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Effect of Hydrophile-Lipophile Balance (HLB) of Mixed Surfactants on In-Vitro Release Profile of Ibuprofen from Semi-Synthetic Suppository Bases

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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 can be of significant effect.

Objective: The study aimed at evaluating the effect of HLB of the incorporated mixed surfactants on the physical and release properties of Ibuprofen suppositories formulated with semi-synthetic fatty bases.

Methodology: The preparations were carried out using 1 g mould. Ibuprofen suppositories, each containing 200 mg of Ibuprofen with semi-synthetic fatty bases (Witepsol® H15, Suppocire® CM), were prepared by fusion method. 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. The physical properties and release profile of the suppositories were evaluated using established procedures.

Results: The physical properties of the suppositories met the standard specified in the BP. Addition of mixed surfactants greatly influenced the release of the Ibuprofen from the formulations with optimum release at lipophilic HLB (4.3) and hydrophilic HLB (12.0) for formulations in Suppocire® CM and Witepsol® H15, respectively. The release parameters majorly fitted into Higuchi's model. The release mechanism was non-Fickian and Fickian for formulations in Suppocire® CM and Witepsol® H15, respectively.

Conclusion: The variations observed in the release profiles of Ibuprofen from the suppository bases indicate that HLB value of mixed surfactants can be employed in modifying drug release from semi-synthetic fatty bases

Keywords: Ibuprofen; Hydrophilic-lipophilic balance; Mixed surfactants; Semi-synthetic fatty bases; In-vitro release

INTRODUCTION

Ibuprofen (Fig. 1) belongs to the class of drugs referred to as Non-Steroidal Anti-inflammatory Drugs (NSAIDs) (Varrassi *et al.,* 2019; Goma, 2018). It is used in the treatment of fever (including post-vaccination fever), mild to moderate pain (including pain relief after surgery), dysmenorrheal, osteoarthritis, dental pain, headaches, and pain from kidney stone (Mosbah *et al.,* 2016). Ibuprofen, like other NSAIDs, works by inhibiting the production of prostaglandins (Goma, 2018; Dawood, 1993) leading to decrease in the activity of cyclooxygenase (COX) enzymes (Goma, 2018).

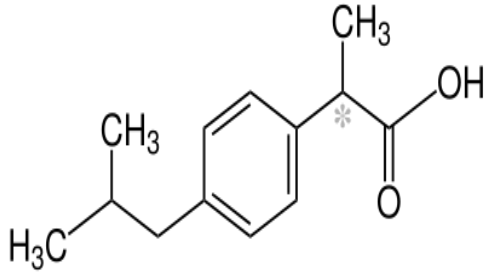

Figure 1: Structure of Ibuprofen

Like other NSAIDS, Ibuprofen has the disadvantages of causing gastrointestinal disturbances and peptic ulcerations (Varrassi *et al.,* 2019; Harirforoosh *et al.,* 2013). Hence, rectal route of administration has been

considered to be of great benefit in avoiding these side effects (Mosbah and Rakesh, 2010). Rectal administration of Ibuprofen as suppository formulation could provide both local and systemic effect (Mosbah *et al.,* 2016), and without the meals interfering with the absorption of the drugs.

Suppository bases used in the formulation of the rectal dosage form constitute the bulk of the preparation in most cases (Oladimeji *et al.*, 2018), which may require modification in other to improve physical and release properties of the suppository (Ogundipe et al., 2017; Okubanjo and Odeku, 2009). Addition of surface active agents to the suppository bases has been a desirable means of altering the physical and the release properties of the resulted suppositories (Oladimeji and Adegoke, 2017; Oladimeji and Bankole, 2017; Niraj *et al*., 2013). The emphasis on the use of surfactants in enhancing drug release from fatty suppository bases has always been on the concentration and type of the surfactants (Oladimeji and Adegoke, 2017; Niraj *et al*., 2013). However, the hydrophile-lipophile balance (HLB) of the surfactants, especially where mixed surfactants are used, can also be of significant effect on the release of the drug from such suppositories. The use of mixed surfactants with resultant different HLB values has been found effective in the formulation of some pharmaceutical products (Iwalewa et al., 2007). Thus, this study aimed at evaluating the effect of HLB of the incorporated mixed surfactants on the physical and release properties of Ibuprofen suppositories formulated with semi-synthetic fatty bases in other to provide information on the relationship between the HLB values of mixed surfactants and release profiles of Ibuprofen from the suppositories.

