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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF METOCLOPRAMIDE HCL RECTAL SUPPOSITORIES

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ABSTRACT
Metoclopramide hydrochloride is a dopamine receptor antagonist, used mostly for stomach and esophageal problems as it is a prokinetic agent. The aim of the present study was to design and evaluate the suppositories of Metoclopramide HCl.
Six different, rectal suppositories were developed by fusion (pour-moulding) method by employing various hydrophilic and hydrophobic polymeric bases like gelatin, PEG-400 and hydrogenated vegetable oil using propylene glycol as plasticizer and beeswax as hardening agent. Metoclopramide HCl suppositories were evaluated for appearance, weight variation, drug content uniformity, liquefaction time and temperature, micro-melting range, disintegration and in-*vitro* release study.
The in-*vitro* release rate data was evaluated statistically and was found that from all the formulations the drug release is by diffusion mechanism. Optimum formulation of batch S1 has shown 83.427% Metoclopramide HCl in a study of 2 hrs. These drug release results are supported by the disintegration time of suppositories. Lesser the disintegration time faster the drug release. All formulations has shown zero, first and Higuchi release kinetics.
The result suggests that the Metoclopramide HCl suppositories can be prepared by employing hydrophilic and hydrophobic polymers.
Keywords: Hydrogenated vegetable oil, *in-vitro* release study, Metoclopramide hydrochloride, suppositories.

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INTRODUCTION

A conventional suppository is a medicated solid dosage form which melts or softens at body temperature. Suppositories are medicated solid bodies suitably shaped for rectal administration[1]. 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. Rectal route of administration is specifically useful for infants and children who have difficulty in swallowing oral medicine[2].

Human rectum remains to be a relatively unexplored route of drug delivery despite its potential as a non-invasive route of drug administration[3]. Drug administered in suppository form can produce not only local effect but also systemic therapeutic action. The presence of dense network of blood vessels has made the rectum an excellent route of drug delivery for both systemic and local effect. Blood draining the lower part of the rectum largely by-passes the liver so that drugs showing a high first-pass metabolism when given orally are more effectively absorbed when administered rectally[4].

Metoclopramide hydrochloride, a dopamine receptor antagonist is indicated in the treatment of gastro oesophageal reflux disease, nausea and vomiting. In long term therapy, it is used for emesis caused due to chemotherapy in cancer patient[5]. Metoclopramide HCl has short half-life of 5±1h[6]. The oral bioavailability of metoclopramide HCl is highly variable showing values between 32 and 98% due to first-pass metabolism. Furthermore, if given by oral route metoclopramide HCl often get vomited[7].

So, all these points favour for the development of rectal delivery systems of Metoclopramide HCl as an attractive alternative.

The aim of this study was to formulate and evaluate sustained release suppositories for metoclopramide HCl to avoid first pass metabolism and thus improve

bioavailability and avoid vomiting limitation of oral route. Suppositories were tested in order to determine weight variation, hardness, friability, drug content uniformity and the release characteristics of metoclopramide HCl from suppositories.

MATERIALS AND METHODS

Metoclopramide HCl was obtained from Unicure Pharmaceutical Limited, Ogun State, Nigeria. Beeswax and gelatin were obtained from Barata Pharmaceuticals, Rivers State Nigeria. HPMC (K4M) and Propylene glycol were obtained from Dana Drugs Limited, Lagos, Nigeria. Methyl Paraben and PEG 400 were obtained from NHC Pharmaceuticals Ltd, Lagos, Nigeria. All other chemicals used were of analytical reagent grade.

Calibration of Mould and displacement value

Before preparing the suppositories, the mould should be calibrated because the moulds may vary in their capacity. The base was melted alone and then filled into the mould and weighed after removing the suppositories; the mean weight was taken as true capacity of the mould. The procedure was repeated for different bases. The calibrated mould capacities ranged from 1.02 to 1.195 g for hydrogenated vegetable oil suppositories and 1.224 to 1.329 g for gelatin base suppositories[8].

Preparation of suppositories

Hydrogenated vegetable oil Metoclopramide HCl suppositories were prepared using fusion (pour-moulding) method. Hydrogenated vegetable oil was taken in a china dish and melted. Metoclopramide HCl was dispersed in the melted oil; after complete dispersion, the melted base along with drug was poured into the pre-calibrated mould (rapid cooling should be avoided as it results in holing of the suppositories).

