East West University

Study on

"Study of sustain release matrix of Diclofenac from hydrophilic polymer"

Prepared by

Rubiyat Naila

Id: 2005-2-70-070

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Prepared for

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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 Rubiyat Naila (ID: 2005-2-70-079) 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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Acknowledgement

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Abstract

The purpose of this study is to establish a sustained release Diclofenac tablet based on physical and chemical properties. Before evaluate the percentage release of drug, necessary to test physical and chemical stability. Control release depends on polymer. Two different hydrophilic polymers were used with different ratios. This study gives idea that how the ratios of polymers alter the physical behavior of granule or tablet. The results also assure us the good compatibility of excipients and API.

Part one describes Diclofenac as well as NSAID, sustain release technology.

Part two discusses use of polymer technology in control drug delivery.

Part three describes the materials were used and method of tests

Part four analyzes results of data which were tested in lab with discussion

Objective

The importance of controlled delivery drug system is that to achieve the high level of drug plasma concentration for a longer period of time. Among the drug delivery system, oral administration is the most convenient. Now-a-days in control release technology can release at constant rate for days to years. Application of such control release technology by oral administration; still have some limitation because of gastrointestinal transit time. Diclofenac sustain release dosage form is effective and would be more compliant to patients. A basic objective of this dosage form is designed to optimize the delivery of medication in the vivo environment where drug release takes place. Other objective is to formulate matrix Diclofenac by using hydrophilic polymer 'Methocel K15MCR' and '100LVCR' in sustain release dosage form.

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PART-01

NSAID, SUSTAIN RELEASE TECHNOLOGY

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

Diclofenac is available as a generic drug in a number of formulations. Over the counter (OTC) use is approved in some countries for minor aches and pains and fever associated with common infections.

Non-steroidal anti-inflammatory drugs, usually abbreviated to NSAIDs or NAIDs, are drugs with analgesic, antipyretic (lowering an elevated body temperature and relieving pain without impairing consciousness) and, in higher doses, with anti-inflammatory effects (reducing inflammation). The term "non-steroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic.

Prostaglandins are a family of chemicals that are produced by the cells of the body and have several important functions. They promote inflammation, pain, and fever; support the blood clotting function of platelets; and protect the lining of the stomach from the damaging effects of acid.

Prostaglandins are produced within the body's cells by the enzyme cyclooxygenase (COX). There are two COX enzymes, COX-1 and COX-2. Both enzymes produce prostaglandins that promote inflammation, pain, and fever. However, only COX-1 produces prostaglandins that support platelets and protect the stomach. Nonsteroidal antiinflammatory drugs (NSAIDs) block the COX enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammation, pain, and fever are reduced. Since the prostaglandins that protect the stomach and support platelets and

blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and promote bleeding.

NSAIDs are used primarily to treat inflammation, mild to moderate pain, and fever. Specific uses include the treatment of headaches, arthritis, sports injuries, and menstrual cramps. Ketorolac (Toradol) is only used for short-term treatment of moderately severe acute pain that otherwise would be treated with opioids. Aspirin (also an NSAID) is used to inhibit the clotting of blood and prevent strokes and heart attacks in individuals at high risk. NSAIDs also are included in many cold and allergy preparations.

NSAIDs vary in their potency, duration of action, how they are eliminated from the body, how strongly they inhibit COX-1 and their tendency to cause ulcers and promote bleeding. The more an NSAID blocks COX-1, the greater is its tendency to cause ulcers and promote bleeding. One NSAID, celecoxib (Celebrex), blocks COX-2 but has little effect on COX-1, and is therefore further classified as a selective COX-2 inhibitor. Selective COX-2 inhibitors cause less bleeding and fewer ulcers than other NSAIDs.

Aspirin is a unique NSAID, not only because of its many uses, but because it is the only NSAID that inhibits the clotting of blood for a prolonged period (4 to 7 days). This prolonged effect of aspirin makes it an ideal drug for preventing blood clots that cause heart attacks and strokes.

Most NSAIDs inhibit the clotting of blood for only a few hours. Ketorolac (Toradol) is a very potent NSAID and is used for moderately severe acute pain that usually requires narcotics. Ketorolac causes ulcers more frequently than other NSAID. Therefore, it is not used for more than five days. Although NSAIDs have a similar mechanism of action, individuals who do not respond to one NSAID may respond to another.

Sustained Release Dosage Form:

The term "controlled release" means those systems from which active drugs automatically released at predefined rates over a long period of time. The coating is designed to release the 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 measure drug delivery system that shows its action for longer period of time after administration of a single dose (figure-1). (Lachman, 1991)

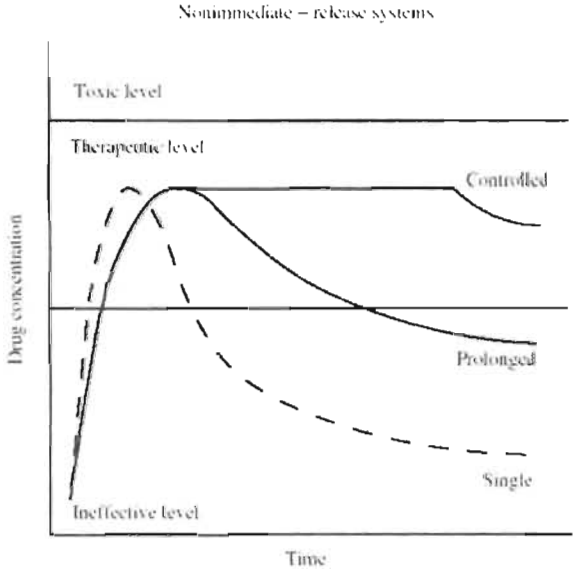


Figure-1: Plot of drug concentration versus time for different release systems.

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)

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. (Banker -501)

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 Aceclofenac.

History of Sustained Release Drug Delivery System:

Because of 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.

Rationale For Sustained Released Dosage Form:

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)

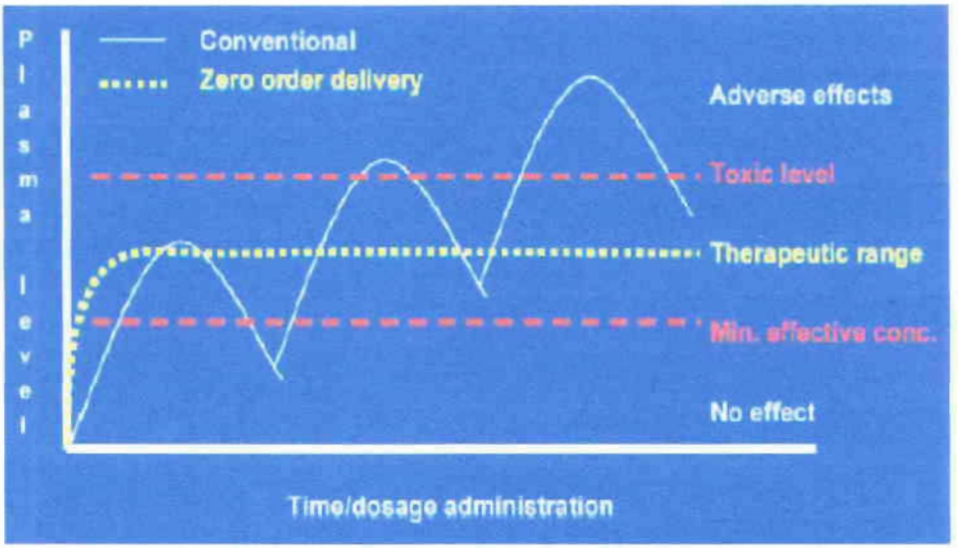


Figure-2: Adverse effects of conventional drug therapy

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

depend on the dose and the dosing interval. But there are several potential problems regarding multiple dose therapy.

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

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

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

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

Types of Controlled or Sustained Drug Delivery System:

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

Examples of oral sustained/extended release products:

Table-1

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

Advantages of sustained release dosage forms:

a) 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.

b) More economical

c) Patient compliance

d) No chance of forgotten

e) 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.

f) 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.

g) Reduction of systemic side effects

h) 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 every 12-hour contributes improved control of therapeutic drug concentration.

Disadvantages of sustained release dosage forms:

a) Chances of dose dumping:

b) Local irritation to GI mucosa:

c) Delayed termination of therapy:

d) Less flexibility of physicians:

e) 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.

f) Undesired by product of degradation may take place.

