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FORMULATION AND EVALUATION ORAL SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM OF EMPAGLIFLOZIN

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Abstract: Empagliflozin loaded Self Microemulsifying Drug Delivery System was developed using eucalyptus oil, tween 80 and PEG 400 as the formulation components. Self Microemulsifying Drug Delivery System containing empagliflozin was formulated by simple admixing method with suitable excipients. Simple Lattice Design was employed to optimize the liquid SMEDDS of Empagliflozin. Surface plot and contour plot were presented for graphical representation of the effect of independent variable on % Transmittance and %CDR. Also for validation of generated mathematical model check point analysis was done. Optimized batches were prepared as per the above design (F1-F10) and evaluated for various parameters. Batches F4 and F8 were observed with good result of various evaluation (% transmittance, emulsification time, %drug content, %CDR). So, they were further evaluated for size, zeta potential, PDI and viscosity. F4 showed better result than F8.The result of F4 that is drug content = 96.20±0.220%, transmittance=98.04±0.860%, drug release= 91.82%, zeta potential= -15.1 mV, PDI= 0.467 and size= 65.5 nm. Optimize (F4) liquid SMEDDS follows Hixon-crowell model (R^2= 0.9786) and First order (R^2= 0.9682) release kinetics. Self Micro Emulsifying Drug Delivery System of Empagliflozin was successfully prepared in order to enhance the solubility and dissolution rate by incorporating the drug in a lipid vehicle.

Keywords: SMEDDS, Simplex design, admixing, Empagliflozin

1.INTRODUCTION

SMEDDS are described as isotropic mixtures of solid or liquid surfactants, natural or synthetic oils, or, equivalently, one or more hydrophilic solvents and co-solvents/surfactants with the special ability to form stable oil-in-water (o/w) microemulsions after mild agitation and dilution in aqueous media, like GI fluids [1]. The GI tract is easily penetrated by SMEDDS, and the intestine's and stomach digestive motility generates the agitation required for self-emulsification. Self emulsifying drug delivery systems (SEDDS), also known as self emulsifying oil formulation (SEOF), and SMEDDS differ primarily in that SMEDDS forms transparent micro emulsions with a droplet size of less than 100 nm, while SEDDS typically produces opaque emulsions with a droplet size between 100 and 300 nm [2]. Additionally, SMEDDS has a lower oil concentration (20%) than SEDDS (40–80%). Emulsions are sensitive, metastable, dispersed forms; in contrast, SMEDDS are easily manufactured, physically stable formulations. In the case of lipophilic drug compounds that display absorption limited by dissolution rate, these systems could potentially enhance absorption rate and extent while producing blood-time profiles that are more consistent. Finding an appropriate oil surfactant mixture that can dissolve the medication at the necessary therapeutic concentration is a crucial first step [3]. Either soft or hard gelatin capsules can be filled with the SMEDDS mixture. Typically, oils, surfactants, and antioxidants are included in SMEDDS formulations. Co-surfactants and co-solvents are frequently added to enhance the properties of the formulation [4].

2.METHOD OF PREPARATION

Solubility Studies

(Screening of Oils, Surfactant and Co-surfactant)

Solubility of Empagliflozin in various oils, surfactant and co-surfactant was examined by supersaturation method. Selected component was taken (2ml) in Eppendorf tube with known quantity (100mg) amount of drug .A vortex mixer was used to facilitate the solubilization. The mixture was kept in orbital shaker at 25±2°C for 24 hrs. After equilibrium each tube was centrifuged at 3000 rpm for 20 min using centrifuge. Supernatant

was filtered and solution was appropriately diluted with 0.1 N HCl and UV absorbance was measured at 224 nm. Concentration of dissolved drug was determined using standard equation [5, 6].

Construction of Pseudo Ternary Phase Diagram

Surfactant (Tween 80) and co-surfactant (PEG 400) were mixed (Smix) in different volume ratios (1:1, 1:2, 2:1). For each phase diagram, oil (Eucalyptus oil) and specific surfactant/co-surfactant ratio were mixed thoroughly in different volume ratios from 1:9 to 9:1 in different glass vials. Pseudo ternary phase diagrams were developed using the aqueous titration method. Slow titration with the aqueous phase was performed for each combination of oil and Smix separately. The amount of aqueous phase added was varied to produce a water concentration in the range of 5% to 95% of total volume at around 5% time intervals. The scale up of proportions is easy, as the system is thermodynamically suitable. After each 5% addition of the aqueous phase to the oil: Smix mixture, visual observation was made and recorded. In similar manner, calculations for the other ratios oil and Smix were also done. For each Smix ratio, a separate phase diagram was constructed, and for each phase diagram visual observations were recorded. The pseudo ternary phase diagram was constructed using Ternaryplot.com software based on the visual observations [7, 8].

FORMULATION OF SMEDDS

The formulation was prepared by initially dissolving required quantity of Empagliflozin in oil. Then surfactant and co-surfactant mixer were added and final mixture was mixed by vortexing until a clear solution was obtained. The formulation was equilibrated at ambient temperature for at least 24 hours and examined for signs of turbidity or phase separation [9].

