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A DESK-TOP LITERATURE FOR RRESEARCH ON MICROSPHERES OF DEXTROMETHORPHAN HYDROBROMIDE

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ABSTRACT

Objective: The existing study is concerned with the design and assessment of DXM microspheres (MS) via ionic gelation. **Methodology:** The microspheres are primed by using the ionic gelation method. All the ingredients were individually weighed and the calcium chloride solution was disseminated in the drug containing an aqueous solution of sodium alginate. The resultant solution has to be added drop-wise with the help of a syringe to the $Cacl_2$ solution. So the microspheres are formed by the isotropic relation between the calcium chloride and sodium alginate which formed the microspheres by the spherical rigid-walled calcium alginate microspheres. **Results:** The parameters of flow properties studies revealed that the set microspheres have good flow properties. They are within the limits. The particle size of DXM microspheres was found to be 42.83µm which is within the limits. The PSA was done by using the optical microscope method. **Conclusion:** The results revealed that with this method we can ensure good establishment of microspheres to allow the drug into the systemic circulation.

KEYWORDS: Dextromethorphan hydrobromide (DXM), Microspheres (MS), Calcium chloride ($Cacl_2$), Particle size analysis (PSA).

INTRODUCTION

A type of innovative drug delivery technology known as the microsphere provides therapeutic options to immediate release in a single dosage form. Microspheres are spherical solid particles with a size range of 1–1000µm.[1] These are spherical, freely flowing particles composed of proteins. In comparison to conventional drug delivery systems, the microspheres created by various processes may differ in terms of drug administration and efficacy. It will result in more consistent drug absorption regardless of formulation. Drug discharge from the stomach is stopped by the microspheres. It has good therapeutic effects but a short half-life. Microspheres will reduce the dose-dumping effect.[2] Microspheres can help incorporate the high amounts. The high medication concentrations can be incorporated into the microsphere. Maintaining the consistency of the medication after synthesis is necessary to ensure a clinically acceptable shelf life. Owing to their regulated particle size and dispersibility, the produced MS are utilized as aqueous injection vehicles.[3]

Dextromethorphan hydrobromide is a popular over-the-counter (OTC) medication used as a cough suppressant. It is commonly found as an active component in cough and cold remedies.[4] The following is a summary of DXM. Treating excessive coughing is done with it since it is an antitussive. Dextromethorphan functions by interfering with the cough reflex in the brain. It temporarily suppresses the cough center in the medulla oblongata, which helps reduce the urge to cough. Dextromethorphan functions by interfering with the cough reflex in the brain. This medicine is primarily intended to treat dry or ineffective coughs.[5] It doesn't treat the underlying cause of the cough, but it can temporarily put an end to the fits of coughing. The mechanism of action of the cough suppressant DXM is NMDA receptor inhibition. Although it is weakly attached and has a low bioavailability (1-2%), it works rapidly. For the development of microspheres to achieve very effective drug absorption, these low bioavailability and brief biological half-life are essential.[6] The microspheres are shown in the Fig.no-1.

