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Preparation, characterization and *in vivo* evaluation of curcumin self-nano phospholipid dispersion as an approach to enhance oral bioavailability

Ahmed N. Allam [a,*], Ibrahim A. Komeil [b], Mohamed A. Fouda [c], Ossama Y. Abdallah [a]

[a] Department of Pharmaceutics, Faculty of Pharmacy, Alexandria University, Egypt
[b] R&D Pharmacist at Medizen Pharmaceutical Industries, Alexandria, Egypt
[c] Department of Pharmacology and Toxicology Department, Faculty of Pharmacy, Alexandria University, Egypt

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ABSTRACT

The aim of this study was to examine the efficacy of self-nano phospholipid dispersions (SNPDs) based on Phosal® to improve the oral bioavailability of curcumin (CUR). SNPDs were prepared with Phosal® 53 and Miglyol 812 at different surfactant ratio. Formulations were evaluated for particle size, polydispersity index, zeta potential, and robustness toward dilution, TEM as well as *in vitro* drug release. The *in vivo* oral absorption of selected formulations in comparison to drug suspension was evaluated in rats. Moreover, formulations were assessed for *in vitro* characteristic changes before and after storage.

The SNPDs were miscible with water in any ratio and did not show any phase separation or drug precipitation. All the formulas were monodisperse with nano range size from 158 ± 2.6 nm to 610 ± 6.24 nm. They passed the pharmacopeial tolerance for CUR dissolution. No change in dissolution profile and physicochemical characteristics was detected after storage. CUR–SNPDs are found to be more bioavailable compared with suspension during an *in vivo* study in rats and *in vitro* release studies failed to imitate the *in vivo* conditions. These formulations might be new alternative carriers that enhance the oral bioavailability of poorly water-soluble molecules, such as CUR.

1. Introduction

Drug delivery systems composed of lipid compounds have gained great importance in medical, pharmaceutical, cosmetic, and alimentary fields. Phospholipids based formulations represent an interesting field of application in the novel research for delivery models (Fricker et al., 2010; Werling et al., 2008). The biocompatibility of phospholipids remains a highly desirable approach in developing stable and safe drug dispersions since their acceptance by regulatory agencies and extensive history of use make them useful excipients in formulations intended for oral, topical, and intravenous delivery (Khani and Keyhanfar, 2014). A further advantage of phospholipids formulations in oral drug delivery is that drugs susceptible to decomposition by enzymes in the GI tract may be protected by formulation with phospholipids (Fricker et al., 2010). The lack of sufficient attention to lipid-based formulations prior to clinical testing on insoluble molecules, especially those with low or variable oral bioavailability in conventional formulations, has led to a dearth of applications for this technology and only 2–4% of the commercially available drug products formulated relies on such technology (Hauss, 2007; Khani and Keyhanfar, 2014).

Phosal® branded products are non-aqueous solutions with phosphatidylcholine (PC) in different concentrations for oral and topical pharmaceutical applications as well as cosmetic products. They can act as solubilizers for insoluble components or function as a source of PC with essential fatty acids (Khani and Keyhanfar, 2014). The additional designations identify the carrier media used, such as medium-chain triglycerides (MCT) and propylene glycol (PG). On reviewing previous studies, there is a limited application with Phosal series in pharmaceutical development; application of Phosal® 50 PG was reported to improve the absorption of highly lipophilic drug, Rapamycin (Carlson et al., 1998). Similarly, Hu et al. (2007) achieved an improvement in oral bioavailability for tumor-inhibiting Src kinase inhibitor TG100435 solubilized in Phosal® 50 PG to possess better bioavailability in comparing with those

* Corresponding author at: Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, El-Khartoum Square, El-Azarita, Alexandria 21521, Egypt. Tel.: +20 10 5422491; fax: +20 3 4873273.
E-mail addresses: ph.a.allam@gmail.com, Allam_basha2000@yahoo.com (A.N. Allam), Ibrahimkomeil393@gmail.com (I.A. Komeil), Mohamed.foudah@alexu.edu.eg (M.A. Fouda), ossama.y.abdallah@gmail.com (O.Y. Abdallah).

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formulations containing aqueous dispersions of Lutrol® F-68 and methylcellulose. Phosal® 50 PG based formulation also raised the bioavailability of mebudipine relative to both its suspension and oily solution formulations, after oral administration (Khani and Keyhanfar, 2014). Another work done by Ge et al. (2008) who prepared a nanoemulsion for Lovastatin from Tween 80 and Phosal® 53 MCT to enhance its oral bioavailability over its suspension form in addition better protection against decomposition by enzymes.

From the previous studies, it is obvious that substances with low aqueous solubility or/and low permeability are good candidates for bioavailability enhancement by phospholipid formulations. These may be formulated into liquid or semi-liquid drug delivery systems with phospholipids.

