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Research Article

PREAPRATION AND IN VITRO EVALUATION OF METOCLOPRAMIDE HCL HOLLOW-TYPE SUPPOSITORY

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ABSTRACT

Metoclopramide HCL is a centrally acting anti-emetic, stimulating the motility of the upper gastrointestinal (GI) tract and possessing par sympathomimetic activity. The aim of this research is to see the possibility of production of metoclopramide HCL hollow-type suppositories as an effective dosage form. We study the influence of base types and suppositories types on in vitro drug release and the physical properties for prepared formulas using various hydrophilic and lipophilic bases in preparation of hollow type suppositories, the selected formula was compared to the marketed suppositories (primperan®10mg) for physical properties and dissolution profile. Also the selected formula were stored at 4°C and 28°C for 30 days to study the effect of storage time and storage temperature on the in vitro drug release and the physical properties for these samples was studied. The release of the drug was found to be enhanced both from witepsol H35 base containing metoclopramide HCL in powder form and solution form (97%, 99% of drug release respectively), while for conventional suppositories prepared from the same base was 20% drug released. The results showed that maximum release rate of the drug were achieve from hollow-type suppositories formulated using witepsol H35 base containing metoclopramide HCL in powder and solution form, also the result indicated there is increasing in drug released for the selected formula in the comparison with the marketed one. On another hand results indicated that the effect of storage on the suppositories prepared from witepsol H35 cause slight increase in physical properties and in release rate of drug from suppository base. Therefore, we can found that the preparation of metoclopramide HCL as hollow type suppositories are consider as a suitable dosage form for rapid release process of drug specially when witepsol H35 is use as a base and the drug is loaded as a powder form.

Keywords: Metoclopramide HCL, Hollow type suppository

INTRODUCTION

Suppositories are solid dosage forms intended for insertion into the body orifices where they melt, soften or dissolved and exert localized or systemic effects. Suppositories are commonly employed rectally or vaginally, occasionally urethral and rarely aurally and nasally. They have various shapes and weights. The shape and size of a suppository must be capable of be easily inserted into the intended site [1].

The rectal absorption occurs mainly by passive diffusion and the drug release from suppository is likely to be an important factor in determining the drug concentration in the rectal fluids and hence its absorption rate. This means, both the drug solubility and the excipients characteristics play a crucial role in the rate of drug absorption [2].

Metoclopramide HCL is a white or almost white, crystals or crystalline powder, very soluble in water freely soluble in alcohol, sparingly soluble in methylene chloride [3]. The antiemetic action of metoclopramide is due to its antagonist activity at Dopamine receptors in the chemoreceptor trigger zone (CTZ) in the central nervous system (CNS); this action prevents nausea and vomiting triggered by most stimuli [4]. Metoclopramide is a centrally acting anti-emetic, stimulating the motility of the upper gastrointestinal (GI) tract and possessing parasympathomimetic activity. Therapeutic indications are gastroparesis or ileus, gastro-oesophageal reflux disease, dyspepsia, nausea and vomiting during migraine or cancer therapy. Its therapeutic range is from 1 mg for pediatric use to 40 mg for adults. The total daily dosage should not exceed 500 µg/kg [5].

Hollow - Type Suppositories, which have a hollow cavity to accommodate drugs in various form as a powder and solution, have been given to a number of patients during the past ten years and their usefulness has been confirmed [6]. Hollow-type suppositories are superior to conventional one that because hollow- type suppositories were found to be less influenced by kinds of the base material than were the conventional types [7] and can carry either powdered or solution forms of drugs also They eliminate the effect of the heating process on the nature of the drug during the preparation of the suppository [8] and they are expected to eliminate interaction between drugs and base materials since the two are separated [9] also It was also reported that drugs were release more rapidly and absorbed more efficiently from a hollow-type suppository than from a conventional suppository [6].

