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Ondansetron loaded pectin based microspheres for nasal administration: In vitro and in vivo studies

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ABSTRACT

The aim of this study was the production of ondansetron hydrochloride loaded polymeric microspheres for delivery via the nasal route with aim to avoid hepatic first-pass metabolism, and enhance residence time. The microspheres were prepared by the spray–drying technique using pectin as the polymer. The objective of this study was to examine extensively the influence of formulation and process variables on the characteristics of the microspheres prepared. The effects of various experimental parameters such as drug to polymer concentration and liquid feed flow rate on particle size and entrapment efficiency were evaluated by means of experimental factorial designs. A 3^2 full factorial design was employed in formulating the microspheres with polymer concentration (X_1) and liquid feed flow rate (X_2) as independent variables and particle size and entrapment efficiency were dependent variables. The results showed that the X_1X_2 interaction had effect on particle size where as X_2 alone effect on entrapment efficiency. The optimal microspheres were evaluated with respect to zeta potential study, drug release kinetic study, ex vivo permeation study, histological examination, stability study and in vivo study. Microspheres were characterized by differential scanning calorimetry, scanning electron microscopy and X-ray diffraction study. Scanning electron microscopy confirmed the smooth spherical surface of microspheres where as kinetic model revealed that drug release followed case II transport. The nasal delivery showed increased bioavailability as compared to oral delivery. In conclusion, the pectin containing microspheres of ondansetron hydrochloride with mucoadhesive property are suitable for nasal delivery.

1. Introduction

Nasal drug delivery has generated interest as an alternative route for administration of drugs and biomolecules that are susceptible to enzymatic or acidic degradation and first pass metabolism. Possible pathways for a drug to permeate across the nasal mucosa are passive transportation carriers mediated, transcytosis and transport through tight junctions. Nasal application of drugs is suggested to be the most viable alternative to the parenteral administration. As a site for drug delivery, nasal cavity has many advantages such as highly vascularized epithelial layer and wide absorption area. In addition, blood is drained directly from the nose into the systemic circulation, thereby avoiding first-pass metabolism in the liver and the intestine by enzymes and secretion by efflux transporters [1]. However nasal delivery has limitation which has restricted its use to the delivery of drug molecules is, the general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism. It has been shown that for both liquid and powder formulations that are not mucoadhesive, the half life of clearance is in the order of 15–20 min. Numerous delivery systems based on mucoadhesive polymers have been developed which are able to increase the residence time of the formulation at the absorption site of the drugs. The use of mucoadhesive system as microspheres is to provide a drug protection from enzymatic degradation and thus increase the contact time with the nasal mucosa [2]. The aim of this work was to study the possible application of pectin for the preparation of mucoadhesive microparticles for the nasal administration of ondansetron hydrochloride. Spray drying is a well established drying process traditionally used for thermolabile materials. It has been used successfully in the pharmaceutical industry to produce products of defined physical and chemical properties. In this study we investigated spray drying as a potential method for the production of micron sized particles. Spray drying is widely used for the microencapsulation of drugs due to reliability, reproducibility and possible control of particle size and drug release. In addition, it has the advantage of being a continuous process which is easy to scale-up. Another important advantage is the fact that microparticles obtained by spray drying are usually free of organic solvents, whereas other methods often result in particles contaminated with organic solvents which may be toxic. The spray drying technique consists of spraying a solution or suspension of polymer and drug through the nozzle of a spray

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dryer apparatus. The solvent evaporates very quickly, leaving behind solid microparticles [3].

Ondansetron hydrochloride (OND) is a selective 5-HT3 receptor antagonist that is used for preventing nausea and vomiting caused by chemotherapy, radiotherapy and postoperative vomiting. Following oral administration, OND is rapidly absorbed and its bioavailability is approximately 60%, mainly due to hepatic first pass and intestinal metabolism. Intravenous and oral dosage forms of OND (film-coated tablets, orally disintegrating tablets, and oral solutions) are commercially available. Considering the limitations of delivering OND orally or intravenously to patients undergoing emetogenic chemotherapy, the nasal route could be a potential alternative to prevent nausea and vomiting associated with such therapy. OND has also relatively short elimination half-life (about 3 h) hence the prolonged drug release is needed [1].