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

Mechanisms of controlled release:

The goal of sustain release to achieve high blood level for a longer period of time. This achievement is fulfilled through four different mechanisms naming below (Sinko, 2006):

- Diffusion
- Degradation
- Swelling followed by diffusion
- Active efflux

Diffusion:

A polymer and active agent might be mixed to form a homogenous system, also referred as matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment. A polymeric controlled release micro sphere represents an example of a matrix controlled release system. (Sinko, 2006)

Swelling followed by diffusion:

Swelling controlled release systems are initially dry, after placing in the body it absorbs water or other body fluids and swell. The swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment. Most of the materials used in the swelling controlled release systems are based on hydrogels. These hydro gels can absorb a significant amount of fluid and at equilibrium, typically comprise 60%-90% fluid and only 10%-40% polymer. (Sinko, 2006)

Degradation:

The system is also referred as biodegradable system where the materials degrade within the body as a result of natural biologic processes, eliminating the need to remove a drug delivery system after completed release of the active ingredients.

Active efflux:

Several drug delivery mechanisms uses the mechanism of elementary osmotic pump, also called as OROS or the gastrointestinal therapeutic system. Theeuwes and Yum first described it. (Sinko, 2006)

In the GI tract, water passes through the semi permeable membrane of the system, expanding the osmotic engine that in turn pushes against the drug layer, releasing drug through a delivery orifice into the GI tract.

Factors affecting controlled release technology:

Physiochemical properties of drug	Biological properties of drug	Patient or disease factor
Aqueous solubility	Biological half life & elimination	Age
Stability	Duration of action	Physiological state
pka value	Side effect of drug	Location of target area
Protein binding	Dose size	
Molecular size and diffusivity	Requirement of acute & chronic therapy	
Absorption characteristics		
Distribution characteristics		
Metabolism		

Table-2

PART-02

POLYMER BASED DRUG DELIVERY SYSTEM

Polymers in Pharmaceutical Technology:

The importance of controlled release technology is very effective for patient compliance. Polymers present a logical and simple approach to control the release of drugs. The polymers are used in pharmaceutical preparation from early 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 excellent in sustain release of 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.

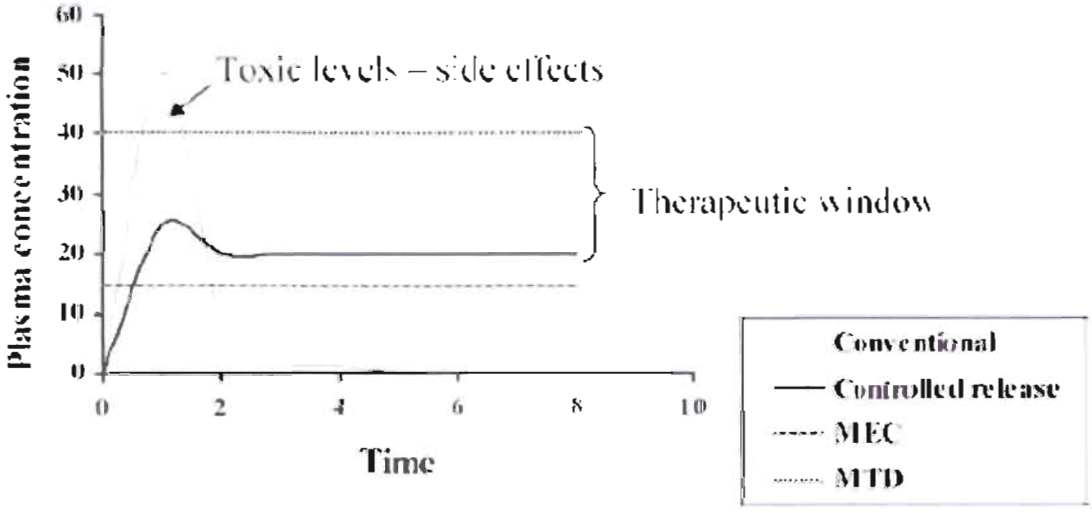


Figure-3: Comparison of typical pharmacokinetic profiles seen for conventional versus controlled release formulations. Abbreviations: MEC, minimum effective concentration; MTD, maximum tolerable dose.

Polymers in Controlled Drug Delivery

The selection of polymers is done according to the following segmentations.

Application	Products Recommended	Typical Use Level	Advantages
Controlled Release Matrix Tablets	METHOCEL K100LV, K4M, K15M, 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
	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:

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. The substitution pattern in methocel can as follows.

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.

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. 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.

PART- 03

MATERIALS AND METHOD

Materials:

Drug: Diclofenac

Polymers: Mehtocel K15 MCR & Methocel 100 LVCR.

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

List of ingredients used in experiment

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

Table-3

Equipments: Shimadzu UV Spectrophotometer Sartorius electronic balance, thickness gauge, Monsanto hardness tester, Roche friabilator, funnel, graduated cylinder, single punch tablet machine.

Chosen Drug (Diclofenac):

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

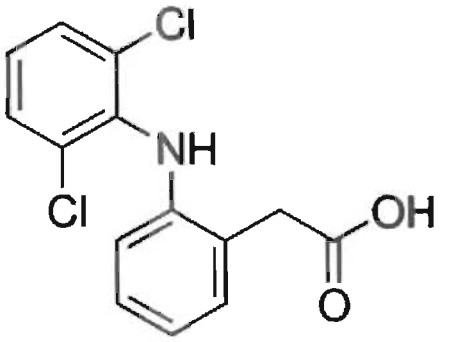


Figure-4: Chemical Structure of Diclofenac

2-(2-(2,6-dichlorophenylamino)phenyl)acetic acid

Formula: $C_{14}H_{11}Cl_2NO_2$

Mol. mass: 296.148 g/mol

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.

Storage: In an airtight container, protected from light.

Pharmacokinetic data
Bioavailability: 100%
Protein binding more than 99%
Metabolism: hepatic, no active metabolites exist
Half life: 1.2-2 hr (35% of the drug enters enterohepatic recirculation)
Excretion biliary, only 1% in urine

Mechanism of action

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

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

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

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

There are marked differences among NSAIDs in their selective inhibition of the two subtypes of cyclo-oxygenase, COX-1 and COX-2. Much pharmaceutical drug design has attempted to focus on selective COX-2 inhibition as a way to minimize the gastrointestinal side effects of NSAIDs like aspirin. In practice, use of some COX-2 inhibitors due to their adverse effects has led to massive numbers of patient family lawsuits alleging wrongful death by heart attack, yet other significantly COX-selective NSAIDs like diclofenac have been well-tolerated by most of the population.

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

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

Indications:

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

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

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

In many countries eye-drops are sold to treat acute and chronic non-bacterial inflammations of the anterior part of the eyes (e.g. postoperative states). A common brand name is Voltaren-ophta.

Diclofenac is often used to treat chronic pain associated with cancer, particularly if inflammation is also present (Step I of the World Health Organization (WHO) Scheme for treatment of chronic pain). Good results (sometimes better than those with opioids) have been seen in female breast cancer and in the pain associated with bony metastases. Diclofenac can be combined with opioids if needed. Combaren, a fixed combination of diclofenac and codeine (50 mg each), is available for cancer treatment in Europe. Combinations with psychoactive drugs such as chlorprothixene and/or amitriptyline have also been investigated and found useful in a number of cancer patients.

Fever due to malignant lymphogranulomatosis (Hodgkin's lymphoma) often responds to diclofenac. Treatment can be terminated as soon as the usual treatment with radiation and/or chemotherapy causes remission of fever.

Diclofenac may prevent the development of Alzheimer's disease if given daily in small doses during many years. All investigations were stopped after it was found that some of the other investigated NSAIDs (naproxen, rofecoxib) caused a higher incidence of death cases due to cardiovascular events and stroke compared to placebo.

Diclofenac has been found to increase the blood pressure in patients with Shy-Drager syndrome and Diabetes Mellitus. Currently, this use is highly investigative and cannot be recommended as routine treatment.

Diclofenac has been found to be effective against all strains of multi drug resistant E. coli, with a MIC of 25 micrograms/mL. Therefore, it may be suggested that diclofenac has the capacity to treat uncomplicated urinary tract infections (UTI) caused by *E. coli.* It has also been shown to be effective in treating Salmonella infections in mice and is under investigation for the treatment of tuberculosis.