MATERIALS AND METHODS

Materials

- Metoclopramide HCL, supplied by Samara's Drug Industry (SDI)
- witepsol H 35, witepsol H 37 supplied by Samara's Drug Industry (SDI)
- Polyethylene glycol (PEG) 1000, Polyethylene glycol 4000, Polyethylene glycol 6000 (BDH chemicals, Ltd., Pool, England)
- Polyethylene glycol 400 (SEARLE Company, HOPKIN & WILLIAMS, (England))
- Propy1ene glycol Supplied by Merk – shuchardt. (Germany)
- Tween 80 Supplied by Merck-shuchardt, (Germany)
- Lactose powder (D (+) – Lactose Supplied by (GCC) Hazard Ltd, (England)
- All other reagents were of analytical grade.
- Primperan®10mg suppositories - Sanofi Avents company, (France)

Methods

Determination of Metoclopramide HCL Melting Point

The electrical melting point apparatus using capillary method measured the melting point of metoclopramide HCL [10].

Determination of λ max of Metoclopramide HCL

Metoclopramide HCL solution in Sorensen's phosphate buffer pH 7.4 was prepared, then the solution was scanned by spectrophotometer from 200-400 nm, and λ max of the drug was determined.

Calibration Curve of Metoclopramide HCL

Calibration curve of metoclopramide HCL in pH 7.4 were obtained by preparing serial dilutions from stock solution (25µg /ml) and the prepared samples were analyzed spectrophotometric ally at λ max 272 nm that determined from above. The measured absorbance of each sample was plotted versus concentrations.

Solubility of Metoclopramide HCL in Phosphate Buffer pH 7.4

The solubility measured by shake-flask method in which a solubility sample is typically prepared by adding an excess amount of metoclopramide HCL to Sorensen's phosphate buffer solution of pH 7.4 in a stoppered flask, then leaving the mixture for 24 hours in a shaking water bath at 37 °C until super saturation achieved. The resultant solution then filtered and analyzed spectrophotometric ally to estimate the ultraviolet absorbance at stated λ max and determined the amount of metoclopramide HCL dissolved [11].

Preparation of metoclopramide HCL suppositories

The fusion method was used to prepare the hollow type suppositories as well as conventional suppositories to best formula. Hollow-type suppositories were prepared by melting various suppository bases using gentle heat(45 °C) in water bath, then the melted bases were poured into 2 gm. suppository molds equipped by cylindrical tube in the center and allowed to stand for 2 hours at room temperature to solidify. After construction of a hollow cavity in the solidified bases, 10 mg metoclopramide HCL powder mixed with lactose powder (used as filler) in ratio (1:9) was added to the cavity [6, 12].

As well as 400 µL of metoclopramide HCL solution prepared by dissolving metoclopramide HCL in aqueous solution of 4 % v/v tween 80, then the resultant solution was mixed with propylene glycol in a percentage of 50 % v/v (for oleaginous bases) [6]. The opening at the back part of the suppository was sealed with the same melted base, each suppository in all formulas contain an equivalent amount 10 mg. of metoclopramide HCL. On the other hand conventional suppositories were prepared by fusion method using witepsol H 35 as a suppositories base. the melting method involved melting of the base by gentle heating(45 °C) on water bath, followed by addition of the drug (10 mg for each suppository) with continuous and gentle stirring until a homogenous preparation was achieved. The mixture was poured into a 2 gram suppository mold and the suppositories were allowed to solidify over a night in a refrigerator [13]. When the suppositories are hard, the mold is removed from the refrigerator and allowed to come to room temperature [14], prepared formulas are shown in table (1)

Table 1: Composition of metoclopramide HCL conventional and hollow-type suppositories

Formula No.	Suppository type	Quantity of metoclopramide HCL (mg)	Type of the base
F1	Hollow-type	10	Witepsol H35
F2	Hollow-type	10	Witepsol H37
F3	Hollow-type	10	PEGs 400:6000 (70:30)
F4	Hollow-type	10	PEGs 1000:6000 (70:30)
F5	Hollow-type	10	PEGs 1000:4000 (70:30)
F6	Hollow-type	10	PEGs 1000:4000 (50:50)
F7	Hollow-type	5 mg in the outer layer(in base)+5 mg in solution form in the inner layer	Witepsol H35
F8	Hollow-type	10 mg as solution	Witepsol H35
F9	Conventional type	10	Witepsol H35

