FORMULATION AND EVALUATION OF ZOLMITRIPTAN CONTROLLED RELEASE MATRIX TABLETS

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IN

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Submitted by

Reg. No: 261210265

Under the guidance of

Mrs. S. BHAMA, M.Pharm.,

Assistant Professor

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTRAJA COLLEGE OF PHARMACY

Kumarapalayam -638 183.

Tamil Nadu.

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF ZOLMITRIPTAN CONTROLLED RELEASE MATRIX TABLETS"** submitted by the student bearing **Reg. No. 261210265** to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on .....

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This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF ZOLMITRIPTAN CONTROLLED RELEASE MATRIX TABLETS"** is a bonafied work done by **Mr. P. VEERAMANI (Reg:No:261210265)**, J.K.K. Nattraja college of pharmacy, in part and fulfillment of the university rules and regulation for award of **Master of Pharmacy** in pharmaceutics under my guidance and supervision during the academic year 2013-2014.

Mrs.S.BHAMA, M. Pharm.,
Assistant Professor,
Department of Pharmaceutics,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam - 638 183.
Tamil Nadu.

Dr.R.SAMBATH KUMAR, M.Pharm.,Ph.D.,
Principal, Head of the Department,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam - 638 183,
Tamil Nadu.

Dr.R.SAMBATH KUMAR,M.Pharm.,Ph.D.,
Principal, Head of the Department,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam - 638 183.
Tamil Nadu.

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"FORMULATION AND EVALUATION OF ZOLMITRIPTAN CONTROLLED RELEASE MATRIX TABLETS"** submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai, was carried out by **Mr.P.VEERAMANI, [REG.NO: 261210265],** for the partial fulfillment of Degree of **MASTER OF PHARMACY** in pharmaceutics under direct supervision of **Mrs.S. BHAMA, M.Pharm.,** Assitiant Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam, during the academic year 2013-2014.

PLACE: Kumarapalayam.
DATE:

Dr.R.SAMBATH KUMAR,M.Pharm.,Ph.D.,
Professor & Principal,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam - 638 183,
Tamil Nadu.

CERTIFICATE

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Dr.R.SAMBATH KUMAR,M.Pharm.,Ph.D.,
Principal and Head of the Department,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam – 638 183.
Tamil Nadu.

Mrs.S.BHAMA, M. Pharm.,
Assistant Professor,
Department of Pharmaceutics,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam - 638 183.
Tamil Nadu.

DECLARATION

The work presented in this dissertation entitled **"FORMULATION AND EVALUATION OF ZOLMITRIPTAN CONTROLLED RELEASE MATRIX TABLETS"** was carried out by me,under the direct supervision of **Mrs.S.BHAMA, M.Pharm**., Assistant professor, Department of pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that, this work is original and has not been submitted in part for the award of any other degree or diploma in any other university.

PLACE: Kumarapalayam

DATE:

Mr P.VEERAMANI,

Reg. No: 261210265

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1. INTRODUCTION

During past few decades, significant advance have been made in the area of controlled release as evidenced by an increasing number of patents, publication, as well as commercial controlled release products for the delivery of variety of pharmaceutical compounds[1]. With a controlled release formulation, predictable and reproducible release rate can be achieved, at the target site for desired duration[2]. This results in optimum biological response, prolonged efficacy, decreased toxicity as well as reduction in required dose levels as compared to the conventional mode of delivery. Hydrophilic polymer matrix is widely used for formulating a controlled release dosage forms.[3, 4]

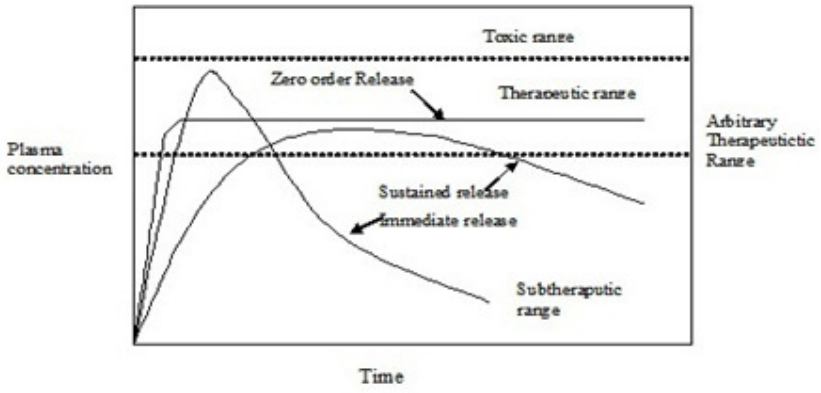


Fig 1: Diagram of controlled release verses sustained release

Oral route still remains the most popular for drug administration by virtue of its convenience to the patient. A sizable portion of orally administered dosage forms so called conventional, are designed to achieve maximal drug bioavailability by maximizing the rate and extent of absorption. While such dosage forms have been useful, frequent daily administration is necessary, particularly when the drug has a short biological half life. This may result in wide fluctuation in peak and trough

steady-state drug levels, which is undesirable for drugs with marginal therapeutic indices. Moreover, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Fortunately, these shortcomings have been circumvented with the introduction of controlled release dosage forms. These dosage forms are capable of controlling the rate of drug delivery, leading to more Controlled drug levels and hence therapeutic action as outlined.

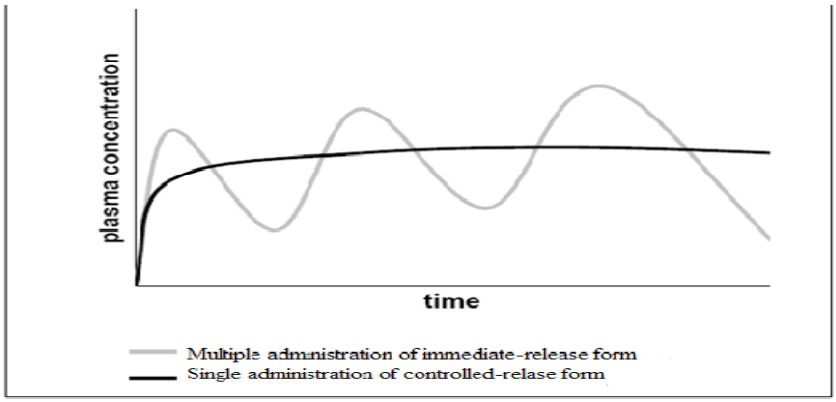


Fig.2: Schematic drawing of plasma concentration-versus-time profiles following administration of three immediate-release dosage forms versus one single controlled-release dosage form.

Terminology

Modified release delivery system may be divided conveniently in to four categories.[6]

A. Delayed Release

These system are those that used repetitive intermittent dosing of a drug from one or more immediate release units incorporated in to a single dosage form.

Examples of delayed release system include repeat action tablets and capsules and enteric coated tablets were timed release is achieved by a barrier coating.

B. Sustained Release

These system include any drug delivery system that achieves slow release of drug over an extended period of time.

I. Controlled release

These system also provide slow release of time over a extended period of time and also can provide some control weather this be of a temporal special nature or both, of drug release in the body, or in other words, the system is successful at maintain constant drug levels in the target tissue or cells.

II. Extended release

Pharmaceutical dosage forms that release the drug slower than the normal manner at predetermined rate and necessarily reduce the dosage frequency by two folds.

C. Site specific targeting

These systems refer targeting of a drug directly to a certain biological location in these cases the target is adjacent to or in the diseased organ or tissue.

D. Receptor targeting

This system refers to targeting directly to certain biological location. In these case the target is particular receptor for a drug with in a organ or tissue. Site specific

targeting and receptor targeting system satisfy the special aspects of the drug delivery and also considered to be controlled drug delivery system.

1.1.1. ADVANTAGES OF MATRIX TABLET[7, 8]

- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.

1.1.2. DISADVANTAGES OF MATRIX TABLET[7, 8]

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusion resistance and/or a decrease in effective area at the diffusion front.
- However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

1.1.3. PHYSICOCHEMICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET

Dose size[9]:

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

Ionization, *pka* and aqueous solubility[10]:

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the *pka* of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of Ph on the release process must be defined. Compounds with very low solubility (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is

the drug's concentration in solution, will be low.

Partition Coefficient[11]:

When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipid; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

Stability:

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation.

1.1.4. BIOLOGICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET

Biological half-life: [12]

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream.

Absorption:

Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23h to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine

Metabolism:

Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-

releasing dosage form. Hence criteria for the drug to be used for formulating Sustained-Release dosage form is

- Drug should have low half-life (<5 hrs.)
- Drug should be freely soluble in water.
- Drug should have larger therapeutic window.
- Drug should be absorbed throughout the GIT

Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

Distribution: Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral CR drug delivery system.

Protein Binding: The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes CR drug delivery system is not required for this type of drug.

Margin of safety: As we know larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of

oral CR drug delivery system due to technological limitation of control over release rates.

$TI = TD_{50}/ED_{50}$

1.1.5. EFFECT OF RELEASE LIMITING FACTOR ON DRUG RELEASE[13,14]

The mechanistic analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusion path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

A. Polymer hydration: It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important step in polymer dissolution include absorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

B. Drug solubility: Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

C. Solution solubility: In view of *in-vivo* (biological) sink condition maintained actively by hem perfusion, it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. In this way a better

simulation and correlation of in vitro drug release profile with *in-vivo* drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

D. Polymer diffusivity: The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion Ed has been acquired by the diffusant is dependent on length of polymer chain segment, cross linking and crystallanity of polymer. The release of drug may be attributed to the three factors viz,

i. Polymer particle size

ii. Polymer viscosity

iii. Polymer concentration

i. Polymer particle size: Malamataris stated that when the content of hydroxyl propyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low. He also justified these results by considering that in certain areas of matrix containing low levels of hydroxyl propyl methylcellulose led to the burst release.

ii. Polymer viscosity: Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution.

iii. Polymer concentration: An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release.

E. Thickness of polymer diffusional path: The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

$$J = D\, dc/dx$$

Where, J is flux of diffusion across a plane surface of unit area D is diffusibility of drug molecule, dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx.

F. Thickness of hydrodynamic diffusion layer: It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer.

G. Drug loading dose: The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases. In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute

drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken in to account.

H. Surface area and volume: The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally. Both the *in vitro* and *in vivo* rate of the drug release, are observed to be dependent upon surface area of dosage form. *Siepman et al.* found that release from small tablet is faster than large cylindrical tablets.

I. Diluents' effect: The effect of diluents or filler depends upon the nature of diluents. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

J. Additives: The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydro soluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate.

Table 1 : Classification of sustained/controlled system

Type of system	**Rate-controlled mechanism**
Diffusion controlled ➢ Reservoir system ➢ Monolithic system	Diffusion through membrane
Water penetration controlled Osmotic system Swelling system	Transport of water through semi permeable membrane Water penetration in to glossy polymer
Chemical control Monolithic system Pendent system Ion exchange resins	Surface erosion or Bulk erosion Hydrolysis of pendent group and diffusion from bulk polymer Exchange of Acidic or Basic drugs with the ions present on resins.
Regulated system Magnetic ultrasound	External application of magnetic field or ultrasound to device

1.1.6. PHARMACODYNAMIC CHARACTERISTICS OF THE DRUG

1. Therapeutic Range:

A drug candidate for controlled/sustained delivery system should have a therapeutic range wide enough such that variations in the release rated do not release in a concentration beyond this level.

2. Therapeutic Index (TI):

The release rate of drug with narrow therapeutic index should be such that the plasma concentration attend is within the therapeutically safe and at effective range. This is necessary becouse such drug have toxic concentration nearer to their therapeutic range. A drug with short half – life and narrow therapeutic index should

be admininistrated more. Frequently than twice a day. Once must also considered the activity of the drug metabolites since controlled delivery system controls the only the release of parent drug but not its metabolism.

3. Plasma concentration-Response relationship:

Drug such as Reserpine, whose pharmacological activity is independent of its concentration,or poor candidates for controlled release system.[3]

1.1.7. DRUG SELECTION FOR ORAL SUSTAINED/CONTROLLED DRUG DELIVERY SYSTEMS

The biopharmaceutical evaluation of a drug for potential use in sustained/controlled rele1ase drug delivery systems requires knowledge on the absorption mechanism of the drug form the G.I tract, the general absorbability, the drug's molecular weight, pKa, solubility at different pH and apparent partition coefficient.

Table2: Parameter for Drug selection[15]

Parameter	**Preferred value**
Molecular weight/size	<100
Pka	Non ionized moiety > 0.1% at pH 1 to pH 7.8
0.1 %Solubilty	> 0.1µg/ml for pH 1 to pH 7.8
Release	Should not be influenced by pH and enzymes
Apparent partition coefficient	High
General absorbability	From all G.I segments
Absorption mechanism	Diffusion

The pharmacokinetic evaluation requires knowledge on drugs elimination half-life, Total clearance, Absolute bio availability, possible first pass effect and the desired study concentration for peak and trough.

Table 3: Pharmacokinetic parameter for drug selection

Parameter	**Comment**
Elimination half-life	Preferably between 0.5 and 8 hrs
Elimination Rate constant	Required for design
Apparent volume of distribution V_d	The larger Vd
Total clearance	And MEC, the larger will be the required dose size
Therapeutic concentration Cssav	Should not be dose dependent
Absolute bio-availability	The lower Cssav and smaller Vd, loss among of drug required
Intrinsic absorption rate	Should be 75% or more Must be greater than release rate
Toxic concentration	A part of the value of MTC and MEC safer the dosage forms. Also suitable for drugs with very short half life

1.1.8. CLASSIFICATION OF MATRIX TABLETS:

On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types.

1. Hydrophobic Matrices (Plastic matrices):[16]

In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused

through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers.

2. Lipid Matrices: [17]

These matrices prepared by the lipid waxes and related materials. Drug release as pore diffusion and erosion. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices: [18]

These systems are called swellable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups,

A. Cellulose derivatives: Methylcellulose 400 and 4000cPs, Hydroxyethylcellulose; Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.

B. Non cellulose natural or semi synthetic polymers: Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

Polymers of acrylic acid : Carbopol-934, the most used variety.

3. Biodegradable Matrices:[18]

They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non enzymatic process in to oligomers and monomers

that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

4. Mineral Matrices:[18] These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid

On the Basis of Porosity of Matrix: [19, 20]

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified:

1. Macro porous Systems:

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2. Micro porous System:

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

3. Non-porous System:

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

1.1.9. POLYMERS USED IN MATRIX TABLET: [21, 22]

Hydro gels:

Polyhydroxyethylemethylacrylate (PHEMA)**,**Cross-linked polyvinyl alcohol (PVA)**,** Cross-linked polyvinyl pyrrolidone (PVP)**,** Polyethylene oxide (PEO)**,** Polyacrylamide (PA)

Soluble polymers:

Polyethyleneglycol (PEG)**,** polyvinyl alcohol (PVA)

Polyvinylpyrrolidone (PVP)**,** Hydroxypropyl methyl cellulose (HPMC)

Biodegradable polymers:

Polylactic acid (PLA)**,** Polyglycolic acid (PGA) **,** Polycaprolactone (PCL)

Polyanhydrides, Polyorthoesters

Non-biodegradable polymers:

Polyethylene vinyl acetate (PVA) **,** Polydimethylsiloxane (PDS)

Polyether urethane (PEU)**,** Polyvinyl chloride (PVC)

Cellulose acetate (CA)**,** Ethyl cellulose (EC)

Mucoadhesive polymers: Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin

Natural gums : Xanthan gum, Guar gum, Karaya gum, Locust bean gum.

1.2. Types of controlled released system[23-26]

A) Diffusion controlled release system:

Diffusion process shows the movement of the drug molecule from a region of a higher concentration to lower concentration. The flux J (in amount/area-time), across a membrane in the direction of decreasing concentration is given by *Fick's law.*

J = -D dc/dx

D = diffusion coefficient in area/time

Dc/dx = change of concentration 'c' with distance 'x'

In common form, when a water insoluble membrane encloses a core of drug ,it must diffuse through the membrane, the drug release rate dm/dt is given by

dm/dt = ADK Δ C/L

where A = area

k = partition coefficient of drug between the membrane and drug core

L = diffusion path length

Δc = concentration difference across the membrane.

i) Reservoir type:

In the system, a water insoluble polymeric material encases a core drug. Drug will partition in to the membrane and exchange with the fluid surrounding the particle or tablet.Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.

Advantages: zero order delivery possible,release rate depend on type of polymer

Disadvantages: High molecular weight compounds difficult to deliver,potential toxic if system fails.

ii) Matrix system:

A solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.

Higuchi has derived the appropriate equation for drug release for this system

$$\mathbf{Q = D\varepsilon/T\ [\ 2\ A - \varepsilon Cs]\ Cst^{1/2}}$$

Where;

Q = weight in gms of drug released per unit area of surface at time t

D = Diffusion coefficient of drug in the release medium

ε = porosity of th matrix

Cs = solubility of drug in release medium

T = Tortuosity of the matrix

A = concentration of drug in the tablet, as gm/ml

Advantages: Easier to produce, can deliver high molecular weight compounds.

Disadvantages: Cannot provide zero order release, required removing reaming matrix.

A third possible diffusional mechanism is the system where a partially soluble membrane encloses a drug core.Dissolution of part of membrane allows for diffusion of the constrained drug through pores in the polymer coat.

The release rate can be given by following equation:-

Release rate = AD/L = [$C_1 - C_2$]

A = area

C_1 = Concentration in the core

C_2 = Drug concentration in the surrounding medium

L = diffusional path length

Diffusion process involves two approaches first matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. Second approach involves enclosing the drug particle with a polymer coat.

B) Dissolution controlled release system:

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or other derivative formation.

i) Reservior type:

Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By altering layers of drug with the rate controlling coats pulsed delivery can be achieved. An alternative method is to administer the drug beads that have coating of different thickness. Since the beads have different coating thickness, their release occurs in a progressive manner.

