Study of Sustained release matrix of Diclofenac from Hydrophilic polymer

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EAST WEST UNIVERSITY

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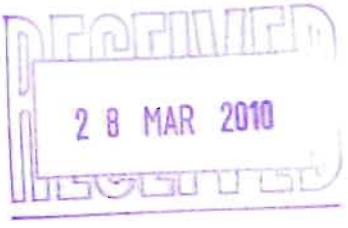
A study paper submitted to the Department of Pharmacy,
East West University in conformity with the requirements
for the degree of Bachelor of Pharmacy



CERTIFICATE

This is to certify that, the thesis 'Study of Sustained release matrix of Diclofenac from Hydrophilic polymer ' submitted to the Department of Pharmacy, East West University, 43 Mohakhali C/A, Dhaka 1212, Bangladesh in partial fulfillment of the requirements for the degree of Bachelor of pharmacy (B. Pharm) was carried out by A.K.M. Rayhan (ID: 2004-2-70-034) under our guidance and supervision and that no part of the thesis has been submitted for any other degree. We further certify that all the sources of information and laboratory facilities availed of in this connection is duly acknowledged.

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I am especially thankful to all the participants without whose enthusiastic cooperation this study would not have been completed.

Finally, I am very grateful to my friends and relatives who encouraged me enormously.

Abstracts

In the entitled study an effort has been delivered to develop once daily-sustained release matrix tablets of diclofenac. The design of Diclofenac SR tablet (NSAID), a cyclooxygenase inhibitor is to achieve more patient compliancy. To prepare tablets of our desired formulation direct compression method were followed which easier and less time is consuming. Since the study concerns with the development of sustained release matrix tablet, a high viscosity and molecular weight (MW>300) of polymer were used. Several ratios of methocel K15 M CR & K100 LVCR (hydrophilic polymer) were used as rate retarding materials. Before compressing the tablets, the granules of different proposed formulations (F-1 to F-9) were evaluated for LBD (0.40-0.435 g/ml), TBD (0.625-0.69 g/ml), % Compressibility Index (30.4-40.03), Total Porosity, Angle of Repose (46.85°-68.96°), Hausner Ratio (1.44-1.90) and % Total Porosity (20.35-30.87 %). The tablets were subjected to thickness, Diameter, weight variation test, hardness and friability test. Depending upon the values of angle of repose and % compressibility index, the granules show poor flow properties. While according to hausner ratio formula F-8 (1.44) shows moderate flow property. In the designing of sustained release product the physical evaluations alone does not indicate a good % release of drugs.

Keywords: Diclofenac, Sustained release, Matrix tablets, Hydrophilic polymer, Direct compression.

List of Contents

Objective of this Study:

The purpose of this work is to evaluate a new method of characterizing flow properties of dry blends of methocel, MCC, Talc and Avicel and to determine if the method can be used to predict the performance of such blends in direct compression tablet manufacturing. It is known that diclofenac is also effective in long-term management of osteoarthritis,Rheumatoid Arthritis (RA) and Ankylosing Spondylitis. preoaration of Diclofenac SR matrix tablet would be more compliant to the patient. Hence to optimize the delivery of medication, the physical evaluation of granules followed by tablets shows transparent view of further proceed in the development of SR matrix tablet of Diclofenac. This study gives idea on how the physical behavior of granules and tablets altered upon the changing of polymer ratio.

CHAPTER-01

(SUSTAINED RELEASED DRUG DELIVERY SYSTEM)

Introduction:

Diclofenac is a COX-2 inhibitor used as an analgesic and anti-inflammatory drug. It has a chondroprotective property, which is useful for long-term management of osteoarthritis. diclofenac is also effective in Rheumatoid Arthritis (RA) and Ankylosing Spondylitis. Chemically it is a phenyl acetic acid molecule, Dichlorophenyl acetic acid. According to the pharmacokinetic property of Diclofenac, it rapidly and completely absorbed after oral administration with peak plasma concentration with in 1.25to 3 hours but highly protein bound (>99%) in plasma having 25 L volume of distribution. The high concentration with rapid absorption of drug causes adverse effect to GIT. Diclofenac has a short biological half-life (about 4 hours), and the usual oral dosage regimen is 100 mg taken twice daily. In Bangladesh Diclofenac is only available as quick release. Of all orally administer dosage form tablet is most preferred because of ease of administration, compactness and flexibility in manufacturing. Direct compression method for the preparation of Diclofenac SR tablet is preferred since this method includes low manufacturing cost and high mechanical integrity of the tablets.

