Research Article

FORMULATION AND EVALUATION OF IBUPROFEN SUPPOSITORIES

Mosbah A. El-Majri ¹, Mokhtar M. El-Baseir ^{2*}

¹Department of Pharmaceutical Industry, Faculty of Pharmacy, Tripoli University, Libya

²Department of Pharmaceutics, Faculty of Pharmacy, Tripoli University, Libya

*Corresponding Author Email: mokhtar79@hotmail.com

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ABSTRACT

In this work suppositories containing Ibuprofen were prepared using water soluble bases (hydrous PEG and anhydrous PEG) and oil soluble bases (Suppocire AML, cacao butter, Witepsol E-75, Witepsol H-15, Novata DE-75, Suppocire AM, and Cacao butter). The prepared suppositories were evaluated for the parameters: weight variation, hardness, melting point, disintegration, melting point and drug content. In vitro drug release study was performed using USP type I apparatus in Sorensen's phosphate buffer pH 7.4 as dissolution media. Results showed that suppositories prepared using water soluble bases were within permissible range of all physical parameters. In vitro drug release from water soluble was greater than that from oil soluble bases. Suppocire AML, Cacao butter, Witepsol E-75 and Witepsol H-15 bases showed the highest values for the released ibuprofen among the tested bases. The lowest amount of drug released was observed with Novata DE-75 base. The study showed that the quality of suppositories is controlled by the type of base used.

KEY WORDS: Ibuprofen, in vitro evaluation, water soluble bases, oil soluble bases, suppositories.

INTRODUCTION

Mucosal drug delivery technique has received wide interest by many researchers. The advantages of this route over other routes of administration include avoiding the first pass metabolism and minimizing gastric irritation. The rectum has a good blood supply, absence of villi and a relatively small surface area (0.02-0.05 m²). Rectum also contains a small volume of viscous fluid (0.5-1.25 ml) spread over the surface with limited buffer capacity. Rectal route of administration is specifically useful for infants and children who have difficulty in swallowing, during nausea and vomiting conditions and when the patient is unconscious¹. In addition this route of administration through the use of suppository can also be suitable for local and systemic therapeutic effects²⁻⁴. However, in spite of being a noninvasive route of administration human rectum remains to be relatively unexplored route of drug delivery. Suppositories are solid dosage form have been prepared using either lipophilic or hydrophilic bases⁵⁻⁸. These suppositories either melt or dissolve in body fluids consequently release the entrapped drug. Ibuprofen (Figure 1) is a non-steroidal anti-inflammatory agent (NSAIA), has been widely used in the management of mild to moderate rheumatoid arthritis, osteoarthritis and primary dysmenorrhea. Like other NSAIA, Ibuprofen causes irritation, nausea, anorexia, gastric bleeding and diarrhea when given orally. Consequently, an alternative route of administration to avoid or minimize these side effects is preferred. Therefore the aim of this work was to prepare Ibuprofen suppositories using different bases.

Figure 1: Chemical Structure of Ibuprofen.

MATERIALS AND METHODS

Materials

Ibuprofen with particle size < 0.3 mm was bought from Ph. Eur., Industrial Chemica Prodotti, Italy. Polyethylene glycol 1400, 4000 were from Union Carbide, New York; Witepsol H-15 and Witepsol E-75 were from Dynamit Nobel, Witten, Germany; Suppocire AML and Suppocire AM were from Gatte Fosse, France; Novata DE-75 was from Hankel International Düsseldorf, Germany; Cacao butter BP grade was from Friedel-De Haen AG, Germany. All other chemicals used in this work were of analytical grade.

