International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-2, 2015 ISSN No: 2277 - 7873

REVIEW ARTICLE

A Review on Sustained Release Oral Drug Delivery System

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Manuscript No: IJPRS/V4/I2/00112, Received On: 29/05/2015, Accepted On: 08/06/2015

ABSTRACT

The advantage of administering a single dose of a drug that is released over an extended period of time instead of numerous doses is now a day's area of interest for formulation scientists in Pharmaceutical industry. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, maximum utilization of the drug, increased safety margin of potent drug, reduction of fluctuation in steady-state drug levels, reduction in healthcare costs through improved therapy and shorter treatment period. Sustained release drug delivery system mainly classified into continuous release, delayed release and delayed transit and continuous. The matrix controls the release rate of drug. The matrices used may be of hydrophilic, hydrophobic, mineral, or biodegradable types. The drug release rate can be studied by *in-vitro* dissolution studies.

KEYWORDS

Sustained Release, Matrix Tablet, Polymers, Diffusion

INTRODUCTION

The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and/or targeting the drug. Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved.

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Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. Matrix system is the release system which prolongs and controls the release of the drug, which 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. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipient by matrix based formulation to desired site. 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 reparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form.[1,2]

Advantages of Oral Controlled Release Formulations

This type of drug delivery has been at the centre of research due to its many benefits over conventional dosage forms, some of which are as follows:

- The frequency of dosing is reduced due to drug being released over a longer period of time unlike conventional tablets.[3] This is extremely valuable for patients with chronic illnesses which require the plasma concentrations of a drug to be within its therapeutic range to avoid breakthrough symptoms, for example, overnight management of pain in terminally ill patients.[4]
- The reduction or avoidance of side effects due to high plasma drug concentrations or 'dose dumping'.[5]
- Improvement in patient compliance due to reduced dosing.[5]
- Better control of therapeutic drug concentration;
- Cost effective manufacturing.[3]

Disadvantages of Oral Controlled Release Formulations[6]

Oral controlled release formulations like other formulations have several disadvantages. These include:

- Development costs: Expensive specialized equipment and inert ingredients may be required for some controlled release formulations.
- Release rate: The drug release rate can be altered by food and gastric transit time; as a result differences may arise in the release rate between doses.
- Cannot crush or chew products: Controlled release products should not be crushed or chewed as it can lead to loss of the 'slow release' characteristics as well as toxicity.

Drug Properties Relevant to Sustained Release Formulation[7,8]

The design of sustained - release delivery systems is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Each of these variables are interrelated and this imposes certain constrains upon choices for the route of delivery, the design of the delivery system and the length of therapy. Properties of drugs are very important for designing a sustained release dosage form mainly physicochemical and biological properties of the drug are most important.

Suitable Candidates for Sustained Drug Release Technology

Table 1: Physicochemical Parameters

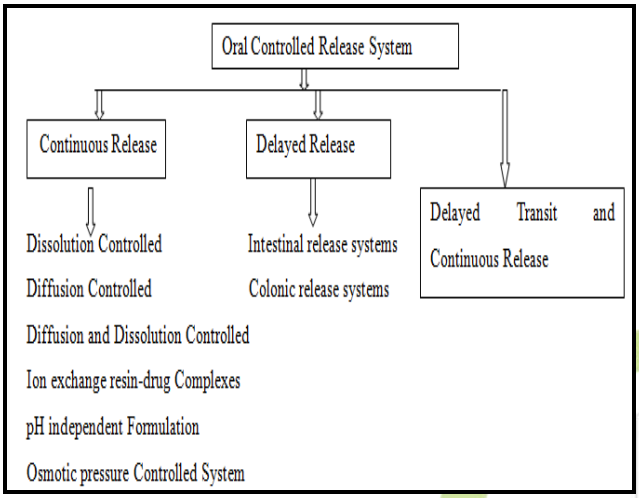
Parameter	Criteria
Molecular Size	<1000Daltons
Aqueous Solubility	More than 0.1mg/ml
Partition Coefficient	High
Absorption Mechanism	Diffusion
Absorption Site	Overall GI Tract

Table 2: Pharmacokinetic Parameters

Parameter	Criteria
Elimination half-life	Between 2 to 8
Apparent Volume of Distribution	Larger Vd and MEC, Larger will be the required dose
Absorption rate constant	Must be higher than release rate

Absolute Bioavailability	Should be more than 50%
Therapeutic Concentration	The lower Css and smaller Vd, the less among of drug required.