For the preparation of gelatin Metoclopramide HCl suppositories, gelatin was added to water and heated. In the mixture of propylene glycol and PEG 400, accurately weighed amounts of drug and preservative (methyl paraben) were added. This solution was then added to the solution of gelatin and heated on water bath at 70- 80°C, stirred to yield homogeneous solution and the solution transferred into the pre-calibrated mould and cooled immediately which is very essential for gelatin suppositories[9]. The prepared suppositories were wrapped in aluminum foil and stored under refrigeration. The composition of all batches of suppositories is shown in Table 1.

Visual characterization

The randomly selected Metoclopramide HCl suppositories (six suppositories from each batch) were cut longitudinally and examined with the naked eye (subjective evaluation) to assess the verified the homogeneity of surface appearance and color of suppositories by Absence of fissuring, Absence of pitting, Absence of fat blooming, Absence of exudation, Absence of migration of the active ingredients. This last test is best accomplished by taking a longitudinal section of the suppository to verify the homogeneity of the active ingredient(s) within the mass[10].

Breaking strength

The breaking strength or crushing strength of Metoclopramide HCl suppositories was determined for measuring fragility or brittleness of suppositories, which assess whether the suppositories will be able to withstand the hazards of packing, transporting and normal handling or not. A plastic disc was fixed horizontally on to one end of the iron rod to which weight are applied and other end had been reduced to sharp point. The sample suppository was placed between the metal plate and the sharp end of the iron rod and placing 200 g weights on to the pan. At 1-minute intervals, 50 g weights are added, and the weight at which the suppository collapses in the breaking point, or the force that determined the fragility of brittleness characterization of the suppositories[11].

Mechanical strength (hardness)

A physical characteristic such as mechanical strength (hardness test) of Metoclopramide HCl suppositories was determined. The hardness of a cylindrical portion (9.6 mm thickness) of suppository, which was obtained by cutting the middle portion of the suppository, was measured in its diameter direction with a Monsanto hardness tester[12].

Weight variation

Twenty Metoclopramide HCl suppositories were weighed and average weight was calculated. Each suppository was then individually weighed by using digital balance. Not more than 2 of the individual masses deviate from the average mass by more than 5 %[13].

Friability

Twenty Metoclopramide HCl suppositories were weighted and placed in the plastic chamber of Roches Friabilator. The chamber was then rotated for 4 minutes at 25 rpm (a total of 100 revolutions). During each revolution suppositories fall from a distance of 6 inches. After 100 revolutions the suppositories were removed and weighed again[14].

$$\% F = \frac{(Wi - Wf)}{Wi} X\ 100$$

Where, Wi was the initial weight of the suppositories before friability testing, Wf was the weight of suppositories after the testing.

Melting point

The melting time is a critical factor in the determination of the release rate of the active ingredient(s) from the suppository. This test is also known as macro melting range test. During this test, the time taken for the entire suppository to melt or disperse is measured when immersed in a water bath maintained at constant temperature (37±1^{o}C). The time required for the whole Metoclopramide HCl suppository to melt or disperse in the surrounding water was noted[15].

Liquefaction or softening time

This important element indicates the physical behaviour of a suppository subjected to its maximum functional temperature (37°C). It consists of a U-tube partially submersed in a constant temperature water bath. This can be carried out at various temperatures from 35.5 to 37oC, as a quality control check and can

also be studied as a measure of physical stability over time. The softening test measures the liquefaction time of rectal suppositories. In this, to measures the time necessary for a suppository to liquefy under pressure similar to those found in the rectum in the presence of phosphate buffer pH 7.4 (5.0 ml) surrounding the water at body temperature[16].

Drug Content

Six Metoclopramide HCl suppositories of each formulation were cut into small pieces. 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. After filtration the content of drug was determined using a UV/Visible spectrophotometer by measuring absorbance of the 272 nm for metoclopramide HCl. Concentrations were determined using standard calibration curve equations[17].

***In vitro* drug release tests**

In vitro release test was carried out using USP type1 rotating basket apparatus (Pharma-test, Germany). Each Metoclopramide HCl 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±0.5^{o}C. Aliquots of 3 ml were withdrawn at appropriate time intervals for a period of 1 h and immediately replaced by 3 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[18].

Drug Release Kinetics

To study the release kinetics, data obtained from all Metoclopramide HCl suppositories formulations were applied to kinetic models such as zero order, first order and Higuchi. The release rate constants (k), and determination coefficients (R^2) were calculated by means Microsoft Excel, 2016 version[19].

