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REVIEW ARTICLE

NOVEL DRUG DELIVERY SYSTEM

AN APPROCH FOR DEVELOPMENT OF ORAL SUSTAINED RELEASE SUSPENSION

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ABSTRACT

The scenario of pharmaceutical drug delivery is rapidly changing; conventional dosage forms are being replaced by new drug delivery system. One such drug delivery is sustained or controlled release drug delivery system the primary objective of sustained release drug delivery system is to ensure safety, improve the efficiency of drug, and also reduces the dose frequency, which also ultimately results in patient compliance. An oral pharmaceutical suspension has been one of the most favorable dosage forms for pediatric and geriatric patients or patients unable to tolerate solid dosage forms. The liquid form is preferred because of the ease of swallowing and flexibility in the administration of doses. More therapeutic and commercial advantages are as high patient compliance, reduction in side effects and improvement of bioavailability could be expected by incorporating a function of sustained drug release into the suspension. Therefore it is desirable to develop, well formulated sustained release suspension.

KEYWORDS

Sustained release, Suspension, Bioavailability, Microencapsulation.

INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintain it constant for the entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dosage form, in a particular dose and at a particular frequency. The oral route of administration is the most popular and successful route used for conventional delivery of drug because of convenience, ease of administration, greater flexibility in dosage form design, ease of production and low cost of such a system and hence adopted wherever possible. Commonly employed dosage form by oral route includes Tablets, Capsules and Liquids [1]. Oral liquid preparations are formulations containing one or more active ingredients, in a suitable vehicle. And are intended to be swallowed either undiluted or after dilution [2]. The choice of a liquid oral preparation rather than a tablets or capsules is often controlled by patient acceptability. While solid dosage forms tablets or capsules are often supplied to adults; the treatment of children is easier with suitably flavored liquids [3]. The ease of drug administration strongly justifies the use of liquid orals particularly to those individuals who have difficulty in swallowing solid dosage forms mainly to geriatric and pediatric patients [4].

Advantages of liquid orals

1. The drug is more readily available for absorption and in most cases is more rapidly and effectively absorbed than the same amount of drug administered in a tablet or capsule
2. Liquids are more easily swallowed than tablets or capsules and are therefore especially suitable for children and elderly.
3. Gastric irritation caused by certain drugs when they are administered as a solid dosage forms, may be reduced or avoided by formulating the drug as a liquid preparations[2].

Disadvantages of liquid orals

1. The drug may be less stable in a liquid formulation rather than in tablets or capsules.
2. Liquid preparation tends to be bulky and therefore inconvenient to store and transport.[5].

Liquid Orals

The solubility of insoluble or sparingly soluble drugs can be enhanced by using co-solvents, which are suitable for oral administration various solubilizing agents can also be used for poorly soluble drugs [6].

Dispersion

The dispersed phase may range in size from particles of atomic and molecular dimensions to particles whose size is measured in millimeter [7]. These systems can be further classified on the basis of the size of the dispersed particles as shown in the following table 1.

TABLE NO.1
TYPES OF DISPER

System	Dispersed Particles	Particle size
True solutions	Small Molecules or Ions	Usually less than 1X 10^{-6}
Colloidal dispersions	Single large molecules or	Larger than those in true solution and have an upper size limit of about 1X $^{10-3}$mm
Coarse dispersion	Aggregates of molecules	Larger than those in colloidal dispersion.

TABLE NO. 2
TYPES OF THE ION EXCHANGE RESIN.

Type	Exchange species	Polymer backbone	Commercial Resins
Strong cation	-So_3H	Polystyrene DVB	Amberlite IR 120
Weak cation	-COOH	Methacrylic acid DVB	Amberlite IRC 50
Strong anion Weak anion	N^+R_3	Polystyrene DVB	Amberlite IR 400, Dowex 1
Strong cation	N^+R_2	Polystyrene DVB	Amberlite IR 4B, Dowex 2

Broadly a dispersion system can be classified into two classes

a) Natural e.g., blood, milk.
b) Synthetic e.g., suspensions, emulsions, aerosols, creams, ointments [8].

