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Sustained release beads: A short review

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Abstract
Sustained release formulations are currently regarded as one of the most significant novel systems for the formulation of essential drugs. The sustained release system exhibits greater therapeutic activity of a drug in comparison to immediate release. This technique has been utilized in an aqueous outer phase for numerous water-insoluble monomers, both with and without the drug. The bead polymerization technique represents an emerging variant of this system, which has attracted considerable attention in pharmaceutical research due to its capacity to sustain therapeutic drug levels, decrease dosing frequency, and improve patient compliance. This review study encompasses a detailed examination of the preparation and evaluation of sustained release beads utilizing both natural and synthetic polymers, along with their physical properties such as particle size, shape, surface morphology, and drug content. This review of the work will undoubtedly serve as a valuable resource for researchers and academicians in various capacities.

Keywords: Sustained release, advantages, polymers, preparation techniques, physicochemical

Introduction
The release of a drug from a microparticle is determined by a number of factors, including the carrier utilized to make the microparticle and the amount of drug contained within it [1]. Beads are one of the most widely employed strategies in continuous release dosage forms. These are spherical particles with a diameter ranging from 50 nm to 2 mm, and include core constituents. To formulate as SRDF, the drug particle's molecular size must be less than 1000 Dalton [2]. Many APIs demonstrate difficulties like limited biological availability and repeated dosing due to poor solubility and penetration across lipid membranes. Oral API administration is the most common route to take medications [3]. Many are restricted in use due to their short for and loss of absorption through a portion of the small intestine. This has an effect on pharmacokinetic action, requiring periodic doses of multiple APIs to get an effective dosage. This increases pill load and reduces patient compliance [4]. Any medication delivery system's objective is to deliver a therapeutic dosage to the right location in the body in order to quickly and sustain the target concentration. That is, throughout a given treatment time, the drug delivery system should administer the medication at a pace determined by the body's demands [5]. The design of effective drug delivery systems an recently become an integral part of the development of new medicines. Hence, research continuously keeps on searching for ways to deliver drugs over an extended period of time, with a well-controlled release profile Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects [6]. For decades, the majority of therapies for both acute and chronic illnesses have involved administering drugs to patients using a variety of traditional pharmaceutical dosage forms, including as pills, suppositories, creams, ointments, squids, aerosols, and injectable as drug carriers. It is well known that this kind of drug delivery device releases the medication quickly. Therefore, it is frequently necessary to take this kind of drug delivery system multiple times a day in order to reach and maintain the drug concentration within the therapeutically effective range required for treatment, which causes a large fluctuation in drug levels. Conventional immediate release formulations of many pharmacological substances offer clinically effective therapy with an acceptable level of patient safety while preserving the necessary balance of pharmacokinetic and pharmacodynamics characteristics [7].

A prolonged release formulation was designed to maintain medication concentration levels. To maintain the effective concentration in the blood for a longer period, the sustained release dosage form releases the drug at a constant rate, while the controlled release dosage form releases the drug at an equal pace [8]. In sustained release dosage forms, an adequate amount of drug is initially made obtainable to the body to cause a desired pharmacological effect [9]. The residual fraction is released occasionally and is required to maintain the maximum early pharmacological activity for some enviable period of time in surplus of time expected from usual single dose [10, 11]. The prolonged release of medications, vaccinations, antibiotics, and hormones can all be achieved with beads. For instance, by utilizing the properties of beads, in addition to their basic advantages, they may be able to offer a greater vehicle area and make it simpler to estimate the behavior of diffusion and mass transfer. Natural polymers are used in the process that is detailed in this study. The primary benefits of natural polymers are their biocompatibility, biodegradability, and ability to cause systemic toxicity during the administration, manufacture, and testing of propranolol HCL beads. It has been attempted to achieve an appropriate oral sustained drug delivery system using biodegradable natural polymers, such as fish gelatin and gelatin B as carriers, by employing physical cross-linking to prevent the toxicity of chemical crosslinking agents [12, 13].

Multiple unit dosage form includes

1. Microgranules/spheroids: Drug wet granulated alone or incorporated into inert granules, and then coated to controlled the release pattern.
2. Pellets: Pellets are prepared by coating inert drug pellets with film forming polymers. The release depends upon coating composition of polymer and amount of coatings.
3. Microcapsules: Microcapsules are prepared by applying relatively thin coating to small particles of solids, droplet of liquid and dispersion.
4. Beads- Microbeads, as the name suggests they are nearly spherical, small with diameter of 0.5-1000µm in size, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles of treatment with various active agents without major side effects. Additionally, the heads maintain functionality under physiological conditions, can incorporate drug to deliver locally at high concentration ensuring that therapeutic levels are reached at the target site while reducing the side effects by keeping systemic concentration low. The microbeads are produced from several polymers such as cationic polymers e.g. chitosan, anionic polymers e.g. sodium alginate, and binding components e.g. gelatin, chondroitin sulfate, avidin in predetermined ratio [14, 15].

