Development of Diclofenac 12H Sustained Release Tablets from Hydrophilic Polymers

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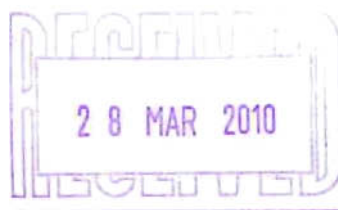
Fall 2009

Submitted by:

Mohamad Tanjib Hussain Chowdhury

ID: 2005-3-70-019

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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

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CERTIFICATION

The project report, entitled **"Development of Diclofenac 12H Sustained Release Tablets from Hydrophilic Polymers"**, submitted by Mohamad Tanjib Hussain Chowdhury, ID: 2005-3-70-019, 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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Table of Content

ABSTRACT

The objective of this study was to develop six formulations for a sustained release Diclofenac tablet 12 hour by direct compression method. In the designing of SR product the polymer played an immense role which regulated drug release for stipulated period. Various ratios of two different hydrophilic polymers (Methocel K15M Premium and Methocel K100 LV CR Premium) were incorporated. Drug content in the proposed formulations (F-1-F-6) were 47.61%, 47.61%, 43.63%, 43.63%, 43.63%, and 48% respectively and drug-polymer ratio has directly influenced steady state drug release from the matrix. Formulations (F-1, F-2, F-4 and F-5) did not fulfill the official drug release for 8 hours. Moreover F-3 and F-6 showed standard release *in vitro* than aforementioned formulations in buffer medium for 12 hours using USP reference dissolution apparatus. Physical criteria of formulations (F-1 – F-6) like loose bulk density (0.221±0.02 to 0.521±0.01), tapped bulk density (0.327±0.02 to 0.457±0.03), compressibility index (11.15±0.03 to 13.35±0.02), total porosity (26.19±0.04 to 34.56±0.01), angle of repose (21.53±0.01 to 29.36±0.01), hardness (3.19±0.01 to 4.35±0.03), friability (0.0 to 0.12±0.02), thickness (4.19±0.12 to 4.90±0.03) and weight variation test (1.132±0.02 to 2.903±0.23) were evaluated. The drug release profile was extrapolated by zero order release kinetics, first order release kinetics, Higuchi release kinetics and Hixson-Crowell release kinetics. This study gives idea on how the release pattern of granules and tablets altered upon the changing of polymer ratio.

Key words: Diclofenac, Sustained release, Methocel K15M Premium and Methocel K100 LV CR Premium, Direct compression, Dissolution study.

ACKNOWLEDGEMENTS

1

INTRODUCTION

Page: 1-4

anti-inflammatory drugs (NSAIDs), widely used for anti-inflammatory, and analgesic purposes, are one of the most frequently used kinds of medicines, for nearly 5% of all prescribed medications (Smalley et al, 1995). Their effects result mostly from the inhibition of cyclooxygenase (COX), an enzyme in the production of prostaglandins which have a strong propensity for inducing inflammation (Tomisato et al 2004). NSAIDs are a chemically heterogeneous group of compounds, often chemically unrelated, which nevertheless share certain therapeutic actions and adverse effects.

Route of Administration

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patience compliance, least sterility constraints and flexible design of dosage forms and control release is the most popular and modern dosage forms of this route (Nellore et al, 1998). The drug controlled delivery systems can be retained in the stomach and assist improved the oral sustained delivery of drugs that have absorption window(s) in particular region(s) of the gastrointestinal tract. The tablet matrix continuously releasing the drug before it reaches the absorption window(s), thus ensuring optimal bioavailability (Alderman, 1984).

1.3 Techniques for Oral Sustained Release Dosage Form

Oral sustained release dosage form by direct compression technique is a very simple approach of drug delivery systems that proved rational demand in the pharmaceutical arena as its ease, compliance, faster production, avoid hydrolytic or oxidative reactions 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 the drug or other active ingredients in such a way that the active agent is released from the material in a redesigned fashion and released the drug at constant rate for desired time period (Lordi et al, 1992).

The fluctuating drug concentrations in blood and tissues coursed by conventional dosages forms lead to insufficient influences on the mechanisms of disease and require the excessive

of a drug. All conventional dosage forms of drug administration except continuous intravenous perfusion do not release the drug at the constant rate. Earlier various oral dosage forms, able to control the rate of delivery of drug in the stomach have been prepared and studied. The main objective of controlled release drug delivery ensure safety and to improve efficacy of drugs as well as patient compliance. So they are designed to provide a therapeutic amount of drug on the specific site for absorption, and then to maintain the desired drug concentration (Longer, 1900).

1.4 Diclofenac

Diclofenac (2-[(2,6-dichlorophenyl)amino]benzene acetic acid, Fig. 1) is commonly prescribed as non-steroidal anti-inflammatory substance (NSAIS) that is taken to reduce inflammation, reducing pain in conditions such as acute injury, musculoskeletal, especially to treat rheumatoid arthritis, osteoarthritis, syondyarthritis, gout attacks, pain management in case of kidney stone. It is very effective in the management of menstrual pain, ovulatory pain, acute migraines, post-operative and post-traumatic pain, female breast cancer and pain associated with bony metastases (Goodman and Gilman's, 2001). Gastrointestinal disturbances are the major adverse effect associated with diclofenac therapy (Haider et al., 2001) and thus, for oral administration, the drug is usually formulated as coated tablets.
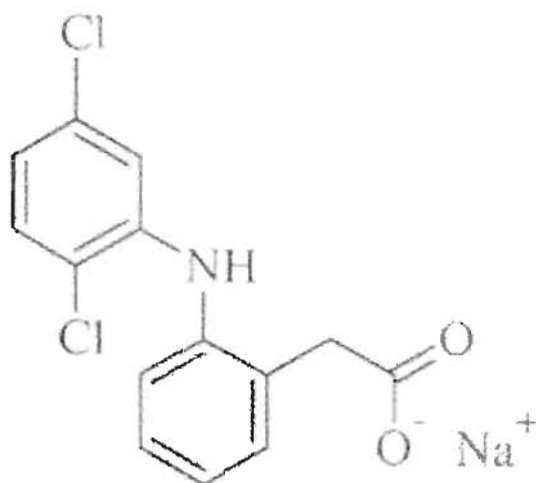
Fig 1 Structural formula of diclofenac

1.5 Diclofenac in Sustained Release Form

Diclofenac formulated for oral sustained releases dosage form, indicated an initial release of drug sufficient to provide a therapeutic dose soon after administration and then a gradual

release over an extended period. So this type of formulation exhibited quick on set of action and continued for prolonged period (Aulton, 1988).

There are number of techniques applied in the formulation as well as in the manufacturing of sustained release dosage form however the matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. Direct compression method has been applied for preparation of tablet matrix that involved simple blending of all ingredients used in the formulations and then under went direct compression. It required fewer unit operations, less machinery, reduced number of personnel and reduced processing time, increased product stability and faster production rate (Shangraw et al., 1989).

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 and are classified as plastic matrix systems. The second class represents hydrophobic and water-insoluble materials, which are potentially erodable and the third group behaves hydrophilic properties (Reza et al, 2003).

The use of controlled release drug product permits the introduction of larger doses with minimum frequencies which reduces chances of dose missing problems. It will also reduce the dose dumping phenomena and some other drug related adverse effects. At the same time administration of larger doses with fewer frequencies will reduce the treatment cost significantly. Moreover, polymer-drug matrix ensure desired drug concentration, effective pharmacological response by localization at the site of action or providing uniform drug delivery for a prolong period of time from the absorption site.

The aim of this work was to evaluate orally administered drug release efficiency of Methocel K15M and Methocel K100 LV CR polymers based formulations of diclofenac sodium sustained release tablet matrix for the better management of inflammation, pyretic and pain.

2

Concept
of
Sustained
Release
Dosage
Form

Concept of Sustained Release Dosage Form:

The term "controlled release" is used to describe 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. Various terms are used to identify drug delivery systems that show its action for longer period of time after administration of a single dose (Figure-2).Thus the commonly used terms are sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot, and repository dosage forms are terms used (Lachman, 1991)
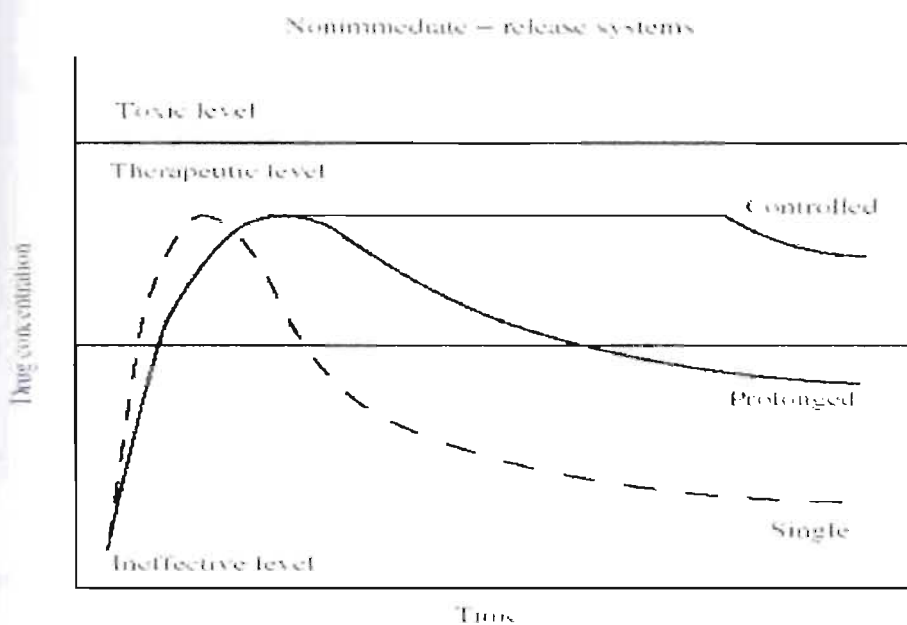
Fig.2. Plot of drug concentration versus time for different release systems.

The variety of dosage forms and dosage levels of particular drug enables 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)

Considerable efforts have been made in the development of new drug delivery systems in recent years. Therapeutic efficacy and safety of drugs administered by conventional methods can be improved by more precise and temporal placement of drug within the body, thereby

reducing both the size and number of doses. During recent years there has been intensive research have been made to provide sustained release formulations. An appropriate designed sustained release formulation with its desired therapeutic efficacy can overcome the problems of conventional dosage forms.

There are several methods present that can be adopted to control release of drugs (Florence, 1988). In the development studies of sustained release formulation, these techniques and approaches are proving their acceptability and feasibility. Among all the methods to design diclofenac SR formulation hydrophilic polymer has been used depending on the physicochemical nature of the active pharmaceutical ingredients (API). The release from hydrophilic matrices uses gelation or diffusion mechanism.

Oral sustained release dosage form by direct compression method is a very modern approach of drug delivery system that meets their demand in pharmaceutical arena in terms of compliancy, cost effectiveness, faster and ease of production rate etc. sustained release dosage formulation by direct compression method are presently gaining importance in order to achieve prolonged action without avoiding multiple dose intake which is commonly needed for maintaining the therapeutic action of the drug for a stipulated period. Depending on the market demand manufacturer is now very much eager in the production of sustained release dosage form.

In general the goal of sustained-release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero-order release from the dosage form. Zero-order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (i.e., a constant release rate). Sustained release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow zero-order fashion (i.e., concentration dependent). Thus systems that are designated as prolonged release can also be considered as attempts at achieving sustained release delivery.

NSAID's are amongst the most commonly prescribed medications in the world attesting to their efficacy as anti-inflammatory, anti-thrombotic, anti-pyretic, and analgesic agents. Thus it is our desire to formulate most effective NSAID (i.e., diclofenac) to increase patient compliance through a prolonged effect and reduce adverse effects as with Diclofenac.

2.2 History of Sustained Release Drug Delivery System:

From the limitation of using conventional dosage form pharmaceutical scientists led to consider therapeutically active molecules in 'extended release' preparations. The research on controlled drug delivery systems first centered on microencapsulation since 1949 with a patent by the Wurster process. This technique utilized a fludizing bed and drying drum to encapsulate fine solid particles suspended in midair. (Aulton, 2002)

Controlled-release technology evolved with matrix technology. Several articles in the 1950s and 1960s reported simple matrix tablets or monolithic granules. In 1952, Smith Kline & French introduced the Spansule, a timed-release formulation that launched a widespread search for other applications in the design of dosage forms (Helfand, 1983).

