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### LIPID MATRIX TABLETS AS SUSTAINED DRUG DELIVERY SYSTEM: A REVIEW

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**Abstract:** Matrix system are favored because of their simplicity, patient compliance etc, than traditional drug delivery which have many drawbacks like repeated administration, fluctuation in blood concentration level etc. It is estimated that 40% of active substances are poorly soluble in water. The improvement of bio-availability of drugs with such properties presents one of the greatest challenges in drug formulations. In recent years, there has been increasing interest in the use of formulations containing lipid based excipients that comprise combinations of synthetic or semi synthetic lipids with surfactants, co-surfactants or co-solvents. The lipid excipients based drug delivery is one of the potential approaches for poorly soluble drugs. The following article present details on the lipid excipients used in the formulations.

**Keywords:** Lipid matrix tablets, Sustained release, Novel drug delivery system



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## INTRODUCTION

According to the USP, tablets are defined as solid dosage forms containing medicinal substances with or without suitable diluents (USP 31 NF 26 2008). Within this definition, tablets can be classified in different types depending on the formulation and the manufacturing process (compressed, molded, coated, chewable, buccal, sublingual, effervescent etc.). The most commonly used tablets are compressed tablets which are prepared by the application of high pressure to a powder or granules using steel punches and dies.<sup>1</sup>

Tablets can be also classified in three major groups depending on their release behaviour i.e. immediate release where the drug is immediately released after ingestion, delayed release where the drug is released after a lag time to avoid a possible destruction or inactivation of the drug in the gastric fluid as well as irritation of the gastric mucosa and sustained release tablets where the drug is released over an extended period of time.<sup>1</sup>

Sustained release tablets are divided into multiparticulate and monolithic tablets. In multiparticulate tablets several units (crystals, particles, granules and pellets) are embedded maintaining their physical and chemical properties. Multiparticulate tablets disintegrate in contact with biological fluids releasing the units with intact properties. The monolithic tablets can either be coated with an inert polymer that releases the drug through diffusion or be matrix tablets where the drug is embedded in a sponge like structure and released through different mechanisms.<sup>1</sup>

The term modified release dosage form is used to describe products that alter the timing and rate of release of drug substance. A modified release dosage form is defined as “one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives” not offered by conventional dosage forms such as solutions, ointments or promptly dissolving dosage forms. The USP/NF presently recognizes several type of modified release dosage forms as:<sup>2</sup>

### **1. Oral dosage forms**

- Modified release dosage forms
- Extended release e.g. Controlled release, Sustained release and Prolonged release

Delayed release e.g. Enteric coated tablets

### **2. Intramuscular dosage forms**

- Depot injections
- Water immiscible injections e.g. oils

### 3. Subcutaneous dosage forms

Implants

### 4. Transdermal delivery systems

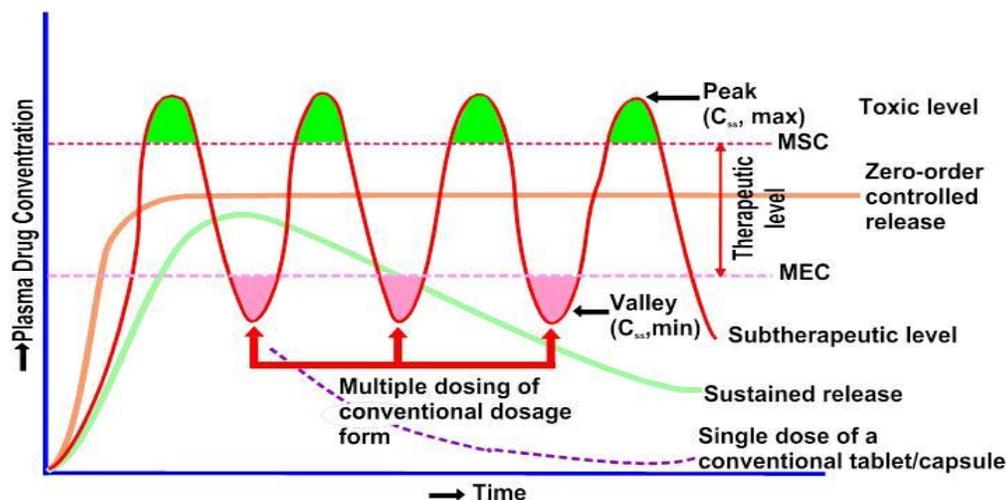
Patches, Creams etc.