Table 1: Composition of SMEDDS of Empagliflozin

Optimized Formulation Code	Oil (%) Eucalyptus oil	Surfactant (%) Tween 80	Co-surfactant (%) PEG 400
F1	30	30	40
F2	10	50	40
F3	10	30	60
F4	20	40	40
F5	20	30	50
F6	10	40	50
F7	23.33	33.33	43.33
F8	13.33	43.33	43.33
F9	13.33	33.33	53.33
F10	16.67	36.67	46.67

3. EVALUATION OF Liquid SMEDDS Formulation [10-16]

3.1. Visual assessment

The quality of SMEDDS was assessed by visual inspection and it was graded in various grades. Empagliflozin SMEDDS (1 ml) of all batches formulation was diluted with purified water (500ml) and gently stirred with magnetic stirrer at 37˚C.

Table 2: Visual assessment of SMEDDS

Grade	Dispersibility and Appearance	Time of self micro-emulsification
I	Rapid forming microemulsion which is clear or slightly bluish in appearance	< 1 min
II	Rapid forming, slightly less clear emulsion which has a bluish white appearance	< 2 min
III	Bright white emulsion	< 3 min
IV	Dull, greyish white emulsion with a slightly oily appearance that is slow to emulsify	>3 min
V	Exhibit poor or minimal emulsification with large oil droplets present on the surface	>3 min

3.2. % Transmittance Test

Stability of microemulsion formulation with respect to dilution was checked by measuring transmittance through UV spectrophotometer. Transmittance of samples was measured at 650nm distilled water as blank and for each sample three replicate assays were performed.

3.3. Determination of Self-emulsification Time

Using a USP Type II dissolving device, the time needed for self-emulsion of different formulations can be measured by adding the formulation drop-wise to a basket filled with water and observing the formation of a clear solution with stirring while agitation is provided by a paddle at 50 rpm. The formulation's self-emulsification efficiency can be ascertained through self-emulsification. The kind of oil phase and the ratio of oil to surfactant were discovered to affect the emulsification rate. Because of the quick expulsion of oil droplets caused by water leaking through the interface, a faster rate of emulsification is seen with a greater surfactant concentration. The emulsification period can also be ascertained visually after the formulation is submerged in 0.1 N HCl with shaking at body temperature, whereby GI conditions can be simulated.

3.4. Determination of Cloud Point

Typically, the cloud point is found by spectrophotometrically measuring the temperature of the water bath into which the formulation is inserted and then progressively raising it. The cloud point, or the temperature above which a clear solution turns cloudy, is the threshold at which the permeability in percentage falls. It is 37 °C; in order for a formulation to maintain its self-emulsifying qualities, it must have a cloud point that is greater than body temperature. Temperatures over the cloud point are frequently associated with phase separation and decreased medication solubilisation due to the surfactant's vulnerability to dehydration. The lipophilicity of the medication and other formulation elements have an impact on the cloud point.

3.5. Drug Content

1 ml of formulation was taken in 10 ml of volumetric flask and at that point diluted with distilled water upto 10 ml. Yet again 1 ml quantity from this solution was taken and diluted with 10 ml if distilled water. Lastly, the absorbance of prepared solution was measured at 224 nm against blank reagent using UV visible spectrophotometer.

3.6. Robustness to Dilution

Robustness to dilution was studied by diluting it 1000 times with water and 0.1 N HCl. The diluted microemulsion was stored for 12hr and observed for any signs and phase separation or drug precipitation.

3.7. Thermodynamic Stability Study

Heating cooling cycle: Six cycles between refrigerator temperatures 4˚C and room temperature with storage at each temperature of not less than 48 hrs was studied. Suitable formulations at these temperatures were subjected to centrifugation test.

3.8. Centrifugation Stability Study

Formulations were passed centrifuged at 3000 rpm for 20 min then were examined for whether the system is monophasic or biphasic.

3.9. *In -vitro* Dissolution Profile

Franz diffusion cell assembly is used for *in-vitro* drug release studies. It consists of two compartments, one of the receptor chambers containing a 0.1 N HCl and another donor compartment containing microemulsion. A dialysis membrane (Mol. wt. 12000-14000) which is previously soaked for 2 h in receptor medium are placed in between these compartments to separate it from each other. To avoid disruption in the ongoing process, it is ensured that no air bubbles are seen between the membrane and liquid surface. During the entire process, the temperature is maintained at 37°C by circulating water bath. At a specific time interval, 1 ml of the sample are withdrawn from the receptor chamber and filled with fresh buffer. Suitable dilution is carried out and the amount of drug release are spectroscopically analyzed.

3.10. Analysis of Size

The kind and concentration of the surfactant have a major influence on the droplet size. For effective medication release, *in vivo* absorption, and stability, the micro-emulsion that forms upon dilution with water

produces droplets with an extremely narrow size and size distribution. Microscopic and spectroscopic methods, including photon correlation spectroscopy, are employed for droplet size analysis. For droplet size analysis, dynamic light scattering methods with a zeta meter can also be employed. Samples need to be diluted enough before determining their size. The size distribution can be reasonably inferred by calculating the polydispersity index (PDI).

3.11. Zeta Potential Measurement

A zeta meter system or a zeta potential analyzer are typically used to measure the zeta potential. After enough dilution, the stability of the emulsion is indicated by the zeta potential value. Good formulation stability is indicated by a greater zeta potential. Free fatty acids cause the zeta potential value to be negative in general; but, when cationic lipids, like oleic-amine, are employed, a positive charge arises. Droplets that are positively charged have the ability to interact with the GIT mucosal surface effectively. Because of the electrostatic nature of these interactions, greater adhesion and increased absorption are to be predicted.