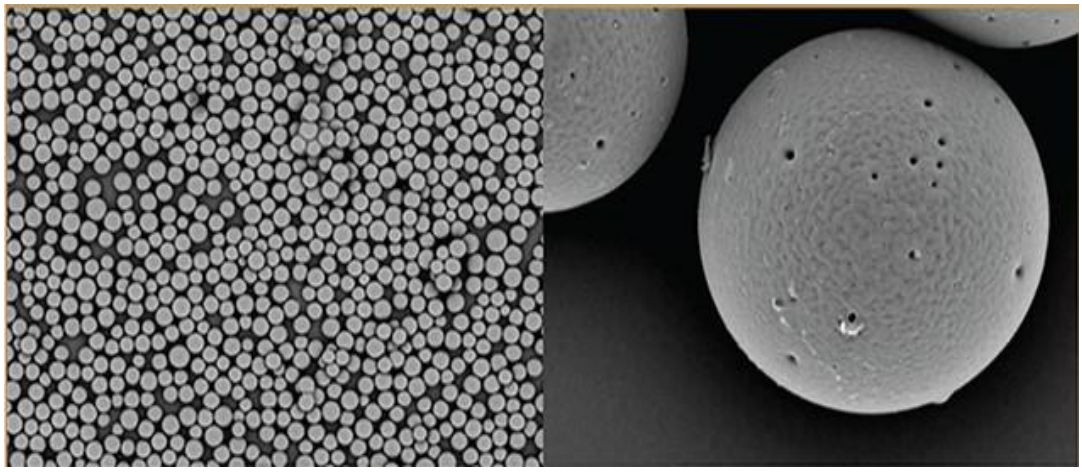

Fig. 1: microsphere image.

Advantages of microspheres

Microspheres

1) Decreasing the size of the particles to improve the drug's low solubility.
2) The medical effect will be long-lasting and steady.
3) By keeping the blood concentration of the medication constant, it promotes patient compliance.
4) Lower the dosage and toxicity.
5) It will reduce the rate of dose, which will improve patient amenability.

Disadvantages of microspheres

1) By lowering the dosage rate, it will make the patient more accommodative.
2) Reproducibility is reduced.
3) The manufacturing and material costs associated with controlled release formulations are higher than those of normal formulations.
4) It might be harmful.

MATERIALS AND METHODS

A complimentary sample of dextromethorphan hydrobromide was provided by Waksman Selman Pharma Pvt.Ltd., located in Anantapur, Andhra Pradesh. Calcium chloride and sodium alginate were provided by Loba Chemicals, Mumbai. Every material that was employed was of an analytical grade.

Solvent Evaporation (SE)

The procedure is emulsifying the solution in an aqueous continuous phase, distributing the medication in the polymer solution, and hardening the polymer in a volatile organic solvent.[7] After that, an organic solvent is removed, leaving behind solid drug-containing microspheres. The therapeutic application is the basis for selecting the medication or active component to be extended. A volatile organic solvent dissolves the chosen polymer.[8] Common solvents are mixtures of solvents, ethyl acetate, and dichloromethane. The solvent of choice is determined by how soluble the polymer is. The polymer solution dissolves the API if it is also soluble in the selected solvent. The medicine may be dispersed as a suspension throughout the polymer solution if it is not soluble. After that, the polymer/drug solution is emulsified. The usual method for doing this is to include the polymer solution into an aqueous phase that contains a surfactant.[9] In the aqueous phase, the polymer/drug solution is formed into tiny drops through the emulsification process. Stirring or agitating the emulsion allows the organic solvent to evaporate precisely. The dispersed droplets become microspheres as the solvent evaporates and the polymer solidifies around them.[10] Upon reaching the required particle size, the microspheres undergo complete solvent evaporation to solidify them. After that, they are usually combined by centrifugation or filtration.[11] To remove any remaining solvent or surfactant, the collected microspheres can be washed. To create the first dry microsphere product, they are dried after washing.[12] The SE method is used to create microspheres that are used in DDS, where it is desirable to have controlled drug release over an extended period of time. Depending on the therapeutic needs, they can be delivered orally, intravenously, or topically.[13]

Spray Drying

This technique entails atomizing the medication and polymer solution into a heated air stream. The solvent quickly evaporates, releasing the microspheres. This technique for making microspheres is quick and effective. This one-step procedure can be used to produce microspheres from a variety of materials.[14] Here, a polymer solution and medication are atomized into a heated air stream to create microspheres. The microspheres are left behind when the solvent quickly evaporates. Both the hot air temperature and the atomizer flow rate can regulate the size of the microspheres. Making microspheres with a broad range of particle sizes, from a few micrometers to several hundred micrometers, is one use for it.[15]

