Symbiosis

www.symbiosisonlinepublishing.com
ISSN Online: 2374-8141

Research Article | Nanoscience & Technology: Open Access | Open Access

Preparation and Evaluation of Mefenamic Acid Loaded Microspheres by Solvent Evaporation Technique

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Received: May 21, 2019; Accepted: June 05, 2019; Published: June 21, 2019

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Abstract

The aim of the present investigation is to prepare mefenamic acid loaded microspheres by solvent evaporation technique. The drug and Ethyl cellulose polymer were dissolved in ethyl acetate under stirring at 700 rpm. The aqueous phase containing a surfactant was kept under stirring. Then the organic phase was added to the aqueous phase under continuous stirring. The obtained microspheres were evaluated for product yield, Drug content, entrapment efficiency and loading capacity. The SEM images clearly reveal that the particles were found to be spherical in shape. The product yield, drug content, entrapment efficiency and loading capacity was found to be 85.3.6%, 65.3%, 75.09% and 37.7% respectively.

Introduction to Microspheres

Microspheres are characteristically free flowing powders consisting of protein or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm [1, 2]. In contrast to drug delivery system, the word novel is searching something out of necessity. The drug has to be delivered for a prolonged period of time and many medicines have to be taken simultaneously in case of chronic patients. Frequent administration of drug is necessary when those have shorter half-life and all these leads to decrease in patient's compliance [3]. In order to overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect, adverse effect decreases by lowering peak plasma concentration [4]. The controlled release dosage form maintaining relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time [3].

One such in Microspheres as carriers of drug become an approach of controlled release dosage form in novel drug delivery system. Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. It has a particle size of (1-1000nm) [4].

Advantages of microspheres

Increase bioavailability

- Alter the drug release & separation of reactive core from other materials.
- Improve the patient's compliance
- Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
- Reduce the reactivity of the core in relation to the outside environment.
- The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in vivo.
- Decrease evaporation rate of the volatile core material.
- Convert liquid to solid form & to mask the bitter taste.
- Protects the GIT from irritant effects of the drug.
- Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
- Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections [7, 8].

Classification of polymers

Microspheres used usually are polymers. They are classified into two types [5]

Synthetic polymers

It is divided into two types

a. Non-biodegradable polymers

E.g. Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

b. Biodegradable polymers

E.g. Lactides, Glycolides & their co polymers, Poly alkyl cyano acrylates, Poly anhydrides

Natural polymers:

It is obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin, and Collagen.

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch.

Chemically modified carbohydrates: Poly dextran, Poly starch.

Recent Applications of Controlled Release Microspheres

Controlled-release microspheres are in development for a number of interesting and important applications, especially for delivery of large, fragile drugs like proteins and nucleic acids. Several recent examples are described below. Controlled-Release Vaccines Vaccination has been highly successful for controlling or even eradicating many important types of infectious diseases, and new or improved vaccines are being heavily investigated for AIDS, hepatitis B, anthrax, and SARS.A frequent problem is the need for repeated administrations. Single-shot Vaccine delivery systems should provide the antigen(s) and adjuvant on a prescribed schedule and maintain the bioactivity of the antigen, both during fabrication of the delivery device and during the often prolonged residence time of the device in the body. To enhance vaccine stability, researchers have been focusing on several approaches, including the use of adjuvants to protect the protein antigens or by choosing different microsphere materials. A major advantage of microspheres for vaccination is that they can be passively targeted to antigen-presenting cells (APCs) such as macrophages and dendritic cells. The ability of APCs to phagocytose particulates is dependent on the particle size. In particular,1- to 10-μm diameter microspheres are optimally taken up by APCs in a number of tissues and have been shown to enhance antigen-specific T-helper lymphocyte (Th) responses thus leading to an enhancement in antigen-specific antibody responses) and elicit a cytotoxic T lymphocyte (CTL) responseT-cell activation in response to antigen encapsulating microspheres has been shown to be 100-1000 fold better than antigen alone [9].

Stabilization of Encapsulated Protein Therapeutics

A major problem with protein encapsulation in polymer particles is loss of protein bioactivity. Damage to proteins can occur during fabrication of the particles via shear stresses or other physical forces, through contact with organic solvents, and by loss of water (e.g., upon lyophilization) as well as during incubation and release in the warm, moist, in vivo environment.

