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Research Article

Formulation and Evaluation of Novel Drug Delivery System Using in Situ Gelling Approach for Antiemetic Drugs Used in Cancer Patients

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Abstract

Nausea and vomiting are symptoms of many different conditions, such as infection, food poisoning and motion sickness. At present, oral and intravenous are the most used routes of antiemetic administration in chemotherapeutic regimens. The effectiveness of conventional drug schedules and formulations is often impaired by difficulties associated with oral or intravenous chemotherapy administration. These problems can be overcome by alternative or new drug delivery systems, hence improving patient compliance. Development of novel delivery systems for antiemetic drugs, as an alternative to conventional preparations, is important in terms of good patient compliance and improving bioavailability. In the present study an antiemetic formulation of Domperidone in the form of an in-situ gel was prepared. The release studies showed very promising results. It was observed that Domperidone was released from the gels in a sustained release manner. The formulation variables such as concentration of polymer affects rate and extent of drug release, which is due to increase in density of polymer and also increase in dissolution path length that the drug molecule has to travel. The developed Domperidone in situ nasal gel formulation showed a more than 11 µg /ml permeation of drug in 6 hours through the epithelium membrane. This local delivery system is anticipated to achieve good patient compliance and improve clinical outcomes as the gel formulation is applied directly to the site of action in the form of solution which upon contact forms a gel.

Keywords: Intranasal, Antiemetic, In-Situ Gel and Release Studies.

1. Introduction

Nausea is an unpleasant, diffused sensation of unease and discomfort, often perceived as an urge to vomit. Nausea and vomiting are not diseases, but are symptoms of many different conditions, such as infection, food poisoning and motion sickness. Nausea and vomiting can sometimes be symptoms of more serious diseases such as central nervous system disorders and some forms of cancer. However, it occurs as side effect with many treatments especially with chemotherapeutic drugs, antibiotics, and NSAID s [1]. A severe acute toxicity occurs with every class of chemotherapeutic cancer agent and these symptoms usually happen within a few minutes to hours after chemotherapeutic treatment is initiated. The inability to adequately alleviate this toxicity can lead to severe complications such as general malaise, weight loss and imbalance in electrolytes. The antiemetic drugs are accordingly used to prevent such complications in the treatment of patients suffering from nausea and emesis [2].

At present, oral and intravenous are the most used routes of antiemetic administration in chemotherapeutic regimens. The effectiveness of conventional drug schedules and formulations is often impaired by difficulties associated with oral or intravenous chemotherapy administration. These problems can be overcome by alternative or new drug delivery systems, hence improving patient compliance. Development of novel delivery systems for antiemetic drugs, as an alternative to conventional preparations, is important in terms of good patient compliance and improving bioavailability [3]. There are several new drug delivery techniques of alternative oral antiemetic drug administration available for emesis induced by chemotherapy. These new systems are being developed, however, currently the research is very limited [2].

Over the recent decades, the interest in intranasal delivery as a non-invasive route for drugs has increased and large number of Pharmaceutical industries are trying to prepare

such formulations but none of them have succeeded so far. The nasal route offers unique superiorities, such as fast and high drug absorption, and high patient compliance. Therefore, a considerable amount of research has been carried out on the development of nasal delivery systems for antiemetic drugs. Since nasal mucosa offers numerous benefits as a target tissue for drug delivery, a wide variety of therapeutic compounds may be administered intra-nasally for topical, systemic, and central nervous system actions. Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. Promising results with enhanced bioavailability have been obtained upon nasal administration and have prompted more extensive investigations in this area [4].

A study was carried out to develop a gel formulation as a topical delivery system containing nanoparticles of Ondansetron using different polymers which could be considered as an attractive alternative to oral and parenteral routes. The nasal route offers fast and high drug absorption, and better patient compliance [3]. One study illustrated the effectiveness of ABHR (lorazepam, diphenhydramine, haloperidol and metoclopramide) gel in relieving the symptoms of nausea and vomiting in hospice patients. The results showed that the formulation of ABHR was highly effective in overcoming the symptoms of nausea and vomiting [5].

