Review Article CODEN: IJPRNK ISSN: 2277-8713
Rajesh Asija, IJPRBS, 2015; Volume 4(1): 439-454 IJPRBS

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

SUSTAIN DRUG DELIVERY SYSTEM: A REVIEW

RAJESH ASIJA, SANGEETA ASIJA, SHAILENDRA BHATT, RASHMI GUPTA
Maharishi Arvind Institute of Pharmacy, Jaipur, 302020.

Accepted Date: 22/02/2015; Published Date: 27/02/2015

Abstract: Sustain Release dosage form is designed to deliver the drug at predetermined rate, in this two type of dose is used, first one is loading dose and second one is maintenance dose. Loading dose is required for immediate attained therapeutic concentration and maintenance dose required for prolong the action of drug. More patient compliance and prevent side effect of conventional dosage form. This system reduced frequency of administration of drug and cured the disease in short time and having less fluctuation in steady state drug level. Various method are used for formulation of sustained drug .this article mainly concentrates on formulation, factor affecting SDDS and advantages and disadvantages. Recent investigation is going on this drug delivery system due to having many advantages.

Keywords: Sustained Release, Loading Dose, Maintenance Dose, Formulation

PAPER-QR CODE

Corresponding Author: DR. RAJESH ASIJA

Access Online On:

www.ijprbs.com

How to Cite This Article:

Rajesh Asija, IJPRBS, 2015; Volume 4(1): 439-454

INTRODUCTION

The term "sustained release" is specified and identified in the medical and pharmaceutical literature for many decades. It has been constantly used to depict a pharmaceutical dosage form formulated to retard the release of therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration.

The term "controlled release" is defined as a meaning that goes beyond the scope of sustained drug action. It also described as predictability and reproducibility in the drug release kinetics, which implies that the arrival of drug from controlled – release drug delivery system proceeds at a rate profile that is surprising kinetically, but also reproducible from one unit to another.

Sustain drug delivery system is used for sustain action, that are specify distinctly to achieve a prolonged therapeutic action by continuously releasing medication over an extend period of time after administration single dose of drug. sustained release (SR) dosage forms the release of the active agent, In the spite of fact that, is lower than in the conventional formulations, The beneficial factor of sustained-release tablets or capsules are that they can often be taken less frequently than immediate formulations of the same medication, and that they keep steadier levels of the drug in the bloodstream. The fundamental reason of controlled release drug delivery system to determined the biopharmaceutical, pharmacokinetic, and pharmacodynamics characteristics of a drug in such a way that its utility is increased, side-effects are diminished and cure or control of the condition is developed.[1]

The USP/ NF presently clearly characterized many types of modified release dosage forms.

- Delayed released dosage forms ex- enteric coated tablets
- Extended released dosage forms ex- sustained released dosage forms, Controlled release dosage forms.

Modified Release dosage form

It is described as one for which the drug release characteristics is chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, tablets and capsules.

1. **Delayed Released dosage form** it is defined as system in which continuous dosing and intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form as delayed release systems include repeat action enteric-coated tablets and tablets and capsules where timed release is achieved by a barrier coating.

2. **Extended-release dosage form** A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate release form.

A Sustained release dosage form is specified as "Any drug or dosage form modification that prolongs the therapeutic activity of the drug". This delivery system is mainly used as a part of the treatment of acute and chronic diseases as they keep the concentration of drug in plasma above the minimum effective concentration to and below the minimum toxic level for an extended period of time. Sustained release, Prolonged action, sustained action, extended action, timed release , controlled release, repository and depot dosage forms are terms used to identify drug delivery system that are designed to approached or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

DESIGN OF SUSTAIN RELEASE DOSAGE FORM

The main aim to designing a sustained release forms is to deliver drug at a predetermined rate to achieve and maintain a constant drug blood level. This is usually accomplished by to attain zero order release from dosage forms. Zero order release elements drug release from dosage form that is independent of the amount of drug in the delivery system. Usually sustained release system do not attain this type of release and try to mimic zero order release by releasing drug in slow first order pattern as described by following equation.

$$\text{Rate in} = \text{Rate out} = K.Cd.Vd$$

Here;

C_d = Desired drug level

V_d = Volume of distribution

K = elimination rate constant

ADVANTAGE OF SUSTAIN DRUG DELIVERY SYSTEM

- To bring down in frequency of dosing of drug and Provide patient compliance
- Uniform release of drug over the period of time.
- Diminished systemic side effect
- Diminished drug accumulation

- Blood level oscillation properties of multiple dosing of immediate dosage form is decreased because a more even blood level.