3.12.Kinetic data analysis

The mathematical models were used to evaluate the kinetics and mechanism of drug release from the SMEDDS. The model that best fits the release data was selected based on the correlation coefficient (r) value in various models he model that gives high r‟ value was considered as the best fit of the release data.

4.RESULT AND DISCUSSION

Table 3: Evaluation parameters of formulation F1-F10

Formulation code	Visual Assessment	% Transmittance (±S.D.) (n=3)	Self-emulsification time (sec) (±S.D.) (n=3)	Cloud Point (˚C)	%Drug Content (±S.D.) (n=3)
F1	I	94.69±0.798	40.16±0.763	80	92.80±0.216
F2	I	92.50±1.482	37.23±0.680	84	94.73±0.561
F3	I	86.84±1.527	47.40±1.509	75	91.15±0.094
F4	I	98.04±0.860	36.90±1.276	83	96.20±0.220
F5	I	84.76±0.868	57.13±1.955	82	87.62±0.578
F6	I	95.40±0.637	56.66±0.577	86	86.3±0.359
F7	I	88.79±0.366	41.63±0.635	78	86.72±0.603
F8	I	96.48±0.408	38.33±1.527	84	95.12±0.474
F9	I	82.86±0.944	48.14±1.221	77	89.40±0.455
F10	I	86.07±0.558	42.66±0.577	82	86.28±0.272

Table 4: Thermodynamic Stability of formulation F1-F10

Formulations	4˚C			Room Temperature		
	Phase Separation	Flocculation	Precipitation	Phase Separation	Flocculation	Precipitation
F1	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
F2	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
F3	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
F4	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
F5	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
F6	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
F7	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
F8	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
F9	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
F10	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen

Table 5: Centrifugation Stability of formulation F1-F10

Formulation code	Phase Separation
F1	Not seen
F2	Not seen
F3	Not seen
F4	Not seen
F5	Not seen
F6	Not seen
F7	Not seen
F8	Not seen
F9	Not seen
F10	Not seen

