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Original Article

ORAL BIOAVAILABILITY ENHANCEMEMENT OF BROMOCRYPTINE MESYLATE BY SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS)

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ABSTRACT

Objective: The purpose of this work was to enhance oral bioavailability of Bromocryptine Mesylate by preparing SMEDDS (self-micro emulsifying drug delivery system)

Methods: Screening of oils, surfactants and co-surfactants were done by solubility study & pseudo ternary diagram. The batches of Bromocryptine Mesylate (BM)–SMEDDS were prepared and evaluated for droplet size analysis, poly dispensability index (PDI), robustness to dilution, zeta potential, *in vitro* dissolution. The optimized batch was compared with commercially available quick release tablets of BM (Brainstar®, 0.8 mg/tablet) by *in vivo* study (Pharmacodynamic study in rats).

Results: Based on the drug's solubility study, Akoline MCM, Tween80 and PEG400 were selected as oil, surfactant and co-surfactant, respectively. By pseudo ternary diagram, the components' ratios were screened. *In vitro* drug release of the optimized batch was lower than the commercial preparation but in *in vivo* study, optimized batch was similar with commercial tablets.

Conclusion: From the study, it was concluded that the group treated with optimized BM-SMEDDS showed better and sustained reduction in blood sugar as compared to control group and the group treated with marketed formulation, indicated improvement in bioavailability of drug.

Keywords: Bromocryptine Mesylate, Type–II Diabetes, Self micro emulsifying drug delivery system, Bioavailability, Pharmacodynamic study

INTRODUCTION

Oral intake has been the most sought-after route of drug delivery by both patients and drug manufacturers for the treatment of most pathological states. Despite tremendous strides made in novel non-oral drug delivery systems, the majority of the drugs available commercially are oral formulations. Nevertheless, with oral delivery, over half of the drug compounds are diminished in the gastrointestinal tract because of their high lipophilicity and consequently poor aqueous solubility [1]. Oral bioavailability of such drugs, being primarily a function of their solubility and dissolution, [2] tends to exhibit inadequate magnitude with high intra-and inter-subject variability. Further, oral bioavailability also depends on upon a multitude of other drug factors such as stability in GI fluids, intestinal permeability, resistance to metabolism by cytochrome P450 family of enzymes present in gut enterocyte and liver hepatocytes and interactions with efflux transporter systems such as P-glycoprotein (P-gp) [3,4].

Type-II diabetes is a growing global pandemic that is estimated to af flict approximately 350 million people by the year 2030 [5]. This growing threat to human health requires medical interventions to lessen the morbidity associated with type-II diabetes. Type-II Diabetes is characterized by elevated fasting and postprandial plasma glucose concentrations which result from increased endogenous glucose production (EGP), decreased insulin-mediated muscle glucose disposal and suppression of endogenous glucose release and inadequate pancreatic insulin secretion. Obesity is a well-established risk factor for type-II diabetes. Extensive experimental evidence indicates that circadian neuroendocrine rhythms play a pivotal role in the development of seasonal changes in body fat stores and insulin sensitivity. Specifically, temporal changes in the interaction of 2 distinct neural circadian oscillations, mediated by dopaminergic and serotonergic neurotransmitter activity, have been shown to regulate the dramatic seasonal alterations in body weight and body composition that are characteristic of all vertebrate classes from teleost to mammals. Data obtained in rats, pigs, and humans suggest that similar mechanisms may play a role in the development of non-seasonal obesity and insulin resistance [6].

Bromocriptine mesylate (BM), an ergot derivative, is a sympatholytic dopamine D2 receptor agonist that exerts inhibitory effects on serotonin turnover in the central nervous system. It has been proposed that bromocriptine can reverse many of the metabolic alterations associated with obesity by resetting central (hypothalamic) circadian organization of monoamine neuronal activities. BM approved by USFDA for treatment Type-II Diabetes (Dec. 2008) is practically insoluble in water [7] and shows pH dependent solubility [8]. Only about 30% of an oral dose is absorbed from GIT bioavailability is only about 6% owing to extensive first-pass metabolism. Bromocriptine improves glycemic control and glucose tolerance in obese type-II diabetic patients. Both reductions in fasting and postprandial plasma glucose levels appear to contribute to the improvement in glucose tolerance. The bromocriptine induced improvement in glycemic control is associated with enhanced maximally stimulated insulin-mediated glucose disposal [6].

