PREPARATION AND IN-VITRO EVALUATION OF WITEPSOL H15-IBUPROFEN SUPPOSITORIES CONTAINING NON-IONIC SURFACTANTS: THE ROLE OF SURFACTANT HLB VALUE AND CONCENTRATION

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ABSTRACT

This paper represents an investigation study results for the role of hydrophilic lipophilic balance (HLB) values and concentrations of non-ionic surfactants on the physicochemical properties of Witepsol H15 suppositories as well as the release kinetic of the entrapped drug. Witepsol H15 suppositories free and containing Brij, Myrj and Tween with different HLB values were prepared using milt method. Suppositories were characterised for physiochemical parameters using British Pharmacopeia methods. The release kinetic study for the entrapped drug from suppositories in absence and presence of surfactant was conducted at 37 ± 1ºC using phosphate buffer pH 7.4 as dissolution medium. The release rate data were then fit to different mathematical models and studied. Results showed that all the prepared suppositories were to satisfy British Pharmacopeia requirements for weight variation, liquification time, hardness, disintegration time and content uniformity. The incorporation of non-ionic surfactants within Witepsol H15 base resulted in changes in physicochemical parameters varied with HLB value and surfactant concentration. The amount of ibuprofen released was also greatly affected by HLB values and concentration of the surfactant used. Analysis of data using linear regression indicated that the release kinetic of ibuprofen from Witepsol H15 base containing 1% of surface active agent followed more than one mechanism.

KEY WORDS: Ibuprofen, in vitro evaluation, Tween, Myrj, Brij, suppositories, HLB

INTRODUCTION

Rectal administration of drugs offers several advantages over other routes of administration. Reduced side effects such as gastrointestinal irritation, avoidance of disagreeable taste and first pass effect are possible[(1)]. It is an alternative route when oral route is not possible in cases of nausea, vomiting, and unconscious conditions. Conventional suppositories are solids at room temperature and melt, soften or even dissolve at rectal temperature[(2,3)]. They are basically made of a base, the incorporated medicament and additives. 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 additives and their concentration in the formulation[(4)]. Surfactant is an amphophilic molecule having a head group and acyl chain and their characteristic is influenced by the concentration and hydrophilic lipophilic balance (HLB) value[(5)]. HLB value is an empirical expression for the relationship of the hydrophilic ("water-loving") and hydrophobic ("water-hating") groups of a surfactant. HLB numbers calculated for non-ionic surfactants are ranging from 0 to 20. Surfactant with HLB numbers >10 have an affinity for water (hydrophilic) and number <10 have an affinity of oil (lipophilic). Non-ionic surfactants are relatively less toxic to biological membranes and with better capacity to dissolve water insoluble drugs. Therefore, showed a wide interest as additives in suppository formulations[(6)]. In the present study non-ionic surfactants with different HLB values and concentrations have been evaluated as release modulator moieties for Non-steroidal Anti-inflammatory Drugs (ibuprofen). Non-steroidal Anti-inflammatory drugs are usually good candidates for the development of conventional or controlled release preparations particularly through the rectal route to reduce or eliminate the gastrointestinal irritation.

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MATERIAL AND METHODS

Materials:

Ibuprofen with particle size < 0.3 mm was from Ph. Eur., Industrial Chemica Prodotti, Italy. Witepsol H15 (WH15), was from Dynamit Nobel, Witen, Germany. Polyoxyethylene glycoldodecyl ether (Brij 30, 35, 58, 78 and 96) and Polyoxyethylene (40) stearate (Myrj 45, 52, 53 and 59) were from Wilmington, USA. Polysorbate 20 (Tween 20, 60, 65, 80, and 85) were from Sigma-Aldrich Chemicals Co, USA. All other chemicals used in this work were of analytical grade and used as received.

Preparation of suppositories:

Witepsol H15 suppositories plain and with surfactants and containing 15 mg/kg of ibuprofen were prepared by fusion method using a metal mould with six cavities. Drug displacement value of the base was first determined and accordingly the amount of drug required was calculated. The drug then mixed with the melted base and molded in stainless steel mould. The suppositories were lefts for overnight at room temperature before characterisation. The suppositories were subjected for weight uniformity,

liquefaction time, hardness, disintegration time as well as content uniformity evaluations.

