5. CONCLUSION

- Our work successes to produce a valuable locally prepared CUR-SPC complex with low cost price and through performing several in-vitro and in-vivo tests. It is concluded that it is a complete similarity with Meriva^{TM}, patently product by Indena, SpA. This approach opens much more chances to produce similar products with low cost price.
- Many advantages are gained on using soft gelatin capsules over hard gelatin capsule as a unit dose for CUR phytosome administration. For example; ability to increase the unit dose of CUR per capsule, using liquified bioactive excipients which affect the bioavailability of CUR and decrease the production loss during production process takes place.
- On formulating PHYTOSOME in a soft gelatin capsule, attention must be performed in selection of excipients (i.e. oils or surfactant) to avoid salting out phenomena due to the difference in the solubility of active herbal drug in different excipients.

CHAPTER II

PREPARATION AND EVALUATION OF CURCUMIN SELF PHOSPHOLIPID NANO DISPERSION: A NOVEL DELIVERY SYSTEM TO ENHANCE CURCUMIN SYSTEMIC BIOAVAILABILITY

1. INTRODUCTION

The gastrointestinal (GI) tract acts as a physiological and chemical barrier setting several challenges for oral drug delivery systems. In this context, increasing knowledge on lipids like lecithin make them more interesting for the formulation of poorly water soluble drugs in the form of fat emulsions, mixed micelles, suspensions and liposomal preparation[210].

Lecithin is defined according to USP as a complex mixture of acetone-insoluble phosphatides which consists chiefly of phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine and phosphatidylinositol combined with various amounts of other substances such as triglycerides, fatty acids and carbohydrates as separated from the crude vegetable oil source. It contains not less than 50 % of acetone insoluble matter [92] and it is isolated from the crude oil obtained from its natural source like soybeans, rape seed and egg yolk by degumming process[210].

After degumming process, crude lecithin undergoes several purification processes yielding phospholipids as shown in (Figure 71). Phospholipids are surface-active, amiphilic molecules with a polar head group with phosphorus and lipophilic tail of two fatty acids chains where the most common phospholipid in lecithin is PC[210].

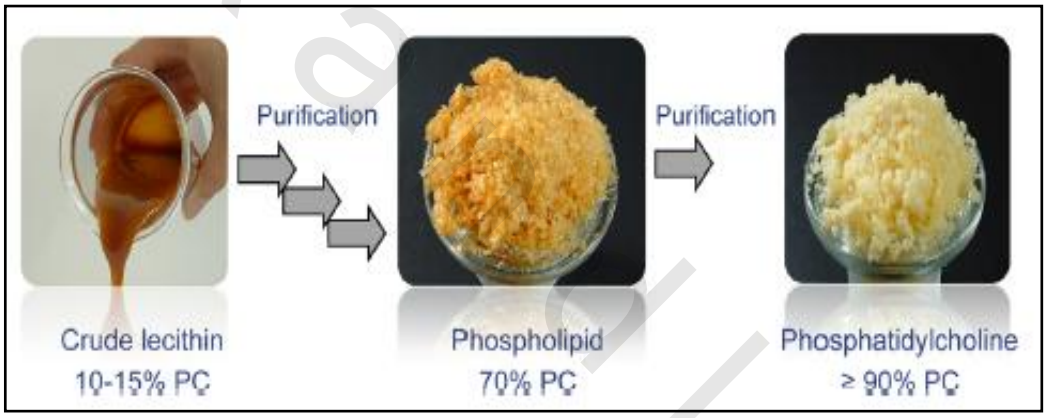

Figure 71: Visual aspect of soybean lecithin fractions with varying PC content.

1.1. Chemical structure

Phospholipids are derived from sn-glycerophosphate. The non-polar region is formed of two fatty acids esterified to the position 1 and 2 of the glycerol backbone while the polar region consists of a phosphate ester at position 3. The functional properties of the various phospholipids are determined by the nature of their polar headgroups as shown in (Figure 72).

