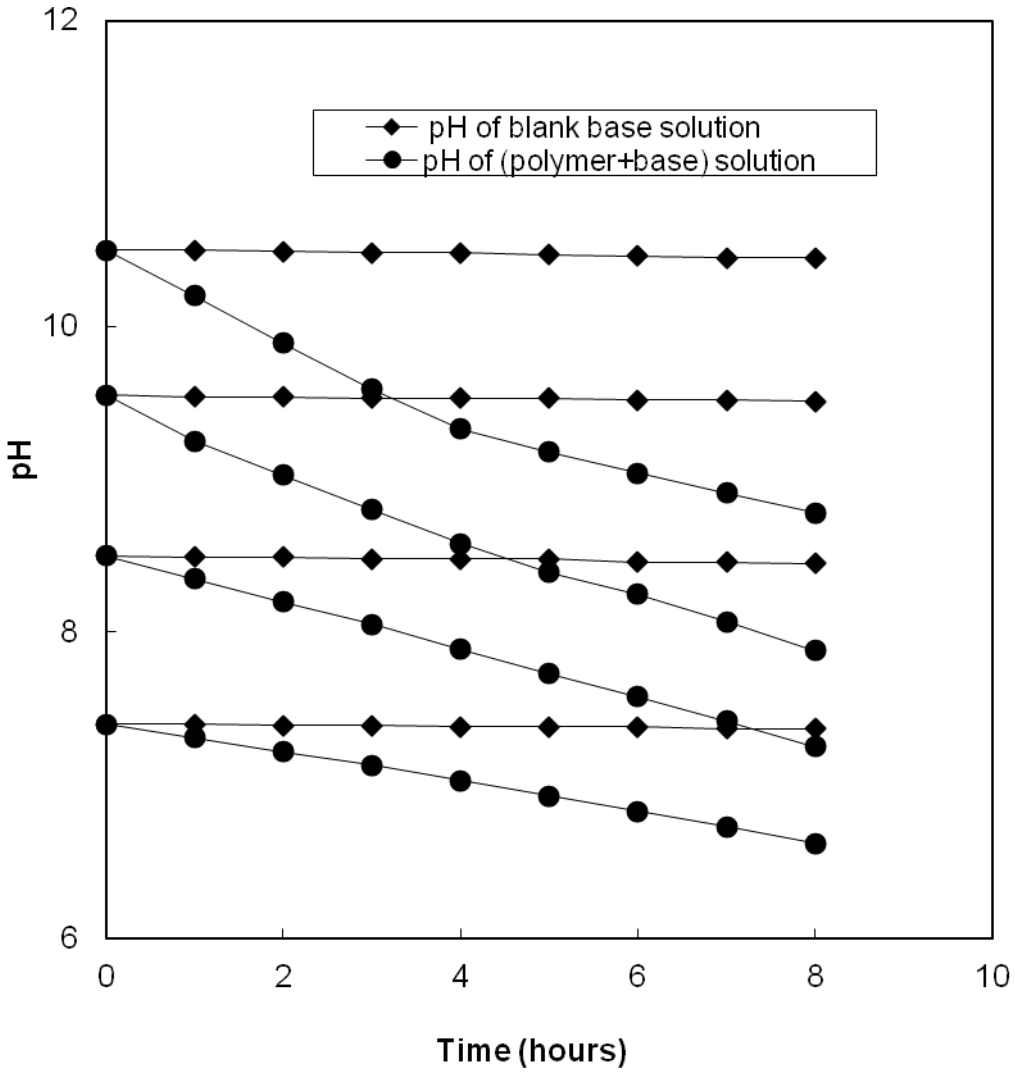


Fig. 5.7: pH Vs time plots of malic acid-adipic acid-butane-1,4-diol co-polyester in sodium carbonate solution of different pH at room temperature.

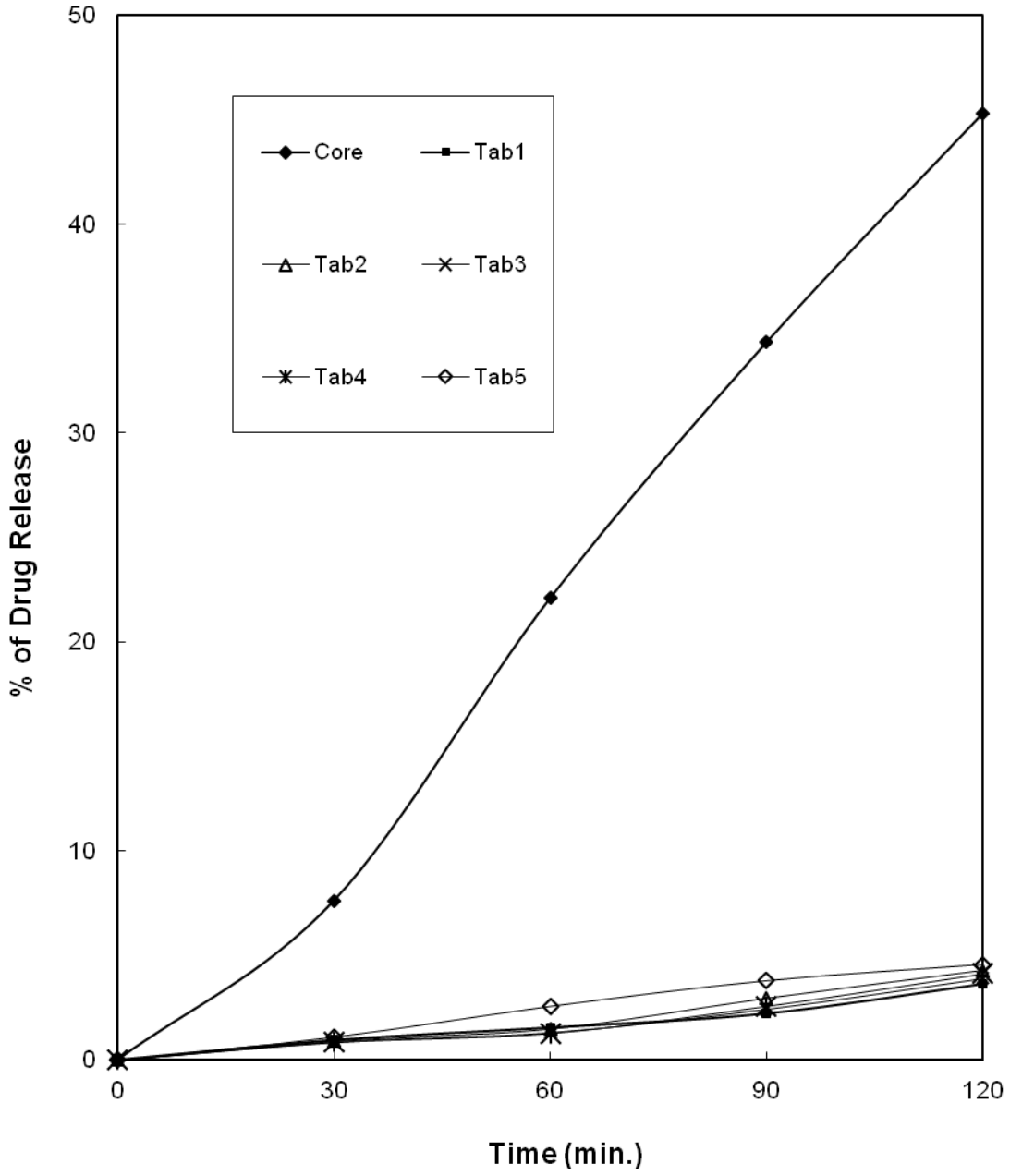


Fig. 5.8: Percent release of diclofenac sodium from core & coated tablets (coated by malic acid-adipic acid-butane-1,4-diol co-polyester) in simulated gastric fluid (pH =1.2).

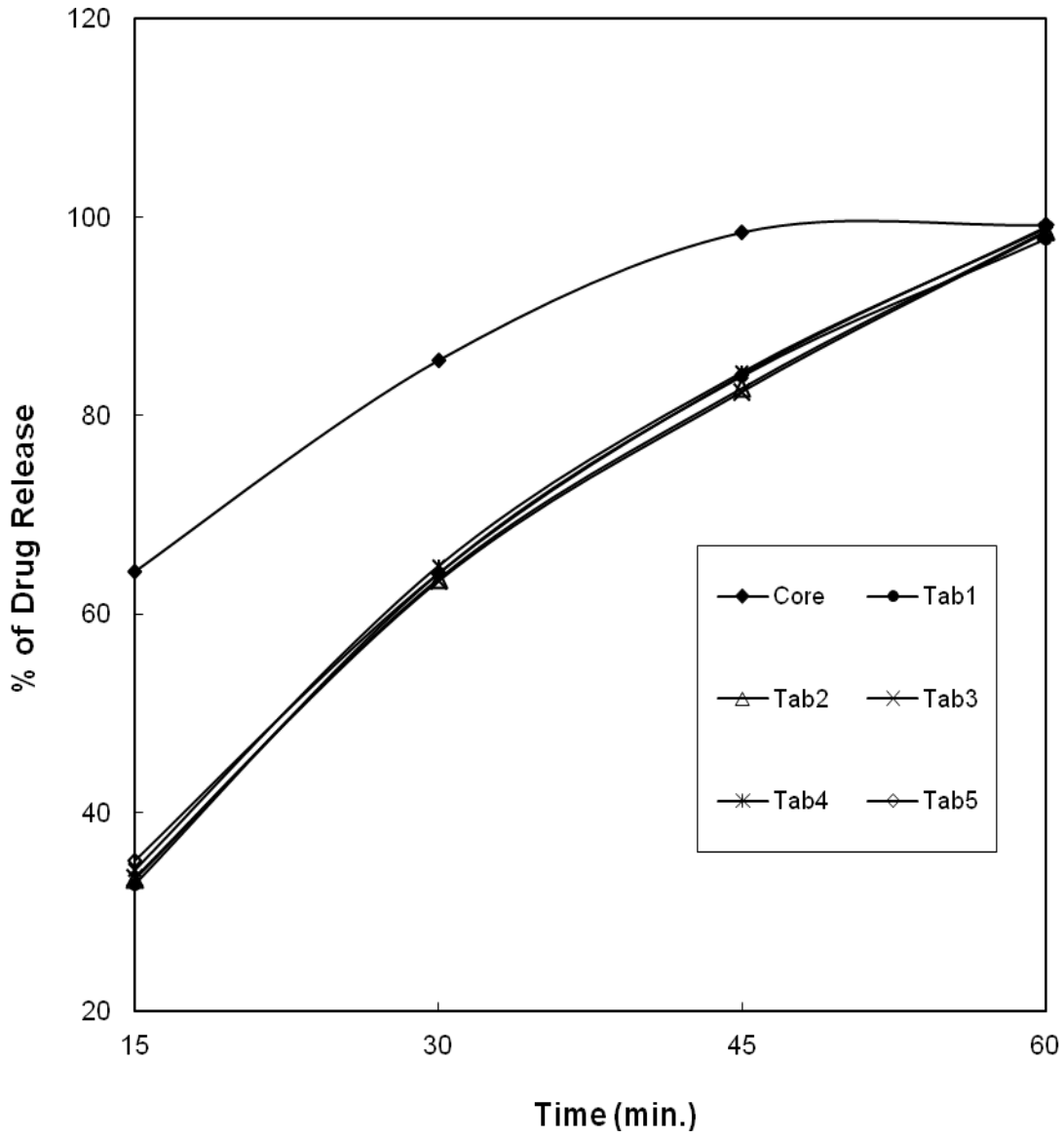


Fig. 5.9: Percent release of diclofenac sodium from core & coated tablets (coated by malic acid-adipic acid-butane-1,4-diol co-polyester) in simulated intestinal fluid (pH =7.4).

