Preparation and *In vitro* Evaluation of Paracetamol and Metoclopramide HCl Double-layered Suppositories for Migraine Treatment

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Abstract: The combination of paracetamol and metoclopramide HCl is commonly used to manage the symptoms of migraine. The aim of the present study was to prepare a double-layered suppository of paracetamol and metoclopramide HCl to increase the efficacy of the two drugs in combination for the effective treatment of migraine headaches, nausea and vomiting. Rectal double-layered suppositories containing 250 mg paracetamol in the first layer and 15 mg metoclopramide HCl in the second layer were prepared by the fusion method using cocoa butter, witepsol W35, different grades of polyethylene glycol (400, 4000, and 6000). Weight variation, drug content, friability, mechanical strength (hardness) and melting time of the formulations were determined. *In vitro* release test was carried out using USP type 1 rotating basket apparatus using phosphate buffer pH 7.4 as dissolution media. For paracetamol, the best release profile was obtained with suppositories prepared from the combination of PEG 400 and PEG 4000 with 94.3% of the drug released in 60 minutes. On another hand, the best metoclopramide HCl release profile was obtained with suppositories prepared using fatty bases prepared from witepsol W35 and cocoa butter with the release of 90.2% and 71.0% of the drug content respectively in 30 minutes. Based on the obtained results, it was concluded that, 1:3 PEG 400: PEG4000 that was used in formula F5, was selected as the base of choice for double-layered suppository since it exhibited optimum physical properties with a reasonable release profile for both drugs. Analysis of the release data of paracetamol proved that the release from all PEG bases followed first order release model, while fatty bases obeyed Higuchi model. The release data of metoclopramide HCl showed that for PEGs based suppositories, the release profile were best explained by Higuchi model, but for fatty bases, the release profile found to follow first order kinetics. It was found that most formulions exhibited n values between 0.5 - 1 indicating anomalous (non-Fickian) release mechanism.
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1. Introduction

Migraine is one of the most frequent disabling neurological conditions encountered in primary practice with a prevalence of 8% in males and 12–15% in females (***Evers et al, 2009***). Migraine is thought to be caused by the widening of certain blood vessels in the brain. It is characterized by recurrent attacks of pulsatile, unilateral headache often accompanied by nausea and vomiting (***Diener et al, 2008***). The oral combination of paracetamol and metoclopramide HCl is commonly used to treat the symptoms of migraine (***Kumar et al, 2014***). The combination therapy has various advantages over monotherapy such as reducing the number of prescriptions and the attendant administrative costs, improving patient compliance and minimizing the dose dependent side effects (***Abebe et al, 2014; Malathi and Khan, 2012***).

Though the oral route is the most common and the easiest way to administer a drug, it suffer from some drawbacks such as its nonsuitability when quick onset of action is required. Further, many patients find it difficult to swallow solid dosage forms such as tablets and capsules resulting in high incidence of non-compliance and ineffective therapy. 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 (***Jannin et al, 2014; Tukker, 2009; Samy et al, 2000; Ryu et al, 1999***). A conventional suppository is a medicated solid dosage form which melts or softens at body temperature. They offer an alternate form of oral medication for systemic action in patients who are in coma or who cannot tolerate oral medication due to periodical episodes of nausea and vomiting or pathological conditions of gastrointestinal tract (***Taha et al, 2004; Gupta, 2007; Noordin et al, 2014; Hermann, 1995***). Double-layered suppository is an improved approach for the successful development of a drug delivery system for the sequential release of two drugs in combination and to separate two incompatible drugs (***Realdon et al, 1997; Yahagi et al, 1999; Marsovna et al, 2015; Chicco et al, 1999***).

Paracetamol is the mostly wide accepted and extensively used common analgesic due to its low toxicity and high therapeutic index. It is used for temporary relief from pain such as headache. It is well absorbed from alimentary tract and on oral ingestion approximately 90 to 95% of a dose is metabolized in liver primarily by conjugation with glucoronic acid (***Basavaraj and Nanjundaswamy, 2005***). Rectal route may present an ideal route of administration of paracetamol as it undergoes firs pass metabolism on oral ingestion. The drug absorbed from the rectum largely bypasses presystemic metabolism as the blood perfusing the rectum (interior and middle hemorrhoidal veins) is not delivered directly into the liver rather than into the systemic circulation (***Gupta, 2007***).

