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Original Article

Lactose coated ceramic nanoparticles for oral drug delivery

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ARTICLE INFO

Article history:
Received 24 November 2012
Accepted 27 December 2012
Available online 11 July 2013

Keywords:
Anthrone
Aquasomes
Co-precipitation
Pimozide
Scanning electron microscopy

ABSTRACT

Background: Drug nanoparticles offer promising applications in drug delivery because of their potential to improve the dissolution rate and oral availability of poorly water-soluble drugs. The present research was aimed at developing three layered ceramic nanoparticles (aquasomes) for the delivery of the hydrophobic drug, pimozide to enhance its dissolution.
Methods: Calcium phosphate ceramic core was prepared by using three different techniques, namely, co-precipitation by reflux, self-precipitation and co-precipitation by sonication. Co-precipitation by sonication was selected based on parameters such as percentage yield and duration of preparation, and further optimization of core synthesis was carried out based on process variables such as reaction volume and sonication time. The core was then coated with the sugar, lactose. Quantification of lactose coating was done by a colorimetric reaction between lactose and anthrone reagent. Pimozide was adsorbed on lactose coated core to obtain the three-layered aquasomal formulation.
Results: SEM morphological studies indicated spherical shaped nanoparticles with a median of 92 nm. *In vitro* dissolution was performed in 0.1 N hydrochloric acid solution and compared with that of pure drug. Enhanced dissolution was observed and the release kinetics of pimozide loaded aquasomes exhibited first order kinetics which is concentration dependent dissolution.
Conclusion: Improved dissolution of the drug was observed when formulated in the form of ceramic nanoparticles.

1. Introduction

Oral drug delivery is the most preferred route for drug administration as it is non-invasive in nature. However, poor solubility, stability, and bioavailability of many drugs make it difficult to achieve therapeutic levels. In oral route, the efficiency of drug delivery is directly related to particle size because particle size can improve the dissolution and thus can enhance bioavailability of the drug. Several strategies and formulations have been employed to overcome these limitations like use of salts of ionic drugs,[1] complexing with cyclodextrins,[2] conjugation to dendrimers,[3] use of co-solvents etc.[4] Though these strategies have been shown to improve drug solubility, universal solubilization methods that can improve the drugs bioavailability significantly are still highly desirable.[5]

Nanotechnology as a delivery platform offers very promising applications in drug delivery, especially through and for

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0974-6943/$ – see front matter
http://dx.doi.org/10.1016/j.jopr.2013.06.015

the oral route. Either direct nanosizing or incorporation into polymeric and lipidic nanoparticles can help deliver drugs with poor aqueous solubility, low permeability, and extensive first pass metabolism.[6] Using nanoparticles, it may be possible to achieve improved delivery of poorly water-soluble drugs by delivering drug in small particle size which increases the total surface area of the drugs thus allowing faster dissolution and absorption in to the blood stream.[7]

Ceramic nanoparticles also called aquasomes, contribute to a new drug delivery systems comprised of surface modified nanocrystalline ceramic carbohydrate composites. These are nanoparticulate carrier systems with three layered self assembled structures. These consist of central solid nanocrystalline core coated with polyhydroxy oligomers onto which biochemically active molecules are adsorbed.[8] For the preparation of nanoparticles core, both polymers (albumin, gelatin or acrylates) and ceramics (diamond particles, brushite, and tin oxide) can be used. Ceramic materials are widely used as they are structurally the most regular materials known, being crystalline high degree of order ensures.[8]

The aim of present investigation is to prepare aquasomes for a poorly soluble drug, pimozide (antipsychotic drug)[9–11] to improve the aqueous solubility on oral administration. Aquasomes can be prepared in three stages, i.e., preparation of ceramic core, carbohydrate coating and drug adsorption. Three different techniques were employed for preparation of ceramic core, i.e., co-precipitation by reflux, self precipitation technique and co-precipitation by sonication. Lactose sugar was adsorbed over prepared ceramic core followed by adsorption of pimozide drug to get the three layered aquasomes.

