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Effect of self-emulsifying phase composition on the characteristics of venlafaxine loaded alginate beads

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ABSTRACT

In this work, different formulations of alginate beads containing venlafaxine were prepared by ionotropic gelation. The drug was solubilized in a self-emulsifying phase composed of different percentages of Labrasol or Labrafil and tocopherol polyethylene glycol 1000 succinate (TPGS).

Beads were characterized and the relationship between the different qualitative and quantitative composition of the self-emulsifying phase and bead properties were studied.

The morphological analysis carried out on Labrasol and Labrafil dried beads evidenced that their mean diameter depended on the quantitative composition of the self-emulsifying phase: systems containing high percentages of liquid excipient (Labrasol or Labrafil) were high in size. Swelling study evidenced that high percentages of Labrasol or Labrafil in the formulation favored the penetration of large quantities of fluid in the systems and were responsible for a rapid and notable swelling. Bead swelling ability, rate of bead erosion and drug release after contact with a fluid were affected by the hydrophilic/lipophilic nature of the liquid excipient in the self-emulsifying phase. Labrafil systems were characterized by a higher fluid resistance than Labrasol ones being Labrafil more lipophilic than Labrasol. Labrafil beads showed low aqueous fluid affinity and were able to prolong the drug release.

1. Introduction

In the last years, self emulsifying drug delivery systems (SEDDS) have been considered a valid solution to overcome oral bioavailability problems of slightly soluble drugs. When SEDDS are put in contact with an aqueous fluid, they give rise spontaneously to a fine oil-in-water emulsion having a droplet size of the dispersed phase in the nanometric range [1]. The combination of the aqueous nature of the gastrointestinal fluid and the gastrointestinal tract motility provides the right condition necessary for autoemulsification [2,3]. Generally, SEDDS are liquid systems that present some disadvantages (low stability, high cost of production, microbiological issues, etc.) that solid SEDDS can overcome. Taking advantage of different techniques (for example spray drying, extrusion and spheronisation, etc.), solid SEDDS are obtained by the solidification of SEDDS into powder useful to prepare solid dosage forms [4,5].

Labrasol and Labrafil are macrogolglycerides able to form microemulsions in gastrointestinal fluids. Labrasol is a mixture of PEG-8 caprylocaproyl macrogolglycerides often used in oral formulations to increase oral bioavailability of many poor water soluble drugs [6–8]. Labrafil consists of mono-, di- and triglycerides and PEG-6 (molecular weight 300) mono- and diesters of oleic (C18:1) acid; it acts as solubilizer for poorly soluble active molecules and as bioavailability enhancer. Compared to Labrasol, it has a higher proportion of glycerides and a lower concentration of free PEG and is less soluble in water. Labrafil is included in several systems according to its ability to self-emulsify in aqueous fluid into emulsion [9,10].

Alginate is a water soluble natural polymer extracted from brown algae; alternating blocks of 1–4 α-L-guluronic and β-D-mannuronic acid residues compose its chains [11]. Alginate forms hydrogels with divalent cations like Ca^{2+}, Ba^{2+}, Sr^{2+}, Zn^{2+} [12–15] and this characteristic is often used to prepare drug loaded beads [16–19].

In a previous work, we studied the technological and biopharmaceutical properties of alginate beads containing a slightly soluble drug dissolved in a self-emulsifying phase able to improve the drug dissolution properties. The self-emulsifying phase proposed was a mixture of three components (ibuprofen; Labrasol as self-emulsifying excipient and D-α-tocopherol polyethylene glycol 1000 succinate, TPGS, as co-emulsifying excipient) and its composition was defined by a trial and error approach [20].

Venlafaxine is one of the most widely used antidepressants of the class of phenethylamines. It is administered orally as hydrochloric acid

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salt, and is worldwide marketed as immediate and controlled release formulations, tablets and capsules. However, venlafaxine hydrochloride is aggressive towards handling equipment and irritating to the skin of personnel who works with the pure drug. On the other hand, venlafaxine free-base exhibits lower water solubility and slower dissolution in water but is easier to handle than its hydrochloride form [21]. In order to improve practical management of pure drug without having significant negative biopharmaceutical impact, the use of venlafaxine base in a self-emulsifying system could represent a good choice.

In the present study, different formulations of alginate beads containing venlafaxine base solubilized in a self-emulsifying phase (drug, Labrasol or Labrafil and TPGS) were prepared and the impact of the quantitative and qualitative composition of the self-emulsifying phase on the morphological, technological and biopharmaceutical characteristics of the beads was evaluated.

2. Experimental methods

2.1. Materials

Venlafaxine was provided as a gift sample from Chemessentia (Novara, Italy). Labrasol (caprylocaproyl macrogol-8 glycerides) and Labrafil M1944CS (oleoyl macrogol-6 glycerides) were kindly donated by Gattefossè (Milan, Italy); TPGS (D-α-tocopherol polyethylene glycol 1000 succinate) was received as free sample by Isochem (Gennevillers, France). Sodium alginate (molecular weight 120,000–190,000 g/mol; ratio of mannuronic-guluronic 1.56) was bought by Sigma Aldrich (Milan, Italy). All other materials were of analytical grade and used as received.

