RESEARCH ARTICLE

Formulation and *In vitro* Evaluation of Piroxicam Conventional and Hollow Suppositories

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ABSTRACT

Objective: The objective of this study was to develop higher and rapid release of piroxicam from suppositories of different types (conventional and hollow) using different bases.

Methods: Thirteen formulas (F1–F13) were prepared (five were conventional, and the rest were hollow type suppositories) by using different bases, such as, witepsol H35, polyethylene glycols (PEGs) with different ratio and glycerinated gelatin. The prepared suppositories were evaluated for physical properties, such as, hardness, melting time, softening time, and for dissolution profile.

Results: All of the prepared suppositories had acceptable physical properties. The maximum percent release of piroxicam was 98, 97, 95, and 91% within 50 minutes were obtained from hollow type suppositories containing piroxicam in a solution form and utilizing witepsol H35 base (F10), glycerinated gelatin base (F13), PEGs 400:4000 (70:30) (F12), and PEGs 200:6000 (70:30) (F11), respectively. Also, they exhibited rapid release of piroxicam, however, F10 and F12 released 65 and 50% of piroxicam within 5 minutes, while, F11 released 57% within 10 minutes.

Conclusion: Hollow type suppositories containing piroxicam in a solution form can be considered as the most suitable formulas (F10–F13). So, hollow-type suppository is useful as a promising approach for enhancing the release of piroxicam to be administered rectally. Also, the study revealed that in addition to the type of suppositories, the type of the base, the grade, and the ratio of PEGs bases are other important factors affecting the physical properties of suppositories and the dissolution profile of piroxicam.

Keywords: Conventional and hollow suppositories, Piroxicam, Types of suppository bases.

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INTRODUCTION

Suppositories are solid dosage form intended for insertion into body orifices, where they melt at body temperature or dissolve in body fluid to exert local or systemic effects. Their action depends on the nature of the drug, concentration, vehicle, and the rate of absorption. Many arguments were indicated for choosing the rectal route for drug administration, among them, to avoid patient gastrointestinal tract problems, unpleasant taste or bad-smelling drugs, first-pass effect, and their convenience for children and unconscious patients.[1-3]

One approach for suppositories is hollow-type suppositories, which have a hollow cavity to accommodate drugs in various forms as a powder or solution. Hollow-type suppositories were found to be less influenced by the kind of the base material than were the conventional types. Also, they eliminate the effect of the heating process on the nature of the drug during the preparation of the suppository, and they are expected to eliminate interaction between drugs and base materials since the two are separated.[4]

Piroxicam is 4-hydroxy-2-methyl-N-(pyridin-2-yl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide. It is a non-steroidal anti-inflammatory drug (NSAID). Therapeutically, it is used as anti-inflammatory, analgesic, and antipyretic in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute gout.[5] Piroxicam belongs to class II with low solubility and high permeability.[6] Piroxicam is readily absorbed after oral or rectal administration, but it is extensively metabolized to inactive metabolites. It is highly bound (approximately 99%) to plasma proteins.[6,7]

This research concerned with the preparation of piroxicam as conventional and hollow-type suppositories for rectal

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administration to achieve higher and rapid release of the drug by utilizing different bases.

MATERIALS AND METHODS

Materials

Piroxcam pure powder (Provizer Pharma, India), di-sodium hydrogen phosphate di-hydrate ($Na_2HPo_4.2H_2O_2$) (E. Merck, Darmstadt, Germany), gelatin and liquid paraffin (Fluka-AG, Switzerland), lactose powder (GCC, Hazard Ltd, England), PEG 200, PEG 4000, and PEG 6000, ethyl oleate, glycerin, and potassium dihydrogen orthophosphate (KH_2PO_4) (BDH Chemicals Limited, England), PEG 400 (Searle Company, Hopkin and Williams, England), tween 80, and propylene glycol (Merck Schuchardt, Germany), and witepsol H35 were supplied by Samarra Drug Industry (SDI) as a gift.

Methods

Two types of piroxicam suppositories were prepared as the following:

- Conventional piroxicam suppositories.
- Hollow type suppositories containing piroxicam in powder or solution form.

Preparation of Piroxicam Conventional Suppositories

Conventional suppositories, each containing 20 mg of piroxicam, were prepared by fusion method using different types and ratios of suppository bases. Witepsol H35, PEGs 200:6000 (70:30), PEGs 200:6000 (50:50), PEGs 400:4000 (70:30), and glycerinated gelatin were used as suppository bases for formula (F1–F5), as shown in Table 1.

