Oral Sustained Release Formulation: Matrix Tablets

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ABSTRACT

Oral drug delivery is the most preferred route for the various drug molecules among all other routes of drug delivery, because ease of administration which leads to better patient compliance. So, oral sustained release drug delivery system becomes a very promising approach for those drugs that are given orally but having the shorter half life and high dosing frequency. Moreover, pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Hence Sustained release dosage forms are good option to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. Sustained release is also providing promising way to decrease the side effects of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body which will improves the therapeutic index of drug concentration. These systems requires numerous considerations, like drug suitability for sustained release dosage forms, techniques of fabrication, evaluation and factors affecting bioavailability of parent drug. Sustained release delivery systems offer numerous advantages when compared to conventional dosage form. These includes less dosage per day, reduced side effects, and improved patient compliance and convenience. In this article basic information regarding sustained release drug delivery system including formulation, evaluation and recent advancements are summarized. Matrix tablets are an interesting option when developing an oral sustained release formulation.

Introduction

A sustained dosage form is defined as any drug or dosage form modification that prolongs the therapeutic activity of drug. The primary objective of sustained drug delivery is to ensure safety and enhancement of efficacy of drug with improved patient compliance. This delivery system is increasingly being used in the treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above the minimum effective concentration and below the minimum toxic level for an extended period of time. Thus, sustained drug delivery results in optimum drug therapy with reduced frequency of dosing and reduced side effects. [1]

The first sustain release tablet were made by Howard Press in New Jerseys in the early 1950's. The first tablet release under his process patent were called nitroglyn and made under license by Key Crop in Florida. Sustain release, prolonged release, modified release, extended release or depot formulation are terms used to identify drug delivery system that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose .[2]

Sustained / Controlled release dosage forms cover a wide range of prolonged action formulation which provided continuous release of their active ingredient at a predetermined rate and for a predetermined time. The majority of these formulations are designed for oral administration; however, recently such devices have also been introduced for parentral administration, ocular insertion and for transdermal application. The most important objective for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance. [3] The concept of sustained or prolonged release of biologically active agents has been well appreciated and rationalized for decades. [4]

There are certain considerations for the preparation of sustained release formulations; if the active compound has a long half life, it is sustained on its own, if the pharmacological activity of the active is not directly related to its blood levels, if the absorption of the drug involves an active transport and if the active compound has a very short half life then it would require a large amount of drug to maintain a prolonged effective dose. Sustained release dosage forms that allow at least a twofold reduction in dosage frequency as compare to that drug presented as an immediate release form. Example controlled release and sustained release. [5]

Drawbacks of conventional dosage form [6,7,8]
- Poor patient compliance
- Increased chances of missing the dose
- Chances of under medication or over medication due to unavoidable fluctuations of drug concentration.
- Difficulty to attain steady state condition.
Plasma drug concentration fluctuations lead to precipitation of adverse effects

Advantages of SR formulations [2,7,9,10,11]
The sustained release formulations may maintain therapeutic concentration over prolonged periods.
- Sustained release formulations reduce dosing frequency of drugs.

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- The use of sustained release formulation avoids the high blood concentration.
- Sustained release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing down the drug absorption.
- Improvement of the ability to provide special effects.
- Minimize the local and systemic side effect.
- Enhancement of activity duration for short half life drugs.
- Improvement in treatment efficacy.
- Improve the bioavailability of some drugs.
- Improve the ability to provide special effects, e.g. morning relief of arthritis through bed dosing.

Disadvantages of SR formulations [2, 7, 9, 10, 11]

- High cost of preparation.
- In case of acute toxicity, prompt termination of therapy is not possible.
- Less flexibility in adjusting doses and dosage regimen.
- Sustained release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.
- The larger size of sustained release products may cause difficulties in ingestion or transit through gut.