Suspensions

Suspension is a heterogeneous system consisting of internal phase or suspended phase, which is made up of the particulate matter, dispersed uniformly with mechanical agitation through out the external phase with the help of suspending agents, which is generally a liquid or semisolid [9]. The particles have diameter for the most part greater than 0.1 µm. The dispersed phase may consist of discrete particles or it may be a network of particles, resulting from particle- particle interaction[10]. Drugs are dispersed as suspensions for different reasons, but the most common one is poor aqueous solubility. The suspension offers greater stability to drug as it is not in solution form and in some cases enhanced bioavailability also occurs [4,11].

Requirement of Pharmaceutical Suspensions

1. The dispersed particles should be small and uniform; they should not settle fast.
2. If the particles settle, they should be easily dispersed.
3. There should be no excess viscosity to interfere with pouring and redispersal.
4. The redispersion should produce uniform dose of administration. [12].

The general choice of suspending agents include the protective collides, viscosity inducing agents, surfactants and dispersing agents. Combinations of various types of agents may be used to achieve desired rheological properties [13, 14].

Depending on particle size suspensions are classified into

Colloidal suspensions: - Suspensions having particle sizes of suspended solid less than about 1µm in size are called as colloidal suspensions.

***Coarse suspensions**:* Suspensions having particle sizes of greater than about 1µm in diameter are called as coarse suspensions [12]. Suspensions contribute to pharmacy and medicine by supplying insoluble and often distasteful substances in a form, which is pleasant to the taste; by providing a suitable form for the application of dermatological material to skin and sometimes to the mucous membranes; and for the parentral administration of insoluble drugs.

The major challenges to be faced in the formulation of suspensions are

1. The diffusion or release of drug into suspending vehicle during storage.
2.The interaction between dispersing vehicle and dispersed phase during storage[13,14].An ideally inert suspending medium is yet to be found, into which drug do not diffuse during storage and which does not change important properties of formulation during storage[15].

Stability of suspension

Particles in the dispersion exhibit repulsive as well as attractive forces. When the forces of repulsion are greater, the particles remain apart. The light fluffy flocks settle rapidly in a suspension to form loosely arranged sediment, which is easy to redisperse. Conversely the individual particles in a well-dispersed deflocculated suspension settle more slowly but have a tendency to form a cake that is difficult to redisperse[16,18].

***The various methods that are available to assess the stability of suspensions** [19]*

- Rate of settling measurement
- Measurement of particle size
- Radio-isotopic methods
- Electro kinetic measurement. [20].

***Approaches used in formulation of sustained-release oral suspension** [21- 23]*

The formulation of oral suspensions that exhibit sustained-release activity presents many challenges due to the substantial loss of the biologically active ingredient to the surrounding suspending medium during storage.

Different approaches have been undertaken to overcome this problem these are mainly

Ion exchange resins

This approach is related to the stable sustained release pharmaceutical compositions comprising a drug resin complex suspended in a liquid carrier for oral administration. Loading of the drug on the resin can be accomplished by well-known techniques, e.g., batch wise process in where in a drug solution is mixed with a resin in a suitable container for the time necessary to obtain maximal loading, or a solution of the drug can be passed through a column of resin until loading is complete.

Sustained release suspension of poorly water-soluble Biologically active Ingredients

Different microencapsulating techniques such as spray congealing, spray drying, solvent evaporation, etc., can be used to prepare slow-release microencapsulated particles for incorporation in a suspension dosage form, the amount of biologically active ingredient leaching out during the shelf life is minimized because of the low solubility of the biologically active ingredient in the aqueous suspending vehicle.

Saturated drug suspension as a suspending medium

A method of preparing sustained-action liquid dosage forms for various compounds by microencapsulating the biologically active ingredient and subsequently suspending the microencapsulated form in a vehicle saturated with the biologically active ingredient is used.

Non-aqueous Vehicles

The use of oleaginous vehicles such as almond oil, sesame oil, sunflower oil, etc., for the preparation of oral liquid suspensions has been described this approach shows enhanced bioavailability, improved absorption characteristics and reduced inter subject variability.

