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Microsphere A Novel Approach For Transdermal Drug Delievery System

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Abstract

In order to increase bioavailability, decrease dosing frequency, and improve patient compliance, the current study's primary goal was to develop and evaluate a gel containing apremilast microspheres. To choose the most effective formulation, a prepared gel loaded with microspheres was assessed for drug interactions using Fourier transform infrared (FTIR), differential scanning calorimetry tests, and scanning electron microscopy (SEM). Pre-formulation studies, spreadability, viscosity, pH measurement, gel strength, homogeneity, drug content, in vitro diffusion tests, drug kinetics, and stability investigations were all performed on the generated formulations (F1–F6). The study used differential scanning calorimeters and FTIR spectroscopy to confirm the drug-excipient interaction and compatibility between medication and excipients. SEM images showed smooth-surfaced particles with regular shapes. All formulations were less effective than the optimized F4 formulation, which had acceptable physical properties like spreadability, viscosity, pH, gel strength, and drug content.

Keywords: Microspheres, Transdermal drug delivery, Apremilast, Formulation and evaluation, Biodegradable polymers

Introduction

Psoriasis and psoriatic arthritis are a chronic skin disease of autoimmune system that is identified as patches of abnormal skin. [1]. An immune-mediated, hereditary condition, psoriasis primarily affects the skin, joints, or both. Diabetes and cardiovascular disorders are closely associated with psoriasis, which is primarily caused by abnormal keratinocyte differentiation and epidermal hyperproliferation. It is a chronic or acute autoimmune disease that is mediated by T lymphocytes.[2-5]

Appremilast inhibits the enzyme phosphodiesterase 4 which leads to spontaneous inhibition of tumor necrosis factor-alpha production from human rheumatoid synovial cell. [6] In addition, the application of oral drug delivery has numerous problems such as abdominal pains, upper respiratory, nasopharyngitis, and depression that often ends in lack of patient compliance. [7] Drugs that are not soluble in water can be entrapped in microsponge pores, which are extremely small, thus the drug functions as microscopic particles, producing a greater surface area and increasing the rate of solubilization. [8]

Microspheres defined as solid spherical particles, approximately the size ranges from 1 to 1000 μm containing dispersed drug molecules either in solution or crystalline forms. [9]

Apremilast (Otezla, Celgene Corporation, Summit, NJ) was approved by the US Food and Drug Administration (FDA) in 2014 and by the European Commission in 2015 for treatment of psoriasis and psoriatic arthritis. [9-10] These are free-flowing, shallow, spherical powders made of synthetic or protein polymers that are biodegradable. [10] The medication is uniformly distributed throughout the polymeric matrix system that makes up microspheres. Polymers such as ethyl cellulose are used for the preparation of matrix-type microspheres of water-soluble drugs to control the dissolution rate of drugs from the dosage forms. [11]

Transdermal gels are made from a liquid and thickened with additional chemicals to create a semisolid system. The drug release through skin membrane and preparation of gelling agent sodium alginate is used. [12]
The present work is to increase bioavailability and reduce the dosing frequency and improve patient compliance by designing formulation and evaluation of gel loaded with microspheres of apremilast for treating psoriasis and psoriatic arthritis.

Advantages [13]

- Microspheres have a long-lasting therapeutic impact.
- Drug distribution by microspheres is regulated, prolonged, and precise.
- Microspheres improve patient compliance by reducing the frequency of doses.
- Microspheres produce more reproducible drug absorption.
- Microspheres also reduce the chances of G.I. irritation.
- Microspheres increase the biological half-life and bioavailability.
- Microspheres Avoids the first pass metabolism.
- Microspheres also mask the taste and odor.
- Microspheres reduce dose dumping.
- Microspheres can provide better therapeutic outcomes for medications with short half-lives.
- Microspheres increase patient compliance by lowering the frequency of doses.
- By preventing drug discharge in the stomach, local adverse effects are lessened.
- Microspheres are easy to inject into the body because of their small size and spherical form.

Disadvantages [14]

- Minimal drug loading is done in the case of parental microspheres.
- It is challenging to entirely eliminate the carrier from the body when microspheres are applied to children.
- The release of formulation can be modified.
- When employing a controlled release dose form, chewing or crushing is not allowed. The following kinds of polymers are utilized in the production of microspheres.
- Any degradation of the release pattern could potentially be harmful.
- It is not advised to chew or crush this type of dosage form.