Oral sustained release preparations are suitable for drugs having intermediary half-life (around 4 hr), not for drugs of too short or too longer half-life. SR preparation is also unsuitable for drugs requiring larger doses. (Lachman, 1991) the unavailability of Diclofenac SR tablet in Bangladesh is also triggered us to start evaluation of prepared Diclofenac granules and tablets. In evaluating Diclofenac as candidate for sustained release formulation certain advantages has been considered. Maintenance of therapeutic effect for longer period of time, reduction of dosage frequency, increasing patient compliances, avoidance of overnight dosing are superior over other conventional dosage forms.

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

Chemical breakdown or interactions between tablet components may alter physical tablet properties, greatly changing the bioavailabilty of a tablet system. The design of a tablet that emphasizes only the desired medicinal effects may produce a physical inadequate product or vice versa. Physical evaluation is the prerequisite to get the unaltered medicinal agent. Thus our only concern has been made towards the physical evaluation of granules and tablets.

In the present work, an attempt has been made to develop once daily sustained release matrix tablets of Diclofenac from Mehtocel K15 MCR & 100 LVCR for compliance of the users.

Concept of Sustained Release Dosage Form:

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

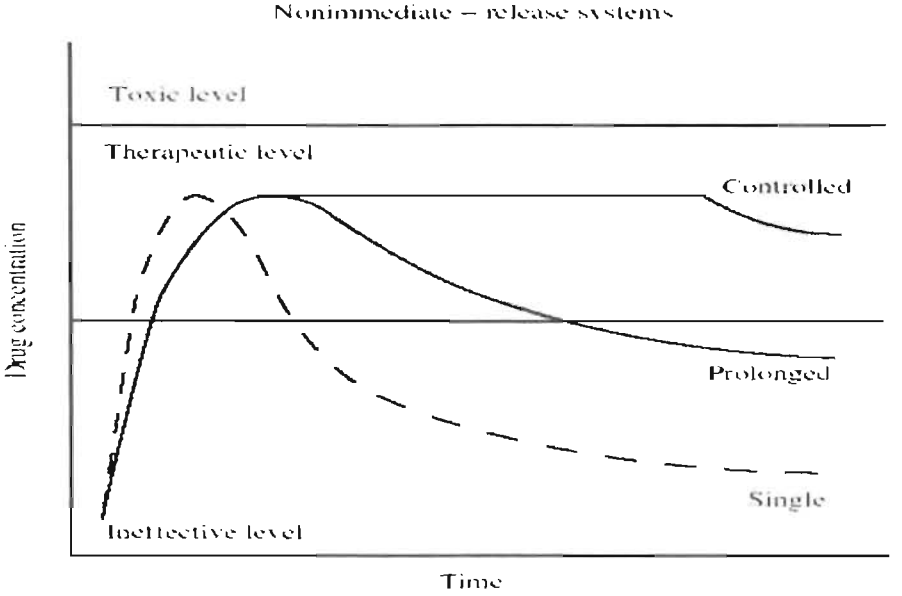

Figure-1.2: Plot of drug concentration versus time for different release systems.

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

In recent years considerable attention has been paid in the development of new drug delivery systems. 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 an upsurge of research into providing 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 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.

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.

One of the first commercially available products to provide sustained release of a drug was Dexedrine Spansules® made by Smith Kline & French. After this many more sustained release products came to the market, some successful, others potentially lethal. (Aulton, 2002)

Rationale For Sustained Released Dosage Form:

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)

