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Stability and Human Bioavailability of Optimized Self-Emulsified Drug Delivery System of Ibuprofen

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ABSTRACT

Ibuprofen self-emulsified drug delivery system (IBSEDDS) has been prepared, characterized and optimized to release 100% drug in one hour. The optimal formulation was subjected to stability and bioavailability studies in human volunteers. The stability was conducted under different storage temperature (4^{o}C, room temperature and 37^{o}C) for 8 months and evaluated for in-vitro drug release, particle size and turbidity. Bioavailability was evaluated after administration of a single oral dose of two formulations, test (HPMC capsule containing IBSEDD) and reference (HPMC capsule containing 50 mg drug in soybean oil), by 6 health human volunteers. The results showed that IBSEDDS was stable under different storage temperatures and the drug was more stable at 4^{o}C. The changes in particle size and turbidity were lesser at room temperature. The pharmacokinetic parameters for test/reference were: the C_{max}, 0.892/0.468 ug/ml, the T_{max}, 1/1.5hr and the $AUC_{0-\infty}$, 3.956/1.986 mg.hr/ml. The % RBof IBSEDDS was 199.114. In a conclusion, the IBSEDD formulation stored at 4^{o}C were more stable regarding drug content but samples stored at room temperature were more stable regarding particle size and turbidity. The IBSEDD formulation showed higher rate and extent of drug absorption and higher bioavailability compared to the oily drug solution.

Keywords*:* Ibuprofen; SEDDS; Stability; Human Bioavailability

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INTRODUCTION

Over one-half of the drug compounds are diminished in the gastrointestinal tract because of their high lipophilicity and consequently poor aqueous solubility. Oral bioavailability of such drugs tends to exhibit inadequate magnitude with high intra- and inter-subject variability[1,2]. Several approaches have been employed to improve the oral bioavailability of these drugs during formulation. Among these, oral lipid-based drug-delivery systems which showed immense potential in improving the poor and inconsistent drug absorption [3,4]. These approaches included various types of lipid suspensions, solutions, and emulsions [5-7].

Self-emulsifying drug delivery systems (SEDDS) are relatively newer, lipid-based technological innovations with immense promise in enhancing the oral bioavailability of drugs. These formulations have been shown to reduce the slow and incomplete dissolution of a drug, facilitate the formation of its solubilized phase, increase the extent of its transportation via the intestinal lymphatic system, and bypass the P-gp efflux, thereby augmenting drug absorption from the GI tract [8-11]. SEDDS are isotropic mixtures of drug, lipids (natural or synthetic oils), and emulsifiers (solid or liquid), usually with one or more hydrophilic co-solvents/co-emulsifiers and form clear dispersions instantaneously in the GI tract that remain stable on dilution[12-14]. Such dispersions are either micro- or nanoemulsions, depending upon the globule size of the SEDDS formulation. These formulations have to be ultimately formulated as an oral solution in soft gelatin capsules or as solid dosage forms in hard gelatin capsules, depending on the final physical nature of the system as liquid or semisolid/solid, respectively[15].

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) and has been proved effective in treatment of rheumatoid osteoarthritis, ankylosing spondylitis, gout, and Bartter's syndrome[16,17]. However, with the demonstrated safety and efficacy, ibuprofen plays a limited pharmaceutical role mainly because of its extremely low aqueous solubility, rapid systemic elimination and inadequate tissue absorption resulting in poor bioavailability. The conventional ibuprofen tablet has low bioavailability and severe stimulatory effect on gastrointestinal tract (GIT). Gastric discomfort, nausea and vomiting are still the most common side effects[18].

Current trends in ibuprofen research have concentrated on the development of potential delivery systems to increase its aqueous solubility and this may increase bioavailability[19-23].

With increasing evidence suggesting that most drugs are substrates for some efflux or uptake transporters, the increase in solubility may not be alone sufficient confirm to enhance drug bioavailability because it does not adequately predict potential in vivo (i.e. physiological) effects.

Based on that, it has been found that individually, these poorly water-soluble. compounds, which are generally classified as 'lipophilic', behave differently in similar vehicles, thus highlighting the need to assess candidate compounds on an individual basis [24].

SEDDS formulations allow better formulation versatility and characterization of lipidic excipients and offer a viable alternative to serve the desired purpose through physicochemical and physiological mechanisms controlling drug absorption [25]. Recently, we developed and optimized ibuprofen self-emulsified drug delivery system (IBSEDDS) with 100% in-vitro drug release in one hour applying Face Centered Experimental Design [26].

