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Effect of Semi-Synthetic Bases and Hydrophile-Lipophile Balance (HLB) Of Mixed Surfactants on In-*Vitro* Release Profile of Ibuprofen Suppositories

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: The emphasis on the use of surfactants in enhancing drug release from fatty suppository bases has always been on the concentration and type of surfactants. However, the Hydrophile-Lipophile Balance (HLB) of the surfactants added, the concentrations and the type of suppository base used have significant effects.

Objective: The study aimed to evaluate the effect of HLB of incorporated mixed surfactants, the concentration, and the type of base used on the physical and release properties of Ibuprofen suppository formulations.

Methodology: Ibuprofen suppositories (200mg) were prepared using Witepsol® H15, Suppocire® CM, Witepsol® W35, Witepsol® E85 semi-synthetic bases. Mixed surfactants (Span® 80 and Tween® 80) were added at 4 %w/w in varied ratios to give HLB values of 4.3 to 15.0, and at 2 and 6% w/w at optimum HLB. The suppositories' physical properties and release profiles were evaluated using established procedures.

Results: The release followed Witepsol® W35>Witepsol® H15>Suppocire® CM>Witepsol® E85. Release from Suppocire® CM and Witepsol® E85 was favored at lipophilic HLB while release from Witepsol® W35 and Witepsol® H15 was favored at hydrophilic HLB. There was a general increase in the release of Ibuprofen with the increase in the concentration of mixed surfactants at the optimum HLBs. The release kinetics were majorly fitted for Higuchi's kinetic model and followed Fickian and Non-Fickian (anomalous) drug transport mechanisms depending on the HLB of the mixed surfactants.

Conclusions: The HLB, concentration of mixed surfactants, and the type of base greatly influenced the variation in the release profile of the Ibuprofen suppository.

Keywords: Ibuprofen; Hydrophilic-Lipophilic Balance; Mixed surfactants; Semi-synthetic fatty bases; In-*vitro* release

INTRODUCTION

Ibuprofen (Fig. 1) is an analgesic compound belonging to Non-Steroidal Anti-inflammatory Drugs (NSAIDs) (Varrassi *et al.*, 2019; Goma, 2018). As an analgesic with a mild antipyretic effect, ibuprofen is used in the treatment of mild to moderate pain (including pain relief after surgery), management of fever, including post-vaccination fever, osteoarthritis, dysmenorrheal, headaches, dental pains, and pain associated with a kidney stone (Adeleke and Oladimeji, 2021; Mosbah *et al.*, 2016). The mechanism of action of ibuprofen involves inhibiting the production of prostaglandins, which then results in the decreased activity of cyclooxygenase (cox) enzymes (Goma, 2018). The major side effects associated with ibuprofen as an NSAID are gastrointestinal irritation and ulcerations, which often affect patient compliance, thus

necessitating the need for alternative routes (Varrassi *et al.,* 2019). The use of suppositories as a rectal drug delivery system in avoiding the gastrointestinal side effects of ibuprofen is gaining wide recognition. Suppositories, in most cases, consist of the drug and the suppository bases that constitute the bulk of the formulation (Oladimeji *et al.,* 2017). Thus, the base's properties, such as solid fat index, hydroxyl value, melting and softening point, iodine value, and polymorphism, influence the physicochemical properties of the final suppository formulation and the release profile of the active ingredient (Happiness, 2006).

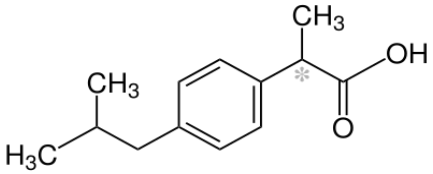

Figure 1: Chemical structure of ibuprofen

In addition, the chemical or physical interaction between the drug and the base also affects the drug's bioavailability (Adeleke and Oladimeji, 2021). Therefore, the selection of the right bases and their modifications is of great importance to achieving and improving the desired physicochemical properties and release profile in the suppository formulation. (Odeku and Okubanjo, 2009).

The emphasis placed on the use of surfactants in modifying suppository bases and enhancing drug release from suppository bases has always been on the concentration and type of surfactants used. There has, however, been limited focus on the hydrophile-lipophile balance (HLB) of the surfactants in relation to the properties of the base used, which also plays a great role in influencing the release profile of the drug (Niraj *et al*., 2013). Mixed surfactants with differed resultants HLB values have been effectively used in the formulation of some pharmaceutical products (Iwalewa *et al*., 2007). In addition, Adeleke and Oladimeji, in their work, were able to establish that the HLB of surfactants at a particular concentration influences the release profile of Ibuprofen in Semi-synthetic (Suppocire CM and Witepsol H15) bases (Adeleke and Oladimeji, 2021). Thus, this study aimed to evaluate and provide information on the effect of the HLB of mixed surfactants, different concentrations of the mixed surfactants at optimum HLB, and the type of semisynthetic base used, on the release profile of ibuprofen from the ibuprofen suppository formulations.

METHODOLOGY

Preparation of Ibuprofen Suppositories:

Each suppository formulation was prepared in a 1g mold using the fusion method and taking into consideration the displacement values of ibuprofen in each of the suppository bases used. The prepared suppository contained 200 mg of ibuprofen in the semi-synthetic fatty bases, without or with the addition of mixed surfactants (Tween® 80 and Span® 80) added at 4 %w/w concentration in varied ratios (Table 2) to give HLB values of 4.3, 6.0, 8.0, 10.0, 12.0, 15.0. At optimum HLB, the mixed surfactant was added at a concentration of 2 and 6 %w/w.

Evaluation of Prepared Ibuprofen Suppositories

Weight Uniformity

The test was carried out as specified in British Pharmacopoeia (BP), 2013. 20 suppositories were selected randomly from each batch of the formulations and weighed individually using a Metler Toledo weighing balance. The mean weight and the deviations from the mean weight of the individual suppository were determined. Deviations of the individual weight from the theoretical weight of the suppository were also determined.

