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Development and Evaluation of a Solid Self-Nanoemulsifying Drug Delivery System for Loratadin by Extrusion-Spheronization

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ABSTRACT

Purpose: Recently the liquid nanoemulsifying drug delivery systems (SNEDDS) have shown dramatic effects on improving oral bioavailability of poorly soluble drugs. The main purpose of this study was to prepare a solid form of self-nanoemulsifying drug delivery system of loratadin by extrusion-spheronization. The liquid SNEDDS are generally prepared in a soft or hard gelatin capsules which suffers from several disadvantages. Therefore incorporation of SNEDDS into solid dosage form is desirable to get together the advantages of SNEDDS and solid multiparticualte systems.
Methods: The SNEDDS was consisted of liquid paraffin, capriole, span 20, transcutol and loratadin as a poorly soluble drug. A multilevel factorial design was used to formulation of SNEDDS pellets, liquid SNEDDS (20 and 30%) was mixed with lactose, microcrystallin cellulose (40%) and silicon dioxide (0, 5 and 10%), and Na-crosscarmelose (0, 5 and 10%). The resulting wet mass transformed into pellets by extrusion-spheronization. The pellets were dried and characterized for size (sieve analysis), shape (image analysis), mechanical strength (friability test), droplet size (laser light scattering) and drug release rate (dissolution test). Selected SNEDDS pellets were also compared with conventional loratadin pellet or tablet formulation.
Results: The resulting SNE pellets exhibited uniform size and shape. Total friability of pellets did not affected by formulation variables. The in vitro release of SNE pellets was higher than the liquid SNE and powder tablets.
Conclusion: Our studies demonstrated that extrusion-spheronization is a viable technology to produce self-emulsifying pellets in large scale which can improve in vitro dissolution with better solubility.

Introduction

In the drug discovery, a large proportion of new chemical entities and many existing drug molecules exhibit poor water solubility and hence poor oral absorption.[1] An innovation strategy which would overcome this barrier is self-emulsifying drug delivery system (SEDDS) that so results in improving the oral bioavailability of poorly water soluble and lipophilic drugs.[2] Self-emulsifying systems have shown lots of unique and reasonable properties compared to other formulation strategies such as application of cyclodextrins, nanoparticles, solid dispersions, permeation enhancers, micronization, co-solubilization, inclusion complexation, nano suspensions and lipid-based formulations.[1-6] Self-emulsifying (SE) systems are able to emulsify rapidly and spontaneously in the gastrointestinal fluids and create fine oil/water emulsions under the gentle agitation provided by gastro-intestinal motion.[7] Small droplets of oil created by SEDDS increase drug diffusion into intestinal fluids (because of large surface area). Moreover, the emulsion droplets lead to a faster and more uniform distribution of drug in the GI tract. They also minimize the mucosal irritation due to the contact between the drug and the gut wall.[7-9]

SEDDS are normally prepared as liquid dosage forms or encapsulated in soft gelatin capsules[10] which have some limitations such as: high production cost, incompatibility problems with capsule shell[6,10-13], low drug portability and stability, drug leakage and precipitation,[1] low drug loading, few choices of dosage forms and irreversible drugs/excipients precipitation. More importantly the large quantity of surfactants in the formulations can induce GI irritations.[13,14] Incorporating liquid SEDDS into pharmaceutical excipients to create solid dosage forms (SE pellets[15] or SE granules[16]) have recently developed by researchers. To some extent, this combination offers the sum of the benefits of both SEDDS and solid dosage forms. From the perspective of the dosage form, pellets have some desired advantages making them of great attraction to