PREPARATION TECHNIQUES

1. Single Emulsion Technique:

This method is mostly used to prepare a number of proteins and carbohydrates. In this technique, natural polymers are first dissolved in aqueous medium and then dispersed in non-aqueous medium (oil phase) followed with next step cross- linking of dispersed globule; which can be achieved by 2 methods: [15]
i. **By Heat:** Addition of dispersion into heated oil, but this method is not suitable for thermolabile drugs.
ii. **By Chemical Cross-linking Agent:** Using glutaryldehyde, formaldehyde, acid chloride etc. as cross-linking agent. Chemical cross- linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation [16-17]

2. Double emulsion technique

This method works with both natural and synthetic polymers and is more suitable for water-soluble medications, peptides, proteins, and vaccinations. This process of creating microspheres requires the production of several emulsions. This method involves dispersing aqueous protein solutions in a lypophllic organic continuous phase that contains the active components. Proteins dispersed in the aqueous phase are encapsulated in polymer solution in the continuous phase. After homogenizing, the original emulsion is added

to an aqueous solution of PVA. After forming Double emulsions, emulsions are processed to remove the solvent by either solvent extraction or solvent. [18]

3. Polymerization Technique:
There are two ways to prepare microspheres using this method:

i. Normal Polymerization:
This kind of polymerization is carried out utilizing a variety of methods, including emulsion, bulk, suspension, and precipitation. In case of bulk, a monomer along with catalyst is heated to initiate Polymerization. The resulting polymer is formed into microspheres, and drug loading can be carried out while the polymerization process is underway. Bulk Polymerization has an advantage of formation of Pure Polymer. In case of suspension, heating of monomers or a mixture of monomers with active Drug as droplet dispersion in continuous aqueous phase. Pearl/bead polymerization is another name for suspension polymerization, which is carried out at a low temperature. In case of emulsion polymerization, there is initiator present in aqueous phase, which later on diffuses at the surface of micelle. [19,20,21]

ii. Interfacial Polymerization:
It involves the reaction of various monomers at the interface between two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. [19,15,22]

4. Emulsion solvent diffusion method
To increase Ketoprofen's residence time in the colon, floating micro-particles of the drug have been produced using the emulsion solvent diffusion technique. The drug/polymer combination was dissolved in a 1:1 mixture of ethanol and dichlromethane (DCM), which was then gradually added to a solution of sodium laurylsulphate (SLS). The solution was stirred for an hour at room temperature using a jet engine agitator running at 150 rpm. The resulting floating microspheres were then rinsed and dried at room temperature in a dryer. Tiny particles below were also gathered and sieved.

5. Spray drying technique
Drug-loaded polymeric mixed microspheres were created using this method. It comprises spraying the resulting combination in the environment for coating solidification, swiftly evaporating its solvent, and scattering the core component to turn it into a liquid coating substance. To make drug loaded microspheres and organic solution of Poly Cprolacton (PCL) and cellulose acetate buty- rate (CAB) in various weight ratios was prepared and sprayed in various experimental conditions. This is quick, but because to the quick drying process, the cryst-line may be lost. [23]

- **Atomization:** Fine droplets were formed from the liquid supply
- **Mixing:** Mixing is the process of passing a stream of hot gas past a spray droplet, which evaporatively removes the liquid and leaves behind dry particles.
- **Drying:** The gas stream is extracted and gathered.[24]

6. Phase Separation Co-acervation Technique:
It is a simple process of separation of a micro molecular solution into two immiscible liquid phases. In order to influence the formation of polymer-rich phases known as coacervates, the coacervation concept entails lowering the solubility of polymers in organic phases. In this method, formation of dispersion of drug particles in a solution of polymer and an incompatible polymer added to the system which makes first polymer to phase separate and engulf the drug particle. [25,26]

7. Solvent Evaporation Technique:
The polymer is dispersed in an organic solvent and the drug is either dissolved /dispersed in the polymer solution. To create an oil in water emulsion, the drug-containing solution is subsequently emulsified into an aqueous phase with appropriate additions (polymers or surfactants). Following emulsion formation, the organic solvent is removed by stirring continuously or by raising the temperature under pressure. The solvent removal leads to polymer precipitation at the oil/water interphase of droplets, forming cavity. [27,28,29]

Characterization of microspheres

1. Particle size and shape

Particle size can be determined by optical microscopy using a calibrated ocular micro-meter. The average particle Once their size is determined, the size of approximately microspheres is calculated. [30]

D mean = Σ n d/Σ n Where, n = number of microspheres checked; d = Mean size

2. Density determination

A multi volume pycno-meter can be used to determine the density of microspheres. A carefully weighed sample is placed in a cup and placed into the multivolume pycnometer. Helium is put into the chamber at a steady pressure and allowed to expand. The pressure within the chamber decreases as a result of this expansion. At various starting pressures, there are two consecutive pressure reduction readings. The volume and density of microsphere carriers are calculated using two pressure readings. [31]

3. Isoelectric point

The isoelectric point can be determined by measuringthe electro-phoretic mobility of microspheres using a micro electrophoresis device. [32] By measuring the period of particle travel across a distance of 1 nm, the mean velocity is calculated at different pH values ranging from 3 to 10.

