ISSN: 0975-766X
Research Article
Available Online through
www.ijptonline.com

DEVELOPMENT, CHARACTERIZATION AND OPTIMIZATION OF IBUPROFEN SELF-EMULSIFYING DRUG DELIVERY SYSTEM APPLYING FACE CENTERED EXPERIMENTAL DESIGN

Abdelazim Zaghloul*, Aly Nada A, Ibrahim Khattab
Department of Pharmaceutics, Faculty of Pharmacy, Kuwait University, PO BOX: 24923, SAFAT 13110, Kuwait.
Email:abdel@hsc.edu.kw

Received on 30-01-2011 *Accepted on 13-02-2011*

ABSTRACT

Ibuprofen (IB) a NSAID, has poor dissolution and many gastrointestinal side effects. Self-Emulsifying drug delivery system (SEDDS) has proved its efficacy to improve the solubility and dissolution of many lipophilic drugs and improve their characteristics. The objectives of this study were to develop, optimize and characterize a IBSEDDS applying Face Centered Experimental Design (FCED). The methods included determination of solubility of IB in different oils, surfactants and co-surfactants. Ingredient showing high drug solubility were used to formulate several IBSEDDS after being tested for physical and chemical compatibility with the drug. A three factor, three level FCED was used for the optimization process. The concentration of oil, surfactant and cosurfactant were the independent variables, X1, X2 and X3 respectively, while the dissolution, turbidity and droplet size were the dependent variables, Y1, Y2 and Y3 respectively. The results showed high solubility and compatibility of IB with soybean oil, Cremophore EL and Capmul MCM-C8. The concentrations of X1- X3 showed significant effects on the responses Y1-Y3.The polynomial equation relating the response Y_1 and variables X1-X3 was obtained. The optimized and predicted values of Y_1 were in close agreement. According to the design, 50% X1, 40% X2 and 10% X3 maximized Y1 up to 100% after 60 min. In conclusion, IBSEDDS with high drug release and reasonable physical properties could be prepared and the experimental design applied helped in understanding the effects and the interaction effects between the three variables applied. The optimized formulation is expected to show high bioavailability with minimal side effects.

Keywords: Self-Emulsifying Drug Delivery System (SEDDS); Ibuprofen; Optimization; Experimental Design.

INTRODUCTION

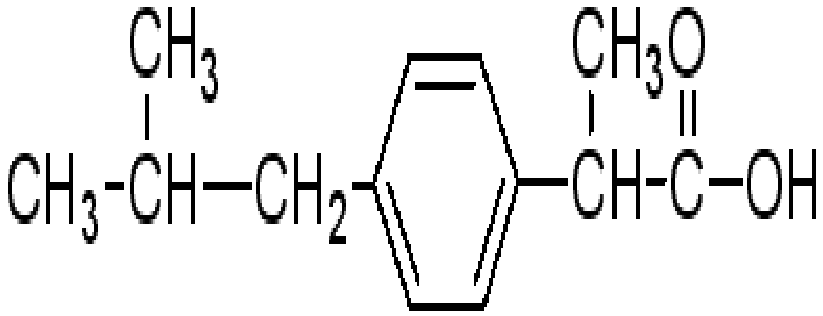
Drug solubility and dissolution are essential factors for therapeutic effectiveness, independent of administration route. They also pose major challenge for pharmaceutical companies developing new pharmaceutical products, since nearly half of the active substances being identified through the new paradigm in high-throughput screening are either insoluble or poorly soluble in water (1). In addition, the resistance of these compounds to being wetted by and dissolved in the fluid of the gastrointestinal tract (GIT) represents a limiting factor for their *in vivo* performance. These compounds, even if they have powerful pharmacological activities, their oral delivery is frequently associated with low bioavailability, high intra- and inter-subject variability, and lack of dose proportionality (2). Therefore, increasing the solubility and dissolution rate of these drugs are important for optimizing bioavailability (3).

Self-emulsifying drug delivery systems (SEDDS) typically comprises a mixture of surfactant, oil and drug which when introduced into the body is rapidly dispersed to form droplets of micrometer or nanometer size. The dispersed systems would be expected to self-emulsify rapidly in the aqueous contents of the stomach or the upper small intestine and forms a thermodynamically stable O/W microemulsion. These small fine droplets have the capability to empty rapidly from the stomach and promote wide distribution of the drug throughout the GIT (4). Additionally, these oil droplets provide large surface area for pancreatic lipases to hydrolyze the glycerides and the fatty constituents of the emulsion and the subsequent drug containment in mixed micelles formed from biliary extracts (5). Recent work proved SEDDS as efficient vehicles for the *in vivo* administration of many lipophilic drugs such as CoQ10 (6), amphotericin B (7), phenytoin (8) and vitamin A (9).

In addition, the stability of the SEDDS is much more higher compared to microemulsion because they do not contain water. For the aforementioned reasons, SEDDS may offer an improvement in both the rate and extent of absorption for drugs subject to dissolution rate limited absorption and drugs greatly influenced by the diet and the flow of bile secretion (10).

The efficiency of oral absorption of the drug compound from the SEDDS depends on many formulation-related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability. Only very specific pharmaceutical excipient combinations will lead to efficient self-emulsifying systems. Although many studies have been carried out in this area, there are few drug products on the pharmaceutical market formulated as SEDDS confirming the difficulty of formulating hydrophobic drug compounds into such formulations. Based on this conclusion and on the fact that almost 40% of new drug compounds are hydrophobic in nature implies that studies with SEDDS will continue, and more drug compounds formulated as SEDDS will reach the pharmaceutical market in the future (11).

