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Abstract

The objective of this study was to develop an oral transmucosal formulation of an antiemetic drug that can not only serve in the active form but also provide a controlled release profile. In this study, sublingual films based on the biodegradable and water-soluble polymers, that is HPMCK-4M and PVPK-30, were developed by the solvent casting method, and were loaded with the antiemetic drug granisetron hydrochloride (granisetron HCl). The entrapment efficiency of the developed formulation was found to be 86%. The *in vitro* profile showed an instant release of the drug from the sublingual film, in a pattern following the first order kinetics array. The *in vivo* studies showed that granisetron HCl was delivered in its active state and showed effective results, as compared to its activity in the marketed formulation.

Keywords: granisetron hydrochloride, HPMC-K4M, PVPK-30, solvent casting method, sublingual film

Introduction

In recent years, various methods have been developed to deliver therapeutic agents through various transmucosal routes, to release a therapeutic amount of drug to a specific site (Marwah et al. 2014), and to maintain the desired therapeutic concentration (Singh et al. 2014c, Malik et al. 2014). The conventional dosage forms, such as tablets (Kaur et al. 2014g) or injections (Kaur et al. 2014d), have many drawbacks such as poor bioavailability (Singh et al. 2014b), poor solubility (Singh et al. 2014a), quick breakdown of the drug *in vivo* (Sharma et al. 2014c), and rapid loss of drug activity (Chaudhary et al. 214). These drawbacks can be overcome through a suitable delivery system, depending on the medical condition (Sharma et al. 2014b, Kaur et al. 2014a). The concept of fast-dissolving films has become popular as a new delivery system (Gagandeep et al. 2014). This delivery system will provide the maximum therapeutic efficacy (Garg 2014) and increase the bioavailability of poorly soluble drugs (Sharma et al. 2014a) with minimum side effects (Garg and Goyal 2014b) and maximum stability (Garg and

Goyal 2014a), improving patient compliance (Rohilla et al. 2014) by reducing the frequency of dosage (Garg and Goyal 2014c), and will also enable the drug to avoid the first pass metabolism, which is a major issue (Kataria et al. 2014).

Nausea and vomiting are common problems that occur in disease and non-disease conditions, and after chemotherapy. These result from the activation of protective physiological mechanisms in order to eliminate the toxins from the body. Granisetron HCl is well-recommended for the treatment of nausea and vomiting following cancer chemotherapy. It is a potent serotonin 5-HT3 receptor antagonist. Its prominent action is to reduce the activity of the vagus nerve, which activates the vomiting center in the medulla oblongata (Nibha and Pancholi 2012, Joshi et al. 2014, Johal et al. 2014).

Several approaches have been developed and implemented, to improve the therapeutic outcomes of granisetron HCl. A transdermal patch has been prepared to control the release (Morie et al. 2014, Goyal et al. 2014b) and provide better therapeutic outcomes for the prevention of chemotherapy-induced vomiting (Garg et al. 2012b, Goyal et al. 2014a). Recently, transdermal patches based on iontophoresis have also been utilized, to increase the bioavailability of granisetron. Studies have demonstrated the feasibility of transdermal transport of granisetron using lutrol-F127 gel, by iontophoresis (Panzade et al. 2012, Garg and Goyal 2012). A provesicular formulation of granisetron HCl has been developed for buccal delivery (Goyal et al. 2013, Garg et al. 2013). Studies have shown that bioadhesive buccal polymers play an important role in the delivery of granisetron (Ahmed et al. 2014).

In the present study, HPMC K-4 and PVPK-30 were selected as polymeric constituents, of which HPMC K-4 acts as a film-forming agent (Nyamweya and Hoag 2000), and PVPK-30 acts as a penetration enhancer (Prajapati et al. 2012). The objective of this study was to formulate and evaluate granisetron HCl-loaded HPMCK-4M and PVPK-30 films for transmucosal delivery via the sublingual route, and to improve therapeutic efficacy and bioavailability by avoiding the first pass metabolism.

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Materials and methods

Materials

Granisetron HCl was obtained from Adley Pharmaceuticals (Solan, India). Water-soluble polymers, that is HPMCK-4M and PVPK-30, were procured from HiMedia Labs, Mumbai, India. All the other chemicals used were of analytical grade.