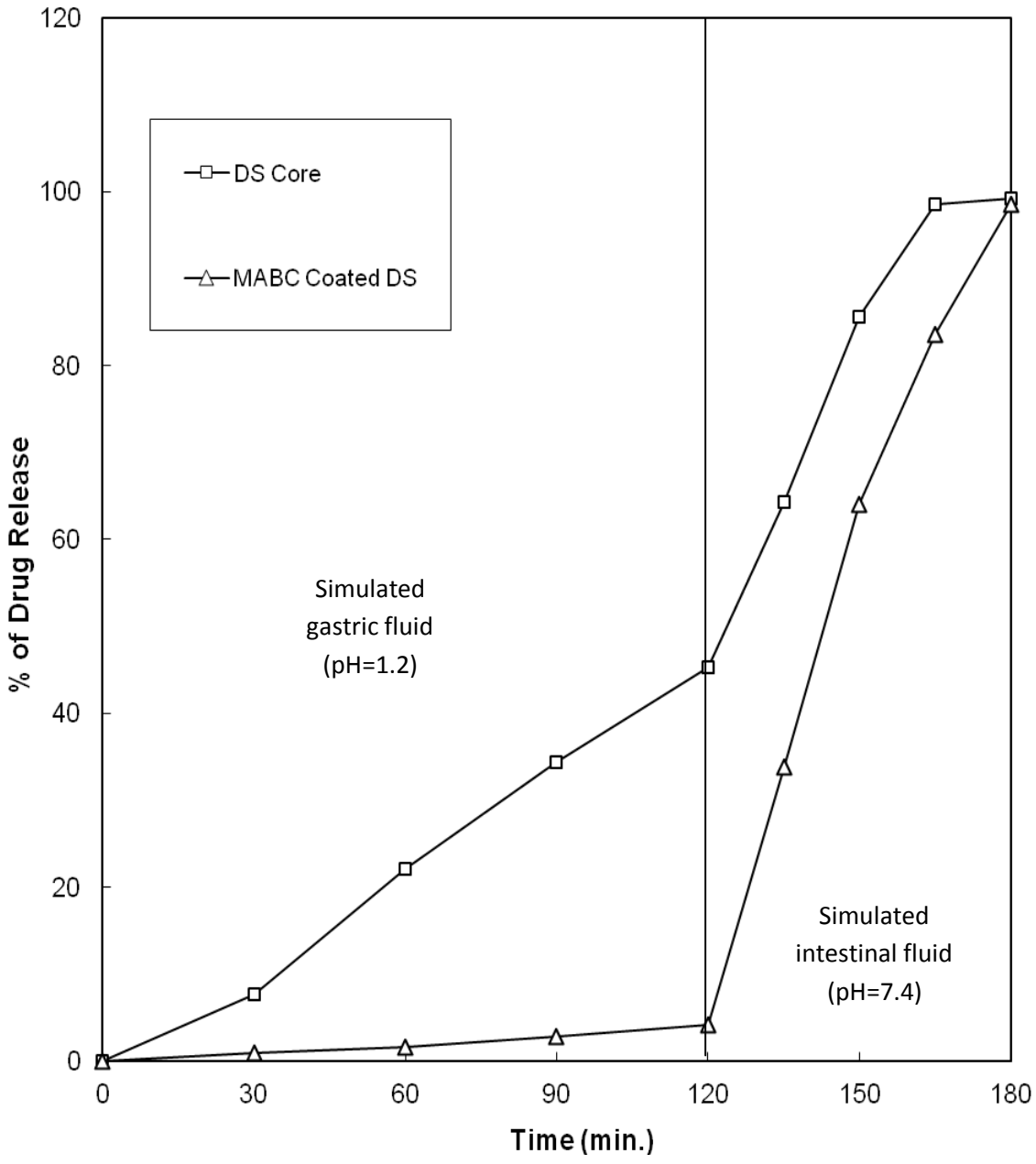


Fig. 5.10: Mean percent release of diclofenac sodium (DS) from core & malic acid-adipic acid-butane-1,4-diol co-polyester (MABC) coated tablets in simulated gastric fluid (pH=1.2) and in simulated intestinal fluid (pH =7.4).

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CHAPTER-6

MALEIC ACID-CITRIC ACID-PROPANE-1,2-DIOL CO-POLYESTER FOR EXTENDED RELEASE DRUG FORMULATION

6.1 INTRODUCTION

So far, oral administration of therapeutic agents represents the easiest, most convenient and user-friendly route for drug delivery. Considering convenience from the patient's perspective, an oral drug formulation presents a challenge to the scientist, who has to design drug delivery systems in such a way that a desirable pharmacokinetic profile may be attained for a given drug[1]. In recent years there has been great interest in the development and use of tablets which after being swallowed can slowly but continuously release the drug in the gastrointestinal tract to achieve a prolonged therapeutic effect over an extended period of time[2,3] .Such tablets are named in various ways, such as slow release, extended release, sustained release, prolonged release, timed release, depot and respiratory dosage forms. There are several reasons for attractiveness of extended release formulations over conventional dosage forms viz. they provide continuous bioavailability of drug, reduce the frequency of drug administration by prolonging the duration of effective blood levels, improve the specific distribution of the drug, reduce the fluctuation of peak-trough concentration and side effects[4,5]. Matrix tablet is one of the least complicated approaches to manufacture extended release dosage forms in which the drug is dispersed in a polymer matrix[6,7]. Biodegradable polymers from poly glycolic acid (PGA) and poly lactic acid (PLA) are the simplest aliphatic polyesters, which are currently

the most widely used synthetic, degradable polymers in human medicine[8,9]. For biomedical applications, a polymer is better to be devised from biocompatible monomers. Pharmaceutical applications of maleic acid has mentioned in Chapter-3. Citric acid occurs naturally in a number of plant species (citrus fruits) and is extensively used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions[10]. On the other hand, propane-1,2-diol is being widely used as a solvent, extractant, and preservative in a variety of pharmaceutical formulations and is generally regarded as a relatively nontoxic material[10].

Choosing these pharmaceutically recognized monomers, maleic acid-citric acid-propane-1,2-diol co-polyester (MCPC) has been synthesized and investigated as a polymer matrix for extended release drug delivery. In this chapter, its synthesis, characterization and bio-degradation will be reported. Incorporation of a suitable drug (dichlofenac sodium) in this polymer matrix and in-vitro release of the incorporated drug will also be discussed.

6.2 EXPERIMENTAL

6.2.1 Synthesis

Apparatus: 1) Dean-Stark apparatus, 2) R. B. flask, 3) Thermometer (range = 0-350^{0}C), 4) Heating mantle with regulator, 5) Condenser and 6) Vacuum desiccator.

Materials: Maleic acid, citric acid and propane-1,2-diol were A. R. grade chemicals and used as such. Anhydrous $FeCl_3$ (A.R. grade chemical), used as catalyst, was freshly sublimed before use.

Procedure: The polycondensation reaction (between the corresponding monomers in desired ratio) was carried out using Dean-Stark apparatus and xylene as the reaction medium. Anhydrous $FeCl_3$ (approximately o.4% of the total weight) was used as catalyst while the reaction temperature and time were 135-140^{0}C and about six hours respectively. The details of synthesis and purification techniques have been described in **Chapter-2**.

In this way, five polymer samples (I-V) were synthesized using maleic acid, propane-1,2-diol (acid/diol mole ratio = 1) along with 0.1, 0.2, 0.3, 0.4 and 0.5% of citric acid, on the basis of total weight of the reactants, respectively. Citric acid was expected to produce random cross-linking throughout the structure

6.2.2 Characterization

The co-polyesters were characterized by their solubility in common organic solvents at the ambient temperature, equilibrium swelling behavior in water and rectified sprit, molecular weight, IR spectra and degradation study in the soil. Equilibrium swelling was measured gravimetrically, where care was given to avoid any loss of solvent during measurement. Molecular weight determination was carried out by end group analysis and viscosity method.

All tests were accomplished through the experimental procedures described in **Chapter-2**.

6.2.3 Hydrolytic Degradation Study

Hydrolytic degradation was carried out to evaluate the degradation characteristics of the synthesized co-polyester in solutions of various pH. This study was done in both acid and alkali solutions of different pH

values. Hydrochloric acid and sodium carbonate were used to prepare these solutions. The change of pH of the solution containing the polymer sample with respect to time in comparison to blank solution was considered as an indication of the degradation of the polyester. The detail of the study was described in **Chapter-2**.

6.2.4 Preparation of Drug-Polymer Matrix Tablets[11]

Maleic acid-citric acid-propane-1,2-diol co-polyester was used as drug carrier and diclofenac sodium was the model drug. Both of the polymer and drug were weighed accurately. The drug was then dispersed in the melted polymer in such a way that each tablet contains 50mg of the drug. After being cooled and meshed, the granules were compressed in a single punch tablet machine to get them in tablet forms. Magnesium stearate was used as a lubricating agent for the punch and die surface of the machine. The detail of the procedure is available in **Chapter-2**.

6.2.5 In-vitro Drug Release Study of the Matrix Tablets [12-13]

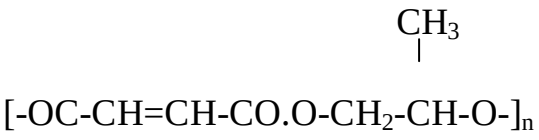
This study was performed to figure out the release kinetics of diclofenac sodium impregnated in polymer matrix. 1000 ml of phosphate buffer (pH 7.4) at 37°C under stirred condition was used as the dissolution medium. A 5 ml aliquot portion of the medium was removed at 30 minutes intervals and its absorbance (after suitable dilution where necessary) was measured at 274nm (λ_{max} of diclofenac sodium) on a Shimadzu UV-VIS (Model: U-1800) spectrophotometer and volume loss of the medium was immediately compensated with the same amount of fresh medium preheated at 37°C±0.5°C. Concentrations of the released drug were then obtained by comparing with standard curves prepared for the pure drug in phosphate buffer solution of pH 7.4 in the appropriate concentration

region. Five samples of drug-polymer matrix tablet were tested in this way and the variations in the concentration values being within 1%.

6.3 RESULTS AND DISCUSSION

6.3.1 Synthesis

Both maleic acid and prpane-1,2-diol are bi-functional monomers and were polycondensed in stoichiometric ratio 1:1. Citric acid (the third reactant) contains three carboxylic groups and one tertiary hydroxyl group. A trace amount of citric acid varying from 0.1 to 0.5% of the total weight of the reactants was used as cross-linking agent. The expected structure of the co-polyester is as follows:



However, the used citric acid would produce random cross-linking throughout the structure. The synthesized MCPC samples were brown in color, solid and slightly sticky at room temperature.

6.3.2 Characterization

Solubility

Solubility of this co-polyester in various organic solvents at the ambient temperature is presented in Table-6.1which reveals that acetone, a mixture of toluene and ethanol (toluene: ethanol =3:1) and ethylacetate are good solvents for MCPC. But it is poorly soluble in ethanol and toluene. However, benzene, xylene, formic acid, rectified sprit (R.S) etc. and water are common non-solvents for this polyester.

Swelling Behavior

Equilibrium swelling values of the five MCPC samples (I-V) in water and rectified sprit (R.S.) at the ambient temperature are presented in the Table-6.2, 6.3 and Fig.-6.1, 6.2 which show that the equilibrium swelling value of the sample-V (containing 0.5wt% citric acid) in each of the two solvents is the lowest. In a given solvent, at a particular temperature, the extent of swelling for a series of chemically similar cross-linked polymers is inversely proportional to the crosslink density in the network[14]. So the results of swelling study indicate that the crosslink density as well as molecular weight follows the order V > IV > III > II > I. More than 0.5% citric acid will certainly increase the crosslink density of the co-polyester domain and thus reduces its solubility in common organic solvents and raises the difficulties to handle it in large scale pharmaceutical applications.