Drug related factors affecting sustained release formulations [2, 6, 7, 9, 10, 11]

Physicochemical factors:

Aqueous solubility

Drugs with low water solubility are difficult to incorporate into sustained release mechanism. The lower limit on solubility for such product has been reported 0.1gm/ml. Drugs with extreme water solubility are equally difficult to incorporate in sustained release system because it is difficult to control release of drug from dosage form.

Partition coefficient

Drugs having lower partition co-efficient values less than the optimum activity are undesirable for oral SR drug delivery system.

Drug pKa and ionization at physiological pH

Only unionized drugs are absorbed and permeation of unionised drug is negligible. pKa range for acidic drug is around 3.0-7.5 and for basic drug is 7.0-11.0.

Drug stability

Drugs that are unstable in stomach, formulation systems that prolong delivery to the entire GI tract are beneficial. Drugs that are unstable in small intestine may demonstrate decreased bioavailability when administered in SR dosage form.

Molecular size and diffusivity

Drugs with large molecular size are poor candidate for oral SR delivery system because the ability of the drug to diffuse polymeric membrane is a function of its diffusivity. Diffusivity depends on size shape of the cavities of the membrane.

Protein binding

The pharmacological response of the drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Protein binding of drug plays a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma, increase biological half life and thus, such type of drug will release up to extended period of time. So there is no need to develop a SR formulation for such type of drug.

Mechanism and Site of absorption

Drugs absorbed by passive diffusion, pore transport and through over the entire length of GIT are suitable candidates for oral SR drug delivery system.

Dose Size

Drug having dose >0.5g is poor candidate for SR formulations. Thus those drugs are good candidate for SR formulations, which having small dose size.

Biological factors:

Absorption

The absorption behavior of a drug can affect its suitability as a sustained release product. The aim of formulating a sustained release product is to place a control on delivery system. It is essential that the rate of release is much slower than rate of absorption. If we assume the transit time of most drugs and device in the absorptive area of GI tract is about 8 to 12 hours, the maximum half life for absorption should be 3 to 4 hours. Drugs that are slowly absorbed or absorb with a variable absorption rate of elimination are poor candidate for oral SR formulation.

Distribution

The distribution of drugs in tissue can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue depending upon the course of drug disposition. Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral SR drug delivery system.

Metabolism

Drug which extensively metabolized is not suitable for SR drug delivery system. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption or first pass effect is poor candidate for SR delivery, since it could be difficult to maintain constant blood level e.g. levodopa and nitroglycerine.

Biological half life

The main target of an oral sustained release product is to maintain therapeutic blood level over an extended period. To implement this, drug must enter in the circulation approximately with the same rate at which it is eliminated. The elimination rate is quantitatively described by half life. Therapeutic compound with short half life are excellent candidate for SR preparations because this can reduce dosing frequency. A drug having biological half-life between 2-8hrs is best suited for oral SR drug delivery system. Because if biological half-life is <2 hrs the system will require unacceptably large rate and large dose, and if biological half-life is >8hrs, it is unnecessary to formulate SR formulation for this type of drug.

Margin of safety

Drugs with large therapeutic index are suitable candidate for oral SR formulation.

Plasma concentration response relationship

Drugs which having pharmacological activity independent of plasma concentration, are not suitable for oral SR drug delivery system, eg. Reserpine.

Concentration dependency on transfer of drug

For formulating a SR dosage form, drug should follow first order kinetics in transfer from one compartment to other.

Sustained release matrix tablets

One of the least complicated approaches to the manufacture of SR 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 retardant. [6]

Advantages of matrix system: [2]

Matrix systems have various advantages. Some of them are:

● Unlike other systems tablets based on matrix system can be manufactured using conventional processes and equipments.

● Development cost and time associated with the matrix system generally are viewed as variables, and no additional capital investment is required.

● Matrix system is capable of accommodating both low and high drug loading.

