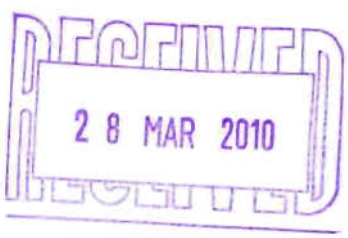
EVALUATION OF DICLOFENAC 12H SR TABLET FROM METHOCEL K-15MCR AND METHOCEL 100LVCR

Department of Pharmacy

EAST WEST UNIVERSITY



Submitted by

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ID: 2005-2-70-018

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A research paper submitted to the Department of Pharmacy, East West University in the partial fulfillment of the requirements for the Degree of Bachelor of Pharmacy.

Submitted by:

Tanjir Ahmed Biswas

ID: 2005-2-70-018

Declaration

I, do hereby declare that the project report, entitled **"EVALUATION OF DICLOFENAC 12H SR TABLET FROM METHOCEL K-15MCR AND METHOCEL 100LVCR"**, Presented to the department of pharmacy , East West University, Bangladesh, is the outcome of investigations performed by me under the supervision of DR. A.S.S.Rauf, professor, Department of pharmaceutical Technology, University of Dhaka, Bangladesh. I also declare that no part of this Project Report has been or is being submitted else where for the award of any Degree of Diploma.

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CERTIFICATION

The project report, entitled **"EVALUATION OF DICLOFENAC 12H SR TABLET FROM METHOCEL K-15MCR AND METHOCEL 100LVCR"**, submitted by Tanjir Ahmed Biswas, ID: 2005-2-70-018, Department of Pharmacy, East West University, Bangladesh, has been accepted as satisfactory for the partial fulfillment of the requirement of the degree of Bachelor of Pharmacy and approved as to its style and contents.

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Acknowledgement

I would first like to express exclusively my gratitude to my supervisor, Dr.A.S.S. Rouf Professor Dept. of pharmaceutical technology, University of Dhaka,Bangladesh, for his adroit supervision, benevolent guidance, positive counseling and constant encouragement.

I also wish to thank my teachers and the office staffs of the Faculty of Pharmacy, for their help and who assisted me in doing my work by opening the laboratory door earlier in the morning.

Special thanks to all of my friends for their great support during my project work.

Finally I am profoundly indebted to the Almighty for providing me the strength and perseverance to carry out the whole work in time.

December, 2009 Tanjir Ahmed Biswas

Abstract

In the present study an effort has been made to formulate 6 dilcofenac SR with Methocel K-15MCR and Methocel 100LVCR polymer to sustain the release of Diclofenac 12H from Diclofenac sustained release tablet Different ratio of Methocel K-15MCR and Methocel 100LVCR as 1:5, 3:4,2:5,4:3,3:3,3:5 of total weight of tablet matrix, were used to prepare sustained release tablet matrix by direct compression The dissolution study of the tablet matrices of different formulations were carried out in the gastric medium (pH 1.3) for first two hours and then in the intestinal medium (pH 6.8) for 10 hours using USP dissolution apparatus. From the release pattern we observed that 2:5 and 3:5 of Methocel K-15MCR and Methocel 100LVCR showed the desired sustained release by direct compression method. The drug release patterns were simulated in different kinetic orders such as Zero Order, First Order and Higuchi release kinetics to assess the release mechanism. From the study we observed that first order was the predominant release mechanism than higuchi and zero Order kinetics. The physical criterion of formula(F-3 and F-6) were evaluated bulk density, compressibility index, total porosity, angle of repose, drug contain for granules hardness, friability, thickness, weight variation test, drug content of finished product.

Objective the present study

Diclofenac SR Diclofenac is an orally administered non-steroidal anti-inflammatory substance (NSAIS). From a clinical efficacy standpoint, diclofenac sodium 75 mg has activity similar to 3.6 g of ASA (Acetyl Salicylic Acid or Aspirin). Diclofenac sodium is similar in activity to equivalent dosages of indomethacin (75 to 150 mg daily) and causes fewer CNS side effects at these doses. Both doctors and patients prefer these types of dosage forms. Sustained release dosage formulation of pharmaceutical products has been widely investigated due to its tremendous demand in the pharmaceutical markets. This happens due to some advantages shown over conventional dosage forms. Among the system that bring about sustained action, SR dosage form has been attracting much attention. This interest is due to the technological simplicity as well as better physiological role in comparison with other controlled release systems developed to achieve oral sustained release.

In the present study an attempt has been made to formulate as Diclofenac sustained release tablet matrix with the addition of release retarding polymers Methocel K-15MCR and Methocel 100LVCR and to evaluate the effect of Methocel K-15MCR and Methocel 100LVCR to sustain the release of Diclofenac from the Diclofenac sustained release tablet matrix. The dosage form were prepared by direct compression that may increase high production, performance, save valuable time in

manufacturing plan, less involvement of labour, reduce cost and increase profit.

In Bangladesh Diclofenac is available as immediate release tablet dosage form. This drug may be a suitable candidate for sustained release dosage form. So sustained release dosage form of Diclofenac SR is introduced with Methocel K-15MCR and Methocel 100LVCR, and then it can provide prolonged action and more compliance to the patient.

CHAPTER 01

INTRODUCTION OF SUSTAIN RELEASE

1.1 General Introduction:

In the last two decades, sustained-release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Preparation of drug-embedded matrix tablet by direct compression technique along with retardant materials and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. Polymers that primarily forming insoluble or skeleton matrices are considered as the first category of retarding materials are classified as plastic matrix systems. The second class represents hydrophobic and water-insoluble materials, which are potentially erodible and the third group behaves hydrophilic properties.

The overall effect of any drug occurs in a sequence of three distinct yet interdependent stages as listed in the following;

Phases of drug action

1. Pharmaceutical Phase : Releases from a dosage form.
2. Pharmacokinetic Phase : Includes absorption, distribution, and elimination.
3. Pharmacodynamic Phase : Includes drug interactions with receptors.

Ideally, a thorough understanding of each of these stages for a given drug is essential for achieving its most effective therapeutic efficacy in patients. The pharmaceutical phase describes the process of a drug's conversion from a chemical form into a dosage form. This phase includes the characterization of physicochemical drug profiles, design and production of dosage forms and biopharmaceutical evaluation of drug products. The pharmaceutical phase can initially influence the pharmacokinetic phase, which is

measured by blood-level-versus-time profiles. The pharmacokinetic phase then directly affects the pharmacodynamic or efficacy phase.

There are a number of techniques applied for the formulation as well as in the manufacturing of sustained release dosage form. But in the development studies of sustained release formulation, several new techniques and approaches are also proving their acceptability and feasibility. Among the systems, matrix tablet has attracted much attention due its technological simplicity in comparison with other controlled release systems developed to achieve the sustained action.

Sustained release dosage formulations by direct compression processes are presently gaining importance in order to achieve prolonged action without avoiding multiple doses taking which is commonly needed for maintaining therapeutic action of the drug for a stipulated period. This type of dosage form can be defined as "the drug delivery system that is designed to have a prolonged therapeutic effect by continuously releasing the active ingredient over an extended period of time after administration of a single dose. Oral sustained release dosage form by direct compression technique is a very modern approach of drug delivery systems that proved demand in the pharmaceutical arena as their ease, compliance, faster production, avoid hydrolytic or oxidative reaction occurred during processing of dosage forms.

Sustained or controlled drug delivery occurs while embedded with a polymer that may be natural or semi synthetic or synthetic in nature. The polymer is judiciously combined with a drug or other active ingredients in such a way that the active agent is released from the material in a redesigned fashion. The main target was that the active agent must be released at constant rate over a stipulated period of time. In most cases, the purpose of controlling or sustaining the drug delivery is to achieve more

effective therapeutic action with eliminating the potential for both under and overdosing.

1.2 History:

The research on controlled drug delivery systems first centered on micro encapsulation since 1949 with a patent by the Wurster process. This technique utilized a fluidizing bed and drying drum to encapsulate fine solid particles suspended in midair.

The first such dosage form was marketed in the USA in 1952 by Smith Kline & French (SK & F) under the trade name "Dexadrin Spanules". At present more than 50 major manufacturers produce about 200 special' delivery products representing nearly. five percent of the total pharmaceutical market.

The popularity and importance of these dosage forms can be appreciated from the fact that for the time in 1985 the official compendia adopted the use of the term "Modified Release" to identify these forms as being different from the conventional dosage forms (USP XXI). Much of the recent research efforts on controlled drug delivery are focusing on site-directed systems as the new technology in the industry. Many scientists believe that the use of liposomes as drug carriers will serve as the leading research topic into the twenty-first century.

1.3 Concept of sustained release dosage from:

Most conventional drug products, such as tablets and capsules, are formulated to release the active drug immediately to obtain rapid and complete systematic absorption of the drug. In recent years, various modified drug products have been developed to release drug products are designed for different routes of administration based on the

physicochemical, pharmacological, and pharmacokinetic properties of the drug. Sustained release, sustained action, prolonged action, controlled release, extended action, time release, depot and respiratory dosage forms are terms used to identify drug delivery, systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of. a single dose. In the case of injectable dosage forms; this period may vary from days to months.

In the case of orally administered forms, however, this period is measured in hours and critically depends on the residence time of the dosage form in the GI tract (BALLARD, 1978).

A more finite explanation of these types of medication has been provided by Nelson (1961) and Parrot (1963). They indicated that a sustained release or sustained action product provides an initial sufficient amount drug to cause a rapid onset of desired therapeutic response, and an additional amount of drug that maintains the response at the initial level for a desired number of hours beyond the activity resulting from conventional dose; the initial desired therapeutic response is maintained because the rate of release of the desired therapeutic concentration is equal to the rate at which the drug is eliminated or inactivated.

1.4 Rationale for Sustained Release Dosages Forms

According to the route of administration, a conventional dosage form of the drug, e.g., a solution, suspension, capsule, tablet, etc., produce a drug blood level versus time profile which does not maintain within the therapeutic range for extended periods of time. This is due to the inability of conventional dosage forms to control temporal delivery. If any attempt is made to maintain drug blood levels in the therapeutic range for longer

periods, for example, by increasing the dose of an intravenous injection, toxic levels may be produced at early a time which is undesirable and the approach therefore is unsuitable. An alternative approach is to administer the drug repetitively using a constant dosing interval as in multiple-dose therapy In this case the drug blood level reached and the time required to reach that level depend on the dose and the dosing interval. There are several potential problems inherent in multiple-dose therapy.

Firstly, if the dosing interval is not appropriate for the biological half-life of the drug, large 'peaks' and 'valleys' in the drug blood level may result. For example, drug with short half-life may require frequent dosing to maintain constant therapeutic levels.

Secondly, the drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states. Thirdly, patient noncompliance with the multiple dose-regimens can result in failure of this approach.
General, controlled delivery attempts to:

a) Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw-tooth kinetic pattern,
b) Localize drug action by spatial placement of a controlled release system (usually rate-controlled) adjacent to or in the diseased tissue or organ,
c) Target drug action by using carriers or chemical derivatization to deliver drug to a particular "target" cell type.

Sustained release dosage forms include those dosage forms in which the drug-release characteristics are different from the conventional dosage

form to saw-tooth pattern of drug delivery (Except continuous IV perfusion) & results in increase adverse effects, decrease therapeutic effect & poor patient compliance (Madan 1985)

So, in recent years considerable attention has been focused on the development of new drug delivery systems by applying the concepts and, techniques of controlled release drug delivery. An appropriately designed sustained release drug delivery system can be a major advance toward solving the problems facing continuously in case of conventional dosage form, thereby reducing both the size and number of doses. It is for this reason that the science and technology responsible for the development of sustained release pharmaceuticals have been and continue to be the focus of a great deal of attention in both industrial and academic laboratories.

1.5 Therapeutic Advantages of Sustained Release Dosage Form

In evaluating drugs as candidates for sustained release formulation, the advantages of such formulations that must be considered include the following:

i. The most important advantage of sustained release dosage forms is to maintain
ii. the therapeutic effect for a longer period of time
iii. Reduction in dosing frequency
iv. Reduced fluctuation in circulating drug levels
v. Increased patient compliance
vi. Avoidance of night time dosing
vii. More uniform effect
viii. Reduction in GI irritation and other dose-related side effects

1.6 Potential Disadvantages of Sustained Release Dosage Form

Not all drugs are suitable candidates for formulation as prolonged action medication.

i. **Drugs with long biologic half-lives (e.g., digoxin - 34 hours)** are inherently long acting and thus are viewed as questionable candidates for sustained release formulation.

ii. Administration of sustained release medication does not permit the prompt termination of therapy when it is desired or required.

iii. The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form design.

iv. **The high cost of sustained release dosage forms must again b taken** into account when the advantages and disadvantages of a particular drug formulation are being considered.

v. Dose dumping is a phenomenon whereby the, relatively large quantity of medication in a controlled release formulation is rapidly systemic circulation.

vi. Reduced potential for dosage adjustment is a major disadvantage of some controlled release products.

vii. Reduced drug absorption is an intrinsic hazard with all controlled release dosage forms.

1.7 Characteristics of Drugs not suitable for Sustain Release Forms

1. Not effectively absorbed in the lower intestine	E.g. Riboflavin, ferrous salts
2. Absorbed and excreted rapidly; short biologic	E.g. Penicillin G., frusemide
3. Long biologic half-lives (>12hr).	E.g. Diazepam, phenytion
4. Large doses required (>1g).	E.g. Sulfonamides
5. Cumulative action and undesirable side effects drugs with low therapeutic indices.	E.g. Phenobarbital, digitoxin
6. Precise dosage titrated to individual is required.	E.g. Anticoagulants,cardiac
7. Not clear advantage for sustained release Formulation.	E.g. Griseofulvin

1.8 Controlled release drug delivery system

The goal of these systems is to supply the optimal concentration of a drug for a longer time than conventional systems allow. Under traditional tablet dosages, medicine is ingested at intervals of specified time. When a tablet is taken, drug concentration raises rapidly, eventually peaks, and then falls until the next tablet is consumed. After the second tablet, the concentration of medicine in the bloodstream again raises, peaks, and falls. The cycle continues.

The problem with this scenario is that optimal concentration cannot be maintained and the peaks may occur at toxic levels. Also, human error may cause additional difficulties if a dosage is delayed or missed. Sustained release systems directly combat the problems associated with the "Hill and Valley" phenomenon described above. Time- release systems eliminate the cyclic nature of multiple tablets and have many advantages over the conventional interval dosages.

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit.

In the exploration of oral sustained release drug administration three potential changes are encountered. These are:

- Development of drug delivery system
- Modulation of gastrointestinal transit time
- Minimization of hepatic first pass elimination

In vitro drug release data, drug release profiles should be generated by a well-designed, reproducible in vitro testing method, such as the dissolution test for solid dosage forms.