Softening and Melting Points

The softening and melting temperatures were determined using the method reported by Oladimeji and Bankole, (2017). A sample from each batch of the suppository was placed in a test tube. The tube was clamped and immersed in a water bath placed on a thermostated heater to raise the temperature of the water gradually. The tube was immersed in the water bath to a depth that allowed the complete immersion of the suppository below the water level. A thermometer was inserted into the tube to take the temperature. The softening temperature was taken at the point when the suppository began to melt, and the melting point was taken at the point when there was a complete liquefaction of the suppository.

Crushing Strength

The crushing strength was determined using Monsato Hardness Tester (Copley Erweka, Germany). The suppository sample was randomly selected and the weight under which the suppository was crushed was

recorded in kilograms and converted to Newton by multiplying by a factor of 10 (Adegoke *et al*., 2016).

Determination of disintegration Time

The Manesty tablet disintegration apparatus (Manesty Machines Ltd., Liverpool, England) was employed using a method similar to that specified for suppositories in BP (2013). For the determination, a suppository was placed in the glass tube each, and a glass disk weighing 3 g was added to the tube (Adebisi and Oladimeji, 2021). The device was set to oscillate, and the time taken for the complete disintegration of the suppository was taken. This is the time it takes for the suppository to be completely deformed. An average of three determinations was taken.

Content Uniformity

The modified method described by Oladimeji and Bankole, (2017) was employed. A suppository was taken at random from each batch of the formulations and weighed. This was placed in a beaker containing 50 ml phosphate buffer (pH 7.4). The suppository was then melted by heating the beaker gradually in a water bath. When the melted suppository had completely dispersed, the mixture was chilled, and the oil layer was removed by filtration using a cotton plug. The resulting aqueous filtrate was further filtered using filter paper. From the aqueous filtrate, 0.5 ml was pipetted and diluted to 100 ml using the phosphate buffer solution. The absorbance of the resulting dilution was measured using a Microprocessor UV spectrometer (Labtronics, Model LT-290, India) at 222 nm. The concentration of the solution was calculated from a plotted standard Beer-Lambert curve of the pure drug.

In-Vitro Release of Ibuprofen from Suppositories

The BP (2013) basket method was used for the in vitro dissolution studies of the samples from each batch of the suppository. The dissolution medium was a phosphate buffer solution having a pH of 7.4. A suppository was selected at random from each batch of formulations and weighed. The weighed medicated suppository was placed in the dissolution basket set at 50 rpm in a flask containing the phosphate buffer maintained at a constant temperature of 37± 1 ˚C. 5ml portion was withdrawn at a fixed time over 180 min and the volume of the medium was kept constant by replacing it with an equal volume of phosphate buffer (pH 7.4) maintained at 37± 1 ˚C. The withdrawn sample was further diluted with an equal volume of the buffer solution and the absorbance of the diluted sample was determined using a UV Spectrometer (Labtronics, Model LT-290, India) at 222 nm. The amount of drug released for each sample withdrawn per sampling time was calculated from a standard Beer-Lambert calibration curve of the pure drug. The average of three readings was used in calculating the drug release from each of the suppositories at the predetermined time of sampling. The percentage of drug release at 60 min (D_{60min}), 180 min (D_{180min}), the time (min) for release of 15 % of the drug and time (min) for release of 25 % of the drug, (T_{15}) and (T_{25}), were used as the release parameters.

Kinetic Analysis of the Release Data

In determining the kinetic of drug release of Ibuprofen from the different formulations, the in-vitro release data were subjected to three kinetic models viz: Zero-order kinetic (Qt vs t) (Gouda *et al*, 2017), First order kinetic model (log (Q0-Qt) vs t) (Gouda *et al,* 2017) and Higuchi diffusion controlled model (Qt vs t1/2) (Suvankata *et al.,* 2010), where Q_t is the amount of drug released at time t, Q_0 is the initial amount of the drug in the formulation (200 mg). The model with the highest correlation coefficient, R^2 was assigned as the kinetic model that fitly describes the release (Mokhtar and Mosbah, 2016). The slope obtained from the linear regression analysis of the plot was used to determine the drug release rate constant. To assign the release mechanism, the profile data was further subjected to Korsmeyer-Peppas kinetic model (logQt vs nlogt) (Gouda *et al.,* 2017; Suvankata *et al.,* 2010) to obtain the value of release exponent, n that was used to assign the release mechanism involved in each formulation.

STATISTICAL ANALYSIS

The dissolution data and statistical analysis (ANOVA and t-test) were evaluated using a Microsoft Excel spreadsheet. A significant difference was considered at $p<0.05$.

RESULTS

Physicochemical Properties of Ibuprofen Suppository

The suppositories fell within 95 to 105 % of the average weight as stipulated in BP 2013 (Table 2). The addition of the mixed surfactant at the various HLBs caused an increase in the standard deviation (SD) and relative deviation from the theoretical value (RDT) in all the bases. The increase in the SD and the RDT can

be attributed to the effect of the weight of the added surfactant to the suppository formulation.

The softening (SP) and the melting points (MP) of the Ibuprofen suppository formulations, in Table 2, show the order Witepsol® E85>Suppocire® CM/ Witepsol® W35>Witepsol® H15. Formulations in Suppocire® CM and Witepsol® W35 had the same temperature range. The high melting range seen with Witepsol® E85 can be attributed to the fact that the base was composed mainly of triglycerides. They are hard fats with a high melting range above body temperatures.

The inclusion of the mixed surfactants caused a general increase in the crushing strengths of the formulations in the different bases at the various HLB values. This change in the crushing strength caused by the addition of the mixed surfactants had been attributed to the effect of the surfactant on the rheology of the formulation (Oladimeji and Adegoke, 2017). The Disintegration times (DT) for the formulations across the bases without mixed surfactants followed the order; Witepsol® E85>Witepsol® W35>Witepsol® H15>Suppocire® CM (Table 2). The disintegration time of Witepsol® E85 was about tenfold higher than the value for the other bases.