Metoclopramide HCl, a centrally acting anti-emetic drug is used to control nausea and vomiting caused by migraine. In addition to its direct anti-emetic effect, metoclopramide HCl also stimulates gastric emptying, which is often delayed during migraine attacks. However the oral bioavailability of metoclopramide HCl is highly variable showing values between 32% and 98% due to extensive presystemic metabolism (***Shiyani et al, 2008; Neha, 2015; Dollary, 1999***). Further, oral forms of metoclopramide HCl often get vomited before systemic absorption compelling other routes of administrations such as parenteral administration where result in low patient compliance. In these conditions, the rectal delivery seems to be an attractive alternative. Therefore, the main objective of present study is the development and *In vitro* evaluation of double-layered suppositories containing paracetamol and metoclopramide HCl as bimodal release system to manage pain, nausea and vomiting associated with migraine. Double-layered suppositories are prepared by fusion method using different bases like, cocoa butter, witepsol W35, PEG 400, PEG 4000 and PEG 6000. The developed double-layered suppositories could reduce drug dosing, enhance the bioavailability, avoid problems associated with oral route and lead to convenient therapeutic effects.

2. Materials and Methods

Materials

Paracetamol, metoclopramide HCl and witepsol W35 were kindly supplied as a gift by Shaphaco Pharmaceutical Industries, Sana'a, Yemen. Polyethylene glycol 400 (HiMedia, Mumbai, India), cocoa butter (B.P. grade), Polyethylene glycol 4000 (ScharLab, Spain) and PEG 6000 (Merck, Darmstadt, Germany) were also used in this work. All the other chemicals used were of high analytical grade.

Methods

Preparation of double-layered suppositories:

Double-layered suppositories each containing 250 mg of paracetamol in the first layer and 15 mg of metoclopramide HCl in the second layer were prepared by the fusion method. Calculated amount of suppository base or base mixtures was accurately weighed and melted on a water bath. Then for first layer preparation, paracetamol powder was incorporated into the melted base along with continuous stirring. Mixing was continued until a homogeneous mass was produced. The determined volume of melted mass was poured into the appropriate suppository metal mould (1 g capacity) and allowed to cool at room temperature to produce the first layer with 250 mg of paracetamol. The second layer was prepared by the same method and the determined volume of melted mass containing metoclopramide HCl was poured into the same mould above the first layer and cooling them again to room temperature to produce the second layer with 15 mg of metoclopramide HCl. Double-layered suppositories were weighed and kept at room temperature for 24h after removal from the mould to allow for uniform solidification. After solidification at room temperature the prepared suppositories were packed in tightly closed containers and placed in a refrigerator at 4 ^{o}C to avoid the development of cracking. Before use, the suppositories were left for 2 hours at room temperature. Code and composition of the prepared formulations are given in Table 1.

Table 1. Code and composition of the double-layered suppositories

Composition*	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Cocoa butter	√					
Witepsol W35		√				
PEG 4000			√			
PEG 6000				√		
1:3 PEG 400 – PEG 4000					√	
1:3 PEG 400 – PEG 6000						√

* The first layer contains 250 mg of paracetamol and the second layer contains 15 mg of metoclopramide HCl.

Weight variation:

The weight variation test was determined according to the British Pharmacopoeia. Twenty suppositories for each formulation were weighed and average weight was calculated. Each suppository was weighed individually on electronic balance. 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 % (***British Pharmacopoeia, 1998***).

Drug Content

Five suppositories of each formulation were cut into small pieces and an appropriate mass was placed into a 250 mL volumetric flask. Phosphate buffer (pH 7.4) was added up to the mark and the volumetric flask was heated slightly to melt the suppository. The suppository was then allowed to cool. 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 245nm for paracetamol and 272 nm for metoclopramide HCl. Concentrations were determined using standard calibration curve equations.

Mechanical Strength (hardness)

The mechanical strength was determined to measure the ability of suppositories to withstand the hazards of packing and transportation. This can be performed by taking suppositories randomly and subjected for crushing using Monsanto hardness tester and the weight required for suppository to collapse was recorded in kilograms (***Allen, 2008; Sankar et al, 2012***). All determinations were done in triplicate.

