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DEVELOPMENT AND CHARACTERIZATION OF RELEASE PROFILE OF NIFEDIPINE AS AN EFFECTIVE CONTROLLED RELEASE SYSTEM BY USING PROPORTION OF VARIOUS AMOUNT OF HPMC WITH DIFFERENT PARTICLE SIZE OF NIFEDIPINE WITH COST BENEFIT POINT OF VIEW

PRIYA TOLIA, MITUL PATEL, HIREN BHAGAT
Arihant School of Pharmacy & Bio Research Institute, Gujarat, India.
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Abstract: Biopharmaceutics Classification System (BCS) class II drugs exhibit low solubility and high permeability characteristics. Nifedipine is a calcium channel blocker of the dihydropyridine type which is mainly used for the treatment of hypertension and angina pectoris. Nifedipine is a suitable candidate for CR administration due to its short elimination half-life of 2-4 hrs, its rapid and complete drug absorption over the entire gastrointestinal tract, despite its low water solubility and the relationship between 3drug plasma concentrations and blood pressure reduction. The importance of reduced peak plasma levels in order to avoid adverse effects such as reflex tachycardia has also been demonstrated.As having low solubility of Nifedipine the paticle size affected in release profile of Nifedipine. Proportion of various amount of HPMC with different particle size of Nifedipine having cost benefit.

Keywords: Ophthalmic, in-situ, osmalirity, precorneal**.**

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Corresponding Author: MS. PRIYA TOLIA

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INTRODUCTION

1.1Conrtolled drug delivery system An oral drug delivery system providing a uniform drug delivery can only partly satisfy therapeutic and biopharmaceutical needs, as it doesn't take into account the site specific absorption rates within the gastrointestinal tract, therefore there is need for developing delivery system that release the drug at right time, at the specific site and with the desired rate[1-2].

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 through 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.[3]

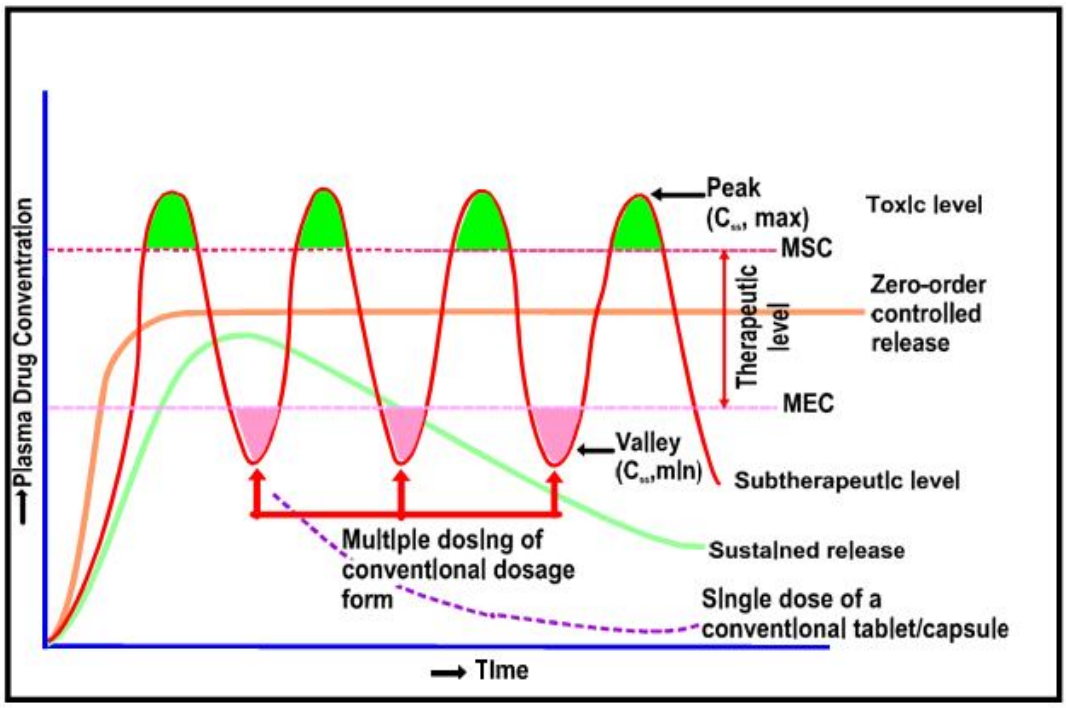

Figure 1.1 Plasma drug concentration profile for conventional tablets or capsule formulations & zero order controlled release formulation