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the pharmaceutical industry. The pellets have improved appearance with fine pharmaceutical elegance, they can decrease the risk of dose dumping and local mucosal irritation, avoid powder dusting in the pharmaceutical industries, also their larger surface area enables better distribution in case of immediate release products.[17] Furthermore, pellets disperse freely in the gastrointestinal tract and invariably maximize drug absorption with a subsequent reduction in peak plasma flactuations, as a result they minimize potential side effects without lowering drug bioavailability. Moreover reduction of intra-and inter patient variability of plasma profiles is achieved by reducing overall transit time.[6]
The method of choice in preparing the pellet dosage forms is extrusion-spheronization since it provides much more benefits than other methods, including large-scale producibility, spherical shape, narrow modal size distribution, good flow, ease of coating,[6] compact packaging, higher density and surface area.[17]
In this study, we intended to prepare and characterize solid self-nanoemulsifying drug delivery system for oral delivery of loratadin as the model insoluble drug. We firstly prepared a liquid SNEDDS formulation containing loratadin.Then solidified it with incorporating liquid SNEDDS into spherical pellets produced by the extrusion-spheronization technique. The developed formulations were characterized by determination of their morphology, size, friability, in-vitro drug release, disintegrating properties, and emulsion droplet size analysis. Optimum SNE pellet formulations were then selected and their in-vitro drug release was evaluated in comparison with liquid SEDDS, conventional loratadin tablets and pellets.

Materials and Methods

Chemicals

Loratadin was kindly donated by Abidi Pharmaceutical Co. (Tehran, Iran). Capriol® and transcutol® were gift from Gattefosse (France). Span® 20, liquid paraffin and hydrochloric acid were provided by Merk (Germany). Aerosil® (silicon dioxide) was purchased from Exir Pharmaceutical Company. Avicel® (MCC, microcrystalin cellulose) from FMC, Biopolymer (USA) was used as a pellet forming material. Sodium crosscarmelose was provided by Fluka, Germany and lactose was purchased from Akbarieh pharmaceutical Co (Iran).

Preparation of the liquid self-nanoemulsifying drug delivery system (SNEDDS)

Based on previous studies,[18] a self-emulsifying system was prepared containing a fixed proportion of loratadin (0.1%), 73.8% of liquid paraffin, 24.55% span 20, and 6.15% capriole as surfactant and co-surfactant, respectively. 0.5% transcutol was added as permeation enhancer. This procedure involved admixing defined amount of the components (oil, surfactant, co-surfactant and transcutol), then adding loratadin 0.1% (w/w) to the mixture. The mixture was stirred at 40 °C for a time period necessary to solve the drug until a solution was obtained. To evaluate self-emulsification properties of the liquid SNEDDS formulation, 1 ml of liquid SNEDDS was added to 0.1 N HCl (100 ml) under continuous stirring (60 rpm) at 37 °C. The formulation was characterized as transparent to milky dispersion.

Experimental design

The solid self-nanoemulsifying drug delivery system (SNE pellets) was prepared using a multi-level full factorial design. Three independent variables, including the percentage of Aerosil (three levels), the Crosscarmellose (three levels), and the amount of liquid SNEDDS (two levels) were used (Table 1). The dependent variables or responses were pellet's disintegration time, friability, MDT and sphericity. The SPSS 16 software was employed for the experimental design and regression analysis of the data to evaluate the effect of the variables on the responses.

Table 1. Independent variables (factors and levels) for factorial design.

Factors	levels		
	-1	0	+1
Aerosil%	0	5	10
Crosscarmelose%	0	5	10
SNEDDS%	20	-	30

Preparation of the SNE pellets

The composition of SNE pellets is shown in Table 2. The pellets were produced by the following processes: initially the resulted liquid SNEDDS was added into Aerosil (or mixture of Avicel and lactose for formulations that had 0% Aerosil), and mixed in a kneader until the liquid SNEDDS were completely adsorbed to form a fine mixture. Then, the adsorbed mixture was blended with other components (MCC, lactose and crosscarmelose) for 5 minutes. After that, drops of distilled water were added until a mass with suitable consistency was obtained for extrusion. The wet mass was extruded at 100 rpm in a screw extruder (Dorsa, Iran) with a die of 1mm thickness and 1mm diameter holes. The extrudates were spheronized for 2 minutes, at 1000 rpm on a spheronizer (Dorsa, Iran). The produced pellets were then dried for 15 h at 40 °C in an oven drier. The pellets were stored in sealed bags.

