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Review Article

Design and Evaluation of Emulgel loaded with Microspheres containing Tecovirimat

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ABSTRACT

Topical gels are becoming more popular due to ease of application and better percutaneous absorption. Topical gels are intended for skin application orto certain mucosal surfaces for local action or percutaneous penetration of medicament or for their emollient or protective action. Transdermal drug delivery systems are a constant source of interest because of the benefits that they afford in overcoming many drawbacks associated with other modes of drug delivery (i.e. oral, intravenous).Microsphere denotes that micrometre in size but the main motto is to deliver the drug and it depends on the routes of administration. Topical delivery of microsphere is one of the most important to deliver the drug into the body. Microsphere can work as a transporter for the drugs in a sustained control release manner. As a result, it clears the potential of the effectiveness of active pharmaceutical ingredients through the barrier of skin by the help of penetration property and vehicle technology of microsphere. In this review, some basic and primitive features of microspheres in the form of topical delivery has been discussed.

Keywords: *Topical gels, Microsphere, surfactant, co-surfactants, penetration*

INTRODUCTION

Microparticles, microspheres, and microcapsules are common constituents of multi particulate drug delivery systems offering numerous advantages based on their structural and functional abilities, and their application is suitable for convenient and tolerable drug administration via several routes. Depending on the formulation, they can be incorporated into different pharmaceutical dosage forms such as solids (capsules, tablets, sachets), semisolids (gels, creams, pastes), or liquids (solutions, suspensions, and even parenterals).

An advantage of micro carriers over nanoparticles is that they do not traverse into the interstitium over the size of 100 nm transported by the lymph, and thus act locally. Possibly toxic substances can be carried encapsulated and liquids can be handled as solids in the form of dried microparticles. In the case of multiparticulates, the dose is distributed in many small separate particles, which carry and liberate a part of the dose, hence the malfunction of an individual subunit does not cause the failure of the whole dosage. Multiparticulate drug delivery systems offer outstanding advantages to experts and patients, such as:

- ✓ choice of dosage form for the desired drug delivery route (peroral tablets, parenteral injections);
- ✓ modified and targeted (even site-specific) drug release and delivery;
- ✓ more expectable pharmacokinetics with reduced intra- or inter-subject variability;
- ✓ more homogenous distribution in the physiological environment;
- ✓ stable fixed-dose combinations of drugs;
- ✓ dose titration and less dose-dumping;
- ✓ patient centricity through better compliance (e.g., patients with dysphagia) and adherence;
- ✓ individual therapy (e.g., for pediatric or geriatric population);
- ✓ improving stability of the medicinal preparations;
- ✓ Isolating the constituents to ensure better compatibility;

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- ✓ Innovative products with a prolonged life cycle through patent protection.

From the viewpoint of technology, microencapsulation provides several advantages: microparticles are formulated in order to protect the core from the environment; masking an unpleasant taste; preserving volatiles or the viability of the cells; separating incompatible substances; protecting the body from the side effects; and optimizing, prolonging, or targeting the effect of a drug. The polymer excipient protects the active pharmaceutical ingredient (API) from the environment (oxidation, temperature, pH) or the body from the irritative, or mucosa-damaging effect of the drug substance. The lesion (e.g., bisectioning) of the multi particulate solid dosage form (i.e., micropellets in spansule or compressed) affects only a small number of units, thus does not result in a significant change of the blood level.

Microspheres can be characterized as matrix systems in which the drug is homogeneously dispersed, either dissolved or homogenously suspended. Microcapsules are heterogenous particles where a membrane shell is surrounding the core forming a reservoir.[1]

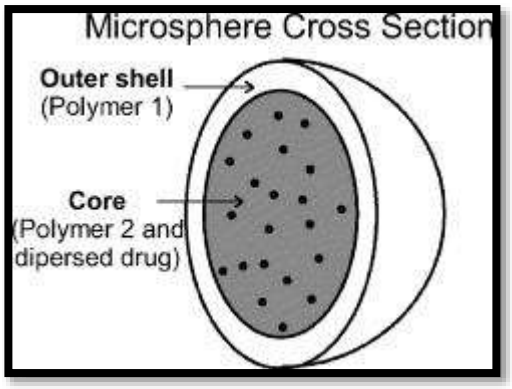

Fig 1: Microsphere cross section

Materials Used

Microspheres used usually are polymers. They are classified into two types.

1. Synthetic Polymers
2. Natural polymers

Synthetic polymers are divided into two types.

(I) Non-biodegradable polymers

• Poly methyl methacrylate (PMMA)

• Acrolein

• Glycidyl methacrylate

• Epoxy polymers

(II) Biodegradable polymers

• Lactides, Glycolides & their co polymers

• Poly alkyl cyano Acrylates

• Poly anhydrides

Natural polymers obtained from different sources likeproteins, carbohydrates and chemically modifiedcarbohydrates.

