Journal of Drug Delivery Science and Technology 111 (2025) 107127

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Solid lipid discs from water-in-oil emulsion as controlled release delivery systems of highly soluble drugs

A. Candiani [a], A. Milanesi [b], G. Diana [a], F. Loda [a], E. Bari [a], M.L. Torre [a], A. Foglio Bonda [b], L. Segale [a,b,*], L. Giovannelli [a,b]

[a] Department of Pharmaceutical Sciences, University of Piemonte Orientale, Largo Donegani 2, 28100, Novara, Italy
[b] APTSol S.r.l., Registered Office, Corso Milano 17, 28100, Novara, Italy

ARTICLE INFO

Keywords:
Lipid excipient
Drug release
W/O emulsion
Solid lipid system
Controlled release

ABSTRACT

Solid lipid systems (SLSs) are widely employed to control the release of highly hydrophilic drugs, and they are, in general, obtained by solubilizing or suspending the drug within melted lipid excipients. This work proposes an advantageous strategy to modulate the drug release of a hydrophilic drug loaded into a lipid matrix using as a starting formulation a water-in-oil emulsion. Therefore, the active ingredient (metoclopramide HCl as a drug model) is solubilized in the emulsion internal phase, and some formulation and process parameters were used as variables for drug release kinetics modulation. Four lipid excipients with different chain lengths of the fatty acids (Dynasan® 114, 116, 118 and Softisan® 154) were selected as external phases by melting them and emulsifying two predefined volumes of 50 % (w/w) metoclopramide HCl aqueous solution to obtain two different drug loadings. Sixteen batches of solid lipid discs were produced by dripping each emulsion into plastic molds and solidifying in an ice bath or at room temperature. The solid lipid discs were compact after the extraction from molds and homogeneous in shape and size. The maximum percentage of residual water in the discs did not exceed 6 %, and their experimental drug content was close to the expected theoretical values. Results indicate that the drug release from the discs can be modulated by changing the percentage of the loaded drug, the length of the fatty acid chain, and the solidification conditions (room temperature or ice). This approach provides a straightforward and exploitable tool for developing other types of SLSs.

1. Introduction

In recent years, solid lipid formulations have steadily gained increasing importance due to their numerous industrial benefits, including cost-effectiveness, ease to handle, and suitability for large-scale manufacturing processes [1]. Lipid excipients show excellent biocompatibility and biodegradability, being naturally present in the human body and included in the human diet. Furthermore, they offer the possibility to obtain highly functional solid dosage forms. The choice of lipids as structuring excipients in solid delivery systems is advantageous for masking the bitter taste of some drugs when they are orally administered, reducing drug gastric irritation [2], increasing the stability of the active ingredient, preserving it from exposure to external factors (such as humidity), improving the bioavailability of drugs that are poorly soluble in water and allowing drug modified release [3–9].

Moreover, lipids also offer several advantages from an operational point of view. For example, they can be processed with techniques that do not require the use of organic or inorganic solvents, offering benefits in terms of both time and cost [10].

In the specific case of solid lipid formulations, the excipients are lipids in the solid state both at room temperature and at body temperature, i.e. long-chain saturated fatty acids (such as myristic, palmitic, and stearic acids), hydrogenated fatty acids, monoglycerides, diglycerides, triglycerides and waxes [11]. As reported by Jannin et al. [12], vegetable oils are one of the primary sources of lipids, and hydrogenated vegetable oils, glycerides, and macrogolglycerides represent their main derivatives. These excipients are produced using specific procedures; first, the catalytic hydrogenation of the unsaturated molecules, responsible for their conversion into hydrogenated vegetable oils with a solid and waxy texture, is ideal for the design of controlled release systems. Partial glycerides, or mono- and diglycerides, can be obtained with transesterification of triglycerides and glycerol and direct esterification between glycerol and selected fatty acids. Some derivatives, such as glyceryl monostearate and glyceryl behenate, containing long-chain

* Corresponding author. Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale, Largo Donegani 2, 28100, Novara, Italy.
E-mail address: lorena.segale@uniupo.it (L. Segale).

https://doi.org/10.1016/j.jddst.2025.107127
Received 21 March 2025; Received in revised form 30 May 2025; Accepted 31 May 2025
Available online 1 June 2025

Table 1
Percentage composition of the W/O emulsions.

Formulation	Dynasan® 114	Dynasan® 116	Dynasan® 118	Softisan® 154	MCP	H_2O	Emulsifier
D114 12.5	73.0				12.5	12.5	2.0
D114 22.5	53.0				22.5	22.5	2.0
D116 12.5		73.0			12.5	12.5	2.0
D116 22.5		53.0			22.5	22.5	2.0
D118 12.5			73.0		12.5	12.5	2.0
D118 22.5			53.0		22.5	22.5	2.0
SFT 12.5				73.0	12.5	12.5	2.0
SFT 22.5				53.0	22.5	22.5	2.0

saturated fatty acids, are valuable in the formulation of prolonged-release systems [12]. Macrogolglycerides, so called in the European Pharmacopoeia, are a defined combination of mono-, di- and triglycerides and mono- and diesters of polyethylene glycols (PEG) with a molecular weight between 200 and 2000 g/mol, obtained from hydrogenated and non-hydrogenated vegetable oils by heat treatment in the presence of an alkaline catalyst. These excipients are easily dispersible in water and helpful in increasing the bioavailability of drugs [12].

In general, solid lipid systems are obtained by solubilization or suspension of the drug within melted lipid excipients. The solubilization of the active ingredient in the lipid carrier and the obtainment of solid solutions have been widely studied for the delivery of lipophilic drugs [13]. However, when it is not possible to identify a combination of lipids capable of solubilizing a specific active ingredient, the most straightforward approach is to opt for a suspension suitable for synthetic, natural, and biotechnological compounds [14].

Recent research works proposed a third option that is the preparation of solid lipid systems starting from water-in-oil (W/O) emulsions [1,15,16]. In this case, the internal aqueous/hydrophilic phase consists of the drug solution, which is dispersed within a hydrophobic external phase composed of melted lipids that, upon cooling to room temperature, return to their original solid state. This strategy has not yet been investigated in depth but the results of some studies reported in the literature outline it as an auspicious approach and particularly suitable in the case of loading a highly water-soluble drug in a lipid system.

Starting from these considerations, this work would contribute to the broader field of lipid-based drug delivery systems by exploring the novel formulation approach, that is the use of water-in-oil emulsion as feeding material, that could be applied to hydrophilic drugs, potentially offering a versatile platform for controlled release applications in pharmaceutical development. In particular, this work aims to modulate the release kinetics of a hydrophilic model drug (metoclopramide hydrochloride, MCP) loaded in solid lipid systems produced by casting and solidification. The novelty consisted in the formulation and preparation of solid lipid systems (in particular solid lipid discs) starting from a W/O emulsion, in which the drug is dissolved in the aqueous phase and the oily phase is a melted lipid. This strategy allows the inclusion in the formulation of a high amount of drug and the obtainment of lipid systems able to control the hydrophilic drug release rate.

To reach this goal, sixteen batches of solid lipid discs were prepared starting from W/O emulsions by modifying some formulation and process parameters.

W/O emulsions were developed using different lipid carriers to obtain, by a melting-solidification process, the solid lipid discs that were characterized concerning appearance, dimensions, hardness, water content, active ingredient content, and *in vitro* drug release behavior.

2. Materials

Metoclopramide hydrochloride (MCP, batch 100220002) was kindly donated by AMSA (Milan, Italy). Dynasan® 114 (glyceryl trimyristate, batch 402156), Dynasan® 116 (glyceryl tripalmitate, batch 207023), Dynasan® 118 (glyceryl tristearate, batch 205046), Softisan® 154 (hydrogenated palm oil, batch 208313) and Imwitor® 600 (polyglyceryl-3 poly-ricinoleate, batch 003153) were a gift of IoI Oleo GmbH (Witten, Germany). Stearic and palmitic acids were purchased by Sigma Aldrich (Sigma Aldrich, Milan, Italy). All other chemicals were of analytical grade and used as received.

