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Development And Optimization of Boswellia Serrata Self-Micro Emulsifying Formulation: An Ameliorative Effort Towards the Herbal Formulation

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Abstract: *Development of self-micro emulsifying drug delivery system (SMEDDS) of herbal extracts is challenging task per se, as the herbal extracts contains many active and non-active constituents with various physicochemical properties. Present work focuses on development and evaluation of self-micro emulsifying formulation of Boswellia Serrata Extracts (BSE). An optimized formulation of BSE-SMEDDS composed of the equal fraction of Capmul-MCM®, Acrysol EL135® and Acconon MC8® was developed by employing the 3^3 Full Factorial experimental design.The optimized formulation having capability to self-micro emulsification within less than one minute and droplet size of 189.3 nm (0.432 PDI) was evaluated for In-vitro drug release and ex-vivo diffusion for its comparison with the marketed formulation of the Boswellia Serrata Extract.*

Keywords- *About five key words in alphabetical order, separated by comma*

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I. INTRODUCTION

Herbal systems of medicine have been acceded by various drug regulatory authorities across the globe. People are preferring this systems of medicines for the treatment of various mild to severe and chronic disease conditions like asthma, arthritis, diabetes, high cholesterol, hypertension, various skin diseases, etc. as another option of allopathic system of medicine[1-4]. The vast reasons for this easy adaptation is the fallacy of "No Side Effect" tag of the herbal formulations[5].Though it is not always true, majority of herbal formulations does not show significant side effects that requires serious medical attention. The herbal formulations can be considered as an advanced version of the ayurvedic formulations. The ayurvedic formulations and other natural formulations utilizesentire parts of medicinal plants as such in raw form, wherein, the herbal formulations utilize extracted constituents of that parts of the medicinal plants. The biopharmaceutical challenges for the herbal constituents are tantamount to the other drug molecules. Limited aqueous solubility and permeability of herbal constituents are also considered as a roadblock against the effectiveness of herbal medical systems. Various advancements in the herbal formulations has been proposed and published to improve effectiveness of herbal constituents[6-10]. Development of novel herbal formulation is even more challenging task as the herbal formulations generally compose of multiple constituents. Every constituent in the herbal extract behaves differently for every formulation that makes development of stable novel formulation a challenging task.

Lipid based formulation have proven its ability to improve bioavailability of drug molecules with limited aqueous solubility and permeability[11-17]. The self-micro emulsifying drug delivery system (SMEDDS) while preserving all the attributes of the micro-emulsion solves physical instability related consequences of the micro-emulsion. The SMEDDS get emulsify spontaneously with the gastric fluid and generate micro-emulsion. As micro-emulsion gets produced spontaneously within the stomach (at the site of absorption) during consumption, there is no space for the discussion on instability of micron sized oil globules.

The Boswellia Serrata is the air-dried gum-resin exudate, obtained by incision in the stem or branches of Boswellia serrata Roxb. ex Colebr.This gummy resin of Boswellia Serrata known as Indian frankincense has the age old history as an anti-inflammatory herbal medicine[18, 19].Key chemical content responsible for anti-inflammatory effects are Acetyl-11-keto-β-boswellic acid (AKBA) and 11-Keto-β-boswellic acid (KBA), which shows poor plasma concentration after oral administration [19-23].Whereas β-Boswelic acid shows hundred fold plasma concentration, that is not pharmacologically active [23, 24].Poor aqueous solubility [25]and high Log P (8.0 and 7.10 respectively) represents AKBA and KBA as BCS Class- II drugs[26].

In the present work, the self-micro emulsifying formulation has been developed and optimized using 3^3 full factorial design as an effort for the improvement of bioavailability and thereby therapeutic effectiveness of Boswellia Serrata herbal formulation.

II. MATERIAL AND METHOD

1.1 Material:

Boswellia Serrata Extract (BSE) was provided by Pharmanza Herbal Pvt Ltd, Tarapur, Dist. Anand, India. Certificate of Authentication describes presence of 18.74% β-boswellic acid, 12.59% acetyl-β-boswellic acid, 5.83% 11-KBA, 3.25% A-11-KBA as percentage content of boswellic acids. Capmul MCM® (oil), and Acconon MC8® (co-surfactant) was provided by the Abitec Corporation. Acrysol EL135® (surfactant) was provided by the Corel Pharma Chem, Ahmedabad, Gujarat. Rest of the excipients of pharma grade were purchased from the local suppliers.