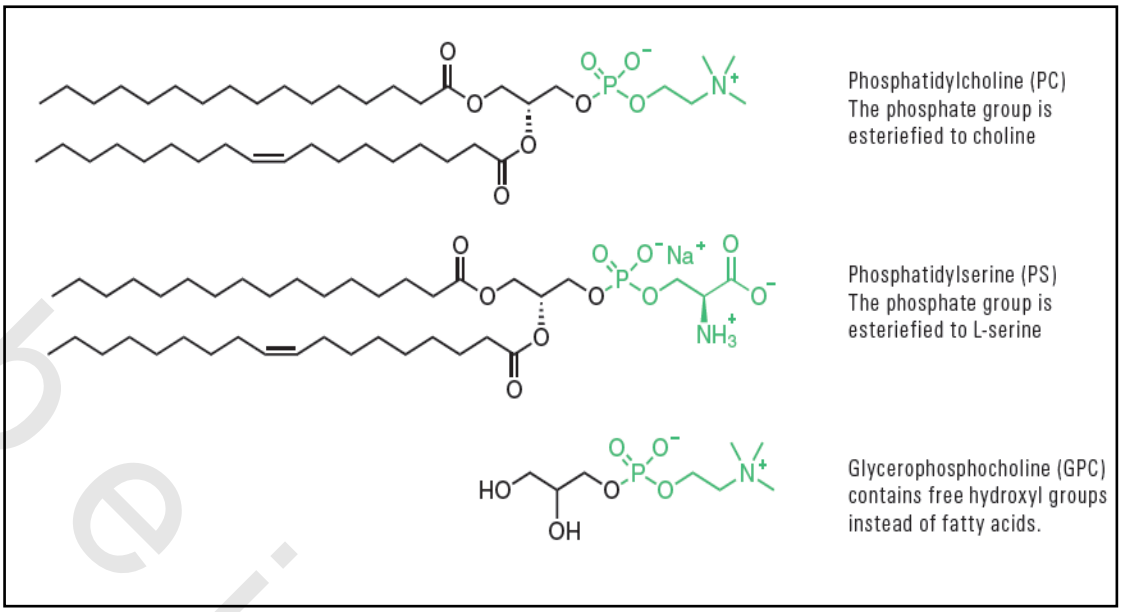

Figure 72: Chemical structures for various phospholipids [163]

1.2. Types of phospholipids

According to the source of phospholipids, it is divided into natural and synthetic phospholipids

1.2.1. Natural phospholipids[210]

Natural phospholipids are defined as phospholipids isolated from natural source as soybean, rapeseed and egg yolk. The phospholipid composition of the lecithin depends on the source of raw material as shown in Table 16.

Table 16: Phospholipid composition of vegetable de-oiled/egg lecithin

Phospholipid	Soybean	Rapeseed	Egg yolk (contains 64-79% PC)
Phosphatidylcholine	20-22%	23-31%	72%
Phosphatidylethanolamine	16-22%	9-15%	17%
Phosphatidylinositol	13-16%	15-18%	-
Phosphatidic acid	5-10%	5-10%	-
Lysophophatidylcholine	<3	<3	2%
Sphingomylein	-	-	2%
Lysophosphatidylethanol amine	-	-	1%

Natural phospholipids may be converted to saturated phospholipids by means of hydrogenation to increase the phase transition temperature for phospholipids in order to produce more physically stable liposomes with increased stability in blood plasma.[210] Also, it should be noticed most of phospholipid products are supplied by *Lipoid GmbH, Germany* with different forms as illustrated in Table 17.

1.2.2. Synthetic phospholipids

Synthetic phospholipids are developed in order to study biophysical/biochemical mechanistic aspects of phospholipids at the molecular level which are homogeneous with respect to the polar head group and fatty acid composition[211] in addition to the growing need to synthesis phospholipids to optimize the drug targeting properties of liposomes as PEG-ylated phospholipids[212] and the cationic phospholipid 1,2-diacyl-P-O-ethylphosphatidylcholine[213].

Table 17: Composition of some commercial products of soybean phosphatidylcholine with different oils and waxes.