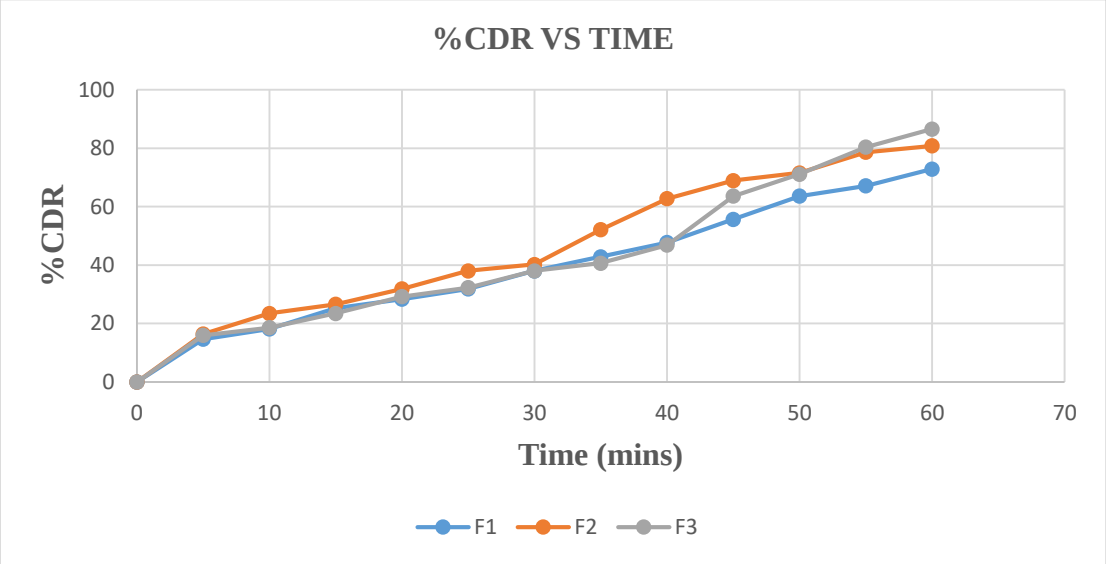

Figure 1: *In-vitro* drug release of F1-F3

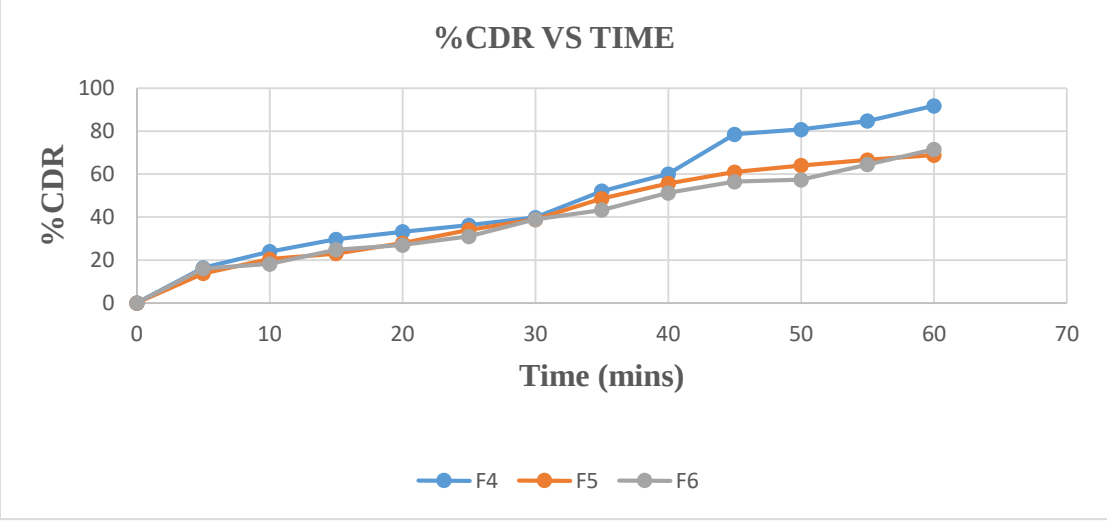

Figure 2: *In-vitro* drug release of F4-F6

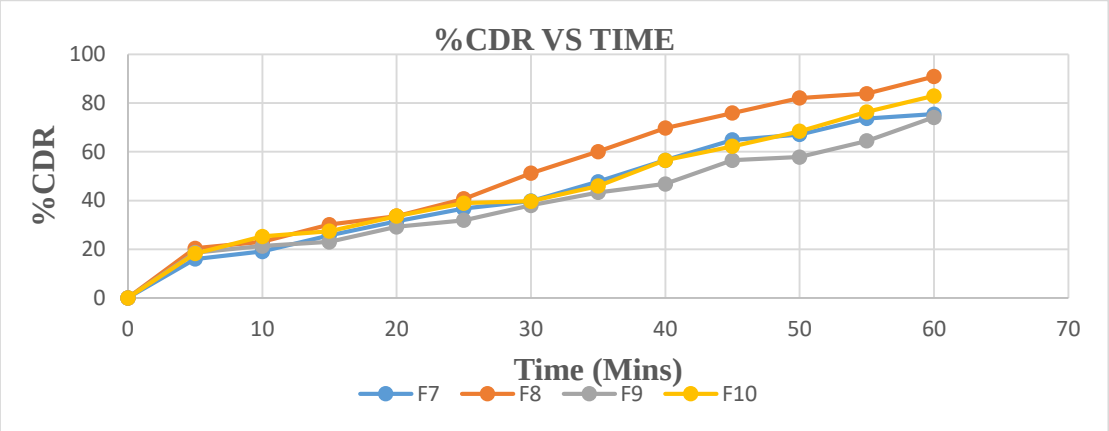

Figure 3: *In-vitro* drug release of F7-F10

Table 6: Size, Polydispersibility index, Zeta potential and Viscosity of SMEDDS Formulation

Formulation	Size (nm)	PDI	ζ (mV)	Viscosity(mPa.s)
F4	65.5	0.467	-15.1	0.897
F8	54.9	0.532	-10.5	0.898

