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Enhanced curcumin permeability by SLN formulation: the PAMPA approach.

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Abstract

Curcumin health benefits are strongly limited by its poor aqueous solubility and low oral bioavailability. This work was focused on the development and characterization of solid lipid nanoparticles (SLNs) for the encapsulation of curcumin for oral administration. High shear homogenization and ultrasonication techniques were employed to prepare Compritol SLNs. The physicochemical characterization of round shaped curcumin-loaded SLNs was carried out by monitoring particle size (lower than 300 nm), zeta potential (-33 mV), drug loading capacity (1.60%), drug entrapment efficiency (80%), TEM analysis and *in vitro* drug release. Stability (4ºC) was investigated over one month. Parallel Artificial Membrane Permeability Assay (PAMPA) showed a considerable increase of curcumin permeated when formulated as SLNs. A modified release profile suggested that curcumin molecules are solubilized into the solid lipid matrix. The developed SLNs were produced without the use of solvents and all excipients were GRAS ingredients; both technology and composition were suitable for food application.

Keywords: curcumin, solid lipid nanoparticles, Parallel Artificial Permeability Assay, *in vitro* release, stability studies.

1. Introduction

Curcumin is a yellow-colored phenolic natural constituent derived from the rhizome of the spice herb *Curcuma longa* L., widely known as turmeric. It has a broad spectrum of biological activities, principally antioxidant (Sharma, Manoharlal, Puri, & Prasad, 2010; Selvam, Subramanian, Gayathri, & Angayarkanni, 1995; Ruby, Kuttan, Babu, Rajasekharan, & Kuttan 1995) anti-inflammatory (Menon & Sudheer, 2007; Rao, Basu, & Siddiqui, 1982), antibacterial (Negi, Jayaprakasha, Jagan Mohan Rao, & Sakariah, 1999), antifungal (Sharma, 1976). Its chemopreventive (Devasena, Rajasekaran, Gunasekaran, Viswanathan, & Venugopal, 2003; Park, 2010) activity has received considerable attention because curcumin influences multiple signaling pathways, modulating more than 30 different proteins, including thioredoxin reductase, cyclooxygenase-2 (COX-2), protein kinase C (PKC), 5-lipoxygenase, activated AMP-activated protein kinase (AMPK) and tubulin. Other molecular targets modulated by this substance included transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis (Aggarwal, Kumar, & Bharti, 2003; Shishodia, Singh, & Chaturvedi, 2007; Aggarwal, Kuiken, Michelle, Laxmi, Kuzhuvelil, & Bokyung, 2009).

Curcumin shows a good safety profile, no studies in either animals or humans have demonstrated any toxicity associated with its use, even at high doses (Shankar, Shantha, Ramesh, Murthy, & Murthy, 1980; Lao, Ruffin, Normolle, Heath, & Bailey, 2006). This safe profile has been reflected by the continuous increase of preparations based on curcumin marketed as food ingredient or constituent of dietary supplements. Despite multiple health benefits, its utility is strongly limited by its poor aqueous solubility and low oral bioavailability. The latter is attributed to poor absorption, extensive intestinal and hepatic metabolism, rapid elimination and clearance from the body (Pan, Huang, & Lin, 1999; Anand, Kunnumakkara, Newman, & Aggarwal, 2007). Formulation of curcumin in effective dosage forms represented a challenge to overcome its poor physicochemical properties. Several strategies such as nanoparticles, liposomes, solid dispersions, microemulsions and complexation with phospholipids and cyclodextrins have been developed to improve the bioavailability of curcumin (Bisht, Feldmann, Soni, Ravi, Karikar, Maitra, & Maitra, 2007; Maiti, Mukherjee, Gantait, Saha, & Mukherjee, 2007; Tiyaboonchai, Tungpradit, & Plianbangchang, 2007; Sanoj Rejinold, Sreerekha, Chennazhi, Nair, & Jayakumar, 2011; Bergonzi, Hamdouch, Mazzacuva, Isacchi, & Bilia, 2014; Chaurasia, Patel, Chaubey, Kumar, Khan, & Mishra, 2015).

This study was focused on the preparation and characterization of solid lipid nanoparticles (SLNs) for oral administration of curcumin (Dhillon, Aggarwal, Newman, Wolff, Kunnumakkara, & Abbruzzese, 2008). Lipid-based drug delivery systems are promising formulations, since lipids are known oral drug absorption enhancers (Porter, Wasan, & Constantinides, 2008; Chakraborty, Shukla, Mishra, & Singh, 2009) and they can be developed in small particle sizes ranging from micro to nanometers (Jia, 2005; Pouton, 2006), that can increase the absorption in the hydrophilic environment of the gastrointestinal tract. SLNs combine these features: they are colloidal carriers of submicron size constituted of solid lipids at body and room temperatures. Substances used to prepare these nanoparticles are physiologic and generally recognized as safe compounds (GRAS ingredients); this aspect makes SLNs carriers without toxicity in humans (Müller, Mehnert, Lucks, Schwarz, Zur mühlen, & Meyhers, 1995). Moreover, they retain the advantages of traditional colloidal systems (Müller, Mader, & Gohla, 2000) such as enhanced physical stability, protection of drug molecules from degradation in the body, controlled drug release, organ or tissue specific targeting, biocompatibility, laboratory to industrial-scalability. SLNs, consist of a lipid core and an outer shell of amphiphilic surfactant. If drug is loaded in the outer shell and on the particle surface, it is quickly released, displaying a burst effect. On the other hand, if it is incorporated into the particle core, it is released in a prolonged way. This make possible a controlled drug release from these carriers, representing an important tool to obtain a prolonged release of the drug (Müller et al., 2000; Reddy, 2005).

A few studies concerning the development of curcumin SLNs have been reported in the literature, but only one paper is dealing SLN for oral administration (Kakkar, Singh, Singla, & Kaur, 2011). This study described the preparation of SLNs using Tween 80, soy lecithin and Compritol with microemulsion technique. *In vivo* pharmacokinetics performed in rats after oral administration of SLNs revealed significant improvement of curcumin bioavailability, but the percentage of Tween 80 in the SLNs is quite high (more than six times higher than the lipid phase). In other studies, the percentage of surfactant is the same or much higher than that of the lipid (Kakkar, Mishra, Chuttani, & Kaur, 2013; Aditya, Macedo, Doktorovova, Souto, Kim, Chang, & Ko, 2014; Hazzah, Farid, Nasra, EL-Massik, & Abdallah, 2015; Sun, Bi, Chan, Sun, Zhang & Zheng, 2013).