### 5. Targeted delivery systems

#### Drawbacks of conventional dosage forms: <sup>3</sup>

- Poor patient compliance.
- Increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak valley plasma concentration time profile is obtained which makes attainment of steady state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index (TI) whenever over medication occur.

In order to overcome the drawbacks of conventional drug delivery systems several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.



### SUSTAINED RELEASE MATRIX TABLET:

In case of sustained release (SR) dosage forms the release of the active agent although is lower than in the conventional formulations. However it is still substantially affected by the external environments into which it is going to be released. Controlled release (CR) systems provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time with the release profiles of predominantly controlled by the special technological construction and design of the system itself. The release of the active constituent is therefore, ideally independent of exterior factors. Extended release formulation is a controlled release formulation designed to produce even and consistent release of active ingredient. Extended release (ER) dosage forms are those which due to special technology of preparation provided, soon after a single dose administration, therapeutic drug levels maintained for 8-12 hrs. Prolong or long action products are dosage forms containing chemically modified therapeutic substances in order to prolong biological half life.<sup>6</sup>

Long term treating of any disease requiring high frequency administration of drug is a cumbersome practice for any patient. To avoid such problems sustain release dosage form are much better alternative compared to conventional dosage form because administration of one single sustain release dose maintain the desired drug plasma level. With the advancement in design of sustain release dosage form drug with higher efficacy are being prepared which release drug at a constant predetermined rate. The release of drug from particle depend on the polymer used to form particle and the quantity of drug contained in it. Extensive *in vitro* and *in vivo* studies of such dosage form are done to make it more safe and effective toward treatment of diseases.<sup>7</sup>

An ideal dosage for the treatment of any disease is the one which immediately attain a therapeutic plasma level and maintain it constant for the entire period of treatment. This is possible through administration of conventional dosage form at a particular frequency. But with conventional dosage form there is unavoidable fluctuation in the drug plasma level which can be overcome by use of sustain release dosage form. Sustain release is a term use to characterize a delivery system which is designed in such a manner to achieve prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The term "control release" has been associated with these systems which release their active principle at a predetermined rate.<sup>7</sup>

Sustained release (also called extended release) tablets are a common dosage form. A sustained release (SR) tablet is typically designed to release drug over 12-24 hrs and might contain three times the dose of drug that is contained in an immediate release tablet. In this way a patient need take a tablet only once a day rather than three times a day if immediate

release tablets were used. This not only has the advantage of convenience for the patient but ideally provides more constant levels of drug in the body. Fluctuating drug levels can result in the patient being exposed to levels of drug which are too high at times, leading to harmful side-effects and sub-therapeutic levels at other times. Sustained release tablets can smooth these fluctuations leading to better control of the patient's illness or symptoms.<sup>8</sup>

Matrix tablet can be made by mixing the drug with suitable excipients (non-active components of the formulation) and compressing the mix in a die at high pressure thereby producing a tablet. Excipients are added to tablets for various reasons. Some are diluents to increase bulk and aid compaction. Others help in manufacture, for example lubricants and flow enhancers while others influence the behaviour of the tablet in water, For example disintegrants added to standard tablets making them break-up when placed in water, are not used in sustained release tablets designed to remain intact. Excipients vary in their physical properties such as water solubility and mechanical properties.<sup>8</sup>

An important excipient in sustained release matrix tablets is the agent to control the drug release. Broadly, either lipids such as fats and waxes or polymers are used. Some polymers, such as hydrogels swell on exposure to water and create a rate-controlling gelatinous layer around the SR tablet. Other polymers, as used in the tablet do not swell markedly but create a matrix through which water can penetrate to dissolve the drug particles and any water soluble excipient particles. The dissolved particles then exist as molecules which diffuse down the concentration gradient, through the water filled pores to be released from the tablet. Several of the authors have been studying matrix tablets made by mixing drug with a polymer and one additional excipient, either lactose a water soluble brittle excipient whose particles might fracture during compression or mannitol a water soluble plastic excipient whose particles plastically deform during compression. Other factors can potentially affect certain characteristics such as the hardness or sustained release behaviour of the tablet includes the particle size of the excipients, proportions of ingredients, compression force and post-compression thermal treatment. This factor can change the tablet porosity due to coalescence of polymer particles to form a coherent polymer network. The amount of drug in the tablet is determined by the total dose to be given to the patient. However, the proportions of the excipients vary with their function and the specific tablet formulation. For example, a lubricant such as magnesium stearate might be used at a 1% level, whereas the level of a rate-controlling polymer would be much higher (10-50%) but preferably the level would be kept as low as possible for cost reasons.<sup>8</sup>