3. Experimental methods

3.1. Selection of the lipid excipients

A preliminary phase was dedicated to the selection of suitable lipid excipients for the production of solid lipid discs by a melting and solidification process. The melting point of single excipients (Softisan® 154, Dynasan® 118, Dynasan® 116, Dynasan® 114, stearic acid and palmitic acid) was determined experimentally (melting point Buchi M 560, Buchi Italia, Cornaredo, Italy), increasing the temperature 3 °C/min from 35 °C to 145 °C. After resolidification, each excipient was tested again to assess any possible variation in its melting temperature.

Solid lipid discs composed only of the selected excipients were prepared according to this procedure: each excipient (2.5 g) was put into a vial and heated above its melting point. Then, the molten lipid was withdrawn by a Pasteur pipette previously heated, dripped into the molds of tablet blisters, and resolidified at room temperature. The solid lipid discs were removed from the blisters and visually inspected for integrity, homogeneity, and ease of handling. The excipients that provided the best responses to these requirements were used for the subsequent steps of the work.

3.2. Formulation and stability of the W/O emulsions

Each lipid was melted by heating and maintained at about 15 °C above its melting point under magnetic stirring. An emulsifier (Imwitor® 600) was solubilized in the lipid. A predefined volume of a MCP aqueous solution (50 % w/w) was added to the lipid phase, and the formulation was kept under magnetic stirring (1100 rpm) to obtain a water-in-oil emulsion. In detail, two different volumes of MCP water solution were added as the dispersed phase of the emulsion to guarantee the obtainment of two drug loadings (12.5 % and 22.5 %). The percentage composition of the emulsions is reported in Table 1.

After 10 min, the stirring was stopped, and the emulsions were then observed for a time compatible with that of the production of the lipid discs (5 min) to assess their stability.

3.3. Production of drug-loaded solid lipid discs

Solid lipid discs were obtained by a melting and solidification method. In detail, each W/O emulsion was dripped into the molds of a tablet blister with an internal diameter between 6.5 and 7.5 mm by using a Pasteur pipette previously heated. For each formulation, the dripping step was carried out by maintaining the blister at room temperature (batches coded “25 °C”) or by inserting it in an ice bath (batches coded “ice”) to accelerate the disc solidification process. The emulsions were then left to solidify and removed from the blister by applying gentle pressure.

Table 2
Experimental melting point of the selected lipids (m.p.1) and after resolidification (m.p. 2) in the capillary.

Excipient	m.p. 1 (°C)	m.p. 2 (°C)
Softisan® 154	58.5–60.4	57.1–57.6
Dynasan® 114	55.7–56.9	56.3–56.6
Palmitic acid	63.2–64.9	64.1–65.0
Dynasan® 116	65.8–67.1	66.1–66.7
Stearic acid	69.4–71.1	69.8–71.2
Dynasan® 118	70.6–72.8	72.0–72.4

For each excipient, solid lipid discs were also prepared starting from a water-free formulation, that is, a suspension of the drug into the molten lipid with two loadings (15 % and 28 %). In this case, MCP was dispersed directly into the molten lipid phase (lipid + emulsifier). The percentage compositions of the suspensions were the following: A - lipid = 83 %, MCP = 15 %, Imwitor® 600 = 2 % and B - lipid = 70 %, MCP = 28 %, Imwitor® 600 = 2 %.

The suspensions were dripped into the blisters and the formed discs recovered after solidification.

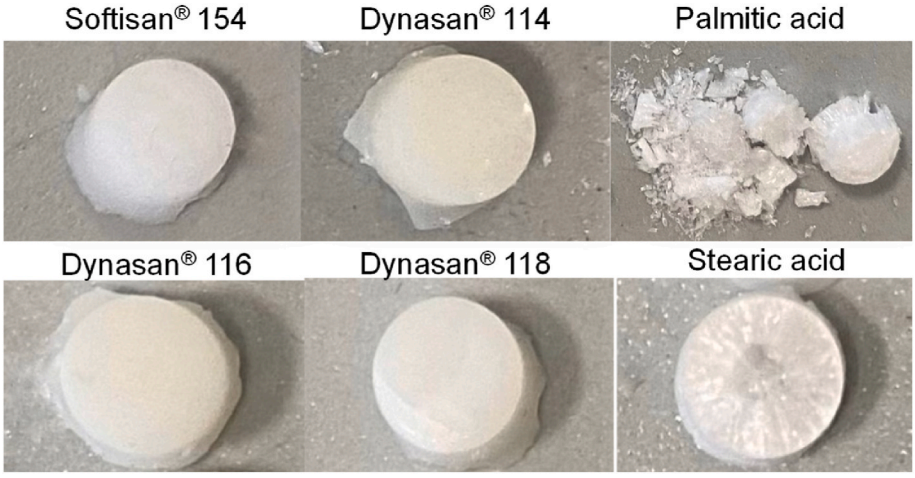

Fig. 1. Solid lipid discs composed only of the selected excipients.

Fig. 2. W/O drug loaded emulsions, a) 22.5 % MCP, b) 12.5 % MCP.

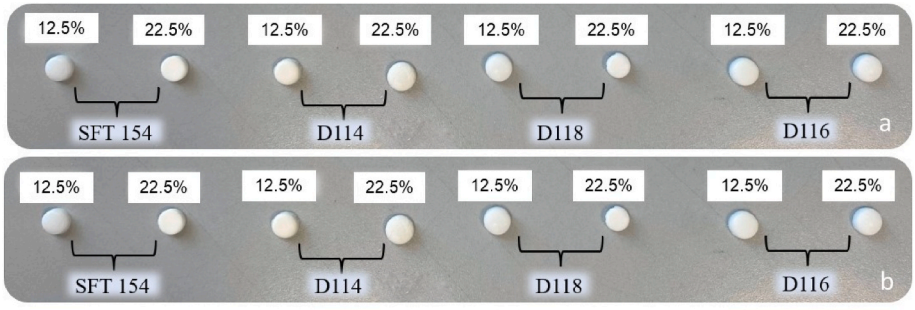

Fig. 3. Solid lipid discs obtained by melting and solidification at room temperature (a) and in an ice bath (b).

Table 3
Properties of the lipid discs.

Formulation		Diameter (mm)	Thickness (mm)	*Aspect Ratio*	Hardness (N)	Experimental MCP content (%)
SFT 12.5	**25 °C**	6.9 ± 0.60	3.2 ± 0.29	2.16 ± 0.01	7.84 ± 0.38	13.14 ± 3.51
	ice	7.4 ± 0.13	3.2 ± 0.41	2.27 ± 0.32	8.82 ± 0.75	11.40 ± 2.20
SFT 22.5	**25 °C**	6.5 ± 0.04	3.0 ± 0.08	2.15 ± 0.07	17.64 ± 1.63	27.34 ± 0.73
	ice	7.4 ± 0.01	4.1 ± 0.09	1.81 ± 0.04	16.66 ± 1.83	25.48 ± 5.28
D114 12.5	**25 °C**	6.5 ± 0.15	3.2 ± 0.06	2.02 ± 0.01	19.60 ± 0.98	12.83 ± 0.68
	ice	6.9 ± 0.01	3.5 ± 0.01	2.00 ± 0.04	15.68 ± 1.14	12.27 ± 1.03
D114 22.5	**25 °C**	7.3 ± 0.13	3.0 ± 0.08	2.47 ± 0.11	16.66 ± 1.09	27.35 ± 0.54
	ice	6.5 ± 0.08	2.9 ± 0.08	2.24 ± 0.03	8.82 ± 0.54	26.93 ± 2.52
D116 12.5	**25 °C**	7.0 ± 0.06	3.2 ± 0.01	2.20 ± 0.01	18.62 ± 0.76	13.90 ± 1.54
	ice	6.5 ± 0.06	2.8 ± 0.13	2.29 ± 0.13	9.80 ± 1.32	11.14 ± 1.18
D116 22.5	**25 °C**	7.1 ± 0.15	3.1 ± 0.01	2.31 ± 0.04	13.72 ± 1.26	25.55 ± 0.38
	ice	6.9 ± 0.17	2.7 ± 0.08	2.56 ± 0.02	10.78 ± 1.04	24.84 ± 2.17
D118 12.5	**25 °C**	6.9 ± 0.19	3.6 ± 0.02	1.91 ± 0.04	10.78 ± 0.73	12.46 ± 4.19
	ice	6.9 ± 0.45	3.3 ± 0.59	2.08 ± 0.51	11.76 ± 1.12	12.16 ± 1.46
D118 22.5	**25 °C**	6.6 ± 0.16	3.4 ± 0.41	1.95 ± 0.19	10.78 ± 1.16	24.62 ± 0.05
	ice	6.4 ± 0.01	4.4 ± 0.18	1.44 ± 0.06	17.64 ± 1.24	28.30 ± 3.87

