

Sustained Release Drug Delivery Systems: A Patent Overview

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Abstract

Sustained Release Drug Delivery System (SRDDS) is 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. Now a day's focus on the development of SRDDS has increased, as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. The major goal of designing SR formulations was intended to modify and improve the drug performance by increasing the duration of drug action, decrease the dosing frequency, reduced side effects, decreasing the required dose employed and providing the shortest possible time by using smallest quantity of drug administered by the most suitable route. SR dosage forms are designed to transport the blood level of a drug instantly to therapeutic concentrations by means of an initial dose portion and then maintain this level for a certain predetermined time with the continuation portion. SR of drugs in GI tract following oral administration is not affected by the absorption process. The major goal of SR dosage forms is the improvement of drug therapy assessed by the relationship between advantages and disadvantages of the use of SR systems. The present review article is useful in knowledge of highlighted formulation approaches, criteria for drug selection, different countries

sustained release dosage form patents and advance novel research for SRDDS. The present review is concerned with the patent study of drug release through controlled or sustained release dosage forms. This patent review is useful in knowledge of sustained release dosage forms for its application.

Keywords: Controlled drug delivery; Polymers; SRDDS Patent; Sustained Release Approaches; Zero order release.

Abbreviations: SRDDS: Sustained Release Drug Delivery System; SR: Sustained Release; US: United States Patent; CN: China Patent; WO: World Intellectual Property Organization (WIPO); EP: European Patent; KR: South Korea Patent; CA: Canadian Patent; JP: Japan Patent; HPMC: Hydroxy Propyl Methyl Cellulose; EC: Ethyl Cellulose; Sodium CMC: Sodium Carboxy Methyl Cellulose.

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Introduction

Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing

medication over an extended period of time after administration of single dose. The main aim of preparing sustained release formulations was intended to modify and improve the drug performance by increasing the duration of drug action, decreasing the frequency of dosing, decreasing the required dose employed and providing uniform drug delivery. During the last 2-3 decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Sustained release dosage forms are prepared by coating the tablets so that the rate of solubility is controlled or individually encapsulating micro particles of varying sizes so that the rate of dissolution can be controlled [1, 2]. Keating listed the following advantages of adsorbing basic nitrogen containing drug onto strong acid cation exchange resins and using them in dosage forms: Prolonged release of drug from the complex for 8-12 hours in the GI tract. SRDDS reduced the toxicity by slowing drug absorption, improved palatability, and availability of formulation in liquid and solid SRDDS, increased stability by protecting the drug from hydrolysis or other degradative changes in the gastrointestinal tract. Very early on, due consideration has to be given to their pharmacokinetics in order to obtain that specific release profile which guarantees optimum therapeutic efficiency. Enclosing drugs in diffusion-controlled membranes is an important basic principle of controlled time release. Combining neutral, permeable polymers with anionic soluble types permits realization of various release mechanisms, while paying due regard to the physicochemical properties of the drug. Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern. Localize drug action by spatial placement of a controlled release system usually rate controlled adjacent to or in the diseased tissue or organ. In short, Sustained release formulations (e.g., Aspirin SR, Dextrin SR) describe the

slow release of a drug substance from a dosage form to maintain therapeutic response for extended period (e.g., 8-24 hours) of time. In oral form it is in hours, and in parenteral's it is in days and months. Controlled release (e.g., Adalat CR tablet for nifedipine, Dynacirc CR tablet for isradipine) dosage form describes the rate or speed at which the drug is released is controlled [3, 4]. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. 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. Ideally a sustained release oral dosage form is designed to release rapidly some predetermined fraction of the total dose into GI tract [5]. This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then releases at a controlled rate. The rate of the drug absorption from the entire maintenance dose into the body should equal to the rate of the drug removal from the body by all the processes over the time for which the desired intensity of pharmacological response is required. Ideally two main objectives exist for these systems: Spatial delivery, which is related to the control over the location of drug release. Temporal drug delivery of the drug is delivered over an extended period of time during treatment [6, 7].