The fusion method involved melting of the base by gentle heating in a water bath, followed by the addition of the equivalent weight of 20 mg piroxicam for each suppository. The melted mass was stirred constantly, but slowly to avoid air entrapment, and then the mixture was poured into 2 grams suppository molds. The molds were allowed to cool thoroughly using a refrigerator, and then any access of congealed mass was removed from the molds by scraping. After that, the molds were opened and the suppositories were removed.[8,9]

For suppositories containing a mixture of PEGs as a base, the higher molecular weight PEGs were first melted, then after, the lower molecular weight one was added and mixed well.[8,10]

On the other hand, glycerinated gelatin base was prepared by heating a mixture of gelatin, glycerin, and distilled water at 70ºC to dissolve the gelatin. Then after, the mixture was stored in a water bath for 48 hours at 50ºC. After that, the mixture was used as a base after removal of the bubbles.[6,8]

Preparation of Hollow-Type Suppositories containing Piroxicam in Solution or Powder Form

These suppositories were prepared by melting various suppository bases using gentle heat in a water bath. The melted bases were poured into 2 grams suppository molds equipped with a cylindrical tube in the center and allowed to stand for 2 hours at room temperature to solidify. After the construction of the hollow-cavity in the solidified bases, piroxicam was placed in the cavity in one of the following forms:

- Powder mixture (400 mg), which was prepared by mixing piroxicam with lactose at 5% (w/w), as shown in Table 2.
- Piroxicam solution (400 µL), which was prepared in two methods according to the type of the base used as below;

Piroxicam solution (a): This solution was prepared when hydrophilic suppository bases (PEGs or glycerinated gelatin) were used by dissolving piroxicam in ethyl oleate, and then mixed with tween 80 at a ratio 70:30 w/w to yield piroxicam solution (a).

Piroxicam solution (b): This solution was prepared when an oleaginous suppository base (witepsol H35) was used by dissolving piroxicam in 4% v/v tween 80 aqueous solution, the resultant solution was mixed with propylene glycol at 50% v/v to yield piroxicam solution (b), as shown below in Table 3.

Each suppository contained an amount of solution or powder equivalent to 20 mg piroxicam. The openings at the back part of the suppositories were sealed with melted bases.[11,12]

Table 1: Composition of piroxicam conventional suppositories of 2 grams mold

Formula No.	*Piroxicam (mg)*	*Suppository base*
F1	20	Witepsol H35
F2	20	PEGs 200:6000 (70:30)
F3	20	PEGs 200:6000 (50:50)
F4	20	PEGs 400:4000 (70:30)
F5	20	Glycerinated gelatin base (glycerin, gelatin, and water)

Table 2: Composition of hollow suppositories containing piroxicam powder

Formula No.	*Piroxicam (mg)*	*Lactose (mg)*	*Suppository base*
F6	20	380	Witepsol H35
F7	20	380	PEGs 200:6000 (70:30)
F8	20	380	PEGs 400:4000 (70:30)
F9	20	380	Glycerinated gelatin base

Table 3: Composition of hollow suppositories containing piroxicam solution

Formula No.	*Piroxicam (mg)*	*Type of the piroxicam solution*	*Suppository base*
F10	20	(b)	Witepsol H35
F11	20	(a)	PEGs 200:6000 (70:30)
F12	20	(a)	PEGs 400:4000 (70:30)
F13	20	(a)	Glycerinated gelatin base (glycerin, gelatin, and water)

Evaluation of Piroxicam Suppositories

Hardness Test (Breaking Strength Test)

Determination of the mechanical strength of suppositories can be valuable to avoid problems with formulation.[13] The breaking strength test was carried out by Erweka hardness tester (Erweka-apparatebau GMBH SBT, Germany). This test was determined, under defined conditions, the resistance of suppositories to rupture was looked on, and it was 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 grams. After 1-minute, a disc of 200 grams weight was added, and this weight addition was continued every minute until the suppository collapsed under the load of the weight. The mass required to crush the suppository was calculated by the sum of the masses weighing on the suppository when it was collapsed, and this was assessed as follows[8]:

If the suppository collapsed within 20 seconds of placing the last disc, then this mass was not taken into account. If the suppository collapsed was 20 to 40 seconds of placing the last disc, then half of this mass was used in calculation, i.e., 100 grams. If the suppository remained uncrushed for more than 40 seconds after the last disc was placed, then all the mass was used in calculation. Six suppositories were used in each measurement.[8]

Determination of the Melting Time

The suppository was placed into a glass tube (2.5 cm diameter), then 2 mL of phosphate buffer solution (pH 7.4) was added. The tube was placed in a water bath at 37 ± 0.5°C. The time required for each suppository to melt completely or to disintegrate was determined.[8]

Softening Time Determination (for Lipophilic Suppositories)

The softening time test indicates how long certain preparation takes to lose its physical structure. A softening time tester (Erweka-apparatebau GMBH SBT, Germany) was utilized for this test. 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 a constant temperature 37°C and a 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 as a softening time.[14]

***In vitro* Drug Release**

The dissolution test was carried out according to the United States Pharmacopoeia (USP) rotating basket method. The rotating basket dissolution apparatus (Copley, Type FH 16-D, Nottingham, UK) was utilized for determination of the *in vitro* release of piroxicam from the various suppository bases. Each suppository was placed in basket and lowered into a flask containing 500 mL of phosphate buffer solution pH 7.4 (as a dissolution medium). The basket was rotated at 50 rpm at a constant temperature of 37 ± 0.5°C. At appropriate time intervals (0, 5, 10, 15, 20, 25, 30, 40, 50, and 60 minutes), 5 mL samples were withdrawn through Millipore filter syringe. 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 formula. Piroxicam samples were analyzed spectrophotometrically at λ_{max} (356 nm), which was determined previously by scanning in UV-visible spectrophotometer. The released amount of piroxicam after each time interval was calculated as a percentage after determination its concentration from the equation of the calibration curve.[13]

Factors affecting Physical Properties of Piroxicam Suppositories and *In vitro* Drug Release

Different formulas of piroxicam suppositories were prepared (Tables 1 to 3) in order to study the effect of different factors as illustrated below:

Effect of the Type of Suppositories

Three types of suppositories composed of the same base were selected to investigate the influence of suppository type on their physical properties and the percent release of piroxicam from them. The first type was conventional suppositories, while the second and the third types were hollow-types suppositories containing piroxicam in powder or solution form.