Preparation of Suppositories

Suppositories free and containing Ibuprofen were prepared by cream melt technique with a metallic suppository mould. Briefly, Adult's suppositories with bullet shape, free and containing 300 mg of ibuprofen homogenised with Anhydrous polyethylene glycol base (carbowaxes 400 and 4000 (4:6), Hydrous polyethylene glycol base (carbowaxes 400, 4000 and water (2:6:2), Witepsol H-15, E-75, Suppocire AML, Suppocire AM, Cacao butter and Novata DE-75 were prepared. Displacement value of Ibuprofen in each base was calculated and considered during formulation. The prepared suppositories

were wrapped in aluminum foil and kept in refrigerator until evaluation.

Evaluation of Suppositories

The prepared suppositories were evaluated for official and unofficial parameters via weight variation, hardness, disintegration, melting point, drug content and in-vitro drug release (dissolution test). The tests were carried out in triplicate and results were tabulated.

Weight Variation

The prepared suppositories were evaluated for weight variation according to method of British Pharmacopoeia⁹. Twenty suppositories made using each respective base were individually weighed using balance (Sartorius AG, Gottingen, Germany) and the average weight calculated. The weight variation was then estimated by subtracting the weight of each suppository from the average weight.

Mechanical Strength (Hardness)

This test was done using Erweka hardness tester (Type SBT, West Germany): The temperature inside the testing chamber was maintained at 25°C by means of circulating water from 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. An initial load (600 gm) was given by the entire suspended block and at regular intervals of one minute a disk of 200 gm was added until the suppository crushed. The mass required to crush the suppository was then calculated as the sum of the initial load and masses added until the suppository collapsed. The measurement of hardness was carried on all suppository formulations with and without ibuprofen.

Disintegration

Disintegration test was performed on six suppositories of each base using USP tablet disintegration (Model PTW, Germany) test apparatus. The suppositories were immersed in 160 ml of distilled water maintained at 37°C. The time for complete disintegration of water soluble bases and complete melting of oily bases was determined.

Melting Point

The ascending melting point method was used to determine the melting point of each base type of suppository. Briefly, capillary tubes of 10 cm in length sealed at one end were filled with the formulation to about 1 cm height. The tubes then dipped in gradually heated electro-thermal thermometer from which the temperature for melting of suppositories was predicted.

Content Uniformity

Ibuprofen is practically insoluble in water; therefore phosphate buffer pH 7.4 was selected as solvent medium. Three randomly selected suppositories for each base were taken in 1000 ml flask containing 100 ml phosphate buffer pH 7.4. The flask was shaken for desired period of time until the suppositories completely dissolved. Samples of the resulting solutions were appropriately diluted and subjected to absorbance measurement on Shimadzu PR240, Kyoto, Japan UV/Vis spectrophotometer at 264 nm using suppository solution prepared without ibuprofen as a blank. Ibuprofen content was calculated using calibration curve equation obtained by plotting the absorbance

for serial concentrations of ibuprofen in phosphate buffer pH 7.4.

In-vitro Drug Release Study

Dissolution test was performed in 900 ml of Sorensen's phosphate buffer of pH 7.4 using USP rotating basket dissolution apparatus (Pharm test, Type PTW Germany). The system was set to rotate at 50 rpm and the temperature maintained at $37 \pm 0.5^\circ\text{C}$. At intervals of 0, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180 and 200 minutes, 5 ml samples were withdrawn, suitably diluted and spectrophotometrically analysed at 264 nm. The volume taken was immediately replaced with an equal volume of fresh dissolution medium. Ibuprofen content in each sample was calculated using the calibration curve equation. In order to identify the release kinetics under the conditions where ibuprofen achieved better dissolution extent, data were fitted to different dissolution kinetic models (Zero-order, First-order and Diffusion). Nonlinear regression to fit the data was used; higher adjusted coefficient of determination (R^2_{adjusted}) was used to select the best model.

Statistical Analysis

Data was analysed using Excel system program (2010). All results were expressed as mean $\pm$ SD of three replicates for each suppository base. Statistical differences were analyzed using ANOVA test. A significant difference was considered at $p < 0.05$.