1.2 Method:

1.2.1 Preparation of BSE-SMEDDS Formulation:

BSE-SMEDDS was prepared by mixing everycomponent in clean screw caped plastic tube of 25 ml and mixed thoroughly by vortex mixture. Each formulation contained 200 mg of BSE. Tubes were sonicated with heating for 30 minute and kept unstirred for 24 hours to attain the equilibrium.

1.2.2 Development of Ternary Phase Diagram:

As shown in Fig. 1, various points from ternary plot were selected for development of Ternary Phase Diagram. Selected ternary graph points were formulated and evaluated for rate of self-emulsification and transparency. Formulations with rate of self-emulsification less than 1 min and transparency more than 90% were tagged in ternary plot. Region with self-emulsifying efficiency, thus explored, was used to determine levels of independent factors in optimization process in later part. Capmul MCM®, Acrysol EL135® and Acconon MC8® were utilized as the oil, surfactant and co-surfactant respectively based on preliminary trials which are not shown here.

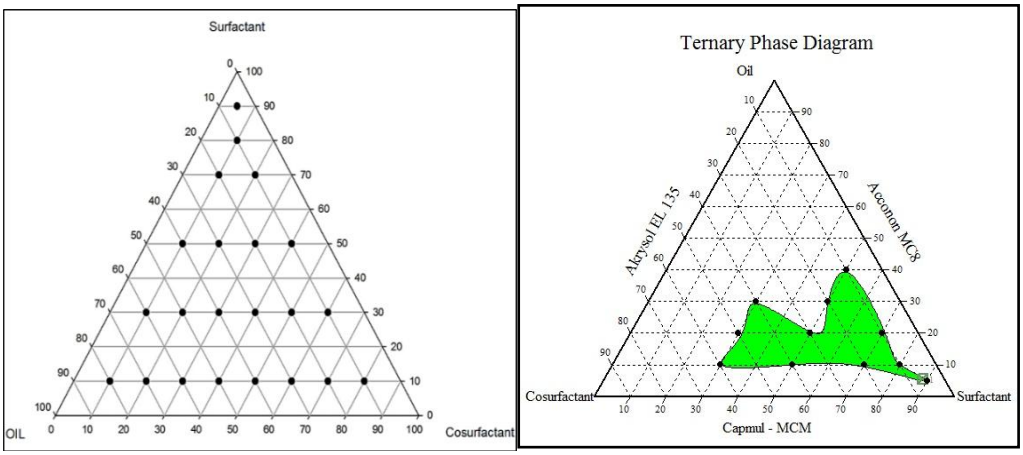

Fig. 1: Ternary plot points selected for evaluation and Ternary Phase Diagram for BSE

1.2.3 Optimization of BSE-SMEDDS Formulation:

Optimization of amount of Capmul-MCM, Acrysol EL 135 and Acconon-MC8 was performed employing 3^3Full-Factorial design. Detail of Independent factor, Coded & Un-coded levels, and design points are given inTable 1.From the ternary phase diagram lowest and highest levels of the independent factors selected. The check point batches were also prepared to evaluate predictability of optimization model. Optimized formula was revealed using Numerical Optimization Tool of SAS 9.1 program. Minimum - droplet size (Y1), PDI (Y2), Rate of Emulsification (Y3), Amount of surfactant (X3) and Maximum amount of oil (X1) were selected as the desirable criteria for the optimization of formulation.

Table 1: Details of 3^3 Full Factorial Design

Independent Factors		**Coded Level (Un-coded amount in ml)**			**Dependent Factors**	
		Low	Medium	High		
X_1 (Capmul MCM in ml)		-1(0.5)	0 (2.25)	+1 (4)	Y_1 = Mean Droplet Diameter in nm	
X_2 (Acrysol EL135 in ml)		-1(3)	0 (3.5)	+1 (4)	Y_2= Polydispersibility Index	
X_3 (Acconon MC8 in ml)		-1(0.5)	0 (2.25)	+1 (4)	Y_3= % Rate of self-emulsification in minute	
Run	X_1	X_2	X_3	Y_1	Y_2	Y_3(SD, n = 3)
BSE1.	-1	-1	-1	1120	1.025	32.8±3.21
BSE2.	-1	-1	0	974.2	0.874	43.8±1.35
BSE3.	-1	-1	+1	969.5	0.861	65.2±4.56