Reconstitution

Ready-made suspensions might be associated with chemical instability of the biologically active ingredient or with physical instability, such as cacking tendencies and dissolution profile changes.

Protective coatings

An enteric coating is usually intended to release the biologically active ingredient after sometime delay, or after the tablet has passed through one part of the gastrointestinal tract into another.

Ion exchange resin

The popular approach to the development of oral sustained release suspension is based on use of ion exchange resin. Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion exchange is reversible and stoichiometric with the displacement of one ionic species by another[24]. Synthetic ion exchange resin has been used in pharmacy and medicine for sustained release of drugs as early as 1950s [25,26,27] . The size of the ion-exchange resins should preferably fall within the range of about 20 to about 200 μm particle sizes substantially below the lower limit are difficult to handle in all steps of the processing. Particle sizes substantially above the upper limit, e.g., commercially available ion exchange resins having a spherical shape and diameters up to about 1000 μm, are gritty in liquid dosage forms and have a greater tendency to fracture when subjected to drying- hydrating cycles

Types of ion exchange resins *[28, 29]*

An ion exchange resin contains positively or negatively charged sites and is accordingly classified as either cationic or anionic exchanger. Within each category, they are further classified as strong or weak depending on their affinity for soluble counter ions.

Equilibrium phenomenon

The principle property of resins is their capacity to exchange bound or insoluble ions with those in solution. Soluble ions may be removed from solution through exchange with the counter ions absorbed on the resin as illustrated in Eq. 1 & 2.

$$Re\text{-}So_3^- Na^+ + Drug^+ \rightleftharpoons Re\text{-}So_3^- Drug^+ + Na^+ \quad \text{---------- 1}$$

$$Re\text{-}N(CH_3)^+ Cl^- + Drug^- \rightleftharpoons Re\text{-}N(CH_3)^+ Drug^- + Cl^- \quad \text{----------2}$$

These exchanges are equilibrium reactions in which the extent of exchange is governed by the relative affinity of the resins for particular ions. Relative affinity between ions may be expressed as a selectivity Co-efficient derived from mass action expression [28] given in Eq. 3.

$$K_{DM} = \frac{[D]_R [M]_S}{[D]_S [M]_R} \quad \text{---------- 3}$$

Where,
$[D]_R$ = Drug concentration in resin
$[D]_S$ = Drug concentration in the solution
$[M]_S$ = Counter ion concentration in the solution
$[M]_R$ = Counter ion concentration in the resin

Factors that influence selectivity include valency, hydrated size, pKa and the pH of the solutions used selectivity coefficient to express the interaction of eleven amino drugs with potassium salt of polacrin, a polycarboxylic acid resin[30,31]

Particle size and form: The rate of ion exchange reaction depends on the size of the resin particles. Decreasing the size of the resin particles significantly decreases the time required for the reaction to reach the equilibrium with the surrounding medium; hence larger particle size affords a slower release pattern [34].

Porosity and swelling: Porosity is defined as the ratio of volume of the material to its mass. The limiting size of the ions, which can penetrate into a resin matrix, depends strongly on the porosity.

Cross-linking: The percentage of cross-linking affects the physical structure of the resin particles. Resins with low degree of cross-linking can take up large quantity of water and swell into a structure that is soft and gelatinous. However resins with high DVB content swell very little and are hard and brittle. Cross-linkage has dramatic effect on loading efficiency. It affects porosity and swelling properties of resin. Low cross-linking agents remarkably upon hydration. Higher grade have finer pore structure thus reducing loading efficacy with increase in cross- linking [34, 35].

Acid base strength
It depends on the various inorganic groups, incorporated into resins. Resins containing sulphonic, phosphoric or carboxylic acid exchange groups have approximate pKa values of <1, 2-3 & 4-6 respectively. Anionic exchangers are quaternary, tertiary or secondary ammonium groups having pKa values of >13, 7-9 or 5-9 respectively. The pKa values of resin will have significant influence on the rate at which the drug will be released in the gastric fluid.