Two types of damage occur most often:

i. Covalent or non-covalent intermolecular aggregation and

ii. Denaturation. Several studies have investigated the mechanisms of damage. Protein stability can be enhanced by the addition of excipients to prevent aggregation and stabilize the folded protein structure or through judicious choice of polymer employed for fabrication of the devices.

Future Challenges

Future challenges of microspheres look bright particularly in the area of medicinal field because of its wide spectrum of application in molecular biology, e.g. microsphere based genotyping platform is used to detect six single nucleotide polymorphism, yittrium-90 microspheres are used to prevent tumour after liver transplantation and it's advanced way in delivery of vaccines and proteins.

Microspheres in cancer therapy

Cancer microsphere technology is the latest trend in cancer therapy. It helps the pharmacist to formulate the product with maximum therapeutic value and minimum or negligible range side effects. Cancer is a disease in which the abnormal cells are quite similar to the normal cells, with just minute genetic or functional change. A major disadvantage of anticancer drugs is their lack of selectivity for tumor tissue alone, which causes severe side effects and results in low cure rates. Thus, it is very difficult to target abnormal cells by the conventional method of the drug delivery system. Microsphere technology is probably the only method that can be used for site-specific action, without causing significant side effects on normal cells [10].

Some Marketed products of microspheres

Table 1: Marketed products of microspheres

Drug	Commercial Name	Company	Technology	Indication
Risperidone	RESPERDA^{R},CONSTA^{R}	Jansenn/Alkermes,inc.	Double emulsion(oil in water)	Schizophrenia;Bipolar1 Disorder
Naltrexone	VIVITROL^{R}	Alkermes	Double emulsion(oil in water)	Alcohol dependence
Octreotide	Sandostatin LAR	Novartis	Phase separation	Acromegaly
Somatropin	Nutropin^{R} Depot^{-a}	Genentech /alkermes	Alkermes prolease^{R}Technology (cryogenic spray drying method)	Growth deficiencies
Bromocriptine	Parlodel LAR	Novartis	Spray drying	parkinsonism
Minocycline	Arestin	Orapharma		Periodontitis

Need and Objective of the study

The treatment for arthritis is to reduce pain and improve the function of joints. The drug used in the investigation is Mefenamic acid. Mefenamic acid is a widely prescribed NSAID and used as first line therapy for the treatment of ailments such as Arthritis and Dysmonorrhoea. MA is available as tablets, capsules and suspensions.MA has a wide range of gastrointestinal disorders, like gastrointestinal bleeding and gastric upset, hypertension. MA biological half-life is 1.5-2hr; frequent administration of drug to maintain the desired steady state level is required. Its usual dose is 200-400mg twice daily. So in order to get a sustained release and to reduce dose, dosing frequency of the drug it was chosen as a drug for the preparation of microspheres.

Methodology

Solvent evaporation method:

Preparation of mefenamic acid microspheres by solvent evaporation method:

General procedure:

Solvent Evaporation method: The drug substance was either dispersed or dissolved in the polymer/solvent system. Then it was added to the aqueous phase by continuous agitation. Agitation of the system was continued until the solvent partitions into the aqueous phase and was removed by evaporation. This process resulted in hardened microsphere which contains the active moiety that is drug.

In this method, the capacity of the continuous phase is insufficient to dissolves the entire volume of disperse phase solvent. Thus, solvent evaporates from the surface of the dispersion to obtain hardened microsphere [11].

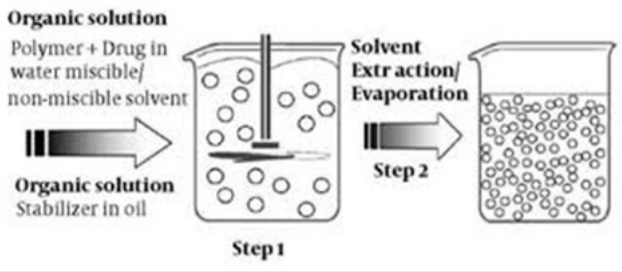

Figure 1: Schematic diagram showing solvent evaporation method.

Optimization parameters

Optimization of organic solvents: Three formulations were prepared by varying different organic solvents such as diethyl ether, Ethyl acetate, and acetone

Table 3.4: optimization of organic solvents

Formulation	Organic solvents
1:01	Diethyl ether
1:01	Ethyl acetate
1:01	acetone

Optimization of stirring speed (rpm): Three formulations were prepared by varying stirring speed 500, 700, & 900 rpm respectively.

