Formulation And Evaluation Of Diclofenac 12H SR Matrix From Hydrophilic Polymer

East West University

Department of Pharmacy

Submitted by:

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ID: 2005-2-70-098

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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:

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CERTIFICATE

This is to certify that, the thesis "Formulation And Evaluation Of Diclofenac 12H SR Matrix From Hydrophilic Polymer" submitted to the Department of Pharmacy, East West University, 43, Mohakhali C/A, Dhaka; in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm) was carried out by Tamanna Fardous (ID# 2005-2-70-098) under our guidance and supervision and no part of the thesis has been submitted for any other degree. We further certify that, all the sources of information and other facilities availed of in this connection is duly acknowledged.

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Abstract:

The study was done to evaluate six formulations of Diclofenac Sodium SR 12H incorporated with two different polymers (Methocel K 15 MCR & Methocel 100 LV CR). The polymers played an important role upon the % drug release. The formulations (F-1 to F-6) polymer ratio was (1:5, 3:4, 2:5, 4:3, 3:3, 3:5). The formulations F-3 & F-6 fulfill the official requirements in 2 hour is simulated acidic (pH 1.3) and 8 hour in buffer (pH 6.8). Dissolution was done by USP reference dissolution apparatus .The physical evaluation such as bulk density, compressibility index, angle of repose, total porosity, hausner ratio, hardness & friability test, thickness, weight variation test was also done. In vitro drug release profile was extra cloated by drug release kinetics Zero order and First order equation.

Keywords: Diclofenac, Sustained release, Matrix tablets, Hydrophilic polymer, Methocel K 15 MCR, Methocel 100 LV CR, Direct compression.

CHAPTER 01

(SUSTAINED RELEASED DRUG DELIVERY SYSTEM)

AN INTRODRUCTION

1.1.Introduction:

Diclofenac sodium is a non-steroidal anti-inflammatory agent, which is widely used in the long-term therapy for rheumatoid arthritis. The biological half-life of Diclofenac sodium is about 1-2 h, therefore it requires multiple dosing to maintain therapeutic drug blood level. The most frequent adverse side effects of Diclofenac sodium on long-term administration are gastrointestinal disturbances, peptic ulceration and gastrointestinal bleeding. Diclofenac sodium is poorly soluble in water and acidic pH (1-3) but is rapidly soluble in alkaline pH (5-8). Hence an attempt was made to formulate a sustained release dosage form containing solid dispersion of Diclofenac sodium for immediate release, which eliminates the need for multiple dosing there by increasing patient compliance and decreasing the occurrence of adverse effects.

The methods of preparation of solid dispersions as well as beads were simple and reproducible. The carriers and polymers used were non-toxic, relatively less expensive and easily available. They were found to be effective in providing a constant release of drug from the formulations for a longer period of time. (Goodman & Gilman)

With many drugs the basic goal of therapy is to achive a steady-state blood or tissu level that is theraputically effective and nontoxic for an extended period of time.The design of the proper dosage regimens is an important element to accomplishing this goal. A basic objective in dosage form design is to optimize the delivery of medication so as to achive a measure of control of the therapeutic effect, in the face of uncertain fluctuation in the in vivo environment in which drug release takes place.This is usually accomplish by maximizing drug availibility,i.e.,by attemting to attain a maximum rate and extent of drug absorption. However, control of drug action through formulation also implise controlling bioavailibility to reducce drug absorption rate.After administration, any drug have to phase three stages into the body.

They are –

1.Pharmaceutical phase- Release from a dosage form

2.Pharmacokinetic phase- Absorption, distribution and elemination

3.Pharmacodynamic phase- Drug interactions with receptor

Oral drug delivery is the largest and the oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration.In solid dosage form of oral drugs tablet is the most popular dosage form because of their greatest capabilities of all oaral dosages form for the greatest dose precision and the least content variability.

Based on their release characteristics, tablet can be classified into three types-

- Immediate release
- Delayed release.
- Extended release

Immediate release - From immediate release tablet the drug is intended to be release rapidly after administration. This is the most common type of tablet.

Delayed release - These systems include that the drug is liberated from the tablet sometime after administration. It is the system that achieves slow release of drug over an extended period of time.

Extended Release - Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds. (Aulton)

The polymers are existed in 2 types. Water-soluble polymer and water insoluble polymers are available. Certain grades of methocel are available among which methocel K15MCR is for controlled release preparation & K identifies different hydroxypropyl methyl cellulose (HPMC) products. While methocel 100 LVCR is also for SR preparation where LV represents low viscosity products. Hence these two water-soluble polymers have been used in the formulation. Methocel is nonionic, retard the influx of water & controls drug diffusion by forming a gelatinous layer on the outer tablet skin. HPMC has good compaction property.

Chemical breakdown or interactions between tablet components may alter physical tablet properties, greatly changing the bioavailabilty of a tablet system. The design of

a tablet that emphasizes only the desired medicinal effects may produce a physical inadequate product or vice versa. Physical evaluation is the prerequisite to get the unaltered medicinal agent. Thus our only concern has been made towards the physical evaluation of granules and tablets.

1.2.Over all concept of Sustained Release Dosage Form:

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot, and repository dosage forms are terms used to identify drug delivery systems that shows its action for longer period of time after administration of a single dose (Figure-1). The term "controlled release" has become associated with those systems from which therapeutic agents may be automatically released at predefined rates over a long period of time. Controlled release coating is designed to release drug at various rates on exposure to gastric or intestinal contents. (Lachman 1991)

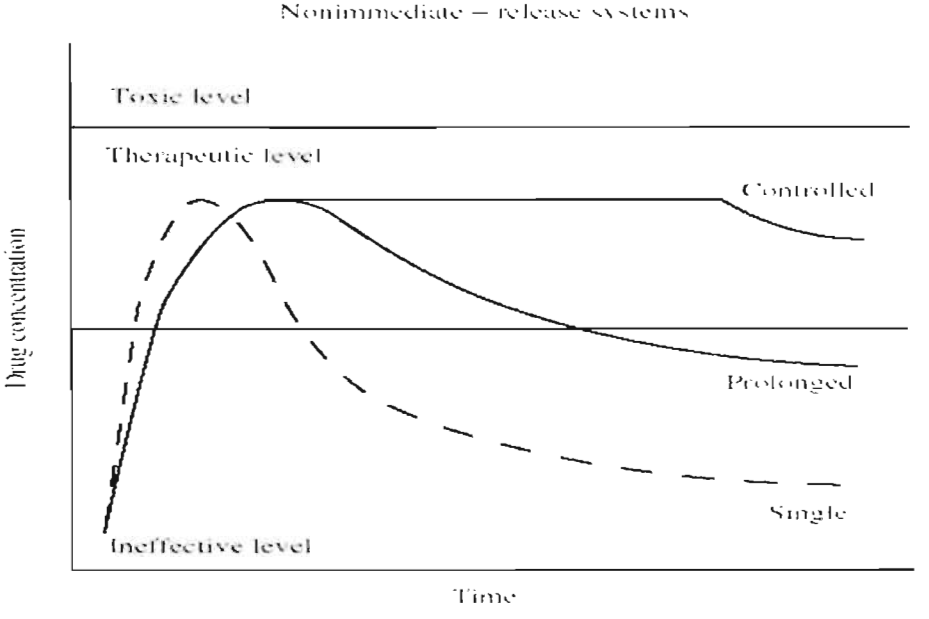


Figure 1.2 (a): Plot of drug concentration versus time for different release systems.

The pharmaceutical industry provides a variety of dosage forms and dosage levels of particular drugs, thus enabling the physician to control the onset and duration of drug therapy by altering the dose or mode of administration. Sustained release dosage form design embodies several approaches to the control of drug action e.g., through a process of either drug modification or dosage form modification, the absorption process, and subsequently drug action can be controlled. (Lachman, 1991)

Sustained release dosages form is the drug delivery system that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time.

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. Typically, sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period.

The sustained plasma drug levels provide by sustained release products often times eliminates the need for night dosing, which benefits not only the patients but the care given as well.The basic rationale of a sustained drug delivery system is to optimize the Biopharmaceutic, Pharmacokinetic and Pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route.

Oral route has been the most popular and successfully used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system. The sustained release systems for oral use are mostly solid and based on dissolution, diffusion or a combination
of both mechanisms in the control of release of drugs.

In this type of dosage forms, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response. The remaining fraction is released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess of time expected from usual single dose.

To design an efficacious sustained release dosage form, one must have a thorough knowledge of the pharmacokinetic knowledge of the drug chosen for this formulation. (Aulton, 2002)

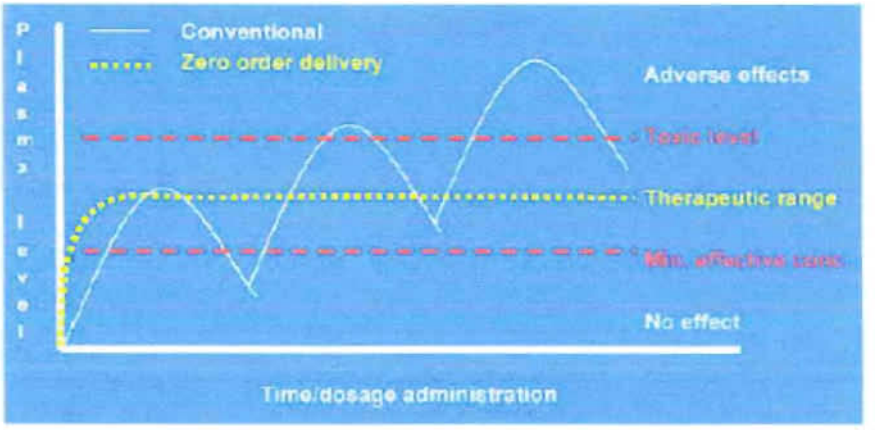


Figure 1.2 (b): Adverse effects of conventional drug therapy

If we consider the route of drug administration, a conventional dosage forms (Figure-2) of the drug. E.g., solution, suspension, capsule, tablet etc produces a drug blood level versus time profile, which does not maintain within the therapeutic range for an extended period of time. It is due to the inability of these conventional dosage forms to control the temporal release of drugs. If any attempt to maintain drug-blood levels

in the therapeutic range for a longer period, e.g., by increasing the dose of an intravenous injection, toxic levels may be produced at early time which is undesirable. For this an alternate option would be administration of drugs repeatedly 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. But there are several potential problems regarding multiple dose therapy.

Firstly, if the dosing interval is not appropriate for the biological half-life of the drug, large peaks and valley in the drug blood level may result. For example, drugs with shorter 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 required for certain disease states.

Thirdly, patient noncompliance of taking the medicine after short intervals can result in failure of this approach.
In those case oral sustained-release dosage forms have been used for improving therapeutic efficacy and patient compliance.

1.3.Types of controlled or Sustained Drug Delivery System:

Table 1.3 - (Sinko, 2006)

Type	Drug Release Pattern
a. Type-1	a. sustained release of active ingredients over an extended period of time
b. Type-2	b. cyclic pattern of release over a long period of time
c. Type-3	c.controlled drug release triggered by environment or other external events (PH changes, temperature, conc. of certain biological active substance)

As we mentioned above, controlled, sustained drug delivery can reduce the undesirable fluctuation of drug levels, enhancing therapeutic action and eliminating

dangerous side effects. There are three general types of controlled / sustained drug release are used that provides different profiles of plasma levels.