Evaluation of suppositories

Breaking strength test

It was carried out using the Erweka hardness tester. This test determines, under defined conditions, the resistance of suppositories to rupture, and it is measured by the mass needed to rupture them by crushing. The temperature inside the testing chamber was controlled at 25°C by means of circulating water from a thermostat connected to the tester. The suppository was placed into the holding device with the tip upwards and the test chamber was then closed with glass plate. At this point, the initial load, which was given by the weight of the entire suspended block, was 600 g. After one minute a disc of 200 g weight, was added and this weight addition was continued every minute until the suppository collapsed under the load of the weight. If the suppository collapsed within 20 seconds of placing the last disc, then this mass was not taken into account. If the suppository collapsed between 20 and 40 seconds of placing the last disc, then half of this mass was used in calculation, i.e. 100 g. If the suppository remained uncrushed for more than 40 seconds after last disc was placed, then all the mass was used in calculation. Ten suppositories were used in each measurement [3]. Determination of the mechanical strength of suppositories can be valuable to avoid problems with formulations [10].

Determination of the melting time

The suppositories were placed into a glass tube (2.5 cm diameter); 2 ml of Sorensen's phosphate buffer$_{\pm}$ solution of pH 7.4was then added. The tube was placed in a water bath at 37°C 0.5°C. The time required for each suppository to melt completely or to disintegrate was determined [6].The release of the active ingredient from the vehicle was related to the melting point of the vehicle and the solubility of the drug in the vehicle. An understanding of these factors and their relationships is critical for evaluating the bioavailability of the final suppository formulation. The higher the melting point, the later the drug effects appear. If too high, the drug effect does not appear [15].

Softening Time Determination

The softening time test indicates how long certain preparation takes to lose its physical structure. The suppository was inserted in the spiral shaped glass basket of the test tube with the tip pointed upwards and the tube was then closed. A thermostat connected to the tester provided circulating distilled water inside the test tube at the constant temperature 37°C and constant flow rate. The time required for the first drop of the suppository base to appear floating on the surface of the water inside the testing tube was considered softening time [16].

In Vitro Drug Release

In vitro release test was carried out according to the USP XXII basket method. The USP rotating basket dissolution apparatus was used for the determination of release rates of metoclopramide HCL from the various suppository bases. Each suppository was placed in basket and lowered into a flask containing 900 ml of phosphate buffer solution (pH 7.4). The basket rotated at 50 rpm at a constant temperature 37°C ± 0.5°C [17]. At appropriate time intervals (0, 5, 10, 15, 20, 25, 30, 40, 50 and 60 minutes), 5-ml samples were withdrawn through syringe Millipore filter, the volume of the dissolution medium was kept constant by replacing the withdrawn volume of the sample with equal volume of fresh dissolution medium maintained at the same temperature. A minimum of triplicate drug release determinations were made for each suppository preparation. Metoclopramide HCL samples analyzed using an ultraviolet spectrophotometric method [6].

Study of factors affecting formulation

Effect of types of suppositories base Used

Six formulas (F1, F2, F3, F4, F5, and F6) selected to investigate the effect of nature of suppository base on the physical properties and in vitro release of metoclopramide HCL of the prepared hollow type suppositories [18].

Effects of Changing the Type and Ratio of Polyethylene Glycols (PEGs)

The effect of changing the type and ratio of polyethylene glycols as suppository base on the physical properties and the drug release was demonstrated [19]. Four formulas (F3, F4, F5 and F6) were selected to study this effect.

Effect of suppository types

Three formulas (F1, F8 and F9) used to investigate the influence of suppository type on the physical properties and the rate of release of Metoclopramide HCL from the prepared suppositories [20].