[A] Proteins:

• Albumin

• Gelatin

• Collagen

[B] Carbohydrates:

• Agarose

• Carrageenan

• Chitosan

• Starch

[C] Chemically modified carbohydrates:

• Poly dextran

• Poly starch

Types of Microsphere

1. Bioadhesive Microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

2. Magnetic Microspheres

This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different

types are therapeutic magnetic microspheres and diagnostic microspheres.

i. Therapeutic Magnetic Microspheres:

It is used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system.

ii. Diagnostic Microspheres:

It can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

3. Floating microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.

4. Polymeric Microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.

i. Biodegradable Polymeric Microspheres:

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bioadhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release.

ii. Synthetic Polymeric Microspheres:

The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles drug delivery vehicles etc and proved to be safe and biocompatible. But the main disadvantage of these kinds of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.[2]

Advantages of microspheres:

1. Particle size reduction for enhancing solubility of the poorly soluble drug.
2. provide constant and prolonged therapeutic effect.
3. provide constant drug concentration in blood there by increasing patent compliance,
4. Decrease dose and toxicity.
5. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.
6. Reduce the dosing frequency and thereby improvethe patient compliance.
7. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
8. Microsphere morphology allows a controllablevariability in degradation and drug release.
9. Convert liquid to solid form & to mask the bittertaste.
10. Protects the GIT from irritant effects of the drug.
11. Biodegradable microspheres have the advantageover large polymer implants in that they do notrequire surgical procedures for implantation andremoval.
12. Controlled release delivery biodegradable microspheres are used to control drug release ratesthereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Limitation:

Some of the disadvantages were found to be as follows

1. The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations.

2. The fate of polymer matrix and its effect on the environment.

3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.

4. Reproducibility is less.

5. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.

6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.3

Methods of Preparation: Different techniques have been tried for the formulation of microspheres using different polymers. Some of these are discussed below:

1. **Single Emulsion Solvent Evaporation Technique:**

This method involves the dissolution of polymers in an organic solvent followed by emulsification in an aqueous phase containing emulsifying agent. The o/w emulsion thus formed is stirred for several hours under ambient conditions to allow evaporation of solvent, which is then filtered, rinsed and dried in desiccators.

2. **Double Emulsification Technique:**

Double emulsion technique involves the preparation of double emulsion either w/o/w or o/w/o. The aqueous drug solution is dispersed in a lipophilic organic continuous phase. The continuous phase that consists of polymer solution eventually encapsulates drug contained in dispersed aqueous phase to form primary emulsion. The pre-formed emulsion is subjected to homogenization or sonication before addition to aqueous solution of polyvinyl alcohol (PVA) to form primary emulsion.

3. **Spray Drying Method:**

Both drug and polymers are dissolved in suitable solvent to form solution which is subjected to spray through nozzle in a spray drier under different experimental conditions.

4. **Spray Congealing:**

Drug is dissolved into melt of lipophilic polymer material to form hot mixture and allowed to atomize with pneumatic nozzle into a vessel that is stored in a carbon dioxide ice bath. Fabricated microparticles are dried under vacuum at room temperature for many hours.

5. **Melt Dispersion Technique:**

Hot mixture of drug and polymer is emulsified into an aqueous surfactant solution that has been heated above polymer melting point to form emulsion which is finally allowed to cool in an ice bath.

6. **Coacervation Phase Separation Method:**

Coacervation is the separation of macromolecular solution into two immiscible liquid phases out of which one is dense coacervate phase while another is dilute equilibrium phase.

7. **Chemical and Thermal Cross – linking Method:**

Aqueous solution of natural polymer containing drug to be incorporated is dispersed in organic phase to form w/o emulsion followed by solidification either by thermal cross linking or addition of chemical cross linking agent such as glutaraldehyde.

8. **Ionic Gelation Method:**

In this method, a hydrophilic polymer is complexed with a multivalent cationic (e.g. calcium chloride) or polyanionic (e.g. sodium tripolyphosphate) to form highly viscous gel particles. An opalescent suspension is obtained. Then the suspension is centrifuged to obtain microspheres. Microspheres are freeze dried followed by lyophilization for 24 hours. The resulting microspheres are formed due to electrostatic interactions between positively charged group and negatively charged anion.4

Topical drug delivery system

Topical drug delivery system is the dosage form which is administered on the skin and other routes of drug delivery get failed or for skin disorders. The topical drug delivery system has the advantage of negotiating the first pass metabolism. It also helps to avoid the risk and inconvenience of i.v route therapy. Topical formulations are prepared in different consistency such as solid, semisolid, and liquid. The topical delivery system is failed in the administration of hydrophobic drug. In each formulation with the active ingredients many excipients are used. Sometimes more than one formulation can be combined to enhance the drug delivery; emulgel is such type of combination. It is the combination of emulsion and gel. Emulgel is prepared both in oil- in- water and water-inoil type emulsion mixed with gel. Oil- in- water type is used for lipophilic drugs and water- in- oil type is used for hydrophobic drugs' delivery. The emulgel have many advantages like thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, bio-friendly, pleasing appearance, transparent and cosmetically acceptable, which also have a good skinpenetration and long shelf- life .The emulsion and gel preparations have their ownproperties. But the gels show some limitations ashydrophobic drug delivery. This limitation is overcomingby emulgel. By the use of gelling agent classical emulsion can be converted in to emulgel.

