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Research paper

Formulation of multiparticulate systems as lyophilised orally disintegrating tablets

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ABSTRACT

The current study aimed to exploit the electrostatic associative interaction between carrageenan and gelatin to optimise a formulation of lyophilised orally disintegrating tablets (ODTs) suitable for multiparticulate delivery. A central composite face centred (CCF) design was applied to study the influence of formulation variables (gelatin, carrageenan and alanine concentrations) on the crucial responses of the formulation (disintegration time, hardness, viscosity and pH). The disintegration time and viscosity were controlled by the associative interaction between gelatin and carrageenan upon hydration which forms a strong complex that increases the viscosity of the stock solution and forms tablet with higher resistant to disintegration in aqueous medium. Therefore, the levels of carrageenan, gelatin and their interaction in the formulation were the significant factors. In terms of hardness, increasing gelatin and alanine concentration was the most effective way to improve tablet hardness. Accordingly, optimum concentrations of these excipients were needed to find the best balance that fulfilled all formulation requirements. The revised model showed high degree of predictability and optimisation reliability and therefore was successful in developing an ODT formulation with optimised properties that were able deliver enteric coated multiparticulates of omeprazole without compromising their functionality.

1. Introduction

Orally disintegrating (dissolving) tablets (ODTs) are solid dosage forms that are placed in the mouth, rapidly disintegrate/dissolve when in contact with the saliva and then easily swallowed without the need for water [1]. The fast disintegrating behaviour of the ODT in the mouth limits the active ingredients that can be incorporated to drugs that exhibit good taste, stability in gastric conditions and have long half-life. Bitter tasting drugs can cause discomfort to patients and consequently reduce their compliance, whereas incorporating drugs that suffer from instability in gastric fluids reduces the efficacy of the dosage form (bioavailability). On the other hand, delivering active drugs that have short half-life in ODTs compromise the practicality of the dosage form as more frequent administration is required. To address these issues, a great deal of interest has been directed towards incorporating multiparticulate drug delivery system in ODT formulations [2].

The multiparticulate drug delivery system comprises of drug particles encapsulated or coated by one or more layers of polymers that control the release of the drug. The polymer can be selected to provide extended, delayed or pulsed drug delivery, allowing the rate of release of the drug to be tailored as required. Therefore, multiparticulate drug delivery systems can mask the unpleasant taste of active drugs, protect acid-labile drugs from possible degradation in the stomach and extend the drug release over several hours. Moreover, they provide many advantages over single-unit dosage forms because of their multiplicity and small sizes including reduced risk of systemic toxicity, enhanced bioavailability, reduced risk of local irritation and reduced patient to patient variability as a result of their more predictable gastric emptying [3]. Accordingly, the formulation of multiparticulate into ODTs can extend their application to more challenging drugs (e.g. acid sensitive) by overcoming restrictions imposed by the nature of these drugs and combine the benefits of ODTs and multiparticulate drug delivery system [2].

The compression of multiparticulate into ODT formulations has attracted substantial attention in both academia and industry and resulted in many scientific publications and patent applications [4]. However, to produce a tablet with good structural integrity, relatively high compression pressures are required. These high pressures can cause damage to the polymer layers of the multiparticulate system, and, as a result, compromise their release controlling properties [5].

Freeze drying is an alternative technique to produce ODTs without application of any compaction force, which could be useful in the formulation of multiparticulate into ODTs. However, three major requirements need to be addressed in order to ensure development of a successful formulation. Firstly, the need for high viscous liquid formulation that is able to suspend the multiparticulate long enough to complete formulation and freezing without

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compromising the disintegration performance. Secondly, minimum interaction between the liquid formulation and the multiparticulate that may lead to unwanted changes in the original properties of the multiparticulate such as early drug leakage. For example, for multiparticulate coated with hydrophobic polymers, the use of thick hydrophilic environment in the formulation reduces premature drug release, whereas for enteric coated multiparticulate, the use of acidic formulation ensures multiparticulate integrity. Thirdly, physical protection against possible damage during freezing and annealing step as a result of ice crystal growth.

The current study aimed to optimise ODT formulations suitable for multiparticulate delivery based on gelatin, carrageenan and alanine. The selection of these excipients can potentially benefit the formulation in many ways. Firstly, the choice of these excipients is based on exploiting the electrostatic associative interaction between the anionic sulphate groups of carrageenan polymer and the positive net charge of gelatin (below its isoelectric point) to produce highly viscous solution at relatively low concentration of both polymer [6], which ensures fast disintegration property and shorter freeze drying cycle [7]. Also, carrageenan has cryoprotectant activity which might be useful to protect the multiparticulate integrity during freezing and annealing steps [8]. Additionally, previous research from our laboratory has shown that gelatin and alanine have superior properties as matrix supporting agents in ODT formulations [9].