The goal behind the development of oral controlled-release formulations at that time was the achievement of a constant release rate of the entrapped drug. On the basis of that concept, the zero-order osmotic delivery system used in Procardia XL became one of the top 10 bestselling medicines in the past century.

From that point in time, the industry has seen a number of innovative oral controlled-release dosage forms patented at a rapid pace, but the main drawback of these technologies continues to be the lack of in vitro–in vivo correlation. Ideally, oral controlled-release systems are reliant upon the dosage form to control the rate of drug release with little or no effect from the intrinsic properties of the drug or the conditions prevailing within the gastro intestinal (GI) tract. Realistic drug candidates exhibit high permeability across the GI epithelium (Class I & II drugs according to the Biopharmaceutics Classification System) such that their absorption rate is controlled exclusively by the rate of release from the dosage form (Löbenberg, 2000).

It is only under these conditions that in vitro dissolution rates can possibly be used to predict in vivo absorption rates and guide formulation development.

After the invention of Smith Kline & French on 1952 many more sustained release products came to the market, some successful, others potentially lethal. (Aulton, 2002)

2.3 Rationale for Sustained Released Dosage Form:

In last 30 year several attempts have been made to market new drug entities of sustained or controlled release drug delivery systems. Because of the therapeutic advantages of controlled drug delivery system over conventional dosage forms, greater attention has been focused on development.

Peroral controlled release or sustained release products are designed to provide either the prompt achievement of a plasma concentration of drug that remains essentially constant at a value within the therapeutic range of the drug for a satisfactorily prolonged period of time or the prompt achievement of a plasma concentration of drug which, although not remaining constant, declines at such a slow rate that the plasma concentration remains within the therapeutic range for a satisfactorily prolonged period of time. 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).
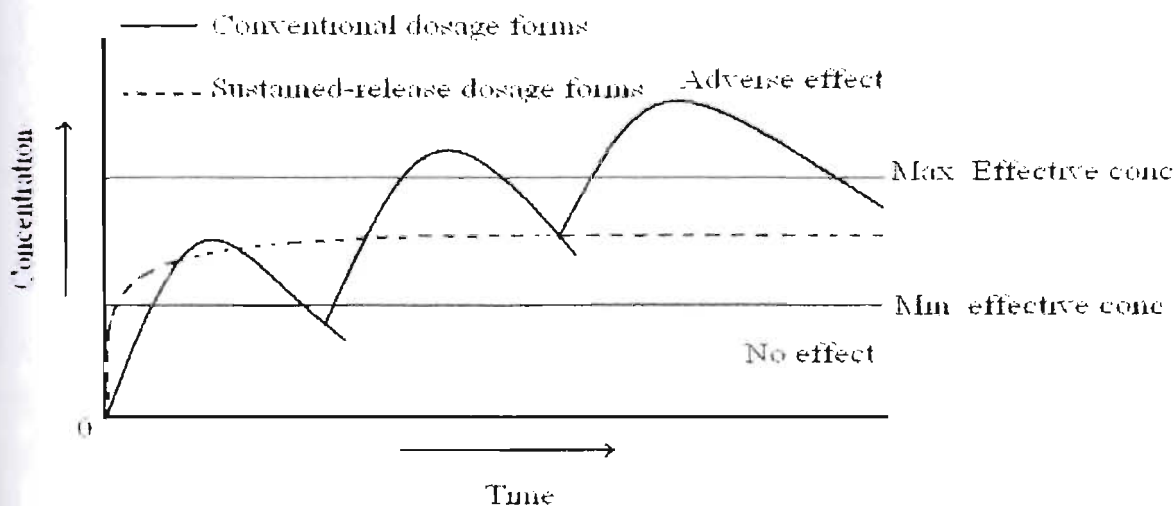
Fig 3 Adverse effects of conventional drug therapy

If we consider the route of drug administration, a conventional dosage forms (Fig3) of the drug. 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

9

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 that case oral sustained-release dosage forms have been used for improving therapeutic efficacy and patient compliance.

2.4 Advantages of Sustained Release Dosage Forms:

• 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.

• 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.

• 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.

• Reduction of dosing frequency: An improved patient compliance resulting from the reduction in the number and frequency of doses required to maintain the desired therapeutic response. For example: One peroral SR dosage form (diclofenac) every 12-hour contributes improved control of therapeutic drug concentration.

2.5 Disadvantages of Sustained Release Dosage Forms:

• Chances of dose dumping: SR dosage forms normally contain a large total amount of drug than the single dose in conventional dosage forms. There is the possibility of unsafe over dosage of an SR product if formulation and other manufacturing procedure are improperly made. As a result the total content of drug therein is released at once resulting in dose dumping.

• 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.

• 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.

• 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.

• Less flexibility of physicians: Physician faces problem in adjusting dosage regimens.

• 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.

• Undesired by product of degradation may take place.

• Using of more costly equipment and process may raise the product price.

3

Polymers in Pharmaceutical Technology

Page: 12-23

3.1 Polymers in Pharmaceutical Technology:

Polymers are used widely in pharmaceutical systems as adjuvants, suspending and emulsifying agents, flocculating agents, adhesives, packaging and coating materials, and increasingly as the basis of drug delivery systems.

Polymers are substances of high molecular weight made up of repeating monomer units. They owe their unique properties of size and often to their asymmetry. The chemical reactivity of polymers depends on the chemistry of their monomer units, but their properties depend to a large extent on the way the monomers are put together; it is this fact that leads to the versatility of synthetic polymers. The monomer units may be linier or branched, and separate linier or branched chains may be joints by cross-links. (Florence, 1988)

Early research into biodegradable systems focused on naturally occurring polymers (collagen, cellulose, etc.) but has recently moved into the area of chemical synthesis. Examples of such polymers include polyanhydrides, polyesters, polyacrylic acids, poly (methyl methacrylates), and polyurethanes. As a result of extensive experimentation with these materials, several key factors have emerged to help scientists design more highly degradable polymers. Specifically, a fast-degrading matrix consists of a hydrophilic, amorphous, low-molecular-weight polymer that contains heteroatoms (i.e., atoms other than carbon) in its backbone and is grown either stepwise or through condensation reactions. Therefore, varying each of these factors allows researchers to adjust the rate of matrix degradation and, subsequently, control the rate of drug delivery.

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.

3.2 History of Polymers:

The use of polymers in pharmaceutical preparation dates back to 3000 B.C., with references in ancient Indian medical text. The use of polymers for oral CR was reported in the modern era, in 1930s, with the use of shellac in aspirin tablets. However elevation of this technology to its current commercial status was catalyzed in the 1970s and 1980s, with a rising need for minimization of toxic side effects and for life cycle management of drugs. (Chaubal, 2006)

13

3.3 Polymers in Controlled Drug Delivery:

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may 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 maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance (Fig-4). While these advantages can be significant, the potential disadvantages cannot be ignored: the possible toxicity or nonbiocompatibility 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 Dow chemical company, 2009).
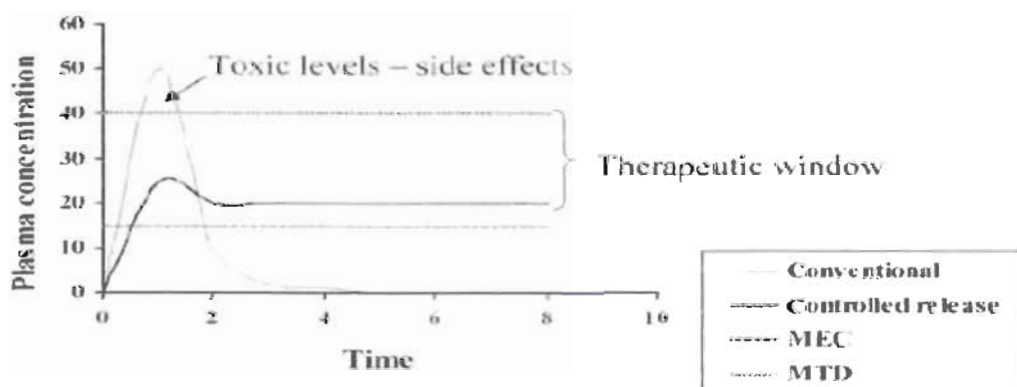
Fig-4: Comparison of typical pharmacokinetic profiles seen for conventional versus controlled release formulations. Abbreviations: MEC, minimum effective concentration; MTD, maximum tolerable dose.

Providing control over the drug delivery can be the most important factor at times when traditional oral or injectable drug formulations cannot be used. These include situations requiring the slow release of water-soluble drugs, the fast release of low-solubility drugs, drug delivery to specific sites, drug delivery using nanoparticulate systems, delivery of two or more agents with the same formulation, and systems based on carriers that can dissolve or degrade and be readily eliminated. The ideal drug delivery system should be inert,

14

biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize.

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.

3.4 Controlled-Release Mechanisms:

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
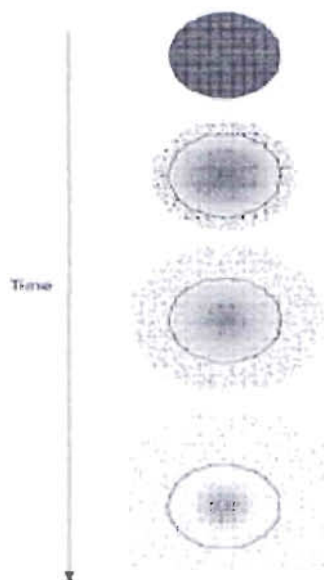
Fig- 5 Drug delivery from a typical matrix drug delivery system
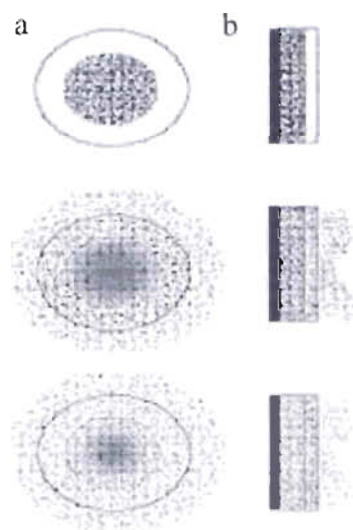
Fig- 6. Drug delivery from typical reservoir devices: (a) implantable or oral systems, and (b) transdermal systems

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. Examples of diffusion-release systems are shown in Figures 5 and 6. In Fig-5, a polymer and active agent have been mixed to form a homogeneous system, also referred to as a matrix system or hydrophilic 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 shown in Figures 6a and 6b, 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. Since this polymer coating is essentially uniform and of a nonchanging thickness, the diffusion rate of the active agent can be kept fairly stable throughout the lifetime of the delivery system. The system shown in Figure 6a is representative of an implantable or oral reservoir delivery system, whereas the system shown in Figure 6b illustrates a transdermal 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 its 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.

3.5 Hydrophilic Matrix System:

Hydrophilic matrix systems have been proven for over four decades. Matrix controlled-release tablets are relatively simple systems that are more forgiving of variations in ingredients, production methods, and end-use conditions than coated controlled-release tablets and other systems. This results in more uniform release profiles with a high resistance to drug dumping. Matrix systems are relatively easy to formulate. The performance of many products is already well documented, providing a body of data to refer to and rely upon. This helps speed development work and can shorten approval times as well.

Matrix systems are easy to produce. Tablets are manufactured with existing, conventional equipment and processing methods. This is true for almost any size tablet, whether it involves direct compression, dry granulation, or wet granulation. Matrix systems are economical.

Beyond the possibility of lower development costs and the use of conventional production methods, the ingredients normally used are cost-effective.

3.6 Selection of Polymer:

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 that was expected from this time-proven excipient family. These polymers improve powder system flowability while maintaining the excellent compressibility, tablet hardness, and controlled release performance for which METHOCEL products have long been known.

Table –1: The selection of polymers is done according to the following segmentations.

Application	Products Recommended	Typical Use Level	Advantages
Controlled Release Matrix Tablet	METHOCEL K100LV, K4M, K100M, E4M, 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
	POLOX 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 Coating	ETHOCEL Standard Premium 4,7,10	3-20%*	Insoluble in water; promotes good diffusion control membrane.
	ETHOCEL Premium blended with METHOCEL E5, E15 Premium	3-20%*	Mixing with METHOCEL Premium moderates diffusion
Microencapsulation	ETHOCEL standard 20, 45, 100 Premium	10-20%	Insoluble in water, can be coacenated (phase separated)

*use rate may vary with dosage form, size and desired release rate   (www.dowchemicals.com)

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.

