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IN-VITRO EVALUATION OF IBUPROFEN RELEASE KINETICS FROM WITEPSOL SUPPOSITORIES

Mosbah A. El-Majri[1] and Mokhtar M. El-Baseir[2]*

[1]Department of Pharmaceutical Industry, Faculty of Pharmacy, Tripoli University, Tripoli, Libya.
[2]*Department of Pharmaceutics, Faculty of Pharmacy, Tripoli University, Tripoli, Libya.

*** Corresponding Author: Dr. Mokhtar M. El-Baseir**
Department of Pharmaceutics, Faculty of Pharmacy, Tripoli University, Tripoli, Libya.

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ABSTRACT
The aim of this work is preparation and characterisation of Witepsol (H5, H15, E75 and W35) suppository formulae containing ionic surfactants (cetrimide and pharmagel B and sodium lauryl sulfate) and non-ionic surfactants (Brij35, Myrj52 and Tween 20). Suppositories were prepared using melt cream method and tested for the physicochemical parameters using British Pharmacopeia (B.P) methods. Release kinetic studies of ibuprofen as a model drug from suppositories were carried out at 37 ± 0.5°C in buffer phosphate as dissolution media. All prepared suppositories were found to satisfy B.P, requirements for liquefaction time, hardness values, disintegration time and content uniformity. The amounts of drug released in 200 min from Witepsol (H15, E75, W35 and H5) W35 and WH5 based suppositories were 65% w/w, 60%w/w, 30%w/w and 23% w/w respectively. Incorporation of Pharmagel B, sodium lauryl sulfate, Myrj52 and Tween 20 surfactants within Witepsol H15 base, significantly enhanced the amount of the ibuprofen released. In this respect sodium lauryl sulfate and Myrj 52 were among the tested ionic and nonionic surfactants found to be superior as additive in preparing ibuprofen suppositories as the released amount of ibuprofen was 95% w/w and 89% w/w in 200 min. Analysis of release kinetics data using different mathematical models indicated that the release of ibuprofen from suppositories containing 1% of surfactant could follow more than one mechanism depending on the base matrix mixture.

KEYWORDS: Witepsol, Ibuprofen, Suppositories, Surfactants. Release kinetics.

INTRODUCTION
Rectal administration of drugs offers several advantages over other routes of administration. It offers reduction in the gastrointestinal irritation and the avoidance of both disagreeable taste and first pass effect. It is also an alternative route when oral route is not possible in nausea, vomiting and unconscious conditions and to treat childrenpp.[1] In general, rectal bioavailability believed to be lower than the corresponding oral values; however, previous study has demonstrated that the bioavailability of rectal Naproxen could be similar to its oral form while its side-effects are lower.[2] Suppository bases are intended to dilute the drug to nonirritating level, control the rate of drug release and representing the drug in an acceptable usable form. Witepsol are commonly used as fatty bases that as they melt at 37˚C. Nine grades of Witepsol are available of which Witepsol H5, Hl5, W35 and E75 attracted the research as suppository bases. Factors including drug solubility in the base, the chemical composition of the base and drug particle size are responsible for drug release from suppository bases. The drug release from the suppositories bases is also influenced by the presence of other additives in the formulation. An increase or decrease in the rate of release was found to depend on the nature of the base and the enhancers concentration.[3] Several studies have examined the use of surfactants as additives in formulating suppositories.[4-7] The surfactant component has a favourable effect on consistency, shortens the disintegration time and frequently accelerates drug liberation, which is mainly due to the change in the moistening ability of the drug, and spreading of the melt on the rectal mucosa.[8] Non-steroidal Anti-inflammatory Drugs (NSAIDs) are usually considered as good candidates for the development of conventional or controlled release preparations particularly through the rectal route to reduce or eliminate the gastrointestinal irritation. Ibuprofen is with pKa value of 4.5 and poorly soluble in water (0.078µg/ml) found to be a good candidate in this study.[9] Therefore, in the present study ionic and nonionic surfactants were incorporated in the formulations and in vitro release characteristics of ibuprofen from hydrophobic suppository bases were evaluated. In order to study the mechanism of the drug release from the base, the release kinetic results were subjected to different mathematical models and studied.