LIMITATION OF SUSTAINED DRUG DELIVERY SYSTEM

- Systemic availability is decreased in comparison to immediate release conventional dosage form
- Poor *invivo*, *invitro* correlation
- Dose dumping possibility may occur due to food, physiologic and formulation variable or chewing or grinding of oral formulation by the patient.
- The possibility of being retrieved of drug is difficult in case of poisoning, toxicity and hypersensitivity action.
- Dosage regimen is not flexible.
- This is designed for normal population on the basis of average drug biologic half- life's.
- First pass metabolism may easily occur.
- It is more costly than conventional release dosage form.

CRITERIA FOR DRUG SUITABLE TO OBTAINED SUSTAIN ACTION

- It should have Desirable half-life.
- It should have High therapeutic index
- It should required Small dose
- Should have Desirable absorption and solubility characteristics.
- Should Desirable absorption window.
- Should have first past clearance.

CRITERIA FOR DRUG UNSUITABLE TO OBTAINED SUSTAIN ACTION

- Drug that have Short elimination half life<2 hour
- Drug that have Long elimination half life>8hour
- Drug which required Large dose

- Drug which have Poor absorption
- Drug having Low or slow drug solubility
- Drug having Extensive first pass clearance

CHARACTERISTICS OF DRUGS REQUIRED FOR SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Factors affecting Design and formulation of Sustained Release Dosage Forms -

The therapeutic efficacy of drug is not simply a function of its intrinsic pharmacological activity but also depends upon the path of the drug molecule from the site of administration to the target site. Different conditions meet by the drug molecule while pass across the path of distribution may alter either the effectiveness of the drug or affect the amount of the drug reaching the receptor site.

A. **Pharmaceutics**: This mentioned to the manufacturing/development of an efficient delivery system in which the drug has greater physiological stability and best bioavailability.

B. **Pharmacokinetics /Bio pharmaceutics**:- This includes the analysis of absorption, distribution, biotransformation and elimination, before and after reaching the target site and evaluation of the relationship between delivery system and therapeutic response.

C. **Pharmacodynamics /Clinical Pharmacology**: It is the of the mechanism of action and clinical efficacy of a drug administered in dosage form in terms of onset, and duration of pharmacological activity.

Factor affecting the Design of Sustained Release Drug Delivery System:

PHYSICOCHEMICAL CHARACTERISTICS [2, 3]

- **Dose size**

If product is taken through the mouth has a dose size greater than 0.5 gm it is a humble candidate for sustained release system. Single dose of 0.5-1.0 gm is esteemed maximal for a immediate dosage form. Some compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid system. Another treatment is the margin of safety in which involved administration of large amounts of a drug with narrow therapeutic range.

- **Aqueous Solubility**

That compound having Low solubility (less than 0.01mg/ml) are intrinsic sustained, since there release over the time course of a dosage form in the GI tract will be restricted by dissolution of the drug. The lower limit for the dissolution of a drug to be formulated in a sustained-release system has been reported to be 0.1mg/ml, so it considered that the solubility of the compound will limit the choice of mechanism to be employed in sustained delivery system.

- **Stability of the drug:**

Orally administered drugs can be subject to both acid base hydrolysis and undergo enzymatic degradation. Degradation will continue at the reduced rate for drugs in the solid state, for drugs that are not stable in stomach; systems that prolong delivery ever the entire course of transit in GI tract are useful. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered form a sustained release dosage from because more drug is delivered in small intestine and hence subject to degradation.

- **PK_a value of the drug:**

The relationship between pKa of compound and absorptive environment introducing drug in an unchanged form is adventitious for drug permeation but solubility decrease as the drug is in unchanged form.

- **Protein binding:**

It is well known that several types of drugs bind to plasma proteins with a attendant influence on the duration of drug activity. Since blood proteins are the most part re-circulated and not eliminated, protein- drug binding can serve as a depot for drug producing a prolonged release profile, especially if a high level of drug binding occurs.

