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Development of Losartan Potassium Self-Microemulsifying Drug Delivery Systems (SMEDDS) for Optimization of Bioavailability

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KEYWORDS

self emulsification, pseudo-ternary

ABSTRACT:

The purpose of the present research work was to formulate, evaluate, and optimize self-emulsifying formulation to enhance drug release. The solubility of formulation was determined in different natural oils, surfactant, and co-surfactants. Self-emulsifying drug delivery system (SEDDS) was prepared by using castor oil, Tween 80, and Carbitol as co-surfactant. S-SEDDS evaluated for globule size and emulsification time. A 3^2 full factorial design was utilized for the optimization purpose. Formulation variables such as quantity of oil (X1) and ratio of surfactant to co-surfactant (X2) were investigated for their effect on globule size and emulsification time. Optimized formulation with minimum globule size was freeze-dried and finally, optimized formulation evaluated for the in vitro drug release study. To recognize the capable self-emulsifying zone, pseudo-ternary phase diagrams were prepared. For knowing the interaction behavior of desired responses, the Box-Behnken framework was used and configured using the appropriate method. At the last, the selected optimized formulation was tested for droplet size analysis, phase separation study, self emulsification time, transmittance, turbidity analysis, and zeta potential. Based on results it is concluded that SMEDDS can be a better choice to optimize the oral delivery of losartan potassium.

Introduction:

Self-emulsifying drug delivery system (SEDDS) attracted substantial attention of the re searchers due to its inbuilt ability to carry drug candidate in dissolved form/state at the site of absorption or action, which is pre-requisite for the drug candidate to be absorbed by biological membrane [1]. SEDDS is defined as an isotropic mixture of the oil, surfactant, and co surfactant/solvent of natural or synthetic origin, which may be in solid or liquid form. These are anhydrous liquid mixtures called as pre-concentrates [2]. SEDDS spreads easily in the gastrointestinal tract whereas intestinal motility provides agitation, which results into the self-emulsification. SEDDS is thermodynamically highly stable system, which is able to form a spontaneous emulsion. Therefore, SEDDS has emerged as the effective drug delivery system, which helps to enhance solubility and bioavailability of water-insoluble active pharmaceutical ingredients [3]. Losartan potassium, a non-peptide molecule, it is Angiotensin-II (Type-I) receptor blocking agent. Losartan is an angiotensin II receptor blocker (ARB). It works by blocking a substance in the body that causes the blood vessels to tighten. Losartan relaxes the blood vessels and lowers the blood pressure. A lower blood pressure will increase the supply of blood and oxygen to the heart [4]. It is BCS class III drug and it reaches mean peak plasma concentration approximately 1.5–2 hours post administration. In such cases it is very essential to enhance onset of action of a drug. Mean peak concentrations of Losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively [5]. To improve the oral bioavailability of a drug by chemical modification, changes were made to its physicochemical properties, using many approaches reported in the literature. The proposed research work,

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have many formulations of losartan potassium SMEDDS with oil (castor oil), Surfactant (Tween 60), and Co-surfactant (Carbitol). The main advantage of this SMEDDS approach is that it keeps the drug in the soluble form, effective drug solubilization depended on how much drug soluble in an oil phase. In drug solubilization, surfactants or co-surfactants play an important role [6]. Non-ionic high HLB with the consequent hydrophilic character of surfactant needed for the immediate production of droplets and rapid dissemination of formulation, providing excellent dissemination and self-emulsion. The goal of this research work is to establish the optimized SMEDDS formula and test it through factorial design experiments with losartan potassium to increase absorption and improve bioavailability.

Material and Method:

Drug losartan potassium was procured as a gift from Alembic Pharmaceuticals Limited, Ahmadabad, India. Castor oil and tween 60 were obtained from National chemicals (Gujarat, India). Glycerol, Carbitol and Tween 80 were bought by S.D. Fine Chemicals (Mumbai, India). There were analytical grades of solvents and chemicals included in the research work.

