Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2018, 10(2):32-39

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Quantitative Evaluation of Effects of Drugs Concentrations and Densities on their Displacement Factors in Suppository Bases

Oladimeji Francis A*, Akinrinola Ibukun A, Dawodu Tolulope A, Ogundipe Omotola D, and Bankole Victor O

Department of Pharmaceutics, Obafemi Awolowo University, Ile-Ife, Nigeria

---

ABSTRACT

Suppositories are formulated on weight basis on the assumption that the medication replaces a portion of the suppository base as a function of its density. The effects of drug concentration (C) and drug type (D) on the displacement factor (DF) of drugs in suppository bases (B) were investigated. Three drugs: paracetamol (PCM), sulphathiazole (STZ) and zinc oxide (ZNO), and two bases: polyethylene glycol (PEG) and shea butter (SB) modified with beeswax were studied. Densities of the drugs and bases were determined. Blank and medicated suppositories were prepared using fusion method and the quantity of base displaced by the drug determined. The densities of the drugs and their DF with respect to the two bases ranked ZNO >>> STZ > PCM. An optimum concentration for each drug was obtained beyond which the DF of the drug in the bases remained constant. The bulkier the drug, the smaller the concentration required to determine the displacement factor. No significant difference (P > 0.05) was found between the calculated density ratios of the drugs/suppository bases and their experimentally determined DF. Based on 2^3 factorial experimental design, the ranking of individual variable effects on the (DF) was D >> C >>> B, while interacting effects' ranking was C-D >>> B-D > B-C. Depending on the bulkiness of the drug, it is suggested that drug concentrations between 10 and 25% w/w should be used for accurate determination of DF in the bases.

Keywords: Displacement factor; Suppository base; Drug concentration; Drug density

---

INTRODUCTION

Rectal suppository formulations containing active drug(s) for local or systemic effect [1,2] hold promise for increasing applications such as when a patient is comatose, unable to swallow or when the drug produces nausea or vomiting with oral administration [3]. It is also becoming attractive because the released drug can avoid hepatic first-pass as well as undesirable effects of meals on its absorption [4]. While suppositories may be classified as solid dosage form, their formulation processes are different from those of tablets and capsules [1]. Suppositories are formulated on weight basis and compounded by volume in the mould [2]. Since the capacity of a specific mould is fixed, determination of how much of the base will be displaced by the drug is required to provide uniform weight and drug content of the suppository [2,5]. Hence, the need for the determination of the displacement factor (DF) of the drug in the base [6].

The DF of drugs in cocoa butter, a widely used and compatible suppository base, are provided in literature [1,2]. However, the relatively higher environmental temperature in the tropics and the poor release of lipophilic drugs from cocoa butter have been setbacks that necessitated the modification of cocoa butter base [7,8] and the use of alternatives like polyethylene glycols (PEG) and semi-synthetic fatty bases. Hence, the need to determine the displacement factors of the drugs in these other bases.

In literature, hardly has any reference been made to the concentration of drug in the determination of its (DF) in the base [9,10]. While it has been suggested that the application of (DF) may not be necessary where the drug content of the formulation is less than 100 mg in a 2 g mould [2], the bulk properties of the drug (bulk density, volume and bulkiness) are essentially important in the determination of the volume of the base displaced and the resulting weight of the medicated suppository. The bulk density of a drug is its physical characteristics as a powder, rather than as individual particles [11]. Therefore, accurate determination of DF of the drug in the base will ensure minimal deviation of the physical weight from the theoretical weight and content uniformity of the suppositories.

In this present study, we have investigated the effects of drug type and its concentration, as well as the type of base employed on the DF of drug in the base. Three drugs namely; paracetamol (PCM), sulphathiazole (STZ) and zinc oxide (ZNO) (having different density and bulk properties) at varied concentrations, with shea butter (SB) modified with beeswax and PEG as the suppository bases were selected for the investigation with a view of determining the minimum drug concentration required for the accurate determination of the drugs' DF in the bases.