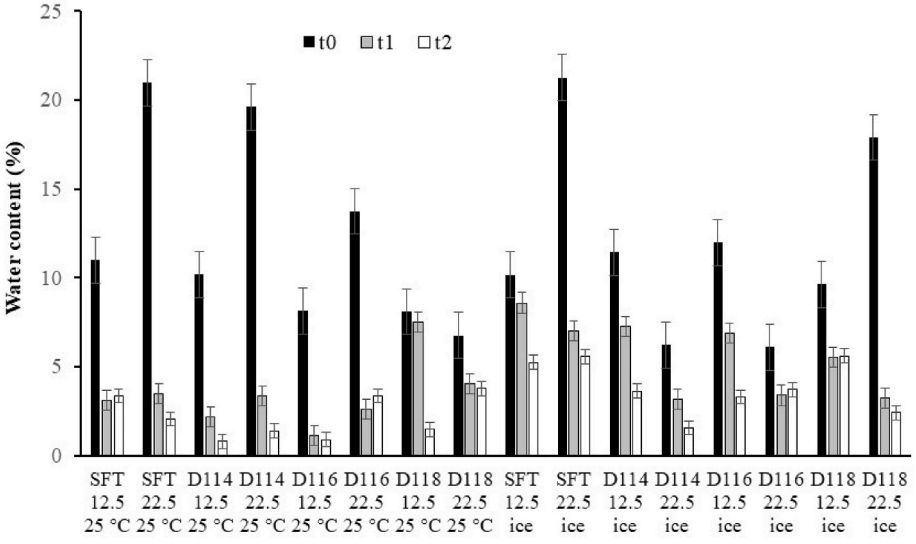

Fig. 4. Percentages of residual water content of the lipid discs (t_0 = just prepared, t_1 = 1-day-aged; t_2 = 2-days-aged).

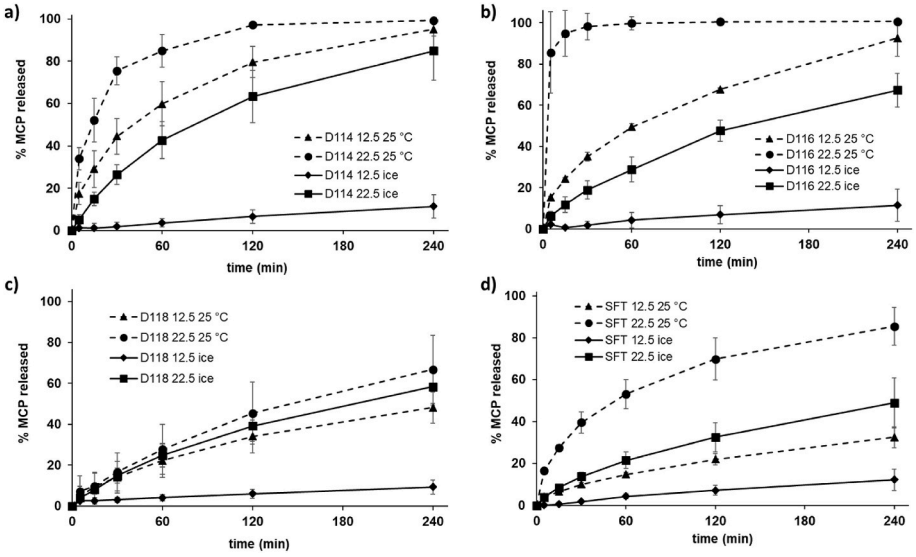

Fig. 5. Comparison of the drug release profiles of the lipid discs containing the same carrier excipients but different drug loading and prepared according to different conditions.

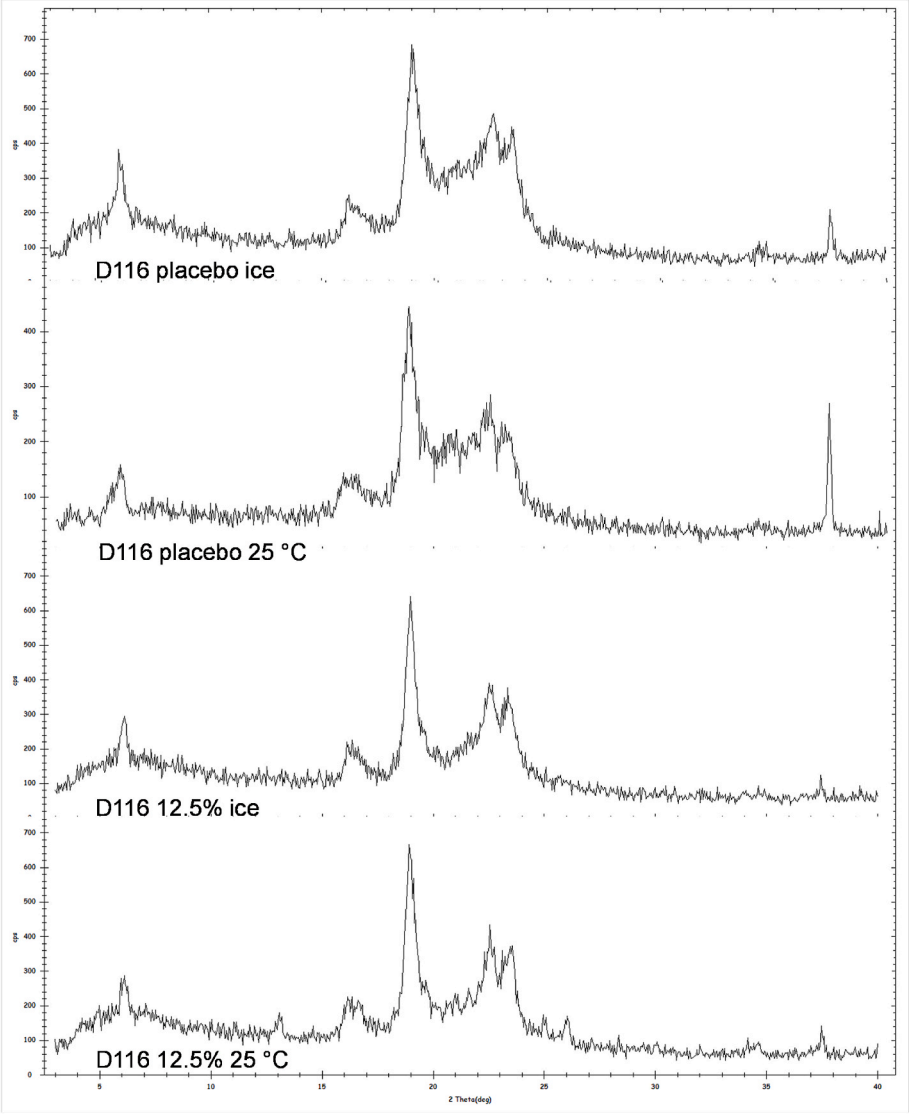

Fig. 6. FTIR spectra of D116 placebo discs and D116 12.5 % 25 °C and ice discs.

