

Research Article**CHARACTERIZATION AND *IN VITRO* EVALUATION OF PIROXICAM SUPPOSITORIES**

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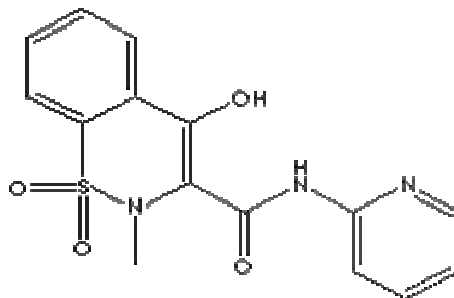
ABSTRACT

Piroxicam is an effective anti-inflammatory agent; it is an inhibitor of prostaglandin biosynthesis. The Principal advantage of piroxicam is its long half-life, which permits the administration of a single daily dose. Piroxicam is approved in the United States for the treatment of rheumatoid arthritis and osteoarthritis. It also has been used in the treatment of Ankylosing Spondylitis, acute musculoskeletal disorders, dysmenorrhea, postoperative pain and acute gout. Therefore, patients with gastrointestinal disorders or after surgery often have difficulties taking drugs by mouth. Rectal administration may be a good alternative to oral administration in these types of situations. Therefore in the present research attempt has been done to formulate piroxicam suppository dosage form in witepsol base. In the present study, the effectiveness of different agents on dissolution and release rate of piroxicam from its suppository base has been studied. Also, the effect of propylene glycol as cosolvent, polysorbate 80 as increasing solubility and colloidal silicon dioxide as suspending agent on the release behavior were investigated. Finally, the best formulation was chosen regarding their release profile, the time needed for 75% release of the drug (t_{75}), and uniformity of formulations.

KEYWORDS Piroxicam, Suppository, Witepsol**INTRODUCTION**

Piroxicam is a weakly acidic and highly lipophilic anti-inflammatory drug (FIG 1) available for oral, parenteral and topical administration. The drug inhibits the synthesis of prostaglandins in inflammation^{1,2}. The pharmacokinetics of piroxicam is characterized by a high oral absorption, and a long biological half-life (50-60 h), which makes possible single daily dose administration of the drug^{3,4}. Currently, several systemic and topical formulations are available as capsules, solutions for injection and gels of piroxicam. In some circumstances such as during nausea and vomiting or in uncooperative patients, oral route becomes impractical. The drug also has gastrointestinal side effects that limits oral route of administration¹. Limitations with the oral route and potential hazards and unacceptability of parenteral formulations prompted

the need for formulation, development and evaluation of suppository formulations of the drug, with the goal of introducing a new formulation to enhance the rate of release of the drug.

**FIG 1. Chemical structure of piroxicam.**

The clinical benefits of rectal piroxicam formulation in children have been demonstrated by Dix et al., 2004⁵, and Labrousse et al., 1989⁶. Also, it has been shown that piroxicam has a lower rate of side effects in lower gastrointestinal tract when compared with indomethacin, and no serious complication occurred⁷. The objective

of this study was to evaluate some suppository bases in order to determine bases capable of ensuring a rapid release of piroxicam. Possibility of improvement of the drug release by incorporation of different excipients was also investigated.

MATERIALS AND METHODS

Materials

Piroxicam and colloidal silicon dioxide were kindly provided by Darupakhsh co. (Tehran, Iran). Witepsol H₁₅ was also provided by Hakim Co., (Tehran, Iran), propylene glycol obtained from a local market, and Polysorbate 80 was purchased from Merck, Germany.

Experimental design

A single factor was varied at each time and a minimum of three replications were made. In the first stage, the single factor varied was the surfactant (Polysorbate 80) concentration, while all other factors (drug concentration, dissolution medium, temperature, dissolution apparatus and agitation) were kept constant. Three different concentrations (0.25, 0.5 and 1 percent) were used. Secondly, the single factor varied was the extent of co-solvent, propylene glycol (PG), incorporated, while other factors as earlier indicated were kept constant. Thirdly, the concentration of thickening agent (silicon dioxide) was the single factor that varied, all other parameters remained the same. Some of the formulations were rejected due to poor consistency and appearance and finally 9 formulations were tested for physical properties and release behavior.

Preparation of piroxicam suppositories

Suppositories containing 20 mg of piroxicam, which was analyzed and proved by potentiometric methods, were prepared by the fusion method using a metal mould with six cavities. The composition of the bases was a blend of Witepsol H₁₅ and component mentioned before. Drug displacement values of the bases used were first determined and the amount of drug required was calculated. The drug powder was passed through a mesh sieve of 100 μm prior to its incorporation into the base. Also, 20 mg of the drug with and without a surfactant (Polysorbate 80) at concentrations indicated in Table 1 were added into the composite base.

Determination of release rates

A paddle model No. 2 USP dissolution test apparatus was used with a 50 rpm rate⁸. The release chamber containing samples was suspended in 900 ml phosphate buffer (pH 6.8) in a 1000 ml beaker and maintained at $37 \pm 1^\circ\text{C}$ ^{9,10}. Samples (5 ml each) were taken at specified time intervals for up to 120 min and assayed for piroxicam. 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 release rate determinations were made for each suppository preparation. Piroxicam samples were analyzed using an ultraviolet spectrophotometric method.

