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Matrix tablets an updated review: Pros and Cons

Dr. Gaurav Tiwari*, Dr. Ruchi Tiwari, Dr. Pranaywal, Ankita Wal, Chitranshu Gupta

Department of Pharmaceutics, Pranveer Singh Institute of Technology, Kalpi Road, Bhauti, Kanpur, U.P., India

ABSTRACT

Oral sustained release (SR) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetics and pharmacodynamic properties of drugs in such a way that it reduce dosing frequency to an extent that once daily dose is sufficient for penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion. Highly water soluble drugs like Diltiazem; Ranitidine has been formulated as sustained release matrix tablets. This article contains the basic information regarding design sustained release formulation and also the different types of the same. Developing oral sustained release matrix tablet with constant release rate has always been a challenge to the pharmaceutical technologist. Most of drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. Hydrophilic polymers have become product of choice as an important ingredient for formulating sustained release formulations.

Keywords: - Extended release, Therapeutic concentration, Patient convenience and compliance.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and Parental routes] that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe in respect to parentral route due to its ease of administration, patient acceptance, and cost effective manufacturing process. [1] Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:

***Corresponding Author:**
Dr Gaurav Tiwari
Dept. of Pharmaceutics,
Pranveer Singh Institute of Technology,
Kalpi Road, Bhauti, Kanpur, U.P. India
E.Mail: drgauravtiwari81@gmail.com
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1) Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs. 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. Controlled drug delivery systems: Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery.

CLASSIFICATION OF MATRIX TABLETS:

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

1. Hydrophobic Matrices (Plastic matrices)

The concept of using hydrophobic or inert materials as matrix materials was firs t 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 and acrylate polymers and their copolymers. The rate controlling step in these formulations is liquid penetration into the matrix. [2] 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.

2. Lipid Matrices

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.

3. Hydrophilic Matrices

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and

broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). 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]

4. 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 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.

5. 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 (Phaephyceae).

Advantages of Conventional Dosage Form

i) **Patient compliance**: Lack of compliance is mainly observed with chronic disease which required long term treatment, as success of drug therapy depends on the patient ability to comply with the drug treatment. Patient compliance is affected by a various factors, like knowledge of disease process, patient faith in treatment, and understanding of patient related to a strict treatment schedule. Also the complication of therapeutic regimens, the cost of therapy and local or systemic side effect of the dosage form. This problem can be resolved to some extent by administering sustained release drug delivery system.

ii) **Reduced 'see-saw' fluctuation**: Drug concentration in the systemic circulation and tissue compartments show ‘see saw’ pattern frequently when the drug administration in conventional dosage form. The magnitudes of

these fluctuations mainly depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' pattern is more prominent just in case of drugs with biological half-life less than four hours, since recommended dosing intervals are by the use of dilute alkali. [4]

Drawback of Conventional Dosage Form

1) Poor patient compliance: Chances of missing of the dose of a drug.

2) The unavoidable fluctuations of drug concentration may lead to under medication or over medication.

3) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of Drawback of conventional dosage form.

4) The fluctuations in drug levels which causes precipitation of adverse effects mainly the drug which having the small Therapeutic Index whenever over medication occur.

Advantages Sustained Release Dosage Form

i) Patient compliance:

Lack of compliance is mainly observed with chronic disease which required long term treatment, as success of drug therapy depends on the patient ability to comply with the drug treatment. Patient compliance is affected by a various factors, like knowledge of disease process, patient faith in treatment, and understanding of patient related to a strict treatment schedule. Also the complication of therapeutic regimens, the cost of therapy and local or systemic side effect of the dosage form. This problem can be resolved to some extent by administering sustained release drug delivery system.[5]

ii) Reduced 'see-saw' fluctuation:

Drug concentration in the systemic circulation and tissue compartments show ‘see saw’ pattern frequently when the drug administration in conventional dosage form. The magnitudes of these fluctuations mainly depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' pattern is more prominent just in case of drugs with biological half-life less than four hours, since recommended dosing intervals arerarely less than four hours. A well designed sustained release drug delivery system can widely reduce the frequency of drug dosing and also maintain a steady drug concentration in blood circulation and target tissue cells.

iii) Total dose reduction:

To treat a diseased condition less amount of total drug is used in Sustained release drug delivery systems. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.[6]

iv) Improvement of deficiency in treatment:

Optimal therapy of a disease requires an effective transfer of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A sustained release dosage form leads to better management of the acute or chronic disease condition.

v) Economy:

The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over an prolong period of time may be less

Disadvantages of sustained release dosage form:

A. Dose dumping: Dose dumping may occur with faulty formulation. [7]

B. Reduced potential for dose adjustment.

C. Cost is more than conventional dosage form.

D. Increase potential for first pass metabolism.

E. For proper medication patient education is necessary.

F. Possible reduction in systemic availability.

G. Poor in vivo and in vitro correlations

Criteria to be met to incorporate the drug into sustained release dosage form:

Some physicochemical parameters for the Selecting of the drug to be formulated in sustained release dosage form which mainly includes the knowledge on the absorption mechanism of the drug form the Gastro Intestinal (G.I.) tract. [8]

BIOLOGICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET:

A. Biological half-life: The simple theory of an oral SR formulation is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter into the blood circulation at almost the same rate at which it is eliminated. Each drug has its own characteristic related to elimination rate, which is the sum of all elimination processes, generally include metabolism, urinary excretion and all the process that permanently remove drug from the blood stream. Drugs with short half life are best candidate for Sustain release formulation. Drugs which having shorter half life less than 2 hours such as levodopa are poor candidates for SR Formulation. Drugs which having longer half life more than 8 hours are also poor candidate in SR formulation, since their effect is already sustained. Examples: Digoxin, Phenytoin. [9]

B. **Absorption**: The goal of forming a SR product is to control the release rate of drug is much slower than the rate of absorption. If we presume that the transit time of most drugs in

the absorptive areas of the GI tract is about 8-12 hours, the extreme half-life for absorption should be in the region of 3-4 hours; otherwise, the dosage form will pass out of the probable absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23h-1 to give 80-95% over this time period. So, it accepts that the absorption of drug should occur at a relatively uniform rate over the entire length of small intestine. If a drug is absorbed by active transport or transport is restricted to a specific region of intestine, SR preparation may be disadvantageous to absorption.

C. **Metabolism**: Decrease bioavailability from slow releasing dosage form shown by Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slow releasing dosage form. a drug which having poor water solubility can be formulated in Sustain release dosage form. For this, various techniques which are available for enhancing the solubility of the drug after the enhancing the solubility Sustain Release formulation is possible. But during this crystallization of the drug is possible when the drug is entering into the systemic circulation, should be prevented and one should be cautious for the prevention of the same. [10]

D. **Distribution**: The rate of elimination of drug is mainly depends upon the apparent volume of distribution. So drugs with high apparent volume of distribution, influence the rate of elimination of the drug, this drugs are consider to be a poor candidate for oral SR drug delivery system. E.g. Chloroquine.

E. **Protein Binding**: To achieve pharmacological response unbound drug concentration is important rather than bound drug concentration and all drug bound to some extent to plasma and or tissue proteins. Protein binding of drug which shows a main role in its therapeutic effect in spite of the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes SR drug delivery system is not required for this type of drug.

F**. Molecular size and diffusivity**: In several sustained release systems Drug must diffuse through a rate controlling membranes or matrix. Ability of a drug to diffuse through membranes, it's so called diffusivity (diffusion coefficient), is a role of its molecular size. An important influence upon the value of the diffusivity. 'D' in polymers is the molecular size for molecular weight of the diffusing species. [11]

G. **Margin of safety**: Safety of drug generally depends upon the therapeutic index, Larger the value of therapeutic index of a drug safer is the

drug. Drugs having less therapeutic index are generally poor candidates for oral SR drug delivery system.