Advantage

1. Reduction in frequency of drug administration.
2. Improved patient compliance.
3. Reduction in drug level fluctuation in blood.
4. Reduction in total drug usage when compared with conventional therapy.
5. Reduction in drug accumulation with chronic therapy.
6. Reduction in drug toxicity (local/systemic).
7. Stabilization of medical condition (because of more uniform drug levels).
8. Improvement in bioavailability of some drugs because of spatial control.
9. Economical to the health care providers and the patient [16-19].

Disadvantage

1. Delay in onset of drug action.
2. Possibility of dose dumping in the case of a poor formulation strategy.
3. Increased potential for first pass metabolism.
4. Greater dependence on G1 residence time of dosage form.
5. Possibility of less accurate dose adjustment in some cases.
6. Cost per unit dose is higher when compared with conventional doses.
7. Not all drugs are suitable for formulating into ER dosage form.
8. Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
9. Poor *In vitro In vivo* correlation.
10. Retrieval of drug is difficult in case of toxicity, poisoning or hypersentivity reactions.
11. Reduced potential for dose adjustment of drugs normally administered in varying strength [20-23].

Review of Literature

Polymers used in the preparation of sustained release beads

Sodium alginate

Another popular mucoadhesive polymer for creating different delivery systems is the sodium version of alginic acid. It is a linear anionic polymer derived from brown algae that is both biodegradable and biocompatible. It possesses high mucoadhesive qualities due to the presence of free carboxyl groups, which enable the polymer to interact with mucin in the mucous membrane through electrostatic and hydrogen bonding. It has been employed in the creation of sustained-release formulations as a matrix material. It administers the medication over an extended period of time because of its hydrogel forming qualities. Both sodium alginate and GG have the ability to go through ionotropic gelation in an aqueous solution with Ca2+, Al3, etc. The mucoadhesive nature of sodium alginate and the gel-forming ability of GG are primarily utilized in pharmaceutical drug design for applications involving controlled drug delivery [24].

Hydroxypropyl methylcellulose (HPMC)

Hydroxypropyl methylcellulose (HPMC) is the most often used hydrophilic carrier material in the creation of oral controlled drug delivery systems. Another name for it is hypromellose. HPMC is classified as a cellulose ether because it contains ether linkages formed by the substitution of more than one of the three hydroxyl groups from the cellulose glucopyranose unit. When making sodium alginate beads, the most often used med polymers are carboxymethyl cellulose, hydroxyl propyl methyl cellulose K100m (HPMC

K100m), etc. Formulations using CMC sodium salt as the matrix agent have the highest rate of drug release, while formulations using HPMC K100M as the matrix agent have the lowest rate. This demonstrates that HPMC created the gel. Despite using a highly viscous CMC sodium salt, it is evident [25].

Cross-linking agents

Various investigations have demonstrated that the type of cross-linker has a significant impact on how pharmaceuticals release from the cross-linked matrix. There are many other physical and chemical ways to cross-link alginates, but generally speaking, alginic acid and calcium chloride combine to generate calcium alginate hydrogel beads [26].

Preparation of Techniques

Ionotropic gelation techniques

Microbeads containing Diclofenac sodium were prepared by Ionotropic gelation technique. The sodium alginate solution was prepared by dispersing the weighed quantity of sodium alginate in deionized water. Accurately weighed quantity (1 g) of Diclofenac sodium was added to 100 ml polymeric solution of Sodium alginate and drug were thoroughly mixed with help of homogenizer at 1500 rpm to get a homogenous drug polymeric mixture. The formed mixture allowed to stand for 1 h to make it bubble free. By following the same procedure the alginate beads of different ratios of drug polymer were prepared. The resulted homogenous dispersion was extruded into 100 ml of 6% cross-linker solution ($CaCl_2$) through hypodermic syringe with flat lip needle (18 G) and stirred at 100 rpm. The formed microbeads were allowed to cure for 30 min in the cross-linker solution to complete the gelation. The beads were removed after the gelation period and washed with ethanol to harden the heads surface and finally with distilled water repeatedly to make free from un-reacted ion. The microbeads were then filtered and dried in hot air oven at 400°C for 18 h [27].