Classification of Oral Sustained or Controlled Release Systems[8,9,10,11,12]



Continuous Release System

Continuous release systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form.

1. Dissolution Controlled Release Systems

The drug present in such system may be the one:

a. Having high aqueous solubility and dissolution rate

b. With inherently slow dissolution rate e.g. Griseofulvin and Digoxin

c. That produces slow dissolving forms, when it comes in contact with GI fluids.

Dissolution-controlled release can be obtained by slowing 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. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer.

The rate of dissolution (dm/dt) can be approximated by following equation:

$$dm/dt = ADS/h \quad ...(1)$$

Where,

A = Surface area of the dissolving particle or tablet

D = Diffusivity of the drug

S = Aqueous solubility of the drug

h = Thickness of the boundary layer

The two types of dissolution-controlled release are:

A. Matrix (or monolith) dissolution controlled systems

B. Reservoir dissolution controlled systems

2. Diffusion Controlled Release Systems[11,13]

In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order, since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusion controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution-controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion controlled device, the rate of drug released (dm/dt) can be calculated using the following equation:

$$dm/dt = ADK\,\Delta C/L \quad ...(2)$$

Where,

A = Area

D = Diffusion coefficient

K = Partition coefficient of the drug between the drug core and the membrane

L = Diffusion path length and

ΔC = Concentration difference across the membrane

In order to achieve a constant release rate, all of the terms on the right side of equation must be held constant. It is very common for diffusion controlled devices to exhibit a non-zero-order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds. Another configuration of diffusion-controlled systems includes matrix devices, which are very common because of ease of fabrication. Diffusion control involves dispersion of drug in either a water-insoluble or a hydrophilic polymer. The release rate is dependent on the rate of drug diffusion through the matrix but not on the rate of solid dissolution.

The two types of diffusion-controlled release are:

A. Matrix diffusion controlled systems

B. Reservoir devices

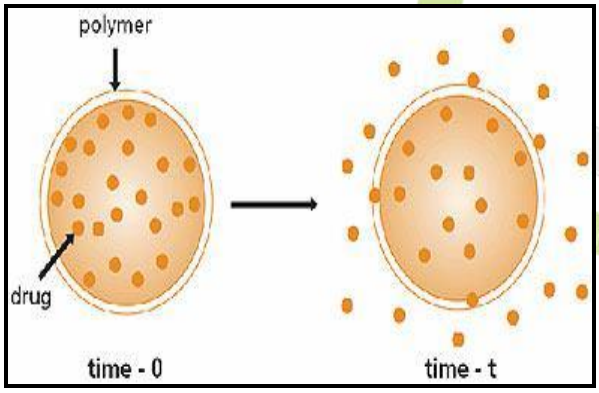


Figure 1: Reservoir Diffusion Controlled System

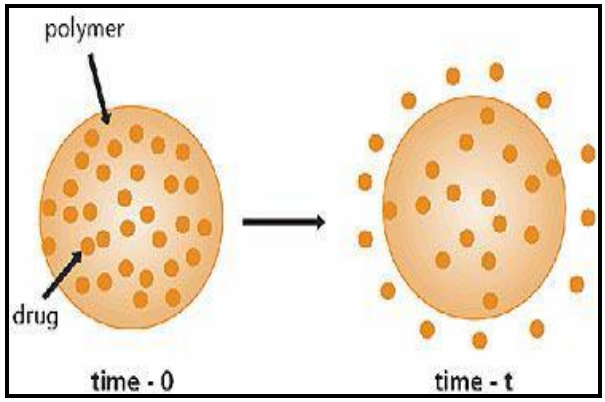


Figure 2: Matrix Diffusion Controlled System

3. *Dissolution and Diffusion Controlled Release Systems*[14]

In such systems, the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug out of the system.

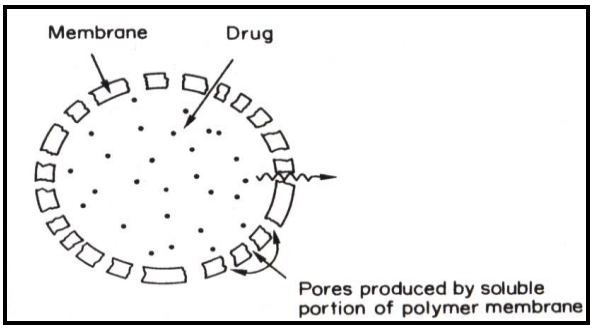


Figure 3: Dissolution and Diffusion controlled release systems

4. *Ion Exchange Resin-Drug Complexes*[14]

It is based on formulation of drug resin complex formed when ionic solution is kept in contact with ionic resins. The drug from this complex gets exchanged in gastrointestinal tract and released with excess of Na^+ and Cl^- present in gastrointestinal tract. This system generally utilize resin compound of insoluble cross linked polymer. They contain salt forming function group in repeating position on a polymer chain.