A calibration curve was generated from a concentration range of the drug (0.01 to 0.06 $\mu\text{g/ml}$) prepared in methanol:glacial acetic acid (199:1) and UV absorbance measured at 325 nm. Following observation that piroxicam suppositories prepared exhibited the best release characteristics, the formulation was

subjected to pharmaceutical quality assessment following the British Pharmacopoeia tests¹¹.

Determination of softening time

A specific liquefaction and softening time apparatus (Erweka model D-61350, Germany) was used. The apparatus was consisted of a 37°C water bath for replacing the suppositories. Three samples of each formulation were tested simultaneously. The time needed for formulated suppositories to soften or liquefying was measured using a digital chronometer.

Content uniformity

The test was according to a modification of USP, 2003 method for indomethacin suppository. Absorbance of filtered solution in phosphate buffer medium pH 6.8 was determined at 353.5 nm using a spectrophotometer (Uvikon, Italy).

Other suppository tests

The mean content of the suppositories, determined using UV spectrophotometric method. The uniformity of appearance, weight and

of each suppository should fall within $\pm 5\%$ of the average value. Content uniformity test was performed in phosphate buffer medium (pH 6.8) according to modification of USP, 2003 method for indomethacin suppository. Capillary tube method was used to determine suppository melting range. All the tests complied with the pharmacopoeia standards.

Data analysis

The extent of drug release was assessed from the total amount of drug present in the dissolution medium at the end of the 120 min drug release experiment. The type of drug release kinetics applicable for the suppository bases was determined by evaluation of three models, zero-order kinetic model (Q vs. t), diffusion-controlled model (Q vs. square-root of t) and first-order model ($\log(Q_0 - Q)$ vs. t), where Q is the amount of drug released at time ' t ' and Q_0 is the initial amount of the drug. Then k , n and SS factors were calculated using a computer program (12). The model that consistently produced the highest correlation among the suppository preparations was used for the assessment of drug

Table 1: Composition and amounts of ingredients in different formulations of Piroxicam suppositories

Formulation	Ingredients				
	Piroxicam (mg)	Witepsol (g)	Polysorbate 80 (%)	Propylene glycol (%)	Silicon dioxide (%)
F ₀₁	20	2.032	-	-	-
F ₁₂	20	2.026	0.25	-	-
F ₁₃	20	2.021	0.5	-	-
F ₁₄	20	2.011	1	-	-
F ₂₅	20	1.827	-	10	-
F ₂₆	20	1.621	-	20	-
F ₃₇	20	2.016	0.25	-	0.5
F ₃₈	20	2.011	0.5	-	0.5
F ₄₉	20	1.806	0.5	10	0.5

content, as well as disintegration tests was evaluated. According to the mentioned reference, weight variation

release rates, and a slope obtained from linear regression analysis of the plot was determined as the drug release rate

constant. The results expressed as mean \pm SD were generated from 3 to 4 replicate determinations for each suppository preparation.

RESULTS AND DISCUSSION

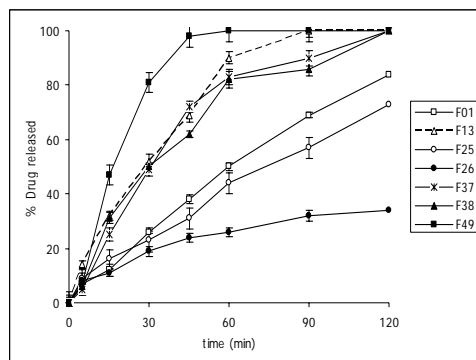


FIG 2. Release profiles of Piroxicam from suppositories of different bases, each containing 20 mg of the drug (n=3-5).

Adequate characterization of drug release rate from suppositories requires the determination of its appropriate release kinetics model. Kinetics of drug release from suppositories may vary from zero-order through diffusion-controlled to first order. Plots of released piroxicam amounts versus time for suppository formulation (F₀₁) showed a 'n' value equaled to 0.846 which indicates that the kinetics of release of the drug can appropriately be described by either a first-order or diffusion controlled model. The time needed for 75% release of piroxicam from different bases, in addition to 'k', 'n', 'SS' and regression coefficients are shown in Table 2, with drug release profiles depicted in fig 2. As it can be seen from Table 2, the time needed for drug release from Witepsol base is too long to have any clinical efficacy. In formulations F₁₂ to F₁₄, While the release rate was significantly increased by addition of Polysorbate 80 ($p < 0.05$), diffusion controlled mechanism was the main kinetic mechanism ($n = 0.576$). Similar results have been reported by Tucker et al.¹³. Also it has been shown that by

increasing the amount of Polysorbate 80 up to critical micelle concentration (CMC), the solubility of benzoic acid increased initially and then decreased gradually after CMC¹⁴.