Emulsion gelation techniques

Another method of beads preparation is emulsion gelation techniques. The sodium alginate solution was prepared by dispersing the weighed quantity of sodium alginate in deionized water. Accurately weighed quantity of drug was added to polymeric solution of Sodium alginate and drug stirred magnetically with gentle heat to get a homogenous drug-polymeric mixture. Specific volume of cross-linking agent were added to form a viscous dispersion which was then extruded through a syringe with a flat tipped needle of size no 23 in to oil containing span 80 and 0.2% glacial acetic acid being kept under magnetic stirring at 1500 rpm. The beads are retained in the oil for 30 min to produce rigid discrete particles. They were collected by decantation and the products thus separated was washed with chloroform to remove the traces of oil the beads were dried at 400°C for 12 h [28].

Emulsion cross-linking techniques

The medication was dissolved in the gelatin solution in this form, which has previously been heated at 40°C for 1 hr. The solution was added drop by drop to liquid paraffin while in 35°C. resulting in w/o emulsion, this mixture was reused at 1500 rpm for 10 minutes. Optional stirring should at 15°C for 10 min. in 5 ml of aqueous glutaraldehyde saturated toluene solution at 28°C for 3 hours for cross-linking the spherically shaped beads were washed three times with acetone and isopropyl alcohol, respectively, air dried and discrete. Then formed beads with a 100 ml. 10 mm glycine solution containing 0.1 percent w/v between 80 and 370C we preserved for 10 min to lump unreacted glutaraldehyde[29].

Dropping method techniques

It's an easy way. It is necessary to use a pipette or a syringe with a needle. It is the technique most frequently used to prepare particles larger than 500 micrometer. The viscosity of the alginate solution and the size of the needle used determine the size of the beads that are produced [30].

Factors affecting of Sustained Release Beads

-Two types of factors involved:

1. Physicochemical factor
2. Biological Factor

Physicochemical factor

Aqueous Solubility

The drug of good aqueous solubility and pH independent solubility are most desirable candidate for sustained-release beads. Poor aqueous solubility possess oral bioavailability problem and drug which having extreme aqueous solubility are unsuitable for sustained release because it is difficult task to control the release of drug from the dosage form.

Partition coefficient

Also called as distribution coefficient, the bioavailability of a drug is greatly influenced by the partition coefficient, as the biological membrane is lipophilic in nature transport of drug across the membrane is depends upon the partition coefficient of the drug. The having low partition coefficient are considered as poor candidate for the sustained release formulation in the aqueous phase.

Drug stability

Sustained release beads is designed to control release of a drug over the length of the gastrointestinal tract (GIT); hence high stability of drug in GI environment is required.

Protein binding

Proteins binding of drug play a key role in its therapeutic. Pharmacological activity of a drug depends on unbound concentration of a drug rather than total concentration. The drugs which bound to some extent of a plasma and tissue proteins enhances the biological half-life of a drug. Release of such drug extended over a period of time and therefore no need to develop extended release drug delivery for this type of drug.

Drug pKa & ionization at physiological pH

If the unionized drug is absorbed and permeation of ionized drug is negligible, but the rate of absorption is 3 to 4 times is less than that of the unionized drug. Since the drug shall be unionized at the site an extent 0.1 to 5%. Drugs existing largely in ionized form are poor candidates for sustained release beads e.g. Hexamethonium.

Molecular size and diffusivity

Diffusivity depends on size & shape of the cavities of the membrane. The diffusion coefficient of intermediate molecular weight drug is 100 to 400 Dalton. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers is very less. e.g. Proteins and peptides.

Dose size

For oral administration of drugs in the upper limit of the bulk size of the dose to be administered. In general, a single dose of 0.5 to 1.0g is considered maximal for a conventional dosage form. This also depends on sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems.

Biological factors

Absorption

To maintain the constant uniform blood or tissue level of drug, it must be uniformly released from the sustained release system & then uniformly absorbed in the body. Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the Gl tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours, otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23 h-1 to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, SR preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds tries to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co- administration results in sustaining effect.

Distribution

Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor for sustained release beads e.g. Chloroquine.

Metabolism

The metabolic conversion of a drug is to be considered before converting into another form. Since as long as the location, rate, and extent of metabolism are known a successful sustain release product can he developed. Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

Half-life of drug

The drug having short biological half-life between <5 but drugs is soluble in water. The drugs should have larger therapeutic window absorbed in GIT. The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the bloodstream [31-33].

Summary and Discussion

The basic goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and nontoxic for extended period of time. Modified-release delivery systems may be divided conveniently into four categories:

1. Delayed release
2. Sustain release
3. Site-specific targeting
4. Receptor targeting

Delayed release systems are those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dose form. Example delayed release system include repeat action tablets, capsules and enteric coated tablet where timed release is achieved by barrier coating. Sustain release system includes any drug delivery systems that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a sustained release beads. Site-specific targeting refers to targeting of drug directly to a certain biological locations. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissue. Receptor targeting refer to the target is particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspects of drug delivery and are also considered to be sustained release beads.

Conflict of Interest

The authors declare that there is no conflict of interest.

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