2.2. Methods

2.2.1. Preparation of alginate beads

All the formulations were prepared by ionotropic gelation using $CaCl_2$ as cross-linking agent [22] and following the same experimental procedure.

Self-emulsifying phase was a mixture of three components: an emulsifying excipient (LAB -Labrasol or Labrafil), a co-emulsifying excipient (TPGS) and venlafaxine (VEN). Three venlafaxine loading percentages were selected considering the drug solubility in the self-emulsifying excipient (40% w/w), the minimum drug percentage compatible with its therapeutic use (10% w/w) and an intermediate value (25% w/w). For TPGS also, three concentration levels were identified (1.0%, 5.5% and 10.0% w/w). Corresponding Labrasol or Labrafil percentages were calculated taking into account that the sum of the three components was 100%.

The composition of the different self-emulsifying phases is reported in Table 1.

Sodium alginate was dissolved, under stirring, in deionized water to obtain a 1.5% w/w solution. In order to prepare self-emulsifying phase, exactly weighed amounts of Labrasol or Labrafil and TPGS were heated at 50 °C to melt TPGS and when a limpid solution was obtained, the drug wad added under stirring until complete dissolution.

Polymeric solution and self-emulsifying phase were then mixed in a 4:1 wt ratio until a homogenous and stable white emulsion was obtained. The emulsion was dropped in the gelling bath ($CaCl_2$ aqueous solution 100 mM) through a 18G needle (1.2 mm internal diameter) under gentle stir. The beads were let to cure in the gelling bath for 15 min under stirring in order to allow the formation of the alginate network [23]. After this time, beads were recovered by filtration, rinsed with purified water to remove the excess of calcium ions and dried overnight in an oven at 40 °C.

Table 1
Percentage composition of different self-emulsifying phases.

	VEN (%)	TPGS (%)	LAB (%)
EXP1	10.0	1.0	89.0
EXP2	10.0	5.5	84.5
EXP3	10.0	10.0	80.0
EXP4	25.0	1.0	74.0
EXP5	25.0	5.5	69.5
EXP6	25.0	10.0	65.0
EXP7	40.0	1.0	59.0
EXP8	40.0	5.5	54.5
EXP9	40.0	10.0	50.0

2.2.2. Drug content determination

To assess drug content, for each formulation 7 mg of dried beads were solubilized in 100 mL phosphate buffer pH 6.8; the obtained solution was filtered (Durapore membrane filters, GVPP, 0.22 μm, Millipore) and analysed spectrophotometrically at 225 nm (PerkinElmer, Lambda 35). The results were the average of three determinations.

2.2.3. Particle size and morphology study

Stereomicroscope (Stereomicroscope Motic SMZ168) equipped with a digital camera was used to evaluate the morphological characteristics and the shape of beads just prepared and after the drying process. Bead size was determined by image analysis (Image J software, National Institute of Health, Bethesda, MD, USA) [24]. For each formulation, a minimum of 50 particles were analysed to determine their mean diameter, area and perimeter. Literature proposed different dimensionless parameters to describe numerically the shape of a particle independently of its size [25]. Among them, *Circularity* (Eq. (1)) is able to identify the degree of roundness of a solid particle from its projected area (A) and perimeter (p) [26].

$$\text{Circularity} = 4\,\pi\,A/p^2 \qquad \text{Eq. 1}$$

This parameter can range from 0 to 1 and 1 is the result obtained in the case of a very regular in shape particle, namely for a particle with a circular projection.

Superficial and internal structure of the dried beads were observed with a scanning electron microscope (SEM, Quanta 200, FEI, Eindhoven), upon covering the samples with a fine gold layer.

2.2.4. Bead swelling study

Swelling studies were performed on dried beads in HCl pH 1.0 and in phosphate buffer pH 6.8. For each formulation, 5 mg beads exactly weighed were placed in a vial with 5 mL of the selected fluid at 37 °C. The vial was left in a thermostatic bath at 37 °C and, after predefined time intervals (5, 15, 30, 60 and 120 min), beads were recovered and weighed again. The swelling percentage was calculated according to Equation (2):

$$Sw_t\ \% = 100\ x\ (W_t - W_0)/W_0 \qquad \text{Eq. 2}$$

where W_t is weight of the beads in the swollen state at time t and W_0 is the initial weight of the dried beads [27].

2.2.5. In vitro drug release study

Drug release studies were carried out in HCl pH 1.0 and in phosphate buffer pH 6.8 using European Pharmacopoeia basket method apparatus (Sotax AT 7 Smart). The receiving phase volume was 500 mL, the stirring rate was set at 100 rpm and the temperature was maintained at 37 °C. At predetermined time intervals (15, 30, 60, 120, 180, 240, 300 min), 5 mL volume samples were withdrawn, filtered by glass fibre filters and analysed using the UV spectrophotometer at 225 nm. The cumulative percentage of drug release in each release medium was plotted as function of time. Each formulation was analysed in triplicates.

