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Sustained Release Suppositories of Metoclopramide HCl: Formulation and *In vitro* Evaluation

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ABSTRACT

The aim of this study was to prepare sustained release suppositories containing metoclopramide HCl, an antiemetic drug for rectal administration. The effect of the water swellable polymer, hydroxylpropylmethyl cellulose (HPMC) and the anionic polymer, xanthan gum on In vitro release of metoclopramide HCl from suppositories was studied. Metoclopramide HCl sustained release suppositories were formulated with the different ratios of release modifier by fusion method. A combination of 1:3 PEG400: PEG4000 was used as hydrophilic suppository base. Weight variation, drug content, hardness (fracture point), disintegration time, friability, melting time and In vitro release experiments were conducted on the prepared formulations. The results indicated that HPMC could sustain drug release more effectively than xanthan gum. Least metoclopramide HCl release rate was shown by suppositories containing 20% HPMC (F7). However, the results of investigation clearly suggest that sustained release suppositories containing 10% HPMC (F6) or 20% xanthan gum (F4) were found more suitable for rectal drug delivery system of metoclopramide HCl and can be successfully designed to achieve suitable sustained delivery of metoclopramide HCl for particular clinical conditions. F4 and F6 showed non-Fickian mechanism and zero order kinetics.

Keywords: Metoclopramide HCl; Xanthan gum; HPMC; Sustained release suppository; Zero order release

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INTRODUCTION

Metoclopramide HCl is a potent and popular antiemetic drug, effective in the treatment of nausea and vomiting induced by drugs, migration and radiation sickness [1]. In long term therapy, it is used for emesis caused due to chemotherapy in cancer patient. Metoclopramide HCl apparently antagonizes dopamine at the Dopamine (D2) receptor sites. This action can explain its extra-pyramidal symptoms when administered in conventional dosage forms [2]. The most commonly reported adverse events with metoclopramide HCl are restlessness, drowsiness, dizziness, diarrhea or constipation, trismus, a bulbar type of speech and breast engorgement [3]. Metoclopramide HCl is rapidly absorbed and eliminated after oral administration. It is usually administered in a dose of 10 to 20 mg four times daily in order to maintain effective concentrations throughout the day. In long term therapy**,** fluctuation in the plasma concentration, with high concentration peaks are common for drugs with rapid absorption and elimination when administered in conventional immediate release dosage forms. The secondary effects of metoclopramide HCl on the central nervous system are in the form of extrapyramidal symptoms, if plasma levels markedly exceed therapeutic levels. Such characteristics make metoclopramide HCl as best suitable drug candidates for controlled drug delivery. The short half-life of metoclopramide HCl (5 ± 1h) also suggests that it is a suitable candidate for sustained drug delivery [3-5]. The patient's compatibility can be improved if drug administered in controlled release dosage form. Furthermore, sustained release dosage forms have the advantages of decreasing side effects, reducing in dosing frequency, reducing fluctuations in circulating drug levels and achieving a prolonged

therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug [6,7].

Conventional oral dosage forms (tablets and capsules) suffer from some drawbacks such as its nonsuitability when quick onset of action is required. In addition, many patients find it difficult to swallow solid dosage forms and thus not comply with prescription that results in high incidence of non-compliance and ineffective therapy. The problem of swallowing is also evident in pediatrics, psychiatric as, elderly patients well as patients who may not have ready access to water.

The oral bioavailability of metoclopramide HCl is highly variable showing values between 32 and 98% as it undergoes variable first-pass metabolism [1,8]. Further, oral forms of metoclopramide HCl often get vomited before systemic absorption compelling parenteral administration which results in low patient compliance. In these conditions, the rectal delivery seems to be an attractive alternative. The rectal route for drug administration was proven to be advantageous over other routes because of the reduced side effects such as gastrointestinal irritation and the avoidance of pH conditions, gastrointestinal enzymes, disagreeable taste and first pass effect [9-13]. A conventional suppository is a medicated solid dosage form which melts or softens at body temperature in the rectum. They are used to deliver drugs either for systemic or local effects and thus offer an alternate form of oral medication, which provide patients with a more convenient means of taking their medication as they overcome the problems associated with oral route [14-16]. Suppository is a new approach for the successful development of sustained release formulation along with many features to provide a way of successful drug delivery system. In the literature, there are several attempts to formulate sustained release suppository dosage forms for many drugs [17-21]. The nature of the suppository base, the use of additives and the solubility of the drug in the suppository base play a crucial role in the absorption of drugs from suppositories. Therefore, there is a need to optimize formulation factors which depend on the drug itself, suppository base and the presence of an adjuvant in the formulation of drug as suppository [22].