Effect of loading dose of metoclopramide HCL in hallow-type suppositories

Tow formulas (F7 and F8) selected to study the effect of in the outer and inner layer on the physical properties Metoclopramide HCL was studied [21].

Comparison of selected formula with brand suppositories (Primperan®)

A final comparison will done for thee selected formula (F1) with the suppositories available in the market (primperan® 10 mg) for physical properties dissolution profile.

Effect of Storage Time and Temperature

To study the effect of storage time and temperature on drug release and physical properties of selected formula (F1), the prepared suppositories were stored at 4°C and 28°C for 30 days [22]. The suppositories were wrapped with aluminum foil, placed in tightly closed containers and stored at the mentioned temperatures for periods indicated [23].

Statistical Analysis

The results obtained statistically analyzed by using one-way analysis of variance (ANOVA). Differences of ($P< 0.05$) considered significant [24].

RESULTS AND DISCUSSION

Physical Properties of Metoclopramide HCL

Determination of Metoclopramide HCL Melting Point

The measured melting point of Metoclopramide HCL was found to be 183 °C with decomposition. This result is the same as reported in references, which indicates the purity of the supplied drug powder [3].

Determination of λ max of Metoclopramide HCL

The UV scan the solution of metoclopramide HCL in solution of Sorensen's phosphate buffer pH 7.4 by UV spectrophotometer at 200-400 nm gave the spectrum shown in figure (1) with a λ max. at 272 nm.

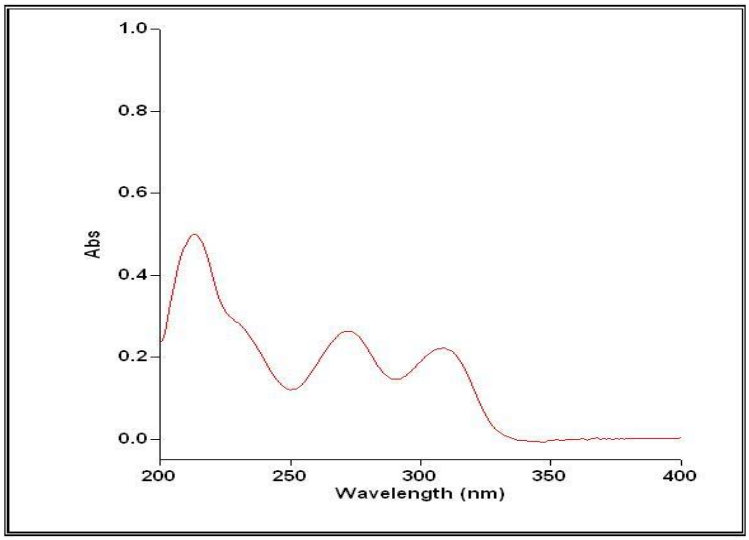

Fig. 1: The UV spectrum of metoclopramide HCL in Sorensen's phosphate buffer pH 7.4 at 37ºC

Determination of Calibration Curve

Figure (2) shows the calibration curve of Metoclopramide HCL in Sorensen's phosphate buffer pH 7.4. A straight line was obtained by plotting the absorbance versus concentration with high regression coefficient (R2 = 0.9981). This indicates that calibration curve obeys Beer-lambert's law at λ max 272 nm within the range of concentration used.