Formulas utilized to demonstrate this effect were F1, F6, and F10, which composed of the same base (witepsol H35 oleaginous base). Also, F4, F8, and F12 utilized PEGs 400:4000 (70:30) as a hydrophilic base, as well as, F5, F9, and F13 composed of glycerinated gelatin base.

Effect of the Type of Suppository Bases

To investigate the effect of type of suppository bases on the physical properties and *in vitro* release of piroxicam from the prepared conventional suppositories, witepsol H35 in F1,

PEGs 200:6000 (70:30) in F2, PEGs 400:4000 (70:30) in F4, and glycerinated gelatin base in F5 were used.

While, F6, F7, F8, and F9 were prepared to investigate the effect of type of suppository bases on the physical properties and *in vitro* release of piroxicam from the prepared hollow type suppositories containing piroxicam powder in their cavity.

On the other hand, F10, F11, F12, and F13 were used for hollow type suppositories containing piroxicam solution in their cavity with different types of bases.

Effect of Changing the Grade and the Ratio of PEGs

The effect of changing the grade and ratio of PEGs as a suppository base on the physical properties and piroxicam release were studied. This was done by either changing the grade of PEGs with same ratio as, PEGs 200:6000 (70:30) in F2 and PEGs 400:4000 (70:30) in F4, or changing the ratio of the same grade as, PEGs 200:6000 (70:30) in F2 and (50:50) in F3, or changing both of them as in F3 and F4.

Statistical Analysis

Analysis of variance (ANOVA) test was used to analyze the difference between many groups, while, Student's t test was used to analyze the difference between two groups by utilizing SPSS18 software window. A probability value ($p < 0.05$) was considered the minimum level of statistical significance.

RESULTS AND DISCUSSION

The physical properties of the prepared suppositories containing 20 mg piroxicam with their corresponding bases were demonstrated in Table 4.

Factors affecting Physical Properties of Suppositories and *In vitro* Drug Release

Effect of the Type of Suppositories

The effect of changing the type of suppository on physical properties of piroxicam suppositories using witepsol H35 as oleaginous suppository base was shown in Table 5. The hardness, melting time, and softening time for conventional suppositories (F1) were 3.57 kg, 14.17, and 6.35 minutes, respectively. While for hollow type suppositories containing piroxicam in powder form (F6) were 3.02 kg, 12.07, and 4.21 minutes, and for those containing piroxicam in solution form (F10) were 2.52 kg, 11.03, and 3.23 minutes, respectively. The results revealed that each of hardness, melting time, and softening time for both hollow types suppositories containing piroxicam in powder (F6) or solution (F10) form were less significantly ($p < 0.05$) than those obtained for conventional suppositories (F1).

This reduction in physical properties may be due to the presence of cavities in hollow type, which might affect the skeleton structure in contrast to the compact backbone of the

Table 4: Composition and physical properties of piroxicam conventional and hollow-type suppositories

Formula No.	*Type of the base*	*Type of the suppositories*	*Hardness (kg)**	*Melting time (min)**	*Softening time (min)**
F1	Witepsol H35	Conventional	3.57 ± 0.43	14.17 ± 1.63	6.35 ± 0.49
F2	PEGs 200:6000 (70:30)	Conventional	3.25 ± 0.38	30.00 ± 0.03	-
F3	PEGs 200:6000 (50:50)	Conventional	3.60 ± 0.33	36.00 ± 3.41	-
F4	PEGs 400:4000 (70:30)	Conventional	3.17 ± 0.41	26.00 ± 3.42	-
F5	Glycerinated gelatin base	Conventional	-	38.00 ± 3.74	-
F6	Witepsol H35	Hollow (piroxicam powder)	3.02 ± 0.44	12.07 ± 1.22	4.21 ± 0.57
F7	PEGs 200:6000 (70:30)	Hollow (piroxicam powder)	2.62 ± 0.37	28.00 ± 3.27	-
F8	PEGs 400:4000 (70:30)	Hollow (piroxicam powder)	2.33 ± 0.34	20.67 ± 3.08	-
F9	Glycerinated gelatin base	Hollow (piroxicam powder)	-	33.00 ± 3.41	-
F10	Witepsol H35	Hollow (piroxicam solution)	2.52 ± 0.42	11.03 ± 1.11	3.23 ± 0.47
F11	PEGs 200:6000 (70:30)	Hollow (piroxicam solution)	2.36 ± 0.28	26.00 ± 3.41	-
F12	PEGs 400:4000 (70:30)	Hollow (piroxicam solution)	2.05 ± 0.36	18.00 ± 2.61	-
F13	Glycerinated gelatin base	Hollow (piroxicam solution)	-	30.00 ± 3.90	-

*Values were expressed as mean ± standard deviation; n = 6

Table 5: Effect of type of suppositories on the physical properties of piroxicam suppositories utilizing witepsol H35 base