The aim of this study was to formulate and evaluate sustained release suppositories for metoclopramide HCl. HPMC or Xanthan gum at various concentrations was used as release modifier for metoclopramide HCl from suppositories made from 1:3 PEG400: PEG4000 base. Suppositories were tested in order to determine weight variation, hardness, friability, drug content uniformity and the release characteristics of metoclopramide HCl from suppositories. The developed sustained release suppositories could reduce drug dosing, enhance the bioavailability and lead to the convenient therapeutic effects with less risk.

EXPERIMENTAL SECTION

Materials

Metoclopramide HCl and hydroxypropyl methylcellulose (HPMC, 400cP) were kindly supplied as a gift by Shaphaco Pharmaceutical Industries, Sana'a, Yemen. Xanthan gum was procured as a gift sample from Pharmacare International Manufacturing CO, Sana'a, Yemen. Polyethylene glycol 4000 (ScharLab, Spain) and Polyethylene glycol 400 (HiMedia, Mumbai, India) were also used in this work. All the other chemicals used were of high analytical grade.

Methods

Preparation of sustained release suppositories:

Conventional and sustained release suppositories composed of metoclopramide HCl were prepared by fusion process in a metallic suppository mold. A total of seven different suppository formulations were prepared using a mixture of PEG 400 and PEG 4000 base at a ratio of 1:3. It should be mentioned here that formulation 1 (F1) did not contain release modifier. The three formulations (F2, F3 and F4) were prepared using xanthan gum as release modifier and the others were prepared using HPMC. The base was fused at 60°C and then metoclopramide HCl and release modifier were added to the melted base and dissolved or dispersed by stirring. The release modifier was added to the base in three different ratios, of 1, 10 and 20%. They were poured into the metallic suppository mold and allowed to solidify at room temperature. Each suppository was formulated to contain 20 mg of metoclopramide HCl. Code and compositions of the prepared formulations are given in Table 1.

Table 1: Code and composition of metoclopramide HCl sustained release suppositories

Formulation No.	Composition of each suppository calculated as percentages of total weight (%)*		
	Suppository base	Xanthan gum	HPMC
F1	100	-	-
F2	99	1	
F3	95	10	
F4	90	20	
F5	99		1
F6	95		10
F7	90		20

*Metoclopramide HCl amount was fixed as 20 mg in each suppository

Weight Variation

The weight variation test was determined according to the British Pharmacopoeia. Twenty suppositories were selected randomly from each batch and weighed individually and also the average weight and the percentage deviation values were calculated. There must be not more than 2 suppositories differ from the average weight by more than 5% and no suppository differs from the average weight by more than 10% [23].

Drug Content

Content uniformity of suppositories was determined by spectrophotometric method. Five suppositories of each formulation were individually melted and dissolved in 250 ml phosphate buffer (pH 7.4). The solution was filtered through doubled layer Whatman filter paper followed by 0.45 µm disc filter. The content of drug was determined using a UV/Visible spectrophotometer by measuring absorbance of the diluted sample at 272 nm. Concentrations were determined using standard calibration curve equations.

Hardness Test (Fracture point)

The hardness test was carried out to evaluate the ability of suppositories to withstand the hazards of packing and transportation. The hardness of three suppositories from each batch was determined using Monsanto hardness tester and the weight required for suppository to collapse was recorded in kilograms [24,25].

Friability

Twenty suppositories of each formulation were weighed and placed in the rotating plastic chamber of Roches Fribilator. The chamber was then rotated for 4 minutes at 25 rpm. After 100 revolutions suppositories were removed and weighed again. A loss of less than 1% in weight is generally considered acceptable [25,26]. Percent friability (% F) was calculated as follows:

$$\% \text{ F } = \frac{\text{Loss in weight (Initial weight} - \text{ Final weight)}}{\text{Initial weight } \times 100}$$

Melting Point Estimation

Melting point is a measure of the time taken for the entire suppository to melt or disperse when immersed in a water bath maintained at 37 ± 1^{o}C [24,27].

