FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE TABLET OF OXAPROZIN

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MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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CERFICATE OF APPROVAL

The foregoing thesis entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE TABLET OF OXAPROZIN"**is hereby approved as creditable study of research topic and has been presented in satisfactory manner to warrant its acceptance as prerequisite to the degree for which it has been submitted.

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CERTIFICATE

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By

MOHAMED HANIF THAHA OM

DECLARATION

We hereby declare that the matter embodied in the dissertation entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE TABLET OF OXAPROZIN"** is a bonafide and genuine research work carried by us under the guidance of **Dr.D.SAKTHIVEL, M.Pharm.,Ph.D.,** Department of Pharmaceutics, PGP College of Pharmaceutical Science and Research Institute, Namakkal-637207.

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CONTENTS

INTRODUCTION

For many decades treatment of an acute disease or a chronic illness hasbeen mostly accomplished by delivery of drugs to patients using variouspharmaceutical dosage forms, including tablets, capsules, pills, suppositories,creams, ointments, liquids, aerosols, and injectables, as drug carriers. This typeof drug delivery system is known to provide a prompt release of drug orimmediate release product. Such immediate release products result in relativelyrapid drug absorption and onset of accompanying pharmacodynamic effects.However, after absorption of drug from the dosage form is complete, plasmadrug concentrations decline according to the drug's pharmacokinetics profile.Eventually, plasma drug concentrations fall below the minimum effective plasmaconcentration (MEC), resulting in loss of therapeutic activity. Before this point isreached another dose is usually given if a sustained therapeutic effect is desired.An alternative to administering another dose is to use a dosage form that willprovide sustained drug release, and therefore,maintain plasma drugconcentrations, beyond what is typically seen using immediate release dosageforms. In recent years, various modified release and/ or the time for drug release.After 20th century investigation of new drug has been retained due to investigation cost of new drug. Therefore, pharmaceutical industries andacademic laboratories have been focused on establishment of novel drugdelivery system / or modified release dosage form rather investigation and
development of new drug.

The basic rationale of a sustained drug delivery system is to optimize the Biopharmaceutic, Pharmacokinetic and Pharmacodynamic properties of a drug insuch a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route.

The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlleddelivery and / or targeting the drug to desired site. The goal of any drug delivery

system is to provide a therapeutic amount of drug to the proper site in the body toachieve promptly and then maintain the desired drug concentration.

There is a continuously growing interest in the pharmaceutical industry for sustained release oral drug delivery systems. There is also a high interest for design a dosage formulation that allows high drug loading, particularly for activeswith high water solubility.

1.1 Modified Release Dosage Form and Drug Delivery

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Early modified release products were often intramuscular/subcutaneous injection of suspensions of insoluble drug complexes, e.g. Procaine penicillin, protamine zincinsulin, insulin zinc suspension or injections of the drug in oil, e.g. Fluphenazine decanoate. Advance in technology have resulted in novel modified release dosage form. In contrast to conventional (immediate release) forms, modified release products provide either delayed release or extended release of drug.

Extended release products are designed to release their medication in a controlled manner, at a predetermined rate, duration, and location to achieve andmaintain optimum therapeutic blood levels of drug.

1.1.1 Sustained Release:

The U.S. Food and Drug Administration (FDA) defines an “sustainedrelease dosage form is one that allows a reduction in dosing frequency from that necessitated by a conventional dosage form, such as a solution or an immediate release dosage form”.

Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. Typically,sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Fig 1). The sustained plasma drug levels provide by sustained release products often tim

eliminates the need for night dosing, which benefits not only the patients but thecare given as well.

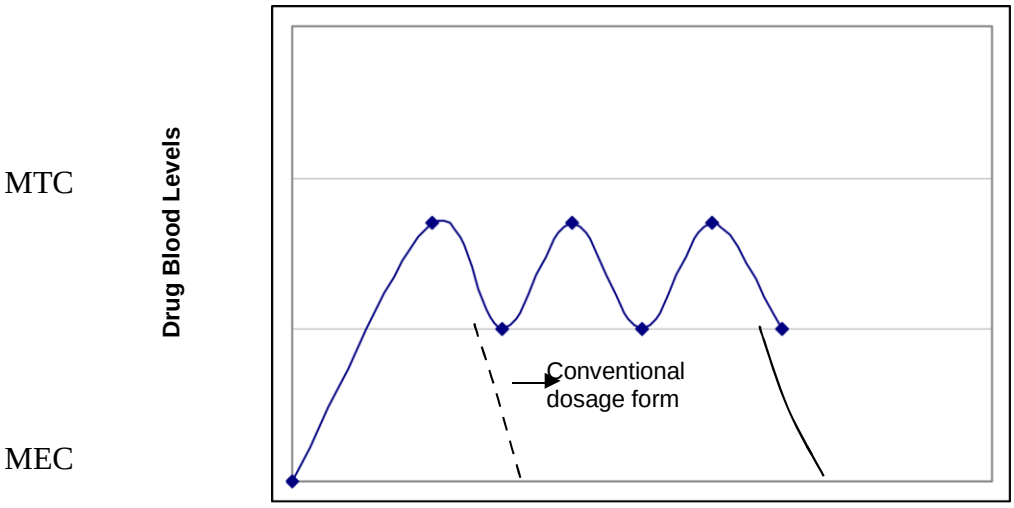
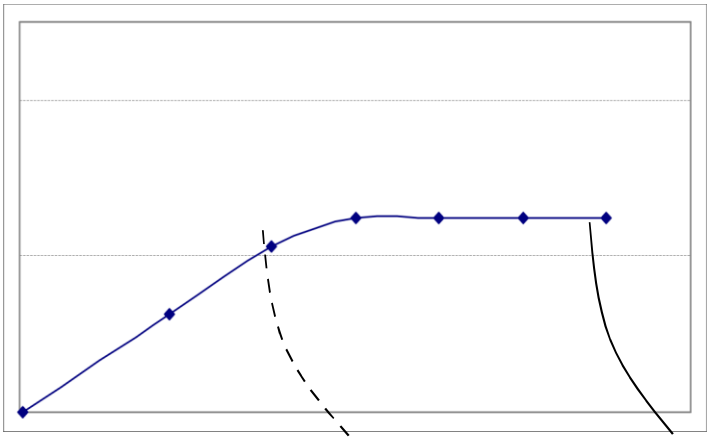


Fig. 1: Hypothetical drug blood level – time coverage for a conventionalsolid dosage form and a multiple action product.

MTC

Drug blood levels



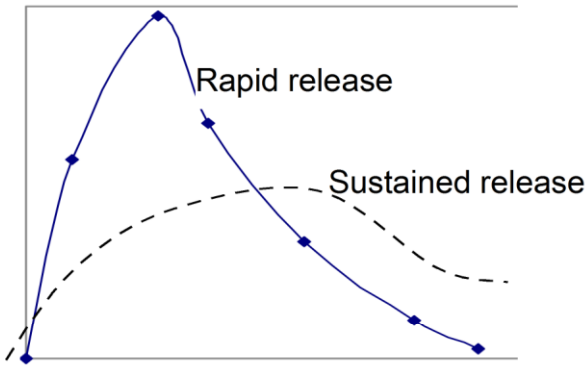
MEC

Time (hr).

Fig. 2: Hypothetical drug blood level – time coverage for a conventionalsolid dosage form and a controlled release product terminology.

1.1.2 Pharmacokinetic Simulation Of Sustained Release Products[8,3]:

The plasma drug concentration profiles of many sustained release products fits an oral one compartment model assuming first order absorption andelimination. Compared to an immediate release product, the sustained release product typically shows a smaller absorption rate constant, because of the slowerabsorption of the sustained release product. The time for peak concentration (t_{max}) is usually longer (fig-3), and the peak drug concentration (C_{max}) is reduced. If the drug is properly formulated, the area under the plasma drug concentration curve should be the same, parameters such as $C_{max,}$ t_{max} and AUC conveniently show how successfully the extended release product performs in-vivo. For example, a product with t_{max} of 3 hours would not be very satisfactory if the product is intended to last 12 hours. Similarly, an excessively high C_{max} is a sign of dose dumping due to inadequate formulation. The Pharmacokinetic analysis ofsingle and multiple-dose plasma data has been used by regulatory agencies to evaluate many sustained release products. The analysis is practical because many products can be fitted to this model even though the drug is not released ina first order manner. The limitation of this type of analysis is that the absorption rate constant may not release to the rate of drug dissolution in vivo.



Drug concentration (µg/ml)

Time (hr.)

Fig 3. Plasma drug concentration of a SR and a regular release product.

Various other models have been used to simulate plasma drug levels of sustained release product (Wellin, 1983). The plasma drug levels from a zero- order, sustained release drug product may be simulated with equation (1)

$$C_p = \frac{D_S}{V_D K}\left(1 - e^{-kt}\right) \quad \text{------(1)}$$

Where, Ds = maintanance dose or rate of drug release (mg/ml),Cp = plasma drug concentration

K = overall elimination constant, andV_D = volume of distribution

In absence of loading dose, the drug level in the body rises slowly to aplateau with minimum fluctuations.

This simulation assumes that

1) Rapid drug release occurs without delay,
2) Perfect zero-order release and absorption of the drug takes place, and
3) The drug is given exactly every 12 hours.

In practice, the above assumptions are not precise, and fluctuations indrug level do occur.

When a sustained release drug product with a loading dose (rapid release) and azero-order maintenance dose is given, the resulting plasma drug concentrations are described by:

$$C_p = \frac{D_i}{V_D (Ka - K)}\left(e^{-kt} - e^{-kat}\right) + \frac{D_S}{V_D K}\left(1 - e^{-kt}\right) \quad \text{-------- (2)}$$

Where, D_i = immediate – release (loading dose) andD_s = maintenance dose (zero-order).

This expression is the sum of the oral absorption equation (first part) andthe i.v infusion equation (second part).

An example of a zero-order release product with loading dose is shown in fig-4 the contribution due to the loading and maintenance dose is shown by the dashed lines, the inclusion of a built-in loading dose in the extended release product has only limited use.

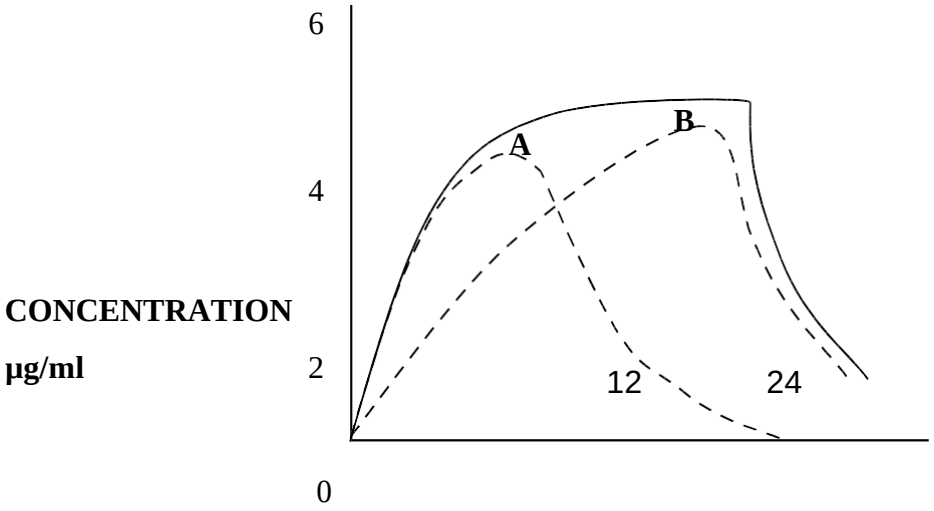


Fig. 4: Simulated plasma drug level of a SR product with a fast releasecomponent (A) and a maintenance component (B). The solid line represents total plasma drug level due to the two components.

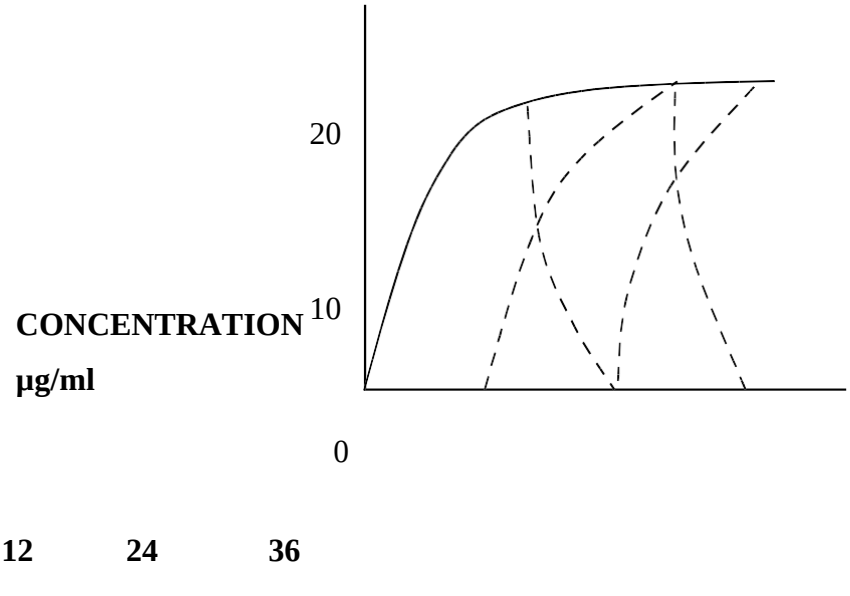


Fig. 5: Simulated plasma drug level of a SR product administered every 12hrs. The plasma level shows a smooth rise to steady state level with no fluctuations.

With most sustained release product, the patient is given more than one dose and there is no need for a built in loading dose with subsequent doses. Putting a loading dose in the body than necessary, because of the topping, effectin situations where a loading dose is necessary, the rapid – release product is used to titrate a loading dose that will bring the plasma drug level to therapeutic level.

A Pharmacokinetic model that assumes first-order absorption of the loading and maintenance dose has also been proposed. This model predicts spiking peaks due to loading dose when the drug is administered continuously fig-9.

1.1.3 Terminology And Sustained Release Concept[3,9-15]:

Over the years, many terms (and abbreviations), such as sustained release(SR), sustained action (SA), prolonged action (PA), controlled release (CD), extended release (ER), timed release (TR), and long acting (LA), have been used by manufactures to describe product types and features. These are terms used to identify drug delivery systems that are designed to active a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of injectable dosage form, this period may vary from days to months. Althoughthese terms often have been used interchangeably, individual products bearing these descriptions may differ in design an performance and must be examined individually to as certain their respective features.

Sustained release

In case of sustained release (SR) dosage forms the release of the active agent, although, is lower than in the conventional formulations, however, it is still substantially affected by the external environments into which it is going to be released.

Controlled release

Controlled release (CR) systems provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, withthe release profiles of predominantly controlled by the special technologicalconstruction and design of the system itself. The release of the active constituent is therefore, ideally independent of exterior factors.

Extended release formulation is a controlled release formulation designed to produce even and consistent release of active ingredient. Extended release (ER) dosage forms are those which due to special technology of preparation provided, soon after a single dose administration, therapeutic drug levels maintained for 8-12 hours.

Prolonged action

Prolonged or long action products are dosage forms containing chemically modified therapeutic substances in order to prolong biological half life (Lee and Robinson, 1987).

These terms are explained in following Fig. 6

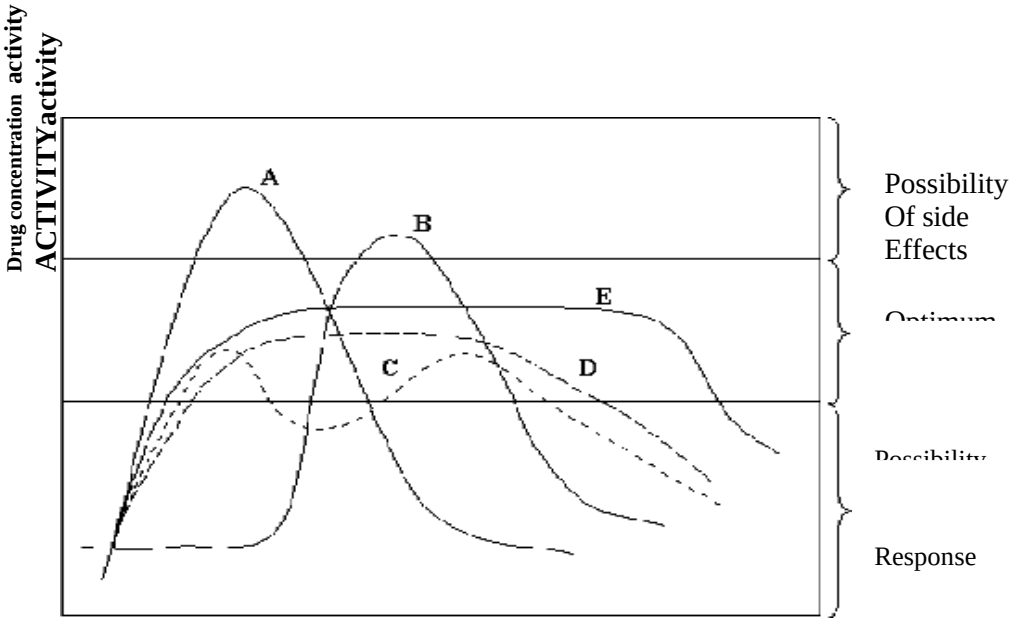


Fig. 6 : Relationship between centration and time for Products Possessing Various Release Profiles

A -Immediate release B -Delayed action C - Repeat action D -

Prolonged release E - Controlled, sustained release

In general, the goal of a 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 dosageform.

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 releaserate). 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 first-order fashion (i.e., concentration-dependent). Systems that are designed as prolonged release can also be considered as attempts at achieving sustained-release delivery. Repeat-action tablets are in alternative method of sustained release in which multiple doses of a drug are contained within a dosage form, and each dose is released at a periodic interval. Delayed–release systems, in contrasts, may not be sustaining, since often the function of these dosage forms is to maintain the drug within the dosage form for some time before release.

1.1.4 CLASSIFICATION[10]:

Modified Release dosage form may be classified asA

.Delayed release

B. Extended release

B.1: Sustained release

B.2: Controlled release

A. Delayed release: [3]

The drug is released at a later time after administration. The delayed action is achieved by the incorporation of a special coat, such as enteric coating, or other time barriers such as the formaldehyde treatment of soft and hard gelatincapsules. The purposes of such preparations are to prevent side effects related to the drug presence in the stomach, protect the drug from degradation in the highly acidic pH of the gastric fluid.

B. **Extended release:** ***B-1): Sustained Release System[13-17]:***

The idealized objective points to the two aspects most important to drug delivery, namely, spatial placement relates to targeting a drug to a specifiedorgan or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed sustained release drug delivery can be a major advance towards solving these two problems. The bulkof research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the new approaches under investigation may allow for spatial placement as well.

The goal of sustained drug delivery are to conserve and maintain effectivedrug concentration, eliminate night time dosage, improve compliance and decrease side effects thus, optimizing drug therapy.

Compliance with a drug regimen depends among other things on the routeand frequency of administration, the type of medication and condition being treated. Oral administration is the most common technique, but patient often forget to take their medication, and the condition, especially when frequent dosing is required.

Products that have been formulated for the purpose of prolonging absorption including oral, parenteral, topical and implants dosage form both for human and veterinary use. Oral sustained release products have gained importance because of the technological advances which achieve zero order release rate of therapeutic substance. Generally the pharmacokinetics of a drug is controlled by its chemical nature. However decreasing the absorption rate by physical means is a useful method to sustain the drug action when it is not feasible to modify the drug compound at its molecular level.

ADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY:[17-21]

The improvement in drug delivery is represented by several potentialadvantages as below.

1. It improves patient compliance.
2. It employs lesser quantity of the drug.

3. It may improve the pathophysiology of the diseases.

   (a) It minimizes or eliminates local side effects.

   (b) It minimizes or eliminates systemic side effects.

   (c) It obtains less potentiation or reduction in drug activity withchronic use.

   (d) It minimizes drug accumulation with chronic dosing.

4. It improves the efficiency in treatment.

   (a) It cures or controls the condition more promptly.

   (b) It improves the control of condition i.e. reduces fluctuation in thedrug level.

   (c) It improves bioavailability of some drugs.

   (d) Make use of special effects, e.g., sustained release aspirin for morning relief of arthritis by dosing before bedtime.

5. Economy:

   (a) In comparison with conventional dosage forms the average costof treatment over an extended period may be less.

   (b) Economy also may results from a decrease in nursing time and hospitalization. Also

   - ❖ Reduce blood level oscillation characteristic of multiple dosing of conventional dosage forms.
   - ❖ Reduce amount of drug administration
   - ❖ Maximizing availability with a minimum dose.
   - ❖ Control of drug absorption; high peak level peaks that maybe observed after administration of high availability drug can be reduced.
   - ❖ Safety margin of high potency drugs can be increased.
   - ❖ Increased reliability of therapy

6. Improved therapy:

The dosage form provides uniform drug availability / blood levels unlike peak and valley pattern obtained by intermittent administration.

a) Attenuation of adverse effects.

The incidence and intensity of undesirable side effects caused by excessively high peak drug concentration resulting from the administration of conventional dosage forms is reduced.

b) It is seldom that a dose is missed because of non-compliance by the patient.

1.2 CONVENTIONAL DRUG THERAPY [4, 22]

In most cases of conventional dosage form the dosing interval is much shorter than the half-life of the drug resulting in a number of limitations.

1. Unless the dosing interval is relatively short, depending on biological half-life of the drug, large peaks and valleys (Fig.7) in the drug level willoccur.
2. Success by this approach is dependent on patient compliance with the dosing regimen. Numerous studies have documented that lack of compliance is an important reason for drug therapy inefficiency orfailure.
3. During the early periods of dosing there may be insufficient drug to generate a favorable biological response, which may be a significant problem in certain disease states.
4. For drugs with short biological half-lives, frequent dosing is needed to maintain relatively constant therapeutic levels of drugs.

There are two ways to overcome such a situation

- Development of new, better and safer drugs with long half-lives and large therapeutic indices.

- Effective and safer use of existing drugs through concepts and techniquesof controlled and targeted delivery systems.

The first approach has many disadvantages, which therefore resulted inincreased interest in the second approach

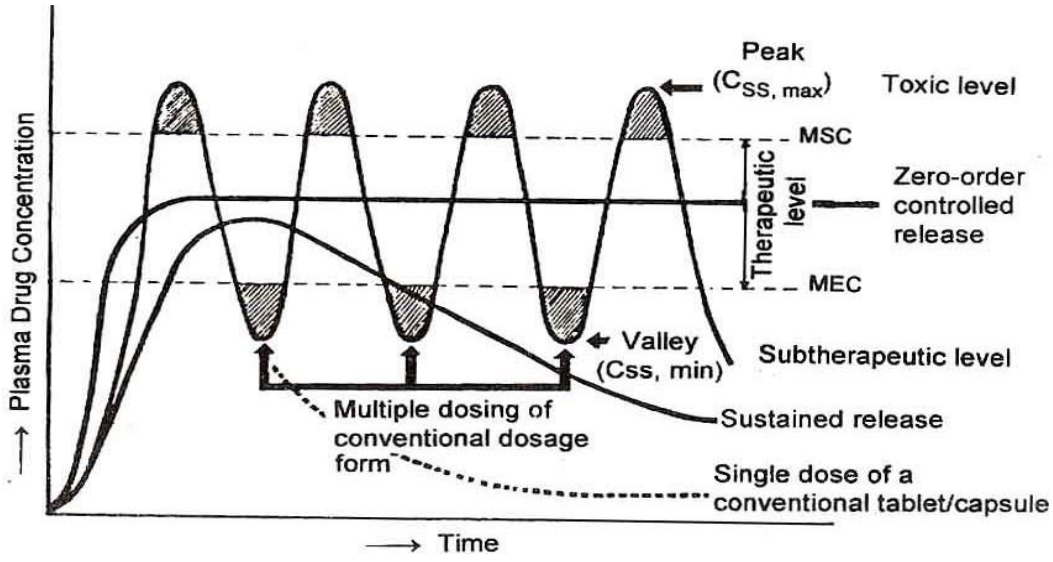


Fig. (7) A hypothetical plasma concentration – time profile from conventional multiple dosing and single doses of sustained and controlleddelivery formulations.

1.3 THEORY OF SUSTAINED RELEASE:[23,17]

Sustained release dosage form may contain:

a) Maintenance dose, and

b) Loading dose

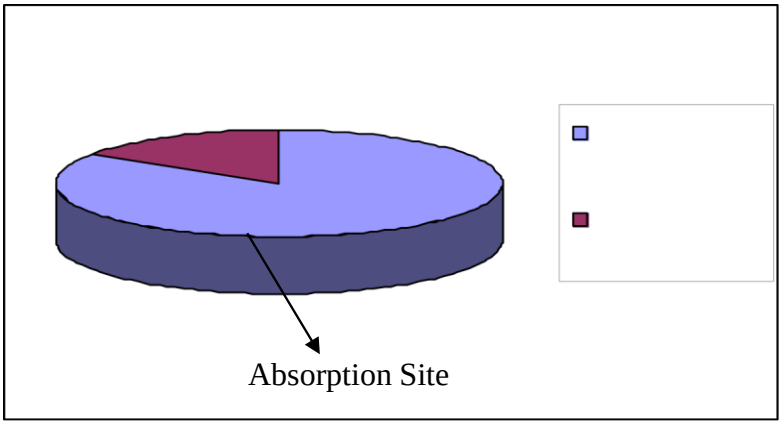


Fig. (8): Schematic representation of sustained release dosage system.

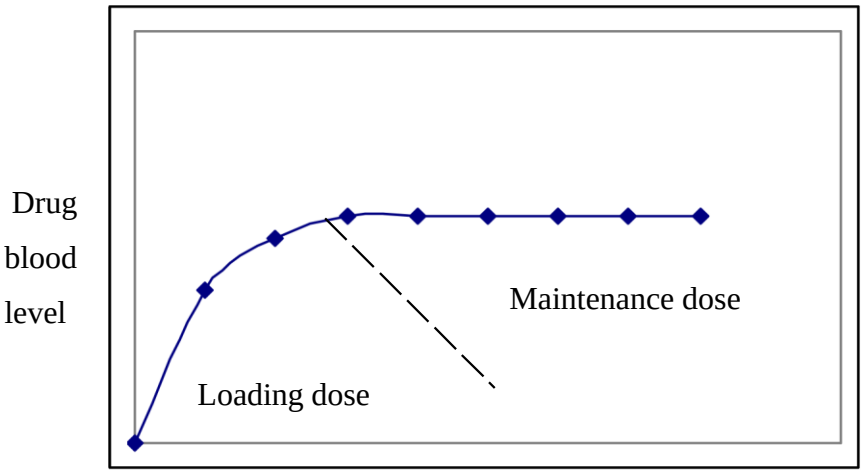


Fig. (9): A hypothetical plasma concentration time profile from sustaineddrug delivery formulation

The maintenance dose or slowly available portion will release the drug slowly and maintain the therapeutic level for an extended period of time. Whilethe loading dose or immediately available portion will held obtaining the therapeutic level quickly

after administration.

The rate of release of the drug from the maintenance dosage should be zero order (independent of the concentration) if the drug at the absorption site is to remain constant. The release of the drug from the loading dose should follows first order kinetics.

Sustained action curve is possible only when the drug from the dosage form is supposed for absorption into the blood, at a constant rate equal to therate constant for the elimination of the drug. From the blood, mathematically this relationship is given as

$$K_2B=R=K_dG \qquad \textbf{(3)}$$

Where, K_2: Rate constant for elimination of drug from blood.B :

Quantity of drug to be maintained to the bloodR :

Replacement rate

K_d : Constant relating the amount that can be absorbed understandard volume and concentration conditions

G : Quantity of drug that the dosage form must supply (maintain) in the depot.

When a fraction, f, of the drug is available because of irreversible binding or degradation, the amount available for absorption must be increased by 1/f. The value for B is usually known or can be ascertained if the drug and its effect can be measured. It is often possible to obtain a value for K_2 by plotting a log of the concentration of the drug remaining in blood versus time. The negative slopeof the elimination rate constant for design purpose.

When the initial dose (D_n) is estimated from the multiple dose data, the dose (D_n) is quantity needed to produce B (quantity of drug that must be maintained at receptor site). The correction for irreversible binding and / ordegradation of the drug in depot (1/f) is not required when Dn is obtained from multiple dose data. Ideally, knowledge of the absorption rate constant K_1, the elimination rate constant (K_2) and the distributive rate constant (K_{12}, K_{21}) should enable the formulation scientist to construct a curve similar to that given for a single dose. Number of methods for determining absorption rate constant have been reported.

The total dose of drug, D_t, in a prolonged action preparation comprises of the normal dose, D_n, and the sustaining dose Ds i.e.

$$D_t = D_n + D_s \text{ ----------} \textbf{(4)}$$

For the system where the maintenance dose D_s provides drug via a zero- order process the total dose is

$$D_t = D_n + K_r^0 T_d \text{ ---------- (5)}$$

Where, K_r^0 is the zero-order rate constant for drug release and T_d is the total time desired for sustained release corresponding to one dosing interval. If the maintenance dose begins releasing drug at time zero it will add on to that which is provided by the initial dose, thus pushing the drug level too high. In this case a correction factor is needed to account for the added drug from themaintenances dose

$$D_t = D_n - K_r^0 T_p + K_r^0 T_d \text{ ---------- (6)}$$

Where the correction factor is the amount of drug provided, during thetime period t = 0 to the time of the peak drug level, T_p. Naturally, if the dosage form is constructed such that the maintanance dose not begin to release drug until the peak blood drug level, no correction factor is needed.

If drug is released via a first-order process, no correction factor is needed.

$$Dt = Dn - \frac{KeCd}{K^1r}Vd \text{ --------- (7)}$$

Where K_e is the total elimination constant for the drug, C_d is the desired blood drug level and K^1_r is the first-order drug release rate constant. The last term in equation (13) results from the approximation.

$$Ds = \frac{KeCd}{K^1r}Vd \text{ ——— --------- (8)}$$

If the maintenance dose begins release of drug from time zero, a correction factor is required similar to the zero-order case. In this case the correctexpression is

$$Dt = Dn - DsK^1rT_p \frac{K_eC_d}{K^1r}V_d \text{ ---------- (9)}$$

B-2: Controlled release formulation:

The controlled release systems is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body.

An ideal controlled drug delivery system is the one, which delivers the drugs at apredetermined rate, locally or systemically, for a specific period of time.

Repeat action preparations

A dose of the drug initially is released immediately after administration, which is usually equivalent to a single dose of the conventional drug formulation. After a certain period of time, a second single dose is released. In some preparation, a third single dose is released after a certain time has elapsed, following the second dose. The main *advantage* is that it provides the convenience of supplying additional dose(s) without the need of re- administration. It has *disadvantage* that the blood levels still exhibit the "Peak and valley" characteristic of conventional intermittent drug therapy.

1.4 ORAL CONTROLLED RELEASE SYSTEM [10]

Oral route has been the most popular and successfully used for controlled delivery of drug because of convenience and ease of administration, greater flexibility in dosage form design(possible because of versatility of GI anatomyand physiology) and ease of production and low cost of such a system.

The controlled release systems for oral use are mostly solids and basedon dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug.

A. Continuous release systems

These systems release the drug for a prolonged period of time along theentire length of GIT with normal transit of the dosage form.

The various systems under this category are:

1. Dissolution controlled release system
2. Diffusion controlled release system
3. Dissolution and diffusion controlled release system
4. Ion exchange resin – drug complexes
5. Slow dissolving salts and complexes
6. pH – dependant formulation

7. Osmotic pressure controlled systems
8. Hydrodynamic pressure controlled system

B. Delayed transit and continuous release system

These systems are designed to prolong their residence in the GIT along with their release systems included in this category are;

1. Altered density systems
2. Mucoadhesive systems
3. Size- based systems

C. Delayed release systems

The design of such systems involves release of drug only at a specific sitein the GIT. The two types of delayed release systems are;

1. Intestinal release systems
2. Colonic release systems

The drugs contained in this system are those that are:

i. Destroyed in the stomach or intestinal site.
ii. Known to cause gastric distress
iii. Absorbed from a specific intestinal site, or
iv. Meant to exert local effect at a specific GI site.

1.4.1 CONTINUOUS RELEASE SYSTEMS:[9,25-27]

Diffusional System:

Diffusional systems are characterized by the release rate of drug being dependent on its diffusion through an inert membrane barrier usually; this barrier is an insoluble polymer. There are basically two types of diffusion devices:reservoir devices and matrix devices.

(a) Reservoir devices:

Reservoir devices, as the name implies, are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system. The releaseof drug from a reservoir device is governed by **fick's first law of dissolution**.

The **fick's first law** states that the amount of drug passing across a unit area is proportional to the concentration difference across that plane. Theequation is given as

$$J = - D \frac{dC}{dX} \quad \text{- - - - - - - - - - - - - -} \quad \textbf{(10)}$$

Where, J = flux in units of amount/area-time,D
= diffusion coefficient,
$\frac{dC}{dX}$ = change in concentration C relative to distance X in the membrane.

(b) Matrix devices:

A matrix device, as the name implies consists of drug dispersedhomogeneously throughout a polymer matrix as represented in following figure(Fig. 12).

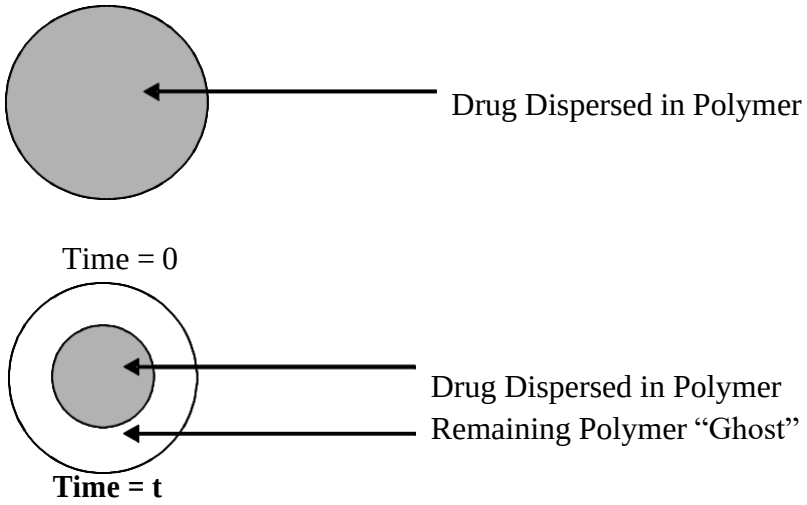


Fig. (10) - Matrix Diffusion system before drug release (time = 0) and afterpartial drug release (time = t)

In this model, drug in the outside layer exposed to the bathing solution isdissolved first and then diffuse out of the matrix. This process continues with the

interface between the bathing solution and the solid drug moving toward the interior.

Derivation of the mathematical model to describe this system involves the following assumptions: (a) a pseudo-steady state is maintained during drug release, (b) the diameter of the drug particles is less than the average distance ofdrug diffusion through the matrix, (c) the bathing solution provides sink conditionsat all times, (d) the diffusion coefficient of drug in the matrix remains constant.

The next equations, which describe the rate of release of drugs dispersed in an inert matrix system, have been derived by **Higuchi**. The following equation can be written based on Fig 4:

$$\frac{dM}{dh} = C_s C_0 \frac{dh}{2} \quad \text{---------- (11)}$$

Where, dM = Change in the amount of drug released per unit area,

dh = Change in the thickness of the zone of matrix that has beendepleted of drug,

C_0 = Total amount of drug in a unit volume of the matrix, C_s = Saturated concentration of the drug within the matrix.

From diffusion theory,

$$dM = \frac{D_m}{C_s} dt \quad \text{----------(12)}$$

Where, D_m is the diffusion coefficient in the matrix, Equating Eqs. (1) and (2),integrating, and solving for h gives

$$M = [C_s D_m (2C_o - C_s)t]^{1/2} \quad \text{---------- (13)}$$

When the amount of drug is in excess of the saturation concentration, that is,$C_o >> C_s$

$$M = (2C_s D_m C_o t)^{1/2} \quad \text{---------- (14)}$$

Which indicates that among the drug released is a function of the square root of time. In a similar manner, the drug release from a porous or granular matrix can be described by

C_a = solubility of the drug in the release mediumT = tortuosity
D_s = diffusion coefficient in the release medium.

This system is slightly different from the previous matrix system in that the drug is able to pass out of the matrix through fluid-filled channels and does not pass through the polymer directly.
For purposes of data treatment, Eq. (14) or (15) can be reduced to

$$M = kt1^{/2} \qquad \textbf{(16)}$$

Where k is a constant, so that plot of amount of drug released versus the square root of time will be linear, if the release of drug from the matrix is diffusion controlled. If this case, then by the Higuchi model, one may control the release of drug from a homogeneous matrix system by varying the following parameters[26, 27]: (a) initial concentration of drug in the matrix. (b) Porosity, (c) tortuosity, (d) polymer system forming the matrix, and (e) solubility of the drug.
E.g. Procan SR.

1.5 MATRIX SYSTEMS:[21]

A matrix is a uniform mixture of drug and excipients. e.g. polymer that is homogeneously fixed in solid dosage form.

The drug substance, which has a solubility S gm /cm^3 in the dissolution medium, is dispersed in the matrix which is insoluble in the dissolution medium, The concentration of drug in the matrix is 'A' gm / cm^3**.** The matrix is porous, with a porosity of **'Є'** and diffusion coefficient of 'D_m'. The drug release from such system can be described by $dQ/dt = 2SD_mAt$. Liquid will intrude from the bulk liquid. The rate and extent of intrusion will follow the following equation:

$$\frac{dL}{dt} = \frac{Qr2}{8\eta L} \qquad \textbf{----------} \ \textbf{(17)}$$

Where, L is the length of the intrusion at time t, r is the average radius ofthe pores, ŋ is the viscosity of the liquid and Q is a constant.

