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FORMULATION AND EVALUATION OF SOLID SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM OF AMITRIPTYLINE DRUG BY USING AEROSIL 200 (SILICON DERIVATIVE) AS SOLID CARRIER

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ABSTRACT

Amitriptyline hydrochloride has been widely used for the treatment of major depressive disorder and general anxiety disorder. However, drug has freely soluble in water which limits its poor bioavailability. Hence, the present investigation was concluded with improvement of solubility and there by improvement of bioavailability by preparing the solid SMEDDS of Amitriptyline hydrochloride. There are many techniques to convert liquid SMEDDS to solid, but an adsorption technique is simple and economic. Hence, the aim of present study was to develop S-SMEDDS of poorly water-soluble drug Amitriptyline HCL using Aerosil 200 as solid carrier. On the basis of solubility study Sesame oil was selected as oil phase. On the basis of emulsification method Tween 80 was selected as surfactant and Propylene Glycol (PG) as co-surfactant. All batches of drug loaded self-microemulsion was characterized for In vitro drug release study. Optimized formulation of self-microemulsion was further evaluated for appearance, viscosity, pH, self-emulsification time, dilution test and drug content. Optimized batch of self-microemulsion was composed of 3.6 ml oil (sesame oil), 3.6 ml Smix (Tween 80 & PG). Finally, solid self-microemulsion was prepared by adsorption technique using Aerosil 200 as the adsorbent and evaluated for bulk density, tapped density, angle of repose, drug content and in vitro drug release study. Stability study of prepared S-SMEDDS was done for one month and the results suggested that the formulation did not show significant change in bulk density, tapped density, angle of repose, drug content and in vitro drug release study. Study

concluded that S-SMEDDS can effectively formulated by adsorption technique with enhanced dissolution rate and concomitantly bioavailability.

KEYWORDS: S-SMEDDS, Amitriptyline HCL, In vitro drug release study, Solubility & bioavailability enhancement.

1. INTRODUCTION

In modern drug discovery techniques, there has been a consistent increase in the number of poorwater soluble drug candidate compounds, and currently more than 50% of new pharmacologically active chemical entities are lipophilic and exhibit poor water solubility. Various techniques are used to improve the bioavailability of those drugs like salt formation, pH change, β-Cyclodextrins complex, micro-emulsion etc. Self micro-emulsifying drug delivery (SMEDDS) is one of the methods for the improvement of oral bioavailability. SMEDDS are class of emulsion that has received particular attention as a means of enhancing oral bioavailability of poorly absorbed drugs. These systems are essentially mixes of oil and surfactant (sometimes with added co-surfactant) that form emulsion on mixing with water with little or no energy input.[1]

Lipid-based formulation approaches, particularly the selfmicro-emulsifying drug delivery system (SMEDDS), are well known for their potential as alternative strategies for delivery of hydrophobic drugs, which are associated with poor water solubility and low oral bioavailability. SMEDDS formulations are isotropic mixtures of an oil, a surfactant, a cosurfactant (or solubilizer), and a drug.[2]

The basic principle of this system is its ability to form fine oil-in-water (O/W) microemulsions under gentle agitation following dilution by aqueous phases (i.e., the digestive motility of the stomach and intestine provide the agitation required for self-emulsification in vivo in the lumen of the gut). This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption.[3]

Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption. Selection of a suitable self-emulsifying formulation depends upon the assessment of the solubility of the drug in various components, the area of the self-emulsifying region as obtained in the phase diagram, and the droplet size

distribution of the resultant emulsion following self-emulsification.[4]According to Nazzal, S. and M.A. Khan (2006), SEDDS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent microemulsions with a droplet size of less than 50 nm. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution ratelimited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles.

The oral route is one of the preferred routes for chronic drug therapy. Approximately 35-40% of new drug candidates has poor water solubility. The oral delivery of such drugs is frequently associated with low bioavailability, high inter and intra subject variability and lack of dose proportionality. Efforts are going on to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy.[5]

Amitriptyline Hydrochloride, a Tricyclic antidepressantdrug, is frequently prescribed to treata number of mental illnesses. These include major depressive disorder and anxiety disorders, and less commonly attention deficit hyperactivity disorder, bipolar disorder. Other uses include prevention of migraines, treatment of neuropathic pain such as fibromyalgia and post herpetic neuralgia, and less commonly insomnia.[6]

The main objective of the study was to develop and evaluate an optimal SMEDDS formulation containing Amitriptyline Hydrochloride and to assess its pharmacodynamic effect in terms of lipid lowering potential. In this research paper, a bioequivalence study was performed where a comparative study between two types of drug (marketed Amitriptyline Hydrochloride and SMEDDS Amitriptyline Hydrochloride was designed and the key pharmacokinetic (PK) parameters for both drugs were assessed. Besides, we examined the stability of the dosage form and then evaluated the influence of the formulation aging on the drug release and subsequently drug bioavailability.