EXPERIMENTAL SECTION

Materials

Paracetamol powder, (PEG) 1500 and 4000 (gifts from Fidson Healthcare Ltd. Sango-Otta, Ogun State Nigeria), sulphathiazole powder (BDH Chemicals Ltd., Poole, England), zinc oxide (Deaborn Chemicals, Ohio, USA), beeswax (Fluka, Switzerland), shea butter (procured at a local market in Shaki, Oyo State, Nigeria), benzene (May and Baker Ltd., Dagenham, England), light liquid paraffin BP (SKG Pharma, Lagos, Nigeria).

Methods

Purification of shea butter:

The purification process of the shea butter (SB) involved the removal of extraneous matter by hot filtration at 60^{o}C in an oven using a silk cloth filter medium placed over a large beaker [12,13]. The filtrate was allowed to solidify at room temperature (28° ± 1°C) for seven days prior to using the sample.

Modification of suppository bases:

SB was modified with beeswax (80:20) [7]. The beeswax was melted in a platinum dish on a water bath regulated at 40° ± 1°C [14]. The SB was chopped to tiny bits and added to the molten beeswax while congealing and stirred until cool.

The PEG base was prepared by mixing PEG 1500 (75%) with PEG 4000 (25%) [15]. PEG 4000 was melted in a platinum dish on a water bath and PG 1500 was added to the molten PEG 4000 and stirred until cool.

Determination of densities of the drugs and bases:

The true densities of paracetamol (PCM), sulphathiazole (STZ) and zinc oxide (ZNO) were determined using the liquid displacement method [16] with a pycnometer having 50 cm^3 capacity. Prior to determination, the drugs were sifted using mesh 120 (125 μm). Benzene was used as the displacement fluid. A 5 g sample was used for the determination. The density (ρ) of each drug was calculated from the equation:

$$\rho = \frac{W_3(W_2 - W_1)}{50(W_2 + W_3 - W_4)} \qquad \text{Eq 1}$$

W_1 = weight (g) of the pycnometer bottle

W_2 = weight (g) of the pycnometer bottle and displacement fluid (benzene)

W_3 = weight of drug sample (5 g)

W_4 = weight (g) of the pycnometer bottle containing the displacement fluid and drug sample

The density of the modified PEG was determined using light liquid paraffin, in which the base was found to be insoluble [17], as the displacement fluid. The modified base was cut into tiny bits and 5 g sample from it was used for the determination. The density of the PEG was calculated using equation 1.

The relative density of the modified SB was determined with distilled water as reference liquid [11]. The 50 cm^3 pycnometer was cleaned and dried in the oven to a constant weight without the stopper (W_5). The pycnometer was filled with freshly distilled water to the brim without the stopper, excess water was wiped off and the bottle weighed (W_6). The modified SB base was melted at 35° ± 1°C [7]. While still fluid, it was poured into the dried pycnometer bottle to the brim at an angular position in order to prevent aeration. The base was allowed to congeal and more of the molted base was added to fill to the brim, excess base was wiped off and weighed after 24 h (W_7). The relative density (ρ) of the base was calculated from the equation 2 (16):

$$\rho = \frac{(W_7 - W_5)}{(W_6 - W_5)} \quad \text{Eq 2}$$

The experiments were carried out under controlled temperature (22° ± 1°C) and repeated in triplicate.

Determination of bulk densities of drugs:

The bulk densities of the drugs were determined using the method described by Sinko [11] as well as Karuppusamy and Venkatesan [16]. A 25 g sample (W_8) of the drug that was previously passed through sieve 20 (840 μm) was carefully introduced into a clean and dry 100 cm^3 graduated cylinder. The cylinder was dropped at ten seconds interval onto a hard wooden surface three times from a height of 2.54 cm. The final volume (bulk volume) of the drug was measured to the nearest cm^3 (V_b). The bulk density (ρ_b) was calculated from the equation:

$$\rho_b = \frac{W_8}{V_b} \quad \text{Eq 3}$$

The experiments were repeated in triplicate.