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 (***Sankar et al, 2012; Varshney and Chatterjee, 2012***). Percent friability (% F) was calculated as follows:

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

Melting time estimation

Macro melting range test was performed with the whole suppository. A suppository from each formulation was placed in a test glass tube (2.5 cm in diameter) with 2 ml of phosphate buffer (pH 7.4), and then the tube was placed in a water bath maintained at constant temperature 37 ± 0.5 ^{o}C. The time required by the whole suppository to melt or disperse in the media was noted (***Allen, 2008; Ranjita and Kamalinder, 2010***).

In vitro drug release tests

Many research groups examined different *In vitro* dissolution techniques for determination of the dissolution rate of drug substances from suppositories. In the present study, *In vitro* release test was carried out using USP type1 rotating basket apparatus (Pharma-test, Germany) (***Zawar and Bhandari, 2012; Hammouda et al, 1993***). 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 2 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 (paracetamol at 245 nm and metoclopramide HCl at 272 nm). For each formulation, the experiments were carried out in triplicate.

Drug Release Kinetics

To study the release kinetics, data obtained from all double-layered suppositories formulations were applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas (***Ertan et al, 2000; Jain et al, 2010; Cobby et al, 1974; Suzuki and Higuchi, 1970; Peppas 1985***). 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). Analysis of variance (ANOVA) was used to test the statistical significance of differences among groups. Statistically significant difference was set at $p < 0.05$.

3. Results and Discussion

Physical and chemical evaluation of the double-layered suppositories

The results of various evaluation parameters are shown in Table 2. Results indicate that all formulations show acceptable physical characteristic regarding uniformity of weight, drug content, mechanical strength, friability and melting time.

The average suppository weight was ranged between 1 and 1.3 g. The weight variation and drug content uniformity of the prepared suppositories were found to comply with the British Pharmacopoeia requirements (***British Pharmacopoeia, 1998***). None of the individual weights deviating from the average by more than 5%. The percentage contents of paracetamol was ranged from 88.3% to 103.0%; while the percentage contents of metoclopramide HCl was ranged from 89.2% to 99.7% which complied with the limits established in the pharmacopoeia.

Table 2. Physical and chemical characterization of the formulated double-layered suppositories

Formula No.	Weight variation (gm) ± sd	% Paracetamol content ± sd	% Metoclopramide HCl content ± sd	Hardness (kg) ± sd	Melting time (min) ± sd	Friability
F1	1.1 ± 0.13	88.3 ± 1.10	99.1 ± 2.20	0.9 ± 0.18	8 ± 0.22	0.35 ± 0.02
F2	1.2 ± 0.32	91. 5 ± 0.45	99.7± 1.22	1.7 ± 0.10	13 ± 0.43	0.50 ± 0.04
F3	1.1 ± 0.24	97. 2 ± 1.81	89.2 ± 0.74	3.1 ± 0.21	28 ± 0.25	0.39 ± 0.05
F4	1.3 ± 0.09	99.8 ± 2.31	91.8 ± 1.52	4.0 ± 0.09	33 ± 0.65	0.48 ± 0.05
F5	1.0 ± 0.04	103.0 ± 1.14	92.1 ± 2.07	2.5 ± 0.13	23 ± 0.37	0.54 ± 0.06
F6	1.2 ± 0.26	102.4 ± 1.06	94. 9 ± 0.09	3.4 ± 0.18	29 ± 0.46	0.44 ± 0.03

The prepared double-layered suppositories exhibited a reasonable degree of hardness ranging between 0.9 and 4.0 kg which proves sufficient mechanical strength for handling and transportation. However, F1 prepared using cocoa butter was found to have the lowest mechanical strength. The hardness of PEG 6000 based suppositories was found to be more than those of the others. Mechanical strength was highly dependent on the melting point of the base. The hardness of the water-soluble base was found to be higher than that for fatty bases, that may duo to the low melting point of the fatty bases while PEG bases has higher melting point but their water soluble properties made them easy to dissolve in the body's fluids (***Kesur et al, 2012***). The friability was found to be within acceptable limits (less than 1 %). The melting time was varied largely, depending on the properties of the suppository base. The melting time for water soluble bases (PEGs) was longer compared to that of fatty bases (cocoa butter and witepsol W35). The melting of suppositories prepared using fatty basesoccurring within 13 minutes. However, in case of PEG bases, it was greater than 23 minutes. The melting and hardness of polyethylene glycols increase as a function of increasing of polymerization of polymer used, that increase with increasing the molecular weight used (***Hashizume et al, 1992***). The appropriate melting properties of a suppository ensures its handling and release of drug after administration in the rectum (***Yahagi et al, 1999***).