1.4.Examples of oral sustained/extended release products:

Table 1.4 - (shargel, 2004)

Type	**Trade Name**	**Rationale**
Erosion tablet	Constant-T Tenuate Dospan	Theophylline Diethylpropion HCI dispersed in hydrophilic matrix
Waxy matrix	tabletKaon *CI*	Slow release of potassium chloride to reduce GI irritation
Coated pellets in capsule	Ornade spansule	Combination phenylpropanolamine HCI and chlorpheniramine with initial- and extended-release component
Pellets in tablet	Theo-Dur	Theophylline
Leaching	Ferro-Gradumet (Abbott)	Ferrous sulfate in a porous plastic matrix that is excreted in the stool; slow release of iron decreases GI irritation
Coated ion exchange Design of Aceclofenac Matrix Tablet 9	Tussionex	Cation ion exchange resin complex of hydrocodone and phenyltoloxamine
Flotation–diffusion	Valrelease	Diazapam
Osmotic delivery	Acutrim	Phenylpropanolamine HCI (Oros delivery system)
Microencapsulation	Bayer timed-release	Aspirin

1.5.Drugs that are Unsuitable for Oral Sustained Release Dosage Form:

Not all drugs are suitable candidates for formulation as prolonged action medication. (Table-1.5) Drugs with long biologic half-lives are inherently long acting and thus are viewed as questionable candidates for sustained release formulations. It is because single doses capable of producing equally prolonged effects often yield significant concentration peaks immediately after each dosing interval.

Table-1.5

Drugs	Characteristics
Griseofulvin is	very insoluble drugs whose absorption limited by the poor solubility of the compound
Cardiac glycoside, Anticoagulants	precise dosage titrated to individual is required
Sulfonamide	large doses required (> 1g)
Diazepam, Phenytoin	long biologic half-lives(>12 hr)
Penicillin G, Furosemide	Absorbed and excreted rapidly, short biologic half-lives (< 1 hr)
Riboflavin, Ferrous salts	not effectively absorbed in lower intestine

1.6.Drug release mechanism for sustained release tablet:

Drug release is controlled by diffusions barriers or by surface erosion. Polymers come in contact with water and increasing the thickness by the gel layer. The outer layer becomes fully hydrated and states dissolving. When water reaches the center of the system and the concentration of drug fells below the solubility value, the release rate of drug begins to reduce. At the same time, an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release.

In general, two major factors control the drug release from swelling controlled matrix system. They include:

1.The rate of aqueous medium infiltration into the matrix, followed by a relaxation process(hydration,gelatin/swelling)

2. The rate of matrix erosion.

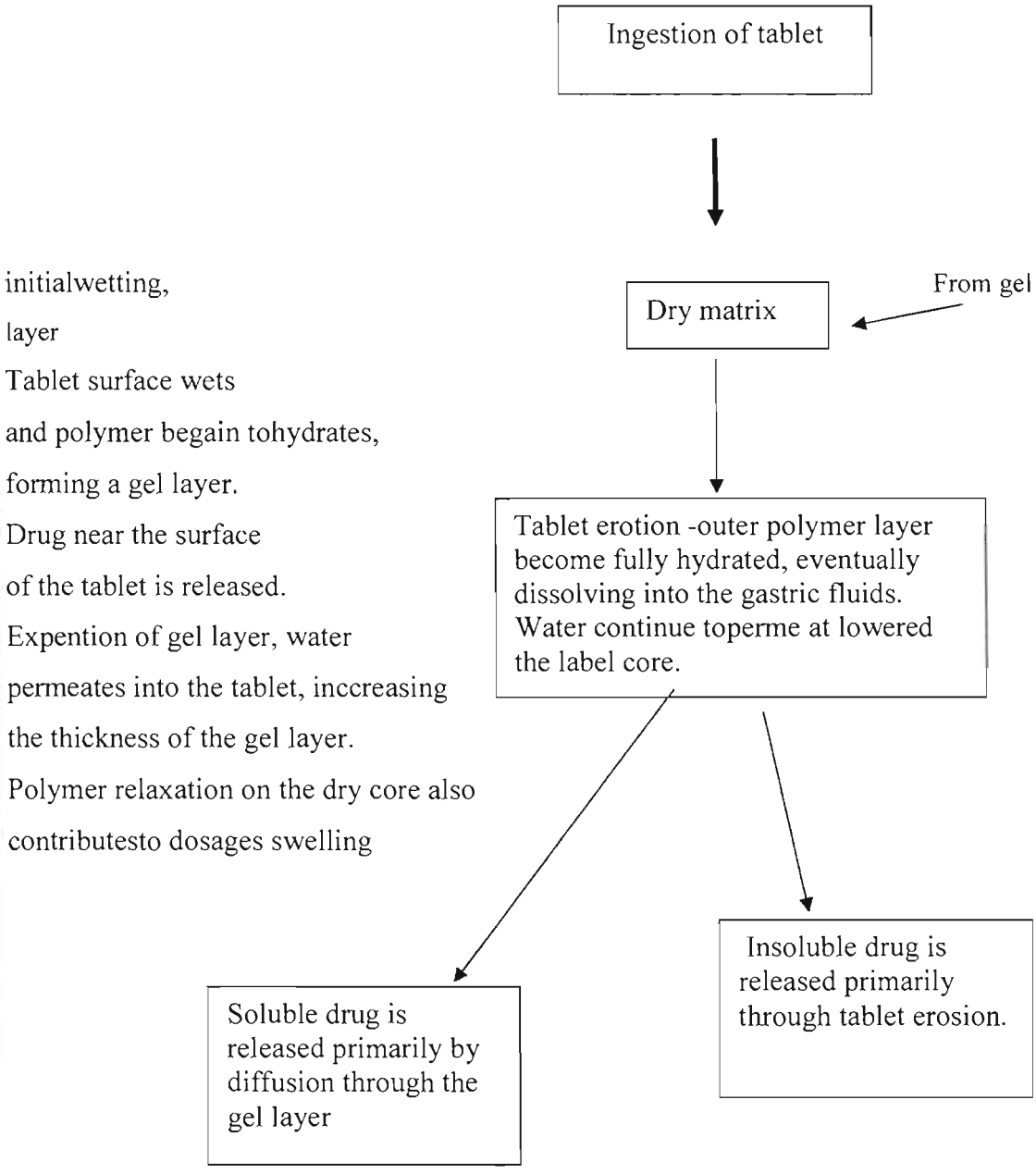


Figure 1.6 (a)-Drug release from a matrix tablet

As a result of these simultaneous processes, two front are evident,

- A swelling front, where the polymer get hydrated, and
-An eroding front.

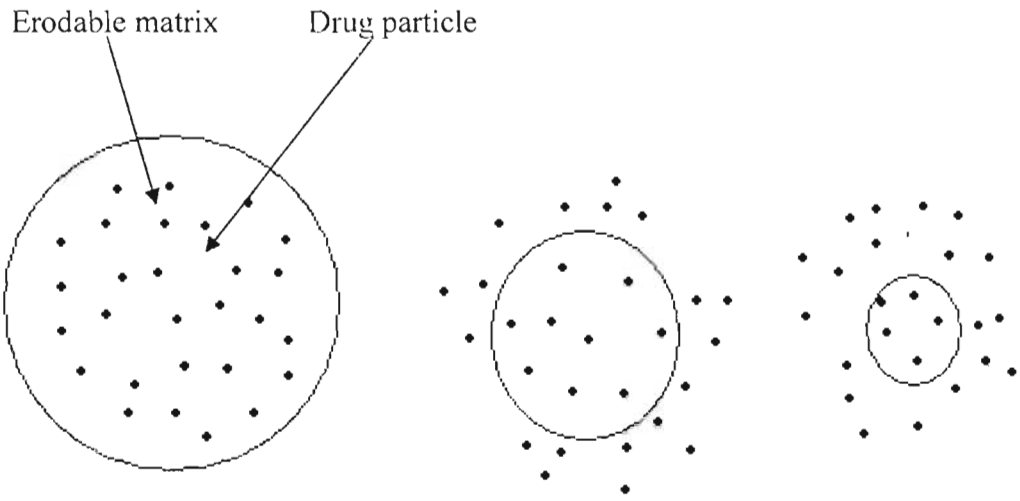


Figure 1.6 (b)- Drug release from the erosion tablet

The distance between these two fronts are called diffusion layer thickness. Diffusion layer thickness depends on the selective rate at which the swelling and eroding fronts move in relation to each other. If the polymer gets slowly, solvent can penetrate deep into the glassy matrix dissolving the drug; there form gel layer thickness and it stability are council in controlling drug release.

Swelling of HPMC matrix tablet was higher for higher a molecular weight. They attributed this to the large hydrodynamic volume occupied by higher molecular weight chain when hydrated. As the polymer chain becomes more hydrated and the gel becomes more dilute, the disentanglement concentration may be reached that is, the critical polymer concentration below which the polymer chain disentangle and detached from gelled matrix.

1.7.Advantages of sustained release dosage forms:

1. Patient Compliance:

Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patient to comply with the regimen. Patient compliance is affected by a combination of several factors, like-

-awareness of disease process,

-patient faith in therapy,

-his understanding of the need to adhere to a strict treatment schedule.

Also the complexity of therapeutic regimens, the cost of therapy and magnitude of local or systemic side effect of the dosage form. The problem of lack of patient compliance can be resolved to some extent by administering controlled release drug delivery system.

2. Reduced total dose:

Controlled release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

3. Economy:

In comparison with conventional dosage forms the average cost of treatment over an extended period may be less. Economy also may results from a decrease in nursing time and hospitalization.

Also,

- Reduce blood level oscillation characteristic of multiple dosing of conventional dosage forms.

-Reduce amount of drug administration.

-Maximizing availability with a minimum dose.

-Control of drug absorption; high peak level peaks that may be observed after administration of high availability drug can be reduced.

-Safety margin of high potency drugs can be increased.

4. Improved therapy:

The dosage form provides uniform drug availability or blood levels unlike peak and valley pattern obtained by intermittent administration. The incidence and intensity of undesirab effects caused by excessively high peak drug concentration resulting from the administration of conventional dosage forms is reduced. It is seldom that a dose is missed because of non-compliance by the patient.

5. Improved efficiency in treatment:

Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A controlled release dosage forms leads to better management of the acute or chronic disease condition.

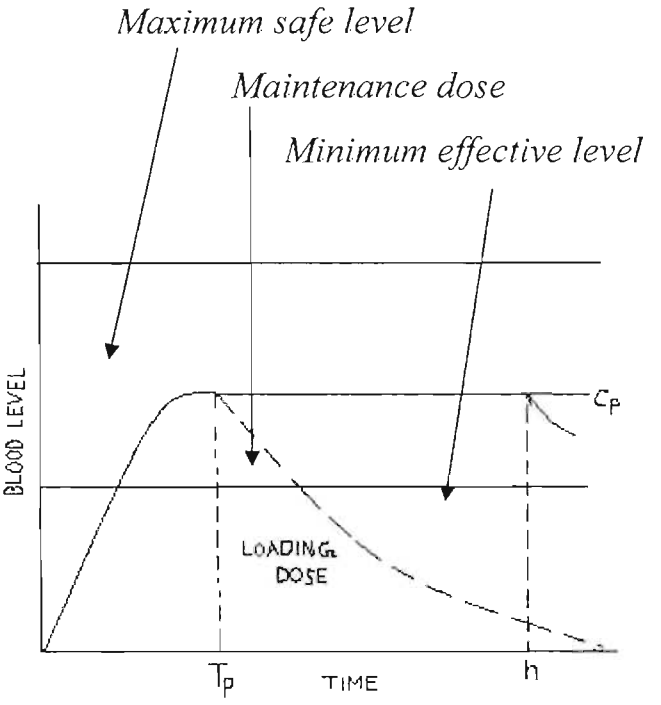


Figure 1.7 -A blood time profile for an ideal sustain release dosages form

6. Reduction in GI side effects:

SR delivery system reduces the incidence and severity of localized gastrointestinal side effects resulting from 'Dose dumping' of irritant drugs e.g., potassium chloride.

7. Reduction of systemic side effects:

This type of delivery system reduces the incidence and severity of untoward systemic side effects related to high plasma peak concentration.

8. Improved maintenance of therapeutic plasma drug concentration:

Sustained released drug delivery system provides improved treatment of many chronic illnesses where symptom breakthrough occurs if the plasma concentration of drug drops below the minimum effective concentration. For example: Asthma, depressive illness.

9. No overnight dosing:

SR drug delivery system maintains the therapeutic action of a drug during overnight no dose periods. For example: overnight management of pain permits improved sleep to ill /elderly patient.

1.8.Disadvantages of sustained release dosage forms:

1. Dose dumping:

Dose dumping is a phenomenon where by relatively large quantities of drug in a controlled release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index.