Nature	Trade name	Composition
Natural phospholipid	LIPOID S 100	Soybean phosphatidylcholine approx. 94%
	LIPOID S 75	Soybean phosphatidycholine approx. 70%
	LIPOID S 40	Soybean phosphatidylcholine ≥ 40%
	LIPOID S 80	Soybean phosphatidylcholine approx. 75%
Hydrogenated phospholipid	PHOSPHOLIPON® 80H	Soybean phosphatidylcholine ≥ 70%
Compounds containing phospholipid	PHOSAL®53MCT	Soybean phosphatidylcholine (≥53%) in caprylic/capric triglycerides and ethanol
	PHOSAL®25MCT	Soybean phosphatidylcholine (≥20%) in medium chain triglyceride
	PHOSAL® 50 PG	Soybean phosphatidylcholine (≥50%) in propylene glycol (33.8-41.2 %) and ethanol
	LIPOID PPL 400	Soybean phosphatidylcholine (≥53%) in hard fat and soybean oil
	LIPOID PPL 600	Soybean phosphatidylcholine (≥37%) in soybean oil and medium chain triglyceride
	LIPOID PPL	Soybean phosphatidylcholine (≥35%) in soybean oil and medium chain triglyceride

1.3. Pharmaceutical applications of phospholipids

1.3.1. Pure phospholipids

Nicolaos *et al* [214] demonstrated the improvement of the oral bioavailability of cefpodoxime proxetil by using a phospholipid based nano emulsion composed of (IMWITOR® 742), MCT and LIPOID S 45 of particle size 230 nm compared to an ethanolic solution, a suspension and an emulsion of the active ingredient .

Wang *et al* [215] utilized phospholipids containing approximately 70-80% soya bean phospholipids (i.e. Lipoid S 75) to make a complex with hydroxysafflower yellow A in a liquified system with application of a surfactant and oil to enhance its oral bioavailability in rats.

Semalty *et al* [216] prepared pharmacosomes (amphilhilic drug-lipid complex) of diclofenac and soybean phosphatidylcholine (Lipoid S 80) resulting in improvement of drug water solubility and diclofenac bioavailability.

Hydrogenated phosphatidylcholine (PHOSPHOLIPON® 80H) (80% PC) was applied by Fini *et al* [217] in the preparation of oral disintegrating tablet of ibuprofen in order to decelerate the release of active material, avoid or weaken its side effects and to mask its taste.

1.3.2. Compounds containing PC

Up to our knowledge, there is no application with LIPOID PPL series in the literature and limited application with PHOSAL series in pharmaceutical development as shown in the following researches:

- Immunosuppressant; Rapamycin is formulated with PHOSAL®50 PG as solubilizer of the highly lipophilic drug. PHOSAL®50 PG is a standardized phosphatidylcholine concentrate with at least 50% PC in propylene glycol containing lecithin, sunflower mono and diglycerides and ascorbyl palmitate. It is shown that the application of phosphatidylcholine improves the absorption, effectiveness and therapeutic index of the active ingredient, while simultaneously enabling the administration of a lower dosage and reducing medication costs side effects [163].

- Hu *et al* [218] achieved an improvement in oral bioavailability by using animal models; rat and dogs for tumor-inhibiting Src kinase inhibitor TG100435 and its metabolite to be solubilized in PHOSAL®50 PG to possess better bioavailability in comparing with those formulations containing aqueous dispersions of Lutrol®F-68 and methylcellulose.

- Ge *et al* [219] prepared a nano emulsion for Lovastatin from Tween 80 and PHOSAL® 53 MCT and spray dried it with a starch matrix with particle size range 135.6-218 nm to enhance its oral bioavailability over its suspension form in addition the active ingredient showed a better protection against decomposition by enzymes.

- Gunasekaran *et al* [220] termed the incorporation of nanotechnology in herbal formulation researches as "nano phytomedine". Where applied nano-based formulations have many advantages including:
-

- Improvement of solubility and bioavailability.
- Protection from toxicity.
- Enhancement of pharmacological activity.
- Improvement of stability.
- Protection from physical and chemical degradation.

From previous researches, it is obvious the growing interest in using phospholipids in different nanotechnology applications (i.e. liposomes, mixed micelles, nano emulsion and nano suspensions) in herbal formulations to maximize their medical benefits. From this point of view, many researchers developed nano herbal formulations based on an expensive type of phospholipid like Aisha *et al* [221] who developed a nano sized liposome of orthosiphon stamineus ethanolic extract in soybean phospholipids (i.e. Lipoid S 75) and Freag *et al* [185] who formulated diosmin in the form of diosmin-phospholipid (i.e. Lipoid S 100) complex.