Self micro emulsifying drug delivery systems (SMEDDS)-isotropic mixtures of the drug, lipids (natural or synthetic oils), and emulsifiers (solid or liquid), usually with one or more hydrophilic co-solvents/co-emulsifiers are relatively newer, lipid-based technological innovations with immense promise in enhancing the oral bioavailability of drugs. [9, 10] These formulations have been shown to overcome the slow and incomplete dissolution of a drug, facilitate the formation of its solubilized phase, increase the extent of its transportation via the intestinal lymphatic system and bypass the P-gp efflux, thereby augmenting drug absorption from the GI tract [11]. This presents the opportunity to prepare the formulation in SMEDDS form to enhance dissolution with the bioavailability of poorly water soluble drug-BM for better treatment of diabetes.

MATERIALS AND METHODS

Materials

Bromocriptine Mesylate (Helios Pharmaceuticals, Baddi, India), Etocas 35 HV-LQ (Croda Europe Ltd., Snaith Goole, United Kingdom), Tween 80 (Hi-Media, Vadodara, India), Captex 500 (Abitec

Corporation, Columbus, USA), Capmul MCM C8 (Abitec Corporation, Columbus, USA), Methanol (Loba Chemie Pvt. Ltd., Mumbai, India), Akoline MCM (Aarhus Karlshamn Sweden AB), PEG 400 (Loba Chemie Pvt. Ltd., Mumbai, India), Potassium Chloride (Merck Specialities Pvt. Ltd., Bengaluru, India), Hydrochloric acid (Merck Specialities Pvt. Ltd.), Crodamol GTCC (Croda Europe Ltd., Snaith Goole, United Kingdom) were used. All other reagents and solvents were of analytical grades.

Screening of oil, surfactants and co-surfactants (solubility study of BM in various oil, surfactants and co-surfactants)

The most important criterion for the screening of components for SMEDDS is the solubility of the poorly soluble drug in oils, surfactants, and co-surfactants. 10 mg of BM was added in each tube containing either oil surfactant or co-surfactant mixed using cyclomixer. After visual assessment of solubility of the drug, the additional drug infraction of 10 mg was subsequently added in each tube to determine the maximum solubility of drug in the particular solvent. The tightly closed tubes were shaken for 48 h at 50 strokes per minute in an isothermal shaker. The procedure was continued till highest solubility observed [12].

Construction of pseudo-ternary phase diagram

The existence of microemulsion regions was determined by using pseudo ternary phase diagram. SMEDDS were diluted under agitation condition using water titration method. The mixture of oil and surfactant/co-surfactant mixture (Smix) at certain weight ratios were diluted with water in a dropwise manner. The ratios of surfactant/co-surfactant were prepared in the specific manner, i.e., 1:1, 1:2 and 2:1 (%w/w). Each of these ratios was mixed with increasing percentage of oil, i.e., 10%, 20%, 30%, 40% up to 90% of oil to get phase diagram. Then, each mixture was titrated with water, and agitation was provided by a magnetic stirrer. The formation of microemulsion regions was monitored visually for turbidity–transparency–turbidity. These values of oil, surfactant and cosurfactant were used to determine the boundaries of microemulsion region in the pseudo-ternary phase diagram. After the identification of microemulsion region in the phase diagrams, the microemulsion formulations were selected at desired component ratios. [12]

Preparation of SMEDDS

A series of microemulsions of SMEDDS were prepared with varying ratios of oil, surfactant, and cosurfactant as mentioned in table 1. Formulations A, B, and C were prepared using Akoline MCM as oil, Tween 80 as a surfactant, and PEG 400 as co-surfactant. In all the formulations, the level of BM was kept constant to 7.5% w/w of SMEDDS. Briefly, oil, surfactant, and cosurfactant were accurately weighed into glass vials according to their ratios. The amount SMEDDS should be such that it solubilizes the drug (single dose) completely. Hence, 0.8 mg of BM was dissolved in 0.125 g of SMEDDS. Then, the components were mixed by gentle stirring and vortex mixing at 26 until clear oily phase was obtained. The formulation was equilibrated at ambient temperature for at least 48 h and examined for signs of turbidity or phase separation prior to self-emulsification and particle size studies [12].