Cellulose nitrate phthalate was synthesized and used as an enteric coating agent for acetyl salicylic acid tablets.

ii) Matrix type:

The most common type of dissolution controlled release dosage form. It can be either drug impregnated sphere or drug impregnated tablet, which will be subjected to slow erosion.

Two types of dissolution – controlled pulsed delivery systems:

a) Single bead – type device with alternating drug and rate- controlling layer

b) Beads containing drug with differing thickness of dissolving coats.

C) Methods using Ion - exchange:

It is based on the formation of drug resin complex formed when a ionic solution is kept in contact with ionic resins. The drug from this complex gets exchanged in GIT and released with excess of Na+ and cl- present in GIT.

Resin + - Drug - + Cl – goes to + Cl- + Drug-

Resin –Drug+ + Na + goes resin – Na++ Drug

D) Methods using osmotic pressure:

A semipermiable membrane is placed around a tablet, particle or drug solution that allows transport of water in to the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating.

Two types of osmotically controlled release sytems are

Type A contains an osmotic core with drug

Type B contains the drug in flexible bag with osmotic core surrounding.

E) pH – Independent formulations:

The GIT present some unusual features for the oral route of drug administration with relatively brief transit time through the GIT, which constraint the length of prolongation, further the chemical environment throughout the length of GIT is constraint on dosage form design.Since most drugs are either weak acids or bases, the release from controlled release form is pH dependent. However buffers such as salts of amino acid, citric acid, Pthalic acid, Phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH there by rendering pH independent drug release.

e.g: Propoxyphene in bufferd controlled release formulation, which significantly increase reproductibility.

F) Alerted density formulations:

It is reasonable to expect that unless a delivery system remains in the victinity of the absorption site until most, if not all of it would have limited utility. To this end several approaches have been developed to prolong the residence time of drug delivery system in the GIT.

High density approach:

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1 – 4 gm/cm^3.

Low density approach:

Globular shells which have an apparent density lower than that of GIT fluid can be used as a carrier of drug for sustained release purpose.

1.3. INTRODUCTION TO MIGRANE

Cluster headache is a relatively rare but extremely debilitating disorder that is characterized by the rapid onset of unilateral, periorbital headache that quickly escalates to maximum intensity. Patients routinely report the pain of an attack as being the most severe they have ever experienced. By the definition of the International Headache Society, attacks typically last from 15 to 180 min when left untreated and are accompanied by one more cranial autonomic feature such as ipsiletaral conjunctiva injection, lacrimation and rhino rhea or nasal congestion[27]. In this case, a rapid onset of pharmacological effect is an often desired from drugs. This can effectively be achieved by parenteral Administration, but this method may not always be convenient for the patient. Therefore there is growing interest in developing new, non-parenteral, reliable and convenient dosage forms using administration routes where a rapidly dissolved drug is immediately absorbed into the systemic circulation.

Zolmitriptan is a second-generation triptan prescribed for patients with migraine attacks, with and without an aura, and cluster headaches. It has a selective action on serotonin receptors and is very effective in reducing migraine symptoms, including pain, nausea and photo- or phonophobia. It is currently available as a conventional tablet, an oral disintegrating tablet and anasal spray (2.5 mg and 5 mg

per dose). The absolute bioavailability of zolmitriptan is up to 40% for both oral and nasal dosage forms.[28]

Vasodialtion of blood leads headache were zolmitriptan drug acts on 5 HT_{1B}& 5HT_{1D} Receptors and constricts the blood vessel thus it prevents headache.

Table4:Physico characteristics of zolmitriptan[29]

S.No	**Parameters**	**Description**
1	Molecular formula	$C_{16}H_{21}N_3O_2$
2	Molecular weight	287.3
3	Physical state of powder	White crystalline powder
4	Melting point	136-141 ºC
5	Solubility	Solubility in water and
6	Dissociation constant	pKa 9.6

2. LITERATURE REVIEW

ziya bayrak et al., (2011)[30] prepared sublingual zolmitriptan tablets.In this study, using different mucoadhesive polymers such as hydroxypropyl methyl cellulose, chitosan and sodium carboxy methyl cellulose at a concentration range of 0.5–5%. The tablets disintegrated rapidly, and dissolution tests revealed that zolmitriptan was dissolved from the formulation within the compendial limits and shows concentration range of polymers is in acceptable limit. It was also concluded that microcrystalline cellulose, spray-dried lactose and sodium starch glycolate are the appropriate excipient and formulated in good proportions. *In-vivo* studies indicated that formulation containing 5% chitosan has the maximum Cmax and AUC and minimum tmax values ($p < 0.05$). As a result, sublingual tablet administration of zolmitriptan formulated with appropriate excipients and especially with chitosan seems promising alternative to traditional routes.

Golam kibria et al.,(2008) [31] Prepared the alfuzosin matrix tablets. The aim of the study was the development and *in vitro* evaluation of a controlled release dosage form of a freely soluble weakly basic drug (alfuzosin hydrochloride). Binary mixer of one hydrophilic polymer (hydroxypropyl methylcellulose) and one hydrophobich polymer (ethyl cellulose) was used in tablets prepared by direct compression.The percent drug released at 1, 6, 12, and 20 h were selected as response.. Dissolution data were fitted to zero order, first order, and Higuchi's release kinetics to evaluate kinetic data. According to Korsmeyer's equation drug release followed both diffusion and erosion mechanism in all cases. Drug release was different from three fillers (microcrystalline cellulose, lactose and dibasic calcium phosphate.

Gurpreet Arora et al.,(2011)[32] Developed, oral controlled release mucoadhesive matrix tablets of domperidone as model drug using natural mucoadhesive material myrrh oleo gum resin (MOGR).The tablets were formulated with the natural polymer in different concentration (5, 10, 15 and 20 % w/w) employing direct compression technology. The prepared batches were evaluated for tablet prepared batches. The tensile strength increases from 0.973±0.09 to 1.687±0.11 MN/m2 and mucoadhesive strength from19.868 to 49.778 N with the increase in natural polymer concentration from 5 to 20 % (M1 to M4). The release kinetic and mechanism of release were calculated by fitting *in-vitro* release data in various models demonstrating that release follows zero order and Hixson Crowell cube root law. The release exponent (n) ranges in between 0.5889 to 0.7389 indicating multiple release mechanisms possibly the combination of diffusion and erosion. These research outcomes clearly specify the potential of MOGR to be used as binder, release retardant and mucoadhesive natural material in tablet formulations.

R. L. C. Sasidhar et al.,(2009) [33] Formulated Losartan Potassium as oral controlled release matrix tablets by using poly(ethylene oxides) {Polyox WSR 303}.And investigated the influence of polymer level and type if fillers namely lactose [soluble filler], microcrystalline cellulose and anhydrous dibasic calcium phosphate [insoluble fillers] on the release rate and mechanism of Losartan Potassium from matrix tablets prepared by direct compression process. Higher polymeric content in the matrix decreased the release rate. At lower polymeric level the rate and extent of drug release was elevated. On the other hand, replacement of lactose with anhydrous dibasic calcium phosphate and microcrystalline cellulose have significantly retarded

the release rate of Losartan Potassium. The formulations F3 & F6 are considered to be best formulations and can further evaluated for *In-vivo* pharmacokinetic studies.

Shefaat Ullah Shah et al.,(2009)[34] Described the formulation and evaluation of controlled release polymeric tablets of Diclofenac Potassium by wet granulation method. Formulations having three grades of polymer Ethocel (7P; 7FP, 10P, 10FP, 100P, 100FP) in several drugs to polymer ratios (10:3 and 10:1) were compressed into tablets using wet granulation method. *In vitro* drug release studies were performed using Phosphate buffer (pH 7.4) as a dissolution medium. The similarities and dissimilarities of release profiles of test formulations with reference standard were checked using f2 similarity factor and f1 dissimilarity factor. Mathematical/Kinetic models were employed to determine the release mechanism and drug release kinetics.

Sandip B. Tiwari et al.,(2003) [35] Studied the effect of concentration of hydrophilic (hy-droxypropyl methylcellulose [HPMC]) and hydropho-bic polymers (hydrogenated castor oil [HCO], ethylcel-lulose) on the release rate of tramadol was studied by wet granulation technique, while hydrophobic (wax) matrix tablets were prepared by melt granulation technique and *in-vitro* dissolution studies were performed using United States Pharmacopeia (USP) apparatus type II. Hydro-phobic matrix tablets resulted in sustained *in-vitro* drug release (>20 hours) as compared with hydrophilic matrix tablets (<14 hours). The presence of ethylcellulose in either of the matrix systems prolonged the release rate of the drug. Tablets prepared by combination of hydrophilic and hydrophobic polymers failed to prolong the drug release beyond 12 hours. The effect of ethylcellulose coating (Surelease) and the presence of lactose and HPMC in the coating composition on the drug release was

also investigated. Hydrophobic matrix tablets prepared using HCO were found to be best suited for modulating the delivery of the highly water- soluble drug, tramadol hydrochloride.

Raja sekharan et al.,(2008)[36] Prepared Theophylline controlled release matrix tablets with guar gum in two ratios and with three different hardness of 5, 6 and 7kg/cm^2. All the formulation showed good flow properties. The compressed tablets were evaluated. All the formulations showed compliance with pharmacopial standards. There was no interaction between drug, polymer and other excipients. It was confirmed by FTIR studies. Among all the formulations F6 (i.e. polymer ratio1:2 and hardness 7kg/cm^2) showed prolong release when compare to other formulations. The drug release kinetics showed zero order. The optimum formulation (F6) was stable when it was stored at $4^0 \pm 2^0$ C, $28^0 \pm 2^0$ C and at $45^0 \pm 2^0$ C for 6 months.

R.K.Kar et al., [37] prepared oral controlled release matrix tablets of Zidovudine (AZT). Tablets were prepared by direct compression method using various proportion of hydrophilic polymer viz; Eudragit RS100 and RL100 along or in combination with hydrophobic polymer ethyl cellulose. All evaluation test are performed. Dissolution study revealed that either Eudragit RS100 or RL100 10%,20% w/w of tablet preparations were able to sustain the drug release up to 9 hours, but 30%, 40% as well as ethyl cellulose combination with 20% and 25% w/w of Eudragit RS100 and RL100 were able to sustaining the drug release for 12 hour. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets followed non-Fickian diffusion mechanism. No compatibility

was observed between the drug and excipients used in the formulation of matrix tablets. The optimized formulation (F13) showed insignificant difference in release mechanism as well as release kinetics (P>0.05) when stability study was done for six months at 40±2 C and 75±5% RH.

Mohammad Usman et al.,(2011)[38] Prepared Mefenamic acid 200 mg controlled release matrices by direct compression and *in vitro* drug dissolution studies were performed to find out the drug release rate and patterns. Methocel was used as rate controlling polymer. Also the effect of several co-excipients was investigated on the drug release rates during *in vitro* dissolution studies. Formulated the drug at 4 different D: P ratios. Phosphate buffer pH 7.2 was used as dissolution medium using PharmaTest dissolution apparatus. Several kinetic models were applied to the dissolution profiles to determine the drug release kinetics.

J. Sahoo, et al.,(2008) [39] A hydrophilic matrix-based tablet using different concentrations of HPMC K15M or Kollidon®SR was developed using direct compression technique to contain 80 mg of propranolol hydrochloride. The resulting matrix tablets prepared with HPMC K15M or Kollidon®SR fulfilled all the official requirements of tablet dosage forms. Formulations were evaluated for the release of propranolol hydrochloride over a period of 12 h in pH 6.8 phosphate buffer using USP type II dissolution apparatus. And seen FTIR and DSC test . Tablets were exposed to 40 °C/75% of RH in open disc for stability. The *in-vitro* drug release study revealed that HPMC K15 at a concentration of 40% of the dosage form weight was able to control the release of propranolol hydrochloride for 12 h, exhibit non-Fickian diffusion with first-order release kinetics where as at 40% Kollidon®SRsame dosage forms show zero-order release kinetics. In conclusion, the

in-vitro release profile and the mathematical models indicate that release of propranolol hydrochloride can be effectively controlled from a single tablet using HPMC K15M or Kollidon®SR.

HamdyAbdelkader et al.,(2008) [40] Investigated the influence of polymer on baclofenac matrix tablets including hydrogenated castor oil (HCO); Eudragit RS100 (E-RS100); Eudragit L100 (E-L100), and some fillers namely mannitol [soluble filler], Dibasic calcium phosphate dehydrate (Emcompress) and anhydrous dibasic calcium phosphate [insoluble fillers] on the release rate and mechanism of baclofen from matrix tablets prepared by a hot-melt granulation process (wax tablets) and wet granulation process (E-RS100 and E-L100 tablets). Higher polymeric content (40%) in the matrix decreased the release rate of drug because of increased tortuosity and decreased porosity. At lower polymeric level (20%), the rate and extent of drug release was elevated. HCO was found to cause the strongest retardation of drug. On the other hand, replacement of Em compress or anhydrous dibasic calcium phosphate for mannitol significantly retarded the release rate of baclofen, except for E-L100 (pH-dependent polymer). Emcompress surface alkalinity and in-situ increase in pH of the matrix microenvironment enhanced the dissolution and erosion of these matrix tablets. The prepared tablets showed no significant change in drug release rate when stored at ambient room conditions for 6 months.

Amir Badshah et al.,(2011)[41] Developed Controlled-release (CR) matrix tablet of 4 mg risperidone using dry granulation–slugging method to improve its safety profile and compliance. Model formulations F1, F2, and F3, consisting of distinct blends of Methocel® K100 LV-CR and Ethocel® standard 7FP premium, were slugged. Each batch of granules (250–1,000 μm), obtained by crushing the slugs, was divided into

three portions after lubrication and then compressed to 9-, 12-, and 15-kg hard tablets. *In-vitro* drug release studies were carried out in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) using a paddle dissolution apparatus run at 50 rpm. The CR test tablet, containing 30% Methocel® and 60% Ethocel® (F3) with 12-kg hardness, exhibited pH-independent zero-order release kinetics for 24 h. The drug release rate was inversely proportional to the content of Ethocel®, while the gel layer formed ofMethocel® helped in maintaining the integrity of the matrix. Changes in the hardness of tablet did not affect the release kinetics. The tablets were reproducible and stable for 6 months at 40±2°C/75±5% relative humidity. Risperidone and its active metabolite, 9-hydroxyrisperidone, present in the pooled rabbit's serum, were analyzed with HPLC-UV at λmax 280 nm. There was a good association between drug absorption *in-vivo* and drug release *in-vitro* (R2=0.7293). The successfully developed CR test tablet may be used for better therapeutic outcomes of risperidone.

Ashishbhandari et al.,(2012)[42]. Designed controlled release matrix tablets of Sildenafil citrate is designed by simplex lattice design and evaluating the relationship and influence of different content levels of HPMC (Hypromellose), Eudragit L100 and Carbopol (Carbomer), in order to achieve a zero-order release of Sildenafil citrate. Tablets were prepared by wet granulation process and evaluated for different pre and post compression parameter, from these matrix tablets drug release was prolonged, leading to achieve an effective therapy with low dosage of the drug, to reduce the frequency of medication.

Silvina A.et al.,(2002) [43] Formulated HPMC matrix tablets of Diclofenac Sodium using microcrystalline cellulose (MCC), starch, and lactose by wet granulation

process. The USP paddle used to perform the dissolution profiles carried out in 900 mL 0.1 N HCl, and phosphate buffer**.** There was no significant difference in drug release between the hydrophilic matrices when the HPMC concentration was modified in low percentage. Release kinetics of Diclofenac Sodium from these swollen matrices was principally regulated by starch (17%) or lactose (17%), even on the presence of MCC. When starch (8.5%) and lactose (8.5%) were mixed at lower concentration in a ratio 1:1, MCC (5% or 7,5%) appeared to control the drug release. The data obtained proved that the formulations are useful for a sustained release of Diclofenac, due to the percentage released after 8 hours is nearly to 70%.

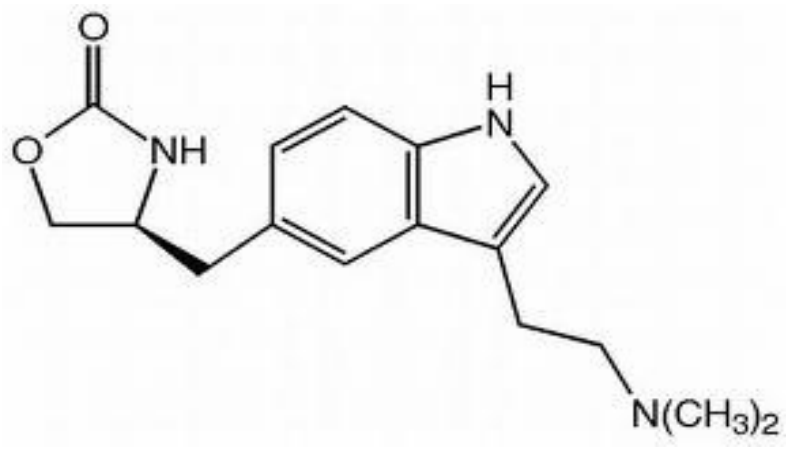
G. Sridhar et al.,(2012) [44] Formulated buccal patches of zolmitriptan by solvent casting method using HPMC E 15, aloe vera, Na CMC and eudragit RS100 as film forming polymers. The developed patches were evaluated for the thickness, folding endurance, bioadhesion strength, *in-vitro* residence time, mucoadhesive strength, *in vitro* drug release studies and *ex-vivo* drug permeation characteristics. Formulation F10 (contains HPMC E 15 &eudragit RS 100) has shown optimum *ex-vivo* mucoadhesion strength (19.4±0.9 g), *in vitro* residence time (6.0±0.14 hrs), *in vitro* drug release (75.06±1.12%) for 8hrs and satisfactory surface PH (6.8±0.02), *ex vivo* drug permeation (94.04±1.04%). The IR spectroscopic studies revealed that there is no evidence for chemical interaction between drug and polymers.