RESULTS AND DISCUSSION

Six suppositories of Metoclopramide HCl suppositories were prepared by fusion method using hydrogenated vegetable oil and gelatin as bases. Bees wax was used to increase the melting point of hydrogenated vegetable oil and propylene glycol was used as plasticizer. The prepared suppositories had a glossy, smooth surface, without showing cracks, white or coloured spots, air bubbles, fat blooming or exudation.

The prepared suppositories were evaluated for appearance, weight variation, drug content uniformity, liquefaction time and temperature, micro-melting range, disintegration and *in-vitro* release study. The results of visual and physicochemical characterization are shown in Table 2 and 3. All the formulations were found to have homogeneous drug distribution with content uniformity, weight uniformity and sufficient mechanical strength to withstand abrasive forces causing disintegration of drug loaded formulation.

The width and length of the randomly selected suppositories was found to be good homogeneity. The weight variation studies for all suppositories were found to be within the acceptable range of <5 %.which indicates that calibration of mould was perfect[20].

All the prepared suppositories showed uniformity of drug content was within the permissible range (95 to100 %) indicating uniformity of drug dispersion in suppositories. The friability was found to be within acceptable limits (less than 1 %). The suppositories should have good mechanical strength for handling and transportation. All suppositories were having good mechanical strength in the range of (2.3±0.37 to 3.6±0. 64 kg/cm^2) showing optimum hardness[21].

The liquefaction time was studies as a measure of physical stability over time. The estimation of drug content in the formulation revealed that the drug was distributed uniformly with low coefficient of variations, indicating batch to batch consistency. The crushing or breaking strength was determined for measuring fragility or brittleness of the suppositories, which assess whether the suppositories will be able to withstand hazards of packaging, transporting and normal handling or not[22]. The formulated rectal suppositories were smooth and fine in texture with mechanical strength (hardness).

Suppositories liquefaction time range was found to be 1:25±0:03-1:49±0:23 min. The softening and disintegration times varied largely, depending on the properties of the lipophilic base and on its interaction with the active pharmaceutical ingredient, having weak or non acidic properties. The disintegration test for suppositories ranges in between 38±0.05-42±0.21 min. The *in vitro* release profile of lornoxicam from different bases are shown Table 4. Maximum release 83.427% was shown by the suppositories of batch S1and minimum 60.39% by the batch S2 in a study of 2 hr. These drug release results are related with disintegration time of suppositories and is inversely proportional to disintegration time[23]. In general release is inversely proportional to the lipophilicity of the base[24]. Suppositories has shown drug release by zero, first and Higuchi kinetic model (Table 4).

CONCLUSION

The influence of the composition on the results of the pharmacotechnical evaluations and on *in vitro* release parameters was assessed for six different prepared rectal suppositories of Metoclopramide HCl.

This study showed ultimate results with respect to the physical characteristics of suppositories (especially hardness and disintegration time) and *in vitro* drug release studies.

The prepared suppositories of sustains the release of Metoclopramide HCl, melts at physiological temperature and has prolonged retention time by adhering to rectal mucosa. About 83.427% Metoclopramide HCl was released from S1 in a study of 2 hrs. On the basis of release and other parameters the formulation of batch S1, consisting of gelatin is considered to be optimum formulation.

The kinetic particularities were adequately described by the zero, first and Higuchi model, confirming the combined role of the contact surface and diffusional resistance. On the basis of different results it can be concluded that rectal suppositories of Metoclopramide

HCl can be prepared by utilizing hydrogenated vegetable oil and gelatin. However, *in vivo* studies are required to ascertain the results obtained with in-*vitro* drug release studies.

CONFLICT OF INTEREST

"No conflict of interest associated with this work".

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Table 1: Table 1: Composition of Metoclopramide HCl suppositories formulations.