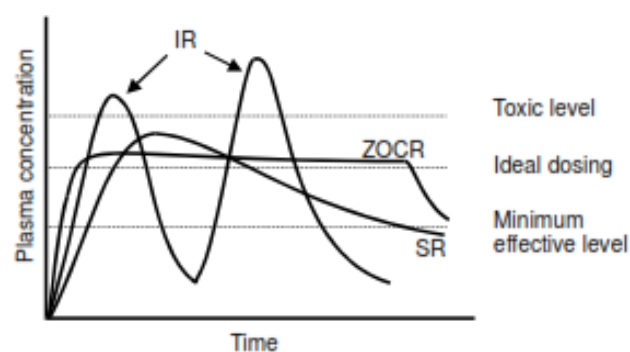


Figure: 1. Graphically representation of plasma concentrations of a conventional Immediate Release (IR), a Sustained Release

(SR) and an idealized zero-order controlled release (ZOCR) drug delivery systems.

Advantages [8]

- Improved patient compliance due to less frequent drug administration.
- Reduced fluctuation in steady-state drug levels.
- Maximum utilisation of the drug
- Increased safety margin of potent drug
- Reduced healthcare costs through improved therapy
- Shorter treatment period
- Less frequency of dosing.

Disadvantages [9]

- Reduced potential for accurate dose adjustment, administering a fraction of a tablet or capsule in order to obtain fine dose adjustment is more difficult with some sustained release products than others.

- If the drug has short half-life, it has to be administered frequently, so there are chances of missing the dose.
- If the drug is not taken at periodic interval, peak valley plasma concentration time profile obtained is not steady.
- The fluctuations of drug plasma level that occurs during conventional release may produce under medication or overmedication.
- Necessitate for additional patient education and counsel. E.g., “do not crush or chew the dosage unit” and “tablet residue may appear in stools”
- Cost of the formulation is high.
- Poor IVIVC (In vitro – in vivo correlation).

Challenges to Sustained Release Drug Delivery [9]

- Biocompatibility
- Cost of formulation, preparation and processing
- Fate of controlled release system if not biodegradable
- Fate of polymer additives, e.g., plasticizers, stabilizers, antioxidants, fillers etc.

Designing Of Sustained Release Formulations [10, 11]

Table 1: Classification of Sustained Release Drug Delivery Systems

Classification of Sustained Release Drug Delivery Systems (SRDDS)	
Diffusion systems	Reservoir Devices Matrix Devices: • Hydrophobic matrix system • Hydrophilic matrix system • Fat-wax matrix system
Dissolution sustained systems	Soluble reservoir system Soluble matrix system Dissolution sustained pulsed delivery system
Ion exchange resins sustained release systems	
Methods using osmotic pressure	Elementary osmotic pump (EOP) Push pull osmotic pump. Osmotic pump with non expanding second chamber Controlled porosity osmotic pump.

	Monolithic osmotic systems. Osmotic bursting osmotic pump. OROS-CT Multi particulate delayed release systems Liquid Oral Osmotic System (L-OROS)
Mineral Matrices	Macro porous systems Micro porous system Non-porous system
pH Independent formulations	
Altered density formulations	
Swelling and expansion systems	
Floating systems	
Bio adhesive or Mucoadhesive systems	
Biodegradable Matrices	
MASRX and COSRX Sustained-Release Technology	MASRx Technology COSRx Technology

Criterion for Drug Selection of SRDDS [12, 13]

The oral route of drug delivery is the most frequently used and is very convenient, safe and simple. There are more specialized groups of per oral dosage form commonly referred as sustained release, long acting, gradual release, slow release dosage form. The scientific frame work required for successful development of oral drug delivery system consists of basic understanding of following aspects includes physiochemical, pharmacokinetics and pharmacodynamic characteristics of a drug, anatomical and physiomechanical characteristics of GI track, and physiomechanical characteristics of drug delivery mode of the dosage form to be designed. The majority of oral sustained release systems rely on dissolution, diffusion or a combination

of both mechanisms, to generate slow release of drug to the GI milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood level time profile similar to that after intravenous constant rate infusion. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation. A number of physicochemical and pharmacokinetic parameters for the selecting of the drug to be formulated in sustained release dosage form which mostly includes the knowledge on the absorption mechanism of the drug form the GI tract. Sustained (zero-order) drug release has been attempted to be achieved, by following classes of sustained drug delivery system.

