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Research Article

Formulation and Evaluation of Coconut Oil - based Diclofenac-loaded Solid Self-Emulsifying Drug Delivery System

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ABSTRACT

Self-microemulsifying drug delivery system (SMEDDS) is one approach for optimizing solubility and consequently the oral bioavailability of class 2 drugs in the biopharmaceutical classification system such as diclofenac which exhibit low aqueous solubility but high lipid permeability. The purpose of this study was to formulate self-microemulsifying drug delivery system based on coconut oil for the delivery of diclofenac, a hydrophobic non-steroidal anti-inflammatory drug (NSAID). Coconut oil was extracted and used in combination with tween 80, polyethylene glycol 400 (PEG400) and propylene glycol at varying ratios for the formulation of diclofenac-loaded solid self-microemulsifying drug delivery system (DCF-loaded solid SMEDDS) which were encapsulated in hard gelatin capsules and evaluated for drug content, emulsification time and in vitro drug release. The results from the study revealed that over 80 % of diclofenac was released from the SMEDDS within 30 minutes and percentage drug content was above 90 % except for BF3, BF5, and BF6 which were 87 %. Emulsification time for all the batches except BF6 were within 120 sec (2 min). It can be concluded that coconut oil in combination with polyethylene glycol 400 (PEG-400) and tween 80 could be used in the formulation of SMEDDS for the delivery of diclofenac for dissolution optimization.

Keywords: *self-microemulsifying delivery, Diclofenac, bioavailabilty, solubility and emulsification.*

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INTRODUCTION

Drugs belonging to class II of the biopharmaceutics classification system (BCS) have poor aqueous solubility and dissolution which result in sub-optimal bioavailability after oral administration of such drugs. Diclofenac sodium, a non-steroidal anti-inflammatory drug belongs to class II of the biopharmaceutics classification system. One of the major problems with this class of drug is low aqueous solubility in biological fluids, which results in poor bioavailability after oral administration. The solubility of diclofenac in aqueous medium is about 0.078 mg/ml. Thus, increasing aqueous solubility and dissolution of diclofenac is of therapeutic value (Kausalya et al., 2011; Bhagwat and D'Souza, 2012). Self-micro emulsifying drug delivery system (SMEDDS) is one approach for improving solubility and consequently the oral bioavailability of drugs in this class.

SMEDDS are usually prepared in a liquid dosage form that can be administered in soft gelatin capsules, however this dosage form has some disadvantages particularly in the manufacturing process as well as possible incompatibility problems with the shells of soft gelatin. Solid SMEDDS have recently been formulated and were found to overcome the disadvantages of liquid SMEDDS as well as exhibit more commercial potential and patient acceptability (Akter and Hossain, 2012).

A major challenge in the oral delivery of lipophilic drugs is low aqueous solubility. Self-micro-emulsifying drug delivery systems (SMEDDS) have the ability to improve solubility and optimize bioavailability of drugs with poor aqueous solubility. Self-micro emulsifying drug delivery systems are isotropic mixtures of oil, surfactant, co-surfactant or co-solvents and can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drugs. Self-microemulsifying drug delivery system can be administered orally in the form of hard or soft gelatin capsule and form fine stable oil-in-water (o/w) emulsion on aqueous dilution resulting from the gentle agitation of gastrointestinal fluid.

The process of self-emulsification of SMEDDS depends on a number of factors such as the type and ratios of oil and surfactant pair, the concentration of surfactant as well as the temperature at which self-emulsification occurs. The primary step in the formulation of a SMEDDS is the identification of these specific combinations of excipients and the construction of a ternary phase plot which shows various concentrations of excipients that possess self-emulsification (Farah et al., 1994).

The incorporation of an active pharmaceutical ingredient to a SMEDDS is critical because the drug interferes with the self-emulsification process to a certain extent, which may lead to a change in the optimal oil–surfactant ratio. So, the design of an optimal SMEDDS requires preformulation solubility and phase-diagram studies. In the case of controlled release SMEDDS, formulation is made by adding a release retarding agent such as polymer or gelling agent (Nazzal and Khan, 2006).