In the present study, the preparation of curcumin SLNs for a suitable oral dosage form was investigated, by using 50 g/kg fat phase and a low content of surfactant (25 g/kg), very suitable for oral administration.

In addition, the development of SLNs was carried out by homogenization-ultrasonication technique without the use of the solvents, technology that can be applied also to an indusial process.

Another key aspect was the analyses by DSC and X-ray diffractometry to investigate the drug-lipid interactions and the crystallinity of both curcumin and lipids, because this aspect could influence the release. Particle size analysis is a necessary, but not a sufficient step to characterize SLN quality. Special attention must be paid to the characterization of the degree of lipid crystallinity and the modification of the lipid, because these parameters are strongly correlated with drug incorporation and release profiles. DSC uses the fact that different lipid modifications possess different melting points and melting enthalpies. By means of X-ray scattering it is possible to assess the length of the long and short spacings of the lipid lattice.

Finally, stability test, release profile and permeability assay were performed to confirm the optimized biopharmaceutical properties of the developed nanovectors. The results confirmed that the developed SLNs offer a promising delivery system for enhancing the oral absorption of curcumin, suitable either for food fortification or as dietary supplements.

2. Materials and methods

2.1 Materials

Compritol 888 ATO, a mixture of mono-, di- and triglycerides of behenic acid (C22), was a gift of Gattefossè (Milan, Italy). Curcumin, Pluronic F68 and 1,7-octadiene were purchased from Sigma Aldrich Corporation (St. Louis, MO, USA). Lecithin was kindly provided by Galeno (Comeana, Prato, Italy). Lipase from porcine pancreas, pepsin from porcine gastric mucose, bile salts and cholesterol were analytical grade from Sigma Aldrich (Milan, Italy). 96-well MultiScreen PAMPA filter plate were purchased from Millipore Corporation, (Tullagreen, Carrigtwohill, County Cork, Ireland). All the solvents used were HPLC grade from Merck (Darmstadt, Germany); 85% formic acid was provided by Carlo Erba (Milan, Italy). Ethanol analytical reagent grade was from Riedel-de Haen Laborchemikalien GmbH & Co. KG, (Seelze, Germany). Water was purified by a Milli-Q_{plus} system from Millipore (Milford, MA). Phosphotungstic acid (PTA) was from Electron Microscopy Sciences (Hatfield, USA). Hydrion Buffer chemvelope pH 7.40±0.02 was purchased from Micro Essential Laboratory (Brooklin, New York, USA).

158 *2.2 High shear homogenization-ultrasonication method*

159 Blank and drug loaded SLNs were prepared using hot homogenization process followed by
160 ultrasonication (Castelli et al., 2005). Two formulations were investigated (SLN-1 and SLN-
161 2) loaded with two different concentrations of curcumin: 0.01 g/g and 0.02 g/g respect to the
162 lipid phase, respectively.
163 Briefly, different amounts of curcumin, (respectively 75 and 150 mg) were accurately
164 weighed and added to melted Compritol (7.5 g, 80ºC). Pluronic F68 (3.75 g) was dissolved in
165 distilled water (138 g) and heated at 85ºC in a beaker. When a clear homogenous lipid phase
166 was obtained, hot aqueous surfactant solution was added to hot lipid phase and homogenized
167 at 9660 x g, by using a high-speed stirrer (Ultra Turrax T25, IKA-Werke GmbH&Co. KG,
168 Staufen, Germany) for five minutes. The temperature was maintained at 80ºC during this step.
169 Then, the coarse emulsion was subjected to probe sonication (Sonopuls HD 2200, 200 W
170 power, probe MS 72, Bandelin Electronic GmbH, Berlin, Germany) for different times. Probe
171 sonication process was suspended for 2' intervals during each cycle, to prevent increase of
172 temperature. Temperature was monitored during the process. Sonication was applied
173 maximum for 15 minutes to avoid metal contamination, by considering also previously
174 published experimental conditions (Silva, González-Mira, García, Egea, Fonseca, Silva,
175 Santos, Souto, & Ferreira, 2011; Müller, Rühl, Runge, Schulze-Forster, & Mehnert, 1997;
176 Nassimi, Schleh, Lauenstein, Hussein, Hoymann, & Koch, 2010; Nayak, Tiyaboonchai,
177 Patankar, Madhusudhan, & Souto, 2010; Vitorino, Carvalho, Almeida, Sousa, & Pais, 2011).
178 Working temperature was kept at least 5ºC above the lipid melting point (85°C) to prevent
179 recrystallization during homogenization and ultrasonication. After ultrasonication, the
180 obtained emulsion (O/W) was cooled in an ice bath in order to solidify the lipid matrix and to
181 form SLNs. Blank and curcumin loaded SLNs were prepared and characterized as well. SLNs
182 dispersions were stored at 4ºC for further analyses.
183

184 *2.3 Particle size analysis and zeta potential measurements*

185 Mean diameter of the population and polydispersity index (P.I.) as a measure of the width of
186 particle size distribution together with the measure of zeta potential values were assessed by
187 photon correlation spectroscopy (PCS) using a Zetasizer Nano ZS (Malvern Instruments,
188 UK). Samples were prepared diluting 10 µl of SLN suspension with 2 ml of deionized water.
189 All measurements were done in triplicate. pH was measured prior to and after dilution,

because it value could alter the zeta-potential. pH resulted 6.1 prior to dilution and 6.3 after dilution.

2.4 Determination of encapsulation efficiency

The percentage of curcumin entrapped in the lipid matrix was determined as follows: a fixed amount of SLNs dispersion was purified by dialysis method, using a membrane (MW=12.400, Sigma Aldrich, Milan, Italy). Then, an amount of material retained in the bag was freeze-dried at -40ºC for 24 h, for following stability studies. The freeze drying process was optimized to obtain a homogenous porous solid and according to TEM and light scattering analyses.