3.4. Characterizations

3.4.1. Dimensional analysis and hardness determination

The diameter and thickness of the solid lipid discs were measured with an LTF caliper, and the aspect ratio was calculated according to the following equation (1):

$$Aspect\ ratio = diameter(mm) \ / \ thickness\ (mm) \quad (1)$$

The hardness of the solid lipid discs was measured two days after preparation by MultiTest 50 Tablet Hardness Tester (Dr. Schleuniger® Pharmatron, Nordring, Switzerland). All the determinations were performed in triplicate.

3.4.2. Morphology

The appearance of solid lipid discs was evaluated using an optical Stereomicroscope S9i – LEICA. Scanning electron microscopy (SEM) investigated the systems' internal and external morphology. The analyses were carried out using a Field Emission Gun Scanning Electron Microscope (FEG-SEM) TESCAN Mira3-XMU operating at the Arvedi CISRic laboratory (University of Pavia).

The images were obtained in high vacuum mode with a 5 kV electron energy at a 15 mm working distance and *via* the secondary electron detector. The samples, appropriately sized by cutting, were fixed, with the help of a carbon-based double-sided conductive tape, to an aluminum support (stub). Their surface was metalized through the deposition of Pt with a Sputter Coater Cressington 208HR to render it conductive.

3.4.3. Residual water determination

Water content was determined on the freshly prepared discs (Wt0), on 1-day-aged (Wt1), 2-days-aged (Wt2) and 4-days-aged (Wt4) discs by coulometric Karl Fischer titration (HI 904 Karl Fischer Coulometric Titrator, Hanna Instruments, Woonsocket, RI, USA). For each batch of discs, one sample was grounded and placed into a vial with 5 mL dichloromethane/methanol mixture (DCM/MeOH ratio: 1/1) and sonicated for 10 min to accelerate their dissolution. Then, 1 mL of the obtained solution was withdrawn by a syringe and immediately inserted into the titration vessel. The results are expressed as the percentage of water recovered (% w/w). The DCM/MeOH mixture was used as a blank, and all the analyses were performed in triplicate.

Water recovery at t0 (Equation (2)) and water loss percentage after 2 days (Equation (3)) were calculated as reported below:

$$Water\ recovery = (Wt0\ (\%)) \ / \ (water\ content\ in\ the\ formulation\ (\%))\ x\ 100 \quad (2)$$

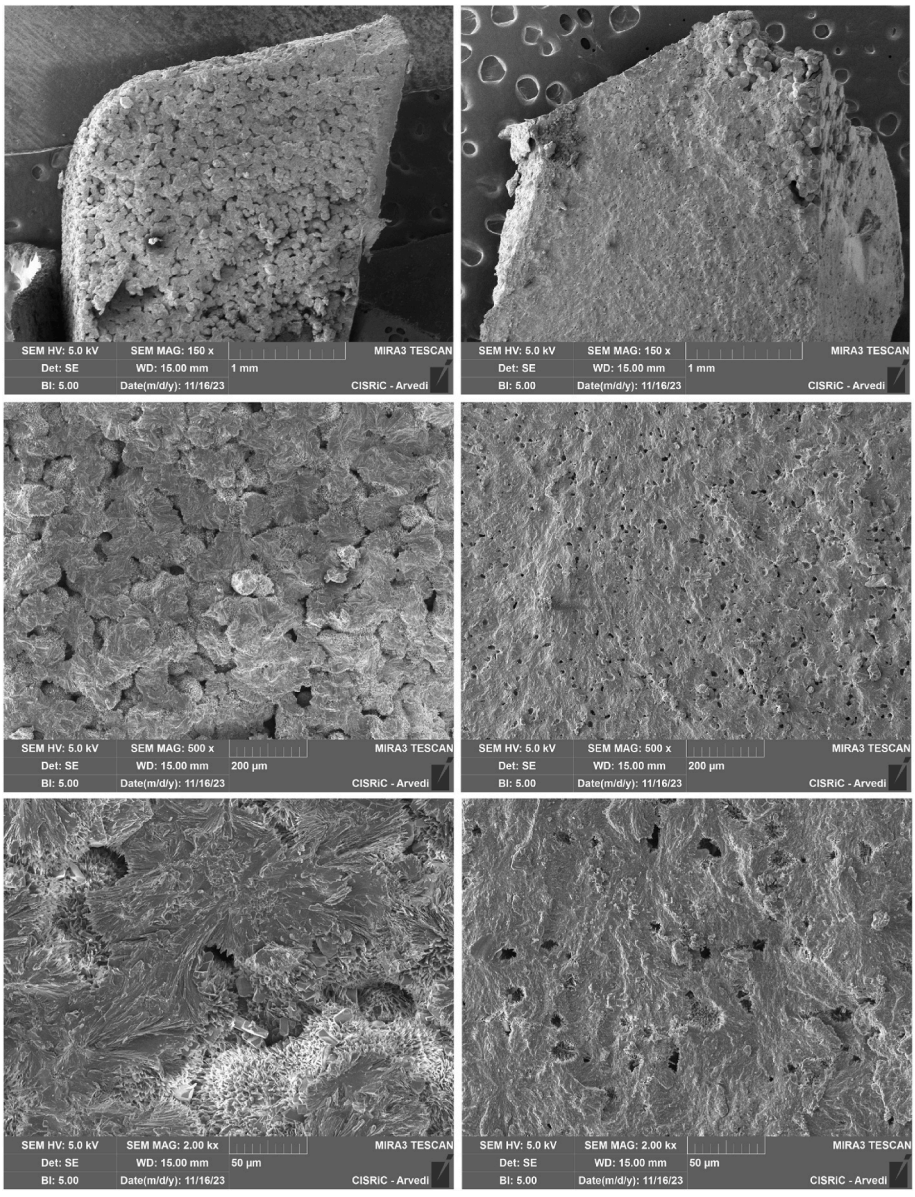

Fig. 7. SEM images of the cross-section of D114 12.5 % 25 °C (left) and D114 12.5 % ice (right) at different magnifications (top 150×, center 500x, bottom 2000x).

$$Water\ loss = (Wt2\ (\%))\ /\ (Wt0\ (\%))\ x\ 100 \quad (3)$$

3.4.4. Determination of drug content

A disc was weighed, added to 500 mL of phosphate-buffer solution (PBS) (0.1 M, pH = 6.8), maintained under magnetic stirring and heated up to a temperature that allowed the melting of the lipid carrier, the subsequent drug release and its solubilization in the medium. 5 mL of this solution were withdrawn, cooled to room temperature, filtered through a 0.22 mm filter and analyzed by UV–Vis spectrophotometer at 273 nm (Beckman Coulter, DU 730 Spectrophotometer).

Drug concentration in the medium and, consequently, the drug content (mg) of the discs was determined according to the calibration curve ($y = 37.041x + 0.0106$; $R^2 = 0.9998$).