When such matrix tablets are placed in water or in the intestinal fluid of the patient, the coherent polymer matrix sustains the release of the drug by keeping the tablet largely intact and by providing a tortuous network through which water penetrates and dissolving the drug

and soluble excipient molecules diffuse out. That is the postulated release mechanism involves penetration of fluid, dissolution of the drug and soluble excipient in the fluid and outward diffusion of molecules of dissolved drug due to the concentration difference between the solution in the tablet and the intestinal fluid. Once released from the tablet, the drug is rapidly absorbed through the patient's intestine into the blood stream. Ideally the delivery rate of the drug from the tablet should be such as to maintain the preferred blood level for an extended time.<sup>8</sup>

Matrix tablets are the type of controlled drug delivery systems which release the drug in continuous manner by dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs which are having different solubility properties, the drug is either dispersed in swellable hydrophilic substances or an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials.<sup>2</sup>

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact a matrix is defined as a well mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed. Intense research has recently focused on the designation of SR systems for poorly water soluble drugs.<sup>9</sup>

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), xanthan gum, sodium alginate, polyethylene oxide and cross-linked homopolymers and copolymers of acrylic acid. It is usually

supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface.<sup>9</sup>

***Advantages of matrix tablet:***

- Easy to manufacture.
- Versatile, effective and low cost.
- Can be made to release high molecular weight compounds.
- Maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in therapy.
- Improvement the bioavailability of some drugs.

***Disadvantages of matrix tablet:***<sup>6,7</sup>

- Chances of dose dumping may occur.
- Less flexibility in acute dose adjustment.
- Poor *in vitro*- *in vivo* correlation.
- In case of accidental failure of the product, effective antidote may be difficult to employ.
- Sustained release medication should not be used with person known to have impaired or erratic gastrointestinal absorption or kidney troubles.
- Drugs having long biological half life are not suitable for presentation in sustained release form.
- Problem in case of elderly people.
- Administration of sustain release medication do not permit the sudden termination of therapy in case of an adverse effect.
- Reduced potential for dosage adjustment of drugs normally administered in varying strength.
- Retrieval of drugs is difficult in case of toxicity or hypersensitive reaction.
- Economic factor should also be considered since costly processing and equipment are involved in manufacturing many sustain release form.

## CLASSIFICATION OF MATRIX TABLETS:

### *On the basis of retardant material used:*

#### **(A) Hydrophobic matrices (Plastic matrices):**

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. 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, acrylate polymers and their copolymers. The rate controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

#### **(B) Lipid (Fat-wax) matrices:**

Lipids are molecules made up of the elements carbon, hydrogen and oxygen but in different proportions to carbohydrates. The most common type of lipid is the triglyceride. Lipids can exist as fats, oils and waxes. Fats and oils are very similar in structure (triglycerides). Examples include fat, waxes, certain vitamins, hormones, and most of the non-protein membrane of the cells. They are non-polar in nature, thus soluble in non-polar environments like chloroform but not soluble in water.

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

Example of lipid matrices : Fatty acids, Natural oils and fats, Semi-synthetic mono, di, and triglycerides, Semi-synthetic polyethylene glycol (PEG) derivatives of glycerides and fatty acids, Polyglyceryl fatty acid esters, Cholesterol and phospholipids.

Example of lipid excipients : Precirol ATO 5, Compritol ATO 888, Peceol, Maisine 35-1, Imwitor 988, Akoline MCM, Capmul MCM, Labrasol, Gelucire 44/14 and 50/13, Cremophol EL.

**(C) Hydrophilic matrices:**

Hydrophilic matrices used in preparation of matrix tablet are hydroxyethylcellulose, hydroxypropylcellulose, polymer of acrylic acid, hydroxypropylmethylcellulose, Na CMC, methylcellulose etc.

**(D) Biodegradable matrices:**

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process into 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 polyesters and poly anhydrides.