To supply drug at the right site means on one hand to deliver locally effective drugs, like antibiotics, anti-inflammatory drugs or cryostatic agents at their target site and on the other hand to release drug with restricted absorption window like Digoxin, Ampicillin, Cefuroxime

axetil etc. To supply drug substances at the right time means to avoid constant plasma levels for drug that develop tolerance like organic nitrates or have biorhythmic dependent action profiles like corticosteroids or antiasthamatic drugs. In this case drug delivery system must ensure altering drug free and effective plasma levels .Drug absorption at the desired rate means, first to reach the effective plasma level within an acceptable short time period, second, to avoid an over shoot in the case of rapidly absorbed drugs and third to maintain effective plasma levels over the desired time period. Although the intensity of pharmacological effect is related to the drug concentration at the site of action, which is in turn, related to the plasma drug concentration, an ideal situation is obtained when the concentration is continuously maintained between minimum effective and maximum safe levels (Therapeutic index). [4]

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 sustained drug levels and hence therapeutic action. 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. With a controlled release formulation a predictable and reproducible release rate can be achieved at the target site for desired duration. 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. The use of controlled release technology in the formulation of pharmaceutical product is becoming increasingly important. Controlled drug delivery involves the application of physical and polymer chemistry to produce well characterized and reproducible dosage forms which control drug entry into the body within the specifications of the required drug delivery profile. In this type of dosage forms the rate of drug release is mainly controlled by the delivery system itself though it may be influenced by external conditions such as pH, enzymes, ions, motility and physiological conditions.[3-4]

1.1.1 Advantages of controlled release drug delivery system:[5-6]

- Avoid patient compliance problems.
- Employ less total drug.
- Minimize or eliminate local side effects.
- Minimize or eliminate systemic side effects.
- Obtain less potentiation or reduction in drug activity with chronic use.
- Minimize drug accumulation with chronic dosing.

- Improve efficiency in treatment.
- Cures or controls conditiomore promptly.
- Improves control of condition (i.e. reduced fluctuation in drug level).
- Improves bioavailability of some drugs.
- Economical (i.e. reduction in health care costs). The average cost of treatment over an extended time period may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

1.1.2 Limitations of controlled release drug delivery system: [5-6]

- Decreased systemic availability in comparison to immediate release conventional dosage forms which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
- Poor *in vitro-in vivo* correlation.
- Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus increased risk of toxicity.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
- High formulation cost.
- More rapid development of tolerance.

1.1.3 Various approaches to achieve controlled release drug delivery: [5-8]

Mechanisms of drug release from oral controlled delivery systems can be broadly divided into following categories:

A) **Dissolution controlled release**

(a) Matrix dissolution control

(b) Reservoir dissolution control

B) Diffusion controlled release

(a) Matrix diffusion control

(b) Reservoir diffusion control

C) **Osmotic controlled release**

D) **Ion exchange resins**

E) **Gastro retentive systems**

F) **Regulated systems**

A) ***Dissolution controlled release*****:**

Dissolution controlled release can be obtained by slowing down the dissolution rate of a drug in the GI medium incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness.

(b) Reservoir dissolution control:

In reservoir dissolution controlled system the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose derivates, polyethylene glycols, polymethacrylates, waxes etc. The resulting reservoirs (coated beads, multiparticulate system, pellets) may be filled as such in hard gelatine capsules (Spansules) or compressed into tablets.

The common multiparticulate systems are microparticles (microspheres or microcapsules), nanoparticles (nanospheres or nanocapsules) and liposomes.

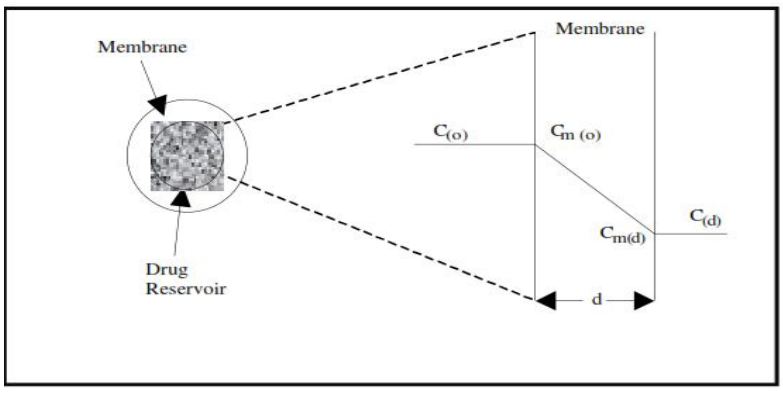

Figure1.3: Schematic representation of dissolution controlled drug release reservoir system

B) Diffusion controlled release:

Diffusion of a drug molecule through a polymeric membrane forms the basis of this controlled drug delivery system. Similar to the dissolution controlled devices these are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix.

