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Review on Formulation of Tramadol Hydrochloride Using Albumin Microsphere

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***Abstract*: Microspheres are small spherical particles with dimensions ranging from 1 to 1000 micrometers. Microspheres are also known as micro particles. Microspheres are homogeneous, monolithic particles that improve treatment by allowing the medicine to be localized at the site of action and extending the drug's release time. According to the findings, the manufactured microspheres containing tramadol (TH) only showed small variations in particle size throughout the stability investigation, with no discernible changes in drug content, indicating that the product was stable in an accelerated environment. Microsphere's efficacy in delaying medication release has been demonstrated in a prior study. As a result, the frequency of dose may be reduced, and patient compliance may be improved in tramadol. Tramadol is a centrally acting analgesic with a multimode of action. It acts on serotonergic and noradrenergic nociception, while its metabolite O-desmethyltramadol acts on the μ-opioid receptor.**

***Keywords*: Albumin microspheres, passive drug targeting, tramadol.**

1. Introduction

Microspheres are homogeneous, monolithic particles that improve treatment by allowing the medicine to be localized at the site of action and extending the drug's release time [1]. The most prevalent types of polymer microspheres are polyethylene2, polystyrene, and expandable microspheres. The goal of any drug therapy is to achieve a therapeutically effective drug concentration in the blood over an extended period of time. This can be accomplished through the use of a well-designed sustained-release dosing regimen [3]. TH is a centrally active oral analgesic that works by binding to opioid receptors and inhibiting the reuptake of nor epinephrine and serotonin. TH has a short plasma half-life of 6 hours, making it ideal for use in a sustained-release drug delivery system. Microencapsulation is a revolutionary strategy for delaying medication release from dosage forms and reducing side effects, resulting in increased patient compliance4. The medication is available in oral, rectal, and parental (IM and IV) delivery formulations [5].

2. Concept of Drug Targeting

Drug targeting is a type of drug delivery in which a pharmacological ingredient is delivered to a specified site of action or absorption. This could be a specific organ structure, a cell subset, or even an area within a cell. The advantages of this delivery method are self-evident: the drug gets to where it's needed, and other tissues aren't exposed to potential harm that could cause an adverse reaction.

There are five different approaches of drug targeting.

- Chemical approach
- Compartmental delivery
- Natural targeting
- Ligand mediated
- Physical approach to targeting

1) Natural or Passive Targeting

This method relies on a careful selection of particle size as well as the carrier system's nature, such as proteins, polysaccharides, synthetic polymers, and erythrocytes. Attempts have been made to employ this strategy to treat lung cancer and emphysema using DNA liposomes, implants, dextrans, silicone capsules, and so on. The carrier has been chosen as human serum albumin, although the efficiency of such microsphere systems has yet to be determined. The trapping of the medication within the microspheres is a key issue. If the particles are smaller than the capillary beds, they will not be confined and will instead enter the systemic circulation, where they will be captured by the Reticuloendothelial system's phagocytic cells (RES). Because the liver's Kupfer cells have a voracious hunger for foreign particles, more than 90% of the particles injected intravenously are routinely sequestered by the liver within 2-3 minutes. As a result, colloidal carriers can be utilized to more effectively target medications to RES cells in disease conditions affecting the RES, such as candidiasis and Leishmaniasis. Colloidal carriers will enter cells via phagocytosis or pinocytosis since the particles are so minute, and will be taken to the cell's lysosomal compartments, which are low pH and rich of enzymes, and these qualities, can be used to offer a regulated mechanism for drug release [6].

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2) Albumin microsphere

Microspheres are discrete, micrometer-sized spherical particles that contain an encapsulated substance in drug delivery. A variety of carrier materials can be used to make them. Macromolecular drug carrier systems have been created in an attempt to change drug tissue localization such that drug effects at desired sites of action are enhanced compared to those at undesirable sites. The strategy is justified by the medication's changed distribution in a stable connection with a macromolecular drug carrier. The qualities of the carrier will have a significant impact on the drug's distribution. Hence tramadol is hydrophilic in nature; it is incorporated in hydrophilic albumin microsphere [7].

