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Nasal inserts containing ondansetron hydrochloride based on Chitosan–gellan gum polyelectrolyte complex: *In vitro–in vivo* studies

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ABSTRACT

The aim of this study was the production of ondansetron hydrochloride loaded lyophilized insert for nasal delivery. The nasal insert was prepared by the lyophilisation technique using Chitosan–gellan gum polyelectrolyte complex as the polymer matrix. The ondansetron loaded inserts were evaluated with respect to water uptake, bioadhesion, drug release kinetic study, *ex vivo* permeation study, and *in vivo* study. Lyophilised nasal inserts were characterized by differential scanning calorimetry, scanning electron microscopy and X-ray diffraction study. Scanning electron microscopy confirmed the porous sponge like structure of inserts whereas release kinetic model revealed that drug release followed non-fickian case II diffusion. The nasal delivery showed improved bioavailability as compared to oral delivery. In conclusion, the ondansetron containing nasal inserts based on Chitosan–gellan gum complex with potential muco-adhesive potential is suitable for nasal delivery.

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1. Introduction

Nasal mucosa has been considered as a potential site of administration to achieve rapid and improved drug absorption due to 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. Hence nasal delivery gained interest among mucosal sites as a non-invasive alternative for systemic delivery of drugs with poor bioavailability [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 macho ciliary 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 [2].

Nasal insert is the novel solid dosage form, which is prepared by lyophilisation, consists of a sponge like hydrophilic polymer matrix and combines the advantages of a solid, single unit dosage for nasal drug delivery by using carrier systems that hydrate quickly after contact with mucosa [3].

The proper choice of polymers can allow mucoadhesion and controlled drug release and due to the dissolution of the gel and/or mucociliary removal toward the nasopharynx, there would be no need to remove the insert mechanically after it is depleted of the drug. Chitosan [4], chitosan/pectin [5], chitosan/hyaluronate [6], hydroxypropyl methylcellulose [7], Xanthan/guar gum [8], Polyvinylpyrrolidone, sodium alginate, carrageenan, Carbomer, sodium carboxymethyl cellulose and xanthan gum [9], were reported as mucoadhesive polymers in preparation of nasal inserts.

Chitosan, a linear polysaccharide composed of randomly distributed β-(1–4)-linked D-Glucosamine (deacetylated unit) and *N*-acetyl-D-Glucosamine (acetylated unit). It is obtained by partial deacetylation of chitin obtained from alkali treated crustacean shells [10]. Chitosan is a hydrophilic, biocompatible and biodegradable polymer of low toxicity. The cationic polyelectrolyte nature of chitosan could provide a strong electrostatic interaction with negatively charged materials [11].

Gellan gum is an anionic hetero polysaccharide produced by aerobic fermentation of the bacterium sphingomonas eloda (formerly known as *Pseudomonas eloda*). The chemical structure made up of repeating units of tetrasaccharide is composed of β-D-glucose, β-D-glucoronic acid, α-L-rhamnose residues in the molar ration of 2:1:1. Because of its ability to form strong, clear gels at physiological ion concentration, it can provide a longer contact time for drug transport across the nasal membrane before the formulation is cleared by mucociliary clearance mechanism. These features, along with bioadhesivity, biodegradability, biocompatibility and absence of toxicity of this polymer, attracted widespread interest in gellan gum as an ion responsive gelling agent [12].The formation of polyelectrolyte complexation (PEC) of either gellan gum or chitosan into solutions of opposite charge is reported [13].

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Ondansetron hydrochloride is a selective 5-HT3 receptor antagonist that is used for preventing nausea and vomiting caused by chemotherapy, radiotherapy and postoperative vomiting. It is rapidly absorbed on oral administration and showed bioavailability approximately 60%, mainly due to hepatic first pass and intestinal metabolism. Intravenous as well as oral dosage forms of ondansetron are commercially available. Oral forms of antiemetic drugs often get vomited out before systemic absorption. Parenteral or rectal administration results in low patient compliance. In this regard, the intranasal delivery seems to be an attractive alternative [14].A nasal mucoadhesive inserts appears very attractive since it is in solid state prior to administration allowing accurate drug dosing. In this study, Chitosan–gellan gum was selected to produce polyelectrolyte complex, with the aim to investigate the possible application of these complex in the preparation of mucoadhesive inserts for the nasal administration of ondansetron hydrochloride.