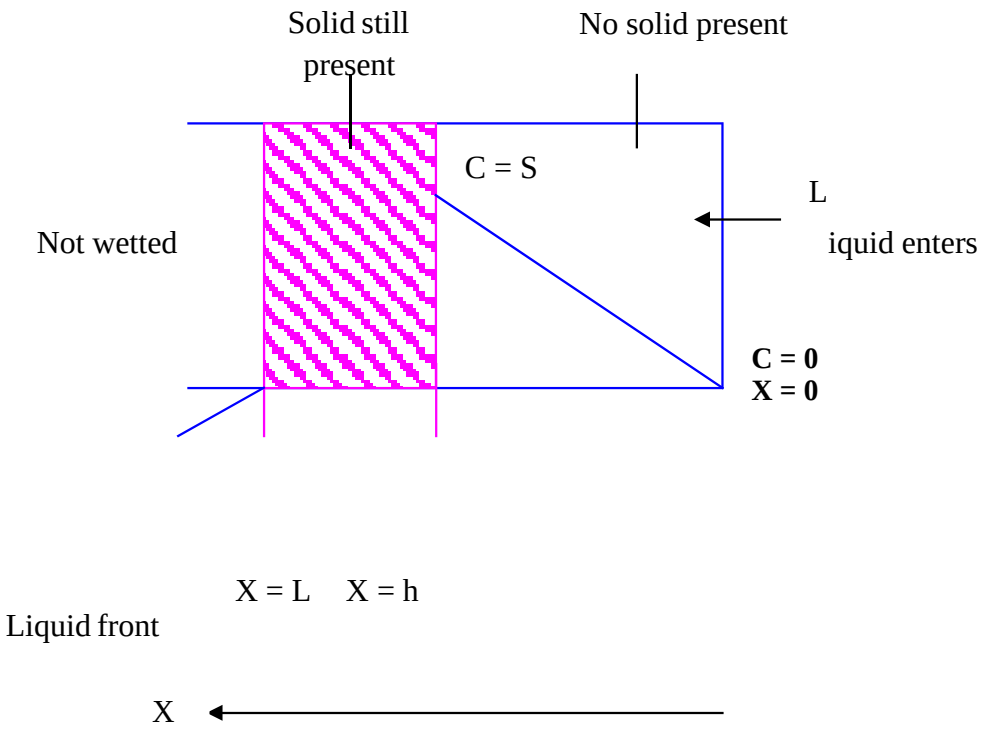


Fig. (11): Dissolution of drug from a solid matrix

1.5.1 HYDROPHILLIC MATRIX SYSTEM:[28,29]

A hydrophilic matrix controlled release system is a dynamic system composed of polymer wetting, polymer hydration and polymer dissolution. At the same time other soluble excipients or drug will also wet, dissolve and diffuse out of the matrix while insoluble materials will be hold in place until the surrounding polymer/ excipients / drug complex erodes or dissolves away.

The main principle is that a water-soluble binder, present throughout the tablet, partially hydrates on the outer tablet "**sink**" to form a gel layer. Throughoutthe life of ingested tablet the rate of drug diffusion (if soluble) out of the wet gel and the rate of tablet erosion control the overall dissolution rate and drug availability.

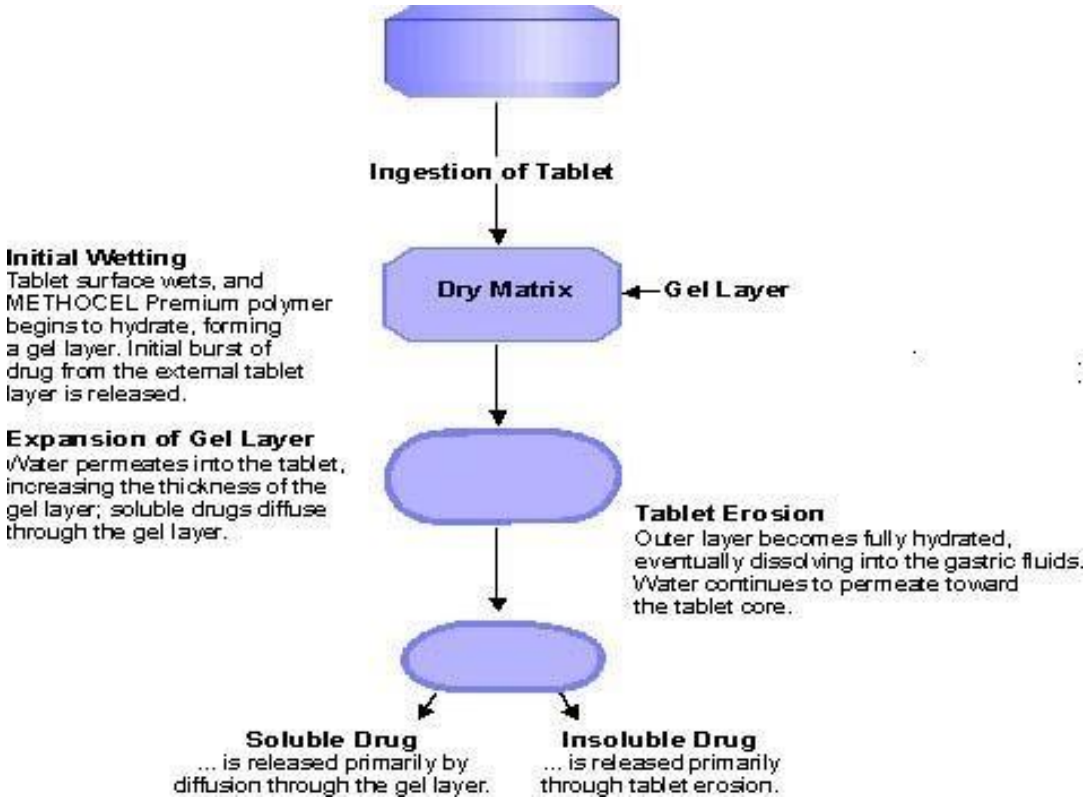


Fig. (12) : Matrix System

The most common controlled delivery system has been the matrix type such as tablets and granules, where the drug is uniformly dissolved or dispersed through out the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period.

Hydrophilic polymers are becoming more popular in formulating oral controlled release tablets, it is well documented that the dissolution curve of drug release from a hydrophilic matrix shows a typical time dependent profile. The release of a dissolved drug inherently follows near first order diffusion either an initially high release rate, due to the dissolution of the drug present at the surfaceof the matrix followed by a rapidly declining drug release rate. The enhanced release rate observed at the beginning for the short time of release process is known as "**burst effect**" and is many a time undesirable since it may, have negative therapeutic consequences. After this burst effect, hydration and

consequent swelling and/or erosion of related polymer occur. These phenomenon's control the release process but with time, the diffusion path lengthincreases and saturation effect is attained, resulting in a progressively slowrelease rate during the end of dissolution span.

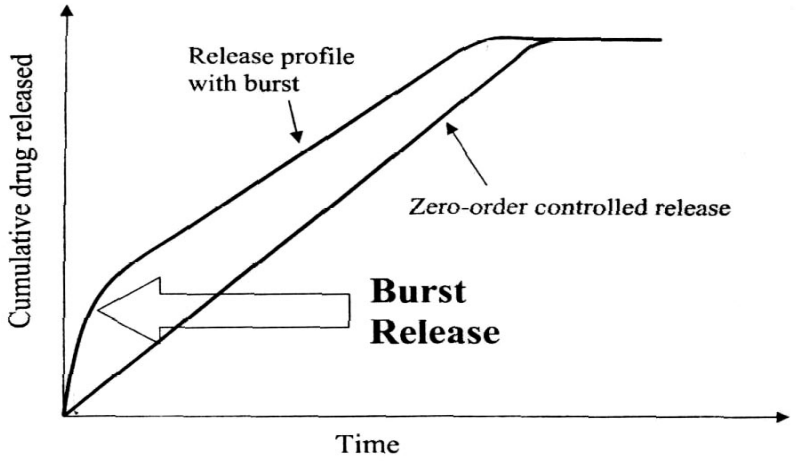


Fig.(13): Schematic showing the burst effect in a zero-orderDrug delivery system.

In many controlled release formulations immediately upon placement in release medium, an initial large bolus of drug is released before the release rate reaches a stable profile. This phenomenon is referred to as '**burst release'**.

SWELLABLE MATRICES AS SYSTEMS FOR ORAL DELIVERY[31-42]

Monolithic devices or matrices represent a substantial part of the drug delivery systems. Matrices containing swellable polymers are referred to ashydro gel matrices, polymeric matrices involving moving boundaries, hydrocolloidmatrices, swellable controlled release systems or hydrophilic matrix tablets. Swellable matrices for oral administration are commonly manufactured as tabletsby the compression of hydrophilic micro particulate powders. Therefore, the mostappropriate classification for these systems is swellable matrix tablets. They are constituted of a blend of drug and one or more hydrophilic polymer. In general drug release from swellable matrix tablets is based on glassy-rubbery transitionof polymer as a result of water penetration into the matrix. Whereas interactions

between water, polymer and drug are the primary factors for release control, various formulations variables, such as polymer grade, drug/polymer ratio, drug solubility, and drug and polymer particle size, can influence drug release rate to greater or lesser degree. However the central element of the mechanism of drug release is the gel layer (rubbery polymer), which is formed around the matrix.The gel layer is capable of preventing matrix disintegration and further rapid water penetration. Water penetration, polymer swelling, drug dissolution anddiffusion and matrix erosion are the phenomena determining gel layer thickness. Finally, drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer. In order to follow gel layer dynamics during drug release in swellable matrices, the boundaries of such a layer have to be defined. It is well known that gel layer is physically delimited by two sharp fronts that separate-different matrix states, i.e. the boundaries separating swollen matrix from solvent and glassy from rubbery polymer. However the possibility of the presence of a third front inside the gel layer has been described. This additional front was termed undissolved drug front or diffusion front and turned out to be a function of drug solubility and loading. Its presence can create conditions such that the release will be more controlled by drug dissolution than by polymer swelling. Thus in swellable matrix tablet three fronts could be expected:

1. The swelling front, the boundary between the still glassy polymer andits rubbery state,
2. The diffusion front, the boundary in the gel layer between the solid, asyet undissolved drug and the dissolved drug and
3. The erosion front, the boundary between the matrix and the dissolution medium.

The measurement of front positions gives the possibility to determinethree important parameters related to the behavior of the matrix, i.e. the rate of water uptake, the rate of drug dissolution and the rate of matrix erosion, associated with the movements of the swelling front, diffusion front and erosion front respectively. These parameters are strictly linked to the drug release kinetics from matrix.

Many attempts have been made in order to control the movement of the fronts and therefore the drug release kinetics. The more successful consists inthe reduction of the matrix-swelling rate by partially coating the matrix surfacewith impermeable or slowly permeable polymeric layer. In this way drug release can be modulated and the release kinetics can be shifted toward the linearity.

1.6 MECHANISM OF DRUG RELEASE FROM MATRIX SYSTEM:[31,51-58]

When a hydrophilic matrix system containing a swellable glassy polymer comes in contact with an aqueous medium, the fall in glass transition temperature leads to an abrupt change from a glassy to a rubbery state, causing swelling of the polymer on the surface and formation of a hydrated gel. Drug release is controlled by this gel diffusional barrier and/or by surface erosion of thegel. Surface leaching of the drug can lead to an initial burst, especially with highlysoluble drugs.

Hydration of individual polymer chains leads to expansion in their end to end distance and radius of gyration to a new solvated state due to lowering of thepolymer transition temperature, a sharp distinction between glassy and rubbery region is observed and the matrix increases in volume because of swelling.

As water infiltrates deep in to the core, the thickness of the gel layer increases with simultaneous dissolution and erosion occurring at the outer layer due to complete hydration.

When the system is hydrated to the core, the drug concentration falls below its solubility value and the release rate of the drug begins to decline. A concurrent increase in the thickness of the barrier layer with time increases the diffusion path length, further reducing the release rate. Drug release kineticassociated with this gel layer dynamics, range initially from Fickian to anomalous (Non-Fickian) and subsequently from quasi-constant (near zero order) to constant. Matrices of highly molecular weight polymers rarely shows all three regimens (Fickian, Non-Fickian and quasi-constant) of drug release because of alow chain disentanglement rate and insufficient external polymeric mass transfer.

Soluble drugs are primarily released by diffusion through aqueous filled porous network formed in the inert matrix former due to dissolution and erosion of the polymer from the surface. Far poorly soluble drugs dispersed in inert polymer systems erosion is the primarily release mechanisms.

There are two major processes that control the drug release from swelling controlled matrix systems, these include:

1. Ingress of aqueous medium into the matrix followed by a hydration, gelation or swelling and
2. Matrix erosion.

Simultaneous occurrence of these processes leads to the formation of twofronts within the hydrating matrix, this are- **a swelling front**, at the junction of the unhydrated glassy matrix and the hydrated matrix and **an eroding front** where the polymer is completely hydrated. Thickness of the diffusion layer, i.e. the distance between the two fronts, depends on the relative rates at which the swelling and erosion occurs.

If the polymer gels slowly, solvent can penetrate deep into the glassy matrix, thus dissolving the drug; therefore, gel layer thickness and its stability are crucial in controlling drug release. Numbers of techniques have been used to study the swelling of matrix tablets and to characterize the gel layer and front movement such as, optical imaging, ^{1}H- NMR, pulsed –filled gradient spin echo NMR, confocal laser scanning microscopy, cryogenic scanning electron microscopy and texture analysis. The gel layer thickness is determined by the relative position of the swelling and erosion front.

ADVANTAGES OF HYDROPHILIC MATRIX SYSTEM:-

A hydrophilic matrix system essentially consists of a drug dispersed in a water swelling viscous polymer. These systems offer a number of advantages over other sustained release technologies namely.

1. Simplicity of formulation.
2. High drug loading as high as 80 % is possible in many cases.
3. The system is usually inexpensive as the rate-controlling agent isusually a GRAS (generally accepted as safe) food polysaccharides.
4. Number of matrix former is available allowing development of formulations that meet special needs and avoid patent infringement.
5. The systems are eroded as they pass the GIT thus there are noaccumulation of "Ghosts" or empty shells.
6. As system depends on both diffusion and erosion for drug release,release is not totally dependent on GI motility.
7. No specialized equipment is required which substantially reduces manufacturing costs.
8. Offer easy scalability and process validation due to simple manufacturing processes.

The above listed advantages overshadow the undesirable propertyof reducing release rates with time.

FACTORS INFLUENCING DRUG RELEASE FROM MATRIX SYSTEMS[57]:-

A number of formulation variables and properties of the rate controlling polymer and the drug itself can be altered to attain a desired release rate from a matrix system. The mechanism by which drug release is controlled in matrix tablets are dependent on many variables, these variables are summarized in figure

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1) Drug solubility
2) Dose/drug content
3) Molecular weight
4) Particle size and shape

ry of factors influencing release rate from Matrix systems.

1.7 Criteria to be met by drug proposed to be formulated insustained release dosage forms. [59-63]

a) Desirable half-life:

The half life of a drug is an index of its residence time in the body. If the drug has a short half life (less than 2 hours), the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage from, and controlled release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

b) High therapeutic index

Drugs with low therapeutic index are unsuitable for incorporation in controlled release formulations. If the system fails in the body, dose dumpingmay occur, leading to fatalities eg. Digitoxin.

c) Small dose:

If the dose of a drug in the conventional dosage form is high, its suitability as a

candidate for controlled release is seriously undetermined. This is chiefly because the size of a unit dose controlled release formulation would become too big, to administer without difficulty.

d) Desirable absorption and solubility characteristics:

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into controlled release formulations is therefore unrealistic and may reduce overall absorption efficiency.

e) Desirable absorption window:

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the *'absorption window'*. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as controlled release dosage form are unsuitable.

f) First pass clearance:

As discussed earlier in disadvantages of controlled delivery system, delivery of the drug to the body in desired concentrations is seriously hamperedin case of drugs undergoing extensive hepatic first pass metabolism, whenadministered in controlled release forms.

2.LITERATURE REVIEW:

Indiran Pather[64] *et.al* **(1998)** have formulated sustained releasetheophylline tablet by direct compression using ethyl cellulose as polymers theyfound that In addition matrices of this polymer display slow surface erosion which can be enhanced by the incorporation of a swelling agent. This property was utilized in an attempt to decrease the attenuation of the release rate that is observed with matrix tablets that follow the Higuchi pattern of drug release.The release rate decreases because of the external layers of the tablet becomedepleted and water must penetrate the deeper layers of the tablet to reach the remaining drug. The Theophyline to ethyl cellulose ratio and the tablet hardness were found to influence the rate of drug release.

Yihong qiu.[65] et.al **(1998)** have used different viscosity grades of HPMC. Along with other excipient including Avicel and lactose for zero order sustained delivery of. Pseudoephedrine HCl they shown that zero – order or near zero – order drug release can be obtained using the new layered matrix designs. In general linear release profiles were observed with the HML and HMH systems. However, formulation and matrix variables in the barrierlayers need to be adjusted for achieving zero – order drug release from the LML system

- **Philip J. Cox**[66] **et.al(1999)** have prepared mini matrix of Ibuprofen by wet granulation technique in which hydrophillic matrix was formed with HPMC. xanthan and Karaya gum along with Avicel PH 101 and found that S(+) ibuprofen mini – matrices can be produced by the wet granulation method using xanthan gum, karaya gum or HPMC as the retarding agents. The crushing strengths used were in the range 23.3 – 28.0 N. Xanthan gum produced a greater sustaining effect on the release of S (+)Ibuprofen than Karaya gum.

- **T.Sing Hua[67] et.al (2000)** have prepared sodium valproate sustained release tablets. The release curve of sustained release tablets were consistent with Depakine Chrono. The pharma cokinetics and bio availability of sustained release tablets was evaluated using the conventional tablets. The plasma concentration were determined by HPLC after a randomized cross overoral administration of a single dose of sustained release tablets and conventional tablets in healthy volunteers.

- **Silvina A. Bravo[68] et.al (2002)** have achieved zero order release of diclofenac sodium by using HPMC matrix in different content level of MCC. Starch and lactose. they studied that Drug release from swollen matrices was principally regulated by starch (17%)j or lactose (17%), even on the presence ofMCC at different levels (5% or 7.5%). However, when starch (8.5%) and lactose (8.5%) were mixed at lower concentration in a ratio 1:1, MCC (5% or7.5%) appeared to control the drug release from the matrices.

- **K. Raghuram Reddy[69]et.al (2003)** have developed sustained release matrix tablet of nicorandil by wet granulation technique they usedHPMC SCMC and sodium alginate as matrix material for granulation they use ethanolic solution of EC and PVP. they found that the hydrophilic matrix of HPMC alone could not control the nicorandil release effectively for 24hours. It was evident from the results that a matrix tablet prepared with HPMC and a granulating agent of a hydrophobic polymer (EC, 4% wt / vol) is a better systemdrug like nicorandil.

- **Owen .I Corrigan[70] et.al (2004)** have studied the swelling and erosion properties of HPMC. In different agitation rate and dissolution medium composition. In their current work, swelling and erosion of HPMC polymers of differing molecular weights were examined by measuring the wet and subsequent dry weights of matrices. The polymers used were K 100 m,

K 15M, K4M, K100 LV and a low viscosity polymer, E50LV, which is slightly more hydrophobic due to increased methoxy substitution. These polymers show a wide range of viscosity's, reflecting molecular weight which causes differences in their swelling and erosion behaviors.

- **Fenq XM [71] et.al (2006)** was prepared and evaluate a new delayed onset sustained release system of propranolol Hydrochloride comprising a sustained release core tablet with HPMC as polymer matrix and an Eudragit polymer coating capable of delaying the drug release

- **Hosseinali Tobandeh [72] et.al (2006)** have prepared sustained release matrix tablets of aspirin with ethyl cellulose, Eudragit RS100 and Eudragit S100 and studying the release profiles and their sensitivity to tablet Hardness

- **Srinivasa Mutalik[73] et.al (2006)** investigation was to prepare glipizide matrix transdermal systems using Eudragit RL – 100/ Eudragit RS -100. The systems were evaluated for various in vitro and in vivo , biochemical parameters. The in vivo results released severe hypoglycemia in the initial hours and they were also effective on chronic application.