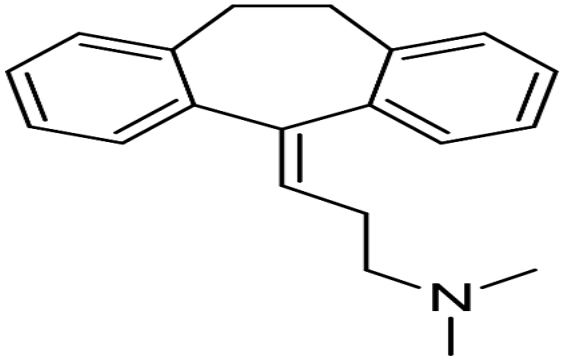


Fig. 1: Chemical structure of amitriptyline HCL.

2. MATERIALS AND METHODS

2.1.Materials: Amitriptyline Hydrochloride was obtained as a gift sample from APY Pharma Ltd., Assam, India. The rest materials such as; Tween 80 (Polyoxyethylene sorbitan monooleate), Tween 60 (Polyoxyethylene sorbitan monostearate), Propylene glycol, Polyethylene glycol 200 (PEG 200) and polyethylene glycol 400 (PEG 400) were bought from Anmol Chemical Pvt. Limited, Mumbai, India. Sesame oil, Coconut oil, and Olive oil were purchased from Shree Hari Private Limited, and Ruchi Soya Ind. Limited, Mumbai, India. Double distilled water was used throughout the study. All other chemicals were of reagent grade.

2.2. Methods

2.2.1. Selection of Self-Microemulsified drug delivery systems components

Oil (Solubility Studies): Solubility of Amitriptyline Hydrochloride was determined in various modified oils, surfactants, and cosurfactants. Two ml of each component was taken in screw cap vials with known quantity (500 mg) of excess drug. A vortex mixer was used to facilitate the solubilization. They were stirred rotary shaker at 37 ± 0.5 °C for24 hours. After equilibrium, All Samplewere centrifuged at 100 rpm for 15 min using a laboratory centrifuge. The Supernatant wastaken and filtered through a 0.45 μm membrane filter.[7] Filtered solution was appropriately diluted with methanol, and UV absorbance was measured at 239 nm. Concentration of dissolved drug was determined using standard equation.

Surfactant (Emulsification study): Different surfactants were screened for its emulsification ability selected in oil phase. Surfactant selection was done on the basis of visual Inspection and ease of emulsification.[7] Briefly, the surfactant was added to oil phase. Each mixture, 100 μl, was then diluted with 50 ml distilled water in glass stopper conical flask. Ease of emulsification was judged by the number of flask inversions required to yield

homogenous emulsion. Emulsion was further observed visually for any turbidity or phase separation.

Co-Surfactant (Emulsification study): The screening was done on the basis of % transparency and ease of emulsification. Mixtures of the co-surfactant, selected surfactant, and the selected oil were prepared and evaluated in similar fashion as described in the above section on surfactants.[7]

2.2.2. Preparation of SMEDDS

A series of micro-emulsions of SMEDDS were prepared with varying ratios of oil, surfactant, and co-surfactant. Formulations $1E_1$, $3E_1$ and $5E_1$ were prepared using Sesame oil as oil, Tween 60 and Tween 80 as surfactant, Propylene Glycoland Polyethylene Glycol 200 as co-surfactant. In all the formulations, the level of Amitriptyline Hydrochloride was kept constant to 5% of SMEDDS.

Preparation of self micro-emulsifications. Amitriptyline HCL (500 mg) was added in accurately weighed amount of oil into a screw-capped glass vial and heated in a water bath at 40°C.The surfactant and co-surfactant were added to the oily mix using positive displacement pipette and stirred with magnetic bar. The formulation was further sonicated for 15 min and stored at room temperature until its use in subsequent studies.[8] SMEDDS formulations were prepared, and their self-emulsifying performance was compared.