In vitro release studies

The *In vitro* release behaviour of paracetamol from varying double-layered suppositories in phosphate buffer pH 7.4 is shown in Figure 1. Percentage cumulative drug releases were found to be 61.4% (F1), 70.3% (F2), 94.0% (F3), 81.7% (F4), 101.2% (F5) and 86.5% (F6) respectively at the end of 120 minutes.

These results indicate that the PEGs released paracetamol to a greater extent than from suppositories prepared using fatty basesand the blend of PEG 400 and PEG 4000 (F5) evidently exhibited the best release characteristics, with 94.3% of the drug released in 60 minutes. The smallest amount of paracetamol was released from formulations prepared from cocoa butter (F1) followed by formulations prepared from witepsol W35 with 42.0% and 51.2% of the drug released in 60 minutes, respectively. Also the results show no significant difference ($p>0.05$) in releasing rate of paracetamol for F1 and F2.

The lower incidence of drug release from fatty bases shows that paracetamol may have a higher affinity for fatty bases than the dissolution medium, also the insoluble nature of the fatty bases increases the dispersion time of the suppositories and drug release time period (***Chicco et al, 1999***). PEG bases which are hydrophilic, easily soluble in aqueous medium and disperses rapidly facilitate penetration of the dissolution medium into the base and has higher rate of release. Also, the enhancement of the dissolution may be due to enhanced solubility of the paracetamol by water-soluble bases as PEG bases have good hydrophilic property and solubilizing effect (***Rcadon and Ragazzi, 2001***).

It is evident from the results that the addition of a low molecular weight polyethylene glycol PEG 400 to high molecular weight polyethylene glycols PEG 4000 (F5) and PEG 6000 (F6) appears to have a significant effect ($p<0.05$) on the release of paracetamol as the amount of drug released was increased to 101.2% (F5) and 86.5% (F6) respectively at the end of 120 minutes. The release is enhanced in one hand by the decreasing of hardness and melting time values and on the other hand, by the solubilizing effect of PEG 400 on the drug (***Rcadon and Ragazzi, 2001***).

Release data of metoclopramide HCl from deferent suppository bases is graphically illustrated in Figure 2. Percentage cumulative drug releases were found to be 98.4% (F1), 99.6% (F2), 67.3% (F3), 74.7% (F4), 99.1% (F5) and 79.6% (F6) respectively at the end of 120 minutes. The data revealed that drug release was more superior from fatty bases. The maximum drug released in 30 minutes was for F2 and F1 as the amount of drug released was 90.2% and 71.0% respectively. On another hand, only between 22.6% to 49.8% of metoclopramide HCl was released in 30 minutes for the other formulations. This result show that there is a significant increase ($p<0.05$) of metoclopramide HCl release from fatty bases suppositories which prepared either from cocoa butter (F1) or witepsol W35 (F2) when compared with the remainder formulations prepared from PEG_S bases.

This may be attributed to the rapid melting of suppositories prepared using fatty baseswhich allowed the rapid release of drug. The poor metoclopramide HCl release from PEG 4000 (F3) and PEG 6000 (F4) suppositories can be attributed to their high melting times leading to unmelted or partially melted base. The lowest amount of drug released was observed in case of PEG 6000 (F4), which exhibited the highest hardness and melting time values (Table 2).