The objectives of this study were to study stability of IBSEDD optimized formulation stored under different storage temperatures and study its bioavailability in human subjects compared with the oily solution of the drug.

MATERIALS AND METHODS

Materials

Ibuprofen, soybean oil and Cremophore EL were purchased from Sigma Chemicals Co. (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.

Preparation and Stability of IBSEDDS optimized formulation

The optimized IBSEDD formulation consisted of 50mg ibuprofen, 50% soybean oil (as solvent), 40% Cremophore EL (as surfactant) and 10% Capmul MCM-C8 (as co-surfactant).

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 200 mg/4ml and stirred to dissolve. The stability study was conducted by keeping samples of the prepared formulation in refrigerator (4^{o}C), room temperature (20-25^{o}C) and incubator (37^{o}C) for 8 months. Samples were withdrawn at zero time and after 1, 2, 4, 6 and 8 months and examined visually for color change, separation and/or sedimentation and characterized for in vitro drug dissolution in distilled water, particle size and turbidity as previously mentioned [26]. Figure. 1-3 show the results of characterization.

Bioavailability study

The bioavailability study of IBSEDDS was carried out with the permission of the Ethical Committee of Al-Azhar University for Bioavailability and Bioequivalence studies, Cairo, Egypt, and in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and to the standard operating procedures (SOP).In

this study, six healthy human male volunteers, their ages ranged from 23 to 34 years and body weights from 60 to 75 kg, were participated in an open randomized single dose two-way crossover study with one week washout period. All subjects gave written informed consent to participate in this study. The selected volunteers were considered healthy on the basis of detailed medical history. Verbal assurance was taken from all of them that they had not administered any drugs during and for one week preceding the study. The participating subjects were fasted overnight before each treatment and for two hours after dosing. On the morning of the study, each subject was allowed to drink 200 ml of water with dosing and required to remain fasted until 2 hours after dosing.

The bioavailability was assessed for test (IBSEDDS) and reference (50mg ibuprofen dissolved in soybean oil). Blood samples (3 ml) were collected in stoppered heparinized tubes immediately before administration and after 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, and 10 hr. of dose administration. The collected samples were centrifuged at 3000 rpm for 5 min to separate plasma. The decanted plasma samples were stored in labeled polypropylene screw-capped tubes at -20°C until analysis. During the experiment, the participants were asked if they feel any hurt burn, gastric pain or any kind of discomfort.

Calibration standards and quality control

Calibrator and quality control samples were prepared by adding of appropriate volumes of standard ibuprofen and internal standard (IS, indomethacin) solution in methanol-water (50:50 v/v) to drug free plasma to give concentrations of 0.1, 0.25, 0.5, 2.5, 5, 7.5, 15.0, 30.0, 50.0 µg/mL. Then a protein precipitating agent acetonitrile (500µL) was added and vortex-mixed for 1 min. The mixture was centrifuged for 10 min at 15,000 rpm. After centrifugation, supernatant was transferred to auto-sampler vials, capped and placed in the HPLC auto-sampler (PerkinElmer-USA). A 30µL aliquot of each sample was injected onto a YMC-C18 (150 X 4.6 mm, 5um) separation column using a mobile phase consisting of acetonitrile : 10 mM acetic acid (56:44) at a flow rate of 1.0 mL per minute. The detection was carried out by UV-diodarray detector set at wave length 220 nm. The obtained chromatograms were analyzed using Total Chrome Navigator Software. The analysis was carried out in triplicate for each concentration. By evaluating a series of method-performance characteristics, including accuracy, precision, recovery, and limit of quantification, the results ensured that the detection method was reliable.

Plasma sample analysis

Plasma concentrations of Ibuprofen were determined according to the method reported by Rustim AM[27] with some modification. Frozen plasma samples were thawed just prior to analysis.

An aliquot of 500µL of plasma sample was spiked with 1mL of acetonitrile containing 1ug IS. The mixture was vortex-mixed for 1 min and centrifuged for 10 min at 15,000 rpm. The supernatant solution was transferred to auto-sampler vials and assayed as mentioned above. The average of three readings of area under the peak of the drug divided by that of the IS was calculated from which the drug concentration is determined.