Sample was dissolved in MeOH under stirring at 80°C for 10 min and then cooled to room temperature to preferentially precipitate the lipid (Nayak, et al., 2010; Tiyaboonchai, Tungpradit, & Plianbangchang, 2007; Sanna, Gavini, Cossu, Rassu, & Giunchedi, 2007). The suspension was centrifuged for 30 minutes at 13148 x g and the supernatant was analyzed by HPLC/DAD analysis using curcumin as external standard. Calibration curves were performed on six solutions in the concentration range 1.38–138 µg/ml. The squared correlation coefficient was >0.99. Curcumin encapsulation efficiency was expressed as drug recovery and calculated from the following equation:

$$Drug\ encapsulation\ efficiency\ (\%) = \frac{mass\ of\ active\ in\ nanoparticles}{mass\ of\ active\ fed\ to\ the\ system} \times 100$$

The drug loading content was the ratio of incorporated drug to lipid (w/w):

$$Drug\ loading\ (\%) = \frac{mass\ of\ active\ in\ nanoparticles}{weight\ of\ lipid} \times 100$$

No lipid interference occurred during UV determination of curcumin (data not shown). Curcumin loaded concentration was assayed by HPLC/DAD analysis performed using a HP 1100 Liquid Chromatograph (Agilent Technologies, Palo Alto, CA, USA) equipped with a HP 1040 Diode Array Detector (DAD), an automatic injector, an auto sampler and a column oven and managed by a HP 9000 workstation (Agilent Technologies, Palo Alto, CA, USA). The UV-Vis spectra were recorded between 220–500 nm and the chromatographic profiles was registered at 420 nm. Separations were performed on a reversed phase column Luna C18 (150 x 4.6 mm, 5 µm, Phenomenex) maintained at 27°C. The eluents were H_2O at pH 3.2 by formic acid (Solvent A) and acetonitrile (Solvent B), using a multi-step linear gradient of 32

min at a flow rate of 0.4 ml/min: 0.10 min 72% A and 18% of B; 10.0 min 56% A to 44% B; 27.0 min 52% A to 48% B; 27.0 min 52% A to 48% B; 32.0 min 20% A to 80% B .

2.5 Transmission electron microscopy (TEM)

The morphological characterization of the systems was obtained by using transmission electron microscopy technique (TEM, CM12 Philips, Netherlands). Samples were deposited on a *formuvar* film-coated copper grid and then stained with one drop of 20 g/L aqueous solution of phosphotungstic acid (PTA), allowing to dry before TEM observation.

2.6 Differential scanning calorimetry (DSC)

DSC was carried out using a Mettler TA4000 apparatus equipped with a DSC 25 cell. Samples (about 10 mg) were accurately weighed (Mettler M3 Microbalance) directly in pierced aluminum pans and scanned between 30 and 250°C at a heating rate of 10 K min^{-1} under static air. DSC thermograms of pure curcumin, Compritol, and curcumin-loaded SLNs were compared.

2.7 X-ray powder diffractometry

X-ray powder diffractograms were obtained with a Bruker D8 advance powder diffractometer, equipped with Cu Kα radiation and operating in ϑ-2ϑ Bragg Brentano geometry at 40 kV and 30 mA. The "SolX" solid-state detector was used. C/Ni Goebel mirrors for the incident beam were used. The samples were analyzed at ambient temperature over the 10–35° 2ϑ range at a scan rate of 0.02 deg s^{-1}.

2.8 In vitro release studies

Dialysis bag method was applied to study the drug release using a mixture of PBS (pH 6.8) and EtOH (150 mL/L ethanol to maintain the sink conditions) or simulated intestinal fluid as dissolution media. Simulated intestinal conditions contained intestinal enzymes (lipase 0.4 mg/ml, bile salts 0.7 mg/ml and pancreatin 0.5 mg/ml) and calcium chloride solution 750 mM at pH 7.0, (Aditya, et al., 2014). Release was monitored for 12 h. The dialysis bags were hydrated in PBS before use. Two milliliter of SLNs dispersion was introduced into the dialysis bag. The bag was placed in a beaker containing 200 mL of dissolution medium maintained at 37ºC under magnetic stirring (50 rpm). Aliquots of the dissolution medium

were withdrawn at different time intervals and replaced with the same volume of fresh medium to maintain the sink conditions. The samples were suitably diluted and analyzed for curcumin determination. All the operations were carried out in triplicate.

2.9 Stability studies

Stability of curcumin SLNs was studied over 1 month. SLNs were kept at 4±1°C and at fixed time intervals; they were assayed for their physical stability. Physical stability was checked by monitoring size, zeta potential and polydispersity of formulation.

2.10 Parallel artificial membrane permeability assay (PAMPA)

The PAMPA assay is a method for predicting passive intestinal absorption. The assay is carried out in a 96-well, MultiScreen-IP PAMPA (Millipore corporation) filter plate. The ability of compounds to diffuse from a donor compartment, through a PVDF membrane filter pretreated with a lipid-containing organic solvent, into an acceptor compartment is evaluated. 5 µL of lecithin (10g/L) and cholesterol (8g/L) in 1,7-octadiene solution were added to the filter of each well. Immediately after the application of the artificial membrane, 150 µL of drug containing donor solutions (free drug or curcumin-SLNs diluted in 0.05 mL/mL DMSO/PBS) were added to each well of the donor plate. In details, SLNs suspension was diluted to obtain in each donor compartment a final concentration of curcumin of 160 µg. A saturated solution of curcumin (0.3 µg of curcumin solubilized in the donor compartment) was used as control. 300 µL of buffer (0.05 mL/mL DMSO/PBS, pH 7.4) were added to each well of the acceptor plate. The acceptor plate was then placed into the donor plate, ensuring that the underside of the membrane was in contact with buffer. The plate was covered and incubated at room temperature under shaking for 24 hours and permeation was evaluated at 1, 2, 4, 6, 19, 24 hours.

3. Results and Discussion

3.1 Preparation of SLNs

The use of solid lipids instead of liquid oils is a very attractive idea to achieve controlled drug release, because drug mobility in a solid lipid should be considerably lower, compared with a liquid oil. SLNs are non-toxic, high biocompatible and easy to produce in large scale. SLN are drug carriers composed of a solid core suitable to target drugs to specific intestine associated systems. The nanoparticles are in the submicron size range. At room temperature

the particles are in the solid state. Therefore, the mobility of incorporated drugs is reduced, which is a prerequisite for controlled drug release.