Drug content (%) was calculated using equation (4):

$$Drug\ content\ (\%) = drug\ amount\ (mg)\ /\ disc\ weight\ (mg)\ x\ 100 \quad (4)$$

Theoretical drug content (%) was calculated on the 2-days-stored discs according to equation (5):

$$Theoretical\ drug\ content\ (\%) = (MCP\ (g)\ /\ waterless\ disc\ (g))\ x\ 100 \quad (5)$$

The entrapment efficiency (EE) was determined according to equation (6):

$$Entrapment\ efficiency\ (EE) = (drug\ content\ /\ theoretical\ drug\ content)\ x\ 100 \quad (6)$$

3.4.5. In vitro drug release tests

In vitro drug release tests were performed to evaluate the quantity of MCP released in phosphate-buffer solution 0.1 M (pH 6.8) over time. Each disc was put in a basket usually adopted for the dissolution studies of the solid dosage forms, placed in 500 mL PBS 0.1 M (pH 6.8) and kept under magnetic stirring (300 rpm) for the whole duration of the test. At predefined time intervals (5, 15, 30, 60, 120, 240 min), 5 mL of fluid were withdrawn without replacement, filtered through a 0.22 mm filter and analyzed spectrophotometrically at 273 nm (Beckman Coulter, DU 730 Spectrophotometer). The concentration of the drug released over time was determined considering the starting MCP content.

Results are reported as the average of at least three determinations.

The release profiles were compared using the f2 similarity factor [17], which assumes values greater than 50 when the two curves are

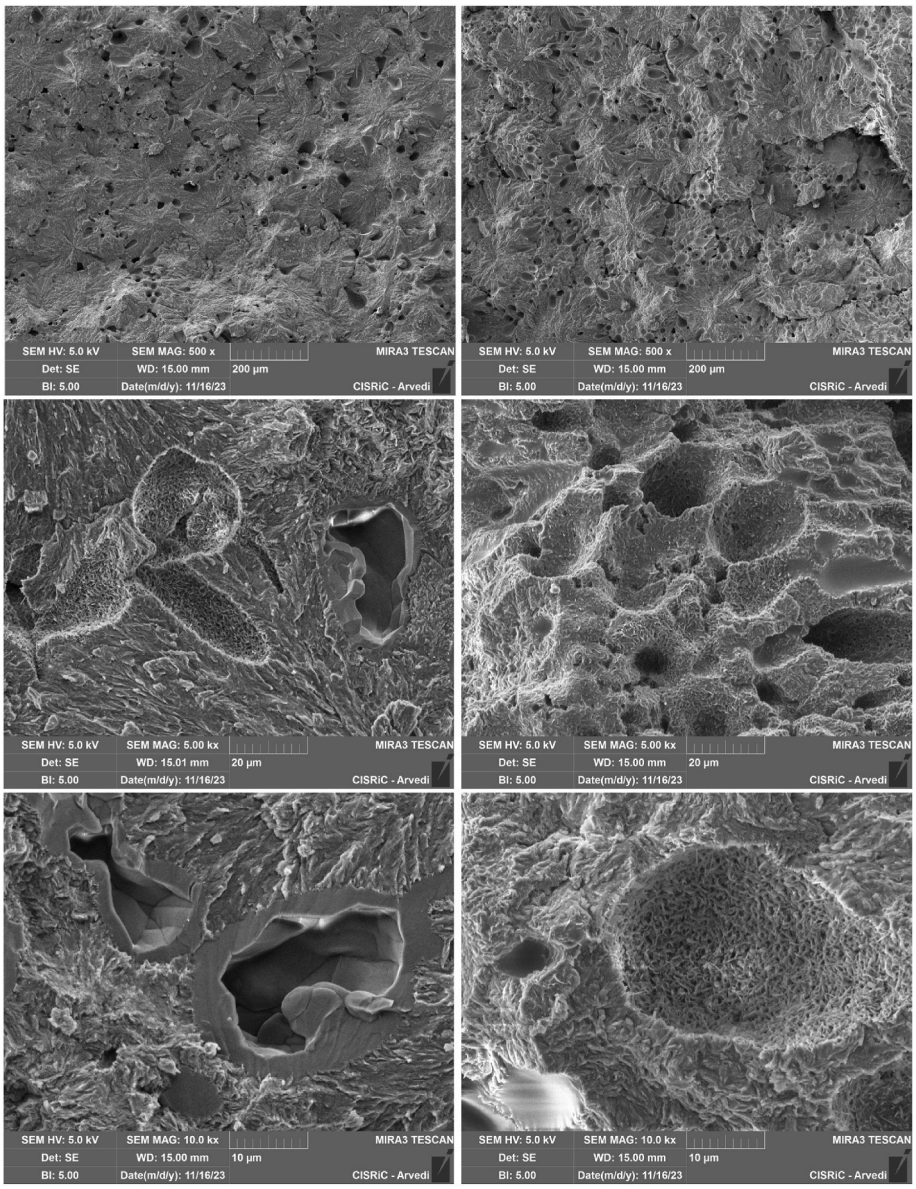

Fig. 8. SEM images of the cross-section of D118 12.5 % 25 °C (left) and D118 12.5 % ice (right) at different magnifications (top 500×, center 5000x, bottom 10000x).

similar.

The mechanism of drug release was evaluated by fitting the MCP release data to the Korsmeyer and Peppas equation (7) [18].

$$M_t / M_\infty = kt^n \quad (7)$$

where M_t/M_∞ is the fractional drug release at time t, k is a constant that includes the structural and geometrical characteristics of the system, and n is the coefficient indicative of the drug release mechanism (n = 0.45 Fickian diffusion, 0.45 < n < 1 anomalous non Fickian, n = 1 Case II).

3.4.6. X-ray Powder diffraction (XRPD)

Selected samples (drug-loaded and placebo solid lipid discs) were submitted to X-ray analysis to evaluate their crystalline structure. X-Ray Powder Diffraction (XRPD) spectra were recorded on an APD 2000 Pro GNR diffractometer at room temperature, using a CuKα tube (40 kV, 30 mA, λ = 1.5418 Å) as an X-ray source and scintillator as detector type.

Data collection was made in 2θ step scan mode, at a scan speed of 0.04°/s in the range of 3°–40° 2θ at a scan speed of 0.02°/s.

4. Results and discussion

The choice of the most suitable excipients for the production of the solid lipid systems was made using Softisan® 154 as a reference, an excipient already selected in a previous work for the preparation of solid lipid microparticles by spray congealing [16]. Softisan® 154 is a hydrogenated palm oil with a melting temperature between 53 and 58 °C that is not excessively low to compromise or hinder the resolidification of the systems at room temperature and, at the same time, not so high to make the production phase difficult or to make this incompatible with the inclusion of thermosensitive compounds in the formulation. Five lipids were selected, and their experimental melting points were determined. Except for stearic acid, in the case of the other excipients, the temperature intervals recorded when the lipid melted after it had been resolidified directly in the capillary (m.p. 2) were narrower compared to those of the excipient as it is (m.p. 1) (Table 2).

The melting point is a crucial characteristic of the excipient in the design of pharmaceutical products that must be obtained by melting and resolidification since its variation can be indicative of a modification of

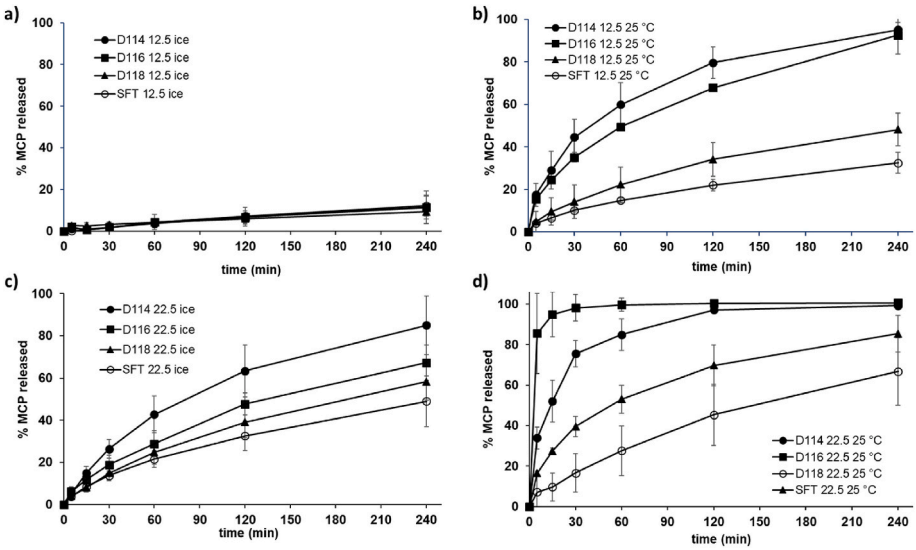

Fig. 9. Comparison of the drug release profiles of the lipid discs containing different drug loading and carrier excipients but prepared according to the same work conditions.