Pharmacokinetic and statistical analysis

From the drug plasma concentration–time profiles, the main pharmacokinetic parameters were calculated: The areas under the curves (AUC), the peak plasma concentration (C_{max}) and the time of its occurrence, T_{max}. The relative bioavailability of the test formulation is obtained by dividing the AUC between the first sample (pre-dosage) and infinite ($AUC_{0-\infty}$) of the test by that of the reference. Analysis of variance (ANOVA) and t-tests were performed to evaluate significant differences between the two formulations. Values were reported as mean ± SD and the data were considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

Stability study

One of the main requirements of a successful pharmaceutical preparation is to remain stable from the date of manufacture till the date of expiration. Since SEDDS contain several components including oil(s), surfactant(s) and co-surfactant(s), possible interactions between one or more of these components with each other and/or with the drug may arise. These interactions may be chemical interactions that may affect the entity of the drug or physical interactions manifested as separation, coagulation, precipitation, texture or color change and so forth. In this study, samples of the optimized IBSEDD formulation were stored at different temperatures for 8 months. The results of dissolution showed no significant decrease of drug content during the stability period compared to the freshly prepared samples. All samples showed more than 95% drug remained at the end of the study. Figure.1 shows the % of drug remained for different samples. It shows that samples kept at 4^{o}C showed higher % of drug remained compared to those stored at room temperature or at 37^{o}C. This may indicate little degradation of drug at higher temperature. The order of % drug remained in different samples was as follow: 4^{o}C> room temperature>37 ^{o}C. Figure. 2 shows the effect of storage temperature on particle size. The change in average particle size for samples kept at room temperature was less compared to those kept at 4^{o}C or at 37^{o}C and the order of this change was as follow: room temperature<37^{o}C< 4^{o}C. The same order was obtained for turbidity change as shown in Figure. 3. This may be due to some coagulation or coalescence of oil droplets at low temperature. The results of particle size and turbidity are in

agreement with those mentioned by other investigators who reported that micro-/nano-emulsions should be kept at 15°C or little higher [28]. All samples showed good dispersability when mixed with water and no separation or precipitation was observed when examined visually. It is worthy to mention here that only samples stored at 37°C showed little color change at the end of experiment and this may be due to the effect of high temperature on drug vehicle.

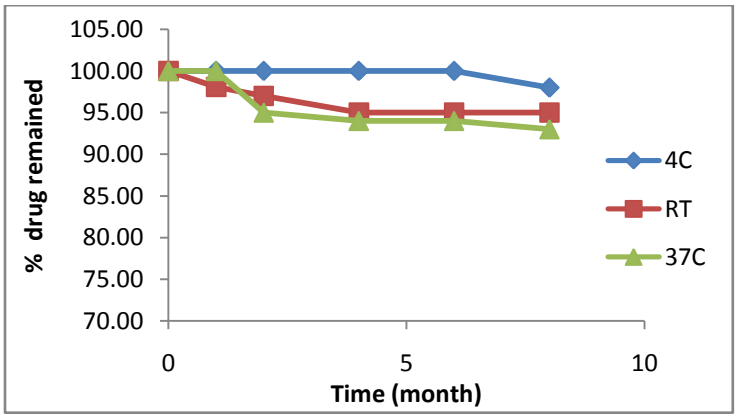

Figure 1: Percentage drug remained for IBSEDDS optimized formulation stored for 8 months at different temperatures.

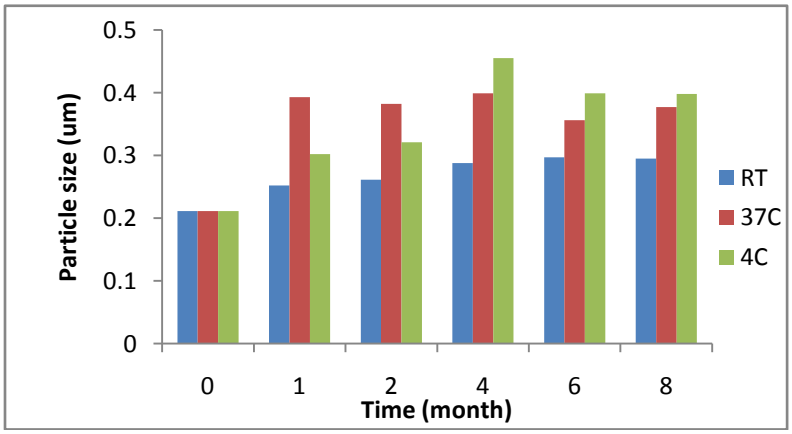

Figure 2: Results of particle size change for IBSEDDS optimized formulation stored for 8 months at different temperatures.