BSE4.	-1	0	-1	963.3	0.842	45.9±2.32
BSE5.	-1	0	0	884.1	0.813	33.9±2.22
BSE6.	-1	0	+1	872.0	0.792	51.9±1.09
BSE7.	-1	+1	-1	856.3	0.781	78.4±3.22
BSE8.	-1	+1	0	845.5	0.776	37.4±5.33
BSE9.	-1	+1	+1	822.1	0.725	32.5±2.19
BSE10.	0	-1	-1	829.2	0.738	47.6±1.90
BSE11.	0	-1	0	784.9	0.713	58.3±4.82
BSE12.	0	-1	+1	765.5	0.701	76.5±1.08
BSE13.	0	0	-1	771.5	0.696	107.3±3.26
BSE14.	0	0	0	745.3	0.687	47.3±2.4
BSE15.	0	0	+1	682.4	0.675	77.5±.2.1
BSE16.	0	+1	-1	677.3	0.662	57.3±3.47
BSE17.	0	+1	0	621.2	0.65	29.4±6.34
BSE18.	0	+1	+1	494.5	0.641	55.8±12.3
BSE19.	+1	-1	-1	432.6	0.628	67.4±9.2
BSE20.	+1	-1	0	378.9	0.619	87.6±7.2
BSE21.	+1	-1	+1	331.6	0.607	34.7±2.1
BSE22.	+1	0	-1	328.9	0.576	56.2±1.7
BSE23.	+1	0	0	287.7	0.546	93.5±5.23
BSE24.	+1	0	+1	276.3	0.54	23.8±2.76
BSE25.	+1	+1	-1	242.3	0.502	48.3±3.45
BSE26.	+1	+1	0	128.4	0.482	67.9±7.23
BSE27.	+1	+1	+1	105.9	0.432	21.7±1.54

1.2.4 Characterization of BSE-SMEDDS:

1.2.4.1 Rate of Self-Emulsification:

Self-emulsification efficiency was measured by visual inspection and qualitative grading method described by Charman, W.N [15]. Self-emulsifying Efficiency was estimated using USP-II (USP 30 NF 25) dissolutionapparatus. 1 ml of formulation was added drop wise to 200 ml of 0.1 N HCL (37^0C). Rotating paddle was kept at 60 RPM speed to provide gentle agitation. Rate of emulsification and quality of emulsion after complete dispersion were measured. Time required for complete dispersion: Rate of emulsification, was measured visually using stop clock.

1.2.4.2 Evaluation of Transparency:

Because of fluctuation in NTU in nephelometric analysis, percentage transparency after dilution of SMEDDS formulation with purified water (1 ml with 200 ml) was determined by UV-Visible spectrophotometer at 560 nm [27, 28].

1.2.4.3 Droplet Size and PDI determination:

Droplet diameter and PDI (Poly Dispersibility Index) was measured by Dynamic Light Scattering technique. Sample was prepared by mixing 1 ml of SMEDDS formulation in to 200 ml double distilled water with gentle agitation. After one-hour sample was subjected to droplet size distribution analysis in Malvern Zetasizer Nano S 90.

1.2.4.4 HPLC Method for Quantitative Analysis:

Instrumentation:

HPLC from Analytical Technologies Ltd, Vadodara, was utilized throughout all studies. UV 2230 Plus detector and P2230 reciprocating pump was employed in instrument. Rhenodye valve injector with 20 µl loop was connected to computer system through USB serial port for data acquisition. Analchrom2006 Version 1.40 was used as graphical user interface layer.

Chromatographic Condition:

Hypersil ODS2 C18 column with 250 × 4.6 mm and 0.5 µm particle diameter was used. Mobile phase [29] was optimized to gradient elution as shown in Table 2. Flow rate was set to 1 ml/min and chromatograph was recorded at 260 nm.