3) Hydrophilic albumin microsphere

Currently, either thermal denaturation at high temperatures or chemical cross linking are used to create albumin microspheres. These approaches yield albumin microspheres that are relatively hydrophobic. This hydrophobicity could be owing to the albumin molecules preferred arrangement at the vegetable oil interface during synthesis. This impact could be boosted by thermal albumin denaturation. The hydrophobic interaction between vegetable oil and albumin causes the albumin molecules to shift shape, exposing the hydrophobic portions of the molecules to the oil in a preferred manner. For a length of time, this results in a hydrophobic "crust" or mantle that is not reversible [8].

The method reported here, on the other hand, entails steric stabilization of aqueous albumin dispersions in organic polymer solutions, resulting in a flexible new class of moderately hydrophilic albumin microspheres.

The hydrophilic microspheres are useful because: in vivo, they may have improved surface physical and chemical properties. Drug release hydrophilicity permits aqueous chemical modification and does not require the surfactants currently employed to prepare aqueous dispersions (of hydrophobic microspheres), which may alter tissue interactions. After manufacturing, high amounts of water-soluble medicines may be introduced into the microspheres. Surface functionality changes could be employed to improve tissue immobilization via covalent or physical binding, particular tissue targeting via bio specific affinity ligands (e.g., tumour-specific antibodies), or diagnostic and immunological test reagents and processes9.

4) Advantage of albumin microsphere

5) They are easily identifiable.

a) Albumin microspheres give a physiological mechanism of obtaining endocytic cell target selectivity. They are quickly phagocytosed and concentrated in the reticulo endothelial system after being removed from the vascular system.

b) They can be tissue localized by blocking capillaries in organs with microspheres of the appropriate size.

c) With the use of an extracorporeal magnetic source

1. Physically and chemically, albumin microspheres are stable.
2. Biodegradable (This is a benefit compared to synthetic polymeric formulations.)
3. Non-antigenic
4. Has the ability to accommodate a wide range of therapeutic compounds in a non-specific manner.

The eventual position of these albumin microspheres is determined only by their size. Microspheres 15-30 microns or larger injected intravenously will pass past the heart and then into the capillary bed of the lungs, where they will deposit with 99 percent efficiency. Microspheres with a diameter of 1-3 microns deposit 90% of the time in the liver, while microspheres with a diameter of less than I microns have a mixed distribution in the liver, spleen, and bone marrow. As a result, microsphere targeting to these organs must be solely based on size. However, drug-loaded spheres can be targeted to other organs or solid tumors using sophisticated angiographic procedures [10].

6) Factors Regulating Drug Release from Albumin Microsphere

Microspheres are typically made from 20-50 percent albumin in water solutions. Although solutions containing 2-5 percent w/v and 70-80 percent w/v have been employed. Heat cross linked microspheres made from higher concentration albumin solutions are denser and release the integrated medication more slowly than those made from lower concentration solutions, especially for heat cross linked microspheres. Prior to spheroidization, the mixture is allowed to equilibrate for 15 to 60 minutes after the drug has been added to the albumin solutions. The many parameters influencing protein binding control the amount of medication bound.

The above relationship is also influenced by the microspheres' particle size. Because of the substantially larger surface area and shorter drug diffusion path length of the smaller spheres, a given weight of tiny microspheres will release a particular amount of a drug faster than the same weight of bigger microspheres holding the same amount of drug.

The particle size can be controlled by adjusting the rate of injection of the drug albumin solution or dispersion into the oil bath, as well as the spheroidization stirring speed. The addition of a small amount of a surfactant, such as tween 80, to the beginning albumin solution influences drug release via altering surface and interfacial tensions.

By adjusting the time and temperature of the heating process during cross linking, the biodegradability and porosity of the microspheres may be adjusted. Higher temperatures and longer heating times, when all other factors are equal, yield tougher, less porous, and slower degradable spheres. The water solubility of the encapsulated medication influences this release behavior to some extent. Water-insoluble medicines, such as steroids, diffuse more slowly and have less dramatic biphasic release profiles than highly water-soluble medications. The first-order release pattern is defined as one in which the rate of drug release is proportionate to the drug concentration remaining in the microspheres [11].

