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DEVELOPMENT AND EVALUTION OF S-SEDDS TABLET DRUG DELIVERY SYSTEM FOR HYDROPHOBIC DRUG

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Abstract: SEDDS and SMEDDS are normally prepared either as liquids or encapsulated in soft gelatine capsules, which have some shortcomings especially in the manufacturing process, leading to high production costs. Moreover, these dosage forms may be inconvenient to use and incompatibility problems with the shells of the soft gelatine are usual. Incorporation of a liquid self-emulsifying formulation into a solid dosage form may combine the advantages of SMEDDS with those of a solid dosage form and overcome the disadvantages of liquid formulations described above. Recently, much attention has been paid to lipid-based formulations with particular emphasis on self-microemulsifying drug delivery systems (SMEDDS) to improve the oral bioavailability of lipophilic drugs. Hence objective of present work is to formulate Solid SMEDDS to enhance solubility, dissolution rate which may improve therapeutic performance and drug loading capacity so as to develop alternative to traditional oral formulations to improve bioavailability. The proposed work developed and evaluated self-microemulsifying drug delivery system (SMEDDS) to improve oral bioavailability of Lamotrigene.

Introduction: The oral intake has been the most compatible route of drug delivery by both patients and drug manufacturers for the treatment of most pathological states. Thus, the important features of drug compounds have to absorb through gastrointestinal (GI) tract, but have limited absorbability because of their high lipophilicity and consequently poor aqueous solubility. Solubility is the most important physicochemical property used in drug discovery and development and thus a good understanding of the concept and methods to predict or determine solubility are significant for the pharmaceutical scientist [1]. Solubility is the property of a solid, liquid, or gaseous hemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation

concentration where adding more solute does not increase its concentration in the solution [2]. The poorly absorbed drugs pose a challenge to the formulation scientists to develop suitable dosage form which can enhance their bioavailability. Broadly, poorly soluble drugs can be formulated in three different forms to overcome the challenge of poor absorption crystalline solid formulations, amorphous formulations, and lipid formulations [3]. Self-emulsifying drug delivery systems (SEDDS) are relatively newer, lipid-based technological innovations with immense promise in enhancing the oral bioavailability of drugs [4]. There are many problems arising from the poor solubility of drug candidates in drug research and development. The general approach in the pharmaceutical industry is selection of compounds that are free from physicochemical problems and their progress in the formulation and development [5-6]. These low solubility profile molecules are often difficult to formulate using conventional approaches and are allied with numerous formulation related performance issues, e.g. poor bioavailability, lack of dose proportionality, slow onset of action and other attributes leading to poor patient compliance. As a result, advanced formulation approaches are of interest in order to improve the dissolution rate and/or apparent solubility of poorly soluble APIs (active pharmaceutical ingredients)6. In the development of novel therapeutics, the ability to develop a suitable pharmaceutical formulation for delivery is of extreme importance [7-8]. The number of poorly water-soluble drug candidates, found in drug discovery and development, it cause increasing problems with poor and changeable bioavailability [9]. For better achievement of pharmacological activity, the molecules must in general display certain solubility in physiological intestinal fluids, to be present in the dissolved state at the site of absorption [10]. The SEDDS are mixtures of oils and surfactants, ideally isotropic, and at times containing co-solvents, which emulsify instantly to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation. They are able to augment the bioavailability of poorly soluble and permeable drugs by avoiding the dissolution step and enhancing the permeability through biological membranes due to the presence of lipid and surfactant [11]. The present work was developed and evaluated the solid dosage form containing S-SEDDS for the oral delivery of poorly soluble drugs with mixtures of oils and surfactants, ideally isotropic, and sometimes containing co solvents/co surfactants, which emulsify spontaneously to produce fine oil-in-water emulsions when initiated into aqueous phase under mild agitation. Hence objective of present work is to formulate Solid SMEDDS to enhance solubility, dissolution rate which may improve therapeutic performance and drug loading capacity so as to develop alternative to traditional oral formulations to improve bioavailability.

Material and Methods:

Preparation of Self Emulsifying Drug Delivery System: Different ratios of oil, lamotrigene, surfactant, and co-surfactant were used for SEDDS formulations, in all the formulations; the drug concentration was kept constant. Oil, co-surfactant was taken inaccurate quantity, for effective mixing vortex mixer and gentle stirring for 15 minutes was utilized. After solubilization of mixture it was heated at 30 – 40°C and then cooled after that Tween 80 was added and for the stable mixture to be formed stirring was done [12].

Solidification of L-SNEDDS: Solidification of L-SEDDS was applying by using the solid carrier adsorption method. Briefly, equivalent to 50 mg drug lamotrigene (50 mg*50 tablets = 25 gm) containing L-SEDDS formulation was blended with 25 gm of microcrystalline cellulose to obtain a wet mass or slug mixture. Now add 2.5 gm of Aerosil 200 (Amorphous colloidal silicon dioxide 200 m^2/g Surface area) was added to the wet slug mixture with granulator mixer to obtain S-SEDDS.