Determination of the displacement factors of the drugs in the suppository bases:

All suppositories were prepared by fusion method using a 1 g metal mould with six cavities. The displacement factors of the drugs in the different bases were determined by the procedure reported by Yousif [18]. The mould was cleaned and lubricated using 50% v/v glycerol. The drugs were sifted through mesh 120 (125 μm). Six unmedicated suppositories were prepared and weighed. Thereafter, six medicated suppositories each containing 5% w/w of drug were prepared and weighed. The displacement factor (DF), which is defined as the number of parts by weight of the drug that displaces one part by weight of the base is given by:

$$DF = \frac{XB}{100\,(A-B)+XB} \quad \text{Eq 4}$$

DF = displacement factor of the drug in the base
X = percentage of the drug used
B = weight of six medicated suppositories each containing X% w/w of the drug
A = weight of six unmedicated suppositories
Medicated suppositories containing 10, 15, 20, 25, 30, 40 and 50% w/w of the drug were further prepared and analysed. Each concentration was prepared in triplicate.

Calculation of density ratios of drugs and bases:

The density ratio (DR) of the drug and the base was calculated from the densities of the drug and the base earlier determined using the equation:

$$DR = \frac{\rho_1}{\rho_2} \quad \text{Eq 5}$$

$\rho_1 =$ density of the drug
$\rho_2 =$ density of the base

Factorial experimental analysis:

Quantitative analysis of the three formulation variables on the DF of the drugs in the suppository bases was based on 2^3 factorial experimental designs [19-21]. The variables: nature of the suppository base (B), concentration of the drug (C) and drug type (D) were employed at a "low" level (denoted by subscript, L) and a "high" level (denoted by subscript, H) resulting in 8 factorial levels. Using the above nomenclatures, the various combinations of variables used in the design were:

$B_LC_LD_L$, $B_LC_LD_H$, $B_LC_HD_L$, $B_LC_HD_H$, $B_HC_LD_L$, $B_HC_LD_H$, $B_HC_HD_L$, $B_HC_HD_H$

Where;
B_L = Nature of the suppository base: fatty base with density <1.0 (modified SB)
B_H = Nature of the suppository base: water soluble base with density >1.0 (PEG)
C_L = Concentration of drug (5% w/w)
C_H = Concentration of drug (50% w/w)
D_L = Drug type: low density with high bulkiness (PCM)
D_H = Drug type: high density with low bulkiness (ZNO)

The combinations were grouped into appropriate sets to enable the assessment of each variable on the DF of the drugs in the bases. The effect of increasing a variable from "low" to its "high" level on DF was determined by summing all the results from samples containing "high" level of the variable and subtracting the sum of the results from samples containing "low" level of the variable as illustrated in Eq. 6. The extend by which the result of the

treatment departed from zero, irrespective of whether positive or negative was a quantitative measure of the effect of the variable on the DF [19,21].

B_L and B_H = ¼[($B_HC_LD_L + B_HC_LD_H + B_HC_HD_L + B_HC_HD_H$)– ($B_LC_LD_L + B_LC_LD_H + B_LC_HD_L + B_LC_HD_H$)] Eq 6

To determine whether there was any interaction between two variables, the results of the combination in which the two variables appear together at either "high" or "low" levels were summed and the sum of other combinations subtracted from this to obtain the interaction coefficient as illustrated in Eq. 7 for B and C (B-C) [19].

B-C = ¼[($B_HC_HD_L + B_HC_HD_H + B_LC_LD_L + B_LC_LD_H$) – ($B_HC_LD_L + B_HC_LD_H + B_LC_HD_L + B_LC_HD_H$)] Eq 7

A result of zero indicated no interaction, but a significant departure from zero implied that the two variables were interacting with each other, with the extent of departure from zero being a measure of the magnitude of the interaction [19,20].