2.2.3. Evaluation parameters of amitriptyline HCL -Loaded SMEDDS

Emulsification time: The emulsification time (the time for a preconcentrate to form a homogeneous mixture upon dilution) was monitored by visually observing the disappearance of SMEDDS and the final appearance of the microemulsion in triplicate. A visual test to assess the self-emulsification properties of SMEDDS formulation was performed by visual assessment as previously reported.[9] In this method, a predetermined volume of formulation (1 mL) was introduced into 300 mL of water in a glass beaker that was maintained at 37°C, and the contents mixed gently using a magnetic stirrer. The time to emulsify spontaneously and progress of emulsion droplets were observed.

Determination of drug content: Amitriptyline HCL from SMEDDS formulation was extracted in methanol using sonication technique. The solutions were filtered, using

Whatman filter paper. The methanolic extract was analyzed for the Amitriptyline HCL content spectrophotometrically (UV-1700, Shimadzu) at 239 nm using standard curve.

In-Vitro dissolution studies: Dissolution test was carried out by using IP type I apparatus. The paddle was rotated at 100 rpm. 0.1 N HCL was used as dissolution medium (900 ml) and was maintained at 37±0.5˚C. Samples of 5 ml were withdrawn at predetermined intervals (0, 15, 30, 45, 60, 90 and 120, 150,180 min) filtered and replaced with 5 ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, where ever necessary and were analyzed for the drug at 239 nm by using Shimadzu UV-1700 spectrophotometer. Each dissolution study was performed for three times and mean values were taken.

Optical clarity: Each formulation (1 mL) was diluted with 100 mL of water in glass beaker. Absorbance of dispersion was measured at 400 nm using a UV spectrophotometer immediately after microemulsions formation, and after 0 hrs, 6 hrs, and 24 hrs, respectively.[10]

3. RESULTS AND DISCUSSIONS

3.1. Solubility study (Screening of oil): Solubility studies were aimed at identifying a suitable oily phase for the development of the Amitriptyline HCL SMEDDS. Identifying the suitable oil having the maximal solubilizing potential for the drug under investigation is very important to achieve optimum drug loading.[11] The solubility of Amitriptyline HCL in various oils and surfactants is presented in Table 1. Among the various oily phases that were screened, Sesame oil could solubilize maximum amount of Amitriptyline HCL (170 mg/mL). The selection of the surfactant or cosurfactant in the further study was governed by the emulsification efficiency rather than the ability to solubilize Amitriptyline HCL.

Table 1: Solubility of Amitriptyline Hydrochloride in few oils, Surfactants and Cosurfactants.

Vehicle	Function in SMEDDS	Avg. solubility *(mg/mL)
Sesame oil	Oil	170 mg/ml
Coconut oil	Oil	120 mg/ml
Soyabean oil	Oil	80 mg/ml
Olive oil	Oil	60 mg/ml
Hydrogenated Vegetable oil	Oil	40 mg/ml

Tween 20	Surfactant	94.19±0.84
Tween 40	Surfactant	112.13±0.72
Tween 60	Surfactant	103.00±0.13
Tween 80	Surfactant	134.00±0.21
Span 20	Surfactant	91.02±0.15
Propylene Glycol	Co-Surfactant	289.00±0.33
Polyethylene Glycol -200	Co-Surfactant	229.97±1.44
Polyethylene Glycol -400	Co-Surfactant	30.02±0.41
Polyethylene Glycol -600	Co-Surfactant	116.05±1.66

3.2.Preliminary screening of surfactants: Non-ionic surfactants are generally considered less toxic than ionic surfactants. They are usually accepted for oral ingestion.[12] Results inferred that the oily phase Sesame oil exhibited the highest emulsification efficiency with Tween 80for the homogenous emulsion formation. On the other hand, Sesame oil showed poor emulsification properties with other surfactants employed, requiring a higher number of flask inversions. The aforementioned results suggested the use of Sesame oil as an oily phase with Tween 80 as a surfactant for further study.

3.3.Preliminary screening of cosurfactants: Addition of a co-surfactant to the surfactant-containing formulation was reported to improve dispersibility and drug absorption from the formulation.[13] Herein, the solubility of the drug in different cosurfactants may judge the final selection. Results of the solubility study demonstrated in Table 1 inferred a higher solubility. This could contend the importance of co-surfactant addition to the surfactantcontaining dispersions.

3.4.Evaluation of the SMEDDS: In the self-emulsifying systems, the free energy required to form an emulsion was very low, thereby allowing a spontaneous formation of an interface between the oil droplets and water. Moreover, since the drug released will be in nanosize, it will increase the effective surface area for dissolution.

3.4.1. Emulsification time: The efficiency of self-emulsification could be estimated primarily by determining the rate of emulsification which is an important index for the assessment of the efficiency of emulsification, that is, the SMEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation. The emulsification time of these formulations was in the range of 15 to 35 sec.