POLYOXTM Water-Soluble Resins, national formulary (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.

3.7 Justification of Selecting METHOCELL

HPMC is a cellulose ether, derived from alkali treated cellulose that is reacted with methyl chloride and propylene oxide. Methocel cellulose products are available in two basic types:

❑   Methyl cellulose (MC)

❑   Hydroxypropyl methyl cellulose (HPMC)

Both type of methocel backbone have the polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose unit. 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 hydroxypropyl substitution on the anhydroglucose units. (Fig-7) The substitution pattern in methocel can as follows. **(Table-2)**

Table-2: Degree of substitution for METHOCEL products

Product	Degree of substitution	Methoxyl %	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
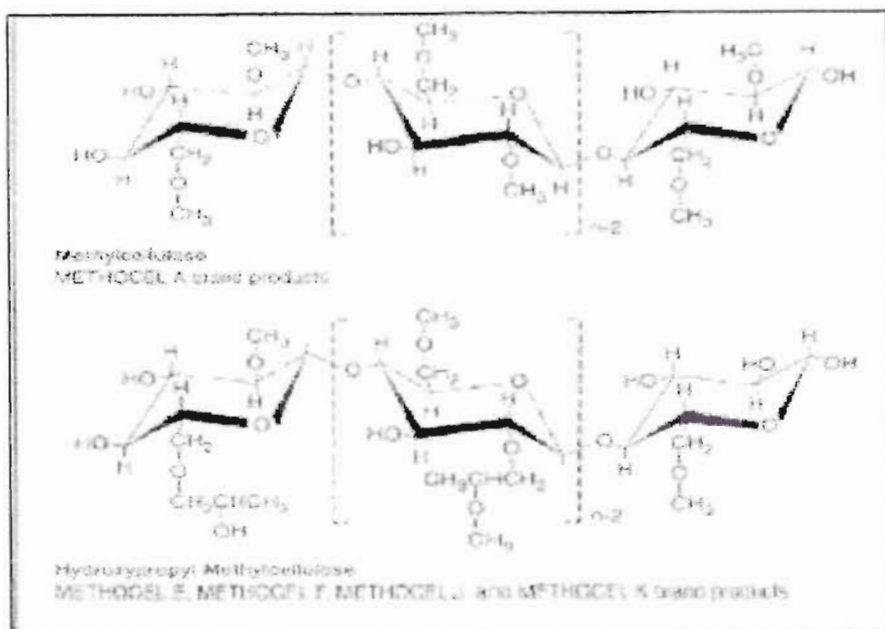
Fig-.7. Typical Chemical Structure of Methocel Products

3.8.1 General Properties of METHOCEL Cellulose Ether

General properties common to METHOCEL cellulose ether products are listed below. Individual METHOCEL products exhibit these properties to varying degrees and may have additional properties that are desirable for specific applications.

Water solubility: METHOCEL cellulose ethers dissolve in water with no sharp solubility limit. This feature provides exceptional handling flexibility and control of solubilization rate. Although METHOCEL powders are soluble in cold water, they must first be thoroughly dispersed in the water to prevent lumping. The maximum concentration is limited only by solution viscosity.

Organic solubility: Certain types and grades of METHOCEL cellulose ethers are also soluble in binary organic and organic solvent/water systems, providing a unique combination of organic solubility and water solubility.

No ionic charge: METHOCEL cellulose ethers are nonionic and will not complex with metallic salts or other ionic species to form insoluble precipitates.

Thermal gelation: Aqueous solutions of METHOCEL products gel when heated above a particular temperature, providing controllable quick-set properties. Unlike gels formed by protein thickeners, the gels go back into solution upon cooling.

Surface activity: METHOCEL products act as surfactants in aqueous solutions to provide emulsification, protective colloid action and phase stabilization. Surface tensions range from 42 to 64 mN/m. The surface tension of water is 72 mN/m; a typical surfactant has a surface tension of 30 mN/m

Film Formation: METHOCEL products form clear, flexible films.

pH stability: METHOCEL cellulose ethers are stable over a pH range of 2.0 to 13.0

Enzyme resistance: Enzyme-resistant METHOCEL products provide excellent viscosity stability during long-term storage.

Low taste and odor: METHOCEL cellulose ethers have excellent (low) flavor and aroma properties, which is important in food pharmaceutical and nutraceutical applications.

Thickening: METHOCEL cellulose ethers thicken both aqueous and nonaqueous systems. The viscosity is related to the molecular weight, chemical type and concentration of the specific METHOCEL product.

Metabolic inertness: Used as food and drug additives, METHOCEL products do not add calories to the diet.

Binding: METHOCEL cellulose ethers are used as high-performance binders for pharmaceutical products.

Suspending: METHOCEL products are used to control settling of solid particles, for example, solids in antacid suspensions.

Protective colloidal action: METHOCEL products are used to prevent droplets and particles from coalescing or agglomerating.

Emulsification: METHOCEL cellulose ethers stabilize emulsions by reducing surface and interfacial tensions and by thickening the aqueous phase.

According to provided data it is obvious that METHOCEL Premium products can be used in controlled-release formulations. Typical products used in controlled release include METHOCEL K100 Premium LV CR, K4M Premium CR, K15M Premium CR, K100M Premium CR, E4M Premium CR, and E10M Premium CR. (Table 2). The physical form of these products is an off-white powder.

3.8.2 Typical Properties:

- **Acidity/alkalinity:** pH = 5.5–8.0 for a 1% w/v aqueous suspension.
- **Angle of repose:** 40–508
- **Autoignition temperature:** _3608C
- **Degree of substitution:** 1.64–1.92
- **Density (bulk):** 0.276 g/cm3
- **Density (tapped):** 0.464 g/cm3
- **Density (true):** 1.341 g/cm3
- **Melting point:** begins to brown at 190–2008C; begins to char at 225–2308C.
- **Refractive index of solution:** n_D^{20} = 1.336 (2% aqueous solution). (Rowe et al, 2006)

Solubility: Practically insoluble in acetone, methanol, chloroform, ethanol (95%), ether, saturated salt solutions, toluene, and hot water. Soluble in glacial acetic acid and in a mixture of equal volumes of ethanol and chloroform. In cold water, methylcellulose swells and disperses slowly to form a clear to opalescent, viscous, colloidal dispersion.

Surface tension: 53–59mN/m (53–59 dynes/cm) for a 0.05% w/v solution at 258C; 45–5mN/m for 0.1% at 208C. Interfacial tension of solution versus paraffin oil is 19–23mN/m for 0.1% w/v solution at 208C.

Viscosity (dynamic): Parious grades of methylcellulose are commercially available that vary their degree of polymerization. Aqueous solutions at concentrations of 2% w/v will

produce viscosities between 5 and 75 000 mPa s. Individual grades of methylcellulose have a stated, narrowly defined viscosity range measured for a 2% w/v solution. The viscosity of solutions may be increased by increasing the concentration of methylcellulose. Increased temperatures reduce the viscosity of solutions until gel formation occurs at 50–608C. The process of thermogelation is reversible, with a viscous solution being reformed on cooling. (Rowe et al, 2006)

3.9 Functional Category: Coating agent; emulsifying agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

3.10 Applications in Pharmaceutical Formulation or Technology: Methylcellulose is widely used in oral and topical pharmaceutical formulations; (Table 3). In tablet formulations, low- or medium-viscosity grades of methylcellulose are used as binding agents, the methylcellulose being added either as a dry powder or in solution. Highviscosity grades of methylcellulose may also be incorporated in tablet formulations as a disintegrant. Methylcellulose may be added to a tablet formulation to produce sustained-release preparations.

Table 3: Uses of methylcellulose.

Use	Concentration (%)
Bulk laxative	5.0-30.0
Creams, gels, and ointments	1.0-5.0
Emulsifying agent	1.0-5.0
Ophthalmic preparations	0.5-1.0
Suspensions	1.0-2.0
Sustained release tablet matrix	5.0-75.0
Tablet binder	1.0-5.0
Tablet coating	0.5-5.0
Tablet disintegrant	2.0-10.0

Tablet cores may also be spray-coated with either aqueous or organic solutions of highly substituted low-viscosity grades of methylcellulose to mask an unpleasant taste or to modify the release of a drug by controlling the physical nature of the granules. Methylcellulose coats are also used for sealing tablet cores prior to sugar coating.

Low-viscosity grades of methylcellulose are used to emulsify olive, peanut, and mineral oils. They are also used as suspending or thickening agents for orally administered liquids,

methylcellulose commonly being used in place of sugar-based syrups or other suspension bases. Methylcellulose delays the settling of suspensions and increases the contact time of drugs, such as antacids, in the stomach.

High-viscosity grades of methylcellulose are used to thicken topically applied products such as creams and gels.

In ophthalmic preparations, a 0.5–1.0% w/v solution of a highly substituted, high-viscosity grade of methylcellulose has been used as a vehicle for eye drops. However, hypromellosebased formulations are now preferred for ophthalmic preparations. Therapeutically, methylcellulose is used as a bulk laxative; it has also been used to aid appetite control in the management of obesity, but there is little evidence supporting its efficacy. (Rowe et al, 2006)

4

FDA Regulation of Oral Controlled-Release Drugs

Page: 24-33

4.1 FDA Regulation of Oral Controlled-Release Drugs

In the 1980s, FDA introduced rigorous regulations governing bioequivalence and in vitro–in vivo correlations for controlled-release products. Required pharmacokinetic evaluations involve

- Relative bioavailability following single dose
- Relative bioavailability following multiple doses
- Effect of food
- Dose proportionality
- Unit dosage strength proportionality
- Singe-dose bioequivalence study (experimental versus marketed formulations at various strengths)
- In vivo–in vitro correlation
- Pharmacokinetic/pharmacodynamic (PK/PD) relationship.

In general, for drugs in which the exposure–response relationship has not been established or is unknown, applications for changing the formulation from immediate release to controlled release requires demonstration of the safety and efficacy of the product in the target patient population. When an NME is developed as a controlled-release dosage form, additional studies to characterize its absorption, distribution, metabolism, and excretion (ADME) characteristics are recommended.

4.2 Guidelines for THE Design and Evaluation of Oral Prolonged Release Dosage

Forms: Ministry of Health and Welfare, Japan (March 11, 1988) stated that: In recent years, in association with progress and innovation in the field of pharmaceutical technology, there has been an increasing effort to develop prolonged release dosage forms for many drugs. Correspondingly, a growing number of new prolonged release dosage forms have been submitted for regulatory approval. Prolonged release dosage forms have many advantages in safety and efficacy over immediate release drug products in that the frequency of dosing can be reduced, drug efficacy can be prolonged and the incidence and/or intensity of adverse effects can be decreased.

However, some prolonged release dosage forms have less clear rationale or are developed for active ingredients which are not appropriate for prolonged release dosage forms. In other cases, prolonged release dosage forms are designed without full consideration of the basic

properties of the drugs. Moreover, standards for dissolution tests, which are important for evaluating prolonged release dosage forms, have not appropriately been established. As a result, it is often difficult to evaluate whether a prolonged release dosage form is acceptable or not. Incomplete or undesirable prolonged release drugs may merely cause therapeutic confusion and, in addition may interfere with development and spread of good quality drugs. As part of the effort to ensure and promote drug availability, it appears necessary to establish appropriate guidelines for the design and evaluation of prolonged release dosage forms.

The present guidelines are prepared for oral prolonged release dosage forms, mainly for drugs with new pharmaceutical forms. However, many of the general principles of the guideline are also applicable to other controlled release dosage forms.

4.2.1 Factors to be Studied in Dosage Form Design

The properties of the active ingredient The following characteristics of drugs are critical in ensuring their efficacy and safety. Therefore they should be sufficiently studied to fulfill characterize the drug.

I) **Elimination half life**: Drugs with long elimination half lives are generally undesirable for prolonged release dosage forms unless designed to prevent toxic effects due to a peaking effect or to reduce the dose.

II) **The first pass effect**: Bioavailability may be significantly impaired if the release rate is retarded for drugs that suffer from an extensive first pass effect.

III) **The absorption site**: If the absorption site is limited, absorption is likely to decrease and variable bioavailability will occur for typical prolonged release dosage forms.

IV) **Adverse reactions**: Undesirable adverse reactions may develop by using prolonging drug release.

4.2.2 It is desirable to clarify following factors:

I) Correlation of clinical response with blood-drug concentrations or tissue concentrations at the site of action.

II) Induction or inhibition of drug metabolizing enzymes by the prolonged blood concentration, casual change of pharmacological response and the possibility of tolerance or addiction for the drug.