Table 3.5: optimization of stirring speed

formulation	Stirring speed
1:01	400
1:01	600
1:01	700

By varying stirring speed, formulations were prepared. The formulations were evaluated for percentage yield and 700 rpm formulation was found to show good results

Optimization of organic –aqueous phase ratio: Three formulations were prepared by varying organic to aqueous phase ratios 1:5, 1:10 1:15 respectively

Table 3.6: optimization of organic-aqueous ratio

Formulation	Organic –aqueous ratio
1:01	1:05
1:01	1:10
1:01	1:15

By varying organic to aqueous phase ratio, formulations were prepared. The formulations were evaluated for product yield and 1:10 ratio formulation was found to show promising results.

Results and discussion

Study of drug excipient-interaction: There are several methods available to determine drug-excipient interaction. The most commonly used processes are the obtained nanoparticles were evaluated for Particle size, product yield, Drug content, entrapment efficiency and loading capacity.

Determination of Particle size

Study of surface morphology of micro sphere by scanning electron microscope (SEM): The prepared amorphous nanoparticles were dispersed in deionised water and sonicated for30 minutes. A circular metal plate is taken on to which carbon double tape (1mm×1mm) is stickered; a drop of the resultant dispersion is

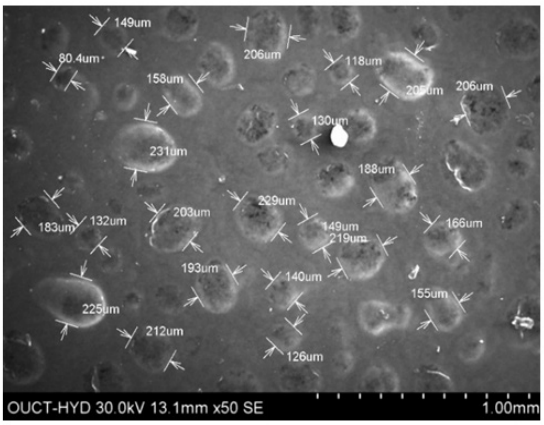

Figure 2 : SEM image of aspirin loaded ethyl cellulose microspheres

placed on to the tape and allowed to dry for a while. Then it is scanned under SEM for morphology. The obtained microspheres were found to be spherical in shape.

Product yield: The yields of the prepared microspheres was calculated. The dried micro particles were weighed and the yield of micro particles was calculated using the following formula:

$$Percentageyield = \frac{Amountofmicroparticlesobtained}{Theoreticalamount} \times 100$$

The product yield was observed as 90.6%

Drug content: To determine the drug content, 50mg drug equivalent to formulation was weighed accurately and transferred into three necked RBF containing 50ml of methanol. The solution was stirred at 700rpm for 3hrs by using magnetic stirrer8. The resultant solution was filtered and the amount of the drug in the filtrate was determined after suitable dilution by ultraviolet (UV) spectrophotometer. The drug content was found to be 80.3%.

Entrapment efficiency: For determination of drug entrapment, the amount of drug present in the clear supernatant after centrifugation was determined (*w*) by UV-spectrophotometry. A standard calibrationcurve of concentration versus absorbance was plotted for this purpose. The amount of drug in supernatant was then subtracted from the total amount of drug added during the preparation (*W*). Effectively, (*W-w*) will give the amount of drug entrapped in the pellet. Then percentage entrapment is given by Equation 2

$$\frac{w - w}{w} \text{X}100$$

The entrapment efficiency of the formulation was found to be 23.9%.

Loading Capacity: The loading capacity (L.C) refers to the percentage amount of drug entrapped in microspheres. Equation 3

$$Loaingcapacity = \frac{Totalamountofdrug - Amountofunbounddrug}{Nanoparticlesweight} \times 100$$

The loading capacity was observed as 4.1%

Conclusion

Mefenamic acid loaded ethylcellulose microspheres were prepared by solvent evaporation technique .The obtained microspheres were evaluated for product yield, drug content, entrapment efficiency and loading capacity. The SEM images clearly reveal that the particles were found to be spherical in shape. The product yield, drug content, entrapment efficiency and loading capacity was found to be The product yield, drug content, entrapment efficiency and loading capacity was found to be 85.3.6%, 65.3%, 75.09% and 37.7% respectively.

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