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Formulation and Characterization of Bromocriptine Mesylate as Liquid Self-Nano Emulsifying Drug Delivery System

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Abstract

Bromocriptine mesylate is a semisynthetic ergot alkaloid derivative with a potent dopaminergic activity, used in the treatment of pituitary tumors, Parkinson's disease (PD), hyperprolactinemia, neuroleptic malignant syndrome, and type 2 diabetes, the oral bioavailability is approximately 6%.Therefore, the aim is the preparation and evaluation of bromocriptine mesylate as a liquid self-nano emulsifying drug delivery system to enhance its solubility, dissolution and thermodynamic stability of the formulation. Solubility study was made in different vehicles to select the best one for dissolving bromocriptine mesylate. Pseudo-ternary phase diagrams were constructed at 1:1, 2:1, 3:1 and 4:1ratios of surfactant and co-surfactant. Four formulations were prepared, using various concentrations of castor oil, tween 80 and ethanol. All the prepared formulations were evaluated for particle size distribution, polydispersity index, drug content, thermodynamic stability, dispersibility and emulsification time, robustness to dilution and *in vitro* drug dissolution. It was found that, the rate and extent of release for all prepared formulations were significantly higher ($p \leq 0.05$) than that in crude drug powder. From the study, it was concluded that self-Nano emulsifying drug delivery system is a promising approach to improve solubility, dissolution and stability of the formulation.

Keywords: Bromocriptine Mesylate, Pseudo-ternary phase diagram, Dissolution rate, SNEDDS.

إعداد وتقييم دواء بروموكربتين ميسيلات كمستحلب سائل نانوي دقيق تلقائي التكوين

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الخلاصة

بروموكربتين ميسيليت هومشتق شبه قلوي ارجوت شبه اصطناعي مع نشاط دوبامينامي قوي، يستخدم في علاج أورام الغدة النخامية , مرض باركنسون ، فرط نشاط هرمون الحليب في ا لدم،المتلازمة الخبيثة للذهان، وداءالسكري من النوع ٢ , التوافر البيولوجي الفموي هوما يقارب ٦ ٪ . وبالتالي نهدف الى إعداد وتقييم بروموكريبتين ميسيليت بشكل نظام سائل الاستحلاب نانوي ذاتي التكوين لتعزيز الذوبان ،الحل والاستقرار. أجريت دراسة قابلية الذوبان في مركبات مختلفة لتحديد أفضل السواغات لحل بروموكريبتين . تم بناء المخططات الطورية الزائفة في ١: ١ ، ٢: ١ ، ٣: ١ و ٤: ١ من نسبة الفاعل بالسطح و المادة الخافضة للتوتر السطحي. تم تحضيرأربع تركيبات باستخدام تراكيزمختلفة من زيت الخروع , توين ٨٠ وايثانول . تم تقييم جميع التركيبات المعدة بمؤشر التشتت وحجم الجسيمات , الثبات الديناميكي الحراري , السهولة في التخفيف وتفكيك الدواء في المختبر , محتوى الدواء , القابلية المعدة لتوزيع حجم الجسيمات ووقت الاستحلاب . وجد أن معدل الإطلاق ومدى كل التركيبات المحضرة كانت أعلى بشكل ملحوظ من مسحوق الدواء العادي. نستخلص من الدراسة ان نظام الاستحلاب النانو الذاتي هو نهج واعد لتحسين الذوبان , حل و استقرار بروموكربتين ميسيليت.

الكلمات المفتاحية : بروموكريبتين ميسيليت، مخطط المرحلة الزائفة الثلاثية ، معدل الحل،SNEDDS .

Introduction

Self - nano emulsifying drug delivery system (SNEDDS) is isotropic uniform pre-concentrate mixtures of oil , surfactant , co-surfactant and drug that rapidly form fine oil-in-water (o/w) nanoemulsions when introduced into the aqueous medium under mild agitation [(1)].