Table 2: Physicochemical and pharmacokinetic parameters for drug selection

Parameters	Criteria for drug selection
Physicochemical parameters for drug selection	
Molecular size	< 1000 Daltons
Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8

Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability from all GI segments	Release Should not be influenced by pH and enzymes
Pharmacokinetic parameters for drug selection	
Elimination half-life ($t_{1/2}$)	Between 2 to 8 hours
Absolute bioavailability	Should be 75% or more
Absorption rate constant (K_a)	Must be higher than release rate
Apparent volume of distribution (V_d)	Larger V_d and MEC, Larger will be the required dose
Total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration (C_{ss})	The lower C_{ss} and smaller V_d , the loss among of drug required.
Toxic concentration	Apart the value of MTC And MEC safer the dosage form

Progression of the Research Topics As Examined By Top Cited Papers

Over the Past 30 years, polymers have been one of the most widely used options for the formulation of sustained release compounds with a view to modulating the release profiles of drugs in a satisfactory way, and in this scenario it is common to discover mixtures of different kinds of polymer. This is why a profound knowledge of the factors affecting the release rates of

drugs is critical for the correct scientific development of sustained release systems. As the topics in Table 3 indicate, novel research techniques in drug delivery have advanced from understanding the drug release mechanisms and disclose background on the different drug formulations and review of sustained release drug delivery as review in Table 3. The following are the general categories which are used in controlled release drug delivery.

Table 3: Leading novel researches on sustained release tablet formulations

Drug/s	Polymer used	Ref.
Indomethacin	HPMC K100LV, HPMC K4M, HPMC K15 M	[14]
Metformin HCl	HPMC K100M, Xanthan gum	[15]
Metformin HCl & Gliclazide	HPMC K4M, HPMC K15M, PVP K90 D	[16]
Ambroxol HCl	HPMC K15M, Eudragit RSPO	[17]
Metformin HCl	HPMC K100M, HPMC K4M, HPMC K15 M, PVP K30	[18]
Repaglinide	HPMC K15M, HPMC K100M, Guargum	[19]
Carbamazepine	HPMC K100M Eudragit RLPO, Eudragit RSPO,	[20]
Glimepiride & Metformin HCl	Eudragit L100, Eudragit RSPO, PVP K30	[21]
Amisulpride	HPMC K4M, PVP K30, Polyox, Carbopol 71G, Cross Povidone, Kollidone SR, Xanthenes Gum	[22]

Tramadol HCl	HPMC K15M, HPMC K100M, PEO N80	[23]
Metformin HCl & Glimepiride	HPMC K15M, HPMC K100M, Guargum, Sodium alginate, Carbopol 934, Carbopol 940	[24]
Galantamine HCl	HPMC K15M, HPMC K100M, Starch	[25]
Isosorbide mononitrate	HPMC K4M, Polyox WSR 303, PVP K30	[26]
Flupirtine Maleate	HPMC K4M, HPMC K100M	[27]
Diclofenac Sodium	HPMC K4M, Sodium CMC, Sodium alginate	[28]
Diclofenac Sodium	HPMC, Cashew nut tree gum, Carbopol	[29]
Diclofenac Sodium & Tramadol HCl	HPMC K4M, HPMC K15M, HPMC K100M	[30]
Diclofenac Sodium	HPMC K100M, EC	[31]
Diclofenac Sodium	HPMC, Sodium alginate, Sodium CMC	[32]
Diclofenac Sodium	HPMC, Cashew gum, Xanthan gum	[33]

Patented Sustained Release Dosage Forms

This is an updated report on recent patents on therapeutic application of sustained release dosage forms. These patents have been reviewed to demonstrate the variety of the controlled or sustained release drug delivery. These systems grip a leading market share in the drug delivery products as demonstrate by means of the number of products in the market and patents granted in the most recent few years. As a result of modulating assorted formulation aspects, it is probable toward use these systems to carry drugs of diversify nature at a pre-programmed rate.