Size distribution of SNE pellets

25 mg of SNE pellet formulations were vibrated by a set of standard sieves (0.35, 0.5, 0.71, 1.18, 1.4, and 1.7 mm) for determination of size distribution. The subsequent tests were carried out on the modal size fraction (1180-1400 µm).

Table 2. Compositions of the SNE pellets

-	Aerosil %	crosscarmelose %	lactose%	avicel%	SNEDDS%	Water (mL) (mL)
F1	10	10	10	40	30	9
F2	10	5	15	40	30	8
F3	10	0	20	40	30	5
F4	5	10	15	40	30	7
F5	5	5	20	40	30	9
F6	5	0	25	40	30	3
F7	0	10	20	40	30	9
F8	0	5	25	40	30	7
F9	0	0	30	40	30	5
F10	10	10	20	40	20	10
F11	10	5	25	40	20	11
F12	10	0	30	40	20	8
F13	5	10	25	40	20	12
F14	5	5	30	40	20	9
F15	5	0	35	40	20	3
F16	0	10	30	40	20	9
F17	0	5	35	40	20	7
F18	0	0	40	40	20	3

Image analysis of SNE pellets

Shape analysis was performed using a stereo microscope (ZSM-1001-3E, Iran) and a digital camera connected to a personal computer with SCION image analysis software. This test was performed on 50 pellets within the 1180-1400 (µm) fraction and two shape factors were determined using projected two-dimensional images of pellets:[19]

$$Aspect\ ratio = d_{max}/\ d_{min} \qquad (1)$$

$$Sphericity\ (circularity) = 4\pi\ A/{P_m}^2 \qquad (2)$$

Where d_{max} and d_{min} are maximum and minimum ferret diameters of pellets, Ferret diameter is the distance between two tangents on opposite sides of the particle parallel to some fixed direction; so, based on direction several Ferret diameters can be determined for the particle. A is the pellet's projected area and P_m is the pellet's perimeter.

Friability test of SNE pellets

5 mg SNE pellets (d ≥1mm) were placed in the friabilator (ERWEKA, Germany) together with 5 (g) of glass spheres, and rotated for 15 minutes at 25 rpm. Then the rotated SE pellets were sieved by mesh 60 sieve and weighed in order to determine friability.[6]

$$\%\ F = \frac{Mb-Ma}{Mb} \times 100 \qquad (3)$$

Where M_b is the weight of pellets before friability test, and M_a is the weight of pellets after friability test.

Disintegration of SNE pellets

Using a disintegration apparatus (ERWEKA, Germany) 50 mg pellet samples from each formulation were tested (n=3) in 700 ml distilled water at 37 °C, and the end point was taken as the time at which no obvious particles were remained on the sieve in each disintegration baskets.[1]

Dissolution test

The dissolution tests were carried out on, liquid SNEDDS, SE pellets, conventional pellets and tablets formed by drug powder in order to compare drug release profiles. The dissolution medium was 900 ml of HCl 0.1N solution at 37± 0.5 °C. Each formulation weighed to be equivalent to 3 mg loratadin. The USP dissolution apparatus (basket method) was used for pellets and tablets and paddle method was used for liquid SNEDDS, at 50 rpm. 2 ml of dissolution medium was sampled at predetermined intervals and fresh dissolution medium was replaced in flasks to achieve sink condition.[20] The samples were assayed by a UV spectrophotometer at 276 nm to determine the dissolved drug concentration[18] (it was found that SEDDS or pellet compositions had no considerable absorbance in this wavelength), the dissolution data were then converted to mean dissolution time (MDT) by following equation:[21]

$$MDT = \frac{\sum \bar{t}_i.\Delta Mi}{\sum \Delta M_i} \qquad (4)$$

$$\bar{t}_i = \left(t_i + t_{i+1}\right)/2 \qquad (5)$$

$$\Delta M_i = \left(M_{i+1} - M_i\right) \qquad (6)$$

Where t_i is the midpoint of the time period during which the fraction ΔM_i of the drug has been released from the dosage form. A high MDT value for a drug delivery system means that it has a slow in vitro drug release.