MATERIAL AND METHODS

1. Materials

Ibuprofen with particle size < 0.3 mm was from Ph. Eur., Industrial Chemica Prodotti, Italy. Witepsol H5 (WH5), Witepsol H15 (WH15), Witepsol W35(WW35) and Witepsol E75(WE75) were from Dynamit Nobel, Witen, Germany. Cetrimide, Pharmagel B and Polysorbate 20 (Tween 20) were from Sigma Aldrich. Sodium lauryl sulfate (SLS), Polyoxyethylene glycoldodecyl ether (Brij 35) and Polyoxyethylene (40) stearate (Myrj 52) were from Wilmington, USA. All other chemicals used in this work were of analytical grade and used as received.

2. Methods

2.1. Preparation of ibuprofen Suppositories

Suppository bases namely, Witepsol H5, Witepsol H15, Witepsol W35 and Witepsol E75 each weighing 2g plain and containing 300 mg of Ibuprofen each were prepared by the fusion method. The prepared suppositories were left for 24 hours at 25^{o}C before testing. Displacement value was calculated based on the following equation:

$F = (100\times(E-G))/(G\times x)+1.$

Where Fis the displacement value, E is the weight of the suppository without active substances (the calibration value of the mould for the certain base) G is the weight of the suppository with active substances and x is the active substance content in percentage.[10] Suppositories containing anionic and nonionic surfactants with concentrations of 1% w/w were also prepared using the same procedure.

2.2. Characterisation of suppositories

2.2.1. Weight Uniformity

The procedure was carried out according to British Pharmacopoeia B.P 1998 method. Weigh 20 suppositories individually then together and calculate the average weight according. There must be not more than 2 suppositories differ from the average weight by more than 5% and no suppository differs from the average weight by more than 10%.

2.2.2. Liquefaction time

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 1cm height. The tubes then dipped in gradually heated electro-thermal thermometer from which the temperature for melting of suppositories was predicted.

2.2.3. Hardness Test

Hardness test was carried out using the Erweka hardness tester. The temperature inside the testing chamber was controlled 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. At this point, the initial load, which was given by the entire suspended block, was 600 gm. After one minute a disk of 200 gm. was added and this weight addition was continued every minute until the suppository crush 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 (including the initial mass of the device i.e. 600 gm.).[11] For satisfactory results, hardness should lay between 1.8 and 2 kg.

2.2.4. Disintegration

Disintegration test was performed on six suppositories of each base using USP tablet disintegration (Model PTW, Germany) test apparatus. Disintegration time (D.T.) for suppositories was determined in water maintained at 37±0.5°C. Disintegration criteria (British Pharmacopoeia 1998) was followed to calculate the D.T. of test suppository.[12]

2.2.5. Content Uniformity

Ibuprofen content as carried out in phosphate buffer pH 7.4 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 until the suppositories completely dissolved. Samples of the resulting solutions were appropriately diluted, filtered through doubled layer Whatman filter paper followed by 0.45µm disc filter 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.

2.2.6. In-vitro Drug Release Studies

Dissolution test was performed in 900 ml of Sorensen's phosphate buffer of pH 7.4 using USP rotating basket dissolution apparatus (VK 7000 Dissolution Testing Station, Vankel Industries, Inc., NJ) following the USP paddle method. The system was set to rotate at 50 rpm and the temperature maintained at 37 ± 0.5°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.

2.2.7. Drug release kinetics

In order to identify the release kinetics under the conditions where ibuprofen achieved better dissolution extent, data were fitted to various release kinetic models viz. zero-order, first-order, Higuchi equation and Korsmeyer-Peppas models. The zero-order kinetic model was obtained by plotting cumulative % drug release vs. time. The first-order kinetic model was analyzed by plotting log cumulative % of drug remaining vs. time. The Higuchi model was evaluated by plotting cumulative

% drug release vs. square root of time, while the Korsmeyer–Peppas model was analyzed by plotting log cumulative % drug release vs. log time. Nonlinear regression to fit the data was used; higher adjusted coefficient of determination ($R^2_{adjusted}$) was used to select the best model. In order to select the proper mechanism for drug release, n values for Korsmeyer -Peppas model was applied.