The key elements for in vitro release are:

- ❖ **Reproducibility of the method**
- ❖ Proper choice of medium
- ❖ Maintenance of perfect sink conditions
- ❖ Good control of solution hydrodynamics

Controlled release dosage form are also called as-

- ✓ Sustained release dosage form (SR)
- ✓ Prolonged release dosage form
- ✓ **Delayed release dosage form**
- ✓ Timed-release dosage form
- ✓ Retarded release dosage form,
- ✓ Extended action dosage form
- ✓ **Depot dosage form**
- ✓ Repeat action dosage form
- ✓ Repository dosage form

1.9 Factors to be considered in Controlled — Release technology

Factors	Considerations
1. Physicochemical	□ Aqueous solubility of the drugs
	□ **Stability of the drug**
Properties of the drug	□ Partition co-efficient of the drug
	□ p K_a value of the drug
	□ Protein binding of the drug
	□ **Molecular size & diffusivity**
	□ Absorption characteristics of the drug
	□ Distribution characteristics of the drugs
	□ Metabolism of the drugs

2 Biological properties of the drugs	Biological half-life & elimination of the drugs
	Duration of action of the drugs
	Margin of the drugs
	Role of disease state & tissue injury
	Side effects of the drug
	Dose size
	Acute or chronic therapy required
	Age & physiological state of the patients
3. Patient/disease factors	Ambulatory or bedridden patient
	Duration of the drug action desired
	Location of the target area
	Pathology of disease state

1.10 Techniques for the Development of Sustained Release Dosage Forms

Name of the Method	Description
Coaling	Coating material gives a more uniform release and control the rate of availability of drug from the dosage form (Lachman et a!; 1979)
Beads & spheres	This dosage form contains beads or spheres of the drug that are coated with a material that differs on thickness from beads at which the drug will be released by diffusion through pores.
Enieric-coated beads	The rate of drug release depends on the

	stomach-emptying rate of the beads.
Mixed-release granules	Two sets of granules are used in the preparation of the compressed tablets.
Ion-exchange resin	This method involves the administration of a dosage form containing salts of drugs complexes with an ion-exchange resin that exchanges drugs for ions as it passes through the GIT.
Complexation	Complex or slats of active drugs are used that are less soluble in the GIF.

Microencapsulation	The release of the drug through the microencapsulated particles takes place by diffusion rather than simple dissolution.
Osmotic tablet	The product operates the principle of osmotic pressure that develops as GIF permeate the semi permeable membrant & reach the core.
Gel forming hydrocolloids	The gastric fluid swells the outer most hydrocolloid to form a gelatinous barrier, preventing further penetration of GIF.
Matrix tables	Release of drug is controlled by the polymer solubiityof the drug and its diffusivity in the polymer matrix.

1.11 Polymers in controlled drug delivery

Controlled drug delivery occurs when a polymer, whether natural or synthetic, judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a pre designed manner. The release of the active agent ma be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under and overdosing

Other advantages of using controlled-delivery systems can include the n of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored: the possible toxicity or no biocompatibility of. the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations.

The goal of many of the original controlled-release systems was to achieve a delivery profile that would a high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood follows the profile shown in Figure 1.6 a, in which the level rises each administration of the drug and then decreases until the next administration. The traditional drug administration is that the blood level of the agent should remain a maximum value, which may represent a toxic level, and a minimum value, below which drug is no longer effective. In controlled drug delivery systems designed for long-term administration, the drug level in the blood follows the profile shown in Figure 1.6 remaining constant, between the desired maximum and minimum, for an

extended period of time. Depending on the formulation and the application, this time may be anywhere from 24 hours (Procardia XL) to I month (Lupron Depot) to 5 years (Norplant).

In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. For example, current controlled release systems can respond to changes in the biological environment and deliver-or cease to deliver-drugs based on these changes. In addition, materials have been developed that should lead to targeted delivery systems, in which a particular formulation can be directed to the specific cell, tissue, or site where the drug it contains is to be delivered. While much of this work is still in its early stages, emerging technologies offer possibilities that scientists have only begun to explore.

1.12 Comparison among controlled, conventional and ideal drug release profiles

The conventional oral and intravenous routes of drug administration do not ideal pharmacokinetic profiles especially for drugs, which display high toxicity and/or narrow windows. For such drugs the ideal pharmacokinetic profile will be one wherein the drug concentration reached therapeutic levels without exceeding the maximum tolerable dose and maintains concentrations for extended periods of time till the desired therapeutic effect is reached. One of the ways such a profile can be achieved in an ideal case scenario would be by encapsulating the drug in a polymer matrix. The technology of polymeric drug delivery has been studied in details over the past 30 years and numerous excellent reviews are available.

1.13 The three key advantages that polymeric drug delivery products can offer are:

1.13.1 Localized delivery of drug

The product can be implanted directly at the site where drug action is needed and hence systemic exposure of the drug can be reduced. This becomes especially important for toxic drugs, which are related to various systemic side effects (such as the chemotherapeutic drugs).

1.13.2 Sustained delivery of drug.

The drug encapsulated is released over extended periods and hence eliminates the need for injections This feature can Improve patient compliance especially for drugs for chronic indications, requiring frequent injections (such as for deficiency of certain proteins).

1.13.3 Stabilization of the drug

The polymer can protect the drug from the physiological environment and hence improve its stability in vivo This particular feature makes this technology attractive for the delivery of labile drug such as proteins

1.14 Controlled release mechanisms of matrix system:

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale-as through pores in the

polymer matrix- or on a molecular level, by passing between polymer chains.

A polymer and active agent have been mixed to form a homogeneous system, also referred to as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release:

For the reservoir systems in the drug delivery rate can remain fairly constant. In this design, a reservoir-whether solid drug, dilute solution, or highly concentrated drug solution within a polymer matrix is surrounded by a film or membrane of a rate — controlling material. The only structure effectively limiting the release of the drug is the polymer layer surrounding the reservoir. The system shown in Figure 1.1 is representative of an implantable or oral reservoir delivery system, whereas the system shown in Figure 1.2 illustrates a transermal drug delivery system, in which only one side of the device will actually be delivering the drug.

For the diffusion-controlled systems described thus far, the drug delivery device is fundamentally stable in the biological environment and does not change it size either through swelling or degradation. in these systems, the combinations of polymer matrices and bioactive agents chosen must allow for the drug to diffuse through the pores or macromolecular structure of the polymer upon introduction of the delivery system into the biological environment without inducing any change in the polymer itself.

1.15 Environmentally responsive system

It is as also possible for a drug delivery system to be designed so that it is incapable of releasing its agent or agents until it is placed in an appropriate biological environment. Swelling-controlled release systems are initially dry and, when placed in the body will absorb water or other body fluids and swell. The swelling increases the aqueous solvent content within the foundation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment. Examples of these types of devices are shown in Figures 1.3 and 1.4 for reservoir and matrix systems, respectively. Most of the materials used in swelling-controlled release systems are based on hydro gels, which are polymers that will swell without dissolving when placed in water or other biological fluids. These hydrogels can absorb a great deal of fluid and at equilibrium, typically comprise 60-90% fluid and only 10-30% polymer.

One of the most remarkable, and useful, features of a polymer's swelling ability manifests itself when that swelling can be triggered by a change in the environment surrounding the delivery system. Upon the polymer, the environmental change can involve PH, temperature, or ionic strength, and the system can either shrink or swell upon a change in any of these environmental factors. A number of these environmentally sensitive or "intelligent" hydrogel materials are listed in Table 1.2 (page 22). For most of these polymers, the structural changes are reversible and repeatable upon additional changes in the external environment. The diagrams m Figure 1 4 illustrate the basic changes m structure of these sensitive systems. Once again, for this type of system, the drug release is accomplished only when the polymer swells. Because many of the potentially most useful pH-sensitive polymers swell at high pH values and collapse at low pH values, the triggered drug delivery occurs upon an increase in the pH of the environment. Such materials are idea for systems

such as oral delivery, m which the drug is not released at low pH values m the stomach but rather at high pH values m the upper small intestine.

1.16 Environment sensitive polymers for drug delivery.

Stimulus	Hydrogel	Mechanism
pH	Acidic or basic hydrogel	Change in pH-swelling of drug
Ionic strength	Ionic hydrogel	Change in ionic strength-change in concentration of ions inside gel-change in selling-release of drug
Chemical species	Hydrogel containing electron-accepting groups	Electron donating compounds-formation of change/transfer complex-change in swelling-release of drug
Enzyme-substrate	Hydrogel containing immobilized enzymes	Substrate present-enzymatic conversion-product change swelling of gel-release of drug.
Magnetic	Magnetic particle dispersed in alginate microshperes	Applied magnetic filed-change in pores in gel- change swelling-release of drug.
Thermal	Thermoresponsive hydrogel poly (N-isorpro-pylacrylamide)	Change in temperature-change in polymer-polymer and water-polymer interactions-change in swelling-release of drug
Electrical	Polyelectrolyte hydrogel	Applied electric filed-membrane charging-electrophoresis of charged drug-change in swelling-release of drug
Ultrasonund irradiation	Ethylene-vinyl alchol hydrogel	Ultrasound-irradiation temperature increase-release of drug.

1.17 Mathematical expression of drug release mechanism from controlled release dosage from

The release of drug from controlled dosage form is controlled by several processes. These extraction or diffusion of drug from matrix and erosion of matrix alternatively; drug j be dissolved in the matrix material and be released by diffusion through membrane. Matrices may be prepared from soluble, insoluble or erodable materials. In some cases drug may be released by osmotic process.

1.17.1 First order release:

Most sustained release formulation tends to give first order release pattern. This release on is based on Fick's law, described as

dc/dt - DA. (CmCr)Ih

Where

dc/dt = the mass of drug which diffuses in unit time

A = cross sectional area

D = diffusion constant

Cm = the initial concentration in the dosage form

Cr = the concentration in the dissolution me

H = thickness of the barrier

Under sink condition, the equation becomes

$dC_m/dt = - K_t C_m$

Where,

E_t = constant

Integration of the above equation gives the first order equation

$LogC_m = \log C°_m — ktI2.303$

Where,

C_m = the concentration at time t

K = the first order release rate constant

1.17.2 Zero order release mechanism

A zero order release of drug is needed for the dosage form, which means that the rate of drug is independent of drug concentration, expressed by the following equations..

$$dc/dt = k_{ro}$$

or

$$dM/dt = k_{ro}$$

At times it is not possible to generate a constant release product and a slow first-order release of drug is employed.

1.17.3 Higuchi release mechanism

Obviously, for this system to be diffusion controlled the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolute drug leaving the matrix. Deviation of mathematical model to describe this system involves the following assumption.

- ✓ A pseudo-steady state is maintained during drug release
- ✓ The diameter of drug particles is less than the average distance of drug dissolution through the matrix

- ✓ The bathing solution provides sink conditions at all times
- ✓ The diffusion coefficient of drug in the matrix remains constant, (i.e. no change occurs in the characteristics of the polymer matrix)

Higuchi has derived the rate of release of drugs dispersed in an inert matrix system This equation is -

$$dM/dh = Co.dh --- Cs/2$$

Where,

dM = Change in the amount of drug release per unit area

dh = Change in the thickness of the zone of matrix that been depleted of the drug

Co = Total amount of drug in a unit volume of the matrix

Cs = Sustained concentration of the drug within the matrix

1.18 Matrix Devices

Matrix devices are monolithic devices which are responsible for controlling the release of drugs. Because they are relatively easy to fabricate, compared to reservoir devices, and there is not the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. In such a device, the active agent is present as dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or, in the case of porous matrices, the solubility in the sink solution within the particle's pore network, and also the tortuosity of the network (Singh et al, 1968) (to a greater extent than the permeability of the film), dependent on whether the drug is dispersed in the polymer or dissolved in the polymer. For low

loading of drug, (0 to 5% W/V) the drug will be released by a solution-diffusion mechanism (in the absence of pores). At higher loading (5 to 10% W/V), the release mechanism will be complicated by the presence of cavities formed near the surface of the device, as the drug is lost: such cavities fill with fluid from the environment increasing the rate of release of the drug.

It was found that the choice of matrix material, amount of drug incorporated in matrix additives, the hardness of the tablet, density variation and tablet shape could markedly affect the release rate of drug (Capan, 1989).

Table 1.1: Hydrophilic, Hydrophobic & Plastic Polymers which are commonly used in sustain released dosage form:

	Hydrophilic Polymer	Hydrophobic Polymer	Plastic
1.	Alginic Acid	Avicel PH 101	Eudragit RL PO
2.	Cabomer 940	Avicel PH 102	Eudragit RL 100
3.	Gelatin	Bees wax	Eudragit RS PO
4.	Guar Gum	Cellulose acetate (CAP)	Eudragit RL 100
5.	Hydroxypropyl methyl cellulose-Methocel K15M	Carnauba wax	Eudragit RL 100
6.	Hydroxypropyl methyl cellulose-Methocel K 100 LVCR	Cetyl alcohol	Kollidon SR
7.	Kollicoat IR 0000	Ethyl cellulose	

8.	Ludipress LCE	Glyceyl monosterarate (GMS)	
9.	Ludipress	Hydroxy propyl methyl cellulose phthalate 40 cst (HPMCP 40 cst)	
10.	Modified starch	Hydroxy propyl methyl cellulose p phthalate 170 cst (HPMCP 40cst)	
11.	Polyethylene glycol 1500 (PEG 4000)	Stearic acid	
12.	Polyethylene glycol 40000 (PEG 4000)	Stearic alcohol	
13.	Polyethylene glycol 6000(PEG 6000)	Stearic alcohol	
14.	Polyethylene glycol 20,000 (PEG 20,000)		
15.	Polyvinyl alcohol		
16.	Sodium carboxy methyl cellulose		

	8000cps (NaCMC 8000 cps)		
17.	Sodium carboxy methyl cellulose 10000 cps (NaCMC 10000 cps)		
18.	Sodium Alginate		

1.19 Factors affecting biodegradation of polymer

- Chemical structure.
- Chemical composition.
- Distribution of repeat units in multimers.
- Presents of ionic groups.
- Presence of unexpected units or chain defects.
- Configuration structure.
- Molecular weight.
- Molecular-weight distribution.
- Morphology (amorphous/semi crystalline, microstructures, residual stresses).
- Presence of low-molecular-weight compounds.
- Processing conditions.
- Annealing.
- Sterilization process.
- Storage history.
- Shape.

- Site of implantation.
- Adsorbed and absorbed compounds (water, lipids, ions, etc.).
- Physicochemical factors (ion exchange, ionic strength, pH).
- Physical factors (shape and size changes, variations of diffusion coefficients, mechanical stresses, stress- and solvent-induced cracking, etc.).
- Mechanism of hydrolysis (versus water).

1.20 Release mechanisms from matrix

The release mechanism from the polymer is rather complex, specially, with dosage forms made of polymer, as not only erosion of the polymers takes place, but also diffusion of the liquid trough the polymer and even diffusion of the drug through the liquid located within the polymer also take place.

There are two other problems also of interest:

- When the solubility of the drug is low in acid gastric fluid as well as the rate of dissolution, and when it is necessary to help the drug dissolve in this liquid by provoking the extraction of the drug out of the dosage form.
- When the solubility is very low in the acid gastric liquid, and rather high in the intestine where the pH is around 8.