POLYMERS USED IN THE MATRIX

The polymers most widely used in preparing matrix system include both hydrophilic and hydrophobic polymers

(A) Hydrophilic Polymers: Hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose(HPC), hydroxyl ethyl cellulose (HEC), Xanthan gum, Sodium alginate, poly(ethylene oxide), and cross linked homopolymers and co-polymers of acrylic acid.

(B) Hydrophobic Polymers: This usually includes waxes and water insoluble polymers in their formulation. [12]

(C) Waxes: Carnauba wax, bees wax, candelilla wax, micro crystalline wax, ozokerite wax, paraffin waxes and low molecular weight polyethylene.

(D) Insoluble polymers: ammoniomethacrylate copolymers (Eudragit RL100, PO, RS100, PO), ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate and latex dispersion of meth acrylic ester copolymers.

FACTORS AFFECTING DRUG RELEASE FROM MATRIX TABLETS

1. Swelling characteristics of polymers
2. Polymer erosion
3. Drug loading
4. Drug solubility

ADVANTAGES OF MATRIX TABLETS [13]

1. Easy to manufacture.
2. Versatile and effective.
3. It has low cost.
4. Can be made to release high molecular weight compounds.
5. Suitable for both non degradable and degradable systems.
6. No danger of dose dumping in case of rupture.
7. Can be fabricated in a wide range of sizes and shapes.

DISADVATAGES OF MATRIX TABLETS

1. The remaining matrix must be removed after the drug has been released.
2. The drug release rates vary with the square root of time.
3. Achievement of zero order release is difficult.
4. Not all drugs can be blended with a given polymeric matrix.
5. Water soluble drugs have a tendency to burst from the system.
6. Poor in vitro – in vivo correlation.
7. Possibility of dose dumping due to food, physiologic or formulation variables.

8. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

9. Reduced potential for dosage adjustment of drugs normally administered in varying strengths.

10. Stability problems.

11. Increased cost.

12. More rapid development of tolerance and counseling.

13. Need for additional patient education and counseling. [14]

EVALUATION OF SUSTAINED RELEASE TABLETS

Before marketing a sustained release product, it is must to assure the strength, safety, stability and reliability of a product by forming in-vitro and in vivo analysis and correlation between authors have discussed the evaluating parameters and procedures for sustained release formulations. [15]

A. In-Vitro Methods

These are:-

a. Beaker method

b. Rotating disc method

c. Rotating Bottle method

d. Rotating Basket method

e. Stationary Basket Method

f. Oscillating tube method

g. Dialysis method

h. USP dilution method us

B. In–Vivo Methods

Once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct in-vivo evaluation and establish in-vitro in-vivo correlation. The various in-vivo evaluation methods are. [16]

a. Clinical response

b. Blood level data

c. Urinary excretion studies

d. Nutritional studies.

e. Toxicity studies

f. Radioactive tracer techniques

C. Stability Studies:

Adequate stability data of the drug and its dosage form is essential to ensure the strength, safety, identity, quality, purity and in-vitro in-vivo release rates that they claim to have at the time of use. A sustained release product should release a predetermined amount of the drug at specified time intervals, which should not change on storage. Any considerable deviation from the appropriate release would render the sustained release product useless. The in-vitro and in-vivo release rates of sustained release product may be altered by atmospheric or accelerated conditions such as temperature & humidity. The stability programmes of a sustained release product include storage at both nominal and accelerated conditions such as temperature & humidity to ensure that the product will withstand these conditions. [17]