Again, the equilibrium swelling values in the two solvents are in order: rectified sprit > water (Table-6.4). This is probably because of the better solvent property of rectified sprit than that of water. On the basis of swelling behavior sample-V was selected for the subsequent experiments.

Fractionation

The synthesized polymer was fractionated at (20±1)°C by precipitation technique (described in **Chapter-2**) using acetone as solvent and water as non-solvent. The result obtained from the experiments was given in Table-6.5.

Molecular Weight Determination

A. End group analysis

The number average molecular weight ($\overline{M}_n$) of each fraction of MCPC was determined by end group analysis. The values of $\overline{M}_n$ for different

fractions were found 22945, 19530, 17253, 13638 and 11220 respectively. The weight percentages (wt%) of the fractionated polymer in un-fractionated polymer sample are shown in Table-6.5 & Fig.-6.3. These indicate that the fraction no.-iii of the sample (mol. wt. 17253) is the highest in quantity in un-fractionated polymer sample.

B. Viscosity method

For each fraction of the polyester, a number of solutions of different known concentrations (g/ml) were made. The efflux time of each solution was measured using Ostwald viscometer and then relative viscosity, specific viscosity and reduced viscosity were calculated, which are presented in Tables-6.6-6.10. Reduced viscosity Vs concentration graph was plotted and extrapolated to zero concentration for each fraction as shown in Fig.-6.4. The ordinate intercept of the straight line gave the intrinsic viscosity. The values of intrinsic viscosities and their corresponding molecular weights (obtained by End Group Analysis) of each fraction of the polyester sample are given in Table-6.11. The logarithms of the intrinsic viscosities of these polymer fractions were plotted against the logarithms of their molecular weights ($\overline{M_n}$) and a linear curve was obtained (Fig.-6.5) whose intercept and slope gave the values of Mark-Hauwink constants[15] 'K' and 'a' respectively.

According to Mark-Hauwink equation the relationship between viscosity average molecular weight ($\overline{M}_v$) and intrinsic viscosity can be expressed as:

$$[\eta] = K\left(\overline{M}_v\right)^a = 15.8\times10^{-3}\left(\overline{M}_v\right)^{0.73}$$

Table-6.11 also shows the comparative values of the molecular weights of different fractions of this polymer sample obtained by end group

analysis and the same obtained by viscosity method and it was observed that molecular weight obtained by viscometry ($\overline{M}_v$) is greater than that of the same found out by end group analysis ($\overline{M}_n$).

IR Spectra

The broad band representing the –OH group at the region 3100-3500cm^{-1} in the spectrum of the diol almost disappeared in the spectrum of the MCPC (Fig.-6.6). The >C=O stretching frequency at the region 1700-1710cm^{-1} of the spectrum of the maleic acid shifted to 1714.7 cm^{-1} region and a new band representing the ester linkage appeared at the 1155cm^{-1} region in the spectrum of polyester. All these indicate the reaction between –OH and –COOH groups forming ester linkage in the sample[16].

Elemental Analysis

Calculated for expected structure: C = 53.85%, H = 5.12 %, and found for co-polyester sample-V: C = 53.21% and H = 5.45%. It is seen that the percentage composition of the sample obtained by calculation matches with the same obtained by analysis. The product is accordingly confirmed.

Soil Degradation Test

Table-6.12 and Fig.-6.7 show the gradual weight loss of the polymer buried in soil[17, 18] and after 55 days it ultimately mixed with the soil. This is an indication of the total soil degradation of the polyester sample.

6.3.3 Hydrolytic Degradation Study

At room temperature, hydrolytic degradation study (Table: 6.13 & 6.14 and Fig.-6.8 & 6.9) showed that the co-polyester sample remained almost intact in the acid medium (pH 1.2-6.0) but gradually degraded in basic

medium (pH>7.0). In acid region the polymer sample swells insignificantly. But in alkaline region it swells and the ester linkage is hydrolyzed resulting in the meaningful decrease of the pH of the polymer sample containing solutions with respect to time. Such pH responsive time dependent degradation nature of this polyester led us to figure out its possible application in controlled release oral formulations. However, it was observed that the co-polyester could not produce soft continuous film on glass substrate. Because of this it was better tried as drug carrier for extended release drug-polymer matrix tablets rather than enteric coating material. In this connection, its *in-vitro* drug release behavior needs to be investigated.

6.3.4 In-vitro Drug Release Study of the Matrix Tablets (Drug Dissolution Study)

A diclofenac sodium loaded MCPC polymer matrix tablet was immersed in phosphate buffer solution of pH 7.4 at 37°C (simulated intestinal fluid) under stirred condition and in-vitro release kinetics of drug was monitored[12,13]. The tablet was found to maintain its shape and physical integrity while decreasing in size gradually during the first 10 hours. Thereafter, the matrix began to disintegrate into small pieces, which completely dissolved in the buffer within the next 4 hours. Cumulative release and percent release/hour of diclofenac sodium from drug-loaded polymer matrix tablets in simulated intestinal fluid are presented in Table-6.15 and 6.16 respectively. The mean percent of drug release is shown in Table-6.17 and Fig.-6.10, which reveal a constant rate of release (zero order) up to 10 hours and around 90% of the drug released within first 12 hours, afterwards release of the drug was negligible.

The decrease in the thickness and the maintenance of the structural integrity of the tablet as well as zero order drug release kinetics suggest that, drug release takes place predominantly by surface erosion[19] of the tablet and that the diffusional release of drug is minimal. A high rate of release in the first hour arises from the fact that the free drug particles on tablet surface go into the solution as soon as it is placed in the buffer. Such high initial rate of drug release has also been observed by other researchers[20].

TABLES OF EXPERIMENTAL DATA

Table 6.1: Solubility behavior of maleic acid-citric acid-propane-1,2-diol co-polyester (MCPC) at ambient temperature.

Solvent	Solubility
Acetone	+ +
Ethylacetate	++
Mixed Solvent (Toluene: Ethanol =3:1)	++
Toluene	+
Ethanol	+
Acetic acid	-
Benzene	-
Xylene	-
Chloroform	-
Formic acid	-
Phenol	-
Carbon tetrachloride	-
Diethyl ether	-
Rectified sprit (R.S)	-
Water	-

Here (+ +), (+) and (-) indicate high solubility, low solubility and no solubility respectively.

Table 6.2: Swelling behavior of maleic acid-citric acid-propane-1,2-diol co-polyesters in water at ambient temperature (M, C & P represent maleic acid, citric acid & propane-1,2-diol respectively).

Swelling Time (hour)	% Swelling (w/w)				
	Sample-I M:P=1 C = 0.1%	Sample-II M:P=1 C = 0.2%	Sample-III M:P=1 C = 0.3%	Sample-IV M:P=1 C= 0.4%	Sample-V M:P=1 C = 0.5%
3	16.0	12.0	6.0	4.0	1.0
9	25.5	21.0	17.0	13.0	6.5
15	34.0	29.5	25.5	21.5	14.5
21	41.0	37.0	34.0	29.0	23.0
27	49.0	44.5	41.5	38.0	32.0
33	56.0	52.0	48.0	44.0	39.0
39	62.0	58.0	54.0	50.0	45.5
45	68.5	63.5	60.5	55.5	51.0
51	74.0	69.0	65.5	61.0	57.0
57	79.0	74.0	70.5	66.0	62.0
63	83.5	78.5	75.0	71.0	67.5
69	87.0	82.5	79.5	75.0	72.0
75	90.5	86.0	83.0	79.0	75.5
81	93.0	88.0	85.5	82.0	78.0
87	94.5	89.5	86.5	83.5	79.5
93	95.0	90.0	87.0	84.0	80.0
99	95.0	90.0	87.0	84.0	80.0

Table 6.3: Swelling behavior of maleic acid-citric acid-propane-1,2-diol co-polyesters in rectified sprit at ambient temperature (M, C & P represent maleic acid, citric acid & propane-1,2-diol respectively).

Swelling Time (hour)	% Swelling (w/w)				
	Sample-I M:P=1 C = 0.1%	Sample-II M:P=1 C = 0.2%	Sample-III M:P=1 C = 0.3%	Sample-IV M:P=1 C= 0.4%	Sample-V M:P=1 C = 0.5%
3	36.0	26.0	20.0	17.0	12.0
9	48.0	40.0	32.0	26.0	20.0
15	59.0	49.5	41.0	34.5	29.0
21	70.0	58.0	53.0	43.5	36.5
27	79.5	70.0	60.0	54.0	44.5
33	88.0	79.5	69.5	63.0	53.0
39	94.5	87.0	78.0	72.0	62.0
45	102.0	94.0	86.5	80.5	70.0
51	105.0	98.0	93.0	87.0	77.5
57	107.0	102.5	96.0	92.0	83.0
63	109.0	105.0	100.0	95.0	86.5
69	110.5	107.5	102.5	96.5	88.5
75	111.0	108.0	103.0	97.0	89.0
81	111.0	108.0	103.0	97.0	89.0

Table 6.4: Comparison between equilibrium swelling of maleic acid-citric acid-propane-1,2-diol co-polyesters in water and rectified sprit at ambient temperature.

Polymer (MCPC)	Acid/diol mole ratio	% of Citric acid	% of equilibrium swelling (w/w) in	
			Water	Rectified sprit
I	1	0.1	95.0	111.0
II		0.2	90.0	108.0
III		0.3	87.0	103.0
IV		0.4	84.0	97.0
V		0.5	80.0	89.0

Table 6.5: Molecular weight distribution of fractionated maleic acid-citric acid-propane-1,2-diol co-polyester in un-fractionated polymer.

Polymer fraction no.	Weight % of fraction	Mol. wt. by end group analysis ($\overline{M_n}$)
i	8.9	22945
ii	25.5	19530
iii	36.4	17253
iv	18.6	13638
v	10.6	11220

Table 6.6: Viscosity data for maleic acid-citric acid-propane-1,2-diol co-polyester ($\overline{M}_n$=22945) in acetone at 26^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (acetone), t_0 = 124.8sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00400	145.9	1.1691	0.1691	42.28	24.87
0.00350	142.3	1.1402	0.1402	40.05	
0.00200	133.2	1.0673	0.0673	33.65	
0.00175	131.8	1.0561	0.0561	32.06	

Table 6.7: Viscosity data for maleic acid-citric acid-propane-1,2-diol co-polyester ($\overline{M}_n$=19530) in acetone at 26^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (acetone), t_0 = 124.8sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00520	153.3	1.2284	0.2284	43.92	22.28
0.00450	147.8	1.1843	0.1843	40.96	
0.00380	142.9	1.1450	0.1450	38.16	
0.00225	134.1	1.0745	0.0745	33.11	

Table 6.8: Viscosity data for maleic acid-citric acid-propane-1,2-diol co-polyester ($\overline{M}_n$=17253) in acetone at 26^0C.
Volume of the solution taken in viscometer = 10 ml
Efflux time for 10 ml solvent (acetone), t_0 = 124.8sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00550	152.3	1.2204	0.2204	40.07	20.37
0.00430	144.0	1.1538	0.1538	35.76	
0.00360	139.7	1.1194	0.1194	33.17	
0.00275	135.1	1.0825	0.0825	30.00	

Table 6.9: Viscosity data for maleic acid-citric acid-propane-1,2-diol co-polyester ($\overline{M}_n$=13638) in acetone at 26^0C.
Volume of the solution taken in viscometer = 10 ml
Efflux time for 10 ml solvent (acetone), t_0 = 124.8sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00570	150.7	1.2075	0.2075	36.40	17.31
0.00450	142.9	1.1450	0.1450	32.22	
0.00380	138.9	1.1130	0.1130	29.74	
0.00285	134.2	1.0753	0.0753	26.42	

Table 6.10: Viscosity data for maleic acid-citric acid-propane-1,2-diol co-polyester ($\overline{M}_n$=11220) in acetone at 26^0C.