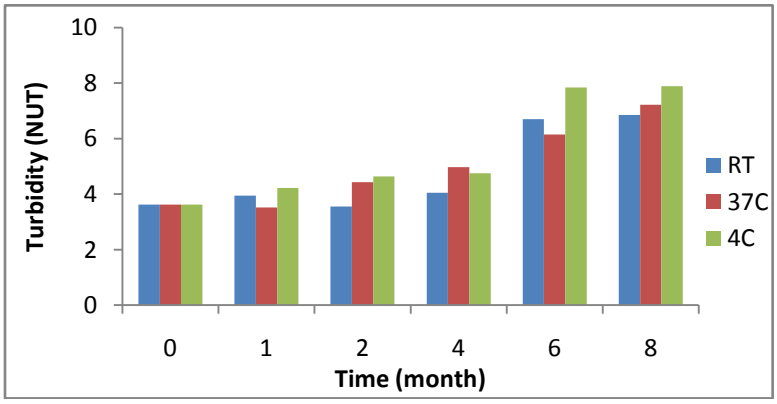

Figure 3: Results of turbidity change for IBSEDDS optimized formulation stored for 8 months at different temperatures.

Bioavailability study

Drug absorption from an oral DDS can simplistically be considered as a consecutive process of dissolution and permeation. Accordingly, as per the BCS, ibuprofen is a class II drug characterized by low dissolution and once the drug is dissolved, it will permeate easily through the GIT membrane. Class II drugs tend to exhibit dissolution-limited bioavailability and in most of the times, the *in vivo* physiological performance correlates well with their *in vitro* dissolution, resulting eventually in good *in vitro/in vivo* correlations [29]. For accomplishing better solubility or dissolution rate of BCS class-II drugs, techniques such as micronization[30] co-solvents[31] micellar solubilization[32], solid dispersions[33] and complexation[34] have been employed successfully but with modest improvement at bioavailability enhancement. Most studies aiming at investigating the bioavailability enhancement effect of SEDDS have been carried out in laboratory animals; only in a few studies, human volunteers were used. In this study we aimed to investigate the in-vivo performance of our IBSEDD optimal formulation and to confirm whether there is IVIVC when using human volunteers. Tables 1 and 2 show the drug concentrations in human plasma for IBSEDD and reference formulations, respectively. Figure 4 shows the average of these concentrations against time. The pharmacokinetic parameters were tabulated in table 3. The results show that IBSEDDS formulation had higher onset and extent of drug absorption compared to the oily drug solution manifested as increase in C_{max} and AUC and decrease in T_{max} results. Several literatures attributed the enhancement in bioavailability of SEDDS to the contents of lipids and surfactants. Lipids are responsible for promoting the transport of lipophilic drugs through the lymphatic system by stimulating the production of chylomicrons[35]. Being transported this way, the drug bypass the hepatic first-pass [8,36]. Furthermore, the drug which has been encapsulated in oil droplets, is further protected from the hatch chemical and enzymatic environment of the GIT [37]. In addition to the role of lipids, surfactants also play a key in augmenting the bioavailability of SEDDS through increasing the dissolution rate of drugs, disrupting the phospholipid bilayer of intestinal membranes which along with unstirred aqueous layer forms the rate-limiting barrier to the absorption of drugs [9, 38]. Further, less susceptibility of SEDDS to gastric emptying delays and lipolysis in the GIT as well as their high thermodynamic stability and robustness to dilution, all these factors keep the drug in solubilized state during the absorption phase and reduce variability in bioavailability[28]. IBSEDDS contain soybean oil which contains mainly long chain fatty acid esters. These are secreted from the intestinal cells by exocytosis into the lymph vessels. The contents of cremophor El which is a polyoxyl 35 castor oil and the capmul MCM which is a mono-diglyceride of medium chain fatty acids (mainly

caprylic and capric), both act as solubilizers and emulsifiers for lipophilic compounds and increase membrane fluidity, facilitating trans-cellular absorption, causing reversible opening of the tight junction to allow para-cellular transport and increase intracellular drug concentration and residence time. Further, being nonionic in nature, they are considered to be safer than the ionic ones [39]. The results obtained for SEDDS were in agreement with those obtained by other investigators. In this regard. The optimized cyclosporine SEDDS showed a 1.2-fold increase in bioavailability compared to Sandimmune Neoral[40]. Likewise, a 1.075-fold increase in the bioavailability of fenofibrate SMEDDS compared with Tricor® tablets [41]. Subramanian et al. reported a relative bioavailability of 132% when celecoxib was administered as SMEDDS compared with conventional marketed brand[42].It is worthy to mention here that the authors did not receive any complain from the volunteers after drug administration.