Tablet Preparation of S-SEDDS: The solid mass powder containing lamotrigene (50 mg) loaded S-SEDDS was previously prepared by using the solid carrier adsorption method and compressed to tablet dosage forms. The required drug containing LM-SE-T tablet were prepared by mixing required quantities of Microcrystalline cellulose (Avicel PH - 102) (45 mg) and starch potato (25mg) as internal binder. The ingredients were mixed until a uniform mixture was obtained and was again sieved #80. The complete batch of powder was collected and mixed with talc (5 mg) as glidant and magnesium stearate (5 mg) as lubricating agent. The granules were compacted into tablets using single-punch tablet compression machine (Khera Instruments Pvt. Ltd., New Delhi), fitted with 8.0 mm flat-faced punches. Compression was controlled to produce a 5-kg tablet-crushing strength [13].

Characterization of S-SEDDS-T

Flow properties of granules: The flow properties of drug powder were characterized in terms of Carr's index (%), Hausner's ratio and angle of repose (ɵ). The Carr's index ((I_C)) and Hausner's ratio (H_R) of drug powders were calculating according to previous discuss equations.

Thickness: The thickness of tablets was performed on 20 tablets from each formulation. The Vernier caliper was used for the study.

Weight variation: Not more than two of the individual weights deviate from the average weight by more than the percent shown below and none deviates by more than twice that percent.

Hardness: Hardness of tablet is defined as the force required to break a tablet a in a diametric direction. A tablet was placed between two anvils. Force was applied to anvils and crushing strength that causes

the tablet to break was recorded. Hardness is thus the tablet crushing strength. Monsanto tester is used for hardness testing.

Friability: Weigh 10 tablets and place in a friabilator chamber rotated at 25 rpm and they are dropped on distance of 6 inches. The chamber is allowed to rotate for 100 revolutions. Then the tablets are removed, dusted and again the weight is taken. The difference in the weigh is calculated and the weight loss should not be more than 1%.

Percent Drug content: 20 tablets from all batches were taken randomly and crushed in pestle-mortar. The weight equivalent to one tablet was taken in volumetric flask (100ml) and dissolved in 0.1 N HCL and filtered. This solution was analyzed in UV spectrophotometer at λmax 268 nm.

***In vitro* Dissolution study:** performed using USP dissolution apparatus type II containing 900 mL of 0.1N HCl as dissolution medium maintained at 37±0.5°C with the paddle speed of 100 rpm. LM-SE-T1 - LM-SE-T3 equivalent to 50 mg drug was directly introduced into the dissolution medium and a suitable aliquot of sample was collected at upto 1h. The sample withdrawn were suitably diluted with 0.1N HCl and analyzed spectrophotometrically at 268 nm. An equivalent volume of fresh dissolution medium maintained at 37±0.5°C was added to compensate the loss due to sampling [14].

Result and Discussion: The LM-SE-T tablets are the composition for identified the solubility and dissolution profile of drug-S-SEDDS for oral drug delivery system. The Carr's index (%), Hausner's ratio and angle of repose (ɵ) were found 13.92 – 14.87, 1.13 – 1.17, 23.1 – 26.2° respectively. The examination showed that, as the Carr's index (%), Hausner's ratio and angle of repose (ɵ) were within in the range of standard value of Good flow-ability. Tablet Thickness of formulations diameter was 7.97 mm – 8.11 mm and height were 2.01 mm – 2.35 mm. The weight variation of formulations was 1.9 % - 2.1 %. The tablet hardness of formulations was found to be in the range of 4.1 – 4.5 kg / cm^2 and friability for all the tablets was found to be approximately 0.579 – 0.621 %. The drug content of granules were determine found in the range of 98.89 – 100.03 %. All the evaluation results were found within the range given in Indian pharmacopeia and standard books. The amount of Avicel PH – 102 (MCC) and internal binder potato starch content may affect the hardness, friability and weight variation. The formulation (LM-SE-T3) tablet was showed good hardness and friability with affective physical properties of materials. The in-vitro Release profile of tablets was characterized for release percentage and release rate **k**. Release data within the linear range were selected and fitted to a zero-order mathematical model: Q = C + kt

Where Q is the release percentage at time t; k is the slope of the fitted linear equation and here represents release rate; and C is the intercept of the linear equation. T_{lag} is defined as the time of the start of drug release and calculated here from the fitted equation, setting Q=0: $T_{lag} = - C / k$.