5. *pH-Independent Formulation*[11,14]

Most of the drug are either weak acid or weak base, the release from sustain release formulation is pH dependent. However, buffer such as salt of citric acid, amino acid, tartaric acid can be added to the formulation, to help to maintain to constant pH their by retarding pH independent drug release. A buffer sustain release formulation is prepared by mixing a basic or acidic drug one or more buffering agent, granulating with appropriate excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agent adjusts the fluid inside to suitable constant pH there by rendering a constant rate of drug release.

6. Osmotic Pressure Controlled Systems[15,16]

A semi permeable membrane is placed around the tablet, particle or drug solution that allows transport of water into tablet with eventual pumping of drug solution out of the tablet through the small delivery aperture in tablet core.

- **Single chamber osmotic pump**
- Elementary osmotic pump (EOP)
- **Multi chamber osmotic pump**
- Push pull osmotic pump.
- Osmotic pump with non expanding second chamber.
- **Specific types**
- Controlled porosity osmotic pump.
- Monolithic osmotic systems.
- Osmotic bursting osmotic pump.
- OROS – CT
- Multi particulate delayed release systems (MPDRS)
- Liquid Oral Osmotic System (L-OROS)

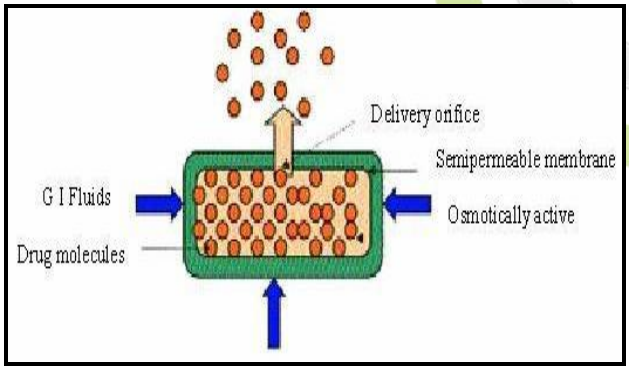


Figure 4: Elementary Osmotic Pump

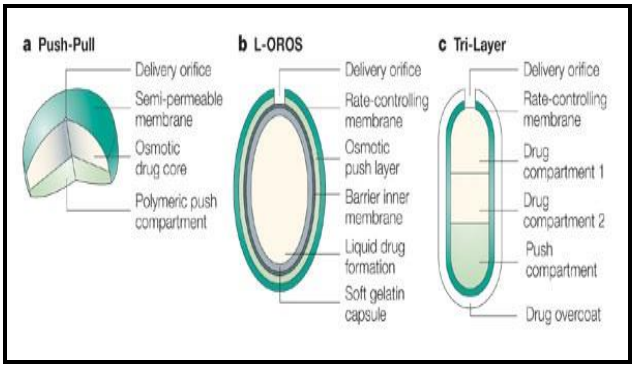


Figure 5: Specific Type Osmotic Pump

Delayed Release Systems[8,9]

The design of such systems involves release of drug only at specific site in the GIT. The drugs contained in such a system are those that are:

a) Known to cause gastric distress

b) Destroyed in the stomach or by intestinal enzymes.

c) Meant to extent local effect at a specific GI site.

d) Absorbed from a specific intestinal site.

The two types of delayed release systems are:

1. Intestinal release systems
2. Colonic release systems

Delayed Transit and Continuous Release Systems[10]

These systems are designed to prolong their residence in the GI tract along with their release. Often the dosage form is fabricated to detain in the stomach and hence the drug present therein should be stable to gastric pH. Systems included in this category are mucoadhesive systems and size based systems.