Although their successful approaches in optimization the bioavailability of herbal drugs, they were unable to develop their work to be administrated in a dosage form products in a large scale production due to high cost of phospholipids as a raw material and production process difficulties.

Therefore, there is a need to develop a low cost nano delivery system for herbal drugs by reducing the cost of used raw materials and develop a simple production steps to produce a suitable oral dosage form containing nano based formulations.

AIM OF THE WORK

Our present work aims to prepare a self phospholipid nano dispersion (SPND) for CUR encapsulated in soft gelatin capsule by using low cost phosphatidylcholine product known as PHOSAL®53 MCT via a simple method and fast production process. This is in order to enhance the oral systematic bioavailability of CUR.

2. EXPERIMENTAL

2.1. Materials

- Curcumin powder was purchased from Shenzhen chemrider, China
- Approximately 53% soy phosphatidylcholine (SPC) phospholipid in medium-chain triglycerides (PHOSAL® 53 MCT) was a gift sample from Lipoid Co., Ludwigshafen, Germany
- Polyoxyl 35 hydrogenated castor oil (Cremophore EL) was purchased from Basf, USA.
- Capric/caprilic triglyceride (Miglyol 812) was purchased from Gattefosse' Corp, USA.
- Polyethylene glycol 400 (PEG 400) was purchased from Dow chemical company, USA.
- Sodium lauryl sulphate was purchased from Basf, USA
- Polyethylene glycol (PEG) -7- glyceryl cocoate was a sample gift from Galaxy, India
- Potassium chloride, Ammonium acetate and Acetonitrile were of analytical grade.

2.2. Equipments

- Eight stations dissolution apparatus,(SR 8 plus, Hanson research, USA)
- Malvern Zeta Sizer (Malvern Instruments, UK)
- Transmission electron microscope (model JEM-100S microscope, Jeol, Japan)
- Thermostatically shaking water bath,(Bunsen, India)
- UV-1800 double beam spectrophotometer (Shimadzu, Japan)
- Magnetic mixer,(IKA T25, Germany)
- Sensitive electronic balance,(AND, Japan)
- Homogenizer (IKA, Germany)
- HPLC instrument (Agilant, USA)

3. METHODOLOGY

3. 1. Solubility studies of CUR

Saturation solubility of CUR in Phosal®53 MCT, Phosal®50 PG, PEG-7-glyceryl cocoate and CRM EL was determined by using standard shake flask method. An excess quantity of CUR was added to the vehicle in a tightly capped conical flask. To achieve uniform mixing, samples were constantly agitated at conditions (100 rpm, 37℃ and 24 h) in a reciprocating water bath. Samples were centrifuged at (4000 rpm, 15 min) after 24h equilibrium where aliquots of supernatant were diluted to appropriate concentrations with Acetone. The samples were analyzed using spectrophotometer at wavelength 420 nm using acetone as a blank.

3.2. Preparation of CUR self phospholipid nano dispersions formulations.

Composition of CUR self phospholipid nano dispersion (SPND) formulations are illustrated at Table 18.

F1 was prepared by mixing CUR with Phosal®53 MCT in a beaker placed in thermostatic water bath adjusted at 40℃ for 30 mins till obtaining a clear viscous liquid while F2 was prepared by mixing Phosal®53 MCT with surfactants for 5 mins before addition of CUR to be prepared in the same previous mentioned conditions.

On other hand F3 – F6 were prepared by simple mixing of CUR with other ingredients for 15 mins in a beaker without application of heat till obtaining a deep orange solution with very low viscosity.

Table 18: Composition of CUR self phospholipid dispersion formulations

Material (mg)	F 1	F 2	F 3	F 4	F 5	F 6
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

3.3. Characterization of CUR self phospholipid dispersion formulations

3.3.1. Physical robustness to dilution.

SPND formulations were exposed to different folds of dilutions (100, 500 and 1000) with media (water, 0.1N HCl and phosphate buffer pH 7.4). Diluted formulations were stored on shelf for 6 hours where any physical changes were monitored. Percentage of transmission was then measured by using spectrophotometer at wave length 638.3 nm[222-224].