3. DRUG PROFILE

3.1. ZOLMITRIPTAN [45, 46, 47, 48]

- Product name : ZOLMITRIPTAN
- Chemical name : (4S)-4-({3-[2-(dimethyl amino)ethyl]-1H-indol-5- yl}methyl)-1,3-oxazolidin-2-one
- Molecular formula : $C_{16}H_{21}N_3O_2$
- Molecular weight : 287.3

Structure of Zolmitriptan:



PHARMACOKINETICS

- Absorption : approximately 40%
- Distribution : 8.4± 3.3 L/kg
- Metabolism : Hepatic
- Elimination : renal and fecal
- Protein binding : 25%

- Half life : 3 hours
- Solubility : readily soluble in water, freely soluble in 0.1 N Hcl
- Dose : 2.5mg, 5mg
- Available trade names : AscoTop, Zomig, Zomig, Rapimelt, Zomigon
- Adverse drug reaction : Myocardial infarction, hypoesthesia, parahtesia,B.P
- Adverse interactive drug

Storage: Store between 20^0C – 25^0C.Protect from sun light.

Dosage form: Dose 2.5mg or 5 mg of tablet or powder form. Not recommended for pediatric and neonates

Overdose/Toxicity: Symptoms include low B.P, confusion, agitation, sweating, convulsion, chest pain, heart pain.

Warnings:should not be used within 24 hours of treatment with another 5-HT1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide, and should not be administered to patients with hemiplegic or basilar migraine.

Mechanism of action:

It has a selective action on serotonin receptors and is very effective in reducing migraine symptoms, including pain, nausea and photo or phonophobia. Vasodialtion of blood leads headache were Zolmitriptan drug acts on 5 HT_{1B}& 5HT_{1D} Receptors and constricts the blood vessel.

3.2 POLYMER PROFILE:

HYDROXYPROPYL METHYL CELLULOSE [HPMC] [49, 50]

1. Nonproprietary name:

BP : Hypromellose

Jp : Hydroxy propyl methyl cellulose

PhEur : hypromellosem

USP : hypromellose

2. Synonyms:

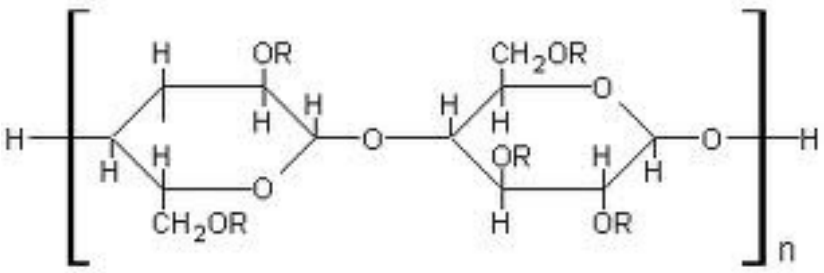
Benecel MHPC; E464;Methocel;Methyl Cellulose Propylene Glycol Ether; Methyl Hydroxyl Propyl Cellulose; Metolose; tylopur.

3 Chemical name: cellulose hydroxypropylmethylether.

4 CAS registry number: [9004-65-3]

5. Empircal formula: $CH_3CH(OH)CH_2$

6. Structural formula:



7. Molecular weight: 10000 to 1500000

8. Functional category:

Coating agent; film-former; rate-controlling polymer for controlled release; stabilizing agent; suspending agent; tablet binder; viscosity – increasing agent.

9. Description: It is odorless and tasteless, white or creamy-white fibrous and granular powder.

10. Typical properties:

Acidity/ Alkalinity: pH is 5.5- 8.0 from a 1 % w/w aqueous solution.

Density: Bulk – 0.341 gm/cm^3

Tapped - 0.557 gm/cm^3

True - 1.326 gm/cm^3

Melting point: Browns at 190 – 200 ^{0}C, chars at 225-230 ^{0} C. Glass transistion temperature is 170- 180 ^{0}C.

Moisture content: It absorbs moisture from the atmosphere, the amount of water absorbed depends up on the initial moisture content, the temperature and relative humidity of the surrounding air.

Solubility: Soluble in cold water forming a colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixture of ethanol and dichloro methane, mixture of methanol and dichloro methane, and mixture of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixture of dichloromethane and propan-2-ol and other organic solvents.

Viscosity (dynamic): A wide range of viscosity types are commercially available. Aqueous solution are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohol such as ethanol and propan-2-ol provided the alcohol content is less than the 50 % w/w. Dichloromethane and ethanol mixture also a\may be used to prepare viscous hypromellose solution. Solution prepared using organic solvents tend to be more viscous and concentration also produces more viscous solution. The designations of the HPMC refer to viscosities in 2% aqueous solution, for example K4M has a viscosity of 4000 mPas and K15M has a viscosity of 15000 m pas.

11. Applications of polymer in pharmaceutical formulation or technology

- Uses oral, ophthalmic and topical pharmaceutical formulations.
- Emulsifier, Suspending Agent, and Stabilizing Agent In Topical Gels And Ointments.
- As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

12. Incompatabilites:

It is incompatibile with some oxidizing agents. Since it is non ionic, it will not complex with metallic salts or with ionic organics to form insoluble precipitates.

3.2 CELLULOSE ACETATE PTHALATE (CAP) [51]

Non proprietary Names:

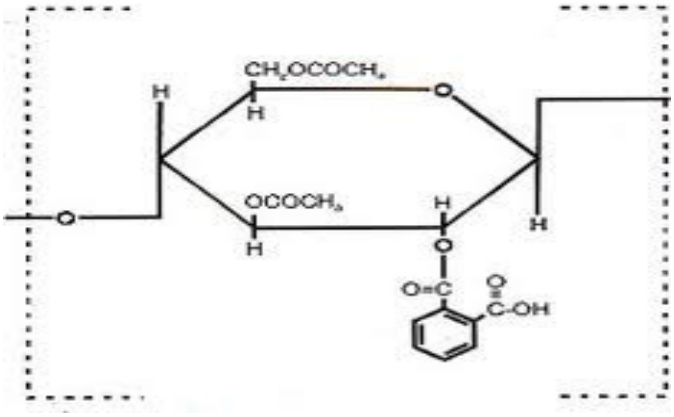
- BP : Cellacephate
- PhEur : Cellulosiacetaspthalas
- USPNF : Cellulose acetate phthalate

Synonyms:

Acetyl pthalyl cellulose; CAP ; cellacefate; cellulose acetate hydrogen 1,2 benzenedicarboxylate; cellulose acetate hydrogen phthalate; cellulose acetate monopthalate; cellulose acetopthalate; cellulose acetylpthalate.

Chemical Name: Cellulose, acetate, 1, 2-benzenedicarboxylate

Structure:



Functional category: coating agent

Melting point: 192 ^{0}C.Glass transition temperature is 160 – 170 ^{0}C

Applications in pharmaceutical formulation or Technology

- Used as enteric film coating material or as matrix binder for tablets
- It is used as a pharmaceutical excipient to solid dosage forms either by coating from organic or aqueous solvent systems,or by direct compression
- It is used in concentration of 0.5 to 0.9%of the core weight.
- Adittion of plasticizers improve water resistance more when compared to the cellulose alone.
- It is also used as other coating form in combination with other agents to control drug release.

Description:

It is a hygroscopic, white, free flowing powder or colorless flakes. It is tasteless and odorless, or may have a slight odor of acetic acid.

Typical properties:

Hygroscopicity:

Cellulose acetate phthalate is hygroscopic and precautions are necessary to avoid excessive absorption of moisture.

Solubility: Practically insoluble in alcohols, chlorinated hydrocarbons, hydrocarbons and water; soluble in cyclic ethers, esters, ether alcohols, ketones and certain solvent mixtures. Also soluble in certain buffered aqueous solution at greater than pH 6.

Stability and storage condition:

It hydrolyzes slowly under prolonged adverse conditions such as high temperature and humidity, with a resultant increase in free acid content, viscosity and odor of acetic acid. If its moisture content is above 6 % w/w, fairly rapid hydrolysis occurs. However acetate phthalate is stable if stored in a well closed container in a cool dry place.

Incompatibilities :

Cellulose acetate phthalate incompatible with ferrous sulfate, ferric chloride, silver nitrate, sodium citrate, aluminum sulfate, calcium chloride, mercuric chloride, barium nitrate, basic lead acetate, and string oxidizing agents such as strong alkalis and acids. It should be noted that one carboxylic acid group of the pthalic acid moiety remains un esterified and free for interactions. Accordingly, in compatibility with acid sensitive drug may occurs.

Safety: Regarded as free from adverse effects and nontoxic.

LACTOSE MONOHYDRATE: [51]

Non – proprietary names:

- BP : Lactose
- PhEur: Lactose Monohydrate
- Jp: Lactose Hydrate
- USP_NF : Lactose Monohydrate

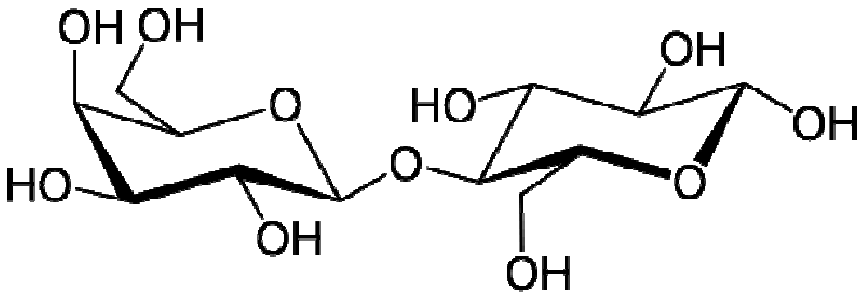
Synonyms: CapsuLac; Lactochem; Lactosummonohydricum; Monohydrate; pharmatose; Prismalac, Sach Lac; SorboLac; SpheroLac;SuperTab 30GR; Tablettose.

Chemical Name: O-b-D-Galactopyranosyl-(1,4)-α-D-glucopyranose monohydrate

Empirical formula: $C_{12}H_{22}O_{11}\_H_2O$

Molecular weight: 360.31

Structural formula:



Description:

In the solid state, Lactose appears as various isomeric forms, depending on the crystallization and drying condition, i.e. Lactose monohydrate, ß-lactose

anhydrous and a lactose anhydrous. The stable crystalline forms of lactose are α-lactose monohydrate, β-lactose anhydrous and stable α-lactose anhydrous. it occurs as white to off white crystalline particles or powder. Lactose is odorless and slightly sweet tasting; α-lactose is approximately 20% as sweet as sucrose, white β-lactose is 40% sweet.

Functional category:

Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluents and filler.

Typical Properties:

Loss on drying: Typically 0.2 % for Monohydrate 80M, Monohydrate Impalpable; and 0.1 – 0.2 % for Meggle products.

Melting point: 201-202 ^{0}C (for dehydrated α- lactose monohydrate)

Moisture content: Lactose monohydrate contains approximately 5% w/w water of crystallization and normally has a range 4.5% - 5.5% w/w water content.

Hygroscopicity: Povidone is very Hygroscopic significant amount of moisture being absorbed at low relative humidities.

Particle size distribution: 90 > 50µm, 50%> 100 µm,5%>200 µm in size for kollidon 25/30; 90%>200 µm,250 µm in size for kollidon 90.

Solubility: solvent solubility at 208 ^{0} unless otherwise stated, chloroform practically insoluble, Ethanol practically insoluble, Ether Practically insoluble.

Tensile Strength : 2.987 MPa (at compression pressure 189.5 MPa); 2.517 MPa.

Density : 1.545 fm/cm^3

Storage and stability: Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. The purities of different lactose's can vary and color evaluation may be important, particularly if white tablets are being formulated. solution shows mutarotation. it should be stored in a well- closed container in a cool, dry place.

Safety: Adverse reactions to lactose are largerly attribute to lactose in tolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase.

Applications in Pharmaceutical Formulations or Technology:

- Widely used as a filler and more limited extent in lyophilized products and in infants formulation.
- It is used as diluents in Dry- powder inhlation.
- Lactose is added to freeze dried solutions to increase plug size and aid cohesion.with the combination of sucrose used as sugar coating solution.

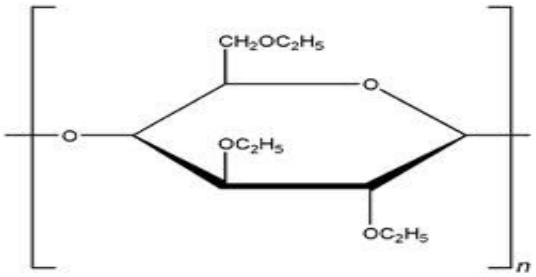
ETHYL CELLULOSE [EC]: [51]

Ethyl cellulose (EC) is available under the brand name Ethocel 7 cps was sourced from DOW Chemicals Company. The chemical name of ethyl cellulose is Cellulose ethyl ether (CAS no. 9004-57-3). The product has approved regulatory status as per USP-NF, Ph.Eur. JP and BP. It is a derivative of cellulose in which some of the hydroxyl groups on the repeating glucose units are converted into ethyl ether groups.

Bulk density:

0.3 – 0.4 gm/cm^3

Structure:



It is available as free flowing powder, white or light tan in color with a density of 0.4g/cm2. It is practically insoluble in water, glycerol and propane-1-2-diol, but soluble in organic solvents. Ethyl cellulose containing 46-48% of ethoxyl group is freely soluble in ethanol, methanol, chloroform and ethyl acetate. Neutral to litmus, with LOD not more than 3%. It is mainly used as a thin-film coating material. In addition to being useful in a variety of pharmaceutical applications. It also features a fine particle (FP) range for use in extended release matrix surface area. This flexibility is further enhanced by the ability to modify release profiles

when ETHOCEL™ is used in combination with water-soluble excipients such as Colorcon's METHOCEL™ premium cellulose ethers175, 176. Ethyl cellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalies. Ethyl cellulose is prone to oxidative degradation in presence of UV light. Ethyl cellulose should be stored at a temperature not exceeding 32 ^{0}C in a dry area and away from heat .

TALC :

1. Non – proprietary names:

- BP : Purified talc
- PhEur: Talcum
- Jp: Talc
- USP_NF : Talc

2. Synonyms:

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; *Luzenacpharma;*magenisium hydrogen metasilicate; magsil*osmanthus;*Magsil star; powdered talc; Purified French chalk; *purtalc;* soap stone; steatite; Superiore.

3. Chemical Name and CAS Registry Number: Talc [14807-96-6]

4. Empirical formula: $Mg_6(Si_2O_5)_4(OH)_4$

5. Functional category:

Anticaking agent; glidant; tablet and capsule diluents; tablet and capsule; lubricant

6. Typical Propertes: Acidity/alkalinity:

pH = 7-10 for a 20% w/v aqueous dispersion

Hardness: 1.0-1.5

Moisture content:

Talc absorbs insignificant amounts of water at 25 ^{0} C and relative humidites up to about 90%.

Particle size distribution:

Varies with the source and grade of material. Two typical grades are ≥ 99% through a 74 µm (# 200 mesh) or ≥ 99% trough 44 µm (#325 mesh)

Refractive index: *n20*,D = 1.54 – 1.59

Solubility: Practically insoluble in dilute acids and alkalis, Organic solvents and water

Specific gravity: 2.7-2.8

Specific surface area: 2.41 – 2.42 m^2/g.

7. Description: Talc is very fine, white to grayish –white, odorless, impalpable, unctuous, crystalline Powder. It adheres readily to the skin and is soft to touch and free from grittiness.

8. Stability and storage Conditions:

Talc is a stable and may be sterilized by heating at 160 ^{0} C for not less than 1 hour or to ethylene oxide or gamma irridation. Talc should be stored in a well-closed container in a cool, dry place.

9. Applications in Pharmaceutical Formulation or Technology:

Talc was once widely used in oral solid dosage formulations as a lubricant and diluents, dissolution retardan although today it is less commonly used.

MAGNESIUM STEARATE

1. Non – proprietary names:

- BP : Magnesium stearate
- PhEur: Magnesiistaras
- Jp: Magnesium steriate
- USP_NF : Magnesium steriate

2.Synonyms:

Magnesium octadecanoate

Octadecanoic acid, Magnesium salt

Stearic acid, Magnesium salt

3. Chemical Name and CAS:

Chemical name and CAS registry number octadecanoic acid magnesium salt and [557-04-0].

4. Empirical Formula and Molecular weight:

$C_{36}H_{70}MgO_4$ and 591.34

5. Functional Category:

Tablet and capsule lubricant

6. Typical Properties:

Crystaline forms

High-purity magnesium stearate has been isolated as a Tri hydrate, a Di hydrate and An hydrate.

Bulk denity: 0.159 gm/cm^3

Tapped density: 0.286 gm/cm^3

True density: 1.092 gm/cm^3

Flash point: 250 ^{0} C

Flowability: Poorly flowing, coahesive powder

Melting range:

- 117-150 ^{0} C (commercial samples)
- 126-130 ^{0} C (high purity magnesium stearate)

Solubilty:

Practically insoluble in ethanol, ethanol 95%, ether and water slightly soluble in warm benzene and warm ethanol 95%

Specific surface area:

1.62-14.8 m^2/gm

7. Stability and storage conditions:

Magnesium stearate is stable and should be stored in a well closed container in a cool, dry place.

8. Incompatibilities:

Incompatibile with strong acid, alkalis and Iron salts. Avoid mixing strong oxidizing materials. Magnesium stearate cannot be used in products containing Aspirin, some vitamins and most alkaloidal salts.

9. Description:

Magnesium stearate is a very fine, light white, precipitated or milled, Impalpable powdered of low bulk density, having faint odor of stearic acid and characteristic taste, The powder is greasy to the touch and readily adheres to the skin.

10. Applications in Formulation or Technology:

It is primarly used as lubricant in capsule and tablet manufacture at concentrations at between 0.25% and 5.0% w/w. It is also used in barrier creams.