Selected SLNs consisting of a core of Compritol were stabilized with Pluronic F68. Compritol was selected because it is a mixture of mono, di and triglycerides. Moreover, Compritol in enhancing the oral bioavailability in comparison to other lipid matrices was previously highlighted (Paliwal, Rai, Vaidya, Khatri, Goyal, Mishra, Mehta, & Vyas, 2009).

Compritol–based nanoparticles were heterogeneous with better drug-loading and release characteristics as compared with the other formulations. Accordingly, SLNs containing lipids with highly crystalline structure can give drug expulsion. On the other hand, the imperfections (lattice defects) of the lipid structure could offer more loading space to accommodate drugs (Westesen, Bunjes, & Koch, 1997; Muller et al., 2000; Silva, González-Mira, García, Egea, Fonseca, & Silva, 2011; Freitas & Müller, 1999; Mehnert & Mäder, 2012) while the use of a mixture of different oils as lipophilic can benefit the encapsulation efficiency. Compritol was also chosen as the lipid component because it gives stable dispersions with smaller particles. Two formulations with different amount of curcumin (0.01 g/g and 0.02 g/g respect to the lipid phase, SLN-1 and SLN-2 respectively) were prepared and fully characterized.

Homogenization-ultrasonication method was selected because economical, efficient and reproducible process to produce SLNs. Effect of different process variables on size, P.I., zeta potential, encapsulation efficiency was analyzed, and the results were reported on Table 1. Homogenization time was maintained constant at 10 minutes, time necessary to obtain a good emulsification of lipid (Das, Ng, Kanaujia, Kim, & Tan, 2011).

Sonication time (5, 10 and 15 minutes) showed huge influence on particle size. Sizes significantly decreased with increasing sonication time and the samples resulted always homogeneous. The best results in terms of P.I. values were found in the formulations SLN-1 and SLN-2, when 15 minutes of sonication were applied.

All formulations were negatively charged, the zeta potential varied from -10 to -45 mV indicating a relatively good stability and dispersion of the system. The negative value of zeta potential of SLNs was attributed to the presence of behenic acid into the lipid matrix surface and also to Pluronic. This is a non-ionic surfactant used in the production of relatively stable dispersions. Although non-ionic surfactant could not interact with charging group like ionic ones, but it can influence the particle/water interface and electric double layer. Pluronic can also provide additional steric stabilization of particles (Schwarz & Mehnert, 1999; Lim & Kim, 2002).

The quantity of curcumin loaded in the system increased the dimensions of SLNs: with 2% (0.02 g/g) the sizes ranged from 415 to 270, by increasing the sonication time. Particle size slightly increased with higher drug concentration; this is probably due to the presence of curcumin inside of lipidic core.

The data in Table 1 shows that all formulations possessed high entrapment efficiency (E.E. %) ranged from 70.7±2% to 80.2±2%. Encapsulation efficiency was not significantly different among SLN-1 and SLN-2, resulting around of 70%; such values might be related to the structure of the lipid which had a great influence on drug incorporation. Lipids which form highly crystalline particles with a perfect structure lead to drug expulsion (Westesen et al., 1997), while, more complex lipids such as Compritol, being mixtures of mono-, di- and triglycerides, produce less perfect structures with many imperfections offering space to accommodate curcumin (Müller et al., 2000). Another feature of Compritol that favors the encapsulation of lipophilic curcumin was the high hydrophobicity due to the long chain fatty acids attached to the triglycerides.

The formulation selected on the basis of the best properties in terms of size, P.I. and zeta potential was SLN-2-15, loaded with 0.02g/g of curcumin and sonicated for 15 minutes: it showed also an encapsulation efficiency of 80% and was selected for further investigations.

3.2 TEM analysis

TEM was conducted to investigate the morphology of solid lipid nanoparticles SLN-2-15. It was evident from TEM images that nanoparticles were almost spherical with smooth morphology, appeared as black dots, well dispersed and separated (Figure 1). This description agrees with a previous observation that the use of chemically heterogeneous lipids in combination with heterogeneous surfactants favors the formation of ideally spherical lipid nanoparticles (Mehnert & Mader, 2001). The mean diameter was in the range of 250-300 nm.

3.3 DSC and X-ray diffractometry assay

DSC and X-ray diffraction were performed for the assessment of the drug–lipid interactions and the crystallinity of curcumin and lipid matrices, because this aspect could influence the *in vitro* and *in vivo* release of the compound from the systems (Müller et al., 2000). Lipid crystallization is an important point for the performance of the SLN carriers. In fact, less perfect crystals with many imperfections can offer space to accommodate the drug (Müller et al., 2000) and also it can modulate the mobility of the drug during the release process

(Mehnert & Mäder, 2001; Silva et al., 2011; Mehnert & Mäder, 2012). The lack of crystallinity is also highly required to avoid extrusion of drug during storage.

The following samples were analysed: pure curcumin, Compritol, unloaded and loaded SLNs SLN-2-15. Figure 2 depicts the DSC thermograms obtained. As Compritol is not composed of pure triacylglycerols, the observed melting peak at 72.1ºC might be due to a mixture of metastable polymorphic β and β' forms. The thermogram showed also a relatively small endothermic shoulder at around 55ºC; this small shoulder corresponds to the melting of a very unstable modification of Compritol which is the α modification (Souto et al., 2006), that clearly disappears after the nanoparticles preparation. DSC analysis of curcumin showed the melting point at 173.17ºC. In the DSC thermograms of blank SLNs (unloaded) and loaded SLNs, a small endothermic peak was observed at 50ºC. This peak indicates the presence of Pluronic either in the form of coating surrounding the nanoparticles or as residue after dialysis and lyophilization.

Curcumin melting peak was not recorded in the SLN formulation attributed to the solubility of the drug within the solid lipid matrix.