3.3.2. Particle size, Zeta potential and polydispersity index

The mean particle size (PS), polydispersity index (PDI) and zeta potential (ZP) for CUR SPND formulations (F1-F6) were measured by using dynamic light scattering technique (DLS) where samples were sonicated for 10 mins diluted with distilled water before measurements.

3.3.3. *In vitro* dissolution study

Official dissolution test for CUR mentioned in USP 32[(92)] was used where 900 ml of 1% SLS dissolution medium operated at 100 rpm by apparatus II for 120 mins. In addition, water was used as a comparative dissolution medium with the same pharmacopeial conditions to study the dissolution pattern for CUR phospholipid dispersion formulations relative to the official system.

40 mg (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 intervals; 15, 30, 60, 120 min and replaced by fresh corresponding medium be diluted and analyzed by spectrometer at wave length 420 nm.

3.3.4. Transmission electron microscope (TEM)

Morphological examination of vesicles for some selected formulations F 1 and F 5 was carried out using TEM. Samples were diluted with distilled water and sonicated for 10 mins. A drop of the resultant dispersions was placed onto a carbon-coated copper grid, leaving a thin liquid film. The film was dried by air then viewed.

3.3.5. *In vivo* CUR absorption study

3.3.5.1. Experimental animal protocol

Study of CUR absorption from selected $SPND_s$; F1 and F 5 through gastrointestinal tract (GIT) was taken place by using 9 wistar rats (200 – 250 gm) obtained from animal house of faculty of pharmacy (Alexandria, Egypt) compared to CUR powder suspended in 1% methyl cellulose[(225)].

Experiments were performed in accordance with the European Community Guidelines for the use of experimental animals and were approved by the institutional ethics committee. The rats were housed in a temperature and humidity controlled room (23℃, 55%) with free access to water and standard rat chow. The rats were acclimated for at least 5 days and fasted overnight but supplied with water and libitum before the experiment. The animals were received in triplicates unformulated and formulated CUR at 340 mg/kg (in terms of CUR) by oral gavage[(130)].

After 60 min, they were exsanguinated under terminal anesthesia and the whole blood was collected by cardiac puncture into heparinised tubes, centrifuged immediately at 7,000 rpm for 15 min, plasma was then decanted and stored at -20°C until analysis.

Gastro intestinal tract from stomach to anus (i.e. 40 cm) was isolated then flushed from inside with normal saline solution to be collected in 15 ml acetone to be analyzed via HPLC system where GIT was stored at -20°C till analysis.

3.3.5.2. Samples preparation

Samples from GIT and plasma were prepared by slightly modified method from that stated by Marczylo *et al* [130] as shown below.

- ***Gastrointestinal tract:*** 1.15% of KCl was added to the isolated gastrointestinal tract and homogenized with a blade homogenizer at top speed, then vortexed with 5 ml acetone. The samples were centrifuged at 10,000 rpm and the supernatant was analyzed by HPLC system.
- ***Plasma:*** 0.1 ml Acetonitrile was added to 0.1 ml plasma then centrifuged at 4000 rpm for 5 mins, then the supernatant was subjected to be analyzed by HPLC system.

3.3.5.3. HPLC analysis

3.3.5.3.1. HPLC system suitability[130]

HPLC analysis was performed using (Agilant series, USA) supplied with C 18 column (4.6 x 150 mm, 3µm) with guard column (4.6 x 20 mm, 3µm), kept at 35°C. The mobile phase was composed of two components; A: 10 mM of ammonium acetate buffer solution with adjusted pH= 4.5 and B: Acetonitrile. The flow rate was adjusted to be 1.5 ml/min and UV detector was adjusted at 426 nm. The elution was encountered to be gradient elution starting with 95% A and 5% B, to be changed to 55% A and 45% B at 20 mins then changed to 5% A and 95% B at 33 mins.

3.3.5.3.2. Calibration curve of CUR in rat plasma

Serial concentrations were prepared 0.02, 0.04, 0.06 and 0.08 mg/ml of CUR in acetone. 0.1 ml of dissolved CUR was mixed with 0.1 ml of rat plasma then 40 µl of acetonotrile was added to the previous prepared mixture. The samples were centrifuged at 4000 rpm for 3 mins and supernatants were isolated and injected to be analyzed by HPLC system.