Table 1: Three composition of SMEDDS (containing 7.5 mg BM % w/w)

Vehicle (%w/w)	A	B	C
BM	7.5	7.5	7.5
Akoline MCM (Oil)	4.5	9.0	13.5
Tween 80 (Surfactant)	70.9	67.2	63.4
PEG 400 (Cosurfactant)	34.1	32.4	30.5

Characterization of SMEDDS

Dispersibility test

Self-emulsification efficiency of the prepared formulation was assessed using a standard USP XXII dissolution apparatus. 0.5 ml of each formulation was added to 500 ml of distilled water at 37±1.0 °C. A standard stainless steel dissolution paddle rotating at 50 rpm was used to provide gentle agitation. Emulsification time was assessed visually and *In vitro* performance of the formulations was visually assessed using the following grading system [1].

Robustness to dilution

0.5 ml of SMEDDS was mixed with 500 ml of 0.1 N HCl. The diluted microemulsions were stored for 12 h at room temperature and observed for any signs of phase separation or drug precipitation [1].

Droplet sizes analysis

Microemulsion globule size was determined using a photon correlation spectrometer (Malvern Zetasizer Nano S90, Malvern Instruments, Worcestershire, UK) based on the laser light scattering phenomenon which analyzes the fluctuations in light scattering. Light scattering was monitored at 25 °C at a 90 ° angle. Properly diluted samples of microemulsion (0.1 ml) were dispersed in 50 ml of buffer pH 1.2 and were taken for droplet size analysis. Average droplet size was determined [1].

Zeta potential determination

Zeta potential was measured by photon correlation spectroscopy using zeta sizer (Malvern Zetasizer Nano ZS, UK; Malvern Instruments, Worcestershire, UK), which measures the potential range from−120 to 120 V. Zeta potential results of all SMEDDS formulations taken after diluted 20 times with buffer pH 1.2 [1, 13].

***In vitro* dissolution study**

BM SMEDDS formulation was filled in size '3' hard gelatin capsules. *In vitro* release profiles of SMEDDS of BM was studied using USP XXIII apparatus type I (Electrolab India, Mumbai, India) at 37±0.5 °C and 120 rpm in 0.1N hydrochloric acid as the dissolution media (500 ml) and an aliquot (5 ml) of sample was collected at predefined time intervals (0, 5, 15, 30, 45 and 60 min) from the dissolution medium and replaced with fresh media. The amount of BM released in the dissolution medium was determined by fluorescence spectrometer (Perkin Elmer LS55, USA) at $\lambda_{Excitation}$ 315 nm and λEmission 425 nm. The results were analyzed for statistical significance by student's t-test using Graph pad Prism software. All data were expressed as mean±S. E ($P<0.05$). Group means were considered to be significantly different at $P<0.05$ [13].

***In vivo* study**

Wistar rats with weighing>200g were utilized for this *in vivo* study. Animals were housed in an air-conditioned animal room at 25±1 °C and 55% relative humidity with a 12 h light/dark cycle and maintained with free access to water and food Italic. The experimental protocol was approved by institutional animal ethics committee vide (Protocol No RPCP/IAEC/2011-2012/MPH-PT-06). All experiments were conducted as per the norms of the committee for the purpose of control and supervision of experiments on animals (CPCSEA). Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) (60 mg/kg) [14] (Sigma, St. Louis, MO, USA) freshly dissolved in a 0.1 M citrate buffer (pH 4.3). After 2 d, rats with blood glucose levels≥300 mg/dL were selected for the study [15, 16]. (STZ produces DNA damage to pancreatic icelet cells which leads to hyperglycemic state and blood glucose level increased to>300 mg/dl. so animals showed hyperglycaemia.)

The rats were assigned to three different groups-5 rats each and treated as follows:

Group I: Diabetic Control, no drug treatment (given only distilled water)

Group II: Diabetic treated with BM SMEDDS (0.8 mg/kg) (dispersed outside and equivalent dose administered).