X-ray diffraction studies evidenced that diffraction pattern of bulk Compritol (Figure 3) presents two main typical signals at 21.5° (2θ) and 23.5° (2θ), significantly modified when formulated into nanoparticles. Besides, another signal arises at 19.4° (2θ) after SLN preparation, corresponding to the most stable polymorphic form of triacylglycerols β (Souto, Mehnert, & Müller, 2006). These results might indicate that the final formulation is composed of the most stable polymorphic state of Compritol: SLNs seem to lose part of their crystallinity by transforming from a mixture of β and β' polymorphs in the most stable β polymorph and allowing curcumin to penetrate in the molecular gaps.

3.4 In vitro release studies

The release of curcumin from SLN-2-15 formulation was tested *in vitro* in of PBS (pH 6.8) and simulated intestinal medium. Due to the poor aqueous solubility of curcumin, ethanol (150 mL/L) was used in the receptor medium to mimic sink condition, as already described in literature (Kakkar et al., 2011; Mulik, Mönkkönenc, Juvonend, Mahadika, & Paradkarb, 2010). Cumulative drug release percentage versus time was plotted to demonstrate the release patterns (Figure 4). In both dissolution media a sustained/prolonged release. Curcumin reached about 40% of the amount loaded in the formulation during 12 hours in PBS. This may be attributed to the curcumin released slowly from the lipidic solid matrices, through diffusion and dissolution mechanisms (zur Mühlen et al., 1998; Mehnert & Mäder, 2012). Although the

release rate of SLNs could be influenced by complex factors, it was reported that among the factors, the large surface area and high diffusion coefficient due to small molecular size or low viscosity in the matrix are preponderant (zur Mühlen, Schwarz, & Mehnert, 1998).

The release profile was similar, but more intense during the incubation of SLNs in simulated intestinal medium. After 12 h the percentage reached about 60%. The presence of enzymes and bile salts caused a pronounced release, probably due to degradation of the lipid carrier and the subsequent solubilization of curcumin in colloidal species, like mixed micelles and swollen micelles (Noack, Oidtmann, Kutza, & Mäder, 2012).

3.5 Stability studies

Stability of curcumin solid lipid nanoparticles was studied over 1 month. Physical stability was checked by monitoring size, zeta potential and P.I. during time, by DLS measurements. There was no modification neither of the particle size nor of the zeta potential (Figure 5). Furthermore, polydispersity was stable over time, no vesicle size alterations occurred over the tested period.

3.6 Parallel artificial membrane permeability assay (PAMPA)

An approach for rapid assessment of absorption potential include the Parallel Artificial Membrane Permeability Assay (PAMPA) (Kansy, Avdeef, & Fischer, 2004). Pampa is based on a 96-well microplate technology and allows reasonable throughput, although it lacks similarity to natural membranes because it does not possess pores or active transport mechanism. It enables fast determination of the trends in the ability of the compounds to permeate membrane by passive diffusion and it is thus suited for the screening of large libraries. Due to their small particle size, SLNs may exhibit bioadhesion properties to the gastrointestinal tract wall or enter in the intervillar spaces thus increasing their residence time in the gastrointestinal tract and releasing the active drug encapsulated. This increase in adhesion results in enhanced bioavailability.

The experiment was carried out measuring the ability of curcumin to diffuse from our SLNs suspension to a donor compartment through a PVDF membrane.

A showed a strong increase of permeated curcumin was found in the case of SLNs suspension when compared with a saturated solution of curcumin used as control (Figure 6). In the case of SLNs, 4.2 µg, 7.9 µg and 9.3 µg of curcumin permeated to the acceptor compartment after 6, 19 and 24h, respectively; within the same timeframe, 0.03 µg, 0.03 µg and 0.04 µg

412 respectively of curcumin permeated from saturated solution. We can observe also that in the
413 case of aqueous saturated solution, the amount of permeated curcumin remains constant
414 during the test while, in the case of SLNs, permeated curcumin increases with time during 24
415 h of test.
416
417 **4. Conclusions**
418 In this study the poorly-soluble curcumin was incorporated into SLNs by homogenization and
419 ultrasound technique without the use of solvents.
420 Compritol demonstrated good solubilization of curcumin and formulation was obtained in
421 terms of drug loading, surfactant percentage and sonication time. Pluronic F68 was selected
422 as surfactant in the amount of 28 g/L of the formulation. SLN-2-15 formulation showed good
423 values of encapsulation efficiency, size, P.I., zeta potential and stability.
424 These SLNs resulted round shape with homogeneous size distribution, as confirmed by TEM
425 analysis. Size of the particles is a key factor for improve oral performance of poorly soluble
426 drugs and the average particle size of the developed nanoparticles was maintained below 300
427 nm, like other effective formulations, such as microemulsions or submicron emulsions. The
428 increased permeability of curcumin loaded in SLNs was confirmed by PAMPA, a simple
429 technique to evaluate *in vitro* passive gastrointestinal performance of innovative carriers. A
430 prolonged release profile was observed suggesting that curcumin is solubilized into the solid
431 lipid matrix. An increase in saturation solubility and, consequently, an increase in the release
432 rate of the drug allows it to reach high concentrations in the gastrointestinal tract. It is
433 expected a better *in vivo* performance of SLN because Pluronic may increase the permeability
434 through the intestinal membrane and they may promote the bioadhesion to the GI wall. Also,
435 the incorporation of curcumin into SLNs solid lipid matrix reduces its enzymatic degradation
436 during the process of absorption.
437 SLNs are very versatile carriers, particularly for the oral administration, they can be easily
438 transformed into powder (by spray-drying or lyophilization) and converted into solid dosage
439 forms, such as tablets, hard gelatin capsules, pellets or powders. The obtained powders can be
440 also dispersed in water or juice prior to administration.
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Figure captions

Figure 1: TEM micrographs of curcumin of SLN-2-15 sample (loaded with 0.02g/g of curcumin and obtained with 15 min of sonication) (A) with details of single SLN (B; C).

Figure 2: DSC thermographs of Compritol; pure curcumin; blank and loaded solid lipid nanoparticles (SLN-2-15 sample, loaded with 0.02g/g of curcumin and obtained with 15 min of sonication).

Figure 3: X-ray diffraction pattern of Compritol; pure curcumin; blank and loaded solid lipid nanoparticles SLN-2-15 sample, loaded with 0.02g/g of curcumin and obtained with 15 min of sonication).

Figure 4: *In vitro* release profile of curcumin from SLN-2-15 sample (loaded with 0.02g/g of curcumin and obtained with 15 min of sonication). Each data represent the mean ± standard deviation of three experiments.