Hintendra demonstrated that metoclopramide nasal gel delivery system was feasible for nasal administration and its antiemetic effect was rapid and the optimized gel showed increased bioavailability of metoclopramide compared to the oral drug solution [6]. Belgamwar et al. prepared a gel containing Dimenhydrinate and the results showed the overall performance of this in situ gel and concluded that it was an effective delivery system for the nasal route [7]. Ozsoy and Sevgi demonstrated that in situ gel formulation of nanoparticles systems gave promising nasal formulation and they found that the nasal route offers unique superiorities, such as fast and high drug absorption and patient compliance [3]. In another study, they evaluated and reviewed several approaches, including permeation enhancers, in situ gel formulations and micro- and Nano particulate systems. The study stressed on the importance of nasal delivery of antiemetic drugs. The results obtained were promising and indicated that nasal formulations of some antiemetic drugs may enter the market soon [3]. concluded that nasal delivery systems are an attractive alternative and showed better stability and bioavailability compared to oral and parenteral routes [4]. developed Transdermal Delivery System of Dexamethasone, Palonosetron and Prepatent for combination antiemetic therapy and concluded that the optimized gel could be utilized for the simultaneous transdermal delivery of dexamethasone, palonosetron and aprepitant [8]. Carried out research on formulation of transdermal patch for antiemetic therapy and concluded that the patch achieved desired therapeutic action with no signs of skin irritation [9]. Demonstrated that the patch of Palonosetron as an antiemetic showed a controlled release, with longer duration of action without any signs of skin irritation and were found to be stable and better than oral administration [10]. A controlled release formulation of Palonosetron hydrochloride was developed using novel parenteral drug delivery system by. They concluded that such drug delivery technology can reduce the total number of injections throughout the drug therapy period and will be truly advantageous in terms of compliance and to improve the quality of the therapy. This formulation involved less complicated fabrication and easy administration [11]. Innovative in situ gelling suspension for effective nasal delivery of fluticasone was developed by. Pectin, gellan gum and sodium hyaluronate were used as gelling/thickening agents, and Tween 80 as a suspending agent. The highest effect on the gel viscosity, strength and fluticasone release profile was observed for gellan gum, hence it was recognised as a crucial parameter for the optimisation of overall therapeutic effect [12].

A study of direct nose-to-brain (N2B) delivery of antipsychotics via the olfactory epithelium was developed by Tan et al. They concluded that nnanotechnology can optimize the drug stability, mucosal absorption, and cerebrospinal fluid (CSF)-bioavailability. This could avert peripheral ADRs by maximizing cerebral drug concentrations and reducing drug levels in the periphery [13]. Recently a study was done on the preparation of in situ gelling formulations by Khatri et al. They were found to have the ability to undergo a sol -gel conversion when exposed to biological stimuli (temperature-responsive, pH-responsive and ion responsive). They illustrated the ability to prolong the residence time of formulation in the nasal cavity, thereby serving better for complete uptake of the drug across the nasal mucosa [14]. This study was designed to formulate an in-situ gel containing Domperidone (using 22 factorial design) along with polymers Kolliphor P 407, Carbopol 934 and HPMC K 100M, and find the one which helps in rapid permeation and helps the drug to reach the blood stream in the shortest time.

2. Materials and Methods

2.1 Materials: Antiemetic drug Domperidone was provided as a gift sample from Oman Pharmaceutical Products Oman. Kolliphor P 407 was a gift sample from BASF /USA. Polymers namely Hydroxy propyl methylcellulose (HPMC), Carboxymethyl Cellulose CMC and Carbopol 934P, preservatives including methyl paraben and propyl paraben were procured from National Pharmaceutical Industries (NPI) Oman. Other Chemicals including Sodium chloride (NaCl), Potassium chloride (KCl), Disodium phosphate (Na2HPO4), Monopotassium phosphate (KH2PO4), Phosphoric acid H3PO4, 0.5N NaOH (Sodium hydroxide) were provided by National University of science and Technology, College of Pharmacy lab.

2.2. Methods

Preparation of in Situ Gels: The formulation was prepared using the cold method [15]. Thermosensitive Kolliphor P 407 20% was prepared, stirred, and kept in the refrigerator at 4ºC for 24 hrs. to dissolve completely and form a clear solution. The other excipients like HPMC, CMC and Carbopol 934 P and 0.5% drug were finally added to the gel formulation and stirred at room temperature. A 2*2 factorial design was used to study the best formulation. The advantage of a

factorial design includes greater precision. It allows examination of the effect of one variable when other factors are changed, something which is not possible using traditional methods of investigation. The formulae are given in Table 1.