Group III: Diabetic treated with marketed formulation, 0.8 mg/kg of Brainstar tablet, USV Limited, India. (Tablet disintegrated outside and equivalent dose administered)

The above-mentioned doses were administered once a day up to 28th day of study. Blood was collected from the tail vein on day 0, 7, 14, 21 and 28. Blood glucose level was determined using glucometer (Johnson and Johnson) based on the glucose oxidase/peroxidase method. The results were analyzed for statistical significance by two-way analysis of variance (ANOVA) test using Graph pad prism software. All data were expressed as mean±SD ($P<0.05$). Group means were considered to be significantly different at $P<0.05$.

RESULTS AND DISCUSSION

Solubility study

The solubility of BM was checked in a number of solvents and presented in a graphical manner in fig. 1. Based on the solubility data, Akoline MCM was selected as oil phase, Tween 80 as surfactant and PEG 400 as co-surfactant since these solvents showed better solubility.

Pseudo ternary phase diagram

To determine the optimum concentration of oil, surfactant, and cosurfactant, phase diagrams were constructed. SMEDDS forms microemulsion when titrated with water under agitation condition. The particle size of the microemulsion is less than 100 nm and as the energy required to form microemulsion is very low, it is a thermodynamically spontaneous process.

This process is facilitated by the presence of a surfactant. The surfactant forms a layer around oil globule in such a way that polar head lies toward aqueous and nonpolar tail pull out oil and thereby reduces surface tension between oil phase and an aqueous phase. Another factor affecting the formation of the microemulsion is the ratio of surfactant and co-surfactant. The lipid mixtures with a different surfactant, co-surfactant, and oil ratios lead to the formation of SMEDDS with different properties. Since surfactant and co-surfactant adsorb at the interface and providing a mechanical barrier to coalescence, selection of oil, surfactant, and cosurfactant and mixing ratio to S/CoS play an important role in microemulsion formation [12].

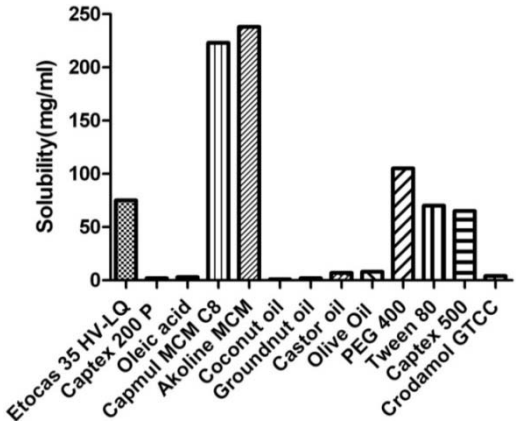

Fig. 1: Graph showing solubility of BM in different various oils, surfactants and co-surfactants

Three different formulations were prepared using different oils, surfactants, and cosurfactants in varying ratios. SMEDDS were formulated using same excipients with three different S/CoS ratios of 2:1, 1:1, and 1:2 and diluted to get microemulsion region as mentioned in fig.2. Microemulsion regions were observed visually. Initially, the concentration of oil taken was.

Table 2: Percentage of water required for microemulsion formation

Oil: mix	Surfactant: cosurfactant (1:2)			Surfactant: cosurfactant (1:1)			Surfactant: cosurfactant (2:1)		
	% Akoline MCM	% Tween 80	% PEG 400	% Akoline MCM	% Tween 80	% PEG 400	% Akoline MCM	% Tween 80	% PEG 400
1:9	7	64	29	4	34	62	-	-	-
2:8	16	64	20	15	62	23	7	27	66
3:7	31	46	23	22	51	26	18	42	39
4:6	36	36	29	29	43	29	25	38	38
5:5	44	30	26	38	38	23	31	31	38
6:4	52	22	26	44	30	26	40	27	33
7:3	59	15	26	50	21	29	42	18	39
8:2	67	7	26	60	15	25	55	14	31
9:1	1	28	71	64	7	29	56	6	38