Factors Influencing Oral Sustained-Release Dosage Form Design

Mainly two factors involved in oral sustained-release dosage form design:

A. Physicochemical factor

B. Biological factor

A. Physicochemical Factor

1. Molecular size and Diffusivity

Diffusivity depends on size & shape of the cavities of the membrane. The diffusion co-efficient of intermediate molecular weight drug is 100-400 Daltons; through flexible polymer range is 10^{-6}-10^{-9} cm^2/sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10-12 cm^2/sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.[17]

2. Ionization, and pKa

only unionized drugs are well absorbed and permeation of ionized drug is negligible, since its rate of absorption of ionized drug is 3 to 4 times less than that of the unionized drug. pKa range for acidic drug where ionization is pH sensitive is around 3.0 to 7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0 to 11.0 are ideal for optimum positive absorption. Drug shall be non-ionized at the site to an extent 0.1 – 5.0%. Drugs existing largely in ionized form are poor candidates for oral ER drug delivery system. e.g. Hexamethonium.[22]

3. Aqueous Solubility

Compounds with very low solubility (less than 0.01mg/ml) are inherently sustained, since there release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained-release system has been reported to be 0.1mg/ml, so it is obvious that the solubility of the compound will limit the choice of mechanism to be employed in sustained delivery system. Diffusional systems will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.[20]

4. Partition Coefficient

When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.[18,19]

5. Stability

When drugs are orally administered, they come across acid-base hydrolysis and enzymatic degradation. In this case, if the drug is unstable in stomach, drug release system which provides medication over extended period of time is preferred, whereas in contrast the drug unstable in intestine will face problem of less bioavailability.[18]

B. Biological factor[20,21,22,23]

1. 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.

2. Absorption

The purpose of forming a sustained release product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the gastrointestinal tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23 h-1 to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds

this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, sustained release preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds try to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bio-adhesive material.

3. Metabolism

Drug, which extensively metabolized is not suitable for ER 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 ER delivery, since it could be difficult to maintain constant blood level e.g. Levodopa, Nitroglycerine. Drugs that are metabolized before absorption, either in lumen or the tissues of the intestine, can show decreased bioavailability from the extended releasing systems. Most intestinal walls are saturated with enzymes. As drug is released at a slow rate to these regions, lesser drug is available in the enzyme system. Hence the systems should be devised so that the drug remains in that environment to allow more complete conversion of the drug to its metabolite.

4. Distribution

The distribution of a drug into vascular and extravascular spaces in the body is an important factor in its overall elimination kinetics. Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in the tissue is that in plasma at the steady state called T/P ratio. The magnitude of the apparent volume of distribution can be used as a guide for additional studies and as a predictor for a drug dosing regimen and hence there is a need to employ a controlled-system.

5. Protein Binding

There are some drugs which having tendency to bind with plasma proteins (eg. Albumin) and causes retention of the drug in the vascular space. The main force of attraction responsible for binding is vanderwals forces, hydrogen bonding and electrostatic forces. In general, charged compounds, because of electrostatic effects. If a drug with protein then the distribution of the drug into the extravascular space is governed by the equilibrium process of dissociation of the drug from the protein.

The drug-protein complex can serve therefore as a reservoir in the vascular space for controlled drug release to extravascular tissues, but only for those drugs that exhibit a high degree of binding. Thus, the protein binding characteristics of a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form. Extensive binding to plasma proteins will be evidenced by along half-life of elimination for the drug and such drugs generally does not required a controlled release dosage form, however, drugs that exhibit a high degree of binding to plasma protein also might bind to biopolymers in the GI tract, which could have an influence on controlled-drug delivery.

6. Margin of Safety

There are very few drugs whose specific therapeutic concentrations are known. Instead, a therapeutic concentration range is listed, with increasing toxic effects expected above this range and a falloff in desired therapeutic response observed below the range. The most widely used measure of the margin of safety of a drug is its therapeutic index, (TI). For very potent drugs, whose therapeutic concentration range is narrow, the value TI is small. In general, larger the value of TI, Usually are poor candidates for formulation into controlled-release product. A drug is considered to be relatively safe if its TI value exceeds 10.

Classification of Matrix Tablets[2,25,26,27]

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 first introduced in 1959. The drug is mixed with an inert or hydrophobic polymer which is not soluble in gastro intestinal fluid and then compress into a tablet. In sustained release formulation the drug is dissolved and diffused through a network of channels that exists between compacted polymer particles or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The liquid penetration into the matrix is the rate limiting step. The diffusion is the possible mechanism of the release of drug in such type of matrices. In presence of gastro intestinal fluid and water such type of matrix tablet inert in nature.

2. Lipid Matrices

Lipid waxes and related materials are used to prepare these types of matrices. The pore diffusion and erosion are mechanism of drug release from such lipid matrices. 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. In this type the hydrophilic polymer with high gelling capacities is used as base excipient. Normally matrix is defined as well mixed composition of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems. It can be divided into three broad groups depending on polymer used in the preparation of hydrophilic matrices.