Precipitation

Using this technique, a non-solvent is added to a polymer and drug solution. The microspheres are created when the polymer precipitates out of the solution. Precipitation is a simple and straightforward method of obtaining the

microspheres.[16] A variety of materials can be turned into microspheres using this one-step procedure. A non-solvent is added to the medication and polymer solution in order to precipitate microspheres. The microspheres are formed when the polymer precipitates out of the solution.[17] The kind, concentration, and mixing speed of the non-solvent can all be used to rank the microsphere size. Microspheres with a wide range of particle sizes, from a few micrometers to several hundred micrometers, can be fixed using the precipitation process.[18]

Freeze Drying

This process entails sublimating the solvent away after freezing a polymer solution containing an active pharmaceutical ingredient (API). The microspheres are subsequently created by powdering the leftover solid.[19] A gentle method for creating microspheres is the freeze-drying mode. Making microspheres out of delicate substances like proteins and peptides is a common application for it. The polymer and API solution must first be frozen in order to prepare microspheres via freeze-drying. Following the solvent's sublimation, a solid matrix is left behind.[20] The solid matrix is then ground into a powder to form the microspheres. The microsphere size can be meticulous by the freezing rate and the grinding speed.[21] A flexible method for creating microspheres from a variety of polymers. To create an oil-in-water (O/W) emulsion, a polymer solution is dispersed in an oil phase. Microspheres are created after the polymer is solidified by chemical crosslinking or solvent evaporation.[22] To create microspheres, a biocompatible and biodegradable polymer is usually utilized. Poly (lactic acid) (PLA), Poly (lactic-co-glycolic acid) (PLGA), and Poly (caprolactone) (PCL) are a few examples. A medication or another active ingredient may be the material to be compressed. a solvent that dissolves the medication as well as the polymer. To make a polymer solution, it is cast off.[23] To create a polymer solution, the polymer is dissolved in an appropriate organic solvent. The dispersed phase of the emulsion will be this solution. After that, the polymer solution is separated using techniques like homogenization, ultra sonication, and mechanical stirring in an aqueous phase that contains a surfactant. The polymer solution forms droplets that are dispersed throughout the aqueous phase as a result of this emulsification process.[24] The polymer is then solidified by cooling the emulsion or letting the solvent drain, creating solid microspheres that contain the medication. The final microspheres undergo a typical washing process to remove any remaining surfactant or solvent. Following collection, the microspheres can undergo additional processing to determine their size, drug content, and other characteristics.[25]

Double Emulsion Technique

The polymer's aqueous solution needs to be distributed throughout the oil/organic phase homogenization process. Therefore, the emulsion needs to be introduced to the PVA aqueous solution before creating additional emulsions. Add a substantial aqueous phase to the numerous emulsions, and denaturation or hardening may be carried out. Next, it is necessary to separate, erode, and desiccate the microspheres in the solution. It is necessary to gather the resulting microspheres.[26]

Coacervation

This method is used to create microspheres that are intended to encapsulate medications or other active ingredients. It is especially useful in the pharmaceutical industry. Microspheres are little particles with diameters typically in the micrometer range.[27] Phase separation is used in the coacervation process to split a polymer solution into two liquid phases, one of which forms a coacervate, a dense liquid droplet phaser.[28] The API is encapsulated in this coacervate phase, which solidifies to form microspheres. Choosing a suitable polymer that can undergo coacervation is the first step in the procedure. Sodium alginate, ethyl cellulose, and gelatin are examples of frequently utilized polymers. To make a polymer solution, the chosen polymer is solidified in a solvent.[29] In the following procedures, the solvent should readily evaporate and be compatible with the polymer. To the active ingredient that has to be encapsulated, is put the medication or the polymer solution. Either the drug particles are suspended in the solution or the API is dissolved in the polymer solution. By altering the polymer solution's conditions, aggravation is brought on. This can be achieved by adjusting variables like pH, temperature, or the addition of salts or other coacervating agent.[30] The polymer solution experiences phase separation into two liquid phases as a result of the circumstances changing: the more dilute phase and the higher concentration polymer-containing coacervate phase. Drug-containing droplets are created as a result of the API's partitioning into the coacervate phase. After that, the coacervate droplets solidify to create microspheres.[31] This can be accomplished in several ways such as cooling, solvent evaporation, or chemical cross-linking, depending on the nature of the polymer used. The resulting. The usual method for gathering microspheres is filtration or centrifugation. Further processing steps may be required, for instance, cleaning to eliminate any leftover solvent or unencapsulated drug.[32] The size, drug content, and release characteristics of the prepared microspheres are assessed to make sure they fulfill the required requirements. To give a controlled release or targeted distribution of the encapsulated medicine, the final Microspheres can be incorporated to pharmaceutical dosage forms like tablets or capsules.[33]