2.2.8. Statistical Analysis

Data was analysed using Excel system program (2010). All results were expressed as mean ± 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 AND DISCUSION

In the present study, ibuprofen suppositories were prepared using Witepsol (H5, H15, E75 and W35) as fatty bases. The weight of suppositories was optimised and found to comply with British Pharmacopoeia (BP) standards.[12] The percentage deviation in weight of all prepared suppositories was less than 0.5 from the average weight. The data obtained from physicochemical parameters (liquefaction time, hardness, disintegration time, drug content) are shown in (Table 1). Liquefaction time for plain suppositories prepared without surfactants was ranged from 7.0 to 9.8 min. These values are within the acceptable limit (30 minutes) required for complete melting. [] Exceptionally WE75 showed high liquefaction time (44.5 min). Results in Table 1 indicated no significant change ($p > 0.5$) in the liquefaction time for suppositories after incorporation of ionic surfactants (Cetrimide, Pharmagel B and SLS). Liquefaction time however, was significantly reduced from 9.8 min for plain witepsol to 4.0, 4.6 and 5.5 and min after incorporation of 1%w/w non-ionic surfactants (Brij35, Myrj52 and Tween 20). Hardness values were ≤ 3.3 kg/cm^2 for all formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress condition while handling even after incorporation of surfactants within the base matrix. Disintegration time was ranged from 9 to 23 min depending on the type of base that significantly reduced with the incorporation of all nonionic surfactants and with Pharmagel B as ionic surfactant. Ibuprofen content in different suppository formulations was highly uniform with the range from 99.3% w/w to 100.3% w/w that is within the limits (95‑105%) specified by British Pharmacopeia, BP. Ideally, a sustained release suppository should release the required quantity of drug in order to maintain an effective drug plasma concentration. In general, drug release from suppository bases depends on the drug solubility in the base, the chemical composition of the base and drug particle size. The effect of suppository base type on the in-vitro release of drugs has been described in several investigations.[13,14] In the present study it was found that the release of Ibuprofen from suppositories was varied according to the type of matrix forming the base. Dissolution test results showed that were 65% w/w, 59% w/w, 31% w/w and 23% w/w Ibuprofen was released in 200 min from WH15, WE75, WW35 and WH5 bases (Fig.1). The percentage drug released in 200 min from the selected bases can be set in the descending order WH15 > WE75 >WW35>WH5. The highest percentage drug release achieved by witepsol H15 base may be attributed to its good emulsifying properties and pores formed in the base by penetrating solution into the suppository. The explanation for lower value for the released percentage of drug in general could be that ibuprofen is a lipophilic drug and it has high solubility in hydrophobic bases like witepsol. Therefore, it is expected to have a low tendency to diffuse out the hydrophobic bases into the dissolution medium. It is obvious that because of long time required for drug release, none of the investigated bases is an ideal for ibuprofen suppository formulation. Numerous studies have shown that drug release from suppository bases is 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 not only the nature of the base but also on the additive and its concentration considering the safety, efficacy and compatibility with other ingredients of the formulation.[13,15] WH15 base formulation showed the highest percentage (65% w/w) of ibuprofen released in 200 min among the tested bases, therefore, selected as a model for further study of the effect of surfactants on suppositories. Results in this work showed that the release of ibuprofen could be enhanced by incorporation of some surfactants. Fig 2 shows the in vitro release profile for ibuprofen from WH15 base containing 1% w/w ionic surfactants. It can be seen that suppository formulation resulted in 95% w/w and 88% w/w of ibuprofen were released in 200 min using WH15+SLS and WH15+Pharmagel B formulations respectively. Incorporation of cetrimide within WH15 however, showed no enhancement in the release rate of ibuprofen compared to plain base without surfactant. Findings indicate that cetrimide is not a suitable additive in formulation of suppositories compared to other surfactants tested in this work. Fig 3 shows the release profile for ibuprofen from WH15 base containing nonionic surfactants. WH15+Myrj 52, WH15+Tween 20 and WH15+Brij35 mixtures resulted in 90% w/w, 75% w/w and 65% w/w of ibuprofen was released in 200 min respectively. Generally, a significant enhancement in the release rate for ibuprofen was observed with incorporation of Merji52 and Tween 20 surfactants compared to the control base without surfactant. The mechanism of dissolution enhancement effect of surfactants is complex and not fully understood. The main possible mechanisms could be as a result of their moistening effects which increased the surface area of the suppository mass and also shortening disintegration times of lipophilic suppositories, which is caused by changing their lipophilic characteristics to a lipohydrophilic nature. Moreover, incorporation of cetrimide and Brij35 into WH15 suppository base had almost no effect on drug