Table 2
Drug content percentages of dried alginate beads.

	Theoretical drug content (% w/w)	Labrasol formulations	Labrafil formulations
		Experimental drug content (% w/w)	Experimental drug content (% w/w)
EXP1	9.43	14.01 ± 0.11	10.25 ± 0.05
EXP2	9.43	12.38 ± 0.31	13.54 ± 0.29
EXP3	9.43	13.02 ± 1.07	13.73 ± 0.37
EXP4	23.58	30.05 ± 0.94	21.79 ± 0.59
EXP5	23.58	34.80 ± 1.19	23.52 ± 0.21
EXP6	23.58	32.28 ± 0.78	23.41 ± 0.13
EXP7	37.74	39.53 ± 0.17	34.99 ± 0.31
EXP8	37.74	48.68 ± 0.02	37.14 ± 0.40
EXP9	37.74	48.91 ± 2.64	37.41 ± 0.79

2.2.6. Photon correlation spectroscopy study (PCS)

Photon correlation spectroscopy was selected as useful tool to highlight the ability of self-emulsifying phases to form micellar structures when dispersed in an aqueous fluid.

Dried beads (about 5 mg) were dissolved in phosphate buffer pH 6.8 (10 mL) and the resulting dispersion was analysed by PCS with a Zetasizer 3000HS (Malvern Instrument, UK) in order to evaluate the presence of micellar structures and measure their average size and distribution (polydispersity index).

3. Results and discussion

Formulations of alginate beads containing venlafaxine solubilized in a self-emulsifying phase (drug, Labrasol and TPGS or drug, Labrafil and TPGS) of different composition were prepared by ionotropic gelation. The beads had an average drug content ranging between 10.25% and 48.91% (Table 2) and standard deviation indicated a homogeneous distribution of the drug in the formulations.

All Labrasol formulations showed a drug content always exceeding the theoretical value. This can be justified considering that Labrasol is water dispersible and during the hardening time, this liquid excipient partially transferred from the beads to the $CaCl_2$ solution. As demonstrated in a previous work, the decrease of Labrasol percentage leads to the increase of the drug content in the beads [28]. This result was shown also by some Labrafil beads, although Labrafil is less hydrophilic than Labrasol ($HLB_{Labrafil} = 9$ *vs* $HLB_{Labrasol} = 14$) and has a reduced water miscibility. In details, venlafaxine experimental content was higher than the theoretical one in the case of EXP1, EXP2 and EXP3 formulations, in which the self-emulsifying phase had the highest Labrafil content (more than 80%). For these systems, Labrafil shows the same behavior of Labrasol that comes out of the beads during the curing step. Probably, the high level of this excipient in the self-emulsifying phase is the driving force that pushes it out of the polymeric network of the beads and causes the increase of the drug content.

Immediately after the preparation, beads exhibited a smooth and homogeneous surface. Labrasol systems had different colors linked to the different amounts of drug loaded: the formulation containing the lowest percentages of venlafaxine (namely EXP1, EXP2 and EXP3) were glossy and transparent, while an intense white color was evident and associable to the high levels of drug in the Labrasol systems (Fig. 1a). On the contrary, Labrafil beads were opaque white independently of their drug content (Fig. 2a).

Labrafil wet beads were characterized by a quite regular shape as confirmed by the images reported in Fig. 2a and by circularity factor values close to 1 (Table 3). On the contrary, some Labrasol wet beads (EXP1, EXP7 and EXP6) are elliptical rather than spherical.

After drying, in general, the morphological characteristics of beads changed: the surface became irregular and wrinkled, the systems lost their regular shape (circularity factors were far from 1, Table 3) and there was a decrease in their size due to water evaporation and bead structure shrinkage (Figs. 1b and 2b). Stereomicroscope images suggest that, for Labrasol systems, the formation of wrinkles on the bead surface during drying process is reduced by the increase of the liquid excipient concentration. In fact, EXP1, EXP2 and EXP3 Labrasol dried beads are transparent with a quite smooth surface. Labrafil beads showed a denser morphology compared to Labrasol systems and a wrinkly surface is particularly evident in formulations containing the lowest Labrafil concentrations (EXP7, EXP8 and EXP9).

SEM images demonstrated that beads are solid and without cracks on their surface; bead surface was not perfectly smooth but characterized by the presence of asperities, like little rods for Labrasol systems and flakes for Labrafil ones (Fig. 3a and b).

Mean diameter of Labrasol beads immediately after the preparation was between 2.3 and 2.7 mm and it was between 2.5 and 3.2 mm in the case of Labrafil formulations (Table 3). The significant differences ($p < 10^{-8}$) between the dimensions of Labrasol and Labrafil beads could be ascribed to some differences between the dripped starting emulsions (for example viscosity).