Formula No.	*Type of the suppositories*	*Hardness (kg)**	*Melting time (min)**	*Softening time (min)**
F1	Conventional	3.57 ± 0.43	14.17 ± 1.63	6.35 ± 0.49
F6	Hollow (piroxicam powder)	3.02 ± 0.44	12.07 ± 1.22	4.21 ± 0.57
F10	Hollow [piroxicam solution (b)]	2.52 ± 0.42	11.03 ± 1.11	3.23 ± 0.47

*Values were expressed as mean ± standard deviation; n = 6

conventional type with more rigid and consolidated structure than the hollow-type.[8,15]

The effect of changing the type of suppositories on the *in vitro* release of piroxicam from witepsol H35 base for F1, F6, and F10 was illustrated in Figure 1.

Piroxicam released by melting of the oleaginous base (witepsol H35). The percent release of piroxicam for F1, F6, and F10, during the first 5 minutes was found to be 9 ± 2%, 5 ± 2%, and 65 ± 3%, respectively. While, after 50 minutes, the percent release of piroxicam was increased to 21 ± 3%, 7 ± 2.5%, and 98 ± 2.5% for F1, F6, and F10, respectively. Drug release was attributed to the melting of the suppository base.[15] However, hollow type suppositories (F10) loaded with piroxicam in solution (b) exhibited significant ($p < 0.05$) rapid, and highest percent release of piroxicam in contrast to the conventional F1 and hollow-type containing powder F6. Since, piroxicam was already present in solution form and ready for release after melting of the base. Otherwise, dissolution process was required before release of piroxicam for F1 and F6 in which the drug dispersed or in powder forms,[8] as well as, the effect of changing the type of suppositories on the physical properties and *in vitro* dissolution rate was represented by suppositories containing a mixture of hydrophilic bases (PEGs 400:4000 at ratio 70:30), such as, conventional F4, hollow-type containing piroxicam powder F8, and hollow-type with piroxicam in solution (a) F12. The hardness and melting time were 3.17 kg and 26 minutes for F4, 2.33 kg and 20.67 minutes for F8, and 2.05 kg and 18 minutes for F12, respectively, as shown in Table 6. Each of hardness and melting time for both hollow types suppositories containing piroxicam in powder F8 or solution F12 form were less significantly $p < 0.05$, than those obtained for conventional suppositories F4. These results also attributed to the compact back bone of the conventional type with more rigid and consolidated structure than the hollow-type.[15]

Piroxicam released by dissolving the hydrophilic bases (PEG 400 and 4000). A significant difference ($p < 0.05$) was observed in the percent release of piroxicam for F4, F8, and F12 in many time intervals, such as, after 5 minutes, it was found to be 28 ± 3.25%, 15 ± 2%, and 50 ± 3.25%, respectively (Figure 2). In addition, the time needed for 50% of the drug to be released was 10, 15, and 5 minutes for F4, F8, and F12, respectively. However, F12 exhibited more rapid and highest release profile than others. After 50 minutes, the percent release of piroxicam was increased to 90 ± 2.5%, 87 ± 2.25%, and 95 ± 2.5% for F4, F8, and F12, respectively. However, the drug exhibited little affinity to these hydrophilic suppository bases so, it partitioned out to the buffered media. Also, these results were attributed to solubilizing of the bases in this media.

In addition, the same observations were obtained when glycerinated gelatin base was used in F5, F9, and F13, as shown in Figure 3 and Table 7. The results revealed that, both hollow types suppositories containing piroxicam in powder F9 or solution F13 form exhibited a significant decrease in the melting time ($p < 0.05$) as compared with conventional one F5. Also, there was significant ($p < 0.05$) increase in the percent release of piroxicam from F13, as compared with F9 and F5. After 50 minutes, it was found to be 97 ± 3%, 85 ± 2.7%, and 83 ± 2.75%, respectively.

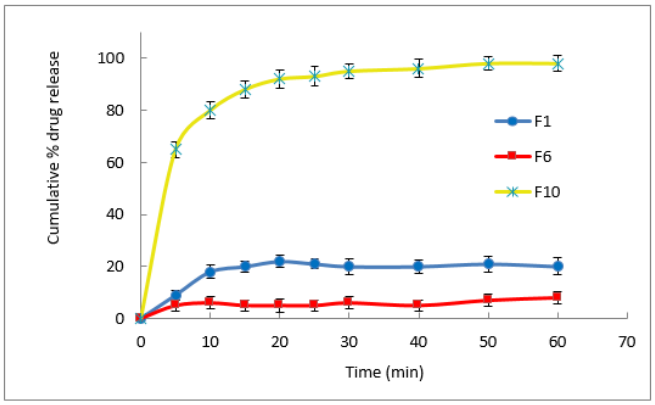

Figure 1: Effect of type of suppositories on the *in vitro* release of piroxicam from witepsol H35 base in phosphate buffer pH 7.4 at 37ºC [F1: conventional, F6: hollow containing piroxicam powder, and F10: hollow containing piroxicam solution (b)]