release profile of ibuprofen and therefore cannot be considered as suitable additives. A good knowledge of the drug release kinetics will provide a proper understanding of the drug release mechanism. Four mathematical models were applied for analysis: Zero order, First-order, Higuchi and Korsmeyer-Peppas models. The values of the correlation coefficients (R^2) are presented in Table 2. According to the R^2-values, the in-vitro drug release profiles for the formulations WH15 and WE75 could be best expressed by zero order equation, as the plots showed high linearity with R^2 values of 0.9775 and 0.9824. Formulations WH15+cetrimide, WH15+pharmagel B and WH15+Tween 20 showed similar trends towards zero order kinetics. WH5, WW35, WH15+SLS, WH15+Brij35 and WH15+Myrj52 formulations found to follow Higuchi equation drug release model and diffusion mechanism is suggested for drug release from these formulations. The release exponents (n) value for the Korsmeyer-Peppas model will enable to understand the drug release mechanism.[16] For Fick diffusion values of n, would be < 0.5, between 0.5 <n< 1.0, or n = 1.0, for mass transfer following a non-Fickian model. The parameter (n) values observed after fitting the drug release data to Korsmeyer-Peppas equation was between 0.45 and 0.85 for all formulations. The results suggested that non-Fickian diffusion model could be applied for the tested formulations and the release of ibuprofen from these systems can involve more than one mechanism. In addition, the study generally indicate that WH15+SLS and WH15+Myrj52 were most suitable as suppository formulations for ibuprofen as a rectal dosage form among the tested formulations, however, considering the irritation effect of SLS as additive, WH15+Myrj 52 is more to be selected.

Table 1. Physicochemical Characterisation data of Ibuprofen Witepsol H15 Suppositories containing ionic and non-ionic surfactants.

Formula	Parameters				
	Liquefaction time (min)	Hardness (Kg)	Disintegration Time (min)	Content uniformity	Entrapment efficiency (%w/w)
WH5	9.0	3	15	299 ± 0.91	99.7
WH15	9.8	2	9	300.2 ± 0.76	100.0
WW35	7.0	3.25	10.5	300 ± 0.97	100.0
WE75	44.5	3	23.5	298.5 ±1.06	99.3
WH15+Cetrimide	10	2.4	12	299.6 ± 0.28	99.7
WH15+Pharmagel B	11	3.2	6	301 ± 0.87	100.3
WH15+SLS	9	3	11	300 ±1.21	100.0
WH15+Brij35	4.6	2.60	6.6	298.5 ± 0.32	99.5
WH15+Myrj52	5.5	2.75	5.68	298 ± 1.01	99.3
WH15+Tween 20	4.0	3.00	6.5	300 ± 0.08	100.0

WH5=Witepsol H5, WH15=Witepsol H15, WW35=WitepsolW35, WE75=Witepsol E75. SLS=sodium lauryl sulfate.

TABLE 2: Kinetic Parameters for Analysis of ibuprofen Release Data

Formula	Model				
	Zero order	First order	Higuchi	Korsmeyer–Peppas	
	R^2	R^2	R^2	R^2	n
WH5	0.8964	0.9615	**0.9862**	0.9877	0.6103
WH15	**0.9775**	0.8028	0.9663	0.9559	0.6965
WW35	0.8948	0.8916	**0.9848**	0.9757	0.6266
WE75	**0.9824**	0.8242	0.9681	0.9845	0.7165
WH15+Cetrimide	**0.9894**	0.8048	0.9598	0.9931	0.7127
WH15+Pharmagel B	**0.9725**	0.7709	0.9585	0.9887	0.8495
WH15+SLS	0.7562	0.9308	**0.9770**	0.9227	0.7216
WH15+Brij35	0.9101	0.9475	**0.9933**	0.9467	0.7216
WH15+Myrj52	0.9548	0.8148	**0.968**	0.9904	0.8213
WH15+Tween 20	**0.9888**	0.7773	0.9428	0.9968	0.8252

WH5=Witepsol H5, WH15=Witepsol H15, WW35=Witepsol W35, WE75=Witepsol E75. SLS=sodium lauryl sulfate, R^2, Correlation coefficient, n, exponent.