Emulsion droplet size determination

To determine the size of the droplets formed by liquid SNEDDS and SNE pellets 1 ml of liquid SNEDDS and 1 g of selected pellet formulations were gently agitated in 50 ml distilled water with a magnetic stirrer. After 30 minutes, samples were filtered through 0.45 µm micropore filters.[1] Then the resulted size of the emulsion droplet was determined by laser diffraction (Scatteroscope Qudix I, Korea). The experiments were carried out in triplicates and reported as mean droplet size and poly dispersity index (PDI).

Statistical analysis

The effects of independent variables on the experimental response were modeled using a second order polynomial equation with a backward, stepwise linear regression technique. Only significant terms (p<0.05) were chosen for the final model. ANOVA and modeling process were performed using SPSS for Windows®, Version 16.0 (SPSS Inc., USA). The related surface plots were obtained by Statgraphics for Windows®, Version 5.1 plus (Statistical Graphics Corp., USA).

Results and Discussion

Preparation and characterization of SNE pellets

Size distribution

Acceptable loratadin SNE pellets were successfully prepared by extrusion-spheronization technique, using different factors and levels applied in this study. The calculated pelletization yield for most of the formulation was over 80% (Table 3).

Quality assessment of the produced pellets was made by evaluating their size and shape,[22] and percentages of the SE pellets in the sieve fraction are shown in Table 3. The size of modal fraction was 1 – 1.7 mm which more than 60% of pellets were in this range.

Table 3. Results of sieve analysis and experimental responses of different SE pellets.

Formulation	Sieve Analysis							Friability (%)	MDT (min)	Sphericity	Aspect ratio	Disintegration Time (min)
	Total weight(g)	0.5-0.71 (mm)	0.71-1 (mm)	1-1.18 (mm)	1.18-1.4 (mm)	1.4-1.7 (mm)	Formulation yield (%)					
1	14.5	6.6	10.3	23.9	44.6	7.4	86.1	0.2±0.3	9.7±0.30	0.53±0.11	1.24±0.13	4.66±2.08
2	21.5	1.9	5.9	21.8	34.3	35.8	97.8	0±0	23.0±2.68	0.56±0.09	1.17±0.09	38±2.64
3	21.42	0.3	3.3	10.4	21.2	55.6	90.4	0.6±0.04	24.7±5.41	0.57±0.07	1.23±0.22	158.67±5.50
4	11.07	11.2	18.3	21.4	42.5	1.5	83.7	3.8±0.05	12.0±1	0.58±0.08	1.16±0.1	0.97±0.05
5	22.47	0.1	1.2	5.1	12.2	72.5	91.1	0.2±0.09	14.9±2.07	0.59±0.10	1.13±0.09	13.33±3.21
6	15.6	4.2	8.4	17.2	31.7	38.3	95.6	0.4±0.1	15.1±1.46	0.57±0.08	1.17±0.13	34.67±5.50
7	17.54	1.8	5.4	10.1	37	46.6	99	1.2±0.04	7.4±0.2	0.63±0.08	1.18±0.11	0.51±0
8	20.5	0.1	0.9	6.1	16.3	59.9	83.2	4.6±0.8	8.6±0.11	0.63±0.12	1.21±0.09	1.5±0
9	19.7	0.1	0.3	4.1	11.9	51.2	67.5	0.6±0.54	9.8±1.17	0.63±0.07	1.19±0.07	27.33±3
10	18.53	2.7	3.9	10.1	14.1	68.2	96.3	0.4±0.62	19.0±0.85	0.63±0.09	1.15±0.1	107±45
11	19.5	1	2.6	7.1	20	27.3	57	0.6±0.09	25.8±2.56	0.58±0.11	1.17±0.14	95.33±35
12	20.4	1.7	5.4	17.6	40.2	34.3	97.6	0.1±0.78	26.6±0.37	0.59±0.06	1.20±0.14	100.67±5.03
13	10.08	1.8	4.4	12.9	52.4	10.1	79.8	0±0.54	15.1±3.71	0.64±0.07	1.21±0.10	41±17
14	22	0.6	2	6.1	15.2	73.9	97.2	0.4±0.4	22.8±3.84	0.64±0.09	1.16±0.10	95.67±2.08
15	20.04	0.5	1.5	5	13.3	76.4	96.3	0.1±0.71	18.5±2.47	0.64±0.06	1.16±0.09	108.33±10.7
16	11.25	9.9	11.3	13.7	54	7.6	86.6	1±0.67	7.1±0.33	0.65±0.09	1.14±0.07	2.5±1
17	14.6	8.2	11.5	18.8	44	12	86.3	0±0.025	7.8±0.92	0.62±0.08	1.18±0.09	4±1
18	21.54	0	0.3	2.8	9.5	66.5	79.1	0.3±0.6	10.8±2.69	0.64±0.09	1.17±0.09	13.33±6.1