4. AIM AND OBJECTIVE

The aim of this work is to develop a matrix tablet to completely deliver Zolmitriptan in controlled manner over a prolonged period which have low half life requiring frequent administration.

Zolmitriptan is an oral antimigrane agent, which is a commonly prescribed for the treatment of patients with migrane attacks. Zolmitriptan is a weak base(pKa = 9.6). soluble in water and 0.1N HCl acid environment and highly soluble less permeable (class III) drugs according to the Biopharmaceutical Classification System (BCS).

The oral absorption is uniform, slow with a bioavailability of nearly 40% and reported to have a short biological half-life (3±0.6 hrs) requiring it to be administered in 2 to 3 doses of 2.5 to 5mg per day. CR formulations that would maintain plasma levels of drug 8 to 12 hrs might be sufficient dosing for Zolmitriptan. SR products are needed for Zolmitriptan to prolong its duration of action and to improve patience compliance.

The polymer selected for the present work was Hydroxypropyl methylcellulose (HPMC) K4M, K15M, K100M Grades, and combination with Ethyl cellulose (EC), and Cellulose Acetate phthalate (CAP). The effect of polymer types and drug: polymer ratio on release also studied. Hydrophilic polymer matrix system are widely used for designing oral controlled release delivery systems because of their flexibility to provide a desirable drug release profile, cost effectiveness, and a broad regulatory acceptance.

In this formulation method combination of Ethyl cellulose and Cellulose acetate phthalate with different grades of HPMC K4M, K15M, K100M were used to control the drug release from the polymer. Formulation with these polymers will leads to slow release of drug from the polymer matrix either by diffusion or by dissolution method following drug kinetic release.

Formulation of Zolmitriptan in the form of matrix tablets leads to prolonged action of drug where the drug binds to the receptor site and drug released from the matrix slowly either in the diffusion or dissolution process and shows action on the target site for long time.

4. PLAN OF WORK

STAGE-I: PREFORMULATION STUDY

1. Pre Formulation Study of Pure Drug

2. Compatibiity Study

    Fourier transforms infrared spectroscopy (FT-IR)

3. Preparation of standard curve of zolmitriptan

STAGE-II: FORMULATION& EVALUATION

Formulation and evaluation of controlled relaese matrix tablets

1. Precompression parameter

2. Formulation of zolmitriptan controlled release matrix tablets

3. Evaluation of zolmitriptan controlled release matrix tablets

    a) Physical evaluation

    b) Drug content study

    c) Dissolution study

    d) Kinetic study

STAGE-III

Accelerated stability study of the optimized formulation.

5. MATERIALS AND METHODS

List of material and equipments used was given in table No. 5 & 6

Table 5: List of material used

S.No	Materials	Manufacturer
1	Zolmitriptan	Reddys labs Ltd, Hyderabad
2	HPMC K4M	Colorcon Asia Pvt Ltd
3	HPMC K15M	Colorcon Asia Pvt Ltd
4	HPMC K100M	Colorcon Asia Pvt Ltd
5	EC	Signet chemicals
6	CAP	Signet chemicals
7	Lactose	Vilin Bio med Ltd,Roorkee,Ind
8	Aerosol	Stumester lab
9	Talc	S.D.Fine chemicals Pvt.Ltd
10	Magnesium Stearate	HimediaPvtLtd,Mumbai

Table 6: List of equipments used

S.No	Equipments	Company
1	Sixteen station rotary tablet punching machine	Cadmach, Ahmadebad, India
2	Electronic digital balance	Shimadzu corp., Japan
3	Double beam UV-spectrophotometer	Elicopvt India Ltd, Hyderabad.
4	Dissolution tester (USP)	Lab India
5	Rotary shaker	RemiEquipments Ltd
6	Roche friabilator	INCO Instruments and chemicals Pvt Ltd; Ambalacity,India
7	Digital verniercallipers	Mitutoyo Corp, Kawasaki,japan

METHODS

5.1. PREFORMULATION STUDIES:

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances in order to develop stable, safe and effective dosage forms.

The following preformulation studies were Performed:

- Study of organoleptic properties
- Solubility analysis
- Melting point of drug
- Drug powder characterization
- drug-excipients compatibility study by FT-IR

5.1.1 Organoleptic properties:

Colour :a small quantity of pure Zolmitriptan powder was taken in a butter paper and viewed in well illuminated place.

Taste and odour : very less quantity of Zolmitriptan was used to get taste with the help of tongue as well as smelled to get the odour.

5.1.2. Solubility analysis:

Solubilityis an important pre-formulation parameter because it affects thedissolution and bioavailability of drug.

Method: Solubility of Zolmitriptan was determined in methanol, water,dicholoro methane, toluene and0.1N HCl.Solubility studies were performed by taking excess amount of Zolmitriptan in different beakers containing the solvent. The mixture was shaken for 10 hrs at regular intervals. The solution was filtered by using whatmann filter paper.

5.1.3. Melting Point

The melting point of Zolmitriptan was determined by capillary method, using small quantity of Zolmitriptan was taken and placed in apparatus and determined the melting point and matched with standards.

5.1.4. Loss on drying

Determined on 1 g by drying in an oven at 100°C to 105°C for 3 hours. Mixed and accurately weighed the substance to be tested. Tare a glass stopper, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Weighed the empty bottle (W1). Put the sample in bottle, replaced the cover, and accurately weighed the bottle with contents (W2). By gently, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm. Placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature in a desicator before weighing. Weighed the bottle (W3).The difference between successive weights should not less than 0.3%.

The loss on drying is calculated by the formula:

$$\%LOD=\frac{(W2-W3)}{(W2-W1)} x100$$

Where, W1 = Weight of empty weighing bottle

W2 = Weight of weighing bottle + sample

W3 = Weight of weighing bottle + dried sample

5.1.5. Drug Powder characterisation

5.1.5.1. Angle of repose: Angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles. The internal angle between the surface of the pile and horizontal surface is known as the angle ofrepose and is related to the density, surface area and co-efficient of friction of the raw material.

Method: Angle of repose was determined by using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed blend is allowed to pass through the funnel freely on the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

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

Where, h = height of heap, r = radius of heap, θ = angle of repose.

Table7: Limits

Angle of repose	Flow property
<25°	Excellent
25-30°	Good
30-40°	Passable
>40°	Very poor

5.1.5.2. Bulk density: Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more spherical in shape, bulk density was increased. In addition as the granule size increases bulk density decreases.

Method: A quantity of 4gm of powder weighed and transferred to a measuring cylinder. The bulk volume and weight of the powder was determined.Bulk density was calculated using the formula.

Bulk Density = Bulk Mass / Bulk Volume

5.1.5.3. Tapped density: It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder.Then the tapping was done and the tapped volume was noted. The tapped density was calculated using the following formulae

$$\textbf{Tapped Density} = \frac{\mathrm{m}}{\mathrm{V}f}$$

Where, m = initial weight of material in gm, V*f*= volume of material aftertapping.Generally replicate determinations are desirable for the determination of thisProperty.

5.1.5.4. Measurement of Powder Compressibility:

Based on the apparent bulk and the tapped density, the percentage compressibility of bulk was determined by the following formula.

Compressibility index: $= 100 \frac{(V_o - Vf)}{V_o}$

Where, V*f*= final tapped volume, V*o* = initial un tapped volume

Table-8: Limits

S.No	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	>40	Extremely poor

Hausner's Ratio: $= \frac{V_\circ}{Vf}$

Where, Vf = final tapped volume, V_o = initial un tapped volume.

Table-9: Limits

S.No	Hausner's ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

5.2. COMPATIBILITY STUDY:

Drug excipient compatibility studies :

IR spectra of drug, polymer and drug and polymers, individual excipients,drug and polymers and excipients were obtained using bruker.

Method: Drug and excipients were analyzed by IR spectral studies by using KBr pellet technique. In this method, the drug and KBr were mixed at the ratio of 1:100. Then these mixtures were pressed in to a pellet. The FT-IR spectra were recorded using bruker alpha in the region 400-4000 cm^{-1}. Spectra were recorded for pure drug,excipients, and physical mixture of drug and polymer, drug, polymer and excipients.

5.3. STANDARD CURVE OF ZOLMITRIPTAN

Calibration curve of Zolmitripitan was plotted in 0.1N HCl buffer and was estimated spectrophotometrically at λ max of 283nm.

5.3.1. Preparation of 0.1N Hcl solution:

Weighed 8.5 ml concentrated HCl was dissolved in 1000ml of distilled water to prepare 0.1N HCl solution.

5.3.2. PREPARATION OF STANDARD SOLUTION

1. Stock solution

First stock solution of Zolmitriptan was prepared by dissolving 100mg in 100ml of 0.1 N HCl. So as to get solution of 1mg/ml concentration.

2. Standard solution

10 ml of 1mg/ml stock solution was diluted to 100ml with 0.1 N HCl buffer thus giving a concentration of 100 µg/ml from the above 10ml of prepared solution diluted to 100ml with buffer thus giving a concentration of 10 µg/ml. Accurately measured aliquot portion of standard drug solution (10 µg/ml) 0.5ml, 1.0ml, 1.5ml, 2.0ml, 2.5ml, 3.0ml, 3.5ml, 4.0ml, 4.5ml, 5.0ml were transferred in to a 10 ml volumetric flask and was diluted up to the mark with the buffer thus the final concentration ranges from 5-50 µg/ml. Absorbance of each solution was measured at 283nm against buffer. A graph of concentration of drug vs absorbance was plotted.

5.4. FORMULATION DEVELOPMENT

Zolmitriptan matrix tablets were prepared by mixing manually in poly bags with different viscosity grades of HPMC such as HPMC K4M, HPMC K15M, HPMC K100M and in combination with EC and CAP. Tablets were prepared by direct compression method to observe the *in vitro* dissolution of drug from HPMC polymers at different concentration such as 10%,20%,30% to the target weight (100 mg) which was kept constant in all formulation F1 to F15. Accurately weighed quantity of drug,polymer and lactose were directly mixed uniformly and then the mixed blend was pre-lubricated with talc and Aerosil and finally lubricated with magnesium stearate manually in polybags for 5-10 min. The concentration of the HPMC K4M, HPMC K15,HPMC K100 in different formulation are (10%), (20%),(30%). The lubricated blend was evaluated for precompression parameter to determine the flow property of the powder and compressed into tablet by using 6.0mm punch. The formulation composition of F1 to F15 was given in table No.10.

Table 10 Formulation composition of zolmitriptan tablet (qty. in mg)

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
1	Zolmitriptan	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
2	HPMC K4M	10	20	30	-	-	-	-	-	-	-	-	30	-	-	30
3	HPMC K15M	-	-	-	10	20	30	-	-	-	-	20	-	-	20	-
4	HPMC K100M	-	-	-	-	-	-	10	20	30	10	-	-	10	-	-
5	Cellulose acetate Pthalate	-	-	-	-	-	-	-	-	-	-	-	-	5	5	5
6	Ethyl cellulose	-	-	-	-	-	-	-	-	-	5	5	5	-	-	-
7	Lactose	79.25	69.25	59.25	79.25	69.25	59.25	79.25	69.25	59.25	79.25	69.25	54.75	79.25	69.25	59.25
8	Aerosil	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
9	Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
10	Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
11	Total weight	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

5.4.1. Pre compression parameter

The lubricated blend of all formulation was examined for pre-compression parameter like angle of repose, bulk, density, tapped density, carr'sndex, hausner's ratio, as given in preformulation section.

5.5 EVALUATION OF CONTROLLED RELEASE MATRIX TABLET OF ZOLMITRIPTAN

5.5.1. PHYSICAL EVALUATION

5.5.1.1. Tablet Thickness

Ten randomly selected matrix tablets from each abtch were used for thickness determination. Thickness of each tablets was measured by using Digital vernier caliper. Mean and standard deviation were computed and reported

5.5.1.2. Weight variation

The USP weight variation test was carried out by weighing 20 tablets individually, calculating the average weight, comparing the individual tablet weight to average weight.

% Deviation = (Individual weight – Average weight / Average weight)×100

Table11: Pharmacopoecial Specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablets (mg) (U.S.P)	Maximum Percentage difference allowed
1	Less than 130	10
2	130-324	7.5
3	More than 324	5

5.5.1.3. Hardness

Hardness of tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides aslongaguage in the barrel to indicate the force. Mean and standard deviations were computed and reported. It is expressed in kg/cm^2.

5.5.1.4. Friability

The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus, which was given 100 revolutions. After which the tablets were reweighed. The percentage friability was calculated.

$$\text{Percentage friability} = \frac{\text{Initial weight - Final weight X 100}}{\text{Initial weight}}$$

5.1.1.5. Drug Content

Five tablets of each formulation were weighed and powdered. The quantity of powder was equivalent to 10 mg. The equivalent weight zolmitriptan was transferred in to 100 ml volumetric flask and dissolved by using pH 6.8 as the extracting solvent and samples were analysedspectrophotometrically 227nm.

5.5.2. SWELLING INDEX STUDY

Swelling behavior of different viscosity grades of HPMC, Ethyl Cellulose, Cellulose Acetate Pthaltein the 0.1 N Hcl dissolution medium.

The mechanism of drug release from hydrophilic polymeric matrice involves solvent penetration, hydration and swelling of the polymer, diffusion of the dissolved drug in the matrix. Initially, the diffusion coefficient of drug in the dehydrated polymer matrix is low it increases significally as the polymer matrix imbibes more and more water and forms a gel as time progresses. The hydration rate of the polymer matrix, and there by the gel formation depends significantly on polymer proportion, viscosity and to a lesser degree on polymer particle size. So swelling study was performed according to the method reported by AL-Taani and Tashtoush to understand the influence of swelling behaviour on drug release and to determine the effect of polymer viscosity on swelling. For determination of swelling index one tablet from each formulation was kept in the petri dish containing 0.1 N HCl. After every2 hrs tablet was with drawn, soaked with tissue paper and weighed. The process is continued for 12hrs.

Swelling index of formulation was calculated using following formula.

$$S.I = \frac{Mt - Mo}{Mo} \times 100$$

Where, SI = Swelling index, Mt = Weight of tablet at time ‘t’ And Mo = weight of tablet at time ‘f ’.

5.5.3. *IN-VITRO* DISSOLUTION STUDY

Table 12: *In-vitro* dissolution study [52, 53]

Apparatus	Dissolution test apparatus (USP XXIII)
Method	USP type 2 apparatus (paddle method)
Dissolution medium	0.1N HCl
Volume	500ml
Temperature	37 ± 0.5^{0} C
Speed	50 rpm

Procedure:

The tablet was placed inside the dissolution vessel. 5ml sample were withdrawn at time intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,12 hrs.The volume of dissolution fluid adjusted to 500 ml replacing fresh 5 ml of dissolution medium after each sample withdrawing. The release studies were conducted with 3 tablets and the mean value were plotted vs time. Each sample were analyzed at 283nm. The drug concentration was calculated using standard calibration curve.

According to USP-29 specification

At 1^{st} hour - between 10-25%

At 9^{th} hour - between 45-85%

At 12^{th} hour - no less than 70%

5.5.4. Kinetic study

Various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on fickian diffusion Eq. (3). TheHixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$$C = k_o t \quad (1)$$

Where, Ko is zero-order rate constant expressed in units ofconcentration/time and t is the time.

$$LogC = LogCo - kt/2.303 \quad (2)$$

Where, Co is the initial concentration of drug and K is firstorder constant.

$$Q = kt^{1/2} \quad (3)$$

Where, K is the constant reflecting the design variables of the system.

$$Q_0\ 1/3 - Qt\ 1/3 = kHC\ t \quad (4)$$

Where, Qt is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and KHC is the rate constant for Hixson-Crowell rate equation. The following plots were made: *cumulative % drug releasevs. time*(zero order kinetic model); *log cumulative of %drugremaining vs. time* (first order kinetic

model); cumulative *%drug release vs. square root of time* (higuchi model) and *cube root of drug % remaining in matrix vs. time* (hixsoncrowell cube root law).

Mechanism of Drug Release

Korsmeyer et al derived a simple relationship whichdescribed drug release from a polymeric system (Equation 5).Tofind out the mechanism of drug release, first 60% drugrelease data was fitted in Korsmeyer–Peppas model by plotting log cumulative % drug releaseVs log time:

$$Mt / M\alpha = kKPt^{n} \quad (6)$$

Where Mt / M$\alpha$is fraction of drug released at time t, kKP is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table for cylindrical shaped matrices. The value of n≤0.45 indicates a classical fickian diffusion-controlled (case I) drug release, n = 0.89 indicates a case II relaxational release transport; non-fickian, zero-order release and n>0.89 indicates super case II (increased plasticization at the relaxing boundary) type of release. Values of n between 0.45 and 0.89 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and the polymer relaxation) commonly called anomalous transport.

5.6. STABILITY STUDY

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of variety of environemntl factors such as temperature, humidity and light. And to establish a

retest for the drug substance or a shelf life for the drug product and recommended storage conditions.

The storage conditions used for stability studies were accelerated condition ($40^oC \pm 2^oC/75\%RH$). Stability study was carried out for the optimized formulation. Tablets of optimized formulation were striped packed and kept in humidity chamber for 90 days on above mention temperature.

The following tests are performed at an interval of 30 days for 90 days.

Test performed

- Drug content
- Dissolution profile
- Test for other physical parameters (hardness, weight variation, friability)

6. RESULTS AND DISCUSSION

6.1. PREFORMULATION STUDY

6.1.1. Observation of organoleptic properties

Table No: 13

Test	Specification	Observation
Colour	White to off-white	crystalline powder
Odour	-	Odourless

6.1.2. Solubility analysis

Zolmitriptan sample are examined and it was found to be readily soluble in methanol, sparingly soluble in dichloromethane,practically insoluble in toluene.