To enhance the solubility of piroxicam in suppository base formula, propylene glycol (PG) was added in exactly 10 and 20 percents (F₂₅ and F₂₆). As shown in Table 3, addition of PG increased 't_{75%}' in both formulations. While the mechanism of release from F₂₅ can be described by either First-order or Diffusion controlled model, the Diffusion controlled mechanism mainly governs the drug release. It has been previously reported that the presence of PG decreases softening time of suppository bases¹⁵. As shown in Table 3 for F₂₅ and F₂₆, the presence of PG not only has not increased the rate of drug release, but also significantly decreased it. Although in formulation F₄₉ the addition of polysorbate 80 to PG has improved the release rate. The phenomenon can be probably due to the ability of the surfactant to increase the contact area between lipophilic base and aqueous nature of PG, which subsequently enhances water absorption property of PG, and so improves drug solubility. Thickening agent, colloidal silicon dioxide was added to enhance physical stability and homogeneity of the drug in suppository base. The appropriate percentage of silicon dioxide, which was 0.25% w/w, significantly improved homogeneity and appearance of the suppositories F₃₇ and F₃₈. The release mechanism from silicon dioxide containing bases was mainly diffusion controlled mechanism ($n = 0.576$). The release rate from F₃₈ was somewhat slower than F₃₇, probably due to micelle formation above the critical micelle concentration which increases drug solubility in the hydrophilic base and drug encapsulation in formed micelles¹⁶. However, addition of PG to the

formulation (F₄₉) significantly increased the drug release ($p < 0.01$). Also the results showed that the addition of colloidal silicon dioxide significantly increased melting point of the base. It has been previously reported that the presence of colloidal silicon dioxide may increase softening time of suppository bases¹⁵.

and its solubility in hydrophilic bases is expected to be low. Consequently, the drug has a higher tendency to diffuse out of hydrophilic bases. Another important factor that can influence the drug release is the water-absorbing property of the base which can facilitate penetration of the dissolution medium into the base with

Table 2: Statistics data for the release of different formulations

Formulation	Statistics			
	k	n	SS*	r
F ₀₁	1.5	0.864	23.7	0.9948
F ₁₂	36.6	0.288	173.0	0.9635
F ₁₃	79.2	0.567	226.0	0.9025
F ₁₄	34.5	0.189	46.2	0.8897
F ₂₅	1.7	0.782	26.7	0.9972
F ₂₆	4.2	0.443	13.6	0.9570
F ₃₇	6.5	0.596	308.0	0.9948
F ₃₈	6.8	0.576	57.2	0.9196
F ₄₉	17.3	0.408	1130.0	0.6710

*weighed sum of squares

Table 3: Weight, melting range, the time needed for the release of 75% of the drug (t_{75%}), and softening time data for different formulations (n=3-5).

Formulation	characteristic			
	Weight (g) Mean±SD	melting range (°C)	softening time (min)	T _{75%} (min)
F ₀₁	2.065±0.007	30-33	11.75±0.50	101
F ₁₂	2.105±0.019	31.8-35.5	11.28±0.73	80
F ₁₃	2.105±0.014	32-35.5	14.50±0.55	60
F ₁₄	2.110±0.014	31.7-35.5	14.19±0.98	73
F ₂₅	2.134±0.014	31.5-35	13.00±0.30	123
F ₂₆	2.127±0.004	31-35.5	12.50±1.40	297
F ₃₇	2.107±0.019	31-34	14.25±0.90	67.5
F ₃₈	2.119±0.015	29.5-31.5	16.00±0.00	71
F ₄₉	2.111±0.010	31-33	13.25±0.75	46.5

Though incompatibilities of Witepsol with some drugs have been reported¹⁷, the chemical class of drug to which piroxicam belongs, has not exhibited any physical or chemical incompatibility with the base. Thus, the release pattern observed may be related to the solubility of piroxicam in the base, its diffusibility from it and its subsequent solubility in the dissolution medium. Piroxicam is a lipophilic drug

subsequent wetting and desorption of the embedded drug. The literature abounds with reports on improvement of dissolution of poorly water-soluble drugs from polyethylene glycol - based solid formulations and, this is due to the water-absorbing properties of polyethylene glycols with their subsequent solubility-enhancing effects^{18,19}. It has been previously shown that polyethylene glycol is an

optimal base for the formulation of suppositories containing poorly water-soluble drugs^{20,21}. It can therefore be asserted that the hydrophilic character of the suppository base promotes the release of piroxicam.

CONCLUSION

In conclusion, combination of Witepsol and a hydrophilic ingredient, propylene glycol, was established to be superior to the lipophilic base alone, in terms of their ability to release the drug from the suppository formulations. Incorporation of non ionic surfactant at different concentrations did not result in improvement of the drug release. The low extent of *in vitro* availability of piroxicam is most likely a major factor of the very poor water-solubility of the drug. There is a need for further studies to enhance piroxicam release for optimization of mixture of Witepsol and propylene glycol suppository formulation of the drug. This may be achieved through development of modalities, such as complexation with beta-cyclodextrin, for possible improvement of the drug solubility.

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