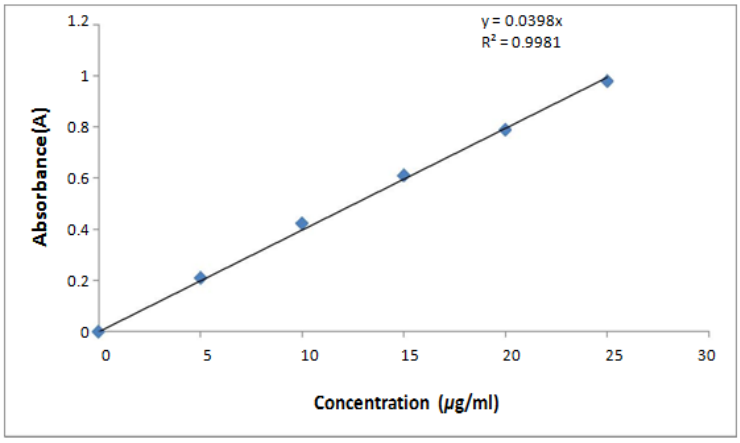

Fig. 2: Calibration curve of metoclopramide HCL in Sorensen's phosphate buffer pH 7.4 at 37°C

Solubility Determination

The measured saturated solubility of metoclopramide HCL in Sorensen's phosphate buffer pH 7.4 was found to be 1.415 g /ml.

Physical Properties and In-vitro Drug Release Studies

Effect of type of suppository base used

Table (2) show that the melting time for hydrophilic bases (polyethylene glycols) was to be longer compared to that of lipophilic bases (witepsol H 35 and witepsol H 37). Suppositories made up of polyethylene glycol (PEG) base, which may soften or melts after considerable time in the rectum due to its relatively high melting point and thus cannot rapidly adsorbed in rectal mucous membranes [21]. On the other hand, lipophilic bases melt quickly at body temperature [25].

Also the hardness of the water-soluble base was found to be higher than that for oleaginous bases, that may duo to the low values of the oil soluble suppositories are attributed to the low melting point of the bases while PEG bases has higher melting point but their water soluble properties made them easy to dissolve. PEG bases suppositories do not melt at body temperature but rather dissolve slowly in the body's fluids [26].

The results show that there is no significant differences (P>0.05) in hardness between water-soluble bases specifically formulas 5 and 6 and an oleaginous bases, that may be due to the melting point and hardness of polyethylene glycols increase as a function of increasing of polymerization of polymer used, that increase with increasing the molecular weight used [25].

Figure (3) show that the release rate was significantly greater for suppositories prepared from oleaginous bases specially (F1) than those prepared from hydrophilic bases.

Drug partitioning is a function of the nature of base and it corresponds to the affinity of the drug towards bases. When there is low affinity between the drug and the base, the release rate of the substances having high solubility in aqueous media is expected be high [27]. Metoclopramide HCL is very soluble in water and it is affinity for lipophilic bases is less compare to lipid soluble drugs, so it leaves the bases easily in to dissolution medium [3]. Also in addition to hydrogenated vegetable oil, they contain emulsifiers and suspending agents [28].

On another hand the release of metoclopramide HCL from witpsol H35 was found higher than that from and Witpsol H37. This may attributed to the rapid melting of witepsol H35 (about 8 minutes) compare to witepsol H 37 which allowed the rapid release of drug [29].

Table 2: Effect of type of suppository base used on the physical properties of hollow-type suppositories

Formula No.	Softening time (min.)	Melting time (min.)	Hardness (Kg)
F1	7	11	2.8
F2	10	14	3
F3	-	26	3.2
F4	-	30	3.4
F5	-	24	2.6
F6	-	30	3

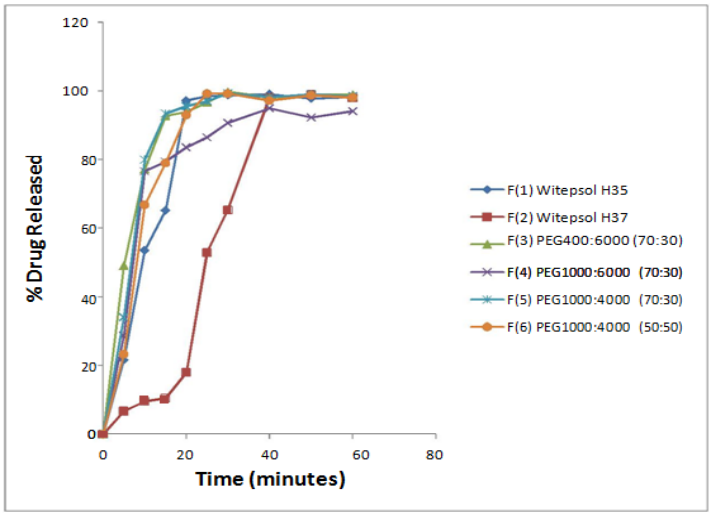

Fig. 3: Effect of type of suppository base used on the in vitro release of metoclopramide HCL in Sorensen's phosphate buffer pH 7.4 at 37 °C