Image analysis

The image analysis was based on the consideration that for a perfect spherical particle the aspect ratio shows the value of unity and values deviating from unity (greater than 1) indicate the degree of spheroid elongation. For the sphericity a value of unity considers a perfect spheroid and smaller values show the deviation from spherical form.

Details of shape analysis results are brought in Table 3. The regression analysis did not show any significant relevancy between aspect ratio and studied formulation factors; while it is indicated that the sphericity could be affected by the factors. As shown in the surface plot (Figure 1) increasing the amount of Aerosil as an absorbent and pelletization aid lead to improve pellets sphericity. Although the amount of crosscarmelose as disintegrating agent and the percent of SNEDDS had no significant effect on sphericity, in formulations containing higher levels of Aerosil, increasing the amount of crosscarmelose showed a negative impact on pellets' sphericity.

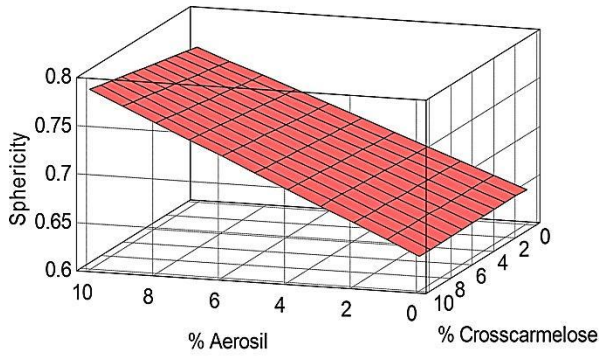

Figure 1. Effect of %Aerosil and %Crosscarmelose on pellets sphericity.

Friability test

The summary of friability test results is shown in Table 3. In this study the mechanical strength of pellets was not significantly affected by studied factors. However it is reported that increasing the amount of SEDDS of the pellets or granules would weaken the interaction within the pellets due to incomplete adsorption on pellets components and decrease their hardness.[1,22] This could be attributed to utilization of different amounts of granulating water in different formulations to achieve suitable consistency which can affects the pellets mechanical strength.

Disintegration of SNEDDS pellets

The effect of both Aerosil and crosscarmelose on disintegration time is shown as a surface plot (Figure 2). The plot demonstrates that increasing the amount of crosscarmelose lead to faster pellet disintegration. It is well known that crosscarmelose possesses wicking and swelling abilities and hence favors the water ingress inside the pellets and improve disintegration of pellets.[23] Moreover, increasing the quantity of Aerosil as a pelletization aid would be useful to improve pellets integrity and the disintegration time. As we found out in this test and according to a previous study, adding the lactose had less effect on disintegration time, but would be useful to improve appearance of the pellets.[1] However, the amount of liquid SNEDDS, had no significant effect on disintegration time.