Release properties of the Ibuprofen Suppository

The plots of the % Cumulative amount release of the Ibuprofen against time in all the bases at different HLBs are shown in figures 2-5. The release parameters (T15, T25, $D_{60,}$ and D_{180}) are also shown in Table 3. The release of Ibuprofen from the suppository base after 180 min was generally low, below 30%. The release in formulations without mixed surfactants followed the order of Witepsol® W35>Witepsol® H15>Suppocire® CM>Witepsol® E85. Drug release from suppositories is dependent on the drug solubility in the base and the chemical composition of the base (Oladimeji and Bankole, 2017). Ibuprofen is a lipophilic drug, having a high affinity for lipophilic base and low solubility in water. Therefore, the low release of Ibuprofen can be attributed to the solubility of Ibuprofen in the lipophilic bases, its diffusion from them, and the subsequent solubility in the dissolution medium (Oladimeji *et al*., 2006).

The higher release of Ibuprofen from the Witepsol® W35 bases can be attributed to the higher proportion of monoglyceride present in its composition compared to the other lipophilic bases. This is reflected in the hydroxyl values, a number that indicates the amount of free hydroxyl groups in the base (Calis *et al.,* 1994). The presence of monoglycerides in the semisynthetic bases acts as an emulsifying agent, facilitating the dispersion of the active ingredient to the surrounding dissolution media, thus aiding the liberation of the drug easily from the formulation (Mosbah *et al*., 2016; Oladimeji and Bankole, 2017).

Witepsol® H15 and Witepsol® E85 had the same range of hydroxyl value of 5-15 but the lowest release was observed with formulations in the latter. The lowest release seen with formulations of Witepsol® E85 may be attributed to the melting range. Witepsol® E85 had the highest melting range of 40˚-46˚C compared to the other bases with lower melting range. The release of drugs from bases with low melting ranges has been found to be higher than those from comparatively higher melting ranges (Mosbah and Rakesh, 2010). Thus, the softening point of these suppositories can be concluded as the rate-limiting step in the release of the drug from Witepsol® E85 with a high melting range (Mosbah and Rakesh, 2010).

The use of surfactants to improve the release rate of drugs has been widely reported (Ilomuanya *et al*., 2012; Mosbah *et al*., 2016). The mechanism by which surfactant improves the release of lipophilic drugs from lipophilic bases has been reported to include: increasing the surface area of the suppository mass due to the moistening effects, ability to decrease the surface and interfacial tensions of the molten bases, and facilitating the drug's penetration of the dissolution medium thereby aiding desorption of the embedded drug out of the suppository bases matrix, shortening disintegration time of the lipophilic suppositories because of the changes from lipophilic characteristics to a lipo-hydrophilic nature (Ilomuanya *et al*., 2012).

Table 1: Codes and composition of Ibuprofen suppository formulations

Formulation Code	Base used	Mixed surfactants	Ratio of Tween® to Span® in the surfactants mix.	HLB of mixed surfactants
S0	Suppocire® CM	-	-	0
S4	Suppocire® CM	Present (4%w/w)	0/100	4.3
S6	Suppocire® CM	Present (4%w/w)	16/85	6.0
S8	Suppocire® CM	Present (4%w/w)	35/65	8.0
S10	Suppocire® CM	Present (4%w/w)	53/47	10.0
S12	Suppocire® CM	Present (4%w/w)	72/28	12.0
S15	Suppocire® CM	Present (4%w/w)	100/0	15.0
SC2	Suppocire® CM	Present (2%w/w)	16/85	6.0
SC6	Suppocire® CM	Present (6%w/w)	16/85	6.0
H0	Witepsol® H15	-	-	0
H4	Witepsol® H15	Present (4%w/w)	0/100	4.3
H6	Witepsol® H15	Present (4%w/w)	16/84	6.0
H8	Witepsol® H15	Present (4%w/w)	35/65	8.0
H10	Witepsol® H15	Present (4%w/w)	53/47	10.0
H12	Witepsol® H15	Present (4%w/w)	72/28	12.0
H15	Witepsol® H15	Present (4%w/w)	100/0	15.0
HC2	Witepsol® H15	Present (2%w/w)	72/28	12.0
HC6	Witepsol® H15	Present (6%w/w)	72/28	12.0
E0	Witepsol® E85	-	-	0
E4	Witepsol® E85	Present (4%w/w)	0/100	4.3
E6	Witepsol® E85	Present (4%w/w)	16/84	6.0
E8	Witepsol® E85	Present (4%w/w)	35/65	8.0
E10	Witepsol® E85	Present (4%w/w)	53/47	10.0
E12	Witepsol® E85	Present (4%w/w)	72/28	12.0
E15	Witepsol® E85	Present (4%w/w)	100/0	15.0
EC2	Witepsol® E85	Present (2%w/w)	16/84	6.0
EC6	Witepsol® E85	Present (6%w/w)	16/84	6.0
W0	Witepsol® W15	-	-	0
W4	Witepsol® W15	Present (4%w/w)	0/100	4.3
W6	Witepsol® W15	Present (4%w/w)	16/84	6.0
W8	Witepsol® W15	Present (4%w/w)	35/65	8.0
W10	Witepsol® W15	Present (4%w/w)	53/47	10.0
W12	Witepsol® W15	Present (4%w/w)	72/28	12.0
W15	Witepsol® W15	Present (4%w/w)	100/0	15.0
WC2	Witepsol® W15	Present (2%w/w)	72/28	12.0
WC6	Witepsol® W15	Present (6%w/w)	72/28	12.0

**Each suppository contains 200 mg Ibuprofen as the active drug*

Table 2: Physical Parameters for the Ibuprofen Suppositories formulated with mixed surfactants of varied HLB values