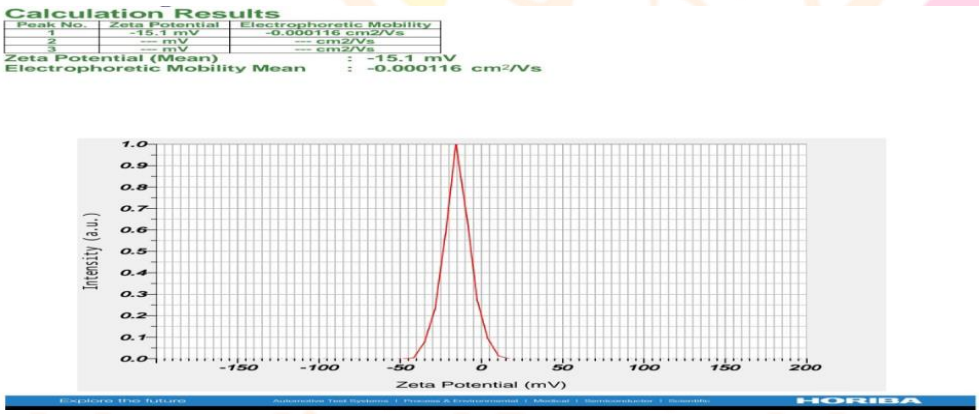

Figure 4: Zeta Potential of F4

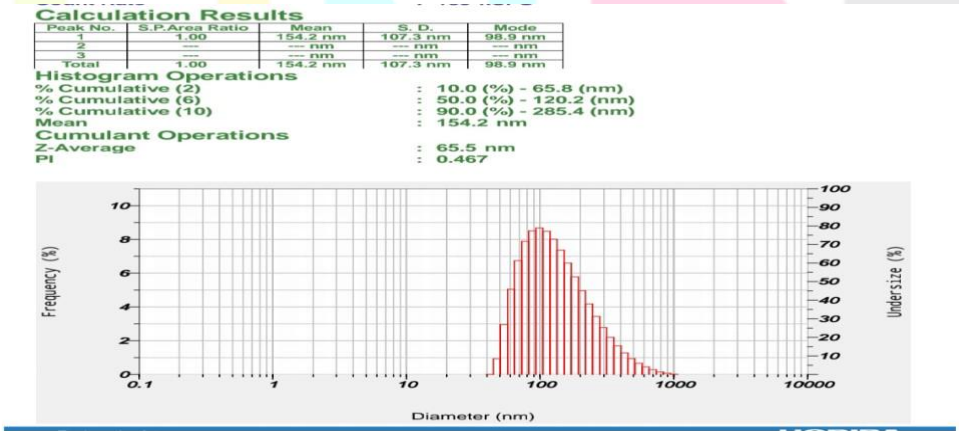

Figure 5: Size of F4

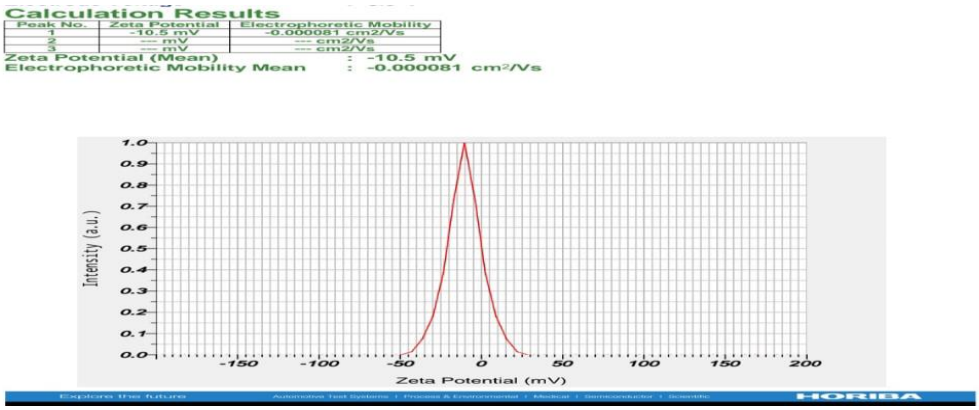

Figure 6: Zeta Potential of F8

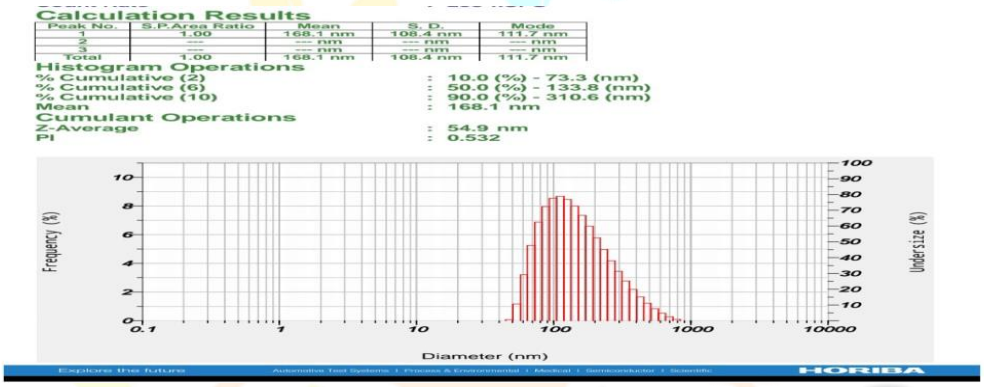

Figure 7: Size of F8

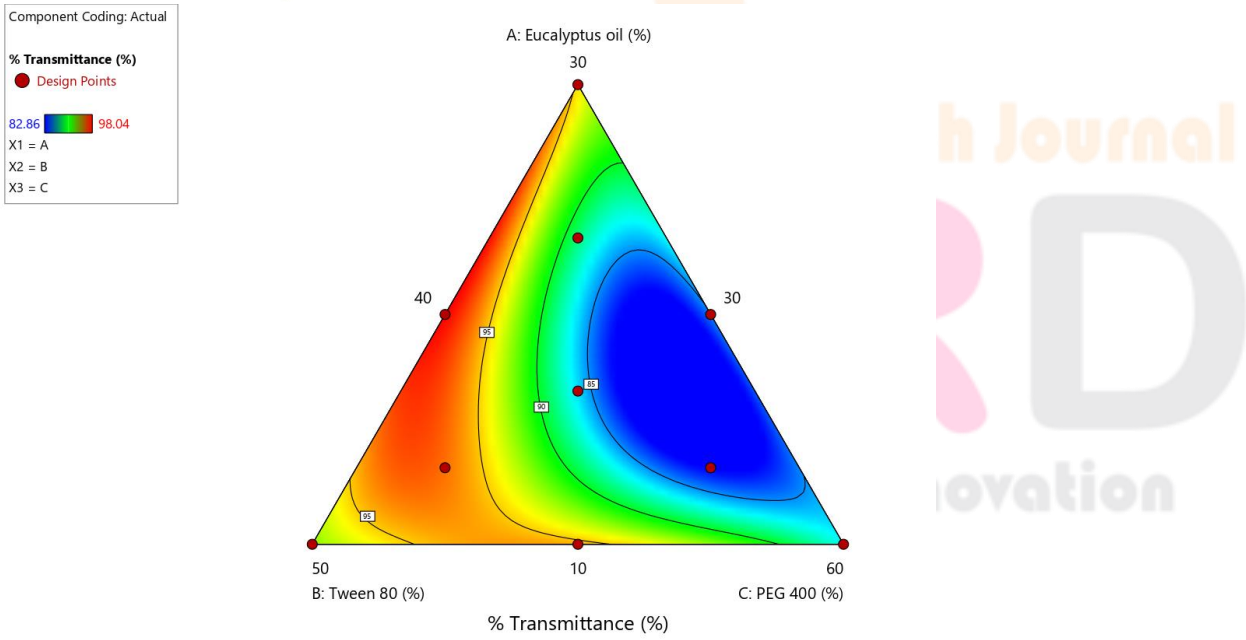

Figure 8: Contour plot showing the effect of Eucalyptus oil (X1), Tween 80 (X2) and PEG 400 (X3) of SMEDDS on Transmittance (%)

The polynomial equation for % transmittance proposed by the model is as follows:

$Y_1 = +94.71[X_1] +92.52 [X_2] +86.86[X_3] +17.85[X_1 X_2] -23.95[X_1 X_3] +22.99[X_2 X_3]$

Synergistic effects of X_1, X_2, X_3, $X_1 X_2$ and $X_2 X_3$ and antagonistic effects of $X_1 X_3$.