Effect of Changing the Type and Ratio of Polyethylene Glycols

Table (2) shows the effects of changing the type and ratio of polyethylene glycols on the physical properties of hollow-type suppositories. The result indicated that F4 showed higher melting time compare to F3.

On another hand the higher melting time of F6 compare to F5, this melting time increases in order (F6=F4>F3>F5) as shown in table (2). This may be as mention previously related mainly to the fact that the melting point and hardness of polyethylene glycols increase as a function of increasing of polymerization of polymer used, that increase with increasing the molecular weight used [16].

Also it was found that the % drug release show no significantly differences (P>0.05) in the dissolution rate of metoclopramide HCL from formulas 3, 5 and 6 but there is slightly decrease in release rate of drug of F4 as show in figure (3). This may be due to water solubility and hygroscopicity of polyethylene glycols (PEG) decrease with increase average molecular weights [30].

Effect of Suppository Type

Table (3) shows that there is a reduction in physical properties (hardness and melting time) for both F1 and F8 compare to F9. This reduction may be due to the presence of cavities that might affect the skeleton structure of the hollow-type suppositories, also may be attributed to the compact back bone of conventional type with more rigid and consolidated structure than the hollow-type one [30].

Figure (4) shows that in first 5 minutes approximately (21%), (20%) and (10%) of metoclopramide HCL was released for F1, F8 and F9 respectively. The maximum drug released (approximately (97% and 99% of metoclopramide HCL was released in 20 minutes for F1 and F8 respectively, on anther hand (approximately 20% of metoclopramide HCL was released in 30 minutes) for F9. This result show that there is a significant increase ($P<0.05$) of metoclopramide HCL release from two different hollow - type suppositories which containing either solution in their cavities (F8) or the other one which containing powder in their cavities (F1) when compared with the remainder one F9. This may be attributed to the rapid melting of witepsol H35 (about 8 minutes) which allowed the rapid release of metoclopramide HCL powder form or solution form solution. In addition, the increase in release of drug may attribute that the presences of propylene glycol, which increase the dissolution, rate of the drug from the suppository [14, 31]. Also the results show no significant difference ($P>0.05$) in releasing rate of metoclopramide HCL for F1 and F2. This may be in addition to higher water solubility of metoclopramide HCL powder, the presence of lactose powder, which used as a filler, in ratio of (1:9) (metoclopramide HCL powder: lactose powder) lead to enhance drug powder dissolution [32].

Table 3: Effect of changing the suppository type on the physical properties of Metoclopramide HCL suppositories

Formula No.	Softening time (min.)	Melting time (min.)	Hardness (Kg)
F1	7	11	2.8
F8	6	8	2.2
F9	7	13	3.4