Formulation Codes	Mean Weight (g)	RDT	Softening Point (˚C)	Melting Point (˚C)	Crushing Strength (N)	Disintegration Time (Min)
S0	0.97±0.01	1.36	34±0.5	39±0.5	5.0±0.0	2.33±0.07
S4	0.99±0.01	3.03	37±0.5	42±0.5	5.2±0.8	1.86±0.10
S6	0.99±0.01	3.61	36±0.5	39±0.5	4.7±0.6	2.35±0.11
S8	0.98±0.01	2.51	36±0.5	40±0.5	7.0±0.0	0.87±0.14
S10	1.00±0.01	4.29	36±0.5	41±0.5	25.3±1.2	2.54±0.05
S12	0.98±0.01	2.41	36±0.5	40±0.5	25.7±4.0	2.67±0.22
S15	0.98±0.01	2.46	36±0.5	40±0.5	5.3±0.6	2.03±0.09
E0	0.97±0.01	0.77	40±0.5	46±0.5	34.3±2.3	41.00±0.32
E4	0.98±0.01	0.00	38±0.5	44±0.5	30.0±0.0	32.22±0.13
E6	0.98±0.01	0.19	38±0.5	44±0.5	47.7±1.4	24.15±0.41
E8	0.97±0.01	1.03	39±0.5	45±0.5	23.7±2.3	26.57±0.54
E10	0.98±0.01	0.72	39±0.5	45±0.5	48.8±2.9	28.23±0.44
E12	1.00±0.03	3.04	39±0.5	45±0.5	51.7±7.6	25.48±0.82
E15	0.98±0.01	0.31	40±0.5	44±0.5	24.8±0.3	23.19±0.24
H0	0.97±0.01	1.40	33±0.5	38±0.5	8.0±0.0	3.50±0.14
H4	0.99±0.01	2.97	33±0.5	38±0.5	9.3±1.8	3.03±0.20
H6	1.01±0.01	5.51	33±0.5	38±0.5	22.0±2.0	3.79±0.15
H8	0.98±0.01	2.29	33±0.5	38±0.5	7.5±0.1	4.51±0.10
H10	0.99±0.01	3.25	34±0.5	38±0.5	30.7±1.2	3.71±0.47
H12	0.99±0.01	3.59	35±0.5	37±0.5	20.7±1.3	2.50±0.16
H15	0.98±0.01	2.29	33±0.5	38±0.5	25.0±3.0	2.90±0.11
W0	0.99±0.01	3.76	34±0.5	39±0.5	6.0±0.0	3.79±0.04
W4	0.99±0.01	3.03	34±0.5	39±0.5	20.0±0.0	0.72±0.05
W6	1.03±0.02	7.12	34±0.5	39±0.5	29.7±1.5	2.58±0.05
W8	0.98±0.01	2.56	34±0.5	38±0.5	13.3±0.6	1.78±0.13
W10	0.98±0.01	2.19	33±0.5	38±0.5	18.3±2.3	1.60±0.06
W12	0.99±0.01	3.50	34±0.5	39±0.5	32.3±2.5	1.04±0.10
W15	0.99±0.01	3.13	34±0.5	39±0.5	14.5±0.9	1.14±0.17

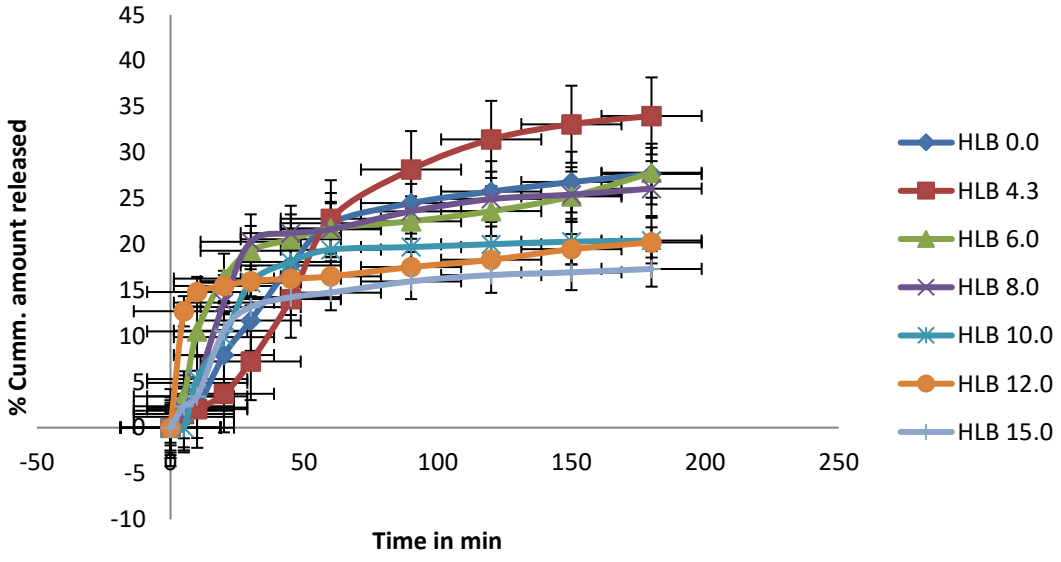

Fig 2: Release Profile of 200 mg Ibuprofen in Suppocire CM base with surfactant conc. of 4 %w/w at different HLBs

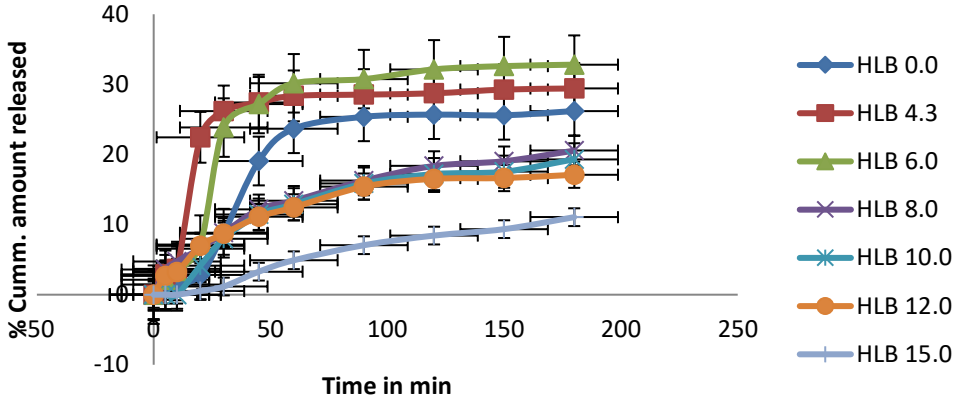

Fig 3: Release Profile of 200 mg Ibuprofen in Witepsol E85 base with surfactant conc.of 4 %w/w at different HLBs

