A REVIEW ON: SUSTAINED RELEASE TECHNOLOGY

Sarika S. Lokhande*, Phalke N. N. and Badadare S. S.

Maharashtra India.

*Corresponding Author: Sarika S. Lokhande
Maharashtra India.

ABSTRACT

Oral drug delivery is the most preferred and expedient option as the oral route provides greatest active surface area among all drug delivery system for administration of various drugs. The attractiveness of these dosage forms is due to consciousness to toxicity and ineffectiveness of drugs when administered by oral predictable method in the form of tablets & capsules. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, maximum consumption of the drug, increased safety margin of potent drug, reduction of fluctuation in steady-state drug levels, decrease in healthcare costs through enhanced therapy and shorter treatment period. The principal goal of sustained release forms is the improvement of drug therapy assessed by the relationship between advantages and disadvantages of the use of sustained release system.

KEYWORD: Matrix type system, oral drug delivery system, Conventional dosage form, Mechanism of drug release, Advantages & disadvantages, bilayer tablet.

INTRODUCTION

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is necessary to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.[1-5] compensation of administering a single dose of a drug that is released over an extensive period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. drug delivery dosage forms can be traced to the 1938.

patent of Israel Lipowski. This work concerned coated pallets for extended release of drug and was most probably forerunner to the development of the coated particle approach to sustained drug delivery that introduced in the early 1950s.[6] The novel system of drug delivery offer a means of improving the therapeutic effectiveness of included drugs by providing sustained, controlled delivery and / or targeting the drug to desired site.[7] The goal of any drug delivery system is to make available a therapeutic quantity of drug to the proper site in the body to achieve rapidly and then maintain the desired drug concentration.[8] Sustained release systems include any drug delivery system that achieves slow. Release of drug over an comprehensive period of time. If

the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system.[9]
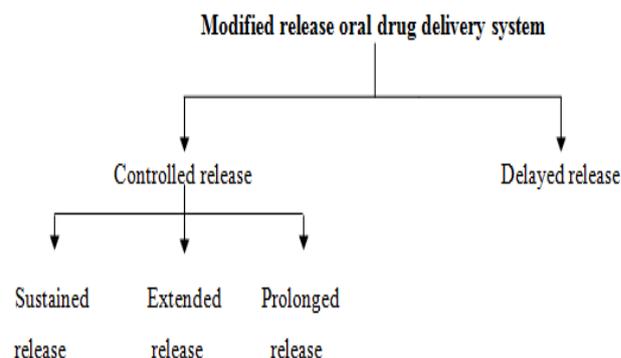
Figure 1: Classification of Modified Release Drug Delivery System.[10]

Advantages of Sustain Release Dosage Forms
1. Decrease in frequency of intakes.
2. Reduce side effects.
3. Uniform release of drug over time.
4. Enhanced patient compliance.[11]

Disadvantages of Sustained Release Drug Delivery
1. Increased cost.
2. Toxicity due to dose dumping.
3. Unpredictable and often poor *in vitro-in vivo* correlation.

4. Risk of side effects or toxicity upon rapid release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
5. Increased potential for first- pass clearance.
6. Need for additional patient education and counseling.[12]

Objectives of oral sustained released dosage form
1. To maintain the concentration of drug at constant level for a preferred period of time.
2. To reduce the frequency of doses administrated as compared to conservative dosage form
3. It should deliver active entity directly to site of action, minimizing or eliminating side
4. effects.[13]
5. This may necessitate delivery to specific receptors or to localization to cells or to definite areas of the body.
6. The safety margin of potent drugs can be improved.
7. Incidence of both local and systemic adverse side effects can be reduced in sensitive patient.[14]