METHODOLOGY

Materials

Ibuprofen powder (donated by Fidson Healthcare Plc., Sango-Otta, Nigeria); Witepsol® H15 (Cremer Oleo GmbH & Co. KG, France); Suppocire® CM (Gattefosse SAS, France); Tween® 80 (Guangdong Guanghua Sci-Tech Co., Ltd., Guangzhou); Sorbitan Monooleate, Span® 80 (Fluka Analytical, Germany); Sodium hyroxide (Qualikems Laboratory Reagents, Delhi); Potassium dihydrogenorthophosphate (Tianjin Kermels, China).

Methods

Preparation of Ibuprofen Suppositories The suppositories were prepared by fusion method using 1 g mold putting into consideration the displacement values of Ibuprofen in the Suppository bases. Each suppository contained 200 mg of Ibuprofen with semi-synthetic fatty bases (Witepsol® H15, Suppocire® CM) and the mixed surfactants (Span® 80 and Tween® 80) added at 4 %w/w concentration in varied ratios (Table 1) to give HLB values of 4.3, 6.0, 8.0, 10.0, 12.0, 15.0. Ibuprofen Suppositories without the mixed surfactants (HLB 0) were also prepared and the formulations' codes are indicated in Table 1.

Evaluation of Prepared Ibuprofen Suppositories

Weight Uniformity

The test was carried out as specified in British Pharmacopoeia (BP), 2013. Twenty suppositories were randomly selected from each batch of the formulations and weighed individually using the 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 the 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 in the tube to take the temperature. The softening temperature was taken at the point when the suppository begins to melt and the melting point was taken at the point when there was a complete liquefaction of the suppository.

Table 1: Codes and composition of Ibuprofen suppository formulations

Formulation Code	Base used	Mixed surfactants @ 4%w/w	Ratio of Tween® to Span® in the surfactants mix.	HLB of mixed surfactants
S0	Suppocire® CM	**-**	**-**	**0**
S4	Suppocire® CM	**Present**	0/100	**4.3**
S6	Suppocire® CM	**Present**	16/85	**6.0**
S8	Suppocire® CM	**Present**	35/65	**8.0**
S10	Suppocire® CM	**Present**	53/47	**10.0**
S12	Suppocire® CM	**Present**	72/28	**12.0**
S15	Suppocire® CM	**Present**	100/0	**15.0**
H0	Witepsol® H15	**-**	**-**	**0**
H4	Witepsol® H15	**Present**	0/100	**4.3**
H6	Witepsol® H15	**Present**	16/84	**6.0**
H8	Witepsol® H15	**Present**	35/65	**8.0**
H10	Witepsol® H15	**Present**	53/47	**10.0**
H12	Witepsol® H15	**Present**	72/28	**12.0**
H15	Witepsol® H15	**Present**	100/0	**15.0**

NB: Each suppository contains 200 mg Ibuprofen as the active drug

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 kilogram and converted to Newton by multiplying with 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 the 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 (Oladimeji and Bankole, 2017). 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 on a water bath. The content was gently stirred while melting proceeded. 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 pipette and diluted to 100 ml using the phosphate buffer solution. The Absorbance of the resulting dilution was measured using Microprocessor UV spectrometer (Labtronics, Model LT-290, India) at 222 nm. The concentration of the solution was calculated from a plotted standard Beer-Lambert's 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 Tablet dissolution test apparatus was employed (Electrical India, model 112). The dissolution medium was phosphate buffer solution having pH 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 and lowered into the flask containing the phosphate buffer maintained at a constant temperature of 37± 1 ˚C. The basket was set to rotate at a constant speed of 50 rpm. 5ml portion was withdrawn at a fixed time over a period of 180 min and the volume of the medium was kept constant by replacing with equal volume of phosphate buffer (pH 7.4) maintained at 37± 1 ˚C. The withdrawn sample was further diluted with equal volume of the buffer solution and the absorbance of the diluted sample was determined using 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 suitable for the release of Ibuprofen from the different formulations, the in-vitro release data were subjected to three kinetic models viz: Zero-order kinetic (Q_t vs t) (Gouda *et al*, 2017; Gautam and Mahaveer, 2011), First order kinetic model (log (Q_0-Q_t) vs t) (Gouda *et al*, 2017) and Higuchi diffusion controlled model (Q_t vs $t^{1/2}$) (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. In other to assign the release mechanism, the profile data was further subjected to Korsmeyer-Peppas kinetic model ($logQ_t$ 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 Microsoft Excel spreadsheet. A significant difference was considered at $p<0.05$.