Stability
The ion exchange resins are inert substances at ordinary temperature and excluding the more potent oxidizing agent are resistant to decomposition through chemical attack. These materials are indestructible. They get degraded and degenerated in presence of gamma rays.

Purity and toxicity
Since drug resin combination contains 60% or more of the resin, it is necessary to establish its toxicity. Commercial product cannot be used as such. Careful purification of resins is required. Resins are not absorbed by body tissue and are safe for human consumption. Test for toxicological tolerance showed that it does not have any pronounce physiological action at recommended dosage and is definitely non-toxic[36,37].

Gastrointestinal sustained release mechanism
Bioavailability of drug adsorbed on ion exchange resins depends on both transits of the particles through the G.I. tract and drug release kinetic.Additionally release is not instantaneous, and the drug must diffuse through the resin from the internal exchange sites.If the drug resin complex is administered orally a small amount of drug may be released. This would be followed by significant and continuous release in the stomach where drug is exposed to high acid and chloride concentrations. Anionic exchange resins and strong cation exchangers release a limited amount of drug in the stomach as shown in Eq. 4& 5.

$$Re\text{-}So_3^- Drug^+ + H^+ \rightleftharpoons Re\text{-}So_3^- H^+ + Drug^+ \quad \text{----------4}$$

$$Re\text{-}N(CH_3)^+ Drug^- + Cl^- \rightleftharpoons Re\text{-}N(CH_3)^+ Cl^- + Drug^- \quad \text{---------- 5}$$

In contrast drug bound to weakly acidic carboxylic acids released much more readily in the stomach as illustrated in Eq.6

$$Re\text{-}COO^- Drug^+ + H^+ \rightleftharpoons Re\text{-}COOH + Drug^+ \quad \text{---------- 6}$$

The high effective pKa of the resin drives the equilibrium towards the formation of undissociated acid in a low pH environment. This may promote rapid drug release. In the intestine the neutral pH should keep all ionic sites on the resins ionized and the exchange process should occur continuously. The highly insoluble resin is not absorbed. It is simply eliminated from the body with the counter ions that have replaced the drug. Biphetamine^R a capsule containing an equal quantity of amphetamine & dextroamphetamine complexed to a sulphonic acid cation exchange resin has been used for antiobesity agent and for behavioral control of children [37].

Several preparations involving resinate of strong sulphonic acid cation exchange resin are marketed as well as reported in the literature. They provide more moderate release than the carboxylic acid resins [38] .Another example is Pennkinetec system by Pennwalt corporation, USA marketed as Penntuss^R where codeine and chlorpheniramine polystyrex contains both drugs complexed with sulphonic acid cation exchange resin wherein the chlorpheniramine resin complex is uncoated and codeine resinate particles are coated with release controlling ethyl cellulose membranes [45].

Sulphonic acid type resinates containing antitussive phenyltolaxamine and dihydrocodeinone have been marketed as Histionex^R and Tussionex ^{R}, [39] compared the duration of the antitussive effect of Noscapine hydrochloride (Longatin $^{R)}$, a commercial resinate of noscapine and a sulphonated cross linked polystyrene resin. In another study microencapsulated Tramadol-resin complex showed slow release[40] . Resinate of propranolol hydrochloride[41] Chlorpheniramine maleate[42] and phenyl propanolamine[43] have been described to show the sustained release. Microparticulates of ion exchange resin drug complex have been used for ophthalmic drug delivery of Betaxolol, an antiglaucoma agent[44]. A recent review describes the use of ion exchange resin microparticulates for ophthalmic drug delivery [].

Taste masking (Chewable or Dispersible tablet of bitter drugs)

Certain drugs that have very bitter taste can be made relatively tasteless by adsorbing the drug on ion exchange resin although all the ion exchange resins can be useful for this purpose, the proper selection on ionic character of drug and release characteristics. Weak cation exchange resins can be used to formulate chewable or dispersible tablet of bitter drugs, for example Rodec decongestant tablet containing pseudoephedrin. Weak cation exchangers are most preferable for their ability to remain undissociated at alkaline pH of mouth, and thus masking the taste of bound drug and further releasing it rapidly at acidic pH of stomach. Reported taste masking of highly bitter antibiotic, sparfloxacin with Indion 204 weak cation exchanger[36].