Various Mechanisms of Medicament Release
1. Diffusion is rate limiting
Diffusion is heavy force where the movement of drug molecules occurs from elevated concentration in the tablet to lesser concentration in gastro intestinal fluids.[15] This movement depends on surface area uncovered to gastric fluid, diffusion pathway, drug concentration gradient and diffusion coefficient of the system (**Fig. 1**).
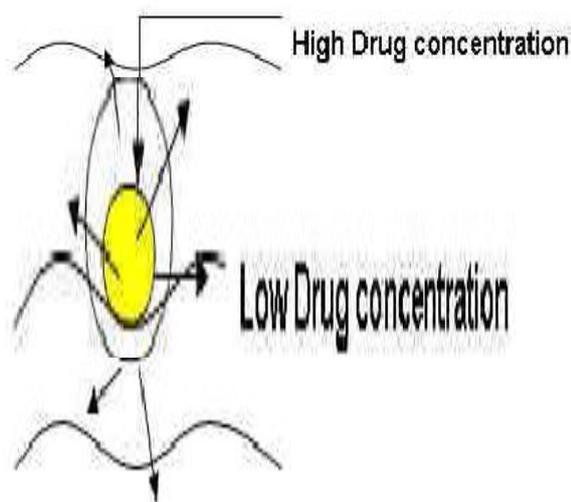
Figure 2: Diffusion Release Pattern.

In practice, we can follow either of the two methods,
a. The drug is formulated in an insoluble matrix; the gastric fluid penetrates the dosage form and dissolves the medicament and liberate the drug through diffusion.
b. The drug particles are covered with polymer of defined thickness so as the portion of drug slowly diffuse through the polymer to maintain constant drug level in blood.[15]

2. Osmotic pressure is rate limiting
Osmosis is a phenomenon in which the flow of liquid occurs from lower concentration to higher concentration through a semi permeable membrane which allows transfer of liquid only. The entire drug is coated with a semi permeable membrane with a hole on one end of tablet made by a laser beam. The gastric fluid penetrates through the membrane, solubilizes the drug and increases the interior pressure which pumps the drug solution out of the aperture and releases the drug in gastric environment.[16]

Classification of Oral Sustained or Controlled Release Systems
The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:
1. Continuous release systems
2. Delayed transit and continuous release systems
3. Delayed release systems.[17]

1. Continuous release systems
Continuous release systems release the drug for a extended period of time along the entire length of gastrointestinal tract with normal transportation of the dosage form. The various systems under this category are as follow:
A. Diffusion controlled release systems
B. Dissolution controlled release systems
C. Dissolution and diffusion controlled release systems
D. Ion exchange resin- drug complexes
E. pH-independent formulation
F. Osmotic pressure controlled systems.[18]

A. Diffusion controlled release systems[19]
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 exhausted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems.

B. Dissolution-controlled release systems[20]
The drug present in such system may be the one Having elevated aqueous solubility and dissolution rate 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.[24] The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer.

C. Dissolution and diffusion controlled release systems[21]
In such systems, the drug core is encased in a partly 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.

Formulation strategy for oral SRDDS[22]
1. Diffusion Sustained System
2. Dissolution Sustained System
3. Methods using ion exchange
4. Methods using osmotic pressure
5. pH independent formulation
6. Altered density formulation

Bilayer tablet
Over 90% of the formulations manufactured today are ingested orally. This show that this class of formulation is the most accepted worldwide and major attention of the researcher is towards this direction. The most important aim of sustained drug delivery is to decrease frequency of dosing. The design of modified release drug product are to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the partial dosing interval providing greater patient compliance and convenience. Bilayer the tablet is the new era for the successful growth of controlled release formulation.[23]

Bi-layer tablets suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is instantaneous release as initial dose and second layers is maintaince dose there are various applications of the bi-layer tablets as it consists of monolithic partly coated or multilayered matrices. Generally predictable dosage form produce wide ranging variation in drug concentration in the blood stream and tissue with unwanted toxicity and poor effectiveness. This factor repetitive dosing and unpredictable absorption led to concept of controlled drug delivery system. The main objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs.[24]

Advantages of bilayer tablet
1. Superior chemical and microbial stability compared to other oral dosage forms.
2. Separation of incompatible component thus minimizes physical and chemical incompatiies.
3. Objectionable odor and taste can be masked by coating technologies.
4. It can be designed in such a manner as to modified discharge of the layers can be kept as extensive and the other as instant release.
5. Cost is lesser as compare to other dosage forms.
6. Suitable for large scale production.
7. Easy to swallowing with least tendency for hang up.[25]