The aim of the study therefore was to evaluate the effect of coconut oil on the self-emulsifying properties of diclofenac loaded solid self-emulsifying drug delivery system.

MATERIALS AND METHODS

Materials: Diclofenac sodium was procured from Sigma chemical Co. (NJ, USA), Tween 80 (BDH chemical, Poole, England), Polyethylene glycol (BDH chemical, Poole, England), Propylene glycol (Manali Petrochemicals, India), Lactose (Loba Chemie, Mumbai, India), and Talc (Loba Chemie, Mumbai, India). Coconut oil was freshly prepared in the laboratory.

Extraction of coconut oil from *Cocos nucifera*: Fruits of coconut were procured from a local market in Abraka, Delta State, Nigeria and their pericarps which consist of epicarp, mesocarp and endocarp were removed. The coconut seeds were sliced into small sizes using a grater. The size-reduced coconut was soaked in 1000 ml of distilled water for 30 minutes. The solution was filtered using muslin bags in order to remove the chaff. The filtered solution was left overnight in the refrigerator. Thereafter, the coagulated interphase of the solution was heated using a heating mantle until the water evaporated thereby leaving the oil. The oil obtained was stored for evaluation and further use.

Characterization of *Cocos nucifera* (coconut) oil

Determination of Specific gravity: This was done using the specific gravity bottle. The bottle was first rinsed with distilled water, and dried in oven for 15 minutes, cooled, stoppered with a cap and weighed. The same specific gravity bottle was filled with the coconut oil sample, closed and again weighed. The weight of sample per ml was determined by subtracting the initial weight from the final weight.

Determination of Refractive index: This was performed using a Refractometer (ABBE model) as described by a previous researcher (Kirk and Sawyer, 1991). Refractive index is specific for oils, within certain limits. It is related to the degree of binding / bonding saturation, but it is affected by other factors such as free fatty acids content, oxidation, and thermal treatment.

Determination of pH: This was done using a pH/ORP meter, model HI 2211 (Hanna Instrument) at a temperature of 25°C ± 2°C.

Pseudo-ternary phase diagram construction: Pseudo-ternary phase diagram of oil, surfactant, and co-surfactant was constructed using the water titration method at 25 ± 2°C. Coconut oil was combined with surfactant mix, Smix (containing surfactant and co-surfactant) in ratios of 9 **:** 1, 8 **:** 2, 7 **:** 3, 6 **:** 4, 5 **:** 5, 4 **:** 6, 3 **:** 7, 2 **:** 8, 1 **:** 9 w/w in a glass vial for 5 minutes. Each ratio of oil and Smix was then titrated with distilled water in increments of 0.5% w/w of water, and the sample was mixed vigorously for at least 2 min and then kept at 25^{O}C for 10 min to equilibrate before next addition of water. The process was repeated until the sample turned turbid or until 90.9% w/w addition of water. The phase behaviour of each ternary phase system was observed during the titration. Samples with clear or slightly bluish appearance were taken as micro emulsion region. The percentage composition of each component in the ternary system was determined, and the results were plotted on the triangular coordinates to construct the phase diagram using Prosim® F-31312 (Ternary diagram software, Labege Cedex, France).

The concentration of oil, surfactant and co-surfactant that gave clear emulsions were selected as the self micro emulsions for the formulation of the Diclofenac SMEDDS and were labelled as BF1, BF2, BF3, BF4, BF5, and BF6 (Borhade *et al*., 2008; Ahmad *et al*., 2013; Syed and Peh, 2014.