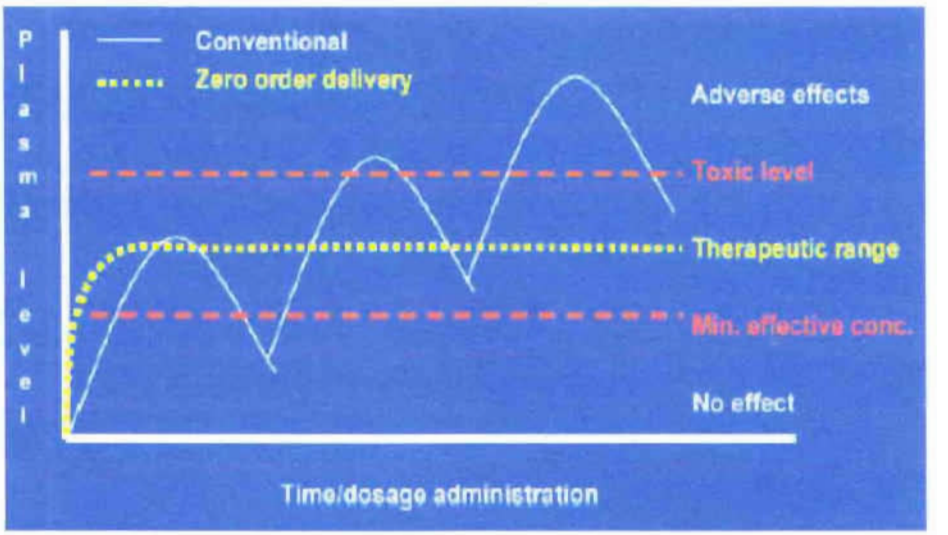

Figure 1.4: Adverse effects of conventional drug therapy

If we consider the route of drug administration, a conventional dosage forms (Figure-2) of the drug. E.g., solution, suspension, capsule, tablet etc produces a drug blood level versus time profile, which does not maintain within the therapeutic range for an extended period of time. It is due to the inability of these conventional dosage forms to control the temporal release of drugs. If any attempt to maintain drug-blood levels in the therapeutic range for a longer period, e.g., by increasing the dose of an intravenous injection, toxic levels may be produced at early time which is undesirable. For this an alternate option would be administration of drugs repeatedly using a constant dosing interval as in multiple dose therapy. In this case the drug blood level reached and the time required to reach that level depend on the dose and the dosing interval. But there are several potential problems regarding multiple dose therapy.

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

Secondly, the drug blood level may not be within the therapeutic range at sufficiently early times required for certain disease states.

Thirdly, patient noncompliance of taking the medicine after short intervals can result in failure of this approach.

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

Advantages of sustained release dosage forms:

a) 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.

b) 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.

c) 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.

d) 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.

e) Reduction in GI side effects:

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

f) More economical.

Potential disadvantages of sustained release dosage forms:

a) 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.

b) 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.

c) 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.

d) 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.

e) Less flexibility of physicians:

Physician faces problem in adjusting dosage regimens.

f) 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.

g) Undesired by product of degradation may take place.

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

Chapter- 02

POLYMER BASED DRUG DELIVERY SYSTEM

Polymers in Pharmaceutical Technology:

The emergence of controlled release (CR) technology as an effective way to enhance patient compliance and extend the life cycle of a drug has led to the need for novel ways of controlling the drug release profiles. Polymers present a logical and simple approach to control the release of drugs. The use of polymers in pharmaceutical preparation dates back to 3000 B.C.E, 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)

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

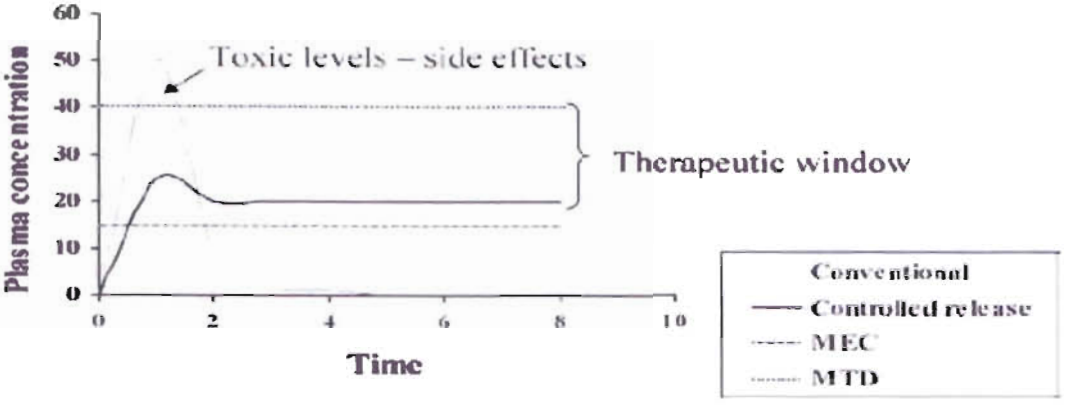

Figure 2.1: Comparison of typical pharmacokinetic profiles seen for conventional versus controlled release formulations. Abbreviations: MEC, minimum effective concentration; MTD, maximum tolerable dose.