Successful development of new pharmaceutical formulations requires extensive and comprehensive research to determine the significant factors that influence formulation, understand their effects (individually and collectively) and optimise them to obtain high quality products. For lyophilised ODTs, traditional experimentation approach can be time and material consuming and consequently is associated with high cost, due to the existence of multiple factors that influence the formulation performance and manufacturing process. Recently, design of experiment (DoE) supported by statistical software has been reported as an efficient and powerful tool in the development and optimisation of pharmaceutical dosage forms [10]. The design evaluates the influence of various formulation parameters and their interaction with the lowest number of experiments, hence reducing the cost and time of the work [11]. Moreover, design of experiment is considered an essential part of quality by design paradigm (QbD), which is recommended by the FDA as a new regulatory requirement for approval of generic drugs [12].

Response surface modelling (RSM) was applied in this study to evaluate the influence of varying the concentration of the selected excipients (independent variables) on four crucial responses: disintegration time, hardness, viscosity and pH. Quantitative estimation of the significant model terms (linear, polynomial and interactive) was used to build statistical model for each response that can describe the relationship between the dependant and the independent variables. These models were used to optimise the concentration of the excipients that maximise the quality of the formulation. Furthermore, ODTs containing therapeutic dose of enteric coated pellets of omeprazole were prepared based on the optimised formulations and fully characterised to evaluate their feasibility as drug delivery system. Omeprazole was chosen as a model drug that is challenging to formulate as ODTs due to its acid labile nature and, therefore, needs to be incorporated in enteric coated pellets in order to tolerate the formulation of ODTs.

2. Materials

Gelatin from bovine skin, type B (Bloom strength ~ 75), lambda carrageenan and L-alanine (C3H7NO2, Reagent plus™ ⩾99%) were all purchased from Sigma–Aldrich Chemicals (Pool, UK). Enteric coated pellets of omeprazole (8.5% omeprazole, batch number: OME-020907) were supplied by MKPPL (Pune, India). Concentrated hydrochloric acid (specific gravity of 1.80), acetonitrile, phosphate buffered saline tablets (PBS) and standard solutions at pH 4.0 and 7.0 were all purchased from Fisher Scientific (Loughborough, UK). All the materials were used as received.

3. Methods

3.1. Design of experiment

The statistical experimental design in this study was performed using MODDE software version 8 (Umetrics Inc., NJ, USA). The top RSM (response surface modelling) design choice suggested by the software was a central composite face centred (CCF) that composed of 34 experiments in total, 15 fractional factorial runs in duplicate (15×2) and four replicated centre points. The concentration of gelatin (X_1), carrageenan (X_2) and alanine (X_3) was selected as independent variables at three levels. The three factorial levels for each independent factors, low, medium and high, were coded as -1, 0 and 1, respectively. The disintegration time (Y_1), hardness (Y_2), viscosity (Y_3) and pH (Y_4) were investigated as dependant variables (responses).

3.2. Preparation of ODTs for RSM experiments

A required amount of gelatin was solubilised in 100 ml double distilled water at about 40 °C to obtain a concentration of 3%, 4% and 5% (w/v). Carrageenan was added slowly in small portions under continuous stirring to the solution at concentration of 0.2%, 0.5% and 0.8% (w/v). After obtaining clear solution, alanine was added at concentration of 2%, 3.5% and 5% (w/v) and the formulations were kept under stirring until alanine dissolved completely. A constant mass of 1.50 g of the formulation was poured in a tablet mould with internal diameter of 13.50 mm, frozen at −80 °C for about 60 min, annealed in −20 °C a pre-cooled freezer for 12 h and then transferred back to the −80 °C freezer. The frozen formulation was freeze-dried (ADVANTAGE Freeze-dryer, VirTis Inc., USA) according to an optimised regime (primary drying for 48 h at a shelf temperature of −40 °C and secondary drying for 10 h at a shelf temperature of 20 °C and under constant vacuum of 50 mTorr throughout primary and secondary drying). The optimised formulation was prepared by the same method and the observed (experimental) and the predicted (from the model) values for the responses were compared with evaluate the validity of the model.

3.3. Viscosity and pH measurements

The viscosity of the formulation was measured using a Brookfield viscometer (LVT, Stoughton, MA, USA) with its spindle number 3 rotating at speed of 20 rpm at room temperature in a 100-mL beaker with the spindle guard.

The pH was measured using pH meter (MP230, Mettler Toledo, Ohio, USA). The pH meter was calibrated using standard solutions at pH 4.0 and 7.0.

3.4. Disintegration time

Disintegration time is the time required for ODTs to disintegrate completely without leaving any solid residue. In vitro disintegration time for lyophilised ODTs was evaluated using US pharmacopoeia monograph (USP General Chapter 2008, ⟨7 0 1⟩ disintegration). A disintegration tester (Erweka ZT3, Heusenstamm, Germany) was used in this study as a disintegration appa-