D. In vitro- In vivo Correlations:

The requirement of establishing good in-vitro invivo correlation in the development of sustained release delivery systems is self-evident. To make a meaningful invitro in-vivo correlation one has to consider not only the pharmaceutical aspect of sustained release drug delivery system but also the biopharmaceutics and pharmacokinetics of the therapeutic agent in the body after its release from the drug delivery system and also the pharmacodynamics of therapeutic agent at the site of drug action. A simple in vitro-in vitro relationship can be established by conducting in-vitro and in-vivo evaluations of a potential drug delivery system simultaneously to study and compare the mechanism and rate profiles of sustained drug release. When the in-vivo drug release mechanism is proven to be in good agreement with that observed in the in-vitro drug release studies, then in-vitro in-vivo correlation factor is derived. For capsule type drug delivery system the factor can be represented as: [18]

(Q/t) In-vivo Q= (Q/t) In-vitro

Where, Q/t = Rate of release

'Q' values are dependent profiles of drug delivery systems. upon the sites of administration and environmental conditions to which the animals are exposed during treatment (study)

The above relationship can be used for optimization of sustained release Levy has classified In-vivo-In-vitro correlation in to:

a] Pharmacological correlations based on clinical observations;

b] Semi-quantitative correlations based on blood levels or urinary excretion data;

c] Quantitative correlation arising from absorption kinetics. While most of the published correlations are of semi-quantitative nature, the most valuable are those based on absorption kinetics.

E. Bioavailability Testing:

Bioavailability is generally defined as the rate and extent of absorption of unchanged drug from its site of application to the general circulation. Bioavailability is defined in terms of a specific drug moiety, usually active therapeutic entity, which may be the unchanged drug or as with prodrug, for instance, a metabolite. In contrast, the term "absorption" often refers to net transport of drug related mass from its site of application into the body. Hence, a compound may be completely absorbed but only partially bioavailable as would occur, when low bioavailability is caused by incomplete absorption. Pharmaceutical optimization of the dosage form may be warranted to improve absorption characteristics of the drug and thereby also its bioavailability. Bioavailability studies are

ordinarily single dose comparisons of tested drug product in normal adults in a fasting state. A crossover design, in which all subjects receive both, the product and reference material on different days is preferred. Guidelines for clinical testing have been published for multiple dose studies. Correlation of pharmacological activity or clinical evidence of therapeutic effectiveness with bioavailability may be necessary to validate the single significance of sustained release claims. While single dose studies are usually sufficient to establish the validity of sustained release dosage form design; multiple dose studies are required to establish optimum dosing regimen. They are also required when difference may exist in the rate but not the extent of absorption. When there is excessive subject-to subject variation or when the observed sblood levels after a single dose are too low to be measured accurately. A sufficient number of doses must be administered to attain steady state blood levels. According to an extensive study of sustained release Theophylline products; for example, encapsulated forms showed less peaking during multiple dosing and therefore better control of blood level within the desired limits.

CONCLUSION

By the above discussion, it can be easily concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility. More over all these comes with reasonable cost. The dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance.

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Table 1: Characteristics of drug unsuitable for Peroral sustained release forms

Characteristic	Drugs
Not effectively absorbed in the lower intestine	Riboflavin, Ferrous salts
Absorbed and excreted rapidly short biological half-life<1hr	Penicillin G, Furosemide
Long biologic half life(>12 hr)	Diazepam, Phenytoin
Large dose required > 1gm	sulfonamide
Cumulative action and desirable side effect drug with low therapeutics indices	Phenobarbital, Digitoxin
Precise dosage titrated to individual is required	Anticoagulants, Cardiac glycosides

Table 2: Physicochemical parameters for drug selection

Parameters	Criteria
Moleicular size	< 1000 Daltons
Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability From all GI segments	release Should not be influenced by pH and enzymes

Table 3: Pharmacokinetic parameters for drug selection

Parameters	Comment
Elimination half-life	Between 2 to 8 hrs
Absolute bioavailability	Should be 75% or more
Absorption rate constant (Ka)	Must be higher than release rate
Apparent volume of distribution (Vd)	Larger Vd and MEC, Larger will be the required dose
Total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration (Css)	The lower Css and smaller Vd, the loss among of drug required
Toxic concentration	Apart the value of MTC And MEC safer the dosage form