1.21 There are four basic release systems from matrix formulations:

i) Inert non-bioerodible system

ii) Bioerodible system

- ✓ Bioerodible with cross linking
- ✓ Bioerodible without cross linking

iii) Swelling controlled system

iv) Magnetically controlled system

In matrix system, the release is controlled of several physical processes. These include:

- Permeation of the matrix by water -
- Leaching (extraction or diffusion) of the drug from the matrix
- Erosion of the matrix material

1.22 Drug Profile

1.22.1 Introduction

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic reducing pain in conditions such as arthritis or acute injury. It can also be used to reduce menstrual pain, dysmenorrhea. The name is derived from its chemical name: 2-(2, 6-**dichlo**ranilino) **phenyl** acetic acid.

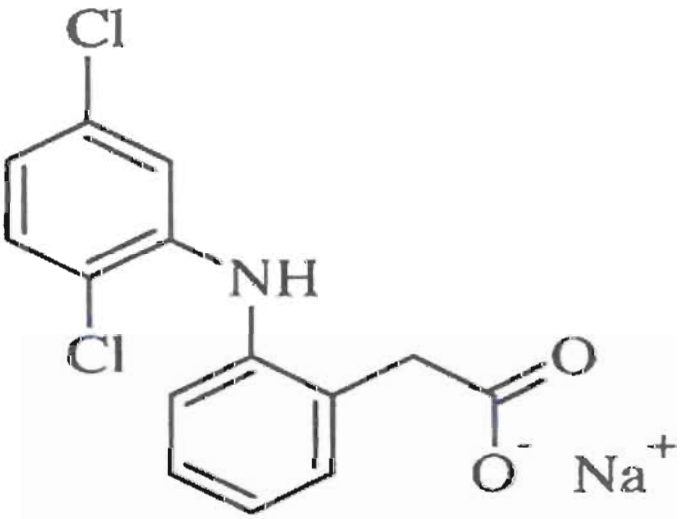


Fig. 8. Structural formula of diclofenac.

1.22.2 Pharmacology of Diclofenac

Diclofenac sodium is the active ingredient in Voltaren, a nonsteroidal anti-inflammatory drug designed by selection of appropriate physicochemical and steric properties. Its

pharmacologic activity, specifically its effects in acute and subchronic inflammation, and its analgesic activity have been assessed in animal models. The tolerability of the compound as judged by several parameters (i.e., ratio between the acute lethal dose or the dose inducing gastrointestinal blood loss and the desired pharmacologic activity) is favorable in comparison with other nonsteroidal anti-inflammatory drugs. Diclofenac sodium acts by potent cyclo-oxygenase inhibition, reduction of arachidonic acid release, and enhancement of arachidonic acid uptake. It thereby results in a dual inhibitory effect on both the cyclo-oxygenase and lipoxygenase pathways.

1.22.3 Dose of Diclofenac :

Nonsteroidal anti-inflammatory drug Diclofeanc have the initial daily dose of 75mg twice a day and maximum daily dose 200mg.The dosing interval of diclofenac is 6-12 hours.

1.22.4 Distribution:

Diclofenac sodium is extensively bound (99%) to serum albumin. The apparent volume of distribution is 0.12 to 0.17 L/kg.

1.22.5 Biotransformation:

Diclofenac undergoes single and multiple hydroxylation and methoxylation, producing 3'-, 4'-, 5-hydroxy, 4'-5-hydroxy and 3'-hydroxy-4'-methoxy derivatives of diclofenac. These phenolic metabolites are largely inactive and (along with the parent compound) are mostly converted to glucuronide conjugates.

1.22.6 **Elimination:**

Plasma clearance of diclofenac is 263±56 mL/min. The mean terminal drug half-life in plasma is 1.8 hours after oral doses. In humans about 60% of the drug and its metabolites are eliminated in the urine and the balance through bile in the feces. More than 90% of an oral dose is accounted for in elimination products within 72 hours. About 1% of an oral dose is excreted unchanged in urine.

1.22.7 Indications

Diclofenac is used for musculoskeletal complaints, especially arthritis, rheumatoid arthritis, Polymyositis, Dermatomyositis, osteoarthritis, spondylarthritis, ankylosing spondylitis, gout attacks, and pain management in cases of kidney stones and gallstones. An additional indication is the treatment of acute migraines. Diclofenac is used commonly to treat mild to moderate post-operative or post-traumatic pain, particularly when inflammation is also present, and is effective against menstrual pain and endometriosis.

As long-term use of diclofenac and similar NSAIDs predisposes for peptic ulcer, many patients at risk for this complication are prescribed a combination (Arthrotec) of diclofenac and misoprostol, a synthetic prostaglandin analogue, to protect the gastric mucosa.

An external, gel-based formulation containing 3% of diclofenac (Solaraze) is available for the treatment of facial actinic keratosis which is caused by over-exposure to sunlight. Some countries have also approved the external use of diclofenac 1% gel to treat musculoskeletal conditions.

1.22.8Contraindications

- Hypersensitivity against diclofenac
- History of allergic reactions (bronchospasm, shock, rhinitis, urticaria) following the use of Aspirin or another NSAID
- Third-trimester pregnancy
- Active stomach and/or duodenal ulceration or gastrointestinal bleeding
- Inflammative intestinal disorders such as Crohn's disease or ulcerative colitis
- Severe insufficiency of the heart (NYHA III/IV)
- Recently, a warning has been issued by FDA not to use to treat patients recovering from heart surgery
- Severe liver insufficiency (Child-Pugh Class C)
- Severe renal insufficiency (creatinine clearance <30 ml/min)

- Caution in patients with preexisting hepatic porphyria, as diclofenac may trigger attacks
- Caution in patients with severe, active bleeding such as cerebral hemorrhage
- NSAIDs in general should be avoided during dengue fever.

1.22.9 Side effects

- Diclofenac is among the better tolerated NSAIDs. Though 20% of patients on long-term treatment experience side effects, only 2% have to discontinue the drug, mostly due to gastrointestinal complaints.

Cardiac

- Following the identification of increased risks of heart attacks with the selective COX-2 inhibitor rofecoxib in 2004, attention has focused on all the other members of the NSAIDs group, including diclofenac. Research results are mixed with a meta-analysis of papers and reports up to April 2006 suggesting a relative increased rate of heart disease of 1.63 compared to non users. Professor Peter Weissberg, Medical Director of the British Heart Foundation said, "However, the increased risk is small and many patients with chronic debilitating pain may well feel that this small risk is worth taking to relieve their symptoms". Only Aspirin was found not to increase the risk of heart disease, however this is known to have a higher rate of gastric ulceration than diclofenac.
  A subsequent large study of 74,838 users of NSAIDs or coxibs, published in May 2006 found no additional cardiovascular risk from diclofenac use.
- Diclofenac has similar COX-2 selectivity to celecoxib. Perhaps related to this selectivity, a review of this constantly changing topic by FDA Medical Officer David Graham concluded in September, 2006 that diclofenac does increase the risk of myocardial infarction.

Gastrointestinal

- Gastrointestinal complaints are most often noted. The development of ulceration and/or bleeding requires immediate termination of treatment with diclofenac. Most patients receive an ulcer-protective drug as prophylaxis during long-term treatment (misoprostol, ranitidine 150 mg at bedtime or omeprazole 20 mg at bedtime).

Hepatic

- Liver damage occurs infrequently, and is usually reversible. Hepatitis may occur rarely without any warning symptoms and may be fatal. Patients with osteoarthritis more often develop symptomatic liver disease than patients with rheumatoid arthritis. Liver function should be monitored regularly during long-term treatment. If used for the short term treatment of pain or fever, diclofenac has not been found to be more hepatotoxic than other NSAIDs.

Renal

- Studies in Pakistan showed that diclofenac caused acute kidney failure in vultures when they ate the carcasses of animals that had recently been treated with it (see below at Ecological problems). Species and individual humans that are drug sensitive are initially assumed to lack genes expressing specific drug detoxification enzymes.
- NSAIDs "are associated with adverse renal [kidney] effects caused by the reduction in synthesis of renal prostaglandins" in sensitive persons or animal species, and potentially during long term use in non-sensitive persons if resistance to side effects decreases with age. Unfortunately this side effect can't be avoided merely by using a COX-2 selective inhibitor because, "Both isoforms of COX, COX-1 and COX-2, are expressed in the kidney... Consequently, the same precautions regarding renal risk that are followed for nonselective NSAIDs should be used when selective COX-2 inhibitors are administered." However, diclofenac appears to have a different mechanism of renal toxicity.

Other

- Bone marrow depression is noted infrequently (leukopenia, agranulocytosis, thrombopenia with/without purpura, aplastic anemia). These conditions may be life-threatening and/or irreversible, if detected too late. All patients should be monitored closely. Diclofenac is a weak and reversible inhibitor of thrombocytic aggregation needed for normal coagulation.

- Diclofenac may disrupt the normal menstrual cycle.

1.23Excipent Profile

1.23.1 Hydrooxypropyl Methylcellulose

Hydroxypropyl methylcellulose (HPMC) was petitioned as an ingredient of hard capsules used for encapsulating
powdered herbs. This use is petitioned as an alternative to gelatin (animal based) capsules. HPMC has many other
uses as an emulsifier, thickening agent, stabilizer, gellant, and suspending agent.
HPMC is a cellulose ether, derived from alkali treated cellulose that is reacted with methyl chloride and propylene
oxide. The NOSB approved powdered cellulose, a less processed material usually derived from wood pulp fiber, for
use as a filtering aid and anti-caking agent in October of 2001.

Composition:
C56H108O30

1.23.3 Identification

1 This Technical Advisory Panel (TAP) review is based on the information available as of the date of this review. This review addresses the

requirements of the Organic Foods Production Act to the best of the investigator's ability, and has been reviewed by experts on the TAP. The

substance is evaluated against the criteria found in section 2119(m) of the OFPA [7 USC 6517(m)]. The information and advice presented to the

NOSB is based on the technical evaluation against that criteria, and does not incorporate commercial availability, socio-economic impact, or other

factors that the NOSB and the USDA may want to consider in making decisions.

1.23.4 Chemical Name(s):

hydroxypropylmethyl cellulose, 2-hydryoxypropyl ether

of methyl cellulose

1.23.5 Other Name(s):

propylene glycol ether of methylcellulose, 2-

hydroxypropyl methyl ether, modified cellulose,

hypromellose, HPMC, MHPC, carbohydrate gum

1.23.6Uses

HPMC has many pharmaceutical uses, as a drug carrier, a coating agent, a tabletting agent, an emulsifier in ointments

(Greminger, 1973). It is also used in ophthalmic solutions (Robert, 1988, USP 1995) and as a slow release agent. It is

widely used in personal care products as a thickening agent and foam stablizer (Dow, 2002).

The petitioned use is as an ingredient of hard capsules used for encapsulating powdered herbs. These are considered to be

"vegetable" capsules, as they are an alternative to gelatin (Smithers, 2002).

1.23.2 Aerosil:

Synonyms: Colloidal silicon di oxide, Cab-O-Sil, fumed silica, silicic anhydride etc

Molecular weight: 60.08 g/mole

Functional category: suspending and thickening agent, glidant, tablet disintegrants, anticaking agent

Physical appearance: bluish-white colored, odorless, tasteless, amorphous powder

pH: 3.5-4.4

Bulk density:0. 029-0.042g/cc

Tapped density: 0.05-0.1

Flow ability: 35.52% (Carr's compressibility index)

Solubility: practically insoluble in water, organic solvent, acids except hydrofluoric acid

Figure 1.1: Silica Di-Oxide (SiO2)

1.23.3Talc:

Synonyms: Hydrous magnesium-calcium silicate, hydrous magnesium silicate, purified French chalk, magnesium hydrogen metasilicate

Functional category: Anticaking agent, glidant, tablet & capsule diluent, tablet & capsule lubricant

Physical appearance:

White to grayish white powder, odorless, powder pH: 7-10

Solubility: practically insoluble in dilute acids & alkalis, water & organic solvents

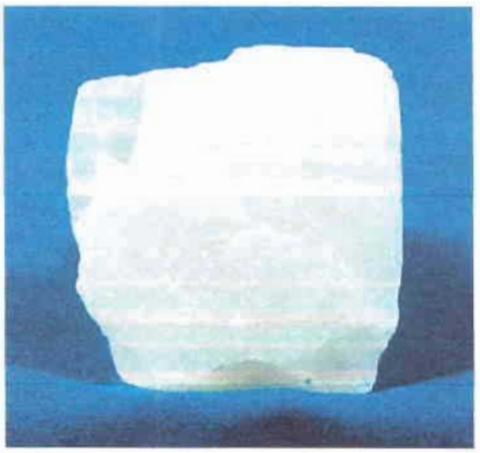


Figure 1.2 : Talc

Type Talc content min. wt% Loss on ignition at 1000 °C, wt % Solubility in HCl, max. wt % A 95 4 – 6.5 5 B 90 4 – 9 10 C 70 4 – 18 30 D 50 4 – 27 30

Empirical formulae: $3MgO.4SiO_2H_2O$

Melting point: 1500°c

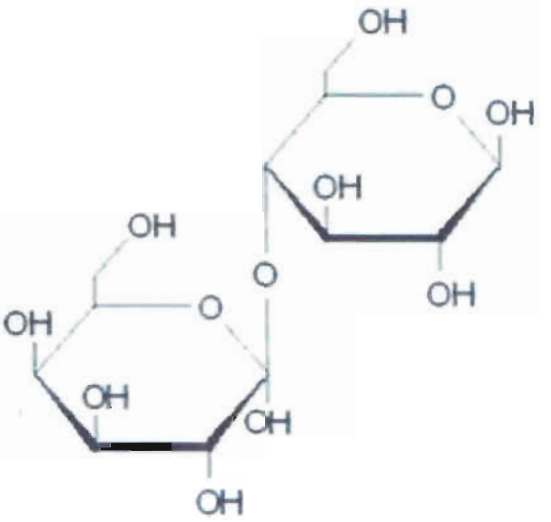
Amount uses:

Use	concentration (%)
Dusting powder	90-99
Glidant & tablet lubricant	1-10
Tablet & capsule diluent	5-30

1.23.4Lactose

Lactose is a sugar that is found most notably in milk. Lactose makes up around 2–8% of milk (by weight), although the amount varies among species and individuals. It is extracted from sweet or sour whey. The name comes from *lacte*, the Latin word for milk, plus the -ose ending used to name sugars.

Figure 1.3: Chemical Formula:



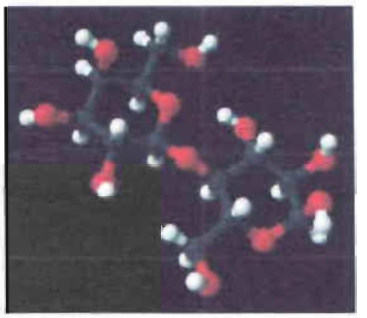


Figure 1.4 : **Alpha-lactose-from-xtal-3D-balls.png**

Synonyms

Milk Sugar

Description

White, odorless, slightly sweet-tasting powder.