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Recently, attention has been drawn toward self-nano emulsifying drug delivery systems (SNEDDS) and Solid nanosuspensions (NS) for improving the oral bioavailability of Biopharmaceutics Classification System (BCS) class II drugs through enhancing their solubility. SNEDDS can form nanoemulsion with 20-200 nm size range upon dilution with no need to perform a dissolution step. SNEDDS spread instantly in the gastrointestinal tract (GIT) fluids and its motility provide the necessary dispersion of the nanoemulsion[2,3].
After administering orally, lingual and pancreatic lipases act on the oily phase of the SNEDDS that result in the formation of emulsified mono-glycerides, diglycerides and fatty acids, resulting in the formation of intestinal mixed micelles in the presence of bile acids.When these mixed micelles pass through the enterocytes, chylomicrons are formed. These can drain the drug into the lymphatic vessels and not in the blood vessels. Thus, bypassing the first pass effect, the oral bioavailability will be increased [4].

SNEDDS improve the oral bioavailability of the poorly water-soluble drug by enhancing the solubility and keeping the drug in a dissolved state, in small globules of oil, during its transit through the gastrointestinal tract [5].

Bromocriptine mesylate is a semisynthetic ergot alkaloid derivative with a potent dopaminergic activity. It is a dopamine agonist that used in the treatment of pituitary tumors, Parkinson's disease (PD), hyperprolactinemia, neuroleptic malignant syndrome, and type 2 diabetes[6]. It is practically insoluble in water, freely soluble in methanol, soluble in ethanol (96 %), sparingly soluble in methylene chloride, belonging to class II according to biopharmaceutical classification system (BCS)[7].

Bromocriptine mesylate is rapidly absorbed after oral administration. The absorption from the gastrointestinal tract is only about 28% to 37%. In addition to that, the drug undergoes first-pass metabolism in the liver, such that the oral bioavailability is only approximately 6% [8].

Thus, this research aimed to formulate and evaluate bromocriptinemesylate as liquid self-nano emulsifying drug delivery system to enhance its solubility, wettability, dissolution and stability of dosage form for better delivery of BM through the oral cavity.

Materials and Methods

Materials

Bromocriptine mesylate was purchased from Aopharm (China). Castor oil was brought from Now food (USA). Tween 80 was purchased from Pure chemistry (Germany). Ethanol, methanol were purchased from Sigma-Aldrich (Germany). Hydrochloric Acid was purchased from Avantor performance materialsInd. Netherlands. Allother chemicals used were of analytical grade.

Methods

Differential scanning calorimetry (DSC)

The DSC technique was used to provide qualitative information about the physicochemical status of the drug in the solid SNEDDS formula and compatibility problems. This test was done to assess the Thermotropic properties and thermal behavior of the drug (BM). Procedures include taking about ten mg of sample, sealing it in an aluminum pan in DSC instrument, and heated at the rate of 10°C/min, covering a temperature range of 40 to 300°C[9].

Solubility Studies

The saturation solubility test was made to detect the best vehicle for dissolving BM.The solubility of BM in (various oil phases, surfactants, co-surfactant/co-solvents mixtures, 0.1N HCl solution) was determined by dissolving an excess amount of drug in 2 ml of each of selected vehicle contained in stoppered vials (10 ml capacity) separately.The resultant liquids were mixed using a vortex and then sonicated for 10 min , then were shaken using a water bath shaker at 25±1°C for 48h to reach equilibrium. The equilibrated samples were removed from the shaker and centrifuged (3000 rpm) for 20 min. The supernatants were taken out and filtered through a membrane (0.45 µm Millipore filter) [10, 11]. The concentration of BM in various phases was determined by UV spectrophotometer at their respective λ max (309 nm in methanol ,y =0.0136x-0.0064 and 306 nm in 0.1N HCl , y = 0.013x-0.002).

Construction of pseudo-ternary phase diagrams

Based on the individual solubility studies and the hydrophilic-lipophilic balance (HLB) value, the oil, surfactant and co-surfactant were chosen for the construction of pseudo-ternary phase diagramusing aqueous titration method[12]. The surfactant and co-surfactant are mixed in different ratios (1:1, 2:1,3:1 and 4:1) ; these S mix ratios were chosen in increasing concentration of surfactant with respect to co-surfactant. Phase diagrams are constructed for each ratio; the data obtained was subjected to CHEMIX Software for construction of the ternary plot.