Statistical Analysis

All the data for comparative analysis were subjected to either the student t-test or F-test using Microsoft Excel and GraphPad Prism 5 software with minimum level of significance established at 5% [7].

RESULTS AND DISCUSSION

Effects of Drug Concentration, Drug Type and Suppository Base Type on Displacement Factor

The effects of drug concentration on DF of drugs in PEG and SB as the suppository bases are indicated in Figures 1 and 2, respectively. The DF of the drugs in PEG were higher than in SB. The DF of the drugs increased with increase in concentration of the drug in the formulation until a point where the value became constant. The DF at such points and the equivalent concentrations of the drugs in the base are indicated in Table 1. While the DF of the drugs in the bases varied for the different drugs, the concentrations of drugs required to achieve constant DF in PEG and SB varied with the drug types. The trend was ZNO > STZ > PCM in PEG and ZNO > STZ = PCM in SB. The coefficient of determination (R^2) between the DF and the drug concentrations were very low; 0.247, 0.472 and 0.426 for PCM, STZ and ZNO in PEG, respectively, and 0.639, 0.596 and 0.648 for PCM, STZ and ZNO in SB, respectively. These low correlation values suggested that the relationship was not in arithmetic progression. It also buttressed the findings that the DF remained fairly constant at a particular drug concentration at which further increase in the drug concentration in the base caused no significant change in the DF. Several workers [22-24] have calculated the DF of drugs in bases using suppositories formulated at varied concentrations of the drugs. It is obvious from this study that such variation in the concentration of the drug would affect the DF obtained as the amount of base displaced by the drug at each drug concentration did not follow arithmetic progression.

The bulk properties of the drugs are indicated in Table 2. The bulk and true densities of the drugs were in the order: ZNO > STZ > PCM. The bulkiness of the drugs suggests that the PCM occupied more volume per unit weight than the ZNO and, hence, would displace more volume of the base than ZNO. The densities of the bases showed that they are less dense than the drugs (Table 2) and, therefore, the DF with reference to the three drugs should be expected to be greater than 1.0.

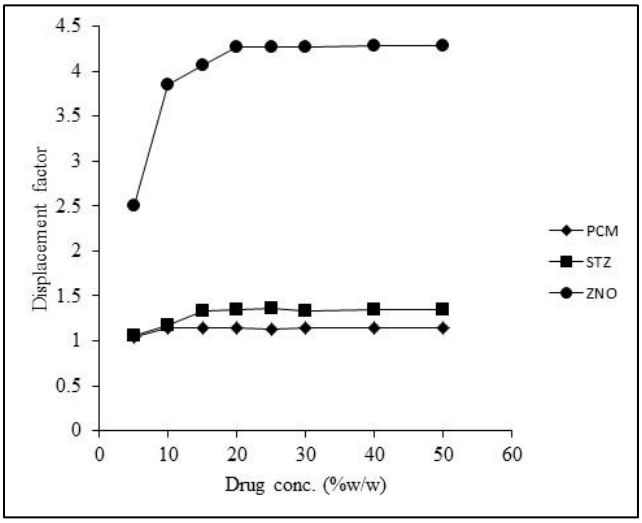

Figure 1: Effects of paracetamol (PCM), sulphathiazole (STZ) and zinc oxide (ZNO) concentrations on their displacement factors in polyethylene glycol suppository base

The volume of the base displaced by the drug could also be determined using the density ratio (DR) of the drug to the base. The DR of PCM, STZ and ZNO calculated with reference to the densities of the bases are indicated in Table 2. The relatively high DR obtained for ZNO in the two bases compared with those of PCM and STZ was due to large differences between the densities of ZNO and the bases (Table 2). A *t*-test statistical analysis between the DR and DF values showed no significant difference (P>0.05) between the two set of values. The relationship between the drug density and DR/DF in the two suppository bases is illustrated in Figure 3. The coefficients of determination (R^2) between DR and drug density and between DF and drug density in the two bases were 1.00 and 0.999, respectively, indicating perfect correlation.