Lactose is a disaccharide, two simple sugars in one molecule. In this case, the sugars are galactose and glucose.

Uses

Lactose is mainly used as a fermentation substrate for lactic acid bacteria in dairy products such as yogurt and cheese. These bacteria break down lactose into lactic acid, which solidifies the milk, and creates an acid environment that favors the benign lactic acid bacteria over those that are more harmful.

CHAPTER 02

METHODS & MATERIALS

2.1 Dissolution (chemistry)

Dissolution is the process by which a solid or liquid forms a homogeneous mixture with a solvent (solution). This can be explained as a breakdown of the crystal lattice into individual ions, atoms or molecules and their transport into the solvent.

Dissolution testing is widely used in the pharmaceutical industry for optimization of formulation and quality control.

2.1.1 What is Tablet Dissolution?

Tablets or capsules taken orally remain one of the most effective means of treatment available. The effectiveness of such dosage forms relies on the drug dissolving in the fluids of the gastrointestinal tract prior to absorption into the systemic circulation. The rate of dissolution of the tablet or capsule is therefore crucial.

One of the problems facing the pharmaceutical industry is to optimise the amount of drug available to the body, i.e. its 'bioavailability'. Inadequacies in bioavailability can mean that the treatment is ineffective and at worst potentially dangerous (toxic overdose).

Drug release in the human body can be measured 'in-vivo' by measuring the plasma or urine concentrations in the subject concerned. However, there are certain obvious impracticalities involved in employing such techniques on a routine basis. These difficulties have led to the introduction of official 'in-vitro' tests which are now rigorously and comprehensively defined in the respective Pharmacopoeia.

Tablet Dissolution is a standardised method for measuring the rate of drug release from a dosage form. The principle function of the dissolution test may be summarised as follows:

- Optimisation of therapeutic effectiveness during product development and stability assessment.
- Routine assessment of production quality to ensure uniformity between production lots.

• Assessment of 'bioequivalence', that is to say, production of the same biological availability from discrete batches of products from one or different manufacturers.
• Prediction of 'in-vivo' availability, i.e. bioavailability (where applicable).

Although initially developed for oral dosage forms, the role of the dissolution test has now been extended to 'drug release' studies on various other forms such as topical and transdermal systems and suppositories.

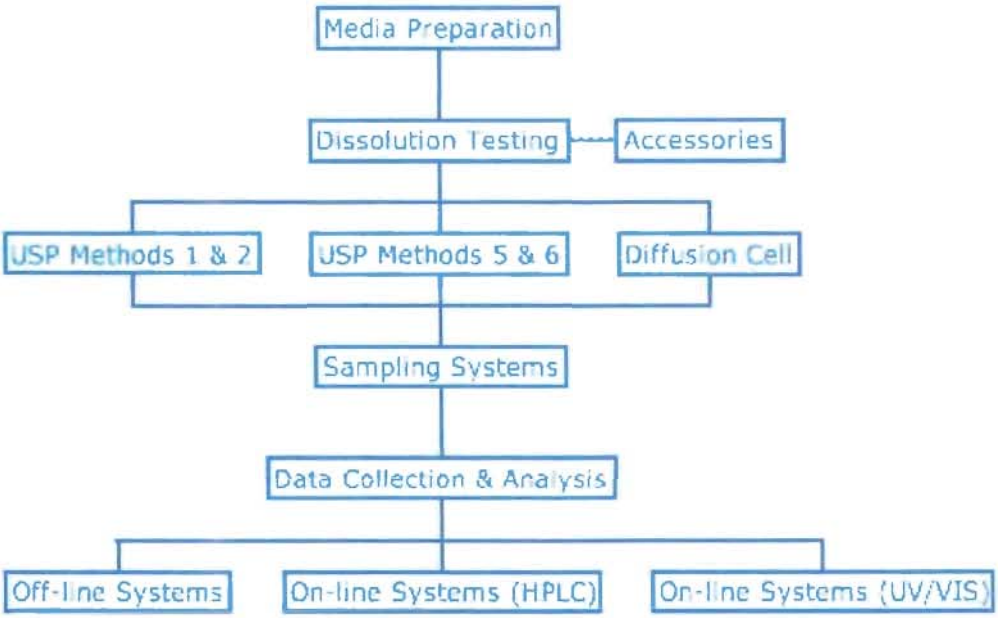


Figure2.1: Flow Chart of Stages in the dissolution testing process

2.2 Materials

Table 2.1 List of Instruments and Equipments used in the Experiments

Serial no	Name	Model
1.	UV-Visible Spectrophotometer	HACH Spectrophotometer
2.	Tablet Dissolution Tester	PHARMA TEST

		Model –DR 70
3.	**Electronic Balance**	**Denver Instrument** **Model-M-310**
4.	**Tablet Compression Machine**	**Single Punch Machine ,India**
5.	**pH Meter**	**PHS-25LIDA Instruments**

This machines are very sophisticated and it handled with great care.

]

Figure: **HACH Spectrophotometer**

Figure: **Tablet Dissolution Tester**

Figure: **Electronic Balance**

Figure: Single punch machine

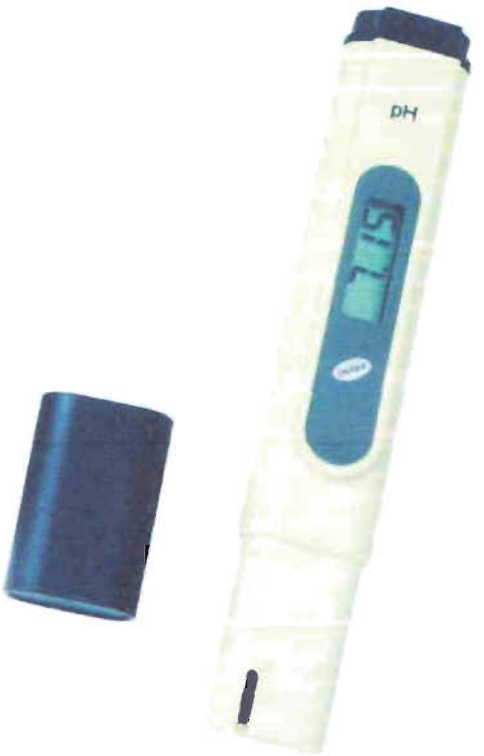


Figure: pH meter

Table 2.2 : List of Ingredients Used in Diclofenac

Name of the material	Function
Diclofenac	API (Active Pharmaceutical Ingredients)
Methocel K15 MCR	Rate controlling polymer, Binder
Methocel 100 LVCR	Rate controlling polymer, Binder
Lactose	Disintegrate
Aerosil (colloidal silicon di oxide)	Filler
Talc	Lubricant

2.3 List of Apparatus were used throughout this project:

1. Plastic Container
2. Mortar & pastels
3. Test Tubes
4. **Volumetric Flasks**
5. Volumetric Pipette
6. Micropipette
7. Pipette
8. **Measurin Cylinder**
9. Measuring Flask
10. Beaker
11. **Laboratory Mixer**
12. Spatula
13. Glass Rod
14. Disposable Syringe

Table 2.4 : Formulation of Diclofenac SR

Table 12: Formulation of diclofenac (F-1 – F-6)

	Diclofenac		K15 MCR		100LV CR		Lactose		Talc		Aerosil		Total
	%	Mg	%	mg	%	mg	%	mg	%	mg	%	mg	mg
F1	48.5	110	5	11.34	25	56.7	20	45.36	0.5	1.13	1	2.27	226.8
F2	43.5	110	15	37.93	20	50.57	20	50.57	0.5	1.26	1	2.53	252.87
F3	43.5	110	10	25.29	25	63.22	20	50.57	0.5	1.26	1	2.53	252.87
F4	43.5	110	20	50.57	15	37.93	20	50.57	0.5	1.26	1	2.53	252.87
F5	48.5	110	15	34.02	15	34.02	20	45.36	0.5	1.13	1	2.27	226.8
F6	38.5	110	15	42.86	25	71.43	20	57.14	0.5	1.43	1	2.86	285.71

2.6 Preparation Matrix Tablet :

Direct Compression method was chosen to prepare The matrix tablet of Diclofenac SR.Diclofenac SR tablets were formulated in 6 batches each containing 10 tablets.

Step 1: At first all the formulation materials were weighted out carefully through the electronic balance for each batch.

Step 2: Then Methocel K-15MCR,methocil K-100LVCR,Arocil,lactose,talc were mixed properly.

Step 3: Then Diclofenac was added and mixing properly within 5 minutes.

Step 4: Then Lactose was added and mixing properly within 5 minutes.

Step 5: After mixing Talc for 2 minutes, Then they were dried in oven at 60.c temperature for an hour. The mixture was then compressed with (5-5.5) TON compression pressure at specified weight using a single manually operated compression machine.

Step 6: Aerosil was added and mixed for 2 minutes.

2.7 Physical Study:

Angle of Repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation (Sinko, 2006)

Angle of repose, $\theta = tan^{-1} h/r$

Where,

h = Height of the powder cone.

r = Radius of the powder cone

Design of Aceclofenac Matrix Tablet 34

The suitable range is given below:

ANGLE OF REPOSE	TYPE OF FLOW
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

Bulk Density:

LBD (Loose Bulk Density) and *TBD* (Tapped Bulk Density) were determined by taking 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was placed into a 10ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The reading of tapping was continued until no further change in volume was noted. Using the following equation *LBD* and *TBD* was calculating (Desai et al, 1997):

LBD = Weight of the powder / volume of the packing.

TBD = Weight of the powder / Tapping volume of the packing.

Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index (Aulton, 2002):

Carr's index (%) = $\{(TBD - LBD) \times 100\}/TBD$

% COMPRESSIBILITY	FLOW DESCRIPTION
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair
23 – 28	Poor
28 – 35	Poor
35 – 38	Very Poor
> 40	Extremely Poor

Hausner Ratio:

It is very important parameter to be measured since it affects the mass of uniformity of the dose. It is usually predicted from Hausner ratio and angle of repose measurement.

Hausner Ratio = Tapped Density / Bulk Density

HAUSNER RATIO	TYPE OF FLOW
Less than 1.25	Good Flow
1.25 – 1.5	Moderate
More than 1.5	Poor Flow

Total Porosity:

Total porosity was determined by measuring the volume occupied by a selected weight of powder (V_{bulk}) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space (V)

$$\text{Porosity (\%)} = V_{bulk} - V / V_{bulk} \times 100$$

Hardness & Friability test:

For each formulation, the hardness and friability of 5 tablets were determined using the Monsanto hardness tester and the Roche friabilator respectively.

Thickness:

The thickness of the tablet was determined using a thickness gauge. Five tablets from each batch were used, and average values were calculated.

Weight Variation Test:

To study weight variation, 10 tablets from each formulation were weighed using an electronic balance and the test was performed according to the official method.

2.8 Assay Method

Drug content of the sample solution i.e; the quantity of drug released in the dissolution medium from the compressed tablets of Diclofenac was determined after appropriate dilution (where necessary) by spectrophotometric analysis using UV-Visible spectrophotometer at 275nm. 0.1 N HCL acid & phosphate buffer solution was used as the blank solution. From each value of absorbance, the concentration of the corresponding sample solution was calculated by using the equation of the standard curve for Diclofenac and then the amount of drug released in each vessel was determined. The percentage of drug release from the tablets were calculated and plotted against time.

CHAPTER 03

RESULT & DISCUSSION

3.1 Result and Discussion:

The proposed formulations (F-1 to F-6) of Diclofenac SR tablet matrix were built by utilizing different percentages of Methocel K100 LV CR and Methocel K15M polymers (**table-12**).

Table 12: Formulation of diclofenac (F-1 – F-6)

	Diclofenac		K15 MCR		100LV CR		Lactose		Talc		Aerosil		Total
	%	mg	%	Mg	%	mg	%	mg	%	mg	%	mg	mg
F1	48.5	110	5	11.34	25	56.7	20	45.36	0.5	1.13	1	2.27	226.8
F2	43.5	110	15	37.93	20	50.57	20	50.57	0.5	1.26	1	2.53	252.87
F3	43.5	110	10	25.29	25	63.22	20	50.57	0.5	1.26	1	2.53	252.87
F4	43.5	110	20	50.57	15	37.93	20	50.57	0.5	1.26	1	2.53	252.87
F5	48.5	110	15	34.02	15	34.02	20	45.36	0.5	1.13	1	2.27	226.8
F6	38.5	110	15	42.86	25	71.43	20	57.14	0.5	1.43	1	2.86	285.71

The physical parameters of the granules of proposed formulations (F-1 to F-6) were measured, where, LBD (g/ml) were 0.221±0.02 and 0.521±0.01, TBD (g/ml) were 0.327±0.02 and 0.475±0.03, Compressibility Index (%) were 11.15±0.03 and 13.35±0.02, Total Porosity (%) were 26.19±0.04 and 34.56±0.01, Angles of Repose were 21.53±0.01 and 29.36±0.01, Drug Content (%) were 89.19±0.03 and 102.63±0.02 respectively. All the data were in an expectable range for the evaluation of the granules (**table- 13**).

Table 13: Physical parameters of proposed formulation (F-1 – F-6)

Parameter (n = 6)	**Parameter value (Mean ± SE)**					
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
LBD (g/ml)	0.401 ± 0.02	0.521 ± 0.01	0.371 ± 0.03	0.453 ± 0.01	0.211 ± 0.03	0.221 ± 0.02
TBD (g/ml)	0.387 ± 0.01	0.462 ± 0.02	0.327 ± 0.02	0.352 ± 0.02	0.475 ± 0.03	0.339 ± 0.01
	0.96	0.88	0.88	0.77	2.25	1.53

Hausner Ratio						
Compressibility Index (%)	11.15 ± 0.03	12.58 ± 0.02	12.49 ± 0.03	11.17 ± 0.01	11.45 ± 0.01	13.35 ± 0.02
Total Porosity (%)	32.29 ± 0.02	26.19 ± 0.04	29.36 ± 0.01	34.56 ± 0.01	26.73 ± 0.02	34.13 ± 0.01
Angle of Repose	22.56 ± 0.03	24.31 ± 0.01	22.47 ± 0.03	29.36 ± 0.01	24.76 ± 0.01	21.53 ± 0.01

Hausner Ratio is in between 0.77 to 2.25. Formulation (F-1 - F-4) is less than 1.25 which indicate good flow property. Formulation (F-6) show moderate and formulation (F-5) possess poor flow property (**Table 13**).

Compressibility Index (%) were 11.15±0.03 and 13.35±0.02. Generally, compressibility index values up to 15% result in good to excellent flow properties. For Carr's compressibility index, the values are reliable only if certain equipment specifications and working protocols are adopted. While Carr's compressibility index was somewhat useful in predicting capsule-filling performance (Trowbridge et al., 1997) could not identify a relationship to tablet ting performance.

The results of angle of repose (°) ranged from 21.53°±0.01 and 29.36°±0.01. The results of angle of repose ($<30^0$) indicate good flow properties of granules. All the formulae having good flow property.