Volume of the solution taken in viscometer = 10 ml

Efflux time for 10 ml solvent (acetone), t_0 = 124.8sec.

Concentration C (g/ml)	Efflux time t sec.	Relative viscosity $t/t_0 = \eta_r$	*Specific* viscosity $\eta_r - 1 = \eta_{sp}$	Reduced viscosity η_{sp}/C (ml/g)	*Intrinsic* viscosity, $[\eta]$ (ml/g)
0.00600	149.5	1.1979	0.1979	32.98	15.29
0.00510	144.4	1.1571	0.1571	30.80	
0.00430	139.8	1.1202	0.1202	27.95	
0.00300	134.0	1.0737	0.0737	24.57	

Table 6.11: Comparison between molecular weights obtained by end group analysis and the same obtained by viscosity method.

Fraction no.	*Intrinsic* viscosity, $[\eta]$ ml/g (from graph)	$K \times 10^3$ (from graph)ml/g	a (from graph)	Molecular weight by	
				End group analysis($\overline{M}_n$)	Viscosity method($\overline{M}_v$)
i	24.87	15.80	0.73	22945	23960
ii	22.28			19530	20609
iii	20.37			17253	18228
iv	17.31			13638	14585
v	15.29			11220	12304

Table 6.12: Soil degradation of MCPC at normal weathering condition.

Time (days)	% of weight loss
7	17.3
14	32.5
21	46.4
28	58.0
35	67.9
42	78.2
49	87.5
56	94.6
63	97.8
70	100.0

Table 6.13: pH-responsive characteristics (hydrolytic degradation study) of maleic acid-citric acid-propane-1,2-diol co-polyester in acid media [HCl solution] at 25^0 C.

Reading	Time (hour)	Initial pH=1.20		Initial pH=2.67		Initial pH=3.70		Initial pH=5.00		Initial pH=6.70	
		pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)	pH of blank acid solution	pH of (polymer + acid solution)
1	0	1.20	1.20	2.67	2.67	3.70	3.70	5.00	5.00	6.70	6.7
2	1	1.18	1.18	2.67	2.67	3.68	3.67	4.98	4.97	6.70	6.67
3	2	1.18	1.18	2.66	2.65	3.67	3.65	4.98	4.95	6.68	6.64
4	3	1.17	1.16	2.65	2.64	3.66	3.64	4.97	4.93	6.68	6.60
5	4	1.16	1.15	2.63	2.62	3.66	3.63	4.96	4.90	6.67	6.57
6	5	1.14	1.13	2.60	2.61	3.65	3.62	4.95	4.88	6.65	6.54
7	6	1.13	1.12	2.59	2.59	3.64	3.60	4.95	4.86	6.65	6.50
8	7	1.10	1.10	2.58	2.57	3.63	3.59	4.94	4.84	6.64	6.45
9	8	1.10	1.09	2.58	2.57	3.62	3.58	4.93	4.81	6.63	6.40

Table 6.14: pH-responsive characteristics (hydrolytic degradation study) of maleic acid-citric acid-propane-1,2-diol co-polyester in basic media [Na_2CO_3 solution] at 25^0 C.

Reading	Time (hour)	Initial pH=7.40		Initial pH=9.15		Initial pH=10.52		Initial pH=11.58	
		pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)	pH of blank basic solution	pH of (polymer + basic solution)
1	0	7.40	7.40	9.15	9.15	10.52	10.52	11.58	11.58
2	1	7.40	7.35	9.15	9.03	10.51	10.30	11.58	11.32
3	2	7.39	7.30	9.14	8.91	10.51	10.11	11.57	10.96
4	3	7.39	7.25	9.14	8.80	10.50	9.88	11.57	10.64
5	4	7.38	7.19	9.14	8.67	10.50	9.68	11.56	10.33
6	5	7.38	7.14	9.13	8.53	10.48	9.49	11.56	10.07
7	6	7.37	7.08	9.12	8.38	10.47	9.30	11.55	9.81
8	7	7.37	7.03	9.12	8.23	10.46	9.12	11.55	9.60
9	8	7.37	6.98	9.11	8.07	10.46	9.00	11.55	9.44

Table 6.15: Release profile of diclofenac sodium loaded maleic acid-citric acid-propane-1,2-diol co-polyester matrices in phosphate buffer of pH=7.4 (simulated intestinal fluid).

Absorbance measured at 274nm

Sample	Cumulative Percent of Drug Release												
	01h	02h	03h	04h	05h	06h	07h	08h	09h	10h	11h	12h	13h
Tab.-1	15.3	23.9	31.6	39.0	46.3	53.6	60.8	67.9	75.0	81.9	87.3	90.6	92.7
Tab.-2	15.4	24.2	31.7	39.1	46.5	53.8	61.1	68.3	75.3	82.1	87.6	91.3	92.9
Tab.-3	15.6	24.1	31.8	39.4	46.9	54.3	61.6	68.8	76.0	82.8	87.9	90.7	92.4
Tab.-4	15.8	24.2	32.0	39.6	47.1	54.6	62.0	69.3	76.5	83.4	88.2	91.1	92.6
Tab.-5	16.0	24.3	32.0	39.5	46.9	54.2	61.5	68.7	75.8	82.6	87.3	90.4	92.2

Table 6.16: Release profile of diclofenac sodium loaded maleic acid-citric acid-propane-1,2-diol co-polyester matrices in phosphate buffer of pH=7.4 (simulated intestinal fluid).

Absorbance measured at 274nm

Sample	Percent of Drug Release/hour												
	01h	**02h**	**03h**	**04h**	**05h**	**06h**	**07h**	**08h**	**09h**	**10h**	**11h**	**12h**	**13h**
Tab.-1	15.3	8.6	7.7	7.4	7.3	7.3	7.2	7.1	7.1	6.9	5.4	3.3	2.1
Tab.-2	15.4	8.8	7.5	7.4	7.4	7.3	7.3	7.2	7.0	6.8	5.5	3.7	1.6
Tab.-3	15.6	8.5	7.7	7.6	7.5	7.4	7.3	7.2	7.1	7.0	5.1	2.8	1.7
Tab.-4	15.8	8.4	7.8	7.6	7.5	7.5	7.4	7.3	7.2	7.0	4.8	2.9	1.5
Tab.-5	16.0	8.3	7.7	7.5	7.4	7.3	7.3	7.2	7.1	6.8	4.7	3.1	1.8

Table 6.17: Mean percent of diclofenac sodium release from drug-polymer matrices in phosphate buffer of pH=7.4 (simulated intestinal fluid).

Time	**01h**	**02h**	**03h**	**04h**	**05h**	**06h**	**07h**	**08h**	**09h**	**10h**	**11h**	**12h**	**13h**
Cumulative % Release	15.62	24.14	31.82	39.32	46.74	54.10	61.40	68.60	75.72	82.56	87.66	90.82	92.56
% Release/hour	15.62	8.52	7.68	7.50	7.42	7.36	7.30	7.20	7.10	6.90	5.10	3.16	1.74

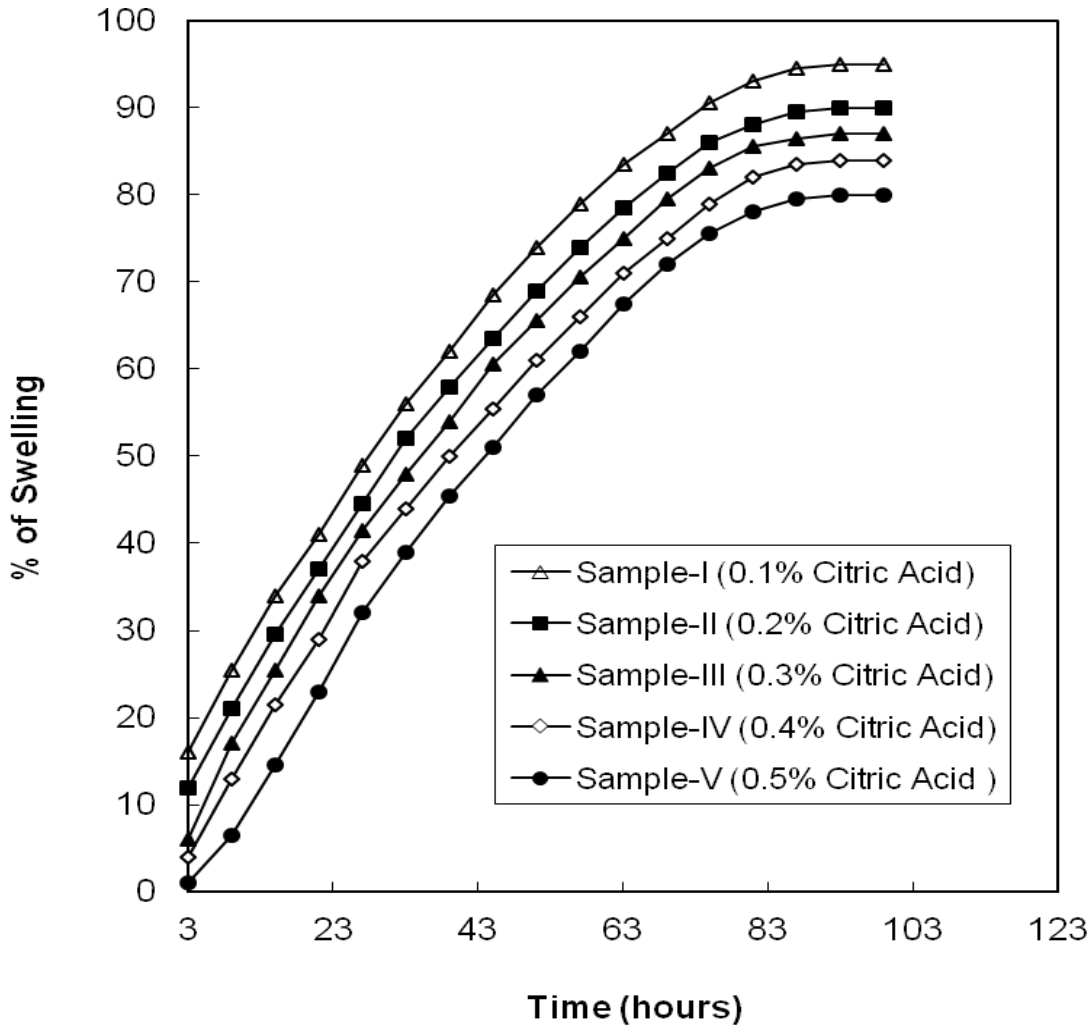


Fig. 6.1: Swelling behaviour of co-polyesters from maleic acid, citric acid and propane-1,2-diol in water at ambient temperature.