Experimental methods:

Solubility Studies: The most important criterion for the screening of components for SMEDDS is the solubility of poorly soluble drug in oils, surfactants, and co-surfactants. The solubility of LP in various oils was determined by adding an excess amount of drug in 2 ml of selected oils and surfactants and co-surfactants in 5 ml capacity stopper glass vial and heated to 60 °C for 2 min in a water-bath. then centrifuge at 3000 rpm for 15 min, then 0.5 mL supernatant was taken and filtered through a 0.45 µm membrane filter. The concentration of LP in the samples was determined using ultraviolet (UV) spectrophotometer by measuring the absorbance of samples at 218 nm [7-8].

Phase Diagram Study: Construction of pseudo-ternary phase diagrams In order to find out the concentration range of components for the existing range of microemulsions, pseudo-ternary phase diagram was constructed using the water titration method. Ternary plots were constructed using oil, surfactant and co-surfactant containing different proportion of surfactant: Co-surfactant, that is specific surfactant/co-surfactant (Smix) ratio were mixed thoroughly with different volume ratios from 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) in different glass vials. Pseudo ternary phase diagrams were developed using the aqueous titration method. Lipid-based drug delivery Systems have been demonstrated to be useful in enhancing the bioavailability of highly lipophilic compounds because they can keep the drug in the dissolved state until it is absorbed, thus overcoming the barrier of slow dissolution rates. In practice, lipid formulations range from pure oils to formulations containing some proportions of surfactants, co-surfactants or co-solvents. The mixtures of oil and surfactant and co-surfactant at certain weight ratios were diluted with water, under moderate stirring. After being equilibrated, the mixtures were assessed visually and determined as being microemulsions or coarse emulsions. The data obtained was used for the construction of ternary plots by using CHEMIX software based on the visual observations noted [9].

Preparation and Characterization: The aim of present work was to prepare and characterize SEDDS of Losartan to enhance solubility and bioavailability of hypolipidemic drug. Self-Emulsifying Drug Delivery System was prepared by simple emulsification techniques. The drug losartan potassium (LP) (20 mg) was added in the mixture containing oil (Castor oil), Surfactant Tween 20) and Co-surfactant (Carbitol) (Table 1). Next the components were mixed by gentle stirring and mixing, and heated at 40˚C.The mixture was stored at room temperature until used. So, prepared SMEDDS was the concentrate of oil, surfactant, co-surfactant and drug 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 60 was added and for the stable mixture to be formed stirring was done [10].

Experimental Design:

This experimental work involves a three-component system: the oil X1 (castor oil), the surfactant X2 (Tween 60), and the co-surfactant X3 (Carbitol). For the optimization of the SMEDDS box, Behenken factorial design was employed by varying its components/factor. For the designing of this experimental work Design

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expert version, 12 software was used. For the optimization and selection of suitable formulation, twenty experimental runs were applied one by one, as well as three central points, were assumed, and according to experimental procedure surfactant, co-surfactant and oil were mixed in a different ratio. Two variables were selected as responses, such as droplet size (Y1) and turbidity (Y2), Optimized formulation was screened based on the positive and negative results of these responses. It was important to convert the parts by weight of X1, X2, and X3 to the percentage by weight using Design-Expert version 12 before the results review. After an experimental run, an effective quadratic equation for each response was obtained [11].

Table 1: Matrix of Box-Behnken Design for formulation parameters for Losartan potassium (LP)

S. No	Std.	Run	Batch	Oil (ml)	Surfactant (ml)	Co-surfactant (ml)
1	50	1	L_1	3.7	3.7	4.5
2	30	1	L_2	3.7	3.7	2.5
3	50	1	L_3	3.6	3	2.5
4	30	1	L_4	3.6	3	0.5
5	**50**	1	L_5	**5**	**5**	2.5

Evaluation of the Formulation

The obtained SEDDS formulation (F5) was selected and characterized for various attributes viz. Assessment of emulsification time, Emulsification time, Droplet size analysis, Zeta potential measurement, transmission and Electron Microscopy, Viscosity Determination, drug content, percentage transmittance, drug release study.

Optical microscopy: The opted formulation of SEDDS observed under optical microscope (Lambed) and it was found that the developed formulation contained the droplets in emulsion.