Ionic gelation method

Microspheres are tiny, spherical particles that range in size from a few micrometers to several millimeters. The ionic gelation method is frequently used to create these particles. These microspheres are capable of ensnaring medications, proteins, or other bioactive substances meant for regulated release. The following is how the ionic gelation method has been modified to create

microspheres: The polymers that are considered suitable for forming microspheres via ionic gelation often include polyanions, such chitosan or sodium alginate, in addition to polycations, like tripolyphosphate or calcium chloride. To make a polymer solution, the polyanion-sodium alginate, for example is dissolved in an aqueous solution. In accordance with this, the polycation, for example, calcium chloride is dissolved in a different aqueous solution. To produce a homogeneous mixture, the medicine or bioactive ingredient is emulsified or distributed throughout the polymer solution.[34] After the dispersed bioactive material is added to the polymer solution, it is extruded or dispensed into a solution that contains the polycation, which is used as a crosslinking agent. The droplets undergo ionic crosslinking between the polyanion and polycation upon contact with the polycation solution, which promotes the production of microspheres. Firm microspheres are produced as a result of the initiation of polymer gelation upon interaction with the polycation solution. Following solidification, the microspheres are usually collected by filtration or centrifugation after being cleaned with an appropriate solvent to get rid of any unreacted ingredients or contaminants.[35]

Formulation of dextromethorphan hydrobromide microspheres

Sodium alginate in an aqueous solution and calcium chloride were used in the ionic gelation method to create the 200 mg of dextromethorphan hydrobromide microspheres. The key idea was the isotropic relationship between sodium alginate and calcium chloride, which results in the formation of rigid-walled, spherical calcium alginate microspheres. Sodium alginate stabilizes and thickens the properties by creating gels. The creation of controlled-release microspheres requires the use of hydrocolloids such as alginate.

Now, weigh each component used to create the microspheres. Prepare a 2% w/v sodium alginate solution and a 5% w/v Cacl2 solution. The 1000 mg of API must be evenly distributed throughout 100 ml of a 3%w/v sodium alginate aqueous solution. Using a syringe, add the subsequent solution drop-wise into the 5% w/v calcium chloride solution. To allow the produced microspheres to solidify, they are set aside for roughly half an hour. After filtering, the resulting microspheres were collected and completely cleaned with water before being dried.[36]

Table 1: Composition of Dextromethorphan hydrobromide microspheres.

Ingredients	Quantity
Dextromethorphan hydrobromide	200 mg
Sodium alginate 3%	20 ml
Calcium chloride	100 ml

Evaluation of dextromethorphan hydrobromide microspheres

Particle Size analysis (PSA)

By utilizing optical microscopy, the size distribution and average PS of microspheres were investigated. The size of around 100 microspheres was determined in order to compute the average PS. A fixed line designed to pass through the center of each particle is used to measure the component portions. One millimeter is divided into 100 equal divisions in the stage micrometer, therefore each division is equal to 10 mm. This formula was used to get the average diameter.[37]

Average diameter= End / En × C.F.