Preparation of bromocriptinemesylate liquid self-nanoemulsifying drug delivery systems

BM was prepared as liquid self-nano emulsifying drug delivery systems using tween 80 as surfactant and ethanol as co-surfactant in ratios (1:1, 2:1, 3:1 and 4:1) respectively and oil: S mix ratio keeping constant as 1:9 illustrated in (Table 1). BM was dissolved in castor oil in a screw-capped glass container and mixed with other components at the concentration of (2.5 mg / 0.3 ml) and heated in a water bath at (50 -60°C) to facilitate homogenization. The components were mixed by vortex mixing for 5 min to obtain a clear, uniform mixture and again cooled to room temperature followed by equilibrating the mixture on a sonication at a room temperature for 10 min, after that the formulations were kept under visual observation for at least 48h (at room temperature) and examined for any signs of turbidity or phase separation prior to droplet size distribution studies [13-15] .

Table 1.Composition of bromocriptine mesylate liquid self-nanoemulsifying drug delivery systems (% w/w)

Formulas–code	S mix ratio	Oil: Smix ratio	castor oil %	Tween80%	Ethanol %
SNEDD-1	1: 1	1: 9	10	45	45
SNEDD-2	2: 1	1: 9	10	60	30
SNEDD-3	3: 1	1: 9	10	67.5	22.5
SNEDD-4	4: 1	1: 9	10	72	18

Evaluation of the prepared bromocriptine mesylate liquid self-nanoemulsifying drug delivery systems

Thermodynamic stability studies

All the prepared formulations were subjected to different thermodynamic stability tests (Centrifugation, Heating-cooling cycle and Freeze-thaw cycle). All the prepared SNEDDS formulations were centrifuged at 3500 rpm for 30 min and observed for phase separation, creaming and cracking. Formulations which are stable, were subjected to heating-cooling cycle. Six cycles between refrigerator temperature 4 and 45º C with storage at each temperature for not less than 48 h. Formulations, that are stable at these temperatures, were subjected to Freeze-thaw cycle. Three freeze-thaw cycles between -21ºC and +25ºC with storage at each temperature for not less than 48h was carried out. Formulations, which passed these thermodynamic stress tests, were taken for further studies [16].

Droplet size measurement and polydispersity index (PDI)

Mean droplet size and polydispersity index (P.I.) were estimated for all stable SNEDDS formulations by applying 100 µL of SNEDDS which was diluted to 250 ml 0.1N HCl in a beaker and gently mixed using a glass rod at 25°C. The estimations were performed using particle size analyzer instrument (Brookhaven Corp 90 Plus, NY, USA) in which the light scattering was monitored at 25ºC and 90 angles [16, 17,18].

Robustness to dilution

All the prepared SNEDDS formulations were diluted to 50, 100, 1000 and3000 fold with distilled water, phosphate buffer (pH 6.8) and 0.1N HCl in three separated glass vials. The diluted formulations were shaken and then visually inspected after 24 hours (at room temperature) for any form of phase separation, coalescence of droplets or drug precipitation [19].

Dispersibility tests and self-nano emulsification time

The efficiency of dispersibility and self-nano emulsification time was assessed using a USP XXII dissolution apparatus II. From each SNEDDS formulation, 0.5ml was added to 500 mL of distilled water maintained at 37 ± 0.5ºC, with paddle rotating at 50- rpm for gentle agitation. The *in vitro* efficacy of the formulations was visually assessed until a transparent homogenous system was seen to determine the time (in a min.) required for completing nano emulsification using the grading system as shown in table 2 [20,21].

Table 2. Grading system of *in vitro* performance of the SNEDDS (Dispersibility and self-nano emulsification time)

Grade	Time required for Nanoemulsion formation	Appearance
A	Rapidly forming (within 1 min) Nanoemulsion,	Having a clear or bluish appearance
B	Rapidly forming (within 1 min)	Slightly less clear emulsion, having a bluish white appearance
C	Formed within 2min	Fine milky emulsion
D	Slow to emulsify (longer than 2 min).	Dull, greyish white emulsion having slightly oily appearance
E	Slow to emulsify (longer than 2 min).	Exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Drug content

SNEDDS formulation containing bromocriptine mesylate equivalent to one dose (2.5mg) was added in 100 ml volumetric flask containing methanol (100 ml) and mixed it well. The extracted solution was suitably filtered, diluted and analyzed for drug content using UV-spectrophotometer at its λ max nm in methanol [22].