III) Interactions with other drugs due to protein binding.

4.2.3 Pharmacodynamics: The major purpose for developing prolonged release formulations of the drug is generally to maintain the blood concentration of the active ingredient at therapeutically effective levels. Therefore, it is desirable that average minimum effective concentration and optimal therapeutic concentrations be clarified for each drug by evaluating blood concentrations of the active ingredient or therapeutic moiety(s) including active metabolite(s) in relation to drug efficacy. The intra- and intersubject variations should be investigated for further confirmation of those levels. It is also desirable to investigate toxic blood drug concentrations.

If the effective blood drug concentration is not known, estimates should be made from dose levels, blood concentrations, and clinical data based on the immediate release drug product. If effective blood drug concentration is unclear, the usefulness of the prolonged release dosage form should be demonstrated by well-designed clinical studies.

4.2.4 Biopharmaceutics: Information on the biopharmaceutical properties of the active ingredient for a prolonged release dosage form is essential in rational formulation design. Particular attention should be given to the following six factors: 1) location of major absorption sites or specificity in the site of absorption, 2) absorption rate, 3) the elimination half life of the drug, 4) whether absorption is non-linear due to the saturated drug absorption, first pass effects, or other reasons, 5) whether elimination is non-linear due to drug metabolism saturation or other factors, and 6) inactivation or metabolism of the drug in the body, including the gastrointestinal tract. The above points should be clarified in humans if possible or in animals if the evaluation in humans is difficult. It is also desirable that the effect of food, drugs likely to be used concurrently and physiological factors such as renal or hepatic function on the absorption, distribution, metabolism and excretion of the drug be studied and evaluated. In addition, it is useful to study effects of age, sex and smoking on the pharmacokinetics of the drug.

4.2.5 Chemistry and Physico-Chemistry: Chemical and physicochemical properties of drugs, especially, pH- solubility characteristics should be clarified.

4.2.6 Factors Due to Physiological Condition: The release of an active ingredient from a prolonged release dosage form, and its absorption are inevitably affected by physiological factors in the gastrointestinal tract. Prolonged release dosage forms are more susceptible to these factors than immediate release dosage forms. Therefore, the possible effects of the physiological factors should be fully considered for the dosage form design. If the drug is intended for use in a specific subpopulation, attentions should be paid to the specific physiology of the subpopulation.

4.2.7 Transit Characteristics of The Dosage Form Through The Gastrointestinal Tract: The transit rate of a dosage form through the gastrointestinal tract is known to depend on the formulation properties such as size, form, specific gravity and adhesiveness of the preparation and physiological properties such as the length, size and motility of the gastrointestinal tract; and on the composition and volume of the gastrointestinal content. It is also affected by food, diseases, posture, and stress. The bioavailability of drugs often depends on the gastrointestinal transit rate of the dosage form. Therefore, the traveling characteristics of the dosage form through the gastrointestinal tract should be fully considered in designing advantageous dosage forms.

4.2.8 Physiology of The Gastrointestinal Tract: The physiological characteristics of the gastrointestinal tract (the volume, composition, pH, surface tension and viscosity of the gastrointestinal content; and gastrointestinal motility) vary greatly from site to site. Prolonged release dosage forms remain in the gastrointestinal tract longer than conventional preparations. Therefore, physiological conditions of the gastrointestinal tract can affect the release of active ingredients of these forms much more than release from conventional forms. Note worthily, gastric pH varies from acidic to neutral, and these variations can affect release of the active ingredient from the dosage form. These points should be considered when a formulation is being designed and assessed.

4.2.9 Prototype Dosage Forms and Selection of The Final Dosage Form: Desirable criteria of performance for prolonged release dosage forms are: duration of appropriate blood drug concentration for a sufficient time with minimal influence of food and physiological conditions of the gastrointestinal tract; and minimal contribution to intra- and intersubject variation. To select the best possible dosage form, all candidate forms should be fully tested

for release characteristics. Moreover the pharmacokinetic profile should be evaluated in an appropriate species of animal or volunteer.

4.2.10 Factors to be Studied in The Final Dosage Forms:
4.2.10.1. Evaluation of the final dosage form

i) Release characteristics:

A. Evaluation of the release characteristics: The release of the active ingredient from the preparation in the gastrointestinal tract is affected by many physiological factors including the mechanical force exerted by the digestive tract in relation to its movement, and the volume, composition, pH, surface tension, and viscosity of the gastrointestinal fluid. Therefore, the in vitro release behaviors should be investigated under as many conditions as possible to understand possible effects of gastrointestinal variables on in vivo release. To achieve stable blood concentrations, it is generally desirable to prepare prolonged release dosage forms whose release rates are minimally pH dependent. Therefore, release of the active ingredient should be evaluated at multiple levels of pH, such as 1.2, 4.0 and 6.8, representing typical gastrointestinal pH variation. Considering the variation in gastrointestinal motility; agitation rates should also vary more than 2 levels among 50, 100 and 200 rpm, when the paddle method is used, at an appropriate pH. If it is anticipated that the release rate is influenced by the wettability, ionic strength and composition of the test medium, their effects should also be investigated. It is also desirable to perform release tests using different kind of apparatus.

On the other hand, taking into consideration the variation of mechanical stress in the gastrointestinal tract, the drug release from prolonged release dosage forms containing an active ingredient with a narrow therapeutic window should be tested by the methods having a high mechanical stress, such as JP disintegration test method, the rotating flask method using beads and solubility simulator.

B. Specifications for dissolution testing: The specifications for drug releases should be established for quality control of prolonged release dosage forms. Basically, it is desirable to employ the release tests which can predict the blood level profile of the drug as precisely as possible. It is also desirable to set the specification including sampling time and amount of drug to be released so as to show the release profile as accurately as possible. The tolerable

29

range of the drug release change depending on the effect of the release rate on absorption or a related pharmacodynamic property (therapeutic window, toxicity or adverse reactions). Therefore, based on the relation between release rate and blood concentration or pharmacological effects, the tolerable range should be set within limits which do not allow great changes in blood concentrations or in clinical efficacy. The narrow tolerance limits should be set as much as possible to decrease the variation in drug release which will provide stable clinical effects.

If the relation between the release rate and blood concentration is not clear, or if sufficient data are not available to prove the correlation, it is difficult to set rational specification. In such a case it is desirable to set specifications using the second method (paddle method) in the Japanese Pharmacopoeia at sampling time points of 20-40%, 40-60%, and more than 70% of the labeled amount of the active ingredient is released. If 100 rpm and 900 ml of test fluid was used for the paddle method, the tolerance ranges at 1st, 2nd and 3rd points should be set within _15%, _15% and _10% of the average release, respectively. At the 3rd sample point, only lower limit is acceptable instead of the tolerance range. The acceptance criteria of the drug release follow the criteria of dissolution or release tests of JP XI or USP XXI.

C. Stability test: Specimens for long term stability tests should be subject to dissolution testing and comply with the standards of the specifications.

ii) Pharmacokinetics:

A. Comparison of the prolonged release dosage form with an immediate release dosage form: As far as possible, the pharmacokinetics of the prolonged release dosage form should be compared with the immediate release product in healthy volunteers. Pharmacokinetic evaluation should be made, based on blood concentration data, except for the case that the concentrations of the active ingredient can be determined at the site of action whose effective concentrations are known. Data on drug concentration in the urine, saliva, or other body fluids will be accepted only when the concentrations of the active ingredient in the blood or at the site of action are correlated with that in these fluids.

Unless the drug shows linear pharmacokinetics within the clinical dose range, the investigation should be made at two dose levels, high and low.

a. **Single dose study:** The usefulness of the new prolonged release dosage form given according to the dosage regimen should be evaluated by comparing the blood concentration with that of the immediate release dosage form or alternative forms such as solution or a powder; or with a prolonged release product which has already been approved, when better prolonged release characteristics are claimed. The parameters to be compared are AUC (zero to the final sampling time), AUC $(0-\alpha)$, C_{max}, the duration of the minimum effective concentration, or optimal effective concentrations of the active ingredient if these concentrations are known or can be estimated. It is desirable to determine the time to reach the minimum effective concentration or the optimal effective concentration, T_{max}, absorption rate constant, elimination rate constant, clearance, extent of absorption and MRT and VRT by the moment analysis method.

b. **Multiple dose study:** Prior to a multiple dose study, a blood concentration profile at steady state for multiple dosing of both standard and test dosage forms should be simulated from the single dose pharmacokinetic trials. In the multiple dose studies, it should be ascertained that C_{max} and C_{min} at steady state are within the estimated ranges, and the usefulness of the prolonged release dosage form should be evaluated by comparing it with the reference product in 1) C_{max}, 2) C_{min}, 3) the difference between C_{max} and C_{min} or the ratio (dosage form index, C_{max}/C_{min}), and the duration of the minimum effective concentration or that of optimal effective concentration. For drugs with non-linear absorption or elimination, those with a narrow therapeutic window, or those which may cause severe adverse reactions, the blood concentration profile at steady state should be characterized by multiple dose studies. When multiple dose studies in healthy volunteers are not done, the usefulness of the prolonged release dosage form should be shown using the simulated parameters, where it is necessary to confirm that C_{max} and C_{min} are within the predicted range, by monitoring blood concentrations in clinical studies.

B. Effect of dosing conditions and physiological factors: Factors which might affect the pharmacokinetics of a prolonged release dosage form should be studied in which food is particularly an important factor because it is know to affect transit of dosage forms in

gastrointestinal tracts, disintegration, and release of the drug. Therefore, the blood concentration profiles of the prolonged release dosage form should be compared between fasting and fed conditions. If a significant effects of food was observed, a special caution should be included in the dosage regimen (i.e. indication of drug administration only after meals), and it should be clarified whether the food effect was related to the drug itself or dosage forms by performing similar food studies using the drug solution or the immediate release product, although the studies are not needed when there is published evidence. In addition, as far as possible, it is desirable to clarify other factors of food (e.g., the volume and composition of meal, and intervals between food and drug administration) affecting the in vivo release and absorption.

It is also desirable to investigate diurnal variations of pharmacokinetic parameters.

iii) Clinical efficacy: The clinical usefulness of the prolonged release dosage form should be shown comparing it with its already approved immediate release product or its already approved prolonged release product (if a better prolonged release dosage form is claimed).

If the relation between the pharmacological effectiveness and blood concentration is unclear, the usefulness should be proved by the well-controlled clinical studies where the effective and toxic concentrations should be investigated by monitoring blood concentrations of the drug.

4.2.10.2 Establishment of dosing regimen: The appropriate dosing regimen should be established during Phase I and II clinical studies in which it is recommended that the blood concentrations are monitored during phase II clinical trials to establish a better dosing regimen.

i) **Factors of particular importance in establishing dosing regimen:**

   a. Overdose or dose dumping: Sustained release dosage forms might be more likely to produce significant adverse and toxic effects than immediate release dosage forms in case of overdose or dose dumping because of the higher doses of active ingredients which are absorbed over a prolonged time. Dose dumping, e.g. resulting from crushing by the teeth, may be another problem with prolonged release dosage forms. This is of particular concern for drugs with a narrow therapeutic window, and so

studies are desired to establish preventive measures and actions to be taken in such cases.

b. Disease state: The physiological changes in gastrointestinal tract, liver, kidneys, or heart due to diseases often affect absorption, distribution and elimination of drugs and there is a possibility that prolonged release dosage forms are particularly susceptible to the changes. In such cases, the dosing regimen should be studied and established as to reflect the pathological changes.

c. Combination therapy: If any other drug is used concurrently, it may affect the absorption, distribution, and elimination of the drug contained in the prolonged release dosage form. As a result, blood concentrations of the drug may be changed, and this may affect the efficacy. The possible effect of drugs which might be used together in practice should be studied, and suitable indications and special warnings for the concurrent use of other drugs should be established.

ii) **Dosing guidelines:** Recommendations for dosing conditions, frequency of dosing per day, and dose levels (initial dose, maintenance dose, dose adjustment for insufficient response, and the maximum tolerable dose) should be established, based on the available pharmacokinetic data during Phase 11 clinical studies. The action to be taken if toxic signs or adverse effects develop should also be specified in these guidelines.

Detailed dosing guidelines including information about dose adjustment based on blood concentration monitoring or changes in renal clearance of each patient may be useful to maximize the therapeutic efficacy by making the utmost use of the advantages of the prolonged release dosage form.