3.4.2. In vitro drug release: Dissolution studies were performed for the SMEDDS formulations in phosphate buffer pH 6.8, and the results were compared with the pure

drug. There is no any significant difference in dissolution of all SMEDDS formulations. As the emulsification time is below 35 s, about 21.3% of the drug is released within 15 min in case of SMEDDS, while plain drug showed only 32.4% dissolution at the end of 15 min. The dissolution studies were conducted for 1 hr to observe the variation or occurrence of precipitation over a time. The in vitro dissolution studies indicate that formulation of Amitriptyline HCL in the form of SMEDDS formulation enhances the dissolution properties.

3.4.3. Drug content: Irrespective of difference in composition, the drug content of formulations $1E_1$, $3E_1$ and $5E_1$ was found in range of 96.1-98.9%.

3.4.4. Optical clarity: Optical clarity measured by directly taking the absorbance of the diluted SMEDDS is a measure of droplet stability. The result indicates that formulation.

Table 2: Composition of Micro-emulsion formulationsafter dilution.

Weight/weight percentage component in micro-emulsion formulation				
S. no	**Formulations**	**S/CoS Ratio**	**oil**	**Water**
1	$1E_1$	3.6 (1:1)	3.6	2.8
2	$3E_1$	3.6 (3:1)	3.6	2.8
3	$5E_1$	3.6 (2:1)	3.6	2.8

Table 3: Evaluation parameters of formulations.

Formulation Code	Emulsification time (sec)*	Globule Size	Avg. Drug Content with S.D.
$1E_1$	30 sec	92(µm±S.D)	95.9
$3E_1$	45 sec	105(µm+S.D)	94.8
$5E_1$	52 sec	120(µm+S.D)	93.2

Table 4: Viscosity of various SMEDDS formulations.

S. no.	Formulation of emulsion	Viscosity (cp)
1.	$1E_1$	385.4
2.	$3E_1$	346.5
3.	$5E_1$	341.6

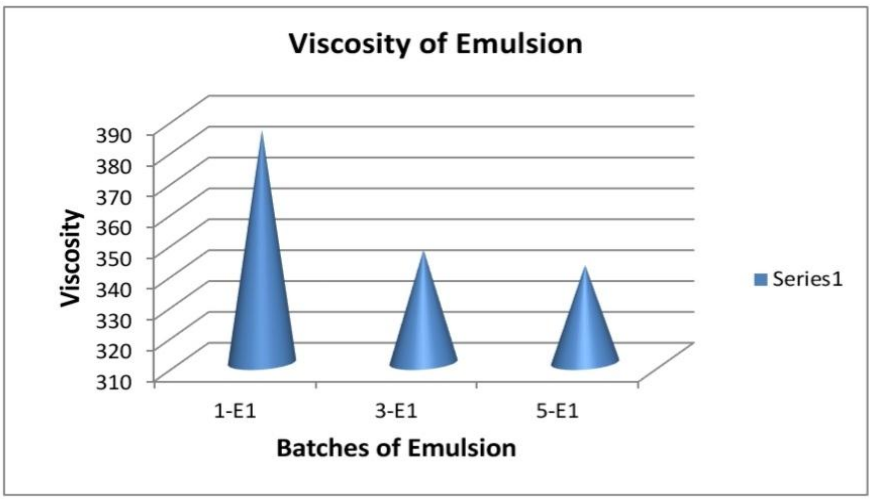


Figure 2: Viscosity of emulsion of optimize batches.

Table no. 5: *In-vitro* dissolution of SMEDDS after real time study.

Time (min)	% Drug released		
	$1E_1$	$3E_1$	$5E_1$
0	0	0	0
5	84.60	83.23	82.93
10	92.01	91.10	91.04
20	96.36	96.22	96.02
30	98.76	98.55	98.05
45	99.48	99.2	99.03
60	96.21	95.57	92.35