Chewing gum for buccal absorption

Nicorette is a widely used patented product for smoking cessation program. It contains nicotine adsorbed on an ion exchange resin with carboxylic acid functionality and formulated in a flavored chewing gum base provides gradual drug release through buccal mucosa as the gum is chewed offering fresh saliva as solvent for elution [47] .

Drug stabilization

Complexing active ingredients with ion exchange resins prevents harmful interaction with other components e.g. Vitamin B_{12}.

Vitamin B_{12} deteriorates on storage. This necessitates addition of overages, leading to significant increase in the cost of the formulations. The stability of Vitamin B_{12} can be prolonged by complexing it with a weak acid cation exchange resin (INDION 264). This complex is as effective as the free form of the Vitamin [48]. Thus the introduction of INDION 264 in the formulation significantly reduces the overages. Ion exchange resin can also be used as carrier for immobilized enzymes to provide extended activity at localized sites.

Bioadhesive system for treatment of gastric mucosa

Ion exchange resin may have inherent bioadhesive properties similar to those of highly charged polyanions[49]. Hence ion exchange resins may be useful in mucoadhesive systems for topical treatment of stomach such as H. pylori infection for prolonging the gastric residence of amoxycillin and cimetidine[50].

Tablet Disintegration

Many tablets disintegrant owe their action to capacity to absorb water and swell up. Fine particle size ion exchange resins have shown superiority as disintegrating agent due to their considerable swelling pressure upon hydration [51].

Advantages of ion exchange resins over conventional disintegrating agents are

1. Rate of permeation of water and subsequent swelling is very fast and cut down the disintegration time.
2. Ion exchange resins do not have adhesive tendency on hydration; hence tablet disintegrates evenly without formation of lumps.

Because of their unusually large swelling capacities polymethacrylic carboxylic acid ion exchange resins have found usage in pharmacy as tablet disintegrants; for example pollacrilline a potassium salt of weakly acidic cation exchange resin with methacryllic acid divinyl benzene matrix.[52, 53] .Investigated chances of interference of cation exchanger disintegrants with drug availability and assay [54].

Targeted drug delivery system [Anticancer drug]

This concept is based on the chemoembolishment of drug-loaded microspheres via the tumor arterial supply. Because of their physical size microspheres can be entrapped in the capillary beds along with their load of cytotoxic drugs can be delivered to well vascularised tumor tissues [55] has studied the in vitro release of cytotoxic agents from cytotoxic agents from ion exchange resins.

Cholesterol reducer *[56]*

Cholestyramine resin USP, when used as an active ingredient binds bile acids, this leads to replenishment of bile acids; through increased metabolism of serum cholesterol resulting in lowered serum cholesterol levels.

Multiparticulate dosage forms *[57, 58]*

Multiparticulate dosage forms include

1. Ion-exchange resin particles.
2. Microcapsules.
3. Microspheres.
4. Pellets/non-pariel seeds

More expensive to manufacture and develop, but also more reliable in their biopharmaceutical behavior, are oral dosage forms containing active ingredient divided into many individual units, so-called subunits. Upon ingestion, the particles mix with the chyme, pass the pylorus at the stomach exit unhindered and spread over a large section of the gastrointestinal tract. Enclosed particles behave like small diffusion cells. As long as undissolved drug is present in the core, its release occurs at a constant rate, i.e. according to a zero-order. Once the entire drug load of the diffusion cell is dissolved, however, release follows first-order reaction. According to Higuchi, release from matrix particles occurs proportionally to $\sqrt{t}$, i.e. fast at the beginning and then ever more slowly.

CONCLUSION

From this review article it can be concluded that the primary requirement of a successful

sustained release product focuses on increase patient compliance and attend desired therapeutic concentration in the minimum dosage frequency. This can be achieved by formulating sustained release suspension.

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