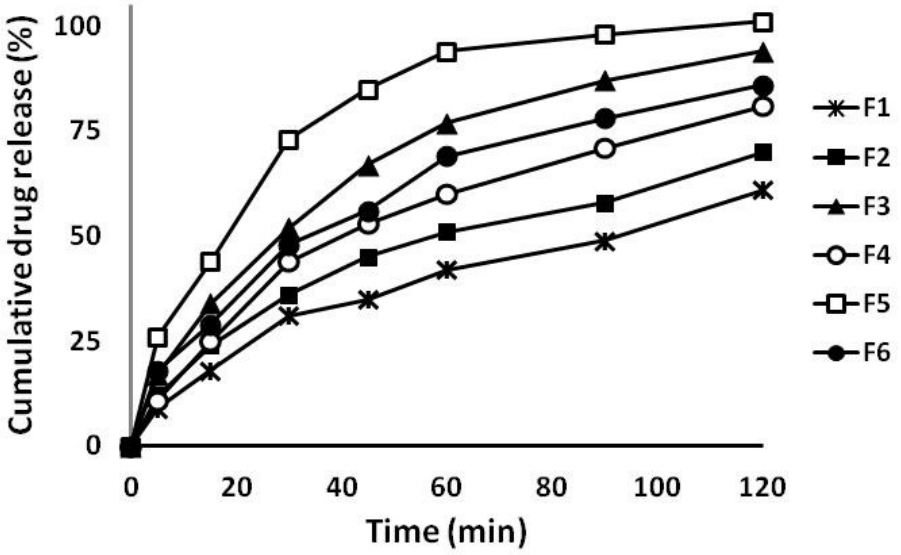

Figure 1. The *In vitro* release profiles of paracetamol from double-layered suppositories

The addition of PEG 400 to the high molecular weight PEGs lead to decrease hardness and melting time and significantly enhance ($p<0.05$) metoclopramide HCl dissolution. The amount of drug released from formulation (F5) was 99.1% at the end of 120 minutes which is similar to suppositories prepared using fatty bases. The results showed that the complete melting of a suppository in a dissolution vessel is required for metoclopramide HCl to have the potential to be released completely during *In vitro* testing.

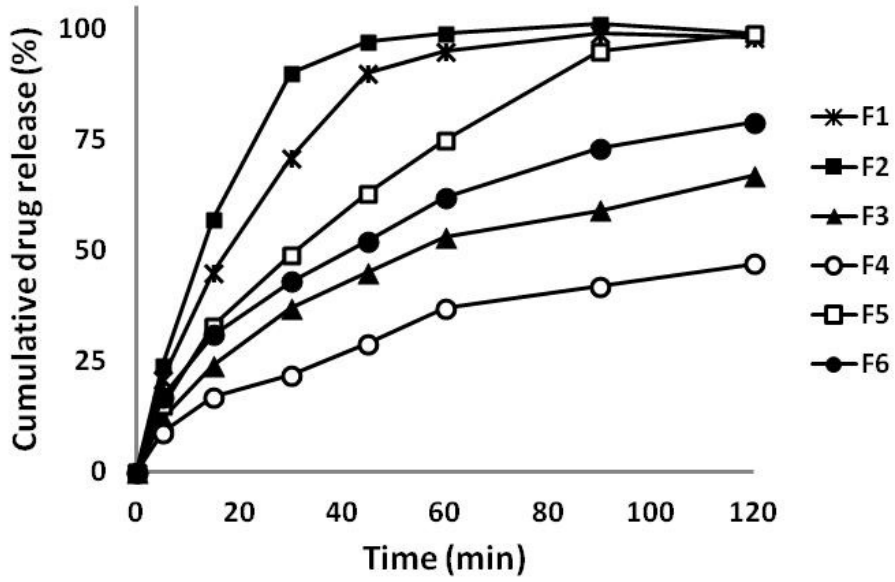

Figure 2. The *In vitro* release profiles of metochlopramide HCl from double-layered suppositories.

It is therefore clearly evident that the release of both drugs from the formulated double-layered suppositories is influenced by the melting of a base and the affinity of the drug towards bases. If the affinity between the drug and the base is low, then the release rate of the substances having high solubility in aqueous media is expected be high. Metoclopramide HCl is very soluble in water and it is affinity for fatty bases is less compare to paracetamol so it leaves the fatty bases easily in to dissolution medium. Further, the cacao butter based suppositories (F1) has the lowest hardness (0.9 kg) and melting time (8 min) but it gave slightly lower release of both paracetamol and metoclopramide HCl compared with witepsol W35 based suppositories (F2). This can be attributed to the high monoglyceride content in the witepsol W35 base which acts as emulsifying agent, thus facilitating the dispersion of the medicament to the surrounding media (***Chicco et al, 1999; Ofoefule et al, 2004***). However, it was found that the % drug release show no significantly differences ($p>0.05$) in the dissolution of two drugs from F1 and F2. Similar results were obtained by Nair and Bhargava who concluded that, the dissolution rate of fluconazole was greater from witepsol W45 than from cocoa butter (***Nair L and Bhargai'a, 1999***). On another hand, drug released from the PEGs based suppositories is dependent upon of the progressive dissolution of PEG in the dissolution media rather than melting. Further, as the average molecular weights of polyethylene glycols (PEG) increase the water solubility and hygroscopicity decrease and vice versa (***Coben LJ and Lieberman, 1986***). From the above results, it can be concluded that the *In vitro* dissolution of both paracetamol and metoclopramide HCl was found out to be satisfactory for F5 containing 1: 3 PEG 400: PEG 4000 bases.