RESULTS

The physicochemical characteristics of suppositories were studied according to the methods described and the results are shown in Table 1. Weight variation of the prepared suppositories found to comply with British Pharmacopoeia standards. The percentage deviation in weight of all prepared suppositories was less than 0.51 from the average weight. Significant increase in the hardness values after incorporation of ibuprofen was observed. Hardness values of 2.8 kg for Suppocire AM, 3 kg for Suppocire AML, and Witepsol E-75, 3.4 Kg for Anhydrous PEG and > 6.2 Kg for Novata DE-75 bases containing ibuprofen were observed. The hardness of Witepsol H-15 and cacao butter based suppositories however, was reduced after inclusion of ibuprofen. Incorporation of ibuprofen had no effect on the hardness of Hydrous PEG based suppositories. A Disintegration time was significantly ($P > 0.05$) reduced for all formulations after incorporation of ibuprofen in comparison to plain suppositories without ibuprofen (Table 1). Disintegration time of suppository was within 30 minutes for fat based suppositories. Results showed that Novata DE-75 based suppositories were exceptionally with disintegration time of more than 60 minutes as plan and containing ibuprofen. According to the melting range and liquefaction time, the suppository bases can be ranked in the following descending order; Cacao butter $<$ Suppocire AML $<$ Witepsol H-15 $<$ Suppocire AM $<$ Witepsol E-75 $<$ hydrous PEG $<$ (Novata DE-75= anhydrous PEG). Excluding Suppocire AM and Witepsol H-15 bases, the addition of ibuprofen has led to decline in the melting range of the studied bases. The drug content (%) for all bases, was within the limits established in British Pharmacopoeia (B.P)⁹. Figure 2 illustrates the release profile of ibuprofen from deferent suppository bases. Ibuprofen release from water soluble bases (hydrous PEG and anhydrous PEG) was generally higher than that from oil soluble bases. The percentage of ibuprofen released in 3 hrs. from hydrous and anhydrous suppository bases was up to 100 % w/w respectively. These results are in consistence with the results reported for

flurbiprofen suppository dosage forms¹⁰. In contrast for oil soluble bases the release of ibuprofen did not exceed 60% w/w in 3 hrs. The release of ibuprofen from Novata DE-75 and Suppocire AM did not exceed 30 %w/w respectively. According to the release pattern of ibuprofen, the oil soluble suppository bases can be arranged as Suppocire AML> Cacao butter > Witepsol E-75> Witepsol H-15 > Suppocire AM> Novata DE-75 (Figure 2). With the exception of cacao butter, results showed that the release of drug from bases with low melting

range was higher than from those with high melting range. Suppocire AML with melting range (33-36°C) resulted in the highest amount of drug released (97.76%) followed by Witepsol E-75 with melting range (36-39°C), which released about (55.25%) of ibuprofen in 3 hours. The lowest amount of drug released was observed with Novata DE-75, which exhibited the highest melting range (41-44°C) followed by Suppocire AM with melting range (36-38°C).

Table 1: Ibuprofen Suppositories Parameters Using Different Bases

Suppository Base	Weight Variation (mg ±SD) n= 20	Hardness (Kg)		Disintegration time (min)		Melting Range (°C)		liquefaction Time (min.)		Ibuprofen Entrapment Efficiency %
		C	FM	C	FM	C	FM	C	FM	
Anhydrous PEG	1.98 ± 0.02	3.2	3.4	14.0	12.0	40-41	38-47	10.0	9.5	100.0
Hydrous PEG	1.79 ± 0.02	3.9	3.9	15.0	13.0	42-43	38-44	12.0	13.0	99.8
Suppocire AML	1.78 ± 0.11	2.8	3.0	13.4	3.45	35-36	33-36	4.0	3.5	99.5
Cacao butter	1.65 ± 0.04	2.9	2.4	6.0	3.41	30-35	32-35	4.0	5.5	100.0
Witepsol E-75	1.86 ± 0.02	2.4	3.0	30.0	23.34	37-39	36-39	42.0	45.0	100.0
Witepsol H-15	1.69 ± 0.05	2.4	2.0	11.25	8.58	34-36	34-36	9.0	8.5	100.0
Suppocire AM	1.87 ± 0.02	2.6	2.8	8.7	6.40	34-37	36-38	8.0	7.0	100.0
Novata DE-75	1.65 ± 0.04	>6.2	>6.2	>60	>60	40-42	41-44	>120	>120	100.0

