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Preclinical evaluation of dual action intranasal formulation intended for postoperative/cancer associated therapies

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ABSTRACT

Granisetron hydrochloride is a potent antiemetic yet experiencing first pass metabolism. Ketorolac tromethamine is a potent analgesic NSAID that is known to cause gastrointestinal complications. The purpose of this study is to prepare combined *in situ* nasal copolymer thermal gel combining both drugs for the management of postoperative and cancer associated nausea, vomiting and pain while avoiding the problems associated with their therapy. *In situ* gelling nasal formulations with/without different mucoadhesive polymers were prepared and evaluated. Viscosity of different formulations was measured and correlated to *in-vitro* drug release. Selected formulae were evaluated for *in-vivo* mucociliary transit time. Based on *in-vitro* release pattern and mucociliary transit time, the selected formula F4 was evaluated for chemical and thermal anti-nociception activity in rats following intranasal or intraperitoneal administration. Only the intra-nasal administration of the selected formulation F4 showed significant analgesia against chemical nociception during both the early and late phases. Also, intranasal administration of the selected formulation F4 showed significant analgesia against thermal nociception. F4 intranasal formulation may offer higher therapeutic value than oral administration as it may not only avoid granisetron first pass metabolism but may also minimize ketorolac gastrointestinal adverse effects as well.

1. Introduction

Granisetron hydrochloride and ketorolac tromethamine are two drugs used for postoperative and cancer associated therapies. Granisetron is a highly selective 5-hydroxytryptamine-3 ($5HT_3$) receptor antagonist, it is used as a potent antiemetic in postoperative nausea and vomiting and in acute and delayed emesis in cancer chemotherapy (Aapro, 2004). Ketorolac is a potent analgesic NSAID used in severe to moderate postoperative pain (Buckley and Brogden, 1990). Ketorolac has also been found effective in the treatment of trauma-related pain as well as pain associated with cancer (Angeles, 2009; Joishy and Walsh, 1998; Mercadante et al., 2002). Granisetron suffers from reduced oral bioavailability (≈60%) due to hepatic metabolism (Sweetman, 2002). Ketorolac can cause gastrointestinal complaints associated with all NSAIDs such as gastrointestinal bleeding, perforation and peptic ulceration (Gillis and Brogden, 1997).

The use of the nasal cavity as a route for drug delivery has been a growing area of great interest. Intranasal administration offers a simple, practical, noninvasive, convenient, cost effective, and an alternative route for rapid drug delivery to systemic route. Other advantages include avoidance of liver or gastrointestinal metabolism, avoidance of the gastrointestinal irritation, and enhanced patient compliance by self-medication (Costantino et al., 2007). Also, it is an attractive alternative for patients not able to take medications orally, or who are experiencing nausea or vomiting (Singla et al., 2010).

Intranasal administration may provide a more convenient form of drug delivery for ambulatory patients when administration by intravenous and intramuscular injection cannot be continued after the patient is discharged (Singla et al., 2010).

Since a rapid onset of action is required and because of problems and side effects associated with granisetron and ketorolac administration; intranasal route seems to be a promising alternative to oral and parenteral route {granisetron is currently available as oral, intravenous and transdermal formulations, while ketorolac is available as oral, parenteral and nasal (spray) formulations}.

Liquid nasal formulations (solutions and sprays) are easily and accurately instilled in the nasal cavity but they suffer from rapid

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mucociliary clearance that limits the time for effective drug uptake (Ugwoke et al., 1999).

Bioadhesive powders and gels have been studied to increase the residence time of the drug in the nasal cavity as well as to facilitate permeation of the drug through the mucosa by loosening the tight junctions between the epithelial cells (Callens et al., 2003). Accurate dosing of conventional bioadhesive gels is problematic due to their high viscosity; on the other hand, bioadhesive powders can cause irritation to the nasal cavity and require sophisticated delivery devices for ideal deposition and accurate dosing. (Li et al., 2014).

Nowadays, *in situ* gels are being preferred widely because they are liquid at room temperature and hence can be easily administered into the nasal cavity as drops that will form a firm gel at the temperature of the nasal cavity. Such types of gels provide accuracy in dose administration which is difficult in case of conventional gels (Hu et al., 2009; Zaki et al., 2007).

The aim of this study is to prepare dual effect mucoadhesive copolymer *in situ* nasal gel containing both drugs to help management of postoperative and cancer associated nausea, vomiting and pain nevertheless avoiding most of problems associated with their therapy. The nasal gel aimed to be of gelation temperature suitable for nasal cavity, adequate pH and release properties, and suitable *in-vivo* mucociliary transit time. The work also aimed to preclinically evaluate the selected formula (e) for analgesic effect.