Binding of drug to plasma proteins will be defined by a long half-life of elimination for drugs and such type of drugs generally most require a sustained release dosage form. However drugs that show high degree of binding to plasma proteins also might bind to bio-polymers in GI tract which could have influence on sustained drug delivery. The vicinity of hydrophobic moiety on drug molecule also increases the binding potential.

- **Molecular size and diffusivity:**

The capacity of drug to diffuse through membranes it's so called diffusivity & diffusion coefficient is function of molecular size (or molecular weight). usually, values of diffusion coefficient for intermediate molecular weight drugs, through adaptable polymer range from 10-8 to 10-9 cm2/sec. The diffusion coefficient in various polymers frequently is so small that they

are difficult to evaluate i.e. less than 16-12 cm2/sec. Thus high molecular weight drugs and/or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

B. biological properties of drug

- **Absorption**

The rate-limiting step in drug delivery from a sustained release product is release, from its dosage form rather than absorption. The rate, extent, and uniformity of absorption of a drug are important factors when considered its formulation into a sustained release system. The main advantage of sustain drug release is high absorption rate.

- **Distribution:**

It not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extracellular fluid. Apparent volume of distribution and the ratio of drug concentration in the tissue are two basic parameters to define distribution characteristics.

- **Metabolism:-**

Drugs that are fundamentally metabolized before absorption, either in the lumen or tissue of the intestine can show decreased bioavailability from slower-releasing dosage forms.

Metabolism to other active form can also be considered as sustained effect. The extent of metabolism should be identical and predictable when the drug is administered by different routes.

- **Elimination Half Life**:

Oral sustained release product is to maintain therapeutic blood levels over prolonged period. To this, drug must enter the circulation at approximately the same rate at which it is eliminated. Smaller the t½, larger the amount of drug to be incorporated in the sustained release dosage form. Drug with its half life in the range of 2 to 4 hours make good candidate (propranolol) and long half-life need not be used in such type of preparation e.g. Amlodipine.

- **Side Effect and safety criteria**:-

The incident of side effects can be minimized by controlling the concentration of the drug exists in plasma at any given time. Hence sustained release formulation appears to offer a solution to this problem. A drug is considered to be relatively safe if its TI value exceeds 10.[2]

- **Formulation and development of oral sustained release drug delivery system**[3,4,5]

Sustained release systems depend upon dissolution, diffusion or a combination of both mechanisms, to produce slow release of drug to the gastrointestinal tract. Theoretically and desirably a sustained release delivery device, should release the drug at zero-order process which would result in a blood level time profile similar to that after intravenous constant rate mixture.

Oral controlled drug delivery systems can be divided into following class based on their mechanism of release the drug.

Diffusion controlled extended release- Diffusion systems are characterized by the release rate of drug being dependent on its diffusion through an inert membrane barrier. In general, two types or subclasses of diffusion systems are recognized reservoir devices and matrix devices.

1) Reservoir system:- Reservoir devices are characterized by a core of drug, the reservoir encompass by a polymeric membrane. The nature of the membrane defined the rate of release of drug from the system sustained release. For this to obtained good results, the polymer itself should not dissolve, yet rather should permit the drug to diffusion through the polymer membrane to the outside, on account of oral drug conveyance, into the gastrointestinal tract.

2) **Matrix system**:- Matrix device, includes of drug dispersed homogeneously throughout a polymer matrix. In this object, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process to exist with a particular action with the interface between the bathing solution and the solid drug moving towards the interior portion.

B. Dissolution controlled extended release-

These types of systems are easiest to depicted. The drug present in such system may be the one:

- With intrinsic slow dissolution rate e.g. Digoxin and Griseofulvin.
- That creates slow dissolving forms, when it keeps in contact with GI fluids.
- Having high water solubility and dissolution rate.
- Drugs which having high aqueous solubility and dissolution rate, shows competition in controlling their dissolution rate.

Dissolution-controlled release can be obtained by decreasing the dissolution rate of a drug in the GI medium, fusing the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of different thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous border layer. The solubility of the drug to make available the source of energy for drug release, which is countered by the stagnant-liquid diffusion layer. The rate of dissolution (dm/dt) can be approximated by Equation 1.

$$dm/dt = ADS/h$$

Where

S = Aqueous solubility of the drug.