Since DF was observed to vary at lower concentrations of the drugs, the application of DR, which is independent of drug concentration [2] may, therefore, be more accurate for the calculation of the amount of the base displaced by the drug. However, this may require a tedious process of determining the densities of the drug and the base when these values are not available in literature.

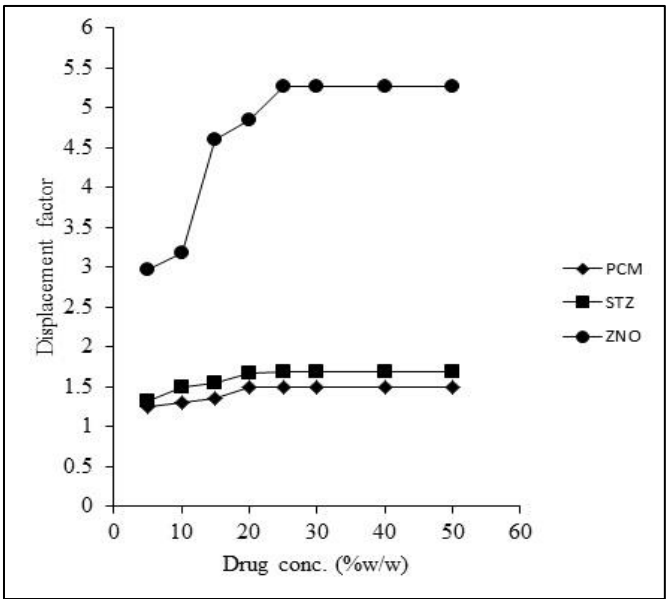

Figure 2: Effects of paracetamol (PCM), sulphathiazole (STZ) and zinc oxide (ZNO) concentrations on their displacement factors in modified shea butter suppository base

Table 1: Displacement factors of drugs in the bases and minimum concentration of drug required for the determination

Base/parameter	Drug		
	Paracetamol	Sulphathiazole	Zinc oxide
PEG			
Displacement factor	1.14	1.34	4.27
*Drug conc. (%w/w)	10	15	20
Shea butter			
Displacement factor	1.49	1.67	5.26
*Drug conc. (%w/w)	20	20	25

*Minimum drug concentration at which a constant displacement factor was obtained

Table 2: Derived densities of drugs and suppository bases and their density ratios

Drug/base	Bulk density (g/cm^3)	Bulkiness (cm^3/g)	True density (g/cm^3)	Calculated density ratio of drug to base	
				PEG	Modified shea butter
Paracetamol	0.323 ± 0.005	3.096	1.362 ±0.001	1.148	1.524
Sulphathiazole	0.439 ± 0.010	2.278	1.487 ± 0.020	1.254	1.66
Zinc oxide	0.593 ± 0.009	1.686	4.893 ± 0.019	4.127	5.473
PEG	Nr	Nr	1.186 ± 0.018	Nr	Nr
Shea butter	Nr	Nr	0.894 ± 0.012	Nr	Nr