Limitations of matrix system:

● Matrix system lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. [7]

● For some products that require unique release profiles, more complex matrix based technologies are required. [2]

Types of matrix:

Matrixes are classified in following classes:

● Hydrophilic matrix system
● Hydrophobic matrix system
● Fat-wax matrix system

➢ **Hydrophilic matrix system**

Hydrophilic matrix can be utilized as a means to control the drug release rate. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic carriers. [6]

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell when in contact with aqueous solution and form a gel layer on the surface of the system. When the release medium is thermodynamically compatible with the polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer undergoes a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. [2] Polymers used in hydrophilic matrix system are hydroxyl propyl methyl cellulose, hydroxyl propyl cellulose, xanthan gum, carbopol 934 and alginates. [7]

➢ **Hydrophobic matrix system**

It is also called as plastic matrix system. The concept of using hydrophobic or inert material as matrix materials was first introduced in 1959. [6] This is the only system where the use of polymer is not essential to provide sustained drug release, although insoluble polymers are used. The primary rate controlling components of hydrophobic matrix are water insoluble in nature. These includes waxes, glycerides, fatty acids and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymer. [2] The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. As such diffusion of active ingredient from the system is the release mechanism and the corresponding release characteristic can be described by Higuchi equation known as square root of time release kinetics. [7] Hydrophobic matrix systems are of two types: [6]

a) Biodegradable matrices
b) Mineral matrices

➢ **Fat-Wax matrix system**

The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray drying technique. In the bulk congealing method, a suspension of the drug and melted fat wax is allowed to solidify and then comminuted for sustained release tablets. [7]

In this the mixture of active ingredients, waxy materials and fillers can also be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender and granulating with a solution of waxy material or other binders. [6]

Matrix system can also be classified according to their porosity and consequently, macro-porous, micro-porous and nonporous system can be identified as: [10]

Macro-porous matrix system

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

Micro-porous matrix system

Diffusion in this type of system occurs essentially through pores. For micro-porous systems, pore size ranges between 50-200A^0, which is slightly larger than diffusant molecules size.

Non-porous matrix system

These 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.

Drug release from matrix tablets [6,7]

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.

Polymers used in matrix tablets [6,7]

Following polymers are used to formulate sustained release matrix tablets and the effect of drug polymers on drug release are summarized in table 1.

Hydrogels

Polyhydroxyethyle methylacrylate (PHEMA)

Cross-linked polyvinyl alcohol (PVA) and Cross-linked polyvinyl pyrrolidone (PVP)

Polyethylene oxide (PEO) and Polyacrylamide (PA)

Soluble polymers

Polyethylene glycol (PEG)

Polyvinyl alcohol (PVA) and Polyvinyl pyrrolidone (PVP)

Hydroxypropyl methyl cellulose (HPMC)

Biodegradable polymers

Polylactic acid (PLA)

Polyglycolic acid (PGA)

Polycaprolactone (PCL)

Polyanhydrides

Polyorthoesters

Nonbiodegradable polymers

Polyethylene vinyl acetate (PVA) and Polyvinyl chloride (PVC)

Polydimethyl siloxane (PDS)

Polyether urethane (PEU)

Cellulose acetate (CA)

Ethyl cellulose (EC)

Mucoadhesive polymers

Polycarbophil and Polyacrylic acid

Methyl cellulose and Sodium carboxymethyl cellulose

Tragacanth and Pectin

Natural gums

Xanthan gum, Guar gum and Karaya gum

Table 1: Summarizes drugs, polymers and techniques used in sustained release tablets