Curcumin (CUR), a natural polyphenol, found in the turmeric rhizomes has been reported to have a widespread use in variety of biological activities, including antioxidant activity, antitumor, anti-inflammatory, antidiabetic, antirehumatic, wound healing, antiviral, hepatoprotective, and anti-HIV (Sun et al., 2012). Despite the promising biological effects of CUR, poor bioavailability in both rats and humans as reported in several pharmacokinetic studies (Sharma et al., 2001; Zhongfa et al., 2012). Extremely low aqueous solubility or extensive pre-systemic metabolism may be responsible for the unfavorable pharmacokinetics of this molecule (Sun et al., 2012). Although 10 or 12 g of curcumin administered orally in humans showed curcumin levels in serum to be approximately 50 ng/ml, this resulted in a minimum availability of curcumin in the blood circulation to achieve its therapeutic effects (Yallapu et al., 2012). Low oral bioavailability causes intersubject variability and poor therapeutic effects; therefore, developing new formulations to improve the solubility and bioavailability of CUR is a challenging task.

The aim of this investigation was to examine the efficacy of self-nano phospholipid dispersions (SNPDs) based on commercially available Phosal® branded products to enhance the oral bioavailability of curcumin (CUR). A simple developmental and manufacturing method was utilized and different physicochemical characterization for the prepared SNPDs were assessed. The *in vivo* oral absorption of selected formulations in comparison to drug suspension was evaluated in rats. Furthermore, Formulations were assessed for *in vitro* characteristic changes before and after storage for 3 months.

2. Materials and methods

2.1. Materials

Curcumin powder was purchased from Shenzhen chemrider, China; Phosal® 50 PG and Phosal® 53 MCT were gift samples from Lipoid Co., Ludwigshafen, Germany, Polyoxyl 35 castor oil (CRM EL) and Polyoxyl 40 hydrogenated castor (CRM RH40) by Basf, USA; Capric/caprilic triglyceride (Miglyol 812) by Gattefosse' Corp, USA; Polyethylene glycol (PEG)-7-glyceryl cocoate was a sample gift from Galaxy, India. Sodium lauryl sulphate (SLS) by Evonik Degussa, UK; All other reagents and chemicals were of analytical grade.

2.2. Solubility study of curcumin

Saturation solubility of CUR in Phosal® 53 MCT, Phosal® 50 PG, PEG-7-glyceryl cocoate and CRM EL was determined using standard shake flask method. Briefly, excess CUR was added to the vehicle in a tightly capped conical flask. Samples were constantly agitated at conditions (100 rpm, 37 °C and 24 h in a reciprocating water bath (Bunsen, India). Samples were centrifuged at (4000 rpm, 15 min) after 24 h equilibrium where aliquots of supernatant were diluted to appropriate concentrations with acetone. Samples were analyzed spectrophotometrically (Shimadzu, Japan) at wavelength 420 nm.

2.3. Preparation of CUR self-nano phospholipid dispersions

Compositions of different CUR–SNPDs are presented in Table 1. F1 was prepared by mixing CUR with Phosal® 53 MCT in a beaker placed in thermostatic water bath (Bunsen, India) adjusted at 40 °C for 30 min till obtaining a clear viscous liquid while F2 was prepared by mixing Phosal® 53 MCT with surfactants for 10 min before addition of CUR and heating at 40 °C for 30 min, respectively. In contrast, F3–F6 did not need heat and were simply prepared by mixing of CUR with other ingredients for 10 min in a beaker till obtaining a deep orange solution with very low viscosity.

2.4. Characterization of CUR self-nano phospholipid dispersions

2.4.1. Physical robustness to dilution

SNPDs were exposed to different folds of dilutions (100, 500 and 1000) with different media (water, 0.1N HCl and phosphate buffer pH 7.4). Diluted formulations were stored on shelf for 6 h where any physical changes were monitored. Percentage of transmission was measured by using spectrophotometer (Shimadzu, Japan) at wavelength 638.3 nm (Elnaggar et al., 2009; Elsheikh et al., 2012; Gupta et al., 2011)

2.4.2. Particle size, zeta potential and polydispersity index

The mean particle size (PS), polydispersity index (PDI) and zeta potential (ZP) for CUR–SNPD formulations (F1–F6) were measured by using dynamic light scattering technique (Malvern Zeta sizer, Malvern instruments, UK) where samples were sonicated for 10 min and diluted with distilled water before measurements.

2.5. In-vitro *dissolution study*

In-vitro dissolution test was carried out according to USP 32 (USP, 2011) for dissolution of CUR, where 900 ml of 1% SLS was used as a dissolution medium with application of apparatus II (Hanson, USA) at 100 rpm for 120 min at 37 °C ± 0.5 °C. In addition, water was also used as a comparative dissolution medium with the same pharmacopeial conditions to study the dissolution pattern for CUR–SNPDs relative to the official system.

Forty milligram (in terms of CUR) from each formula was weighed in a hard gelatin capsule and placed in the dissolution test apparatus where 10 ml sample was withdrawn in triplicates at different intervals, filtered, replaced by fresh corresponding medium and analyzed spectrophotometrically at wavelength 420 nm. Shifting from visible absorbance to UV absorbance over time, signifying the disappearance of characteristic curcumin peak at 420 nm, can be used as a measurement of degradation (Leung et al., 2008).

Table 1
Composition of CUR phospholipid dispersion formulations.

Material (mg)	F1	F2	F3	F4	F5	F6
CUR	60	60	60	60	60	60
Phosal® 53 MCT	1160	1000	300	300	300	300
Miglyol 812	–	–	–	61	183	305
CRM EL	–	80	80	50	50	50
PEG-7-glyceryl cocoate	–	80	780	749	627	505