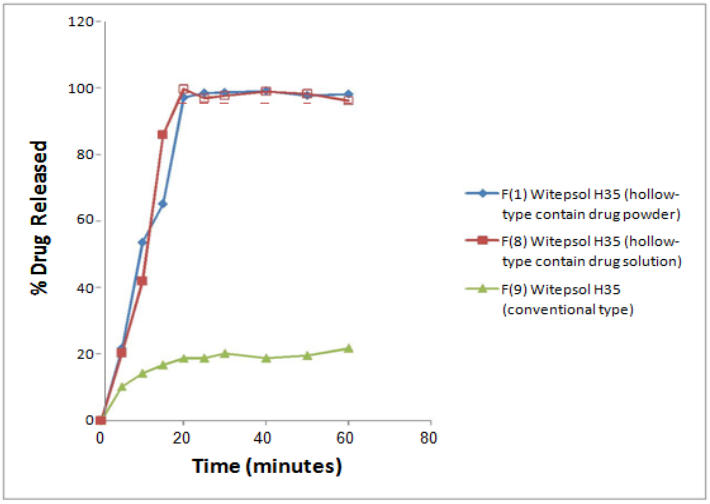

Fig. 4: Effect of suppositories type on the in vitro release of Metoclopramide HCL in Sorensen's phosphate buffer pH 7.4 at 37 °C

Effect of Loading the Dose of the Metoclopramide HCL in the Outer and Inner Layers

Table (4) shows that the physical properties (melting time, softening time and hardness) were not significantly ($P>0.05$) changed by dividing the dose of the metoclopramide HCL in the outer and inner layers, since both formulas contain hollows in their structures [33].

Figure (5) shows the release profiles of these suppositories revealed that there was no significant ($P>0.05$) change in the time of 100% of drug release for F7 and F8. This may because of rapid release of metoclopramide HCL in solution form, so all the drug was available in a solution form to be absorbed [34].

The results indicated that hollow-type suppositories contain the drug in inner and outer layers (F7) show faster release rate than that contain drug in inner layer (F8). This may be to the continuous release of the drug from both an outer and inner layers until the suppository was completely dissolved [20].

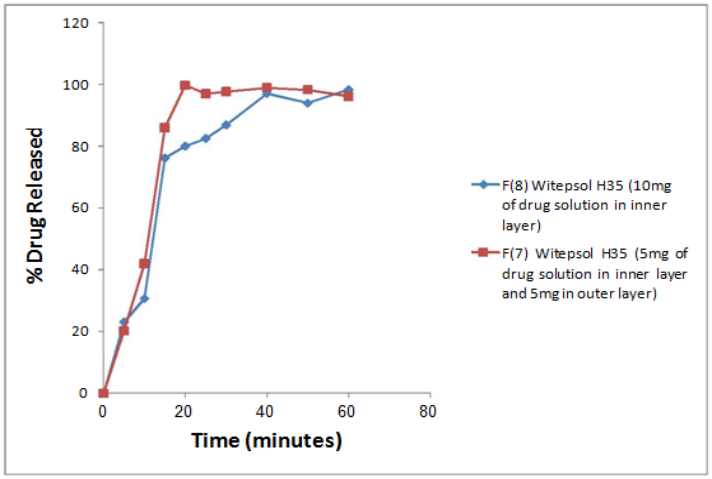

Fig. 5: Effect of loading the dose of the Metoclopramide HCL in the outer and inner layers using witepsol H 35 base in Sorensen's phosphate buffer pH 7.4 at 37 °C

Comparison of Selected Formula with Brand Suppositories (primperan®)

Table (5) appears that primperan® 10 mg suppositories have a longer melting point and higher hardness compare to F1. This is as mention previously may be due to the presence of cavities fill off drug that might affect the skeleton structure of the hollow-type suppositories [30].

Figure (6) indicates that there is a significant increase (P<0.05) of drug release for hollow type (F1) when compared with primperan® 10 mg suppositories. Watanabe.et.al demonstrated that drug released more rapidly and absorbed more efficiently from a hollow-type suppository than from a conventional suppository [6].