2.Local irritation to GI mucosa:

SR product may become lodge at some site along the GI tract resulting in high concentration of the slow released drug causes local irritation.

3. Patient variation:

The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

4. Local irritation to GI mucosa:

SR product may become lodge at some site along the GI tract resulting in high concentration of the slow released drug causes local irritation.

5. Administration of large doses:

Since SR delivery mechanism comprising maintenances dose, the physical size of the SR dosage form will provide the difficulty in swallowing.

6. Delayed termination of therapy:

SR dosage form administration does not permit the prompt termination of the therapy. Sometimes immediate changes in therapy is required if significant adverse effects are noted.

7. Less flexibility of physicians:

Physician faces problem in adjusting dosage regimens.

8. Influences of physiological factor:

Physiological factors like: gastrointestinal pH, enzyme activities, gastric & intestinal transit rates, food, and severity of any diseases often influences bioavailability. Also interferes with the precision of control of release.

Chapter 02

(POLYMER BASED DRUG DELIVERY SYSTEM)

2.1.Polymers in Pharmaceutical Technology:

Polymers are capable of providing sustained release of an encapsulated drug, within its therapeutic window. This leads to reduced peaks and valleys typically associated with immediate release dosage forms. Typically natural polymers or their derivatives (such as cellulose and methyl cellulose) as well as synthetic nondegradable polymers [such as poly (vinyl pyrrolidone) and polymethacrylates] are used for oral CR applications. (Chaubal, 2006)

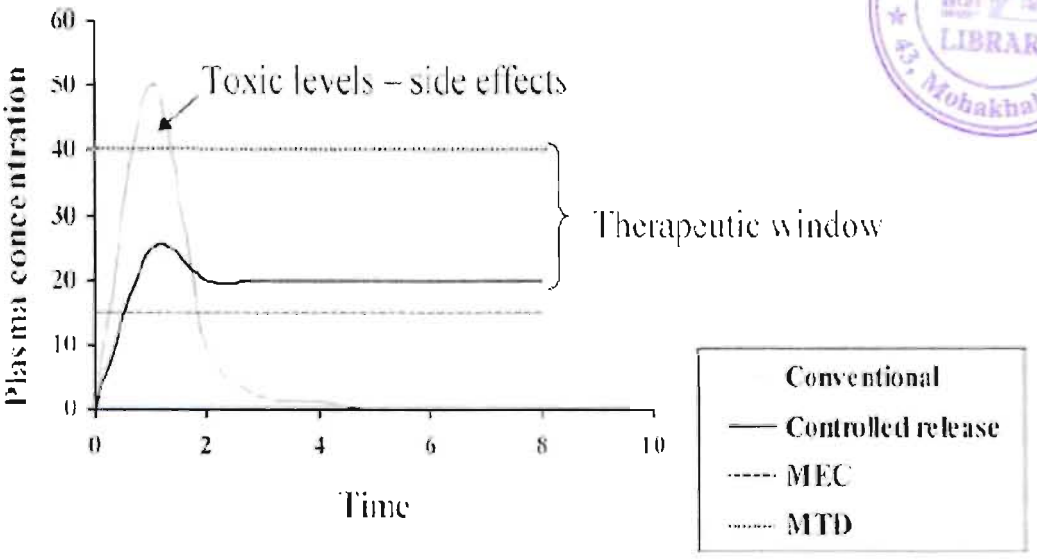


Figure 2.1: Comparison of typical pharmacokinetic profiles seen for conventional versus controlled release formulations
Abbreviations: MEC, minimum effective concentration; MTD, maximum tolerable dose.

The polymer must not only permit CR of the drug, but also be biocompatible and nontoxic. Several drug delivery applications also require the polymer to be biodegradable-degrading into by-products that are safe and can be cleared from the body.

2.2.Polymers in Controlled Drug Delivery:

The selection of polymers is done according to the following segmentations.(Table-2.2)

Table -2.2

Application	Products Recommended	Typical Use Level	Advantages
Controlled Release Matrix Tablets	METHOCEL K100LV, K4M, K15M, K100M, E4 M, E10M Premium (all available in Controlled Release, CR grade	20 – 55%**	METHOCEL K premium has the fastest hydration rate of the METHOCEL family and is often preferred
	POLYOX WSR-205 NF, WSR-1105 NF, WSR N-12K NF, WSR N-60K NF, WSR-301 NF, WSR-303 NF, WSR Coagulant NF	20 – 90%	Molecular weight can be selected to tailor release profile
Controlled Release Coatings	ETHOCEL Standard Premium 4, 7, 10	3 – 20%**	Insoluble in water; provides good diffusion control membrane. Mixing with METHOCEL Premium moderates diffusion
	ETHOCEL Premium blended with METHOCEL E5, E15 Premium	3 – 20%**	
Microencapsulation	ETHOCEL Standard 20, 45, 100 Premium	10 – 20%	Insoluble in water, can be coacervated (phase separated)

** Use levels may vary with dosage form, size, and desired release rate

2.2.1. METHOCEL™ Premium Direct Compression (DC) Grade Hypromellose Polymers have been developed to achieve the production economies of direct compression while assuring the multi-functional performance you expect from this time-proven excipient family. These polymers improve powder system flow ability while maintaining the excellent compressibility, tablet hardness, and controlled release performance for which METHOCEL™ products have long been known.

2.2.2. ETHOCEL* Premium ethyl cellulose resins are among a small number of water-insoluble polymers that are approved and accepted globally for pharmaceuticals. They are most frequently used in controlled release and solid dosage formulations. They are also useful as granulation binders, as film-formers to improve tablet integrity and appearance, and in taste masking of actives.

2.2.3. POLYOXTM Water-Soluble Resins, NF Grade include a range of free-flowing poly (ethylene oxide) hydrophilic resins in a wide variety of molecular weight grades. They offer a long history of successful use including controlled release solid dose matrix systems, tablet binding, and mucosal bioadhesives.

2.3.Selection of Polymer:

Methocel cellulose products are available in two basic types:

- Methyl cellulose (MC)
- **Hydroxypropyl methyl cellulose (HPMC)**

Both types of METHOCEL have the polymer backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units.

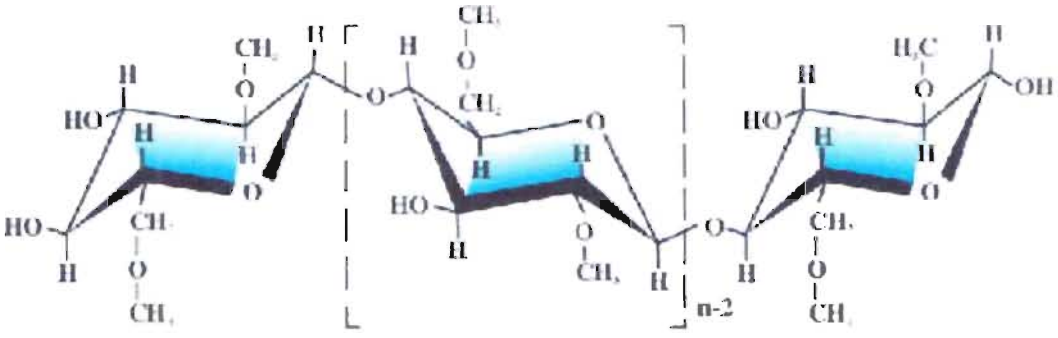


Figure 2.3 (a)- Methylcellulose - METHOCEL A Products

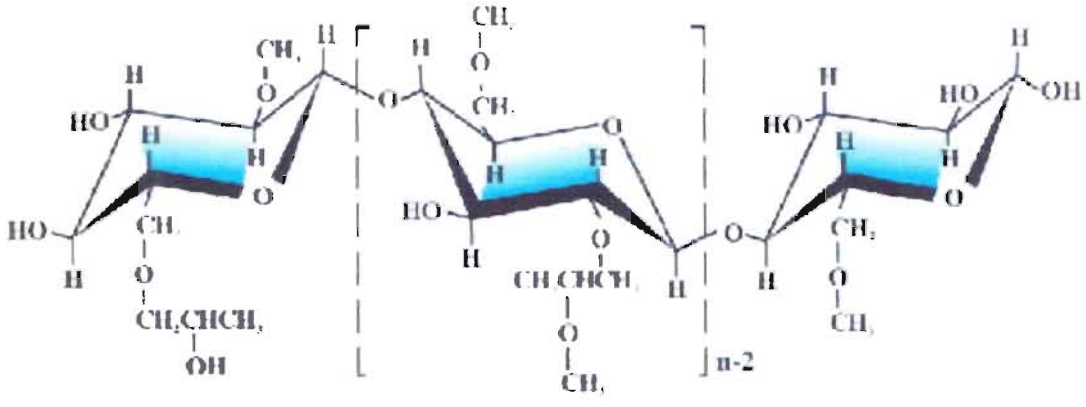


Figure 2.3(b)-Hydroxypropyl Methylcellulose - METHOCEL E, F, K, and 40-Series products

Methylcellulose is made only using methyl chloride. These are named as METHOCEL A products. For hypromellose products (Methocel E, F, K), propylene oxide is used in addition to methyl chloride to obtain htdroxypropyl substitution on the anhydroglucose units. (Figure-2.3(b)) The substitution pattern in methocel can as follows. (Table-2.3)

Table 2.3: Degree of substitution for methocel products

Product	methoxy degree of Substitution	Methoxyl %	Hydroxypropyl molar substitution	Hydroxypropyl %
Methocel A	1.8	30	-	-
Methocel E	1.9	29	0.23	8.5
Methocel F	1.8	28	0.13	5.0
Methocel K	1.4	22	0.21	8.1

2.4.Nomenclatures for Polymers (Methocel):

METHOCEL™ is a trademark of The Dow Chemical Company for a line of cellulose ether products. An initial letter identify as the type of cellulose ether, its "chemistry." "A" identify as methyl cellulose (MC) products. "E," "F," and "K" identify different Hypromellose products. METHOCEL™ E and METHOCEL™ K are the most widely used for controlled release drug formulations.

The number that follows the chemistry designation identifies the viscosity of that product in millipascal-seconds (mPa·s), measured at 2% concentration in water at 20°C. In designating viscosity, the letter "C" is frequently used to represent a multiplier of 100, and the letter "M" is used to represent a multiplier of 1000.

Several different suffixes are also used to identify special products. "LV" refers to special low-viscosity products, "CR" denotes a controlled-release grade, and "LH" refers to a product with low hydroxypropyl content. "EP" denotes a product that also meets European Pharmacopoeia requirements; "JP" grade products also meet Japanese Pharmacopoeia requirements.

To understand the nomenclature for Methocel polymer the following pictorial presentation could be helpful. (Figure-2.4).

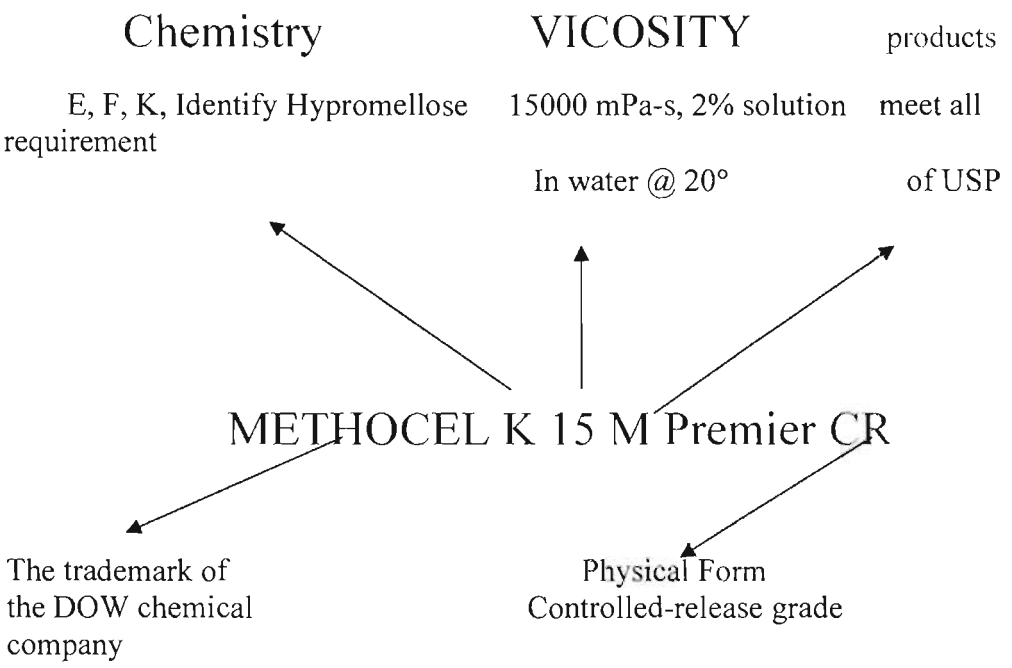


Figure 2.4: Nomenclature for a methocel K15M CR

2.5.Hydrophilic Matrix Device:

Hydrophilic matrix systems are among the most widely used means of providing controlled release in solid oral dosages forms. Diclofenac is a hydrophilic matrix system tablet. This hydrophilic matrix system is widely use, for all control release in solid oral dosage form. Polymers are use widely in pharmaceutical system as the basis of drug delivery system. Only methocel premium product can be use in the controlled release formulation of hydrophilic matrix system as the controlled release agent.