DRUG	POLYMER	TECHNIQUE	CONCLUSION	REFERENCE
Valsartan	Guar gum, Pectin	Direct compression method	Guar gum was found better polymer for SR tablets as compared to pectin.	[12]
Venlafaxine Hydrochloride	Xanthan gum, EC, HPMC(K4M, K15M, K100M)	Direct compression method	Hydrophilic and hydrophobic polymer combination found to sustain the release for 24 hrs.	[13]
Lornoxicam	HPMC K4M, Carbopol	Direct compression method	HPMC K4M was found to give better SR than carbopol	[14]
Indomethacin	PVP K-30, EC, Eudragit L100, Cellulose acetate phthalate	Wet granulation method	On basis of drug release it was found that combination of cellulose acetate phthalate and Eudragit L100 sustained the release up to 14-16 hrs.	[15]
Metformin hydrochloride	HPMC K15M, HPMC K100M, SCMC	Wet granulation method	On basis of stability studies it was concluded that formulation containing 24% HPMC K100M and 3.13% SCMC is suitable for ER tablets.	[16]
Phenytoin Sodium	HPMC, CMC, PVP-K90	Co-Evaporation method	Formulation having HPMC was found to sustain the release upto 12 hrs and formulation having CMC and PVP-K90 control the release upto 8 and 6 hrs.	[17]
Lamivudine	HPMC, EC	Wet granulation method	Release study showed that drug release is highly influenced by HPMC grade.	[18]
Cephalexin	HPMC	Direct compression method	Prepared tablets were found to sustain the release upto 6hrs.	[19]
Lamotrigine	Eudragit L-30D, Methocel K4M, Methocel K100LV	Wet granulation method	In-vitro release of prepared tablets showed that combination of hydrophilic and hydrophobic polymer showed less release than alone.	[20]
Naproxen and Ranitidine hydrochloride	Methocel K4M, Methocel K15M	Direct compression	On the basis of evaluation results it was found that combined technique is more useful without using coating.	[21]
Indomethacin	HPMC-K4M, PEG 6000, Avicel PH-112, Ac-di-so	Direct compression	Prepared tablets showed sustained release upto 24 hrs.	[22]
5-amino salicylic acid	HPMC K15, Xanthan gum, MCC	Direct compression	Hydrophilic polymers can be used as an effective matrix former; to extend the release of 5- amino salicylic acid where coated matrix tablet remains intact in 0.1 N HCl for 2 hrs and showing 5 hrs lag time for effective colon targeting system.	[23]
Silymarin	Xanthan gum, Guar gum	Direct compression	Silymarin controlled release tablets were successfully prepared.	[24]
Losartan Potassium	HPMC, EC, Xanthan Gum	Wet granulation method	Formulation containing drug-polymer ratio 1:1.5 exhibited drug release pattern very close to theoretical profile. Release kinetics of the drug was decreased on increasing polymer ratio.	[25]
Cephalexin	HPMC 15cps	Direct compression	The dissolution result shows that on a higher amount of HPMC result in decrease drug release.	[5]
Pregabalin	HPMC K-100, PVP K-30, MCC (101 & 102)	Direct compression	In-vitro dissolution study reveals that above a particular concentration of MCC-101, HPMC K-100 and PVP K-30 are capable of providing sustained release.	[26]
Propanolol Hydrochloride	HPMC	Wet granulation method	Tablets which exhibit a combination of floatation and adhesion for prolonged release in stomach have been successfully developed.	[27]
Lornoxicam	HPMC (K4M, K15M, K1OOM)	Direct compression method	Formulation containing drug: HPMC K4M 1:1 ratio was found to be optimized formulation among all.	[28]