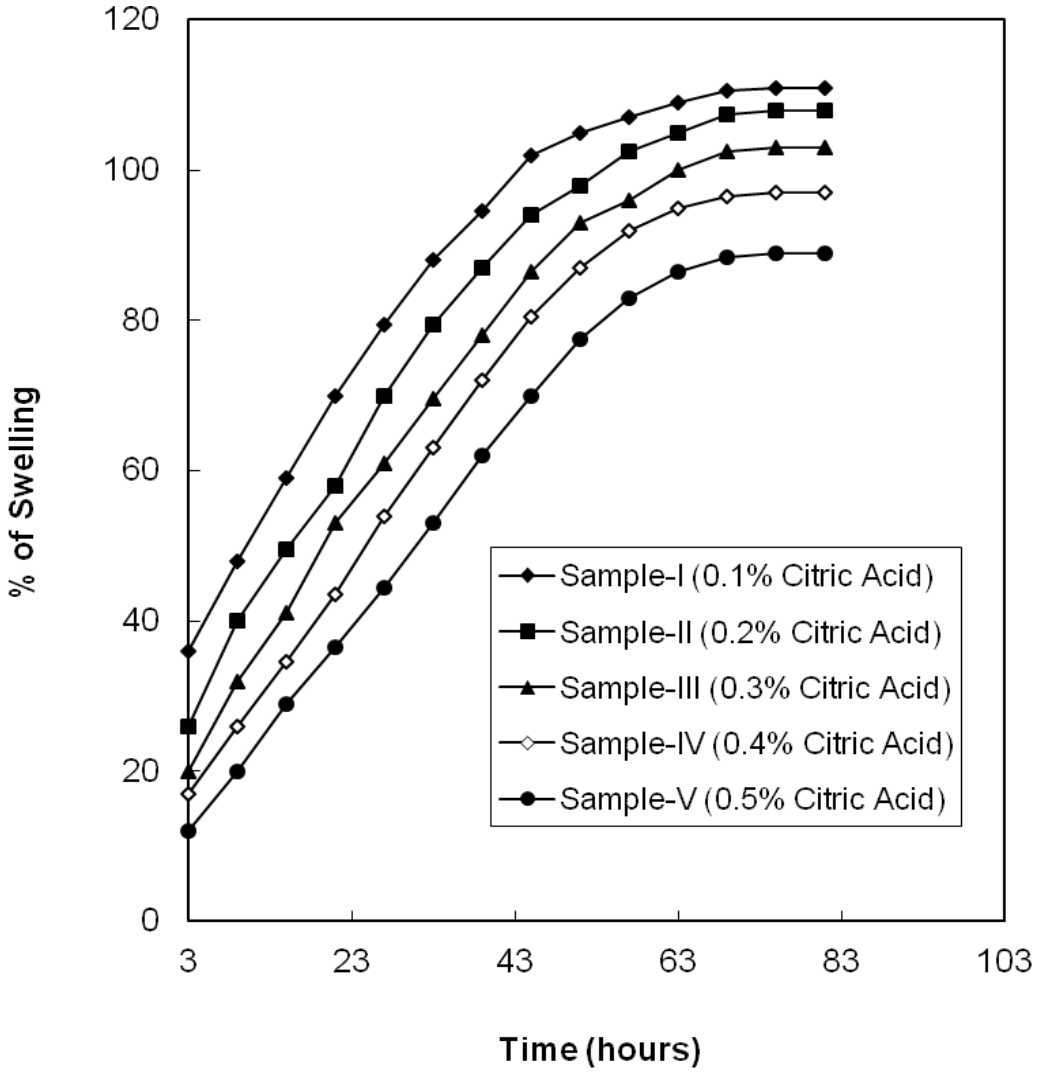


Fig. 6.2: Swelling behaviour of co-polyesters from maleic acid, citric acid and propane-1,2-diol in rectified sprit at ambient temperature.

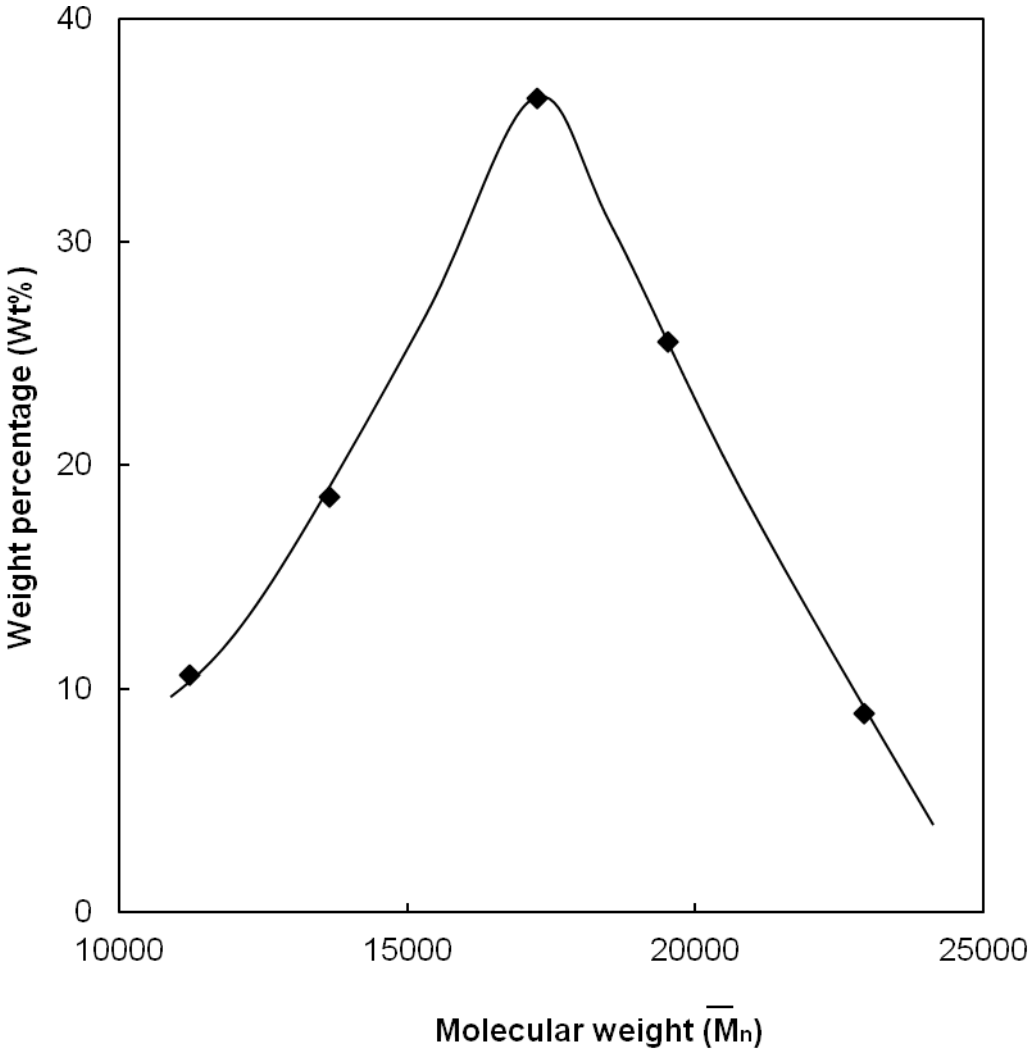


Fig. 6.3: Molecular weight distribution curve of fractionated maleic acid-citric acid-propane-1,2-diol co-polyester in unfractionated sample.

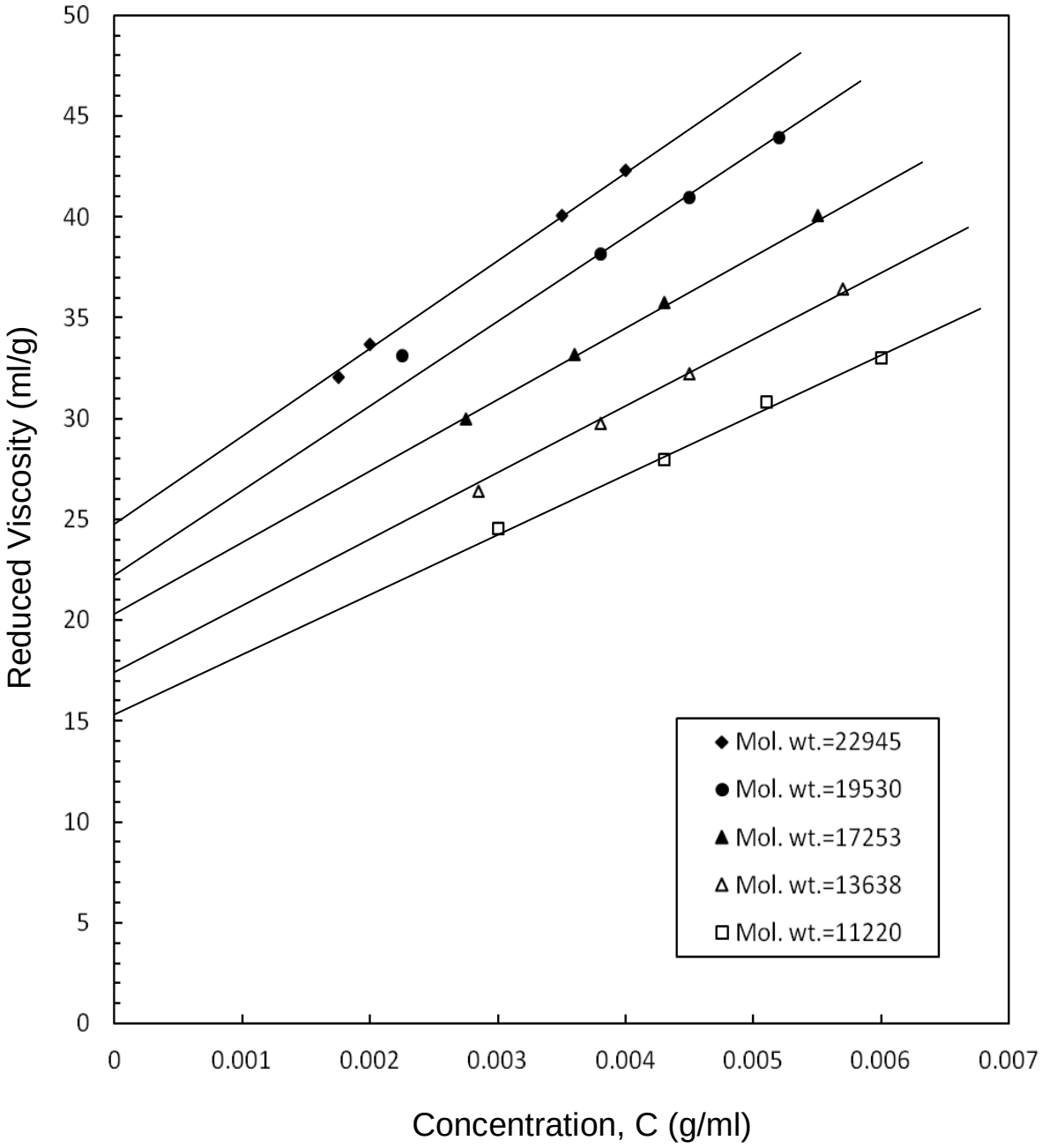


Fig. 6.4: Plots of concentration Vs reduced viscosity for maleic acid-citric acid-propane-1,2-diol co-polyester of different fractions in acetone at 26^0C.