Table 2: Gradient Elution Parameters

Time (min)	**Mobile Phase-A**	**Mobile Phase-b**
0-12.5	16→6	84→94
12.5-13.5	6→0	94→100
13.5-15.0	0	100
Mobile Phase-A	phosphoric acid: water R (0.1:99.9 V/V)	
Mobile Phase-B	phosphoric acid : acetonitrile R (0.1:99.9 V/V)	

Preparation of Standard Solution:

Accurately weighed 50 mg standard BSE powder was dissolved in 25 mL of methanol to get a standard solution: 2 mg/mL that represents to 116.6 µg/mL of 11-Keto Boswellic Acid and 65 µg/mL of Acetyl-11-Keto Boswellic Acid. Concentration of KBA and AKBA are calculated using Equation 1 and

Equation 2.

$$\text{Concentration of KBA } (\mu g ml^{-1}) = \frac{A_1 * 116.6}{A_2}$$

Equation 1: Calculation of concentration of KBA

$$\text{Concentration of AKBA } (\mu g ml^{-1}) = \frac{A_1 * 65}{A_2}$$

Equation 2: Calculation of concentration of AKBA

1.2.4.5 *In vitro* Dissolution Profile Comparison:

According to the Lipid Formulation Classification System (LFCS) Consortium, this formulation comes under type IIIA/IIIB. Such formulation does not require digestion of lipid. So, Dissolution media as prescribed in official compendia, wasselected[30]. Dissolution test procedure described in USP320-NF25 was employed for study. Dissolution study was performed using the USP-II apparatus using 900 ml of 0.1N HCl as dissolution media and 50 RPM as paddle rotation speed. Sample collected at each time points were filtered with Whatman® filter paper and subjected to quantitative analysis by HPLC method of analysis.Dissolution profile of BSE-SMEDDS Tablet (25 mg) formulation (Formulation of BSE-SMEDDS Tablet is not discussed here) is compared with the marketed formulation Shallika 250 mg Capsule.

1.2.4.6 Ex-vivo Diffusion Comparison:

Ex-vivo drug diffusion study was performed to prove bioavailability improvement in test product than reference product [31]. *Ex-vivo* drug permeation study of BSE-SMEDDS Tablet (MB-1T) were performed by intestinal sac method [32-35]. A non-everted chick ileum was used for *Ex-vivo* drug release study. Test and reference sample were prepared by mixing powdered tablet of test or reference in to 10 ml of physiological salt solution. One end of small specimen of chick ileum (5 cm) was tied with thread and from another end, and either of test or reference sample was introduced with syringe. After filling with sample in to chick ileum, another open end was also tied with thread. Intestinal sac thus formed was placed in glass beaker containing 100 ml of PSS with constant aeration at 37^0C. Constant stirring was allowed with the help of magnetic stirrer at 100 ± 10 RPMs. 10 ml of sample was collected at different time interval and replaced with 10 ml fresh aerated PSS. Sample was than analyzed for amount of drug released using HPLC method of analysis.

III. RESULT AND DISCUSSION

3.1Optimization of BSE-SMEDDS:

Phase boundary lines of the ternary phase diagram has been utilized for determination of minimum and maximum levels of the independent factors. Fit statistics and effect estimate of each dependent factors have been calculated using SAS 9.1 and shown inTable 3. Fit statistics of Y_3 represents poor fit of model and none of the independent factor have significant effect over the dependent factors. The polynomial equations for Y_1 and Y_2 have been utilized for prediction of responses of check point batches. Chi^2 Test between predicted and actual results, clearly represents the predictive capability of the polynomial equation. With the help of numerical optimization tool of SAS 9.1 software and the contour plot of Y_1 and Y_2 has been utilized for optimization of BSE-SMEDDS. Minimum globule size, poly-dispersibility index and minimum rate of self-emulsification was considered as desirable property of the optimized formulation. Optimized formulation of BSE-SMEDDS is tagged in the overlain contour plot as shown in Fig. 2.Each of the components has been selected in same proportion as an optimized formulation of BSE-SMEDDS. Transparency and overall performance of an optimized BSE-SMEDDS can be observed through the Fig. 3.As shown in Fig. 4, Malvern Zeta sizer analysis report shows Z-avg. globule size of 189.3 nm and 0.432 PDI for an optimized formulation which is not significantly different from the predicted value.

Table 3: Fit Statistics of Y_1, Y_2 and $Y_3$and Result of Check Point batches.