Diclofenac is an antiuricosuric

Contraindications

- Hypersensitivity against diclofenac
- History of allergic reactions (bronchospasm, shock, rhinitis, urticaria) following the use of Aspirin or another NSAID
- Third-trimester pregnancy
- Active stomach and/or duodenal ulceration or gastrointestinal bleeding
- Inflammative intestinal disorders such as Crohn's disease or ulcerative colitis
- Severe insufficiency of the heart (NYHA III/IV)

- Recently, a warning has been issued by FDA not to use to treat patients recovering from heart surgery
- Severe liver insufficiency (Child-Pugh Class C)
- Severe renal insufficiency (creatinine clearance <30 ml/min)
- Caution in patients with preexisting hepatic porphyria, as diclofenac may trigger attacks
- Caution in patients with severe, active bleeding such as cerebral hemorrhage
- NSAIDs in general should be avoided during dengue fever.

Side effects

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

Gastrointestinal

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

Hepatic

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

Renal

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

Other

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

- Diclofenac may disrupt the normal menstrual cycle.

Excipient profile:

Methocel: Discussed previous

Microcrystalline cellulose (Avicel 101):

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

Molecular weight: ≅ 36000 g/mole

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%
Loss on drying	Not more than 6% 3600
Water soluble substances	Not more than 12 mg/5 grams 3002
Residue on ignition	Not more than 0.005% 3601
Heavy metals	Not more than 0.001% 3601
pH, NF procedure	5.5 to 7
Appearance, visual inspection	White

Aerosil:

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

Molecular weight: 60.08 g/mole

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

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

pH: 3.5-4.4

Bulk density:0. 029-0.042g/cc

Tapped density: 0.05-0.1

Flow ability: 35.52% (carr compressibility index)

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

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

Empirical formulae: $3MgO.4SiO_2H_2O$

Melting point: 1500°c

Amount uses:

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

Methods

Tablet Granulation:

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.

Preparation of matrix tablet of diclofenac:

The tablet was prepared by simple blending of active ingredient with polymers, tablet disintegrant, diluent, glidant followed by direct compression.
Properly weighed Methocel, talc, Aerosil and the active ingredient were then taken 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.

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 (Cooper J and Gunn C, 1986)

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

Where,

h = Height of the powder cone.

r = Radius of the powder cone

The suitable range is given below:

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

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 (%) = $\{(TBD - LBD)\ X\ 100\}/TBD$

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

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)

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.

Dissolution study:

These studies were conducted at 37±0.5^{0}C on an USP specification dissolution rate test type II apparatus (Paddle apparatus) with six section assembly according to the USP XXII procedure with monitor 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 stimulated gastric medium (0.1 N HCl pH 1.2)
For 0.1 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 10000 ml adjusting pH by addition of 1.2 ml *O*-phosphoric acid. The dissolution test was performed using 900 ml medium at 37±0.5^{0}C and 50 rpm.

The medium was preheated to 37^{0}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.

PART- 04

RESULT AND DISCUSSION

Result and Discussion:

The proposed formulations (F-1 to F-6) of diclofenac sodium SR tablet matrix were built by utilizing different percentages of Methocel K100 LV CR and Methocel K15MCR polymers (**table-4**).

Table 4: Formulation of diclofenac (F-1 – F-6)

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

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

Table 5: Physical parameters of proposed formulation (F-1 – F-6)

Parameter (n = 6)	**Parameter value (Mean ± SE)**					
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
LBD (g/ml)	0.401 ± 0.02	0.521 ± 0.01	0.371 ± 0.03	0.453 ± 0.01	0.211 ± 0.03	0.221 ± 0.02
TBD (g/ml)	0.387 ± 0.01	0.462 ± 0.02	0.327 ± 0.02	0.352 ± 0.02	0.475 ± 0.03	0.339 ± 0.01
Hausner Ratio	0.96	0.88	0.88	0.77	2.25	1.53
Compressibility Index	11.15	12.58	12.49	11.17	11.45	13.35

(%)	± 0.03	± 0.02	± 0.03	± 0.01	± 0.01	± 0.02
Total Porosity (%)	32.29 ± 0.02	26.19 ± 0.04	29.36 ± 0.01	34.56 ± 0.01	26.73 ± 0.02	34.13 ± 0.01
Angle of Repose	22.56 ± 0.03	24.31 ± 0.01	22.47 ± 0.03	29.36 ± 0.01	24.76 ± 0.01	21.53 ± 0.01

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

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 and fulfilled the official requirement for both the granules and the finished product itself.

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

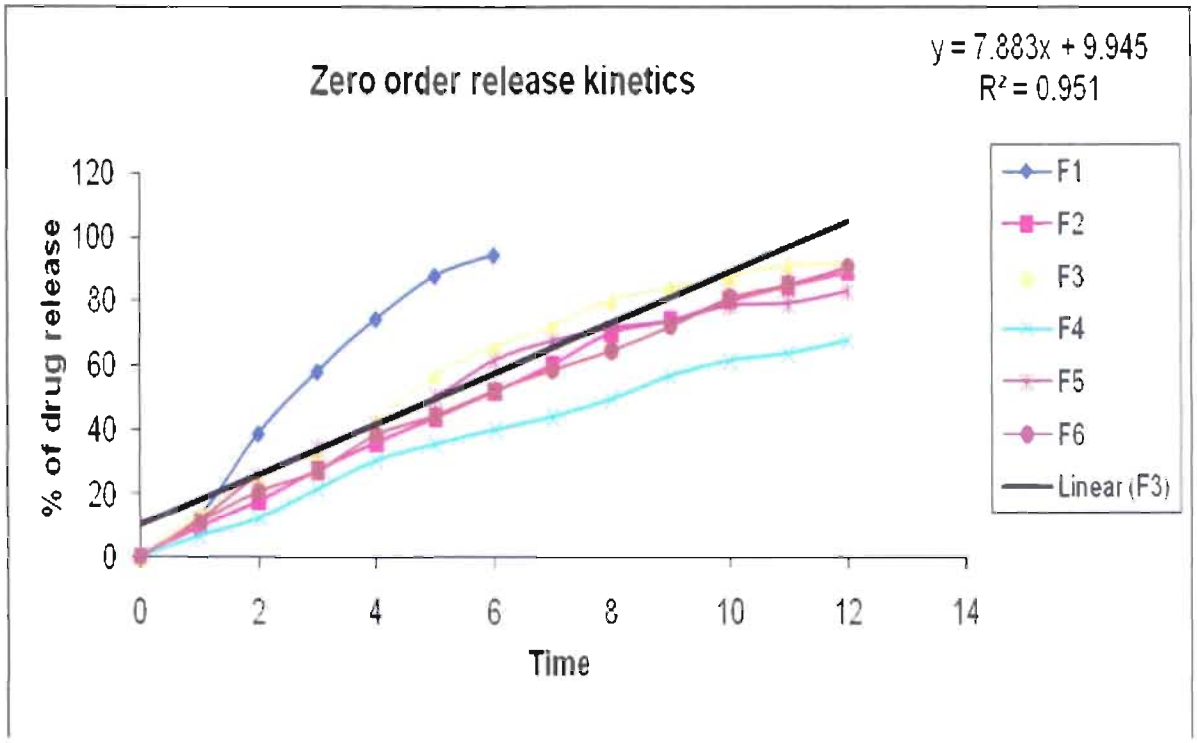
Parameter	Parameter value (Mean ± SE)					
	F-1	F-2	F-3	F-4	F-5	F-6
Hardness (n = 6) (kg/cm^2)	3.5 ± 0.23	4.35 ± 0.03	4.15 ± 0.02	4.275 ± 0.021	3.19 ± 0.01	3.265 ± 0.02
Friability (n = 10) (%)	0.00	0.00	0.12 ± 0.02	0.00	0.00	0.00
Thickness (n = 6) (mm)	4.59 ± 0.02	4.43 ± 0.03	4.19 ± 0.12	4.90 ± 0.03	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 8^{th} hours in simulated intestinal medium.