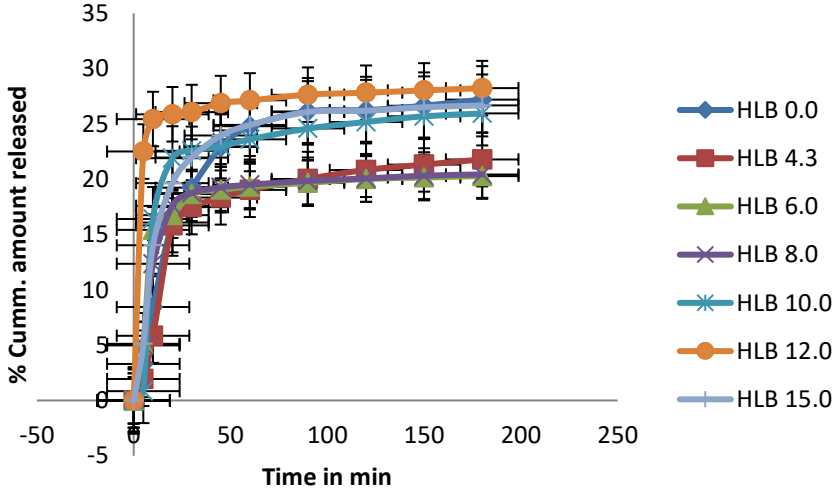

Fig 4: Release Profile of 200 mg Ibuprofen in Witepsol H15 base with surfactant conc. of 4 %w/w at different HLBs

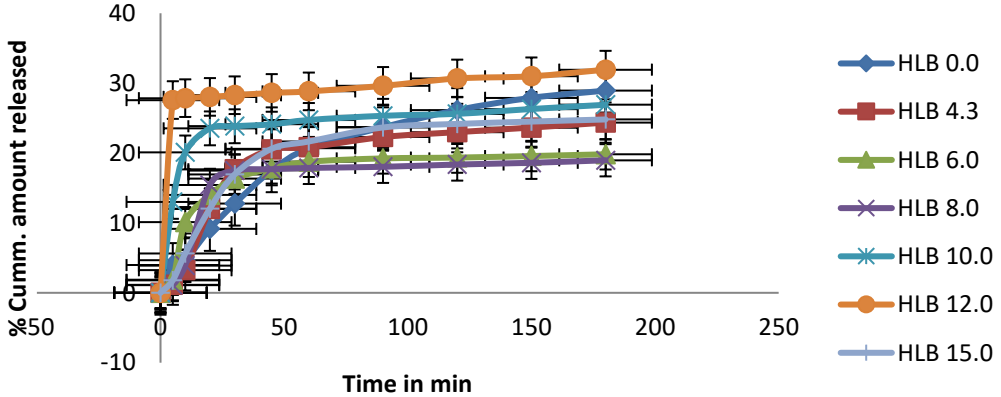

Fig 5: Release Profile of 200mg Ibuprofen in Witepsol® W35 base with surfactant conc. of 4%w/w at different HLBs

Table 3: In vitro release parameters for the ibuprofen suppository formulations with mixed surfactants of various HLB values

Formulation Codes	Time for 15% release (T_{15}) (min)	Time for 25% release (T_{25}) (min)	Percentage released in 60 min (D_{60min})	Percentage released in 180 min (D_{180min})
S0	38	100	22.3	27.7
S4	49	70	22.8	34.0
S6	18	150	21.7	27.8
S8	22	120	21.6	26.1
S10	28	>180	19.4	20.4
S12	16	>180	16.5	20.6
S15	64	>180	14.7	17.3
SC2	70	145	12.7	27.7
SC6	13	23	39.1	52.2
E0	39	74	23.7	26.2
E4	17	24	28.4	29.4
E6	25	33	30.2	32.8
E8	78	>180	13.4	20.6
E10	80	>180	12.9	19.3
E12	86	>180	12.5	17.1
E15	>180	>180	4.9	11.1
EC2	>180	>180	6.1	11.9
EC6	60	114	15.0	33.0
H0	19	62	24.8	27.2
H4	20	>180	19.0	21.8
H6	10	>180	19.3	20.3
H8	14	>180	19.5	20.4
H10	8	110	23.6	25.9
H12	4	10	27.1	28.2
H15	9	68	24.9	26.7
HC2	4	25	26.4	28.1
HC6	2	5	30.6	34.8
W0	38	110	20.7	28.9
W4	24	>180	20.8	24.4
W6	24	>180	18.8	19.8
W8	20	>180	17.9	19.0
W10	7	58	24.7	26.9
W12	4	6	28.8	31.9
W15	26	>180	21.65	24.81
WC2	9	18	28.9	31.2
WC6	4	5	32.2	35.2

The release of the Ibuprofen from the suppository mass was greatly improved with the addition of the mixed surfactant at HLB 4.3 and 6.0 for Suppocire® CM and Witepsol® E85, respectively. However, there was a reduction in the release as the HLB increased from 8.0 to 15.0. Thus, the release of Ibuprofen from Suppocire® CM base and Witepsol® E85 was favored by surfactants that had more lipophilic properties. This was evident with the release parameters; D_{180}, $D_{60,}$ $T_{25,}$ and T_{15} shown in Table 3.