Figure 5: Particle size (A), polydispersity index (P.I., B) and zeta potential (C) evolution of curcumin solid lipid nanoparticles (SLN-2-15 sample, loaded with 0.02g/g of curcumin and obtained with 15 min of sonication) at storage conditions (30 days, 4ºC). (Mean±S.D.; n=3).

Figure 6: Permeation profile of free curcumin and curcumin loaded SLNs by Parallel artificial membrane permeability assay (PAMPA). Amount of curcumin is referred to each well. Black: control; grey: SLN-2-15 sample, loaded with 0.02g/g of curcumin and obtained with 15 min of sonication. (Mean±S.D.; n=3).

Table 1. Characterization of developed blank and curcumin loaded SLNs; effect of sonication time and amount of curcumin on size, polydispersity index (P.I.), encapsulation efficiency (EE%) and drug loading (D.L.%). SLN-1, SLN-2 are solid lipid nanoparticles loaded respectively with 0.01 and 0.02g/g of curcumin. 5, 10 and 15 indicate sonication time. Each data represent the mean ± standard deviation of three experiments.

Formulation	**Time of sonication (min)**	**Curcumin (g/g)**	**Size (nm)**	**P.I.**	**ζ Potential (mV)**	**EE (%)**	**DL (%)**
Blank SLN	5	-	333±1	0.28±0.02	-36±3	-	-
	10	-	254±6	0.25±0.01	-24±2	-	-
	15	-	241±9	0.33±0.03	-10±1	-	-
SLN-1-5	5	0.01	320±18	0.31±0.03	-45±2	76.4±4.9	0.76
SLN-1-10	10	0.01	238±4	0.31±0.04	-34±4	74.2±16	0.74
SLN-1-15	15	0.01	199±23	0.26±0.02	-39±4	76.4±4.6	0.76
SLN-2-5	5	0.02	415±6	0.31±0.08	-39±3	70.7±2	1.41
SLN-2-10	10	0.02	313±13	0.33±0.01	-29±4	77.8±8	1.56
SLN-2-15	15	0.02	270±15	0.29±0.01	-33±3	80.2±2	1.60