4. Angle of repose

Angle of repose of microspheres is used to calculate the resistance to particle flow and is calculated as

$\tan \Theta = 2h/d$

Thus, after the microspheres have flowed out of the glass funnel, 2h/d is the area of the microspheres' free standing height. [33]

5. Fourier transform infrared spectroscopy (FTIR)

FTIR can be used to assess drug polymer interaction and microsphere disintegration. [34]

6. Drug entrapment efficiency

Microspheres are weighed and crushed. Then, using a stirrer, dissolve it in a buffer solution and filter it. Using a calibration curve the filtrate is tested with a UV spectrophotometer at a certain wavelength. [35]

To calculate the effectiveness of drug entrapment, divide the actual weight of microspheres by the theoretical weight of the drug and polymer 100.

7. Percentage yield

This is computed by multiplying the weight of microspheres collected from each batch by the total weight of medicine and polymer used to make that batch. [36]

Applications of Microspheres

1. Microspheres in vaccine delivery

Protection against the microbe or its harmful product is a requirement of a vaccination. Efficacy, safety, usability, and cost must all be met by the ideal vaccination. Safety and the reduction of unfavorable reactions are challenging issues. [37] The tissue of level of antibody response development safety are both intimately related to the technique of application. The drawbacks of conventional vaccines might be overcome by biodegradable vaccine delivery systems for parenteral immunizations.[38] Parenteral (Subcutaneous, Intramuscular, Intradermal) carriers are appealing because they provide a number of benefits, including.

- Adjuvant activity increases antigenicity
- Regulation of antigen release
- Stabilization of antigen.

2. Monoclonal antibodies

Immune micro-spheres are monoclonal antibodies that target microspheres. This targeting is used to target certain areas with precision. Monoclonal antibodies are molecules with a high level of specificity. Any of the following ways can be used to attach maps to micro-spheres:

- Non-specific adsorption and specific adsorption
- Immediate coupling
- Using reagents to couple

3. Targeting drug delivery
The concept of site-specific drug targeting is an established doctrine that is gaining a lot of traction. The therapeutic efficacy of a medication is determined by its ability to reach and engage with its receptor. [39]

4. Topical porous microspheres
Porous microspheres with several interconnected spaces that range in size from 5 to 300 micrometers are known as micro sponges. These micro sponges are utilized as topical carriers because they may entrap a wide range of active substances such as emollients, perfumes, and essential oils. [40]

5. Imaging
When employing radio-labeled microspheres to image specific areas, the particle size range of the microspheres is a crucial consideration. The intravenous particles will become caught in the lung capillary bed if they are administered outside of the portal vein. Labeled human serum albumin microspheres are used to take advantage of this phenomena in order to perform scintigraphic imaging of lung tumor masses.

6. Medical Application: [41]
- Release of proteins, peptides and hormones over the extended period of time.
- Passive targeting of leaky tumor vessels, active targeting of tumor cells, antigens, by intra arterial/intravenous application.
- Magnetic microspheres are useful for bone marrow purging and stem cell extraction.
- Used in many diagnostic tests for bacterial, viral, and fungal infectious diseases.

Future perspective:
The formulation of a gel with Apremilast microspheres for transdermal delivery holds rich scope for future research and therapeutic applications. Further adjustment of formulation parameters, such as cross-linking agents, particle size, and ratio of polymer, can enhance drug loading efficiency and extend drug release. To compare penetration efficiency, pharmacokinetics, and systemic bioavailability with traditional oral formulations, we need to do more advanced in vitro and in vivo studies, especially on human skin models. Using cutting-edge technologies like penetration enhancers, microneedle-enhanced delivery, or nanocarrier integration may also make it easier for apremilast to get through the skin. Also, a lot of safety and long-term stability tests must be done to make sure the product is safe for patients and works as it should.

Conclusion:
This review paper indicates that psoriasis and psoriatic arthritis may be successfully treated with a gel containing apremilast microspheres. A gel loaded with microspheres of apremilast was prepared to deliver the drug through the transdermal route, providing a quicker onset of action compared to oral routes. Good physicochemical characteristics, such as solubility and dissolution, were exhibited by the gel and APR-crystals. Solid state characterization using DSC, XRD, and FTIR studies confirmed the formation of a new crystalline phase. The gel was formulated into a topical gel using Carbapol-940 and HPMC as independent variables. The new crystalline form of APR with saccharine increased solubility and dissolution rate, making it suitable for oral drug administration.

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