Table 2: Marketed Sustained Release Tablets

BRAND NAME	ACTIVE INGREDIENT(S)	MANUFACTURER
Pari-SR Tab	Proxitine HCl	Ipca, Mumbai
Gluconorm-SR Tab	Metformin HCl	Lupin, Baddi (HP)
Gabaneuron-SR Tab	Gabapentin and Methylcobalamin	Aristo, Baddi (HP)
Lithosum-SR Tab	Lithium Carbonate	Sun Pharma, J and K
Etomax-ER Tab	Etodolac	Ipca, Mumbai
Augmentin-XR Tab	Amixicillin and Potassium Clavulanate	Glaxosmithkline, Mumbai
Sentosa-ER Tab	Venlafaxine	Nicholas Piramal, Baddi (HP)
Embeta-XR Tab	Metoprolol Succinate	Intas, Ahemdabad
Venlor-XR Tab	Venlafexine HCl	Cipla Protect. Baddi (HP)
Carvidon-MR Tab	Trimetazidine HCl	Microlab, Banglore
Zetpol CR Tab	Carbemezapine	Sun Pharma, J and K
Gluconorm G Tab	Metformin HCl	Lupin, Baddi (HP)
Valprol-CR Tab	Metoprolol Succinate and Amlodipine	Intas, Ahemdabad
Intalith CR	Lithium Carbonate	Intas, Ahemdabad
Reolol-AM 25/5 Tab	Metoprolol Succinate	Ipca, Mumbai
Etura Tab	Etodolac	Dr'Reddy, Hydrabad
Vasovin-XL Tab	Nitroglycerine	Torrent, Ahemdabad
Sporidex-AF Tab	Cefalaxin	Ranbaxy, Ponta Sahib
Altiva-D Tab	Fexofenadine HCl and Pseudoephidrine sulphate	Sidmak
Glycomet-1GM Tab	Metformin HCl	USV, Mumbai
Licab-XL Tab	Lithium Carbonate	Torrent, Ahemdabad
Metocontin Tab	Metoclopromaide HCl	Modi-Mundi Pharma, Meerut
Fecontin-F Tab	Ferrous glycine sulphate and Folic acid	Modi-Mundi Pharma, Meerut
Diucontin-K 20/250 Tab	Furosemide	Modi-Mundi Pharma, Meerut
Unicontin-E Tab	Theophyllin	Modi-Mundi Pharma, Meerut
Wellbutrin-XL Tab	Biproprion HCl	Glaxosmithkline, Mumbai
Revolol-XL tab	Metoprolol Succinate	Ipca, Mumbai
Metaride Tab	Glimipiride and Metformin HCl	Unichem, Mumbai
Glizid-MR Tab	Gliclazide	Panacea Biotech, Lalru(CHD)
Metzok Tab	Metoprolol Succinate	USV, Mumbai
Tegritol-CR Tab	Carbemezapine	Novartis, Goa
Supermet-XL Tab	Metoprolol Succinate	Piramal Healthcare, Baddi (HP)
Diva-OD Tab	Divalproex Sodium	Intas, Ahemdabad

Evaluation of Sustained Release Tablets [2, 7, 9]

To design a tablet and later monitor its quality, quantitative evaluation and assessment are done on the basis of its physical, chemical, and pharmacokinetic properties. Various authors have discussed the evaluating parameters and procedures for sustained release tablets. Evaluation of tablets can be classified in three steps:

- *In-vitro* methods
- *In-vivo* methods
- Stability studies

➢ ***In-vitro* methods**

These are:-
a) Beaker method
b) Rotating disc method
c) Rotating bottle method
d) Stationary basket method
e) Oscillating tube method
f) Dialysis method
g) USP dissolution method

➢ ***In-vivo* methods**

Once the satisfactory *in-vitro* profile is achieved, it becomes necessary to conduct *in-vivo* evaluation and establish *IVIVC*. Various methods are used for *in-vivo* evaluation. These are as follows:
a) Clinical response
b) Blood level data
c) Urinary excretion data

d) Nutritional studies
e) Toxicity studies
f) Radioactive tracer techniques

➢ **Stability studies**

Adequate stability data of the drug and dosage form is essential to ensure the strength, safety, identity, quality, purity and in-vitro in-vivo release rates that they have claim to have at the time of use. The stability programmes of a sustained release tablet include storage at both nominal and accelerated conditions such as temperature and humidity to ensure that the product will withstand these conditions. [9]

Various sustained release tablets available in the market are summarized in table 2.

Conclusion

It can be easily concluded that sustained release formulations are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility. 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. A number of drugs are now marketed in a variety of different sustained release products. The market for sustained release drug delivery has come a long way and will continue to grow. There are varied technologies for manufacturing sustained release tablets with significant advantages and some limitations. To be a successful sustained release product, the drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal

residence time, and absorbed at rate which replace the amount of drug being metabolized and excreted.

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