The drying process was responsible for an evident reduction of bead volume and size caused by water evaporation and decrease of the distance among polymeric chains. The average diameters of dried beads were between 1.3 mm and 2.1 mm (Table 3) and were about 30% lower than wet bead diameters. For each Labrafil formulation, the relative standard deviation was about 10% but in the case of Labrasol systems, this value exceeded 20% indicating a very wide particle size distribution.

Dried Labrasol and Labrafil systems were allowed to swell in HCl (pH 1.0) and in phosphate buffer (pH 6.8) at 37 °C to evaluate their swelling ability. The percentage of weight gain between dried and wet alginate beads was calculated to determine the swelling percentage of the systems as a function of time (Figs. 4 and 5). As expected, the swelling ability of both Labrasol and Labrafil beads was affected by the pH of the swelling fluid: in acidic fluid, the swelling percentage was more restrained than in phosphate buffer solution.

In details, during the first minutes of acidic phase, Labrasol beads swelled increasing their weight, which has been kept almost constant until the end of the test (Fig. 4a). After 5 or 15 min, these systems reached their maximum swelling level, which did not exceed 65%. The restrained swelling ability in the acidic environment is due to the protonation of carboxylic acid group of alginate, which makes insoluble the polymer and preserves the polymeric structure of the beads. In this fluid, beads did not show significant physical alterations and remained intact without evident erosion/disintegration throughout the duration of the experiment.

Fig. 4a shows clearly that at pH 1.0 the system swelling attitude improved by increasing the percentages of Labrasol in the self-emulsifying phase of the beads. Probably high amounts of liquid excipients allowed having a greater distance between the polymer chains in the structure, favoring the fluid up-take.

In general, Labrafil beads needed more time (at least 60 min) compared to Labrasol ones to swell completely in HCl. EXP1 and EXP5 Labrafil formulations showed an anomalous swelling behavior. After contact with the acidic fluid, beads slightly absorbed fluid, hydrated and swelled but these events were not associated with a weight gain but rather with its decrease. This behavior is reported also by other authors [29] and it could find explanation in a significant drug release not associated to a relevant fluid absorption.

In phosphate buffer, all beads swelled quite rapidly and reached a maximum swelling at least four times higher than that showed in the acidic fluid. In phosphate buffer, the electrostatic repulsion between the ionized carboxylic groups onto the polymer chains results in an important expansion of the chain network and in the bead swelling. As reported by Soppimath et al. [30], as a consequence of the ionization, the counter ion concentration inside the polymeric network increased and caused an osmotic pressure difference between the inside and the outside of the beads that promotes water up-take. In this fluid, the

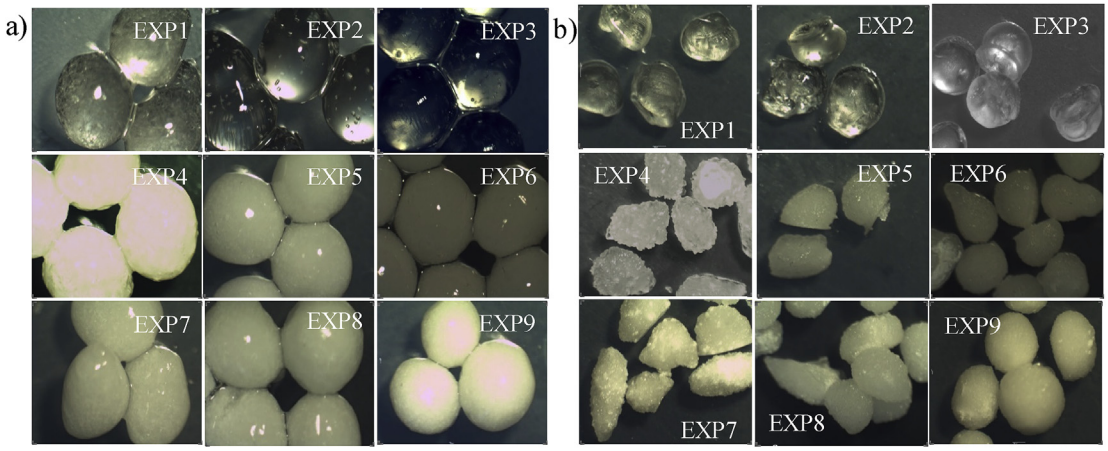

Fig. 1. A) Labrasol beads just prepared (magnification 2X); b) Labrasol beads after drying (magnification 2X).

weight of particles grows rapidly, reaches the maximum and then, in some cases, decreases abruptly because of the erosion/disintegration of the beads. This behavior finds explanation in an ion exchange reaction between Na^+ (present in the phosphate buffer) and Ca^{2+}. In the initial phase of the swelling process Ca^{2+} ions present in polymannuronate blocks are exchanged with Na^+ ions present in the buffer solution causing the chain relaxation and enhancing the fluid up-take and the increase in weight/volume of the system. In the later stage of swelling process, the Ca^{2+} ions bonded with $–COO^-$ groups of the guluronic units and forming the tight *egg-box* structure also start to exchange with Na^+ ions of the buffer medium, causing the structure erosion.