Table 1:
Composition of selected self-micro emulsion of Oil, Surfactant and co-surfactant

Batch	Composition (% v/v)		
	Coconut oil	**Tween 80**	**PEG 400**
BF1	35	20	20
BF2	32	20	23
BF3	40	20	20
BF4	30	25	20
BF5	20	20	30
BF6	25	20	20

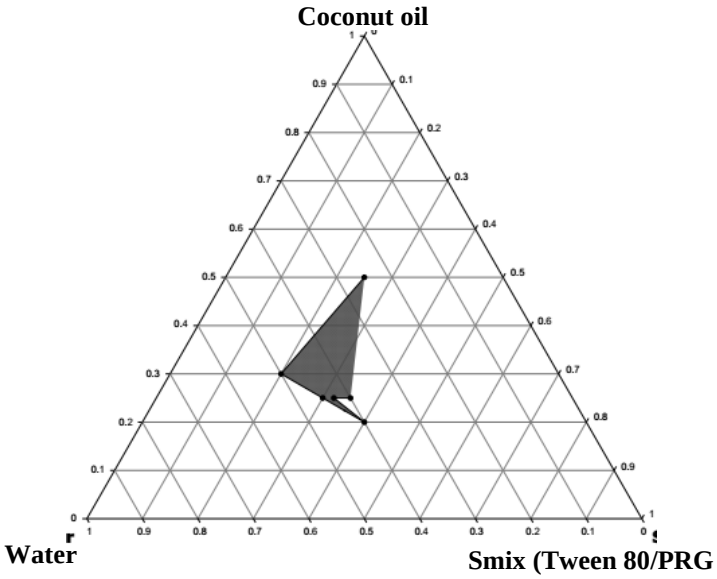

Figure 1:
Pseudoternary phase diagram showing the microemulsion region (shaded region)

Table 2:
Composition of DCF-loaded solid SMEDDS based on coconut oil

	Ingredients (g)							
Batch	**Coconut 0il**	**Tween 80**	**PEG400**	**propylene glycol**	**Diclofenac sodium**	**Lactose**	**Talc**	**Total**
BF1	0.332	0.216	0.228	0.281	2.0	6.84	0.1	10
BF2	0.295	0.216	0.262	0.281	2.0	6.85	0.1	10
BF3	0.3682	0.216	0.228	0.225	2.0	6.86	0.1	10
BF4	0.2762	0.27	0.228	0.281	2.0	6.84	0.1	10
BF5	0.1841	0.216	0.338	0.338	2.0	6.82	0.1	10
BF6	0.2300	0.2700	0.285	0.281	2.0	6.83	0.1	10

(Batch size: 20 capsules)

Evaluation of Self micro emulsions: The selected concentrations of oil, surfactant and co- surfactant that produced self micro emulsion (SME) labelled BF1 to BF6 were evaluated for p^H, viscosity, conductivity and refractive index (Porter *et al*., 2007).

Viscosity*:* Viscosity of the different SMEs were measured at 25°C using a NDJ-8S digital viscometer (Shanghai Precision and Scientific Instrument, Shanghai, China) with a No 1 spindle at 60 rpm.

Conductivity*:* Electrical conductivity was determined using a conductivity meter (DDS-11C, Shanghai San-Xin Instrumentation Inc, Shanghai, China)

Refractive Index: Refractive index measurement was done with Abbe Refractometer (Shijiazhuang Optical Instrument Factory, Xiamen, China).

pH: The pH measurement was carried out using a pH/ORP meter, model HI 2211 (Hanna Instruments) at a temperature of 25°C ± 2°C.

Preparation and encapsulation of DCF-loaded solid SMEDDS granules: The preparation of diclofenac SMEDDS batch formulation was done according to the quantities stated in Tables 2. In each case, weighed amounts of coconut oil, surfactants (tween 80), co-surfactant (PEG400) and co-solvent (propylene glycol) were mixed manually with stirring for 5 min in a beaker over a water bath at 50^0C. A 2 g quantity of diclofenac sodium (equivalent to 20 capsules, each holding 100 mg) was weighed and dissolved in the SME. After which lactose (solid carrier) was added and was properly mixed to form a wet mass. The wet mass was sieved using 800μm sieve. The granules were dried and dry sieving was done using 600 μm sieve, and then dried again in an oven 60^0C. Talc was added to the dried granules.