Table 4
Fitting parameters of the Peppas equation.

	n	K	R^2
D114 12.5 ice	0.6215	0.3068	0.897
D114 22.5 ice	0.7916	1.6099	0.988
D114 12.5 25 °C	0.4861	8.0373	0.996
D114 22.5 25 °C	0.4417	16.397	0.992
D116 12.5 ice	1.0145	0.0521	0.973
D116 22.5 ice	0.6312	2.1928	0.999
D116 12.5 25 °C	0.4745	6.9828	0.999
D118 12.5 ice	0.3337	1.2105	0.856
D118 22.5 ice	0.7086	1.2776	0.997
D118 12.5 25 °C	0.6043	1.8284	0.999
D118 22.5 25 °C	0.6104	2.2704	0.978
SFT 12.5 ice	1.1857	0.0251	0.977
SFT 22.5 ice	0.6532	1.4275	0.998
SFT 12.5 25 °C	0.5471	1.5875	0.997
SFT 22.5 25 °C	0.4593	7.9758	0.998

the characteristics of the solid state of the material (for example, crystalline form, crystalline or amorphous state) and consequently, its ability to release the active ingredient loaded into the dosage form. For this reason, in the formulation phase, excipients that maintain unchanged melting points after fusion-resolidification are preferable. Furthermore, as suggested by the literature, when the production process requires heat treatment, it is more appropriate to choose lipids with higher physical stability instead of more heterogeneous and sensitive excipients [19].

Solid lipid discs composed of single excipients were produced by dripping the molten lipids into the molds of a tablet blister. Softisan® 154, Dynasan® 114, Dynasan® 116 and Dynasan® 118 gave solid, compact, intact and homogeneous in shape and size systems; palmitic acid discs were very friable with a tendency to break during ejection from the blister, while stearic acid discs were characterized by non-homogeneous surfaces (Fig. 1). Therefore, stearic and palmitic acids were discarded and not used to formulate the W/O emulsion.

The drug-loaded W/O emulsions were prepared, and their stability was evaluated. The emulsions appeared iridescent regardless of the lipid used as the component of their external phase and the percentage of the loaded drug, as shown in Fig. 2.

This result corroborates what was already demonstrated in a previous work [16]: the iridescence is attributable to the presence of metoclopramide and water in a 1:1 ratio and was not ascribable to the nature of the other components of the formulation.

The emulsions were stable over time: they did not show phase separation and were suitable for the preparation of solid lipid discs.

The choice of the emulsion as a starting point is rather unusual, but it can offer considerable advantages, especially when the active ingredient has hydrophilic characteristics that are poorly suited to a lipophilic carrier. On the other hand, treating a solution (i.e. a system in which the drug is dissolved in the melted lipid excipient) or a suspension represents the most common approach because it is more flexible and, in many cases, simpler to manage. However, in this work, it was not possible to prepare lipid discs suspending the drug into the lipid carrier because the resulting formulation was not homogeneous and was not suitable for dripping into tablet blisters.

The solid lipid discs obtained starting from drug-loaded W/O emulsions were intact and compact after the extraction out of the blisters (Fig. 3), independently of the percentage of loaded drug (12.5 or 22.5 %) and of the conditions of resolidification (at room temperature or in an ice bath).

The diameter and thickness of the discs, as well as the aspect ratio, were in a quite narrow range (6.4–7.4 mm, 2.8–4.4 mm and 1.4–2.6, respectively) (Table 3).

The dimensions of the systems were comparable, even if not identical, because of the unequal dimensions of the molds. On the other hand, the hardness of the lipid discs was quite variable and ranged between 7.84 and 19.60 N, and it was not possible to establish a relation between these values and the type of lipid carrier in the formulation and/or the solidification method used during the production process. Only in the case of Softisan® discs, it was possible to evidence that the hardness increased by increasing the loaded drug. As reported by Oliveira et al. [20], the mechanical properties of the systems are linked to the type of glycerides and fatty acids that compose the lipid-based excipients and to the characteristics of the materials.

Considering the water evaporation during the production step, it was mandatory to determine the actual residual water content of the discs. As expected, the residual water percentages in the solid lipid discs were lower than those present in the starting W/O emulsions. After the extraction of the discs from the blisters, the rate of residual water in the systems progressively decreased over time (Fig. 4): it was maximum in the discs just prepared (t_0), and it gradually reduced. Two and four days after the preparation and the extraction from the blister, the residual water in the discs was the same: it did not exceed 4 % and 6 %, in the case of the discs solidified at room temperature and in the ice bath,

respectively. Therefore, two days are enough to reach an equilibrium and a constant value of residual water. The water evaporation rate changed according to the solidification conditions used during the production of the discs. When it was carried out at room temperature, the systems rapidly lost their water content, and after one day, in most cases, it had already decreased by more than 70 % compared to its starting value. When the solidification of the discs took place in an ice bath, the water moved away more slowly, probably because the systems were characterized by a more packed internal structure, which made the path that the water had to take to escape from the disc tortuous.

The experimental drug loadings are close to the expected theoretical values defined according to the actual residual water content of the lipid discs (Table 3).

The influence of the formulation, the type of excipient and the preparation protocol on the drug release performance of the solid lipid discs was evaluated.

The results highlighted that for all the discs, regardless of the solidification conditions, the amount of drug loaded into the systems profoundly influenced their release behavior and release rate. When the amount of MCP was high (22.5 %), the drug was delivered more quickly than when it was low (12.5 %) (Fig. 5), and the release profiles can be considered dissimilar according to the f2 parameter values less than 50. This behavior can be justified by assuming that the release mechanism is diffusive and, therefore, powered by the concentration gradient. Furthermore, a faster release could also be attributed to the fact that, if the drug content is high, as a consequence of its passage into solution, porosities are generated within the system. The dissolution fluid can penetrate more quickly and efficiently into the inner layers of the lipid structure [21].

Moreover, for the same drug loading, independently of the type of lipid carrier, the discs obtained in an ice bath released MCP more slowly than those solidified at room temperature. For example, in the case of D116 12.5 discs, after 60 min from the beginning of the tests, the percentages of the drug in solution were 4.24 % and 49.43 % in the case of systems obtained in an ice bath and at room temperature, respectively (Fig. 5b). According to these results, it is evident that the cooling and solidification method has a significant impact on the performance of the lipid systems produced. The literature reports that if the lipid solidifies in different crystalline forms, the resulting solid system can be characterized by different wettability [8,22] and, consequently, may guarantee a different drug release rate. The structure that forms under slower cooling at room temperature is more unstable and less dense than that typical of an instantaneously solidified system (in an ice bath). Rapid cooling is responsible for the rearrangement of the structure to the most stable form. As stated by Lutton [23], the structures relating to the presence of β and β' crystalline forms, which are also the most stable, are denser in cross-section than the α (more unstable) form.

To evaluate if this theory could justify the different release behavior of the lipid discs obtained at room temperature and low temperature, the structure of the systems was characterized at the molecular level by X-ray diffraction. The results have highlighted the presence of the lipid in β form in all the samples analyzed (both drug-loaded discs and placebo discs, used as reference) and the absence of significant differences between their diffraction spectra (Fig. 6).

It can be deduced that the different solidification rates of the discs were not sufficient to guarantee the solidification of the lipids in two distinct crystalline forms (α or β) or that the transformation from α or β′ to β form was so rapid that it was not possible the identification of the less stable polymorph (α or β') but only of the stable one (β).