Disadvantage of bilayer tablet
1. Some drug resist compression into impenetrable compacts, due to amorphous nature, low density nature.
2. Bilayer rotary presses are expensive.
3. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen
1. may require encapsulation or coating.
4. Inaccurate individual layer weight control.
5. Insufficient hardness, layer separation reduced yield.[26]

Homogenous type
Bilayer tablets are preferred when the release profiles of the drugs are unusual from one another. bilayer allows for designing and modulating the dissolution and release characterstics. bilayer tablets are prepared with one layer of drug for instant release while second designed to release drug, either as second dose or in an extensive release manner.

Heterogeneous type
Bilayer tablet is appropriate for sequential release of two drugs in combination, separate two incompatible substances.[27]

Need of bilayer tablet
1. For the administration of fixed dose combination of different active pharmaceutical ingredient, extend the drug product life cycle, buccal delivery system; fabricate novel drug delivery system such as chewing device and floating tablet for gastro-retensive drug delivery.
2. Controlling the delivery rate of either single or two different active pharmaceutical Ingredients.[28]

General properties of bilayer tablet dosage forms
1. Bilayer tablet should have elegant product identify while free of defect like chips, cracks,
2. discoloration and contamination.
3. It should have adequate strength to withstand mechanical shock during its production, shipping and dispensing.
4. It should have chemical and physical stability to maintain its physical attributes over time.[29]

Various Approaches Used In the Bilayer Tablet
1. Floating drug delivery system
2. Polymeric Bioadhesive system
3. Swelling system/unfolding system

Types of Bilayer Tablet Press
A. Single sided tablet press
B. Double sided tablet press
C. Bilayer tablet press with displacement monitoring.[30]

Marketed Preparation of Bilayer Tablets[31]

Sr. no.	Product Name	Chemical Name	Developer
1	ALPRAX PLUS	Sertraline, Alprazolam	Torrent Pharmaceuticals Ltd.
2	DIAMICRON®XRMEX500	Gliclazide, Metformin Hcl	Sedia® Pharmace -uticals Pvt. Ltd
3	DIUCONTIN-K®20/250	Furosemide, Potassium chloride	T.C. Health Care Pvt. Ltd.
4	Glycomet®-GP2Forte	Metformin hydrochloride, Glimepiride	USV Limited
5	New cold Plus	Levocetrizine Hcl, Phenylpropanolamine Paracetamol	Piramol Healthcare Ltd.
6	Revelol®-Am 25/5	Metoprolol succinate, Amlodipine besilate	Ipca Laboratories Ltd.
7	TRIOMUNE 30	Nevirapine, Lamivudine, Stavudine	Cipla Ltd.

Introduction of matrix tablet

As sustained release (SR) has given a new. Breakthrough for novel drug delivery system (NDDS) in the field of pharmaceutical technology. It excludes multifaceted production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is extensively used for formulating an SR dosage form.[32]

Advantages of SR Matrix DDS

1. The frequency of drug administration is reduced.
2. Patient compliance can be enhanced.
3. Drug administration can be made more suitable as well.
4. The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.[33]
5. Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduce.
6. The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
7. The total amount of drug administered can be reduced, thus maximizing availability with minimum dose. Minimize or eliminate local side effects. Minimize or eradicate systemic side effect. Reduce drug accumulation with chronic dosing.[34]

Disadvantages of SR Matrix DDS

1. Probability of dose dumping.
2. Reduced potential for dose adjustment.
3. Cost of single unit higher than predictable dosage forms.
4. Increase potential for first pass metabolism.
5. Requirement for additional patient education for proper medication.[35]

General mechanism of drug release from polymer

There are three primary mechanisms by which active agents can be released from a delivery system namely; Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. Diffusion occurs when the drug passes from the polymer matrix into the exterior surroundings.