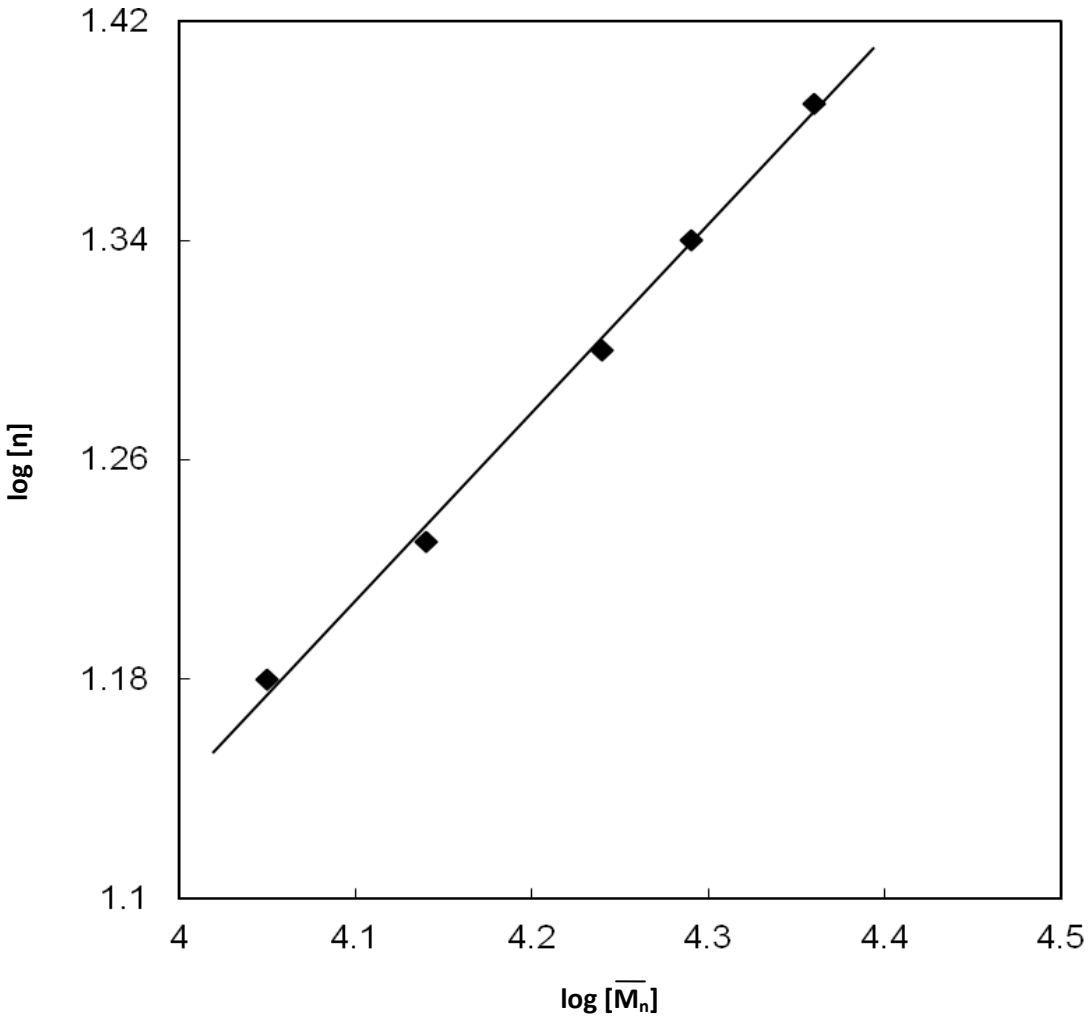


Fig. 6.5: log of intrinsic viscosity Vs log of molecular weight relationship for maleic acid-citric acid-propane-1,2-diol co-polyester in acetone at 26°C.

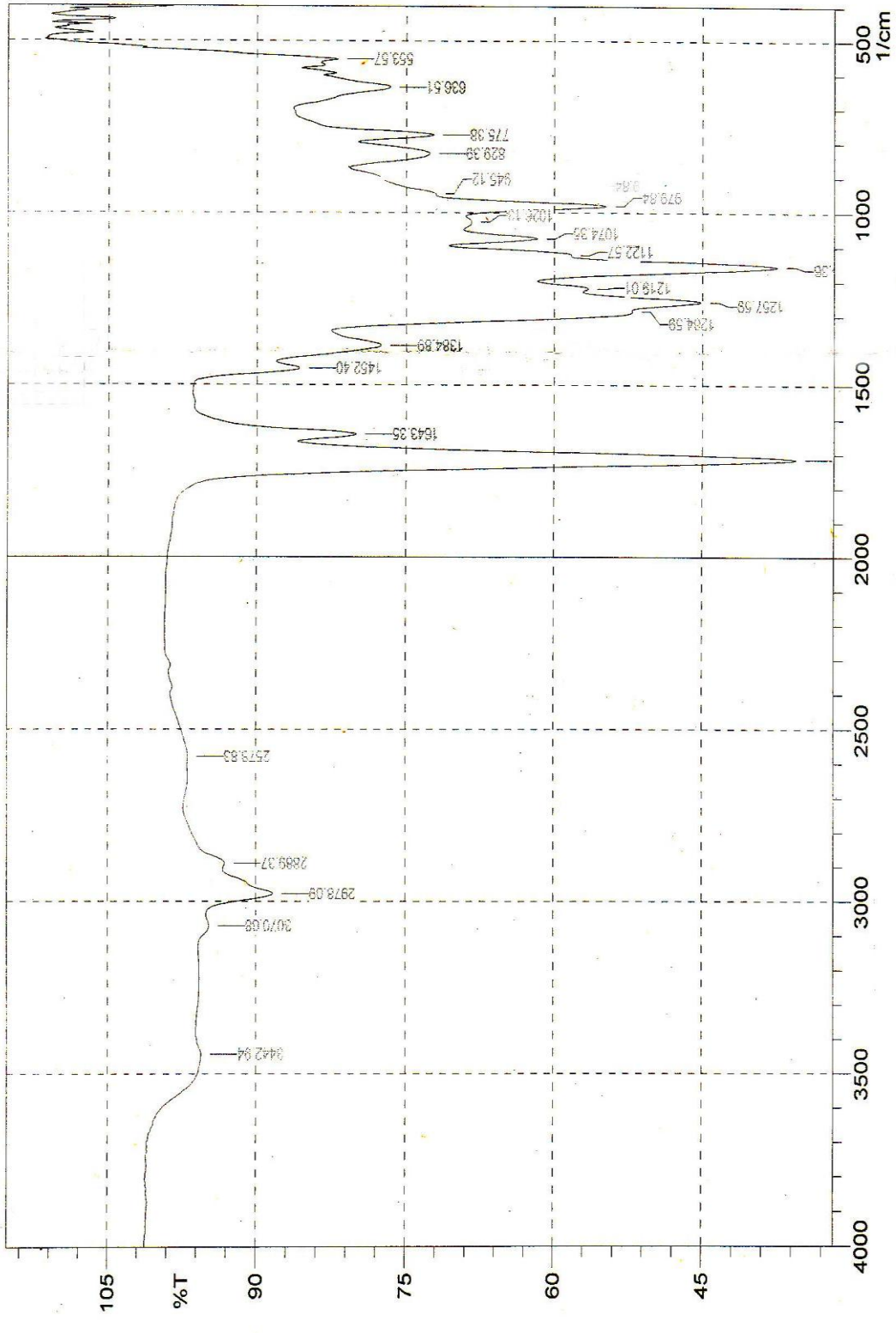


Fig. 6.6: IR-spectrum of maleic acid-citric acid-propane-1,2-diol co-polyester

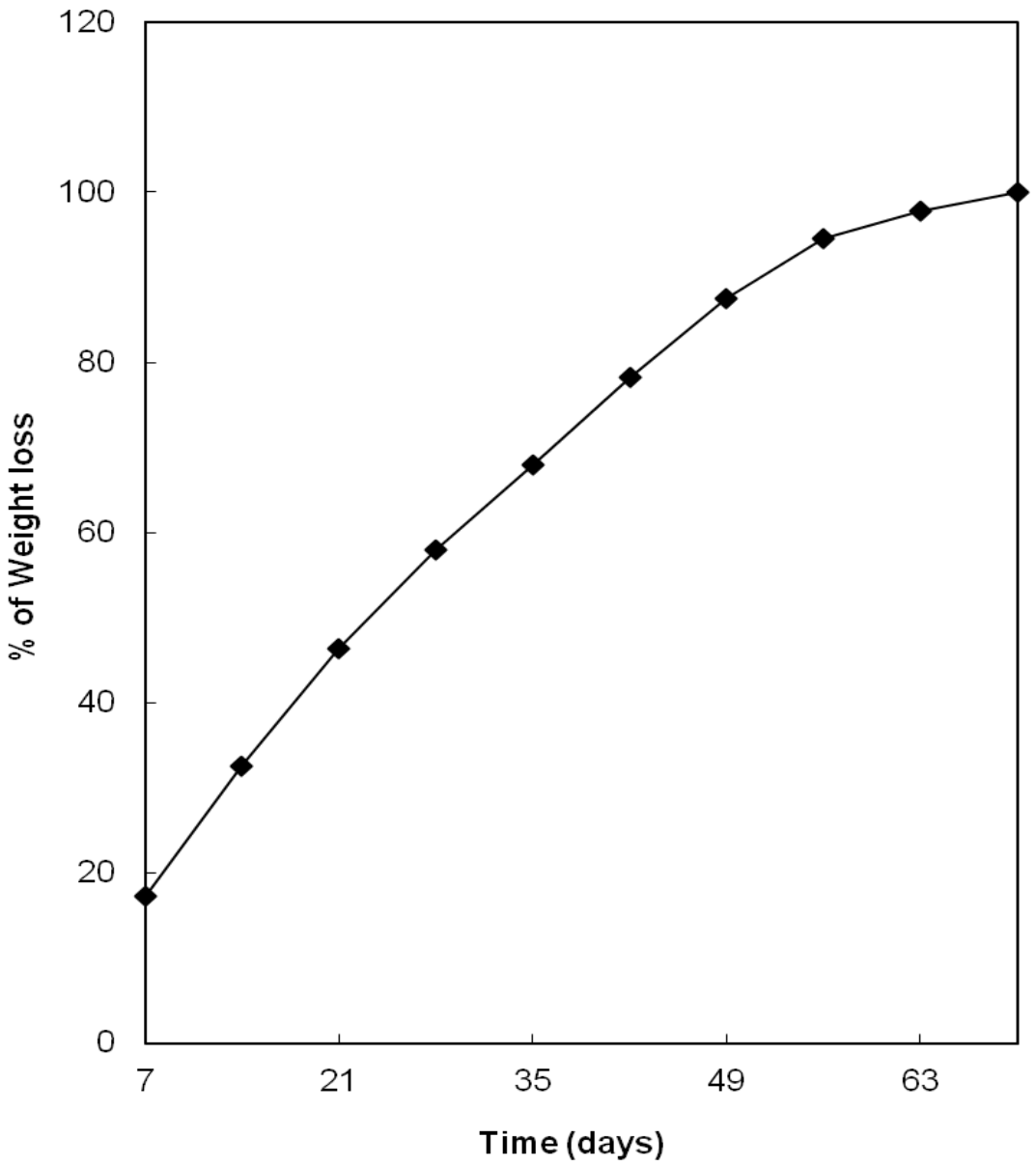


Fig. 6.7: Soil degradation of maleic acid-citric acid-propane-1,2-diol co-polyester at normal weathering condition.

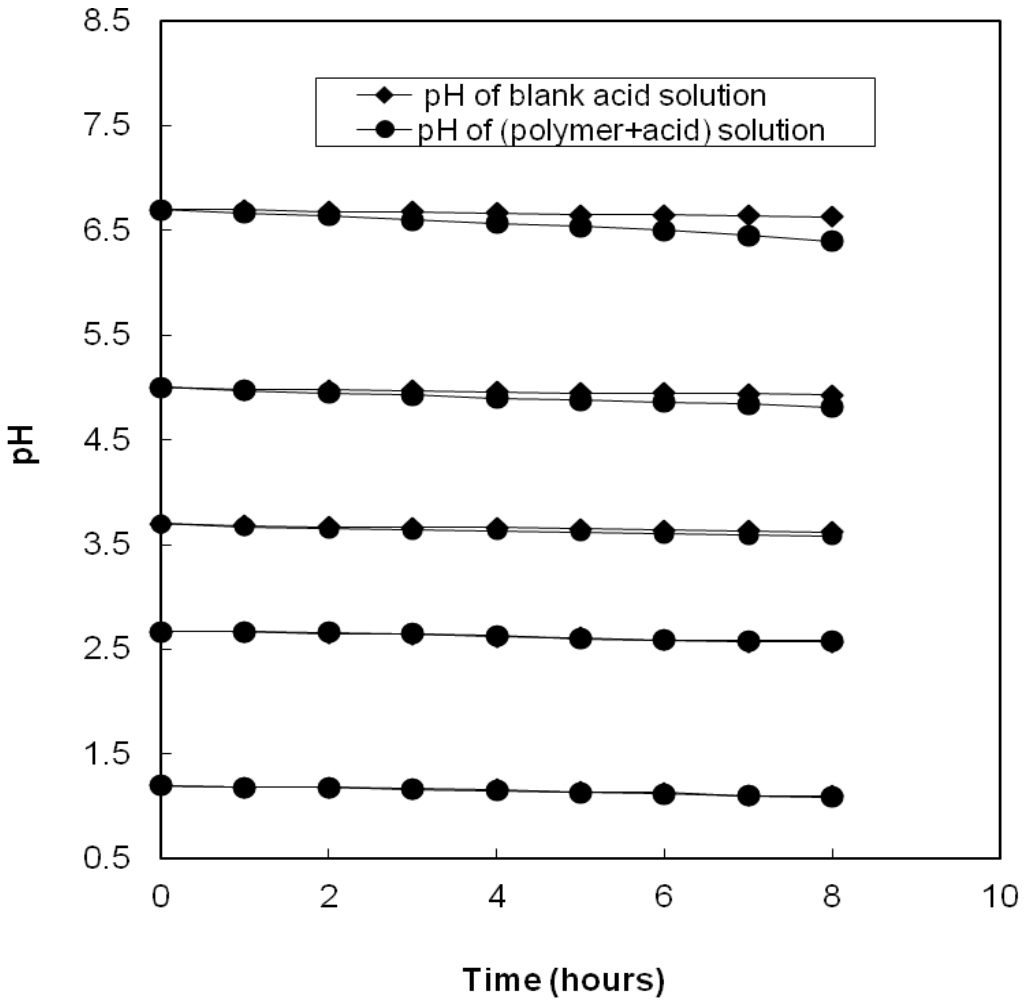


Fig. 6.8: pH Vs time plots for maleic acid-citric acid-propane-1,2-diol co-polyester in hydrochloric acid solution of different pH at room temperature.