Patel VS has developed (EP0250038 A3) SR pharmaceutical capsule for oral administration comprising, in a capsule shell, a particulate mixture comprising an Active Pharmaceutical Ingredient (API) which is a weak acid, neutral, or a weak base, PVP and carboxyvinyl polymer [34].

Kitchell JP et al. invented (US5486362) controlled and SR delivery system for treating drug dependency. The present innovation also pertains to a method for treat an individual for drug dependence and includes, for example, treating an individual for nicotine dependence, i.e., termination of smoking or chewing nicotine containing products. The delivery system includes a Physical Constriction Modulation System (PCMS™) containing lobeline. The method includes administering the

drug substitute, e.g., lobeline, to the individual in a controlled, SR behavior such that long-term curative levels of the drug substitute, e.g., lobeline, are provided to the individual. This method preferably is carried out using the drug delivery systems described above. The drug substitute, e.g., lobeline, may be administered to the individual at time periods easily integrated with behavioral amendment support programs. Also described are methods of using the drug delivery systems in treating other drug dependency and its kits [35].

Belenduik GW et al. generated (CA2238930) SR pharmaceutical composition comprising a highly soluble pharmaceutical agent, such as selegiline, in a pharmaceutical carrier comprising a hydrophilic polymer dispersed in a hydrophobic matrix. A hydrophilic microenvironment is created in a hydrophobic matrix by incorporating hydrophilic polymers within a hydrophobic matrix. Optionally, a binder, preferably a polyhydroxylated compound, can also be added [36].

Stefely JS et al. patented (US20020164290) biocompatible compounds for SR pharmaceutical drug delivery systems. The present invention relates to the use of relatively low molecular weight biocompatible polymeric compounds for pharmaceutical drugs delivery formulations, and, in particular, to the use of such compounds as drugs solubilizing and drug stabilizing aids and/or to provide SR of drug. Biodegradable polymers have

long been study for their use in providing SR of drugs and have also been used to make biodegradable medical products. For example, polymeric esters of preferred hydroxycarboxylic acids or their derivatives (e.g., lactic acid, glycolic acid, p-dioxanone, etc.) are known to be highly biocompatible with, and biodegradable in, the human body. Such polymers are degraded into their constituent hydroxycarboxylic acids, which are metabolized and eliminated from the body, over periods typically ranging from several weeks to several years. Accordingly, compounds of this type have been utilized for such things as degradable sutures, preformed implants, and SR matrices [37].

Brubaker MJ et al. prepare (WO/2002/053128 A2) SR drug delivery devices with multiple agents. The present invention is directed to an improved sustained release drug delivery device for delivering multiple agents comprising a drug core, a unitary cup, and a permeable plug [38].

Drizen A et al. displayed (US20030175354) antiemetic, anti-motion SRDDS. This discovery relates to a stable, sterilized, purified composition having a polymer matrix and a therapeutically effective amount of a drug, wherein the drug can be used to prevent or treat drug-induced, alcohol-induced, biologically-induced, trauma-induced or pain-induced nausea, vomiting, dizziness and other adverse effects arising from but not limited to motion sickness, cancer therapy, and pregnancy. In scrupulous, the polymer matrix may be conformable to topical application on animal skin [39].

Viscasillas S has demonstrated (US20040219181 A1) on SR devices with coated drug cores. The present invention is directed to an improved SR devices comprising a drug core comprising a polymer coated inner core and an impermeable cup or reservoir [40].