Fit Statistics	Mean	R-square	RMSE	CV
Dependent Factor				
Y_1	636.66	94.37%	78329	12.30
Y_2	0.688	95.97%	0.0306	4.451
Y_3	54.81	24.58%	21.72	39.63
Polynomial Equation				

$Y_1 = 636.66+321.8*X_1-90*X_2-50.13*X_3$								
$Y_2 =0.688-0.14*X_1-0.061*X_2-0.0264*X_3$								
Check point Batch			Y_1			Y_2		
			Predicted	Actual	Chi^2 Test (p-Value)	Predicted	Actual	Chi^2 Test (p-Value)
0.5	0.5	0.5	405.6	394.8	0.42775	0.573	0.423	0.9966
-0.5	-0.5	-0.5	867.7	843.8		0.804	0.780	
0.5	-0.5	0.5	495.8	473.7		0.635	0.621	
-0.5	0.5	-0.5	777.6	753.5		0.742	0.723	

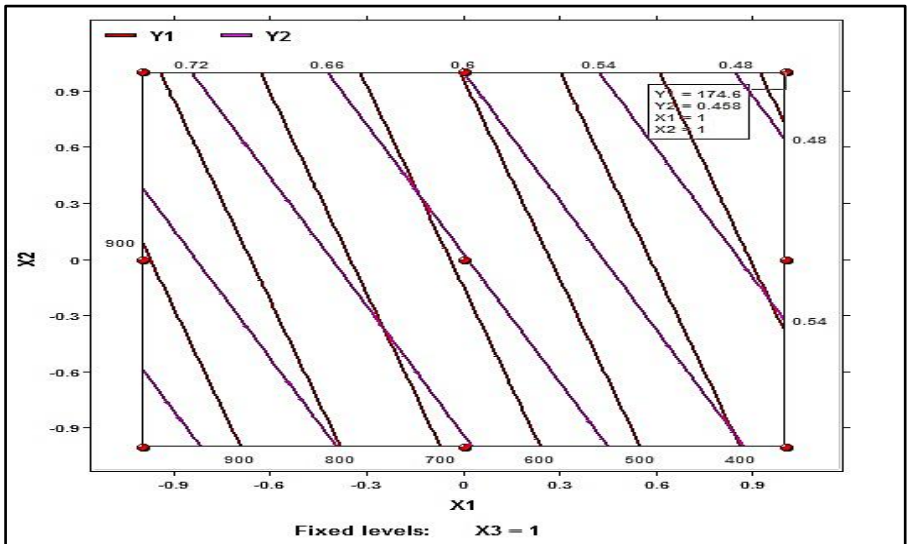

Fig. 2: Overlain Contour for Optimization of BSE-SMEDDS.