Similarly the physical parameters of tablet were Hardness (kg/cm^2) 3.19±0.01 and 4.35±0.03, Friability (%) 0.0 and 0.12±0.02, Thickness (mm) 4.19±0.12 and 4.90±0.03, Weight Variation Test (%) 1.132±0.02 and 2.903±0.23. All the values were found to be in expected range (**table-14**) and fulfilled the official requirement for both the granules and the finished product itself.

Table- 14: Properties of the matrix tablet for the proposed formulations (F-1 – F-6)

Parameter	Parameter value (Mean ± SE)					
	F-1	F-2	F-3	F-4	F-5	F-6
Hardness (n = 6) (kg/cm^2)	3.5 ± 0.23	4.35 ± 0.03	4.15 ± 0.02	4.275 ± 0.021	3.19 ± 0.01	3.265 ± 0.02
Friability (n = 10) (%)	0.00	0.00	0.12 ± 0.02	0.00	0.00	0.00
Thickness (n = 6) (mm)	4.59 ± 0.02	4.43 ± 0.03	4.19 ± 0.12	4.90 ± 0.03	4.51 ± 0.02	4.39 ± 0.01
Weight Variation Test (n = 20) (%)	2.153 ± 0.02	2.903 ± 0.23	2.342 ± 0.01	2.528 ± 0.03	2.503 ± 0.01	1.132 ± 0.02

Available six formulation (F-1 to F-6) of diclofenac sodium SR tablets were studied for their *in vitro* dissolution behavior in simulated gastric medium (pH 1.2) for 2 hours time period and in simulated intestinal medium (pH 6.8) for 10 hours time period using USP reference dissolution apparatus and show release kinetics of the matrix tablets *in vitro* dissolution specification 80% drug release within 10 hours in simulated intestinal medium.

Table 15: Zero order release kinetic profiles

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	12.6	9.2	12.8	6.3	11.3	10.7
2	38.5	17.4	25.1	11.9	25.4	20.4

3	57.8	27.1	33.3	21.1	33.8	26.9
4	74.2	35.8	42.6	30	41.1	38.1
5	87.6	43.6	57.3	35.2	49.9	44.2
6	94.1	51.7	65.8	39.7	61.3	51.9
7		60	72.4	43.7	67.2	58.3
8		69.9	80.3	49.1	71.3	64.2
9		73.7	84.2	56.4	73.5	71.7
10		79.9	87.6	61.1	78.3	80.6
11		84.5	91.2	63.3	79	84.7
12		88.7	91.6	67.2	82.7	90.1

Due to substandard formulations, four of the national brands (F-1, F-2, F-4, and F-5) were failed to fulfill the USP *in vitro* dissolution specification i.e., 80% drug release within 8th hours in simulated intestinal medium and one national brand (F-1) released 80% drug within 5th hours in the simulated intestinal medium. The amount of drug present in each tablet was determined by spectroscopic method.

In-vitro dissolution studies of all the proposed sustained release formulations (F-1 to F-6) throughout the consequent hours gave a theoretical release profile of the drug with multiple coefficients (r^2) by zero order release kinetics, first order release kinetics which indicated the highest linearity of the formulation. The highest linearity of standard formulation F-6 and F-3 followed zero order release ($r^2 = 0.9928$) and ($r^2 = 0.9514$).

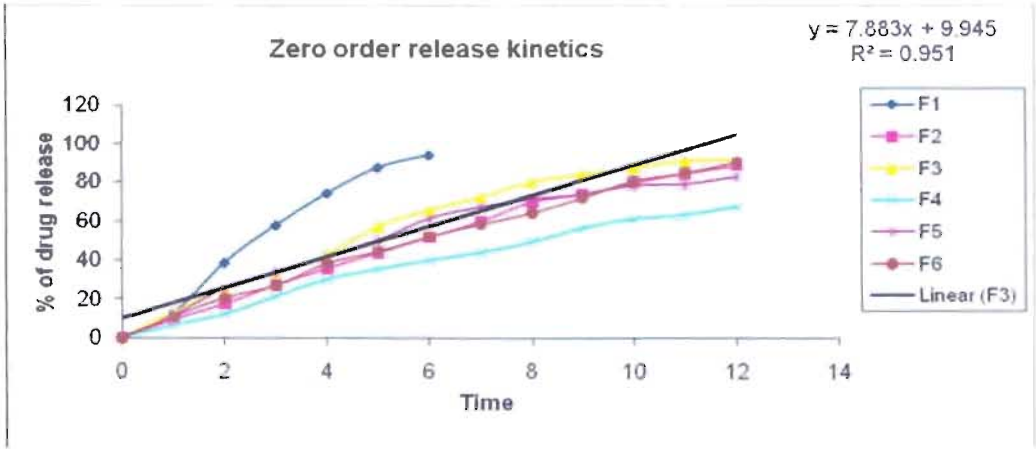


Table 16: First order release kinetic profiles

Time	F1	F2	F3	F4	F5	F6
0	2	2	2	2	2	2
1	1.941511	1.958086	1.940516	1.97174	1.947924	1.950851
2	1.788875	1.91698	1.874482	1.944976	1.872739	1.900913
3	1.625312	1.862728	1.824126	1.897077	1.820858	1.863917
4	1.41162	1.807535	1.758912	1.845098	1.770115	1.791691
5	1.093422	1.751279	1.630428	1.811575	1.699838	1.746634
6	0.770852	1.683947	1.534026	1.780317	1.587711	1.682145
7		1.60206	1.440909	1.750508	1.515874	1.620136
8		1.478566	1.294466	1.706718	1.457882	1.553883
9		1.419956	1.198657	1.639486	1.423246	1.451786
10		1.303196	1.093422	1.58995	1.33646	1.287802
11		1.190332	0.944483	1.564666	1.322219	1.184691
12		1.053078	0.924279	1.515874	1.238046	0.995635

It is denoted from this evaluation that the *in vitro* drug release from the matrix of the tablet was directly related to the type of polymers used in the formulations. Here, Methocel K100 LV CR and Methocel K15M, the hydrophilic polymers, allowed the drug release by hydration, gel formation and finally through diffusion process. The release rate determining step was primarily the time required for hydration of polymer with physiological fluids, channel formation for dissolution of drug and excipients.

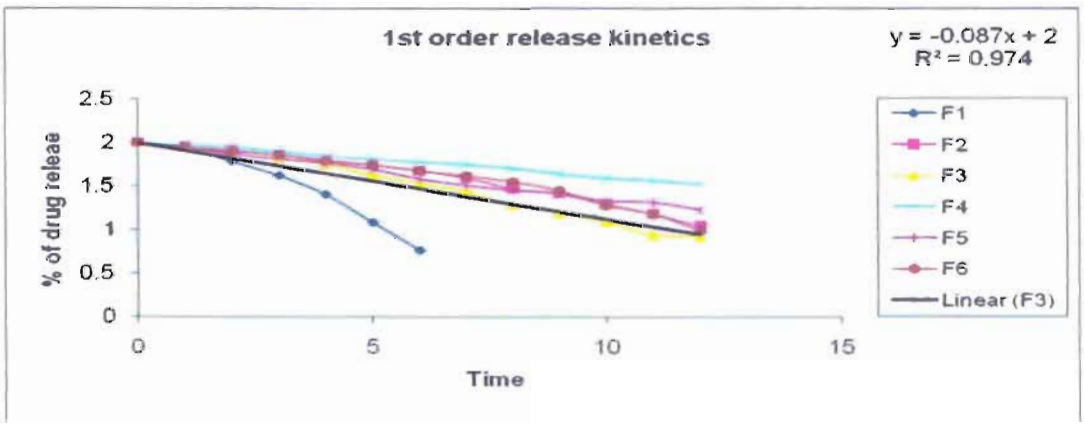


Table: Effect of Methocel K-15MCR and Methocel 100LVCR on Diclofenac SR from proposed formulation 1 to 6 in gastroin testinal fluid and intestinal fluid (Higuchi plot)

SQRT	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	12.6	9.2	12.8	6.3	11.3	10.7
1.414214	38.5	17.4	25.1	11.9	25.4	20.4
1.732051	57.8	27.1	33.3	21.1	33.8	26.9
2	74.2	35.8	42.6	30	41.1	38.1
2.236068	87.6	43.6	57.3	35.2	49.9	44.2
2.44949	94.1	51.7	65.8	39.7	61.3	51.9
2.645751		60	72.4	43.7	67.2	58.3
2.828427		69.9	80.3	49.1	71.3	64.2
3		73.7	84.2	56.4	73.5	71.7
3.162278		79.9	87.6	61.1	78.3	80.6
3.316625		84.5	91.2	63.3	79	84.7
3.464102		88.7	91.6	67.2	82.7	90.1

Figure Table: Effect of Methocel K-15MCR and Methocel 100LVCR on Diclofenac SR from proposed formulation 1 to 6 in gastroin testinal fluid and intestinal fluid (Higuchi plot)