Table 5: Comparison between formula 1 and marketed brand suppositories in physical propertie

Formula No.	Softening time (min.)	Melting time (min.)	Hardness (Kg)
F1	7	11	2.8
Primperan® 10 mg suppositories	7	14	3.6

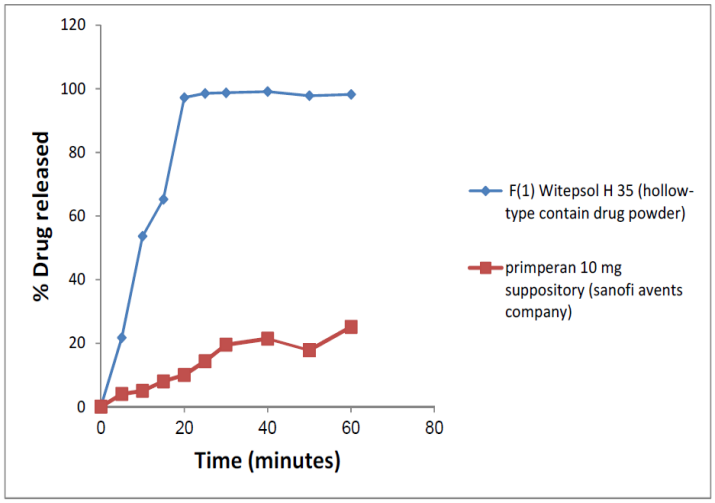

Fig. 6: Comparison of selected formula with brand suppositories (Primperan® 10mg) on the release of Metoclopramide HCL in Sorensen's phosphate buffer pH 7.4 at 37 °C

Effect of Storage Time and Temperature

Table (6) shows the effect of storage period and temperature on the physical properties for the selected formula. F1 was chosen because it gave optimum and uniform release profile and good physical properties. Samples were selected from this formula and stored for 30 days at 4°C and 28°C. The results indicated that on storage of F1 at 4°C and 28°C there was no significant (P>0.05) change in the physical properties, but the slightly increase in the softening time and melting time and hardness for F1 may be due to polymorphic transition of some semi-synthetic fatty suppository bases [13].

Beside the dissolution behavior of metoclopramide HCL from this formula during the storage at a various temperatures was found to be no significant (P>0.05) change as shown in figure (7) .

Table 6: Effect of storage time and temperature on the physical properties of hollow-type suppositories storage for 30 days

Formula No.	Storage temperature	Softening time (min.)	Melting time (min.)	Hardness (Kg)
F1	4°C	8	12	3
F1	28°C	7	11	2.6

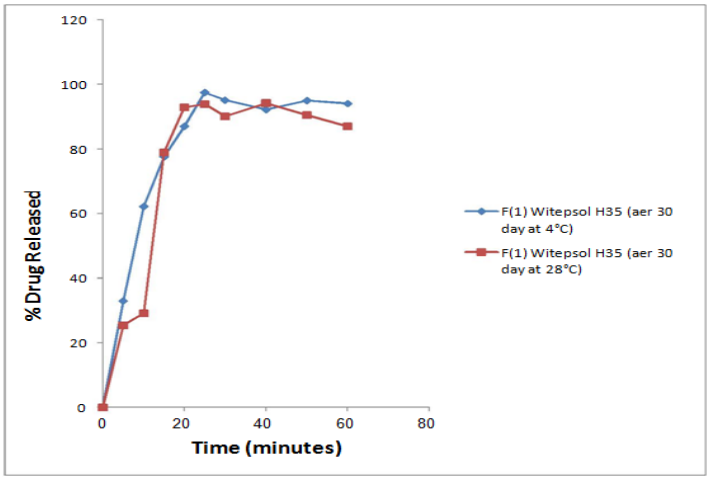

Fig. 7: Effect of storage period and temperature on the release of Metoclopramide HCL from hollow-type suppositories using witepsol H 35 base in Sorensen's phosphate buffer pH 7.4 at 37 °C

CONCLUSION

The physical properties of the prepared suppositories were found to be affected by changing the nature of the bases and the suppository type employed in the study.

Also the maximum release rate of the drug was achieved from hollow-type suppositories containing drug as a powder form or solution form formulated by using witepsol H35. The drug release was better from hollow type suppositories containing drug in powder form compared with conventional suppositories formulated from the same base. So hollow-type suppositories are useful as a promising approach for enhancing the release of drugs administered rectally to gate a rapid pharmacological effect.

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