6.1.3. Melting point of Drug

The melting point of zolmitriptan was determined by capillary method, melting point of zolmitriptan was found to be 139º C melting point compared with USP standards that showed that drug is pure.

6.1.4. Loss on drying

It was determined as per procedure given in methodology. The results are as follows.

Table No : 14 Observations for loss on drying

Test	Loss on drying	Observation
Loss on drying	Not more than 0.5%	0.31%

The loss on drying of drug was founded as 0.31 which is with in the limit.

6.1.5. Drug Powder characterization

6.1.5.1. Angle of repose

It was determined as per procedure given in material and methodology section 5.1.5.1.

Table No: 15

Material	Angle of repose
Zolmitriptan raw material	27º56"

The result indicating that the raw material has very good flow property.

6.1.5.2. Flow properties

Flow property of pure drug determined according to the procedure given in methodology 5.1.5.2, 5.1.5.3, 5.1.5.4, section the results were given in table No. 16

Table No:16 Flow propertie of pure drug

Material	Bulk density	Tapped density	Carr's index (%)	Hausner ratio (%)
Zolmitriptan raw material	0.34gm/ml	0.546gm/ml	15.05	1.57

The results are clearly indicating that the zolmitriptanhas good flow property.

6.2. Drug – Excipient compatibility test

FTIR study on drug, drug with different polymer such as HPMC K4, HPMC K100M, EC, CAP were performed. The FTIR peak value spectrum were given in Table No : 17 to 20 and Fig No. 3 to 12

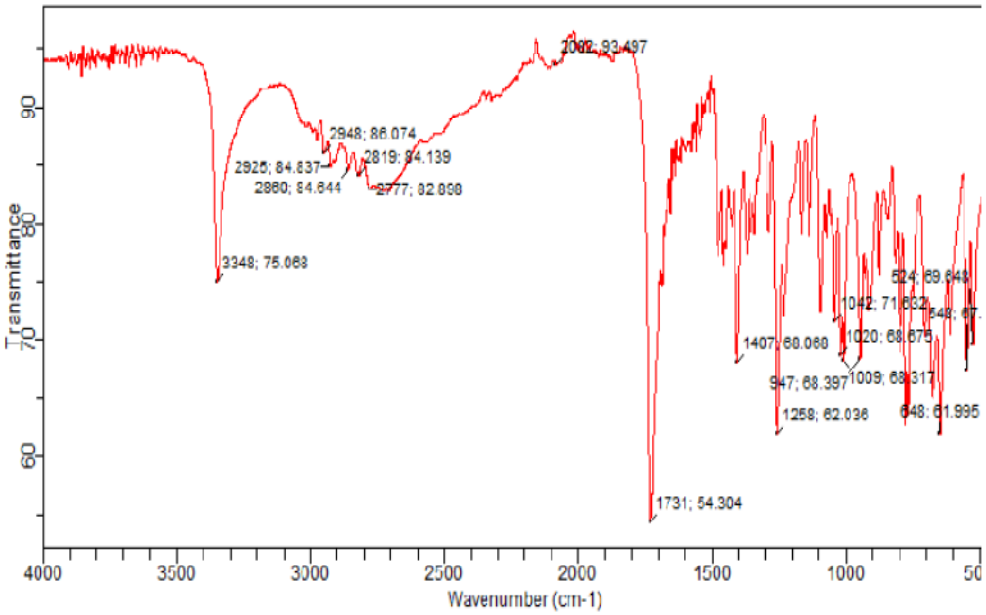


Fig. 3 FTIR study of Zolmitriptan

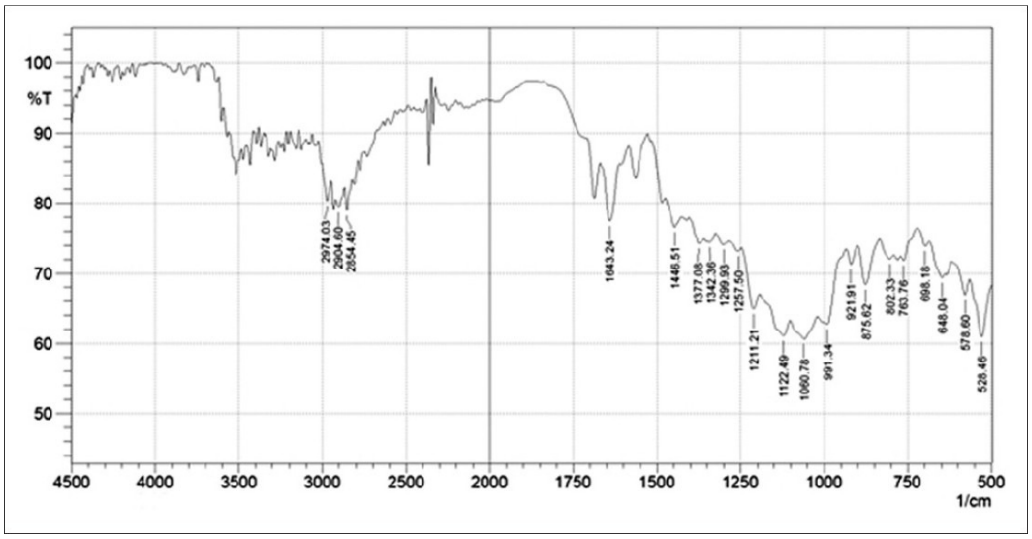


Fig. 4 FTIR study of Zolmitriptan with HPMCK4 Polymer

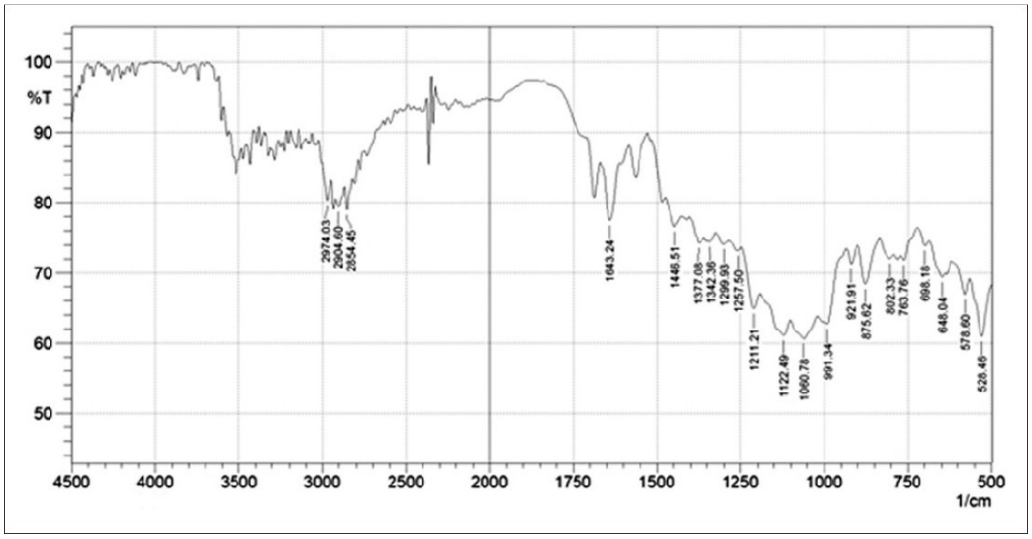


Fig. 5FTIR study of Zolmitriptan with HPMCK4 + EC

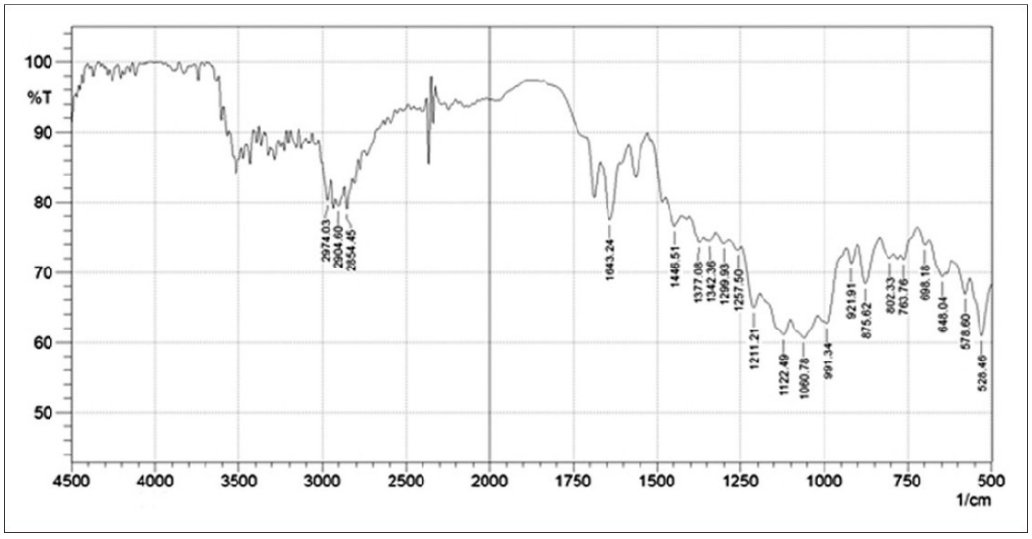


Fig. 6FTIR study of Zolmitriptan with HPMCK4 + CAP

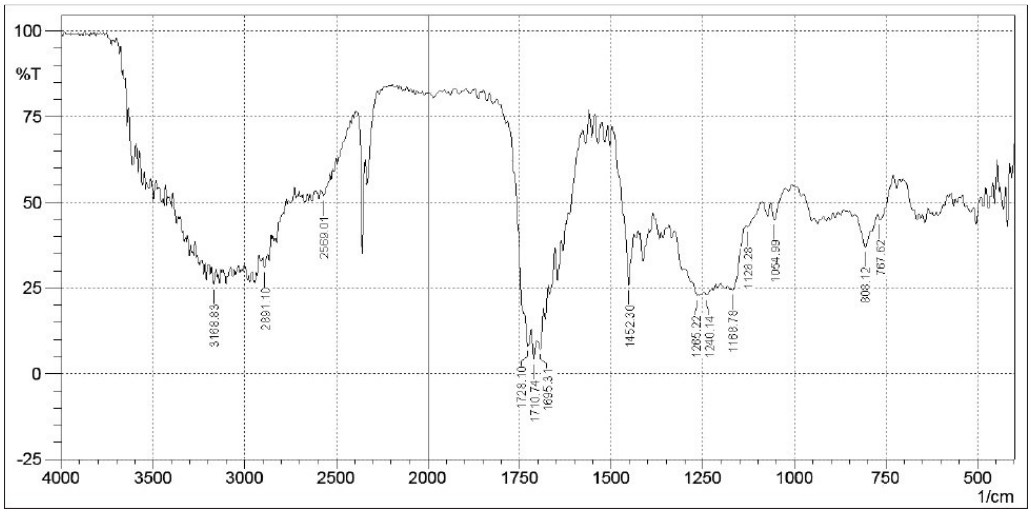


Fig. 7FTIR study of Zolmitriptan with HPMCK15

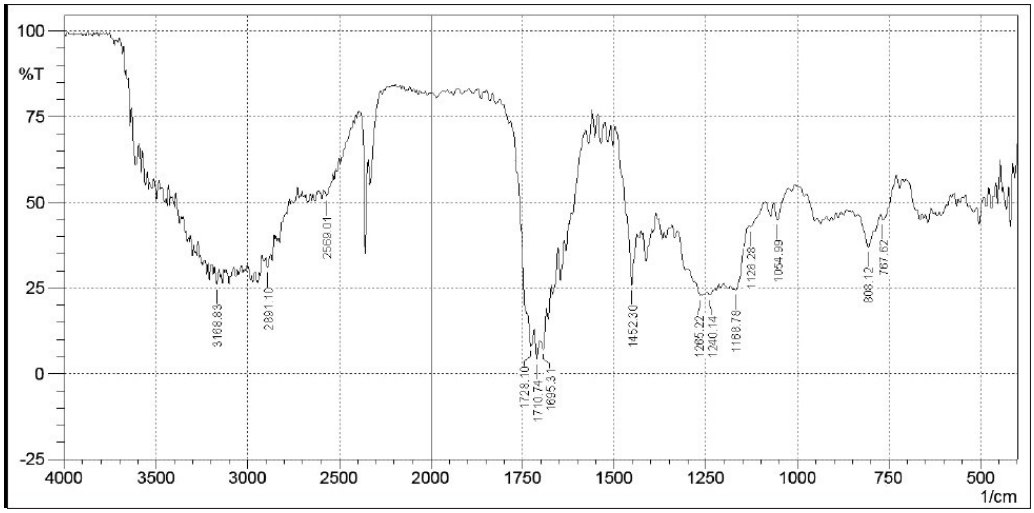


Fig. 8 FTIR study of Zolmitriptan with HPMCK15 + EC

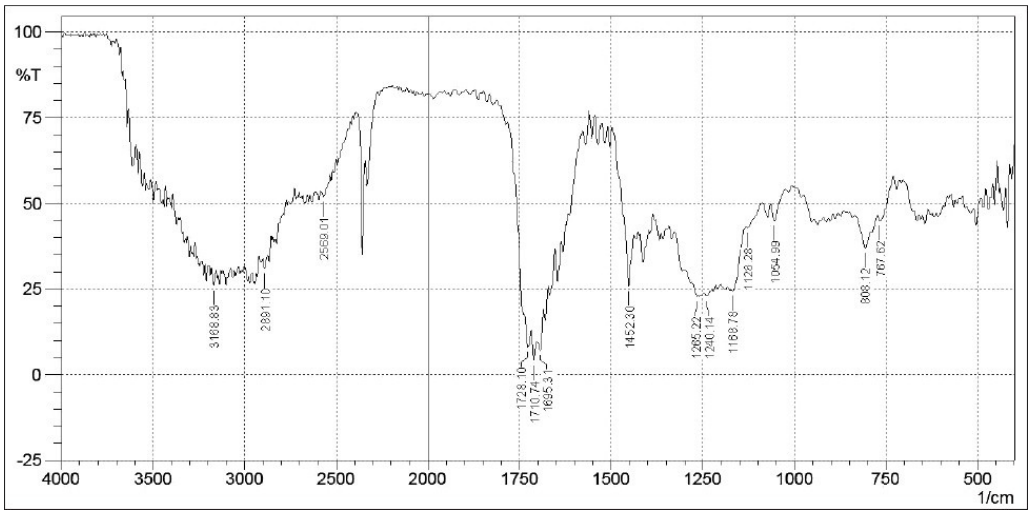


Fig. 9 FTIR study of Zolmitriptan with HPMCK15 + CAP

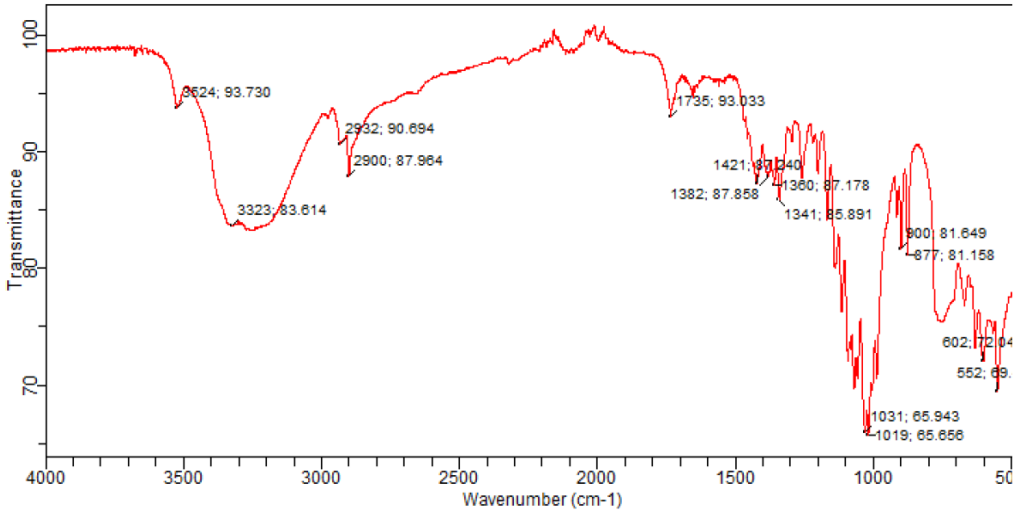


Fig.10FTIR study of Zolmitriptan with HPMCK 100 polymer

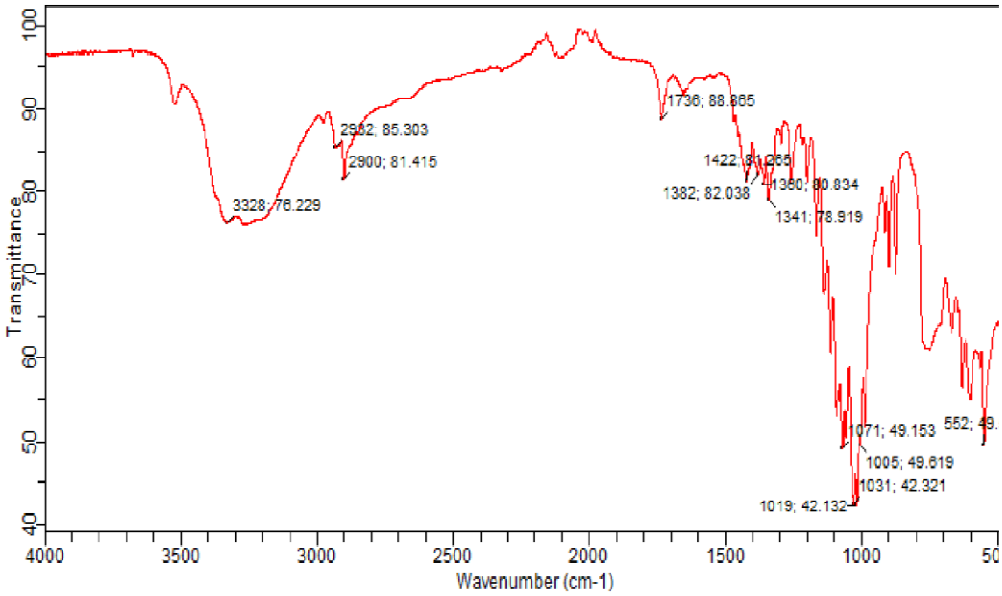


Fig.11FTIR study of Zolmitripitan with EC+HPMCK100(10%)