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) commonly used in the treatment of post-operative, epidural, dysmenorrheal and dental pain in addition to migraine, rheumatoid arthritis and other musculoskeletal disorders. It shows poor water dissolution and tableting behaviour due to its hydrophobic substituted isobutyl benzene. Additionally, its high coalescence results in low flowability and processibility (12). Similar to other drugs of this group, it has a wide spectrum of gastrointestinal side effects ranging from mild dyspepsia to gastric bleeding. One of the reasons for gastric irritation is due to the free carboxylic acid group in its chemical formula.



To overcome these problems, as well as to fulfill drug therapy for some chronic disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis, several trials have been made to control drug release through preparing different dosage forms such as tablets (13), gels (14), osmotic pumps (15), beads (16), spherical crystal agglomerates (17), microspheres and microcapsules (18) and nanoparticles (19) or reduce the

particle size through preparing nanosuspension (3) or microemulsion (20). High local concentrations of the NSAIDs should be avoided during oral administration, by diluting them with food or administering them as a dilute aqueous solution. In this respect, it is important to have the drug available in a highly soluble chemical form or a rapidly dissolving solid dosage form (3). One of the recent methods to increase the drug solubility and dissolution is to prepare the drug in self emulsified lipid formulations. It is assumed that by this way, the absorption and bioavailability could be improved and also the side effects could be reduced.

The main objectives of this study were to prepare, characterize and optimize ibuprofen self-emulsifying drug delivery systems (IBSEDDS) applying Face Centered Experimental Design (FCED) in trials to enhance its solubility and dissolution. As part of the optimization process, the main effects, interaction effects, and quadratic effects of the formulation ingredients on drug release were investigated.

MATERIALS AND METHODS

Materials

Ibuprofen, soybean oil, olive oil, corn oil, peanut oil, Cremophore EL and Pluronic acid F-68 were purchased from Sigma Chemicals Co. (NJ, USA). Labrafil M 1944 CS, Labrafil M-2125-CS and Labrasol were obtained as a gift from Gattefosse Corporation **(**Paramus, NJ, USA). Capmul MCM-C8 was gifted from Abitec Corp. (Jamesvills, WI, USA). Hydroxypropyl methylcellulose (HPMC) capsules were gifted from Qualicaps (Whitsett, NC, USA). All other chemicals were of analytical grade and were used as received.

Methods

Determination of the solubility of IB in different oily and aqueous solutions

The solubility of IB in the following oils and in 10% of the following surfactants and co-surfactants was determined: soybean oil, olive oil, corn oil, peanut oil Labrafil M-1944-CS, Labrafil M-2125-CS, Labrasol, Cremophore EL, Pluronic acid F-68, Capmul MCMC-8, Transcutol P, propylene glycol and glycerol. Solubility determination was carried out applying saturation solubility method. This was done by preparing saturated solutions of the drug in these reagents, shaking for 48 hrs at 20^{o}C, and 50 rpm (New Brunswick Scientific Excella E5 Platform Shaker, New Brunswick Scientific CO., Inc, USA), centrifugation, taking a

sample from the supernatant layer containing the dissolved drug and using HPLC for analysis. The results of solubility study are shown in Table 1.

Table-1: Solubility study of IB in different oils, surfactants and co-surfactants.

Reagent	Solubility (%w/v)
Corn oil	5.281
Peanut oil	4.980
Soybean	8.799
Olive oil	3.689
Labrasol,10%	0.418
Labrafil M-1944-CS, 10%	0.419
Labrafil M -2125- CS, 10%	0.414
Cremophor EL, 10%	0.464
Pluronic acid F-68, 10%	0.018
Transcutol.P, 10%	0.014
Capmul MCM-C8, 10%	0.831
Propylene glycol, 10%	0.009
Glycerol, 10%	0.006

Chromatography

The method of analysis was as described in Araya et. al (21) with some modification. The HPLC instrument consisted of 2690 Waters separation module and a 996 photodiode array detector set at a wavelength of 252 nm (Waters Corporation, Milford, MA, USA). The HPLC column was hypercil ODS-AGILENT 4x125mm, 5

um, mounted on HPLC Agilent cartridge holder 125 mm.The mobile phase was methanol : water : phosphoric acid (7:3:1) with a flow rate: 1 ml/min. The injection volume was 50 ul and the retention time was 4.2 min. Ethyl acetate was used as an intermediate solvent to help mixing the oil with the mobile phase.

The chromatographic data were managed using Waters empower 2 software (Waters Corporation, Milford, MA, USA).

Compatibility study of IBSEDDS components

The compatibility of different ingredients of IBSEDDS was investigated physically and chemically. The physical compatibility (miscibility and spontaneity of emulsification) was inspected visually while the chemical compatibility between the ingredients and IB was demonstrated using Differential Scanning Calorimeter (DSC) and Fourier Transform Infrared Spectroscopy (FTIR).

DSC and FTIR

DSC measurements (DSC 50, Kyoto, Shimadzu Corp and Japan) were carried out by taking approximately 2 mg of IB powder and IBSEDDS in sealed aluminum pans and analyzing under nitrogen purge. Thermal analysis was carried out between 10 ^{o}C and 200 ^{o}C at a heating rate of 5 °C/ min. An empty aluminum pan was used as a reference and indium was used as instrument calibration standard.