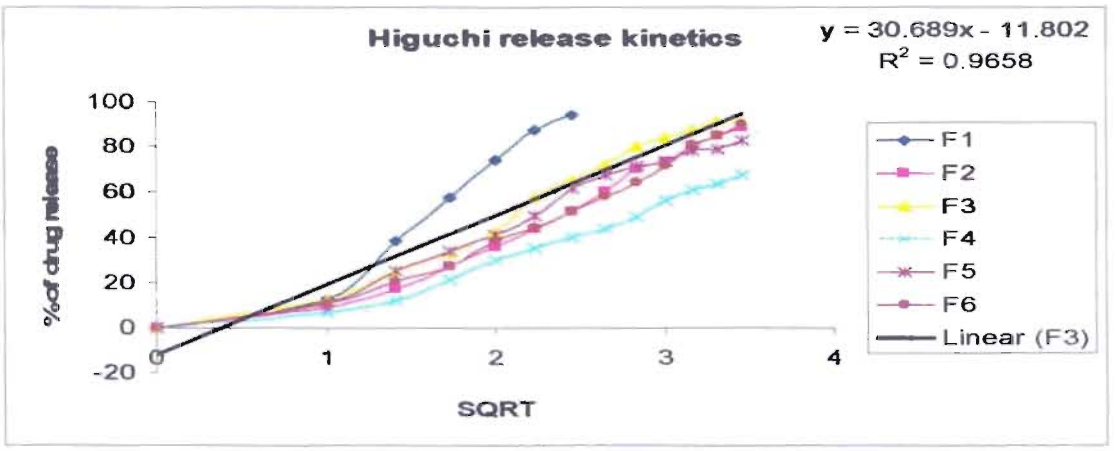


Figure: Zero order Plot for proposed formulation 1

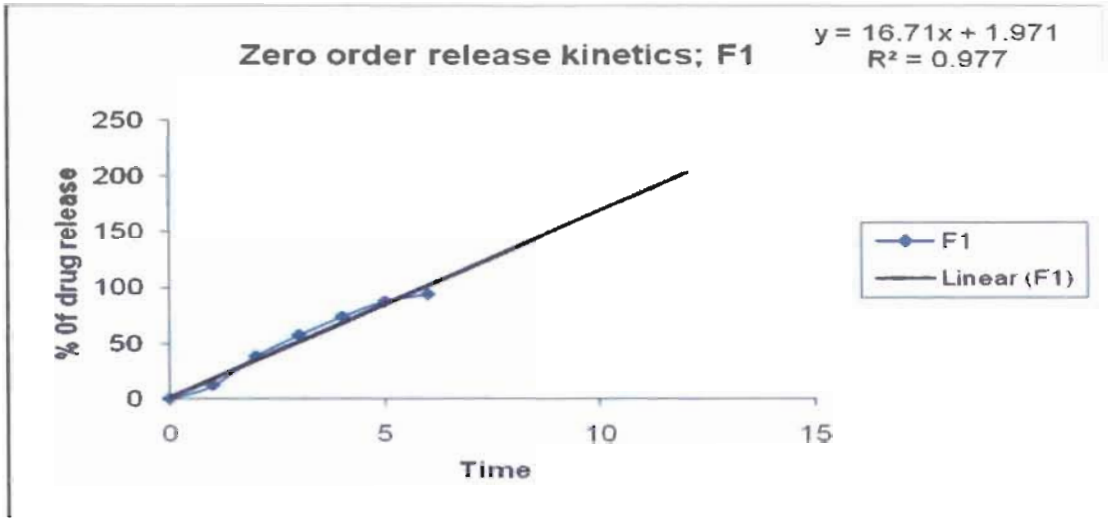


Figure: Zero order Plot for proposed formulation 2

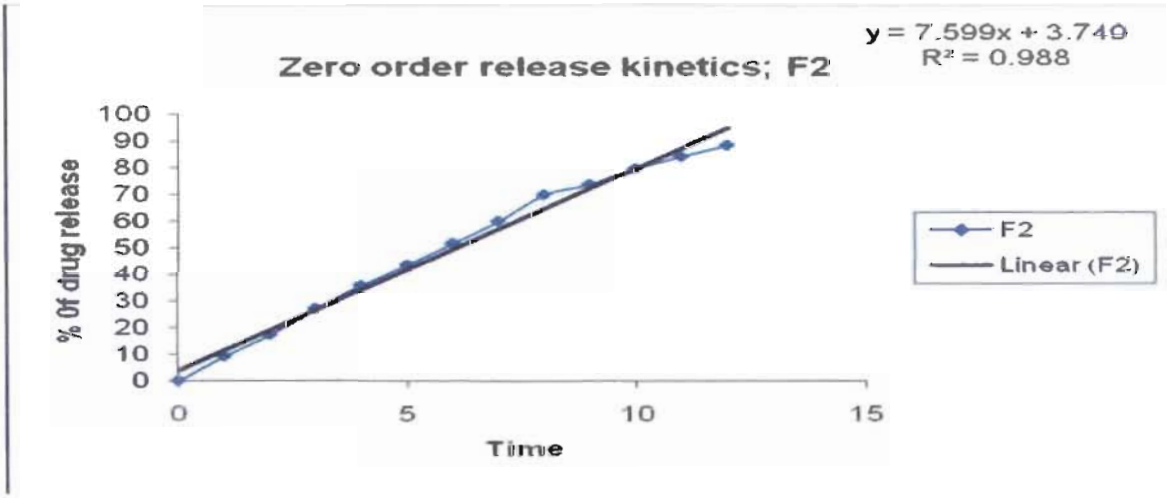


Figure: Zero order Plot for proposed formulation 3

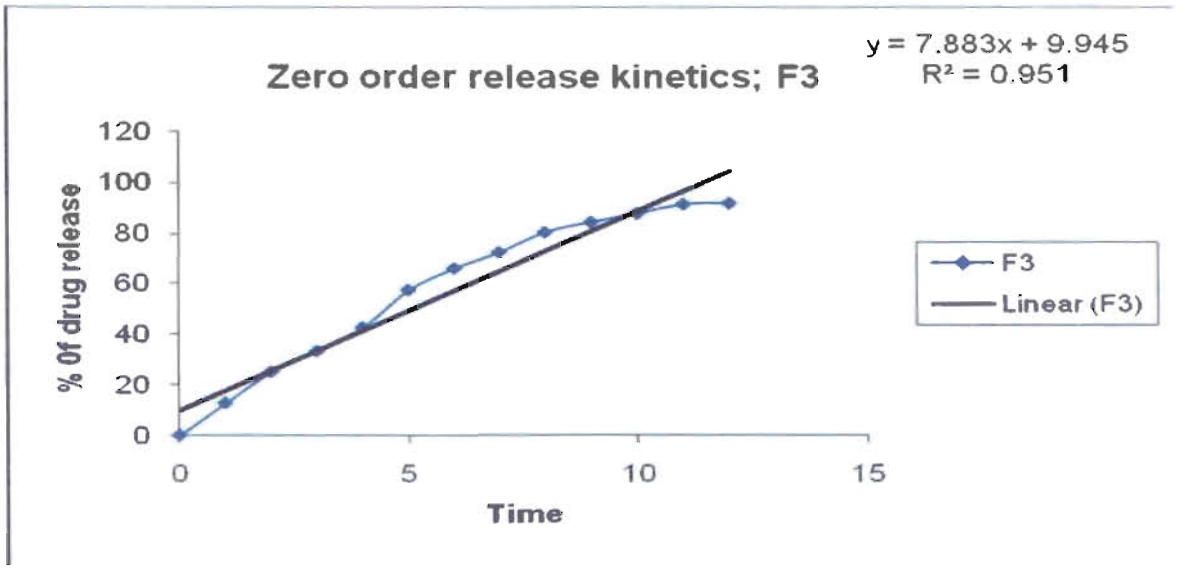


Figure: Zero order Plot for proposed formulation 4

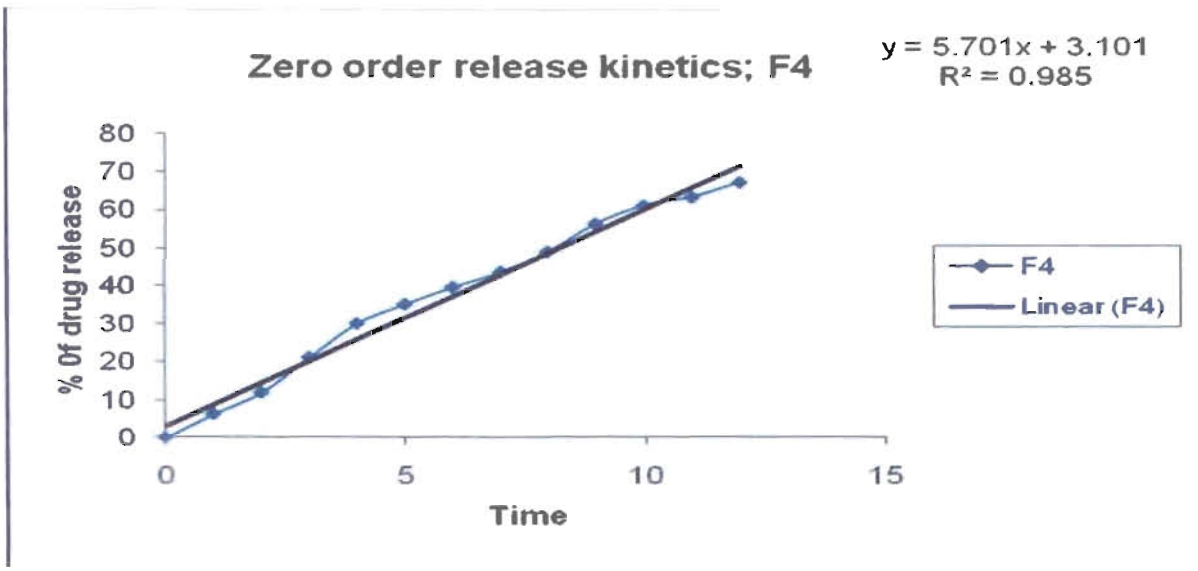


Figure: Zero order Plot for proposed formulation 5

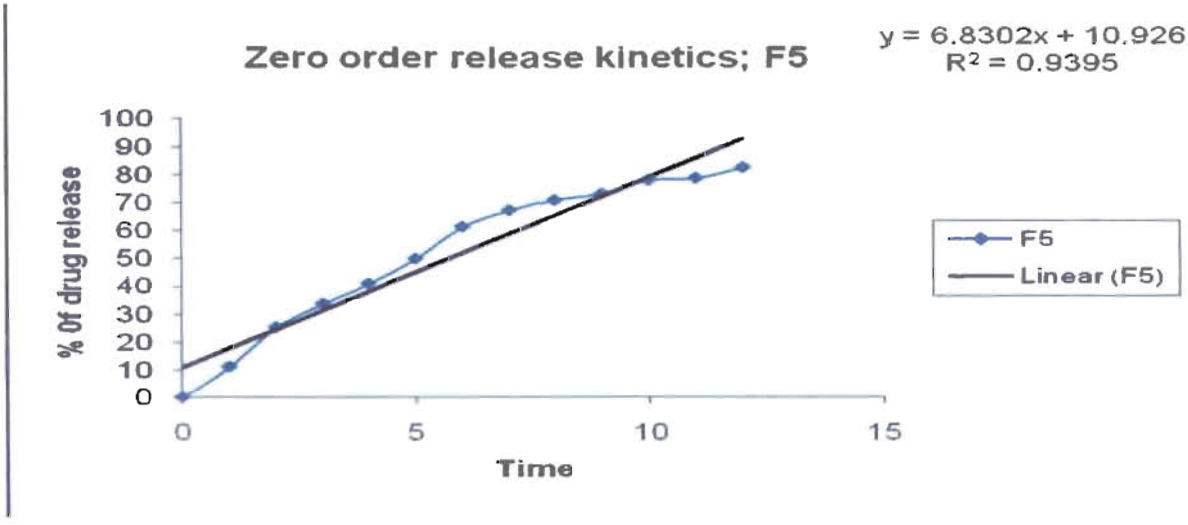


Figure: Zero order Plot for proposed formulation 6

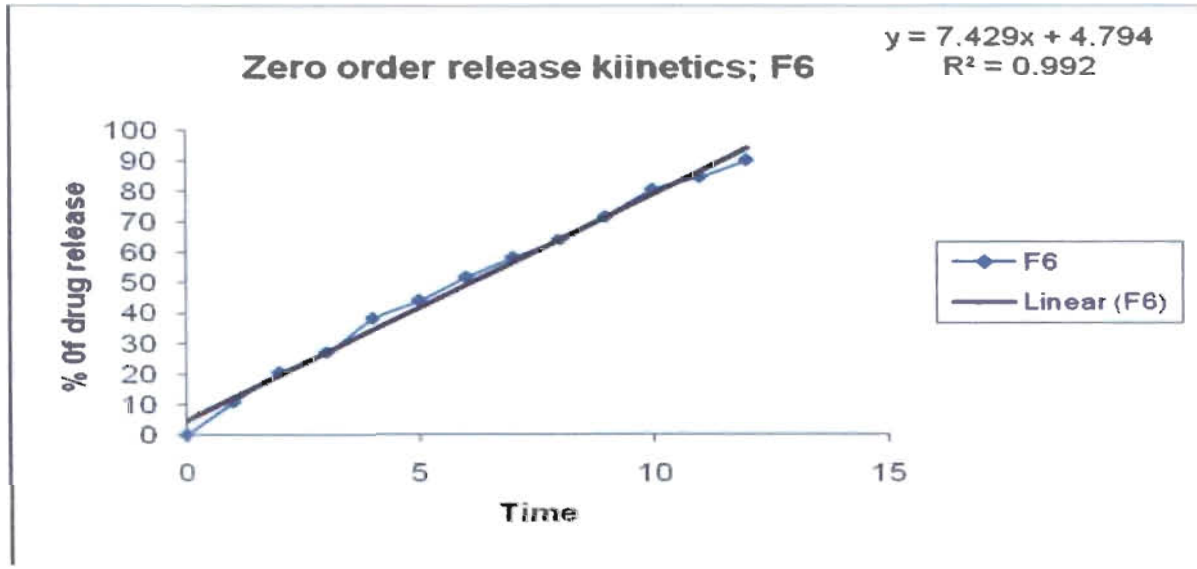


Figure First order plot of the proposed formulation 1

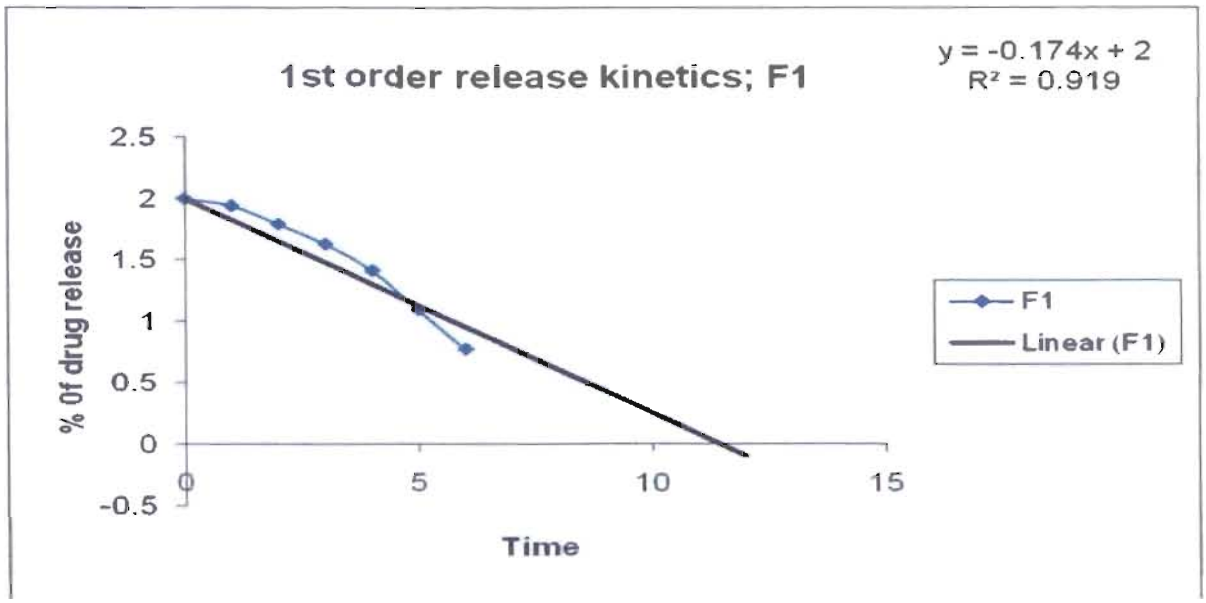


Figure: First order plot of the proposed formulation 2

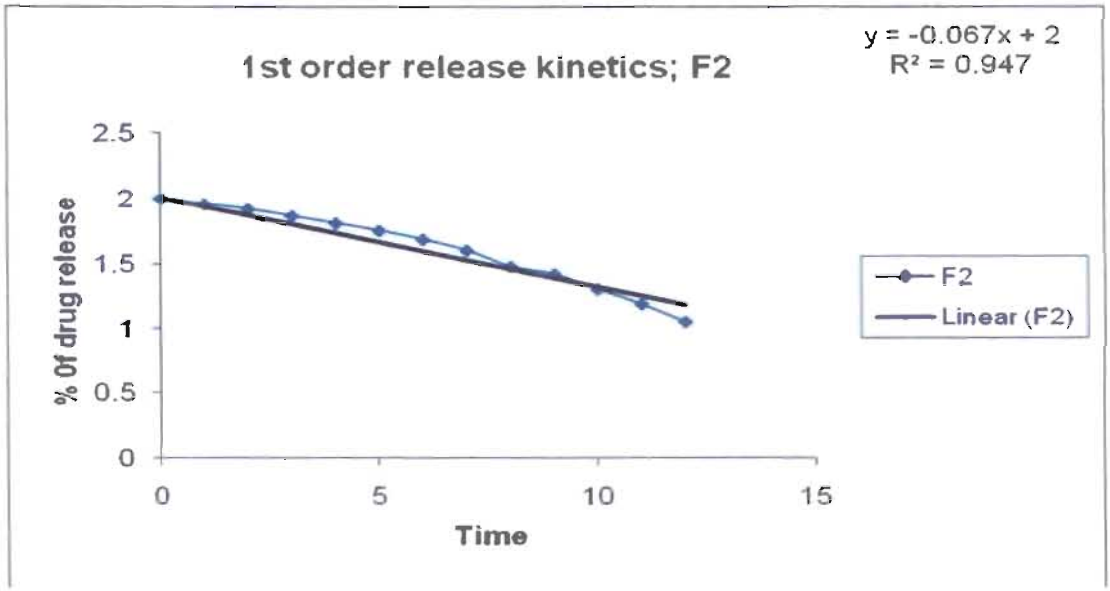


Figure: First order plot of the proposed formulation 3

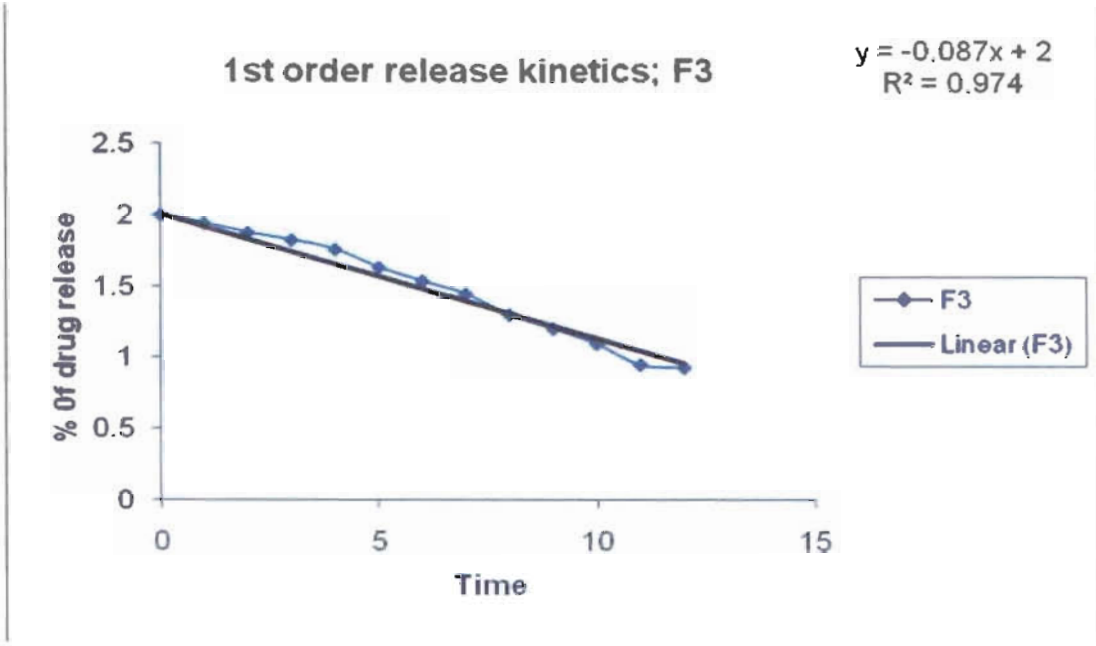


Figure : First order plot of the proposed formulation 4

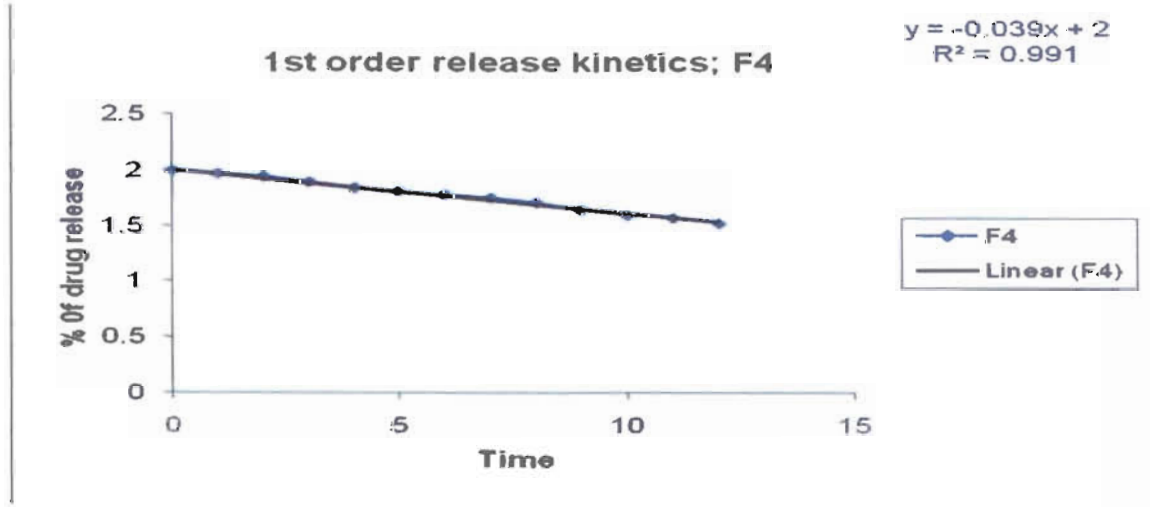


Figure : First order plot of the proposed formulation 5

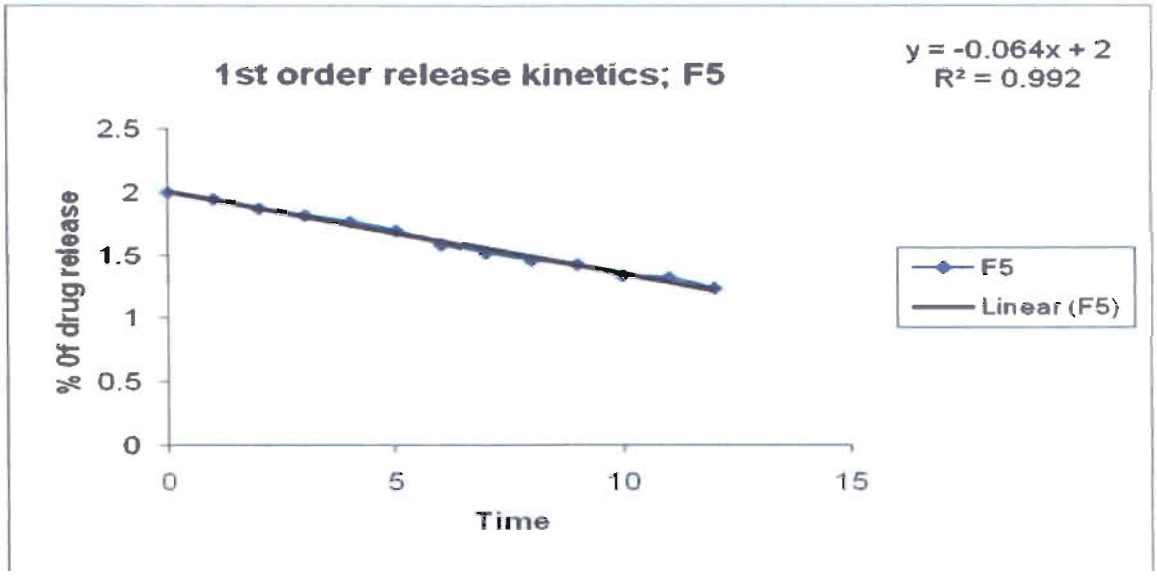


Figure: First order plot of the proposed formulation 6

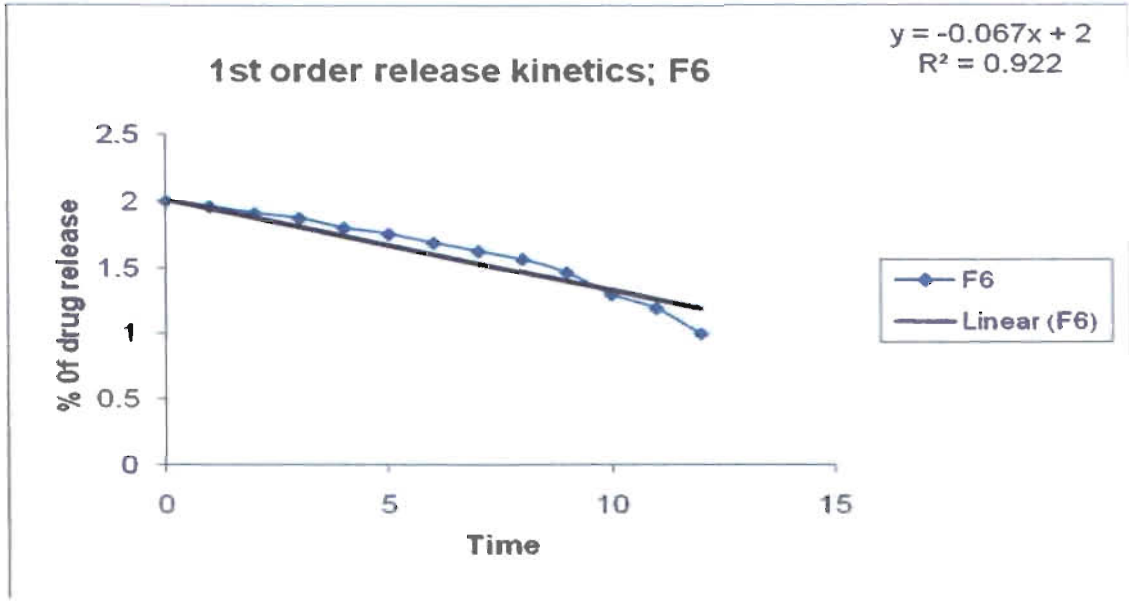


Figure: Higuchi plot for the proposed formulation 1

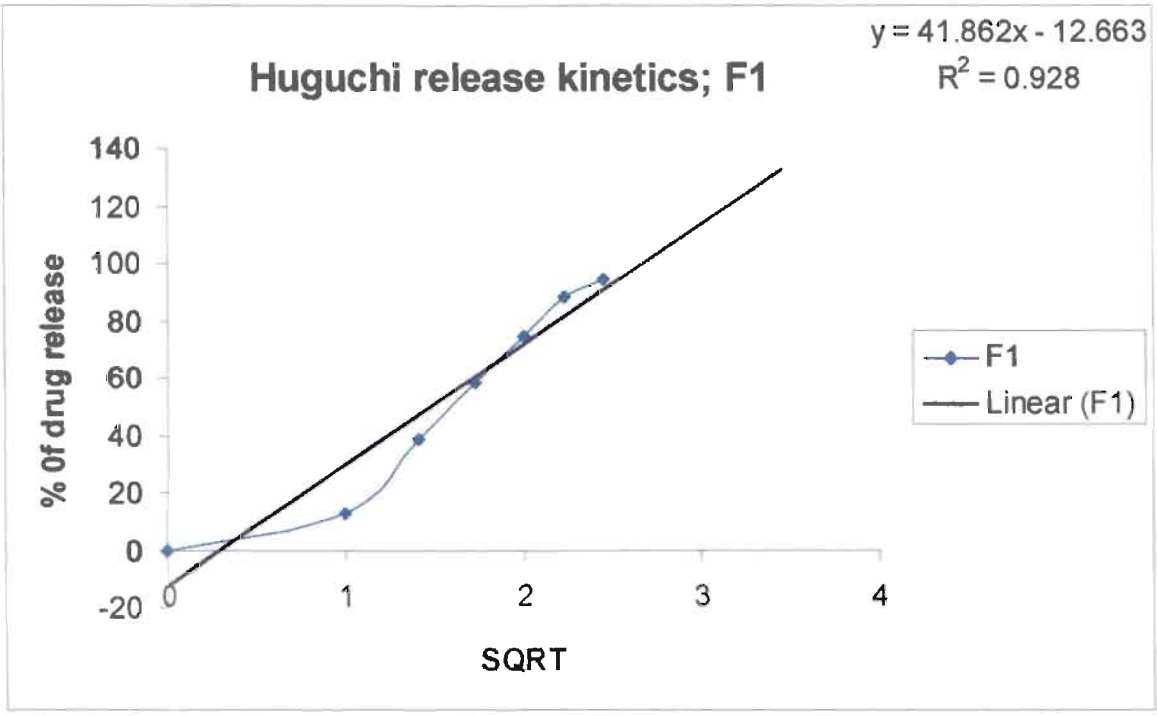


Figure: Higuchi plot for the proposed formulation 2

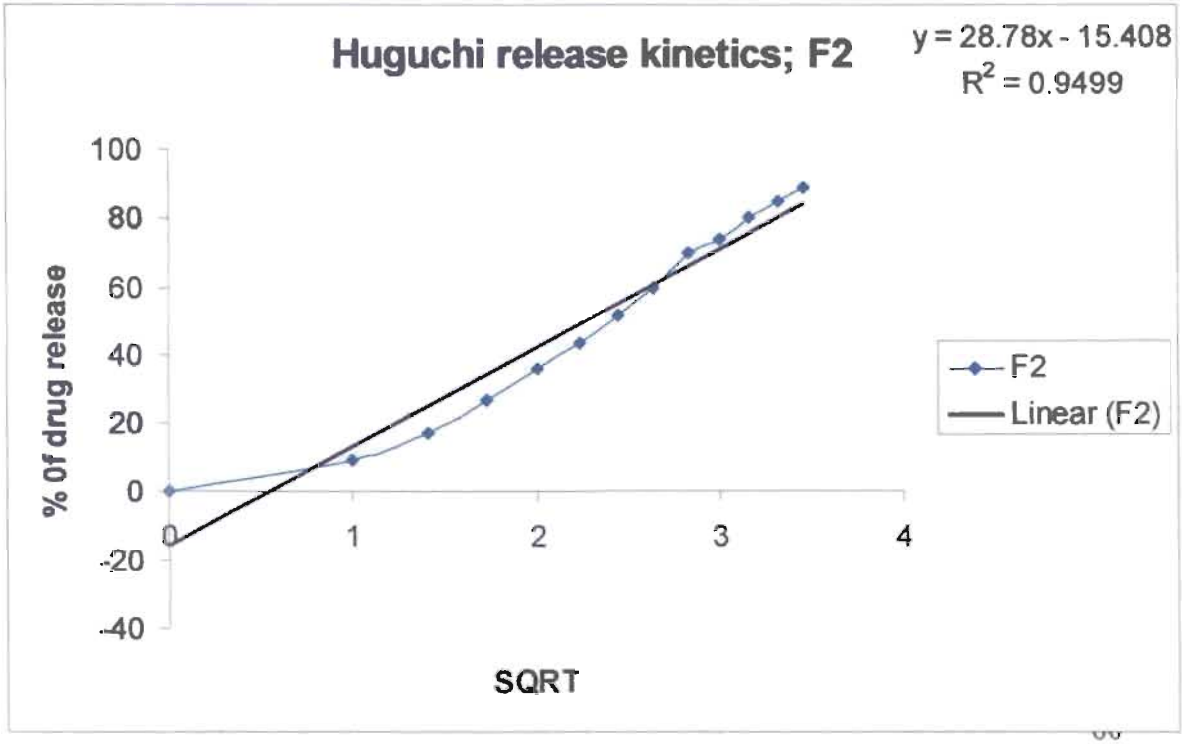


Figure: Higuchi plot for the proposed formulation 3

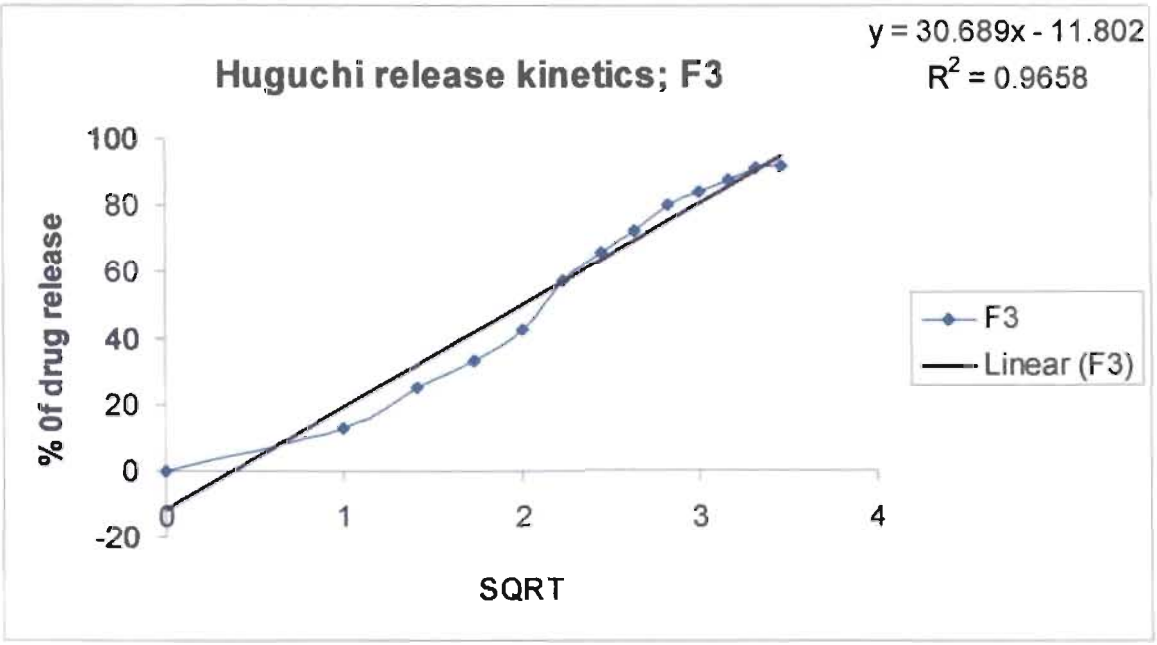


Figure: Higuchi plot for the proposed formulation 4

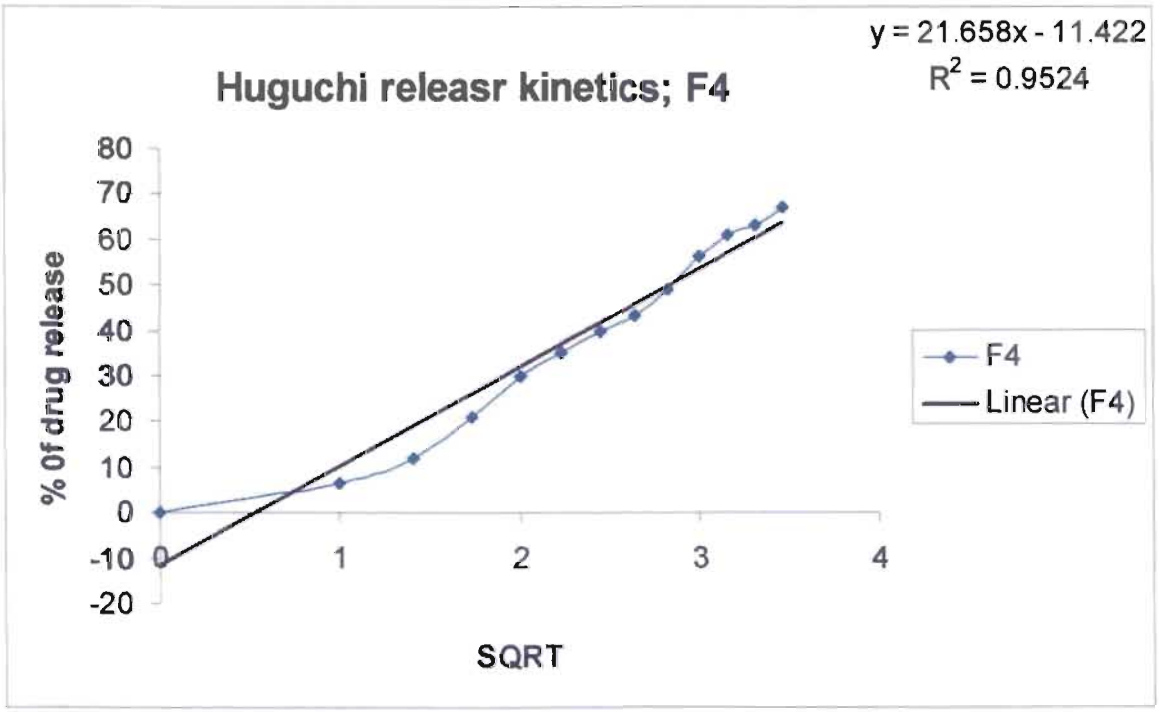


Figure: Higuchi plot for the proposed formulation 5

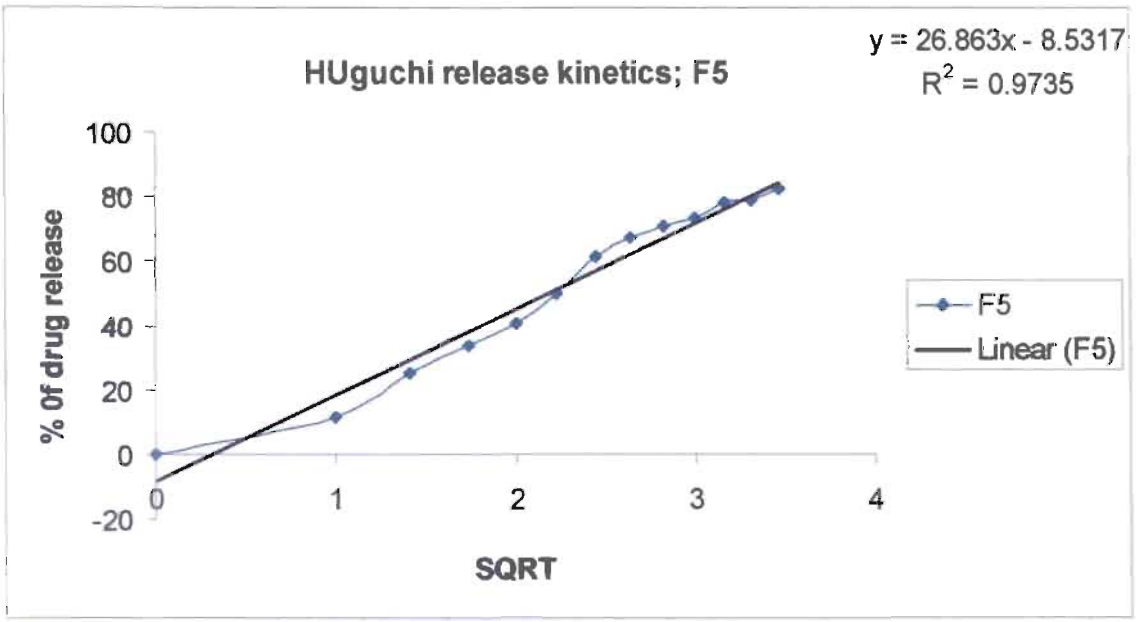
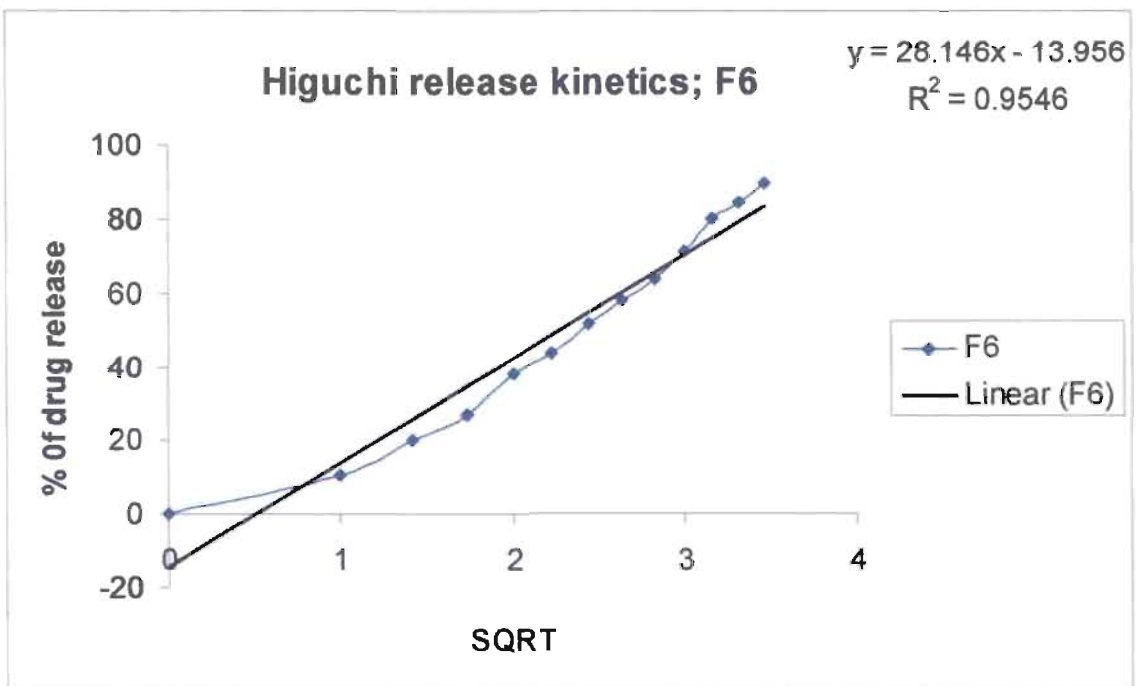


Figure: Higuchi plot for the proposed formulation 6



3.2 Discussion:

In this study, Methocel K-15MCR & Methocel 100LVCR were used for the development of the Diclofenac SR tablet matrix by direct compression method. The effect of Methocel K-15MCR & Methocel 100LVCR on Diclofenac SR dosage was assessed. Different ration of Methocel K-15MCR & Methocel 100LVCR as 1:5, 3:4, 2:5, 4:3, 3:3, 3:5of total tablet matrix, containing tablet matrices were added in the dissolution media according to design of study. In contact with the dissolution media drug was released from the tablet matrix and came into the dissolution media. The ration release from all respective polymer matrix system plotted against time to get the plot. It was that the ration of drug release was increases with decreasing the amount of Methocel K-15MCR & Methocel 100LVCR in the proposed formulation F-1 to F-6.