In phosphate buffer, Labrasol beads took up fluid and increased promptly their weight. In only 30 min, they reached their maximum swelling (the Sw% value was on average about 200%) and then, in almost all cases, they lost mass because of the erosion/disintegration of the beads. Only EXP3 Labrasol formulation showed complete and rapid collapse and erosion of the polymeric network before the end of the test.

On the other hand, at pH 6.8 Labrafil systems showed not only a different swelling behavior but also a different swelling degree (270% maximum swelling percentage for Labrasol beads *versus* 180% for Labrafil beads). All Labrafil systems swelled gradually during all the test-time, they reached the swelling equilibrium in about 60 min and after 120 min of contact with the fluid, they did not show erosion/disintegration signs but a completely hydrated and gelled structure. The lipophilic nature of Labrafil self-emulsifying phase limited water affinity of Labrafil beads and aqueous fluid up-take. This resulted not only in a moderate swelling performance of these systems but also in a slower erosion/dissolution tendency.

Drug release performance of beads was studied in HCl at pH 1.0 and in phosphate buffer solution at pH 6.8 and the obtained results evidenced that the release behavior is independent of pH of the release medium (Figs. 6 and 7) but was lightly influenced by the qualitative composition of the self-emulsifying phase. In both fluids, venlafaxine release profile reached a plateau in about 60 min for Labrasol systems and after about 120 min for Labrafil ones and in general drug release rate was lower for Labrafil formulations compared to the others. All formulations containing Labrasol were able to release more than 50% of the drug in less than 30 min, while this was not true for Labrafil systems, which required more time to reach the same objective. This can be justified considering the lipophilic nature of Labrafil beads, which possesses a reduced aqueous affinity and shows a slow release.

To investigate the ability of the self-emulsifying phase and of its amphiphilic component to form micelles (structures able to improve drug absorption), Labrasol and Labrafil beads were solubilized in phosphate buffer at pH 6.8 and the obtained systems were analysed by PCS.

The results demonstrated that after dissolution, Labrasol or Labrafil beads were able to generate quite small structures like micelles, with average diameters in the range 138–356 nm (Table 4). To verify if the reduced dimensions of micellar structures can be attributable only to the self-emulsifying excipient selected (Labrasol or Labrafil in combination with TPGS), PCS analysis was carried out also on the single components of self-emulsifying phase solubilized in phosphate buffer. Venlafaxine is not able to form micelles, Labrasol or Labrafil alone were responsible for the formation of large micelles and the combination of

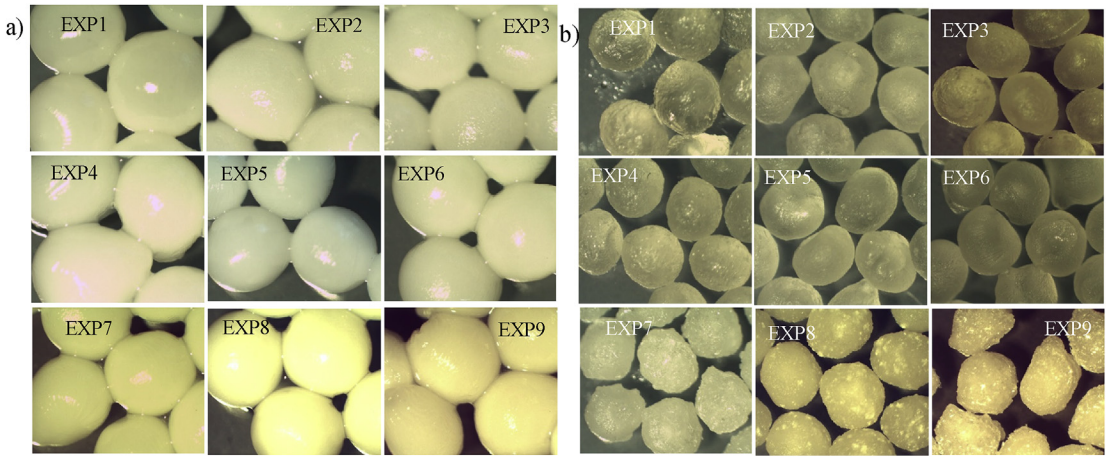

Fig. 2. A) Labrafil beads just prepared (magnification 3X); b) Labrafil beads after drying (magnification 3X).

Table 3
Average diameters and circularity factors of wet and dried beads.