FTIR spectra were obtained using FTIR spectroscopy (Perkin Elmer System 2000, USA). The method included dissolving IB or IBSEDDS in suitable volatile solvent to form a thin film on the spectroscopy plate and leave to dry before the operation.

Preparation and characterization of IBSEDDS: Screening study

The results of solubility showed that soybean oil (solvent), Cremophore EL (surfactant) and Capmul MCM-C8 (co-surfactant) demonstrated the highest solubility and compatibility among the investigated reagents, that why these reagents were used to prepare different IBSEDDS.

Preparation of IBSEDDS

Different self-emulsifying systems were prepared with varying concentrations of soybean oil, Cremophore EL and Capmul MCM-C8. The oil was accurately weighed into a screw-capped glass vial. Cremophore and Capmul were mixed and added while stirring with a magnetic bar until a clear mixture was obtained. The drug

was added at a final loading of 300 mg/4ml and stirred to dissolve. Table 2 shows the concentration of different ingredients in SEDDS formulations.

Table 2: Design and results of characterization of different IBSEDDS formulations (screening study).

Form #	Drug (mg)	Oil (%)	Surf. (%)	Co-surf. (%)	Turbid. (NTU)	Mean droplet size(um)	Visual observation
1	300	90	8	2	4.1	0.51	fair
2	300	80	16	4	5.2	0.42	fair
3	300	70	24	6	4.8	0.41	fair
4	300	60	32	8	6.4	0.33	fair
5	300	50	40	10	4.4	0.23	good
6	300	40	48	12	4.9	0.39	good
7	300	30	56	14	3.4	0.23	good
8	300	20	64	16	3.1	0.29	good
9	300	10	72	18	2.7	0.31	good

Characterization of IBSEDDS

The prepared formulations were characterized for the following:

Emulsion droplet size analysis

One ml of each formulation was diluted with pure water, pre-equilibrated at room temperature to 1000 ml in an Erlenmeyer flask and gently mixed by hand. The mean droplet size distribution of the resultant emulsions was determined by Coulter N4 plus submicron particle sizer and the data obtained were analyzed using N4 Plus software (Coulter Corporation, Miami, FL, USA). The data were collected for 60 seconds and the droplet size was calculated from the volume size distribution.

Turbidity measurements.

The procedures included diluting one ml of the formulation with pure water, pre-equilibrated at room temperature to 1000 ml in an Erlenmeyer flask and gently mixed by hand. The turbidimeter (HACH 2100N IS, HACH Company, Loveland, CL, USA) was first calibrated with Formazin Standards Kit and turbidity measurements were performed on 30 ml of the emulsion stored in a clear screw-capped sample vials. The readings were given in nephlometric turbidity units (NTU).

Visual observation

Spontaneity of the emulsification of different IBSEDDS was carried out by mixing one ml of the formulation with 900 ml of pure water in a glass Erlenmeyer flask at room temperature and the contents were gently stirred. A scale with poor, fair and good was used to judge the tendency of the mixture to spontaneously form a transparent emulsion. The results of characterization of different formulations were shown in Table 2.

Dissolution studies

Dissolution studies of HPMC capsules (size 00) filled with IBSEDDS or IB dissolved in soybean oil without any other additives (blank) were determined using USP rotating paddle apparatus (Erweka® GmbH, Type DT80, Germany) at 37 ± 0.5 ◦C and a rotating speed of 50 rpm in 900 ml of distilled water. Capsules were held to the bottom of the vessel using copper sinkers. Samples of 2 ml were withdrawn after 10, 20, 30, 45 and 60 min, filtered (hydrophilic syringe filter PTFE 0.45um, Millipore Millex - LCR), properly diluted and assayed for the drug applying the HPLC method previously mentioned. Figs. 1&2 show the dissolution profiles of IBSEDDS formulations in the screening study while Figs. 3-5 show the dissolution profiles of IBSEDDS optimized formulations.

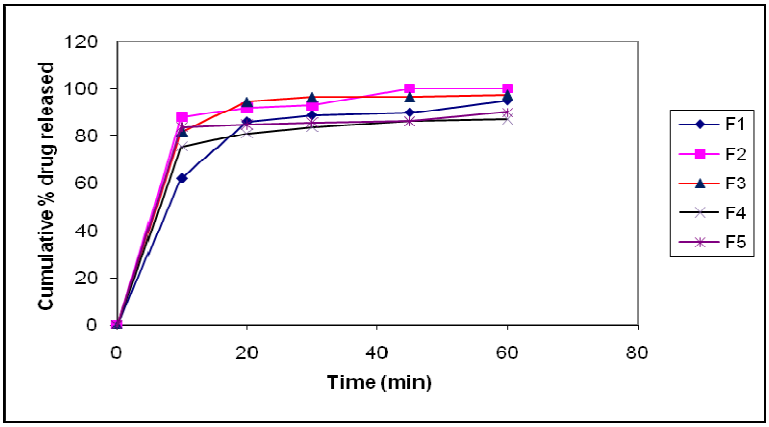


Fig-1: Dissolution profiles of IBSEDDS screening formulations (F1-F5) in distilled water.