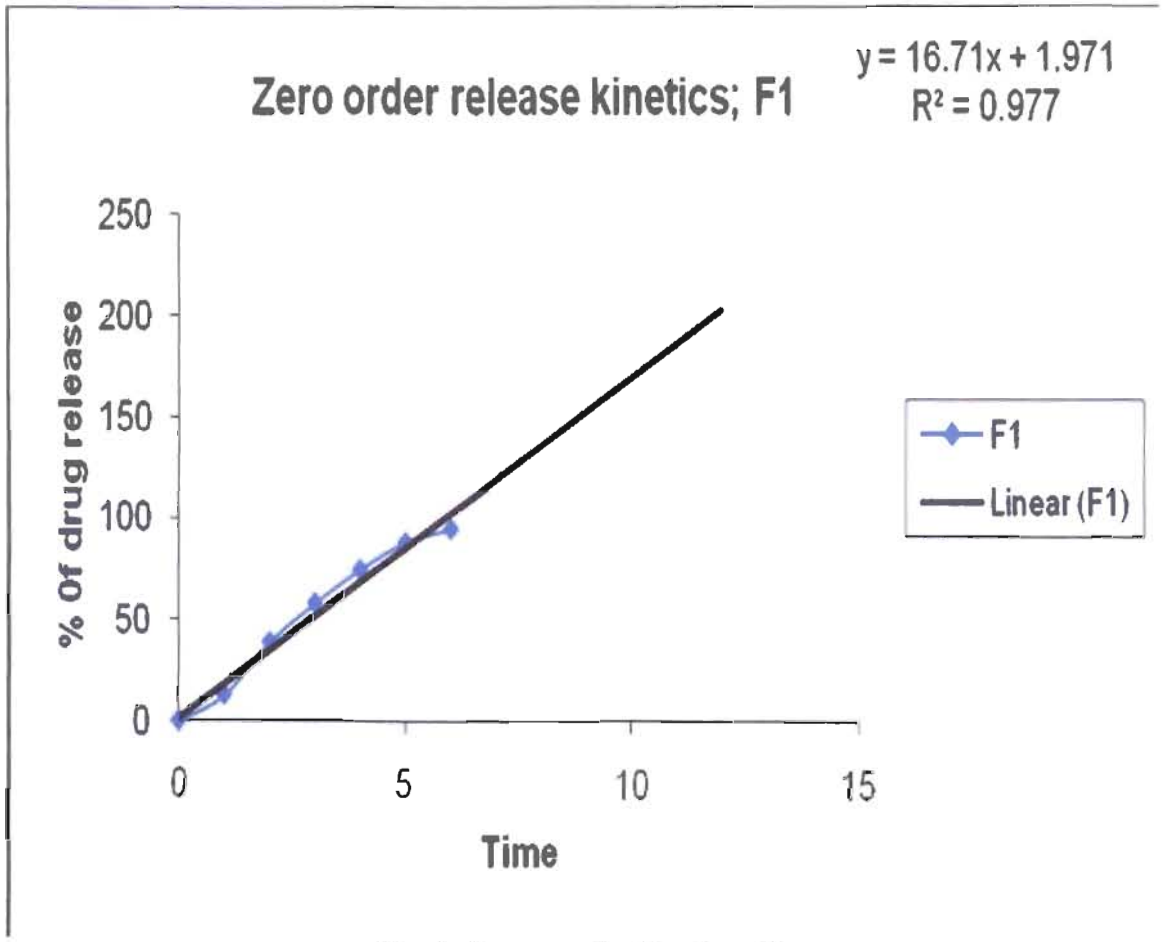
Table 7: Zero order release kinetic profiles

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

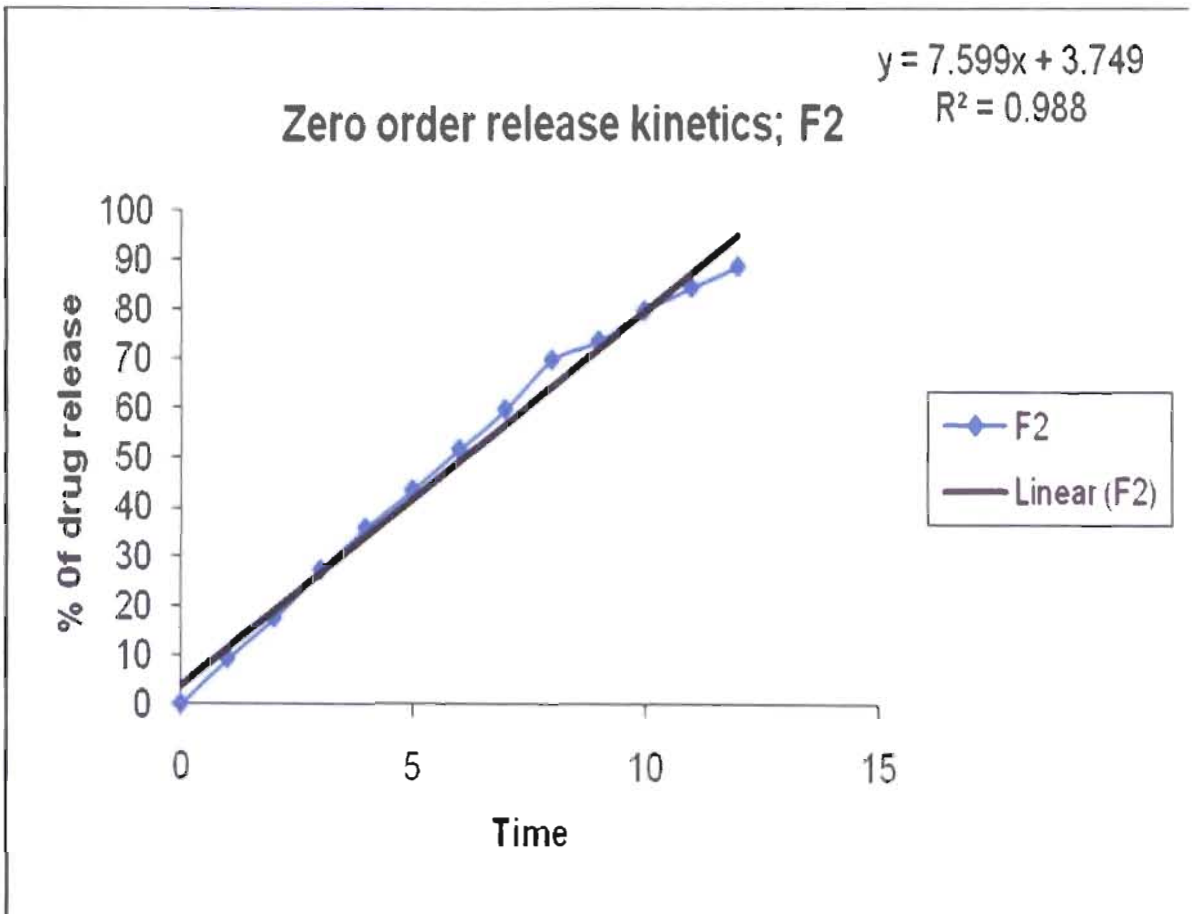
7		60	72.4	43.7	67.2	58.3
8		69.9	80.3	49.1	71.3	64.2
9		73.7	84.2	56.4	73.5	71.7
10		79.9	87.6	61.1	78.3	80.6
11		84.5	91.2	63.3	79	84.7
12		88.7	91.6	67.2	82.7	90.1