As the release continues its rate normally decreases with this type of system since the active agent has a increasingly longer distance to travel and therefore requires a longer diffusion time to release. In these systems, the combinations of polymer matrices and bioactive agents chosen must allow for the drug to diffuse through the pores or macromolecular structure of the polymer upon introduction of the delivery system into the biological environment without inducing any change in the 15 polymer itself. Biodegradable polymer degrades within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed.[36]

Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically satisfactory and progressively smaller compounds. For some degradable polymers, most notably the polyanhydrides and polyorthoesters, the degradation occurs only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the drug delivery system.

They are initially dry and when placed in the body will absorb water or other body fluids and swell. The swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen16 network into the external environment.[37]

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.

On the other hand, sustained release implies slow release of drug over a time period. Sustain released formulation may or may not be controlled release. From the above discussion, we can concluded that development of SRDDS depend upon a variety of factors such as Biopharmaceutics, Pharmacokinetic and Pharmacodynamic characteristics of drug. Sustained release drug delivery system has leaded no difficulty of market penetration as replacement of oral predictable drug delivery system.

Release formulations are a promising way to improve the patient compliance by reducing dosing interval and minimizing undesirable effect.

ACKNOWLEDGEMENT

REFERENCES

1. John C, Morten C. The Science of Dosage Form Design, Aulton: Modified release peroral dosage forms. 2nd ed. Churchill Livingstone, 2002; 290-300.
2. Mandal S, Ratan GN, Mulla JS, Thimmasetty J, Kaneriya A, "Design and In Vitro Evaluation of Gastro Retentive Sustained Release Tablets of Tizanidine Hydrochloride", Indian Journal of Novel Drug delivery, 2010; 2(4): 144-152.
3. Chien Y. W. Novel Drug Delivery System, 1992; 2: 139 – 140.
4. Dixit Navin, Sheo, DM. Bhanu, Sagar PS. Sustained Release Drug Delivery System. Indian Journal of Research in Pharmacy and Biotechnology, 2013; 1(3): 305.
5. Chugh I, Seth N, Rana AC, Gupta S. Oral sustained release drug delivery system: an overview. International research journal of pharmacy, 2012; 3(5): 57-62.
6. Gupta S, Singh RP, Sharma R, Kalyanwat R, Lokwani P. Osmotic pumps: A review. Int. journal of comprehensive pharmacy, 2011; 6: 1-8.
7. Jantez GM, Robinson JR. Sustained andcontrolled release drug delivery systems. In: Banker GS, Rhodes CT, editors. Modern pharmaceutics. 3rd edition. New York: marcel dekker inc, 1996.
8. Jantzen GM and Robinson JR, Sustained and controlled-release drug delivery systems, In Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, Third Ed., Revised and Expanded, Drugs and The Pharmaceutical Sciences, vol 72. Marcell Dekker, Inc., New York, 1995; 575-609.
9. Brahmankar D. M. and Jaiswal S. B. in "Biopharmaceutics and Pharmacokinetics", "A Treatise," Vallabh Prakashan, 1st Edition, 1995; 347- 352.
10. Sampath Kumar KP, Debjit B, Shweta S, Shravan P, Dutta AS. Sustained release drug delivery system potential. The Pharma Innovation, 2012; 1(2): 46-56.
11. Lachman. L. Herbert, A.Tablet dosage Forms, The theory and practice of industrial pharmacy; 3rd edn Varghese publishing house, Bombay, 1991; 296-298,293-345,430.
12. Pawar, R.G., formulation and evaluation of pregabalin sustained release matrix tablet; Ind. J. pharm. Res & Devpt, 2011; 4(02): 153-159.
13. Jain NK. Controlled and novel drug delivery. CBS publishers and distribution, 1997; 1-25.
14. Hoffman A, "Pharmacodynamics aspects of sustained release preparations", Advance Drug Deliv Rev., 1998, 33, 185-199.
15. Asija Rajesh, Rathi Harish, Asija Sangeeta. Sustained Released Drug Technology: A Review. IJRPS, 2012; 2(4): 1-13.
16. Modi SA, Bankar VH, Pawar SP. Sustained Release Drug Delivery System: A Review. International journal of pharmaceutical research and development 2011; 2(12):147-160.
17. Chang R.K., Robinson J.R., Sustained drug release form tablets & particles through coating, In: Liberman H.A., Lachman L.S., Chwartz J.B.," Pharmaceutical Dosage Form: Tablets" vol 3,2nd edn., Marcel Dekker, New York, 2015; 199-287.
18. Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances. 1st ed. Vallabh prakashan; 2002; 156-189.
19. Sahilhusen IJ, Mukesh RP, Alpesh DP. Sustained Release Drug Delivery Systems: A Patent Overview. Aperito J Drug Designing and Pharmacology 2014; 1(1): 1-14.
20. Shalin AM, Gaikwad PD, Bankar VH, Pawar SP. Sustained release drug delivery system: a review. Int J Phama Res Dev., 2011; 2(12): 147-60.
21. Gandhi A, Hari Kumar SL. Recent Trends in Sustained Release Drug Delivery System.
22. Jain N.K. Controlled and Novel Drug Delivery. CBS Publiser, new Delhi, 1-2, 2002: 676-698.
23. Dusane AR, Gaikwad PD, Bankar VH, Pawar SP, "A review on: Sustained released technology", IJRAP, 2011; 2(6): 1701-1708.
24. Patel. S. Jaldhara, Thakkar Divya, et al, A Review on Bilayer Tablet, Journal of Drug Discovery and Therapeutics, 2013; 1(3): 40 – 48.
25. Syan Navneet , Mathur Pooja, Aggarwal Swati, Biliayer Tblet Technology Opening New Ways Journal of Research in Pharmaceutical and Biomedical Sciences.
26. Bindu Hima, Gopipant. C, Nischala : An overview on Bilayerd Tablet Technology , Journal of Global Trends in Pharmaceutical Scinences, April- June 2013; 4: 1077-1085.
27. Bhatia K Evneet, Vaishy Prabhanshu, Mishra Ashwani, et al Bilayer Tablet Techology: A Review, International Journal of Pharmaceutical and Biological Archives., 2014; 5(4): 9-18.
28. Morsu Ashok, P. Vishnu. Et al.., An Overview on Bilayer Tablet, International Journal of Research and Review in Pharmacy and Applied science, 2014; 4(1): 957- 974.
29. Kavitha, K, A.Divya,et al, Bilayer Tablet Techonolgy, An Overwiew: Journal of Applied Pharmaceutical Sciences, 2011; 08: 43- 47.
30. Altaf AS, Friend DR, MASRx and COSRx Sustained-Release Technology in Rathbone MJ, Hadgraft J, Robert MS, Modified Release Drug

