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A REVIEW ON SUSTAINED RELEASE TECHNOLOGY DRUG DELIVERY SYSTEM

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Abstract: In all drug delivery system, Oral drug delivery remains the most preferred system for administration of various drugs. 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. 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. Sustained release system are considered a wiser approach for the drugs with short half-lives and which require repeated dosing, they are easy to formulate and are irrespective of absorption process from gastrointestinal tract after oral administration. Hydrophilic polymers have become product of choice as an important ingredient for formulating sustained release formulations.

Keywords: Sustained drug delivery, Half-life, Diffusion, Oral drug delivery

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INTRODUCTION

Sustained release drug delivery system

The Important role of novel drug delivery system that improve the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and or targeting the drug to desired site. The aim of any drug delivery system is to provide a therapeutic amount of drug to the specific site in the body to achieve promptly and then maintain the desired drug concentration. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system includes any drug delivery systems that achieves slow release of drug over prolong period of time.

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. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patients, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems.

Controlled Release Drug delivery System

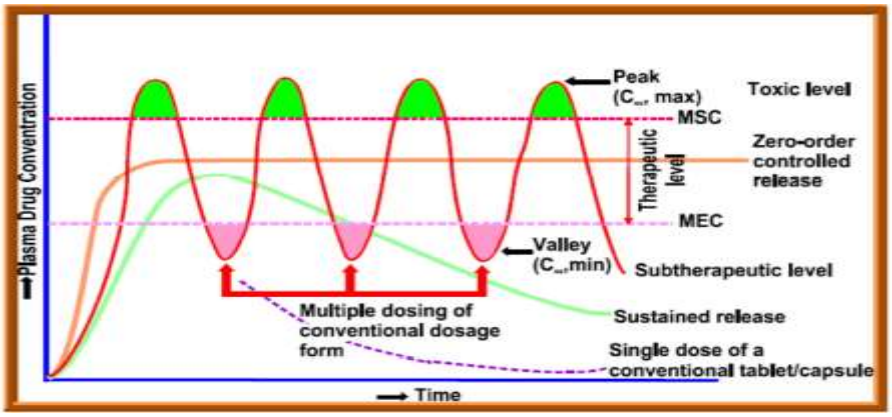
The dosage form in which the drug is released in planned, predictable and slower than conventional dosage form.

Extended release drug delivery system

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate and necessarily reduce the dosage frequency by two folds

Delayed Release Drug Delivery System

This is the specific type of modified release dosage form that releases the drug at a particular time. E.g Enteric coated tablet



(Figure 1.A hypothetical plasma concentration-time profile from conventional multiple dosing and single dose of sustained and controlled delivery formulation)

ADVANTAGE OF SUSTAINED DRUG DEIVERY SYSTEM

- Enhance patient compliance and convenience.
- Reduction in dosing frequency.
- Reduced fluctuation in circulating drug levels.
- More uniform effect.
- Reduced toxicity due to overdose.
- Enhanced bioavaibility.
- Elimination of wastage of drug and inconvenience of nighttime administration of drug.
- Enhanced duration of activity for short half-life drugs.

DISADVANTAGE OF SUSTAINED DRUG DELIVERY SYSTEM

- Increased cost.
- Toxicity due to dose dumping.
- Unpredictable and often poor in vitro-in vivo correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Need of additional patient education counseling.

- Increased potential for first pass clearance.

DRUG SELECTION FOR SUSTAINED RELEASE DRUG DELIVERY SYSTEM

There are some physiochemical parameters for the drug selection to be formulated in sustained release dosage form.

Table 1.2 physiochemical parameters for drug selection

Parameters	Preferred value
Molecular weight	<1000 Daltons
Solubility	>0.1mg/ml for pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segment
Release	Should not influenced by pH and enzyme

Table 1.3 Pharmacokinetic parameters for drug selection

Parameters	Comments
Elimination half-life	Preferably between 2 to 8hrs
Total clearance	Should not be dose dependent
Elimination rate constant	Require for design
Apparent volume of distribution(Vd)	The larger Vd and MEC, the larger will be the required dose size
Absolute bioavaibility	Should be 75% or more
Intrinsic absorption rate	Must b greater than release rate
Therapeutic concentration(Css0	The lower Css and smaller Vd, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very

VARIOUS MECHANISMS OF MEDICAMENT RELEASE

1. Diffusion is rate limiting

Diffusion is driving force where the movement of drug molecules occurs from high concentration in the tablet to lower concentration in gastro intestinal fluid. This movement depends on surface area exposed to gastric fluid, diffusion pathway, drug concentration gradient and diffusion coefficient of the system (Fig.1)