Disintegration Time Test

The disintegration time is a critical factor in the determination of the release rate of the active ingredient(s) from the suppository. The disintegration times were recorded utilizing USP tablet disintegration apparatus (Electrolab ED-2L) [28]. Randomly six suppositories were selected from each batch for disintegration test. The suppository was completely immersed in a water bath maintained at constant temperature (37 ± 1°C) and the time taken for the suppository to melt or disperse in phosphate buffer pH 7.4 was recorded.

***In vitro* Drug Release Tests**

In vitro release test was carried out according to the USP XXII basket method [21,29]. The USP rotating basket dissolution apparatus (Pharma-test, Germany) was used for the determination of release rates of metoclopramide HCl from the various suppositories. Each suppository was placed in basket and lowered into a flask containing 900 ml of phosphate buffer solution (pH 7.4). The basket was rotated at 50 rpm at a constant temperature 37^{o}C ± 0.5^{o}C. Aliquots of 5 ml were withdrawn at appropriate time intervals for a period of 5 h and immediately replaced by 5 ml fresh phosphate buffer.

The amount of drug released in the time course from suppositories was spectrophotometrically determined after a suitable dilution with phosphate buffer at 272 nm. For each formulation, the experiments were carried out in triplicate.

Drug Release Kinetics

Data obtained from *In vitro* drug release studies were fitted to various kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas to predict the drug release mechanism [30-34]. The release rate constants (k), release exponent (n), and determination coefficients (R^2) were calculated by means of a computer program (Microsoft Excel, 2007 version).

Statistical Analysis

The data were expressed as mean ± standard deviation (sd). For comparisons a one way analysis of variance was applied. The difference was considered as significant when $P<0.05$.

RESULTS AND DISCUSSION

Physicochemical Properties

The combination of 1:3 PEG 400: PEG 4000 was found out to give suppositories with satisfactory physicochemical properties as discussed in a previous paper [35]. Different from lipophilic bases, the drug is released from PEG system as a consequence of the progressive dissolution of PEG into the dissolution medium [22]. Therefore, the suppository base composed of 1:3 PEG 400: PEG 4000 was selected and used in all metoclopramide HCl sustained release suppositories. The physicochemical characteristics of suppositories were determined according to the methods described. The results are listed in Table 2. The suppositories were found to be in accordance with BP (British pharmacopoeia) requirements for weight uniformity with standard deviation less than 5% [20]. The results revealed that the average weight for all the suppositories ranged from 0.91 to 1.32 g. The percent drug content was found to be in the range of 85.6 to 101.3%, indicating that metoclopramide HCl contents were homogeneous for all suppositories.

Table 2: Physical and chemical characterization of metoclopramide HCl sustained release suppositories

Code	Weight variation (gm) ± sd	% Metoclopramide HCl content ± sd	Hardness (kg) ± sd	Friability	Melting time (min) ± sd	Disintegration time (min)
F1	1.01 ± 0.04	91.3 ± 1.20	2.7 ± 0.25	0.46 ± 0.05	53 ± 0.08	25 ± 0.30
F2	0.94 ± 0.02	93. 4 ± 0.23	2.8 ± 0.10	0.34 ± 0.12	59± 0.37	22 ± 0.52
F3	1.32 ± 0.54	101.3 ± 0.72	3.4 ± 0.54	0.37 ± 0.32	66 ± 0.22	28 ± 0.34
F4	1.12 ± 0.08	86.2 ± 1.32	4.1 ± 0.23	0.51 ± 0.11	74± 0.55	37 ± 0.70
F5	0.91 ± 0.30	97.4 ± 2.03	2.5 ± 0.04	0.46 ± 0.09	67± 0.43	24 ± 0.81
F6	0.93 ± 0.02	99.0 ±0.10	3.7 ± 0.09	0.41 ± 0.23	71 ± 0.04	32 ± 0.42
F7	1.12 ± 0.56	85.6 ± 0.22	4.4 ± 0.27	0.50 ± 0.61	86± 0 02.	46 ± 0.08

sd: standard deviation

The fracture point (hardness) values indicated that all the prepared suppositories exhibited an acceptable degree of hardness ranging between 2.5 to 4.4 kg which proves sufficient mechanical strength to ensure the structural rigidity during storage or transportation processes. The conventional suppositories were found to have lower fracture points than those of the others. On the other hand, as the concentration of release modifier increases, the hardness increases. The friability was found to be within acceptable limits (less than 1%).