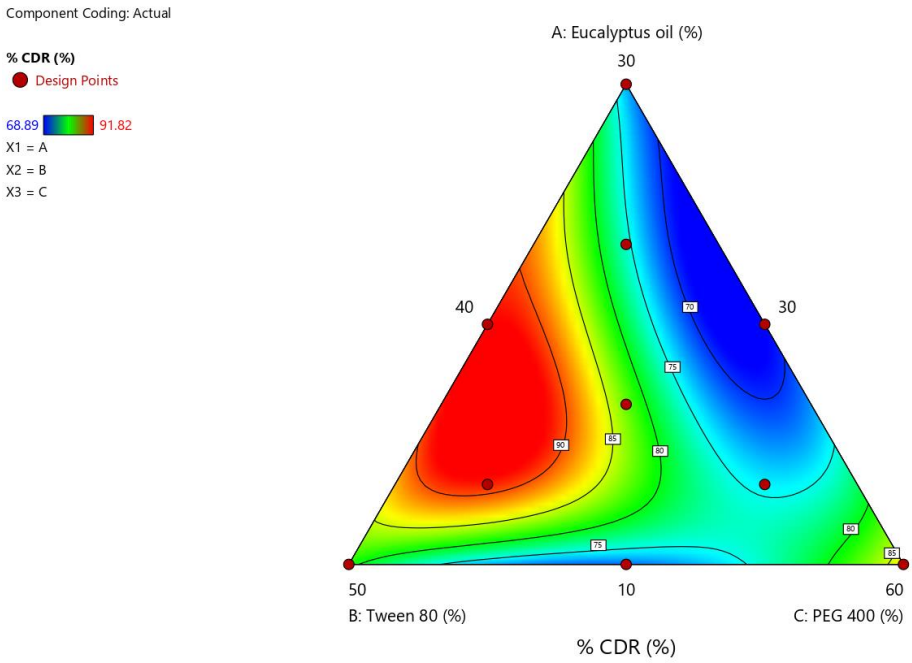

Figure 9: Contour plot showing the effect of Eucalyptus oil (X1), Tween 80 (X2) and PEG 400 (X3) of SMEDDS on CDR (%)

The polynomial equation for % CDR proposed by the model is as follows:

$Y_2 = +72.82[X_1] +80.75 [X_2] +86.48[X_3] +59.82[X_1 X_2] -43.36[X_1 X_3] -48.66[X_2 X_3]$

Synergistic effects of X_1, X_2, X_3 and $X_1 X_2$ and antagonistic effects of $X_1 X_3$ and $X_2 X_3$.

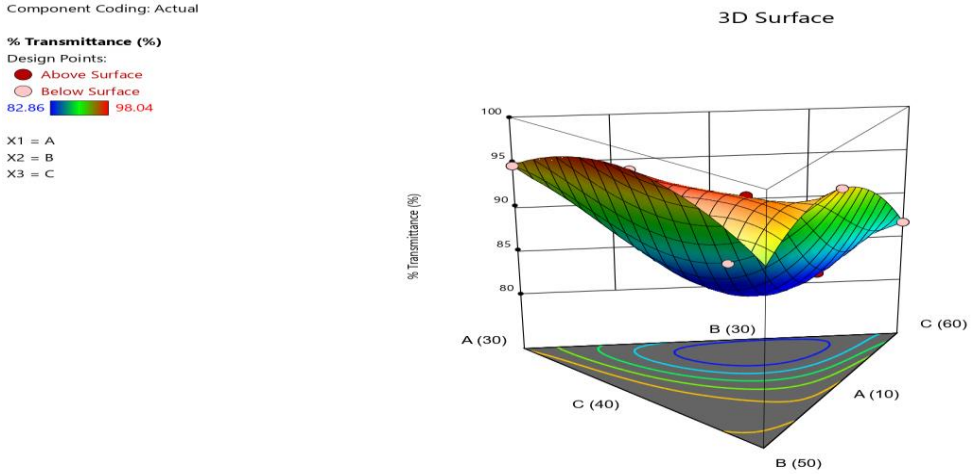

Figure 10: Response surface plot showing the effect of Eucalyptus oil (X1), Tween 80 (X2) and PEG 400 (X3) of SMEDDS on response Y1 Transmittance (%)

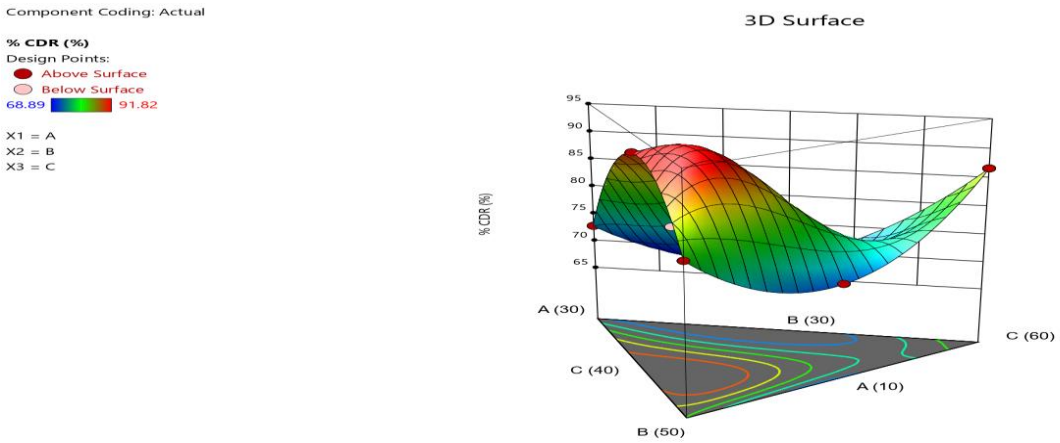

Figure 11: Response surface plot showing the effect of Eucalyptus oil (X1), Tween 80 (X2) and PEG 400 (X3) of SMEDDS on response Y2 CDR (%)