Where, n = no. of microspheres

D = diameter of microspheres

F. = calibration factor

Drug loading and Entrapment efficiency

Drug loading is the amount of medication per weight unit of the nanoparticle. Entrapment efficiency is the overall amount of drug trapped. This was accomplished by carefully weighing, adding, and shaking 100 mg of microspheres in 100 ml of 7.4 pH phosphate buffer until every microsphere was dissolved. Using a UV-visible spectrophotometer set to detect absorbance at 272 nm, the solution was filtered and appropriately diluted.[38]

%drug loading= Actual drug content in microspheres/weight of microspheres ×100

%entrapment efficiency=Particle drug loading/theoretical drug loading × 100

Flow properties

Bulk density (BD)

It was determined by adding a properly weighed sample to a 100 ml graduation cylinder. The initial weight and volume were noted. For the microspheres, the following formula is used to compute this.[39]

BD = Weight of the microspheres/bulk volume

Tapped density (TD)

A graduating cylinder with the known mass of the microspheres is inserted to compute it. The ratio of the microspheres' total mass to their tapped volume determines it. It is determined by using the following formula represented in gm/cm^3.[40]

TD = Mass of the powder/ Tapped volume

Hausner's ratio (HR)

It is defined as the tapped density divided by the bulk density.[41]

Hausner's ratio= Tapped density/ Bulk density

Carr's index(CI)

This property is also known as the compressibility index which is indirectly related to flow rate and particle size.[41]

It is a potential strength metric that is computed using the following formula.

Carr's index= tapped density-bulk density/tapped density × 100

Angle of Repose

It is described as the greatest angle that can exist between the powder pile's surface and a horizontal plane. You can calculate it by using the formula.[42]

The angle of repose ($\tan\theta$) = h/r

h = height of pile

r= radius of the base of the pile

Invitro drug release studies

The drug release studies were carried out via a USP-type 1 (Basket) dissolution apparatus. The dissolution medium used was 900ml of phosphate buffer pH 6.8, which was kept at 37 ± 0.5 at 50 rpm. They have used microspheres in an amount equal to 100 mg of DXM. 5mg of samples were taken out at intervals of 1, 2, 3, 4, 5, and 6 hours. To ensure sink withdrawal, equal volumes of new dissolution medium were added right away. The samples were then spectroscopically examined at 272 nm.[43]

RESULTS

Particle Size analysis

Optical microscopy was used to define the size of the particles. It is crucial to the medication release from microspheres. The batch-produced microspheres had a consistent avg. particle size of 42.83µm. The particle size of microspheres is shown in the table.no-2.

Table 2: Particle size of the microspheres.

No.of microspheres	Particle size of microspheres (µm)	No.of microspheres	Particle size of microspheres (µm)	No.of microspheres	Particle size of microspheres (µm)
1	39.74	36	40.56	71	40.76
2	41.84	37	41.84	72	41.84
3	41.45	38	39.84	73	42.83
4	42.83	39	42.83	74	40.87
5	40.39	40	39.76	75	41.84
6	39.84	41	39.98	76	40.00
7	39.73	42	42.83	77	41.30
8	41.84	43	39.85	78	41.18
9	42.83	44	40.56	79	41.18
10	41.84	45	40.56	80	42.83
11	40.50	46	41.84	81	42.83
12	42.83	47	39.99	82	41.84
13	39.84	48	39.98	83	42.83
14	41.66	49	40.56	84	40.00
15	41.84	50	42.83	85	39.98
16	41.84	51	39.99	86	40.25
17	40.77	52	41.84	87	41.76
18	42.83	53	39.76	88	41.84
19	41.84	54	38.80	89	42.83
20	42.83	55	39.99	90	42.83
21	39.78	56	40.56	91	41.82
22	42.83	57	41.84	92	40.00
23	41.84	58	42.83	93	41.84
24	41.12	59	41.83	94	42.83
25	42.83	60	41.84	95	40.00
26	41.84	61	40.00	96	42.83
27	39.85	62	41.84	97	41.84
28	39.76	63	40.30	98	42.83
29	42.83	64	40.76	99	39.99
30	41.84	65	41.84	100	42.83
31	40.90	66	42.83		
32	39.99	67	42.83		
33	40.26	68	39.99		
34	41.84	69	39.99		
35	42.83	70	40.73		

Drug loading & Entrapment efficiency

The percentage drug loading was found that 168.7% and the percentage entrapment efficiency was found to be 18.1%.