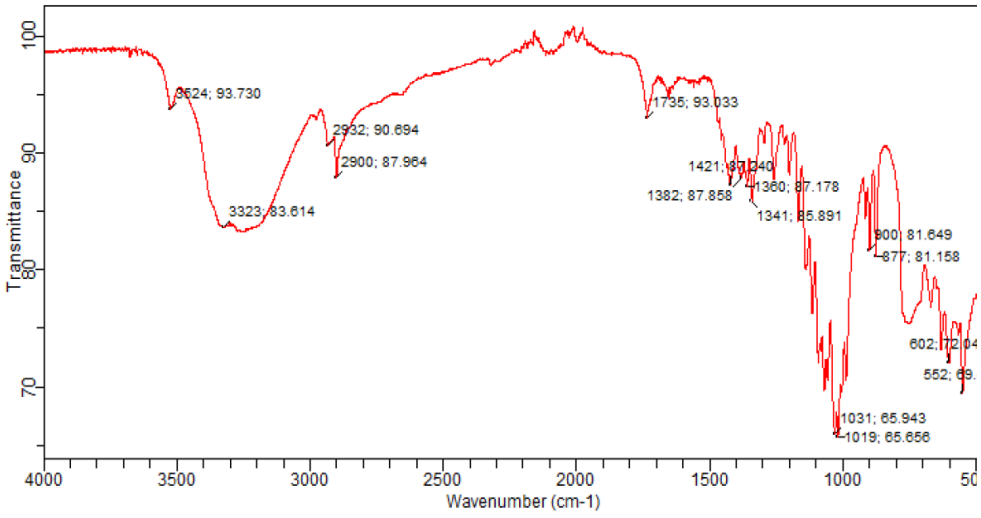


Fig.12FTIR study of Zolmitripitan with CAP+HPMCK100(10%)

Table No : 17 FTIR peaks of various components of zolmitriptan

S.No	Peak in pure drug (cm^{-1})	Functional group	Type of vibration
1	3348.75	Amine (-N-H)	Stretch (medium)
2	2948.75	Aromatic (-C-H)	Stretch(medium)
3	1731.54	Amide (C=O)	Stretch(strong)
4	1407.68	Methylene cyclo hexane	Stretch(scissoring)
5	1047.68	Sulfoxide	Stretch(strong)
6	1020.63	Aromatic plane bending (C-H)	Stretch(medium)
7	1009.64	Aromatic (C=C)	Stretch (weak multiple)

The FTIR spectral analysis showed that there is change in percent transmittance which may be due to change in crystalline and there is no appearance of disappearance of any characteritstic peaks of pure drug Zolmitriptan and in the physical mixture of drug and polymer, which confirms the absence of chemical interaction between drug and polymers.

Table No : 18 FTIR spectrum zolmitriptan with HPMC K_4 Ec and CAP

pepared Formulation

Zolmitriptan	Drug+HPMC K4M	Drug+HPMC K4 (10%)+EC	Drug+HPMC K4 (10%)+CAP
526.69	529.60	532.60	545.69
567.67	604	1010.49	660.72
649.61	632.53	1019.42	878.81
967.60	1019.39	1041.45	900.81
1008.68	1038.40	1081.49	1019.65
1031.68	1071.47	1368.74	1034.65
1044.71	1258.74	1350.80	1347.85
1258.62	1347.76	1352.84	1387.75
1407.62	1359.60	1477.81	1389.87
1731.54	1429.78	1756.88	1389.87
2085.93	1739.89	2979.85	1425.87
2877.82	2915.82	2900.80	1733.93
2917.84	3337.75	3376.75	2900.87
2860.62	3629.88	-	2937.90
2925.82	-	-	3337.65
2933.68	-	-	-
3556.72	-	-	-

Table No : 19 FTIR spectrum peak of Zolmitriptan with HPMC K_{15},EC,CAP.

Zolmitriptan	Drug+HPMC K15M	Drug+HPMC K15 (10%)+EC	Drug+HPMC K15 (10%)+CAP
556.69	568.75	587.79	590.65
54867	603.51	1005.49	602.72
649.61	637.74	1017.47	877.47
956.68	1017.49	1037.42	910.81
1008.69	1047.61	1071.49	1026.68
1026.68	1058.61	1349.76	1037.68
1047.71	1268.74	1368.80	1374.69
1259.65	1351.76	1389.65	1369.87
1407.68	1359.76	1422.87	1386.95
1756.54	1422.78	1746.88	1389.65
2087.65	1756.87	2936.65	1427.87
2778.65	2900.80	2900.84	1737.93
2819.84	3337.74	3326.84	2954.84
2860.65	3526.89	-	2937.65
2926.65	-	-	3327.65
2948.75	-	-	3624.43
3346.85	-	-	-

Table No:20 FTIR spectrum peak point of Zolmitriptan with HPMC $K_{100,}$EC,CAP.

Zolmitriptan	Drug+HPMC K 100M	Drug+HPMC K 100(10%)+EC	Drug+HPMC K100(10%)+CAP
524.69	552.45	552.49	552.69
548.67	603.51	1005.49	602.72
648.61	632.53	1019.42	877.81
947.68	1019.39	1031.42	900.81
1009.68	1031.40	1071.49	1019.65
1020.68	1071.47	1341.78	1031.65
1042.71	1260.78	1360.80	1341.85
1258.62	1341.76	1382.82	1360.87
1407.68	1359.79	1422.81	1382.87
1731.54	1422.78	1736.88	1382.87
2082.93	1736.86	2932.85	1421.87
2777.82	2900.80	2900.81	1735.93
2819.84	3338.73	3328.76	2900.87
2860.84	3524.89	-	2932.90
2925.84	-	-	3323.83
2948.75	-	-	3624.93
3348.75	-	--	-

6.3 Standard calibration curve for Zolmitriptan

Initially the pure zolmitriptan was scanned in between UV-range such as 200-400nm.The maximum absorbance for zolmitriptan was found at 283 nm. A standard concentration of zolmitriptan in the range of 5-50 µg/ml was prepared in 0.1 N HCl buffer and the absorbance was measured at 283nm. Zolmitriptan is showing good linearity between 5-50 µg/ml with a correlation coefficient of 0.999.

Table : 21 Standard value of zolmitriptan

Concentration(µg/ml)	Absorbance(nm)
0	0
5	0.097
10	0.178
15	0.266
20	0.355
25	0.442
30	0.539
35	0.617
40	0.728
45	0.807
50	0.907

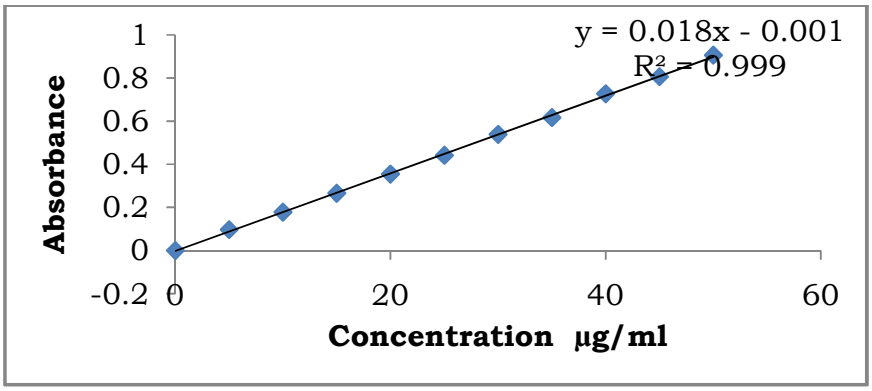


Figure:13 Standard curve of zolmitripitan in 0.1 N HCl

6.4 Pre compression Parameter

The lubricated blend of all formulation examined according to standard procedure given in methodology and results were given in table No. 22

Table : 22 Pre compression Parameter

Formulation Code	Angleof repose (degree± SD)	BD (gm/ml± SD)	TD (gm/ml± SD)	Carr's index (%± SD)	Hausner ratio (%± SD)
F1	26.81±0.02	0.42±0.02	0.52±0.02	16.71±0.02	1.16±0.05
F2	27.71±0.09	0.43±0.09	0.53±0.09	17.28±0.09	1.18±0.04
F3	28.54±0.06	0.45±0.06	0.54±0.06	15.44±0.06	1.16±0.02
F4	29.73±0.08	0.43±0.08	0.56±0.08	13.44±0.08	1.19±0.04
F5	27.54±0.07	0.45±0.07	0.58±0.07	15.69±0.07	1.14±0.06
F6	25.61±0.09	0.46±0.09	0.59±0.09	17.76±0.09	1.13±0.06
F7	28.61±0.06	0.53±0.06	0.53±0.06	14.46±0.06	1.19±0.03
F8	27.73±0.08	0.49±0.08	0.52±0.08	14.44±0.08	1.15±0.01
F9	26.33±0.02	0.52±0.02	0.51±0.02	15.44±0.02	1.18±0.03
F10	27.38±0.09	0.41±0.09	0.54±0.09	14.64±0.09	1.17±0.05
F11	26.66±0.08	0.47±0.08	0.53±0.08	16.28±0.08	1.16±0.04
F12	28.52±0.06	0.45±0.03	0.58±0.03	15.18±0.03	1.17±0.02
F13	27.53±0.04	0.42±0.02	0.57±0.02	14.28±0.02	1.15±0.01
F14	26.52±0.08	0.49±0.01	0.52±0.01	15.72±0.01	1.19±0.04
F15	29.75±0.09	0.43±0.04	0.53±0.04	16.18±0.04	1.18±0.06

The angle of repose values were ranged from 25º61"±0.06 to 29º75"±0.09. The results were found to be below 30; hence they have good flow ability. The Carr's Index value ranged from 13.44±0.08 to 17.76±0.09 and Hausner ratio value ranged from 1.13±0.06 to 1.19±0.04,For all formulations hence they have good flow and free flow ability. It was suitable for direct compression technique. So according to F1 to F15 the tablets were formulated by direct compression technique. as per the procedure given in 5.4.

6.5 EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF ZOLMITRIPTAN

6.5.1 Physical evaluation various physiochemical properties were studied and summarised in table no:23

Table : 23 Physical parameters of the prepared Zolmitriptan matrix tablet

F. Code	Weight variation (mg)	Thickness (mm)	Tablet hardness(kg/cm^2)	Friability(%)	Drug content(%)
F1	98.9±0.33	2.42±0.66	6.2±0.44	0.40	98.12±1.2
F2	97.5±1.31	2.52±0.08	6.3±0.46	0.54	98.2±0.2
F3	99.2±1.42	2.63±0.09	6.9±0.54	0.65	98.48±0.62
F4	100.2 ±1.33	2.54±0.09	6.9±0.05	0.36	98.5±0.96
F5	99.5 ±1.37	2.48±0.09	6.2±0.43	0.40	97.25±0.86
F6	98.9±1.39	2.60±6.08	7±0.16	0.36	99.1±0.05
F7	101.2±1.45	2.50±0.08	6 ±0.51	0.38	98.2±0.097
F8	102±1.32	2.57±0.06	7.3±0.45	0.36	99.56±0.097
F9	99.5±1.35	2.64±0.09	6.6±0.52	0.38	98.56±0.91
F10	98.2±1.42	2.58±0.094	6.7±0.54	0.41	101±0.082
F11	99.5±1.35	2.42±0.081	6.6±0.51	0.31	100.1 ±0.091
F12	98.2±1.42	2.58±0.091	6.7±0.54	0.41	101±0.082
F13	99.8±1.35	2.42±0.081	6.6±0.51	0.31	100.1±0.091
F14	101±1.5	2.40±1.38	6.9±0.51	0.33	101.2±1.2
F15	101±1.5	2.40±1.38	6.9±0.51	0.36	99.9±0.91

Acceptable physiochemical properties were observed for the prepared matrix tablets. F1 to F3 which is containing HPMC K4 (10%, 20%, 30%). Friability of the prepared matrix tablets F1, F2, F3 was (0.40, 0.54, 0.65%) respectively, Indicating that friability is with in the acceptable limits. Hardness of the tablets was found to be good depending up on compression force applied (4-6.9 kg/cm^2). The thickness of the tablets were found to be in the range of (2.42mm-2.63 mm).All the formulation shown uniform thickness which indicates good mechanical strength of the tablet. Drug content of the prepared matrix tablets was found to be in the range of 98.12-98.48%. which is in the range as per the requirement of pharmacopoeia.

Acceptable physiochemical properties were observed for the prepared matrix tablets. F4 to F6 which contain HPMC K15 10%, 20%, 30% respectively.Friability of the prepared matrix tablets was (0.36%,0.40%,0.36%). Indicating that friability is with in the acceptable limits. Hardness of the tablets was found to be good depending up on compression force applied (6.9-7 kg/cm^2). The thickness of the tablets were found to be in the range of (2.54mm-2.60mm).All the formulation shown uniform thickness which indicates good mechanical strength of the tablet. Drug content of the prepared matrix tablets was found to be in the range of 98.5-99.8%. which is in the range as per the requirement of pharmacopoeia.

Acceptable physiochemical properties were observed for the prepared matrix tablets. Friability of the prepared matrix tablets was (0.38%, 0.36%, 0.38 %),F7 to F9 which contain HP mc k100 10%,20%,30% respectively indicating that friability is with in the acceptable limits. Hardness of the tablets was found to be good depending up on compression force applied (6-6.6kg/cm^2). The thickness of the tablets were found to be in the range of (2.50mm-2.64mm).All the formulation

shown uniform thickness which indicates good mechanical strength of the tablet. Drug content of the prepared matrix tablets was found to be in the range of 98.56-101%. which is in the range as per the requirement of pharmacopoeia.

Acceptable physiochemical properties were observed for the prepared matrix tablets F10 to F11 contained combination of Hpmck$_{100}$10%,K$_{15}$20%,K$_4$30% with ethyl cellulose. Friability of the prepared matrix tablets was (0.41%, 0.31%, 0.41%). Indicating that friability is with in the acceptable limits. Hardness of the tablets was found to be good depending up on compression force applied (6.6-6.7 kg/cm^2). The thickness of the tablets were found to be in the range of (2.42mm-2.58mm).All the formulation shown uniform thickness which indicates good mechanical strength of the tablet. Drug content of the prepared matrix tablets was found to be in the range of 100-101%. which is in the range as per the requirement of pharmacopoeia.

Acceptable physiochemical properties were observed for the prepared matrix tablets F12 to F15 which contained combination of Hpmc k$_{100}$10%,K$_{15}$20%,K$_4$30% with cellulose acetyl phalate Friability of the prepared matrix tablets was (0.31,0.33,0.36%). Indicating that friability is with in the acceptable limits. Hardness of the tablets was found to be good depending up on compression force applied (6.6-6.9 kg/cm^2). The thickness of the tablets were found to be in the range of (2.40mm-2.42mm).All the formulation shown uniform thickness which indicates good mechanical strength of the tablet. Drug content of the preparedmatrix tablets was found to be in the range of 99.9.-100.1%.

6.5.2. SWELLING INDEX

Swelling index for all formulation F1 to F15 determined according to procedure given in 5.5.2. The results were summarised in Table No.24 to Table No. 28 and Fig:14 to 18.

Table: 24 Swelling index of Zolmitriptan matrix tablets prepared with HPMC K4M (10%,20%,30%)

Time in hrs	HPMC K4M 10%	HPMC K4M 20%	HPMC K4M 30%
0	0	0	0
2	114	140	164
4	117	162	180
6	121	178	210
8	134	181	258
10	111	200	259
12	107	170	200

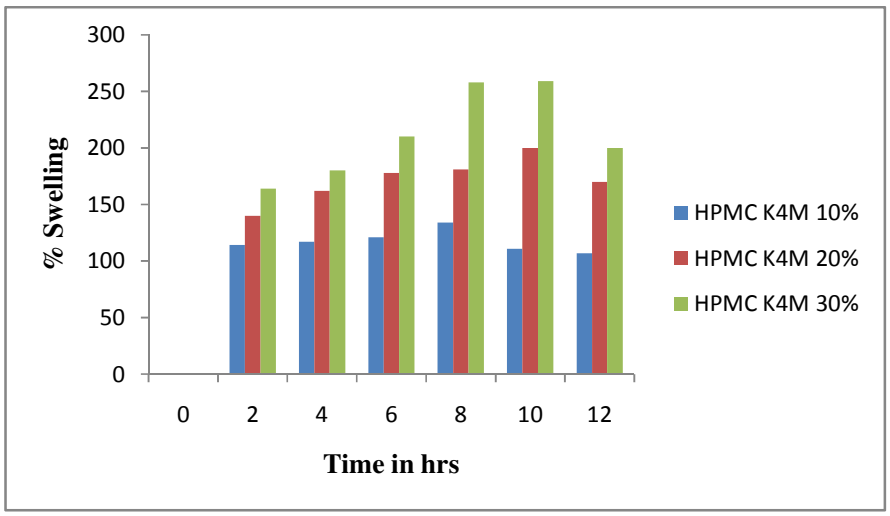


Fig: 14 Swelling index vs.time of Zolmitriptan matrix tablets F1 to F3.