RESULTS AND DISCUSSION

Physical Properties of Ibuprofen Suppositories

All the suppositories fell within 95 % to 105 % of the average weight as stipulated in BP (2013) (Table 2). Generally, the inclusion of the mixed surfactant caused an increase in the standard deviation (SD) and relative deviation from the theoretical value (RDT) (Table 2). There was an increase in RDT as the HLB increases from 4.3 to 10.0 followed by decrease at HLB 12 and 15. For formulations in Witepsol® H15, there was, generally, an increase in the RDT with the addition of the mixed surfactants. However, there is no observed corresponding increase in the RDT with the increase in HLB.

The SP and MP of the formulations in Suppocire® CM and Witepsol® H15 are indicated in Table 2. Inclusion of the mixed surfactants caused an increase in the SP of formulations with Suppocire® CM. Formulations with Witepsol® H15 had their SP at 33 ˚C and the MP fell within the range of 37˚-38 ˚C except formulation at HLB 12 (S12) that had SP of 35 ˚C. The softening and melting points play vital role in the release of drug content from formulations in fatty base (Mosbah and Rakesh, 2010). The release of drug from fatty base follows softening/ melting of the suppository, the dissolution of content in the rectal fluid and absorption of the drug through the rectal mucosa (Pushkar *et al*., 2013; Othman and Muti, 1986). A softening temperature of 32˚ to 37˚C is desirable for suppositories of fatty bases in the tropic. This allows the suppository to maintain its solid state in the temperature obtainable in the tropics and also allow fast release of the drug content when inserted into the rectum (Taylor *et al.*, 1992). Incorporation of surfactant into suppository formulations had been reported in literatures to cause a change in the SP and MP of the suppository formulations which could be attributed to alteration in the rheological properties of the suppositories (Ilomuanya *et al.*, 2012). The increase in the melting range for the formulations in Suppocire® CM base with incorporation of mixed surfactants could result to a greater stability of the suppository in the tropic. However, this could also lead to delay in the release of the drug when inserted into the rectum.

The crushing strengths for the formulations are indicated in Table 2. The inclusion of the mixed surfactants caused a general increase in the crushing strengths of the formulations in the different bases which had been attributed to the effect of the surfactant on the rheology of the formulation (Oladimeji and Adegoke, 2017). However, there is no trend observed between the increase in the crushing strength and the increase in the HLB values. There was an increase in the crushing strength of formulations with Suppocire® CM base as the HLB increases from 4.3 to 12.0, with the exception at HLB 6.0 (S6). Formulations with Witepsol® H15 have crushing strength in the range of 7.5-30.7 N at the various HLB values with the highest value of 30.7 N observed at HLB 10.0 (H10). The effects of the mixed surfactants on the crushing strength of the suppositories were more evident at the hydrophilic HLB values. Hydrophilic nature of surfactants had been reported to support the formation of stronger bonds which, in turn, causes an increase in the crushing strength of the suppository (Odeku and Itiola, 2003).