- **Varshosaz Jaleh[74] et.al (2006)** Used hydrophilic natural gums such as HPMC. Guar gum and xanthan gum for sustaining release of tramadol hydrochloride in matrix form and find that Guar gum alone cannot efficiently control drug release, and Xanthan gum has higher drug retarding ability than Guar gum . The Combination of each n gum with HPMC leads to a greater retarding effect as compared with a mixture of 2 natural gums.

- **Yeole PG[75] et.al (2006)** developed sustained release matrix tablet of diclofenac sodium by using xanthan gum as a matrix former and micro

crystalline cellulose as diluent. The inverse relationship was found between amount of gum and release rate of diclofenac sodium. Increasing the amount of gum in the formulation form 0.12% w/w to 0.28% w/w resulted in slowerrate and decreased amount of drug release from the tablet.

- **Achutha Nayak Usha[76] et.al (2007)** have prepared Oxaprozin agglomerates by spherical crystallization technique using a three solventsystem comprising acetone, dichloromethane water, Hpmc – 50 cps. In different concentration was used as a hydrophilic polymer. The effect ofspeed of rotation and amount of bridging liquid on spherical agglomeration were studied. The agglomerates were subjected to various physicochemical evaluation such as practical yield, drug content, LOD, IR , Spectroscopy, DSCand Dissolution studies. The agglomerates showed improved micromeritic properties as well as dissolution behaviour. In comparison to conventional drug crystals.

- **Mandal U[77] et.al (2007)** have design oral sustained release matrix tablets of metformin hydrochloride and to optimize the drug release profile using response surface methodology. Tablets were prepared by non –aqueous wet granulation method using HPMC K – 15M as matrix forming polymer. The evaluation parameter helped in finding the optimum formulation with sustained release Drug.

- **Srinivasa Mutalik[78] et.al (2007)** studied the significant effect of chitosan on improving the dissolution rate and bioavailability of oxaprozin . Chitosan was precipitated on oxaprozin crystals using sodium citrate as the salting out method with different concentrations of chitosan were characterized in terms of solubility, X –ray diffraction etc. wasassessed by preclinical pharmacodynamic (analgesic and anti – inflammatory activity). The in vivo studies revealed that the optimized crystal

formulation provides rats besides exhibiting improved pharmacokineticparameters in rats.

- **S Mutalik[79]et.al (2007)** studied was to develop "once daily" sustained release tablets of oxaprozin hydroxyl profile methyl cellulose – K4 M (HPMC). The solubility, in vitro drug release , analgesic, pharmacokinetic and toxicity studies and clinical pharmacokinetic studies were conducted.

- **Venkadari Gupta[80]et.al (2007)** prepared Celecoxib spherical agglomerates with polyvinylpyrrolidone (PVP) using acetone , water and liquid respectively. The agglomerates were characterized by differential scanning calroimetry (DSC) etc. The results indicated the absence of studies showed a decrease in crystallinity in agglomerates. An increase in PVP concentration the studies showed that the crystal possess surface.

- **Meyyanathan S.N[81] et.al (2008)** have prepared sustained release matrix tablets of Dextromethorphan hydrobromide by wet granulation using (HPMC k – 100) as the hydrophillic rate controlling polymer. The physical parameter and invitro dissolution were studied .The extent of Absorption of drug from the sustained release tablets was significantly higher than that for marketed Dextromethorphan hydrobromide tablets because of lowerelimination rate and longer half life.

- **Li CJ[82] et.al (2008)** have prepared verapamil Hydrochloride in cup tablet with tri layered tablet and core tablet separately which can provide biphasic release with double pulsatile and multiphasic release, core tablets were prepared by direct compression method and core in cup tablets by dry compression coated technology. The release rate increased with HPMC K – 100. This is determined by erosion rate of inhibitor layers.

- **Tiwari S. B.[83] et** al**, (2019)**studied the effect of concentration of hydrophilic(hydroxypropyl methyl cellulose [HPMC] and hydrophobic polymers (hydrogenated castor oil [HCO], ethyl cellulose). Hydrophobic matrix tablets resulted in sustained in vitro drug release (>20 hours) as compared with hydrophilic matrix tablets (<14 hours). The presence of ethyl cellulose in either of the matrix systems prolonged the release rate of the drug. The effect of ethyl cellulose coating (Surelease) and the presence of lactose andHPMC in the coating composition on the drug release was also investigated.Hydrophobic matrix tablets prepared using HCO were found to be the best suited for modulating the delivery of the highly waster-soluble drug, tramadol hydrochloride

- **Mandal U[84] et.al, (2020)** studied a fixed dose combination of bilayer matrixtablets of metforming sustained release and glipised as immediate release with HPMC k – 15 M and HPMC K- 100M. In this three different grades of HPMC (HPMC K - 4M, HPMC K – 15M and HPMC K – 100M) were used.By using polymer tablet shows release profile.

AIM AND OBJECTIVE

Aim of work

In pharmaceutical practice several approaches exist for administration of drugs to the patient. If the drug is given in conventional dosage form it has to be administered several time to produce desired therapeutic effect. Because of this frequent dosing fluctuation in plasma drug level occur. The pronounced fluctuation resulting from the conventional drug administration are likely to yield period of therapeutic effects, when the concentration falls below the minimum therapeutic level. Drug concentration can be controlled within the narrow therapeutic range by the use of sustained release systems, which will minimize the severity of side effects

Oxaprozin is an Non Steroidal Anti Inflammatory Drug , with half life of

4 – 4.3 hours and requires Single daily doses to maintain adequate plasma concentrations. So it is selected to prepare a sustained release tablets. The objective of this present study to develop a competitive sustained release tablets Oxaprozin which release the drug in a sustained manner over a period of 24 hours, by using different polymers and study on there effect on release pattern.

3. PLAN OF WORK

The following experimental protocol was therefore designed to allsystematic approach to the study.

1) *Drug selection*

2) *Literature Survey*:-

3) *Preformulation study*: Compatibility evaluation was carried out between drug and polymers in physical observation and by using FT- IR spectral study.

4) *Preparation of standard curve* for Oxaprozin in phosphate buffer pH 6.8 .

5) *Formulation development* of sustained release matrix tablets of usingdifferent release retardant.

6) The following *evaluation parameters* were studied based on laboratoryexperiments.

i) Evaluation of granules

- Angle of repose
- Apparent bulk density
- Tapped bulk density
- Percent compressibility
- Loss on drying
- Hausner Ratio

ii) Evaluation of tablets

- Tablet dimensions
- Hardness
- Friability
- Weight variation
- Content uniformity of active ingredient
- *In-vitro* dissolution study

7) Stability study of optimized batch

5.1 Materials Used in study

Table 1

Material Used

Sr.No	MATERIALS USED
1.	Oxaprozin
2.	Microcrystalline cellulose (Avicel pH 101)
3.	PVP k 30
4.	HPMC K 4M
5.	HPMC K 15M
6.	Acrypol 934 P
7.	Aerosil
8.	Isopropyl Alchol

ALL THE CHEMICALS USED IN UNIT WERE OF ANALYTICALGRADE AS PER INDUSTRY SPECIFICATIONS.

5.2. Instruments Used in study:

Table No. 2

Instruments Used

Sr. No	INSTRUMENTS	MANUFACTURER
1	Electronic Balance & Top loading Balance,	Shimadzu Corporation, AW 220 and BX 6205
2	Tray Dryer	Erweka Pvt. Ltd.
3	Coating machine	Erweka Pvt. Ltd.
4	Dissolution Apparatus (USP) Auto Sampler	Electrolab Pvt. Ltd.
5	Shaking Water Bath	Equitron
6	Tablet Hardness tester	Monsanto
7	Friability test apparatus	Electrolab Pvt. Ltd. EF 2 USP
8	Ultra Violet Visible spectro photometer	Shimadzu Corporation UV-1700
9	FT-IR Spectrophotometer	Shimadzu Corporation, 8400S
10	Tap density Appratus	Erweka Pvt. Ltd.
11	Granulate Flow Tester	Erweka Pvt. Ltd.
12	Vernier Caliper	Digimatic
13	pH Meter,	Systronics (335)
14	LOD apparatus	Sartorius
15	Tablet punching machine	CADMACH 16 station

5.3 DRUG PROFILE [85-88]

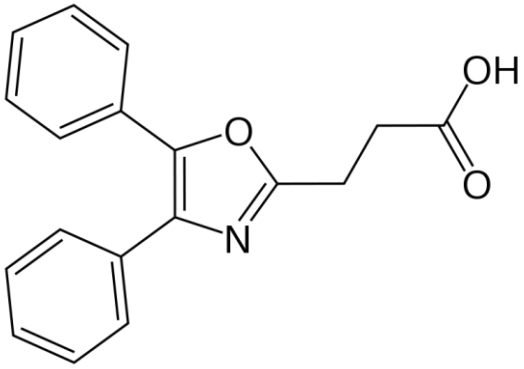
OXAPROZIN

Oxaprozin is one of the emerging NON STEROIDAL ANTI INFLAMMATORY DRUG molecules for arthritis treatment. it is a newerderivative of diclofenac and has less gastrointestinal complications. the successful treatment of arthritis depends on the maintenance of effective drugconcentration level in the body for which a constant and uniform supply of drug is desired. Sustained release dosage forms deliver the drug at a slow release rate over an extended period of time and achieve this objective. the short biological half-life 9about 4 h) and dosing frequency more than one per day make oxaprozin an ideal candidate for sustained release.

To reduce the frequency of administration and to improve patient compliance, a once-daily sustained release formulation of oxaprozin is desirable. For sustained release systems, the oral route of drug administrationhas, by far, received the most attention as it is natural uncomplicated, convenient and safer route. Matrix tablets composed of drug and release retarding material offer the simplest approach in designing a sustained release system. Matrix tablets are prepared by wet granulation.

The objective of the present study was to develop “one daily” sustainedrelease tablets of oxaprozin by wet granulation. The solubility studies of oxaprozin were conducted to select suitable dissolution media. The drug excipient mixtures were subjected to preformulation studies. The tablets were subjected to physicohemical, in vitro drug release and stability studies.

Structural Formula:



Official	In Indian Pharmacopoeia
Molecular formula	$C_{16}H_{13}C_{12}N0_4$
Molecular weight	354.19
Chemical name	(2,6-dichlorophenyl)aminophenylacetoxyacetic acid
Solubility	Drug is freely soluble in acetone and insoluble in water
Appearance	White or almost white powder
Shape	Crystalline Powder
Identification	When examined in the range of 220 nm to 370 nm. The 0.002% w/v solution in Methanol shows Maximum absorption at 275 nm It contains not less than 99.0% not more than 101.0% of its compounds calculated on the driedbasis (IP 2007)
Biopharmaceutical Classification	Class Second (High Permeability and Low Solubility)
Category	First –line drugs in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

Mechanism of pain & Inflammation:

Prostaglandins are implicated in the inflammatory response and are sensitizing nociceptors to the actions of other Mediators, occurring during acute and chronic inflammatory illness, prostaglandins are produced at thesite of inflammation where it is believed that they mediate many of symptoms of inflammation such as oedema and pain.

Arachidonic acid is released from cell membranes by phospholipases, cyclooxygenases catalyze the addition of molecular oxygen to arachidonic acid to form in initially the endoperoxide intermediate prostaglandin G2. The same enzymes also process peroxidase activity, which catalyzes the reduction of these prostaglandins to form PGH2. PGH 2 may then react with anumber of enzymes sometimes called isomerases to become one of the prostaglandins or thromboxanes.

Clinical Pharmacology :

Pharmacodynamics –

Oxaprozin is a novel NSAIDS known to exhibit multifactor mechanism of action.Oxaprozin was developed in order to provide a highly effective pain relieving therapy with a reduced side effect profile

1. Oxaprozin directly blocks PGE2 secretion at the site of inflammation by inhibiting IL-1 BETA & TNF in the inflammatory cells(Intracellular Action).Oxaprozin has been demonstrated to inhibit cyclooxygenase (COX) activity and to suppress the PGE2 production byinflammatory cells,which are likely to be a primary source of PGE2.Oxaprozin and 4-hydroxyoxaprozin penetrates the inflammatorycells like active metabolites diclofenac and 4-hydroxydiclofenac which inhibit IL-1 and TNF released by the inflammatory cells and therefore suppress production of PGE2 at the site of inflammation.

2. Oxaprozin stimulates the synthesis of the extracellular matrix ofthe Human Articular Cartilages.

Oxaprozin blocks degeneration and stimulates synthesis of extracellular matrix of cartilages by inhibiting the action of different cytokines.Oxaprozin and the metabolites inhibit IL-6 production by human chondrocytes.This leads to inhibition of increase of inflammatory cells in synovial tissue,inhibition of IL-1 amplipification,inhibition of increased MMP synthesis and thus ensuring proteoglycan production.Oxaprozin also inhibit IL-1 and TNF production by human chondrocytes,inflammatory cells and synovial cells and therefore blocks suppression of GAG and collagen synthesis and stimulates growth factor mediated synthesis of GAG and collagen.4`-hydroxyoxaprozin,a metabolite of oxaprozin inhibits pro MMP1 and pro MMP3 produced by synovial cells (Rheumatoid Synovial Cells) in serum and in synovial fluid and thus inhibits progressive joint destruction by MMPs.

3. Oxaprozin inhibits Neutrophil Adhesion & Accumulation at the inflammatory site in the early phase and thus blocks the pro-inflammatory actions of Neutrophils.

Pharmacokinetic Profile:

Absorption:

Oral Absorption : Rapidly absorbed orally

Oral Bioavailability : Almost 100%

Distribution:

Plasma protein binding 99.7%

Volume of distribution : 20-30 L

Effective Concentration : 60%

Metabolism : Oxaprozin is probably metabolized via CYP2C9 to the main metabolite 4-hydroxyoxaprozin.

Elimination:

Plasma half life : 4 – 4.3 hours

Excretion : Urinary 95 %

Dosage and Administration

The dose of Oxaprozin SR should be titrated according to the severity of the pain and the clinical response of the individual patient. The recommended dose of Oxaprozin SR in adults and adolescents over theage of 12 years in 200 mg once a day. The tablets are to be taken whole, not divided or chewed, with sufficient liquid, irrespective of food intake.

Indications : Relief of moderate to severe pain.

Contraindications

Oxaprozin is contraindicated in:

- Individuals with known hypersensitivity to Oxaprozin or any of its excipients
- In patients in whom substances with a similar action (e.g. Aspirin or other NSAIDS) precipitate attack of asthma,bronchospasm,acuterhinitis or urticaria
- Severe heart failure or severely impaired hepatic or renal organ function
- Oxaprozin must not be used during the last three months of pregnancy..

Adverse Effects:

- Generally mild:epigastric pain,nausea,headache,dizziness,rashes.
- Gastric ulceration and bleeding are less common.
- Reversible elevation of serum amino-transferases can occur.
- Kidney damage is very rare.

USES

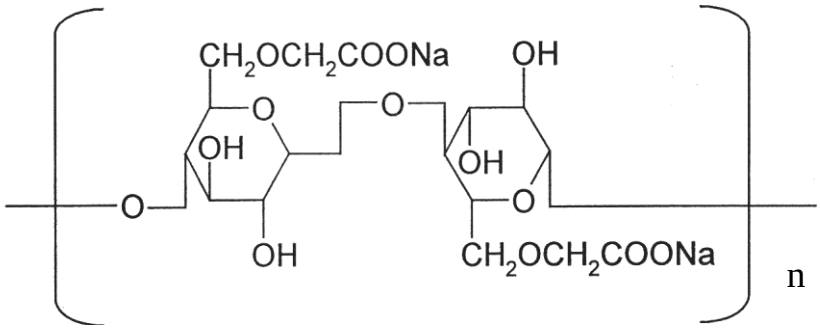
- IN OSTEOARTHRITIS
- IN RHEUMATOID ARTHRITIS
- IN ANKYLOSING SPONDYLITIS
- IN DENTAL PAIN
- IN POSTOPERATIVE PAIN
- IN DYSMENORRHOEA
- IN ACUTE LUMBAGO
- IN MUSCULOSKELETAL TRAUMA
- GONALGIA (KNEE PAIN)

Oxaprozin SR tablets are available at strength 100mg or 200mg dose in themarket

5.4 POLYMER PROFILE [89-92,61]

1) HYDROXYPROPYL METHYLCELLULOSE:

It is also called as methyl hydroxypropylcellulose, propylene glycol ether of methylcellulose, methylcellulose propylene glycol ether. Chemically it is cellulose, 2-Hydroxypropyl methyl ether, cellulose Hydroxypropylmethylether.



Empirical Formula: $C_8H_{15}O_6 – (C_{10}H_{18}O_6)$ n – $C_8H_{15}O_5$

Description: It is an odorless tasteless, white or creamy white fibrous or granular powder

Molecular Weight : 86,000 Bulk

Denisity 0.25-0.75 g/cm^3

Solubility

Soluble in cold water forming a viscous colloidal solution, insoluble in alcohol,ether and chloroform, but soluble in mixtures of methyl alcohol and methylenechloride. Certain grades are soluble in aqueous acetone, mixtures of methylene chloride and isopropyl alcohol and other organic solvents

Viscosity: 2% solution

HPMC K100M –80000-120000 cps
HPMC K15M-11250-21000 cps
HPMC K4M-3000-5000 cps

Stability and Storage Conditions:

Very stable in dry conditions. Solutions are stable at PH 3.0-11.0. Aqueous solutions are liable to be affected by microorganisms. When used asa viscosity increasing agent in ophthalmic solutions, an anti-microbial agent, such as benzalkonium chloride, should be incorporated. Store in a tight container, in a cool place.

Incompatibility:

Extreme pH conditions, oxidizing materials.

Uses:

It is used as film former (2-10%), binder (2-5%). High viscosity grades are used to retard the release of water- soluble drugs. It is also used as emulsifier, suspending agent and stabilizer in gels and ointments Adhesive in plastic bandages.

2) MICROCRYSTALLINE CELLULOSE

Synonyms **:** Avicel, Crystalline cellulose Emcocel

Description : It is purified, partially depolymerised cellulose, which occurs as white, odorless, tasteless, dry powder composed of porous particles. It is available in various particle size and moisture grades.

Functional Categories : Adsorbent, Suspending Agent, Tablet and Capsulediluent and tablet disintegrant.

Tablet disintegrant :5-15%
Tablet diluent : 20-90%
Solubility : Slightly soluble in 5% sodium hydroxide practically insoluble in water.
Specific surface area 1.18m2g for avicel pH 101pH :
5.0 to 7.0

Grade	Bulk Density	Tapped Density	Nominal Mean Particle Size
PH 101	0.320 g/cm^3	0.386 g/cm^3	50 Micro meter
PH 102	0.307 g/cm^3	0.3709/Cm^3	100 Micro Meter

Stability and storage conditions : It is hygroscopic and stable one and itshould be stored in well closed container.

Incompatibilities : Incompatible with strong oxidizing agents.

Applications : It is widely used in pharmaceuticals and food products. It is used as binder or diluent in oral tablet or capsule formulation where it is usedin both wet granulation and direct compression. It is also used as lubricant ordisintigrant.

3) MAGNESIUM STEARATE

It is also called as metallic stearate. Chemically it is octadecanoic acid.

Empirical formula: $C_{36}H_{70}MgO_4$

Molecular weight: 591.3

Description: Fine, white, precipitated or milled, impulpable powder of low bulk density. Odour and taste are slight but characteristic. The powder is unctuous, and readily adheres to the skin.

Density: 1.03 – 1.08 g/cm^3

Stability and Storage Conditions:

Stable, non-self-polymerizable, store in a cool, dry place in a well-closed container.

Incompatibilities:

Acidic substances, alkaline substances, iron salts, avoid mixing withstrong oxidizing materials. Use with caution with drugs which are incompatible with alkali.