Chen J et al. invented (CA2530113 and US20050025834) bioerodible SRDDS. The present invention relates to SRDDS, medical devices incorporating said systems, and methods of use and manufacture thereof. The inventive systems feature bioerodible drug delivery devices that include biocompatible solid and biocompatible fluid compositions to achieve desired sustained release drug delivery [41, 42].

Cho SH et al. displayed (KR20050001734) SRDDS system which sustains drug releases effectively in GI tract. Provided is a SRDDS which sustains drug-releases effectively in the gastrointestinal tract and controls drug-release time. The system involves no orifice forming which occurs in the tablet and exhibits zero-order release of pharmaceutically active ingredients. The SRDDS is characteristically composed of a crystalline nucleated material, a water absorption promoting layer which is formed on the outer surface of the crystalline nucleated material, a pharmaceutically active ingredient containing layer which is formed on the outer surface of the water absorption promoting layer, and a multiporous layer which is formed on the outer surface of the Active Pharmaceutical Ingredient (API) containing layer [43].

Hughes PM et al. showed (US20050271705) Retinoid containing SR intraocular drug delivery system and related methods. Biocompatible intraocular implants include a retinoid component and a biodegradable polymer that is effective to assist release of the retinoid component into an eye for an extended period of time. The therapeutic agents of the implants may be associated with a biodegradable polymer matrix, such as a matrix that is substantially free of a polyvinyl alcohol. The implants may be placed in an eye to treat or reduce the occurrence of one or more ocular conditions, such as retinal damage, including glaucoma and proliferative vitreoretinopathy [44].

Hollenbeck GR has patented (US20060134148) on aqueous SRDDS for extremely water-soluble electrolytic drugs. The present discovery relates to liquid SR suspension dosage forms comprising ionized forms of water-soluble drugs. In particular, the innovation encompasses a liquid form controlled release drug composition comprising a dispersed phase comprising an ion-exchange matrix drug complex comprising a pharmaceutically tolerable ion-exchange matrix and a water-soluble electrolytic drug associated with the ion-exchange matrix, wherein the surface charge of the ion-exchange matrix is opposite that of the electrolytic drug wherein the dispersed phase further comprises a non-electrolytic, soluble component having low molecular weight and a diffusion controlling

membrane and a dispersion medium substantially free of diffusible counterions, further comprising an excipient capable of associating with water and impeding water activity such that drug dissolution is inhibited prior to administration. The invention also provides methods for preparing such compositions and methods of treatment [45].

Hughes PM *et al.* generated (US20060182783) SR intraocular drug delivery systems. Biocompatible intraocular drug delivery systems include an anti-angiogenic macromolecular curative agent and a polymeric component in the form of an implant, a microparticle, a plurality of implants or microparticles, and combinations thereof. The therapeutic agent is released in a biologically active form, for example, the therapeutic agent may retain its three dimensional structure when released into an eye of a patient, or the curative agent may have an altered three dimensional structure but retain its therapeutic activity. The therapeutic agent contains a component selected from the group consisting of anti-angiogenesis peptides and nucleic acid agents. The implants may be placed in an eye to treat or reduce the occurrence of one or more ocular conditions, such as retinal damage, including glaucoma and proliferative vitreoretinopathy among others [46].

Desai DS *et al.* displayed (US20060099254) SRDDS and method. The present invention relates to a pharmaceutical delivery system comprising a gel-like structure that comprises at least one water-soluble polymer, such as, for example, povidone or hydroxypropyl cellulose, and at least one fatty acid, such as, for example, stearic acid or lauric acid. The invention further relates to a sustained release drug delivery composition comprising the gel-like structure and at least one drug trapped or dissolved therein, wherein said system is capable of releasing the drug in a dissolution medium at a controlled rate. The creation is also directed to a method for preparing the sustained release drug delivery composition [47].