2. Materials and methods

2.1. Materials

Pimozide was a gift sample from Vasudha Pharma Chem Ltd, Hyderabad. Calcium chloride dihydrate, disodium hydrogen orthophosphate and lactose monohydrate were from S.D. Fine Chemicals Ltd., Mumbai, India. Anthrone reagent was from Loba chemicals, Mumbai, India. Other chemicals and reagents were of analytical grade.

2.2. Methods

2.2.1. Preparation of the core

2.2.1.1. Co-precipitation technique by reflux. 0.19 N diammonium hydrogen phosphate solutions was added drop wise with continuous stirring to 0.32 M calcium nitrate solution maintained at 75 °C in a three-necked flask bearing one charge funnel, a thermometer, and a reflux condenser fitted with a CO_2 trap.[12]

The reaction involved is:

$$3(NH_4)_2HPO_4 + 3Ca(NO_3)_2 \rightarrow Ca_3(PO_4)_2 + 6NH_4NO_3 + H_3PO_4$$

During the addition, the pH of calcium nitrate was maintained in the range 8–10 using concentrated aqueous ammonia solution. The mixture was then stirred for 4–6 days at the same temperature and pH. The precipitate was filtered, washed thoroughly with double distilled water, and finally dried at 100 °C overnight.

2.2.1.2. Self-precipitation technique. In this method, the simulated body fluid of pH 7.2 containing sodium chloride (134.8 mM), potassium chloride (5.0 mM), magnesium chloride (1.5 mM), calcium chloride (2.5 mM), sodium hydrogen carbonate (4.2 mM), disodium hydrogen phosphate (1.0 mM), and disodium sulfate (0.5 mM) was used. The pH of the solution was adjusted to 7.26 every day with hydrochloric acid. This solution was transferred to a series of polystyrene bottles of 100 ml capacity. The bottles were tightly sealed and kept at 37 ± 1 °C for one week. The formation of precipitate was then observed on the inner surface of the bottles. The precipitate was filtered, washed thoroughly with double distilled water, and finally dried at 100 °C.[12]

2.2.1.3. Co-precipitation technique by sonication. 0.75 M solution of disodium hydrogen phosphate was slowly added to 0.25 M solution of calcium chloride under sonication at 4 °C.[13] The reaction involved is:

$$3Na_2HPO_4 + 3CaCl_2 \rightarrow Ca_3(PO_4)_2 + 6NaCl + H_3PO_4$$

The precipitate (calcium phosphate) was separated by centrifugation at 15,000 rpm for 1 h and then washed five times with double distilled water to remove sodium chloride formed during the reaction. The precipitate was resuspended in the double distilled water and passed through a 0.2 μm millipore filter to collect particles less than 0.2 μm. This filtrate containing the calcium phosphate nanocore was used for further processing.

In this method, the effect of process variables like reaction volumes of reactants (20 ml, 40 ml and 60 ml) and sonication period (1 h, 2 h and 3 h) on the percentage yield of the core formation was evaluated and optimized to achieve highest core yielding.

2.2.2. Carbohydrate coating onto the ceramic core particles

Carbohydrate was coated on the ceramic core using incubation method.[12] Specified quantity of sugar (200 mg) was weighed and dissolved in double distilled water. Ceramic core was added to sugar solution. The solution was sonicated using probe sonicator (at 30% pulse and 18 W, Bandelein, Germany) and was shaken for 3 h, 100 rpm, 25 °C. Then non-solvent (acetone, 1 ml) was added and allowed the sugar to get adsorbed onto the core by keeping the solution aside for approximately 20 min. The dispersion was then centrifuged at 2000 rpm, 25 °C and 15 min. The supernatant was decanted off and the sugar coated core was washed twice with double distilled water and dried at 70 °C in a hot air oven (Biotechnics, Mumbai).

2.2.3. Quantification of sugar coating – anthrone reagent

50 mg of sugar coated core was accurately weighed and dissolved in 5 ml of distilled water. 2 ml of the above solution was added to 5.5 ml anthrone reagent and boiled (10 min, 100 °C). The solution was cooled rapidly and the absorbance was estimated at λ_{max} of 625 nm.[14,15]

2.2.4. Adsorption of pimozide on the sugar coated ceramic core

Pimozide solution of 1.5% w/v in ethanol was added to volumetric flask containing an accurately weighed amount of