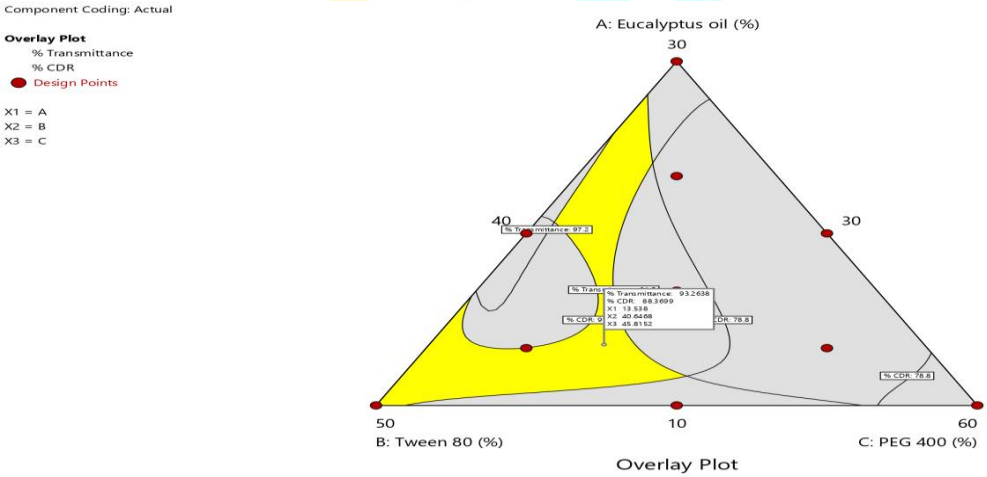

Figure 12: Overlay Plot

Table 7: Overlay Plot for formulation

Formulation	Parameters	Predicted Value	Observed Value	%Error
FP1	% Transmittance	93.2638	92.137	1.12
FP1	% CDR	88.3699	87.141	1.22