Preparation of the sublingual film

The sublingual film of granisetron HCl was prepared by the solvent casting method. Aqueous solution 1 was prepared by dissolving the polymer (100/22) in 10 ml of distilled water, and stirred to produce a clear solution, which was kept for 1 h to remove all air bubbles. Then, aqueous solution 2 was prepared by adding the drug, plasticizer, and sweetener, in a specific proportion, (50 mg/20 mg/1.5 ml) to distilled water. Subsequently, solution 1 was added to solution 2, under mixing, and left to be for stirred for 1 h. Then, the solution was cast in a petri dish of 9 cm in diameter, and was dried in oven at 45°C for 24 h. The film was then carefully removed from the petri dish and checked for any imperfection, and cut according to the size required for testing (a square film of 2 cm length, 2 cm width). The samples were stored in a glass container maintained at a temperature of 30°C and a relative humidity of 60% ± 5%, until further analysis (Nafee et al. 2004).

Characterization and evaluation

Measurement of tensile strength

The mechanical property was evaluated using the model TexturePro CT V1.3 Build 15. Film strips of a special dimension and free from air bubbles or physical imperfections were held between two clamps which were positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp at a rate of 100 mm/min, and the force was measured when the film broke (Garg et al. 2012a).

Tensile strength is calculated by the following equation:

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross-section area of the sample (mm}^2\text{)}}$$

Drug entrapment efficiency

The drug entrapment efficiency (DEE) of the film was calculated by dissolving the prepared film of the dimension of 2 cm × 2 cm in 20 ml of simulated salivary fluid of (pH 6.8), with continuous shaking for 30 min. The amount of drug in the solution was determined by UV spectroscopy at 301 nm (Kaur et al. 2014e, 2014f). The percentage of entrapment was calculated using the following formula:

$$\% \text{DEE} = \frac{\text{Total Amount of drug added} - \text{Amount of drug in supernatant}}{\text{Total amount of drug added}} \times 100$$

In vitro dissolution study

The *in vitro* dissolution profile of the sublingual film of granisetron HCl was conducted in a USP type 2 (basket apparatus) with 900 ml of simulated salivary fluid of pH 6.8 as the dissolution medium (stirred at 50 rpm), maintained at 37 ± 0.5°C, for 8 h. Samples were withdrawn every 30 min and replaced with the same amount of fresh medium. Absorbance was determined by a UV spectrophotometer at the λ_{max} of 301 nm. The prepared formulation was also compared with granisetron tablets (Mashru et al. 2005, Kaur et al. 2014c, Kaur et al. 2014b).

Ex vivo permeability study

Drug permeability studies were carried out using freshly excised goat tissue. The receptor compartment of the Franz diffusion cell was filled with freshly prepared simulated salivary solution (pH 6.8). The freshly excised tissue was fixed by clamps between the donor and the receptor compartments in such a way that its epithelial surface was oriented towards the donor compartment. The release studies were carried out at 37°C. Samples were withdrawn every 30 min. After each sampling, the volume removed was replaced with fresh medium. The amount of drug present in the release medium was determined by UV spectroscopy at a λmax of 301 nm. The release experiments of each sample were performed in triplicate, and average values were reported. The percent drug release was calculated using the calibration curve of the drug in the simulated salivary solution (pH 6.8) (Semalty et al. 2008, Modgill et al. 2014).

In vivo study

The studies were carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India (ISF/CPCSEA/IAEC/2014). The blood samples were taken from the ear vein route through a syringe (Satishbabu and Srinivasan 2008, Pv et al. 2011, Pabreja et al. 2014). The study was performed in four different groups, each group being administered a different formulation, as follows:

F_1: Nothing is put just below the tongue of the rabbit.
F_2: A blank film is applied under the tongue of the rabbit.
F_3: 200 mcg of granisetron HCl loaded in a film is applied below the/under the tongue of the rabbit.
F_4: 200 mcg of granisetron H film-coated tablets are given orally to the rabbit.

Results and discussion

Transmucosal sublingual patches were successfully prepared by the solvent casting method. During the formulation, PVP K-30 was used, in association with HPMC K-4M. PVP K-30 provided a better dissolution profile; while addition of HPMC K-4M in the developed film may improve the mucoadhesivity, along with modulating the release of the drug. The solvent casting method selected is very simple and effective, to prepare uniform sublingual patches.

Optimization of the drug-loaded film

Table I shows the influence of the polymer ratio on film uniformity. Based on the data, it can be seen that the

Table I. Influence of polymer ratio on film uniformity.

Formulation code	HPMCK4M/ PVPK30	PEG (ml)	Mannitol (mg)	Drug (mg)	Observation
GSF1	10/2	1	20	50	Film breaking/non-uniform weight of film
GSF2	10.1/5	1	20	50	Film breaking/ Non-uniform weight of film
GSF3	100/2.2	1	20	50	Film breaking/non-uniform weight of the film
GSF4	**100/2.2**	**1.5**	**20**	**50**	**No film breaking/uniform weight of the film**
GSF5	150/2.2	2	20	50	Film forming/uniform weight, but not able to sustain its integrity, breakage after some time

Bold row signifies optimized formulation and selected for further studies.

formulation code GSF4 shows the best results, as compared to other formulations.