2. Materials and methods

2.1. Materials

Granisetron hydrochloride and ketorolac tromethamine (kind gifts from Amriya for Pharmaceutical Industries, Alexandria, Egypt). Pemulen™ TR-2 (P TR-2, gift from Luna Pharmaceutical Co., Cairo, Egypt; it is a polymer of acrylic acid, modified by long chain (C10–C30) alkyl acrylates, and crosslinked with allylpentaerythritol). Carbopol® 974P (CP 974P, Lubrizol Advanced Materials Inc., USA). Hydroxypropylmethylcellulose (HPMC K15M, Colorcon, England). Calcium chloride dihydrate, formaldehyde solution (Formalin, 34–38%), Sodium chloride, potassium chloride and triethanolamine (El-Nasr Pharmaceutical, Chemical Co., Egypt). Pluronic F127 (P F127, Sigma–Aldrich Inc., Germany). Benzalkonium chloride (Sigma Chemical Co., USA). Urethane (Sigma–Aldrich Inc., USA). Amaranth (standardcon, Pvt. Ltd., India). Normal saline (Sodium chloride Intravenous Infusion 0.9% w/v, B.P, Ateco Pharma, Egypt).

2.2. Derivative spectral characteristics of granisetron and ketorolac in simulated nasal electrolyte solution (SNES) pH 5.5

Scanning in the UV range 200–400 nm for granisetron and ketorolac was carried out in SNES pH 5.5 (SNES is composed of 7.45 mg/ml NaCl, 1.29 mg/ml KCl and 0.32 mg/ml $CaCl_2 \cdot 2H_2O$) (Cheng et al., 2002; Callens et al., 2003). A zero order, first derivative and second derivative spectra were computed for each drug. The first derivative and second derivative of the ratio spectrum were calculated and the zero crossing method was used to detect the suitable wave lengths for each drug (Shimadzu UV-1601PC UV–Vis Double beam Spectrophotometer, Koyo, Japan).

2.3. Recovery study of granisetron and ketorolac mixtures in SNES pH 5.5

Mixtures of known concentrations of granisetron and ketorolac in SNES pH 5.5 were prepared. The amplitude of each drug in SNES at the predetermined wave length was measured, and then the concentration was back calculated. The recovery percentage (R%) was calculated for each mixture.

2.4. Compatibility study of granisetron, ketorolac and different pharmaceutical excipients using infrared spectroscopy (IR)

Samples of individual drugs, excipients and physical mixtures weighing about 2–3 mg were mixed with about 400 mg of dry potassium bromide powder in micronized IR grade using pestle and mortar. The powder was compressed into discs under pressure of 10,000–15,000 psi. The infrared spectra of the samples were recorded over a wave number range of 4000–500 cm^{-1} (Genesis II, TM, Mattson Instruments, USA).

2.5. Preparation of in situ nasal gels

2.5.1. Preparation of non mucoadhesive in situ nasal gels containing different concentrations of Pluronic F127

The cold method described by Schmolka (1972), was applied. P F127 gels were prepared at different concentrations (16%, 17%, 18%, 19% and 20% w/w) with or without granisetron (0.5% w/w) and ketorolac (5% w/w) to determine the lowest possible concentration that exhibits thermoreversible property between 29 and 34 °C. Formulations were prepared on weight basis, the drugs (medicated gels) were completely dissolved in distilled water, the solutions were cooled down to 4 °C and then a weighed amount of P F127 was added slowly with continuous stirring. The dispersions were then stored in a refrigerator until clear solutions were obtained.

2.5.2. Preparation of mucoadhesive in situ nasal gels

The method of preparation is the same as that mentioned under the previous section except that benzalkonium chloride and the mucoadhesive polymer were accurately weighed and stirred in the calculated quantity of distilled water together with granisetron and ketorolac prior to cooling and subsequent addition of P F127. Various prepared mucoadhesive *in situ* nasal gel formulations are given in Table 1.

2.6. Characterization of different prepared in situ nasal gels

2.6.1. Measurement of gelation temperature

An aliquot of 10 ml of each formulation was put into a beaker (25 ml) placed on thermostatically controlled magnetic stirrer at room temperature (Model SB 162, Thermolyne Corporation, USA). A thermometer was immersed in the sample solution. The solution was gradually heated under continuous stirring using a magnetic bar. The temperature at which the magnetic bar stopped moving

Table 1
Composition of the different prepared mucoadhesive *in situ* nasal gels.

Formula	Pluronic F127 (%w/w)	HPMC (%w/w)	Pemulen™ TR-2 (%w/w)	Carbopol® 974P (%w/w)
F1	17	0.5	–	–
F2	17	1		–
F3	17	1.5	–	–
F4	17	–	0.05	–
F5	17	–	0.1	–
F6	17		0.2	
F7	17	–	–	0.1
F8	17	–	–	0.2
F9	17	–	–	0.3

Each Formula Contains 0.001% w/w Benzalkonium Chloride, 5% w/w Ketorolac Tromethamine and 0.5% w/w Granisetron Hydrochloride.
Non medicated non mucoadhesive nasal gels were coded as P; medicated non mucoadhesive nasal gels were coded as M throughout the manuscript.