Cho SH *et al.* patented (US20070275066) to a SRDDS composed of a water insoluble polymer, and more particularly, to a SRDDS comprising: a crystalline core material; an active ingredient layer which is created on an outer surface of the crystalline core material and comprises a pharmacologically

active ingredient and a water insoluble polymer; and a sustained release layer which is formed on an outer surface of the active ingredient layer and comprises a sustained release film forming material. The present invention also relates to a SRDDS which releases an effective drug in an aqueous solution or a body fluid for 24 hours by using a SR film forming material and a plasticizer together to provide SR of a pharmacologically active ingredient [48].

Jiang DY has displayed (WO/2007/089876 A3) on preparation for gastric buoyant SRDDS. Disclosed is a floating SR pharmaceutical dosage form including a drug that is adapted to release the drug over an extended period of time. The buoyant pharmaceutical dosage form provides extended gastric residence time of the formulation so that substantially the entire drug is release in the stomach over an extended period. The pharmaceutical dosage form is formulated with low molecular weight rigorous milk proteins to provide buoyancy or optimism to the dosage form which can float in gastric fluid for an extended period, including up to about 48 hours [49].

Ameri M *et al.* have demonstrated (US20090117158 A1) transdermal SRDDS. Provided herein are microprojections and microprojection arrays wherein a microprojection is coated with at least two layer. One layer comprises a biologically active agent, for example, a PTH agent and optionally other excipients. Another layer, which is generally, at first devoid of active agent comprises a polymer or a mix of polymers to provide controlled release, for example SR, of the biologically active agent contain in the first layer. Microprojections coated with multiple layers, some layers containing a biologically active agent and other layers containing a polymer for controlled release are also contemplated herein [50].

Amidon GE *et al.* patented (EP2172199 A1) SR tablet comprising pramipexole. SR pharmaceutical compositions are in the form of an orally deliverable tablet comprising an active pharmaceutical agent having solubility not less than about 10mg/ml, dispersed in a matrix comprising a hydrophilic polymer and a starch having a tensile strength of at least about 0.15kNcm⁻² at a solid fraction representative of the tablet [51].

Robinson MR *et al.* generated (US20100247606) intraocular SRDDS and methods for treating ocular conditions. Biocompatible, bioerodible SR implants and microspheres for intra-cameral or anterior vitreal placement include an anti-hypertensive agent and a biodegradable polymer effective to treat an ocular hypertensive condition (such as glaucoma) by relapsing therapeutic amount of the anti-hypertensive agent over a period of time between 10 days and 1 year [52].

Arima H *et al.* showed (JP2011068606) SR carrier, drug using the SR carrier and drug delivery system using the drug. To provide a SR carrier that is derived from a naturally occurring substance, has a film-forming property and exerts excellent water retention even in the presence of a salt, a drug using the SR carrier, and a drug delivery system using the drug. The SR carrier is prepared by dissolving sacran derived from *Aphanothece sacrum* in water or a solvent containing water, and adding a trivalent cation to the resulting solution so as to form gel. The drug can be carried by the resulting gel. The drug is prepared using the SR carrier. In the drug delivery system, the amount of the drug released can be adjusted by first administering the drug to a living body and subsequently administering a preparation containing a chelating agent, a trivalent cation or an enzyme that cleaves a sugar chain in sacran so as to act on the sacran gel [53].

Chang JN *et al.* patented (US20110034448) carbonic anhydrase inhibitor SR intraocular drug delivery systems. Biocompatible intraocular drug delivery systems include a carbonic anhydrase inhibitor therapeutic agent and a polymeric component in the form of an implant, a microparticle, a plurality of implants or microparticles, and combinations thereof. The therapeutic agent is released in a biologically active form, for example, the therapeutic agent may retain its three dimensional structure when released into an eye of a patient, or the therapeutic agent may have an altered three. The implants may be placed in an eye to treat or reduce the incidence of one or more ocular circumstances, such as retinal damage, including glaucoma and proliferative vitreoretinopathy among others [54].