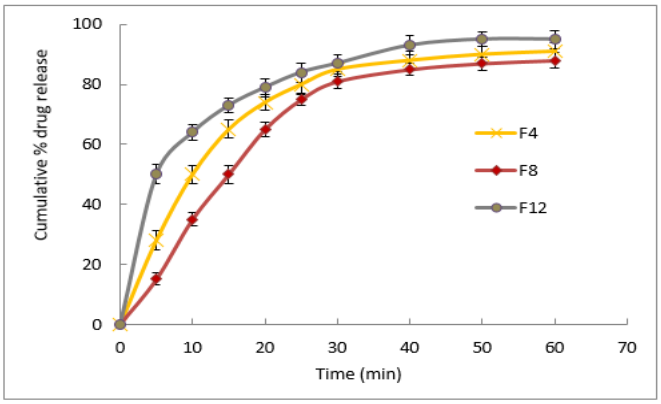

Figure 2: Effect of type of suppositories on the *in vitro* release of piroxicam from PEGs 400:4000 (70:30) base in phosphate buffer pH 7.4 at 37ºC [F4: conventional, F8: hollow containing piroxicam powder, and F12: hollow containing piroxicam solution (a)]

Table 6: Effect of type of suppository on the physical properties of piroxicam suppositories using PEG 400 and 4000 at ratio of (70:30) as hydrophilic base

Formula No.	*Type of the suppositories*	*Hardness (kg)**	*Melting time (min)**
F4	Conventional	3.17 ± 0.41	26 ± 3.42
F8	Hollow (piroxicam powder)	2.33 ± 0.34	20.67 ± 3.08
F12	Hollow [piroxicam solution (a)]	2.05 ± 0.36	18 ± 2.61

*Values were expressed as mean ± standard deviation; n = 6

Table 7: Effect of type of suppository on melting time of piroxicam suppositories using the glycerinated gelatin as hydrophilic base

Formula No.	*Type of the suppositories*	*Melting time (min)**
F5	Conventional	38 ± 3.74
F9	Hollow (piroxicam powder)	33 ± 3.41
F13	Hollow [piroxicam solution (a)]	30 ± 3.9

*Values were expressed as mean ± standard deviation; n = 6

Table 8: Effect of type of suppository bases on physical properties of conventional suppositories

Formula No.	*Type of the base*	*Hardness (kg)**	*Melting time (min)**
F1	Witepsol H 35	3.57 ± 0.43	14.17 ± 1.63
F2	PEGs 200:6000 (70:30)	3.25 ± 0.38	30 ± 3.03
F4	PEGs 400:4000 (70:30)	3.17 ± 0.41	26 ± 3.42
F5	Glycerinated gelatin base	-	38 ± 3.74

*Values were expressed as mean ± standard deviation; n = 6

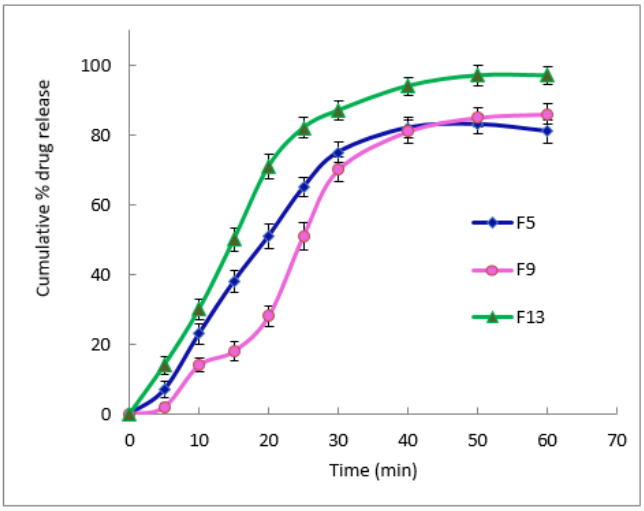

Figure 3: Effect of type of suppositories on the *in vitro* release of piroxicam from glycerinated gelatin base in phosphate buffer pH 7.4 at 37ºC [F5: conventional, F9: hollow containing piroxicam powder, and F13: hollow containing piroxicam solution (a)]

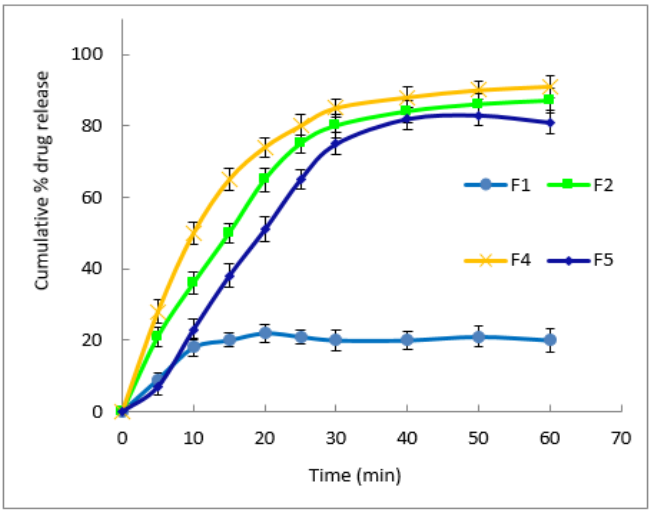

Figure 4: Effect of type of suppository bases on the *in vitro* release of piroxicam from conventional suppositories in phosphate buffer pH 7.4 at 37ºC [F1 (witepsol H 35), F2 (PEGs 200:6000 70:30), F4 (PEGs 400:4000 70:30), and F5 (glycerinated gelatin base)]