A hydrophilic matrix, controlled-release system is a dynamic one involving polymer wetting, polymer hydration, gel formation, swelling, and polymer dissolution. At the same time, other soluble excipient or drugs will also wet, dissolve, and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away.

The mechanisms which drug controls release in matrix tablets are dependent on many variables. The main principle is that the water-soluble polymer, present throughout the tablet, hydrates on the outer tablet surface to form a gel layer (Figure-2.5). Throughout the life of the ingested tablet, the rate of drug release is determined by diffusion (if soluble) through the gel and by the rate of tablet erosion.

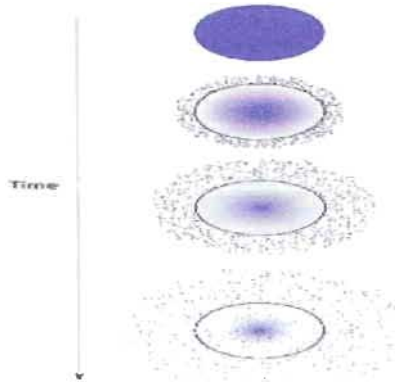


Figure 2.5: Drug delivery from a typical matrix drug delivery system.

2.6.Polymer property:

Different type of products are used in controlled release, METHOCEL products have different polymer grades, such as: METHOCEL K100 Premium LV, K4 M Premium, K15 M Premium, K100 M Premium and E10 M Premium CR. All of these products are available in controlled release (CR) grades which are specially produced, ultra fine particle materials. Only METHOCEL premium product can be use in controlled release formulation. The product description of METHOCEL premium product has given below.

Table 2.6(a)- The product description of METHOCEL premium products-

Physical form	Off- white powder
Particle size Premium grades	 99%<40 mesh screen K series , min 90%<100 mesh screen
Packaging	50-lb, multiwall paper bags 25-kg and 50-kg fiber drums
Shelf life:	Bags:3 years Drums:5years.

In this experiment METHOCEL K100 Premium LV and METHOCEL E10 Premium CR was used. Characteristically they are much closer to each other. There pH range is around 5.5-8. Percentage of methoxyl in METHOCEL-K100 premium LV is 19%-24% and in METHOCEL-E10 premium CR is 28%-30%. The amount of hydroxypropoxyl in METHOCEL-K100 premium LV and in METHOCEL-E10 premium CR is7%-12%. So the properties of these two HPMC has given below which has used in this experiment.

Table 2.6(b)-The properties of METHOCEL K100 Premium LV and METHOCEL E10 Premium CR polymer

METHOCEL Premium product grade		K100 Premium LV	E10 Premium CR
Methoxyl,%	USP	19-24	28-30
Hydroxypropyl,%	USP	7-12	7-12
USP substation type	USP/EP	2208	2910
Chlorides, max %	EP	0.5	0.5
Apparent viscosity, 2% in water at 20 C ,cp	USP	80-120	7500-14000
Apparent viscosity, 2% in water at 20 C , mPas	EP	78-117	4646-7070 [5673 Nom]
ID test A,B,C	USP	Pass	Pass
ID test A,B,C,D,E,F	EP	Pass	Pass
Opalescence of solution	EP	Pass	Pass
Solution color, yellowness, 1% in water	EP	Pass	Pass
pH, 1% in water	EP	5.5-8.0	5.5-8.0
Loss on drying, max,%	USP/EP	5.0	5.0
Organic impurities, volatile	USP	Pass	Pass
Residue in ignition, max,%.	USP	1.5	1.5
Ash, sulfated, max,%	EP	1.0	1.0
Heavy metals, as Pb, max, ppm	USP/EP	10	10

2.7.Selection of METHOCEL polymer:

For the selection of the METHOCEL or hydroxy propyl methyl cellulose few factors have to take under consideration. They are-

1. Type of the HPMC polymer:

In controlled release formulation the two polymer grade of METHECEL are widely use, they are-K(HPMC 2208 USP) and E(HPMC 2910 USP).

A fast rate of hydration followed by quick gelation and polymer/polymer coalescing is nacessary for a rate controlling polymer to form a protective gelatinious layer around the matrix. Thus prevent the tablet from immediatly disintegrating, resulting in premature drug release.Fast polymer hydration and gel layer formation are particularly critical when formulating with water soluble drug and water soluble excipience.

The hydration rates of the various grades of METHOCEL product differ because of varying proportion of the two chemical substituents, hydroxylpropoxyl and methoxyl substitution, attach to the cellulose backbone of HPMC. The hydroxylpropoxyl substitution is relatively hydrophilicin nature and greately contributes to the rate of hydration of METHOCEL.The methoxyl substitution is relatively hydrophobic in nature and dose not contribute significantly to the rate of hydration of METHOCEL.

2. Polymer level:

There must be sufficient amount of polymer present in a matrix to form a uniform barrier which protects the drug from immediately releaseing into the dissolution medium.The hydrophilic matrix tablets containing HPMC absorb water and swell, the polymer level in the outermost hydrated layers decreased with time.

It is important to note that polymer level in a formulation may not always affect drug release in the same way because of potential drug/excipient/polymer inter action. Most studies indicate that higher polymer levels result in slower release rates.

The effect of slower release for higher polymer levels is due to the longer period of time required disentanglement concentration at the tablet surface, which in turns equate to greater resistance to surface erosion.

3. Molecular weight and viscosity factor:

Water soluble polymer have an ability to increase the viscosity of solvent at low concentration. The rate of solution of the water soluble polymer depends on molecular weight. The larger the molecule, the stronger are the forces holding the chains together. The molecular weight in the HPMC polymer in a matrix tablet and the viscosity is important in determining the drug release properties. The difference in molecular weight in various METHOCEL product is reflected in the viscosity of an aqueous solution of a standard concentration. Viscosity of polymer solution is the result of hydration of polymer chains.

4. Particle size distribution and its flow property:

Fraction of HPMC polymers with smaller particle size containing matrix have more surface area which provide better polymer-water contact that leads the more effective formation of the protective gel barrier that slowed both water penetration into the tablet and drug release out of the matrix. As Diclofenac is water insoluble drug it is much easy to control its erosion. The interaction between the drug and HPMC that negatively impact polymer hydration are relatively rare.

Within the general scheme for categorizing the powders, METHOCEL premium products would be classed as "very fine". It is essential that the powder be quite fine for it to function as a rate controlling polymer and the METHOCEL cellulose ethers has the satisfactory flow property.

5. Effect of pH on viscosity:

METHOCEL products are non ionic. The viscosity of their solution is generally stable over a wider pH range than are the viscosities of polymers that are ionic in nature.

6. Solubility factor:

Higher solubility drugs release at faster rates in because their diffusional driving force would be highest. Also drug dose is an important issue, in that a high solubility drug at a dose higher than its solubility in the matrix can have an increased erosional release component because of a dissolution limitation.

Hydrophilic matrices have been proven useful in the formulation of drugs with a wide range of aqueous solubilities Formulation of very highly soluble drugs at very high dosage levels are the most difficult because of the extreme demands on polymerhydration and gelation.

CHAPTER 03

(MATERIALS AND METHODS)

3.1. Materials:

Drug: Diclofenac

Polymers: Methocel K15 MCR & Methocel 100 LVCR.

Other excipients: Lactose, Talc, Aerosil (colloidal silicon dioxide).

List of ingredients used in experiment:

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	Disintegrant
Aerosil (colloidal silicon di oxide)	Filler
Talc	Lubricant

Equipments: Shimadzu UV Spectrophotometer (Shimadzu, Model UV-160A, Tokyo, Japan), electronic balance (Denver Instrument Company-USA), Thickness gauge (Campbell Electronics, India), Monsanto hardness tester (Campbell Electronics, India), Roche friabilator (Campbell Electronics, India), funnel, graduated cylinder, Single punch tablet machine (PERKIN- ELMER Hydraulic press-UK), Dissolution machine.

Figure 3.1 (a): Weighing Machine & Fribilator used

Figure 3.1 (b): Single Punch Tablet Machine

Figure 3.1 (c): Digital-Tablet-Friability-Test-Apparatus

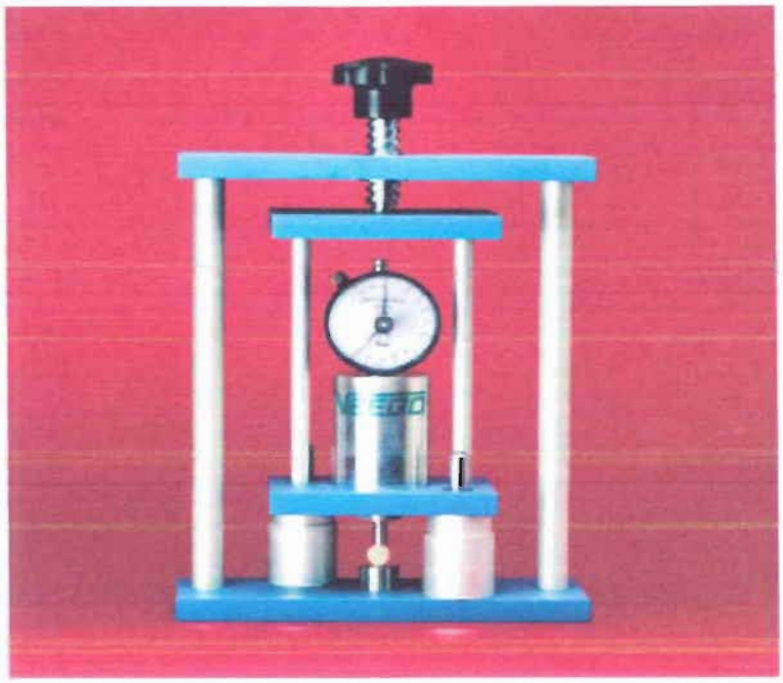


Figure 3.1 (d): Tablet-Hardness-Tester

Figure 3.1 (e): Tablet-Dissolution-Test-Apparatus

3.1.1.Diclofenac the API:

Diclofenac sodium is a benzene-acetic acid derivative. It is available as delayed-release tablets for oral administration. The chemical name is 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt. The molecular weight is 318.14. Its molecular formula is $C_{14}H_{10}Cl_2NNaO_2$, and it has the following structural formula.

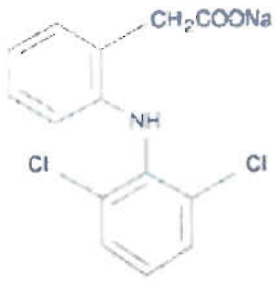
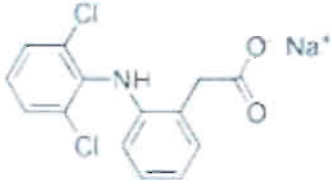


Figure 3.1.1: Chemical structure of diclofenac

The inactive ingredients in Diclofenac sodium include: hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, povidone, propylene glycol, sodium hydroxide, sodium starch glycolate, talc, titanium dioxide.