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)	content (mg)
S0	0.97±0.01	1.36	34±0.5	39±0.5	5.0±0.0	2.33±0.07	199.0±13.9
S4	0.99±0.01	3.03	37±0.5	42±0.5	5.2±0.8	1.86±0.10	199.0±13.9
S6	0.99±0.01	3.61	36±0.5	39±0.5	4.7±0.6	2.35±0.11	199.0±13.9
S8	0.98±0.01	2.51	36±0.5	40±0.5	7.0±0.0	0.87±0.14	199.0±13.9
S10	1.00±0.01	4.29	36±0.5	41±0.5	25.3±1.2	2.54±0.05	199.0±13.9
S12	0.98±0.01	2.41	36±0.5	40±0.5	25.7±4.0	2.67±0.22	199.0±13.9
S15	0.98±0.01	2.46	36±0.5	40±0.5	5.3±0.6	2.03±0.09	199.0±13.9
H0	0.97±0.01	1.40	33±0.5	38±0.5	8.0±0.0	3.50±0.14	207±9.1
H4	0.99±0.01	2.97	33±0.5	38±0.5	9.3±1.8	3.03±0.20	207±9.1
H6	1.01±0.02	5.51	33±0.5	38±0.5	22.0±2.0	3.79±0.15	207±9.1
H8	0.98±0.01	2.29	33±0.5	38±0.5	7.5±0.1	4.51±0.10	207±9.1
H10	0.99±0.01	3.25	34±0.5	38±0.5	30.7±1.2	3.71±0.47	207±9.1
H12	0.99±0.01	3.59	35±0.5	37±0.5	20.7±1.3	2.50±0.16	207±9.1
H15	0.98±0.01	2.29	33±0.5	38±0.5	25.0±3.0	2.90±0.11	207±9.1

The crushing strengths for the formulations are indicated in Table 2. The inclusion of the mixed surfactants caused a general increase in the crushing strengths of the formulations in the different bases which had been attributed to the effect of the surfactant on the rheology of the formulation (Oladimeji and Adegoke, 2017). However, there is no trend observed between the increase in the crushing strength and the increase in the HLB values. There was an increase in the crushing strength of formulations with Suppocire® CM base as the HLB increases from 4.3 to 12.0, with the exception at HLB 6.0 (S6). Formulations with Witepsol® H15 have crushing strength in the range of 7.5-30.7 N at the various HLB values with the highest value of 30.7 N observed at HLB 10.0 (H10). The effects of the mixed surfactants on the crushing strength of the suppositories were more evident at the hydrophilic HLB values. Hydrophilic nature of surfactants had been reported to support the formation of stronger bonds which, in turn, causes an increase in the crushing strength of the suppository (Odeku and Itiola, 2003).

The disintegration time (DT) range for formulations in Suppocire® CM is 0.87-2.70 min (Table 2). The disintegration time for formulations in Witepsol® H15 falls within the range of 2.50-4.51 min (Table 2). A short disintegration time will favor the instant release of the Ibuprofen from the formulation (Oladimeji and Adegoke, 2017). There is no trend observed with the changes in the DT as the HLB increases from 4.3 to 15.0. The change in the disintegration time of the suppositories with the addition of the surfactant has been attributed to the change in rheology of the suppository and the particle-particle interaction caused by the added surfactants (Odeku and Itiola, 2003).

The mean drug contents (Table 2) of all the formulation were found to fall within 100±15 % stipulated in the British Pharmacopoeia (2013). Thus, the batch to batch variations in strength of the suppository remains within the stipulated acceptance limit for suppository and the quality of the suppository, in terms of strength, assured.

Release properties of the Ibuprofen Suppository

The plots of the % Cumulative amount release of the Ibuprofen against time in the two bases at different HLBs are shown in figures 2 and 3. The release parameters ($T_{15,}$ and T_{25}) are also shown in Table 3. The release of Ibuprofen from the suppository base after 180 min is generally low for the two bases; below 30 %. This is in consistence with the results reported by Mosbah *et al*, 2016 for the release of Ibuprofen suppository in semisynthetic bases (Suppocire AM). Drug release from suppository 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 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 poor diffusion from them and the subsequent solubility in the dissolution medium. The same effect has been reported in the work done by (Oladimeji *et al*., 2006) on the release of Halofantrine HCl, a lipophilic drug, from lipophilic and hydrophilic bases. There is a significant difference ($p<0.05$) in the release of Ibuprofen from the two bases, an indication that the release of Ibuprofen from the suppository formulations is dependent on the kind of base used. The release from Witepsol® H15 was greater than that obtainable from Suppocire® CM.