3.6. Shelf stability for CUR SPND formulations.

F 1 and F 5 SPND formulations were subjected to shelf stability study for 3 months under normal room conditions (25°C, 65% RH) to be stored in well closed container and in soft gelatin capsule as a final dosage form.

3.6.1. Shelf stability in closed containers.

3.6.1.1. *In vitro* dissolution study

In vitro dissolution study for F 1 and F 5 $SPND_S$ was performed in the USP dissolution system (i.e. 1% SLS, 900 ml, apparatus II at 100 rpm) and water dissolution medium with the same procedures of experiment 3.3.3.

3.6.2. Shelf stability in soft gelatin capsules.

3.6.2.1. *In vitro* dissolution study

In vitro dissolution study for F 1 and F 5 $SPND_S$ injected in air-filled soft gelatin capsules was performed with same procedures in experiment 3.3.3

3.6.2.2. Transmission electron microscope (TEM)

F 1 and F 5 $SPND_S$ from soft gelatin capsule were photographed with the same procedures of experiment 3.3.4.

4. RESULTS AND DISCUSSION

4.1. Solubility study of CUR in non aqueous vehicles

As shown in (Figure 73), saturated solubility of CUR in Phosal®53 MCT was reached to 51.72 mg/gm which encountered to be higher than in case of Phosal® 50 PG, this attributed to the presence of PG as a major ingredient in the product which in turns limit the solubility of CUR. (Experimental solubility of CUR in PG is 2.64 mg/gm).

In case either using different type of hydrophilic surfactants, it was shown that using of CRM EL or PEG 7 glyceryl cocoate provides better solubility for CUR to reach 41 mg/gm.

4.2. Preparation of CUR self phospholipid nano dispersion formulations

Formulation strategy of CUR SPND depends on preparation of CUR with other excipients in a solubilized form; Phosal® 53 MCT was selected to provide 53% of soybean PC in the formulation in addition to CRM EL and PEG 7 glyceryl cocoate as a hydrophilic surfactants and Miglyol 812™ as the lipophilic member in the formulations.

Application of heat and long time of mixing were required in the preparation of F 1 and F 2 due to high content of viscous liquefied substance Phosal® 53 MCT in such formulations to solubilize CUR powder in contrary to F3-F6 formulations preparation method so there is no need for heat and long time mixing due to presence of much lower concentration of viscous Phosal® 53 MCT and high concentration of surfactants.
CUR SPND formulations were divided into 3 different categories:

- ***Category A (F 1):*** According to the previously mentioned solubility data, 60 mg CUR was able to be solubilized in 1160 mg of Phosal® 53 MCT as shown in F 1.

- ***Category B (F 2 and F 3):*** In F 2, 13% of total hydrophilic surfactants (i.e. Composed of CRM EL and PEG 7 glyceryl cocoate in ratio (1:1)) was utilized to promote the emulsification of CUR on dispersion in water in the presence of 1 gm of Phosal®53 MCT. It must be noticed that 1 gm of Phosal® 53 MCT provides 530 mg PC.

In contrary F 3 was composed of relative higher surfactant concentration than F 2. It was composed of CRM EL and PEG 7 glyceryl cocoate in ratio (1:9.8) reaching to 70.5% of total weight of the formula in addition to 300 mg of Phosal® 53 MCT providing 150 mg PC. The PC quantity was reported to be sufficient for CUR-phospholipid complexation[129].

Referring to the toxicological assessment for using CRM EL and PEG 7 glyceryl cocoate in oral use, it was concluded the systematic toxicity of CRM EL[226] more than PEG-7 glyceryl cocoate. The LD_{50} of CRM EL was concluded to reach 1.466 gm /Kg[227] however, LD_{50} of PEG-7 glyceryl cocoate was reported to be $\geq$ 19,900 mg/Kg [228].

Although CRM EL provided the same solvent capacity towards CUR powder like PEG - 7 glyceryl cocoate, PEG-7 glyceryl cocoate was preferred to be used as a main solvent for such formulations over CRM EL according to previously mentioned reasons. It must be noticed the importance of using CRM EL in CUR SPND formulations due to its biological activity in inhibition CYP 450 3A [208, 209] which affects on the intestinal metabolism for CUR [137].