The melting time and disintegration time values are important parameters to be determined as they play an important role in the disintegration and availability of the drug for absorption from the rectal route. The melting time of all the formulations was found in the range of 53 to 86 min. The conventional formulation showed lower melting time (53 min) than those containing the release modifier. The melting time was found to be highest for F7 formulation owing to its high HPMC content and its hard nature.

According to BP the disintegration time of each suppository should be less than 60 min for hydrophilic suppository. Disintegration time of all formulations was found to be within limit as ranged from 22 to 46 min. F4 and F7 showed delayed disintegration because of its hard nature and disintegrated around 37, 46 min, respectively. It is also observed that the samples containing HPMC disintegrate in a time longer than those of the formulations which contain xanthan gum as inert matrix material. The implications of these factors on drug release will be discussed later.

In vitro Release Studies

In vitro release tests were conducted on both conventional and sustained-release suppository formulations as shown in Figure 1. Metoclopramide HCl was completely released within 2 h from conventional suppository (F1). The fast drug dissolution from F1 was due to the high hydrophilicity and solubility of both PEG bases and drug. The amounts of metoclopramide HCl released from F2 and F5 coded formulations in which the release modifier is 1%, are very close to that of conventional suppository (F1) and did not show any significant effect ($p>0.05$). Therefore, 1% of release modifier is not suitable for sustained-release suppository formulations.

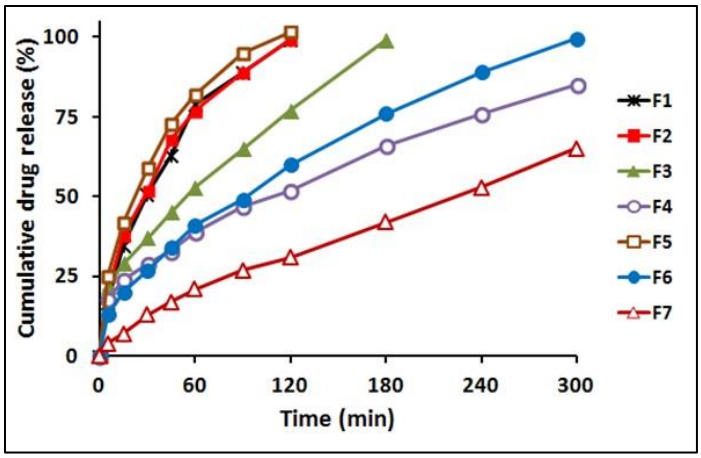

Figure 1: The *In vitro* release profiles of metoclopramide HCl suppositories

It was observed that with increase in the polymer concentration the drug release rate was found to be decreased. The dissolution of the drug was 99.04% after 3 h from F3 (10% xanthan gum) and about 85.04% from F4 (20% xanthan gum) after 5 h. While dissolution of the drug from F6 (10% HPMC), and F7 (20% HPMC) was about 99.42% and 65.04% after 5 h respectively. Least metoclopramide HCl release rate was shown by suppositories containing 20% HPMC (F7) as about 65.04% metoclopramide HCl was released in 5 hours. In the rectum where only 3-5 ml of rectal fluid exists, it is expected that the release from F7 will be highly minimized. So 20% HPMC (F7) seems to be not suitable for sustained release of metoclopramide HCl. On the other hand, the formulations F4 and F6 both could give metoclopramide HCl suppositories with reasonable sustained release profiles. They have also high disintegration time and fracture point. Also it was found that the% drug release show no significantly differences ($P>0.05$) in the dissolution rate of metoclopramide HCl from F4 and F5 but there is slightly decrease in release rate of drug of F4 as show in Figure 1. The previous results could be due to gel generating properties exhibited by the release modifiers [36,37]. Gel formation with generating the viscous environment from polymer hydration could modulate the amount and penetration rate of the medium and also the drug diffusion into the test medium which apparently sustained the drug release. However, at low concentration (1%), the release modifier did not clearly demonstrate this behavior owing to its too minimal interconnected polymer network to form the sufficient strong viscous gel, where at high concentrations (10-20%) the viscosity of the matrix might markedly increase forming network structure and the drug diffusion is hindered.