Suppocire® CM has a hydroxyl value of less than 10 while Witepsol® E85 has a range of 5-15. The addition of mixed surfactants at an HLB that is lipophilic could improve the polarity of the base, improving the lipo-hydrophilic property of the base. However, as the HLB increased, the hydrophilicity property of the bases increased because of the increase in the amount of the Tween® 80 present in the mixed surfactant. With the increase in HLB, the formation of the emulsion may be enhanced at that particular concentration of 4 %w/w and the drugs could be entrapped, preventing release into the dissolution medium (Ilomuanya *et al*., 2012; Yousfan and Haisan, 2015).

On the other hand, the release of Ibuprofen from Witepsol® H15 and Witepsol® W35 decreased with the addition of the mixed surfactant at HLB 4.3, followed by a gradual increase in the release as the HLB increased from 6.0 until there was an optimum release at 12.0, then followed by a reduction in the release at HLB 15.0. This was also evident in the release parameters; D_{180}, $D_{60,}$ $T_{25,}$ and T_{15} in Table 3.

The reduction in release experienced with the addition of mixed surfactant at lipophilic HLB could be explained on the basis that surfactants having HLB 4-6 act as water in oil emulsifiers (Emmanuel and Musliu, 2014). This could aid the formation of water

in oil micelles, thus entrapping the drug content from being released into the dissolution medium. Also, the high hydroxyl value in Witepsol® W35 and Witepsol® H15 could form a water-in-oil emulsion, which would generally result in a very slow transfer of drug molecules from the inner aqueous phase, leading to retarded release at the lipophilic HLB (Yousfan and Haisan, 2015). At HLB higher than this (7-9), the surfactants act as wetting agents which could allow the easy spreading of the molten mass in the dissolution media and facilitate the penetration of the drug into the dissolution medium (Emmanuel and Musliu, 2014). As the HLB increases, the lipo-hydrophilic properties of the base increase, thus, reducing the affinity of the lipophilic Ibuprofen for the lipo-hydrophilic bases (Ilomuanya *et al*., 2012). This could explain the reason for the increase in the release as the HLB increased beyond 6. In addition, surfactants at HLB 10-15 act as solubilizers, promoting the solubilization of poorly soluble drugs like Ibuprofen in the hydrophilic dissolution media (Emmanuel and Musliu, 2014). Thus, we had the highest release at HLB 12.0. However, beyond HLB 15, there is a reduction in the solubilizing effect of the surfactant (Mokhtar and Mosbah, 2016). The surfactant, having higher hydrophilic properties, behaves as an oil-in-water emulsifier leading to the formation of micelles at critical micelle concentration (Szulc-musioł *et al*., 2019). With the formation of micelles, the drugs are entrapped and there is a reduction in the amount of Ibuprofen released into the dissolution medium. The result, therefore, indicates that an optimum HLB value is required for surfactants to be effective in enhancing the release of Ibuprofen from lipophilic suppository bases.

At the HLB of the mixed surfactant around where we had the highest release for the release of the Ibuprofen in each of the bases, an increase in the concentration from 4%w/w to 6%w/w resulted in a general increase in the amount of Ibuprofen released at 180 min. However, a reduction in the concentration to 2 %w/w did not influence a distinct change or reduction in the release of the Ibuprofen from the bases (Table 3). The only exception was for formulations in Witepsol® E85 where a reduction in the concentration of the mixed surfactant led to a reduction in the amount of Ibuprofen released. The increase in the release with an increase in the concentration of the mixed surfactant at the optimum HLB for release can be attributed to an increase in the effect of the surfactant at that HLB in causing the release of the Ibuprofen from the molten mass. As earlier explained, the mechanism for such action includes increasing the moistening effect on the base, solubilizing effect on the drug, and changes in the lipophilic properties of the base to lipo-hydrophilic (Ilomuanya *et al*., 2012).

Kinetics of Ibuprofen Release from the Suppository Formulations

The release profiles of the Ibuprofen suppository formulations are depicted in Figures 2-5. The R^2 and the release rate constants for Higuchi, Zero-order, First-order kinetic, and Kormeyer-Peppas kinetic models are shown in Table 4. The kinetic model with the highest R^2 value was selected to best characterize the release of Ibuprofen in the different formulations (Mokhtar and Mosbah, 2016).

From the results, the release constant was zero for all the formulations when fitted into a first-order kinetic model at the different HLBs and concentrations. This indicates that the release did not follow a First order release kinetics. Across the formulations without mixed surfactants in the different bases, the release constants showing the release rate, for the Higuchi model and Zero kinetic models were found to be in this order across the bases: Witepsol® E85>Suppocire® CM>Witepsol® W35>Witepsol® H15. The addition of the mixed surfactant at different HLBs resulted in a change in the rate of release of the Ibuprofen from the formulations based on the HLB of the added mixed surfactant. The addition of the mixed surfactants to the formulations in Suppocire® CM at HLB 4.3 caused an increase in the release rate constant for both Higuchi and Zero order kinetics, the effect which was seen in the higher release at this HLB compared to the formulation without mixed surfactants. However, this was followed by a decrease as the HLB increased. Increasing the concentration of the mixed surfactant from 4 to 6 %w/w at HLB 6.0 caused a two-fold increase in the rate constant for both Higuchi and Zero order and a greater release rate when compared to what was obtainable for the formulation without mixed surfactant. At a concentration of 2 %w/w, the rate constant was higher than what was obtainable with the formulation without mixed surfactants but with little significant difference to the rate constant at 4 %w/w of the mixed surfactants.

The addition of the mixed surfactant to formulations in Witepsol® E85 at HLB 4.3 first resulted in a decrease in the rate constant for both Higuchi and zero-order kinetic models compared to the formulation without mixed surfactants. However, there was a surge in the release constant at HLB 6.0, which was higher than what was obtained from the formulation without mixed surfactants. Increasing the HLB to 8.0 and beyond led to a gradual decrease in the rate constant observed.