	Labrasol formulations				Labrafil formulations			
	wet bead diameters (mm)	dried bead diameters (mm)	wet bead circularity	dried bead circularity	wet bead diameters (mm)	dried bead diameters (mm)	wet bead circularity	dried bead circularity
EXP1	2.480 ± 0.163	1.637 ± 0.367	0.83 ± 0.07	0.81 ± 0.06	3.227 ± 0.151	2.129 ± 0.227	0.89 ± 0.02	0.87 ± 0.04
EXP2	2.668 ± 0.137	1.697 ± 0.150	0.86 ± 0.05	0.81 ± 0.09	2.979 ± 0.150	2.016 ± 0.190	0.90 ± 0.01	0.86 ± 0.04
EXP3	2.399 ± 0.078	1.768 ± 0.331	0.90 ± 0.04	0.86 ± 0.05	2.570 ± 0.207	1.843 ± 0.202	0.89 ± 0.01	0.89 ± 0.04
EXP4	2.577 ± 0.096	1.623 ± 0.396	0.88 ± 0.03	0.80 ± 0.06	2.607 ± 0.197	1.796 ± 0.156	0.90 ± 0.01	0.87 ± 0.02
EXP5	2.636 ± 0.164	1.480 ± 0.344	0.89 ± 0.02	0.84 ± 0.06	2.732 ± 0.130	1.858 ± 0.214	0.90 ± 0.01	0.87 ± 0.04
EXP6	2.449 ± 0.102	1.380 ± 0.514	0.82 ± 0.02	0.72 ± 0.11	2.866 ± 0.184	1.882 ± 0.208	0.87 ± 0.01	0.83 ± 0.04
EXP7	2.350 ± 0.211	1.525 ± 0.448	0.82 ± 0.05	0.78 ± 0.07	2.688 ± 0.79	1.861 ± 0.154	0.93 ± 0.01	0.86 ± 0.02
EXP8	2.600 ± 0.144	1.588 ± 0.395	0.86 ± 0.08	0.80 ± 0.07	2.548 ± 0.209	1.808 ± 0.124	0.95 ± 0.02	0.89 ± 0.02
EXP9	2.378 ± 0.234	1.421 ± 0.293	0.87 ± 0.02	0.87 ± 0.06	2.532 ± 0.130	1.816 ± 0.202	0.92 ± 0.02	0.84 ± 0.04

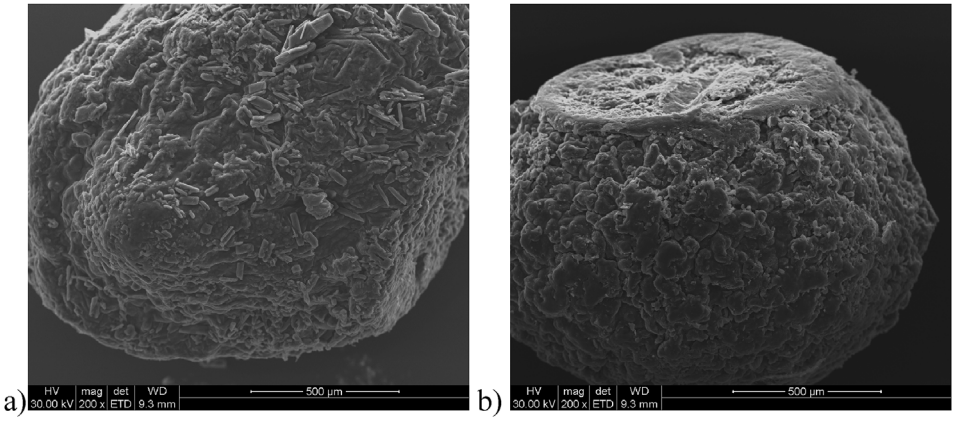

Fig. 3. SEM images of EXP9 Labrasol (a) and EXP9 Labrafil (b) dried beads.

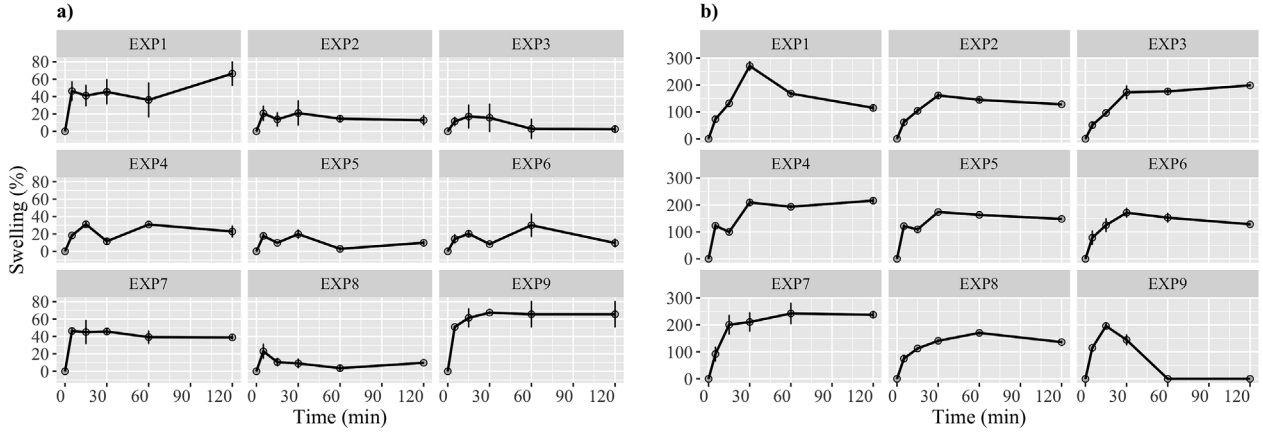

Fig. 4. Swelling percentage of Labrasol beads in hydrochloric acid at pH 1.0 (a) and in phosphate buffer at pH 6.8 (b).