***In vitro* dissolution study**

The *in vitro* drug release profile of all the prepared SNEDDS formulations were determined using USP dissolution apparatus-II (paddle method). The dissolution medium, according to the monograph of bromocriptine mesylate in USP (2009), is 0.1N HCl as the dissolution media (500 ml), at 37±0.5°C and 50 rpm, using dialysis bag technique (Molecular cut off 12000 Da)[23]. SNEDDS formulation containing bromocriptine mesylate equivalent to one dose (2.5mg) was placed in the dialysis bag and five mL of dissolution medium was withdrawn every 10 min over 60 min (10, 20, 30, 40, 50, 60) and replaced with fresh media (0.1N HCl) in each withdrawal. The quantity of dissolved drug was determined using UV-Spectrophotometer method at its λ max in 0.1N HCl (306nm)[22].

Statistical analysis

The results of the experiments were given as a mean of triplicate samples ± standard deviation and were analyzed according to the one way analysis of variance (ANOVA) to determine if the changes in the applied factors are statistically significant at level of ($P \leq 0.05$) and non-significant at level of ($p>0.05$).

Results and Discussion

Differential scanning calorimetry

The DSC technique has been performed to determine the thermal stability of drug. DSC thermogram of BM illustrated in (Figure 1).Pure BM showed a characteristic sharp endothermic peak at (204.03°C) which corresponding to its melting point ,which is near the reported one (192-196) [24].

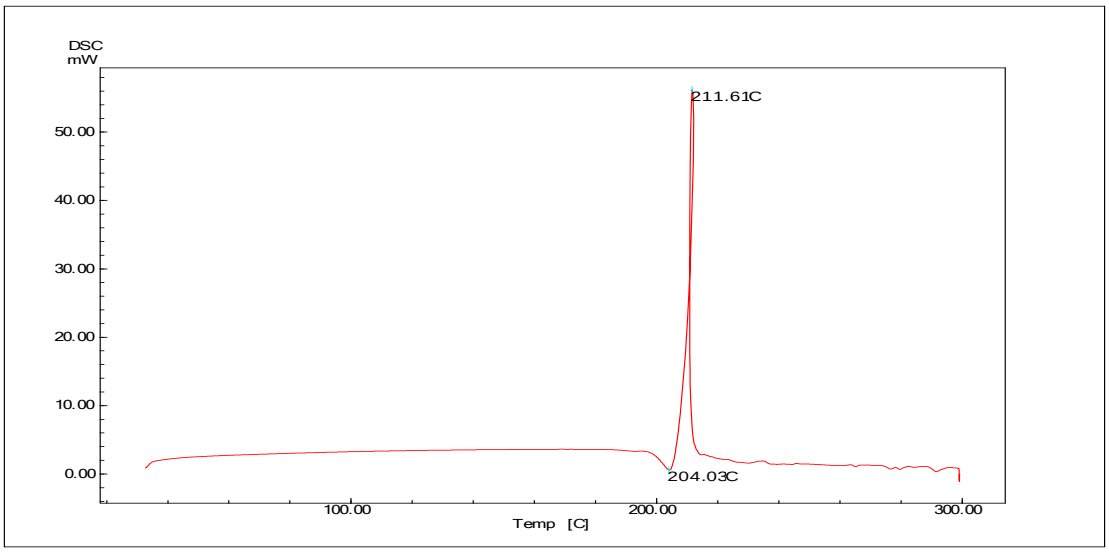

Figure 1. DSC thermogram of bromocriptinemesylate

Determination of saturation solubility of bromocriptine mesylate in different oils, surfactant, and co-surfactant

It was found that, the solubility of the drug at acidic media was significantly higher than that obtained at phosphate buffer (pH 6.8) as given by the (Table 3), this is due to the nature of the drug [6], as it will be in an ionized form in the acidic medium. While upon increasing pH, the unionized species predominated, which explains the sharp decrease in the solubility at buffer (pH 6.8) that can be predicted by the application of the Henderson-Hassel Balch equation [25].Amongst the various oils that were screened (Table 3), castor oil could solubilize the dose of BM (2.5mg) at relatively small volume and BM shows high solubility in this oil. As shown in (Table 3), tween 80 showed a high ability to dissolve BM and therefore was selected for the study.From the results of saturation solubility, castor oil is used as an oil component, tween 80 as surfactant and ethanol as co-surfactant.