Molecular structure:



Melting point: 288-290°C

solubility: H_2O: 50 mg/mL

Appearance: white off white crystalline powder.

Usage: Allay a fever, easing pain. Applicable to fever caused by rheumatoid arthritis, osteoarthrosis and operation pain etc.

Storage: Store at room temperature below 86 degrees F (30 degrees C) away from light and moisture. Do not store in the bathroom. Keep all medicines away from children.

3.1.2.Mechanism of action:

The exact mechanism of action is not entirely known, but it is thought that the primary mechanism responsible for its anti-inflammatory, antipyretic, and analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX) and it appears to inhibit DNA synthesis.

Inhibition of COX also decreases prostaglandins in the epithelium of the stomach, making it more sensitive to corrosion by gastric acid. This is also the main side effect of diclofenac. Diclofenac has a low to moderate preference to block the COX2-isoenzyme (approximately 10-fold) and is said to have therefore a somewhat lower incidence of gastrointestinal complaints than noted with indomethacin and aspirin.

The action of one single dose is much longer (6 to 8 hours) than the very short half-life that the drug indicates. This could partly be due to a particular high concentration achieved in synovial fluids.

Diclofenac may also be a unique member of the NSAIDs. There is some evidence that diclofenac inhibits the lipoxygenase pathways, thus reducing formation of the leukotrienes (also pro-inflammatory autacoids). There is also speculation that diclofenac may inhibit phospholipase A_2 as part of its mechanism of action. These additional actions may explain the high potency of diclofenac – it is the most potent NSAID on a broad basis.

Besides the well-known and often cited COX-inhibition, a number of other molecular targets of diclofenac have recently been identified which could contribute to its pain-relieving actions. These include:

Blockade of voltage-dependent sodium channels (after activation of the channel, diclofenac inhibits its reactivation also known as phase inhibition) Blockade of acid-sensing ion channels (ASICs) Positive allosteric modulation of KCNQ- and BK-potassium channels (diclofenac opens these channels, leading to hyperpolarization of the cell membrane).

3.1.3.CLINICAL PHARMACOLOGY:

3.1.3.1.Pharmacodynamics:

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Diclofenac sodium, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

3.1.3.2.Pharmacokinetics:

Absorption:

Diclofenac is 100% absorbed after oral administration compared to IV administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. Food has no significant effect on the extent of diclofenac absorption. However, there is usually a delay in the onset of absorption of 1 to 4.5 hours and a reduction in peak plasma levels of < 20%.

Distribution:

The apparent volume of distribution (V/F) of diclofenac sodium is 1.4 L/kg.
Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Serum protein binding is constant over the concentration range (0.15-105 μg/mL) achieved with recommended doses.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism:

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'hydroxy-4'-methoxy diclofenac. In patients with renal dysfunction, peak concentrations of metabolites 4'-hydroxy- and 5-hydroxy-diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects. However, diclofenac metabolites undergo further glucuronidation and sulfation followed by biliary excretion.One diclofenac metabolite 4'-hydroxy- diclofenac has very weak pharmacologic activity.

Excretion:

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac, dosing adjustment in patients with mild to moderate renal dysfunction is not necessary. The terminal half-life of unchanged diclofenac is approximately 2 hours.

3.1.4.INDICATIONS:

Diclofenac Sodium is indicated:

For relief of the signs and symptoms of osteoarthritis

For relief of the signs and symptoms of rheumatoid arthritis

For acute or long-term use in the relief of signs and symptoms of ankylosing spondylitis

3.1.5.DRUG INTERACTIONS:

Aspirin:

When Diclofenac sodium is administered with aspirin, its protein binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

Methotrexate:

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Cyclosporine:

Diclofenac sodium, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with Diclofenac sodium may increase cyclosporine's nephrotoxicity. Caution should be used when Diclofenac sodium is administered concomitantly with cyclosporine.

ACE Inhibitors:

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Furosemide:

Clinical studies, as well as postmarketing observations, have shown that Diclofenac sodium can reduce the natriuretic effect of furosemide and thiazides in some patients.

This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure,as well as to assure diuretic efficacy.

Lithium:

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Warfarin:

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

3.1.6.DOSAGE AND ADMINISTRATION:

Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

After observing the response to initial therapy with Diclofenac Sodium, the dose and frequency should be adjusted to suit an individual patient's needs.

For the relief of osteoarthritis, the recommended dosage is 100-150 mg/day in divided doses (50 mg b.i.d. or t.i.d., or 75 mg b.i.d.).

For the relief of rheumatoid arthritis, the recommended dosage is 150-200 mg/day in divided doses (50 mg t.i.d. or q.i.d., or 75 mg b.i.d.).

For the relief of ankylosing spondylitis, the recommended dosage is 100-125 mg/day, administered as 25 mg q.i.d., with an extra 25-mg dose at bedtime if necessary.

Different formulations of diclofenac sodium enteric-coated tablets; diclofenac sodium extended-release tablets; diclofenac potassium immediate-release tablets are not necessarily bioequivalent even if the milligram strength is the same.

3.2.Excipient profile:

3.2.1.Methocel: Discussed at chapter 2.

3.2.2.Aerosil (Colloidal silicon dioxide):

Aerosil is pure silicon dioxide, made from vaporized silicon tetrachloride oxidized in high-temperature flame with hydrogen and oxygen. Aggregated amorphous nano-sized primary particles gives free flow to powder materials. It gives suspending and thickening effect and thixotropy by dispersing to liquid materials. It also work as free-flowing agent, glidant, tablet disintegrants and anticaking agent. It is insoluble in organic solvents, water and acids, except hydrofluric acid. Standard hydrophilic products are made of primary particles from 7 nm to 40 nm, and also these products are surface modified to hydrophobic. Molecular weight is 60.08 g /mole. Aerosil is bluish-white colored, odorless, tasteless, amorphous powder and the pH is3.5-4.4, bulk density is 0. 029-0.042g/cc, tapped density is 0.05-0.1; the flow ability is 35.52%. The synonyms of Aerosil are Colloidal silicon di oxide, Cab-O-Sil, fumed silica, silicic anhydride etc.

Aerosil 200 is a colloidal silicon dioxide manufactured in a patented, vacuum-based densification process that increases the tapped density by nearly 140% to 120 g/L from 50-60g/L while reducing dusting during processing and handling. By packing the high performance excipients into half of the space, the densified fumed silica Aerosil 200 delivers powerful, tangible cost savings in freight, packaging, handling and storage.

Aerosil 200 is a pharmaceutical excipient that delivers: free flow, anti-caking and Compaction properties for strengthening tablet and capsule formulations.(Handbook of Pharmaceutical Excipients)

3.2.3.Talc:

Talc is Hydrated Magnesium Silicate, it is a versatile material, also know as steatite or soapstone, hydrous magnesium-calcium silicate, purified French chalk, magnesium hydrogen metasilicate. Talc is a very fine, white to grayish- white colour. It is odorless and crystalline powder. Due to its softness, chemical inertness and adsorption properties it is widely used as anti-sticking, anti-caking, glidant, tablet &capsule lubricant and diluent. It is also use as a dissolution retardant in the development of controlled release products. The pH of talc is 7-10 and practically insoluble in dilute acids & alkalis, water & organic solvents. Melting point is 1500°c. Empirical formulae is $3MgO.4SiO_2H_2O$.

Amount uses:

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

(Handbook of Pharmaceutical Excipients)

ISO standard for quality (ISO 3262)

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

Figure 3.2.3: Talc

3.2.4.Lactose:

The molecular formula of lactose is $C_{12}H_{22}O_{11}$ molar mass is 342.30g/mol. Lactose is white solid molecule. It is Soluble in water and ethanol. The solubility of lactose in water is 18.9049 g at 25°C, 25.1484 g at 40°C and 37.2149 g at 60°C per 100 g solution. Its solubility in ethanol is 0.0111 g at 40°C and 0.0270 g at 60°C per 100 g solution.

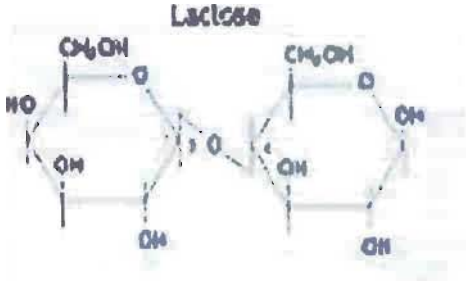


Figure 3.2.4 (a): Molecular structure of Lactose

The molecular structure of α-lactose, as determined by X-ray crystallography.

Lactose is a disaccharide that consists of galactose and glucose fragments bonded through a β-1→4 glycosidic linkage. Its systematic name is β-D-galactopyranosyl-(1→4)-D-glucose. The glucose fragment can be in either the α-pyranose form or the β-pyranose form, whereas the galactose fragment can only have the β-pyranose form: hence α-lactose and β-lactose refer to aromatic form of the glucopyranose ring alone. (Handbook of Pharmaceutical Excipients)

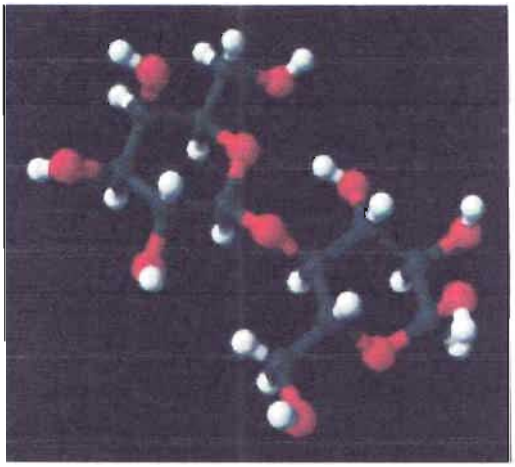


Figure 3.2.4 (b): Three dimensional structure of Lactose

3.3.Methods:

3.3.1.Tablet Granulation:

Granulation is the process in which primary powder particles are made to adhere to form larger, multi particle entities called granules. Pharmaceutical granules typically have a size range. Granules are used in the production of tablets or capsules.
Granulation is performed since it causes:

-Prevention of segregation of the constituent of powder mix,
-Improvement of the flow property of the mixture,
-Improvement of the compaction characteristics of the mixture.

3.3.1.2.Preparation of matrix tablet of Diclofenac:

The tablet was prepared by simple blending of active ingredient with polymers, tablet disintegrant, diluent, glidant (flow promoter) followed by direct compression (Table 3.3.1.2). Properly weighed Methocel, Talc, Aerosil, Lactose and the active ingredient were then taken into a beaker. A glass rod was rotated unidirectional to avoid static charges. Mixing was performed for around 20 minutes to ensure thorough mixing and homogenization. All the prepared granules were stored in airtight containers at room

temperature for further study. Prior to compression, the granules were evaluated for several tests. After that 20 tablets were prepared for each proposed formulae by direct compression method.

Table 3.3.1.2: Mixing of the ingredients

Contents taken in order	Time of mixing
Drug + Methocel K 15MCR + Methocel 100LV CR	**5 – 7 minutes**
Added Lactose	**3 minutes**
Added Talc and Aerosil	**2 minutes**
To prepare mixing for one formulation	**Total time: 12 minute**

3.3.2.Physical evaluation of granules:

3.3.2.1.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.

3.3.2.2.Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index (Aulton ME, 1988):

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

% 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

3.3.2.3.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. (Cooper J and Gunn C, 1986)

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

Where,

h = Height of the powder cone.

r = Radius of the powder cone

The suitable range is given below:

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

3.3.2.4.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).

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

3.3.2.5.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

3.3.2.6.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.

Figure 3.3.2.6: Digital-Tablet-Friability-Test-Apparatus

3.3.2.7.Thickness:

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

3.3.2.8.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. Weight values were reported in milligrams. The standard deviation for upper and lower rang was calculated by the following process-

Upper % deviation = (Average weight of 20 tablets – Upper weight) x 100/Average weight of 20 tablets. And
Lower % deviation = (Average weight of 20 tablets – Lower weight) x 100/Average weight of 20 tablets

Official weight variation tests for tablets are given in the U.S.P. The USP 24/NF19 Supplement 1 indicate that each tablet "shall be not less than 90% and not more than 110% of the theoretically calculated weight for each unit." Diameter of the tablets.