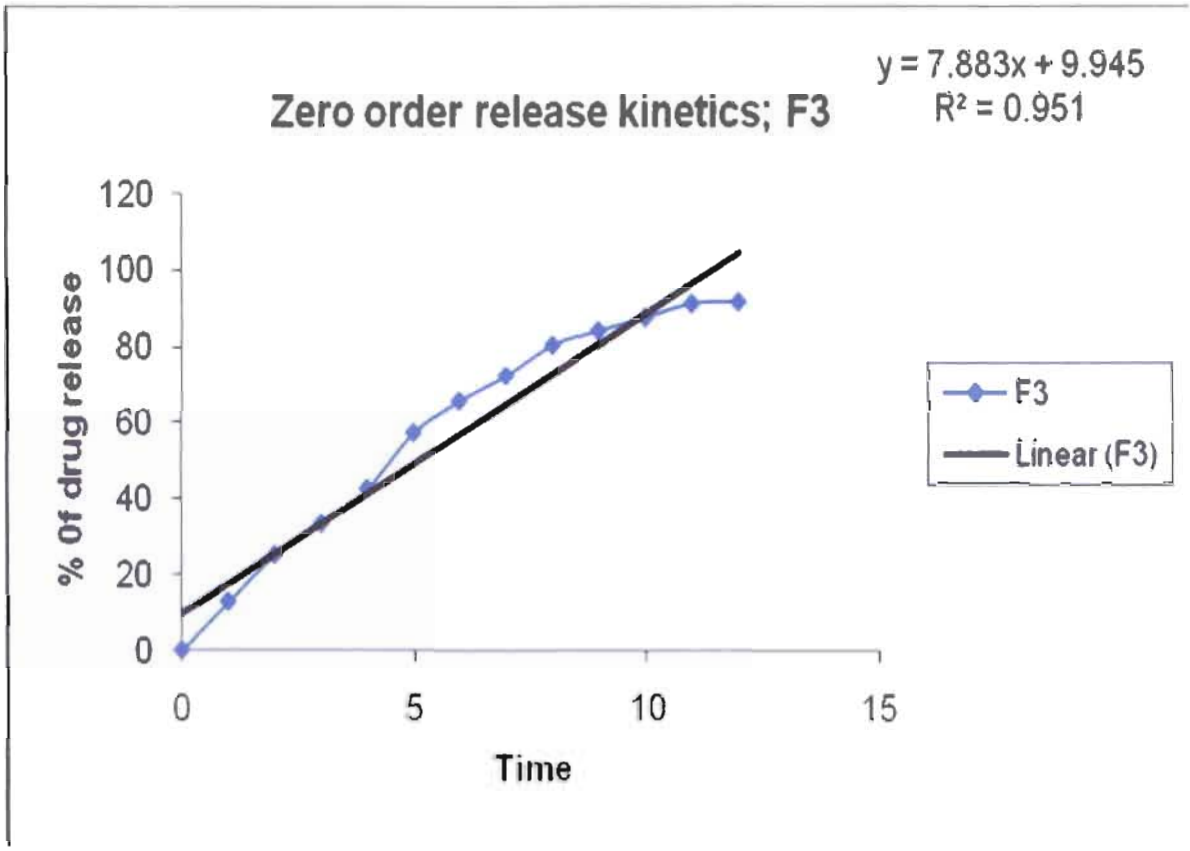
Graph-1: zero order release kinetics



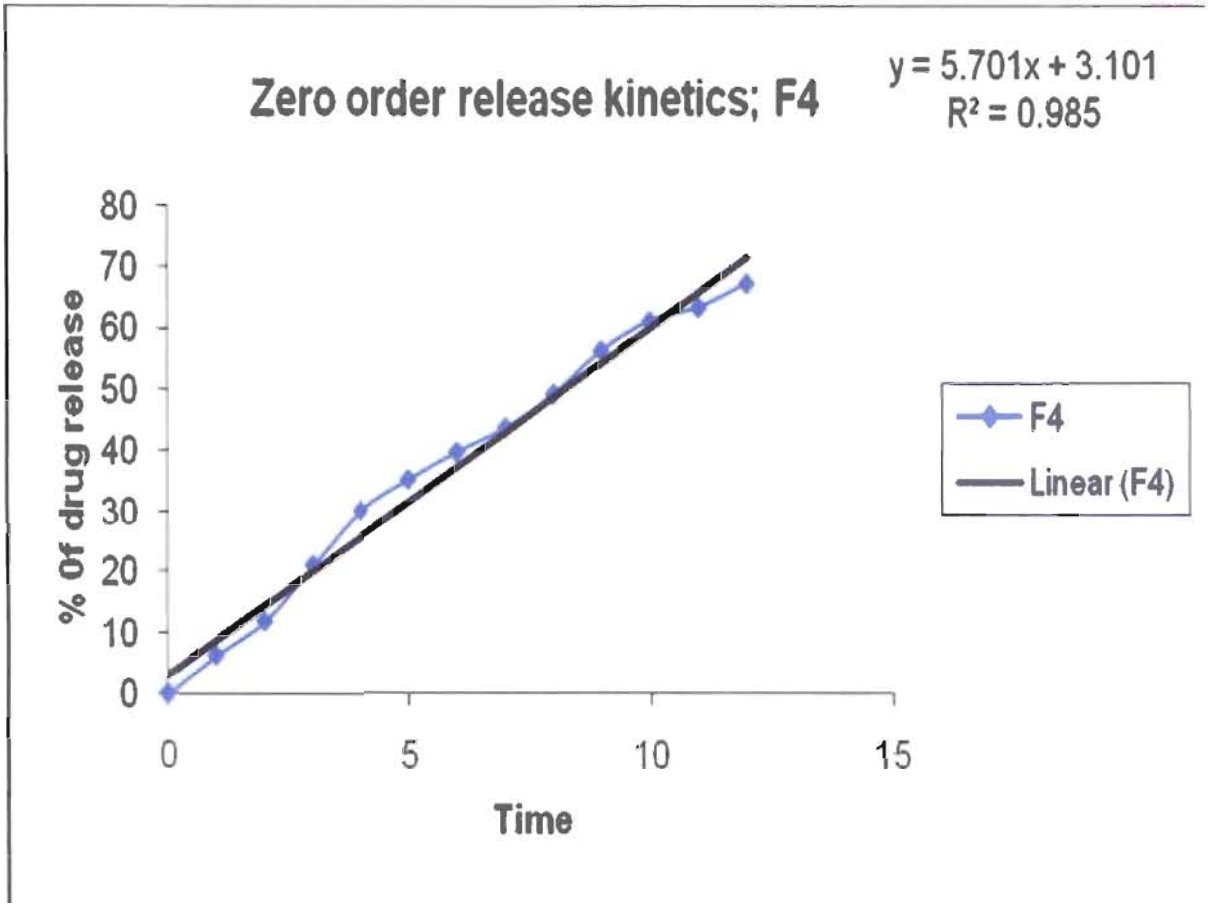
Graph-2: zero order kinetics; F1



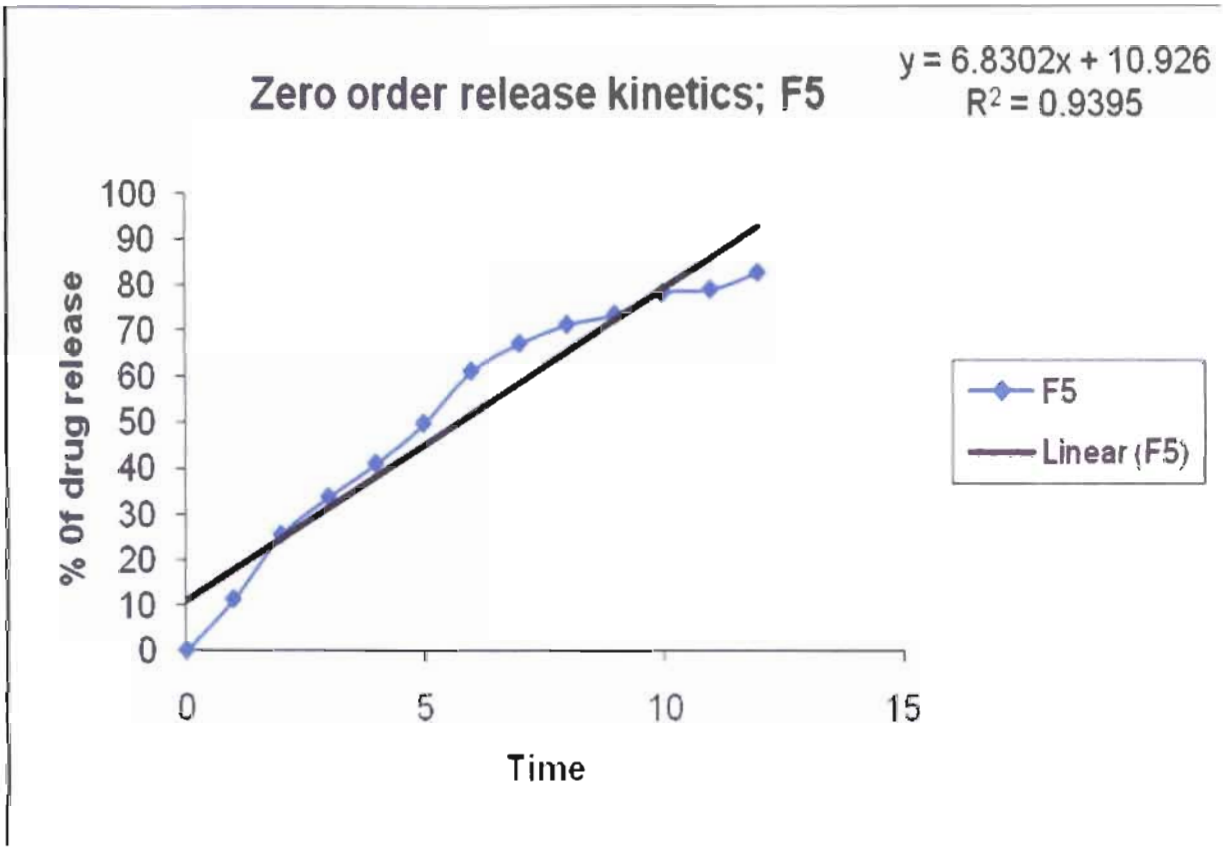
Graph-3: Zero order release kinetics; F2