Table 3. Saturation solubility of bromocriptine mesylate in different media

medium	Solubility (mg/ml) mean ±SD*
Coconut oil	3.744± 0.048
Sunflower oil	6.366 ± 0.075
Peppermint oil	5.15 ± 0.074
Castor oil	67.135 ± 0.15
Oleic acid oil	59.85 ± 0.1
Tween 80	125.098 ± 0.07
0.1 N HCl	0.19 ± 0.02
Phosphate buffer PH 6.8	0.0254±0.0004

Pseudo- ternary Phase Diagram Construction

Pseudo-ternary phase diagrams were constructed to optimize the concentration of the oil (castor oil), surfactant (tween 80) and co-surfactant (ethanol) to identify their effect on the nanoemulsion formation. In the pseudo-ternary phase plot, the shaded area represents the area of nanoemulsions while unshaded area represents the area of the emulsion. The plot with a larger shaded area indicates the presence of perfect nano emulsifying activity of formulated nanoemulsions and beneficial interaction among the S mix, oil and aqueous phase [26]. Pseudo-ternary phase diagram plot for different S mix ratio (tween 80 : ethanol 1:1, 2:1, 3:1, 4:1)are shown in figures 2 respectively. As ratio of tween increase give larger shaded area indicates the presence of perfect nano emulsifying activity of formulated nanoemulsions, usually, the addition of surfactant alone cannot lower the oil/water interfacial film sufficiently to form nanoemulsion and addition of short to medium chain length alcohol is imperative as a co-surfactant [27].

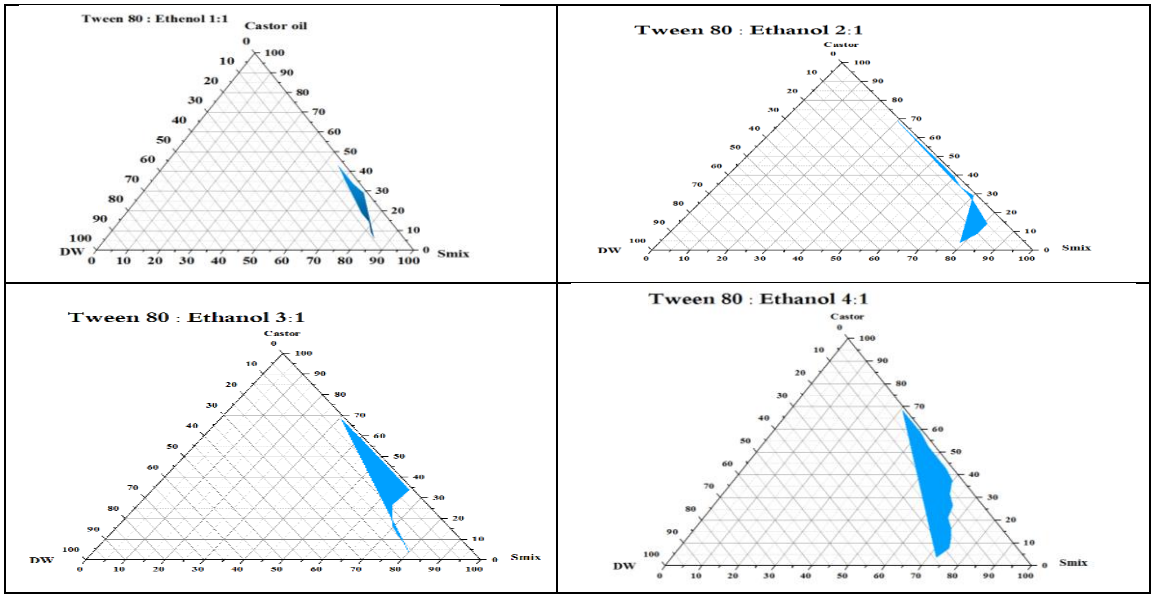

Figure 2 .Pseudo ternary phase diagrams for different S mix ratio (tween 80: ethanol 1:1, 2:1, 3:1, and 4:1)

Preparation of bromocriptinemesylate liquid self-nano emulsifying drug delivery systems

All the SNEDD formulations show yellow and clear mixtures without phase separation orvisually noticed drug precipitation, resulting in four successful formulations.