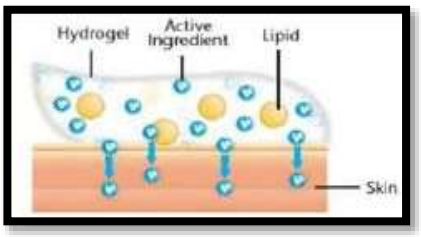

Fig 2: Emulgel structure

Advantages of emulgel

- ✓ Incorporation of hydrophobic drugs
- ✓ Better loading capacity
- ✓ Better stability
- ✓ Controlled release
- ✓ No intensive sonication
- ✓ Avoiding first pass metabolism
- ✓ Avoiding gastrointestinal incompatibility

- ✓ More selective for a specific site
- ✓ Improved patient compliance
- ✓ Convenient and easy to apply

Disadvantages of emulgel

- ✓ Skin irritation on contact dermatitis
- ✓ The possibility of allergenic reactions
- ✓ The poor permeability of some drugs through the skin
- ✓ Drugs of large particle size are not easy to absorb through the skin
- ✓ The occurrence of the bubble during formulation of emulgel

Formulation of Emulgel

For the preparation of emulgel some constituents are used including drug, which are:

- ➢ **Vehicle**

Vehicle should follow the ideal characters given in the Pharmacopeias

- ➢ **Aqueous material**

The aqueous phases used are water, alcohol, etc.

- ➢ **Oil**

Oils are used for preparation of emulsion. Mineral oils and paraffin are used either alone or in combination.

- ➢ **Emulsifiers**

Emulsifiers used for preparation of emulsion. Some examples are span 80, tween 80, stearic acid, sodium stearate.

- ➢ Gelling agents

Gelling agents are used for prepare gels, which enhance consistency of preparation.

- ➢ Penetration enhancers

Penetration enhancers help to absorb drug to the skin

- ➢ pH adjusting agent[5]

Microsphere based gel

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1µm to 1000 µm). Microspheres are sometimes referred to as microparticles. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. There are two types of microspheres;

- ✓ Microcapsules
- ✓ Micromatrices

In microcapsules entrapped substance is distinctly surrounded by distinct capsule wall and inmicromatrices entrapped substance is dispersing throughout the microspheres matrix. Solidbiodegradable microspheres incorporating a drug dispersed or dissolved through particle matrix havethe potential for the controlled release of drug. They are made from polymeric, waxy, or other protectivematerials (i.e. Biodegradable synthetic polymers and modified natural products).

Advantages

- ✓ Microspheres provide constant and prolonged therapeutic effect.
- ✓ Reduces the dosing frequency and thereby improve the patient compliance.
- ✓ They could be injected into the body due to the spherical shape and smaller size.
- ✓ Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- ✓ Microsphere morphology allows a controllable variability in degradation and drug release.

Disadvantages

- ✓ The modified release from the formulations.
- ✓ The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- ✓ Differences in the release rate from one dose to another.
- ✓ Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- ✓ Dosage forms of this kind should not be crushed or chewed.

Evaluation parameters

- ✓ Particle size and shape
- ✓ Entrapment efficiency
- ✓ Density determination
- ✓ Isoelectric point
- ✓ Swelling Index
- ✓ Angle of contact
- ✓ In vitro study[6]

Encapsulation of microsphere

Microencapsulation is a process by which very thin coatings of inert natural or synthetic polymeric materials are deposited around micronized particles of solids or droplets of liquids.

Products thus formed are known as microparticles, covering two types of forms: microcapsules, micrometric reservoir systems, microspheres, and micrometric matrix systems (Figure 1). These systems consist of two major parts. The inner part is the core material containing one or more active ingredients. These active ingredients may be solids, liquids, or gases. The outer part is the coating material that is usually of a high molecular weight polymer or a combination of such polymers. The coating material can be chosen from a variety of natural and synthetic polymers and must be nonreactive to the core material, preferably biodegradable, and nontoxic. Other components, such as plasticizers and surfactants, may also be added.

CONCLUSION

Topical delivery of microsphere shows an impactful future in various pharmaceutical applications in the coming years as they have unique properties like enhanced product performance and elegancy, extended-release, reduced irritation, improved thermal, physical, and chemical stability so flexible to develop novel product forms. Not only it is using in facial moisturizer, sunscreen type cosmetic products but also it is using in anti-inflammatory, anti-fungal, anti-dandruff, etc. The various types of works are going on about it in the research area and they're having lots of hope to overcome various challenges and we will go towards the light.[7]

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