(a) Matrix diffusion control:

Matrix devices are very common because of ease of fabrication. Diffusion controlled involves dispersion of drug in either water insoluble or a hydrophilic polymer. Drug

[C] **Osmotic controlled release:**

Oral osmotic pump popularly known as ORAS® based on principle of osmotic pressure to release the drug at constant rate. The rate of drug release from the products is determined by the constant in flow of the water across semi permeable membrane into reservoir which contains osmotic agents. The drug is either mixed with the agent or is located in the reservoir. The dosage form contains a small hole from which the dissolved drug moves out at a rate determined by the rate of entrance of water due to osmotic pressure. The rate of release is constant and can be controlled within tight limits yielding relatively constant blood concentrations. The advantage of this type of product is that the release is unaltered by the environment of the GIT and it relies simply on the passage of the water into the dosage form. Altering the osmotic agent and the size of the hole can modify the rate of release.

[D] Ion exchange resins:

Drugs can be bound to ion exchange resins and when ingested, ionic environment within the GIT determines the release of the drug. The drug is released slowly by diffusion mechanism from the resins particle structure.

[E] Gastro retentive systems:

Variability in GI transit time is a concern for oral controlled drug delivery system. Drugs with a narrow absorption window in the GI tract are particularly susceptible to variation in both bioavailability and times to achieve peak plasma levels. Gastro retentive controlled release formulations could offer a potential solution to the problem by offering a prolonged gastric residence time. Gastro retentive delivery

Systems (GRDS) are beneficial for such drugs by improving their bioavailability, therapeutic efficacy and by reduction of dose. Apart from these advantages, these systems offer various pharmacokinetic advantages like maintenance of constant therapeutic levels over a prolonged

period. This would lead to reduction in fluctuation in therapeutic levels and therefore minimizing the risk of resistance especially in case of antibiotics. Gastrointestinal retention depends on many factors such as density of the dosage form, size of the dosage form, fasting and fed condition, nature of the meal taken, sleep, posture etc. It also depends strongly on a complicated and unpredictable gastric emptying with migrating myoelectric complex motility of the stomach. Various delivery systems like floating, swellable, mucoadhesive, high-density formulations etc. have been developed to achieve gastro retention.

[F] Regulated systems:

These devices are capable of releasing therapeutic agents by well defined kinetics and have significant improvement over conventional controlled release systems. In these devices drug output is adjusted in response to a physiological need. Regulated systems can be classified into two types i.e. one is externally regulated system and the other is self regulatory system. Externally regulated devices can alter their drug output only in response to an intervention externally. For example, control of diabetes is achieved by delivering insulin in response to blood glucose levels. While self regulated devices can act without external intervention. The response to changes in temperature or pH within the system leads to drug release. An example of this type of system is insulin release from pH sensitive polymers. This approach utilizes pH changes resulting from the conversion of glucose to gluconic acid by glucose oxidase. Increase in glucoronic level would reduce the pH which leads to erosion of polymer and insulin release.

1.2 Matrix Drug delivery System:

These are the type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials[7].

Moreover drug release from matrix tablet depends on other factors such as pore permeability, shape and size of matrix, drug solubility, polymer molecular weight, drug loading, compression force and hydrodynamic conditions. The compression force has major control over the porosity which directly influences the release characteristics of the tablet. Drug solubility, hydrophilicity of the polymer and tablet porosity determines the rate of liquid penetration into the tablet and thus influences drug release rate. It has been found that pore size distribution of the matrix and the permeation pressure of the release media are defined by its surface tension and contact angle.[8]

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.[8]

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 control 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.[9]

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 those systems which release their active principle at a predetermined rate. [9]

Controlled release also called sustained/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. [10]

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 behavior 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.

An important excipient in sustained release matrix tablets is the agent to control the drug release.

1.2.1Advantages of matrix tablet: [7 –]

- 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 change in gastrointestinal tract.
- Minimize the local and systemic side effects. Improvement in therapy.
- Improvement the bioavailability of some drugs. 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.