A = Surface area of the dissolving molecule.

D = Diffusivity of the drug and

h = Thickness of the boundary layer.

C. **Osmotic controlled extended release** - A semi permeable membrane is placed surrounding a tablet, micro particle or drug solution that favours transport of water into the tablet with ultimate pumping of drug solution out of the tablet by way of a small delivery aperture in tablet coating.

Osmotically sustained systems are defined as two types-

Type A includes an osmotic core with drug

Type B includes the drug in flexible bag with osmotic core surrounding.

D. **Ion exchange resin-in this method** irreversible drug complex is formed by upon prolongs exposure of drug to the resin. Later then drug get exchanged in GIT and are released with excess of Na^+ and Cl^- present in gastrointestinal tract. The release of drug containing opposite charge retarded by the addition of ion exchange resin to HPMC-matrices due to formation of complex between drug and resin.

There are two types of resin-

Anionic resin- amino or quaternary ammonium groups

$Resin^+ – Drug^- + Cl^- \text{----------}>> resin^+Cl^- + Drug^-$

Cationic resin- carboxylic groups, or sulfonic groups in repeating positions on the chain.

$Resin^- – Drug^+ + Na^+$ ----------->>$resin^- Na^+ + Drug^+$

In this system, Water insoluble cross linked polymer compounds are used.

E. **pH– Independent formulations**– some of drugs are weak acid or weak bases, and release from Sustained release formulations is pH dependent. Buffers such as amino acid salts, citric acid, phosphoric acid phthalic acid or tartaric acid can be added to the formulation to help to maintain a constant pH thereby rendering pH independent drug. These salts adjust the pH to the desired value when dosage form move across the gastrointestinal tract.

F. **altered density formulation**-

1) Low density approach-globular shell that have low density than gastric fluid is used as carrier of drug as sustain release.

2). In high density approach- the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4g/cm3. I

RECENT RESEARCH IN SRDDS

• **Gobbo O et al (2015)** formulated dry powder inhaler (DPI) with appropriate formulation stability, biological action and suitable physicochemical and aerosolisation characteristics that provide a viable alternative to parenteral formulations. The present study planned to create sugar-based nanoporous/nanoparticulatemicroparticles (NPMPs) loaded with a therapeutic peptide – salmon calcitonin(SCT) The physicochemical properties of the powders and their suitability for pulmonary delivery of(SCT) were resolved. Generation of powders composed of (SCT) loaded into raffinose or trehalose with or without hydroxypropyl-β-cyclodextrin was done using a laboratory scale spray dryer. Spray dried microparticles were spherical, porous and of small geometric size (≤2 µm). Aerodynamic assessment showed that the fine particle fraction (FPF) less than 5 µm ranged from 45 to 86%, depending on the formulation. The mass median aerodynamic diameter (MMAD) varied between 1.9 and 4.7 µm. Compared to unprocessed (SCT), SCT:raffinose composite systems presented a bioactivity of approximately 100% and Sct:trehalose composite systems between 70–90% after spray drying. Storage stability studies explained composite systems with raffinose to be more stable than those containing trehalose. These sugar-based salmon calcitonin-loaded NPMPs retain reasonable Sct bioactivity and have micromeritic and physicochemical properties which indicate their suitability for pulmonary delivery. Formulations presented a similar pharmacokinetic profile to Sct solution. Hence the benefits of a dry powder formulation is its non-invasive delivery route and ease of administration of the Sct[11]

• **Chang D.etal (2014)** Inorganic mesoporous silica material, as drug carriers, and a natural organic polymer alginate (ALG),both are used to establish a sustained drug delivery system for the poorly water-soluble drug Indomethacin (IND). Mesoporous silica nanospheres (MSNs) were synthesized using an organic template method and then functionalized with aminopropyl groups through postsynthesis.The effects of surface chemical groups and ALG layer on IND release were systematically studied using scanning electron microscopy (SEM), transmission electron microscopy (TEM), nitrogen adsorption, zeta-potential analysis and TGA analysis. The results showed that sustained release of IND from the designed drug delivery system was mainly due to the blockage effect from the coated ALG. This simple skill will have used in producing sustained drug systems for poorly water-soluble drugs[12]