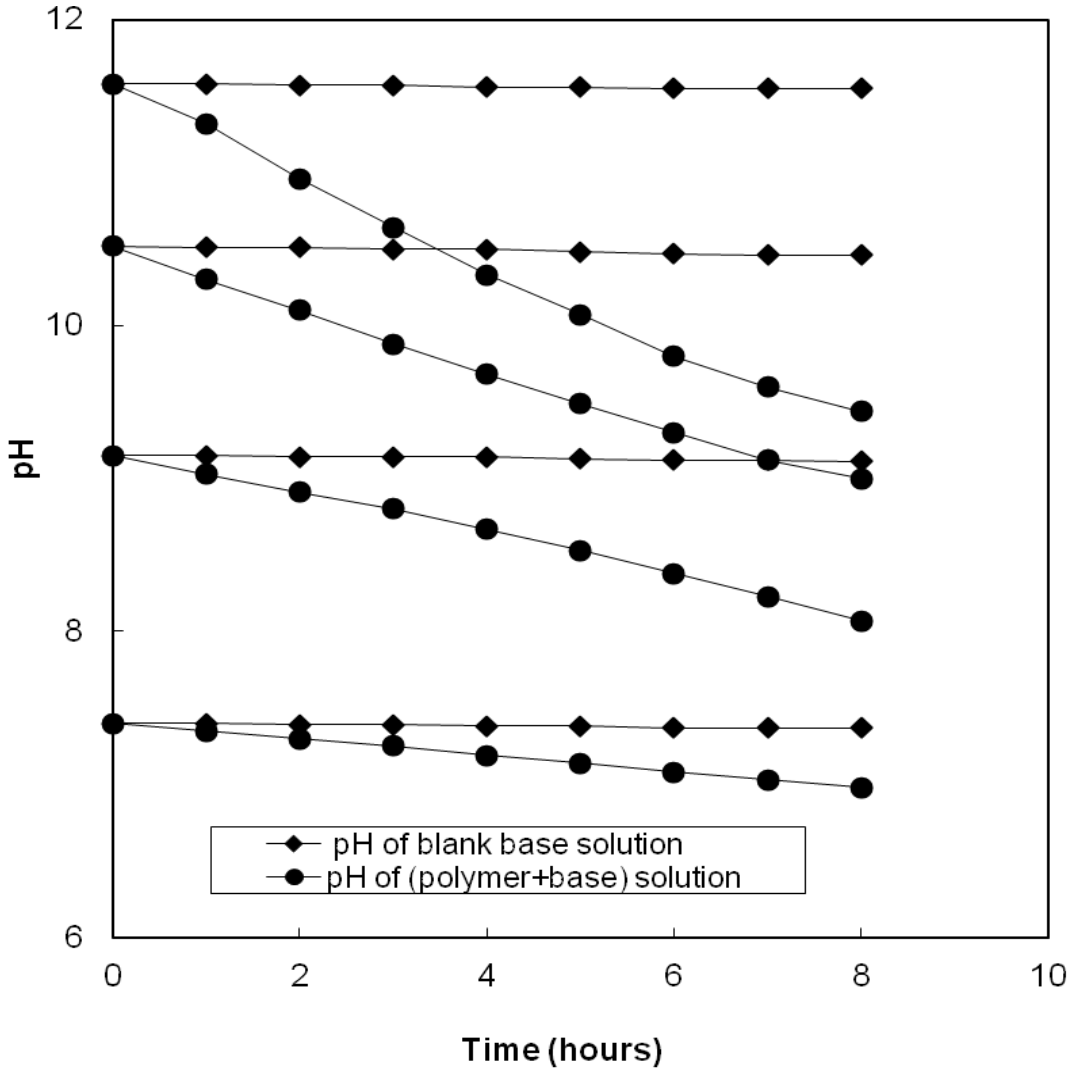


Fig. 6.9: pH Vs time plots of maleic acid-citric acid-propane-1,2-diol co-polyester in sodium carbonate solution of different pH at room temperature.

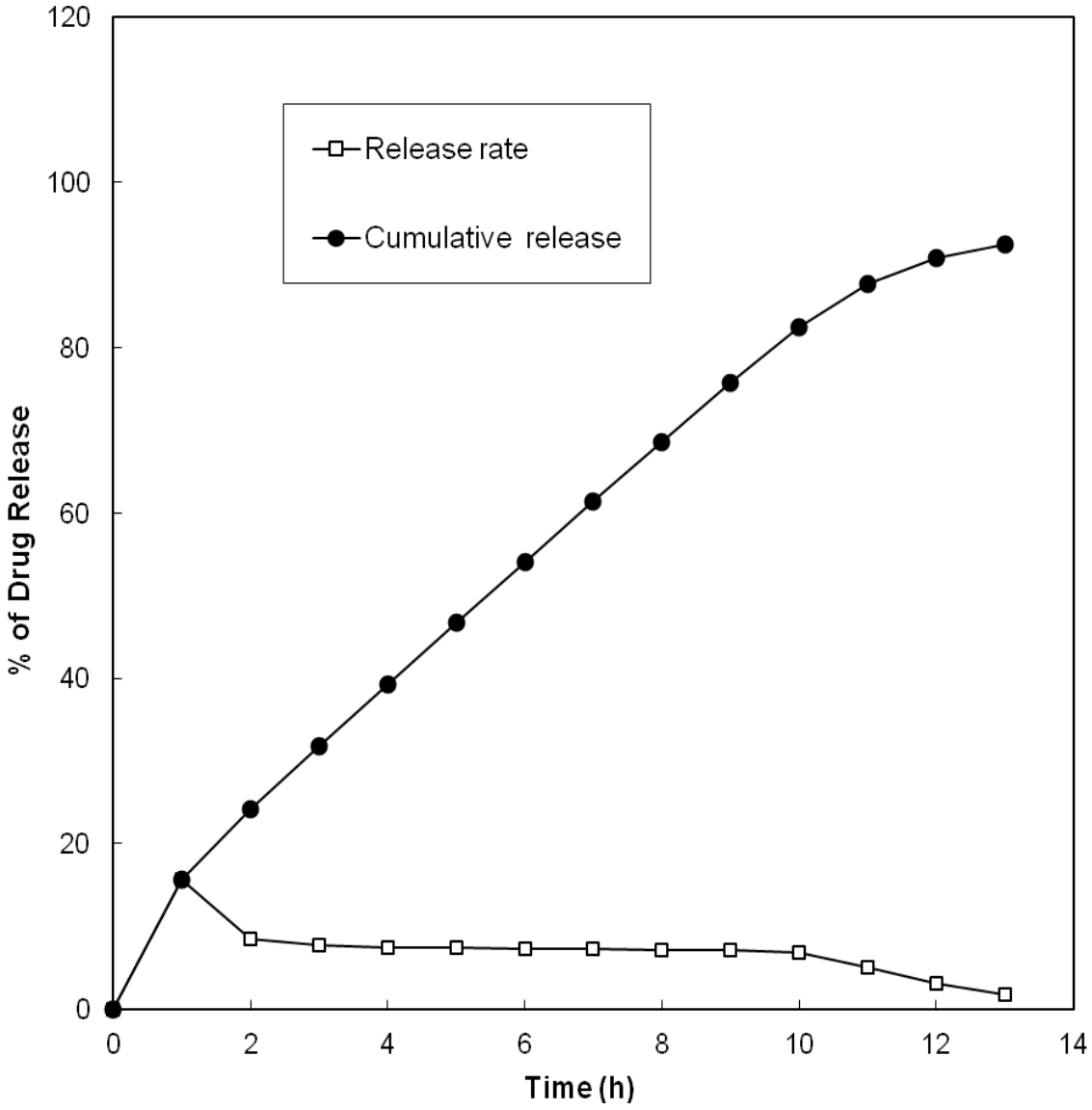


Fig. 6.10: Mean percent release of diclofenac sodium from maleic acid-citric acid-propane-1,2-diol co-polyester matrix tablets in simulated intestinal fluid (pH =7.4).

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SUMMARY

The present thesis entitled **"BIODEGRADABLE POLYMERS: DRUG RELEASE CHARACTERISTICS"** embodies six chapters and reports four novel biodegradable polymers, their synthesis and characterization, their hydrolytic and soil degradation and their application as either enteric coating materials or as carriers for controlled and sustained release of drugs. A brief discussion on each of the chapters is given bellow.

Chapter 1: GENERAL INTRODUCTION

Because of the inconveniences as well as environmental concerns that occur due to non-degradable synthetic polymers, considerable interest is being focused on the development of biodegradable polymers. This chapter begins with the definition of biodegradable polymers. Then, factors of biological environment responsible for polymer degradation, structural feature for polymer degradation, mechanisms of polymer degradation and scope of biodegradable polymers are discussed with special attention to pH responsive biodegradable polymers for drug release. After that, pH distribution and physiology of GIT, various types of controlled-release oral dosage forms, mechanism of drug release and site targeted oral drug delivery systems have been illustrated. Literatures have also been reviewed at this stage. The chapter finally ends up with the proposal of the present work and its purpose.

In recent time, biodegradable polymers are being used for many medical, agricultural and ecological purposes. Various biodegradable polymeric drug products have been developed to release the active medicament at a

controlled rate and/or at the intended site. From the last few decades, the search of polymers which change their structures and properties in response to environmental stimuli such as pH is going on. These pH-responsive smart polymers have been being tried in site controlled oral drug delivery systems because the most pronounced pH variation in the human body occurs in the gastrointestinal tract (GIT).

Enteric-coated products are designed to keep the drug intact in the stomach and then to release it in the neutral or slightly alkaline environment of the intestine. The polymers used for enteric coatings remain unionised at low pH, and therefore remain insoluble. As the pH increases in the gastrointestinal tract the acidic functional groups are capable of ionisation, and the polymer swells or becomes soluble in the intestinal fluid. Thus, an enteric polymeric film allows the coated solid to pass intact through the stomach to the small intestine, where the drug is then released and being absorbed to exert its pharmacologic effects.