It also followed the same process. All data for the diameter of different formulation were approximately same because all the time used the same die for the formulations. The diameter of the tablets were determined by using a slide calipers scale. 5 tablets from each batch were used and average values were calculated as calculated earlier for the measurement of thickness of the tablets.

3.3.2.9.Friability:

For each formulation, the hardness and friability of 5 tablets were determined by using the Roche friabilator machine. Tablets were weighted before and after testing and friability were expressed as a percentasge loss on pre-test tablet weight. Officially the friability range should be below from 1%.

3.3.2.10.Dissolution:

The transfer of molecules or ions from a solid state into solution is known as dissolution.

Solid drugs need to dissolve before they can be absorbed. The dissolution of drugs can be described by the Noyes-Whitney equation.

$dC/dt=DA(Cs-C)/h$

Where, dC/dt is the rate of dissolution of the drug particles,

D is the diffusion coefficient of the drug in solution in the gastrointestinal fluids,

A is the effective surface area of the drug particles in contact with the gastrointestinal fluids,

h is the thickness of the diffusion layer around each drug particle,

Cs is the saturation solubility of the drug in solution in the diffusion layer and

C is the concentration of the drug in the gastrointestinal fluids.

Dissolution-controlled extended-release systems can also be obtained by covering drug particles with a slowly dissolving coating. The release of the drug from such units occurs in two steps:

The liquid that surrounds the release unit dissolves the coating (rate-limiting dissolution step).

The solid drug is exposed to the liquid and subsequently dissolves. (Aulton)

Dissolution testing and interpretation can be continued through three stages if necessary. In stage 1(S_1), six tablets are tested and are acceptable if all of the tablets are not less than the monograph tolerance limit (Q) plus 5%. If the tablets fail S_1, an additional six tablets are tested (S_2). The tablets are acceptable if the average of the twelve tablets is greater than or equal to Q and no unit is less than Q minus 15%. If the tablets still fail the test, an additional 12 tablets are tested. The tablets are acceptable if the average of all 24 tablets is greater than or equal to Q and if not more than 2 tablets are less than Q minus 15%.

Industrial pharmacists routinely test their formulations for dissolution. Their results are plotted as concentration versus time. (Lachman)

3.3.3.Drug Release Kinetics:

The in vitro drug release kinetic data were tested with the following Mathematical Model.

3.3.3.1.Zero Order Equation:

The equation assumes that the cumulative amount of drug release vs time. The equation may be as follows -

$C=K_0t$ ----------(1)

Where, K_0 is the zero order rate constant expressed in unit concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

3.3.3.2.First order equation:

The release behavior of first equation expressed as log cumulative percentage of drug remaining vs time. The equation may as follows -

$LogC = LogC_0 - kt/2.303$ ----------(2)

Where, C is the amount of drug undissolved at t time, the C_0 is drug concentration at t=0, k corresponding release rate constant.

Chapter 04

(RESULTS AND DISCUSSIONS)

4.1.Result and Discussion:

The proposed formulations (F-1 to F-6) of Diclofenac Sodium SR tablet matrix were built by utilizing different percentages of Methocel K100 LV CR and Methocel K15M polymers. (table –4.1 (a))

Table 4.1 (a) 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- 4.1 (b))

Table 4.1 (b): 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
Hausner Ratio	0.96	0.88	0.88	0.77	2.25	1.53
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 4.1(b)**)

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-4.1(c))** and fulfilled the official requirement for both the granules and the finished product itself.

Table 4.1(c): 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 8th hours in simulated intestinal medium.