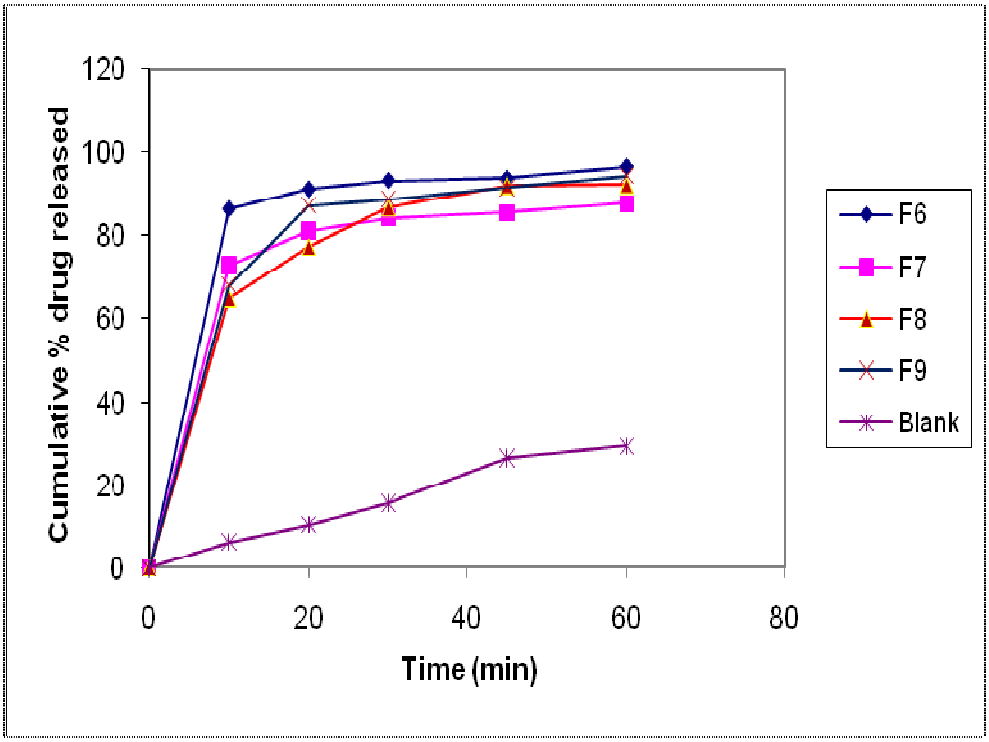


Fig-2: Dissolution profiles of IBSEDDS screening formulations (F6-F9) and blank formulation in distilled water.

Optimization of IBSEDDS applying experimental design

A three factor, three level Face Centered Experimental Design (FCED) was used for the optimization process. This design is suitable for exploring quadratic response surfaces and constructing second order polynomial models. It provides information on direct effects, pair wise interaction effects and curvilinear variable effects. The non-linear quadratic model generated by the design is of the form: $Y = A_o + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_1X_2 + A_5X_2X_3 + A_6X_1X_3 + A_7X_1^2 + A_8X_2^2 + A_9X_3^2 + E$, where Y is the measured response associated with each factor level combination; A_o is an intercept; A_1-A_9 are the regression coefficients; X_1, X_2 and X_3 are the factors studied and E is the error term. In this design, the concentration of oil, surfactant and co-surfactant represented the independent variables X_1, X_2 and X_3 respectively while cumulative percent drug dissolution after 60 min, turbidity and droplet size represented the dependent variables Y_1, Y_2 and Y_3 respectively. The limits of independent and dependent variables used in the design were listed in Table 3.

Table 3: Variables in the Face Centered Experimental Design.

Independent variables
X1 = % of oil (10, 50, 90)
X2 = % of surfactant (8, 40, 72)
X3 = % of co-surfactant (2, 10, 18)
Dependent variables
Y1 = Drug released after 60 min (%)
Y2 = Turbidity (NTU)
Y3 = Droplet size (um)

RESULTS AND DISCUSSION

Solubility and compatibility of IB different oily and aqueous solutions

Table 1 shows the results of solubility of IB in different oils, surfactantas and cosurfactants. From these reagents, soybean oil, Cremophore EL and Capmul MCM-C8 were used to prepare IBSEDDS because they showed high solubility and chemical compatibility with the drug when tested by DSC and FTIR (results are not shown). The mixture also showed physical compatibility where no phase separation was observed on mixing. Soybean oil is an unmodified edible oil and provides the most natural bases for lipid formulations in addition to increasing the fraction of lipophilic drugs transported via the intestinal lymphatic system. Unfortunately, because of its poor ability to dissolve large amounts of hydrophobic drugs and phase separation might occur on dilution with water, it needed to be mixed with one or more surfactant. Addition of Cremophore EL and Capmul MCM-C8 increased the drug uptake and improved the emulsification efficiency. Cremophore EL is a nonionic surfactant made by reacting castor oil with ethylene oxide. It is recommended as a solubilizer and emulsifer and is particularly suitable for the production of liquid preparations. Capmul is composed of mono and diglycerides of medium chain fatty acids (mainly caprylic). It is an excellent solvent and emulsifier for many organic compounds. In addition, it is affirmed GRAS (generally recognized as safe) by the manufacturer (22).

Since alcohol and other volatile co-solvents comprised in the conventional SEDDS are known to migrate into the shells of soft gelatin or hard gelatin capsules, resulting in drug precipitation (23), they were excluded from our formulations.