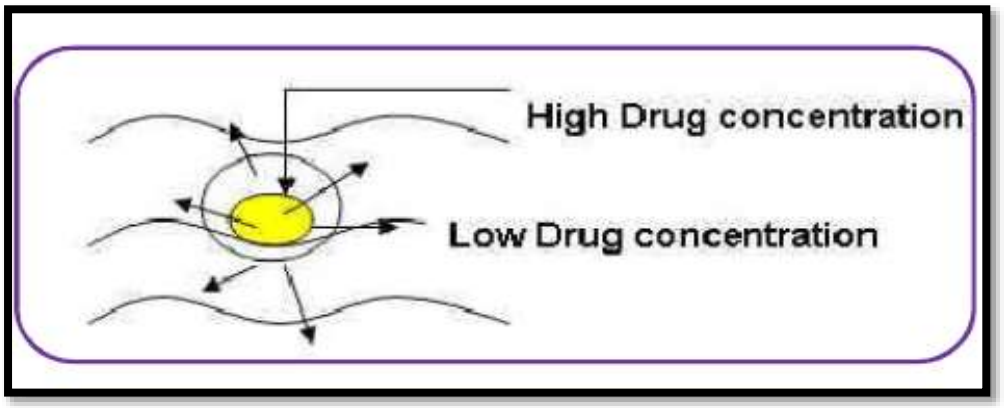


Figure 2: Diffusion Release pattern

In practice, we can follow we can either of the two method,

a. The drug is formulated in an insoluble matrix; the gastric fluid penetrates the dosage form and dissolves the medicament and release the drug through diffusion.

b. The drug particles are coated with polymer of defined thickness so as the portion of drug slowly diffuse through the polymer to maintain constant drug level in blood

2. Dissolution is rate limiting

The drugs with poor water solubility (BCS class 2 and 4) are inherently sustained release forms. While for water soluble drugs, it's possible to incorporate a water insoluble carrier reduce dissolution of the drug particles are coated with this type of materials e.g. polyethylene glycol. One may skip the use of disintegrating agent to promote delayed release.

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 whole 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 internal pressure which pumps the drug solution out of the aperture and releases the drug in gastric environment. The delivery rate is constant provided that the excess of drug present inside the tablet. But it declines to zero once the concentration drops below saturation.

4. Release is controlled by ion exchange

Ion exchangers are water insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried form a beads which are tabulated. The drug release depends upon high concentration of charged ions in gastro intestinal tract where, the drug molecules are exchanged and diffused out of the resin into the surrounding fluid. This mechanism relies upon the ionic environment of resin and not pH or enzyme on absorption site.

CLASSIFICATION OF SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Depending upon the manner of drug release, this system has are classified as follows:

A. Continuous Release system

a) Diffusion sustained system

Reservoir type.

Matrix type

b) Dissolution sustained system

Reservoir type.

Matrix type

c) Methods using Ion-exchange

d) Methods using osmotic pressure

e) pH independent formulations

B. Delayed Transit and Continuous Release System

these systems are designed prolong their residence in the GIT along with their release.

C. Delayed Release System The design of such systems involves release of drug only at specific in the GIT. The drug contained in such a system is those that are destroyed in the stomach or by intestinal enzymes. Known to cause gastric distress. Absorbed from a specific intestinal site.

A. Continuous release system

a. Diffusion controlled system

Reservoir devices

This system involves a membrane which controls the release of drugs from the matrix system.

The characteristics of reservoir diffusion system are

- Zero order drug release is possible.
- The release rate is dependent on the type of polymer.
- High molecular weight compounds are difficult to deliver through the device.
- Matrix type

A solid drug is distributed into an insoluble matrix and the release rate of drug which generally depend on the rate of drug diffusion and the rate of solid dissolution. The characterstics of Matrix type

- Zero order release can not be obtained.
- Easy to produce than reservoir devices.
- High molecular weight compounds are delivered through the device.

b. Dissolution controlled Release system

A drug which having a slow dissolution rate this drugs are naturally sustained and for those drugs with high water solubility, decrease their dissolution rate through appropriate salt or derivative formation.

Soluble reservoir system

In this system drug is coated with erodible coat, which is slowly dissolved in the contents of GI tract by alternating layers of drug with the rate controlling coats. Soluble matrix system (Monolith)

As the drug is homogenously dispersed throughout rate controlling medium, this system is also called monolithic system.

c. Dissolution and Diffusion Controlled Release Systems

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

d. pH-independent formulation

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.

METHODS OF PREPARATION

1. Direct Compression

In this process powdered materials are compressed directly without changing the properties of the drug like physical and chemical properties.

2. Wet Granulation

In this method weighed quantities of drug and polymer are mixed with sufficient volume of granulating agent. After enough cohesiveness was obtained, then screening of wet mass. The granules are dried and screening of dry granules, then blending with lubricant and disintegrate to produce “running powder “tablets are compressed using a single-punch tablet compression machine.