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.

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

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 nonenzymatic 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 by the use of dilute alkali.

1) On the Basis of Porosity of Matrix

Matrix system can also be classified according to their porosity,

❖ *Macro porous Systems*

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

❖ *Micro porous System*

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

❖ *Non-porous System*

Non-porous systems have no pores and the molecules diffuse through the network meshes.

Table 3: Marketed Drug Products[17]

Sr.no.	Type	Brand Name	Drug	Manufacturer
1.	Diffusion Controlled release	Welbutrin XL	Bupropion	GlaxoSmithKline
2.	Matrix Tablet	Ambien CR	Zolpidem Tartarate	Sanofi-Aventis
3.	Ion Exchange	Tussionex Pennkinetic ER suspension	Hydrocodone Polistirex & Chlor-pheneramine Polistirex	UCB Inc.
4.	Osmotic Pressure-Elementary Osmotic Pump	Efidac 24®	Chlorpheniramine Maleate	Novartis
5.	pH independent	Inderal® LA	Propranolol HCl	Wyeth Inc.
6.	Altered Density Approach	Modapar	Levodopa & Benserazide	Roche Products, USA

In this case, only the polymeric phase exists and no pore phase is present.

Material Used as Release Retardants in Matrix Tablet Formulation[27,28]

These classes of retardant materials are used to prepare matrix tablet formulations.

a. Water insoluble inert materials

e.g. polyethylene, polyvinyl chloride, methyl acrylate, methacrylate copolymer, ethyl cellulose.

b. Insoluble, erodible materials

e.g. Steryl alcohol, stearic acid, polyethylene glycol, carnauba wax, caster wax, polyethyleneglycol monosterate, triglycerides.

c. Hydrophilic materials

e.g. Hydroxy propyl methylcellulose, sodium CMC, methylcellulose, hydroxy ethyl cellulose.

Natural gums: Galactomannose (guargum), chitosan, gum acacia, locust bean gum, sodium alginate, karaya gum, pectins, xanthan gum.

d. Natural polymers

eg. Ispaghula husk, tamarind seed polymer.

CONCLUSION

Thus, it can be concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient compliance. Matrix forming polymers can be successfully used to prepare Matrix tablets, releasing drug in a controlled manner. This suitability of polymers, to various drug delivery systems preparation confirms the importance of these specialized excipients in pharmaceutical application. They represent the choice solution for many oral delivery problems like fluctuating drug plasma levels, low bioavailability, more frequent dose administration etc. So Sustained release formulations can overcome the above problems of conventional oral drug delivery.

ACKNOWLEDGEMENTS

The authors are thankful to Trustees, Bhujbal Knowledge City, MET's institute of pharmacy, Adgaon, Nasik, Maharashtra, India for providing the necessary facilities to carry out this work.

REFERENCES

1. Modi, S. A., Gaikwad, P. D., Bankar, V. H., & Pawar, S. P. (2011). Sustained release drug delivery system: a review. *International*

Journal of Pharma Research and Development, *2*(12), 147-59.