Uses:

Tablet and capsule lubricant, glidant or antiadherent (0.25 – 2.0%).Carbomar

It is a high molecular weight polymer of acrylic acid cross linked withallyl ether of sucrose

It having different varieties of grade that are in such a manner

Carbomer 934

Carbomer 934 P

Carbomer 940

Carbomer 941

Carbomer 1342

Carbomer Co polymer

These trade are official U.S.P

Carbomer 934 P

It is a high molecular weight polymer of acrylic acid cross linked withallyl ethers of sucrose.

It is dried in vaccum at 80^0 C for one Hour

It contains not less than 56.0% not more than 68% of COOH groups The Viscosity of a neutralized 0.5% aqueous dispersion of carbomer 934 P is between Viscosity of this is between 29,400 & 39,400 centipoises.

Applications

Carbomer is used in

- Sustained release
- Matrix beads
- Site specific drug delivery to esophagus
- Additionally used in preparation of SR Tablets. by using dry orwet binder & as rate controlling excipient

4) COLLOIDAL SILICON DIOXIDE

Synonyms: Aerosil, Cab-O-sil, Colloidal silica, Fumed silica.

Description

It is submicroscopic fumed silica with a particle size of about 15 nm. Itis a light, loose, bluish-white colored, odorless, tasteless, nongritty amorphouspowder.

Functional categories

Adsorbent, anticaking agent, glidant, suspending agent, tablet disintegrant,

viscosity-increasing agent.

Solubility

It is insoluble in water, organic solvents & acids, except hydrofluoric acid. It is soluble in hot solution of alkali hydroxide.

Typical Properties

pH: *3.5 – 5.5*

Loss on drying: □ *2.5%*

Density (bulk)*:* *0.029-0.042 gm/cm*^{3}

Density (tapped): *0.050 gm/ cm*^{3}

Stability and storage conditions

It is hygroscopic & absorbs large quantities of water without liquefying.

Should be stored in well-closed container in a cool, dry place.

Incompatibilities Incompatible with diethylstilbestrol preparation.

Applications

It is widely used in pharmaceuticals, cosmetics & food products. It is used as a glidant. It is also used to stabilize emulsions & as a thixotropic thickening & suspending agent in gels & semisolid preparations. It is alsoused as tablet disintegrant. In aerosol, except those for inhalation, it is used topromote particulate suspension, eliminate hard settling & minimize the clogging of spray nozzles.

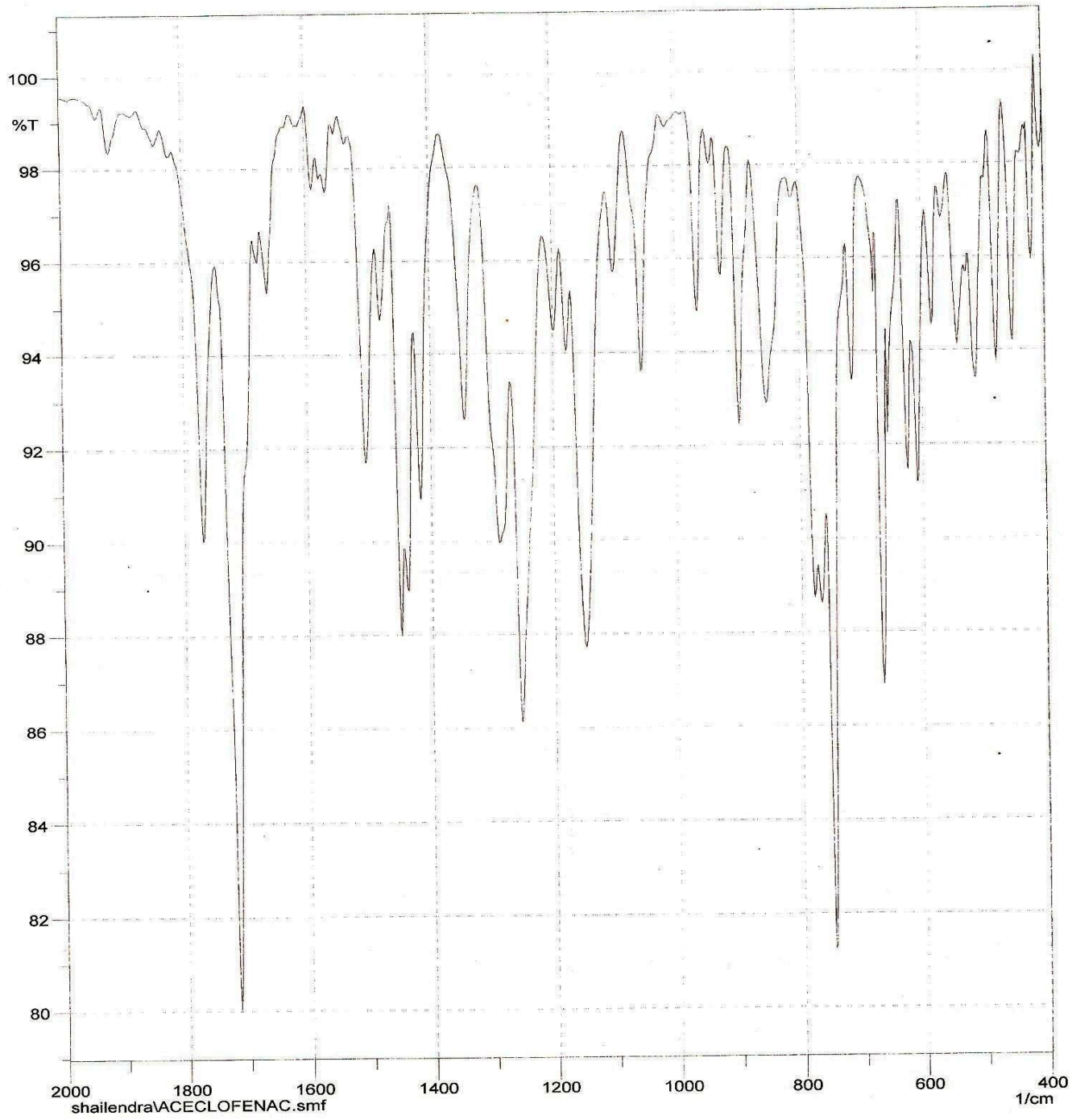
5.5 PREFORMULATION STUDY[93-94]

Preformulation stability studies are usually the first quantitativeassessment of chemical stability of a drug as well as stability in presence of other excipients. The primary objectives of this investigation are identification of stable storage conditions for drug in the solid state and identification of compatible excipients for a formulation.

Identification of Drug

The identification of drug was done by FT-IR Spectroscopy.

Method: Triturate 1-2 mg of the substance to be examined with 300-400 mg, unless otherwise specified, of finely powdered and dried potassium bromideor potassium chloride . These quantities are usually sufficient to give a disc of10-15 mm diameter and a spectrum of suitable intensity. Infraredspectrophotometers are used for recording spectra in the region of 4000 – 650.



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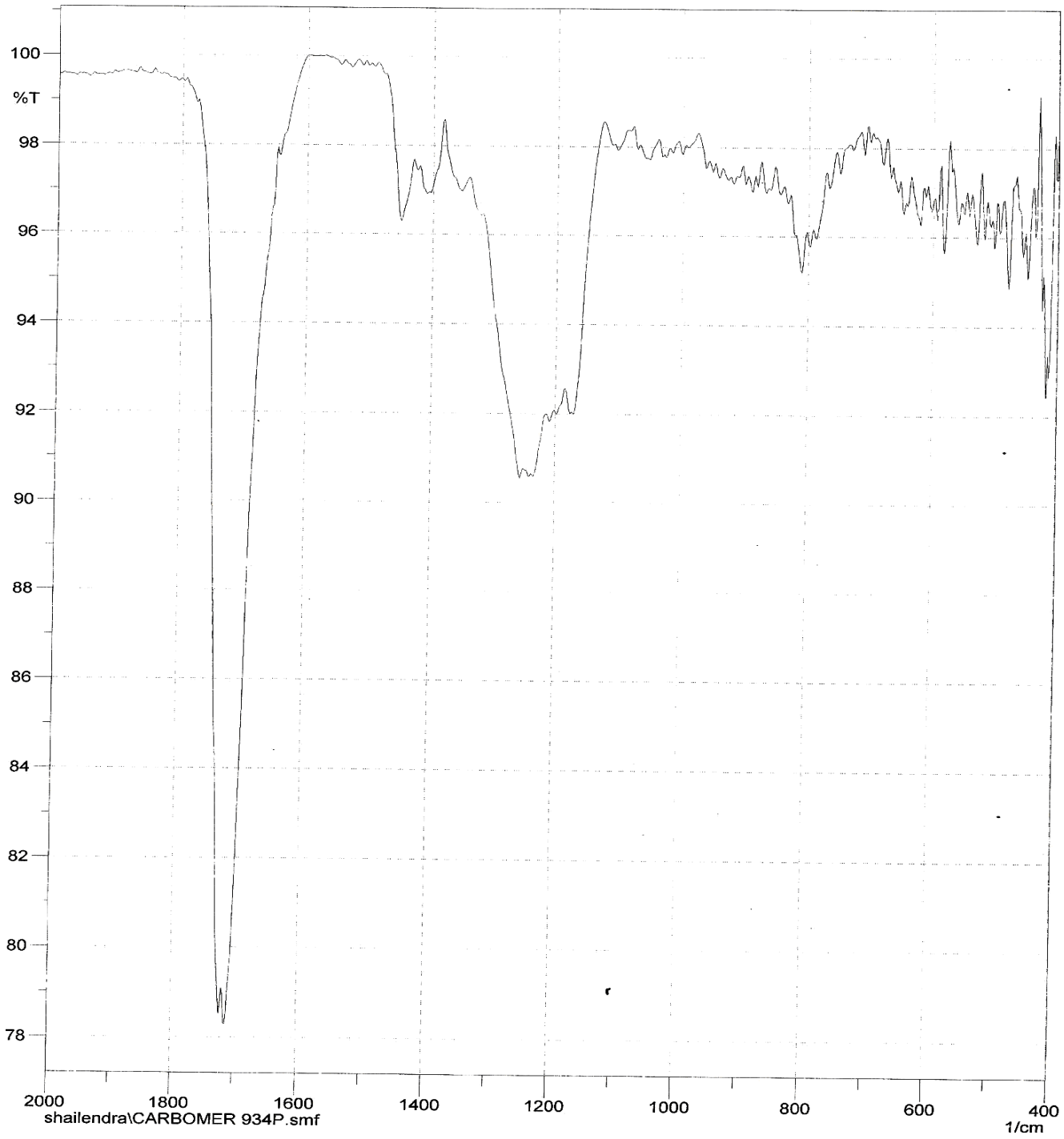

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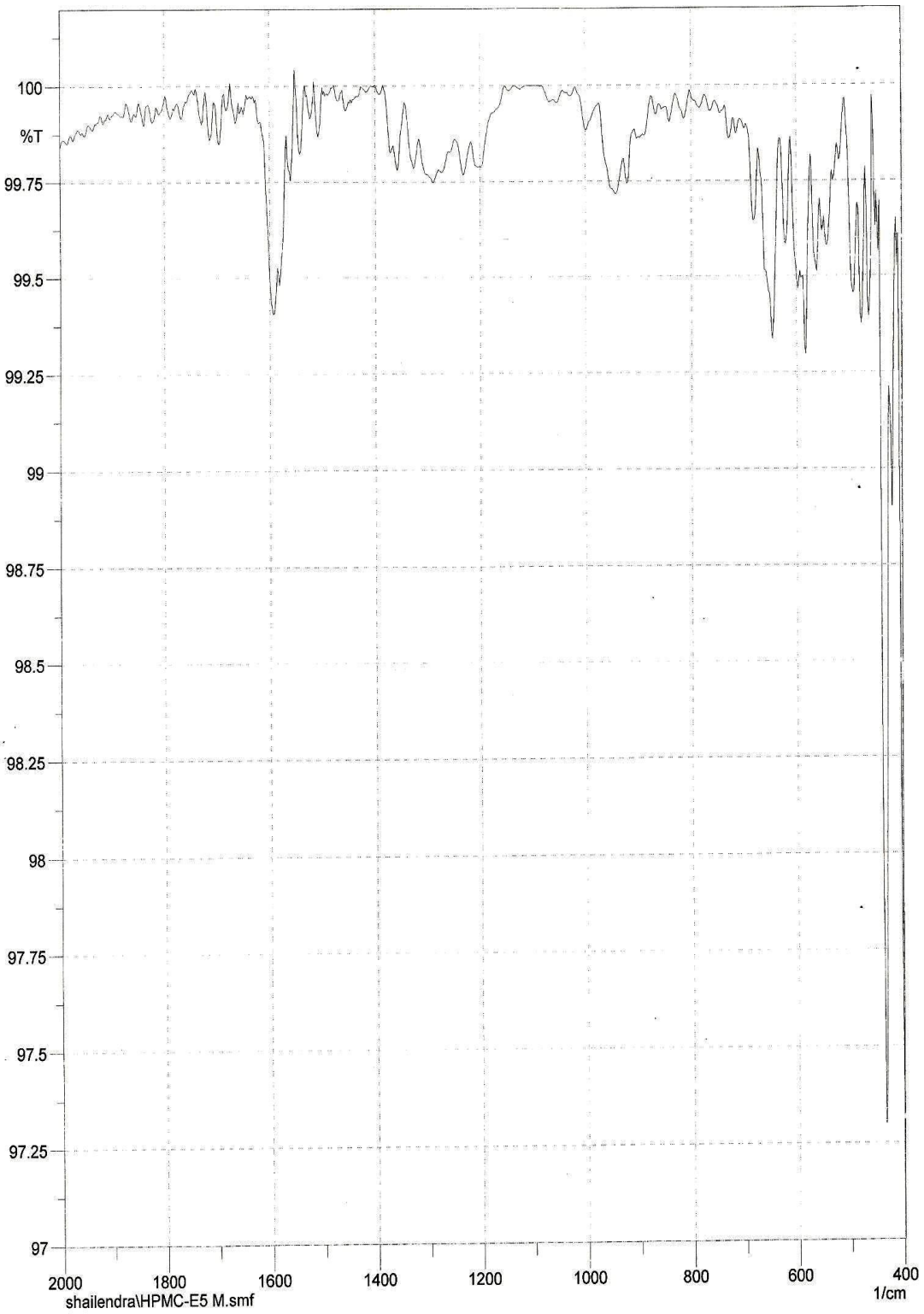

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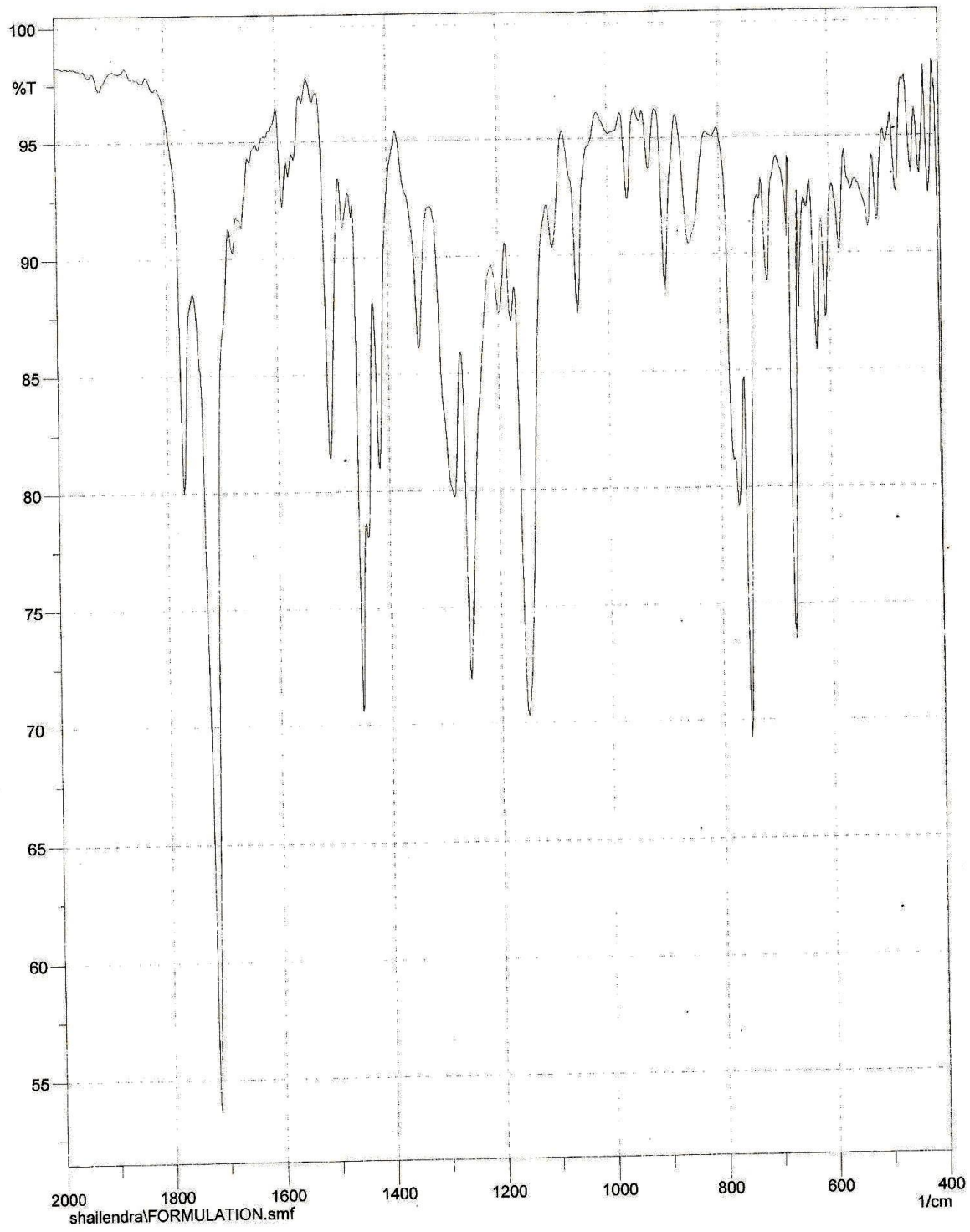

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Drug – Excipient Compatibility Study :

Compatibility studies were conducted to investigate and predict physicochemical interaction between drug substance and excipents and therefore to select suitability of chemically compatible excipients.

Table No.3

Physical observation of compatibility study :

Drug & Excipients (Ratio 1 : 1)	**Observation**			**Result**
	Initial	**30ºC±2/65% ±5 RH after 30 days**	**40ºC±2/75%±5 RH after 30 days**	
Oxaprozin	White to off White powder	White to off White powder	White to off White powder	Compatible
Oxaprozin + HPMC K15 M	White to off White powder	White to off White powder	White to off White powder	Compatible
Oxaprozin + HPMC K 4M	White to off White powder	White to off White powder	White to off White powder	Compatible
Oxaprozin + Carbomer 934P	White to off White powder	White to off White powder	White to off White powder	Compatible
Oxaprozin + PVP K 30	White to off White powder	White to off White powder	White to off White powder	Compatible
Oxaprozin + Mg. Stearate	White to off White powder	White to off White powder	White to off White powder	Compatible
Oxaprozin + Mcc	White to off White powder	White to off White powder	White to off White powder	Compatible

5.6 STANDARD CURVE OF OXAPROZIN

Preparation of phosphate buffer pH 6.8

Accurately weighed quantity of 27.218 g of potassium dihydrogen phosphate was dissolved in distilled water and diluted with distilled waterupto 1000 ml. 50ml of above solution was taken in a 200 ml of volumetric flask, 22.4 ml of 0.2 M NaOH was added to the solution and then diluted with distilled water upto volume.