Jain S *et al.* showed (US20110244034) controlled release dosage form comprising a therapeutically effective amount of a

active pharmaceutical agent, illustrated by Acyclovir, that would release in about 12 hours not more than about 90% of the said active agent in a simulated gastric juice in a first order rate of release in a USP type 1 dissolution test, and not containing a solubilizer or a swelling enhancer or both, comprising (a) a tablet made from polymer matrix of at least two biocompatible polymers, illustrated by Carbopol 974P and polyethylene oxide, the said pharmaceutically active agent and acceptable excipients; the said tablet capable of rapid swelling without disintegration in the said simulated gastric juice to a size that shall result in its gastric retention in the stomach and start controlled release of the said active agent by initial controlled erosion as well as diffusion immediately after coming into contact with the said gastric juice, or (b) microspheres of ungrafted chitosan or a chitosan derivative illustrated by thiolated chitosan and trimethyl chitosan, or Carbopol incorporating the said active agent, wherein the said pharmaceutically active agent is not a polymeric molecule and after administration in stomach, the said microspheres adhere to the gastric mucosa for a long time releasing the active agent in a controlled way [55].

Davis RD *et al.* demonstrated (US8012504) novel pharmaceutical modified release formulation of guaifenesin and dextromethorphan. The formulation may comprise a hydrophilic polymer, preferably a HPMC, and a water-insoluble polymer, preferably an acrylic resin, in a ratio range of about 1:1 to about 9:1, more preferably a range of about 3:2 to about 6:1, and most preferably in a range of about 2:1 to about 4:1 by weight. These formulations are capable of providing therapeutically effective bioavailability of guaifenesin for at least 12 hours after dosing in human subjects. The invention also relates to a modified release product which has two portions: a first portion having an immediate release formulation of guaifenesin and a second portion having a SR formulation of guaifenesin, wherein one or both portions further comprises dextromethorphan. The modified release product has a maximum guaifenesin serum concentration equivalent to that of an immediate release guaifenesin tablet, and is capable of providing therapeutically

effective bioavailability of guaifenesin for at least 12 hours after dosing in a human subject [56].

Chen J *et al.* invented (US20120016467) polymer-based SRDDS. Disclosed is a SR system that includes a polymer and a prodrug having solubility less than about 1.0 mg/ml dispersed in the polymer. Advantageously, the polymer is permeable to the prodrug and may be non-release rate limiting with respect to the rate of release of the prodrug from the polymer. This permits improved drug delivery within a body in the vicinity of a surgery via SR rate kinetics over a prolonged period of time, while not requiring complicated manufacturing processes [57].

Dongling S *et al.* have displayed (CN1842321) bioerodible SRDDS. The present invention relates to SRDDS, medical devices incorporating said systems, and methods of use and manufacture thereof. The inventive systems feature bioerodible drug delivery devices that include biocompatible solid and biocompatible fluid compositions to achieve desired SRDD [58].

Farinas KC *et al.* showed (US20120101260 A1) SRDDS. A drug composition comprising a charged moiety coupled to a therapeutic compound is disclosed. The charged moiety is configured to interact with at least one type of component of opposite charge in a biological tissue to create an in situ depot for prolonged drug delivery. The biological tissue may be eye tissue or any tissue containing charged components [59].

Buan CV *et al.*, generated (WO/2012/154563 A1) SR paracetamol formulations. The present invention is directed to twice daily SR pharmaceutical composition of paracetamol having an immediate release phase of paracetamol and a SR phase of paracetamol, said composition having unique and advantageous pharmacokinetic properties and a pharmaceutical composition comprising only a SR phase of paracetamol having unique and advantageous pharmacokinetic properties [60].

Trogden JT *et al.* patented (US20130280272) SRDDS comprising a water soluble therapeutic agent and a release modifier. A biocompatible SR intraocular drug delivery system is comprises a protein or polynucleotide therapeutic agent and polymeric carrier for the therapeutic agent and a long chain fatty alcohol release modifier. The biocompatible, SR intraocular

drug delivery system can be used to treat an ocular condition [61].