2. Libermann, H., Lachman, L. and Schwartz J. (1990). *Pharmaceutical Dosage forms: Tablets*, 2nd Edn, Vol 3, Marcel Dekker, New York, 201-243.
3. Maderuelo, C., Zarzuelo, A., & Lanao, J. M. (2011). Critical factors in the release of drugs from sustained release hydrophilic matrices. *Journal of Controlled Release*, *154*(1), 2-19.
4. Aulton, M. E. (2008). *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, 3rd ed. Philadelphia, USA: Churchill Livingstone Elsevier, 99-102,
5. Kojima, H., Yoshihara, K., Sawada, T., Kondo, H., & Sako, K. (2008). Extended release of a large amount of highly water-soluble diltiazem hydrochloride by utilizing counter polymer in polyethylene oxides (PEO)/polyethylene glycol (PEG) matrix tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *70*(2), 556-562.
6. Nokhodchi, A., Raja, S., Patel, P., & Asare-Addo, K. (2012). The role of oral controlled release matrix tablets in drug delivery systems. *BioImpacts: BI*, *2*(4), 175.
7. Brahmankar, D. M., Jaiswal, S. B. (2009). *Biopharmaceutics and Pharmacokinetics: Pharmacokinetics*, 2nd Edn, Vallabh Prakashan, Delhi. 399-401.
8. Ankit, B., Rathore, R. P. S., Tanwar, Y. S., Gupta, S., & Bhaduka, G. (2013). Oral sustained release dosage form: an opportunity to prolong the release of drug. *International Journal of Advanced Research in Pharmaceutical and Bio sciences*, *3*(1), 7-14.
9. Dusane, A. R., Gaikwad, P. D., Bankar, V. H., Pawar, S. P. (2011). A Review On Sustained Released Technology. *International Journal Research in Ayurveda and Pharmacy*, *2*(6), 1701-1708.
10. Patel, P. N., Patel, M. M., Rathod, D. M., Patel, J. N., & Modasiya, M. M. K. (2012). Sustain Release Drug Delivery: A Theoretical Prospective. *Journal of Pharmacy Research*, *5*(8), 4165-4168.
11. Jantzen, G. M. and Robinson, J. R. Sustained and controlled-release drug delivery systems, Banker GS, Rhodes CT (Eds.) (1995). Modern Pharmaceutics Revised and Expanded Drugs and The Pharmaceutical Sciences, 3rd Edn Vol 72, Marcell Dekker, Inc., New York: 575-609,
12. Nanditha and Anka Rao. (2014). An Overview: Oral Sustained Release Technology. *Asian Journal of Biochemical and Pharmaceutical Research*, *1*(4), 96-106.
13. Mandal, S., Ratan, G. N., Mulla, J. S., Thimmasetty, J., & Kaneriya, A. (2010). Design and in vitro evaluation of gastro retentive sustained release tablets of tizanidine hydrochloride. *Indian Journal of Novel Drug delivery*, *2*(4), 144-152.
14. Parashar, T., Singh, V., Singh, G., Tyagi, S., Patel, C., & Gupta, A. (2013). Novel oral sustained release technology: A concise review. *International Journal of Research and Development in Pharmacy and Life Sciences*, *2*(2), 262-269.
15. Kamboj, S., Gupta, G. D., & Oberoy, J. (2009). Matrix tablets: An important tool for oral controlled-release dosage forms. *Pharmainfo.net*, *7*(6). 1-9.
16. Bechgaard, H., & Nielsen, G. H. (1978). Controlled-release multiple-units and single-unit doses a literature review. *Drug Development and Industrial Pharmacy*, *4*(1), 53-67.
17. Ratnaparkhi, M. P., & Gupta Jyoti, P. (2013). Sustained release oral drug delivery system-an overview. *Terminology*, *3*, 4.
18. Asija, R., Rathi, H., Asija, S. (2012). Sustained Released Drug Technology: A Review. *International Journal of Research in Pharmacy and Science*, *2*(4), 1-13.

19. Isha, C., Nimrata, S., Rana, A. C., & Surbhi, G. (2012). Oral sustained release drug delivery system: an overview. *International Research Journal of Pharmacy*, *3*(5), 57-62.

20. Jain, N. K. (1997). *Controlled and Novel drug delivery*, CBS Publisher and Distributors, 1st Edn, New Delhi, 1-25.

21. Remington: *The Science and Practice of Pharmacy*, 21st Edn, Vol 1, Published by: Wolter Kluwer Health India, 939-964.

22. Banker, G. S., Rhodes, C. T., *Modern Pharmaceutics Drug and Pharmaceutical Science*, 2nd Edn, Dekker Marcel: 501-527.

23. Gupta, M. M., & Ray, B. (2012). A Review On: Sustained Release Technology. *International Journal of Therapeutic Applications. (8)*, 1-23.

24. Chauhan, M. J., & Patel, S. A. (2012). A concise review on sustained drug delivery system and its opportunities.

25. Maderuelo, C., Zarzuelo, A., & Lanao, J. M. (2011). Critical factors in the release of drugs from sustained release hydrophilic matrices. *Journal of Controlled Release*, *154*(1), 2-19.

26. Hemnani, M., Patel, U., Patel, G., Daslaniya, D., Shah, A., & Bhimani, B. (2011). Matrix tablet: A tool of Controlled drug delivery. *American Journal of Pharm Tech Research*, *1*(4), 127-143.

27. Pundir, S., Badola, A.,Sharma, D. (2013). Sustained release matrix technology and recent advance in matrix drug delivery system - A review. *International Journal of Drug Research and Technology*, 3(1), 12-20.

28. Jaimini, M., & Kothari, A. H. (2012). Sustained release matrix type drug deliery system: a review. *Journal of Drug Delivery and Therapeutics*, *2*(6).