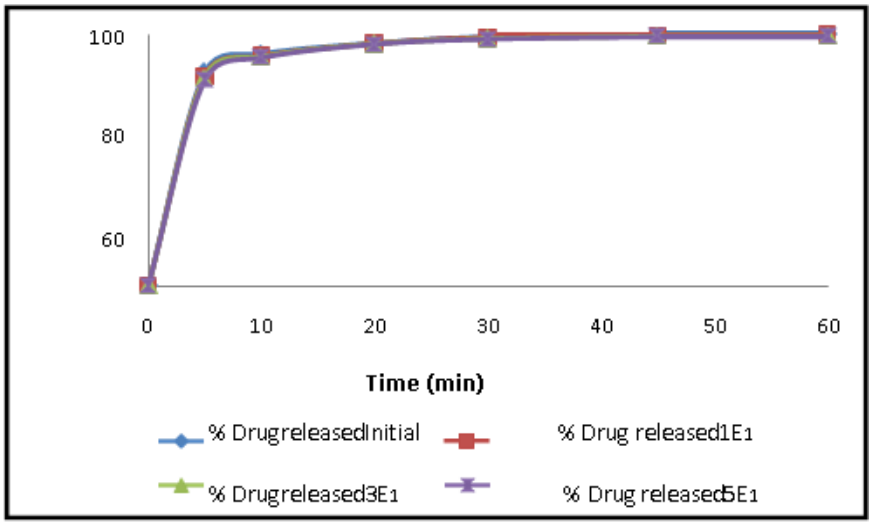


Figure 3: *In-vitro* dissolution of Batch ($1E_1$) after real time.

Table no. 6: Powder characteristics of all adsorbent after adsorption of liquid SMEDDS.

Adsorbent	Evaluation parameters					Inference
	Bulk density (gm/ml)	Tappeddensity (gm/ml)	% yield	Carr's index (%)	Hausner's ratio	
$1E_1$	0.594	0.744	15.0	1.25	0.594	Excellent
$3E_1$	0.397	0.543	14.6	1.36	0.397	Passable
$5E_1$	0.471	0.601	13.2	1.27	0.471	Passable

Table no. 7: *In vitro* release of Amitriptyline HCL from free flow powder of different Adsorbents.

Time (min)	% Drug Released from Free Flow Powder		
	$1E_1$	$3E_1$	$5E_1$
0	0	0	0
5	35.18± 2.3	58.23± 1.5	51.84± 3.6
10	50.84± 3.0	67.40± 2.0	63.71± 4.7
20	68.27± 2.5	79.72± 3.6	80.69± 2.1
30	80.34± 1.8	82.37± 1.4	89.78± 3.3
45	92.16± 2.0	85.14± 2.2	90.12± 2.5
60	92.67±3.2	90.32± 1.7	91.54± 2.8

***Mean of n=3**

The graphical representation of *in-vitro* study release ofAmitriptyline from free flow powder of different adsorbents with standard errors is as shown below in Fig.

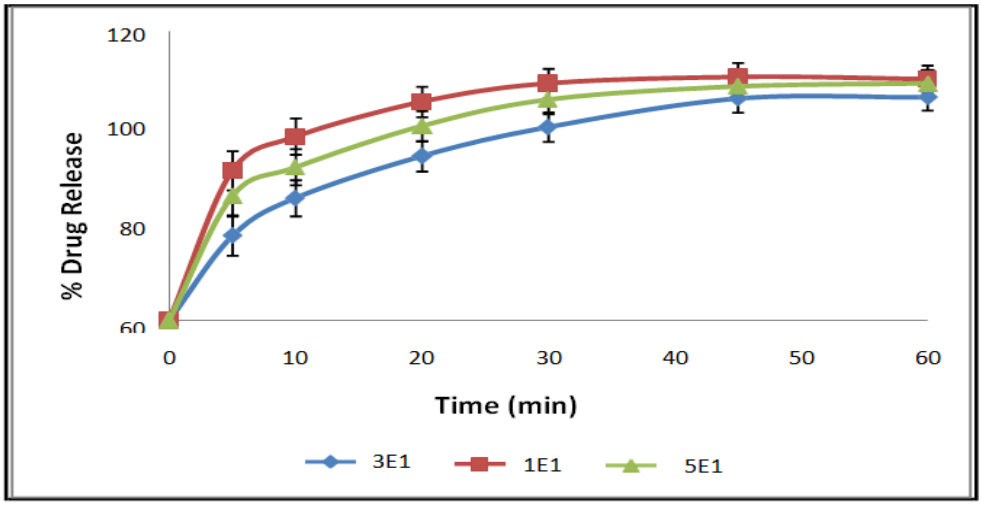


Figure 4: *In-vitro* dissolution study of drug from various adsorbent.

Table no. 8: Evaluation parameters for S-SMEDDS Tablet of Amitriptyline.