Ashton P *et al.* showed (US20140037746) polymer-based SRDDS. Disclosed is a SR system that includes a polymer and a pharmaceutically active agent dispersed in the polymer. The agent is in granular or particulate form, and has a rate of release from the system that is limited primarily by the rate at which the agent dissolves from the granules into the polymer matrix. Advantageously, the polymer is permeable to the agent and is non-release-rate-limiting with respect to the rate of release of the agent from the polymer [62].

Wu CW *et al.* displayed (US20140086974) biodegradable drug delivery systems, such as extruded implants, for the sustained delivery of a protein to an ocular region of the eye or intra-articular region in the body are described. The drug delivery systems may be used to treat a variety of ocular and medical conditions, including macular deterioration. Methods for using and making the drug delivery systems are also described. The drug delivery systems can be in the form of extruded filaments configured for placement in an ocular region such as the vitreous body or anterior chamber of the eye [63].

Shi R *et al.* invented (WO/2014/066658 A1) Ketorolac-containing SRDDS. Biodegradable intra-ocular and intra-articular drug delivery system comprising ketorolac and a biodegradable polymer matrix that can release ketorolac into an eye or joint for an extended period of time are described. The drug delivery system may be in the form of an extruded implant and may be used to treat one or more medical and ocular conditions, such as post-operative pain and inflammation following an ocular surgery such as cataract surgery [64].

Characterization of Sustained Release Tablets [9]

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.

➤ Pre and post compression parameters

Most widely used parameters are bulk density, tapped density, compressibility index, hausner ratio, total porosity, flow rate, angle of repose, hardness, friability, weight variation test and uniformity of drug content etc.

➤ In-Vitro Methods

The various types of methods used are beaker, rotating disc, rotating bottle, rotating basket, stationary basket, oscillating tube, dialysis and USP dissolution method.

➤ 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.

Future Opportunities

The oral SRDDS market is the largest piece of the drug delivery market, and there is no sign that it is slowing down. With pharmaceutical companies increasingly turning to drug delivery to extend the revenue-earning lifetime of their biggest products, and seeking to tap into the growing elderly population that requires products with a level of ease-of-use and cost benefit. Oral drug delivery provides the definitive break down of the markets. Benefits for short half-life drugs, sustained release can mean less frequent dosing and thus better compliance reduce variations in plasma or blood levels for more consistent result. This would provide the desired impetus to the product

development scientist, facilitating further evolution of research on SRDDS innovations and next-generation product launches. This patent overview provides an updated bird's eye view survey account on the publications and patents of different novel sustained release delivery approaches used for its applications.

Conclusion

SRDDS is usually apprehensive with maximum drug availability by attempt to get a maximum rate and extent of drug absorption however; controls of drug action through formulation also imply controlling bioavailability to decrease drug absorption rates. Oral dosage forms characterize one of the leading edge areas of sustained release drug delivery system (SRDDS). SR formulations are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compliance and expediency due to less frequent drug administration. The present overview further provides an insight into assorted commercial platform technology, criteria for drug selection, advance novel research and patents for SRDDS. The SRDDS may be used to deliver drugs at a sustained rate over a period of 24 hours. The dosage form design is to optimize the delivery of medication to bring about the control of curative effect in the face of uncertain fluctuation in the vivo environment in which drug release take place. In the future, design of oral SR formulated products used to obtain the desired drug accessibility rate from sustained action dosage form include increasing the particle size of the drug, embedding the drug in matrix, coating the drug or dosage form containing drug or microencapsulation, forming complexes of the drug with material such as ion exchange resins. SR formulations are easy to optimize and tremendously useful in case of the antibiotics in which irrational use of the similar possibly will perhaps result in resistance. I hope that my effort is going to find new application or new application in near future.

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