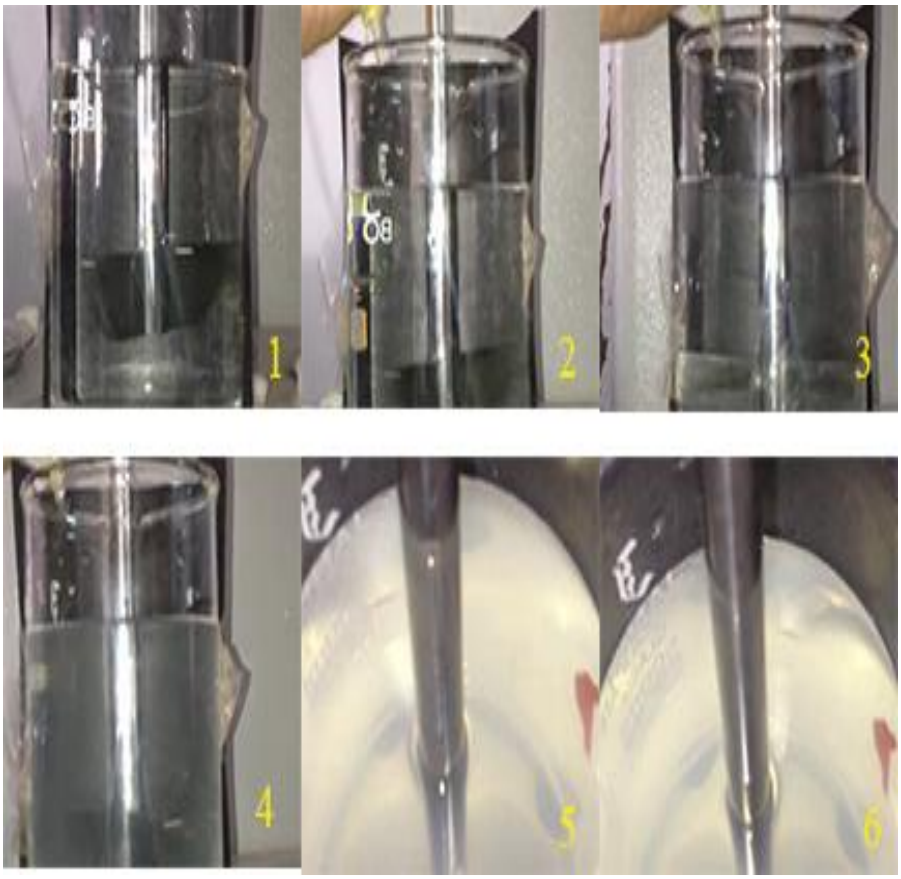

Fig. 3: Performance of BSE_SMEDDS in USP-II Apparatus

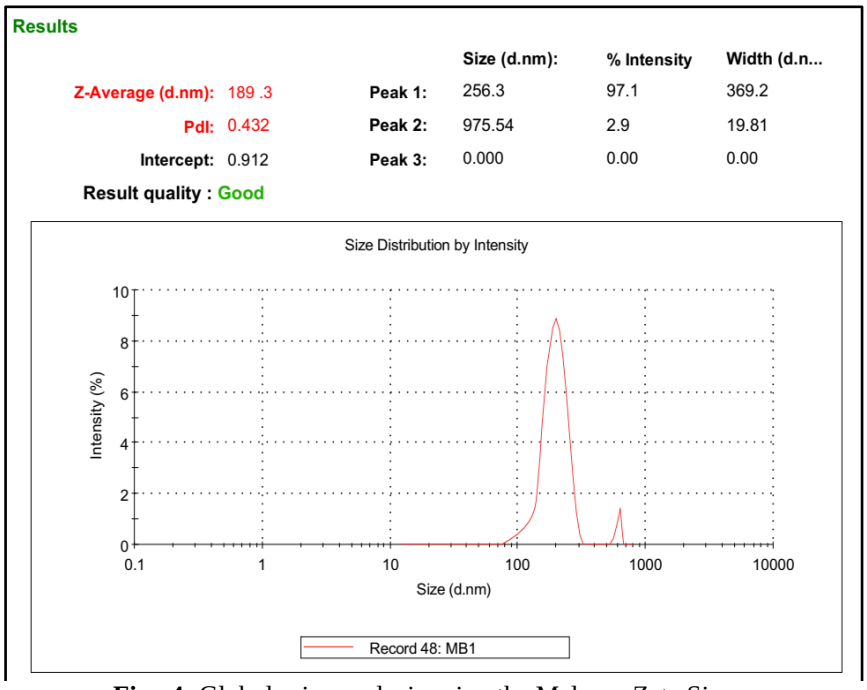

Fig. 4: Globule size analysis using the Malvern Zeta Sizer.

3.2In-vitro Dissolution Profile Comparison:

Dissolution profile comparison as shown in Fig. 5, apparently represents the significant difference between the BSE-SMEDDS Tablet and marketed formulation. BSE-SMEDDS Tablet releases more than 80% of active constituents within 30 minutes.