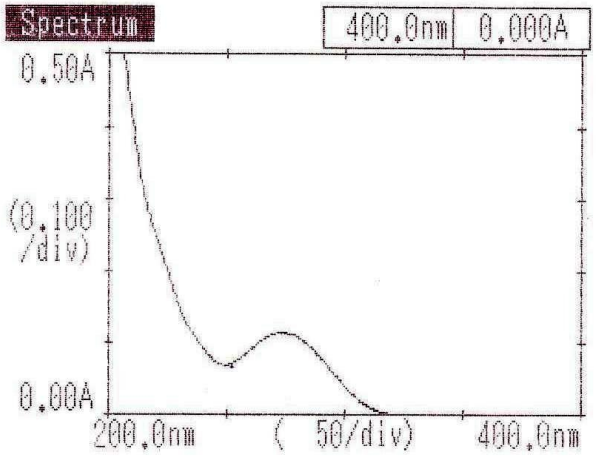
Preparation of standard curve in 6.8 pH buffer

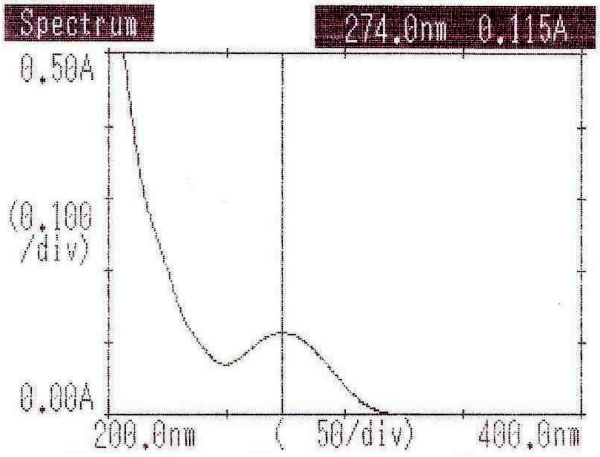
100 mg equivalent weighed of Oxaprozin was dissolved in 100 ml of phosphate buffer pH 6.8. The 10 ml of above solution was further diluted upto 100 ml with phosphate buffer pH 6.8. The resulting solution was serially diluted with phosphate buffer pH 6.8. to get drugconcentration 5,10,15,20,25 µg/ml. The absorbance of the solutions was measured against phosphate buffer pH 6.8 as a blank at 274.0 nm using double beam UV visible spectrophotometer.. The plot of absorbance v/s concentration (µg/ml) was plotted and data was subjected to obtain linear regression analysis.

Observation

The standard calibration curve of drug in phosphate buffer pH 6.8 depicted as Figure. The data of absorbance was shown in Table . The datahad correlation coefficient of 0.9992.

SCANNING OF ACECLOFENAC IN PHOSPHATE BUFFER IN pH 6.8





Peak detection

Abscis.	ABS
274.0	0.115

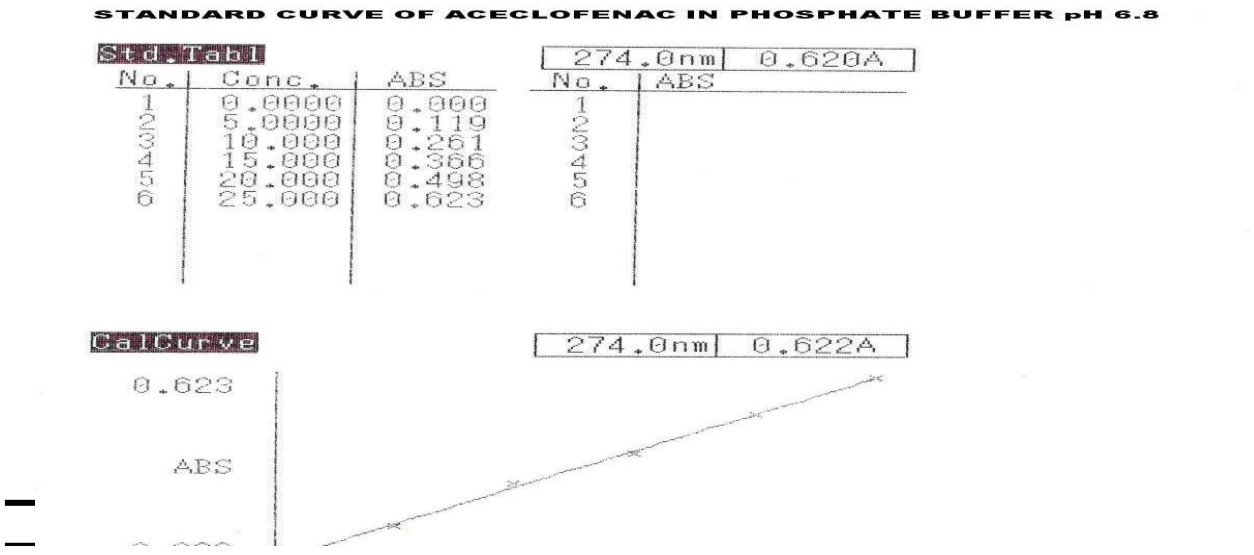
6.1 Manufacturing procedure of sustained release tablet of Oxaprozin

Wet Granulation Method

Weight accurately Drug + HPMC K15M + PVP K-30 and Microcrystaline cellulose pass through 40 no sieves and mix properly for 3-5 minutes in a steel tub.

Prepare binder solution by dispersing PVP K30 in isopropyl alcohol.

Granulation of above mixture is done by prepared binder solution by kneading up to granulation end point is obtained(Dough mass) .Pass the dough mass through 12 mess and keep it in a tray dryer for drying and finaly keep the loss on drying(LOD) up to 2-3 %.Remove the driedgranules from oven and pass through 20 mess sieve to get optimum size granules.Lubrication is done by using Mg.stearate and passed through 60 mesh of the granules for 3 to 4 min. in a steel tub and then in polybag.



Compression is done by using 16 station single rotary CADMACHmachine by using 9.6 mm round , biconcave ,both side plane punch .

6.2 DESIGN AND DEVELOPMENT OF OXAPROZIN SRMATRIX TABLETS

Table No. 4 Formulation of Batch T-1 to T-5

Formulation Ingredients	TRIAL BATCHES				
	ASR - 01	ASR - 02	ASR - 03	ASR - 04	ASR – 05
Oxaprozin	200	200	200	200	200
MCC	67	63	62	74	72
PVP K – 30	10	9	10	8	10
I.P.A	Q.S	Q.S	Q.S	Q.S	Q.S
HPMC K4M	-	20	15	10	10
HPMC K 15	15	10	15	10	-
ACRYPOL 934 P	10	-	-	-	10
MAG STEARATE	5	5	5	5	5
AEROSIL	3	3	3	3	3
TOTAL WEIGHT	310 mg	310 mg	310 mg	310 mg	310 mg

6.2.1 DESIGN AND DEVELOPMENT OF OXAPROZIN SRMATRIX TABLETS

Table No. 4.1 Formulation of Batch T-6 to T-10

Formulation Ingredients	TRIAL BATCHES				
	ASR - 06	ASR - 07	Final	ASR - 09	ASR - 10
Oxaprozin	200	200	200	200	200
MCC	71	67	49	53	42
PVP K – 30	11	10	10	10	10
I.P.A	Q.S	Q.S	Q.S	Q.S	Q.S
HPMC K4M	-	10	-	20	25
HPMC K 15	5	10	23	-	-
ACRYPOL 934 P	15	5	20	19	25
MAG STEARATE	5	5	5	5	5
AEROSIL	3	3	3	3	3
TOTAL WEIGHT	310 mg	310 mg	310 mg	310 mg	310 mg

7. EVALUATION STUDIES [93,95-98]

7.1 EVALUATION OF GRANULES

7.1.1 Determination of bulk density and tapped density

An accurately weighed quantity of the powder (W) was carefullypoured into the graduated cylinder and the volume (V_o) was measured then the graduated cylinder was closed with lid, set into the densitydetermination apparatus (Bulk density apparatus, electrolab, mumbai). The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density and tapped density were calculated using the following formulas:

Bulk density $= W/V_o$

Tapped density $= W/V_f$

Where V_o =initial VolumeV_f = final Volume

7.1.2 Compressibility index & Hausner Ratio

The Compressibility index and Hausner ratio are measures of theproperty of a powder to be compressed. As such, they are measures of therelative importance of inter particulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, they are frequently greater inter particle interaction, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner Ratio. The compressibility index and Hausner ratio may be calculated

using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped})as follows :

$$\text{compressibility index} = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \times 100$$

$$\text{Hausner ratio} = \frac{\rho_{tapped}}{\rho_{bulk}}$$

7.1.3 Loss on drying

Determination of loss on drying of granules are important dryingtime during granulation was optimized depending LOD value. LOD of each batches were tested at 105° c for 2.5 minutes by using “Sartorius” electronic LOD apparatus.

7.1.4 Angle of repose

The flow characteristics are measured by angle of repose.Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible betweenthe surface of a pile of the powder and the horizontal plane.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} h/r$$

where h = height of pile

r = radius of the base of the pile

θ = angle of repose

Table No.5

Characterization of Trial Blends

B.No	Bulk density*	Tapped density*	Loss on Drying in % *	Compressibility Index*	Hausner Ratio *	Angle of Repose( )*
T1	0.442 □. 0.024	0.506 □ 0.014	1.7 □ 0.011	12.65 □ 0.015	1.14 □ 0.014	34□ □2
T2	0.486 □ 0.018	0.556 □ 0.026	1.2 □ 0.014	12.59 □ 0.022	1.14 □ 0.016	31□ □3
T3	0.529 □ 0.016	0.593 □ 0.021	1.5 □ 0.018	10.79 □ 0.021	1.12 □ 0.014	31□ □2
T4	0.512 □ 0.019	0.574 □ 0.025	1.4 □ 0.016	10.80 □ 0.019	1.12 □ 0.018	28□ □3
T5	0.544 □ 0.022	0.601 □ 0.022	1.4 □ 0.011	9.48 □ 0.014	1.10 □ 0.019	28□ □ 2
T6	0.539 □ 0.017	0.586 □ 0.021	1.3 □ 0.013	8.02 □ 0.016	1.09 □ 0.021	26□ □3
T7	0.499 □ 0.018	0.564 □ 0.016	1.8 □ 0.017	11.52 □ 0.024	1.13 □ 0.022	32□ □2
T8	0.523 □ 0.018	0.602 □ 0.017	2.2 □ 0.012	13.12 □ 0.021	1.15 □ 0.017	35□ □2
T9	0.524 □ 0.014	0.596 □ 0.024	1.5 □ 0.016	10.74 □ 0.019	1.14 □ 0.015	31□ □ 2
T10	0.527 □ 0.019	0.587 □ 0.024	1.2 □ 0.016	11.59 □ 0.017	1.13 □ 0.018	31□ □ 3

7.2 EVALUATION OF TABLET

All the prepared sustained release tables were evaluated forfollowing official and unofficial parameters.

7.2.1 Weight Variation

7.2.2 Dimensions

7.2.3 Hardness Test

7.2.4 Friability Test

7.2.5 Drug content

7.2.6 Dissolution study

7.2.1 Weight Variation

Method

Twenty tables were randomly selected form each batch and individually weighed. The average weight an standard deviation of 20 tablets was calculated. The batch passes the test for weight variation testif not more then two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table 7 and none deviate by more than twice the percentage shown.

Observations:

The average weight and standard deviation of the tablets of eachbatch were given in Table 6

Percentage deviation allowed under weight variation

Percentage deviation allowed under weight variation test.	
Average weight of tablet (X mg)	**Percentage deviation**
X< 80 mg	10
80 < X < 250 mg	7.5
X > 250 mg	5

7.2.2 Dimensions

Twenty tablets were randomly selected form each batch and therethickness and diameter was measured by using digital vernier caliper.

Observations:

The average thickness and diameter with standard deviation of thetablets of each batch were given in Table No.7

7.2.3 Hardness Test

Hardness was measured using Monsanto hardness tester. For eachbatch ten tablets were tested given in Table No.7

Observations:

The measured hardness (N) of tablets of each batch was rangedfrom 4-6 kg/cm2

7.2.4 Friability Test

Twenty tables were weighed and placed in the Electorlabfriabilator and apparatus was rotated at 25 rpm for 4 minutes. Afterrevolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$\% F = \{ 1- (Wt/W)\} \times 100$

Where %F = friability in percentageW =

Initial weight of tablet

Wt = weight of tablet after revolution

Observations:

The results of measured % friability are given in Table 7

Table No.7

Physical parameters of tables of each batch

B.No	Weight Variation (mg)*	Thickness (mm)*	Hardness (kg/cm2)*	Friability (%)	Drug Content (%)
T1	310□1.97	4.66□0.2	6	0.62□0.03	101.65
T2	310□1.68	4.63□ 0.0	4	0.62□0.02	98.22
T3	310□3.05	4.37□0.3	4	0.42□0.05	103.99
T4	310□3.01	4.72□0.2	5	0.49□0.04	100.83
T5	310□1.84	4.69□0.3	6	0.65□0.03	96.98
T6	310□2.36	4.66□0.2	6	0.59□0.04	96.89
T7	310□3.14	4.60□0.3	4	0.67□0.02	96.42
T8	310□2.15	4.66□0.2	4	0.53□0.03	99.25
T9	310□3.14	4.60□0.3	6	0.65□0.03	99.73
T10	310□1.87	4.69□0.2	4	0.45□0.02	100.75

* Each value represents the mean □ standard deviation (n = 10)

7.2.5 Drug Content of Oxaprozin by HPLC

Column : µ bonda pack C18 (1-30 cm; d = 4mm) Waters Eluent : Add to 900 ml of water, 4 ml of ammonia 25% and 5ml of conc. Phosphoric acid. Shake and to bring on pH = 2.1 with phosphoric acid. Add 100ml acetonitril. Filtrate under vacuum

Flow rate : 1.0 ml/min

Detection : 2.70 nm

Injection : 20 µl. Autosampler Spark Holland.

Temperature : room temperature (15-25°C) Solutions

Standard : Accurately weigh 100 mg of **Oxaprozin** reference standard into a 100.0 ml volumetric flask, dissolve inmethanol and dilute to volume.

Sample to : Accurately weigh an amount of tablet powder, equal 100mg of **Oxaprozin** into a 100.0 ml volumetricflask, and add methanol to volume. Stir during onenight to allow the Oxaprozin to dissolve. Centrifugeand inject the clear solution.

Calculation :

$$\frac{\text{area Sa x th.wgh.S x wgh.St area St}}{\text{X th. wgh. St x wgh. sa}} \quad X\ 100\% = \text{assay \%}$$

Where :

area Sa = The area of the sample solution

area St = The area of the standard solution

th.wgh.St	=	The theoretical weight of the sample solution
th.wgh.st	=	The theoretical weight of the standard solution
wgh.Sa	=	The real weight of the sample solution
wgh.St	=	The real weight of the standard solution

7.2.6 Dissolution Study

Medium	:	6.8 pH phosphate buffer
Volume	:	900ml
Apparatus	:	Paddle
Rotation	:	75 rpm
Time	:	24 hours
Detection	:	UV, 274nm
St. stock solution	:	Weigh an amount of **Oxaprozin,** reference standard equal to 103.27 mg **Oxaprozin** into a 100.0 ml volumetric flask which was dissolve in medium
Std. solution	:	Dilute 10.00 ml St, Stock solution to 100ml with medium
Sample Solution	:	Take 10ml solution of sample from each vessel and filtered and take absorbance at 274 nm on double beam UV spectrophotometer and replace thevolume with dissolution medium maintaining the temperature.

Calculation :

$$\frac{\text{Ex. S x th.wgh.St x 10 x 900 x purity}}{\text{Ex.St x wgh. St x 100 x 1 x 100}} \times 1000$$

Where :

Ex.S	=	The extinction of the sample solution
Ex.St	=	The extinction of the standard solution
th.wgh.St	=	The theoretical weight of the reference standard calculated on the assay of the reference standard
wgh.St	=	The real weight of the reference solution

Table No.8

Dissolution Profile of batch No. T-1 to T-10 and marketed sample in 6.8 pH phosphate buffer

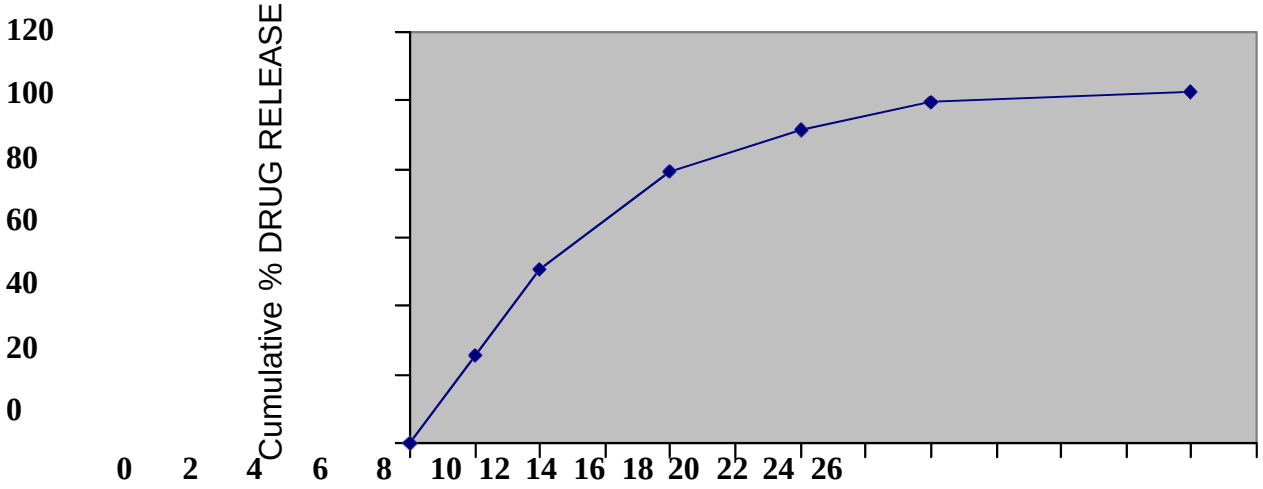
B.No	**Time in Hours (cumulative % drug release)**						
	6.8 PH buffer						
	0	**2**	**4**	**8**	**12**	**16**	**24**
T1	0	25.65	50.48	79.25	91.25	99.52	102.
T2	0	22.68	40.17	72.58	89.24	97.77	100.
T3	0	18.85	39.45	65.95	90.58	99.01	100.
T4	0	20.65	40.25	72.56	92.68	99.67	102.
T5	0	26.98	49.65	75.82	95.62	101.24	101.
T6	0	24.98	42.78	70.98	85.24	92.57	101.
T7	0	25.64	45.65	75.58	90.14	99.65	102.
T8	0	15.56	25.63	69.85	82.46	92.05	99.5

T9	0	17.56	30.64	75.52	80.97	95.41	101.
T10	0	14.69	22.57	65.24	75.68	88.52	97.2
Market Sample	0	11.41	21.63	71.64	78.46	89.27	100.