Bulk density

The BD of each formulation was determined by dividing the sample weight in grams by the sample's ultimate volume in cm3 inside the 10 ml graduated cylinder. The

bulk density (BD) of the dextromethorphan hydrobromide microsphere range is 1.017 gm/cm^3. Bulk density is usually crucial when considering the size of a product's high-dose capsules or the homogeneity of a low-low-dose formulation where the densities of the API and excipient vary significantly. The anticipated dosage and the measured formulation density can be used to determine the ideal size for a capsule formulation. In microspheres that flow freely, these interfaces are typically less significant since the BD and TD values are closer together.

Tapped density

It was determined by the tapping method. The value of dextromethorphan hydrobromide microspheres was found to be 1.022 gm/cm^3.

Carr's Index and Hausner's ratio

The relative inter-particulate interaction is represented by the hausner ratio and compressibility index, which serve as indicators of the porosity of a microsphere that is to be compressed. Since the values of the BD and TD are closer in free-flowing microspheres, these interactions often have less of an effect there. Because of the enhanced interparticle interactions, materials with poor flow will exhibit greater bulk and tapped densities. These changes are displayed by the hausner ratio and the incompressibility index. Now, powder flow properties can be extensively, quickly, and simply anticipated by utilizing the closely linked HR and the compressibility index. The CI is one method for inferring bulk density indirectly. Size, shape, moisture content, surface area, and cohesiveness of the materials are all relevant since they can all have an impact on the observed compressibility index. It is calculated using the values of BD and TD. The percentage compressibility index was found to be 0.476%. The hausner's ratio, we found, was 100.49.

Angle of Repose

The angle of repose of DXM microspheres was found to be 27.92.

Invitro drug release studies

The drug release is shown in Table.no-3 and the dissolution graph is shown in Fig.no-2.

Table 3: Invitro drug release studies.

Time in (hours)	% Drug Release
0	0
1	75.45%
2	87.2%
3	91.0%
4	91.5%
5	92.3%
6	97.8%

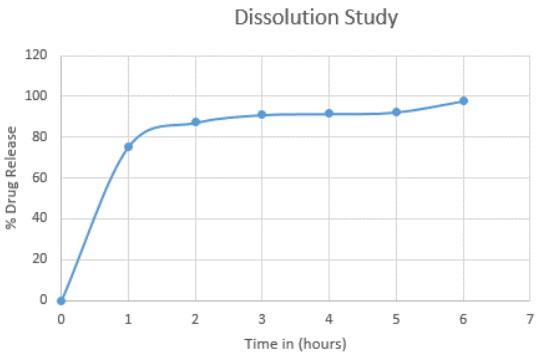

Fig. 2: Dissolution study of microspheres.

DISCUSSIONS

Within the acceptable bounds, the microspheres' particle size is 42.83µm. The results of the tapped density (1.022 gm/cm^3) and bulk density (1.017 gm/cm^3) may have shown that the microspheres are flowing properly and well. The relative inter-particulate interaction is represented by the compressibility index and Hausner's ratio, which are based on the porosity of the microspheres. Thus, these interactions demonstrate the microspheres' good flow characteristics. Based on the above given parameters, 95.5% of the in vitro drug release experiments demonstrated improved drug release. The primary factors influencing the systemic circulation are the medication contained in the microsphere and the size of the particles. Ionic gelation is the method used to do this. Ionic gelation's fundamental significance stems from its ease of use and versatility. A multitude of materials, including synthetic and natural polymers, can be used to make these. Therefore, dextromethorphan hydrobromide has a short biological half-life and a low bioavailability when prepared in microspheres.

CONCLUSION

Calcium chloride works well for microsphere synthesis, while sodium alginate was used to create DXMH microspheres with success using the ionic gelation procedure. Depending on how these excipients are manufactured, their concentration has a significant and interactive impact on microspheres and drug release. Ultimately, it was shown that because the drug has a short biological half-life and low bioavailability, the formulation of these microspheres can provide good drug release.

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