On the other hand, the results indicated that formulations prepared using HPMC showed prolonged release profiles more than xanthan gum. Phaechamud et al. studied the influence of dissolution medium on the role of xanthan gum in controlling drug release from propranol HCl suppositories [38]. The results indicated that drug release was slower in distilled water than in phosphate buffer pH 7.4. This was explained by the freely hydration of xanthan gum, an anionic polymer, in distilled water resulted in higher gel formation which effectively retarded the drug release. Whereas the anionic ions from phosphate buffer could suppress the polymer hydration and decrease the viscous gel formation resulted in lower efficacy to control the drug release from suppository. HPMC, a water swellable polymer, has an inert matrix structure and hence forms cage on the surface of the suppositories, thus preventing release of drug from the suppository to the aqueous medium [39]. Further, the mucoadhesion properties of HPMC also give the formulation prolonged retention time by adhering to rectal mucosa.

Drug Release Kinetics

Table 3 summarizes the kinetic analysis of metoclopramide HCl release data according to zero, first order kinetics and Higuchi model. The release of metoclopramide HCl from conventional suppository (F1) and suppositories containing 1% release modifier either xanthan gum or HPMC showed the best fitting linear relations with the

highest correlation coefficients with the Higuchi diffusion equation, while suppositories containing 10-20% release modifier obeyed zero and Higuchi order release model i.e. showing both the non-Fickian diffusion and dissolution rate dependent upon drug concentration.

Table 3: Release kinetics of metoclopramide HCl from suppositories

Parameter		F1	F2	F3	F4	F5	F6	F7
Zero order	R^2	0.89	0.88	0.99	0.98	0.88	0.97	0.99
	K_0	0.78	0.76	0.44	0.22	0.97	0.29	0.2
First order	R^2	0.92	0.92	0.88	0.86	0.99	0.93	0.95
	K_1	0.03	0.03	0.01	0	0.03	0	0
Higuchi model	R^2	0.99	0.99	0.99	0.93	0.99	0.99	0.98
	K_H	1.9	1.86	1.3	0.76	2.04	1.06	0.55
Korsmeyer-Peppas	R^2	0.99	0.99	0.97	0.97	0.99	0.99	0.98
	K	0.07	0.09	0.11	0.1	0.12	0.06	0.02
	n	0.56	0.51	0.37	0.32	0.47	0.48	0.61

R^2: Determination coefficient. k: Release rate constant for respective models

The dissolution data obtained were subsequently analyzed according to Korsmeyer-Peppas model. Obtained results showed that the release rates of all above formulations were best described with Peppas model (R^2> 0.96). The value of n indicates the drug release mechanism from the nonswellable and swellable devices and the value of n= 0.43 indicates Fickian diffusion. Values of 0.43< n <1.0 indicate anomalous non-Fickian transport, whereas value of n= 1.0 indicates case II or zero-order release [40]. It is clear from the n values shown in Table 3 that all formulations except F3 and F4 exhibited a non-Fickian diffusion mechanism. This type of diffusion contains Fickian and relaxation or gelation properties together i.e., the polymer here swells and then diffusion occurs. n value was 0.37 and 0.32 for F3 and F4 respectively, which is below 0.43 indicating diffusion mechanism.This may be explained by the reduction of xanthan gum hydration in the phosphate buffer media as showed by Phaechamud et al. [38].

CONCLUSION

The investigation was carried out by the addition of variable percentage (1, 10 and 20%) of either HPMC or xanthan gum in 1:3 PEG400: PEG4000 based suppositories of metoclopramide HCl. It can be concluded that physical properties and dissolution profiles of the prepared suppositories are influenced considerably by the type and concentration of the release modifier employed. HPMC can be more useful for sustained release suppositories than xanthan gum. HPMC had a more profound effect on release rate of metoclopramide HCl than that of xanthan gum. However, F4 (20% xanthan gum) and F6 (10% HPMC) coded formulations appear to be suitable for development of a rectal drug delivery preparation for metoclopramide HCl offering reasonable sustained release profiles and can be optional as an alternative way to conventional dosage forms to provide more suitable therapy. This will ensure minimum fluctuations in the plasma drug concentration and reduced dosing frequency which will result into improved patient compliance.

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