Dissolution Profile of batch No. T-1 in 6.8 pH phosphate buffer

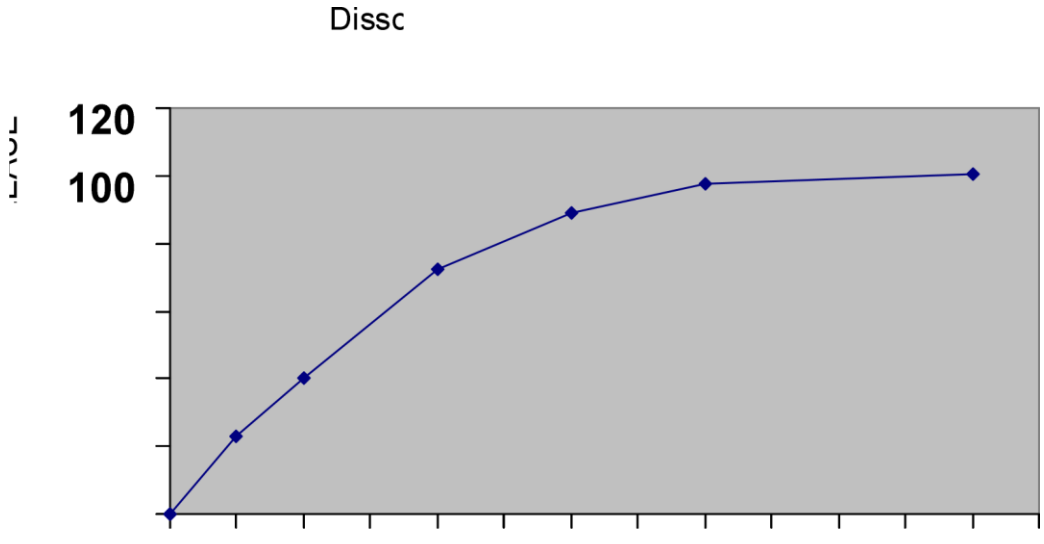
Time in hours	% Drug release
0	0
2	25.65
4	50.48
8	79.25
12	91.25
16	99.52
24	102.69

Dissolution Profile Of Batch T-1



Dissolution Profile of batch No. T-2 in 6.8 pH phosphate buffer

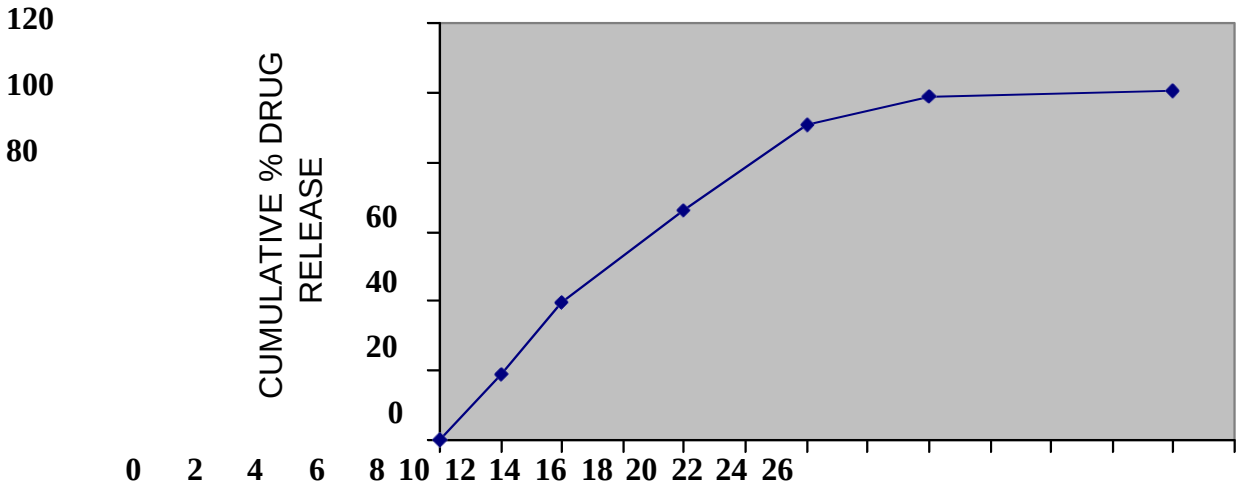
Time in hours	% Drug release
0	0
2	22.68
4	40.17
8	72.58
12	89.24
16	97.77
24	100.25



Dissolution Profile of batch No. T-3 in 6.8 pH phosphate buffer

Time in hours	% Drug release
0	0
2	18.85
4	39.45
8	65.95
12	90.58
16	99.01
24	100.25

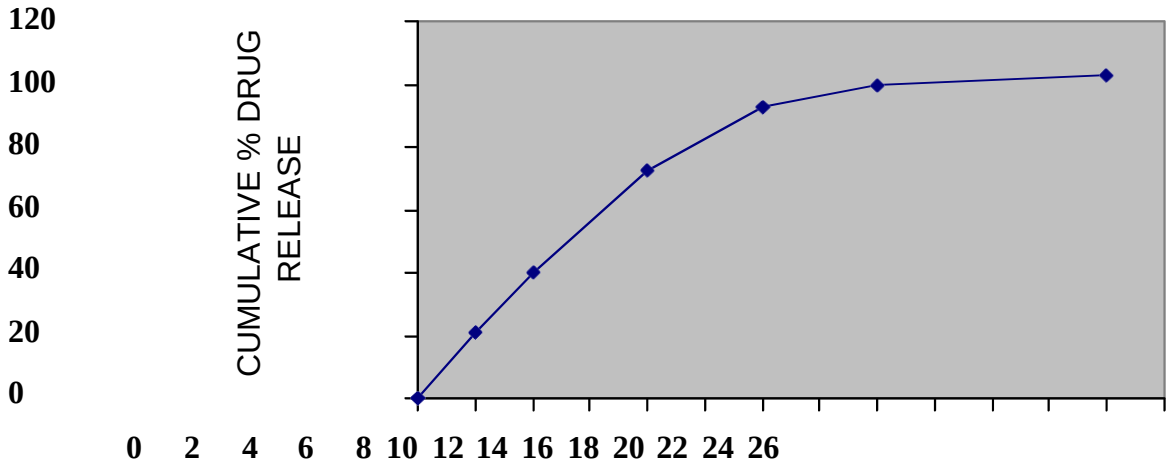
Dissolution Profile Of Batch T-3



Dissolution Profile of batch No. T-4 in 6.8 pH phosphate buffer

Time in hours	% Drug release
0	0
2	20.65
4	40.25
8	72.56
12	92.68
16	99.67
24	102.58

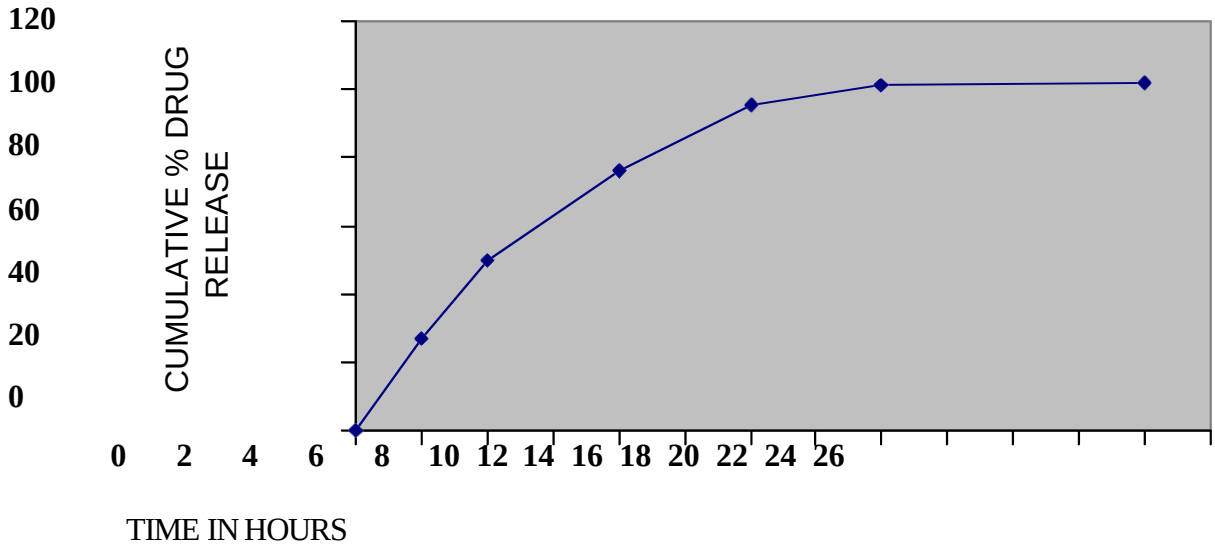
Dissolution Profile Of Batch T-4



Dissolution Profile of batch No. T-5 in 6.8 pH phosphate buffer

Time in hours	% Drug release
0	0
2	26.98
4	49.65
8	75.82
12	95.62
16	101.24
24	101.98

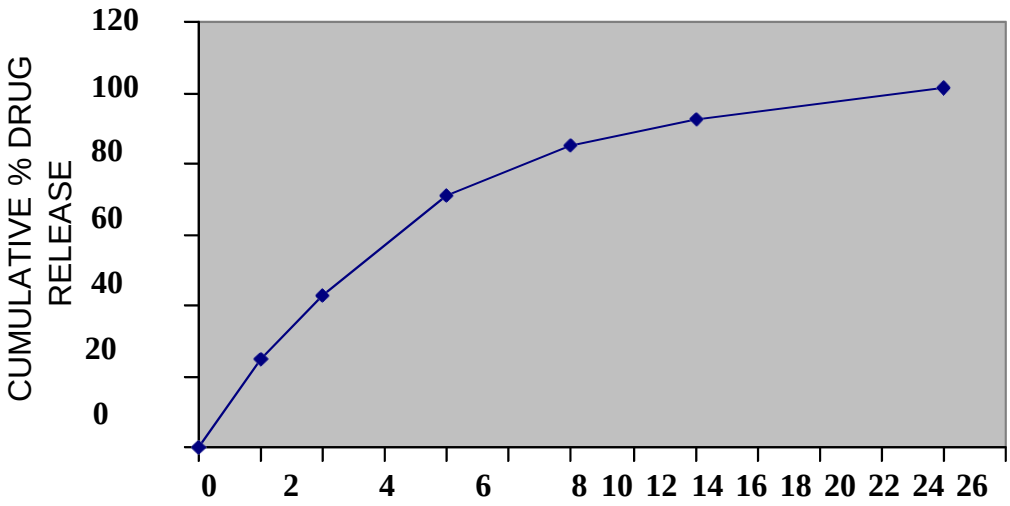
Dissolution Profile Of Batch T-5



Dissolution Profile of batch No. T-6 in 6.8 pH phosphate buffer

Time in hours	% Drug release
0	0
2	24.98
4	42.78
8	70.98
12	85.24
16	92.57
24	101.69

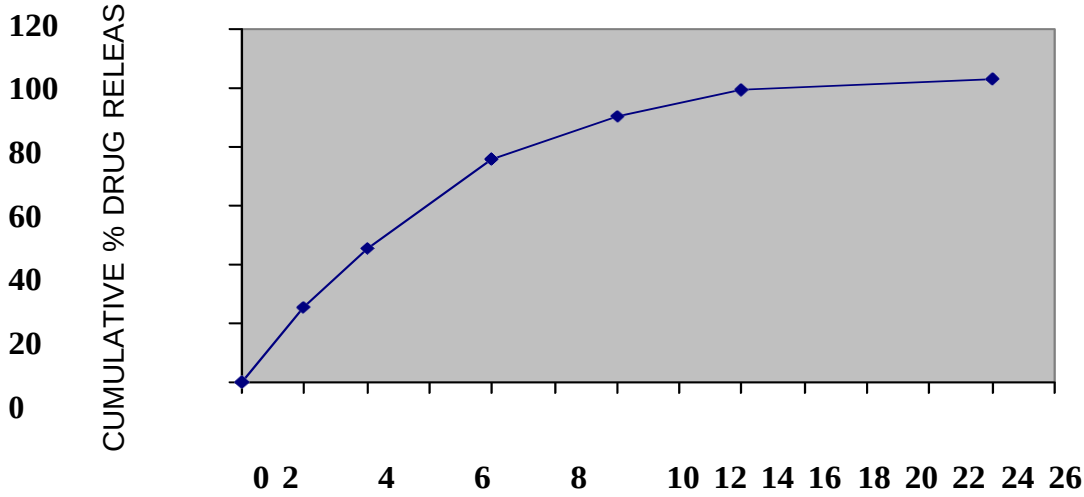
Dissolution Profile Of Batch T-6



Dissolution Profile of batch No. T-7 in 6.8 pH phosphate buffer

Time in hours	% Drug release
0	0
2	25.64
4	45.65
8	75.58
12	90.14
16	99.65
24	102.97

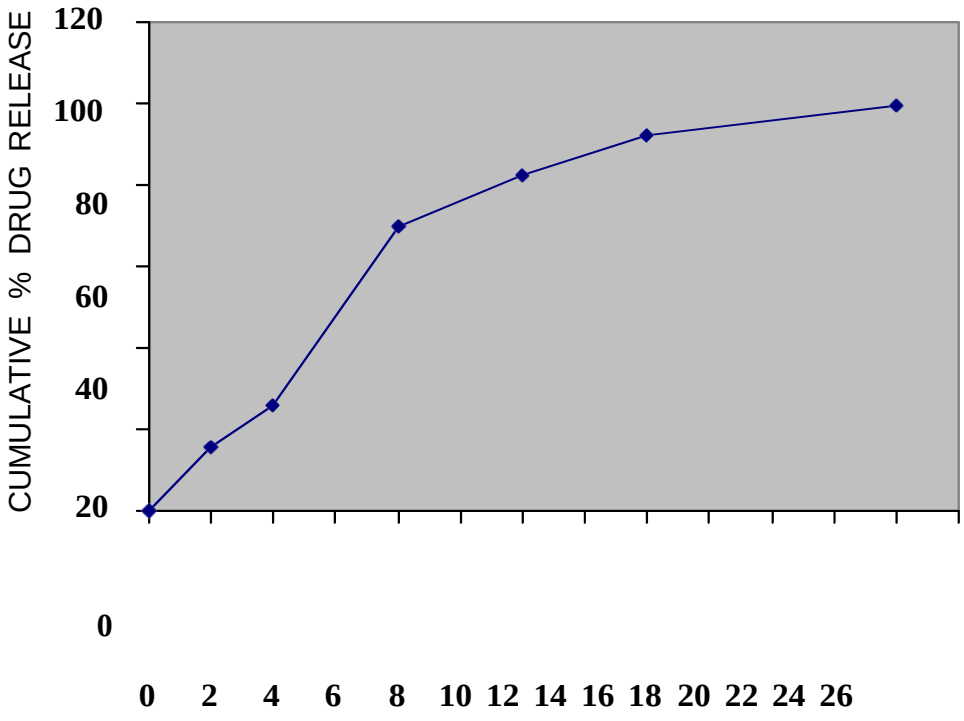
Dissolution Profile Of Batch T-7



Dissolution Profile of batch No. T-8 in 6.8 pH phosphate buffer

Time in hours	% Drug release
0	0
2	15.56
4	25.63
8	69.85
12	82.46
16	92.05
24	99.56

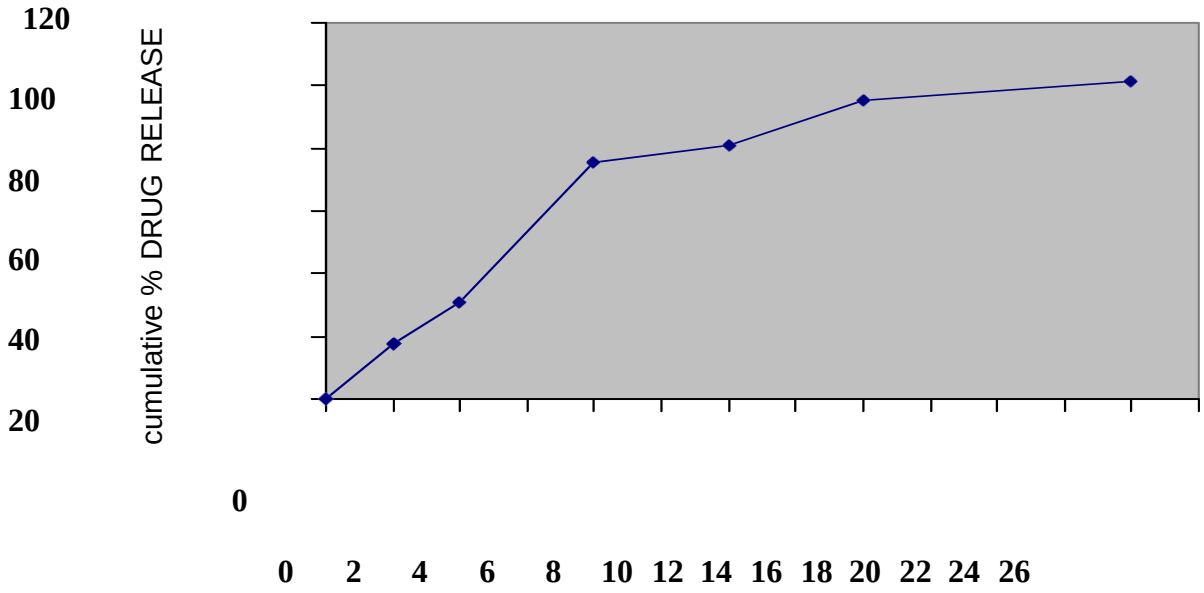
Dissolution Profile Of Batch T-8



Dissolution Profile of batch No. T-9 in 6.8 pH phosphate buffer

Time in hours	% Drug release
0	0
2	17.56
4	30.64
8	75.52
12	80.97
16	95.41
24	101.28

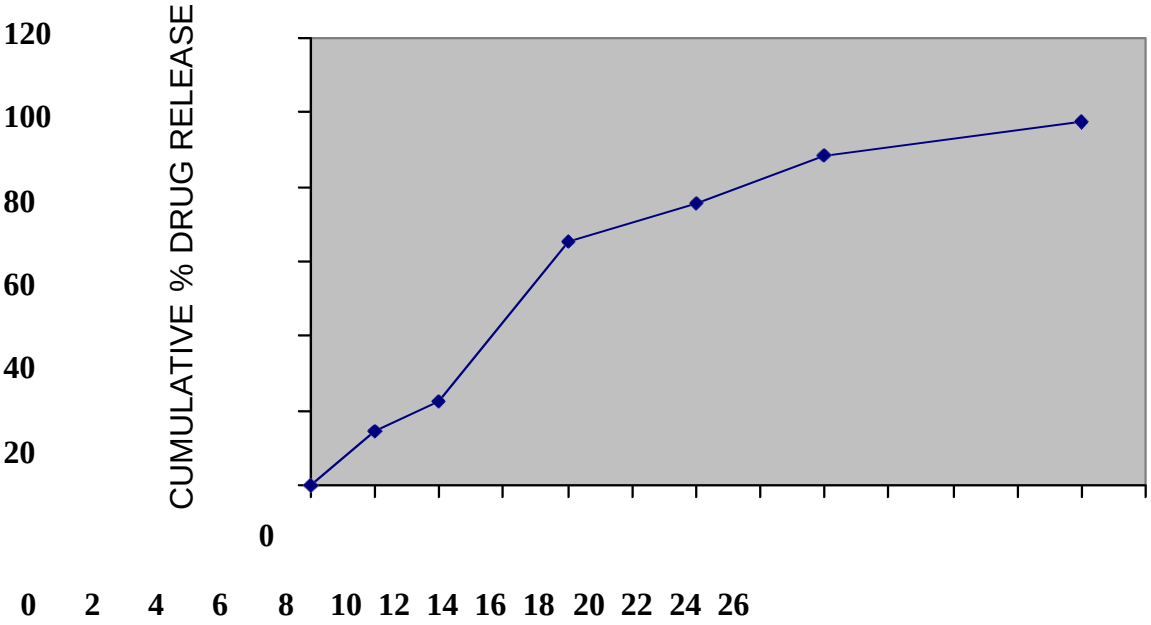
Dissolution Profile Of Batch T-9



Dissolution Profile of batch No. T-10 in 6.8 pH phosphate buffer

Time in hours	% Drug release
0	0
2	14.69
4	22.57
8	65.24
12	75.68
16	88.52
24	97.24