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

Polymers in Controlled Drug Delivery

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

Table –2.2

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

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

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

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, 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.

Selection of polymer:

Based on the above-mentioned polymers and depending on the physicochemical properties methocel polymer had chosen.

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 htdroxypropyl substitution on the anhydroglucose units. (Figure-2.3) The substitution pattern in methocel can as follows. (Table-2.3)

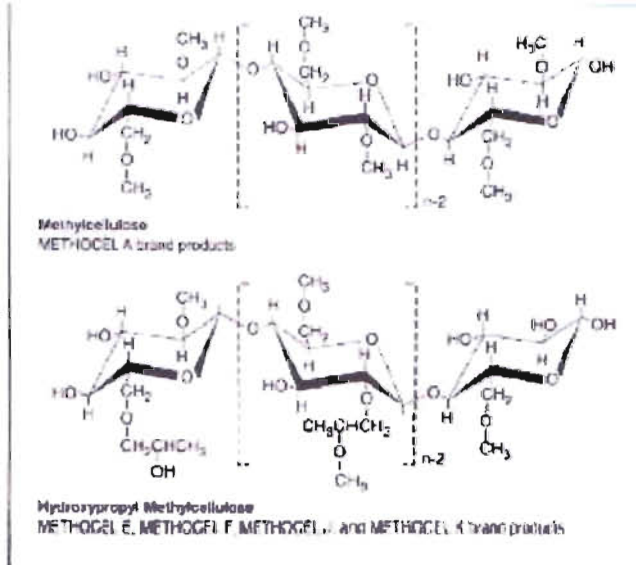

Figure2.3.1: Typical chemical structure of Methocel products

Table-2.3.1: Degree of substitution for methocel products

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

Hence 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 (3.3.1) lists

the typical properties of METHOCEL™ Premium Products generally used for controlled release. The physical form of these products is an off-white powder.

Nomenclatures for Polymers (Methocel):

METHOCEL™ is a trademark of The Dow Chemical Company for a line of cellulose ether products. An initial letter identify as the type of cellulose ether, its "chemistry." "A" identify as methyl cellulose (MC) products. "E," "F," and "K" identify different Hypromellose products. METHOCEL™ E and METHOCEL™ K are the most widely used for controlled release drug formulations. The number that follows the chemistry designation identifies the viscosity of that product in millipascal-seconds (mPa·s), measured at 2% concentration in water at 20°C. In designating viscosity, the letter "C" is frequently used to represent a multiplier of 100, and the letter "M" is used to represent a multiplier of 1000.

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

To understand the nomenclature for Methocel polymer the following pictorial presentation could be helpful. (Figure2.3.2)

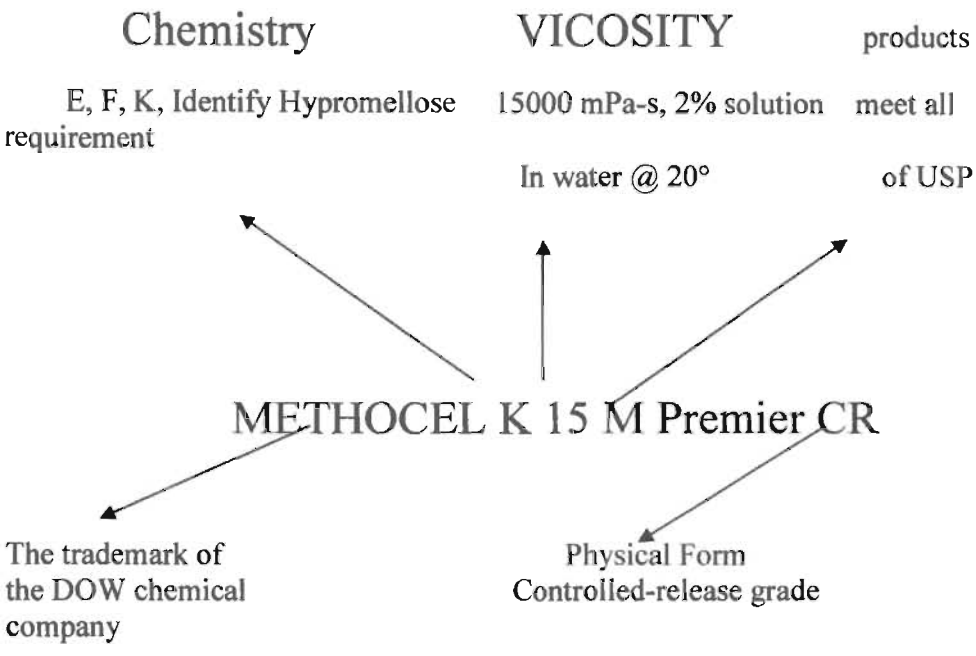

Figure2.3.2: Nomenclature for a methocel K15M CR

Hydrophilic Matrix Device:

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

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

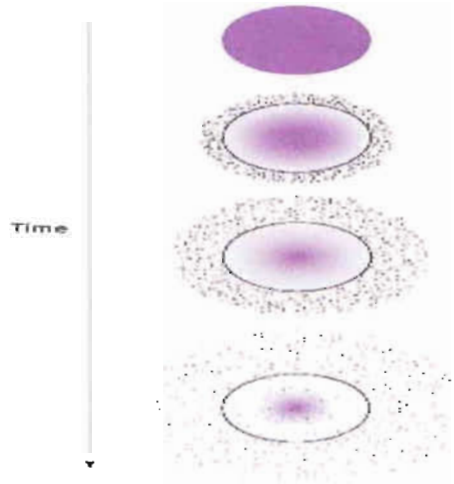

Figure2.5: Drug delivery from a typical matrix drug delivery system.

CHAPTER-03

(MATERIALS & METHODS)

Materials:

Diclofenac Sodium was purchased from Profarmaco Milan, Italy. Hydroxypropylmethylcellulose (Methocel K15M) was supplied by Dow Chemicals, Miami, U.S.A. The viscosity of 2% HPMC aqueous solution is 0.05 Pa.s. Microcrystalline cellulose (Avicel pH 101) was obtained from FMC Corp., Philadelphia, U.S.A. Lactose was purchased from Foremost Whey Products, Div. Wisconsin Dairies, U.S.A. Polyvinylpyrrolidone (PVP) with molecular weight of 35,000 was purchased from Merck, Germany. All other reagents were analytical or pharmaceutical grade.

List of ingredients used in experiment (Table: 4.1)

Name of the material	Function
Diclofenac	API (Active Pharmaceutical Ingredients)
Methocel K15 MCR	Rate controlling polymer, Binder
Methocel 100 LVCR	Rate controlling polymer, Binder
Microcrystalline cellulose (Avicel PH 101)	Disintegrant
Aerosil (colloidal silicon di oxide)	Filler
Talc	Lubricant

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

Figure 4.1(a): Weighing Machine & Fribilator used

Figure4.1 (b): Single Punch Tablet Machine

Chosen Drug (Diclofenac):

Diclofenac is an orally administered phenyl acetic acid derivatives with effects on a variety of inflammatory mediators.

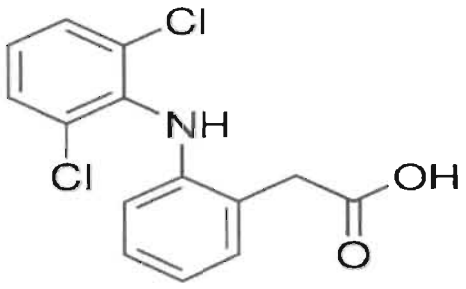

Figure 4.1.1: Chemical Structure of Diclofenac

Diclofenac contains not less than 99.0% and not more than the equivalent of 101.0 percent of dichlorophenyl acetic acid.

It is a white or almost white crystalline powder. It is an effective analgesic and anti-inflammatory agent with a good tolerability profile.

Molecular weight: 296.148 g/mole

Chemical formulae: $C_{14}H_{11}Cl_2NO_2$

Action and use: Analgesic; anti-inflammatory.

Appearance: White or almost white, crystalline powder.

Solubility: Practically insoluble in water, freely soluble in acetone, soluble in alcohol.

Content: 99.0 per cent to 101.0 per cent (dried substance).

Storage: In an airtight container, protected from light.

Indications:

- ✓ Osteoarthritis of the knee,
- ✓ diclofenac decrease pain reduces disease severity and improves the functional capacity of the knee
- ✓ Reduces joint inflammation, pain intensity

- ✓ Reduces the duration of morning stiffness in patients with rheumatoid arthritis.
- ✓ Improvement of spinal mobility in patients with ankylosing spondylitis.