It is desirable to set up corresponding detailed guidelines particularly for prolonged release products containing A) drugs, blood concentrations of which may change strikingly by minimal changes in dose (drugs with non-linear absorption or elimination), B) drugs, the clearance and blood concentrations of which are susceptible to physiological conditions, age and so forth, C) drugs with a narrow therapeutic window, and D) drugs which might cause tolerance and/or severe adverse effects (Ministry of Health and Welfare, Japan, March 11, 1988).

5

Materials

Page: 34-41

34

5.1 Materials:

Drug: Diclofenac (Merk, Germany).

Polymers: Mehtocel K15M CR and Methocel K100LV CR.

Other excipients: Lactose, Aerosil 200 (colloidal silicon di oxide), Talc

### Table 4: List of ingredients used in experiment

Name of the material	Function
Diclofenac	API (Active Pharmaceutical Ingredients)
Methocel K15M CR	Rate controlling polymer, Binder
Methocel K100 LV CR	Rate controlling polymer, Binder
Lactose	Adsorbent, Diluent
Aerosil (colloidal silicon di oxide)	Filler, flow promoter
Talc	Lubricant

5.2 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).
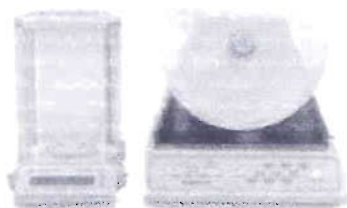
Fig-8(a): Weighing Machine & Fribilator used
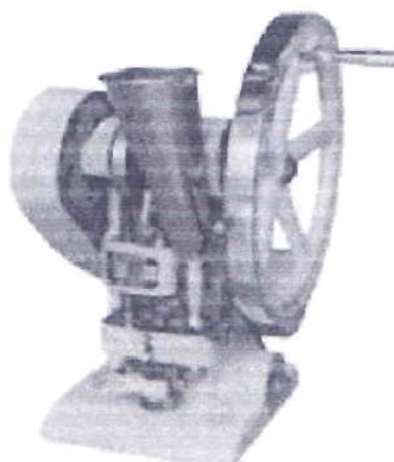
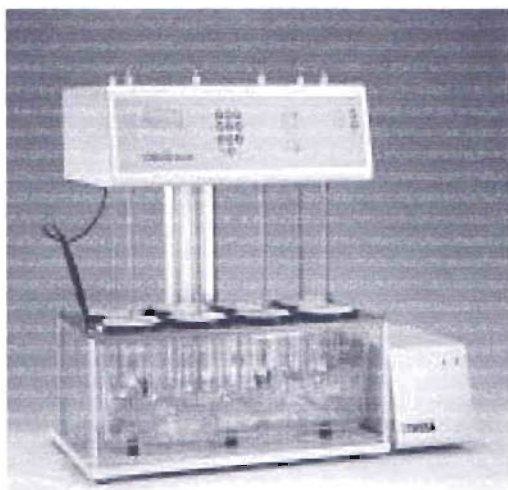Fig-8(b): Single Punch Tablet Machine
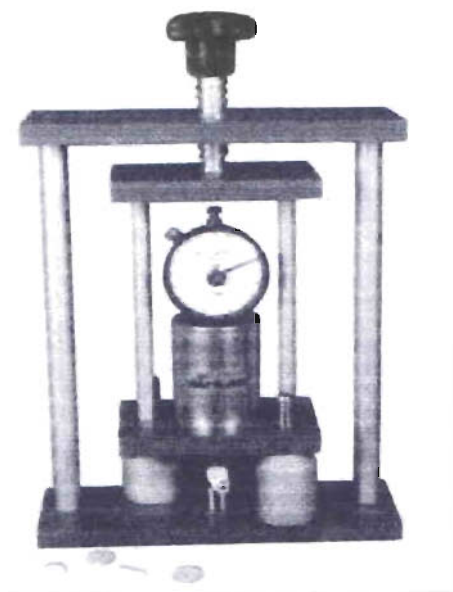
Fig-9 (a): Disolution Aparatus   Fig-9 (b): Monsanto hardness tester

5.3 Diclofenac- the API: Diclofenac (2- [(2,6-dichlorophenyl)amino]benzene acetic acid, Fig.10) is an orally administered non-steroidal anti-inflammatory substance (NSAIS).
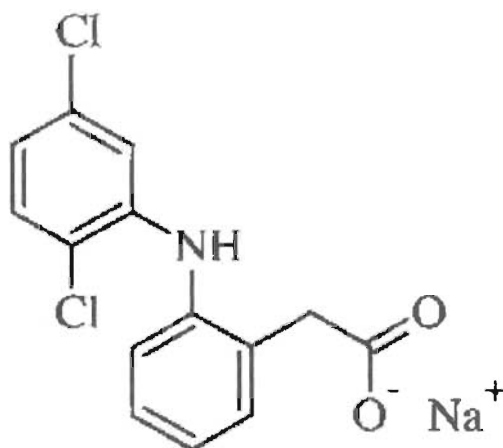

Fig.10. Structural formula of diclofenac.

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The mode of action is not fully known but it does not act through the pituitary-adrenal axis. Diclofenac sodium inhibits prostaglandin synthesis by interfering with the action of prostaglandin synthetase.

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.

Although diclofenac sodium does not alter the course of the underlying disease, it has been found to relieve pain, reduce fever, swelling and tenderness, and increase mobility in patients with rheumatic disorders of the types listed.

Following administration of the slow-release (SR) diclofenac sodium, Cmax is reached at approximately 4 hours or later.

Pharmacokinetics: Absorption: In humans, orally administered diclofenac sodium is rapidly and almost completely absorbed and distributed to blood, liver and kidneys. The plasma concentrations show a linear relationship to the amount of drug administered. No accumulation occurs provided the recommended dosage intervals are observed. Mean plasma concentrations of 13 ng/mL (40 nmol/L) were produced 24 hours after diclofenac SR 100 mg, or 16 hours after diclofenac SR 75 mg following administration of a single dose. Trough levels are approximately 22 to 25 ng/mL (70 to 80 nmol/L) during treatment with diclofenac SR 100 mg once daily, or 16 hours after diclofenac SR 75 mg administered twice daily. In pharmacokinetic studies, no accumulation of diclofenac sodium was found following repeated once daily administration of diclofenac SR 100 mg tablets or repeated twice daily administration of diclofenac SR 75 mg tablets.

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

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.

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.

Indications And Clinical Uses: The symptomatic treatment of rheumatoid arthritis and osteoarthritis, including degenerative joint disease of the hip.

Contra-Indications: Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.

Diclofenac sodium should not be used in patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals.

Significant hepatic impairment or active liver disease.Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored. Diclofenac sodium is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

Suppositories are contraindicated in patients with any inflammatory lesions of the rectum or anus and in patients with a recent history of rectal or anal bleeding.

5.4 Polymers: Discussed earlier in chapter 3.

5.5 Excipients:

A. Lactose:

- **Nonproprietary Names:** Anhydrous lactose
- **Synonyms:** Anhydrous Lactose NF 60M; Anhydrous Lactose NF Direct Tableting; milk sugar; Pharmatose DCL 21
- **Empirical Formula:** $C_{12}H_{22}O_{11}$
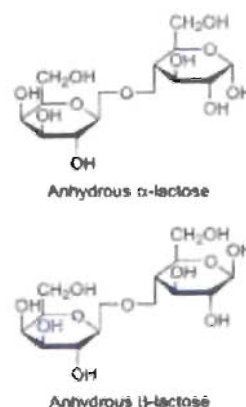- **Molecular Weight:** 342.30
- **Structural Formula:**

Anhydrous α-lactose

Anhydrous β-lactose

Fig- 11. α and β Anhydrous Lactose

- **Functional Category:** Binding agent; directly compressible tableting excipient; lyophilization aid; tablet and capsule filler.
- **Applications in Pharmaceutical Formulation or Technology:** Anhydrous lactose is widely used in direct compression tableting applications and as a tablet and capsule filler and binder. .
- **Description:** Lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous b-lactose and anhydrous a-lactose.
- **Typical Properties**
- **Angle of repose:** 398.
- **Brittle fracture index:** 0.0362
- **Density (true):** 1.589 g/cm3 for anhydrous b-lactose.
- **Density (bulk):** 0.68 g/cm3
- **Density (tapped):** 0.88 g/cm3.
- **Melting point:** 223.08C
- **Solubility:** soluble in water; sparingly soluble in ethanol (95%) and ether.
- **Water content:** 40.5% loss on drying and 41.0% water content for Anhydrous Lactose NF Direct Tableting and Anhydrous Lactose NF 60M.

(Rowe et al, 2006)

B. Aerosil 200 (colloidal silicon di oxide):

- **Nonproprietary Names:** BP: Colloidal anhydrous silica; PhEur: Silica colloidalis anhydrica;

- USPNF: Colloidal silicon dioxide

- **Synonyms:** Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica;

- **Chemical Name:** Silica

- **Empirical Formula:** SiO_2

- **Molecular Weight:** 60.08

- **Structural Formula:** $O=Si=O$

- **Functional Category:** Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

- **Applications in Pharmaceutical Formulation or Technology:** Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders. Colloidal silicon dioxide is also used to stabilize emulsions and suspending agent in gels and semisolid preparations.

- **Description:** 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 compressibility index)

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

(Rowe et al, 2006)

C. Talc:

+ **Nonproprietary Names:** BP: Purified talc; JP: Talc; PhEur: Talcum; USP: Talc
+ **Synonyms:** Altalc; hydrous magnesium calcium silicate; hydrous magnesium silicate; magnesium hydrogen metasilicate; powdered talc; purified French chalk.
+ **Chemical Name:** Talc
+ **Empirical Formula:** Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$.
+ **Functional Category:** Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.
+ **Applications in Pharmaceutical Formulation or Technology:** Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, see Table 1, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant.

Table 5: Uses of talc.

Use	Concentration (%)
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0
Tablet and capsule diluent	5.0–30.0

(Rowe et al, 2006)

6

Methods

6.1 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 between 0.2 and 4.0 mm. Granules are used in the production of tablets or capsules. Granules in such cases are made as an intermediate product and have a typical size range between 0.2 and 0.5 mm.

Granulation is performed since it causes:

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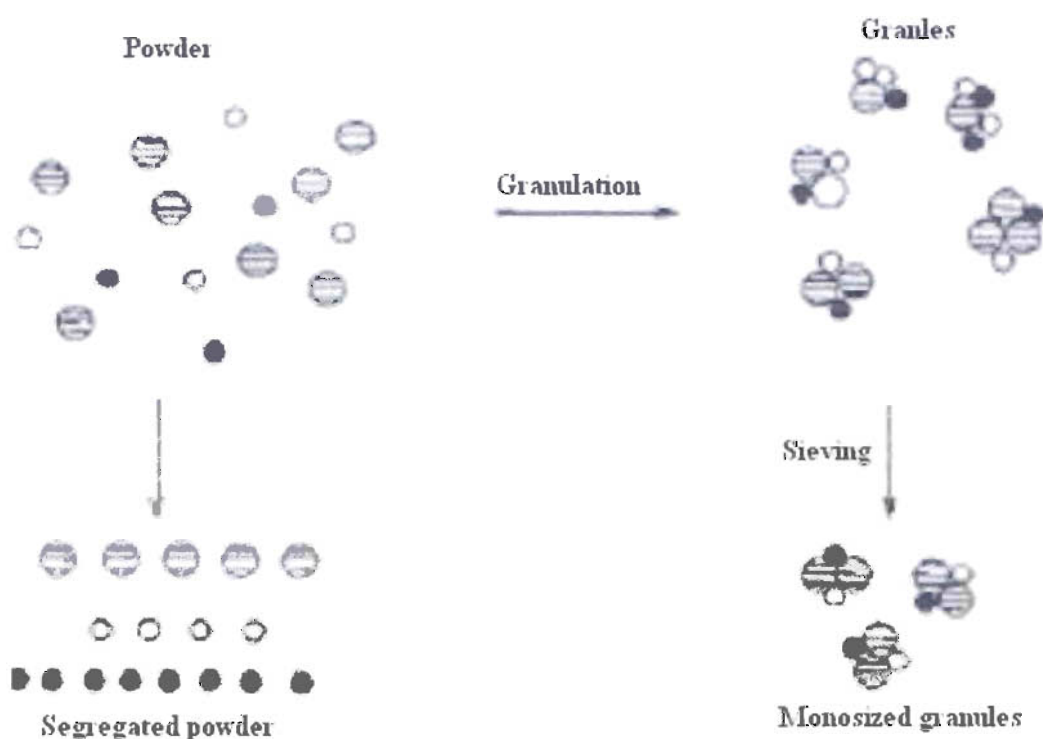- ❑ Improvement of the compaction characteristics of the mixture.