Nr = Not required

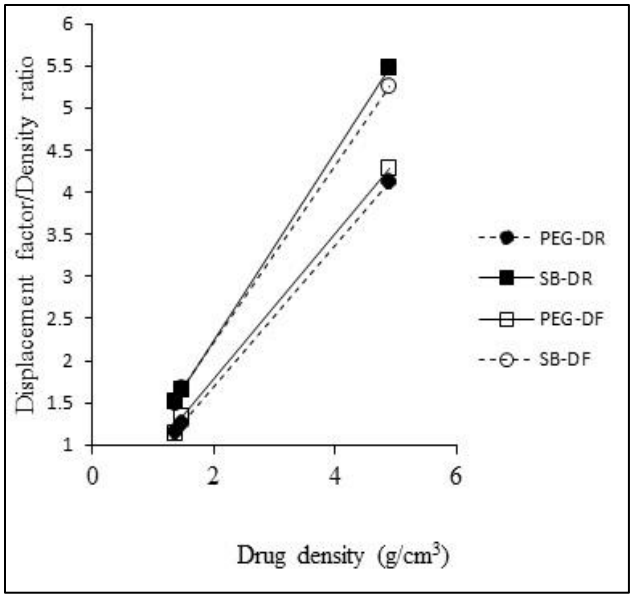

Figure 3: Plot of drug densities against their displacement factors (DF) and density ratios (DR) in the suppository bases

Effects of Interacting Variables on Displacement Factor

The values of DF used for the factorial experiment are presented in Table 3. The use of PCM and ZNO for the 2^3 factorial experimental was justified by the fact that the two drugs presented two opposite extremes of their bulk properties (Table 2). The values were used in calculating the independent and interaction coefficients for the variables (Table 4). Thus, the individual and interaction coefficients provided a clear indication of the quantitative effects of the three variables on the DF of the drugs in the suppository bases [19,20]. In comparing the formulations, the ranking of the independent coefficient values on DF was D > C > B (Table 4). The negative value for B indicated that a change from the base with lower density, SB (B_L) to that with higher density, PEG (B_H) led to decrease in the DF. This finding also held for the DR obtained for the drugs in the two bases (Table 2). The density of the drug (D) was the most influential independent variable that affected the rank-investigated DF of the drugs in the bases (Table 4). The results indicated that the larger the difference between the densities of the drug and the base, the higher the DF and DR. The positive values obtained for C and D is an indication that increase in the concentration of the drug (C) and use of denser drug (D) led to increase in the DF. However, as mentioned earlier, Figures 1 and 2 showed that there was an optimum concentration of the drug beyond which the DF remained constant. Determination of such concentrations for the individual drugs in the different bases was the target in this study.

The interaction coefficients (Table 4) indicate the effects of the variables in combination [19,20]. The values of the interaction coefficients were not arithmetic summation of the independent coefficients, but indicated complex interaction between the variables. The ranking of interaction effects on the DF was C-D > B-D > B-C (Table 4). Since the values of the interaction coefficients deviated from zero, it thus implied that the three variables interacted with each other to influence the DF of the drugs in the suppository bases.

Table 3: Displacement factors of paracetamol and zinc oxide in polyethylene glycol and shea butter bases for factorial experimental design

Variables and combination code	Displacement factor
$B_LC_LD_L$	1.24 ± 0.10
$B_LC_LD_H$	2.97 ± 0.07
$B_LC_HD_L$	1.49 ± 0.06
$B_LC_HD_H$	5.27 ± 0.05
$B_HC_HD_H$	4.28 ± 0.04
$B_HC_HD_L$	1.14 ± 0.03
$B_HC_LD_L$	1.05 ± 0.03
$B_HC_LD_H$	2.51 ± 0.06

Table 4: Quantitative effects of nature of the base (B), concentration of drug (C) and nature of the drug (D) on displacement factors of paracetamol and zinc oxide

Variables	Independent/ interaction coefficient for displacement factors
Independent	
B	-0.5
C	1.103
D	2.528
Interaction	
B-C	-0.173
B-D	-0.228
C-D	0.933

CONCLUSION

The results obtained indicated that there was an optimum concentration for each drug in the different suppository bases above which the DF of the drug in the base remained constant. These concentrations were determined as 10, 15 and 20% w/w for PCM, STZ and ZNO with DF of 1.14, 1.34 and 4.27 in PEG, respectively, and as 20, 20 and 25% w/w for PCM, STZ and ZNO with DF of 1.49, 1.67 and 5.26 in SB, respectively. The drug type (D), as typified by its density, was the most influential independent variable that affected the rank-investigated DF of the drugs in the suppository bases. The dual interaction coefficients showed a departure from zero value, implying interaction between the variables. Thus, based on the fact that the highest dual interaction effect of the variables on DF was that between the drug concentration and the drug type (C-D), it is suggested that drug concentrations between 10 and 25% w/w could be used for accurate determination of DF of drugs in the bases depending on the bulkiness of the drug. The bulkier the drug, the lower the concentration of drug required for the DF determination.