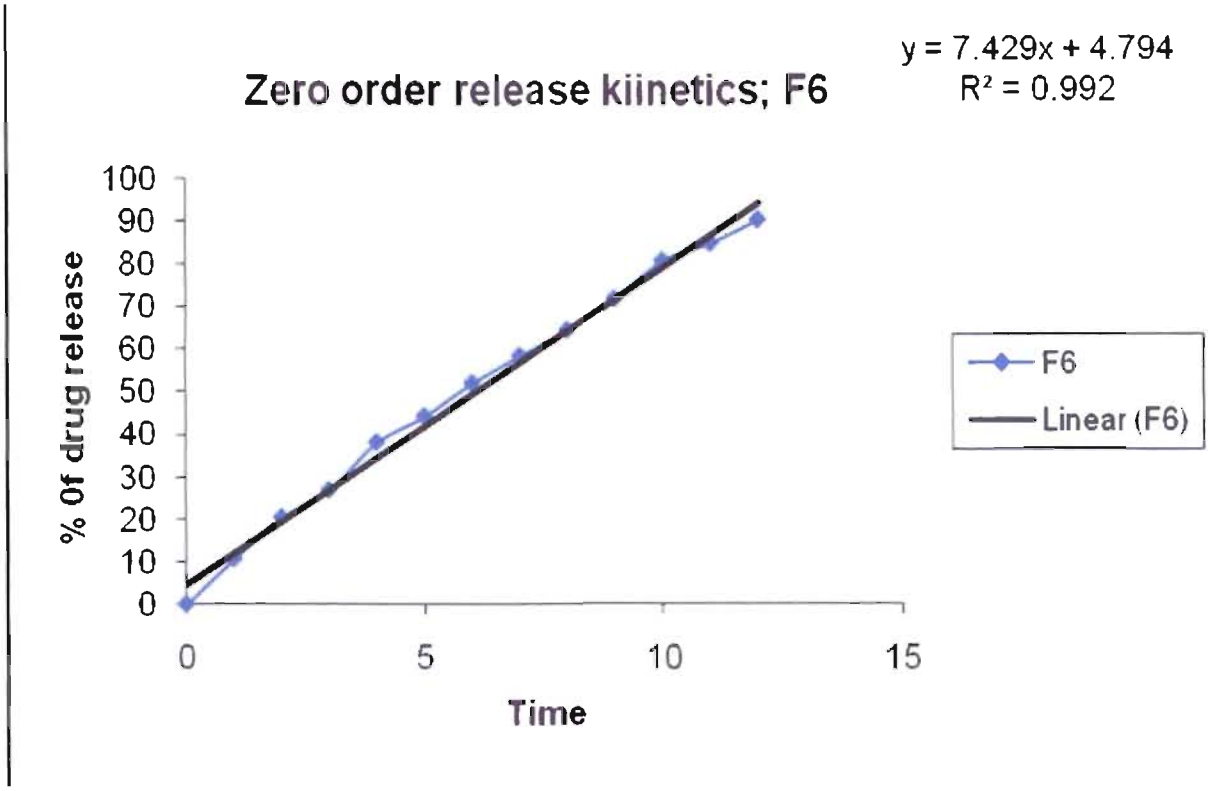
Graph-4: Zero order release kinetics; F3



Graph-5: Zero order release kinetics; F4



Graph-6: Zero order release kinetics; F5



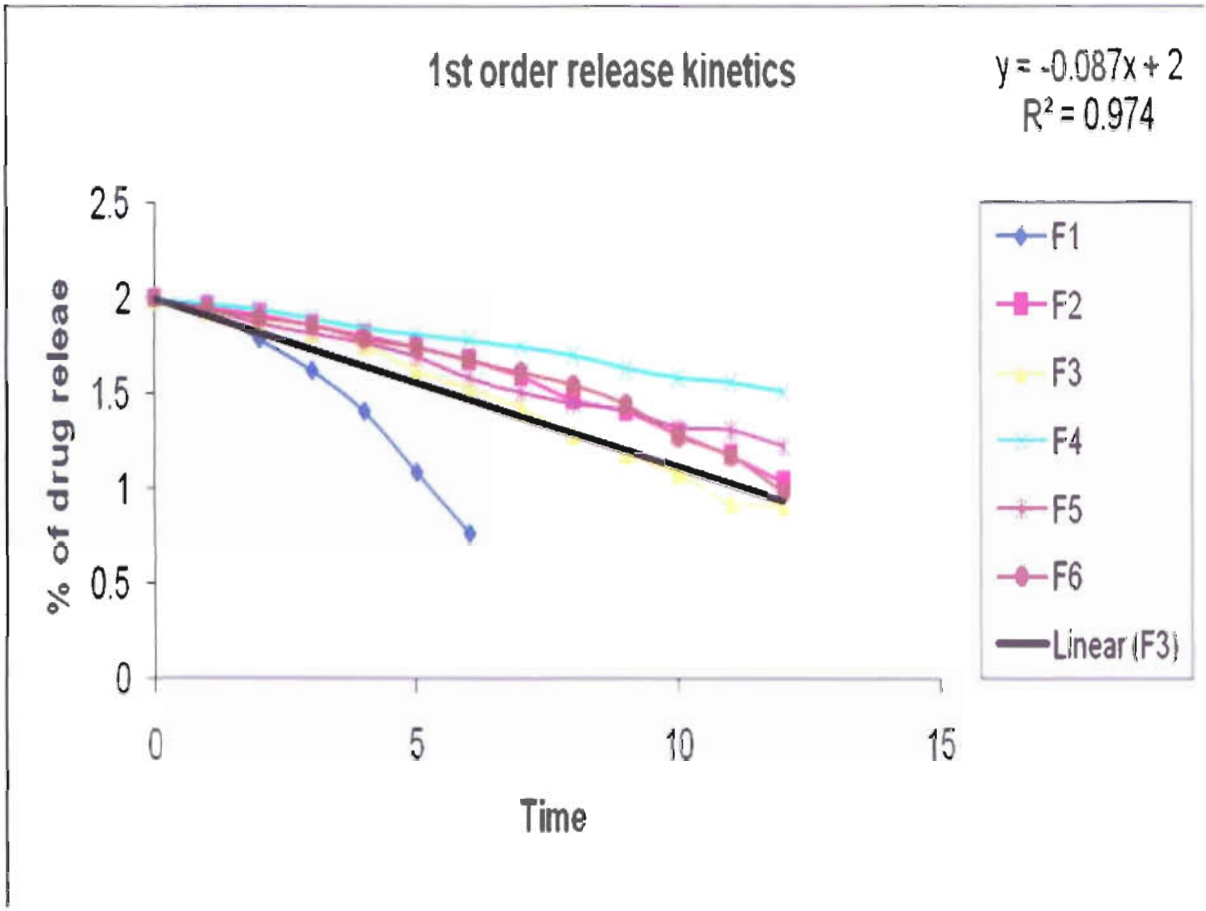
Graph-7: Zero order release kinetics; F6

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

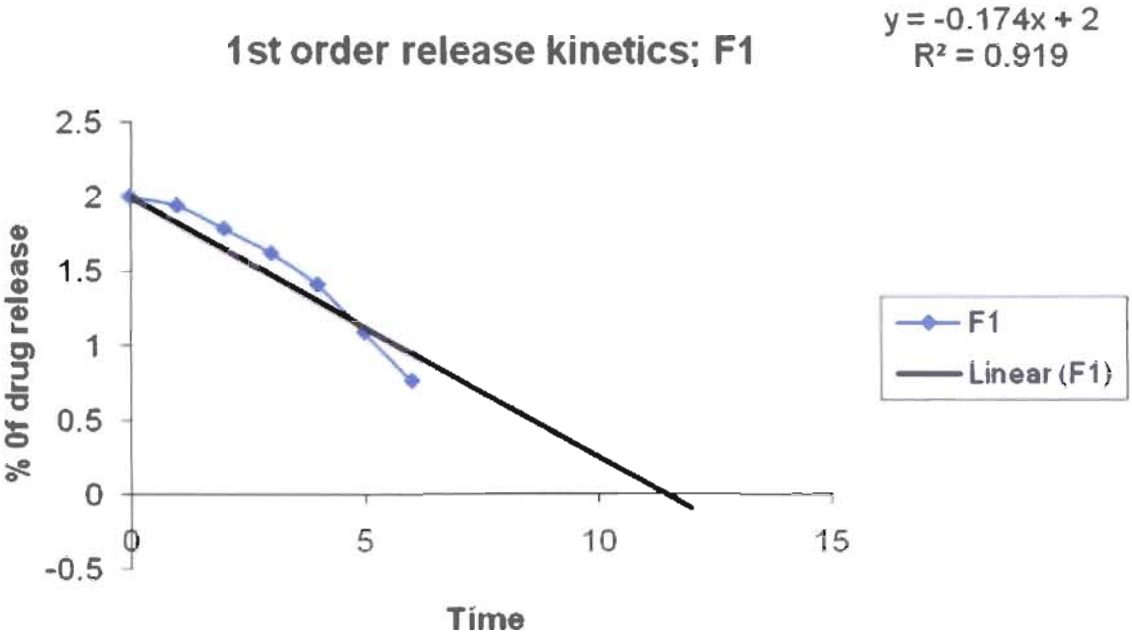
In-vitro dissolution studies of all the proposed sustained release formulations (F-1 to F-6) throughout the consequent hours gave a theoretical release profile of the drug with multiple coefficients (r^2) by zero order release kinetics, first order release kinetics which indicated the highest linearity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