Fig- 12: Tablet Granulation Preventing Segregation

6.2 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 6). Properly weighed Methocel, Lactose, Talc, Aerosil and the active ingredient were then taken

43

into a beaker. A glass rod was rotated unidirectional to avoid static charges. Mixing was performed for 30 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 6: Comparison of major steps involved in the granulation methods.

Step	Direct compression	Dry Granulation	Wet granulation
1	Mixing / blending of API and Adjuvants ↓	Mixing / blending of API and Adjuvants ↓	Mixing / blending of API and Adjuvants ↓
2	**Compression**	Compression in to ↓ slugs	Preparation of binder solution ↓
3		Size reduction of slugs and sieving ↓	Massing of binder solution of step 2 with powder mixture of step 1. ↓
4		Mixing of granules with pharmaceutical aid/s. ↓	Wet screening of damp mass ↓
5		**Compression**	Drying of wet granules ↓
6			Resifting of dried granules and blending with pharmaceutical aid/s. ↓
7			**Compression**

(Gohel et al., 2005)

Table 7: Parameters useful in evaluation of directly compressible

Property	Related Parameters	Comments
Flowability	Bulk density, Tapped density	It decides the ability of the material to undergo compression and final volume of the tablets.
	Carr's index, Angle of Repose, and Hausner's ratio	Carr's index less than 20%, angle of repose less than 32° and/ or Hausner's ratio less than 1.2 indicates good flow. Good flowability is desirable for content uniformity and less weight variation in final tablets.
	Particle size distribution - Mean particle size - Percentage fines	Carr's index, Angle of repose and Hausner's ratio are based on the ability of powder mass to flow. The flowability of the directly compressible adjuvant is influenced by particle size and shape. Too small (less than 200 mesh; 74 micron; fines) particles retard the flow. The particles with uniform size and shape exhibit better flow than irregular shaped same size particles.
Compressibility	Heckel plot, Kawakita and Kuno's constants	The directly compressible adjuvant should exhibit good pressure - volume profile. The Heckel equation is most widely used in recent years (111). The slope, k of the Heckel plot gives a measure of the plasticity of a compressed material and the reciprocal of k is known as the yield value (Py). Yield value reflects the deforming ability of the material. The soft, ductile powders have lower yield value. The agglomerates with low yield value could be plastically deformed as a result of the rebonding of smaller primary crystals (112, 113). Low value of Py (steep slope) reflects low resistance to pressure, good densification and easy compression (12). A large value of slope indicates the onset of plastic deformation at relatively low pressure (40). Kawakita's constant 'a' represents the proportion of consolidation as closest packing is attained and the 'b' represents the packing velocity. The smaller value of constant 'a' for the granules indicates good packing even without tapping. The large value of 'b' for the granules indicates rapid packing velocity (114). Smaller value of Kuno's parameter "k" indicates the slower packaging velocity of the powder or agglomerates. The slow packing velocity corresponds with a proportion of the consolidation of the powder bed per tap (115).

		$\ln\left\|\frac{1}{1-D}\right\| = \rho_K + A$ (Heckel Equation), wherein "k" and "A" are constant. D and P are the packing fraction and pressure respectively. $\frac{n}{c} = \frac{1}{ab} + \frac{n}{a}$ ...(Kawakita's equation) wherein, $a = \frac{V_o - V_{inf}}{V_o}$ $C = \frac{V_o - V_n}{V_o}$, Where "a" and "b" are the constant, n is the tap number, V_o, V_n and V_{inf} are the powder bed volumes at initial, after nth tapping and at equilibrium state respectively. $\rho_c - \rho_n = (\rho_c - \rho_o)\, e^{(kn)}$... (Kunos' equation). wherein, ρ_o, ρ_n and ρ_c is the apparent densities at initial state, after nth tapping respectively, and k is a constant.
Tablet characteristics	Lubricant sensitivity ratio	Lubricant, especially metallic stearates reduce the tensile strength due to reduction of interparticle bonding (116) and/or make the API hydrophobic and thereby prolong the disintegration time or decreases the dissolution of the drug from the tablet. These effects are more pronounced on long intensive mixing (117). The material undergoing plastic deformation is more susceptible to the negative effect of lubricant (116).
	Granular friability	It gives the idea about the toughness of the composite directly compressible adjuvant against the abrasion during mixing or handling. Too tough material is difficult to compress while very soft material generates excessive fines and leads to poor flow on mixing.
	Dilution potential	High dilution potential is desirable to produce tablets with less weight. Compressibility and flowability of the drug has influence on it. Acetaminophen is widely used as a model drug because of its high capping tendency (115).
	Reworkability	It is the ability to reprocess the defective batch. The reworkability is influenced by the deformability of the directly compressible adjuvant on first compression.
	Tensile strength, Friability, and Disintegration time	These are important tools for the quality assurance of the tablets (118). The mechanical properties of a tablet are the consequence of consolidation and expansion phenomenon (119). The increase in particle surface contact promotes the greater possibility for increased bonding (120). Tablets should have sufficient tensile strength to hold the API at lowest compression force. Simultaneously it should give low friability and desired disintegration time.
Others parameters like brittle fracture index, indentation hardness, moisture absorption, storage stability can be used to compare the performance of the directly compressible adjuvants.		

(Gohel et al., 2005)

6.3 Physical Evaluation of Granules:

6.3.1 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

Table 8: The suitable range of angle of repose and type of flow

Angle of Repose	Type of Flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

6.3.2 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, 1965):

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

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

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

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

Table 9: The suitable range of the compressibility index and flow description

% 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

6.3.4 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, 1967).

Hausner Ratio = Tapped Density / Bulk Density

Table 10: The suitable range of Hausner ratio and type of flow

Hausner Ratio	Type of Flow
Less than 1.25	Good Flow
1.25 – 1.5	Moderate
More than 1.5	Poor Flow

6.3.5 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) (Allen et al, 2005).

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

6.3.6 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. (Allen et al, 2005).

6.3.7 Thickness: The thickness of the tablet was determined using a thickness gauge. Five tablets from each batch were used, and average values were calculated. (Allen et al, 2005).

6.3.8 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 (Pharmacopoeia of India, 1996).

6.4 Dissolution Study:

These studies were conducted at 37±0.5°C on an USP specification dissolution rate test type II apparatus (Paddle apparatus) with six section assembly according to the USP XXIII procedure with minor modification (USP XXII and NF XVII, 1995).

For in vitro dissolution studies simulated gastric medium (pH 1.2) and simulated intestinal medium (pH 6.8) were required.

a) Preparation of simulated gastric medium (0.1 N HCl pH 1.2):

For 0.1N HCl, 11.4 ml of Hydrochloric acid (32% w/v) was diluted with sufficient water to produce 1000 ml.

b) Preparation of simulated intestinal medium (Buffer pH 6.8):

20 ml Sodium Hydroxide (25%) was diluted with 0.1 N Hydrochloric acid to 1000 ml adjusting pH 6.8 by addition of 1.2 ml O-phosphoric acid. The dissolution test was performed using 900 ml medium at $37\pm0.5°C$ and 50 rpm.

The medium was preheated to 37°C and then added to the vessels after the medium was placed in the vessels, paddle rotation was started and the system was allowed to equilibrate for 15 min. Each vessel, vessel position, and corresponding tablet result were assigned the same number. Thus, for each sub sample of six tablets tested simultaneously, every individual tablet result was identified with a particular vessel and position. The total duration of dissolution was 12 hours in which the first 2 hours the tablet matrices were subjected to simulated gastric media (0.1N HCl pH 1.3) and the later 10 hours the tablet matrices were subjected to simulated intestinal media (Buffer pH 6.8).

Acid Stage: 900 ml of 0.1N HCl was placed in each vessel and the apparatus was assembled. Six tablets from each formulation were weighed and placed in the baskets. The operation in the acid stage was carried out for 2 hours. After each hour 10 ml of sample solution was withdrawn and filtered. The released drug was assayed by using UV spectrophotometer at 277 nm.

Buffer Stage: After 2 hours operation in the acid stage, 20 ml NaOH (25%) was added to the previous fluid. The pH (6.8 ±0.05) was adjusted with addition of 1.2 ml O-phosphoric acid. The operation was continued for 10 hours.

At every one-hour interval sample (10 ml) of the solution was withdrawn from the dissolution medium and immediately replaced with equal volumes of dissolution medium.

The withdrawn samples (10ml) was then filtered and diluted, analyzed at 277nm for diclofenac sodium by UV spectrophotometer (Shimadzu, Model UV-160A, Kyoto, Japan).

The amounts of drug present in the samples were calculated from calibration curves constructed from the standard solution of USP reference standard test drugs.

6.5 Drug Release Kinetics:

The in vitro drug release kinetic data were tested with the following mathematical model.

6.5.1 Zero Order Equation: The equation assumes that the cumulative amount of drug release is directly related to time. The equation may be as follows (Hadjiioannou et al 1993):

$C = K_0 t$

Where, K_0 is the zero order rate constant expressed in unit concentration/time and t is the time in hour. 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.

6.5.2 First Order Equation: The release behavior of first order equation is expressed as log cumulative percentage of drug remaining vs time. The equation may as follows (Bourne 2002):

$LogC = LogC_0 - kt / 2.303$

Where,

C = The amount of drug undissolved at t time,

C_0 = Drug concentration at $t = 0$,

k = Corresponding release rate constant.

6.5.3 Higuchi Square Root Law: The Higuchi release model describes the cumulative percentage of drug release vs square root of time. The equation may as follows (Higuchi, 1963):

$Q = K\sqrt{t}$

Where, Q (100-C) the amount of drug dissolved at time t. K is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.

6.5.4 Hixson-Crowell Cube Root Law: It is the law that presents idea about the evaluation of drug release pattern changes with the surface area and the diameter of the particles/tablets.

It is mentioned as the cube root of the percentage of drug remaining in the matrix vs time. The equation may as follows (Hixson and Crowell 1931):

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} \times t$$

Where,

Q_0 = Initial amount of the drug in the tablets

Q_t = The amount of drug release in time t

k_{HC} = The rate constant for the Hixson-Crowell cube root law

6.6 Determination of λmax: 0.004 mg/ml Solution was taken & wavelength was set to 200-600 nm ranges. Then scanning was performed & peak absorbance was recorded. The peak absorbance was found at 278 nm.

6.7 Determination of Absorbance of Various Conc. of Solution: Various absorbance of different concentration were found at 277nm. Thus a graph of absorbance vs. concentration was plotted.

7

Result and Discussion

Page: 52-63

Result and Discussion:

The proposed six formulations (F-1 to F-6) of Diclofenac SR tablet matrix were incorporated with two different polymers. They were Methocel K100 LV CR and Methocel K15M. In six formulations they possess six different ratios (**table-11**).

Table 11: Proposed formulation (F-1 – F-6) of Diclofenac 12 H SR tablet

	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 granules' physical properties of proposed formulations (F-1 to F-6) were measured, where, LBD (g/ml) were between 0.221 ± 0.02 to 0.521 ± 0.01, TBD (g/ml) were between 0.327 ± 0.02 to 0.475 ± 0.03, Hausner ratio were between 0.77 to 2.25, Compressibility Index (%) were between 11.15 ± 0.03 to 13.35 ± 0.02, Total Porosity (%) were between 26.19 ± 0.04 to 34.56 ± 0.01 and Angles of Repose were between 21.53 ± 0.01 to 29.36 ± 0.01 respectively. All the data were in an expectable range for the evaluation of the granules (**Table- 12**).

Table 12: Physical parameters of proposed formulation (F-1 – F-6) of Diclofenac 12 H SR tablet

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 indicates good flow property. Formulation (F-6) show moderate and formulation (F-5) possess poor flow property (**Table 13**).

Table- 13: 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

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 formulations possess 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-13**) and fulfilled the official requirement for both the granules and the finished product itself.

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.