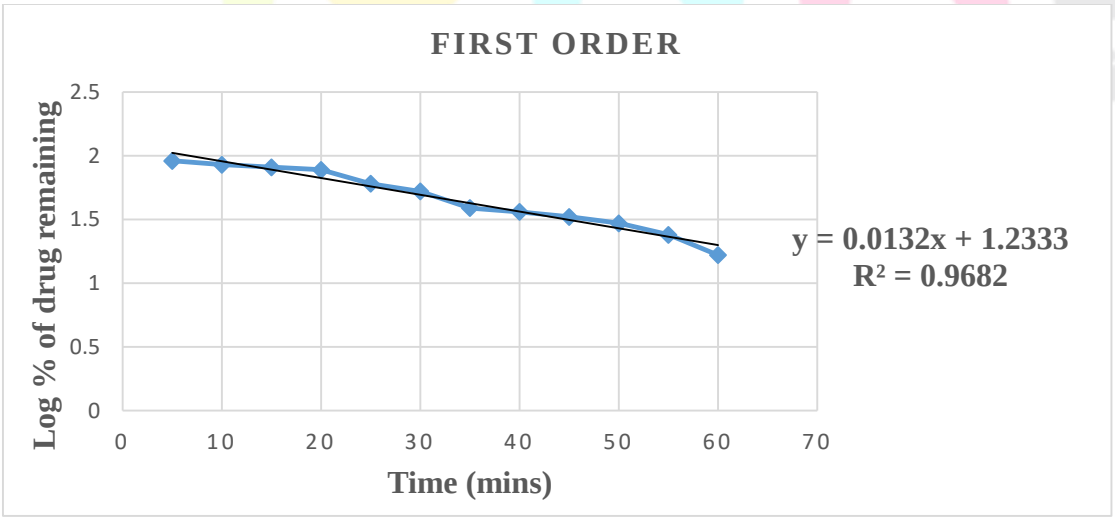

Figure 13: First order graph

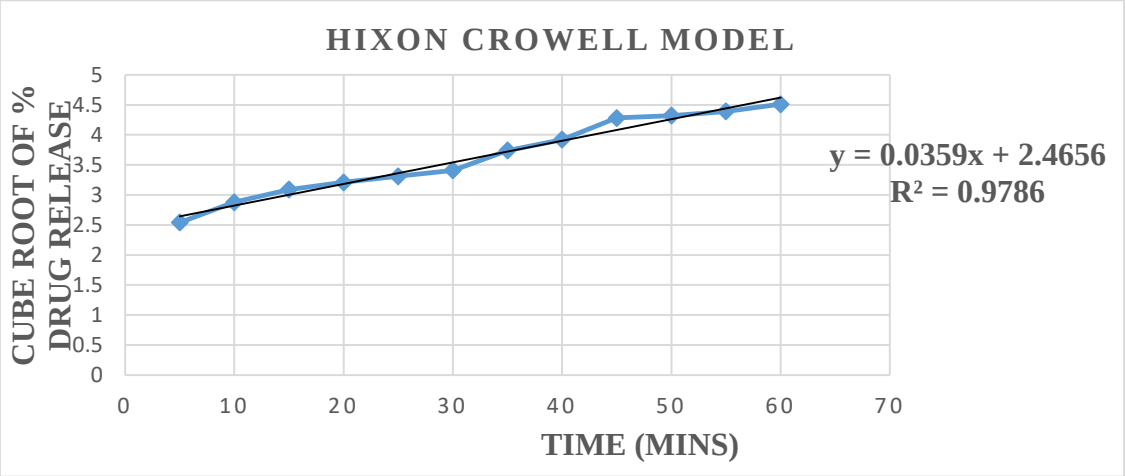

Figure 14: Hixon-crowell model graph

5. CONCLUSION

Empagliflozin is anti-diabetic drug which is used for the management of diabetes. It is lipophilic, its oral bioavailability is low because of its poor solubility. Hence newer approach of self microemulsifying drug delivery system is used to improve the solubility of Empagliflozin. The SMEDDS formulation of Empagliflozin were prepared using Eucalyptus oil, Tween 80 and PEG 400 as oil, surfactant and co-surfactant phase respectively. An optimized formulation of SMEDDS containing Empagliflozin was developed through the construction of ternary phase diagram. As per the phase diagram, stable microemulsion zone was obtained. Formulation were evaluated for visual assessment, self-emulsification time, particle size, zeta potential, PDI and *in-vitro* dissolution study. From the evaluation parameter like particle size 65.5nm, PDI 0.467, zeta potential -15.1mV and *in-vitro* dissolution study 91.82%. F4 formulation was selected as the best formulation out of all.

6. REFERENCES

1. Gangane P, Singh K and Rabade V. 2023. Enhancement of the solubility of lipophilic drug by self-micro emulsifying drug delivery system (SMEDDS) for oral administration. *Ind. J. Pharm. Edu. Res*, 57(3):511-519.
2. Vaghela S, Chaudhary S and Chaudhary A. 2021. A systemic review on the self micro emulsifying drug delivery system. *Int. J. Pharm. Sci. Rev. Res*, 69(1): 184-193.
3. Gangane P, Singh K and Rabade. 2023. Enhancement of solubility of lipophilic drug by self-microemulsifying drug delivery system (smedds) for oral administration. *Indian Journal of Pharmaceutical Education and Research*, 57(3): 511-519.
4. Garg AK, Maddiboyina B, Alqarni MHS, Alam A, Aldawsari HM, Rawat P, Singh S and Kesharwani P.2021.Solubility enhancement, formulation development and antifungal activity of luliconazole niosomal gel-based system. *J Biomater Sci Polym*, 32(8):1009-1023.
5. Bhavani J and Kumar P. 2022. A review on formulation and evaluation of microemulsion. *International Journal of Pharmaceutical Research and Applications*, 7(6): 1644-1654.
6. Halim A, Jindal K and Tarique M. 2021. Solubility enhancement of poorly soluble drug by self emulsifying drug delivery system: comprehensive review." *World Journal of Pharmaceutical Research*, 10(5):840-852.
7. Tushir R, Gupta B, Sharma R and Chauhan A. 2022. A concise review on novel approach for challenging pharmaceuticals through self – micro emulsifying drug delivery system (SMEDDS). *IJPSR*, 13(12):4830-4847.
8. Bhavani J and Kumar P.2022. A review on formulation and evaluation of microemulsion. *International Journal of Pharmaceutical Research and Applications*, 7(6):1644-1654.
9. Tushir R, Gupta B, Sharma R and Chauhan A. 2022. A concise review on novel approach for challenging pharmaceuticals through self – micro emulsifying drug delivery system (SMEDDS). *IJPSR*, 13(12):4830-4847.

10. Ravikant, Rai AK and Upendra. 2022. Compressive Review on Self Emulsifying Drug Delivery System for Diabetes Mellitus. *International Journal of Research and Analysis in Science and Engineering*, 2(1):36–44.

11. Beibeiyan. 2020. Self-microemulsifying delivery system for improving bioavailability of water insoluble drugs. *Journal of Nanoparticle & Research*, 22(1):1-14.

12. Abdulkarim MF, Abdullah GZ, Sakeena MHF, Chitneni M and Mun F .2010. Study of pseudoternary phase diagram behaviour and the effect of several tweens and spans on palm oil esters characteristics. *Int J Drug Deliv*, 3(1):95-100.

13. Li X, Yuan Q and Huang Y. 2010. Development of silymarin self-microemulsifying drug delivery system with enhanced oral bioavailability. *AAPS Pharm Sci Tech*, 11(1):672-678.

14. Jantratid E and Janssen N. 2008. Designing bio-relevant dissolution tests for lipid formulations: case example lipid suspension of RZ-50. *European Journal of Pharmaceutics and Biopharmaceutics*, 69(1):776-785.

15. Salawi A. 2022. Self-emulsifying drug delivery systems: a novel approach to deliver drugs. *Drug Delivery*, 29(1): 1811-1823.

16. Shaikh H and Patil S. 2015. Mathematical models for drug release characterization: a review. *World J. Pharma. Res*, 4(4): 324-338.