The overall results of changing suppository type revealed clearly that hollow-type suppositories containing piroxicam solution had faster and higher percent release, as compared with corresponding hollow-type containing piroxicam powder and conventional suppositories composed of the same base. These results were in good agreement with that obtained with metronidazole and morphine when formulated as conventional and hollow-type rectal suppositories.[16,17]

Effect of Type of Suppository Bases

The effect of changing the type of suppository bases on the physical properties (hardness or breaking strength and melting time) of the conventional suppositories was represented in F1 containing oleaginous base (Witepsol H35), F2 with water-soluble bases (PEGs 200:6000 70:30), and F4 containing PEGs 400:4000 (70:30) bases. Their hardness was 3.57, 3.25, and 3.17 kg, respectively. Meanwhile, their melting time was found to be 14.17, 30, and 26 minutes, respectively, as shown in Table 8. In addition, the melting time for F5 containing glycerinated gelatin base (water-soluble) was 38 minutes. No significant differences ($p < 0.05$) were observed in hardness of F1, F2, and F4, possessing different types of bases. While, significant differences ($p < 0.05$) were observed in melting time of F1, F2, F4, and F5. Suppositories containing lipophilic base F1 exhibited significantly ($p < 0.05$) shorter melting time than suppositories formulated with hydrophilic bases (F2, F4, and F5). This could be due to the mechanism of disintegration of these bases since; lipophilic bases melt quickly at 37ºC, while, PEGs and glycerinated gelatin bases dissolved more slowly.[18] However, these differences attributed to the physiochemical properties of these bases.[6,19]

These results were inconsistent with the results obtained when indomethacin and lornoxicam were formulated as rectal suppositories using oleaginous and hydrophilic bases.[20,21]

On the other hand, the percent release of piroxicam after 50 minutes from these conventional suppositories F1, F2, F4, and F5 were found to be 21 ± 3%, 86 ± 3%, 90 ± 2.5%, and 83 ± 2.75%, respectively, as shown in Figure 4.

Suppositories containing hydrophilic bases, such as, PEGs and glycerinated gelatin as in F2, F4, and F5 produce significantly ($p < 0.05$) higher percent release of piroxicam, in contrast to that formulated with lipophilic base witepsol H35 (F1). This behavior may be due to the low aqueous solubility of piroxicam so that the affinity of the drug to lipophilic base was higher than that to hydrophilic bases. Its solubility was better in a lipophilic base than in hydrophilic one and tended to stay in a lipophilic base longer than in hydrophilic bases.[22] Meanwhile, the higher release of piroxicam from hydrophilic bases may be related to both the low affinity of the drug to these bases and the water solubility of the bases in aqueous medium. These results were compatible with that obtained with diazepam, carbamazepine, and flurbiprofen rectal suppositories when formulated with different hydrophilic and lipophilic suppository bases.[23,24]

The effect of changing the type of suppository bases was also observed in hollow-type suppositories (F6–F9) containing piroxicam in powder form with lipophilic or hydrophilic bases, as shown in Table 9.

The hardness of hollow suppositories containing oleaginous base (witepsol H35) as F6 or hydrophilic bases like PEGs 200:6000 (70:30) as F7, and PEGs 400:4000 (70:30) as F8, were found to be 3.02, 2.62, and 2.33 kg, respectively. By applying ANOVA test, there were significant differences ($p < 0.05$) in hardness of F6, F7, and F8, which may be attributed to the physiochemical properties of these bases.[6] The melting point and hardness of PEGs act as a function of increasing polymerization of PEGs used that increases with increasing the molecular weight.[25] In addition, the melting time of F6, F7, F8, and F9 were 12.07, 28, 20.67, and 33 minutes, respectively. A significant difference ($p < 0.05$) appeared; suppositories containing lipophilic base F6 exhibited shorter melting time than that formulated with hydrophilic bases F7, F8, and F9. This could be due to the mechanism of disintegration of these bases since lipophilic bases melt quickly at 37ºC, while, glycerinated gelatin bases dissolved more slowly than PEGs.[18]

The effect of type of suppository bases used on the dissolution rate of piroxicam from F6, F7, F8, and F9 was demonstrated in Figure 5. According to the results obtained, the percent release of piroxicam after 50 minutes was found to be 80 ± 3.5%, 87 ± 2.25%, and 85 ± 2.7% for F7, F8, and F9, respectively, which were significantly ($p < 0.05$) higher than that for F6 (7 ± 2.5%). This may be due to entrapment of piroxicam in the melted base (oleaginous base, witepsol H35), which resulted in hindered migration of piroxicam. Besides that, the faster release of piroxicam from PEGs mixture and glycerinated gelatin bases might be due to the low affinity of piroxicam to these bases and the water solubility of the bases.[23] Drug partitioning is a function of the nature of base, and it corresponds to the affinity of the drug towards bases. When there is a low affinity between the drug and the base, the release rate of the drug is expected to be high,[26] as well as, effect of utilizing different bases on the physical properties and release profile of piroxicam appeared in hollow suppositories containing piroxicam in a solution form (F10–F13), as shown in Figure 6 and Table 10. The hardness of F10, F11, and F12