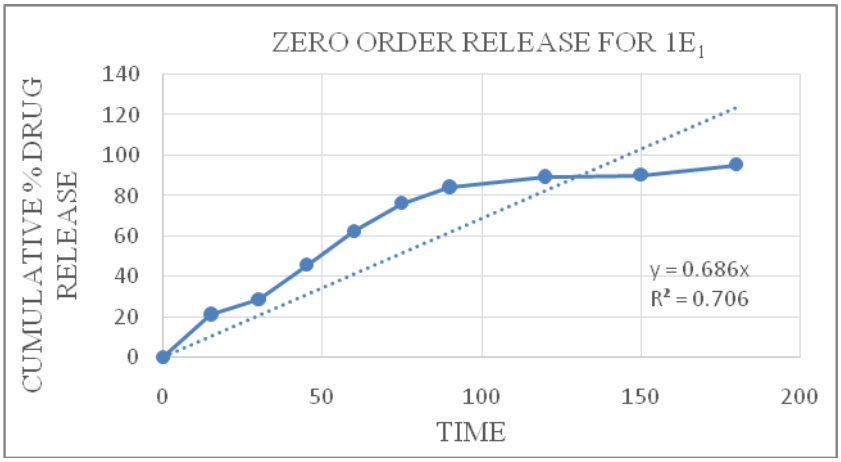
Batch	Evaluation parameters				
	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time (sec)
$1E_1$	201±1.3	2.2	3.15 - 3.24	0.5%	76 (sec)
$3E_1$	198±2.5	2.2	3.11 - 3.22	0.52%	126 (sec)
$5E_1$	200±2.3	2.1	3.14 - 3.28	0.56%	115 (sec)

Table no. 9: *In vitro* dissolution study of S-SMEDDS formulations.

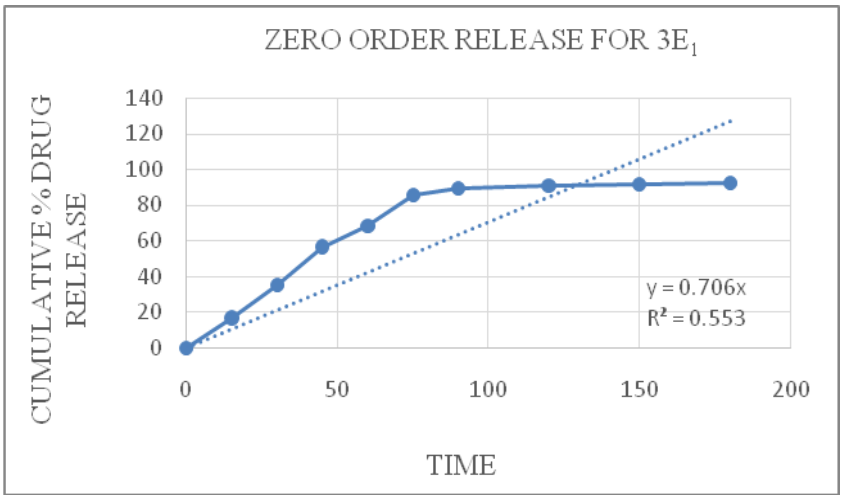
Time (min)	% Drug released		
	$1E_1$	$3E_1$	$5E_1$
0	0	0	0
15	21.3%	16.8%	18.8%
30	28.6%	35.2%	38.4%
45	45.6%	56.4%	66.8%
60	62.3%	68.2%	76.2%
75	76.2%	85.2%	81.2%
90	84.3%	89.2%	86.6%
120	89.2%	90.5%	92.1%
150	90.1%	91.2%	92.0%
180	95.2%	91.9%	91.9%