2. Materials and methods

2.1. Materials

Ondansetron hydrochloride was a gift sample from Alkem Laboratories (Mumbai, India). Chitosan (degree of deacetylation ~79%) from Sigma Aldrich, India, Gellan gum (Low acyl content) obtained as a gift sample from Burzin and Leons, CPKelco division of the Monsanto Company, USA. All other reagents used were of analytical grade.

2.2. Method

Chitosan (0.85% w/v) and gellan gum (0.4% w/v) polymeric solutions were prepared separately in 25 ml of acetate buffer solution (pH 5.0) and stirred at room temperature for 24 h. Ondansetron hydrochloride (1%) and mannitol (0.5% as cryoscopic agent) were added to a mixture of both solutions to produce viscous dispersion. 0.1 ml of the prepared viscous dispersion was placed into blister molds and frozen at −25 °C for 1 h. The samples were then freeze dried (0.25 mbar for 24 h with increasing shelf temperature − 15 to 0 °C and final drying for 2 h at +15 °C and 0.01 mbar (VirTis Benchtop K, Lyophilizer).The inserts were then stored in desiccators until further use.

2.3. Characterization of nasal inserts

Inserts were characterized for general properties like color, appearance and thickness measured by using a digital vernier caliper (Aerospace Digimatic Vernier Caliper, India).

2.4. Water uptake studies

A sponge (7 × 3.5 × 3 cm, household sponge) was fully soaked in the hydration medium (Simulated Nasal Fluid) and placed in a container filled with the same medium to a height of 1 cm in order to keep the sponge soaked during the experiment. Square filter paper (3 × 3 cm) was soaked in the medium and positioned on the top of the sponge. This experimental setup was equilibrated for 30 min and accurately weighed inserts were placed on the filter paper and the water uptake was determined at a time interval of 1 h for 8 h. Whole experiment has been carried in temperature and humidity controlled area using balance with high sensitivity. Percent water uptake of the insert was calculated using the following equation:

$$\%\text{Water uptake (mg/mg)} = W_w - W_d / W_d \times 100 \quad (1)$$

where,

W_w = the weight of wet insert,
W_d = the weight of the insert before water uptake

2.5. Muco adhesion test

One hundred grams of a hot agar/mucin solution (1 and 2%, w/w, respectively, in phosphate buffer pH 6.6) was cast on glass plate (20 cm × 20 cm) and allowed to gel at 4–8 °C for 3 h. The gel was then equilibrated for 1 h to the test conditions of 22 °C and 79% relative humidity in a chamber (Environment Chamber, Remi. India). The inserts were placed on top of the gel, moved downward due to gravity after the glass plate was turned into a vertical position. The displacement in cm was measured as a function of time (n = 6). The adhesion potential was inversely related to the displacement of insert [15].

2.6. In-vitro drug release

In-vitro drug release was carried out USP XXX-NF XXV (Apparatus-1 Basket type) dissolution apparatus, where phosphate buffer pH 6.6 was used as dissolution media maintained at 37 °C ± 0.5 °C at 50 rpm. Drug loaded inserts was placed in the dissolution vessel. 5 ml of aliquot samples was withdrawn at 1, 2, 3, 4, 5, 6, 7, and 8 h and replaced with fresh dissolution media. Samples were then filtered through a 0.45 μm filter and analyzed spectrophotometrically at 310 nm [16].

2.7. Drug release kinetics

In order to investigate the drug release mechanism, the release data were fitted to models representation: zero order (see Eq. (2)) as the cumulative amount of drug released vs time, first order (see Eq. (3)) as log cumulative percentage of drug remaining vs time and Higuchi's model (see Eq. (4)) as cumulative percentage of drug released vs square root of time.

2.7.1. Zero order

$$C = K_0 t \quad (2)$$

where,

K_0 = the zero-order rate constant expressed in units of concentration/time,
t = the time in minutes.

A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

2.7.2. First Order

$$\text{Log } C = \text{Log } C_0 - K * t/2.303 \quad (3)$$

where,

C_0 = the initial concentration of drug,
K = the first order constant and t is the time.

2.7.3. Higuchi

$$Q_t = K * t^{1/2} \quad (4)$$

where,

Q_t = the amount of drug release in time t,
K = the kinetic constant and t is the time in minutes.

A more rigorous test was used to distinguish between the mechanisms of drug release. The release data were fitted to the Peppas exponential model as a log cumulative percentage of drug released vs log

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