Table 8: First order release kinetic profiles

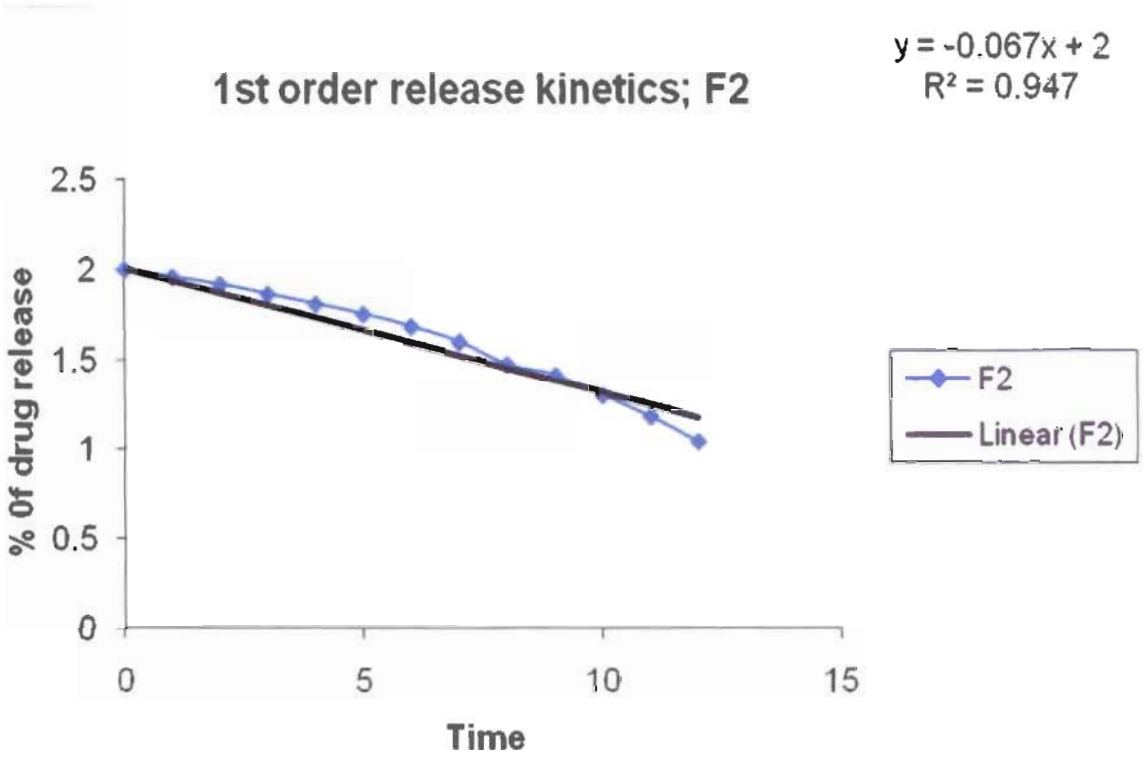
Time	F1	F2	F3	F4	F5	F6
0	2	2	2	2	2	2
1	1.941511	1.958086	1.940516	1.97174	1.947924	1.950851
2	1.788875	1.91698	1.874482	1.944976	1.872739	1.900913
3	1.625312	1.862728	1.824126	1.897077	1.820858	1.863917
4	1.41162	1.807535	1.758912	1.845098	1.770115	1.791691
5	1.093422	1.751279	1.630428	1.811575	1.699838	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