Labrasol or Labrafil and TPGS were responsible for the formation of small structures.

In general, micelles derived from Labrafil systems were characterized by higher dimensions compared to Labrasol micelles. The longest lipophilic chain (oleoyl *versus* caprylcaproyl chains) and the presence of a double bond in Labrafil were probably responsible for the reduced packing ability of molecules, which drives to the formation of dynamic structures with a major particle size.

The polydispersity index was mostly far from zero indicating a broad particle size distribution. This parameter maintained reproducible values (about 0.5) in the case of Labrafil systems, demonstrating that the ability of Labrafil and TPGS to form micelles was not affected by their percentages in the formulation.

4. Conclusions

The presence of a self-emulsifying phase into the composition of a drug delivery system loaded with a slightly soluble or not well-absorbed drug could be a useful tool to improve drug bioavailability. The qualiquantitative composition of self-emulsifying phase affects some technological properties and performances of the final product.

Both the liquid excipients selected for this work (Labrasol or Labrafil) are able to carry out the role of venlafaxine solubilizing agent and self-emulsifying agent, but Labrafil could be considered the first choice. The major advantages of Labrafil systems are the good correspondence between theoretical and experimental drug content, which allows knowing the real system composition reducing drug waste, and the higher mechanical resistance of the systems, which contrasts bead

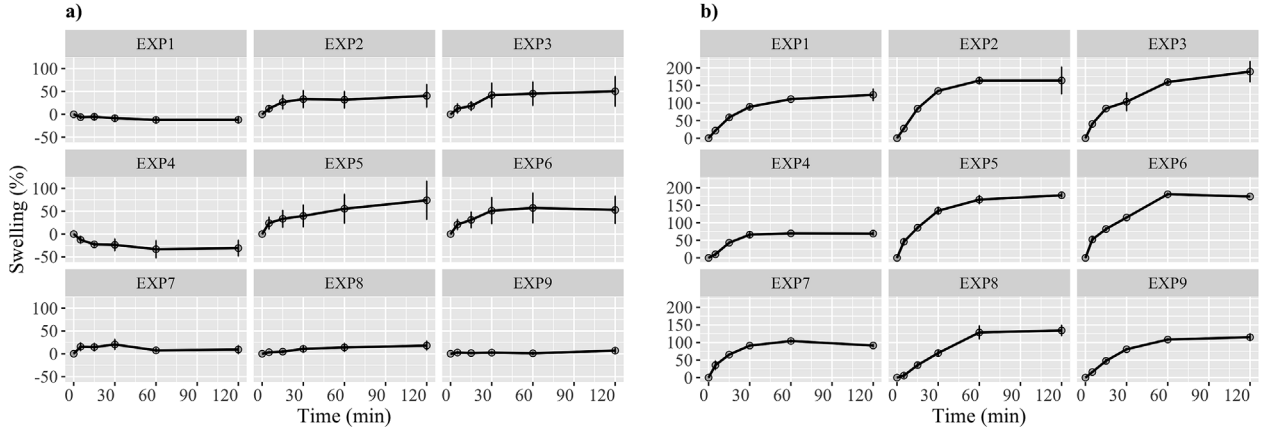

Fig. 5. Swelling percentages of Labrafil beads in hydrochloric acid at pH 1.0 (a) and in phosphate buffer at pH 6.8 (b).