The most convincing hypothesis that justifies the result of the release tests is that the rapid solidification in ice favored the formation of a closely packed internal structure of the system, regardless of the crystalline form of the lipid. SEM images confirmed it. Figs. 7 and 8 compare the internal surfaces of D114 12.5 % and D118 12.5 % lipid discs obtained at room temperature (25 °C) and in an ice bath. It is clear that when the discs were solidified at room temperature, they were characterized by a loosely packed structure in which many empty spaces were present. Otherwise, the rapid cooling in the ice bath was responsible for the formation of a denser structure in which only minimal in-diameter pores were visible.

The comparison of the release profiles of the 12.5 % metoclopramide lipid discs solidified in an ice bath confirmed this hypothesis: a prolonged drug release process characterized the behavior of the systems independently of the structuring excipient. After 1 h, no more than 5 % of the drug passed into solution, and this percentage did not exceed 13 % at the end of the test (Fig. 9a). The curves are similar ($f2 > 50$) and perfectly overlapped. The rapid solidification of the discs and the formation of a very compact structure probably led to eliminating the diversity of drug release behavior associated with the formulation variability, making the entry of fluid into the system and the consequent delivery of the drug solution particularly difficult.

Different results can be observed by comparing the performances of the systems with 12.5 % of drug solidified at room temperature (Fig. 9b), of the systems composed of different lipids with 22.5 % of active ingredient obtained by solidification in an ice bath (Fig. 9c) or at room temperature (Fig. 9d). In the first two cases (Fig. 9b and c), the Softisan® and Dynasan® 118 systems showed similar behavior ($f2 > 50$), while the discs made of Dynasan® 114 released MCP faster than the others. These results agree with the literature, as stated by Kreye et al. [21]; by ranking lipid systems in decreasing order of drug release rate, a consistent pattern can be observed, even when varying the nature and concentration of the active ingredient. The drug release rate decreased according to the following order: Dynasan® 114 > Dynasan® 116 > Dynasan® 118. Koennings et al. [24] and Windbergs et al. [25] confirmed this assumption: they attributed this trend to the chain length of the lipids, highlighting that longer fatty acid chains corresponded to a reduction of the system wettability and drug release rate.

Fig. 9d highlights that when the lipid discs were loaded with 22.5 % of the drug, and the solidification was carried out at room temperature, the release behavior varied significantly depending on the formulation (as confirmed by the f2 values always being less than 50) right from the early stages of the process. In fact, after only 5 min from the beginning of the test, the percentage of drug released from D118 22.5 25 °C is about 7 %, while for the other systems, it exceeds 16 % (SFT 22.5 25 °C), 33 % (D114 22.5 25 °C), and 85 % (D116 22.5 25 °C).

To identify the mechanism that drove the drug release process, the data obtained from *in vitro* release studies were reprocessed using the Peppas equation [26,27] selected for its ability to provide information on both the mechanism and kinetics of drug release. As reported by the authors, this equation has to be applied only to the first 60 % of the drug released. In the case of D116 22.5 25 °C discs, the release data processing was not done because there were only two experimental points under this limit.

The correlation coefficient (R^2) between 0.86 and 0.99 (Table 4), indicates a good correlation with the experimental data. The K parameter values gave information about the rate of the drug release process: low values indicate a slow drug release, while high K values represent a fast release. The results showed that the discs solidified in an ice bath had lower K values than discs obtained at room temperature, and it was confirmed that they released the drug more slowly than the other.

The diffusion exponent n took values within the interval $0.45 < n < 1$, corresponding to an anomalous non-Fickian release, except for SFT 12.5 ice, D116 12.5 ice, D118 12.5 ice and for D114 22.5 25 °C (Table 4). In these cases, the n values were not within the interval, exceeding the limits: n was greater than 1 for the SFT 12.5 ice and D116 12.5 ice, and less than 0.45 for the D118 12.5 ice and D114 22.5 25 °C. Peppas and Korsmeyer [18] state in their work that if the values of n are less than 0.45 or greater than 1, it indicates that during the drug release process, diffusion is involved, as well as another phenomenon.

The n values suggested a release mechanism beyond the Fickian diffusion usually associated with lipid systems, considering their hydrophobicity and insolubility within aqueous media. In general, the

diffusional behaviour characterized the lipid systems regardless of the production method [22]. Still, the literature evidences some exceptions that supported the results of the present work, as presented in the studies conducted by Özyazici et al. [28] and Abd-Elbary et al. [29], where it is underlined the non-Fickian anomalous release of lipid matrix systems. According to Özyazici et al. [28], this behavior can be attributed to a combination of Fickian diffusive release and relaxation of the lipid matrix. This phenomenon is commonly observed in hydrophilic and swellable polymers that form a gel after contact with the dissolution medium. However, it can also be observed in lipid systems, which can undergo minimal swelling without forming a gel under certain conditions, as reported by Quadir et al. [30] and Zhao et al. [31].

As demonstrated by Kreye et al. [21], lipid systems obtained by compression and prepared with various excipients, including Dynasan® 114, Dynasan® 116 and Dynasan® 118, undergo a slight swelling after prolonged contact with phosphate buffer due to the penetration of the medium into the porosity of the structure.

5. Conclusion

The selected lipids were suitable for the formulation of W/O emulsions useful to obtain, through melting and solidification, solid lipid discs with physical and technological characteristics dependent on the nature of the structuring excipient, the drug loading and/or the solidification conditions. This work demonstrated that formulation and process parameters affect the mechanism and rate of drug release: the use of lipids with longer fatty acid chains and lower solidification temperatures will result in a long-lasting drug release. The strategy proposed here, combined with the choice of the most suitable carrier excipient and process conditions, could be useful in obtaining lipid dosage forms able to control the release of a highly soluble drug. This formulation approach is a viable tool that offers new potential lines of research, even for the development of other types of solid lipid systems. Solid lipid microparticles can be produced in industrial applications using the spray congealing process, which can be easily automated, is reproducible and fast scalable.

CRediT authorship contribution statement

A. Candiani: Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation. **A. Milanesi:** Writing – review & editing, Visualization, Validation, Investigation, Formal analysis, Data curation. **G. Diana:** Writing – review & editing, Visualization, Validation, Investigation, Formal analysis. **F. Loda:** Visualization, Investigation. **E. Bari:** Writing – review & editing, Visualization. **M.L. Torre:** Writing – review & editing, Supervision. **A. Foglio Bonda:** Writing – review & editing, Project administration, Methodology, Conceptualization. **L. Segale:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Conceptualization. **L. Giovannelli:** Writing – review & editing, Supervision, Resources.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Lorella Giovannelli and Lorena Segale are members of the company APTSol S.r.l.

Acknowledgments

Centro Interdipartimentale di Studi e Ricerche per la Conservazione del Patrimonio Culturale (CISRiC) – Pavia, Via Ferrata 1–27100 Pavia.

Data availability

The data that has been used is confidential.