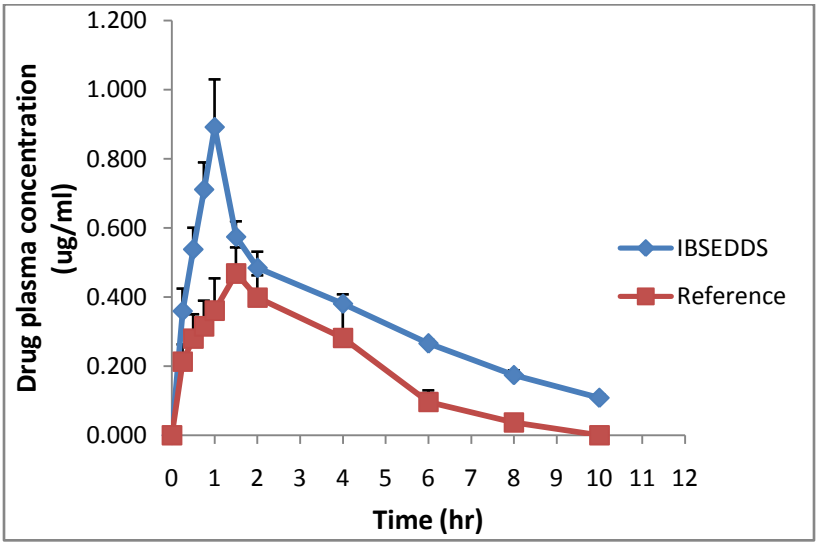

Figure 4: Drug plasma concentration following oral administration of IBSEDDS and reference formulations

Table 1. Drug plasma concentration of IBSEDDS optimized formulation in human volunteers

Time (hr)	H1	H2	H3	H4	H5	H6	Mean	SD
0.25	0.388	0.289	0.298	0.394	0.314	0.473	0.359	0.065
0.5	0.609	0.492	0.447	0.592	0.489	0.596	0.538	0.063
0.75	0.703	0.687	0.603	0.707	0.695	0.869	0.711	0.079
1	0.898	0.789	0.759	0.911	0.816	1.176	0.892	0.139
1.5	0.603	0.526	0.519	0.617	0.548	0.633	0.574	0.045
2	0.491	0.428	0.423	0.513	0.487	0.561	0.484	0.048
4	0.395	0.359	0.338	0.398	0.374	0.421	0.381	0.027
6	0.267	0.256	0.249	0.265	0.271	0.284	0.265	0.011
8	0.178	0.163	0.155	0.189	0.169	0.193	0.175	0.014
10	0.108	0.103	0.096	0.112	0.105	0.128	0.109	0.010

Table 2. Drug plasma concentration of Ibuprofen reference formulation in human volunteers

Time (hr)	H1	H2	H3	H4	H5	H6	Mean	SD
0.25	0.308	0.249	0.198	0.182	0.178	0.165	0.213	0.050
0.5	0.416	0.326	0.235	0.247	0.246	0.208	0.280	0.071
0.75	0.468	0.337	0.267	0.289	0.293	0.238	0.315	0.074
1	0.495	0.489	0.303	0.306	0.301	0.271	0.361	0.093
1.5	0.568	0.537	0.411	0.468	0.484	0.341	0.468	0.076
2	0.473	0.49	0.356	0.386	0.381	0.305	0.399	0.064
4	0.301	0.426	0.118	0.314	0.322	0.209	0.282	0.097
6	0.137	0.123	0.029	0.096	0.101	0.092	0.096	0.034
8	0.043	0.059	0.018	0.041	0.036	0.028	0.038	0.013
10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Table 3. Pharmacokinetic parameters of IBSEDDS optimized and reference formulations

Parameter	IBSEDDS	Reference
Dose, mg	50	50
(t_{max}), hr	1	1.5
C_{max}, ug/ml	0.892	0.468
AUC_{0-24}, mg.hr/ml	3.378	1.8966
$AUC_{24-\infty}$, mg.hr/ml	0.578	0.0902
$AUC_{0-\infty}$, mg.hr/ml	3.956	1.9868
R. Bioavailability %	199.1142	-

CONCLUSIONS

The developed IBSEDDS formulation showed physical stability under different storage temperatures but the drug was more stable in refrigerator. An IVIVC was confirmed after administration of IBSEDDS optimized formulation by human volunteers. SEDDS have significantly increased the C_{max} and AUC of ibuprofen compared to reference capsules and the relative bioavailability of IBSEDDS was 199.11% compared to the oily solution. In a conclusion, SEDDS proved to be a potential system for delivering orally administered hydrophobic compound ibuprofen.

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