Pharmacokinetics:

diclofenac is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after an oral dose.

Protein Bound : High

Absorption : Altered by food

Metabolite: 4'-hydroxyclofenac

Excretion :Renal (70-80%)

Plasma half life: approximately 4 hour

Adverse Drug Reaction:

Diclofenac is well tolerated, with most adverse events being minor and reversible and affecting mainly the GI system. Most common events includes:

- ➢ dyspepsia (7.5%),
- ➢ abdominal pain (6.2%),
- ➢ nausea (1.5%),
- ➢ diarrhea (1.5%),
- ➢ flatulence (0.8%),
- ➢ gastritis (0.6%),
- ➢ constipation (0.5%),

Although the incidence of gastro intestinal adverse events with diclofenac was similar to those of comparator NSAIDS in individual clinical trials, withdrawal rates due to these events were significantly lower diclofenac than with ketoprofen and tenoxicam.

Dosage and Administration

The usual dose of Diclofenac is 100 mg given twice daily by mouth, one tablet in the morning and one in the evening. There is no evidence that the dosage of diclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDS caution should be exercised. (The Merck Manual, 1992)

Excipient profile:

Methocel: Discussed at chapter 2

microcrystalline cellulose (Avicel 101):

Synonym: Avicel PH, cellulose gel, emocel, fibrocel, pharmacel etc (Rowe& Sheskey, 2003)

Molecular weight: ≅ 36000 g/mole

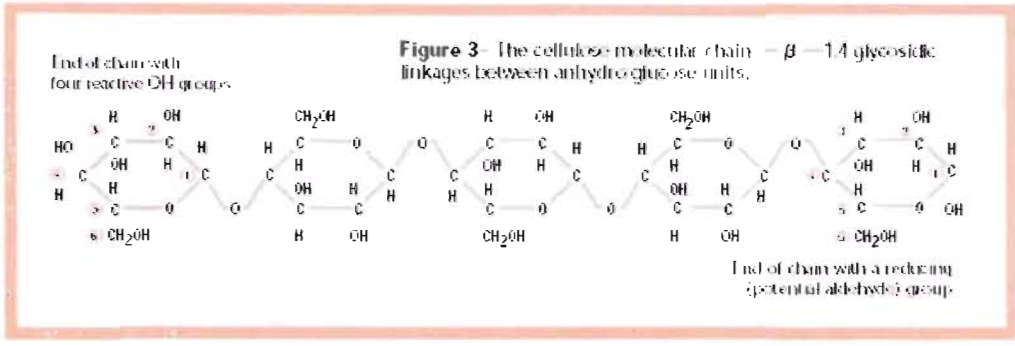

Figure4.2.2: Chemical Structure of Avicel101

Functional category: adsorbent, suspending agent, tablet disintegrants, tablet diluent

Physical appearance:

White, odorless, tasteless and is free from organic and inorganic contaminations.

Solubility: It is partially soluble in water, insoluble in dilute acids and in most organic solvents. It is practically insoluble in sodium hydroxide solution.

Angle of repose: 49°

Bulk density: 0.32 g/cc

Tapped density: 0.45g/cc

Others Chemical and Physical Specifications:

Assay	97.0 to 102.0%
Loss on drying	not more than 6.0% 3600
Water soluble substances	not more than 12 mg/5 grams 3002
Residue on ignition	not more than 0.050% 3601
Heavy metals	not more than 0.001% 3602
pH, NF procedure	5.5 to 7.0
Appearance, visual inspection	white

Aerosil 200:

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

Molecular weight: 60.08 g/mole

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

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

pH: 3.5-4.4

Bulk density:0. 029-0.042g/cc

Tapped density: 0.05-0.1

Flow ability: 35.52% (carr compressibility index)

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

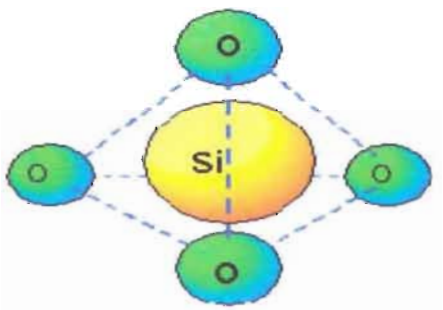

Figure 4.2.3: Silica Di-Oxide (SiO2)

Talc:

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

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

Physical appearance:

White to grayish white powder, odorless, powder

pH: 7-10

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

Figure 4.2.4: Talc

Empirical formulae: $3MgO.4SiO_2H_2O$

Melting point: 1500°c

TABLE 4.2.4 Amount uses:

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

Methods

Preparation and characterization of matrix tablets

The detailed compositions of HPMC matrix tablet formulations are given in Table 1.