Table 3: Visual assessment of SMEDDS

Grade	Dispersibility and appearances	Time of self-micro emulsification
A	Rapid forming microemulsion which is clear or slightly bluish in appearance	<1 min
B	Rapid forming, slightly less clear emulsion, which has a bluish white appearance	<1 min
C	Bright white emulsion (similar to milk)	<2 min
D	Dull, grayish white emulsion with a slightly oily appearance that is slow to emulsify	>3 min
E	Exhibit poor or minimal emulsification with large oil droplets present on the surface	>3 min

Table 4: Result of dispersibility of SMEDDS in distilled water

Batch No	Appearance	Emulsification Time	Grade
SM1	Clear, Slight bluish	<1 min	A
SM2	Clear, Slight bluish	<1 min	A
SM3	Less Clear, bluish white	<1 min	B

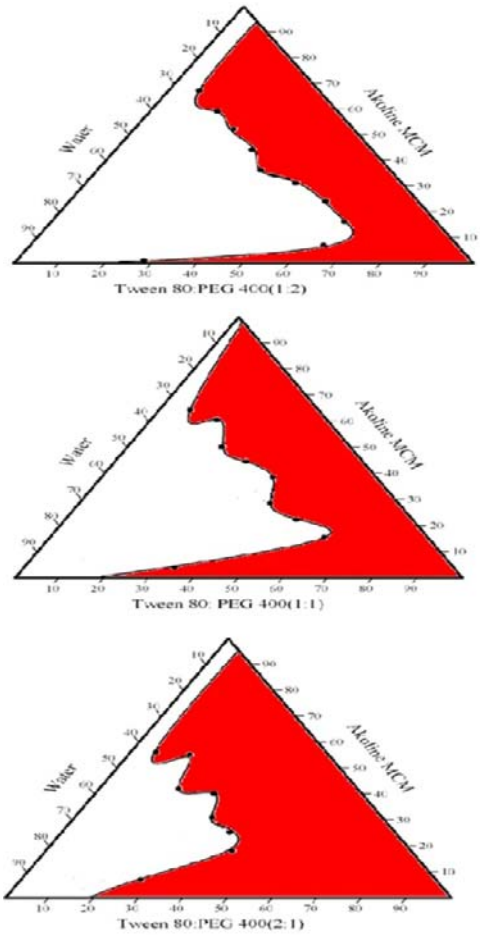

Fig. 2: Phase diagram prepared with the following components: oil-Akoline MCM, surfactant-Tween 80, and co-surfactant-PEG 400. S/CoS ratio of 1:2, 1:1 and 2:1

Maximum, i.e., 90%, and the amount of S/CoS was kept to a minimum, i.e., 10% as per the table 3. Gradually, oil concentration was decreased, and that of S/CoS was increased. It was observed during these experiments that high concentration of oil forms a poor emulsion with entrapment of very less amount of water upon dilution. Another observation was that as the concentration of S/CoS increases, the time estimated to form micro emulsion decreases.

A series of micro emulsions were prepared at different concentrations of oil and S/CoS, but the concentration of oil was found to be a rate-limiting factor, and in all cases, high oil concentration resulted in poor emulsion region. Hence, it was decided to keep the oil concentration less than 10%. Ternary phase diagram of 2:1 w/w S: CoS resulted in higher micro emulsion region as compared to other, so it was selected for formulation development trials.

Dispersibility test

Dispersibility of all the batches was recorded in terms of appearance and self-emulsification time, and all the results were recorded as per table 3.

All the formulations have shown good dispersibility in distilled water as a dispersibility medium. Self-emulsification time for all the batches found within 60 seconds as mentioned in table 4**.** Rapid self-emulsion time was indicated that in GI fluid these formulations rapidly form dispersion with small droplet size. All the formulations have shown good dispersibility in distilled water as a dispersibility medium.

Robustness to dilution

Diluted SMEDDS did not show any precipitation or phase separation on storage in various dilution media. This reveals that all media were robust to dilution.

Droplet sizes analysis

There is a relationship between the droplet size and the concentration of the surfactant being used. As per the earlier research, increasing the surfactant concentration could lead to droplets with smaller mean droplet size. This could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface. On the other hand, As per Literature, the mean droplet size may increase with increasing surfactant concentrations. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to the ejection of oil droplets into the aqueous phase [17].