Table: 25 Swelling index of Zolmitriptan matrix tablets prepared with HPMC K15M (10%,20%,30%)

Time in hrs	HPMC K15M 10%	HPMC K15M 20%	HPMC K15M 30%
0	0	0	0
2	210	221	254
4	230	243	256
6	245	255	268
8	250	267	271
10	259	243	252
12	200	198	220

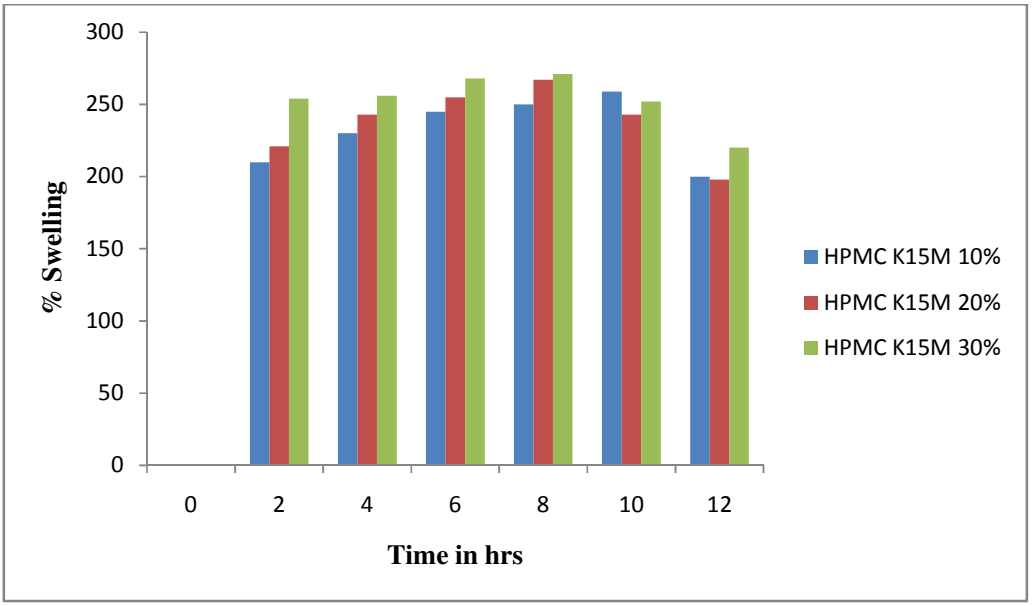


Fig: 15 Swelling index of Zolmitriptan matrix tablets.

Table: 26 Swelling index of Zolmitriptan matrix tablets prepared with HPMC K100M (10%,20%,30%)

Time in hrs	HPMC K100M 10%	HPMC K100M 20%	HPMC K100M 30%
0	0	0	0
2	85	92	122
4	105	115	137
6	116	127	144
8	122	131	151
10	100	104	116
12	93	99	108

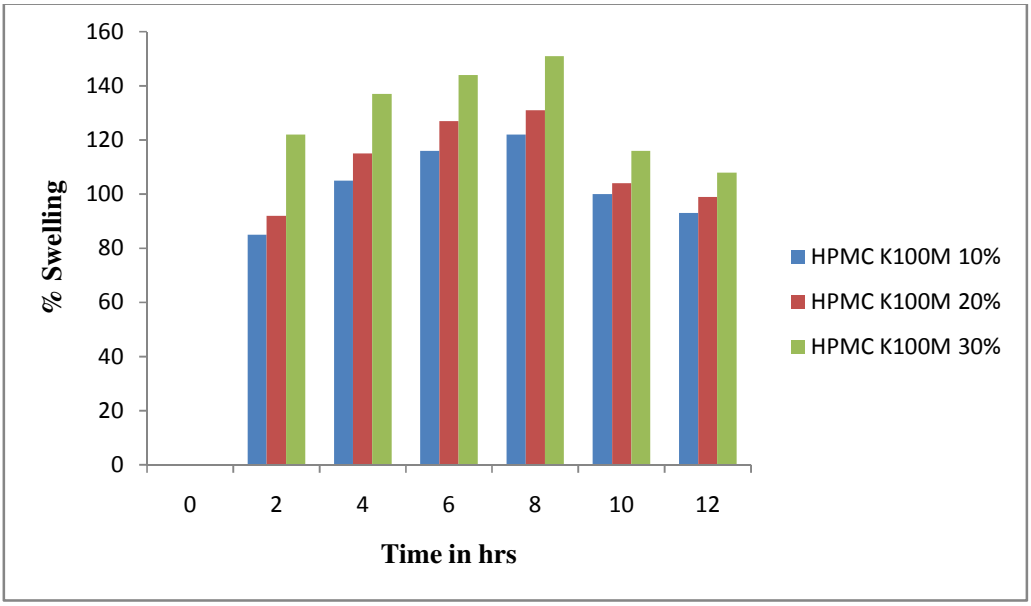


Fig: 16 Swelling index of Zolmitriptan matrix tablets F7 to F9.

Table: 27 Swelling index of Zolmitriptan matrix tablets prepared with Ethyl cellulose HPMCK4-K15-K100M(30%,20%,10%)

Time in hrs	EC+HPMC K4M 30%	EC+HPMC K15M 20%	EC+HPMC K100M 10%
0	0	0	0
2	117	128	133
4	124	139	148
6	135	141	169
8	148	157	178
10	115	119	120
12	108	112	118

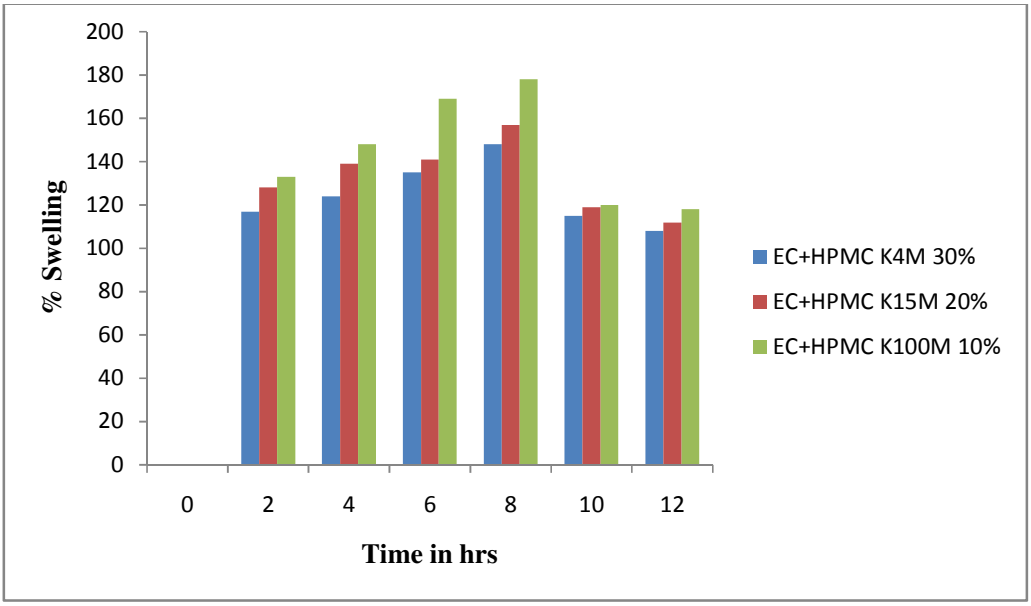


Fig: 17 Swelling index of Zolmitriptan matrix tablets F10 to F12.

Table: 28 Swelling index of Zolmitriptan matrix tablets prepared with Cellulose acetate phthalate HPMCK4-K15-K100M (30%, 20%, 10%)

Time in hrs	CAP+HPMC K4M 30%	CAP+HPMC K15M 20%	CAP+HPMC K100M 10%
0	0	0	0
2	132	148	152
4	145	159	168
6	156	167	176
8	162	188	200
10	127	139	142
12	120	125	136

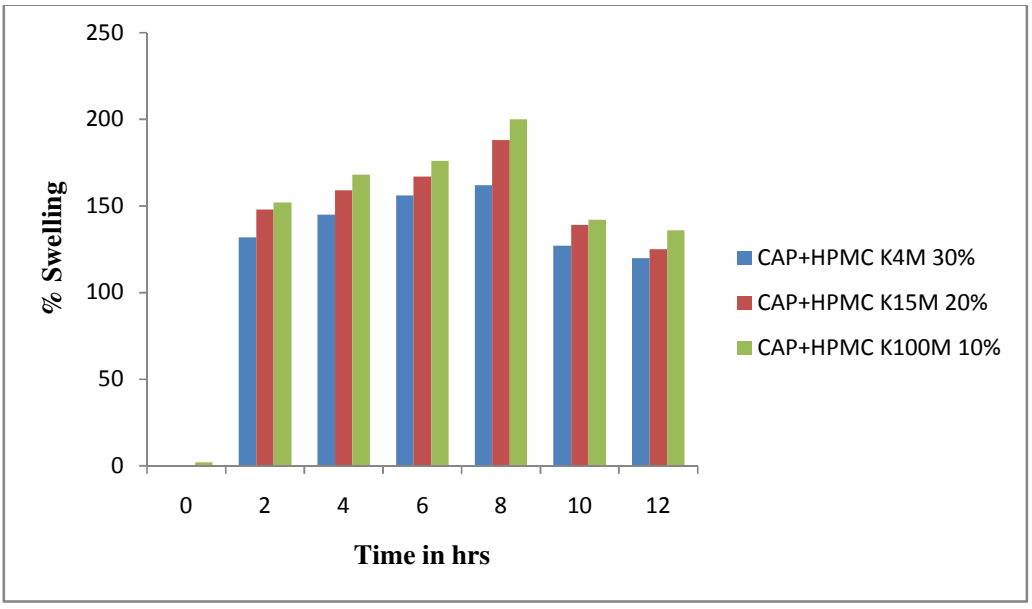


Fig: 18 Swelling index of Zolmitriptan matrix tablets F13 to F15.

The percentage water uptake of the formulations (F1-F15) was calculated Table 24 to 28. Results demonstrated enhancement in the swelling index with an increase in polymer concentration and also time duration. Increase in polymer concentration from 10 to 30% increased the swelling . From 2 to 12 hours in formulation. This may be due to the hydrophilic property of HPMC . Moreover, swelling of the polymer also leads to the formation of matrix, thereby retarding the release of drug from the formulation.

Investigation of polymer swelling and erosion is a valuable exercise to better understand the mechanism of release and the relative importance of participating parameters. Matrix tablets of HPMC were found intact throughout the period of swelling (2 to12) in HCL and also the percent of swelling index was proportionate to the polymer level. On comparing the swelling indices of different matrix formulations, it was observed that, tablets containing combination of hydrophilic-hydrophobic polymer blends swelled less than that of formulations containing hydrophilic polymer alone .This could be due to presence of non-swellable hydrophobic polymers, which minimized the swelling of the matrix tablets.

6.3 *IN VITRO* DISSOLUTION STUDY

Invitro dissolution study was carried out by using USP dissolution 2 apparatus. The release profiles of formulations F1toF15, prepared by using HPMC K4 M, K15 M a K100 M,EC,CAP illustrated in (Table 29) and (Figure 19& 20).

Table: 29 *INVITRO* DRUG RELEASE STUDY OF FORMULATED CONTROLLED RELEASE TABLET

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	40.3±1.20	36.6±2.42	32±1.36	35±1.20	32.7±1.36	30.6±2.38	29±1.2	26±1.6	20±0.43	25±0.76	26±0.87	30±0.45	25±0.99	26±0.56	30±0.84
2	48±2.31	47.1±1.20	42.8±2.54	46±1.40	41±2.42	38±1.54	42±0.59	36±1.2	34.1±0.53	35±0.98	36±0.59	34±0.69	37±1.54	32±1.45	38±1.67
3	59±0.25	58±0.20	53.6±1.56	57.3±2.20	53±2.12	46±1.14	50±0.45	41±1.65	41±0.69	44±1.18	45.7±1.44	37±1.55	46±1.79	40±1.86	40±1.43
4	67±2.42	66.3±1.34	61±0.77	64±0.10	60.8±1.34	50.2±1.10	57±0.75	50±0.97	46±1.23	53±0.56	54±1.87	44±1.98	54±1.63	47±1.78	46.4±1.54
5	76±1.40	73±1.10	68±1.40	72±2.25	68±1.20	59±0.20	62±1.54	58±0.58	50±1.48	62±0.85	63.3±1.90	50±0.97	63±1.34	54±1.98	53±1.98
6	89±1.10	80±0.30	74±3.24	78±1.26	70±0.36	64±0.28	70±1.48	63±1.45	55±1.25	70±1.17	71±1.38	58±1.67	71±0.56	60±1.43	60±0.78
7	98±2.35	89±2.62	81±2.25	84±1.30	79±0.28	70±1.15	75±0.93	71±1.22	59±1.48	75±1.87	76±1.06	64±1.89	76±0.29	65±1.38	66±0.78
8		97±2.10	89±1.15	90±1.38	84±2.56	80±1.64	82±0.45	75±0.67	63±0.45	80±0.99	81±1.54	71±0.98	81±0,88	71±0.57	73±0.98
9			98±0.47	98±0.10	91±1.24	87±2.25	90.2±1.32	83±2.10	70.4±1.82	83±1.57	86±1.39	82±0.43	86±1.43	80±0.65	86±1.26
10					97.8±1.54	94±2.02	97.6±2.05	90±1.28	78±0.96	86±1.54	88±0.82	90±0.84	89±1.68	88±1.43	93±1.42
11						98.8±1.00		98.7±0.62	85±0.76	89	92±0.47	99.1±1.98	91±1.78	94±1.20	99.4±1.38
12									90.2±1.56	92.1	97±0.65		93±1.54	99.7±0.69	

Figure: 19 Dissolution profile of prepared formulation F1-F7

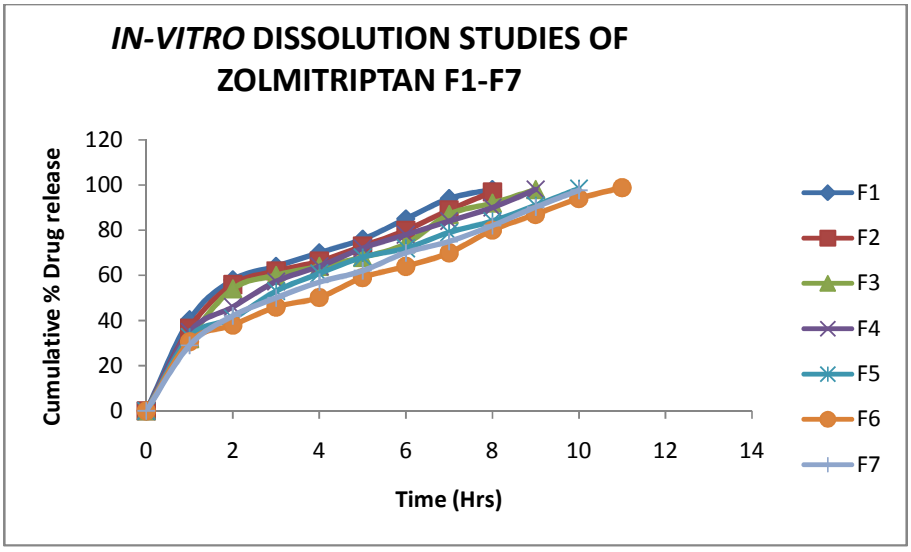
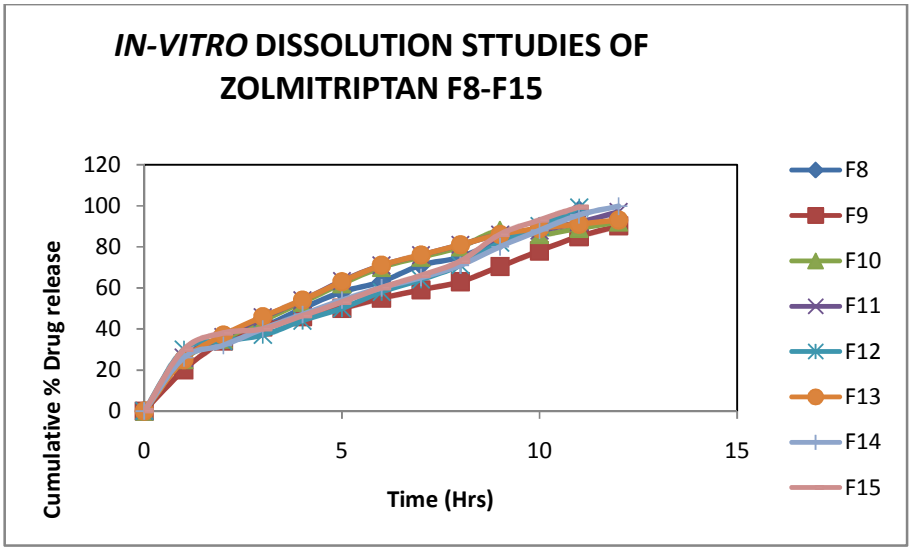


Figure: 20 Dissolution profile of prepared formulation F8-F15



In vitro dissolution studies were conducted in 500ml (500ml distilled water + 4.5 ml 0.1 N Hcl) of 0.1 N Hcl buffer using USP-II apparatus at 50 rpm and the

temperature of 37±0.5^{0}c. Samples of 5ml were collected at different time intervals and analyzed spectrophotometrically at 283 nm.The effect of polymer level on release was studied by varying the levels of HPMC in the matrix tablets. The release pattern of matrix tablet containing 10,20 and 30% w/w HPMC, K4,K15,K15 with EC and CAP was decipated in Figure. The release rate from F1, F2 and F3 was found to be 98, 97 and 98% at the end of 7th, 18th and 9thhrs respectively. profile of zolmitriptan Hcl from HPMC-K15 matrix formulations F4, F5, and F6 were found to be 98, 97.8 and 98.8% at the end of 9 th, 10th and 10th hr respectively. The release profile of Zolmitriptan from HPMC-K100 matrix formulations F7, F8, and F9 were found to be 97.6, 98.7 and 90.2% at the end of 10th ,11th ,&12th hr respectively. The release rate decreased as the concentration of HPMC increased which showed that the presence of a highly water-soluble compound, Zolmitriptan, in a HPMC matrix generates an additional osmotic gradient, thereby resulting in a faster rate of polymer swelling and a large increase in gel thickness. In the presence of a solvent, the mobility of the polymer chains is enhanced, resulting in a gradual transformation of a glassy matrix to a rubbery swollen gel. At higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug. other factors that may contribute to differences in drug dissolution profile as a function of changes in total polymer concentration include differences in water penetration rate, water absorption capacity and polymer swelling .