Droplet size analysis: Droplet size determines the rate and extent of drug release as well as the stability of the emulsion. Formation of SEDDS, which are stable, isotropic and clear o/w dispersions, takes place on reduction of the globule size. SEDDS formulation (F5) was diluted to 100 ml with distilled water in a flask and is mixed gently by inverting the flask. The droplet size was determined by dynamic light scattering (DLS) technique using Zetasizer (Zetasizer Ver. 6.01, Malvern Instruments, (UK)

Determination of self emulsification: The efficiency of emulsification was assessed using a standard US pharmacopoeia XXIII dissolution apparatus type II. Accurate weighed quantity of 1 gm of formulation was added drop wise to 100 ml of at 37 ˚C. Gentle agitation was provided by a standard stainless steel dissolution paddle at 60rpm. The italic performance of the formulation was visually assessed using the following grading system.

Grade A: Rapidly forming emulsion having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that formed within 2 minutes

Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify longer than 2 minutes.

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface [12].

Determination of self emulsification time

Optimized SMEDDS of losartan potasium self emulsification time was determined by using the USP type II dissolution apparatus. To provide gentle agitation 1 ml optimized losartan potassium SMEDDS

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dropwise mixed with 250 ml filtered water by maintained 60 rpm paddle rotation speed at 37 °C. During the process rate of micro emulsification and color produced was observed visually.

Rheological properties determination: The SEDDS systems were loaded in hard gelatin capsules in the present study. So, it can be easily pourable into capsules, and such systems should not be too thick. Viscosity studies are necessary for SEDDS to characterize the system physically and to control its stability. The rheological properties (viscosity, flow) of the microemulsion are evaluated by use of Brookfield viscometer (Japan) DV-E use of spindle RV-6 at 100 rpm at 25°C ± 0.5°C. This viscosities determination conform whether the system is w/o or o/w. If the system has low viscosity then, it is o/w type of the system and if a high viscosity then it is w/o type of the system

Phase Separation Study

A 5 ml distilled water glass tube was taken and 1 ml of SMEDDS was added, then this mixture was held at 25°C. For successful mixing, a Vortex mixer was used for 1 minute. For phase separation analysis, the resulting mixer was kept aside for 2 hours**.**

Experimentation design: To optimize the self-micro emulsifying drug delivery mechanism of oil X1 (castor oil), the surfactant X2 (Tween 60), and the co-surfactant X3 (Carbitol), independent variables have been selected using a three-factor, three-level factorial method (3^3) using Design-Expert version 12 software. The average droplet size (Y1) and turbidity (Y2) were used as the answers. Behenken factorial architecture was then used for SMEDDS box optimization by varying its components/factor. The experimental plan was developed using version 12 of Design-Expert Software. Twenty experimental runs with three central points have been designed by combining separate portions of oil, surfactant, and co-surfactant, as recommended by the experimental plan. To explain and better understand the relationships between the independent and dependent variables, ANOVA, 2D, and 3D plots were developed with the help of software. Based on the point prediction method, the optimized formulation was chosen [13].

Zeta Potential

The zeta potential indicates the physical stability of the colloidal structures by calculating the presence of an electric charge on the surface of the particles. The microemulsion stability is directly associated with the magnitude of the surface charge present of the colloidal particles. The Zeta potential has been calculated by Zeta-Sizer. Experiments were replicated three times at 25 °C**.**

Transmittance and turbidity measurement

The percentage transmittance and turbidity of the optimized microemulsion were measured with the help of UV–Visible spectrophotometer and Nephelometer respectively.

Results and Discussion

Optical microscopy: The opted formulation (L_5) of SEDDS observed under optical microscope (Lambed) and it was found that the developed formulation contained the droplets in emulsion

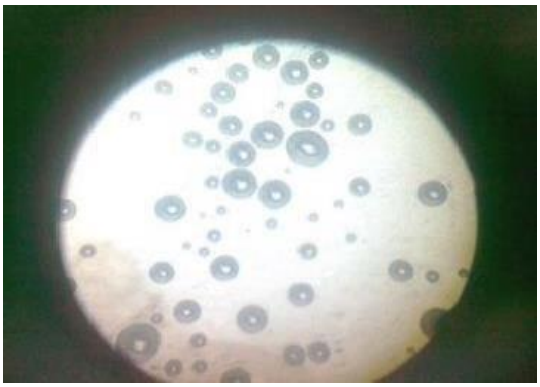

Figure 1: Optical microscopy determination of SMEDDS formulation (L_5)

Droplet Size Analysis

The mean droplet size was found, which was very small. After dilution with water, the SMEDDS were found to be transparent and the preparation was stable for more than one week.