Characterization of drug-loaded film

Table II shows the physical characterization (weight variation, thickness, drug content, folding endurance and tensile strength) of the optimized drug-loaded film. It was observed from the data that the uniformity of weight, thickness, folding endurance, and tensile strength were satisfactory with respect to variation of these parameters between films of same formulation. In the present study, 1.5 ml of PEG was found to be optimized, with respect to the polymer ratio selected for the formulation code GSF 4. As the concentration of HPMC increases beyond 100, there will be a significant increase in viscosity of the resultant solution, which in turn limits the plasticizing effect of PEG, which is also supported by the results of tensile strength and folding endurance, where the respective values were found to be decreased with increasing concentration of HPMC (Garg et al. 2014).

Drug entrapment efficiency

The entrapment efficiency of the sublingual film of granisetron HCl was estimated (Figure 1). All the formulations showed good reproducible results. There are no significant changes observed in the DEE among different formulations; however a relatively higher entrapment efficacy in GSF 4 was found to be 86.73 ± 4.13, which could be associated with the better solubilizing potential of the formulation.

In vitro dissolution study

The data obtained from the *in-vitro* dissolution study of the developed formulations and the marketed formulation, are represented in Figure 2. From the *in-vitro* drug release studies, it was found that of all the three sets of formulations (F1, F2, and F3), the developed formulation showed a high percentage of release of 82% in 7 h, followed by the plain formulation that showed 65% in 7 h, and the marketed formulation that showed 69% in 7 h. *In vitro* drug release studies clearly demonstrated a steady state release from
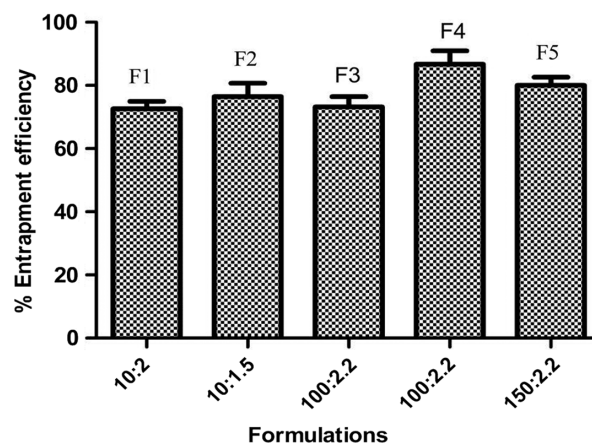

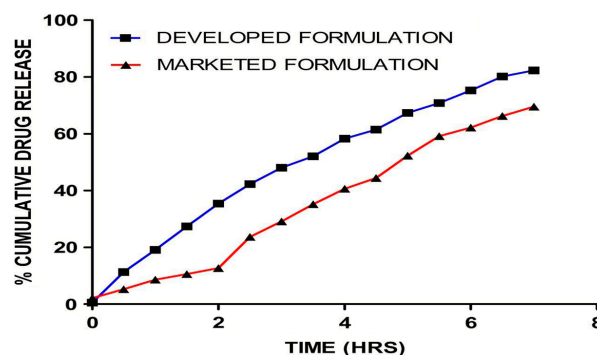Figure 1. Entrapment efficiency of the different formulations.

Figure 2. *In vitro* drug release profiles of developed formulation and marketed formulation.

the developed formulation under the simulated conditions, whereas an initial dump occurred in the marketed formulation, which could be associated to tablet disintegration. The drug release behavior, conceding an initial burst followed by controlled release, was found to be appropriate in the management of anti-emetic therapy. Further, the drug release profile follows first order kinetics ($R2 = 0.9901$), and shows that the rate of drug release depends on the concentration of drug.

Table II. Physical characterization of the optimized drug-loaded film.

Formulation code	Weight variation (mg)	Thickness	% Drug content	Folding endurance	Tensile strength (Kg/ mm^2)
GSF1	64.8 ± 1.00	0.54 ± 0.081	72.63 ± 2.32	280.0	1.141 ± 0.3
GSF2	74.73 ± 1.527	0.56 ± 0.008	76.46 ± 4.23	246.6	0.846 ± 0.2
GSF3	64.16 ± 2.516	0.46 ± 0.052	73.18 ± 3.27	238.3	1.023 ± 0.7
GSF4	**59.1 ± 1.00**	**0.43 ± 0.009**	**86.73 ± 4.13**	**291.6**	**1.444 ± 0.1**
GSF5	94.2 ± 2.516	0.74 ± 0.015	80.07 ± 2.56	270.0	1.151 ± 0.3