Weight Uniformity:
The procedure was carried out according to British Pharmacopoeia B.P 2007 method[7]. Briefly 20 suppositories were weighed individually then together and the average weight then calculated. 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%.

Liquefaction Time:
The time taken for the entire suppository to melt or disperse when immersed in a water bath maintained at 37 ± 1˚C was measured according to suggested method[8]. 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. An average of four determinations was taken as the liquefaction time.

Hardness Test:
This test determines, under defined conditions, the resistance to rupture of suppositories. This test was carried out using the Erweka hardness tester. Briefly, 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 (600 gm) was applied. After one minute a disk of 200 gm was added and this weight addition was continued every minute until the suppository got crushed. 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)[7,9].

Disintegration Time:
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) were followed to calculate the D.T. of test suppository[10].

Content Uniformity:
Ibuprofen content was carried out in phosphate buffer pH 7.4 as solvent medium. Three randomly selected suppositories for each formulation 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 0.45 µm 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.

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 with the buffer medium and analysed at a wavelength of 264 nm using Shimadzu PR240, Kyoto, Japan UV/Vis spectrophotometer. The volume withdrawn at each interval was immediately replaced with an equal volume of fresh dissolution medium. Ibuprofen content in each sample was calculated using the calibration curve equation and the cumulative percent of ibuprofen released then plotted against time. Tests conducted with suppositories in which the active substance is absent have shown negligible absorption in the wavelength considered.

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, diffusion exponent (n) values for Korsmeyer -Peppas model was applied. The n value for different release mechanisms for cylindrical shaped matrices is given in (table 1).

(Table 1) Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

Statistical Analysis:

Data was analysed using Excel system program (2010). All results were expressed as mean ± SD of three replicates for the formulation. Statistical differences were analyzed using ANOVA test. A significant difference was considered at P-value <0.05.

RESULTS AND DISCUSSION

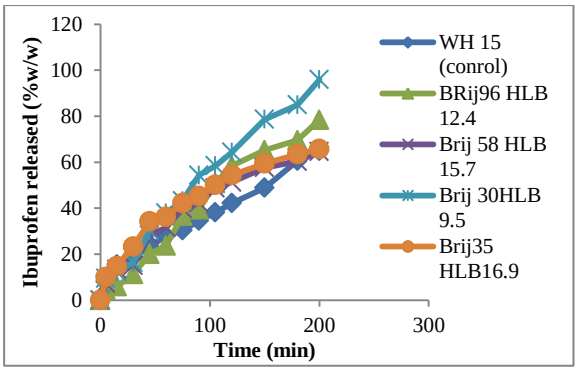
In the present work project, Witepsol H15 suppositories plain and containing non-ionic surfactants (Brij, Myrj and Tween) with different HLB values at the concentration level of 1 % w/w were formulated and studied. Table 2 shows the physicochemical parameters results for these formulations. Liquefaction time was 8.9 min for plain WH15 suppository reduced to 4.0-6.5 min in presence of 1% w/w Brij, Myrj and Tween. However, the variation in liquefaction time showed nonlinear correlation with HLB values but it was generally reduced by the addition of surfactant. The mechanical strength values of all tested suppositories were ranged from 2 to 3.2 kg showing an optimum hardness for handling and transportation. The disintegration time for the formulated suppositories was reduced from 6.65 min for plain suppository without surfactant to range of 3.8 to 6.6 min, 5.5 to 6.6 min and 5.5 to 7.0 min for Brij, Myrj and Tween containing formulations. The results indicate that disintegration time was not greatly affected by the addition of surfactant similar to the hardness (table 2).

(Table 2) Physical parameters for WH15 suppositories containing surfactant (1% w/w) with different HLB values