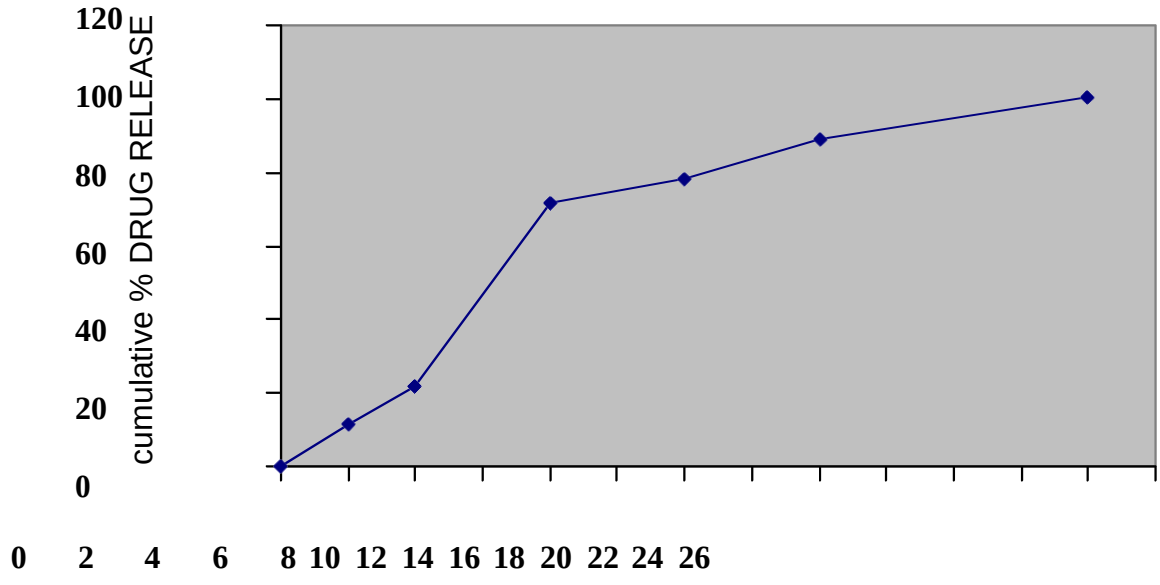
Dissolution Profile Of Batch T-10



Dissolution Profile of Market Sample in 6.8 pH phosphate buffer

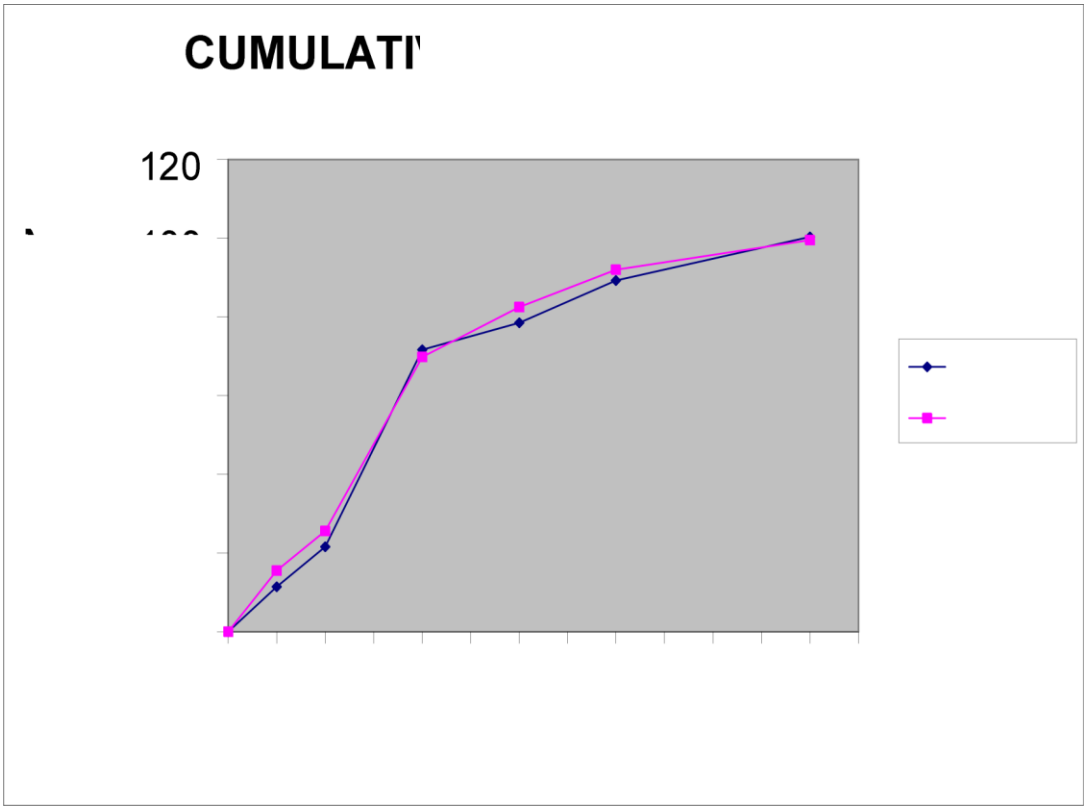
Time in hours	% Drug release
0	0
2	11.41
4	21.63
8	71.64
12	78.46
16	89.27
24	100.35

Dissolution Profile Of Market Sample

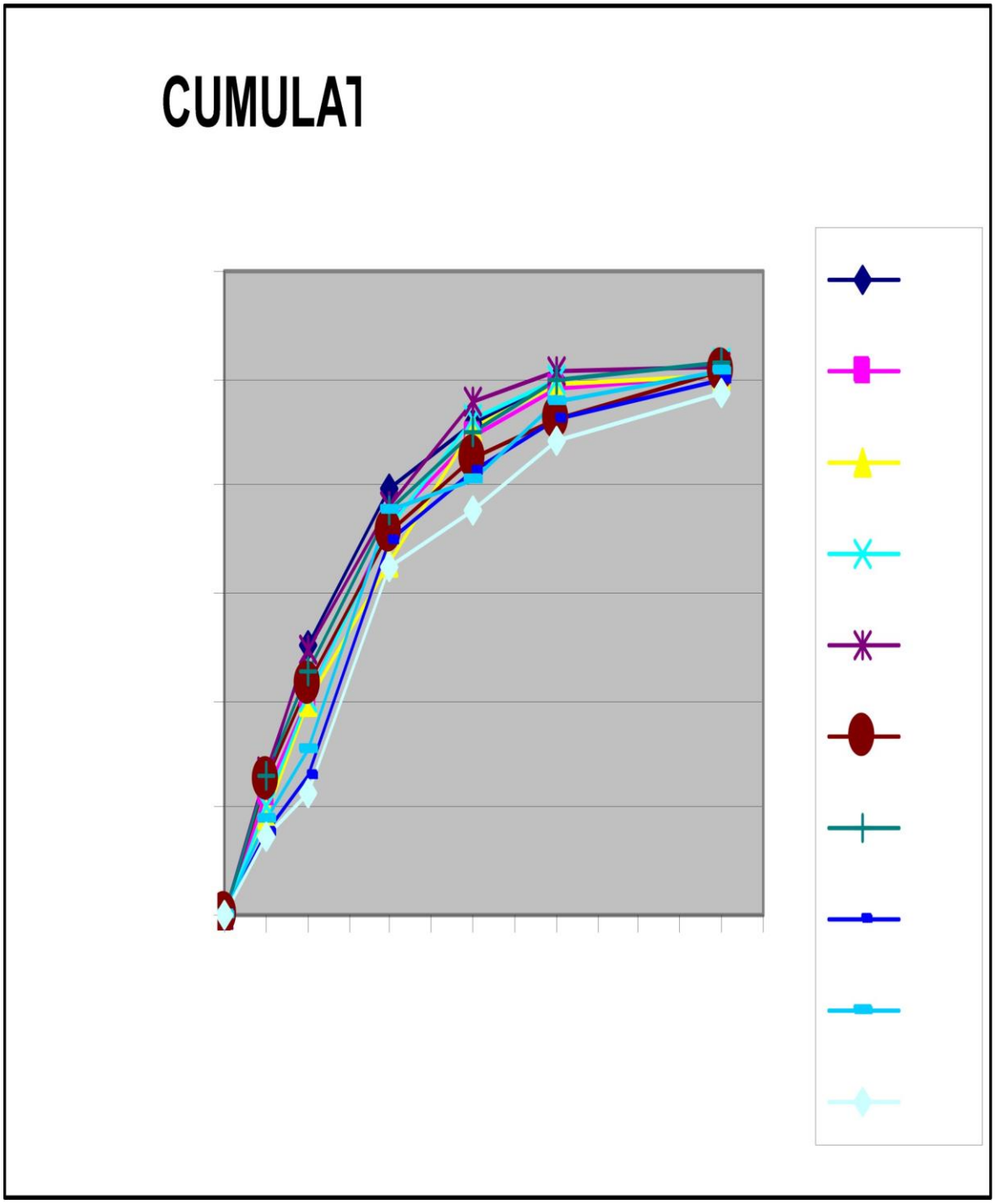


Comparative Dissolution profile of Batch T8 with marketedsample

Time in hours	Market Sample	Batch T8
0	0	0
2	11.41	15.56
4	21.63	25.63
8	71.64	69.85
12	78.46	82.46
16	89.27	92.02
24	100.35	99.56



Comparative Dissolution profile of Batch T1-T10



Determination of Similarity & Disimilarity Factor

Table No.9

Disimilarity Factor

Time (hours)	R	T	R-T	SQR	MOD (sqrt)	Cumulative MOD	CumulativeR	F1
0	0	0	0	0	0	0	0	0
2	11.41	15.56	-4.15	17.22	4.15	4.15	11.41	36.37
4	21.63	25.63	-4	16	4	8.15	33.04	24.66
8	71.64	69.85	1.79	3.20	1.79	9.94	104.68	9.49
12	78.46	82.46	-4	16	4	13.94	183.14	7.61
16	89.27	92.02	-2.75	7.56	2.75	16.69	272.41	6.12
24	100.35	99.56	0.79	0.62	0.79	17.48	372.76	4.68

Table No.10

Similarity Factor:

Time in (hours)	R	T	R-T	(R-T)2	Cumulative (R-T)2	Cum(R-T)2*1/N	Cum(R-T)2*1/N+1	SQRT	1/SQRT	100*1/SQR
0	0	0	0	0	0	0	1	1	1	100
2	11.41	15.56	-4.15	17.22	17.22	2.87	3.87	1.96	0.50	50.83
4	21.63	25.63	-4	16	33.22	5.53	6.53	2.55	0.39	39.11
8	71.64	69.85	1.79	3.20	36.43	6.07	7.07	2.65	0.37	37.60
12	78.46	82.46	-4	16	52.42	8.73	9.73	3.12	0.32	32.04
16	89.27	92.02	-2.75	7.56	59.98	9.99	10.99	3.31	0.30	30.15
24	100.35	99.56	0.79	0.62	60.61	10.10	11.10	3.33	0.30	30.01

STABILITY STUDY OF TABLETS OF BATCH T8[94]

The batch T8 was selected as an optimum batch and the stability studywas carried out at accelerated condition. of 40□C/75 % RH condition for a period of two month.

Method :

Ten tablets were individually wrapped using aluminum foil and packed in ambered color screw cap bottle and put at above specified condition in incubator for 2 months. After two month tablets were evaluated for content uniformity and in- vitro drug release.

Observation :

The results of stability study after two month are given in Table 11 & 12 The plot of cumulative % drug release v/s Time (hr) depicted in graph.

Drug content : Comparative content uniformity of the tablet after twomonth stability.

Table No.11

Drug content of batch T 8 kept for stability

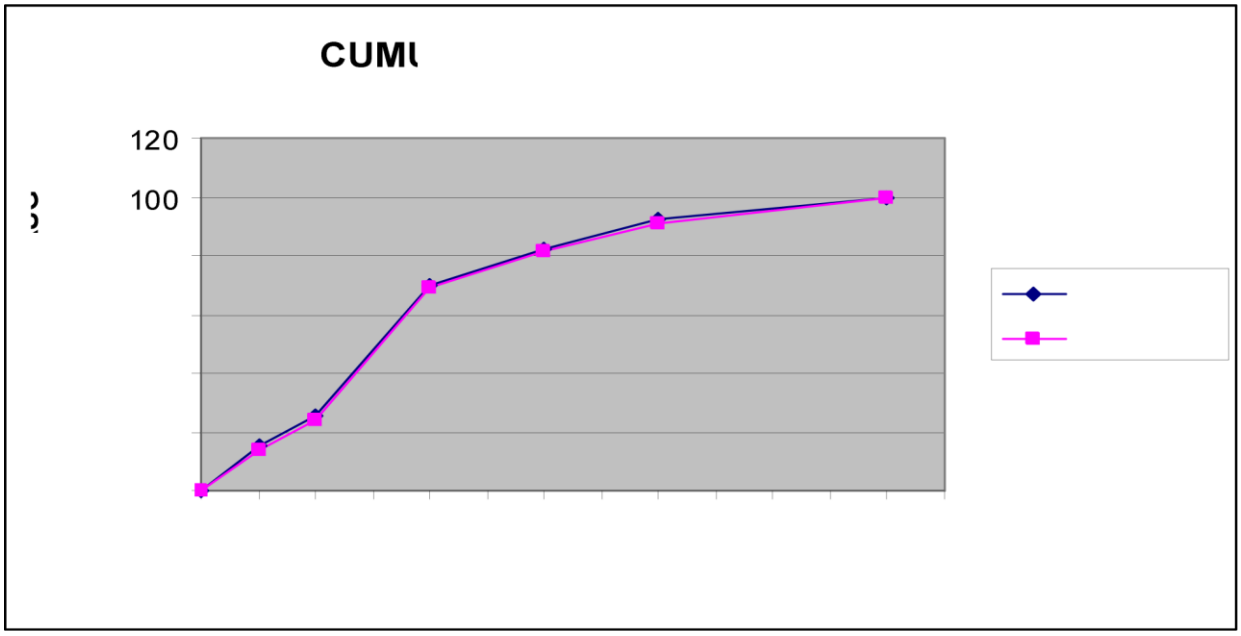
Time	Drug Content (%)
Zero month	99.25
Two month	99.14

Table No.12

Dissolution profile of batch T-8 kept for stability

Dissolut-ion Medium	Time (hrs)	Cumulative % release	
		Initial	Two month
	0	0	0
	2	15.56	14.12
	4	25.63	23.69
6.8pH buffer	8	69.85	69.12
	12	82.46	81.78
	16	92.02	91.23
	24	99.56	99.31

Dissolution profile of batch T-8 kept on stability at 40□C /75% RH



RESULTS AND DISCUSSION:

The procured sample of Oxaprozin was tested for its identification.

The manufacturer also was confirmed of quality and purity of sample.

The drug – excipients compatibility was done at accelerated temperature $40^{o}C/75\% \pm 5\%$ and 30^{o} C/65% ± 5% relative humidity. Opened and closed vial methods were used. The result doesn't show any physical change to the mixture after 30 days. This fact concluded that the drug and Excipient are compatible with each other.

The sustained release tablets of Oxaprozin were prepared by wet granulation method, They were evaluated for weight variation, drug content, friability, hardness, and thickness for all batches (T-1 – T-10).

No significant difference was observed in the weight of individual tablets from the average weight. Tablet weights of all batches were found with in recommended pharmacopoeia limits. The data of uniformity of content indicated that tablets of all batches had drug content within pharmacopoeia limits. The hardness of tablets of all batches are in acceptable limits, as shows in the literature. All the formulation showed % friability less then 1% that indicates ability of tablets to withstands shocks, which may encounter. No significant difference was observed in the thickness of individual tablet from the average weight.

Standard calibration curve of Oxaprozin was prepared in phosphate buffer medium 6.8pH.Correlation coefficient values indicate the linear correlation between concentration and absorbance and following lamberts beers law.

The release of Oxaprozin from sustained release tablet of various formulations varied according to the ratio and degree of the polymer. In case of tablet of T1containing drug & HPMCK15M (quantity in mg). 200:15 : the release profile, was showing the release 102.69%. In case of tablets of T2 containing drug and HPMC K15M & HPMC K4M (in mg). 200:10:20 it was showing 100.25% release in 24 hours. In case of tablets of T3 containing drug polymer's (HPMCK15M, HPMCK4M in mg) 200 : 15 :15 : prepare to be seen in the effect of combination of polymers in release of drug but it was showing same release given 100.25% upto 24 hour. In case of tablets T4 containing drug and HPMC K15M & HPMCK 4M (in mg) 200: 10: 10 the release profile was showing drug release more than 100% .In case of tablets of T5 containing drug and HPMC K 4M & HPMC K15M PVP K30 (in mg) 200: 10: 10:10 . Prepared the tablets. But it cannot maintain the release with in 100%. In case of tablets of T6 containingdrug and HPMC K 15M (in Mg) 200 : 5 . It was seen the increase in release of drug and shown more than 100% drug release in 24 hour profile. In case of tablets T7, containing drug. HPMCK4M & HPMCK15m (in mg) 200:10:10 the release profile was showing drug release more than 100%. In case of Tablets T8 containing drug. HPMCK15M (in mg) 200 : 23. The release profile was showing drug release with in 24 hours. With very slowerrelease than all formulations containing % drug release 99.56.

In case of tablets T9, containing drug. HPMCK4M (in mg) 200:20 the release profile was showing drug release more than 100%. In case of tablets T10, containing drug. HPMCK4M (in mg) 200:25 the release profile was showing drug release less than 100%.

For similarity, F2 calculation was done in 6.8 pH phosphate buffer showing the value of similarity factor (F2) i.e., 73.9

Results of stability studies of batch T-8 indicates that it was stable at $40^{o}C/75\%$ + 5% relative humidity as there was no significant difference was observed for dissolution and average drug content data after two months.

10.Conclusion:

The study was undertaken with an aim to formulate develop andevaluation of Oxaprozin sustained release tablets using different polymers as release retarding agent. Preformulation study of Oxaprozin was done initially and results directed for the further course of formulation. Based on preformulation studies different batches were prepared using selected excipeints. Granules were evaluated for tests LOD, Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets. Tablets were tested for weight variation, thickness, hardness and friability as per official procedure. Dissolution of batch T-8 was carried out in 6.8 pH media and compared with marketed preparation. Based on dissolution tests and F-2 values in pH 6.8 phosphate buffer as release medium, it was concluded that T-8 satisfactory performs in the same manneras that of marketed formulation. F-2 (similarity factor) value of T-6 was found to be 73.90.

From the above results and discussion it is concluded that formulation of sustained release tablet of Oxaprozin containing HPMC K 15M & 200 :23 (in mg) T8 can be taken as an ideal or optimized formulation of sustainedrelease tablets for 24 hour release as it fulfills all the requirements forsustained release tablet and our study encourages for the further clinicaltrials on this formulation.

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