• **Santosh G.etal (2014)** Swellable drug delivery system (SDDS) of Pregabalin was prepared and evaluated containing HPMC K4M, Psyllium Husk, Crosspovidone and Polyvinylpyrolidone, by wet granulation method. Nine formulations were formulated in the different ratio of polymers. PF-1, PF-2, PF-3, PF-4, PF-5, PF-6, PF-7, PF-8 and PF-9 Formulations were composed of Psyllium Husk, HPMC K4M, Crosspovidone and Polyvinylpyrolidone respectively. All the formulations were examined for friability, hardness, weight variation, content uniformity, swelling index and in vitro drug release study. Estimation of pregabalin in the formulated SDDS was done by extracting drug in double distilled water and HCL by measuring the absorbance at 210 nm. *In vitro* drug release study was accomplished in type 2 dissolution test apparatus (paddle) stirrer at 50 rpm using 900 ml of 0.1N HCl maintained at 37ºC ± 0.5ºC as the dissolution medium. PF-5 Formulation was selected as improved formulation. Therefore, it can be concluded that the SDDS may be exploited successfully for the delivery of drugs such as pregabalin[13]

• **Biswas S etal (2014)** Theophylline hydrochloride sustain release tablet were developed using Methocel k 15 MCR, Methocel K4M CR premium and Methocel K100M CR premium in blending and granulation steps of processing and evaluate their physico-chemical properties. Dissolution profile is also compared with the marketed drugs. Tablets were formulated by wet granulation method. The active ingredient, diluents, release retardants, fraction of polymer are mixed together to make wet mass for granulation. The rest of the polymer was slowly mixed in the blending process. The effect of polymer on drug release was examined with other physicochemical properties. Formulations (F-4) containing Methocel k 15 MCR met the desired sustained release pattern as per USP specification (30th edition, 2006) from 1st hour to 8th hour as per in-vitro dissolution studies. The second test trial containing double polymer Methocel K4M CR premium and Methocel K100M CR premium also exhibited desired release pattern slightly deviated from compendia limit against specified time for 1st and 2nd hour. At the same time we also studied comparison of dissolution profile of two marketed product with

our test product. In that case the marketed product revealed irregular dissolution profile in 6 th and 8 th hour in some cases[14]

• **Madhurima SC *et al* (2014)** formulated a sustained release Acebutolol HCl microspheres prepared by solvent evaporation method in which the different concentration ranges of Acebutolol HCl and ethyl cellulose polymer was taken. The reaction mechanism to form sustained release Acebutolol HCl microspheres were determined by optical microscopic method and scanning electron microscope (SEM). The particle size of Acebutolol ranged from 302 to 370 µm. The size of particle was observed to increase with increasing concentration. The present study shows a relatively simple method to design and develop sustained release Acebutolol microspheres and evaluation micromeritics property , invitro study and Drug release kinetics of Acebutolol HCl[15]

• **Vani V.etal (2013)** Controlled release micro beads of Metoprolol Succinate were prepared using Natural polymers, xanthan gum, sodium alginate, and Guar gum as rate controlling polymers.To the management of hypertension, Metoprolol succinate, β1- selective adrenergic receptor- blocking agent is used. The half-life of drug is relatively short (3-6hr) The formulations i.e. F1-F15 were made by applying the Emulsion solvent Evaporation method, to bring about controlled release of Metoprolol Succinate over 16hrs by using varying concentrations of polymers. Drug compatibility studies are examined using Fourier transform infrared spectroscopy (FTIR) to check for the compatibility between the drug and polymers. All the formulations are subjected to evaluated Micrometric properties, Percentage yield, , Particle size analysis, Drug entrapment efficiency, Loose surface crystallography, Swelling studies and in-vitro drug release studies. The best formulation, F15 containing 3.5%w/w guar gum showed sustained release of drug with 82.7 ±0.23% drug release at the end of 16th hour and was in range of USP limits. The Percentage yield, Particle size analysis, Drug entrapment efficiency, Loose surface crystallography and Swelling studies of the best formulations, F15 were found to be 96%, 93.7±1.28%, 535±2.28 µm , 10.8±0.10% and 330.5±11% respectively. The values of correlation (r2) were calculated and were found to be more linear for first order release as compared to zero order. The kinetic data showed to Higuchi model and good regression coefficients were observed. The extended release F15 formulation was found similar and comparable to the innovator product. Therefore, one can supposed that the Metoprolol succinate microbeads are promising pharmaceutical dosage forms by providing sustained release drug delivery systems and avoiding the dose related side effects in the entire physiological region.[16]