Encapsulation of the SMEDDSs from the different batches was done by weighing quantities equivalent 100 mg of diclofenac into a 500 mg capacity hard gelatin capsule. The batch size for diclofenac-loaded SMEDDS was twenty (20) capsules each containing exactly 100 mg diclofenac.

Micromeritic properties of DCF-loaded solid SMEDDS granules

Angle of repose: Diclofenac-loaded SMEDDS granule equivalent to 8 g was weighed and allowed to fall freely from a funnel clamped to a retort stand at a height of 7.5 cm from a horizontal surface. The diameter and the height of the pile formed by the granules were measured using a meter rule. This procedure was also repeated in triplicate for each batch and the result was recorded (Chawla *et al*., 2003).

$$Angle\ of\ repose\ (\Theta) = tan - 1\left(\frac{h}{r}\right) \quad (1)$$

Where, h = height of the pile, r = radius of the base of the pile, Θ = angle of repose.

Bulk and tapped densities: An 8g quantity of granules from each batch was weighed and packed into a 20 ml graduated cylinder. The granules were carefully levelled without compacting and the unconsolidated apparent volume (V_o) was read and recorded as the bulk volume. Thereafter, the cylinder was tapped to constant volume and recorded as the final tapped volume (V_f). The process was done in triplicate and then the bulk density and tapped density in g/ml were calculated using Equations (Bharadia *et al*., 2004).

$$Bulk\ density = \frac{M}{V_0} \quad (2)$$

$$Tapped\ density = \frac{M}{V_f} \quad (3)$$

Where, M = mass of the powder, V_0= bulk or unconsolidated apparent volume of the powder

V_f= final tapped volume of the powder

Compressibility index (Carr's index) and Hausner ratio*:* The Compressibility index and Hausner ratio of the granules were derived from the bulk and tapped densities (Aulton and Wells, 1988).

$$Carr's\ index\ (\%) = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} * 100 \quad (4)$$

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density} \quad (5)$$

Estimation of diclofenac content

Drug content in solid SMEDDS was determined. Accurately weighed diclofenac-loaded solid SMEDDS, equivalent to 100 mg diclofenac, was thoroughly dissolved in 100 ml of phosphate buffer, pH 6.8 in a volumetric flask. The solution was filtered using a 0.45 µm filter paper and assayed for diclofenac content at 276 nm using Shimadzu UV-1601 spectrophotometer. The drug content (%) was estimated by the following formula:

$$DC = \frac{C_p}{C_t} * 100 \qquad (6)$$

Where DC is the percentage of drug content, C_p is the concentration determined by UV Spectrophotometer, and C_t is the theoretical concentration.

Dissolution test: *In vitro* dissolution test was performed using dissolution tester (Erweka apparatus – type: DT, Nr: 56263, Germany), USP dissolution apparatus 1 rotating at 100 rpm in 900 ml phosphate buffer of pH 6.8 at 37 ± 0.5ºC. Aliquot of dissolution medium equal to 5 ml was withdrawn at specified time intervals and replaced with same volume of fresh dissolution medium. The withdrawn samples were diluted accordingly and the concentration of diclofenac was determined spectrophotometrically using Shimadzu UV-1601, Japan at a wave length of maximum absorption of 276 nm by using the regression equation from the standard calibration curve.

Emulsification time: The content of one capsule randomly drawn from each batch was emptied into a beaker containing 250 ml of distilled water with little agitation of the mixture. The time taken for the granule in each beaker to emulsify was noted

RESULTS AND DISCUSSION

The result of the physicochemical evaluation of coconut oil as presented in Table 2 shows that coconut oil with specific gravity of 0.9205 is not as dense as water; while the refractive index value of 1.5609 shows that the extracted coconut oil is not as transparent as water (1.333).