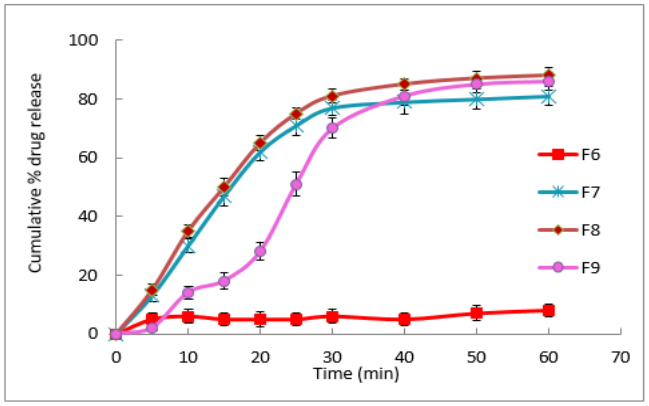

Figure 5: Effect of type of suppository bases on the *in vitro* release of piroxicam from hollow suppositories containing piroxicam powder in their cavities using phosphate buffer pH 7.4 at 37ºC [F6 (witepsol H 35), F7 (PEGs 200:6000 70:30), F8 (PEGs 400:4000 70:30), and F9 (glycerinated gelatin base)]

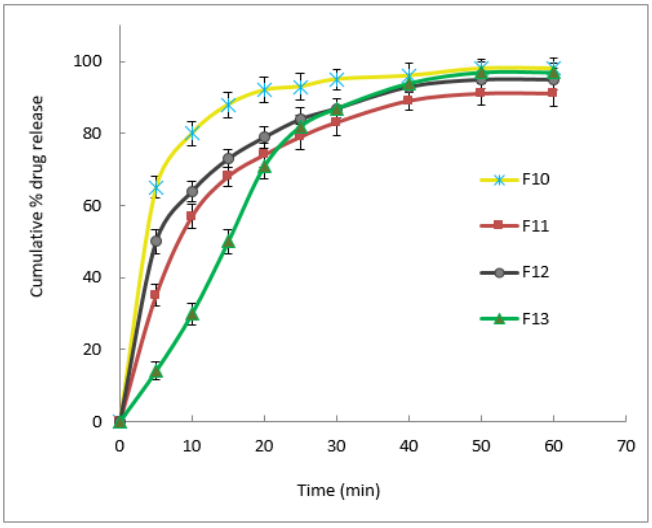

Figure 6: Effect of type of suppository base on the *in vitro* release of piroxicam from hollow suppositories containing piroxicam solution in their cavities using phosphate buffer pH 7.4 at 37ºC [F10 (witepsol H35), F11 (PEGs 200:6000 70:30), F12 (PEGs 400:4000 70:30), and F13 (glycerinated gelatin base)]

Table 9: Effect of type of suppository bases on the physical properties of hollow-type suppositories containing piroxicam in a powder form

Formula No.	*Type of the base*	*Hardness (kg)**	*Melting time (min)**
F6	Witepsol H 35	3.02 ± 0.44	12.07 ± 1.22
F7	PEGs 200:6000 (70:30)	2.62 ± 0.37	28 ± 3.27
F8	PEGs 400:4000 (70:30)	2.33 ± 0.34	20.67 ± 3.08
F9	Glycerinated gelatin base	-	33 ± 3.41

*Values were expressed as mean ± standard deviation; n = 6

Table 10: Effect of type of suppository base used on the physical properties of hollow suppositories containing piroxicam in a solution form

Formula No.	*Type of the base*	*Hardness (kg)**	*Melting time (min)**
F10	Witepsol H 35	2.52 ± 0.42	11.03 ± 1.11
F11	PEGs 200:6000 (70:30)	2.36 ± 0.28	26 ± 3.41
F12	PEGs 400:4000 (70:30)	2.05 ± 0.36	18 ± 2.61
F13	Glycerinated gelatin base	-	30 ± 3.90

*Values were expressed as mean ± standard deviation, (n = 6)

Table 11: Effect of changing grade and ratio of PEGs on the physical properties of piroxicam conventional suppositories

Formula No.	*Base*	*Hardness (kg)**	*Melting time (min)**
F2	PEGs 200:6000 (70:30)	3.25 ± 0.38	30.00 ± 3.03
F3	PEGs 200:6000 (50:50)	3.60 ± 0.33	36.00 ± 3.41
F4	PEGs 400:4000 (70:30)	3.17 ± 0.41	26.00 ± 3.42

*Values were expressed as mean ± standard deviation, (n = 6)

was 2.52, 2.36, and 2.05 kg, respectively. No significant difference ($p < 0.05$) was observed since all of them containing piroxicam solution in their cavities, which diminished the rigidity of suppositories skeleton. On the other hand, a significant difference ($p < 0.05$) appeared in their melting time. However, the melting time of suppositories formulated with oleaginous base, witepsol H35 (F10), was 11.03 minutes. It was significantly ($p < 0.05$) shorter than that of other suppositories containing water-soluble bases F11, F12, and F13, which was 26, 18, and 30 minutes, respectively, for the same reasons that mentioned previously for F6 to F9. These results were in agreement with the previous study reported by Ibtisam G *et al.*[27]