Formula	HLB	Liquefication Time (min.)	Hardness (Kg)	Disintegration Time (min)	Content Uniformity	Entrapment Efficiency (%)	Extent of drug release at 200 min (%)
WH15 (control)	-	9.8	2.0	6.65	301.1 ± 0.09	100.4	64.87
WH15+Brij 30	9.5	4.2	2.6	6.0	300 ±1.08	100.0	95.89
WH15+Brij 96	12.4	6.5	2.6	6.0	304.1±0.001	101.4	78.45
WH15+Brij 78	15.5	4.0	3.0	3.8	299 ± 1.11	99.7	84.45
WH15+Brij 58	15.7	4.0	2.6	4.0	303 ± 0.16	101.0	64.64
WH15+Brij 35	16.9	4.6	2.6	6.6	298.5 ± 0.32	99.5	65.76
WH15+Myrj 45	11.1	5.6	3.00	5.5	300 ± 0.18	100.0	58.9
WH15+Myrj 52	16.9	5.5	2.75	5.7	298 ± 1.01	99.3	88.75
WH15+Myrj 53	17.9	5.51	2.65	7.0	299.6 ± 0.26	99.9	64.23
WH15+Myrj 59	18.9	5.5	2.60	6.6	302 ± 0.07	100.7	61.26
WH15+Tween 65	10.5	5.0	3.0	7.0	299.6 ± 0.28	99.9	84.23
WH15+Tween 85	11.0	5.0	2.0	6.5	301.4 ± 0.09	100.5	88.79
WH15+Tween 60	14.9	5.0	3.2	5.5	301 ± 0.87	100.3	84.76
WH15+Tween 80	15.0	5.0	2.0	6.8	299 ±1.21	99.7	94.87
WH15+Tween 20	16.7	4.0	3.0	6.5	300 ± 0.08	100.0	75.65

WH15=Witepsol H15, HLB= Hydrophilic Lipophilic Balance

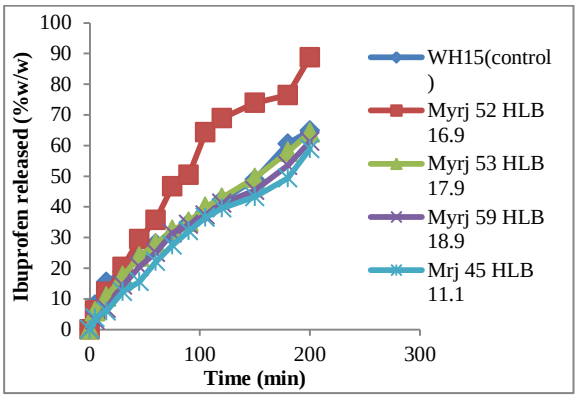
Drug content of 90–110% w/w that agree with specifications of the British Pharmacopeia for suppositories[10]. The effect of suppository bases on the in-vitro release of drugs has been described in several investigations[11,12]. In general, drug release from suppository bases depends on the drug solubility in the base, the chemical composition of the base and drug particle size[13]. Numerous studies have shown that drug release from suppository bases is also influenced by presence of other additives in formulation[14,15]. Figures 1-3 show the release profiles of ibuprofen as a model drug from Witepsol H15 base plain and mixed with non-ionic surfactants (Brij, Myrj and Tween) having different HLB values. According to (figure 1) it is obvious that there is an optimum HLB value for a suitable release of ibuprofen using Brij. An addition of Brij 30 with HLB value of 9.5 resulted in the highest percentage (99% w/w) of ibuprofen was released in 200 min followed by Brij 96 (with HLB value of 12.4) with 89% release. In contrast, there was no improvement in the released amount of ibuprofen using Brij 58 and Brij 35 having HLB values of 15.7 and 16.9. Results indicated an inverse relationship between the extent of drug release and the HLB values for Brij as surfactant. These findings could be explained as that surfactant at lower HLB value behaves as solubliser and therefore affinity of the drug towards the dissolution media enhanced and consequently more drug was released.



(Figure 1) Release profile of Ibuprofen from WH15 suppositories containing Brij with different HLB values.

Insignificant change in the extent of ibuprofen released in 200 min using Brij with higher HLB values 15.9 and 16.9 can be explained by the hydrophlicity of the surfactant at this stage and therefore leading to reduced ability to solubilise the drug and therefore not released to the dissolution medium.

(Figure 2) illustrates the release profile of ibuprofen in presence of Myrj of different HLB values.