Table 2:
Physicochemical characteristics of extracted *Cocos nucifera* (coconut) oil

Parameters	Values
Specific gravity	0.9205
Refractive index (28.5 °C)	1.5609
pH	6.2

Table 3:
Physiochemical characterizations of SMEDDS

Batch	pH	Viscosity (mPa.s)	Conductivity (µs/cm)	Refractive index
BF1	6.4	3000	1.74	1.9543
BF2	6.3	3500	1.22	1.5609
BF3	6.45	3500	1.84	1.5598
BF4	6.99	250	1.21	1.6051
BF5	6.10	300	1.15	1.5944
BF6	6.30	350	1.06	1.5922

Refractive index of diluted SMEDDS was found to be in the range of 1.559 – 1.954. Electrical conductivity was carried out to differentiate between the water-in-oil (w/o), bi continuous or oil-in-water (o/w) micro emulsion. Electrical conductivity is a function of the water content (% w/w) for self-micro emulsifying drug delivery systems (SMEDDS). The conductivity as revealed in Table 3 is in the range of 1.06 -1.84 which is quite low

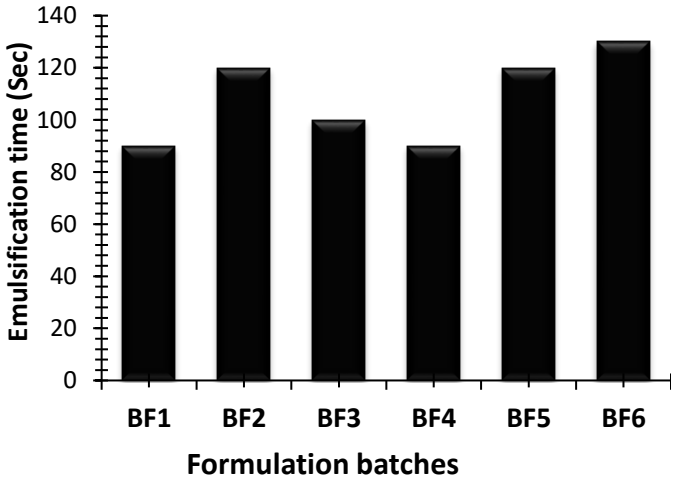

Figure 2:
Emulsification time for the various batches of diclofenac-loaded SMEDDS

The self-emulsification efficiency could be primarily estimated by an assessment the rate of emulsification which is an important index for the determination of the efficiency of emulsification, that is, SMEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation. Emulsification time for all the batches were within 120 sec (2 min) except for batch BF6 as revealed in Figure 2. Batches BF1 and BF4 showed higher self-emulsification efficiency with the lowest emulsification time of 90 seconds apiece.

The results of the micromeritic characterization presented in Table 4 reveal that the tapped densities of the granules were greater than their bulk densities. The angle of repose for BF1 to BF6 ranged from 30-35^0. This falls into the range of good flow property based on angle of repose (Carr, 1965). Batch BF5 gave the best angle of repose value of 30.90 followed by BF6 (33.6^0) and BF1 (33.8^0).

The compressibility index and Hausner ratio are measures of the ease or tendency of a powder to be compressed as well as interparticulate interactions and from the results in Table 4, the values of the Carr's index and Hausner ratio are in the range of 34.7 – 43.13% and 1.53-1.76 respectively which are rather too large and would result in granules being poorly compressible, although these granules are meant to be filled into hard gelatin capsules. However, the suboptimal values of Carr's index and Hausner ratio will also affect the flowability of the granules.