In addition, the percent release of piroxicam after 50 minutes for F10, F11, F12, and F13 was found to be 98 ± 2.5%, 91 ± 3%, 95 ± 2.5%, and 97 ± 3%, respectively. Little differences in percent release of piroxicam were observed between suppositories prepared from hydrophilic bases F11, F12, and F13, and that prepared from oleaginous base F10, as represented in Figure 6. While, there was significant difference ($p < 0.05$) difference in the percent of piroxicam released after the first 5 minutes, which was 65 ± 3%, 35 ± 3%, 50 ± 3.25%, and 14 ± 2.5% for F10, F11, F12, and F13, respectively (Figure 6). This referred to the fast melting of witepsol H35 base and higher solubility of PEGs mixtures (especially mixtures containing a high percentage of the lower grade member as PEGs 400 and 600), as compared with the lower solubility of glycerinated gelatin mixture.[24,28]

Effect of Changing the Grade and Ratio of PEGs' Bases

The effects of changing the grade and ratio of PEGs on the physical properties of the prepared suppositories were shown in Table 11. The effect of changing the grade of PEGs was represented by conventional suppositories F2 and F4, which were formulated with PEGs 200:6000 (70:30), and PEGs 400:4000 (70:30), respectively. The hardness of F2 and F4 was found to be 3.25 and 3.17 kg, respectively. However, there was only slight difference in their hardness and not significant ($p < 0.05$). On the other hand, a significant increase ($p < 0.05$) in the melting time of F2 (30 minutes) in contrast

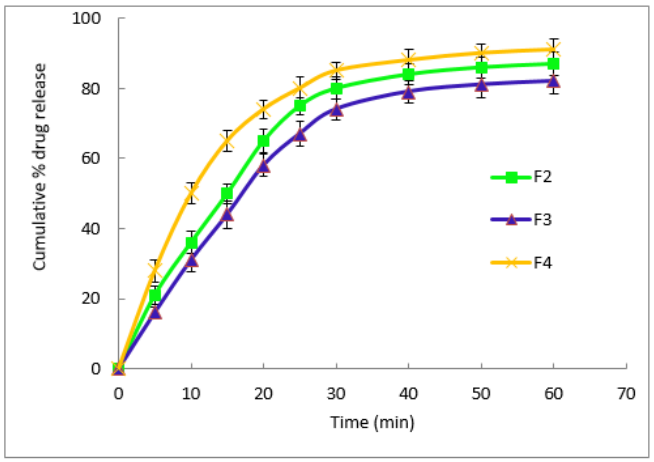

Figure 7: Effect of changing grade and ratio of PEGs bases on the *in vitro* release of piroxicam from conventional suppositories using phosphate buffer pH 7.4 at 37ºC [F2 (PEGs 200:6000 70:30), F3 (PEGs 200:6000 50:50), and F4 (PEGs 400:4000 70:30)]

to F4 (26 minutes) was observed. This may be attributed to the fact that increasing the molecular weight of PEGs (by polymerization) leads to increasing the hardness and melting time of the polymer. Therefore, the impact of PEG 6000 on the melting time and the hardness was more than that of PEG 4000.[18]

The effect of changing the ratio of PEGs was demonstrated in conventional suppositories F2 and F3, since both of them were formulated with (PEGs 200:6000) at 70:30 and 50:50, respectively. Also, not significant increase in hardness of F3 (3.6 kg) as compared with F2 (3.25 kg) but significantly ($p < 0.05$) longer melting time (36 minutes) was observed for F3 in contrast to F2 (30 minutes). So that, increasing the ratio of the higher molecular weight (PEGs 6000) and decreasing the ratio of the low molecular weight (PEGs 200) produced suppositories with little more hardness but significantly longer melting time.[18]

On the other hand, the percent release of piroxicam from F2, F3, and F4 after 50 minutes was found to be 86 ± 3%, 81 ± 2.02%, and 90 ± 2.5%, respectively, as shown in Figure 7. In general, all of them exhibited good release properties.

These results may be attributed to the low solubility of piroxicam in these hydrophilic bases since; it is lipophilic in nature and belongs to class II, according to Biopharmaceutics Classification System (BCS).[6]

In addition, the percent release of piroxicam after 5 minutes was found to be 21 ± 2.75%, 16 ± 1.5%, and 28 ± 3.25% for F2, F3, and F4, respectively. A significant increase ($p < 0.05$) in percent release of piroxicam represented by F4. However, F4 exhibited higher release profile than F2 and F3. These differences in the percent release of piroxicam were either due to the differences in grade F2 and F4, or grade and ratio (F3 and F4) of PEGs bases. However, PEGs of a lower molecular weight resulting in suppositories of higher release profile (high % release) and vice versa.[18] These results were in agreement when these bases were formulated for ibuprofen suppositories.[29]

CONCLUSION

Piroxicam released faster with higher percentage from hollow suppositories loaded with piroxicam in solution form (F10–F13) in addition to their best physical properties, as compared with corresponding conventional suppositories (F1, F2, F4, and F5), and hollow suppositories loaded with piroxicam in powder form (F6–F9) containing the same base.

In addition to the type of suppositories, the type of the base utilized, the grade, and ratio of PEGs bases are other important factors affecting physical properties of suppositories and the release profile of piroxicam.

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