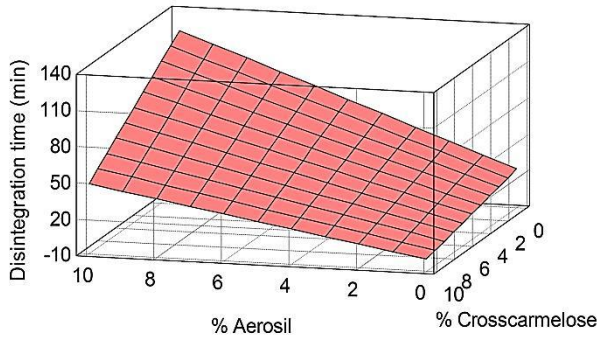

Figure 2. Effect of %Aerosil and %Crosscarmelose on pellets disintegration time.

In vitro dissolution test

In vitro dissolution profile of different pellets formulations are shown in Figure 3. The mean dissolution time (MDT) was used to compare the release profiles easily, (Table 3). The results are shown in Figure 4 as a surface plot. According to the plot increasing amount of Aerosil, increasing the (MDT), is in accordance with the disintegration time of the pellets, while increasing crosscarmelose cause to decrease MDT.

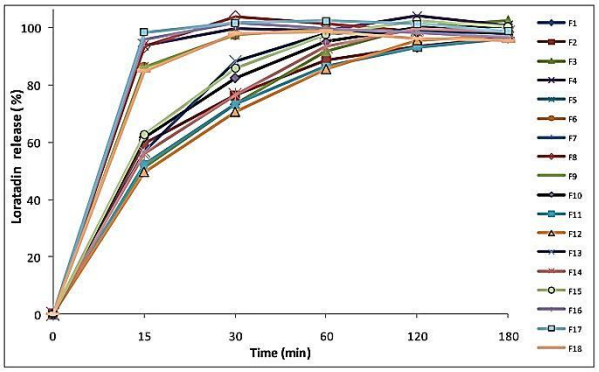

Figure 3. In vitro dissolution profile of different pellets formulation.(n=3)

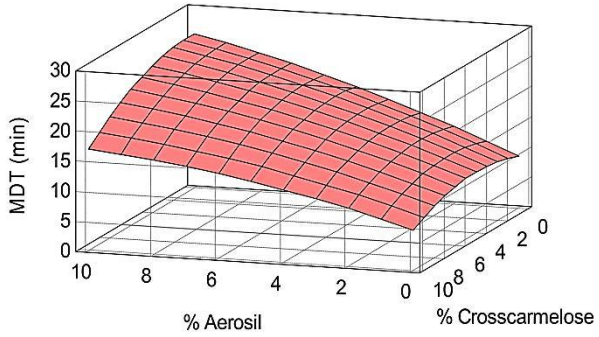

Figure 4. Effect of %Aerosil and %Crosscarmelose on pellets MDT

Formulations F_7 (30% SNEDDS) and F_{16} (20% SENDDS) which had lowest MDT and highest drug release rate, were selected as optimal formulations; moreover, their release profiles were compared with liquid SNEDDS, pellets and tablets, which were prepared in our lab based on powder drug with the same fraction of components as selected formulations (Figure 5).

As shown in Figure 5 and using MDT results, the selected SSNEDDS had a faster drug release than liquid SNEDDS and powder drug pellets ($p<0.01$). This finding could be primarily attributed to the effects of pellet components particularly crosscarmelose on enhancing water absorption into the pellets and improve interfacial surface between liquid SNEDDS and dissolution medium. Secondly the result could be related to the role of fine solid components of pellet formulations as an auxiliary emulsifying agent. It has been shown that finely divided solid particles can be used as emulsifying agents and emulsion stabilizer.[24]

As shown in Table 4, pelletization process did not affect the emulsifying efficiency of the SNEDDS. However, the F_{16} pellets resulted in smaller droplet size compare to the liquid SNEDDS ($p<0.05$). This may explained by emulsifying effect of solid components in the formulation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification and droplet size distribution.[20] The droplet size of the emulsion is a crucial factor in self-emulsification performance because it determines the extent of drug release as well as absorption.[25] Furthermore, F_{16} have a slightly faster drug release than F_7 (Table 4). This result could be related to the smaller droplet size of F_{16}.[26]