Table 4:
Micromeritic characterization of diclofenac- loaded SMEDDS granules

Batch	Angle of Repose (°)	Tapped density (g/ml)	Bulk density (g/ml)	Hausner ratio	Car's index (%)
BF1	33.8 ± 0.95	0.73 ± 0.07	0.427 ± 0.01	1.6 ± 0.10	41.3 ± 0.65
BF2	35.1 ± 1.04	0.73 ± 0.06	0.43 ± 010	1.69±0.15	40.5 ± 0.56
BF3	35.6 ± 1.35	0.75 ± 0.04	0.427 ± 0.01	1.76±0.12	43.13 ± 0.39
BF4	35.1 ± 1.27	0.73 ± 0.00	0.421 ± 0.00	1.73±0.00	42.6 ± 0.32
BF5	30.9 ± 1.20	0.68 ± 0.05	0.440 ± 0.00	1.53±+0.1	34.7 ± 4.70
BF6	33.6 ± 1.95	0.69 ± 0.06	0.427 ± 0.01	1.62±0.12	38.4 ± 4.60

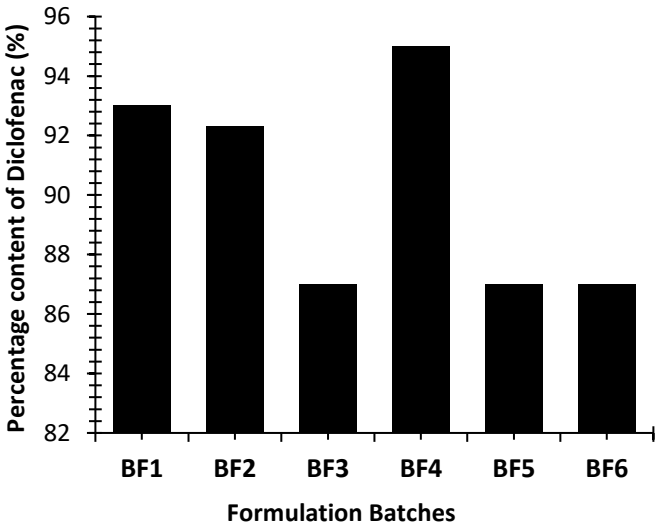

Figure 3:
Drug contents of the various batches of coconut oil based diclofenac-loaded solid SMEDDS

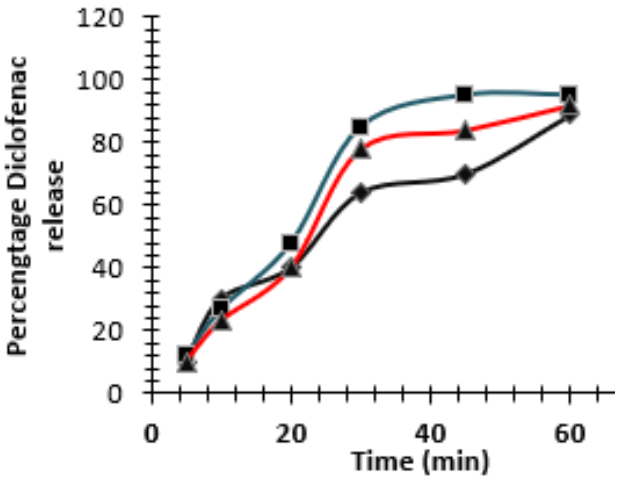

Figure 4:
Release profile of coconut oil based diclofenac-loaded SMEDDS for batches
BFI ♦, BF2 ■ and BF3 ▲

The results of the micromeritic characterization presented in Table 4 reveal that the tapped densities of the granules were greater than their bulk densities. The angle of repose for BF1 to BF6 ranged from 30-35^0. This falls into the range of good flow property based on angle of repose (Carr, 1965). Batch BF5 gave the best angle of repose value of 30.9^0 followed by BF6 (33.6^0) and BF1 (33.8^0).

The compressibility index and Hausner ratio are measures of the ease or tendency of a powder to be compressed as well as interparticulate interactions and from the results in Table 4, the values of the Carr's index and Hausner ratio are in the range of 34.7 – 43.13% and 1.53-1.76 respectively which are rather too large and would result in granules being poorly compressible, although these granules are meant to be filled into hard gelatin capsules. However the suboptimal values of Carr's index and Hausner ratio will also affect the flowability of the granules.