Evaluation of the prepared liquid self-nano emulsifying drug delivery system

Thermodynamic stability studies

All of SNEDDS formulations were passed the thermodynamic stability testing as there was no sign of phase separation or drug precipitation at the end of all cycles. This suggested that the formulations were persisted against the extreme storage conditions. The thermodynamic results of the prepared formulation were shown in table 4 .

Table 4. Thermodynamic stability studies of bromocriptine mesylate liquid self-nano emulsifying drug delivery systems.

Formula-code	Centrifuga-tion test	Heating-cooling cycles test	Freeze-thawing cycles test
SNEDDS-1	pass	pass	pass
SNEDDS-2	pass	pass	pass
SNEDDS-3	pass	pass	pass
SNEDDS-4	pass	pass	pass

Droplet size measurement and polydispersity index (PDI)

The droplet size of the nanoemulsion determines the absorption and bioavailability of the drug, smaller droplets diameter provide a larger surface area, leading to faster drug release into the aqueous medium [28]. It was found that the optimal droplet diameter was in the range of 100–500 nm [29], All the prepared SNEDD formulas show droplet diameter more than 100 nm and The polydispersity index below 0.3, this indicates good uniformity in the droplet size distribution after dilution with water[30,31]. Droplet size measurement and polydispersity index (PDI) results showed in table 5.

Table 5. Droplet size measurement and polydispersity index (PDI) of bromocriptine mesylate liquid self-nanoemulsifying drug delivery systems

Formula – code	Mean droplet diameter (nm)	polydispersity index (PDI)
SNEDDS-1	262.2	0.210
SNEDDS-2	329.5	0.005
SNEDDS-3	181.2	0.131
SNEDDS-4	271.6	0.005

Robustness to dilution

The dilution capability of the formulations was tested to determine the capability of the formulation to withstand possibly infinite dilutions. This was because upon ingestion, the gastrointestinal fluids are responsible for the dilution, and it is impossible to accurately identify the amount of water present to form the emulsion with the formulation, robustness to dilution was performed dilution with an excess of water, standard phosphate buffer pH 6.8 and 0.1N HCl and was stored for 24h. All SNEDDS formulas showed no precipitation or phase separation as illustrated in table 6.The ability of SNEDDS formulation to withstand aqueous dilution was found to be fascinating. The phenomenon was attributed to the high solubilizing properties of the excipients, and also the capability to form a relatively stable emulsion with small droplet sizes. This implied, that these formulations were stable at infinite water dilution [32]. There was no significant effect of pH on the SNEDDS formulations, as non-ionic surfactants are less affected by changes in pH and ionic strength compared to ionic surfactants. It confirms that the preparations were robust to high dilution and variations in pH [33].

Table 6. Robustness to dilution of various bromocriptine mesylate liquid self-nanoemulsifying drug delivery systems

Formula - code	Phase separation			Drug precipitation		
	0.1N HCl	Phosphate buffer pH 6.8	Distilled water	0.1N HCl	Phosphate buffer pH 6.8	Distilled water
SNEDDS-1	pass	pass	pass	pass	pass	pass
SNEDDS-2	pass	pass	pass	pass	pass	pass
SNEDDS-3	pass	pass	pass	pass	pass	pass
SNEDDS-4	pass	pass	pass	pass	pass	pass

Dispersibility tests and self-nano emulsification time

Emulsification studies are an essential method to evaluate the self-emulsifying properties of designed formulations. When subjected to aqueous dilution under mild agitation, SNEDDS should completely and rapidly disperse [34]. The rate of emulsification is an important index for the assessment of the efficiency of emulsification. Since the free energy required to form an emulsion is very low, the formation is thermodynamically spontaneous[35,36]. All the prepared SNEDDS formulations have formed the nanoemulsion in less than 1 min with grade A as illustrated in table 7. Noticed that as the surfactant concentration was increased as the emulsification time was decreased, because surfactants present in the SNEDDS reduce the interfacial tension between oil and aqueous phases and facilitate dispersion and formation of oil in water emulsion [34].