1.2.2 Classification of matrix tablets:

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

(A) Hydrophobic matrices (Plastic matrices):

(B) Lipid (Fat-wax) matrices:

(C) Hydrophilic matrices:

Hydrogel based drug delivery systems are classified as:

Diffusion controlled release system:

(A) Reservoir system:

(B) Matrix system

(A) Reservoir system:

It consists of polymeric membrane surrounding a core containing the drug. The rate limiting step for drug release is diffusion through the outer membrane of the device.

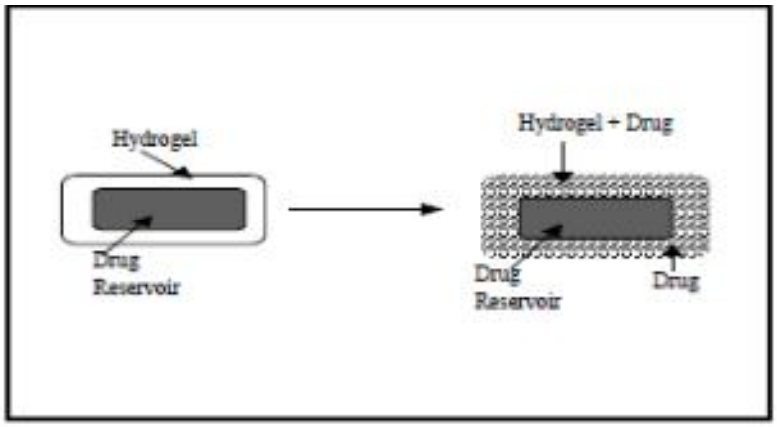

Figure 1.4: Hydrogel formation in reservoir systems

(B) Matrix system

The drug is dispersed throughout the three dimensional structure of the hydrogel. Release occurs due to diffusion of the drug throught out the water filled pores.