The linear equation is based on regression of at least three release data, and only correlation coefficient of over 0.99 is acceptable. The tablets LM-SE-T3 is the best formulations containing effective oil, surfactant, co-surfactant combination for enhancing the solubility profile, thus increase the dissolution profile of solid drug delivery system. The formulation release more than 99 % of the drug in gastric environment upto within a 60 min. Regression analysis was performed and the r^2 values suggested that the curves were fairly linear and slope values were computed from the graph. The release exponent "n" values were in the range of 0.9173 to 0.9469 for LM-SE-T1 to LM-SE-T3**.**

Summary and conclusion:

The optimized L-SEDDS formulations were solidified by adsorption method and the solid content was compressed to solid drug delivery system as tablet with some specific excipients. The LM-SE-T tablets are the composition for identified the solubility and dissolution profile of drug-S-SEDDS for oral drug delivery system. Tablet Thickness, weight variation, hardness, and drug content of were found within the range given in Indian pharmacopeia. The amount of Avicel PH – 102 (MCC) and internal binder potato starch content may affect the hardness, friability and weight variation. The formulation **(**LM-SE-T3**)** tablet was showed good hardness and friability with affective physical properties of materials. The in-vitro study and kinetic graph of all formulations LM-SE-1 - LM-SE-T3 were evaluated and tablets LM-SE-T3 is the best formulations containing effective oil, surfactant, co-surfactant combination for enhancing the solubility profile, thus increase the dissolution profile of solid drug delivery system and release more than 99 % of the drug in gastric environment upto within a 60 min.

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Table 1: Various formulations for Self Emulsifying Drug Delivery System

Formulation code	Drug (mg)	Oil (%)	Surfactant (%)	Cosurfactant (%)
	Lamotrigene	Olive Oil	Tween 80	Glycerol
LSEF1	50	38	37	25
LSEF2	50	39	38	23
LSEF3	50	40	40	20

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Table 2: Various parameters of S-SEDDS-T formulations

Formulation code	Flow Properties			Tablet Thickness (mm)		Weight Variation (%)	Hardness (kg/cm ^{2})	Friability w/w (%)	Drug Content (%)
	Carr's index ^{n} (%)	Hausner's ratio ^{n}	Angle of repose (θ) ^{n}	Diameter	Height				
LM -SE-T1	14.77±0.011	1.16±0.003	25.2±0.081	8.01±0.011	2.31±0.011	1.9±0.019	4.1±0.09	0.601±0.012	99.19±0.01
LM-SE-T2	14.14±0.014	1.15±0.014	24.4±0.001	8.11±0.019	2.35±0.022	1.9±0.021	4.1±0.27	0.601±0.008	99.92±0.21
LM-SE-T3	13.92±0.011	1.13±0.011	23.1±0.014	8.0±0.012	2.03±0.002	2.1±0.016	4.5±0.13	0.579±0.011	99.99±0.17

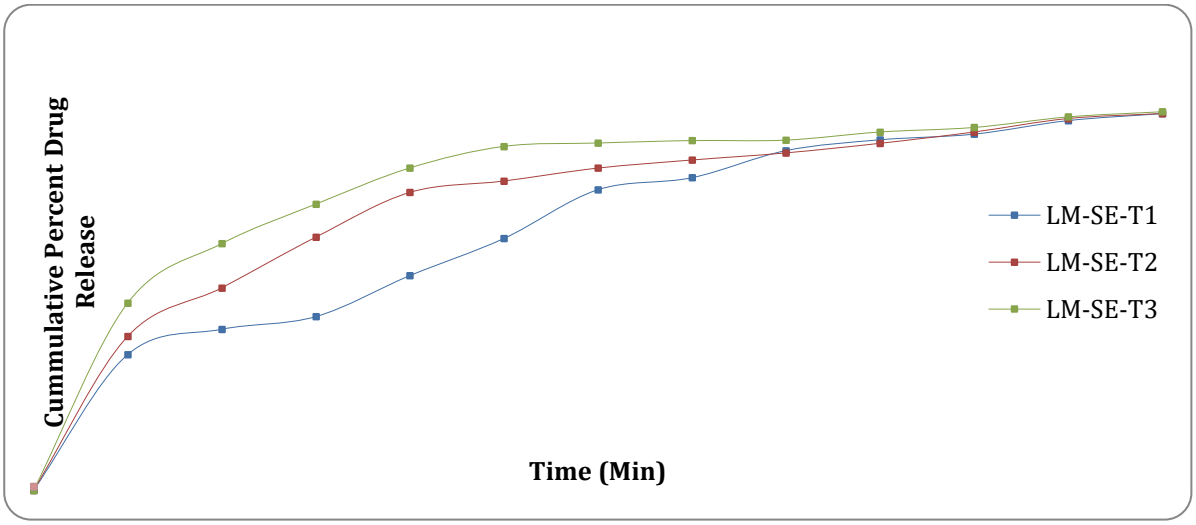

Figure 1: Zero-order kinetic plot of various formulations