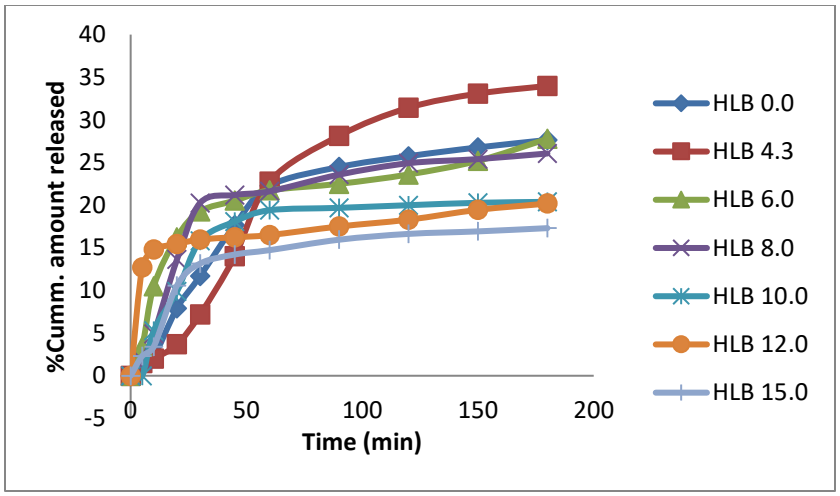

Figure 2: Release Profiles of Ibuprofen suppositories prepared using Suppocire® CM with mixed surfactants and different HLBs.

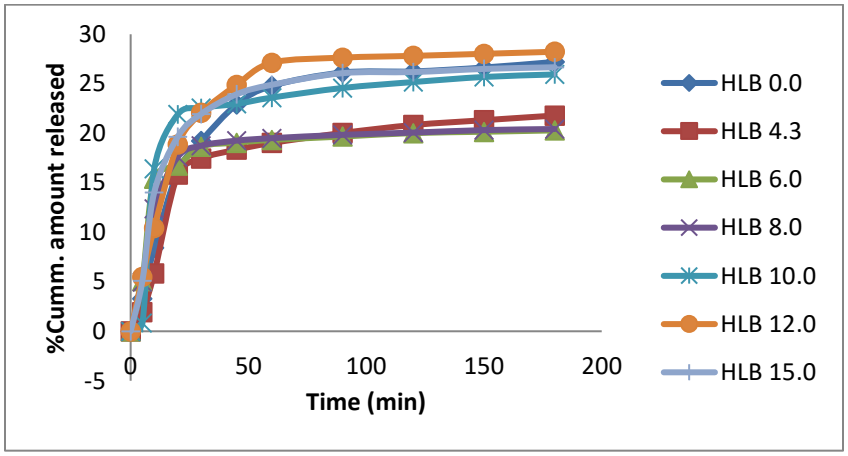

Figure 3: Release Profile of Ibuprofen suppositories prepared using Witepsol® H15 with mixed surfactants and different HLBs

Table 3: In *vitro* release Parameters for the Ibuprofen Suppositories formulated with mixed surfactants of various HLB values.

Formulation Codes	Time for 15% release (T_{15}) (min)	Time for 25% release (T_{25}) (min)
S0	38	100
S4	49	70
S6	18	150
S8	22	120
S10	28	>180
S12	16	>180
S15	64	>180
H0	19	62
H4	20	>180
H6	10	>180
H8	14	>180
H10	8	110
H12	4	10
H15	9	68

However, at HLB 15, there is a reduction in the solubilising effect of the surfactant (Mokhtar and Mosbah, 2016). The surfactant, having higher hydrophilic property, behaves as oil in water (o/w) emulsifier leading to the formation of micelles (Szulc-musioł *et al*., 2019). With the formation of micelles, the drugs are entrapped and there is reduction in the amount of Ibuprofen released into the dissolution medium.