References

[1] S. Bertoni, B. Albertini, J. Ronowicz-Pilarczyk, N. Calonghi, N. Passerini, Solvent-free fabrication of biphasic lipid-based microparticles with tunable structure, Pharmaceutics 14 (1) (2021) 54, https://doi.org/10.3390/pharmaceutics14010054.
[2] N. Dudhipala, A.A. Ay, Amelioration of ketoconazole in lipid nanoparticles for enhanced antifungal activity and bioavailability through oral administration for management of fungal infections, Chem. Phys. Lipids 232 (2020) 104953, https://doi.org/10.1016/j.chemphyslip.2020.104953.
[3] S. Jaspart, G. Piel, L. Delattre, B. Evrard, Solid lipid microparticles: formulation, preparation, characterization, drug release and applications, Expet Opin. Drug Deliv. 2 (1) (2005) 75–87, https://doi.org/10.1517/17425247.2.1.75.
[4] W. Mehnert, K. Mäder, Solid lipid nanoparticles: production, characterization and applications, Adv. Drug Deliv. Rev. 64 (2012) 83–101, https://doi.org/10.1016/S0169-409X(01)00105-3.
[5] V. Mishra, K.K. Bansal, A. Verma, N. Yadav, S. Thakur, K. Sudhakar, J. M. Rosenholm, Solid lipid nanoparticles: emerging colloidal nano drug delivery systems, Pharmaceutics 10 (4) (2018) 191, https://doi.org/10.3390/pharmaceutics10040191.
[6] G.I. Nora, R. Venkatasubramanian, S. Strindberg, S.D. Siqueira-Jørgensen, L. Pagano, F.S. Romanski, N.K. Swarnakar, T. Rades, A. Müllertz, Combining lipid based drug delivery and amorphous solid dispersions for improved oral drug absorption of a poorly water-soluble drug, J. Contr. Release 349 (2022) 206–212, https://doi.org/10.1016/j.jconrel.2022.06.057.
[7] S. Mondal, A. Sirvi, K. Jadhav, A.T. Sangamwar, Supersaturating lipid-based solid dispersion of atazanavir provides enhanced solubilization and supersaturation in the digestive aqueous phase, Int. J. Pharm. 638 (2023) 122919, https://doi.org/10.1016/j.ijpharm.2023.122919.
[8] J.R.J. Lantz, Pa Norristown, M.J. Robinson, N.J. Moorestown, Method of preparing sustained release pellets and products thereof, U.S. Patent No. 3 (146) (1964) 167.
[9] J.B. Schwartz, A.P. Simonelli, W.I. Higuchi, Drug release from wax matrices I. Analysis of data with first-order kinetics and with the diffusion-controlled model, J. Pharmaceut. Sci. 57 (2) (1968) 274–277, https://doi.org/10.1002/jps.2600570206.
[10] K. Becker, S. Salar-Behzadi, A. Zimmer, Solvent-free melting techniques for the preparation of lipid-based solid oral formulations, Pharm. Res. 32 (2015) 1519–1545, https://doi.org/10.1007/s11095-015-1661-y.
[11] R. Kumar, Lipid-based nanoparticles for drug-delivery systems, Nanocarriers for Drug Delivery (2019) 249–284, https://doi.org/10.1016/B978-0-12-814033-8.00008-4.
[12] V. Jannin, J. Musakhanian, D. Marchaud, Approaches for the development of solid and semi-solid lipid-based formulations, Adv. Drug Deliv. Rev. 60 (6) (2008) 734–746, https://doi.org/10.1016/j.addr.2007.09.006.
[13] D. Nakmode, V. Bhavana, P. Thakor, J. Madan, P.K. Singh, S.B. Singh, J. M. Rosenholm, K.K. Bansal, N.K. Mehra, Fundamental aspects of lipid-based excipients in lipid-based product development, Pharmaceutics 14 (4) (2022) 831, https://doi.org/10.3390/pharmaceutics14040831.
[14] S. Chakraborty, D. Shukla, B. Mishra, S. Singh, Lipid – an emerging platform for oral delivery of drugs with poor bioavailability, Eur. J. Pharm. Biopharm. 73 (2009) 1–15, https://doi.org/10.1016/j.ejpb.2009.06.001.
[15] M.O. Salvim, M. Thomazini, F.P. Pelaquim, A. Urbano, I.C. Moraes, C.S. Favaro-Trindade, Production and structural characterization of solid lipid microparticles loaded with soybean protein hydrolysate, Food Res. Int. 76 (2015) 689–696, https://doi.org/10.1016/j.foodres.2015.08.003.
[16] A. Candiani, A. Milanesi, A. Foglio Bonda, G. Diana, E. Bari, L. Segale, M.L. Torre, L. Giovannelli, Solid lipid microparticles by spray congealing of water/oil emulsion: an effective/versatile loading strategy for a highly soluble drug, Pharmaceutics 14 (12) (2022) 2805, https://doi.org/10.3390/pharmaceutics14122805.
[17] P. Costa, An alternative method to the evaluation of similarity factor in dissolution testing, Int. J. Pharm. 220 (2001) 77–83, https://doi.org/10.1016/j.ejps.2014.10.002.
[18] Peppas N.A., Korsmeyer, Hydrogels in Medicine and Pharmacy, 3, 109-136, 198 https://doi.org/10.1201/97804292850977.
[19] C. Reitz, P. Kleinebudde, Influence of thermal and thermo-mechanical treatment: comparison of two lipids with respect to their suitability for solid lipid extrusion, J. Therm. Anal. Calorim. 89 (3) (2007) 669–673, https://doi.org/10.1007/s10973-006-7953-z.
[20] G. Oliveira, M.A. Wahl, J.F. Pinto, Characterization of laminar extrudates manufactured at room temperature in the absence of solvents for the delivery of drugs, Int. J. Pharm. 454 (1) (2013) 90–98, https://doi.org/10.1016/j.ijpharm.2013.06.072.
[21] F. Kreye, F. Siepmann, J. Siepmann, Drug release mechanisms of compressed lipid implants, Int. J. Pharm. 404 (1–2) (2011) 27–35, https://doi.org/10.1016/j.ijpharm.2010.10.048.
[22] Y. Rosiaux, V. Jannin, S. Hughes, D. Marchaud, Solid lipid Excipients—matrix agents for sustained drug delivery, J. Contr. Release 188 (2014) 18–30, https://doi.org/10.1016/j.jconrel.2014.06.004.

[23] E.S. Lutton, Review of the polymorphism of saturated even glycerides, J. Am. Oil Chem. Soc. 27 (7) (1950) 276–281, https://doi.org/10.1007/BF02634906.
[24] S. Koennings, A. Berié, J. Teßmar, T. Blunk, A. Göpferich, Influence of wettability and surface activity on release behavior of hydrophilic substances from lipid matrices, J. Contr. Release 119 (2) (2007) 173–181, https://doi.org/10.1016/j.jconrel.2007.02.008.
[25] M. Windbergs, C.J. Strachan, P. Kleinebudde, Influence of structural variations on drug release from lipid/polyethylene glycol matrices, Eur. J. Pharmaceut. Sci. 37 (5) (2009) 555–562, https://doi.org/10.1016/j.ejps.2009.04.010.
[26] P.L. Ritger, N.A. Peppas, A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs, J. Contr. Release 5 (1) (1987) 23–36, https://doi.org/10.1016/0168-3659(87)90034-4.
[27] N.A. Peppas, J.J. Sahlin, A simple equation for the description of solute release. III. Coupling of diffusion and relaxation, Int. J. Pharm. 57 (2) (1989) 169–172, https://doi.org/10.1016/0378-5173(89)90306-2.
[28] M. Özyazici, E.H. Gökçe, G. Ertan, Release and diffusional modeling of metronidazole lipid matrices, Eur. J. Pharm. Biopharm. 63 (3) (2006) 331–339, https://doi.org/10.1016/j.ejpb.2006.02.005.
[29] A. Abd-Elbary, M.I. Tadros, A.A. Alaa-Eldin, Sucrose stearate-enriched lipid matrix tablets of etodolac: modulation of drug release, diffusional modeling and structure elucidation studies, AAPS PharmSciTech 14 (2013) 656–668, https://doi.org/10.1208/s12249-013-9951-3.
[30] M.A. Quadir, M.S. Rahman, M.Z. Karim, S. Akter, M.T. Awkat, M.S. Reza, Evaluation of hydrophobic materials as matrices for controlled-release drug delivery, Pak. J. Pharm. Sci. 16 (2) (2003) 17–28.
[31] X. Zhao, X. Wang, J. Yan, Water-swelling behavior of hydrophobic porous copolymer resins composed of two kinds of crosslinkers, J. Appl. Polym. Sci. 92 (2) (2004) 997–1004, https://doi.org/10.1002/app.20060.