Preparation and characterization of different IBSEDDS for screening study

The objective was to choose the correct blend of oil with surfactant(s) to get a stable microemulsion. The screening formulations were prepared using oil concentration ranging from 10-90%, surfactant concentration ranging from 8-72% and co-surfactant concentration ranging from 2-18%. The prepared formulations were characterized for droplet size, turbidity and spontaneity of emulsification. Table 2 shows the design and results of characterization of these formulations. Few techniques have been mentioned in the literatures to categorize and characterize the self-emulsifying performance. This performance is based on type and content of lipid phase, surfactant(s) and any other ingredients in the preparation such as cosolvent. The techniques are primarily based on equilibrium phase behavior studies of systems mixed with water. One of these is the visual inspection where the emulsification rate and resultant emulsion are qualitatively described. Spontaneity or the rate of self-emulsification can also be assessed by monitoring the turbidity change and/or the droplet size analysis of the dispersion by appropriate instrumental tools. The results of characterization showed that there was a correlation between spontaneity of emulsification and surfactant concentration. Increasing the concentration of surfactant(s) improved the shape and stability of the emulsion. Out of the 9 formulations, F5-F9 showed no separation or precipitation of the drug even after they were kept at room temperature for 2 months. These formulations were characterized by having small droplet size (ranged from 0.39 to 0.23 um) and low turbidity (ranged from 2.7 to 4.9 NTU). The results also showed some correlation between the droplet size and turbidity. This correlation is acceptable where more light beam scattering will occur on increasing the particle size. In general, formulations exhibiting better dispersion showed better results regarding the droplet size and turbidity and vice versa .

Dissolution studies

For lipophilic drugs, the absorption and bioavailability are dissolution rate dependent. Ideally the SEDDS formulation allows the drug to remain in a dissolved state throughout its transit through the GIT. The primary

mechanism of action which leads to improved bioavailability of drugs from SEDDS is usually avoidance, or partial avoidance, of the slow dissolution process of hydrophobic drugs from solid dosage forms. In this study, HPMC capsules were used to fill the IBSEDDS formulations because of their chemical inactivity, low moisture content, short disintegration time and not coloring the dissolution medium. The dissolution profiles of all IBSEDDS screening formulations (Figs 1, 2) showed dissolution rate over 90% except F4 and F7 (87 and 88% respectively). IB in oil (blank) (Fig 2) showed 29% drug release. The results indicted that SEDDS increased the release of IB tremendously compared to blank formulation. From the results, it seems that there is poor correlation between the results of dissolution and other characterization results such as droplet size and turbidity. This may be due to other factors such as the concentrations and ratio of surfactant/ cosurfactant and their combined HLBs (hydrophil/lipophil balance). The drug could be released or entrapped in the micelles depending on the resulted critical micelle concentration (CMC) as evidenced by Chanana and Sheth (24). This interprets the difficulty in predicting the rate of drug release from SEDDS formulations and shows the necessity of using experimental design for the optimization process.

Optimization of IBSEDDS

From the results of screening study, it was obvious that 10-50% oil, 40-72% Cremophore EL and 10-18% Capmul MCM-C8 resulted in good and stable emulsion which resisted separation when stored for couple of months on shelf. Other formulations showed either separation, drug precipitation or color change after short time. These findings were in agreement with the report stating that the usual surfactant concentration in self-emulsifying formulations required to form and maintain a stable microemulsion in vitro and in vivo is ranging from 30 to 60% (25). Seventeen runs were required for the optimization process based on FCED. Table 3 shows the independent variables and their ranges in addition to the dependent variables. The prepared formulations were characterized as previously mentioned. The concentrations of different ingredients, as per the design, and their results of characterization were mentioned in Table 4. All the formulations showed good emulsification properties with reasonable turbidity and droplet size. None of them showed phase separation, color change or drug precipitation after 6 months stay on shelf at room temperature. The results of dissolution

were shown in Figs 3-5. All the formulations (except F3 and F13) showed above 90% drug release. Ten out of the seventeen preparations showed almost 100% drug release. The polynomial equation relating the response Y_1 and independent variables was:

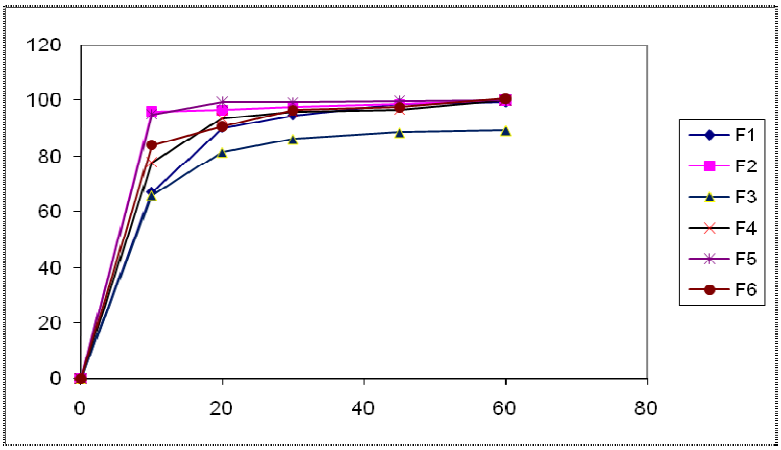


Fig-3: Dissolution profiles of IBSEDDS optimized formulations (F1-F6) in distilled water.