Table 1: Composition (in mg) of 50-mg Diclofenac Sodium matrix tablets.

Formulation	HPMC	MCC	Starch	Lactose
MT 1	162.00	-------	46.00	-------
MT 2	153.90	8.10	46.00	-------
MT 3	149.85	12.15	46.00	-------
MT 4	162.00	-------	-------	46.00
MT 5	153.90	8.10	-------	46.00
MT 6	149.85	12.15	-------	46.00
MT 7	162.00	-------	23.00	23.00
MT 8	153.90	8.10	23.00	23.00
MT 9	149.85	12.15	23.00	23.00

HPMC, at different ratios was blended with the Diclofenac Sodium, microcrystalline cellulose (MCC), starch and/or lactose, in a planetary mixer for 5 minutes. Thereafter, the powders were granulated with 10% w/v PVP/EtOH solution, sieved using a N° 14 mesh screen, and the granules obtained dried in a hot air oven at 40°C for 3 hours. Finally, the granules were dried and sieved using a N° 12 mesh screen before tableting. Tablets of approximately 280 mg weight each were prepared from these granules after addition of starch (4%) and magnesium stearate (3.5%). Tablets were compressed using a single punch-tableting machine Erweka, Heusenstamm-Germany, with 9 mm flat round punches. Three batches were prepared for each formulation. The physical properties of the biopolymeric matrix tablets are given in Table 2. The weight variation of the tablets was evaluated on 20 tablets using an electronic balance (Ohaus TS120S). The flow properties were measured by the angle of repose f. Friability was determined using 6 g of tablets in a Roche friabilator for 4 min. at a speed of 25 rpm. For each formulation the hardness of 10 tablets was also evaluated using an ERWEKA TBT 28 apparatus (Erweka GmbH,Germany).

Table 2: Physical properties of Diclofenac Sodium matrix tablets.

Tablet	Weight (mg)	Friability (%)	Hardness (kp)	Thickness (mm)
MT 1	279.6 ± 2.8	0.62 ± 0.3	7.4 ± 1.1	3.97 ± 0.02
MT 2	281.6 ± 3.1	0.68 ± 0.1	8.1 ± 1.0	3.99 ± 0.01
MT 3	280.7 ± 2.0	0.34 ± 0.4	8.4 ± 1.4	3.98 ± 0.03
MT 4	279.0 ± 3.2	0.17 ± 0.1	7.9 ± 1.2	3.97± 0.04
MT 5	280.1 ± 2.5	0.22 ± 0.2	8.6 ± 1.3	3.99± 0.02
MT 6	279.9 ± 1.9	0.06 ± 0.1	7.8 ± 1.2	3.99± 0.05
MT 7	281.0 ± 2.1	0.45 ± 0.2	7.0 ± 1.1	3.98± 0.07
MT 8	279.8 ± 1.5	0.39 ± 0.5	8.2 ± 1.0	3.99± 0.03
MT 9	280.9 ± 2.7	0.06 ± 0.3	8.6 ± 1.1	3.97± 0.02

The tablet hardness ranged from 7 to 9 Kp. The thickness of the tablets was measured on 10 tablets with a Vernier Calipter (Mitutoyo, Japan).

In Vitro Drug Dissolution Studies

Drug release profiles were evaluated in vitro using a dissolution test apparatus (Hanson Research, SR8 8-Flask Bath). The USP paddle method was selected to perform the dissolution profiles of Diclofenac Sodium from HPMC. The same test for all the formulations was carried out in 900 mL 0.1 N HCl, and phosphate buffer, (USP XXIV) maintained at 37 ± 0.5°C at a paddle rotation speed of 50 rpm. Withdrawing 5 mL filtered samples at preselected intervals up to 8 hours monitored progress of the dissolution. The release rates from these hydrophilic polymeric matrices were conducted in a medium of changing pH by starting with a tablet in HCl solution (pH=1,2) for 2 hours. Then, the tablets were immersed into a phosphate buffer (pH=6.8) for 6 hours. The sample solutions were analyzed for Diclofenac Sodium by UV absorbance at 276 nm using a Spectrophotometer Unicam (UV-Vis, Peltier 178). Cumulative percentage of drug release was calculated and the mean of three determinations was used in data analysis.