The polymer Methocel K-15MCR & Methocel 100LVCR were used alone with as the matrix builder in the proposed formulations F-1, F-2, F-3, F-4, F-5 and F-6 as 1:5, 3:4, 2:5, 4:3, 3:3, 3:5of total tablet matrix respectively. The variable ranges of Methocel K-15MCR & Methocel 100LVCR were selected by considering physicochemical behavior of the polymer in the physiological fluid and physicochemical properties of the drug. According to USP ideal sustain release dosage, percent release in 1st hour should be not more than 30% and in 8th hour not less than 80% (USP 29th Edition, 2006).

The effect of polymer content on drug release as a function of time was found to be significantly different for a specific set of percent of polymer irrespective of their chemical nature. Observation the corresponding release profile for a particular drug and polymer system from 3.1, 3.2 and 3.3 , it is clear that drug release is inversely proportional to the level of rate retarding polymer presenting the matrix system, i.e. the rate and extent of drug release increases with derease in total polymeric content of the matrix.

F-3 and F-6 formula mostly follow the first order kinetics. All over the formula appropriately F-5 follow the zero order kinetics, F-3 and F-6 both are mainly follow the first order kinetics.

From the result, we can say when Diclofenac was contained Methocel K-15MCR & Methocel 100LVCR; the release of Diclofenac followed a first order kinetics with the polymer contain 2.5 and 3.5 ratio.

Reference:

Alderman D.A.; **(1984)**. A Review of Cellulose Ethers in Hydrophilic Matrices for Oral Control Release Dosage Form. *Int J Pharm Tech*. Prod. Manufr.

Allen L.V., Popovich N.G., Ansel H.C.;**(2005)**. Ansels Pharmaceutical Dosage Forms and Drug Delivaru Systems; 8th edition;

Aulton M.E.; **(1988)**. *Pharmaceutics: The Science of Dosage Form Design*, 1st edition, *ELBS/Churchill Livingstone, Edinburgh*,

Burke A., Smyth E., FitzGerald G.A.; **(2001)**. Analgesic–Antipyretic Agents: Pharmacotherapy of Gout. In: L.L. Brunton (Eds.), *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th ed., *McGraw-Hill, USA*, 2006,

Chaubal, M.V.; **(2006)**. Polymeric Excipient for Controlled Release Applications. In Chaubal, M.V., *Excipient Development for Pharmaceutical, Biotechnology and Drug Delivery Systems, USA:Informa Healthcare*,

Desai,S.J., Simonolli, A.P., and Higuchi,W.I., **(1965)**; Investigation factors influencing release rate of solid drug dispersed in inert matrices, Pharm Sci,

Florence AT and Attwood D.; **(1988)**. *Physicochemical Principles of Pharmacy*. 2nd edition. *Macmillan Press Ltd*,

Gohel, M.C., Jogani P.D.; **(2005).** A Review of Co-Processed Directly Compressible Excipient, *J Pharm Pharmaceut Sci* (www.cspscanada.org),

Goodman and Gilman's **(2001)**. The Pharmacological Basis of Therapeutics. 10th edition. *McGraw-Hill Medical Publishing Division*,

Hollinger, MA (1990). "Pulmonary toxicity of inhaled and intravenous talc". *Toxicology letters* **52** (2): 121–7; discussion 117–9.

Haider SS and Ahsan GM **(2001)**. Dissolution Profiles of Commercially Available Enteric Coated Tablets of Non-Steroidal Anti Inflammatory Drugs. *J. Bangladesh Acad. Sci.,*