Kinetics of Ibuprofen Release from the Suppository Formulations

The release profiles of the Ibuprofen suppository formulations are depicted in figures 2 and 3. The R^2 and the release rate constants for Higuchi, Zero-order and First order kinetic models are shown in Table 4. The kinetic model with the highest R^2 value was selected to best characterize the release of the Ibuprofen in the different formulations (Mokhtar and Mosbah, 2016; Ilomuanya *et al*., 2012). All the formulations were best fitted into the Higuchi kinetic model (Table 4). This implies that the release of Ibuprofen from the formulations was majorly diffusion driven.

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 (Singhvi *et al*., 2011), therefore, the release data was also analysed using Korsmeyer-Peppas model (Table 4). The *n* value greater than 0.5 indicates non-Fickian diffusion controlled (anomalous) drug transport mechanism. Anomalous in that more than one type of release phenomenon is involved in facilitating drug release from the formulations aside diffusion transport. It involves both diffusion controlled and erosion controlled mechanisms (Oladimeji and Adegoke, 2017).

All the formulations with Suppocire CM had a non-Fickian transport mechanism at all the HLB values with $n>0.5$, except formulation with HLB 12.0 (S12) ($n=0.11$). The transport mechanism in the formulation without surfactant (S0) and at HLB 4.3 (S4), however, is that of a Supercase II transport, $n>0.89$. This has been attributed to burst effect by the formulation (Mokhtar and Mosbah, 2016). Addition of the mixed surfactants to the formulation resulted in the reduction of the *n* value as the HLB increase from 6 to 15. The release mechanism of formulation S12 (HLB 12) demonstrated perfect diffusion driven transport mechanism as indicated by high R^2 value obtained from Higuchi model (0.953) and very low n value from Korsmeyer-Peppas model (0.11).

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

CODES	HIGUCHI		ZERO OREDR		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
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

The formulations with Witepsol® H15 without surfactant (H0) and at HLB 4.3 (H4) had non-Fickian (anomalous) transport (Table 4). However, as the HLB of the added mixed surfactant increased from 6.0 to 15.0, the release mechanism shifted to diffusion controlled (Fickian) transport mechanism ($n<0.5$) with exception at HLB 10.0 that was non-Fickian (anomalous) transport mechanism ($n=0.636$).

In all, the *n* value is greatly influenced by the addition of the mixed surfactants which in turn dictated the release mechanism of the Ibuprofen from the bases. A comparison of the release criterion, R^2, shows that the release mechanism is better fitted using Korsmeyer-Peppas kinetic model than the Higuchi's model earlier postulated. This is affirmed with the expectation that the release of drug from fatty bases follows melting of the base, partitioning and diffusion of the drug from

the molten base into the medium for dissolution, relatively to the diffusion release phenomenon postulated by Higuchi model (Oladimeji and Adegoke, 2017).

CONCLUSION

The addition of the mixed surfactants conferred different effect on the physical and release profile of the formulations, influenced by the nature of the base and the HLB of the mixed surfactants added. The release in all the formulations was generally low, (less than 30%). There is a significant difference ($p<0.05$) in the release of Ibuprofen from the two bases used. Addition of mixed surfactants to the formulations at different HLB values caused a significant change ($p<0.05$) in the release of the Ibuprofen from the suppository formulations in the two bases. The effect of the HLB on the release of the Ibuprofen is dependent on the bases used and the effect of the base on the release of the Ibuprofen is, also, dependent on the HLB of the mixed surfactants used ($p<0.05$). The study found out that there is an optimum HLB that favours the release of Ibuprofen from the semisynthetic bases. Release was optimum at a lipophilic HLB of 4.3 for Suppocire CM and hydrophilic HLB of 12.0 for Witepsol® H15. The release parameters were found to be best fitted into Higuchi kinetic model. The parameters subjected to Korsmeyer-Peppas model followed majorly a Non-Fickian diffusion mechanism for formulations in Suppocire CM while formulations in Witepsol H15 followed majorly a Fickian diffusion mechanism at the various HLB values of the mixed surfactant. The variations observed in the release profiles of Ibuprofen from the suppository bases indicate that HLB value of mixed surfactants can be employed in modifying drug release from semi-synthetic fatty bases.

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