The data are the mean ± standard deviation of three determinations. C, Control (suppository without ibuprofen). FM, Fresh medicated suppository

Table 2: Release kinetic Results for Ibuprofen from Different Suppository Bases

Suppository Base	Z-order (R ²)	First order (R ²)	Diffusion (R ²)	Suggested model
Anhydrous PEG	0.84	-3.53	0.96	Diffusion
Hydrous PEG	0.79	-5.62	0.97	Diffusion
Cacao Butter	0.93	-2.19	0.95	Diffusion
Suppocire AML	0.88	-4.21	0.96	Diffusion
Suppocire AM	0.96	0.57	0.84	Zero order
Witepsol H-15	0.99	-0.473	0.75	Zero order
Witepsol E-75	0.94	-1.31	0.93	Zero order
Novata DE-75	0.97	0.49	0.86	Zero order

R² is the regression coefficient

Figure 2: Drug Release Profile of Ibuprofen from Suppository Bases

DISCUSSION

The results obtained indicate that the prepared suppositories met official standards with regard to weight and content uniformity as presented in Table 1. Generally, drug release from suppository bases depends upon the drug solubility in the base, chemical composition of the base and drug particle size. The drug release from the suppositories bases is also influenced by the presence of other additives in the formulation and may result in an increase or decrease in the rate of release depending on the nature of the base and that of the additives and its

concentration¹¹. Several techniques have been reported in the literature for enhancing the dissolution of ibuprofen^{12,13}. Results in this study showed that ibuprofen release from water soluble bases (hydrous PEG and anhydrous PEG) was higher than from oil soluble bases. This enhancement in dissolution could be due to enhanced solubility of ibuprofen by water-soluble bases through formation of solid dispersions of ibuprofen with the base¹⁴. Furthermore, PEG bases have good hydrophilic property and solubilising effect¹⁴. It can also be suggested that water present in the hydrous base decreased the affinity of the drug to the base and hence increased the rate of the drug release¹⁵. For

oil soluble bases it could be concluded that softening point of these suppositories was the rate limiting step in release of drug from fatty bases. Cacao butter has low melting range (32-35°C) but gives slightly lower release pattern of medicament compared to Suppocire AML and Witepsol E-75. The presence of monoglycerides in the latter bases act as emulsifying agent thus facilitating the dispersion of medicament to the surrounding media.

Adequate characterisation of drug release rate from suppositories requires the determination of its appropriate release kinetics model. Table 2 shows the calculated regression coefficient (R^2) and the suggested release kinetics model for the studied suppositories bases. Analysis of the drug release data from different suppository formulations revealed that the release of ibuprofen from water soluble bases followed diffusion controlled mechanism with regression coefficient (R^2) of 0.96 and 0.97 %. For oil soluble bases (Suppocire AM, Witepsol H-15, Witepsol H-75 and Novata DE-75) the release profile found to follow Zero order kinetics. Cacao butter and Suppocire AML based suppository exhibited the diffusion kinetics with (R^2) values of 0.95 and 0.96 %.

CONCLUSION

The release of Ibuprofen from water soluble bases was higher than that from oil soluble bases. Incorporation of water in PEG base enhanced the drug release from the tested suppositories. Suppocire AML suppository bases afforded the highest medicament release among oil soluble bases. It can be concluded that the results of suppositories is controlled by the type and hydrophobicity of the base used.

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