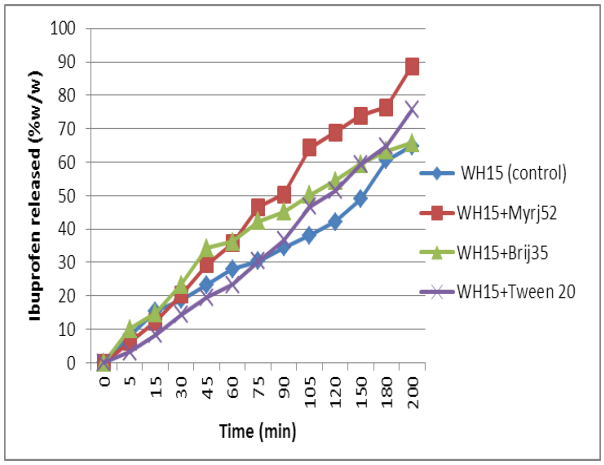

Figure1: In vitro release of Ibuprofen from different suppositories bases. Sorensen's phosphate buffer of pH 7.4 at 37 ± 0.5°C was used as dissolution medium.

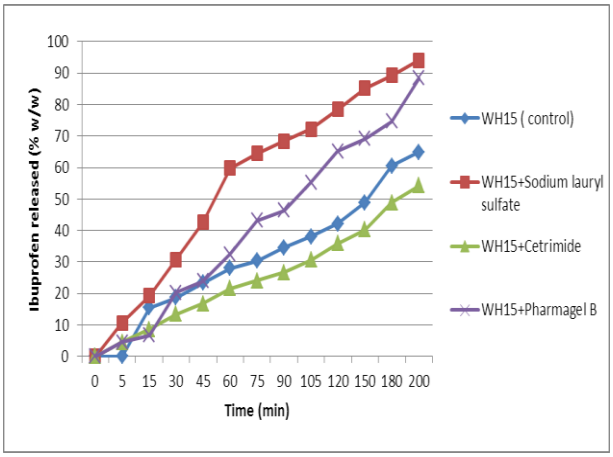

Figure 2. In vitro release profile of ibuprofen from Witepsol H15 (WH15) suppositories containing 1% w/w of ionic surfactants (Sodium lauryl sulfate, Cetrimide and Pharmagel B). Sorensen's phosphate buffer of pH 7.4 at 37 ± 0.5°C was used as dissolution medium.

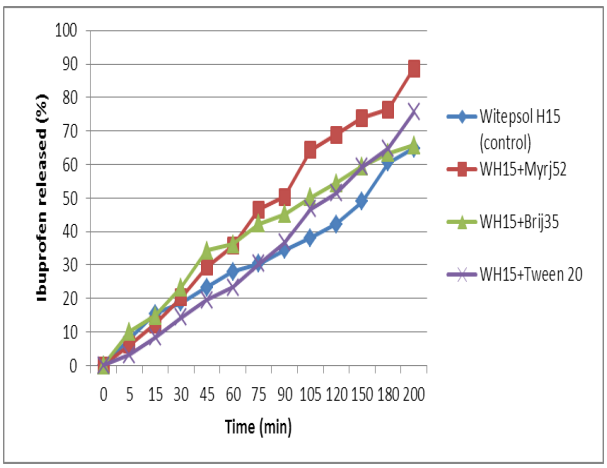

Figure 3. In vitro release profile of ibuprofen from Witepsol H15 (WH15) suppositories containing 1% w/w of nonionic surfactants (Myrj52, Brij35 and Tween 20). Sorensen's phosphate buffer of pH 7.4 at 37 ± 0.5°C was used as dissolution medium.

CONCLUSION

It can be concluded that suppository Formulations and the release profile of the entrapped drug is controlled by the type of base and additives. WH15+ Myrj 52 could be considered as suitable formulation for ibuprofen suppositories among the tested formulations in this study.

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