Drug Release kinetics

Release data of paracetamol and metoclopramide HCl from double-layered suppositories were fitted to the zero order, first order and Higuchi models and the model with the highest R^2 was selected as the best fit. To examine further the release mechanism from the prepared suppositories, the data was plotted using Korsmeyer and Peppas equation. The kinetic parameters are shown in Tables 3 and 4.

Table 3. Release kinetics of paracetamol from different double-layered suppositories

Parameter		**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Zero order	R^2	0.9248	0.8995	0.862	0.8949	0.8138	0.8809
	K_0	0.4670	0.5308	0.7426	0.6421	1.0421	0.6691
First order	R^2	0.9811	0.9815	0.9986	0.9908	0.9945	0.9937
	K_1	0.0069	0.0088	0.0226	0.0129	0.0439	0.0154
Higuchi model	R^2	0.9925	0.9949	0.9846	0.9895	0.9661	0.9903
	K_H	13.940	16.093	22.877	19.463	28.011	20.450
Korsmeyer Peppas	R^2	0.9909	0.9919	0.9924	0.9802	0.9903	0.9907
	K	0.0363	0.0528	0.0692	0.0443	0.1086	0.0749
	n	0.5940	0.5480	0.5823	0.630	0.5374	0.5301

Table 4. Release kinetics of metoclopramide HCl from different double-layered suppositories

Parameter		**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Zero order	R^2	0.8137	0.8410	0.8748	0.9057	0.9085	0.8799
	K_0	1.0849	1.6238	0.5177	0.3679	0.8106	0.6070
First order	R^2	0.9955	0.9965	0.9670	0.9637	0.9534	0.9907
	K_1	0.0525	0.0811	0.0083	0.0046	0.0382	0.0119
Higuchi model	R^2	0.9599	0.9614	0.9901	0.9921	0.9903	0.9943
	K_H	1.7443	2.1156	0.9526	0.6659	1.4639	1.1161
Korsmeyer Peppas	R^2	0.9905	0.9765	0.9872	0.9924	0.9977	0.9960
	K	0.0048	0.0053	0.0032	0.0023	0.0034	0.0048
	n	0.6274	0.6595	0.5448	0.5280	0.6345	0.4904

Analysis of paracetamol release data from PEGs based suppositories revealed that the highest correlation coefficient were exhibited with the first order release mechanism while for suppositories prepared using fatty bases, the release data of paracetamol were best fitted to the Higuchi model as shown in Table 3. On another hand, kinetic assessment of the metoclopramide HCl release data showed that, for PEGs based suppositories, the release profile were best explained by Higuchi model while for suppositories prepared using fatty bases, the release profile found to follow first order kinetics as shown in Table 4. However, from the data illustrated in Table 3 and 4, it was found that most formulations exhibited n

values between 0.5 - 1 indicating anomalous (non-Fickian) release mechanism. Therefore, the release mechanism from the formulated double-layered suppositories involves two or more process as the type of drug release may be controlled by a combination of polymer swelling, erosion and diffusion through the hydrated matrix in addition to the combined effects of melting and drug partitioning (***Peppas, 1985; Korsmeyer, 1983***).

4. Conclusions

In this study, double-layered suppositories with satisfactory physico-chemical parameters were produced. The first layer contained 250 mg of paracetamol and the second contained 15 mg of metoclopramide HCl. PEGs based suppositories had better release profiles than suppositories prepared from fatty bases for paracetamol; while fatty bases suppositories showed better release profiles than PEGs based formulations for metoclopramide HCl. The addition of PEG 400 to PEG 4000 and PEG 6000 bases showed a significant effect on the release of both two drugs from the tested suppositories ($p<0.05$). *In vitro* dissolution of both paracetamol and metoclopramide HCl was found out to be satisfactory for F5 prepared using 1:3 PEG 400: PEG4000.

The results reveal that the prepared double-layered suppositories may be more suitable than conventional formulations for the treatment of migraine by sequential release of the two drugs, enhancing the release of drugs administered rectally and improving bioavailability of drugs with significant first-pass effect to get a rapid pharmacological effect. However, there is a need for further studies to examine other suppository bases and performing *In vivo* evaluation.

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