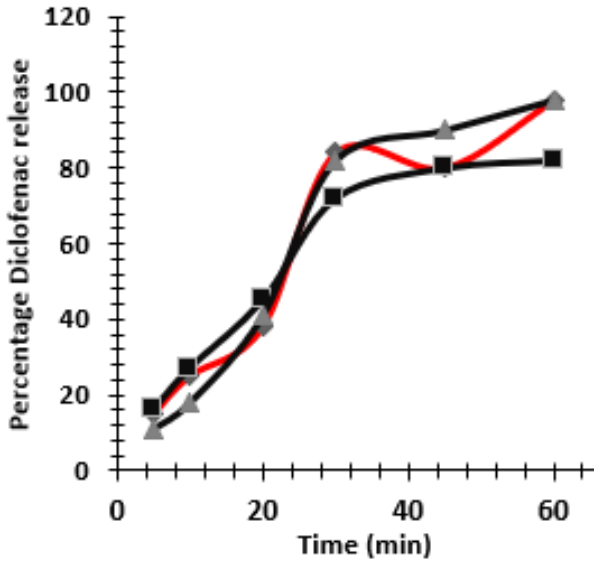

Figure 5:
Release profile of coconut oil based diclofenac-loaded SMEDDS for batches
BF4 ♦, BF5 ■ and BF6 ▲

British Pharmacopoeia specification for content uniformity is 85 to 115% of the labelled claim (B.P., 2013). The Percentage drug contents of diclofenac-loaded SMEDDS batches BF1, BF2, BF3, BF4, BF5 and BF6 were 93%, 92.3%, 87%, 95%, 87% and 87% respectively as presented in Fig. 3. From the result obtained it can be said that all the batches met the B.P specification for content uniformity with batch BF4 having the highest value of 95%.

The results of the dissolution profile of all batches of diclofenac-loaded SMEDDS are presented in Figures 4 and 5. All batches were able to release 80% or more of diclofenac within 60 minutes. But batch BF2 released over 80% of diclofenac in 30 minutes and about 95% of diclofenac in 45 minutes. Batch BF2 can be regarded as the optimized batch having released over 80% in 30 minutes, had percentage diclofenac content of 92.3%, and emulsification time of 120 seconds (2 minutes).

The SMEDDS system showed high viscosity especially for batches BF1, BF2 and BF3 which are batches with the highest concentration of coconut oil. The high viscosity and very low conductivity of the SMEDDS system indicates that it is a water-in-oil emulsion system (Pooja et al., 2011; Ajeet et al., 2009 and Cho et al., 2008).

The *in vitro* Self-emulsification efficiency of the formulations determined by self-emulsification
time and the efficiency of pre-concentrate dispersibility when it is exposed to aqueous dilution was visually assessed and defined using the grade A to E grading scale system reported by previous researcher (Khoo et al., 1998 and Balakumar et al., 2013). The SMEDDS in this study fell into grade C (Fine milky emulsion that formed within 2 min). An emulsification time of 2 min is often recommended for such systems

The overall micromeritic properties of diclofenac-loaded SMEDDS was poor and this may be due to the wet granulation technique employed in preparing the self-emulsifying granules using lactose as adsorbent powder or carrier, and the liquid SEDDS as binder. The adsorption capacity of lactose is low and granulation with SEDDS produces a broader size distribution and aggregation is difficult to control when compared with granulation procedure where water is employed as granulating agent (Franceschinis et al., 2015; Nikolakakis and Partheniadis, 2017).

In conclusion, the study has revealed that coconut oil in combination with tween 80, polyethelene glycol 400, propylene glycol can be used in the preparation of Self-microemulsifying drug delivery system for the delivery of diclofenac. The coconut oil based SMEDDS of diclofenac sodium showed rapid emulsification.

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