Table 7. Dispersibility and self-nano emulsification time of bromocriptine mesylate liquid self-nanoemulsifying drug delivery systems

Formula- code	Grade	Emulsification time(sec)	Formula- code	Grade	Emulsification time(sec)
SNEDDS-1	A	21	SNEDDS-3	A	17
SNEDDS-2	A	19	SNEDDS-4	A	14

Drug content

Drug content of the all prepared BM SNEDDS was more than 97% (from BM loaded dose 2.5mg), and there was no significant difference among the various formulations, which meet united states pharmacopeia (USP) requirements and were within an acceptable range (90%-110%)[37] indicating that, there was no precipitation of drug in any of the prepared formulations. The content percents of BM SNEDDS were illustrated in table 8.

Table 8. The drug content percent of a bromocriptine mesylate liquid self-nano emulsifying drug delivery system (mean ±SD) n=3.

Formula-code	Drug content %	Formula-code	Drug content %
SNEDDS-1	97.67 ± 0.125	SNEDDS-3	98.55 ± 0.163
SNEDDS-2	99.42 ± 0.095	SNEDDS-4	99.33 ± 0.081

***In vitro* dissolution study**

Dialysis membranes were used in this test, since they are less susceptible to blockage and the size of the pores is very small [38]. They were washed with deionized water to get rid of the preservatives and then soaked in the dissolution medium (0.1N HCl) overnight to achieve equilibration state [39]. Moreover, the size of bag chosen was about (12000 Da) to ensure a large surface area exposed to the dissolution medium and avoid acting as a barrier to release of BM from formulation [23, 40]. The *in vitro* drug release studies were made in order to ensure the fast release of the drug in the dissolution medium. The *in vitro* drug release profile of F1to F 4 and pure BM powder were evaluated in 0.1 N HCl and shown in figure 3.

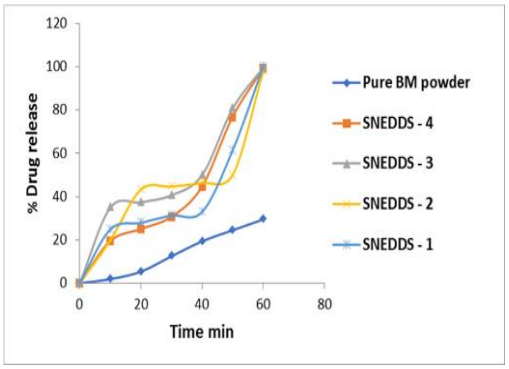

Figure 3. A comparative dissolution profile of BM SNEDDS formulas (F1, F2, F3, F4) and pure BM.

The pure drug showed (29.45%) drug release at the end of 60 min due to its poor aqueous solubility. While prepared BM SNEDDS formulations showed more than 97% of drug release at the end of 60 min. As the drug particles are converted into a dissolved state in the SNEDDS, as the release faster compared to the pure drug. The faster release rate may be attributed to fine particle size and high surfactant mixture concentration, which can easily emulsify the oil rapidly for finer globule [41]. All the prepared SNEDDS formulas have

no significant difference in the rate and extent of release profile ($p > 0.05$), they have a higher significant difference with the rate and extent of the release profile of crude BM powder ($p \leq 0.05$).

Finally, the SNEDDS formulation resulted in the spontaneous formation of a nanoemulsion with a small droplet diameter size, which permitted a faster rate of drug release into the aqueous phase, significantly much faster than pure drug powder.

Conclusions

From this study, we can conclude that SNEDDS provided a useful dosage form for the oral water-insoluble drug. SNEDDS that was prepared from castor oil, tween 80 and ethanol was a promising approach to improve the solubility, wettability, dissolution rate and stability of bromocriptine mesylate. SNEDDS of bromocriptine mesylate was successfully developed and assessed for it's *in vitro* performance. The nano size of these formulations is responsible for the enhancement of drug dissolution, due to the large surface area and, also the lipidic nature of these systems allows delivery of drugs to the lymphatic system.

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