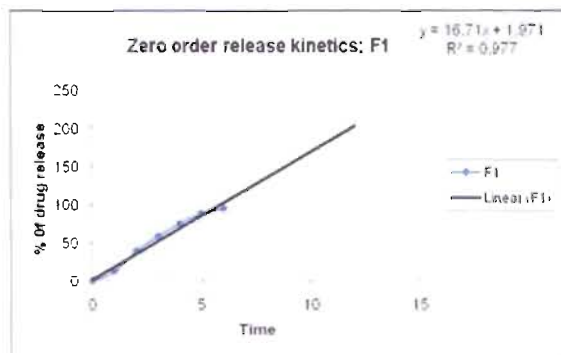**Table 14**: Zero order release kinetic profiles

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

They shoes drug release kinetics of the matrix tablets *in vitro* dissolution specification 80% drug release within 10th hours in simulated intestinal medium.

Fig.13. Zero order drug release kinetic profiles of the proposed formulations (F1-F6) of Diclofenac 12 H SR tablet in Graphical explanation
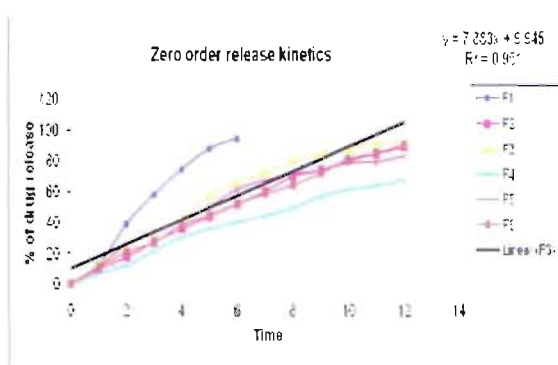
Fig. 13.1. All six Formulations (F1-F6)   **Fig. 13.2. Formulation F1**

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.
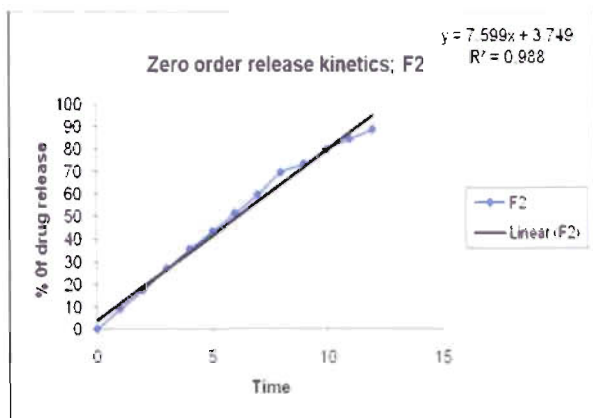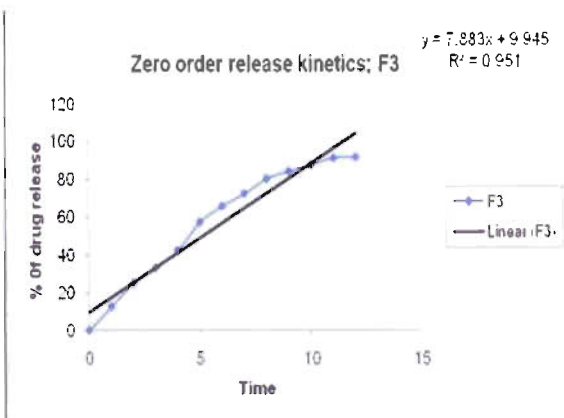

Fig. 13.3. Formulation F2
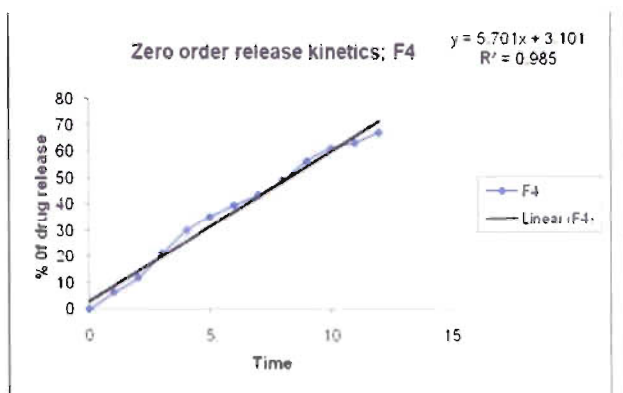

Fig. 13.4. Formulation F3
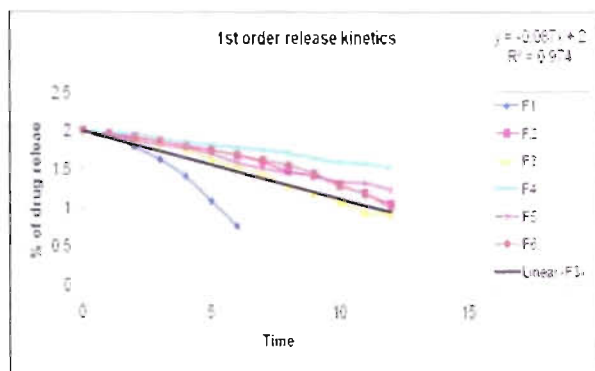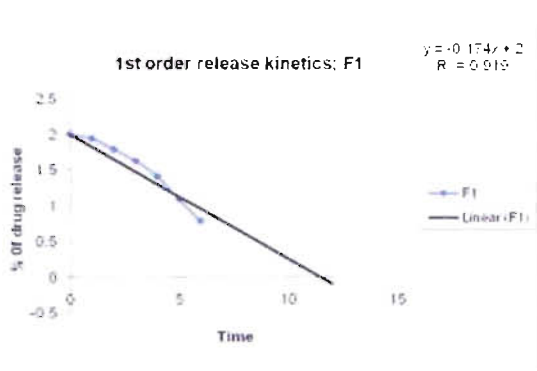

Fig. 13.5. Formulation F4
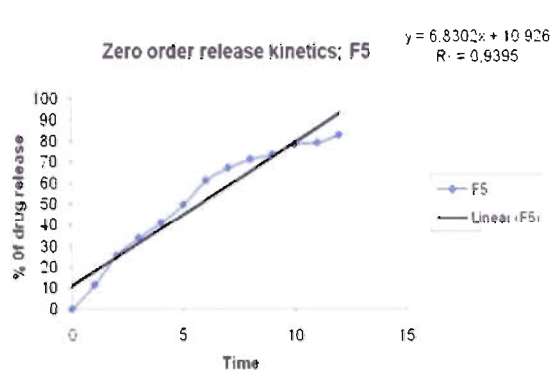
Fig. 13.6. Formulation F5
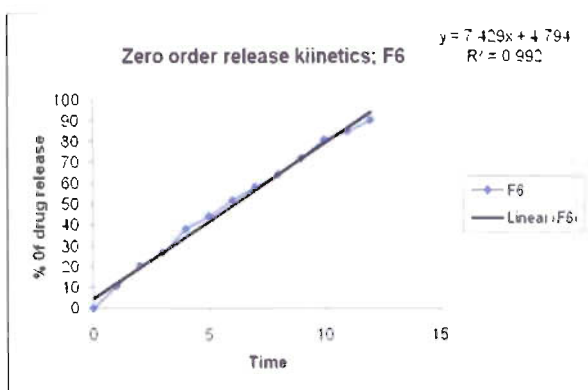
Fig. 13.7. Formulation F6

Using First order drug release kinetic equation we figure out the values of remaining % of drug over the time in *In-vitro* dissolution studies of all the proposed sustained release formulations 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.

Table 15: 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

Fig. 14. First order drug release kinetic profiles of the proposed formulations (F1-F6) of Diclofenac 12 H SR tablet in Graphical explanation

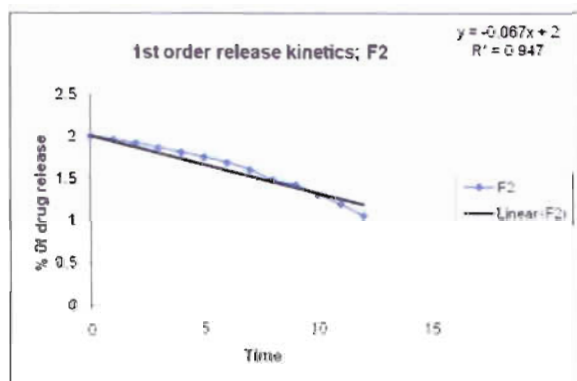**Fig. 14.1. All six Formulations (F1-F6)**   **Fig. 14.2. Formulation F1**
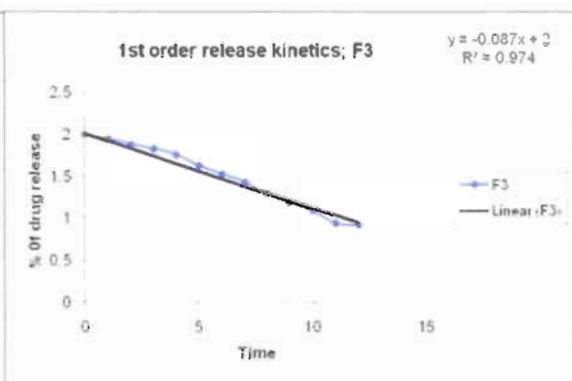
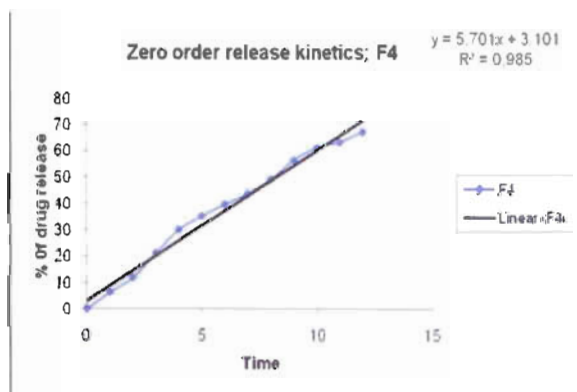**Fig. 14.3. Formulation F2**

Fig. 14.4. Formulation F3

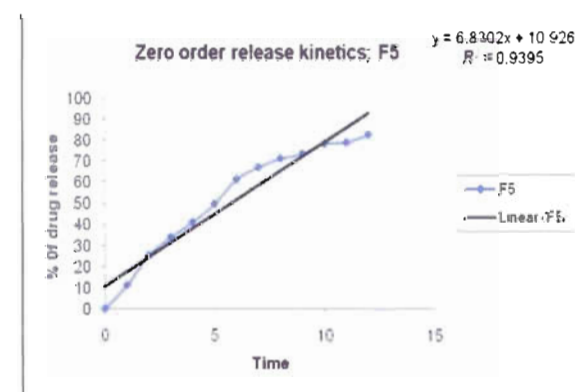**Fig. 14.5. Formulation F4**

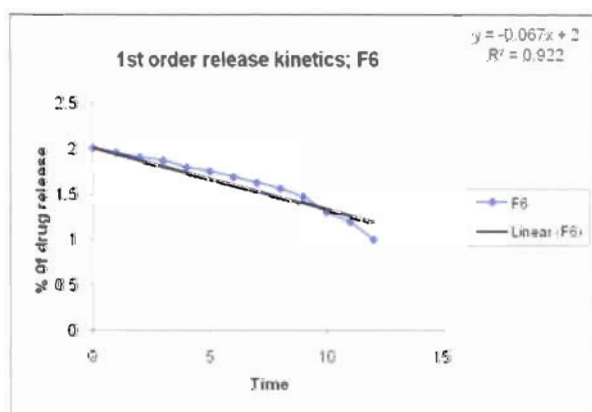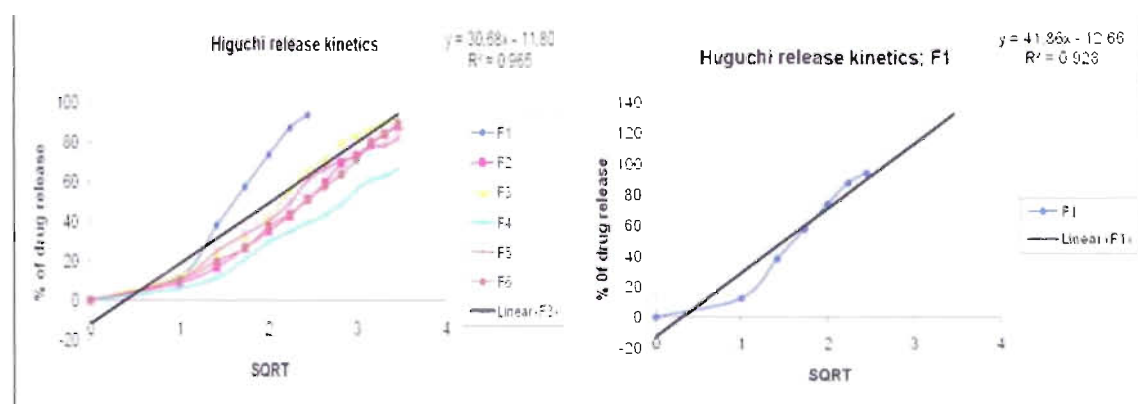

Fig. 14.6. Formulation F5

Fig. 14.7. Formulation F6

Using Higuchi drug release kinetic equation we figured out the SQRT values through *In-vitro* dissolution studies of all the proposed sustained release formulations 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.