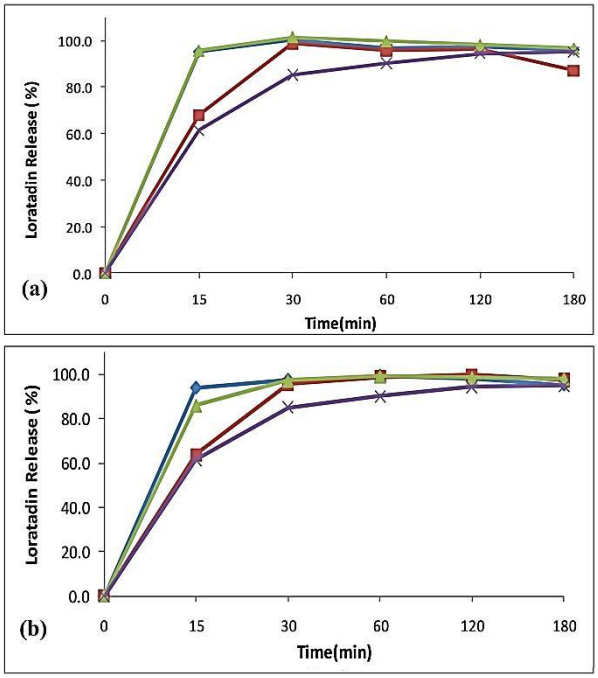

Figure 5. In vitro dissolution profile of the selected SNE pellets (▲), liquid SEDDS(×), tablets(■) and pellets formed by powder drug (♦) ; a: F_7 , b: $F_{16.}$ (n=3)

Table 4. Droplet size, PDI and MDT results of liquid SNEDDS and two selected pellet formulations.

Formulation	Mean Droplet size (nm)	PDI	MDT (min)
Liquid SNEDDS	190±42	0.39	17.6±5.9
SSNEDDS (F_7)	213.3±46	0.34	7.4±0.2
SSNEDDS (F_{16})	87.0±27	0.34	7.1±0.33

Conclusion

The overall results of this study indicated that an improved formulation of loratadin SNEDDS pellets was successfully developed using the extrusion-spheronization technique. The resulting SE pellets exhibit uniform size and spherical shape and suitable hardness. The results of in vitro dissolution revealed that the pelletization process of loratadin SNEDDS not only had no inappropriate effect on its self-emulsification properties, but also improve the drug release rate from resulted nano-emulsions.

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Conflict of Interest

The authors report no conflicts of interest.

References

1. Wang Z, Sun J, Wang Y, Liu X, Liu Y, Fu Q, et al. Solid self-emulsifying nitrendipine pellets: preparation and in vitro/in vivo evaluation. *Int J Pharm* 2010;383(1-2):1-6.
2. Iosio T, Voinovich D, Perissutti B, Serdoz F, Hasa D, Grabnar I, et al. Oral bioavailability of silymarin phytocomplex formulated as self-emulsifying pellets. *Phytomedicine* 2011;18(6):505-12.
3. Aungst BJ. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. *J Pharm Sci* 1993;82(10):979-87.
4. Wong JW, Yuen KH. Improved oral bioavailability of artemisinin through inclusion complexation with beta- and gamma-cyclodextrins. *Int J Pharm* 2001;227(1-2):177-85.
5. Patravale VB, Date AA, Kulkarni RM. Nanosuspensions: a promising drug delivery strategy. *J Pharm Pharmacol* 2004;56(7):827-40.
6. Abdalla A, Mader K. Preparation and characterization of a self-emulsifying pellet formulation. *Eur J Pharm Biopharm* 2007;66(2):220-6.
7. Iosio T, Voinovich D, Grassi M, Pinto JF, Perissutti B, Zacchigna M, et al. Bi-layered self-emulsifying pellets prepared by co-extrusion and spheronization: influence of formulation variables and preliminary study on the in vivo absorption. *Eur J Pharm Biopharm* 2008;69(2):686-97.
8. Charman SA, Charman WN, Rogge MC, Wilson TD, Dutko FJ, Pouton CW. Self-emulsifying drug delivery systems: formulation and biopharmaceutic evaluation of an investigational lipophilic compound. *Pharm Res* 1992;9(1):87-93.
9. Pouton CW. Formulation of self-emulsifying drug delivery systems. *Adv Drug Deliver Rev* 1997;25(1):47-58.
10. Yi T, Wan J, Xu H, Yang X. A new solid self-microemulsifying formulation prepared by spray-drying to improve the oral bioavailability of poorly water soluble drugs. *Eur J Pharm Biopharm* 2008;70(2):439-44.
11. Franceschinis E, Voinovich D, Grassi M, Perissutti B, Filipovic-Grcic J, Martinac A, et al. Self-emulsifying pellets prepared by wet granulation in high-shear mixer: influence of formulation variables