S.N.	Ingredients	S1	S2	S3	S4	S5	S6
1	Metoclopramide HCl (mg)	15	15	15	15	15	15
2	Hydrogenated vegetable oil (g)	-	15	-	16	-	15
3	Beeswax (g)	2.48	2.52	1.96	1.82	1.92	2.46
4	Gelatin (g)	6.00	-	5.00	-	5.00	-
5	HPMC(K4M)	-	3.00	-	6.00	5.00	-
6	Propylene glycol (g)	6	8	10	7	-	8
7	Methyl Paraben (g)	0.3	0.3	0.3	0.3	-	0.3
8	PEG 400 (g)	3.00	-	4.5	-	6.00	-
9	Distilled Water (ml)	5.0	5.0	5.0	5.0	5	5

Table 2: Evaluation of Metoclopramide HCl suppositories for various parameters

Code	Visual characterization of the formulations					Drug Content (mg)	Weight variation (mg)
	Fissuring	Pitting	Fat blooming	Exudation	Migration of active ingredient		
S1	NO	NO	NO	NO	NO	98±0.13	1.13±0.08
S2	NO	NO	NO	NO	NO	97±0.32	1.15±0.12
S3	NO	NO	NO	NO	NO	96±0.45	1.16±0.36
S 4	NO	NO	NO	NO	NO	94±0.35	1.18±0.48
S5	NO	NO	NO	NO	NO	99±0.08	1.14±0.63
S6	NO	NO	NO	NO	NO	95±0.86	1.21±0.41

Table 3: Physico-chemical characterization of Metoclopramide HCl suppositories

Code	Friability (%)	Hardness (kg/cm^2)	Breaking strength (gm)	Liquefaction time (min.)	Melting time (min.)	Disintegration time (min)
S1	0.32±0.12	2.8±0.58	424±15.2	1:25±0:03	23:10±0:02	38±0.05
S2	0.41±0.15	2.3±0.37	425±15.2	1:34±0:15	25:28±0:01	39±0.08
S3	0.43±0.09	2.4±0. 82	428±15.4	1:36±0:07	26:43±0:03	41±0.12
S4	0.46±0.22	3.2±0.51	432±16.2	1:42±0:24	27:29±0:04	42±0.21
S5	0.45±0.31	3.6±0. 64	434±16.4	1:41±0.37	28:48±0:01	39±0.19
S6	0.39±0.43	2.9±0. 38	431±12.5	1:49±0:23	26:57±0:05	40±0.42

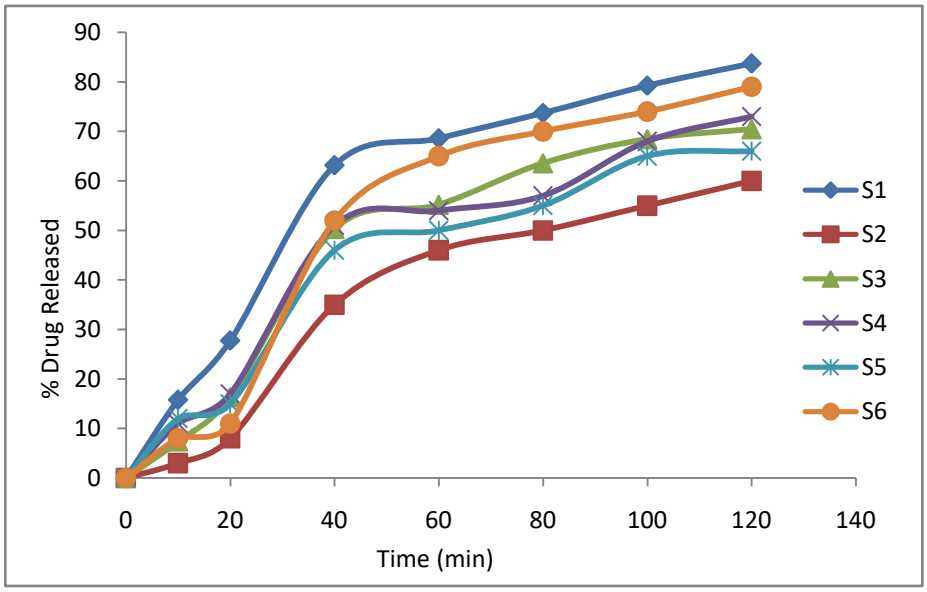

Figure 1: *In vitro* release profile of Metoclopramide HCl from different suppositories formulations

Table 4: Release kinetics of Metoclopramide HCl from suppositories

Parameter		S1	S2	S3	S4	S5	S6
Zero order	R^2	0.87	0.85	0.98	0.96	0.94	0.89
	K0	0.75	0.68	0.59	0.63	0.58	0.64
First order	R^2	0.91	0.90	0.88	0.87	0.94	0.89
	K1	0.02	0.01	0.03	0.02	0.01	0.01
Higuchi model	R^2	0.98	0.97	0.95	0.94	0.96	0.93
	K_H	1.83	1.72	0.9	0.88	1.23	1.36

R^2: Determination coefficient. k: Release rate constant