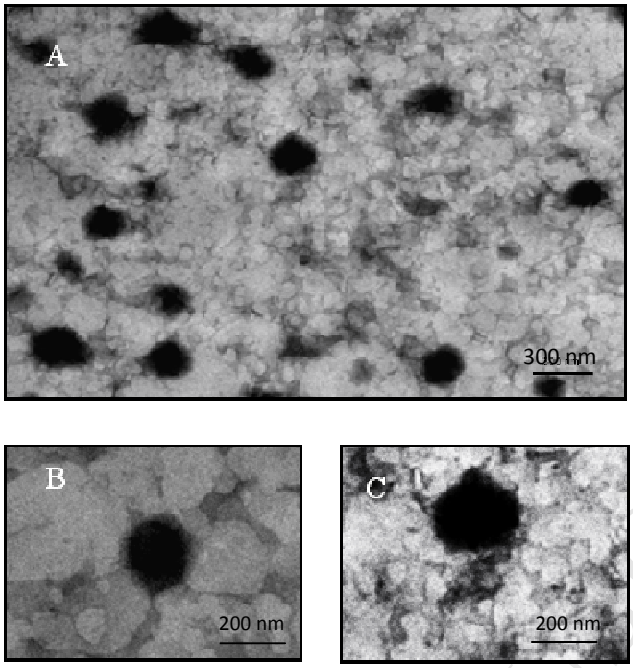

Figure 1

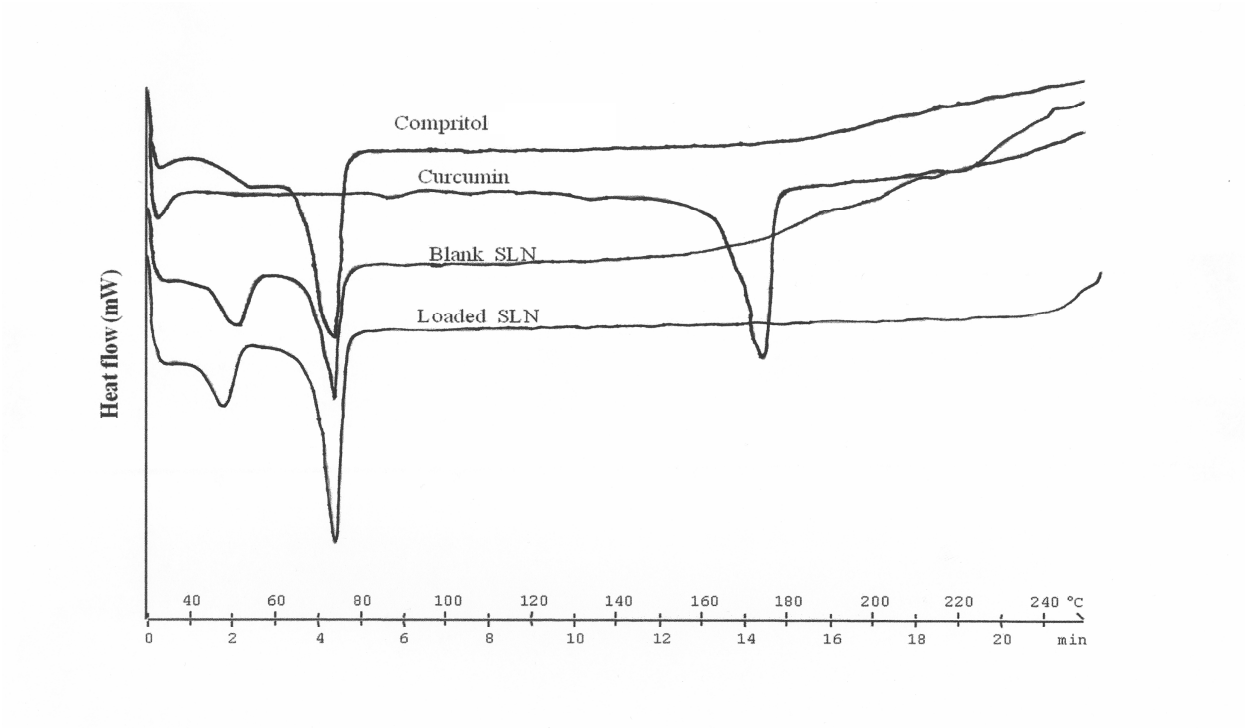

Figure 2

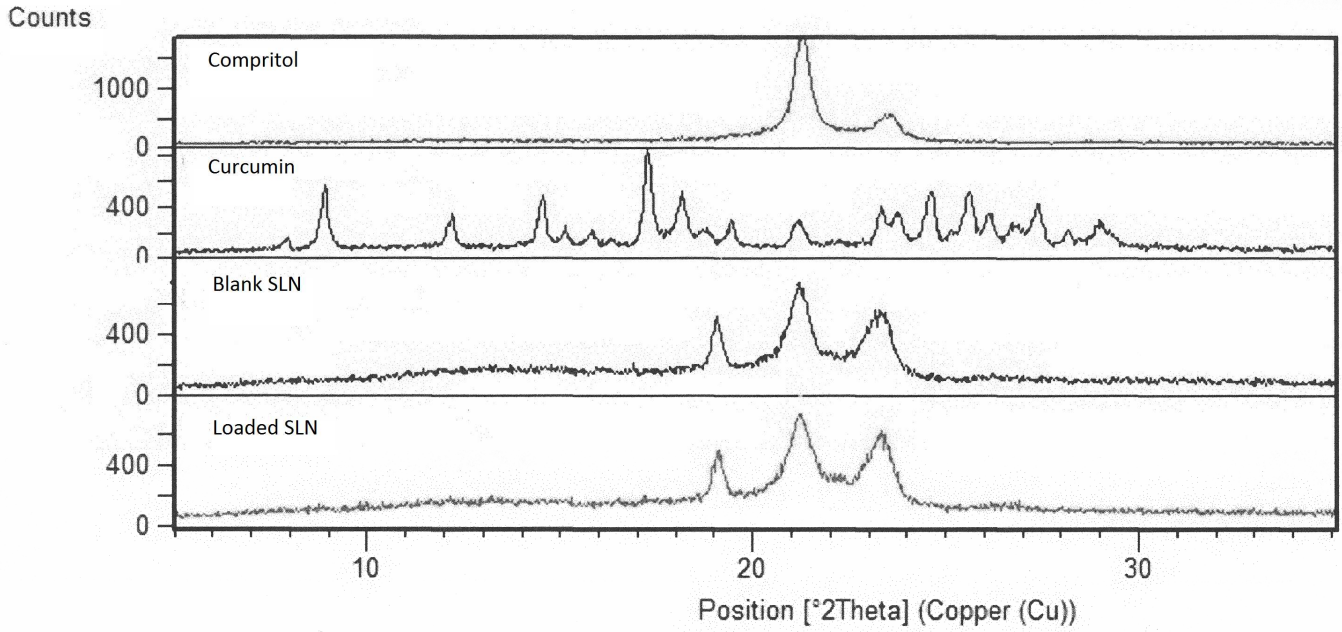

Figure 3

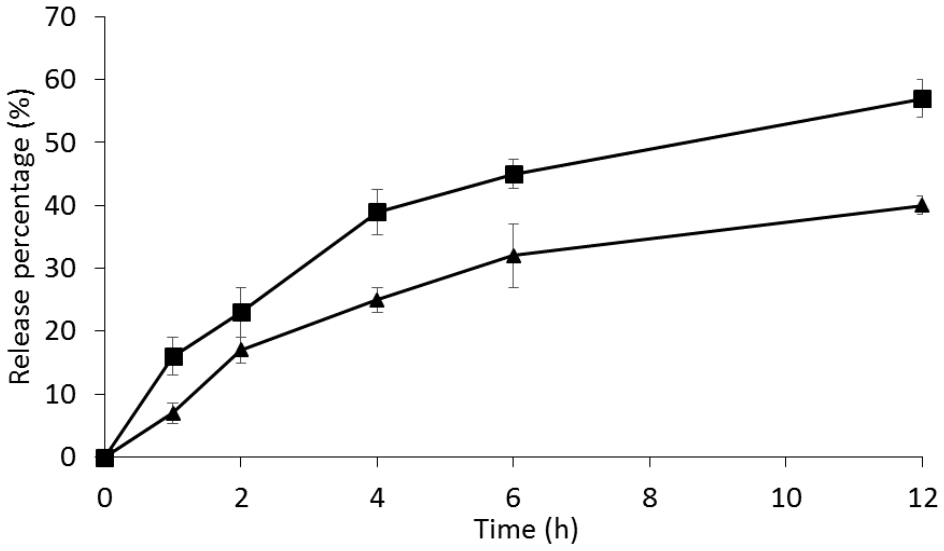

Figure 4

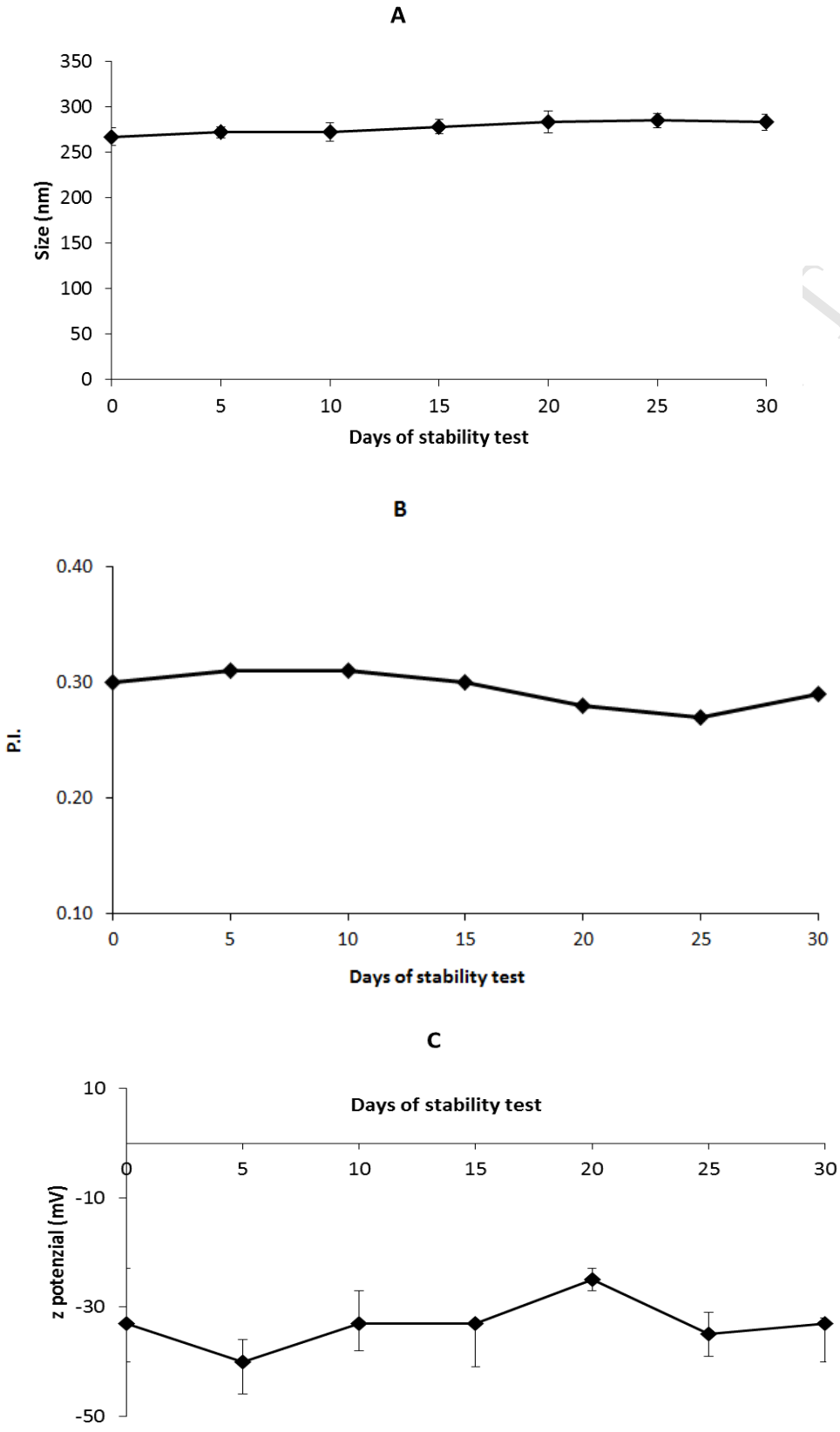

Figure 5

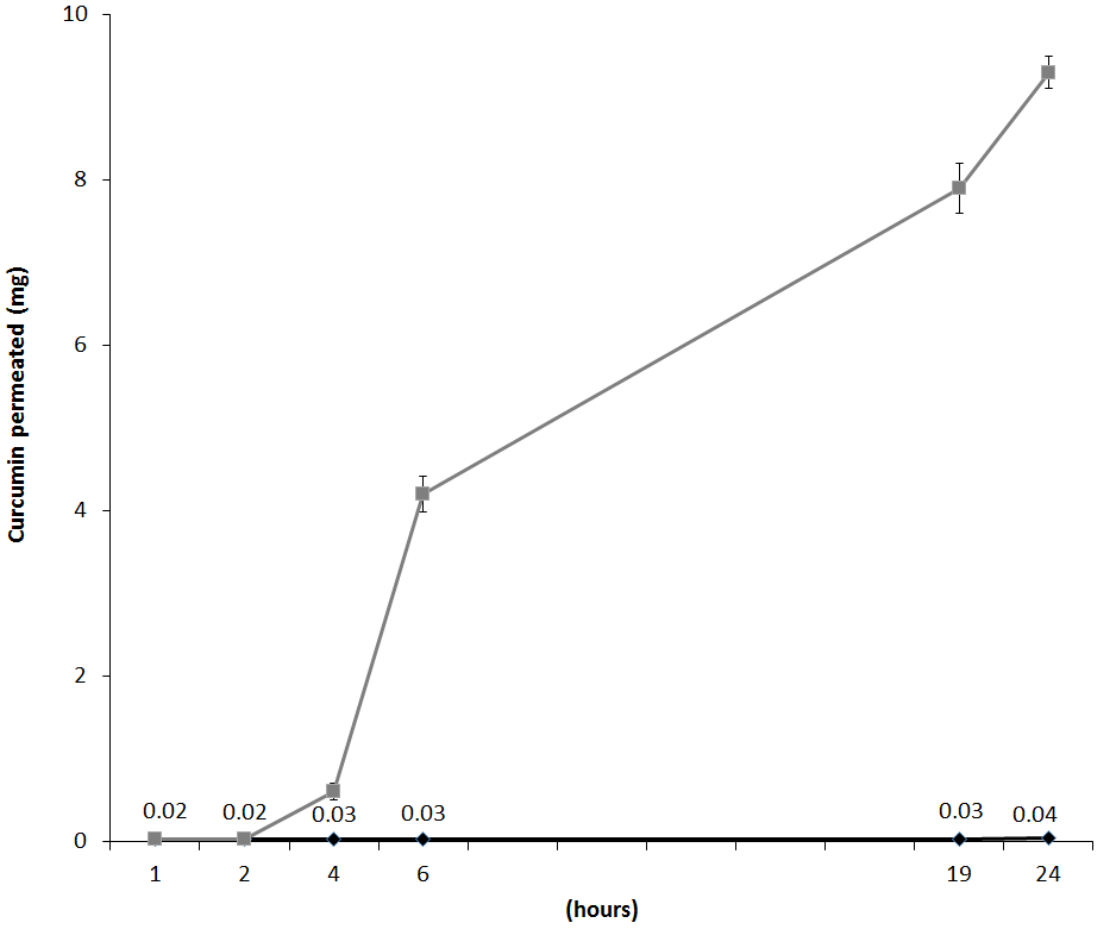

Figure 6

Highlights:

1. Compritol and Pluronic were used to prepare curcumin oral solid lipid nanoparticles.
2. Solid lipid nanoparticles resulted stable over 1 month at 4±1°C.
3. *In vitro* studies showed a good release of curcumin from lipid nanoparticles.
4. Formulation increases the amount of curcumin permeated by 2 orders of magnitude.