and preliminary study on the in vitro absorption. *Int J Pharm* 2005;291(1-2):87-97.
12. Tuleu C, Newton M, Rose J, Euler D, Saklatvala R, Clarke A, et al. Comparative bioavailability study in dogs of a self-emulsifying formulation of progesterone presented in a pellet and liquid form compared with an aqueous suspension of progesterone. *J Pharm Sci* 2004;93(6):1495-502.
13. Tang B, Cheng G, Gu JC, Xu CH. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. *Drug Discov Today* 2008;13(13-14):606-12.
14. Chen Y, Li G, Wu X, Chen Z, Hang J, Qin B, et al. Self-microemulsifying drug delivery system (SMEDDS) of vinpocetine: formulation development and in vivo assessment. *Biol Pharm Bull* 2008;31(1):118-25.
15. Hu X, Lin C, Chen D, Zhang J, Liu Z, Wu W, et al. Sirolimus solid self-microemulsifying pellets: formulation development, characterization and bioavailability evaluation. *Int J Pharm* 2012;438(1-2):123-33.
16. Beg S, Jena SS, Patra Ch N, Rizwan M, Swain S, Sruti J, et al. Development of solid self-nanoemulsifying granules (SSNEGs) of ondansetron hydrochloride with enhanced bioavailability potential. *Colloids Surf B Biointerfaces* 2013;101:414-23.
17. Setthacheewakul S, Mahattanadul S, Phadoongsombut N, Pichayakorn W, Wiwattanapatapee R. Development and evaluation of self-microemulsifying liquid and pellet formulations of curcumin, and absorption studies in rats. *Eur J Pharm Biopharm* 2010;76(3):475-85.
18. Lavanya K, Senthil V, Rathi V. Pelletization technology: a quick review. *Int J Pharm Sci Res* 2011;2(6):1337-55.
19. Zadeh BSM, Dahanzadeh S, Rahim F. Preparation and evaluation of the self-emulsifying drug delivery system containing loratadine. *Int J Adv Pharm Sci* 2010;1(3);239-48.
20. Kleinebudde P. Application of low substituted hydroxypropylcellulose (L-HPC) in the production of pellets using extrusion/spheronization. *Int J Pharm* 1993;96(1-3):119-28.
21. Balakrishnan P, Lee BJ, Oh DH, Kim JO, Hong MJ, Jee JP, et al. Enhanced oral bioavailability of dexibuprofen by a novel solid self-emulsifying drug delivery system (SEDDS). *Eur J Pharm Biopharm* 2009;72(3):539-45.
22. Costa FO, Sousa JJ, Pais AA, Formosinho SJ. Comparison of dissolution profiles of Ibuprofen pellets. *J Control Release* 2003;89(2):199-212.
23. Abdalla A, Klein S, Mader K. A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: characterization, dissolution, in vitro digestion and incorporation into solid pellets. *Eur J Pharm Sci* 2008;35(5):457-64.
24. Rowe RC, Sheskey PJ, Owen SC. *Handbook of pharmaceutical excipients*. 2nd ed. London: Pharmaceutical Press; 2006.
25. Levine S, Sanford E. Stabilisation of emulsion droplets by fine powders. *Can J Chem Eng* 1985;63(2):258-68.
26. Kohli K, Chopra S, Dhar D, Arora S, Khar RK. Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. *Drug Discov Today* 2010;15(21-22):958-65.