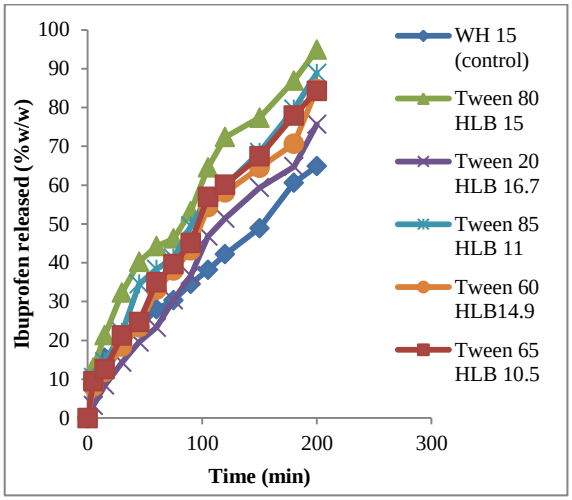


(Figure 2) Release profile of Ibuprofen from WH15 suppository containing Myrj with different HLB values.

Myrj 52 with HLB value of 16.9 showed an optimum release rate (89%w/w) of ibuprofen in 200 min where the addition of Myrj 45, Myrj 53 and Myrj 59 with HLB values 11.1, 17.9 and 18.9 showed nearly no improvement in the release rate of ibuprofen compared to 65 % w/w for plain WH15 base without surfactant. The results indicated no correlation between the HLB value and the release profile for ibuprofen using Myrj as an additive. The results also indicate that an optimum HLB value is required for surfactant to be effective enhancer for the release of drug from suppository.

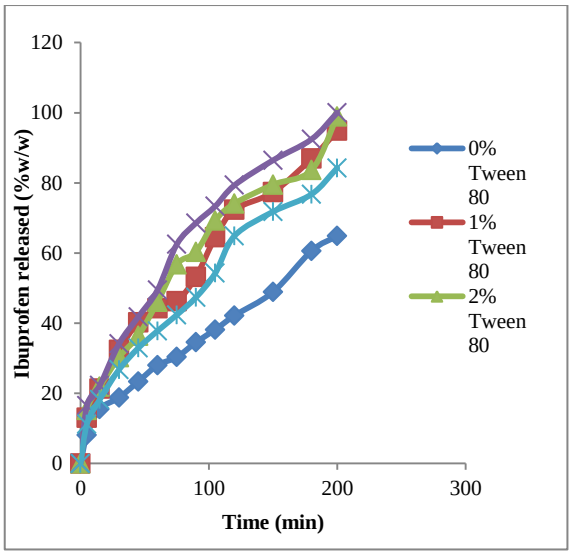
An enhancement in the extent of drug release rate from the suppository formulation to 95% w/w was achieved with Tweens having HLB values of 10.5 to15. However, an addition of Tween 20 with HLB value of 16.7 the extent of the released ibuprofen was improved from 65% w/w for plain base to merely 76 % w/w. The results indicate that by increasing HLB value for the surfactant, the release rate reduced. The release of drug from vehicle or carrier is influenced by several factors (dissolution medium composition, dissolution method setting, pH of the buffer used, temperature, etc). In order to study the relationship between surfactant concentration and the release profile of the entrapped drug, formulations containing 0, 1, 2, 3 and 4% w/w of Tween 80 were prepared and tested for the release rate of ibuprofen.

(Figure 3) illustrates the release profile of ibuprofen in presence of Tween.



(Figure 3) Release profile of Ibuprofen from WH15 suppositories containing Tween with different HLB values

(Figure 4) shows the release profile of ibuprofen from suppositories containing 0, 1, 2, 3 and 4% w/w of Tween 80.



(Figure 4) Release profile of Ibuprofen from WH15 suppository containing different concentrations of Tween 80.

A significant increase in the amount of ibuprofen released in 200 min from 65% w/w for plain WH15 suppository to 95, 99 and 100 % w/w with incorporation of 1, 2 and 3 % w/w of Tween 80. On increasing the concentration of Tween 80 to 4% w/w, the

extent of drug release achieved in 200 min was 85% w/w respectively. The reduced percentage of ibuprofen released in presence of 4% w/w of Tween 80 could be explained as micelle formation at this concentration of Tween 80 that lead to the reduced amount of ibuprofen released into the dissolution media. The other explanation could be due to an increase in the affinity for the drug towards the lipophilic base at this concentration, therefore delayed the release of the drug[16]. Release kinetic results of formulations containing Brij, Myrj and Tweens with different HLB values are summarised in (table 3).