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Table 2: Determination of self emulsification for various SEDDS formulations

Formulation code	Parameter	Size (nm)
L_1	Droplet size	125.89
L_2	Droplet size	121.41
L_3	Droplet size	131.47
L_4	Droplet size	123.14
L_5	Droplet size	129.01
L_1	Droplet size	112.24

Determination of self emulsification: The efficiency of emulsification was assessed0 using a standard US pharmacopoeia XXIII dissolution apparatus type II and the grade of all formulation followed from grade A to grade C.

Table 3: Determination of self emulsification for various SEDDS formulations

Formulation	Grade
L_1	B
L_2	A
L_3	C
L_4	B
L_5	A

Self-emulsification time

The assessment of self emulsification property of any SMEDDS was based on its rate of emulsification, As the SMEDDS system comes in contact with water, with mild agitation it is completely and quickly dispersed into the medium. The result of the experiment shows that the rate of self emulsification depends on the individual formulation composition and the ratio of surfactant, oil, and co surfactant it consists. Higher the percentage of surfactant system greater the spontaneity of emulsification, due to excess diffusion of aqueous phase into oil phase causing significant interfacial disruption and discharge of droplet into the bulk aqueous phase. The losartan potassium-SMEDDS self-emulsifying time was 60 ± 1 s.

Rheological properties: The rheological nature of the losartan SMEDDS is crucial in determining its ability to be kept the prepared formulation in hard or soft gelatin capsules. If the system has very low viscosity, it may enhance the probability of leakage from the capsule and the system with very high viscosity may create problem in pourability. The prepared SMEDDS of losartan potassium L_5 (1ml) was identified more viscous in nature and shown best formulation.

Table 4: Determination of viscosity for various SEDDS formulations

Formulation code	Parameter	Viscosity (cps)
L_1	Viscosity	12.2±0.2
L_2	Viscosity	13.4±0.1
L_3	Viscosity	13.7±0.2
L_4	Viscosity	12.8±0.1
L_5	Viscosity	14.1±0.2

Pseudo Ternary Phase Diagram Study: As SMEDDS come in contact with water with constant agitation, it turns into o/w emulsion. The system's phase behavior was analyzed using multiple surfactants to co-surfactant ratios. In each category, surfactants and co-surfactants (Smix) were mixed in the ratios like 1:1,1:0.5 and 1:2 (w/w). The self-emulsifying properties of the prepared SMEDDS series were visually examined. A pseudo-ternary phase diagram was utilized for the screening of surfactants and identification of the self emulsification region.

Phase Separation Study

Phase separation analysis indicates that for the subsequent study, during a 2-hour phase a mixture of castor oil, the surfactant Tween 60, and the co-surfactant Carbitol has insignificant phase separation.

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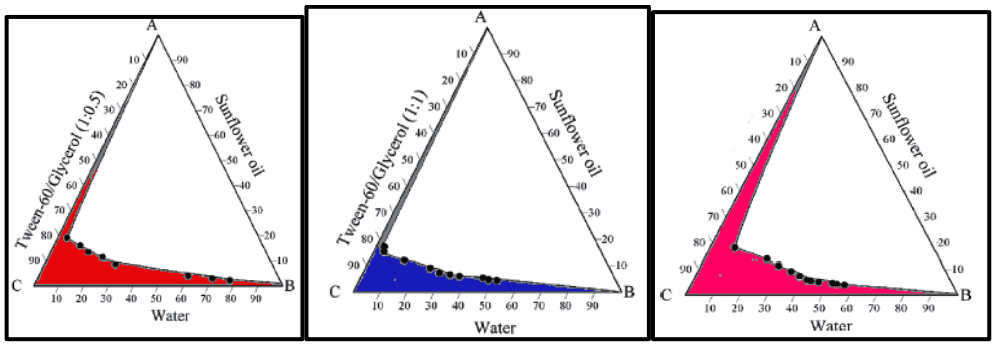

Figure 2: Pseudo ternary phase diagram Shows region of Self emulsification

Determination of turbidity

The turbidity and transmittance of prepared SMEDDS were found to 32.2875 NTU.