3. Melt Granulation

In this process use of a substance, which melts at relatively low temperature? This substance can be added in the molten form over the substrate, which is then heated above its melting point. Different lipophilic binders were tried by using melt granulation technique.

4. Hot-Melt Extrusion Process

In the hot-melt extrusion process, a mixture of the active ingredients, the thermoplastic polymers and other processing aids is fed into the barrel of the extruder through the hopper. The materials are transferred inside the heated barrel by a rotating screw. The materials melt at elevated temperatures and the molten mass is continuously pumped through the die attached at the end of the barrel. Depending upon the dimensions of the die cylinders, films can also be produced from the extruder.

Effect of Release limiting factor on drug release

- Polymer hydration:
- Drug solubility
- Solution solubility
- Polymer diffusivity
- Thickness of polymer diffusional path
- Thickness of hydrodynamic diffusion layer
- Drug loading dose
- Surface area and volume
- Diluent's effect
- Additives

FACTORS INFLUENCING ORAL SUSTAINED RELEASE DOSAGE FORM DESIGN

Two factors involved in oral sustained-release dosage form design.

A. Biological Factors

B. Physicochemical Factors

A. Biological Factors

1. Biological half life

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from

the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-lives shorter than 2 hours such as furosemide or levodopa are poor candidates for SR

preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.

2. Absorption

Since the purpose of forming a SR 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 GI 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, SR preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds tries 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 bioadhesive materials.

3. Metabolism

Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

B. Physicochemical Factors

1. 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.

2. Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

3. Stability

Orally administered drugs can be subject to both acidbase hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propentheline and probanthine are representative example of such drug.

4. Ionization, pka and aqueous solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pka of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release process must be defined. Compounds with very low solubility (<0.01 mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility

of the compound 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.

CHARACTERIZAION OF SUSTAINED RELEASE TABLET

Before marketing a sustained release product, it can be evaluated and characterized by using different parameters including in vitro, ex vivo and by in vivo (Clinical) procedures, and it is must to assure the strength, safety, stability and reliability of a product. A number of techniques have been used to characterize SRDDS and determine the various feasibility or flexibility of their formulation process. Various authors have discussed the evaluating parameters and procedures for sustained release formulations.

1. Pre-compression Parameter:

- **Angle of Repose:**

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height (h) of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = \frac{h}{r}$$

Where, 'h' is the height of the powder cone and ' r' is the radius of the powder cone.

Table: 4.9 Standard limits for Angle of Repose

Type of Flow	Angle of Repose
Excellent	<20
Good	20-30
Passable	30-34
Very poor	>35

- **Bulk Density**

Weigh accurately 5 gm of powder blend, and transferred in 100 ml graduated cylinder. Carefully level the powder blend without compacting, and read the unsettled apparent volume (V0). Calculate the apparent bulk density in gm/ml by the following formula.[23]

Bulk Density = Mass / bulk volume

- **Tapped Bulk Density**

Weigh accurately 5 gm of powder mixture and transferred in 100 ml measuring cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute.[2]Tap the cylinder for 500 times initially and measure the tapped volume (V1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V2). Calculate the tapped bulk density in gm/ml by the following formula.

Tapped Density = Mass / tapped volume

- **Carr's Index:-**

It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by:-

Carr's index (%) = [(TBD - LBD) x 100]/TBD

Where,

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

- **Hausner Ratio**

Hausner ratio is the ratio of bulk density to the tapped density.

Hausner's Ratio = Tapped density / Bulk density

$H.R = T_D / B_D$

Table: 4.10 Effect of Carr's index and Hausner's ratio on flow property

Flow Character	Carr's Index (%)	Hausner's Ratio
Excellent	≤ 10	1.00-1.11
Good	11-15	1.12-1.18
Fair	16-20	1.19-1.25
Passable	21-25	1.26-1.34
Poor	26-31	1.35-1.45
Very poor	32-37	1.46-1.59
Very, very poor	>38	>1.60

2. Post- compression Parameter:

- **Physical appearance:**

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, color, embossing, debossing,

- **Thickness:**

Thickness was determined for 20 preweighted tablets of each batch using a digital vernier scale and the average thickness was determined in mm. The tablets thickness should be controlled within a +/- 5% variation of standard.

- **Weight variation:**

20 tablets were selected randomly from a batch and were weighed individually and then average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Table 4.11: Weight variation limit:

Average Weight of Tablet (mg)	% Deviation
80 mg or less	±10
80-250	±7.5
250 or more	±5

- **Percentage friability:**

In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping. The tablets were rotated in Roche Friabilator for 100revolutions at 25 rpm. The tablets were dedusted and reweighed. The % Friabilator should be not more than 1% w/w of the tablets is being tested. The % friability is expressed as the loss of weight and is calculated by formula

% friability = (wo-wf) / wo x 100

Wo – initial weight of tablets

Wf – final weight of tablets

- **Hardness:**

Hardness of tablet was determined using Monsanto hardness tester. Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness.