**(E) Mineral matrices:**

These consist of polymers which are obtained from various species of seaweeds. Example is alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophyceae) by the use of dilute alkali.

**MECHANISM OF DRUG RELEASE FROM MATRIX TABLET**

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

- a) A pseudo-steady state is maintained during drug release,
- b) The diameter of the drug particles is less than the average distance of drug diffuse through the matrix,
- c) The bathing solution provides sink conditions at all times.

The release behaviour for the system can be mathematically described by the following equation:

$$dM / dh = C_o \cdot dh - C_s / 2 \dots\dots (1)$$

Where,

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

dh = Change in the thickness of the zone of matrix that has been depleted of drug  
 $C_o$  = Total amount of drug in a unit volume of matrix

$C_s$  = Saturated concentration of the drug within the matrix

Additionally, according to diffusion theory:

$$dM = ( D_m \cdot C_s / h ) dt \dots\dots (2)$$

Where,

$D_m$  = Diffusion coefficient in the matrix. h = Thickness of the drug-depleted matrix  
dt = Change in time

By combining equation 1 and equation 2 and integrating:

$$M = [ C_s \cdot D_m ( 2 \cdot C_o - C_s ) t ]^{1/2} \dots\dots (3)$$

When the amount of drug is in excess of the saturation concentration then:

$$M = [ 2 \cdot C_s \cdot D_m \cdot C_o \cdot t ]^{1/2} \dots\dots (4)$$

Equation 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores.

The volume and length of the openings must be accounted for the drug release from a porous or granular matrix:

$$M = [ D_s \cdot C_a \cdot p / T \cdot ( 2 \cdot C_o - p \cdot C_a ) t ]^{1/2} \dots\dots (5)$$

Where,

p = Porosity of the matrix t = Tortuosity

$C_a$  = Solubility of the drug in the release medium

$D_s$  = Diffusion coefficient in the release medium

T = Diffusional path length

For pseudo steady state, the equation can be written as:

$$M = [2.D.C_a .C_o (p / T) t]^{1/2} \dots\dots (6)$$

The total porosity of the matrix can be calculated with the following equation:

$$p = p_a + C_a / \rho + C_{ex} / \rho_{ex} \dots\dots (7)$$

Where,

p = Porosity of the matrix

$\rho$  = Drug density

$p_a$  = Porosity due to air pockets in the matrix

$\rho_{ex}$  = Density of the water soluble excipients  
 $C_{ex}$  = Concentration of water soluble excipients

For the purpose of data treatment, equation (6) can be reduced to:

$$M = k. t^{1/2} \dots\dots (8)$$

Where k is a constant, so the amount of drug release vs. square root of time will be linear, the release of drug from matrix is diffusion controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer system forming the matrix
- Solubility of the drug.

#### MANUFACTURE METHOD FOR MATRIX TABLET: <sup>1</sup>

The process used to prepare matrix tablet can be classified into four major groups: direct compression, dry granulation, hot melt extrusion and wet granulation.

### **Direct compression:**

This process has been used since 1950 especially in process development. The drug and other excipients used to make a compressible mass are mixed and then compressed. The advantages are simplicity of the process saving a lot of steps compared to other process and it is cheap and fast. Furthermore the process is recommended for formulation containing the drug that could be affected by temperature and humidity for increasing their stability. Another advantage is from point of view of documentation. The reduced amount of equipment involved in a process like this reduced validation and other documentation. One of the disadvantages of this process is bad flow property and compressibility of drugs. The difference in particle size of different component of the formulation can lead to segregation of the mixture. This is one of the factors that can directly affect the release of drug.

### **Dry granulation:**

Dry granulation is a process where powder mixture is compacted by a compression process and followed by a milling process. The process is characterized by low energy and cost requirement and shorter procedure time compared to wet granulation. It is used for those drug and excipients that are sensitive to humidity and/or heating. Furthermore the elaboration of granules by compaction and afterword compression increases the disintegration time of the produced tablet. Also the percentage of fine produced during the process is also high. If the percentage exceeds 10-15% a repetition of the compaction is necessary.