Table 1: Composition ratios of in-situ gel formulations (Formulae F1 -F6)

	Domperidone %(w/w)	Kolliphor P 407 %(w/w)	HPMC %(w/w)	CMC %(w/w)	Carbopol 934 %(w/w)
F1	0.5	20	1	2	0
F 2	0.5	20	2	1	0
F 3	0.5	20	0	1	2
F4	0.5	20	0	2	1
F 5	0.5	20	1	0	2
F 6	0.5	20	2	0	1

Gel Formulations Composition

Evaluation of gels

Visual Appearance, Clarity, and pH of Gel: The visual inspection was carried out for the formulations for color and presence of air bubbles. The pH of the medicated formulations was measured using standardized digital pH meter (Martini by Milwaukee Instrument Company) at room temperature by taking adequate volume in a 10 ml beaker and allowing it to equilibrate for 1 min (Table - 2). The experiment was run in triplicate.

Table 2: pH reading of various formulations.

Formulation	Reading 1	Reading 2	Reading 3	Average ±SD
F1	6.52	6.5	6.57	6.53 ±0.0361
F2	6.69	6.72	6.65	6.69±0.0351
F3	6.73	6.61	6.75	6.70±0.0757
F4	6.03	6.07	5.99	6.03±0.0400
F5	6.65	6.72	6.67	6.68±0.0361
F6	6.69	6.71	6.65	6.68±0.0306

In vitro Drug Release Study: The drug release from different Domperidone containing polymer gels was studied using dissolution testing apparatus type 1. One milliliter (1 ml) of the gel was filled inside cellulose bag using 2.5 ml syringe and kept within the basket of the dissolution apparatus. Then it was immersed in 1 liter of prepared buffer in a container. Temperature of 37±0.50 °C and rotations of 100 rpm were maintained throughout the test. Aliquots of 5ml were withdrawn at predetermined time intervals each hour from the release medium and replaced with an equal volume of the prepared buffer. The drug content in the samples was determined at 255nm using UV-Visible spectrophotometer. Figure 1 shows the release profile of different Domperidone gel formulations.

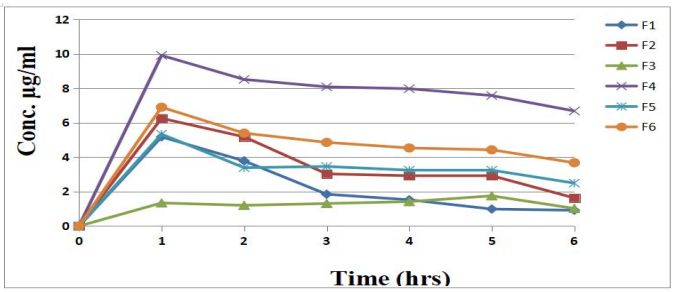

Figure 1: Release Profile for Domperidone Drug from Various Formulations.

In vitro permeation studies: A modified device (modified Franz diffusion cell) using epithelial tissues was used for the study. The facial part of the sheep was taken from the slaughterhouse in Muscat and washed with 0.9% normal saline. The diffusion membrane was used for evaluation of drug permeation. Phosphate buffer pH 6.8 [NaCl (8) g, KaCl (2) g, Na2HPO (41.44) g, KH2PO4 (0.25) g in 1liter of distilled water] was used as the diffusion medium in the receptor chamber. One (1) mL of the optimized formulation gel (F 4) was added to the donor chamber. The donor surface of

the membrane was constantly in contact with tissue and was covered with a piece of Para film® to prevent evaporation. Temperature of 37 ± 0.5 °C was maintained throughout the test. The assembly was put on magnetic stirrer (50 rpm) and equilibrated for 30 minutes. 0.5 mL sample was withdrawn every 1 hour up to 6 hours and replaced with same volume of fresh phosphate buffer fluid to maintain constant volume. The sample was analyzed using a UV spectrophotometer at 255nm (Figure 2). The withdrawn sample was diluted to 5 ml in a test-tube with the prepared buffer and analyzed by UV spectrophotometer at 255 nm. The standard solution for the drug Domperidone was prepared and standard curves were developed as shown in Figure 3.

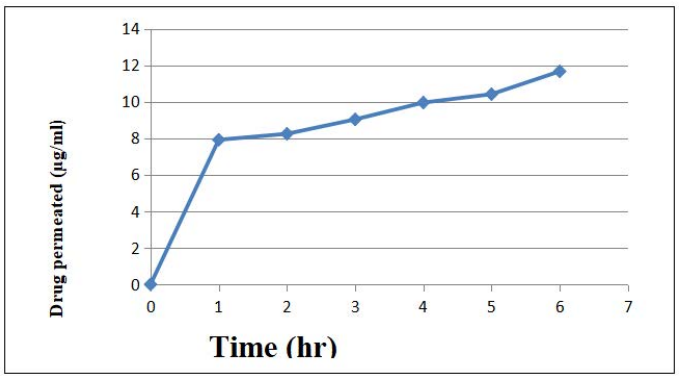

Figure 2: Permeation Profile for Domperidone Drug.