The particle size determination following self-microemulsification is a critical factor to evaluate a self-microemulsion system as droplet size is reported to have an effect on drug absorption. The smaller is the droplet size; the larger is the interfacial surface area provided for drug absorption [17]. The optimization of SMEDDS was based on the particle size of SMEDDS. The mean particle size and PDI for all the SMEDDS and optimized formulation's globule size have been summarized in table 5 and fig. 3 respectively**.** The Results are of triplicate study.

Table 5: Result of globule size analysis in pH 1.2 buffer

Batch no.	Globule size	Poly dispersibility index
SM1	28.53±27.33	0.30±0.07
SM2	12.63±2.65	0.24±0.07
SM3	140.96±57.55	0.23±0.03

Mean of 3 measurements±SD (n = 3)

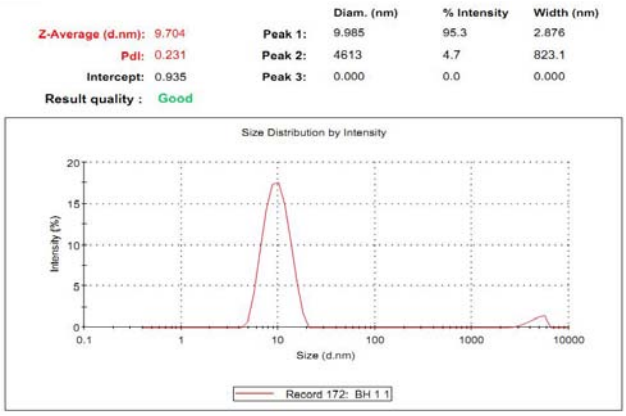

Fig. 3: Globule size of optimized SMEDDS formulation

Poly dispersity is the ratio of standard deviation to the mean droplet size. This signifies the uniformity of droplet size within the formulation. The higher the value of poly dispersity, the lower is the uniformity of the droplet size in the formulation. The poly dispersity values of SMEDDS SM1, SM2, and SM3 are 0.3±0.07, 0.24±0.07, and 0.23±0.03, respectively, which indicates uniformity of droplet size within the formulation. SMEDDS with increased globule size causes agglomeration of globules and suffers with the instability of the system. SMEDDS SM1 and SM2 were found having a particle size less than 100 nm which fill the criteria of the microemulsion and low PDI shows the uniformity of particles. But SMEDDS SM2 having least particle size, Therefore, SMEDDS SM2 was optimized and considered for further *in vitro* and *in vivo* studies.

Zeta potential determination

The Zeta potential of the optimized batch (SM2) was found to be 14.7 mV shown in fig. 4. Barry

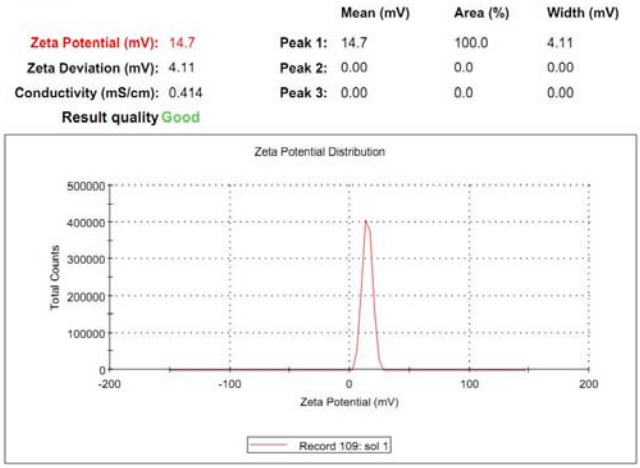

Fig. 4: Zeta potential of optimized SMEDDS formulation

and Eggenton has shown that the intestinal cell interior negatively charged relative to mucosal fluid [18]. The positively charged oil droplets formed by SMEDDS could produce strong interaction with the mucosal surface, improve the adhesion of the positively charged droplets to the intestinal mucosa, and increase drug uptake from the mucosa, further improving the oral bioavailability [13].