Table 4.1 (d): 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

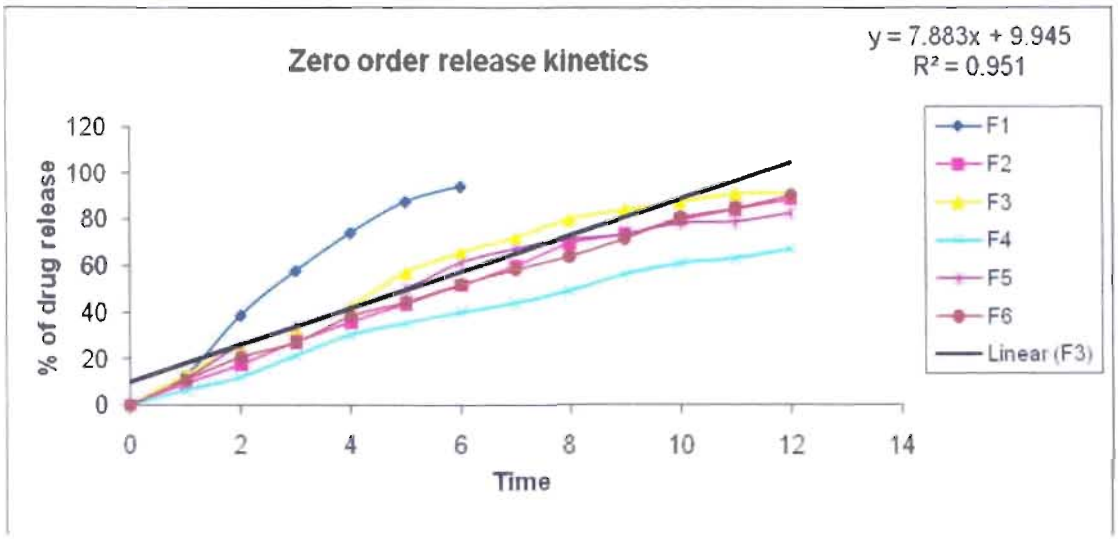


Figure 4.1 (a): Zero Order release Kinetics

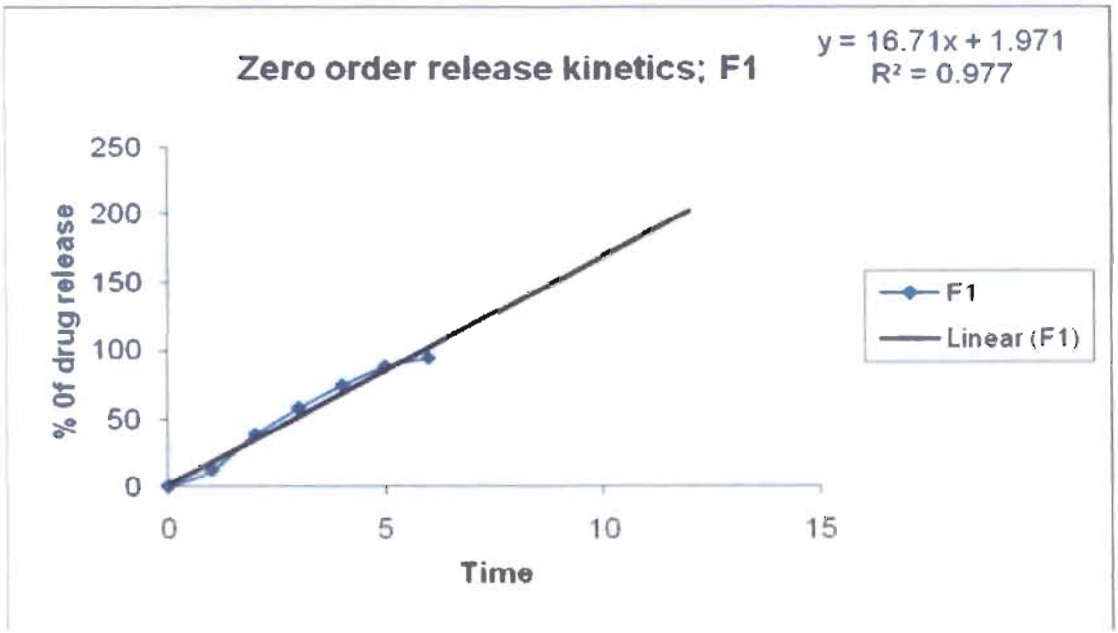


Figure 4.1 (b): Zero Order release Kinetics; F1

Figure 4.1 (c): Zero Order release Kinetics; F2

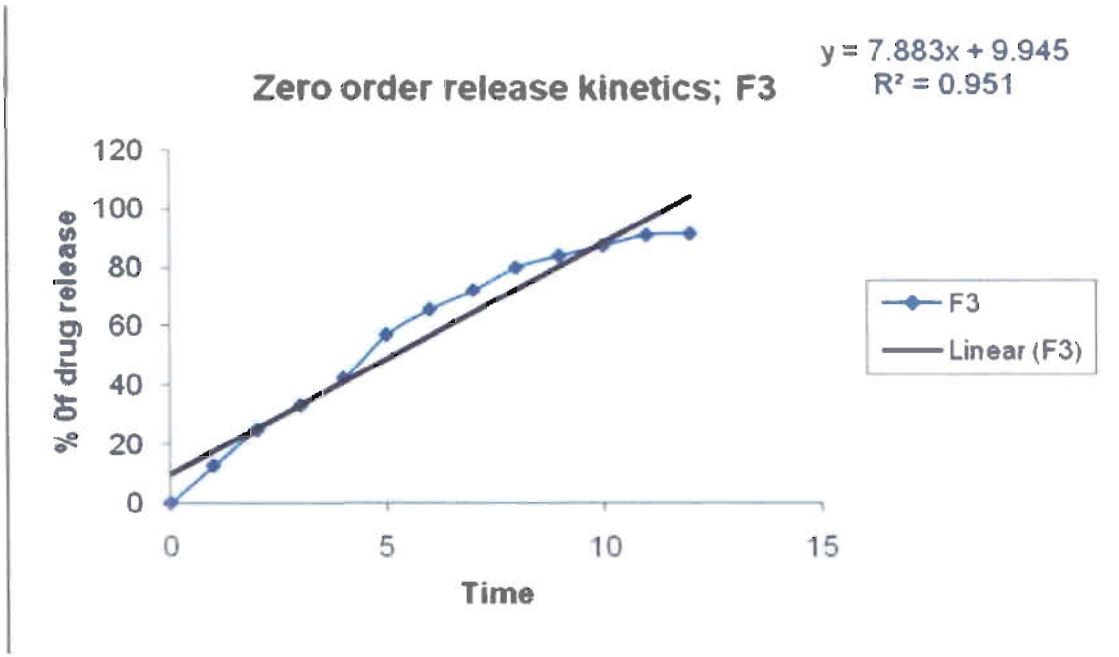


Figure 4.1 (d): Zero Order release Kinetics; F3

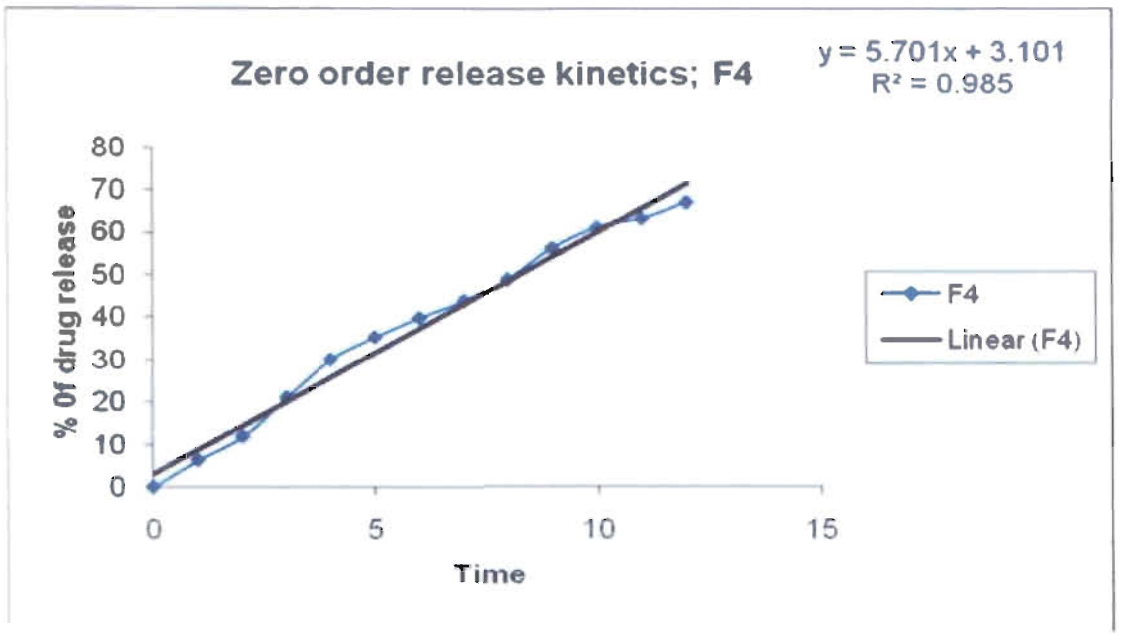


Figure 4.1 (e): Zero Order release Kinetics; F4

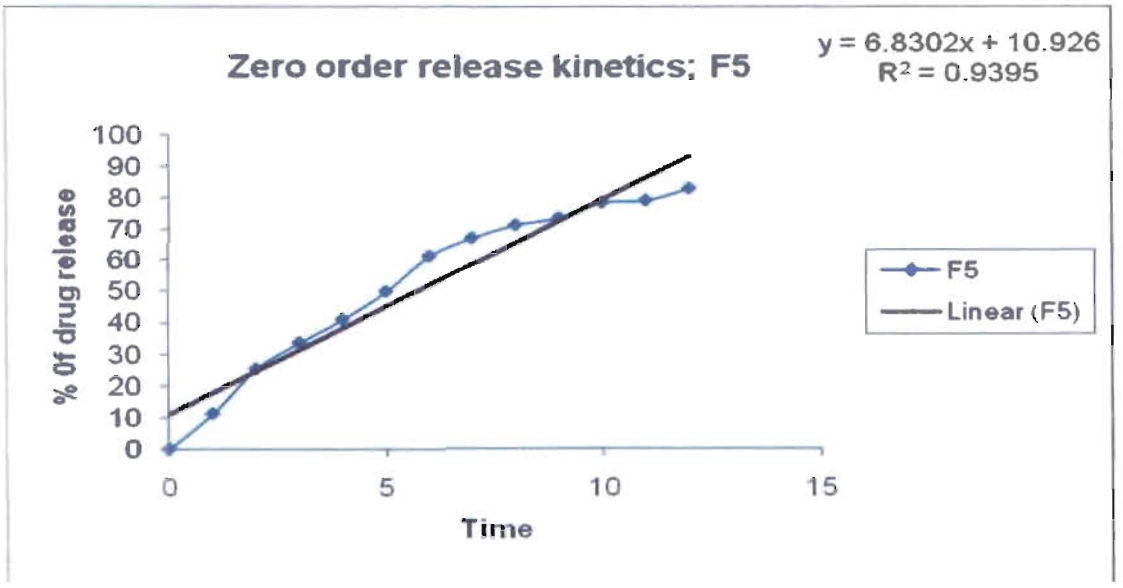


Figure 4.1 (f): Zero Order release Kinetics; F5

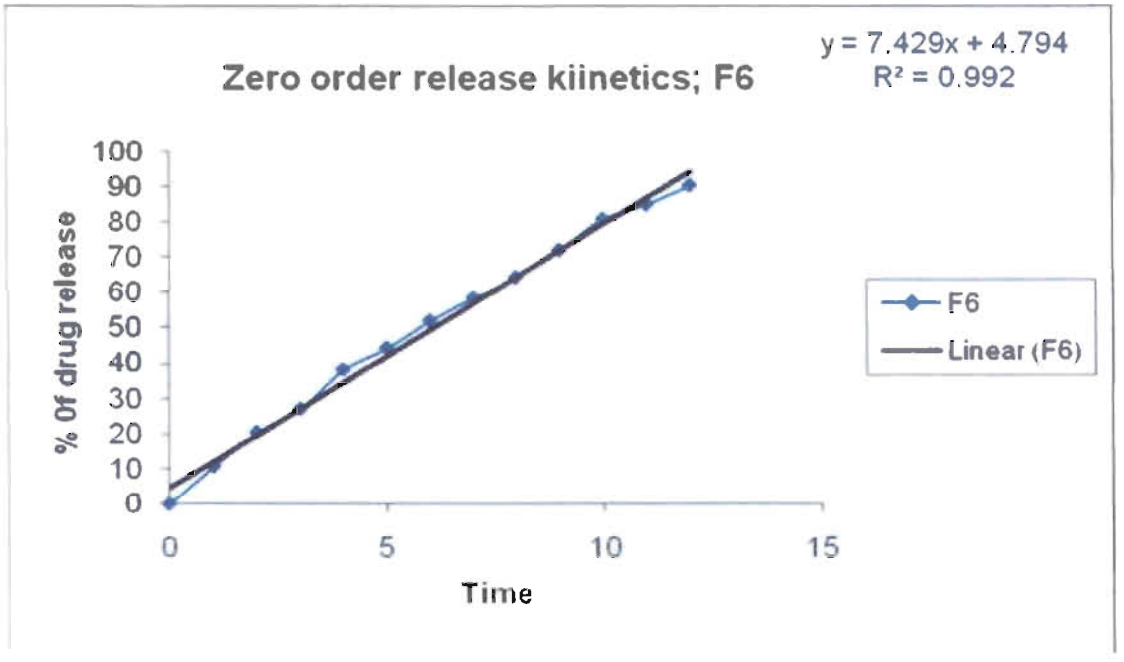


Figure 4.1 (g): Zero Order release Kinetics; F6

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 4.1 (e): 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