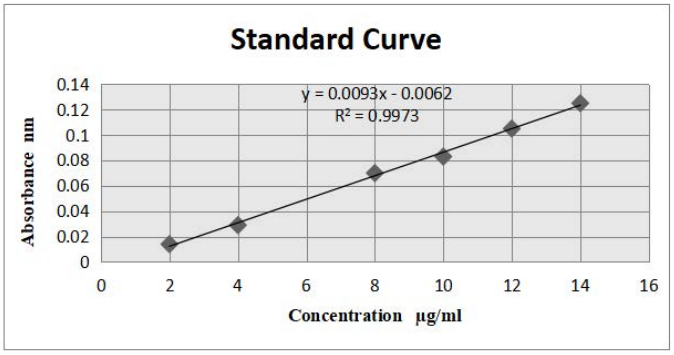

Figure 3: Standard Curve Showing plot of Concentration vs. Absorbance.

3. Results

Evaluation of Gels: pH reading of various formulations is shown in Table 2.

In Vitro Drug Release Study: Figure 1 shows the release profile of different Domperidone gel formulations.

In vitro permeation studies: The standard curves and permeation study results are shown in Figures 2 and 3.

4. Discussion

A severe acute toxicity occurs with every class of chemotherapeutic cancer agent after the chemotherapy. This usually happens a few minutes to hours after chemo is given. Nausea and vomiting can lead to severe complications such as general malaise, weight loss and imbalance in electrolytes and antiemetic drugs are used in the treatment of patients suffering from nausea and emesis [2]. Over the recent decades, the interest in intranasal delivery as a non-invasive route for drugs has increased [3]. Our study showed that all formulated gels of Domperidone had a different release profile of the drug, and it was dependent on the concentration of the polymers.

The release profiles of formulations F4 and F3 were highest and lowest (9.9 µg /ml and 1.3 µg /ml) respectively. It was observed that Domperidone was released from the gels in a sustained release manner. The formulation variables such as concentration of polymer affects rate and extent of drug release, which is due to increase in density of polymer and also increase in dissolution path length that the drug molecule has to travel. It was also revealed that the release of drug from gels was directly proportional to the concentration of polymers [16, 17]. The developed Domperidone in situ nasal gel formulation showed a more than 11 µg /ml permeation of drug in 6 hrs. through the epithelium membrane. Thus, release of Domperidone from gels may be achieved as a desirable property for formulation, treating conditions involving vomiting and migraine. Our result showed higher value in comparison with a study that was done by [18]. This amount is somehow more than the amount released by the same gel in vitro using cellulose bag as a membrane barrier. This may be due to structural differences that exist in vivo and in vitro. This advantage allowed the pharmacological effect over an extended period and the amount was satisfactory and enough to suit good bioavailability of the formulation when used as nasal gel [19, 20].

Moreover, Kolliphor P 407 is triblock copolymer of POE-PPO-POE, and its solution is viscous and can be easily injected. As the temperature increases, dehydration of PPO blocks causes formation of micelle leading to formation of a gel by achieving gelatinization at body temperature. Kolliphor P 407, 20% alone cannot retain the formed gel and maintain in situ formed gel, so addition of HPMC, CMC, and Carbopol to achieve adequate gel strength and stay at the site of application was required. It was observed that F4 (2% CMC & 1% Carbopol) had a good release and was maintained for six hours. The new drug delivery techniques serve as an alternative to oral antiemetic drug administration for emesis induced by chemotherapy and can be used as an alternative method for local delivery system. [21]. The nasal route offers fast and high drug absorption, with improved patient compliance. This local delivery system is anticipated to achieve good patient compliance and improve clinical outcomes as the gel formulation is applied directly to the site of action in the form of solution which upon contact forms a gel [22].

5. Conclusion

Local nasal system as an alternative route for antiemetic drug delivery provides a needle-free, non- invasive method of targeting the brain by passing the BBB and avoiding hepatic first-pass metabolism in delivering the drug to the brain. Nasal gel formation is the best formulation for anti-emetic drug, Domperidone. Hence such drug delivery form could lessen the total number of injections throughout the drug chemotherapy duration. Although epithelial tissue from the goat animal is widely applicable for evaluation of formulation, however, in vivo tests by using volunteers are required to confirm the result. We assume this work will simply add

a new dimension to more modern drug delivery systems, which is nasal gel delivery systems. Domperidone tablet or injection can be replaced with a nasal gel which can provide good absorption.

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