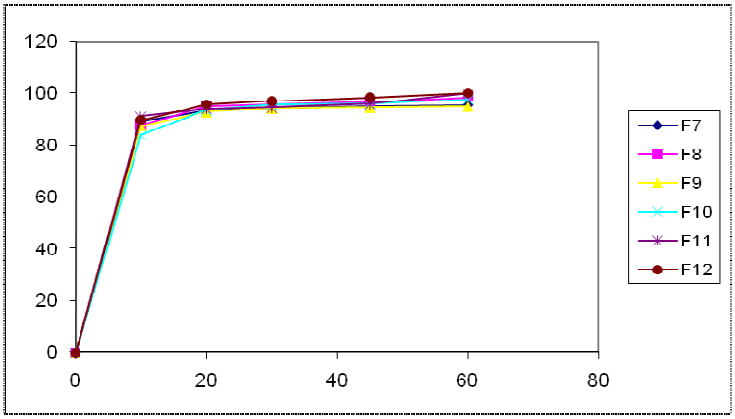


Fig-4: Dissolution profiles of IBSEDDS optimized formulations (F7-F12) in distilled water.

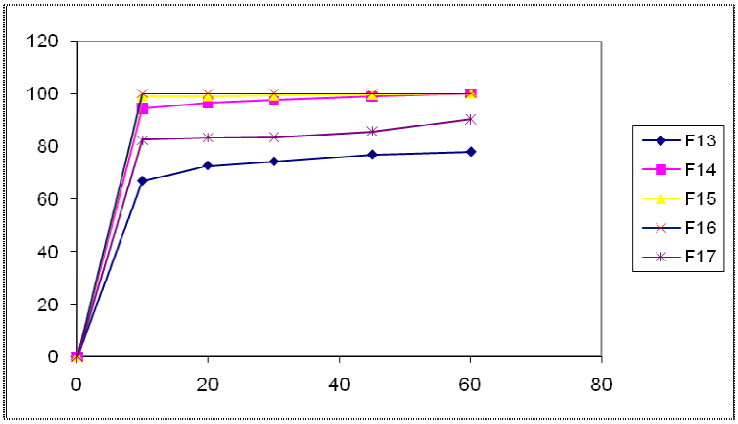


Fig-5: Dissolution profiles of IBSEDDS optimized formulations (F13-F17) in distilled water.

Table 4: Face Centered Experimental Design and results of characterization (optimized runs).

Form#	Oil (part)	S (part)	CoS (part)	Turbidity (NTU)	Droplet size (um)
1	10	8	2	4.53	0.279
2	90	8	2	4.12	0.2883
3	10	72	2	0.119	0.2701
4	90	72	2	3.75	0.261
5	10	8	18	0.514	0.296
6	90	8	18	6.18	0.315
7	10	72	18	0.322	0.2379
8	90	72	18	4.28	0.2874
9	10	40	10	0.446	0.129
10	90	40	10	6.12	0.4887
11	50	8	10	6.13	0.3948
12	50	72	10	1.96	0.2668
13	50	40	2	5.19	0.3264
14	50	40	18	2.13	0.2377
15	50	40	10	3.99	0.2536
16	50	40	10	3.51	0.2731
17	50	40	10	3.24	0.2529

$Y_1 = 96.77 – 0.094X_1 – 0.573X_2 + 2.108X_3 + 0.001X_1X_2 - 0.003X_1X_3 + 0.001X_2X_3 + 0.001X_1^2 + 0.005X_2^2 - 0.083X_3^2$. This equation represents the quantitative effect of process variables; X_1 through X_3; and their interactions on the response Y_1. The values of the coefficients X_1-X_3 refer to the extent of these effects. Coefficients with more than one factor term and those with higher order terms represent interaction terms and quadratic relationships respectively. A positive sign represents a synergistic effect, while a negative sign indicates an antagonistic effect. The values of X_1-X_3 were substituted in the equation to obtain the theoretical values of Y_1. The theoretical (predicted) values and the experimental values were in reasonably good

agreement as seen from Table 5. The relationship between the dependent and independent variables was further elucidated using contour and response surface plots. The effects of X_1 through X_3 and their interaction on Y_1 were given in Figs 6-8. The optimization was performed to obtain the levels of X_1 through X_3, which maximize Y_1 at constrained conditions of Y_2 through Y_3. According to the design, 50% X1, 40% X2 and 10% X3 will maximize the release up to 100%. Using these values, a new formulation was prepared and the obtained Y_1 was in agreement with the predicted value. The dissolution profile for the optimized formulation was shown in Fig 9. The given results demonstrated the reliability of the optimization procedure in predicting the output properties of IBSEDDS.

Table 5: Observed and predicted values for the response (Y1).

Form. #	Observed (%)	Predicted (%)	Residuals
1	99.26	95.67	3.59
2	99.98	98.06	1.92
3	89.11	88.29	0.82
4	99.87	96.92	2.95
5	99.98	102.4	-2.42
6	100.6	100.9	-0.3
7	95.38	96.77	-1.39
8	98.44	101.51	-3.07
9	94.86	95.46	-0.6
10	97.54	99.03	-1.49
11	99.89	102.68	-2.79
12	99.99	99.29	0.7
13	77.86	87.14	-9.28
14	99.99	92.8	7.19
15	99.99	95.32	4.67
16	100	95.32	4.68
17	90.14	95.32	-5.18