Efficacious, nontoxic therapy requires that drug concentration in plasma lies within the therapeutic range, which is bounded below by the minimum effective concentration (MEC) and above by the minimum toxic concentration (MTC). In the conventional method of drug administrations, if a dose is omitted or taken late, the drug concentration in the plasma will drop to the ineffective level and if the patient takes his or her dose at regular intervals the drug concentration in the plasma will keep rising and eventually reach the toxic level causing undesirable side effects. A controlled release system, generally a polymeric material in which the drug is incorporated, should deliver the incorporated drug continuously in a fixed predetermined pattern resulting in a uniform drug concentration in the plasma for a desired span of time. In some cases,

drug activity becomes better in minute quantities, which can be achieved by controlled release system. Further, the entire body exposure of the patient to excess dose can be eliminated by using the regulated release system at the target site. The matrix tablets, which are impregnated with the active ingredients in an inert or polymeric material, have been well known to act as an effective sustained release medicament. However, for controlled release systems involving drug-polymer matrices, two desirable pre-requisites are: (a) the release rate should remain approximately constant so that drug concentration in the plasma remains within the desirable level and (b) matrix should be biodegradable to non-toxic smaller molecules to be excreted or assimilated by the body through normal pathway.

Chapter 2: EXPERIMENTAL

This chapter describes all the experimental procedures which include polymerization technique, method of synthesized polymer purification, techniques for polymer characterization, methods of molecular weight determination and the techniques for the hydrolytic degradation study of the polymer samples. The coating procedure of the uncoated tablets, drug-polymer matrix tablet preparation method and the ways to study *in-vitro* drug release have also been discussed.

The polycondensation reaction (between the corresponding monomers in desired ratio) was carried out using xylene as the reaction medium in Dean-Stark apparatus. Anhydrous $FeCl_3$ or p-toluene sulphonic acid was used as catalyst. The reaction mixture was heated at a suitable temperature in a round bottom flask until elimination of water subsided followed by 1 hour post-curing under the same condition. Water was the

reaction by-product and eliminated azeotropically with xylene. After being cooled, the synthesized polymer was collected from the reaction vessel by dissolving it in an appropriate solvent and purified by precipitating using water as non-solvent.

Molecular weights of the polymers obtained by end group analysis were used to find out the values of Mark-Houwink constants 'K' and 'a' to determine the viscosity average molecular weight. IR spectra of polymers were recorded using a SHIMADZU Model-470 IR-spectrophotometer. Equilibrium swelling values of the polymers in different solvents were found out simply by gravimetric method and their elemental analyses were kindly carried out in the Central Drug Research Institute, Lucknow, India. To evaluate the pH responsive characteristics of the polymers, their hydrolytic tests were conducted in acid medium and also in base medium.

Coating on core (uncoated) tablets was carried out with the 40% solution of the polymer in acetone in a small coating pan with continuous hot air flow. Melted polymer together with drug (drug: polymer=1:2) was taken in a beaker and then mixed well. The polymer-drug mixture was passed through a sieve (mesh no. 25) followed by crushing in a mortar. The granules, thus made, were compressed in a single punch tablet machine to get them in tablet forms.

The *in-vitro* release of drug was performed under simulated physiological environment i.e. in simulated gastric fluid (pH=1.2) and in simulated intestinal fluid (pH=7.4) by dissolution apparatus and the concentration of the released drug was determined spectrophotometrically.

Chapter 3: DRUG RELEASE PATTERN OF MALEIC ACID BUTANE-1,4-DIOL POLYESTER

This chapter illustrates the synthesis, characterization and probable application of maleic acid-butane-1,4-diol polyester (MBP). The polymer was synthesized taking the monomers in their stoichiometric ratio and p-toluene sulphonic acid was used as catalyst. It was characterized by its molecular weight, IR-spectrum, solubility in common organic solvents and elemental analysis. Probable structure of the polyester has been assigned. Hydrolytic degradation and soil burial tests of the polyester have also been discussed.

The number average molecular weight of this polymer was determined by end group analysis and the results were applied to find out the values of Mark-Houwink constants 'K' and 'a' to determine the viscosity average molecular weight. It was seen that the molecular weight obtained by viscosity method ($\overline{M}_v$) was higher than the same obtained by end group analysis ($\overline{M}_n$). The >C=O stretching frequency at the region 1716-1730cm^{-1} and corresponding vibration band at 1163cm^{-1} region in the IR-spectrum of the polymer sample indicate the formation of ester linkage. In soil burial study it was observed that the polyester sample mixed with the soil in 42 days, which is an indication of the total biodegradation of the polyester sample.

From the hydrolytic test it was found that the polyester sample remained almost intact in the acid medium but gradually degraded in basic medium. In acid region the polymer samples swell insignificantly. But in alkaline region they swell and the ester linkage happens to be hydrolyzed. Because of having such pH responsive characteristics, the polymer was

tried as an enteric coating material on diclofenac sodium and naproxen core (uncoated) tablets. Drug release from the polymer coated specimen in simulated physiological environments was investigated and British Pharmacopoeia (B.P.) standard enteric coating properties of the polymer were observed.

Chapter 4: DRUG DELIVERY PROFILE OF MALEIC ACID-ADIPIC ACID-PROPANE-1,2-DIOL CO-POLYESTER

The synthesis and characterization of maleic acid-adipic acid-propane 1,2-diol co-polyester (MAPC) has been discussed in this chapter. The polymer was synthesized taking the monomers in their stoichiometric ratio and anhydrous $FeCl_3$ was used as catalyst. It was then characterized by its molecular weight, IR-spectrum, elemental analysis, hydrolytic test and soil degradation test. Molecular weight determination was carried out by end group analysis and viscosity method. Molecular weight obtained by viscosity method was higher than the same obtained by end group analysis. Probable structure of the co-polyester has also been assigned. The >C=O stretching frequency at the region 1716.7 cm^{-1} and corresponding vibration band at 1161.2 cm^{-1} region in the IR-spectrum of the polymer sample indicate the formation of ester linkage. From the elemental analysis, it has been found that the percentage composition of the sample obtained by calculation matches with the same obtained by analysis. The product is accordingly confirmed. From the hydrolytic degradation study, it was found that the polyester sample remained intact in the acid medium (pH 1.2-6.0) but gradually degraded in basic medium (pH>7.0).

Because of its pH responsive characteristics, the polymer was tried as an enteric coating material. Diclofenac sodium and naproxen were used as model drugs. In-vitro release kinetics of drug from the core and coated tablets were performed in dissolution apparatus in order to evaluating the efficacy of the polymer as an enteric coating material on the release of the drug. The experiment was carried out for 2 hours in simulated gastric fluid followed by 1 hour in simulated intestinal fluid. The experiment and the simulations were performed according to the guidelines of British Pharmacopoeia (B.P.).

It was found that the co-polyester did not degrade or swell in the simulated gastric fluid for two hours when coated on a core tablet and less than 6% either diclofenac sodium or naproxen released from MAPC coated tablets. But in the simulated intestinal fluid the polymer coating gradually degraded and more than 80% of diclofenac sodium or naproxen released within 45 minutes. The mean percent release of diclofenac sodium and naproxen from MAPC coated tablets corresponds to the British Pharmacopoeia (B.P.) drug release pattern of enteric-coated tablets. However, prior to clinical trial as an enteric coating material, toxicological and other pharmacological tests of the co-polyester need to be performed.

Chapter 5: MALIC ACID-ADIPIC ACID-BUTANE-1, 4-DIOL CO-POLYESTER FOR GASTRO-RESISTANT DRUG DELIVERY

This chapter deals with the synthesis and characterization of malic acid-adipic acid-butane 1,4-diol co-polyester (MABC). This chapter also depicts its application as an enteric coating material.

The polycondensation reaction was carried out using Dean-Stark apparatus and xylene as the reaction medium. The mole ratio of the reactants was malic acid: adipic acid: butane 1,4-diol= 1.2:1:2. Anhydrous $FeCl_3$ was used as catalyst while the reaction temperature and time were 130-135^{0}C and about six hours respectively. The synthesized polyester was characterized by its molecular weight, IR-spectrum, solubility in common organic solvents, elemental analysis, hydrolytic degradation study and soil burial tests. Probable structure of the polyester has been assigned. Molecular weight determination was carried out by end group analysis and viscosity method. Molecular weight obtained by viscosity method was higher than the same obtained by end group analysis. IR-spectrum of the polymer sample indicates the reaction between –OH and –COOH groups and thereby ester linkage is formed in the sample. The elemental percentage composition of the co-polyester obtained by analysis matches with the same of the theoretical composition of the polymer, the product structure is accordingly confirmed.

At room temperature, hydrolytic degradation study in solutions of different pH values showed that the co-polyester remained intact in solutions of pH=0-3.0, slight degradation was observed in pH range 3.0-6.0 but it gradually degraded in solutions of pH >6.0. Such pH responsive degradation nature of this polyester led us to investigate its possible application in gastro-resistant drug delivery formulation. The task of the gastro-resistant material is to resist the release of the drug from the solid dosage forms in the gastric environment but assists drug release in the intestine. The mean percent release of diclofenac sodium from MABC coated tablets indicate that the drug release pattern of MABC

corresponds to the British Pharmacopoeia standard drug release profile of gastro-resistant drug delivery formulations.

Chapter 6: MALEIC ACID-CITRIC ACID-PROPANE-1,2-DIOL CO-POLYESTER FOR EXTENDED RELEASE DRUG FORMULATION

This chapter describes the synthesis of maleic acid-citric acid-propane 1,2-diol co-polyester (MCPC), its characterization, its hydrolytic degradation, its soil burial test and its *in-vitro* drug release behavior under physiological condition.

Five polymer samples (I, II, III, IV & V) have been synthesized taking the corresponding monomers in desired ratio. Both maleic acid and prpane-1,2-diol are bi-functional monomers and were polycondensed with stoichiometric ratio (1:1) in all five cases. However, the amount of citric acid was varied (0.1, 0.2, 0.3, 0.4 and 0.5wt % respectively) to synthesize these five polymer samples. The equilibrium swelling values of these polymers in both water and rectified sprit are in order V > IV > III > II > I. Sample-V, containing 0.5wt% citric acid, swell minimally in each of the two solvents, showing maximum cross-linking. Increasing the percentage of citric acid certainly increases the cross-linking of the co-polyester domain, thus reduces its solubility in common organic solvents and raises the difficulties to handle it in pharmaceutical applications. Considering this, sample-V was chosen for the subsequent experiments. Its IR-spectrum confirmed the esterification between the monomers. The number average molecular weight ($\overline{M}_n$) of this polymer was determined by end group analysis and the results were applied to find out the values of Mark-Houwink constants ‘K’ and ‘a’ to determine the viscosity

average molecular weight ($\overline{M}_v$). It was seen that ($\overline{M}_v$)> ($\overline{M}_n$). From soil burial test it was found that it ultimately mixed with the soil after around 55 days. Hydrolytic degradation study of the co-polyester reveals that in acid medium the polymer sample swells insignificantly. But in alkaline medium it swells and the ester linkage happens to be hydrolyzed with respect to time. Because of such time dependent pH responsive nature, this polyester was tried as an enteric coating material but satisfactory result was not found. It was then investigated for extended release drug-polymer matrix tablets and pure dichlofenac sodium was used as the model drug.

Incorporation of dichlofenac sodium in the polymer matrix was done by melt granulation method keeping the drug polymer ratio as 1:2. The prepared granules were compressed in a single punch tablet machine to get them in tablet forms. *In-vitro* drug release from these matrix tablets were studied spectrophotometrically under physiological condition (phosphate buffer of pH 7.4 at 37^0C). The release pattern has shown a bit higher release in the first hour, then a nearly constant release for 10-11 hours followed by declining release for the subsequent few hours. The gradual decrease in the thickness and the maintenance of the structural integrity of the tablets as well as nearly zero order drug release kinetics suggest that drug release takes place predominantly by surface erosion of the tablet and that the diffusional release of drug is minimal.