Pectin is a predominately linear polymer of mainly α-(1–4)-linked D-galacturonic acid residues interrupted by 1, 2-linked L-rhamnose residues. Pectin has a few hundred to about 1000 building blocks per molecule; this corresponds to average molecular weight from about 50,000 to 150,000 Da. The pectin classes based on the degree of esterification are high methoxyl (HM) pectin and low methoxyl (LM) pectin. Degree of esterification values for commercial HM pectin is typically range from 60 to 75% and those for LM pectin is range from 20 to 40%. HM-pectin requires a minimum amount of soluble solids and a pH within a narrow range, around 3.0, in order to form gels. In general, HM-pectin is hot water soluble and often contains a dispersion agent such as dextrose to prevent lumping. HM-pectin, unlike LM-pectin, does not contain sufficient acid groups to gel or precipitate with calcium ions, although other ions such as aluminum or copper cause precipitation under certain conditions. LM-pectin produce gels independent of sugar content. They are not as sensitive to pH as the HM-pectin. LM-pectin requires the presence of a controlled amount of calcium or divalent cations for gelation. Pectin is an interesting candidate for pharmaceutical use as a carrier of a variety of drugs for controlled release applications. Many techniques have been used to manufacture the pectin based delivery systems, especially ionotropic gelation and gel coating. These simple techniques, together with the very safe toxicity profile, make pectin an exciting and promising excipient for the pharmaceutical industry for present and future applications [4].

2. Materials and method

2.1. Materials

Ondansetron hydrochloride was gift sample from Alkem Laboratories (Mumbai, India). Pectin LM (Low Molecular Weight) was kindly provided by Colorcon Limited, Goa, India. All other reagents used were of analytical grade.

2.2. Preparation of microspheres by spray drying

Ondansetron loaded microspheres were prepared using pectin in three different drug to polymer ratios. Pectin was added in distilled water and dissolved by gentle heating with moderate stirring. Drug was added to above polymer solution. Microspheres were obtained by spraying the feed with spray drier (LU222, Labultima, India) using a standard 0.7 mm nozzle. The dispersion was fed to nozzle with a peristaltic pump, atomized by the force of compressed air and blown together with heated air to the drying chamber where the solvent in the droplets was evaporated. The dried microspheres were harvested from the apparatus collector. The process conditions of the spray drying were inlet temperature 105–110 °C; outlet temp 80–90 °C; pump setting of 1 to 3 ml/min; spray pressure 2 kg/cm^2.

2.3. Experimental design

The design of experiments (DOE) technique was used to provide an efficient means to optimize the spray drying process. DOE is an approach for effectively and efficiently exploring the cause and effect relationship between process variables and the output. A 2-factor 3-level factorial central composite experimental design technique was employed to investigate the variables. This technique was applied to quantify the influence of operating parameters on the particle size and entrapment efficiency of microspheres. The dependant variables were polymer concentration and feed flow rate. The factorial design parameters and experimental condition are shown in Table 1. The goal of the experimental design was to find out, with the minimum number of experimental runs, which process variables have the biggest impact on the final product. Various batches of ondansetron hydrochloride loaded microspheres were prepared based on the 3^2 factorial designs. The independent variables were polymer concentration 1 to 3% (X_1) and liquid feed flow rate 1 to 3 ml/min (X_2) and their levels are shown in Table 1.

2.4. Optimization data analysis and model-validation

ANOVA was used to establish the statistical validation of the polynomial equations generated by Design Expert® software (version 8.0.1, Stat-Ease Inc, Minneapolis, MN). Fitting a multiple linear regression model to 3^2 factorial design gives a predictor equation incorporating interactive and polynomial term to evaluate the responses:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}{X_1}^2 + b_{22}{X_2}^2 \quad (3)$$

where Y is the measured response associated with each factor level combination; b_0 is an intercept representing the arithmetic average of all quantitative outcomes of nine runs; bi (b_1, b_2, b_{11}, $b_{12}$and b_{22}) are regression coefficients computed from the observed experimental values of Y and X_1 and X_2 are the coded levels of independent variables. The terms X_1X_2 represent the interaction terms. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms show how the response changes when two factors are changed simultaneously. The polynomial equation was used to draw conclusions after considering the magnitude of coefficients and the mathematical sign it carries, i.e. positive or negative. A positive sign signifies a synergistic effect, whereas a negative sign stands for an antagonistic effect.

In the model analysis, the responses: the particle size of the microsphere and entrapment efficiency of all model formulations were treated by Design Expert® software. The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the coefficient of variation (CV), the multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS), provided by Design Expert® software. Level of significance was considered at $p<0.05$. Three dimensional response surface plots resulting from equations were obtained by the Design Expert® software. Subsequently, the desirability approach was used to generate the optimum settings for the formulations.

Table 1
Factorial design parameters and experimental condition.

Factors	Levels		
	Low(−1)	Medium(0)	High(+1)
X_1 = polymer concentration (%)	1	2	3
X_2 = feed flow rate (ml/min)	1	2	3