(Table 3) Release kinetic parameters for Ibuprofen from WH15 suppositories containing Brij, Myrj and Tween with different HLB values

Additive	HLB	Model				
		Zero order	First order	Higuchi	Korsemeyer-Peppas	
		R^2	R^2	R^2	R^2	n
WH15 (control)		0.9779	0.8028	0.9663	0.9473	0.6971
Brij 30	9.5	0.9841	0.788	0.959	0.9558	0.806
Brij 96	12.4	0.9773	0.8285	0.9366	0.9749	1.6597
Brij 78	15.5	0.9646	0.7735	0.9768	0.9678	0.8373
Brij 58	15.7	0.937	0.9265	0.9819	0.9718	0.7447
Brij 35	16.9	0.9102	0.9475	0.9934	0.9584	0.7854
Myrj 45	11.1	0.9918	0.8707	0.9599	0.965	0.5708
Myrj 52	16.9	0.9928	0.8148	0.968	0.9898	0.8428
Myrj 53	17.9	0.9909	0.8122	0.8637	0.9874	0.7851
Myrj 59	18.9	0.9902	0.7962	0.9739	0.9906	0.8336
Tween 65	10.5	0.9812	0.8279	0.9656	0.965	0.5708
Tween 85	11.0	0.976	0.7806	0.9759	0.9518	0.7812
Tween 60	14.9	0.9802	0.7449	0.959	0.9697	0.8348
Tween 80	15.0	0.9573	0.8187	0.9841	0.9148	0.809
Tween 20	16.7	0.9888	0.7773	0.9428	0.9963	0.8225

WH15=Witepsol H15, HLB= Hydrophilic Lipophilic Balance

According to the correlation coefficient parameter (R^2), formulations containing Brij with HLB values 9.5 and 12.4 found to follow zero order kinetics where Brij with HLB values 15.5, 15.7 and 16.9 found to follow Hughici equation model. Exceptionally formulation containing Brij 96 with HLB value of 12.4 showed n value (1.6597) after Korsemeyer-Peppas model indicating Super case-II transport mechanism. The super case-II release mechanism may be attributed to burst-effect displayed by this formulation. Myrj containing formulations found to fit Zero order kinetics supported with correlation coefficient values (R^2) ranges from 0.9902 to 0.9928 irrespective of HLB value. Formulations containing Tweens with exception of Tween 80 were found to follow Zero order kinetics, with correlation coefficients ranged from 0.976 to 0.9888. Tween 80 containing formulation with HLB value of 15 exceptionally followed Higuchi equation model with correlation coefficient of 0.9841. According to Pappas equation, the mechanism of drug release was suggested to be non-fickian diffusion as its n values were between 0.5 and 1. Results for Tween 80 with concentrations 1, 2, 3 and 4 % w/w showed Zero order rate and non-fickian diffusion mechanism of the drug (table 4).

(Table 4) Release kinetic parameters for Ibuprofen from WH15 suppositories containing different concentrations of Tween 80

Formulation	Tween 80 Concentration (%w/w)	Model					Extent of Drug release at 200 min (%)
		Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsemeyer Peppas		
					R^2	n	
WH15 (control)	0	0.9779	0.8028	0.9663	0.9473	0.6971	64.87
WH15+ Tween 80	1	0.9573	0.8187	0.9841	0.9148	0.809	94.87
WH15+ Tween 80	2	0.943	0.7674	0.9852	0.9186	0.8499	98.89
WH15+ Tween 80	3	0.9309	0.8695	0.9921	0.8939	0.8827	100.00
WH15+ Tween 80	4	0.9658	0.8398	0.9817	0.9311	0.7723	84.24

WH15=Witepsol H15, HLB= Hydrophilic Lipophilic Balance

The release kinetics for these formulations seems not to be affected by the concentration of the surfactants.

CONCLUSION

Rectal route is a promising route for administration of drugs that are sometimes difficult to administer by other routes such as Non-steroidal Anti-inflammatory Drugs (ibuprofen). Non-ionic surfactants are usually added during formulation of suppositories to improve the quality of the base.

In this work WH15 suppositories containing non-ionic surfactants having different HLB values and concentrations were prepared and studied for their physicochemical properties and the release kinetics of the entrapped drug. The results of the study showed that work.

HLB value and concentration of the surfactant can affect the physicochemical properties of the base and the drug release profile from suppositories. It can be concluded that using proper amount of surfactant with an optimum HLB value are essential to control drug release from suppositories.

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