***In vitro* dissolution study**

The *in vitro* dissolution profile of optimized SMEDDS formulation (SM 2) and Brainstar® tablet (marketed formulation) was studied in 0.1N hydrochloric acid. It was observed that optimized SMEDDS formulation SM2 and Brainstar® release more than 85% of Bromocriptine Mesyalte within 15 min. Optimized SMEDDS formulation and Brainstar® tablet showed similar dissolution profile in 0.1 N Hydrochloric acid. The comparative dissolution profile of optimized SMEDDS formulation and Brainstar® tablet have been summarized in fig.5. The dissolution profile of optimized batch was compared with marketed formulation of BM tablet (BrainStar®) and no significant difference between both release profiles was found (P<0.05).

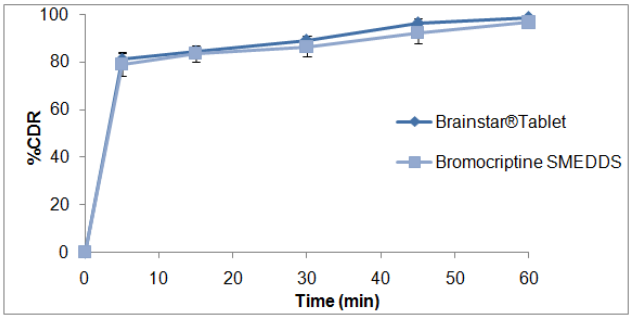

Fig. 5: Comparative dissolution profile of optimized SMEDDS formulation and Brainstar® tablet (Marketed formulation) Mean of 3 measurements±SD (n = 3)

***In vivo* study**

In present study, STZ treated diabetic control animals showed significant increase in blood glucose level from zero to four weeks (study period) during the experiment while a significant reduction was observed in blood glucose level during study period in optimized BM SMEDDS treated diabetic animals as compared to marketed formulation of BM treated diabetic animals mentioned fig. 6.

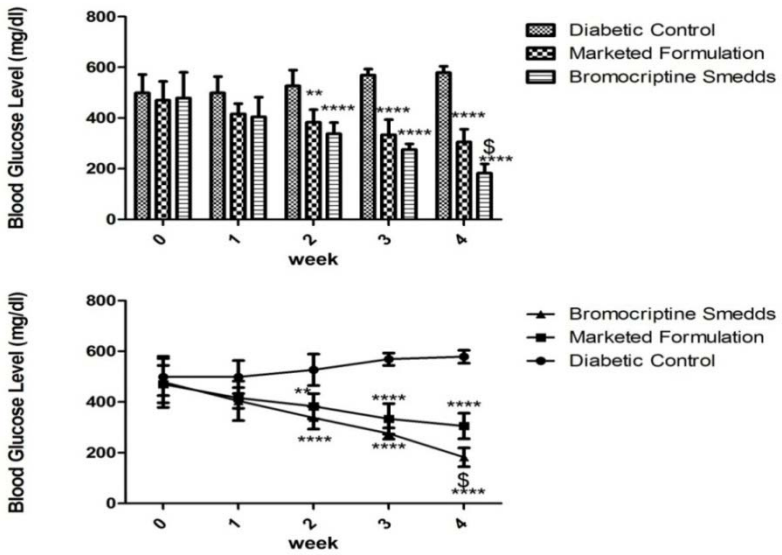

Fig. 6: Result of blood glucose level of rats treated with Bromocriptine SMEDDS and marketed formulation. Values are statistically significant at ** p<0.01 and **** p<0.0001 as compared with diabetic control: $ p<0.05 as compared with the group treated marketed formulation. Mean of 3 measurements±SD (n = 3)

The amount of BM released from SMEDDS formulation, SM2 was 96.50±1.07 % in 60 min comparatively lower than the marketed formulation-Brainstar® (98.36±1.08) shown in fig. 5. But in, *in vivo* study, SMEDDS formulation, SM2 showed a better result than marketed formulation-Brainstar®. This might be because of small globule size and the higher surface area in case of SMEDDS, which permitted faster rate of drug release. The reason behind this might be the use of surfactant-Tween 80 and Cosurfactant–PEG 400 which are good solubilizers, and they enhanced the permeability of the pure drug in, *in vivo.*

CONCLUSION

SMEDDS of BM was prepared and optimized by using *in vitro* parameters like particle size and poly dispersity index. Optimized SMEDDS contains Akoline MCM as the oil phase, Tween 80 as a surfactant and PEG 400 as co-surfactant. This optimized SMEDDS showed similar *in vitro* release as compared with the marketed formulation. *In vivo* pharmacodynamic evaluation of optimized batch showed a significant increase in hypoglycemic activity as compared to the oral marketed formulation. The present study indicates that

the use of oral SMEDDS delivery of BM may be an option to improve its bioavailability. However, pharmacokinetic studies and clinical studies are required to perform to establish therapeutic potential of this system.