REFERENCES

[1] W Lund. The Pharmaceutical Codex: Principle and Practice of Pharmaceutics, 12th Edition, The Pharmaceutical Press, London, **1994**, 170-175.
[2] LV Allen Jr, NG Popovich, HC Ansel. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th Edition, Lippincott Williams and Wilkins, Philadelphia, **2005**, 316-335.
[3] TA Adegboye; OA Itiola. *Trop J Pharm Res.* **2008**, 7(1), 887-896.
[4] T Takatori; N Shimono; N Higaki; T Kimura. *Int J Pharm.* **2004**, 278, 275-282.
[5] I Setniker; F Fontani. *J Pharm Sci*. **1970**, 59, 1319-1324.
[6] E Kalmar; JR Laser; TD Tarry; A Myers; G Szakonyi; G Dombi; G Baki; KS Alexander. *Saudi Pharm J*. **2014**, 22, 338-342.
[7] A Adegoke; FA Oladimeji; AO Oyedele. *J Pharm Res Dev Pract*. **2016**, 1(1), 12-24.
[8] O Taylor; I Igwilo; B Silva; A Nchako; A Adenitan. *J West Afr Pharm.* **1992**, 6, 49-53.
[9] HS Yousif. *Asian J Pharm Sci*. **2011**, 10(2), 68-83.
[10] MO Ilomuanya; ND Ifudu; J Odulaja; C Igwilo. *J Chem Pharm Res*. **2012**, 4(6), 3280-3286.
[11] PJ Sinko. Martin's Physical Pharmacy and Pharmaceutical Sciences. 5th Edition, Lippincott Williams and Wilkins, New Delhi, **2006**; 533-560.
[12] HC Mital; FR Dove. *Planta Medica*. **1971**, 20, 283-288.
[13] AO Oyedele. *Ife J Sci.* **2012**, 14(2), 253-257.
[14] The Pharmaceutical Codex. 11th Edition, The Pharmaceutical Press, London, **1979**, 78.
[15] CO Onyeji; AS Adebayo; CP Babalola. *Eur J Pharm Sci*. **1999**, 9, 131-136.
[16] C Karuppusamy; P Venkatesan. *J Pharm Sci Res*. **2017**, 9(3), 326-331.
[17] RC Rowe, PJ Sheskey, PJ Weller. Handbook of Pharmaceutical Excipients, 5th Edition, Pharmaceutical Press, UK, **2009**, 518-519.
[18] A Yousfan; J Hasian. *J Chem Pharm Res*. **2015**, 7(7), 274-282.
[19] OO Okubanjo; OA Odeku. *Acta Pharm Sci*. **2009**, 51, 281-288.
[20] MA Odeniyi; KT Jaiyeoba. *Trop J Pharm Res*. **2004**, 3(1), 285-290.
[21] RC Woolfall. *Soap Perfum Cosmet*. **1964**, 37, 965-970.
[22] LJ Coben, HA Lieberman. The Theory and Practice of Industrial Pharmacy, 3rd Edition, Lea and Febiger, Philadelphia, **1986**; 564-588.

[23] SJ Carter. Cooper and Gunn's Dispensing for Pharmaceutical Students, 12th Edition, CBS, New Delhi, **2008**, 232-252.
[24] NJ Vidras; VE Roid; NR Bohidar; FM Plakogiannis. *J Pharm Sci*. **1982**, 71, 945-949.