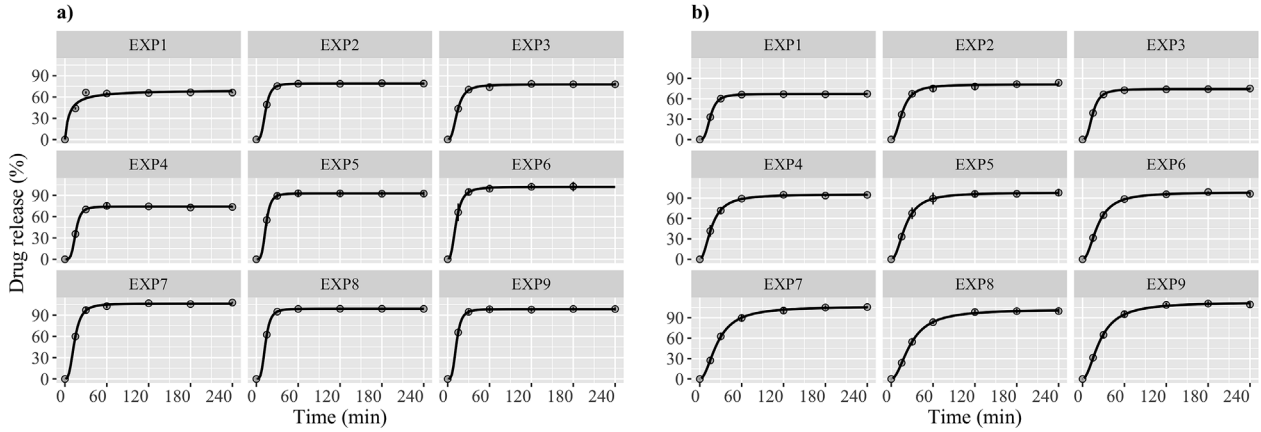

Fig. 6. *In vitro* venlafaxine release profiles of Labrasol beads in hydrochloric acid at pH 1.0 (a) and in phosphate buffer at pH 6.8 (b).

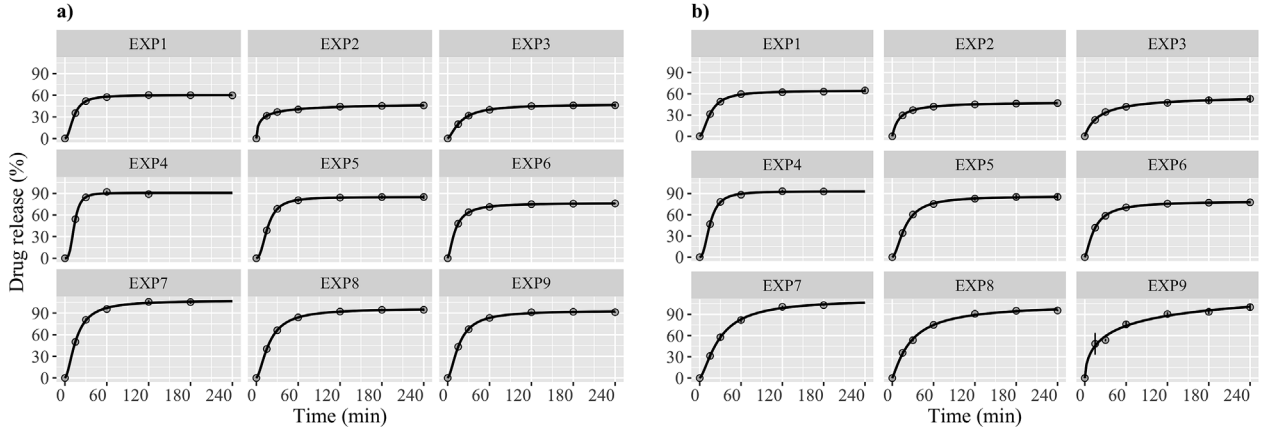

Fig. 7. *In vitro* venlafaxine release profiles of Labrafil beads in hydrochloric acid at pH 1.0 (a) and in phosphate buffer at pH 6.8 (b).

erosion and delays drug release.

Data availability

The raw/processed data required to reproduce these findings cannot be shared at this time as the data are also part of an ongoing study.

CRediT authorship contribution statement

Lorena Segale: Conceptualization, Methodology, Supervision, Writing - original draft. **Lorella Giovannelli:** Investigation, Writing - review & editing. **Andrea Foglio Bonda:** Investigation, Writing - review & editing. **Franco Pattarino:** Formal analysis, Writing - review & editing. **Maurizio Rinaldi:** Formal analysis, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 4
Mean diameter and polydispersity index of micelles obtained solubilizing Labrasol and Labrafil formulations.

	Labrasol formulations		Labrafil formulations	
	mean diameter of micelles (nm) ± sd	polydispersity index ± sd	mean diameter of micelles (nm) ± sd	polydispersity index ± sd
EXP1	230.7 ± 7.6	0.16 ± 0.04	249.6 ± 2.6	0.40 ± 0.02
EXP2	187.9 ± 1.2	0.33 ± 0.03	265.2 ± 7.9	0.45 ± 0.06
EXP3	355.9 ± 187.4	0.73 ± 0.23	274.5 ± 2.2	0.45 ± 0.05
EXP4	242.0 ± 3.7	0.41 ± 0.03	323.3 ± 3.4	0.48 ± 0.15
EXP5	170.4 ± 2.1	0.47 ± 0.01	232.8 ± 3.0	0.48 ± 0.03
EXP6	281.6 ± 4.9	0.54 ± 0.02	310.2 ± 1.5	0.54 ± 0.03
EXP7	240.5 ± 3.6	0.40 ± 0.01	138.1 ± 5.7	0.50 ± 0.08
EXP8	312.3 ± 11.6	0.61 ± 0.10	303.2 ± 3.8	0.48 ± 0.05
EXP9	151.9 ± 10.9	0.56 ± 0.01	302.8 ± 2.0	0.50 ± 0.02

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2019.101483.

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