**Table 16: Higuchi release kinetic profiles**

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

Fig. 15. Higuchi drug release kinetic profiles of the proposed formulations (F1-F6) of Diclofenac 12 H SR tablet in Graphical explanation
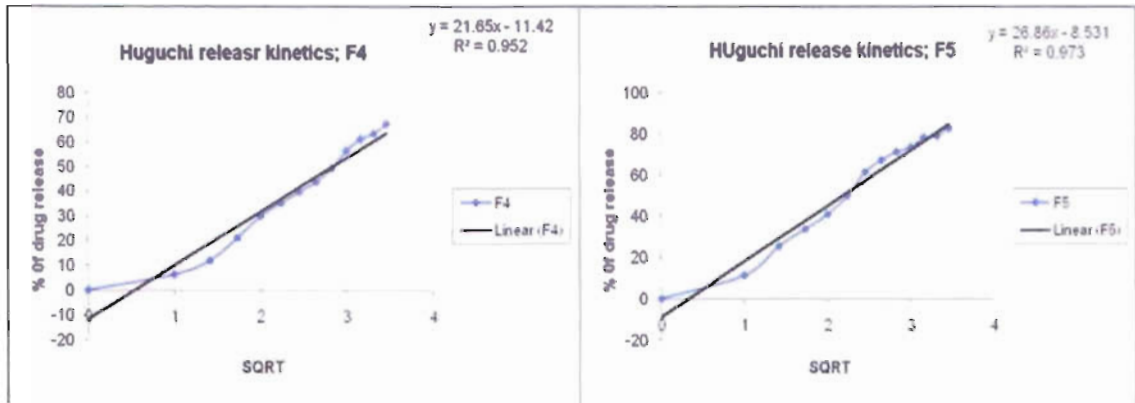

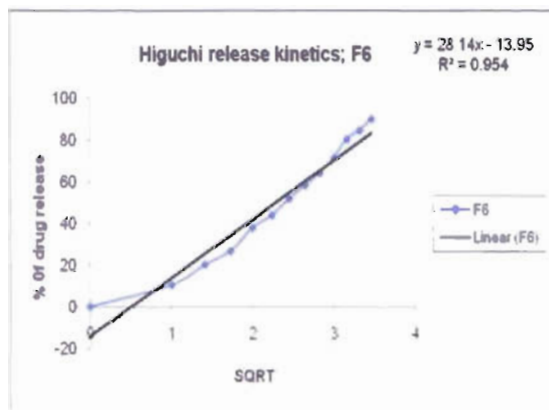**Fig. 15.1. All six Formulations (F1-F6)**   **Fig. 15.2. Formulation F1**
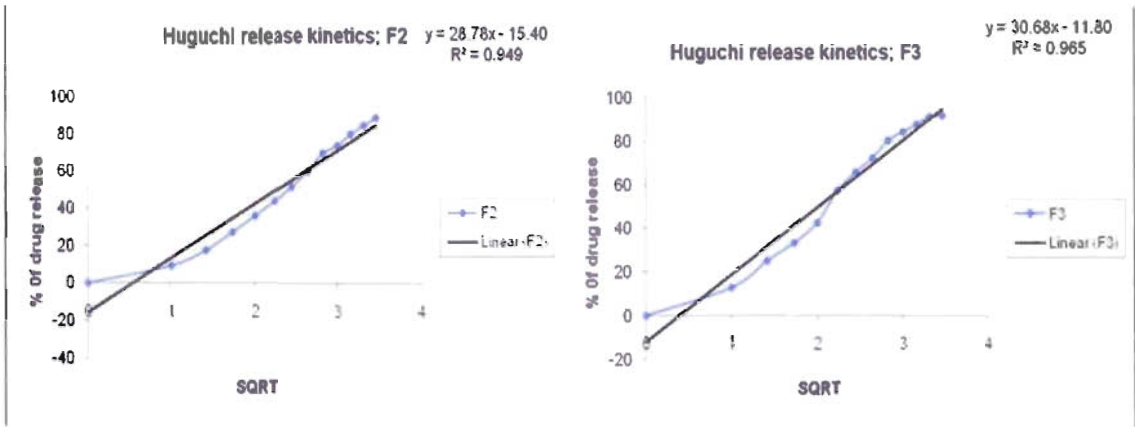
Fig. 15.3. Formulation F2

Fig. 15.4. Formulation F3

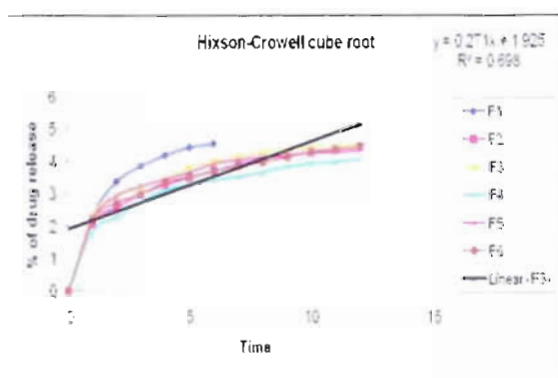Fig. 15.5. Formulation F4

Fig. 15.6. Formulation F5

Fig. 15.7. Formulation F6

60

Using Hixson-Crowell cube root release kinetic equation we figured out the % of drug release values through *In-vitro* dissolution studies of all the proposed sustained release formulations 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.
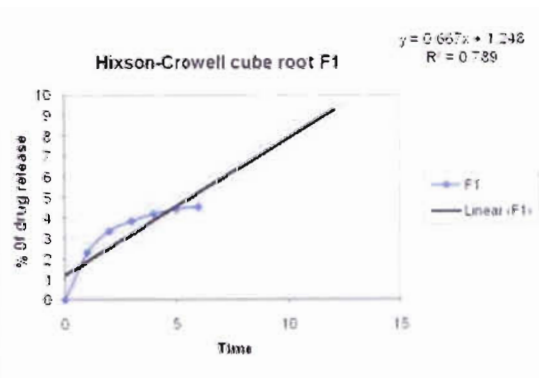
Table 17: Hixson-Crowell cube root release kinetic profiles

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	2.32697	2.09538	2.33921	1.84691	2.24402	2.20358
2	3.37666	2.59129	2.92791	2.28305	2.93953	2.73239
3	3.86642	3.0037	3.21722	2.7633	3.23325	2.99629
4	4.20212	3.2958	3.4925	3.10723	3.45102	3.36492
5	4.44121	3.51962	3.85524	3.27729	3.68157	3.53569
6	4.54845	3.72532	4.03715	3.41138	3.94294	3.73012
7		3.91487	4.16786	3.52231	4.06559	3.87754
8		4.11932	4.31425	3.66179	4.14664	4.00416
9		4.19266	4.38299	3.83495	4.18886	4.15438
10		4.30707	4.44121	3.93865	4.27813	4.31961
11		4.38819	4.50123	3.98536	4.29084	4.39165
12		4.45972	4.50781	4.06559	4.35681	4.48306

Fig. 16. : Hixson-Crowell cube root release kinetic profiles of the proposed formulations (F1-F6) of Diclofenac 12 H SR tablet in Graphical explanation

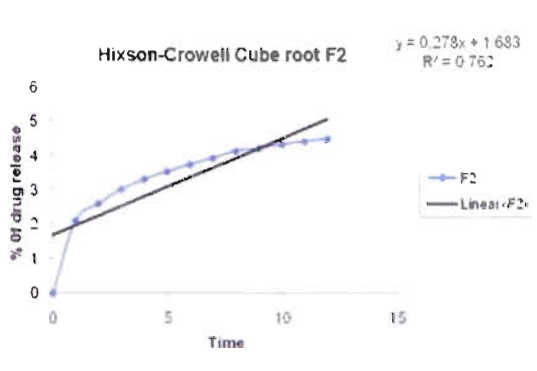**Fig. 16.1. All six Formulations (F1-F6)**   **Fig. 16.2. Formulation F1**
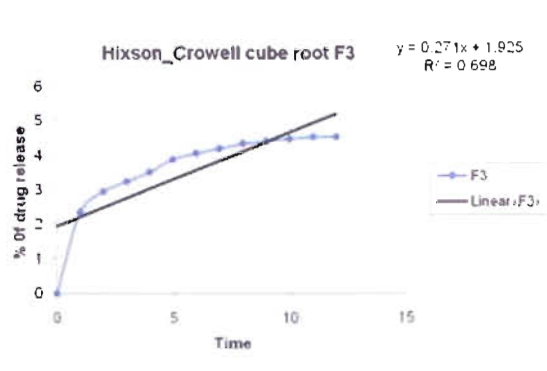
Fig. 16.3. Formulation F2
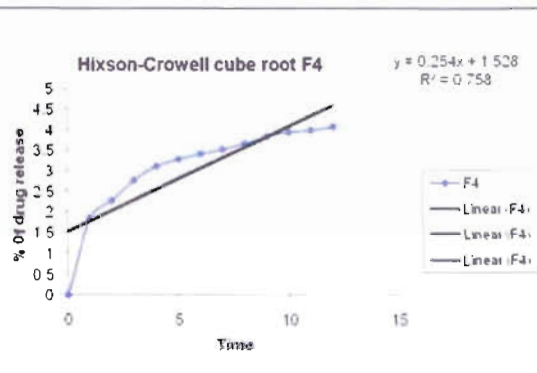

Fig. 16.4. Formulation F3
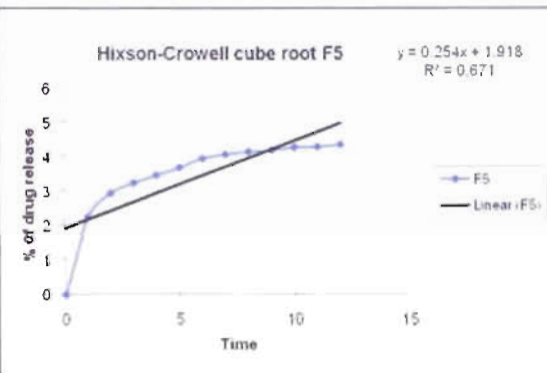

Fig. 16.5. Formulation F4
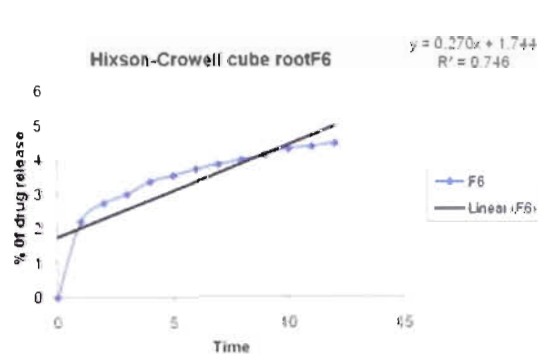

Fig. 16.6. Formulation F5

Fig. 16.7. Formulation 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.

Table 18: Drug release mechanisms (Multiple coefficient [r^2]) of different formulations

Formulation	Multiple Coefficient r^2			
	Zero order	First order	Higuchi	Hixson-Crowell
F-1	0.9772	0.919	0.928	0.7893
F-2	0.9887	0.947	0.9499	0.7628
F-3	0.9514	0.9743	0.9658	0.6982
F-4	0.9851	0.991	0.9524	0.7584
F-5	0.9395	0.9929	0.9735	0.6718
F-6	0.9928	0.9228	0.9546	0.7463

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.

The study for formulation and evaluation of Diclofenac SR tablet matrix with a easy and cheaper process revealed that formulation F-6 at 3:5 of Methocel K15 MCR and 100 KLVCR hydrophilic polymers ratio fulfilled the official requirements. The study also concluded that hydrophilic polymer particles have unique quality to hold drug firmly through matrix formation while compressed into tablet. The predicted values agreed well with the experimental values and the results demonstrated the feasibility of the model. The results also assure us the good compatibility of excipients and API. By doing the little modification of our formulae we may start our further study. However, further study is required for improvement of the formulation F-3 and F-5. The study also emphasize on the formulation of Diclofenac SR tablet in a cheap and easy process in Bangladesh to develop a formulae having better acceptance to the general people of our country.

8

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