Bold row signifies optimized formulation and selected for further studies.
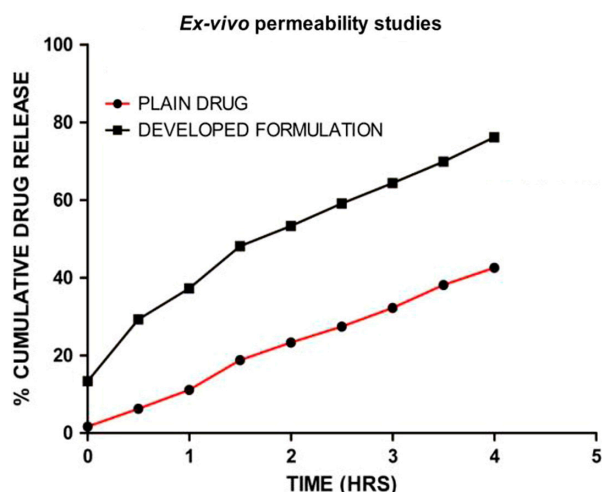
Figure 3. *Ex vivo* permeability study of the developed and marketed formulations.

Ex vivo permeability study

The data obtained from the *ex vivo* study of permeability through the mucosal site are shown in Figure 3. Studies of permeation through the oral mucosa indicated that the extent of permeation of the developed formulation showed the highest percentage of drug permeated, which was found to be 76.08% in 4 h, as compared to the corresponding value for plain drug, which was found to be 42% in 4 h. The higher drug permeability in the developed formulation could be related to PEG, because PEG, owing to its solubilizing properties, enlarges the aqueous channel which facilitates para-cellular transport of the drug. Further, the mucoadhesive nature of the film helps to maintain a concentration gradient of the drug at the absorption site for a sufficient time, necessary for drug absorption via the passive diffusion process.

Comparative study of in vivo bioavailability

A comparative study of *in vivo* bioavailability was done using New Zealand white rabbits ($n = 6$). The graphical representation of plasma concentration of granisetron HCl vs time, relating to the developed and marketed formulation, and a comparison of different pharmacokinetic parameters, are shown in Figure 4 and Table III, respectively.

Table III. Comparison of pharmacokinetic parameters.

Pharmacokinetic parameters	Developed formulation	Marketed formulation (MHRA)
AUC (ng.h/ml)	146.60	140.10
C_{max} (ng/ml)	23.3	10.6
$t_{1/2}$ (h)	4.81	11.3
T_{max} (h)	3.56	2.42

The oral bioavailability of the sublingual film of granisetron HCl was found to be 1.04-fold greater than that of the marketed formulation (film-coated tablets), which indicates that the bioavailability of the drug in sublingual film is maximum, when compared to that of the marketed formulation. The higher bioavailability of the drug in the developed formulation could be related to better drug absorption and the escape of first pass metabolism. Further, a higher Cmax indicated a higher fraction of drug available in the systemic circulation for a longer time, to produce the therapeutic activity. A study of the pharmacokinetics clearly demonstrated a better therapeutic management by granisetron HCl in the developed formulation.

Conclusions

It has been concluded that the granisetron HCl-loaded sublingual film was successfully formulated. The sublingual carrier system will help in achieving improved bioavailability by avoiding first pass metabolism, and resulting in an improvement in patient compliance. The incorporation of the sweetening agent, mannitol, helped to mask the taste.

Acknowledgements

Declaration of interest

The authors confirm that the contents of this article do not have any conflicts of interest.

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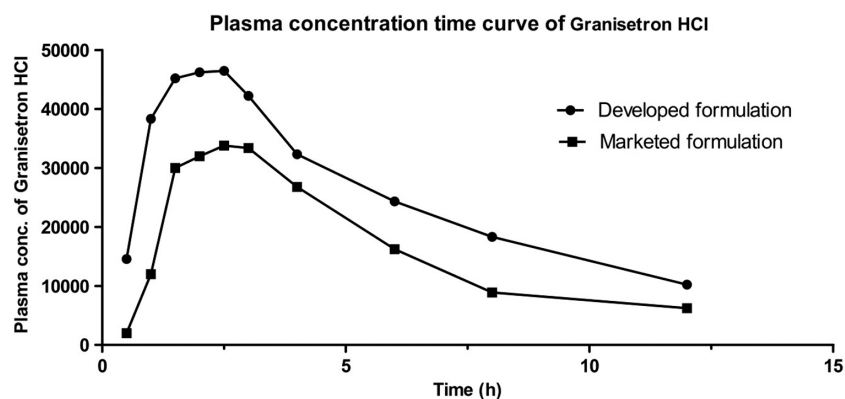

Figure 4. Comparison of plasma drug concentration vs time profile of developed and marketedformulation.

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