### **Hot melt Extrusion:**

In this method drug and excipients are melted together and forced through an orifice or a die producing a product called extrudate. One advantage is the absence of water especially when working with hydrophilic substances. The absence of organic solvents avoids the risk of explosion and cause fewer environmental problems. The easiness of the process makes it suitable for manufacturing of sustained release forms. One main factor providing sustained release properties is high density of the extrudate. Since this is a thermal process, the drying step involved in wet granulation is also deleted saving time and costs. A disadvantage of the process is the impossibility of using thermo sensitive drugs. The equipment used in this process is an extruder and it could be vertical and horizontal. Based on the screw it can be single or twin screw. The extruders have several barrels that can be heated independently. The mixing efficiency of the extruder is an advantage, having dispersive or distributive mixing properties. Therefore a homogeneous product is formed through this process.

### **Wet granulation:**

This process is most widely used even if require higher energy or costs. The drug and excipients get in contact with liquid with the aim of obtaining a homogeneous wet mass. This mass is passed through sieve to obtain granules. The flowability of powder mixture improves with this process. The particle size and distribution of the different component are homogeneous in each granule avoiding the segregation. Binders used during wet granulation can be among others, cellulose derivatives, starches, polysaccharide and synthetic polymers. The binders are added after approximately 2 minutes of mixing. After the binding liquid is added the wet mass can be sieved to obtain granules or it can be dried then granulated. The drying process can takes place on tray in drying oven, fluid bed, and vaccum and microwave devices.

### **MELT GRANULATION:**

Melt granulation is processes by which granules are obtained through the addition of either a molten binder or a solid binder which melts during the process. This process is also called melt agglomeration and thermoplastic granulation. The preparation of tablets by the melt granulation process was investigated to enhance chemical stability of a highly water-soluble drug substance that is susceptible to degradation in presence of moisture. Melt granulation with a lipophilic binder improved the stability of the drug, while still maintaining immediate-release characteristics of the drug product. The drug to binder ratio was shown to impact the degradation behavior of the drug product. With higher binder levels, the sensitivity of the drug to degradation under humidity conditions decreased. It is postulated that the lipophilic binder coated drug particles at the surface protecting them from the influence of moisture. There is no need of drying steps because dried granules are obtained by cooling it to room temperature. Moreover amount of liquid binder can be controlled precisely and the production and equipment costs are reduced. This method can be used for granulating water sensitive material and producing sustained release granulation.

### **EVALUATION**

**Evaluation of granules:** The granules obtained by melt granulation were characterized by carrying out particle size distribution by sieve analysis and by IR to study the drug-binder compatibility. The results are shown in figure no. 1 to 4. The granules were also evaluated for angle of repose, bulk density, compressibility index and Hausner's ratio to check the flowability.

### **EVALUATION OF TABLETS**

**Weight variation test:** To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Adventure OHAUS) and the test was performed according to the official method.

### **Thickness**

Thickness and diameter of tablets was determined using calibrated Vernier caliper. Five tablets from each batch were used, and their average values calculated.

### **Friability**

For each formulation, the friability of 20 tablets was determined using the Roche friabilator (Lab Hosp.). This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed 20 tablets was placed in Roche friabilator, which was then operated for 100 revolutions for 4 minutes. The tablets were then dusted and reweighed.

### **Hardness:**

For each formulation, the hardness of 6 tablets was determined using calibrated Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm<sup>2</sup>. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm<sup>2</sup>.

### **Drug content:**

Five tablets were weighed individually, and these tablets were crushed in mortar. Powder was taken, to distilled water was added. The mixture was heated to melt (as per melting point of meltable binders) and allowed to cool to room temperature. The lipid was solidified and drug solution was filtered through Whatmann No.1 paper. The absorbance was measured after suitable dilution. The drug content was determined.

### ***In vitro* Dissolution Studies:**

*In vitro* drug release study for the prepared matrix tablets using a six-station USP XXIII type II (paddle) apparatus at 37°C ± 0.50°C and 50 rpm speed. The dissolution studies were carried in acid buffer of pH 1.2 and then in Phosphate buffer pH 7.4, under sink condition. At first half an hour and then every 1- hour interval samples of 5 ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at specific wavelength(nm) for drug by a UV-spectrophotometer. The amounts of drug present in the samples were calculated with the help of appropriate calibration curve constructed from reference standard. Also the *in vitro* drug release study for the marketed tablets was conducted.

BRAND NAME	DRUG NAME
Glumet	Metformin
Nikoran	Nicorandil
Claritin	Loratadine
Zyprexa	Olazapine
Feldene	Piroxicam

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