Release Kinetics

To study the mechanism of drug release from the matrix tablets, the release date were fitted to the following equations:

Zero-order equation: $Q = Q_0 - k_0 t$ *(1)*

where Q is the amount of drug release at time t, and k0 is the release rate;

First-order equation: $\ln Q = \ln Q_0 - k_1 t$ *(2)*

where k1 is the release rate constant;

Higuchi's equation: $Q = k_2 t^{1/2}$ *(3)*

Where Q is the amount of drug release at time t, and k_2 is the diffusion rate constant.

Stability study

A stability test was conducted by storing tablets in amber bottles at ambient temperature, 40°C, and 50°C. The content of DS and the dissolution of drug from these matrix tablets were tested monthly for three months. The assay of DS and the dissolution study followed the same procedure as previously described.

Physical evaluation of granules:

Angle of repose:

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

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

Where,

h = Height of the powder cone.

r = Radius of the powder cone

The suitable range is given below:

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

Bulk density:

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

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

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

Compressibility index:

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

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

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

Hausner Ratio:

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

Hausner Ratio = Tapped Density / Bulk Density

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

Total porosity:

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

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

Hardness & friability test:

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

Thickness:

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

Weight variation test:

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

Solubility of Diclofenac in distilled water:

Diclofenac is practically insoluble in water, freely soluble in acetone, soluble in alcohol. (BP-2007). Thus 10 mg of Diclofenac was solubilizing in 250 ml of distilled water by vigorous shaking. The concentration of that prepared solution was 0.004 mg/ml.

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.

Determination of absorbance of various conc. Of solution

Various absorbance of different concentration were found at 278 nm. Thus a graph of absorbance vs. concentration was plotted.

CHAPTER - 04

(RESULTS & DISCUSSION)

Results and Discussions:

Result and Discussion:

The proposed formulations (F-1 to F-6) of Diclofenac SR tablet matrix were built by utilizing different percentages of Methocel K100 LV CR and Methocel K15M polymers (**table-11**).

Table 11: Formulation of diclofenac (F-1 – F-6)

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

Table 12: Physical parameters of proposed formulation (F-1 – F-6)

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

The physical parameters of the granules of proposed formulations (F-1 to F-6) were measured, where, LBD (g/ml) were 0.221±0.02 and 0.521±0.01, TBD (g/ml) were 0.327±0.02 and 0.475±0.03, Compressibility Index (%) were 11.15±0.03 and 13.35±0.02, Total Porosity (%) were 26.19±0.04 and 34.56±0.01, Angles of Repose were 21.53±0.01 and 29.36±0.01, Drug Content (%) were 89.19±0.03 and 102.63±0.02 respectively. All the data were in an expectable range for the evaluation of the granules (**table- 12**).

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

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

Similarly the physical parameters of tablet were Hardness (kg/cm^2) 3.19±0.01 and 4.35±0.03, Friability (%) 0.0 and 0.12±0.02, Thickness (mm) 4.19±0.12 and 4.90±0.03, Weight Variation Test (%) 1.132±0.02 and 2.903±0.23. All the values were found to be in expected range (table-13) and fulfilled the official requirement for both the granules and the finished product itself.

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

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

dissolution specification 80% drug release within 8th hours in simulated intestinal medium.

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

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

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

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

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

Conclusion:

In order to achieve patient compliance against pain relief, formulation of once daily Diclofenac SR tablet matrix is essential for the management of acute and chronic pain, caused by rheumatoid arthritis, osteoarthritis and ankylosing spondylitis etc. Hydrophilic polymer particles have unique quality to hold drug firmly through matrix formation while compressed into tablet. This matrix promotes desired controlled drug release upon hydration, swelling and gel formation with biological fluid. In Bangladesh the absence of diclofenac SR tablet triggers us to develop a formulae having better acceptance to the general people of our country. 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 and also go for dissolution study. In conclusion, Methocel K15 MCR and 100 KLVCR hydrophilic polymer based formulation F-8 at 4:3 ratio fulfilled the official physical data requirements. However, further improvement is required to determine the flow property of granules.

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