Delivery Technology, Marcell Dekker Inc., New York, 2003.

31. Remington. The Science and Practice of pharmacy. Lippincott Williams & Wilkins, 20th Edition, 2006.

32. Kar RK, Mohapatra S, Barik BB. Design and characterization of controlled release matrix tablets of Zidovudine. Asian J Pharm Cli Res. 2009; 2: 54-6.

33. Aulton M.E. Hand Book of pharmaceutics Edition. 2001: 291-295.

34. Chauhan MJ, Patel SA. A Concise Review on Sustained Drug Delivery System and Its Opportunities. Am. J. PharmTech Res 2012; 2(2): 227-238.

35. Wise DL. Handbook of pharmaceutical controlled release technology. Marcel dekker Inc new York: 2002; 432-460.

36. Kumar V, Prajapati SK, Soni GC, Singh M, Kumar N. Sustained release matrix type drug delivery system: a review. World journal of pharmacy and pharmaceutical sciences, 2012 Sep 5; 1(3): 934-60.

37. Pundir S, Badola A, Sharma D. Sustained release matrix technology and recent advance in matrix drug delivery system: a review. International Journal of drug research and technology, 2017 Feb 28; 3(1): 8.

38. Jaimini M, Kothari AH. Sustained release matrix type drug delivery system: a review. Journal of Drug Delivery and Therapeutics, 2012 Nov 15; 2(6).