1. Zero order release of drug

a) Zero order release for $1E_1$



b) Zero order release for $3E_1$



c) Zero order release for $5E_1$

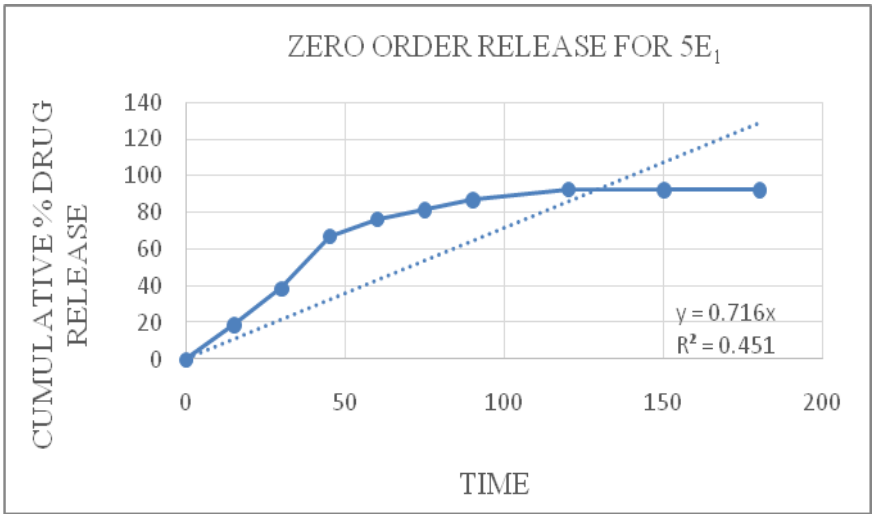
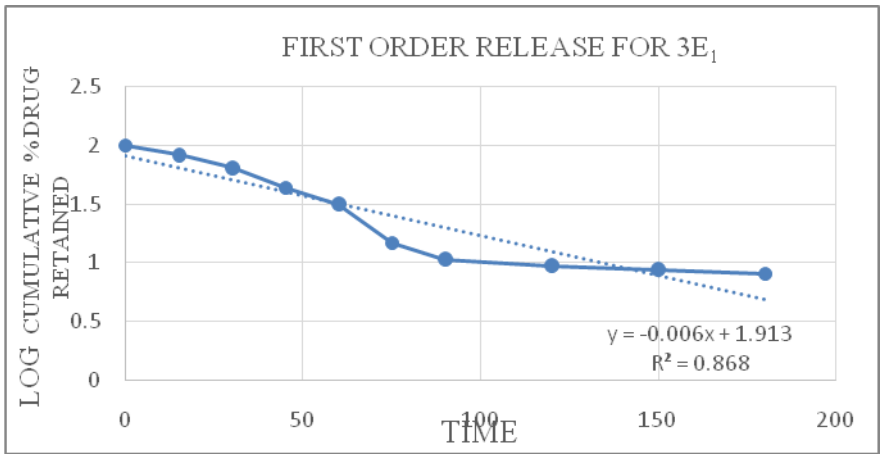


Figure 5: Zero order release kinetics graph of selected formulation.

2. First order release of drug

a) First order release for $1E_1$

b) First order release for $3E_1$



c) First order release for $5E_1$

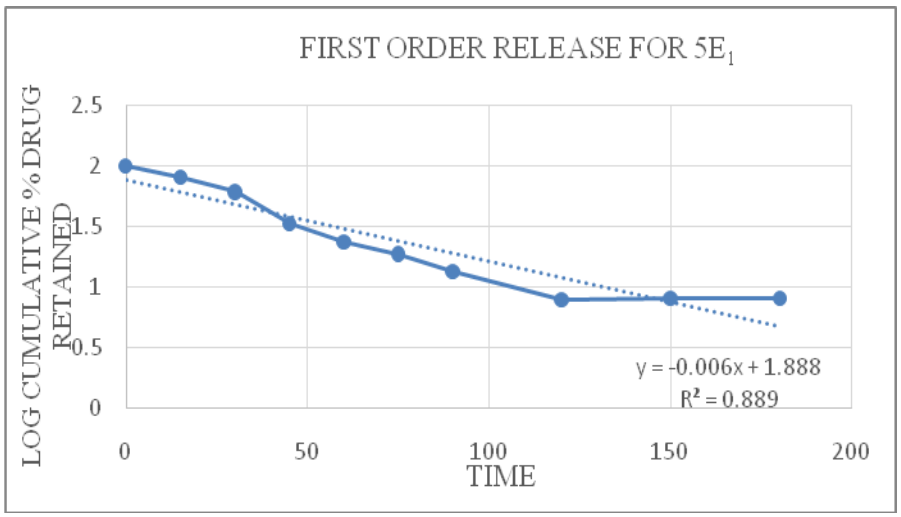


Figure 6: First order release kinetics graph of selected formulation.

Table no. 10: Comparison table of various mathematical models of drug dissolution.

Release kinetics	$1E_1$	$3E_1$	$5E_1$
Zero order release	0.665	0.558	0.451
First order release	0.916	0.868	0.889

Table no. 11: *In-vitro* dissolution comparison of M and $1E_1$.