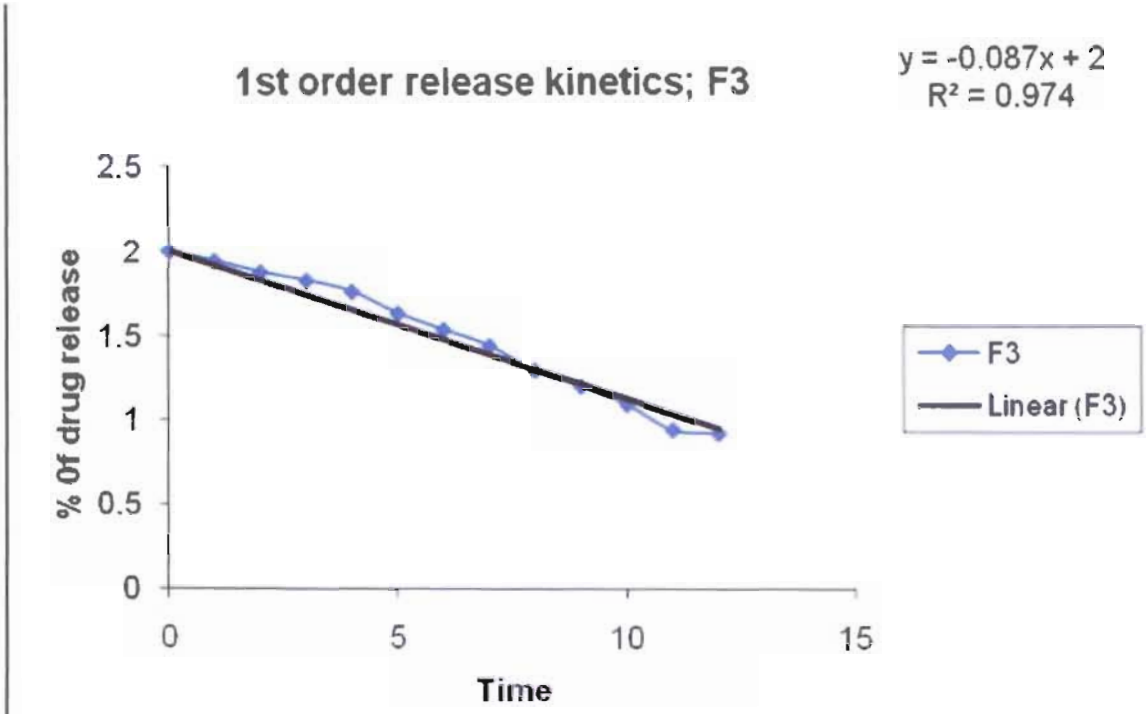
Graph-8: 1st order kinetics



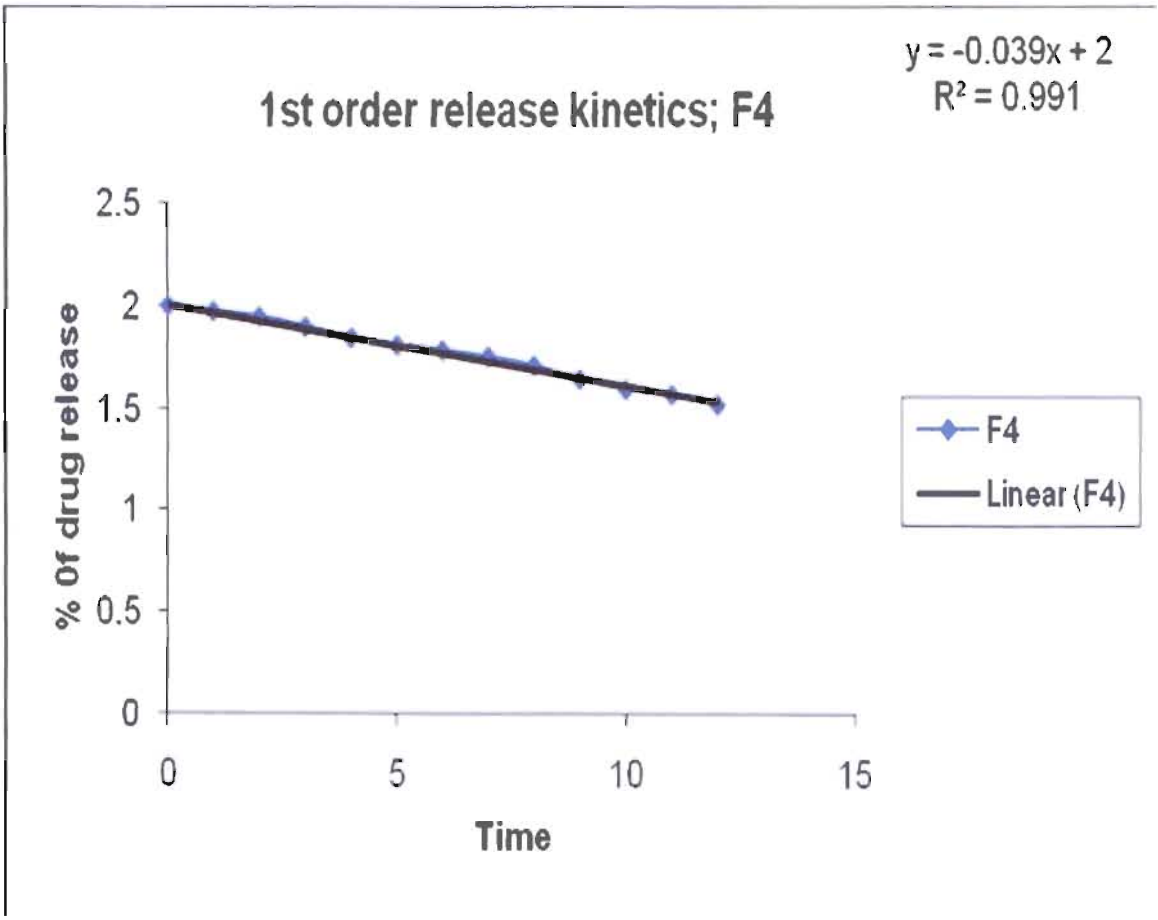
Graph-9: 1st order kinetics; F1



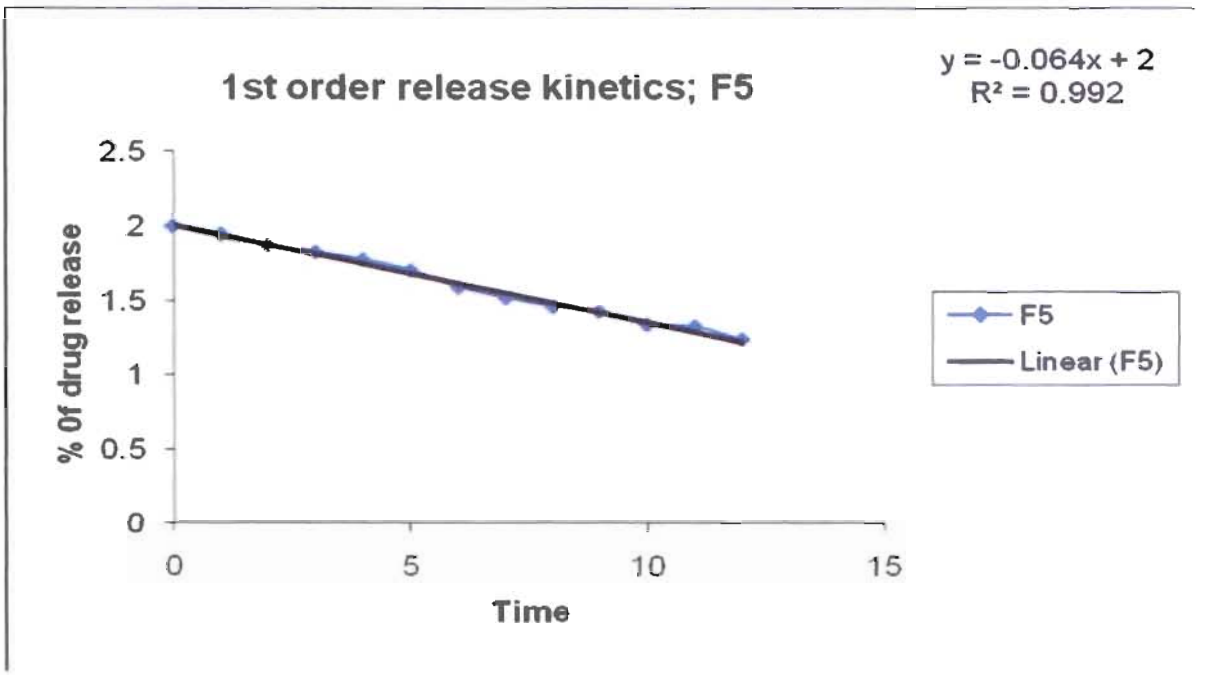
Graph-10: 1st order kinetics; F2



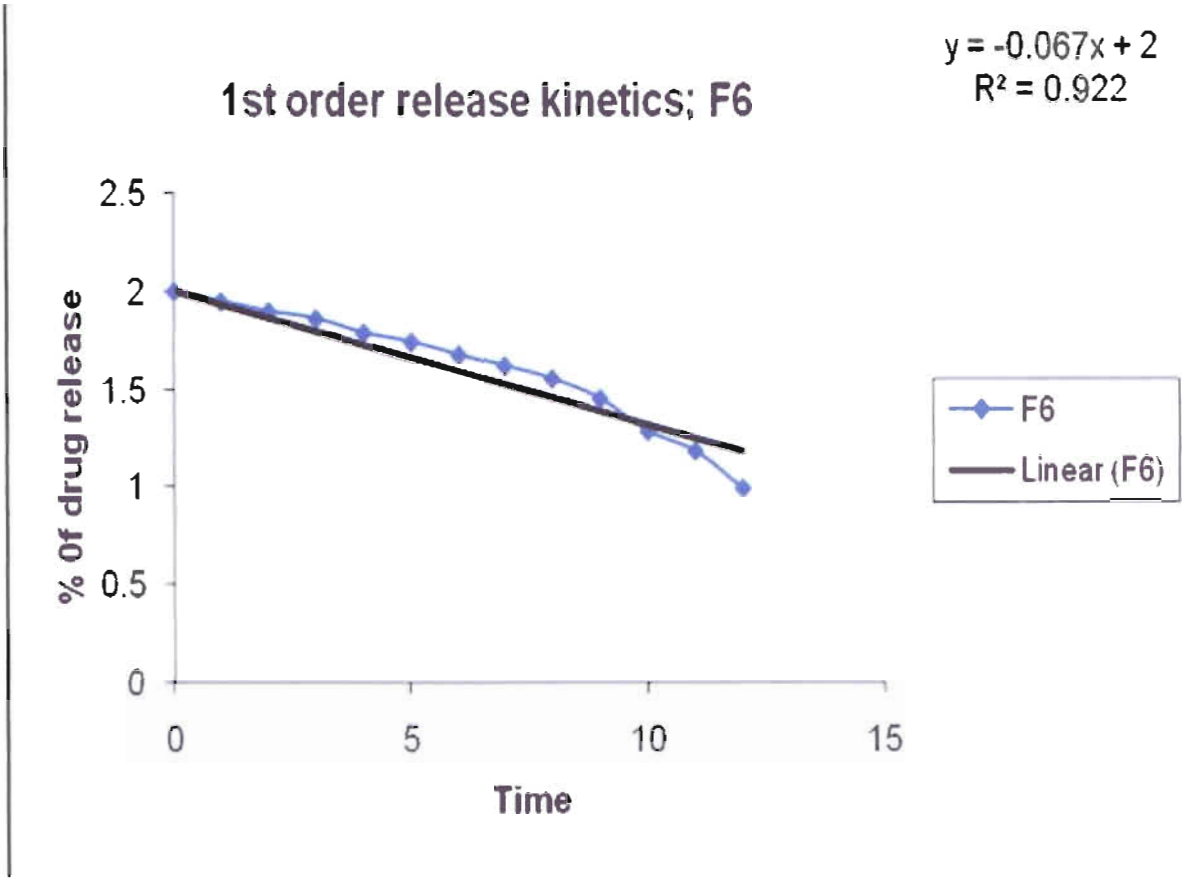
Graph-11: 1st order kinetics; F3



Graph-12: 1st order kinetics; F4



Graph-13: 1st order kinetics; F5



Graph-14: 1st order kinetics; F6

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

Table 9: Drug release mechanisms (Multiple coefficient [r^2]) of different formulations

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

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

Conclusion:

Diclofenac SR tablet matrix is essential for the management of pain caused by osteoarthritis, ankylosing spondylitis etc. Hydrophilic polymer is excellent quality to hold drug in compressed tablet.

Methocel K15 MCR and 100 LVCR hydrophilic polymer fulfilled most of the official physical data requirements.

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