Hausner H,H, **(1967);** Int J Powder Metall. 3, 7-13

Helfand WH, and Cowen DL, **(1983)**. Evolution of Pharmaceutical Oral Dosage Forms, *Pharm Hist.*

Higuchi T., **(1963)**; Mechanism of Sustained Action Mechanism, Theoritical Analysis of Rate Release of Solid Drugs Dispersed in Solid Matrixs. *J. PHARM. Sciences,*

Löbenberg R. and Amidon G.L.; **(2000)**. Modern Bioavailability, Bioequivalence and Biopharmaceutics Classification system. New Scientific Approaches to International Regulatory Standards. *Eur. J. Pharm. Biopharm.*

Longer M.A., and Robinson J.R.; **(1900)**. Sustained Release Drug delivery System. In: *Remington's Pharmaceutical Science* (Gennaro, A.R. and Chase, G.D. (Eds),

Lordi N.G.; Sustained Release Dosage Forms, in Lachman, L., Lieberman, H.A. and Kanig, J. L. (Edts); **(1992)**. *The Theory and Practice of Industrial Pharmacy*, 3rd ed, *Varghese Publishing House, Bombay,*

Ministry of Health and Welfare, Japan; **(1988)**. Guidelines for The Design and Evaluation of Oral Prolonged Release Dosage Forms; *Ministry of Health and Welfare, Japan.* At: http://docs.google.com/viewer?a=v&q=cache:tbsbdpx78XEJ:www.nihs.go.jp/drug/be-guide%28e%29/CR-new.pdf+Ministry+of+Health+and+Welfare,+Japan%3B+%281988%29.+Guidelines+for+The+Design+and+Evaluation+of+Oral+Prolonged+Release+Dosage+Forms%3B+Ministry+of+Health+and+Welfare,+Japan&hl=bn&gl=bd&sig=AHIEtbS7YlK99a83gKhU01nmrUQ0-tiQxw; Viewed on 08/10/2009

Nellore RV, Rekhi GS, Hussain AS, Tillman LG and Augsbruger LL, **(1998)**. Development of Metoprolol Tartrate Extended-Release Matrix Tablet Formulations for Regulatory Policy Consideration. *J. controlled Release*; V-50: 247-256.

Reza SM., Quadir MA, and Haider SS, **(2003)**. Comparative Evaluation of Plastic, Hydrophobic and Hydrophilic Polymers as Matrices for Controlled-Release Drug Delivery, *J Pharm Sci,*

Rowe R. C., Sheskey P. J., Owen S. C.; *Handbook of Pharmaceutical Excipients,* 5th edition, *Pharmaceutical Press,UK*; ***2006****;*

Shangraw RF, Compressed Tablets by Direct Compression in *Pharmaceutical Dosage Forms*: *Tablets*, H.A.Lieberman, L.Lachman, and J.B. Schwartz, Eds, **(1989);** 2nd ed, *Marcel Dekker, Inc., New York.,* Vol-1,

Smalley WA, Ray, J.R. Daughterty, M.R. Griffin, **(1995)** Nonsteroidal Anti-Inflammatory Drugs and The Incidence of Hospitalization for Peptic Ulcer Disease in Elderly Persons, Am. *J. Epidemiol.*

Tomisato W, Tanaka K, Katsu T, Kakuta H, Sasaki K, Tsutsumi S, Hoshino T, Aburaya M, Li D, Tsuchiya T, Suzuki K, Yokomizo K and Mizushima T, **(2004)**. Membrane Permeabilization by Non-Steroidal Anti-Inflammatory Drugs, *Biochem. Biophys. Res. Commun.*

United States Pharmacopeia XXIII & National Formulary XVII (1995*). United States Pharmacopeia Convention, Inc., Rand McNally, Taunton,*