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CONFLICTS OF INTERESTS

There are no conflicts of interest.

REFERENCES

1. SB Bhupinder Singh, Rishi Kapil, Ramandeep Singh, OP Katare. Self-emulsifying drug delivery systems (SEDDS): formulation development, characterization, and applications. Crit Rev Ther Drug Carrier Syst 2009;26:427–521.
2. CM O'Driscolland BT Griffin. Biopharmaceutical challenges associated with drugs with the low aqueous solubility-The potential impact of lipid–based formulations. Adv Drug Delivery Rev 2008;60:617–24.
3. S Yang, RN Gursoy, G Lambert, S Benita. Enhanced oral absorption of paclitaxel in a novel self-micro emulsifying drug delivery system with or without concomitant use of p-glycoprotein inhibitors. Pharm Res 2004;21:261–70.
4. PP Constantinides, KM Wasan. Lipid formulation strategies for enhancing intestinal transport and absorption of P-glycoprotein (P-gp) substrate drugs: *In vitro*/*In vivo* case studies. J Pharm Sci 2007;96:235–48.
5. P Zhang, X Zhang, J Brown, D Vistisen, R Sicree, J Shaw, *et al*. Global healthcare expenditure on diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:293–301.
6. SOH Pijl, M Matsuda, Y Miyazaki, A Mahankali, V Kumar, R Pipek, *et al*. Bromocriptine: a novel approach to the treatment of type-II diabetes. Diabetes Care 2000;23:1154–61.
7. European Pharmacopoeia: European Directorate for the Quality of medicines and healthcare; 2011. p. 1509.
8. MK Juergendrewe, P Guitard, Andre pellet, Britton Johnston, Christophbeglinger. The relevance of pH dependency on *in vitro* release of bromocriptine from a modified–release formulation. J Pharm Sci 1991;80:160–3.
9. CW Poulton and, CJH Porter. Formulation of lipid-based delivery systems for oral administration: Materials, methods, and strategies. Adv Drug Delivery Rev 2008;60:625–37.
10. M Joshi, S Pathak, S Sharma, V Patravale. Solid microemulsion preconcentrate (NanOsorb) of artemether for effective treatment of malaria. Int J Pharm 2008;362:172–8.
11. CJH Porterand, WN Charman. Intestinal lymphatic drug transport: an update. Adv Drug Delivery Rev 2001;50:61–80.
12. SJR Adhvait R Dixit, Samir G Patel. Preparation and bioavailability assessment of SMEDDS containing valsartan. AAPS Pharm SciTech 2010;11:314–21.
13. T Gershanik, Haltner E, Benita S. Charge-dependent interaction of self-emulsifying oil formulations with CACO–2 cell monolayers: binding, effects on barrier function and cytotoxicity. Int J Pharm 2000;211:29–36.
14. Goyal BR, Solanki N, Goyal RK, Mehta AA. The investigation into the cardiac effects of spironolactone in the experimental model of type 1 diabetes. J Cardiovasc Pharmacol 2009;54:502-9.
15. Subhrojit Sen, Moumita Roy, Abhay Sankar Chakraborti. Ameliorative effects of glycyrrhizin on streptozotocin-induced diabetes in rats. J Pharm Pharmacol 2011;63:287–96.
16. Nahla S Barakat, Alanood S Almurshedi. Design and development of gliclazide-loaded chitosan microparticles for oral sustained drug delivery: *in–vitro/in–vivo* evaluation. J Pharm Pharmacol 2011;63:169–78.
17. BS Gursoy RN. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother 2004;58:173–82.
18. RJ Barry, Eggenton J. Membrane potentials of epithelial cells in small rat Intestine. J Physiol 1972;227:201-16.