Time (min)	% Drug released	
	M	$1E_1$
0	0	0
15	32.4%	21.3%
30	68.4%	28.6%
45	85.13%	45.6%
60	91.02%	62.3%
75	97.15%	76.2%
90	98%	84.3%

120	98%	89.2%
150	98%	90.1%
180	98%	95.2%

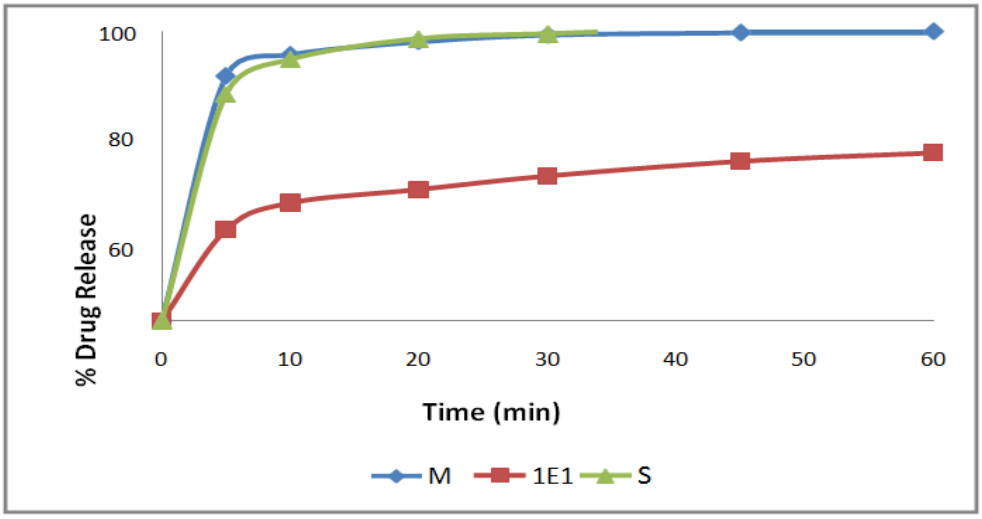


Figure 7: *In-vitro* dissolution comparison of M and 1E.

Table no. 12: Results of accelerated stability study of batch $1E_1$.

Parameters	Initial	1M	2M	3M
Description	White colored, round shaped tablets plain on both side.			
Weight (mg)	300	NC	NC	NC
Hardness (kg/cm2)	2.2	2.2	2.2	2.2
Thickness (mm)	3.15 – 3.24	NC	NC	NC
Friability (%)	0.5%	NC	NC	NC
Assay (%)	99.4	99.3	99.2	99.3

Where, (NC-Not Change)

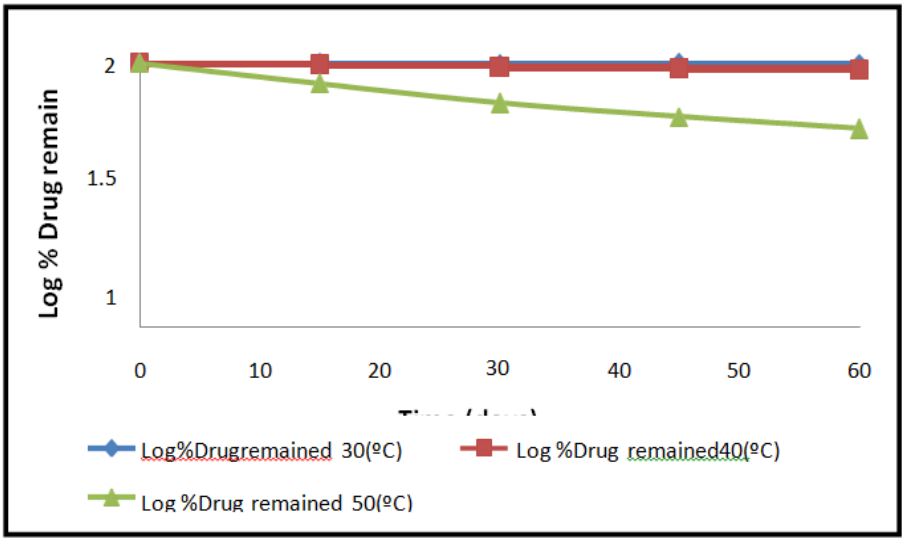


Figure 8: Log percent concentration of drug remaining versus time plot $1E_1$.

3. CONCLUSION

It was concluded that SMEDDS formulations containing Amitriptyline Hydrochloride significantly increase in the dissolution rate and in vitro diffusion rate compared to plain Amitriptyline Hydrochloride suspension. The ex vivo intestinal permeability results showed that the drug diffusion across the intestinal membrane from the SMEDDS is significantly higher than the plain drug suspension. These observations lead us to the conclusion that SMEDDS seems to be a promising drug delivery system, which can provide an effective and practical solution to the problem of formulating drugs with low aqueous solubility and poor systemic bioavailability.

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