Increasing the concentration of the mixed surfactants at HLB 6 from 4 to 6 %w/w resulted in a slight increase in the rate constant for both Higuchi and Zero order kinetics while a decrease to 2 %w/w caused a remarkable reduction in the rate constant. Thus, the rate of release of Ibuprofen from Suppocire® CM and

Witepsol® E85 was favored at a lipophilic HLB. As the HLB increased to a more hydrophilic HLB, however, the rate of release reduced gradually. In addition, the release rates in the two bases were concentration-dependent. The rate of release increased with an increase in the concentration of the mixed surfactants.

Table 4: The release rate constants, correlation coefficient, R^2, and the model that best describes the release of ibuprofen from the suppository formulations

Codes	Higuchi		Zero Order		First Order		Korsmeyer-Peppas		
	K_H(mg/min$^{1/2}$)	R^2	K_0(mg/min)	R^2	K_1	R^2	K_{k-p}	R^2	*n*
S0	5.10	0.92	0.30	0.79	0.00	0.82	-1.80	0.91	0.90
S4	6.85	0.95	0.42	0.89	0.00	0.91	-1.23	0.96	0.99
S6	3.44	0.82	0.20	0.68	0.00	0.72	-0.27	0.80	0.46
S8	3.98	0.78	0.22	0.62	0.00	0.65	-1.00	0.81	0.67
S10	3.24	0.74	0.18	0.56	0.00	0.58	-4.20	0.71	0.85
S12	1.13	0.95	0.07	0.91	0.00	0.92	-0.29	0.95	0.11
S15	2.50	0.77	0.14	0.61	0.00	0.63	-0.85	0.83	0.55
SC2	4.93	0.98	0.31	0.97	0.00	0.98	-2.33	0.99	0.79
SC6	7.81	0.91	0.45	0.78	0.00	0.85	-0.358	0.88	0.63
E0	5.26	0.84	0.30	0.72	0.00	0.73	-1.19	0.89	0.91
E4	4.20	0.60	0.22	0.44	0.00	0.45	-0.69	0.72	0.64
E6	5.85	0.78	0.33	0.62	0.00	0.66	-1.79	0.86	0.82
E8	3.18	0.98	0.19	0.91	0.00	0.92	-0.72	0.99	0.51
E10	3.65	0.94	0.21	0.83	0.00	0.85	-0.33	0.88	1.11
E12	2.77	0.94	0.16	0.83	0.00	0.84	-1.02	0.95	0.56
E15	2.14	0.98	0.13	0.97	0.00	0.97	-0.02	0.91	1.04
EC2	2.12	0.99	0.13	0.97	0.00	0.97	-0.86	0.98	0.81
EC6	6.26	0.99	0.39	0.98	0.00	0.99	-0.73	0.99	1.05
H0	3.86	0.79	0.21	0.62	0.00	0.64	-0.38	0.83	0.52
H4	3.00	0.70	0.16	0.54	0.00	0.56	0.69	0.75	0.57
H6	1.73	0.52	0.09	0.37	0.00	0.39	0.06	0.60	0.27
H8	1.93	0.56	0.10	0.40	0.00	0.41	0.01	0.67	0.30
H10	0.79	0.53	0.15	0.38	0.00	0.41	-0.74	0.52	0.64
H12	0.79	0.78	0.04	0.63	0.00	0.65	-0.49	0.89	0.05
H15	3.11	0.69	0.16	0.52	0.00	0.53	-0.01	0.74	0.37
HC2	1.22	0.83	0.07	0.68	0.00	0.69	0.45	0.89	0.06
HC6	1.22	0.95	0.08	0.97	0.00	0.97	-0.73	0.99	0.53
W0	4.81	0.96	0.29	0.87	0.00	0.89	-0.76	0.97	0.60
W4	3.91	0.78	0.22	0.61	0.00	0.64	-2.10	0.81	0.78
W6	2.25	0.66	0.13	0.49	0.00	0.51	-0.48	0.66	0.50
W8	2.57	0.57	0.14	0.40	0.00	0.41	-1.31	0.69	0.67
W10	1.700	0.64	0.09	0.49	0.00	0.51	0.34	0.75	0.55
W12	0.76	0.95	0.05	0.99	0.00	0.99	0.53	0.83	0.04
W15	3.92	0.81	0.22	0.64	0.00	0.67	-0.98	0.83	0.66
WC2	3.03	0.58	0.16	0.42	0.00	0.46	0.14	0.67	0.32
WC6	1.23	0.86	0.07	0.76	0.00	0.78	0.53	0.92	0.07

The effect produced by the mixed surfactant on the release rate constant for formulations in Witepsol® W35 and Witepsol® H15 was, however, different from the above. The addition of the mixed surfactants to the formulations of Witepsol® H15 and Witepsol® W35 caused a decrease in the release rate constant for both Higuchi and Zero order kinetic models as the HLB increased from 4.3 to 8.0 followed by a gradual increase at 10.0 and 15.0. The addition of the mixed surfactant tended to have a reduction effect on the release rate of Ibuprofen from the formulations as the HLB increased. However, as the HLB increased to a more hydrophilic value of HLB 10, there was a reversal with an increase in the rate at HLB 15. The exception was at HLB 12.0 where there was the lowest release constant.

The first 5 min of release for formulations in Witepsol H15 at HLB 12 was marked by a high rate of release of about 4.5 and with 22.50% of the drug released. The same was evident with the formulation in Witepsol

W35 at the same HLB with a high rate of 5.51 for the first 5 min of release and with 27.58% of the drug released. This was then followed by a gradual reduction in the release rate throughout 180 min. This explains why, although there was the highest release of Ibuprofen at HLB 12, the lowest overall rate constant was obtained.