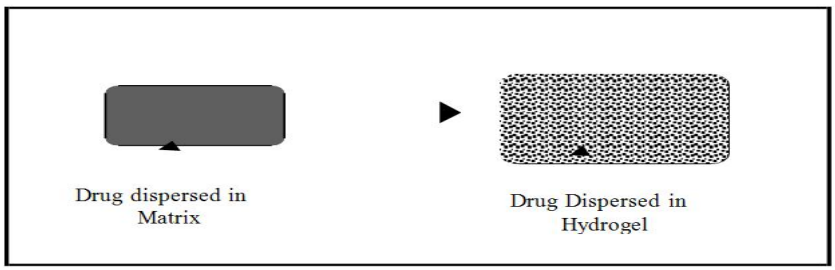

Figure1.5: Hydrogel formation in Matrix System

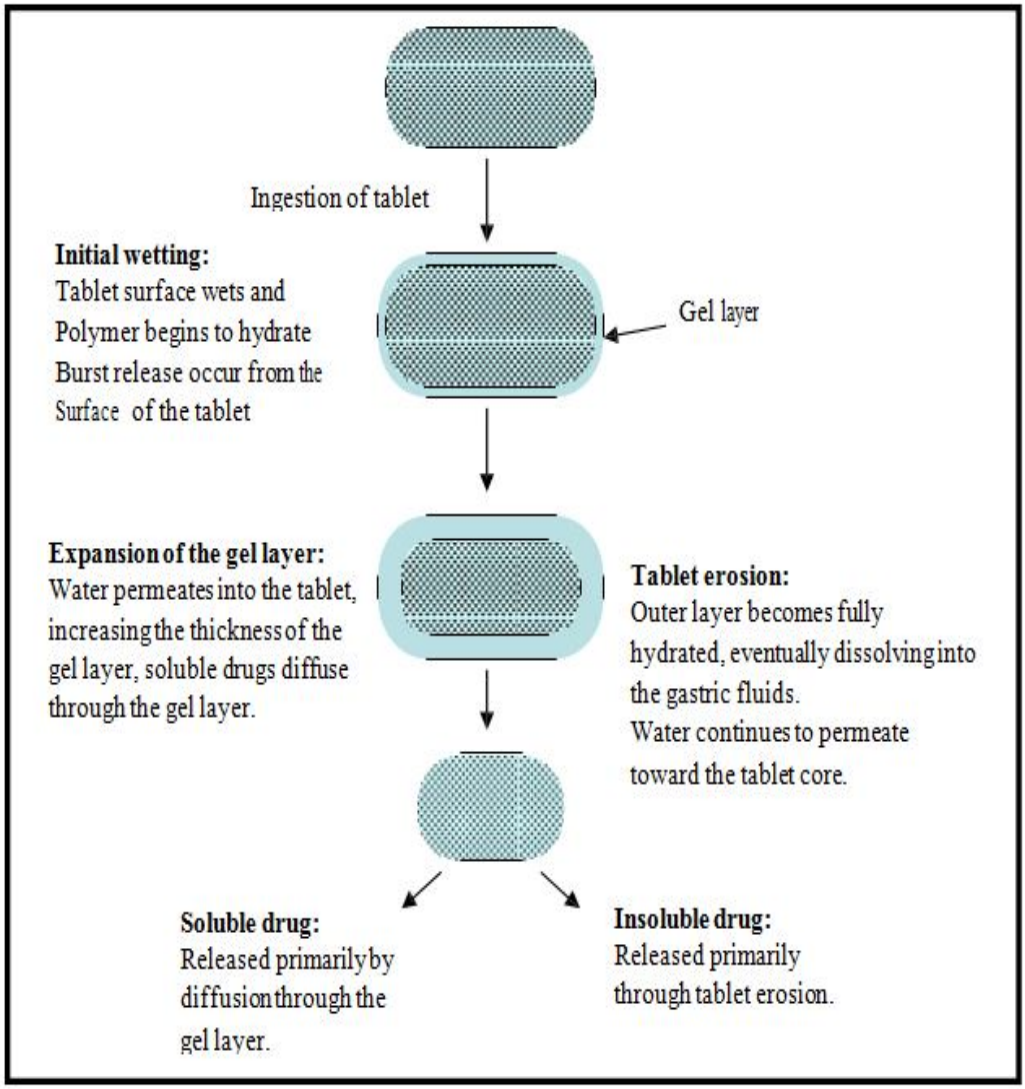

Figure 1.6: Drug release from hydrophilic matrix tablet

Types of matrix system: [14]

I. **Swellable controlled release system**

II. **Non swellable controlled release system**

On the basis of porosity of matrix: [7, 11]

Matrix system can also be classified according to their porosity into macro porous, micro porous and non-porous system.

(A) Macro porous systems:

(B) Micro porous system:

(C) Non-porous system:

1.2.3 Mechanism of drug release from matrix tablet*:* [7, 11]

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.

1.2.4 Factor affecting drug release from matrix tablet: [11,15]

***Biological factors*:**

I. Biological half-life

II. Absorption

III. Metabolism

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. Propentheline and probanthine are representative example of such drug.

1.2.5 Manufacture method for matrix tablet: [16]

The process used to prepare matrix tablet can be classified into four major groups:

Direct compression, dry granulation, hot melts extrusion and wet granulation.

1.3 :Proportion of various amount of HPMC with different particle size of Nifedipine

HPMC is one of the most widely used hydrophilic polymer having GRAS regulatory status and easily available in all the grades. Mostly HPMC is used for the preparation of SR/CR formulations in industry. Biopharmaceutics Classification System (BCS) class II drugs exhibit low solubility and high permeability characteristics. Their oral absorption is mostly governed by *in vivo* dissolution; the solubility and the dissolution rate are therefore key determinants for the oral bioavailability of these drugs. This implies that a small increase in the dissolution rate will result in a multifold increase in bioavailability.

Nifedipine is a calcium channel blocker of the dihydropyridine type which is mainly used for the treatment of hypertension and angina pectoris. Nifedipine is a suitable candidate for CR administration due to its short elimination half-life of 2-4 hrs, its rapid and complete drug absorption over the entire gastrointestinal tract, despite its low water solubility and the relationship between drug plasma concentrations and blood pressure reduction. The importance of reduced peak plasma levels in order to avoid adverse effects such as reflex tachycardia has also been demonstrated. Conventional tablets need to be administered three to four times a day and controlled release formulations of nifedipine would be effective in overcoming the dissolution limitation by slowing supplying the drug from the intact matrix base during its sojourn in the gastrointestinal tract and is thus expected to decrease side effects and improve patient compliance. A controlled release formulation of nifedipine has become available, [5] such as coated granules and matrix tablets. Due to low solubility of Nifedipine, particle size of Nifedipine effected in the dissolution profile & rate of drug release ,mechanism of release profile, kinetics of dissolution of formulation

CONCLUSION :

Zero order release kinetics as controlled release rate profile of Nifedipine can be achieved by using proportion of various amount of HPMC with different particle size of Nifedipine with cost benefit point of view.As Nifedipine is having low solubility & particle size of Nifedipine affected in dissolution rates and HPMC is easily avalabile in various grades.

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