Zeta-Potential Determination

The zeta potential value of the liquid SMEDDS was found to be - 32.0 mV. This Negative zeta potential value of optimized formulations indicated that the formulation was negatively charged and sufficient repulsive force between emulsion globules was present, due to that an un-coagulated stable system was formed

Conclusions:

In the current research, three components, oil (castor oil), the surfactant (Tween 60), and the co-surfactant (Carbitol), were selected. Optimization and screening of these selected components for the preparation of losartan potassium SMEDDS, Box behenken factorial design method was utilized. From the studies performed it was concluded that, prepared liquid SEDDS has good self emulsification efficiency and having globule size in nanometer range which may be physiologically stable. The study was concluded that the optimized formulation of SMEDDS suggest that it could be a successful strategy to devise an efficient novel drug delivery method for solubility and oral bioavailability enhancement of poorly soluble drugs.

References:

1. Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother. 2004;58:173–82.
2. Bali V, Ali M. Study of surfactant combinations and development of a novel nanoemulsion for minimising variations in bioavailabil ity of ezetimibe. Colloids Surf B: Biointerfaces. 2010;76:410–20.
3. Bhupinder S, Ramandeep S, Shantanu B, Rishi K. Optimized nanoemulsifying systems with enhanced bioavailability of carve dilol. Colloids Surf B. 2013;101:465–74.
4. Constantinides PP. Lipid microemulsions for improving drug dissolution and oral absorption: Physical and biopharmaceutical aspects. Pharm Res 1995;12:1561-72.
5. Serajuddin AT, Sheen PC, Mufson D, Burnstein BF, Augustine MA. Effect of vehicleamphiphilicity on the dissolution and bioavailabilityof a poorly water soluble drug from solid dispersion, J. Pharm. Sci. 1988; 77 Suppl 5: 414- 417.
6. Iwanaga K, Kushibiki T, Miyazaki M, Kakemi M. Disposition of lipid-based formulation in the intestinal tract affects the absorption of poorly water-soluble drugs. Biol Pharm Bull 2006;29:508-12.
7. Wu W, Wang Y, Que L. Enhanced bioavailability of silymarin by self-microemulsifying drug delivery system. Eur J Pharm Biopharm 2006;63:288-94.
8. Gupta AK, Mishra DK. Preparation and evaluation of self emulsifying drug delivery system of anti-hypersensitive drug valsartan. Int J Pharm Life Sci 2011;2: 633-639.
9. Khadka P, Ro J, Kim H, Kim I, Kim J, Kim H, Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability, Asian J Pharm Sci. 2014; 9: 304–16.
10. Aungst B, Novel formulation strategies for improving oral bioavailability of drugs with poor

membrane permeation or presystemic metabolism, J. Pharm. Science, 1983; 979–998.

11. Gao Ping, Morozowich Walter, Development of supersaturatable self-emulsifying drug delivery system formulations for improving the oral absorption of poorly soluble drugs Expert Opin, Drug Delivery, 2006, 3(1): 97-110.
12. Beg S, Katare OP, Saini S, Garg B, Khurana RK, Singh B, Solid self-nano emulsifying systems of olmesartan medoxomil: formulation development, micromeretic characterization, in vitro and in vivo evaluation. Powder Technol,. 2016 ; 294:93 –10.
13. Kang BK., Lee, JS., Cho, SK., Jeong, S Y., Yuk, SH., Khang, G., Lee, HB., & Cho, S. H. Development of self-microemulsifying drug delivery systems (SMEDDS) for bioavailability enhancement of Simvastatin in Begale dogs. Int. J. Pharm., 2004; 274: 65–73.