• **Goswami DS *et al* (2013)** developed and evaluated site specific sustained release microspheres for intestinal infection. Hydrocortisone has the anti-inflammatory property so used to treat the intestinal infection so oral Hydrocortisone is prescribed to treat more severe

symptoms of colitis. Coating was done with the colon specific polymer eudragit S100 and sodium alginate used as a matrix polymer and HPMC K4M and gellan gum was used as mucoadhesive polymers. Hydrocortisone mucoadhesive microspheres were prepared by orifice ionic gelation method and characterized the particle size, percentage yield, drug entrapment efficiency, loose surface crystal study, surface accumulation study, % moisture loss, swelling poperties, wash off test and in vitro drug release of mucoadhesive microsphere at different pH up to 12 hrs. The drug entrapment efficiency of all formulations was reported as high profile ranges 80-97.44% and the surface pH in the ranges between 6.80 -7.02. The swelling index in the range 51.11-88.12%. It was found that the F1 shows the best cumulative drug release up to 12 hrs of the period. Hence it was concluded that the polymer possess substantial release with good mucoadhesion properties could be used for sustained drug delivery[17].

• **Bashir S *et al* (2013)** Prepared Nateglinide Microspheres using rate controlling polymers Carbopol-940 and Hydroxypropylmethyl cellulose (HPMC) by Ionic gelation technique .Shape and surface were evaluated with Scanning electron microscopy (SEM). Percentage Yield, Particle size analysis, Encapsulating Efficiency, Micromeritic analysis, Fourier Transform Infra-Red Spectroscopy (FTIR), Differential Scanning Colorimetry (DSC) were done for characterization of Microspheres.The invitro studies were performed at pH 1.2 and 7.2 using USP dissolution type-II apparatus and release rates were analyzed by the application of different pharmacokinetic models. The size of microspheres was found to be varied from 781µm to 853µm. Rheological studies proved excellent flow behavior while percentage yield was found to be varied from 72% to 79%. The microspheres prepared with sodium alginate showed interaction while microspheres obtained from blend of Carbopol-940 plus sodium alginate was smooth and spherical. Maximum entrapment efficiency (71.4%) was achieved for Microspheres with Carbopol -940. The greater retardation in drug release was observed for microspheres containing Carbopol-940 and release pattern followed Higuchi kinetics model[18].

• **Saha N *et al* (2013)** prepared non-steroidal anti-inflammatory drug Ibuprofen microspheres by using Methocel K4M & Eudragit RSPO. These microspheres were prepared by emulsification solvent evaporation method to provide sustained action and to minimize local side effect of Ibuprofen by avoiding the drug release in the upper gastrointestinal tract. The prepared microspheres were evaluated and in-vitro release studies. In-vitro drug release was studied in a paddle type dissolution apparatus (USP Type II Dissolution Apparatus) using Phosphate buffer (pH 7.4) as the dissolution medium at 37.5oC for 6 hours (paddle speed 50 RPM). The release mechanisms were examined with Zero Order, First Order, Higuchi and Korsmeyer-Peppas equations. The correlation coefficients values of the graphs showed that the formulations best fit with Korsmeyer-Peppas release pattern. Microspheres' morphology and chemical integrity

were studied by a scanning electron microscope (SEM) and Fourier transforms infrared spectroscopy (FTIR) respectively[19].

Conclusion

Sustained drug delivery system is widely used for slowed release of drug to obtained prolonged action of drug at predetermined rate. It also known as prolonged drug delivery System. Oral route of sustained drug delivery system is widely used due to its more flexibility. This reduced fluctuation at steady state drug level and provides patient compliance and reduced side effects of conventional dosage form. There are certain considerations to formulated sustained drug system. If drug having long half life it sustained its own and having short half life, required sustained action. There are recent approach is going on this system.

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