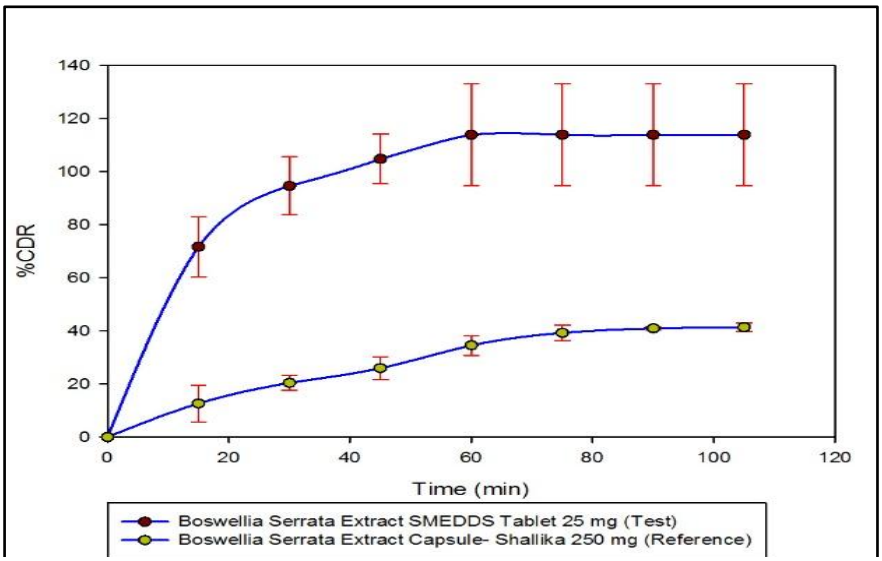

Fig. 5: Dissolution profile comparison between BSE-SMEDDS Tablet and Boswellia Serrata Capsule (Shalilika 250 mg)

3.4Ex-vivo Diffusion Comparison:

Ex-vivo diffusion study of Boswellia Serrata Extract represents clear-cut improvement in absorption in case of BSE-SMEDDS Tablet (MB-1T) than reference product. Graphical comparison of results of diffusion study for both products are shown in Fig. 6. Flux calculation at the end of one hour for test product is 1.17 mg/hr.cm^2 while 0.25 mg/hr.cm^2 in case of reference product.

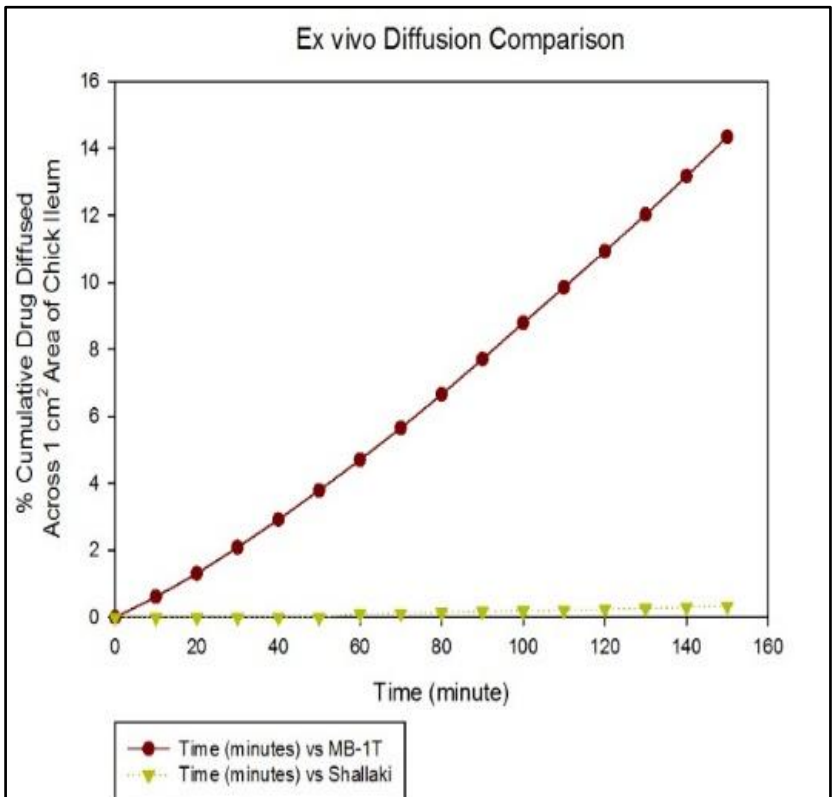

Fig. 6: Ex-vivo Diffusion Study Comparison between BSE-SMEDDS Test and Reference Product.

IV. CONCLUSION

The self-micro emulsifying formulation of Boswellia Serrata Extract can be developed, nevertheless it contains multiple active constituents. The optimized formulation of BSE is capable to produce micro-emulsion spontaneously having average globule size of 189.3 nm (0.432 PDI) within less than one minute. The optimistic results of Ex-vivo diffusion study allowed to presume improvement in bioavailability of Boswellia Serrata Extract. However, a comprehensive in-vivo study is required to prove improvement in the oral bioavailability.

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