- ***Category C (F 4, F 5, F 6):*** In this category of CUR SPND, Miglyol 812™ (i.e. Medium chain triglyceride) was included in these formulations with different concentrations about 5%, 15% and 25% for F 4, F 5 and F 6 respectively. In addition to, hydrophilic surfactants with different concentrations about 65.5%, 55,5% and 45.5% for F 4, F 5 and F 6 respectively to promote CUR emulsification upon dispersion in water under gentle agitation which referred to as the self-emulsifying formulation[8, 229] to form fine colloidal droplets very high surface area. It must be noticed that the presence of surfactants in such formulations leading to a more uniform and reproducible bioavailability[230].

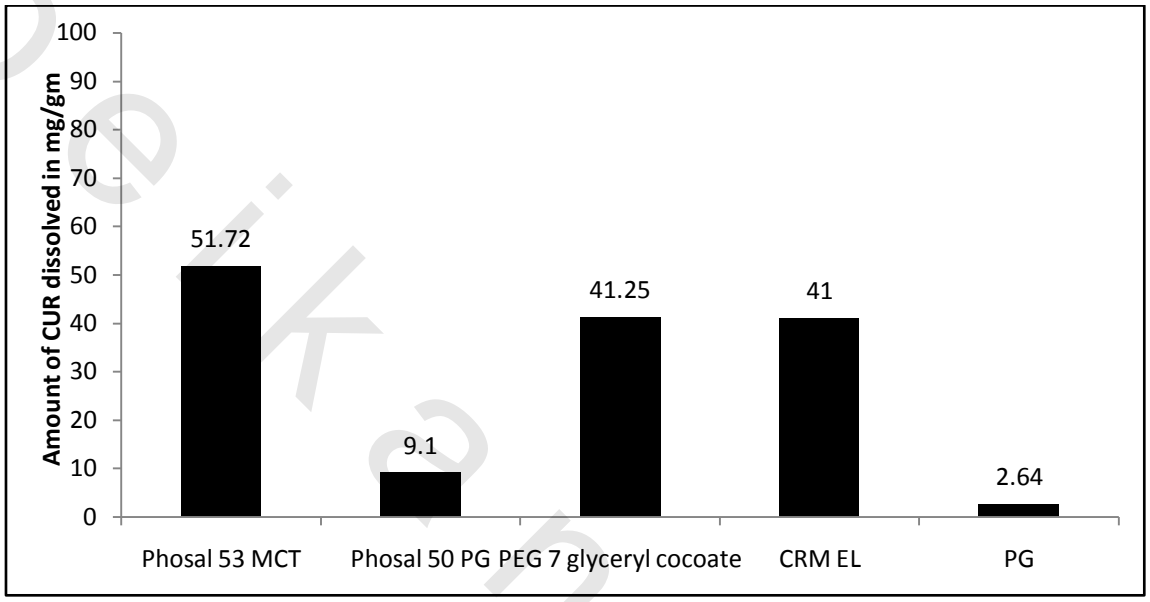

Figure 73: Saturated solubility of CUR in different surfactants and vehicles.

4.3. Characterization of CUR self phospholipid nano dispersion formulation

4.3.1. Physical robustness to dilution

This test was carried out to determine the physical stability of SPND in simulated gastric/intestinal fluid after 6 hours to guarantee the *in-vivo* efficacy for such formulations after oral administration.

Milky dispersion was observed after F1 and F2 dispersion due to absence of surfactants in F1 and low surfactant concentration in F 2 knowing the role of surfactants in promoting physical stability of emulsions [91] leading to a decrease in % of transmission as shown in Table 19. While in higher dilutions, % of transmission increased.

In case of F3 - F6, translucent to transparent dispersions were observed after dispersion for such formulations lead to increase %of transmittance. This was due to presence of high concentration of surfactants in such formulations. It was observed %of transmission in F 6 is less than that of F 4 and F 5, this may be attributed to aggregates from colloidal particles as a result of decreasing in the concentration of total hydrophilic surfactant.