As the proportion of HPMC was increased, there was a progressive decline in the release rate because of formation of thick gel structure that delayed the drug release from the matrices, where hydration of HPMC resulted in extensive swelling and increase in the diffusion path length. Swelling studies of HPMC matrices also showed proportionate increase in the swelling with increase in polymer level. However, the results of the *in vitro*

drug release studies indicated that, matrix tablets prepared using HPMC alone could not efficiently control the release of drug even with increased levels of polymers (up to 30%w/w) and thus indicated the need for hydrophobic polymers in the HPMC matrices for controlling the drug release over a period of 12 hrs. To assess the influence of hydrophobic polymers in controlling the drug release, six matrix formulations containing combination of HPMC-EC (F10-F12) and with equal proportions were prepared in different polymeric levels like 10, 20 and HPMC-CAP (F13-F15)30% w/w. Similarly, the matrices prepared using combinations of HPMC with EC were subjected for dissolution studies. The release pattern of matrix tablets containing HPMC-EC (F10-F12) is depicted in Fig. 20. The release rate from matrix formulations F7, F8, and F9 was found to be 92.1, 97 and 95% at the end of 12^{th} hrs respectively. The release profiles from HPMC-EC formulations showed due more hydrophobic nature of EC. In all the above formulations, delay in drug release was observed due to the presence of hydrophobic polymers like ethyl cellulose and CAP, which restricted the penetration of dissolution medium in side the matrix and also the formation of gel layer around the matrix. The observation is further supported by penetration theory, which states that, when a matrix is composed of a water-soluble drug and a water-insoluble polymer, drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network. As drug release continues, the interconnecting clusters increase the pore network through which interior drug clusters can diffuse with more hydrophobic particles present, and the theory predicts that fewer clusters of soluble drug substance are formed. Furthermore, the presence of finite drug clusters is more statistically plausible. The resulting pore network becomes less extensive and more tortuous resulting in slower drug release. The incorporation of CAP in the matrix not only helped to provide

good initial retardation in the release but also helps to enhance the overall release rate of the drug after a suitable lag time. The release profiles showed tri-phasic with initial burst effect (less than 30min) followed by a polymer-controlled slower release in the second phase. The difference in burst effect was the result of difference in the viscosity of the polymers. As it can be seen from (Figure 1) Polymeric system with low viscosity polymer (HPMC K4 M, K15 M) yielded a faster initial burst effect except HPMC K100 M. There has been considerable interest in using different grades of HPMC in controlled release drug delivery system due to their hydrophilic nature and fast hydration. In conclusion, the matrix tablets prepared with polymeric combination of HPMC-EC and HPMC-CAP showed better controlled release than those prepared using HPMC alone. Among all F1to15 formulation F14 shown better release (99%in 12hrs)so F14 formulation which contain HPMC K15 +CAP was selected as optimised formulation .

6.5.4 KINETIC STUDIES OF ZOLMITRIPTAN CONTROLLED RELEASE MATRIX TABLETS:

Table No: 30

time (hrs)	log time	√time	cumulative % drug release	log cumulative % drug release	cumulative % drug remained	log cumulative % drug remained
1	0	1	26	1.4149	74	1.8692
2	0.301	1.4142	32	1.5051	68	1.8325
3	0.4771	1.732	40	1.602	60	1.7781
4	0.602	2	47	1.672	53	1.7242
5	0.6989	2.236	54	1.732	46	1.6627
6	0.7781	2.4494	60	1.7781	40	1.602
7	0.903	2.6457	65	1.8291	35	1.544
8	0.903	2.828	71	1.8512	29	1.4623
9	0.9542	3	80	1.903	20	1.301
10	1	3.166	88	1.9444	12	1.0791
11	1.0431	3.3166	94	1.9731	6	0.7781
12	1.0791	3.4641	99.7	1.9956	1	0

Fig : 24 Zero Order Plot

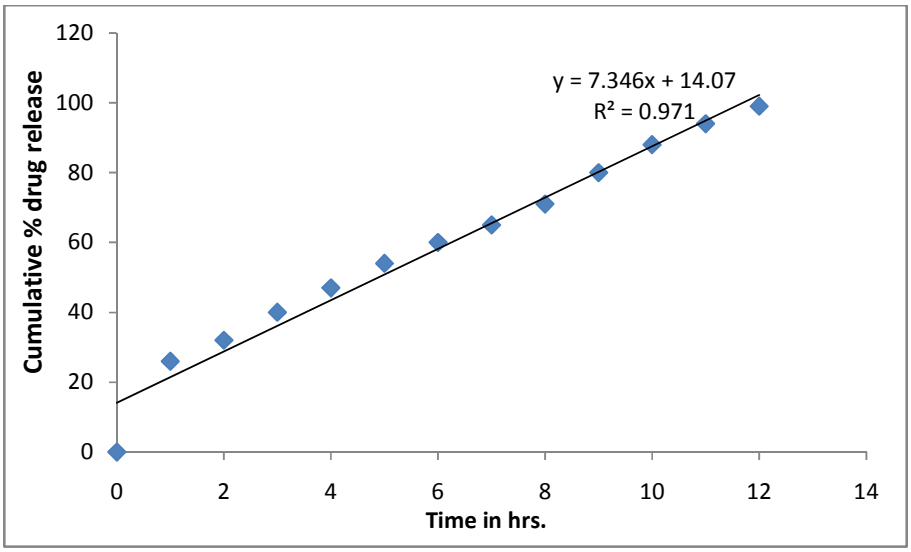


Fig : 25 First Order Plot

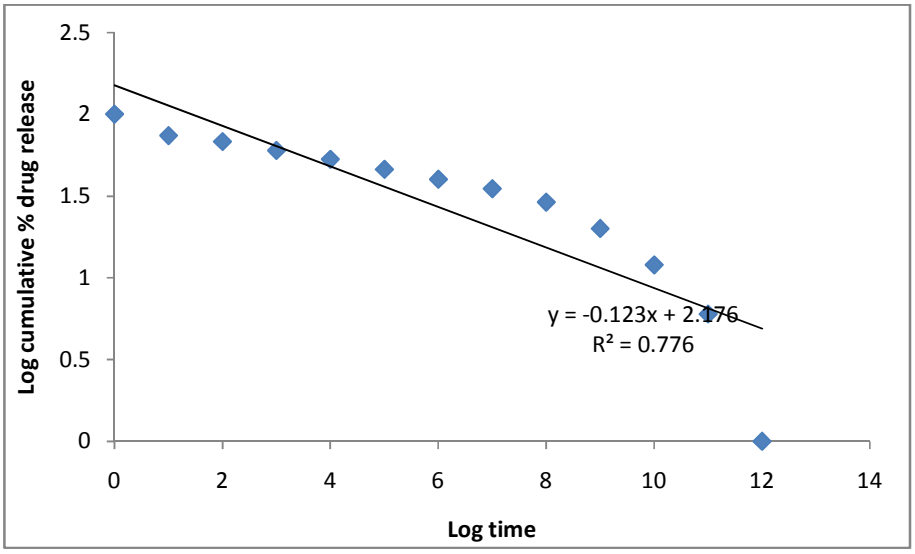


Fig : 26 Higuchi Plot

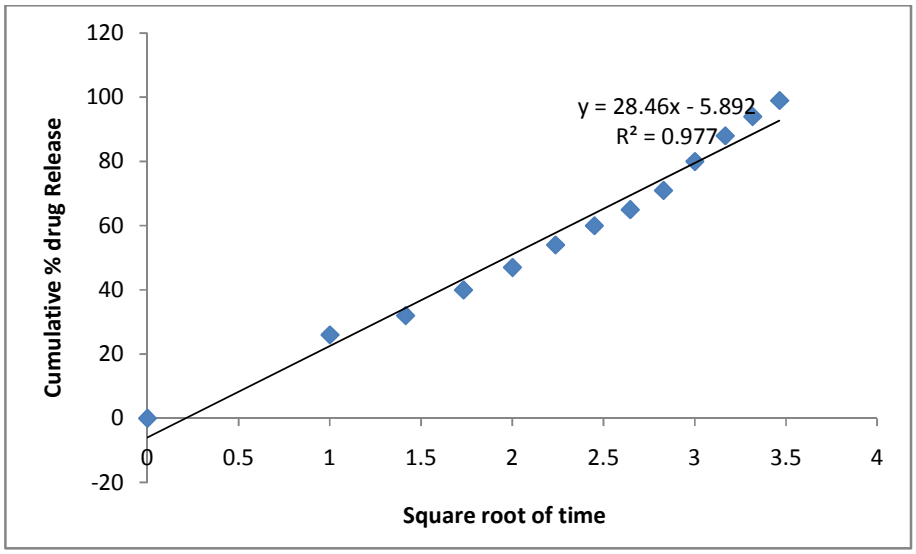


Fig : 27KorsemeyerPeppas Plot

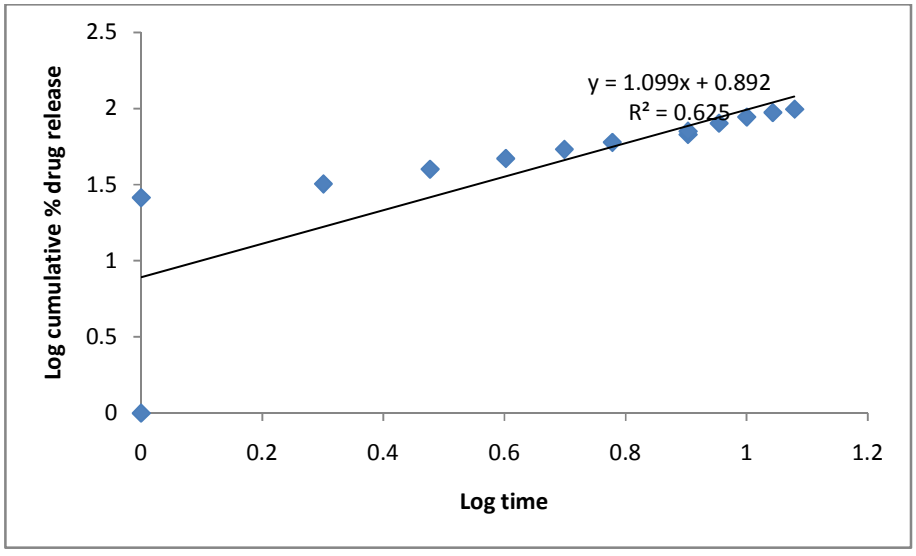


Table No. : 31 KINETICS OF DRUG RELEASE

Formulation	Zero Order Release R^2	First Order Release R^2	Higuchi Release R^2	Peppas R^2	Peppas n	Order of Release
F14	**0.971**	**0.776**	**0.977**	**0.625**	**0.596**	**Zero order Release**

In order to determine the mechanism of drug release from the formulation the *in vitro* dissolution data was fitted to zero order, first order ,higuchi and korsemeyar –peppas's plot and interpretation or release exponent value (n) was calculated and results were shown in Table:31 and fig no:25 to 28.

The model that best fits the release data was evaluated by correlation coefficient (r) [Table 31]. The correlation coefficient (r) values were used as the criteria to choose the best model to describe drug release from the controlled release tablets. The r-values (r^2= 0.977) obtained for fitting the drug release data to the Higuchi equation indicated that the drug release mechanism from these tablets was diffusion controlled. In most of the formulated tablets, the r^2 values (0.971) were higher in zero-order models than in first-order (0.776) model, indicating that the drug release from the tablets was according to zero-order kinetics and thus showing that the drug release rate was independent of the residual concentration of drug. By using the release exponent value of was found to be 0.596 Korsmeyer-Peppas equation, the *n* values obtained were between 0.5221 and 0.8992 [Table 31] for formulation F14. These values are characteristic of anomalous kinetics (non-Fickian)

STABILITY STUDIES

Zolmitriptan control matrix tablet were evaluated for accelerated stability studies at $40^{o}C$ / 75% RH condition. The stability details / results were presented as below.

The product was evaluated for following para meters.

1. Weight variation
2. Hardness
3. Friability
4. Drug content
5. Dissolution analysis

Storage condition : $40^{o}C$ / 75% RH

Pack : HDPE (High Density Polyethylene) container

Storage period : 1 month, 2 months, 3 months.

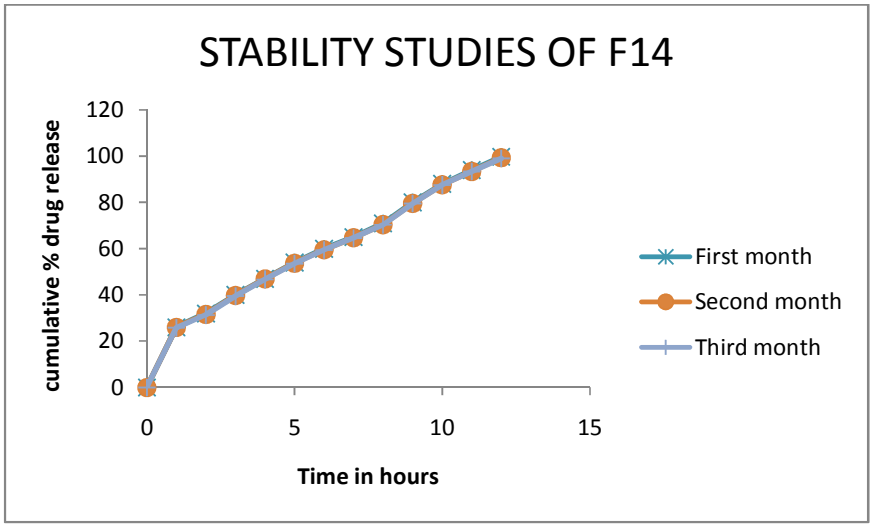
Table No. 31

TEST	**0 Days**	**30 Days**	**60 Days**	**90 Days**
Weigth variation	99.8 ± 1.35	99.5 ± 1.35	98.9 ± 1.39	98.8 ± 1.42
Hardness(kg/cm^2)	7	6.9	6.9	6.6
Friability	0.65	0.54	0.41	0.40
Drug content	99.9 ± 0.91	99.1 ± 0.05	99.56 ± 0.097	99.1 ± 0.093

Table No. : 32 Cumulative dissolution profile of tablets after 1st month, 2nd month and 3rd month stability of F14

Time in hours	0 days	Cumulative % drug release		
		1st month	2nd month	3rd month
0	0	0	0	0
1	26	26	26	25.8
2	32	32	31.6	31.3
3	40	40	39.8	39.5
4	47	47	46.9	46.7
5	54	54	53.7	53.5
6	60	60	59.5	59.4
7	65	65	64.7	64.6
8	71	71	70.4	70.3
9	80	80	79.6	79.5
10	88	88	87.6	87.5
11	94	94	93.4	93.3
12	99.7	99.7	99.3	99

Fig : 28 Dissolution data of Stability for sample F14



The stability studies for optimized formulation F14 was carried based accelerated stability conditions &Studty of various parameters carried out at 0, 30, 60, 90 days of intervals and the results found satisfactoriliy and that reveals that the optimized formulation was stable under accelerated condition.

7. SUMMARY AND CONCLUSION

Controlled release formulations in many case provide significant advantages,including improved theraupetic effect,increased patient compliance by reducing dosing frequency and decrease in incidence and or intensity of adverse effect by a constant blood concentration.The main objective of the present study was to develop controlled release matrix tablet formulation containing 5mg of zolmitriptan for the treatment of migraine.

In the prefomulation, FTIR study was carried out for pure drug (zolmitriptan) zolmitriptan and excipients. It has not shown any interaction. Hence drugs were found to be compatible with excipients.

The angle of repose values for formulations range from 25.61±0.06 to 29.75"±0.09 Bulk and tapped densities were used for the measurement of compressibility index. The bulk and tapped values for formulations range from 0.42± to 0.53±0.06 0.51±0.02±0.59±0.09 and to respectively the car's index and hausner's ratio values for formulations range from1.13±0.06 to 1.19±0.04 to respectively. Thus all formulations exhibited good flow characteristics. The formulations F1 to F15 were prepared by direct compression method.

The prepared controlled matrix tablets were evaluated for various parameters like thickness, weight variation, hardness, friability and drug content uniformity. The thickness of tablets in all formulations were ranged from 2.40±1.38 to2.64±0.09. The weight variation of tablets in all formulations were ranged from 100.2±1.33to102±1.32. The hardness and friability of all the formulations F1-F15

was found to be 6±0.51 to 7.3±0.45 and 0.31 to 0.65respectively.Drug content of all the formulations were ranging from 97.25±0.86 to 101.2±1.2.

Swellling index stugies were carried out indicating that according to the polymer concentration swelling index vary.

The prepared tablets were then subjected to dissolution test for evaluating the *invitro* drug release .The dissolution studies were carried out in 0.1 N Hcl in USP II appatarus at 37±0.5°C. The results of the dissolution studies indicated that the polymer concentration was having a substantial effect on the drug release from the tablets .Formulation F14 which contained HPMC K15 (20%) and CAP have better controlled drug release (99.7% at 12 hrs) andincomparision to the other formulations.

The kinetic study was carried out for F14 formulation which showed that the drug release followed zero order kinetics followed by non-fickian diffusion.

The stability studies were carried out for F14 formulation at 40^{o}C / 75% RH for 3months. Data revelead that there was no considerable difference.

From the above study, concluded that F14 was the optimized formulation, among all the formulation F14 formulation containing CAP+HPMC K15M 20% shows that 99% drug release at the end of 12hrs emerging as best formulation which followed by zero order release kinetics non fickian diffusion release.

In future,the following recommendations are made for continuation of experiment work

1. *In-vivo* studies, 2. Development of suitable packaging material.

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