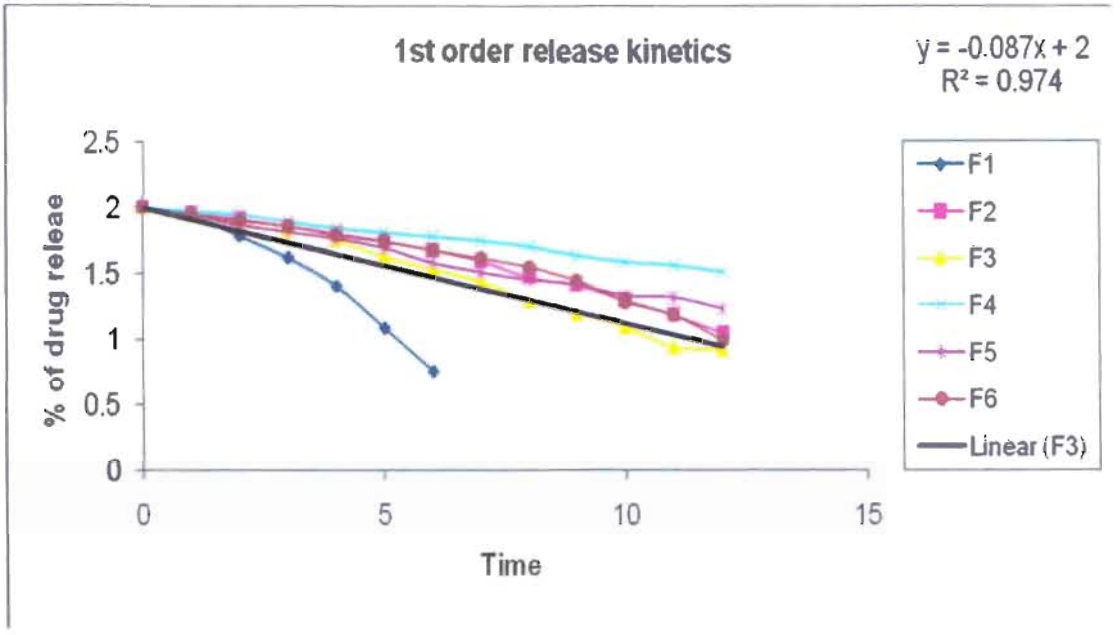


Figure 4.1 (h): First Order release Kinetics

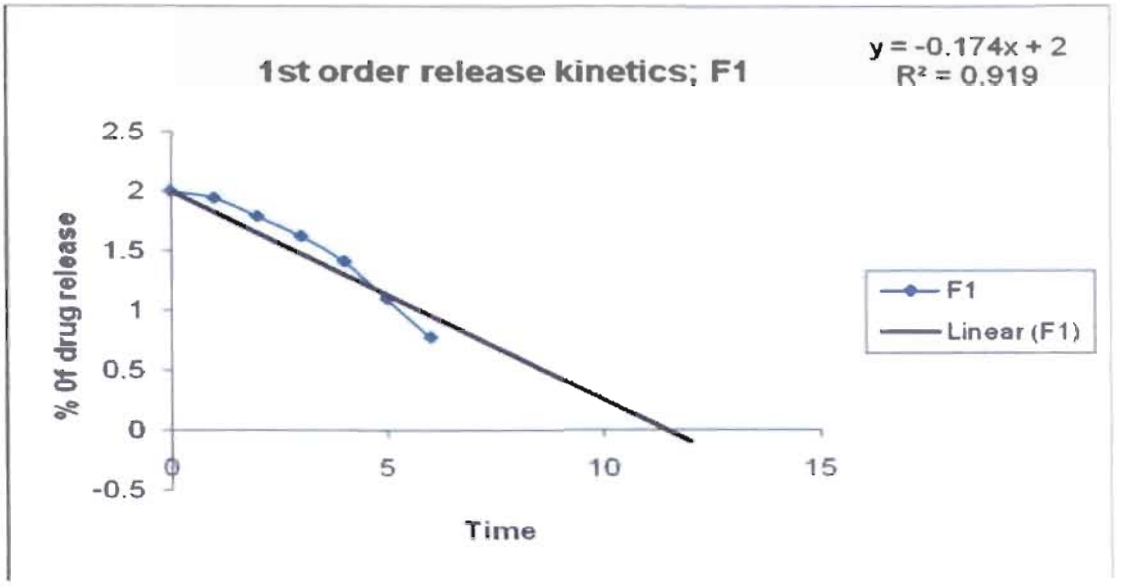


Figure 4.1 (i): First Order release Kinetics; F1

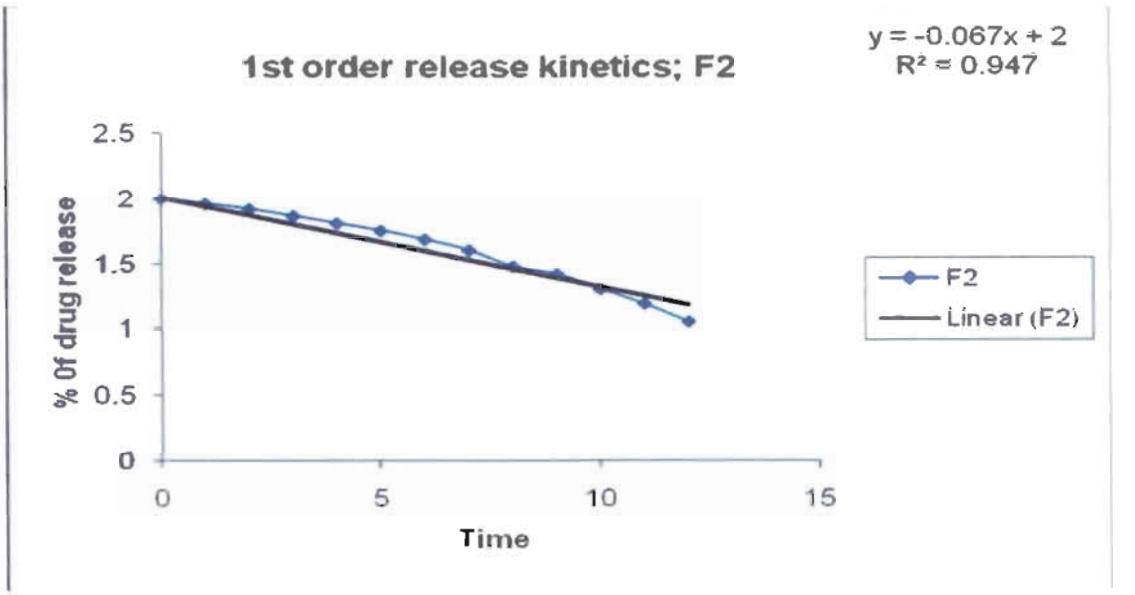


Figure 4.1 (j): First Order release Kinetics; F2

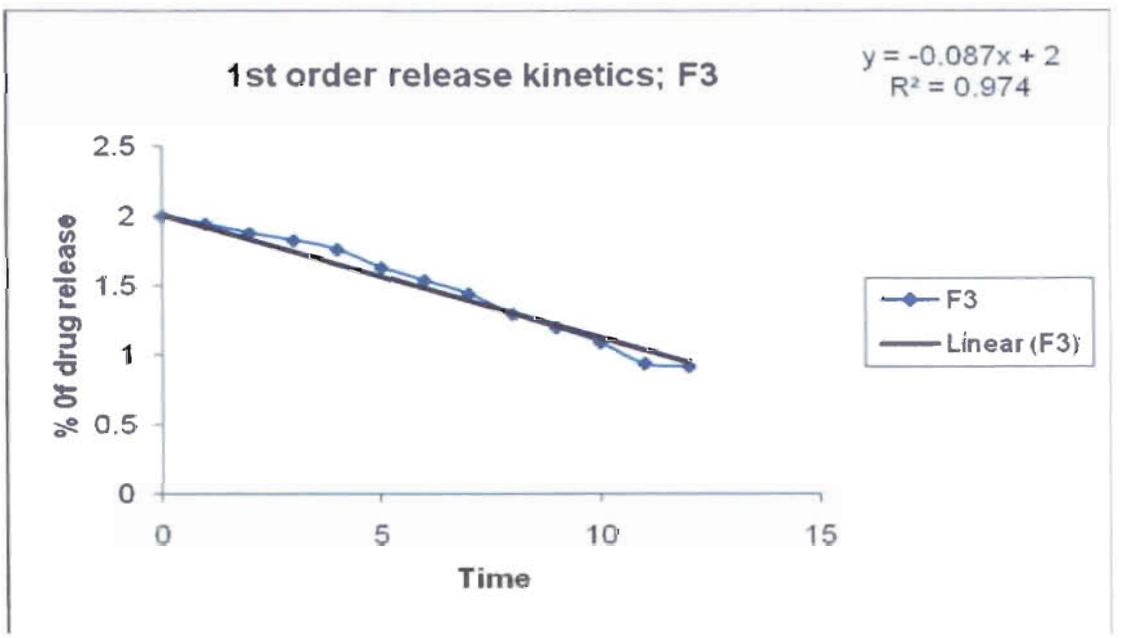


Figure 4.1 (k): First Order release Kinetics; F3

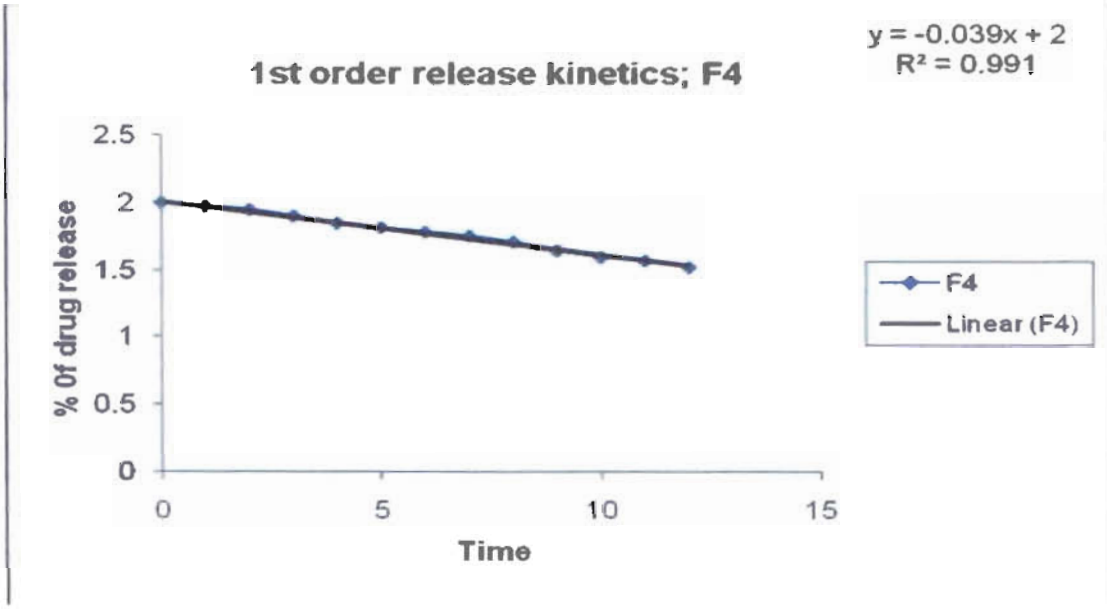


Figure 4.1 (l): First Order release Kinetics; F4

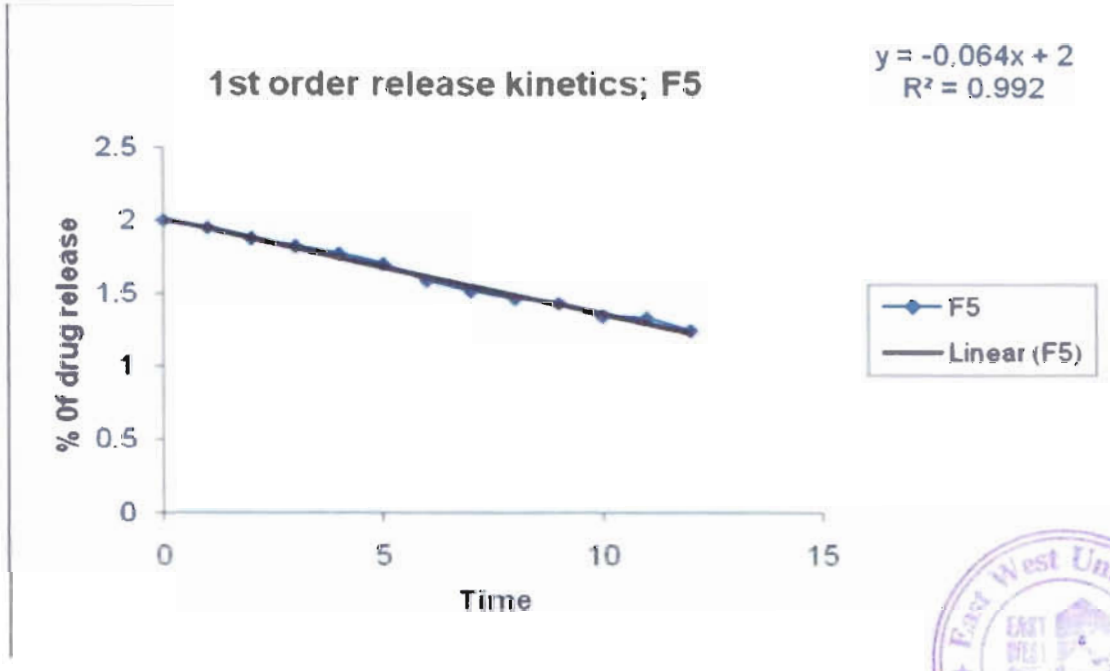


Figure 4.1 (m): First Order release Kinetics; F5

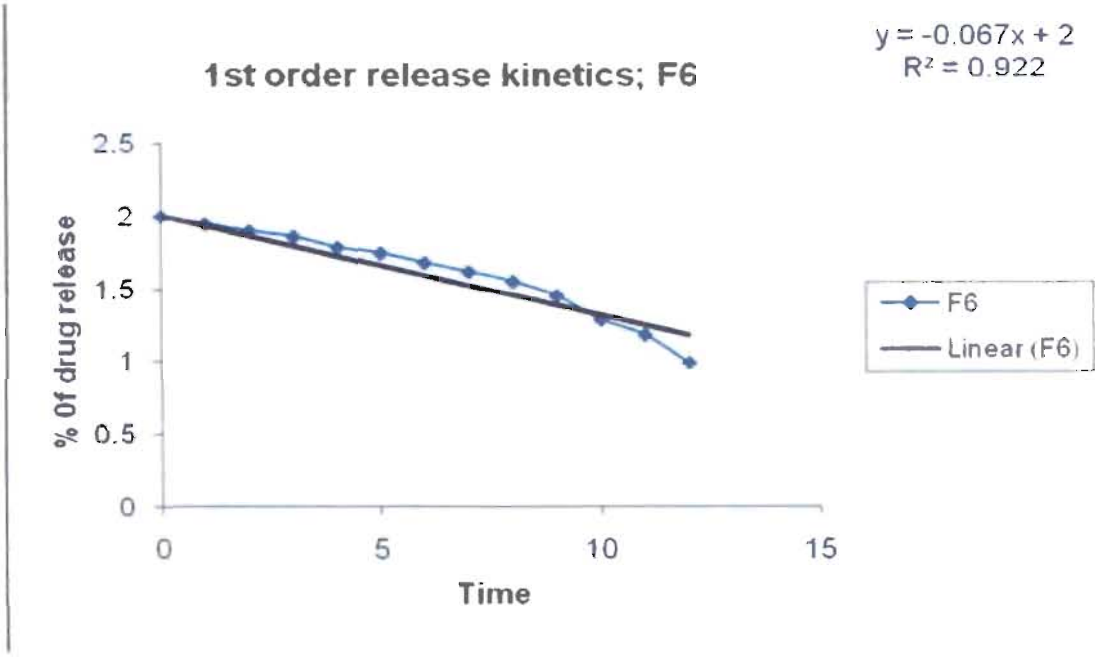


Figure 4.1 (n): First Order release Kinetics; F6

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.

Table4.1 (f): Drug release mechanisms (Multiple coefficient [r^2]) of different formulations

Formulation	Multiple Coefficient r^2	
	Zero order	First order
F-1	0.9772	0.919
F-2	0.9887	0.947
F-3	0.9514	0.9743
F-4	0.9851	0.991
F-5	0.9395	0.9929
F-6	0.9928	0.9228

Besides, the steady state drug release profile for prolong period from the polymers were dependent on symmetric drug-polymer-excipients interactions or cohesive forces developed during granule formation, compaction or compressive force and duration of interaction with the physiological fluid. These polymers can be acted properly with the physiological fluid if they can interact enough with the drug and the excipients used in the formulation at the time of granulation.

Conclusion:

In order to achieve patient compliance against pain relief, formulation of once daily diclofenac SR tablet matrix is essential for the management of acute and chronic pain, caused by rheumatoid arthritis, osteoarthritis and ankylosing sponndylitis etc. Hydrophilic polymer particles have unique quality to hold drug firmly through matrix formation while compressed into tablet. This matrix promotes desired controlled drug release upon hydration, swelling and gel formation with biological fluid.

In this study, the tablets were prepared for different weight by using different percentage of polymers to observe weather they comply with the official specification with different range of the polymers or they show any kind of deviation. Here mainly the physical evaluation had done for the granules and the compressed tablets. By observing all the data for different evaluation for powder granules (before compression) and tablets (after compression) it was seen that all the properties of the prepared formulation were in the acceptable pharmacotechnical properties range and were complied with pharmacopoeias specifications for tested parameters.

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Purpose of the study:

Diclofenac is a non-steroidal anti-inflammatory (NSAID) drug. Through its analgesic and anti-inflammatory properties, diclofenac provides symptomatic relief in a variety of painful conditions. Diclofenac is also effective in long-term management of osteoarthritis, Rheumatoid Arthritis (RA) and Ankylosing Spondylitis.preoaration of Diclofenac SR matrix tablet would be more compliant to the patient. A basic objective in this dosage form design is to optimize the delivery of medication so as to achieve a measure of control of therapeutic effect in the face of uncertain fluctuations in the in vivo environment in which drug release takes place. The other purpose of this work is to evaluate a new method of characterizing flow properties of dry blends of Methocel, Lactose, Talc and Aerosil and to determine if the method can be used to predict the performance of such blends in direct compression tablet manufacturing.