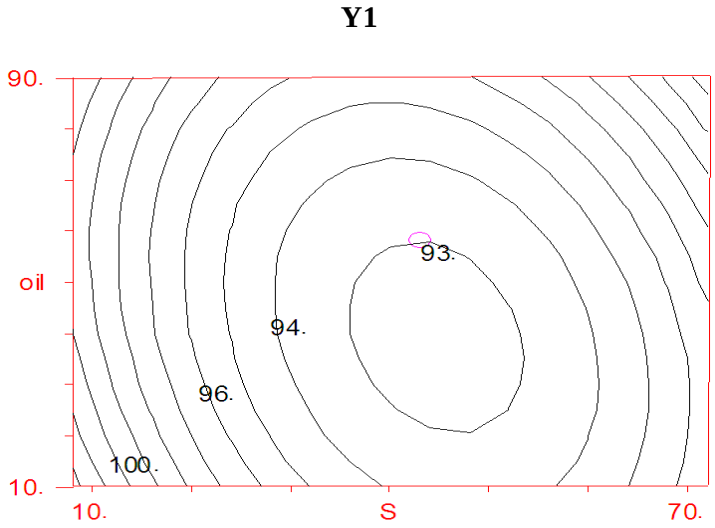


Fig-6: Contour plot showing the effect of oil and surfactant concentrations on dissolution (Y1).

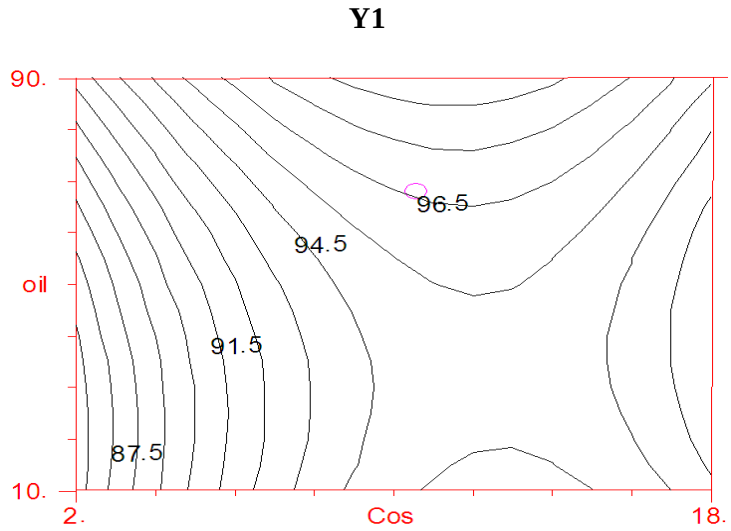


Fig-7: Contour plot showing the effect of oil and co-surfactant concentrations on dissolution (Y1).

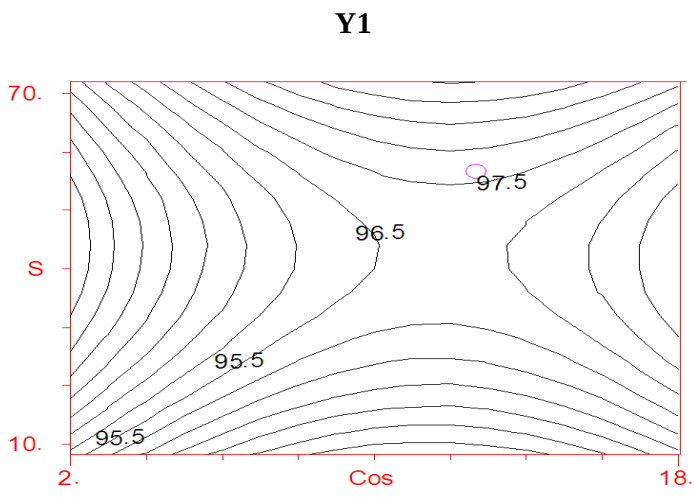


Fig-8: Contour plot showing the effect of surfactant and co-surfactant concentrations on dissolution (Y1).

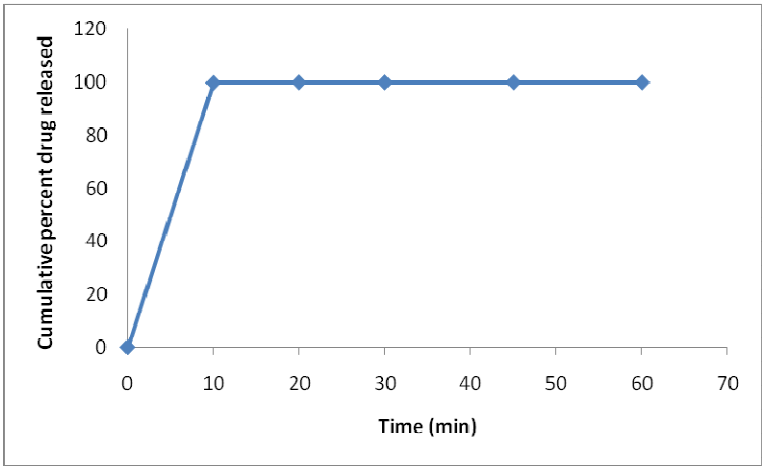


Fig-9: Dissolution profile of IBSEDDS optimized formulation in distilled water.

CONCLUSIONS

IBSEDDS could be prepared without interaction or incompatibility between the ingredients. The prepared IBSEDDS improved the characteristics, increased the dissolution rate several folds compared to the blank formulation. The findings also indicated that the experimental design applied in the optimization study helped in understanding the individual and interaction effects between the three factors applied. The produced IBSEDDS may have the potential to enhance the therapeutic bioavailability of IB. The priority for the future work will focus on studying the stability and bioavailability of the optimized formulations.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Kuwait University for funding this research project (grant No. PP02/06). Thanks is extended to Science Analytical Facilities (SAF) at Kuwait University for their help in DSC and FTIR, Gattefosse and Abitec for their gift supply of some of raw materials, Qualicaps for HPMC capsules and Pharmacist Doha Nabil for the excellent technical assistance.