7) Preparation of albumin microsphere

Heat denaturation was used to create albumin microspheres. A solution of albumin (1 g in 25 ml) was made, and 1 gm of the medication was added to the albumin solution. The ingredients were gently added to a beaker containing 100 ml of preheated

60°C liquid paraffin with tween 80 as an emulsifier and swirled for 1 hour. For the hardening phase, the temperature was decreased to 40°C and held for 25 minutes. The microspheres were then stabilized in a glutaraldehyde solution (25 percent v/v) for 15 minutes. Decantation was used to collect the microspheres, which were then washed in n-hexane and dried at room temperature [12].

3. Pharmacokinetics of Tramadol

In terms of human pharmacokinetics, oral tramadol absorption in the upper small intestine is 95 to 100%, while bioavailability is 70% after administration, single dosages (owing to a 30 percent first-pass failure rate) 90 percent in multiple dose studies with a placebo (metabolism) and 90 percent in single dose studies with a placebo (metabolism). In 36 hours, the steady state has been reached. It is readily absorbed after oral administration within two hours of reaching peak serum concentrations capsules for three hours and five hours for sustained release tablets [13].

1) Drug interaction

When combined with other opioid analgesics, tramadol functions as an opioid agonist, which can increase the risk of side effects (such as morphine, pethidine, tapentadol, oxycodone, and fentanyl) 14. Tramadol can interact with other drugs that work in a similar way. Tramadol is a serotonin–nor epinephrine reuptake inhibitor, which means it can interact with other serotonergic medications (selective serotonin reuptake inhibitors, serotonin–nor epinephrine reuptake inhibitors, tricyclic antidepressants, triptans, cough and cold medications containing dextromethorphan, herbal products containing St. John's wort, and some serotonergic antagonist anti-emetic drugs (ondansetron) may be rendered ineffective as a result [15].

2) Adverse drug reactions

Nausea, dizziness, dry mouth, indigestion, abdominal discomfort, vertigo, vomiting, constipation, sleepiness, and headache are some of the most prevalent side effects of tramadol16, 17. Interactions with other drugs could cause additional side effects. Tramadol, like morphine, has dose-dependent side effects, including respiratory depression 18.

4. Clinical use

1) Acute pain

Tramadol has undergone extensive testing in a variety of surgical specialties, including cardiothoracic19, orthopaedic20, general and paediatric surgery [21].

2) Cancer Pain

Tramadol has been demonstrated to be effective in the treatment of cancer pain across a wide range of cancer pain syndromes, with fewer adverse effects22. When compared to morphine in terms of profile and tolerability, and it has now progressed to the second stage of the World Health Organization's. An organization ladder is required for Step I treatment. Paracetamol and NSAIDs can be added or substituted 23. However, in the early stages of treatment, for extreme pain morphine has proven to be more beneficial (This could be due to tramadol's delayed absorption) 24. Its significance in the long-term therapy of diverse forms of intractable pain still has to be clarified25.

3) Assessment of Drug Incorporation

A number of approaches for estimating the amount of medication linked with albumin microspheres have been developed. The first approach is an indirect method that determines the amount of medication that remains in the system after the microspheres have been collected (including in the emulsion and the washing). The radio labelled medication is used in the second approach. The method allows for direct estimation of drug quantity and is dependent on the availability of radio labelled chemical and acceptance of apparatus contamination. The produced microspheres can also be digested with a mixture of 5% hydrochloric acid and ethanol. The disadvantage of this approach is that it produces erroneous results due to drug degradation and /or the drug assay being hampered by the resultant microsphere particles

The fourth method entails determining the amount of medication contained in non-stabilized microspheres. Because cross linking and heat stabilization have little influence on integration, the approach can be applied quickly. The amount of medication in solution is determined by dissolving the freeze-dried, non-stabilized microspheres in aqueous buffer. To establish the effect of dissolved protein on the drug assay, controls must be performed [11].

5. Conclusion

Microspheres only showed minimal variations in particle size throughout the stability investigation, with no much change in drug content, indicating that the product was stable when tested in an accelerated environment. It has high efficacy in delaying tramadol drug release. As a result, the frequency of dose may be reduced, and patient compliance may be improved.

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