In other to select which kinetic model best fits the characterization of the release profile of the Ibuprofen in the different formulations, the applications of R^2 value as the criterion for selection were employed. The kinetic model with the highest R^2 value was selected to be the best fit (Mokhtar and Mosbah, 2016). Formulations S4, S12, SC2, E8, E15, EC2, EC6, and W0 were best fit for Higuchi while formulations HC6 and W12 were best fit for Zero kinetic order. Other formulations could not be assigned to fit into any of the three kinetic models because the $R^2<0.95$. The selection of EC6 to be the best fit for the Higuchi kinetic model over the first-order kinetic model was due to the K1=0.

The release mechanism from suppositories in lipophilic bases has been reported to involve more than one process which includes, in addition to diffusion, the effect of melting of the base and the drug partitioning (Ilomuanya *et al*., 2012). In order to predict the transport mechanism involved in the release of Ibuprofen whether it is majorly diffusion-driven or other transport mechanisms are involved, the Korsmeyer-Peppas model was employed. The Korsmeyer-Peppas model has been reported to predict the fractional release of the drug as related to time in an exponential manner better than the Higuchi model (Oladimeji and Adegoke, 2017). From Table 4, the *n* value greater than 0.5 indicates a non-Fickian diffusion-controlled or anomalous drug transport mechanism. Anomalous in that more than one type of release phenomenon is involved in facilitating drug release from the formulations aside from diffusion (Oladimeji and Bankole, 2017). Anomalous transport involves both diffusion-controlled and erosion-controlled mechanisms (Adeleke and Oladimeji, 2022).

Considering the drug transport mechanism across the bases without the addition of the mixed surfactant, all the formulations in the different bases had a non-Fickian transport mechanism ($n>0.5$). However, the formulation in Suppocire® CM and Witepsol® E85 followed non-Fickian (Supercase II transport) with *n* values of 0.904 and 0.908, respectively; while formulations in Witepsol® H15 and Witepsol® W35 had non-fickian (anomalous) transport with *n* values of 0.521 and 0.604, respectively. Supercase II transport has been attributed to the burst effect by the formulation (Mokhtar and Mosbah, 2016).

With the addition of the mixed surfactants, all the formulations in Suppocire CM had a non-Fickian transport mechanism at all the HLB values with $n>0.5$. The exception was at HLB 12.0 where there was Fickian transport mechanism ($n=0.111$), meaning that the release was solely controlled by the diffusion process. The transport mechanism at HLB 4.3, however, was that of a non-Fickian (Supercase II transport), $n>0.89$; while the others followed non-Fickian (anomalous) transport, $0.45<n<0.89$. The addition of the mixed surfactants to the formulation resulted in the reduction of the *n* value as the HLB increased from 6 to 15. Decreasing and increasing the concentration of the mixed surfactant at HLB 6.0 to 2 and 6 %w/w still maintained a non-Fickian (anomalous) transport mechanism with *n* values of 0.789 and 0.628, respectively.

The addition of mixed surfactant to formulations in Witepsol® E85 at HLB 4.3 resulted to a shift in the transport from a non-Fickian (Supercase II transport) mechanism in the formulation without mixed surfactants to a non-Fickian (anomalous) transport mechanism as seen in the reduction of the *n* value (Table 4). Increasing the HLB from 4.3 to 15.0 still maintained a non-Fickian (anomalous) mechanism aside at HLB 10.0 ($n=1.113$) and 15.0 ($n=1.04$) where there was a shift to a non-Fickian (supercase II transport) mechanism. Increasing the concentration at HLB 6.0 to 6%w/w resulted in a change from a non-Fickian (anomalous) release mechanism to a non-Fickian (Supercase II transport), $n=1.05$. This implies the increase in the concentration of the surfactant caused a burst effect in the release of the Ibuprofen from the formulation.

The addition of the mixed surfactant to formulations in Witepsol® H15 at HLB 4.3 caused a slight increase in the *n* value (n=0.570) while still maintaining a non-Fickian (anomalous) transport mechanism. However, as the HLB of the added mixed surfactant increased from 6.0 to 15.0, the release mechanism shifted to a diffusion-controlled (Fickian) transport mechanism ($n<0.5$). The only exception was at HLB 10.0 where a non-Fickian (anomalous) mechanism was involved ($n=0.636$). Increasing the concentration of the mixed surfactant at HLB 12.0 to 6 %w/w resulted in a drastic increase in the *n* value and the transport mechanism changed from a Fickian mechanism to a non-Fickian (anomalous) mechanism ($n=0.525$). This is to show that other mechanisms that aid release like erosion were involved aside from the diffusion-controlled process.

The addition of the mixed surfactant to the formulation in Witepsol® W35 resulted in a shift from a non-Fickian (Supercase II transport) of the plain formulation ($n=0.966$) to a non-Fickian diffusion (anomalous) mechanism ($0.45<n<0.89$) at all the HLB

values of the mixed surfactant except at HLB 12.0 (n=0.038) where there was majorly a Fickian diffusion (Higuchi model) controlled mechanism. The change in concentration of the surfactant at HLB 12 from either 2 or 6 %w/w though affected the *n* value (n= 0.318 and 0.067, respectively), but did not change the mechanism of the drug release (Fickian diffusion).

In all, the *n* value was greatly influenced by the addition of the mixed surfactant which in turn dictated the release mechanism of the Ibuprofen from the bases.

CONCLUSION

The addition of the mixed surfactant conferred different effects on the physical and release profiles of the formulations. The release in all the formulations was generally low, (less than 53%). The release in the different bases without the addition of the mixed surfactant follows the order Witepsol® W35>Witepsol® H15>Suppocire® CM>Witepsol® E85. The study provides information on the optimum HLB and the concentration of mixed surfactants that favored the rate of release of Ibuprofen for all the semisynthetic bases. The variations observed with the release profile of Ibuprofen from the suppository influenced by the HLB of the mixed surfactants, change in the concentrations of the surfactant at the optimum HLB, and the type of semisynthetic suppository bases used, indicate that these factors could be employed in modifying drug release and bioavailability of ibuprofen from ibuprofen suppository formulations.

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