REFERENCES

1. Patravale VB, Date AA, Kulkarni RM. Nanosuspensions: a promising drug delivery strategy. *J Pharm Pharmacol. 2004;56*:827–840.
2. Robinson JR. Introduction: Semi-solid formulations for oral drug delivery. *BT Gattefosse. 1996;89*:11–3.

3. Kocbek P, Baumgartner S, Kristl J. Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drugs. *Int J Pharm. 2006;312*:179–186.
4. Devani M, Ashford M, Craig DQ. The emulsification and solubilization properties of polyglycolysed oils in self-emulsifying formulations. *J Pharm Pharmacol. 2004; 56:*307-316.
5. Shah NH, Caravajal MT, Patel CI, Infeld MH, Malick AW. Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving in-vitro dissolution and oral absorption of lipophilic drugs. *Int J Pharm. 1994;106*:15-23.
6. Balakrishnan P, Lee BJ, Oh DH, Kim JO, Lee YI, Kim DD, Jee JP, Lee YB, Woo JS, Yong CS, Choi HG. Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems. *Int J Pharm. 2009:374*:66-72.
7. Wasan EK, Bartlett K, Gershkovich P, Sivak O, Banno B, Wong Z, Gagnon J, Gates B, Leon CG, Wasan KM.. Development and characterization of oral lipid-based Amphotericin B formulations with enhanced drug solubility, stability and antifungal activity in rats infected with Aspergillus fumigatus or Candida albicans. *Int J Pharm. 2009;372*:76-84.
8. Atef E, Belmonte AA. Formulation and in vitro and in vivo characterization of a phenytoin self-emulsifying drug delivery system (SEDDS). *Eur J Pharm Sci. 2008;35*:257-63.
9. Taha E, Ghorab D, Zaghloul A. Bioavailability assessment of vitamin A self-nano emulsified drug delivery systems in rats: A comparative study. *Med Princ Pract. 2007;16:*355-9.
10. Balakrishnan P, Lee BJ, Oh DH, Kim JO, Hong MJ, Jee JP, Kim JA, Yoo BK, Woo JS, Yong CS, Choi HG. Enhanced oral bioavailability of dexibuprofen by a novel solid SEDDS formulation. *Eur J Pharm Biopharm. 2009;72:*539-45.
11. Neslihan G, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. *Biomed Pharmacother. 2004;58:*173-182.
12. Rasenack N, Muller BW. Crystal habit and tableting behavior. *Int J Pharm. 2002;244:*45-57.

13. Majid Khan G, Zhu JB. Studies on drug kinetics from ibuprofen-carbomer hydrophilic matrix tablets: influence of co-excipients on release rate of the drug. *J Control Release. 1999; 57:*197-203.
14. Paavola A, Kilpelainen I, Yliruusi J, Rosenberg P. Controlled release injectable liposomal gel of ibuprofen for epidural analgesia. *Int. J. Pharm. 2000;199*:85-93.
15. Ozdemir N, Sahin J. Design of a controlled release osmotic pump system of ibuprofen. Int *J Pharm. 1997; 158*:91-97.
16. Sipahigil O, Dortunc B. Preparation and in vitro evaluation of verapamil HCl and ibuprofen containing carrageenan beads. *Int J Pharm. 2001;228*:119–128.
17. Nada A, Al-Saidan S, Mueller B. Improving the Physical and Chemical Properties of Ibuprofen. *Pharm Technol. 2005*; 29:1-8.
18. Tamilvanan S, Sa B. Studies on the in vitro release characteristics of ibuprofen-loaded polystyrene microparticles. *J Microencapsul. 2000;17*:57–67.
19. Pignatello R, Bucolo C, Ferrara P. Eudragit RS 100 nanosuspensions for the ophthalmic controlled delivery of ibuprofen. *Eur J Pharm Sci. 2002;16*:53-61.
20. Hiroshi A, Mikio T, Masahiro H. The novel formulation design of O/W microemulsion for improving the gastrointestinal absorption of poorly water soluble compounds. *Int J Pharm. 2005; 305*:61-74.
21. Araya H, Tomita M, Hayashi M. The novel formulation design of self-emulsifying drug delivery systems (SEDDS) type O/W microemulsion III: the permeation mechanism of a poorly water soluble drug entrapped O/W microemulsion in rat isolated intestinal membrane by the using chamber method. *Drug Metab Pharmacokinet. 2006; 21*:45-53.
22. Product Information on Capmul MCM C8, ABITEC bulletin, version #7, 7/28/04, from Abitec Corp.
23. Gershanika T, Benita S. Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. *Eur J Pharm Biopharm. 2000;50*:179-188.
24. Chanana GD, Sheth BB. Particle size reduction of emulsions by formulation design. II: effect of oil and surfactant concentration. *J Pharm Sci Technol. 1995;49*:71–6.

25. Constantinides PP. Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. *Pharm Res. 1995;12:*1561-1572.

Corresponding Author:

Dr.Abdelazim Zaghloul*,

Department of Pharmaceutics,

Faculty of Pharmacy, Kuwait University,

Email: *abdel@hsc.edu.kw*