- **Drug Content:**

The 10 tablets were crushed in mortar and the powder equivalent to 600mg of Pirfenidone was transferred to 1000ml of 6.8pH Phosphate buffer in volumetric flask and filtered through 0.45µm What man filter paper after necessary dilution, sample was measured at 310nm for Pirfenidone using double beam UV-Vis Spectrophotometer. The content of drug calculated from simultaneous equation method.

- ***In Vitro* Dissolution studies:**

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions

Apparatus:- USP Apparatus-II

Medium:-0.1N HCl up to first two hours, 6.8 pH Phosphate buffer for remaining 22 hours.

Rpm:-50

Temperature:-37°C±0.5°C

- **Stability studies :**

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of variety of environmental factors such as temperature, humidity etc

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 clinical response, blood level data, urinary excretion studies, nutritional studies, toxicity studies and radioactive tracer techniques.

- Stability Studies
- In vitro- In vivo Correlation (IVIVC)
- Bioavailability Testing
- In vitro drug release characterization models:
- Mathematical Models .The various types of modals used are zero order release kinetics, first order release kinetics, Higuchi model, Hixson-Crowell cube root law and Korsmeyer-Peppas model.

CONCLUSION

There are several reasons for attractiveness of sustained release drug delivery system, provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak through

concentration and side effects and possibly improves the specific distribution of the drug. From the above discussion, we can concluded that development of SRDDS depend upon various factors such as Biopharmaceutics, Pharmacokinetic and Pharmacodynamic characteristics of drug**.** Sustained release formulations are a promising way to improve the patient compliance by reducing dosing interval and minimizing adverse effect.

REFERENCE

1. Manish JC, Satish AP, "A concise Review on Sustained Drug Delivery System and Its Opportunities," American J. of Pharmtech Res,2012, 2(2), 227-238.

2. Sampath kumar KP, Dutta AS, "Sustained release drug delivery system potential." www.thepharmajournal.com,2012, 1(2), 48-60

3. Anuj PT, Nagarjuna T, "Sustained release drug delivery system: A modern formulation approach." Int J. of Res in Pharmaceutical & nano sci, 2013, 2(5), 586-601

4. Niraj V, Srivastava K, "Sustained and controlled drug delivery system-As a part of modified release dosage form", Int J. of Res in Pharmaceutical and nano sciences, 2015, 4(5), 347-364

5. Bansal BK, Shakya.V, "A new trend in oral sustained release technology," Asian J. of Pharmaceutical Research and Development," 2014, 2(2), 91-95

6. Piyush M, Gayitri J, "Development of Sustained Release Drug Delivery System," Asian Specific J. of Health Sci, 2015, 2(1), 179-185

7. Zalte H.D, Saudagar RB, "Review on Sustained Release Matrix Tablet," Int J. Pharm Bio Sci, 3(4), 2013

8. Pratik P P, Shrenik KS, "A Detailed Review on Sustained Release Drug Delivery System," Int. J. Med. Pharm. Res, 2013, 1(1), 145-151

9. Jaimini M, Kothari A, "Sustained Release Matrix Type Drug delivery system," Journal of Drug Delivery and Therapeutics,2012**,** 2(6), 142-148

10. Tarun P, Vishal S, Gaurav S, " Novel Oral Sustained Release Technology: A Concise Review," Int J. of Res and Development in Pharmacy and Life Sci, 2013, 2(2), 262-269

11. Tarun P, Vishal S, Gaurav S, " Novel Oral Sustained Release Technology: A Concise Review," Int J. of Res and Development in Pharmacy and Life Sci, 2013, 2(2), 262-269

12. Lordi G. Nicholas. Sustained release dosage form, Leon Lechman, Liberman, Kanig, The theory and practice of Industrial pharmacy, 1987;(3) 430-45614

13. Shailesh J. wadher, Satish B. Mehtre, Tukaram M. Kalyankar. Recent (aspects) trend on sustained drug delivery system.International journal of chemical and pharmaceutical sciences.2013;4(2),0976-9390

14. 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.

15. 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.

16. Bechgaard H, Nielson GH. Controlled release multiple units and single unit dosage. Drug Dev & Ind Pharm 1978; 4(1): 53-67.

17. Qiu Y, Zhang G, Wise DL. Handbook of pharmaceutical controlled release technology. New York: Marcell Dekke, 3rd edition 2000.

18. Chugh I, Seth N, Rana AC, Gupta S. Oral sustained release drug delivery system: anoverview. International research journal of pharmacy 2012; 3(5): 57-62.

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

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

21. Davis SS, Hardy JG, Taylor MJ, Whalley DR, Wilson CG. Comparative study of gastrointestinal transit of a pellet and tablet formulation. Int J Pharm 1984; 21: 167-77.