Table 19: Physical robustness to dilution for CUR SPND formulations

No of formula	Dilution	Physical appearance at zero time	%Transmission after 6 hours		
			HCL	Buffer	Water
F 1	100	Milky	1.2%	3.2%	12.5%
	500		26.5%	37.6%	67.8%
	1000		54.3%	62.2%	78.4%
F 2	100	Milky	16.1%	20%	26.7%
	500		45.8%	55.1%	76.5%
	1000		72.7%	71.2%	89.1%
F 3	100	Translucent	32.9%	38.2%	81.6%
	500		86.6%	87%	96.6%
	1000		90.6%	88.2%	98%
F 4	100	Transparent	46%	65%	84.3%
	500		84%	80%	97%
	1000		89%	86.7%	97.3%
F 5	100	Transparent	45.8%	61.6%	85.2%
	500		70.6%	82.3%	95.9%
	1000		81.3%	97.7%	85.2%
F 6	100	Transparent	31.6%	36.6%	37.2%
	500		66.3%	68.9%	84.6%
	1000		80%	79.5%	92.8%

4.3.2. Particle size (PS), Zeta potential (ZP) and polydispersity index (PDI)

Physicochemical characterization of phospholipid dispersions encompassed assessment of PS, ZP and PDI as depicted in Table 20.

- ***Particle size (PS):*** Results revealed that PS of F1 and F2 were 500, 610 nm respectively. They were considered to be relatively higher than other formulations because of containing relatively higher concentration of phospholipid than other formulations resulting in

formation of larger particle size upon dispsersion in water. Also, addition of low concentration of surfactants in F2 didn't show any improvement of the formed globules particle size but it enlarged the particle size, this may be attributed to deposition of surfactant molecule at the surface of the colloids being below the critical micelle concentration (CMC) of CRM EL (i.e. 0.039 mM) [231] and PEG-7-glyceryl cocoate (i.e. 0.2 mM/L) [232]

While in F3, F4, F5 and F6, results revealed much small particle size for colloids to reach 199, 219.7, 165.7 and 158 nm respectively. This decrease may be attributed to the presence of high surfactant concentration in such formulations above their CMC value leading to micelle formation.

- ***Polydispersity index (PDI):*** PDI is a measure of the heterogeneity of sizes of molecules or particles in a mixture[233]. Thus F1 and F2 showed higher PDI values than F3-F6 formulations and this indicates that F3-F6 dispersions showed more mono-dispersable than F1 and F2 dispersions. This may be attributed to formation of dispersed colloids varying in sizes due to high concentration of the used phospholipid in such formulations.

- ***Zeta potential (ZP):*** ZP is a key indicator of the stability of colloidal dispersions. The magnitude of the zeta potential indicates the degree of electrostatic repulsion between adjacent, similarly charged particles in a dispersion [234]. As shown in table 20, a relative high ZP for F1 and F2 compared to F3-F6 which have reduced ZP values to reach -36 mV. Such higher values for F1 and F2 may be attributed to a result of the negative charge of CUR. On other hand F3-F6 have relative smaller values and this may be attributed to the formation of non-ionic micelles at the surface of the colloidal particles being used above their CMC leading to reduce the negative charge at the surface of colloids.

  Shielding effect of non-ionic molecules on the negative charge at the colloid surface was also discussed by Freag *et al* [185] leading to reduce ZP value of SPC on using mannitol as cryoprotectants.

  Figures (74, 75, 76, 77, 78 and 79) illustrate PS, PDI and zeta potential properties for F1, F2, F3, F4, F5 and F6 respectively.

Table 20: Results of PS, PDI and ZP of CUR SPND formulations

Formula no.	Particle size (nm)	PDI	Zeta potential
F 1	500 ± 2.9	0.467 ± 0.016	- 51.87 ± 1.62
F 2	610 ± 6.24	0.56 ± 0.01	-48.7 ± 0.61
F 3	199 ± 8.2	0.351 ± 0.011	-35 ± 1.32
F 4	219.7 ± 1.5	0.381 ± 0.0036	-36,2 ± 1.6
F 5	165.7 ± 5.1	0.31 ± 0.005	-36.4 ± 0.4
F 6	158 ± 2.6	0.42 ± 0.0075	-36.8 ± 1.058

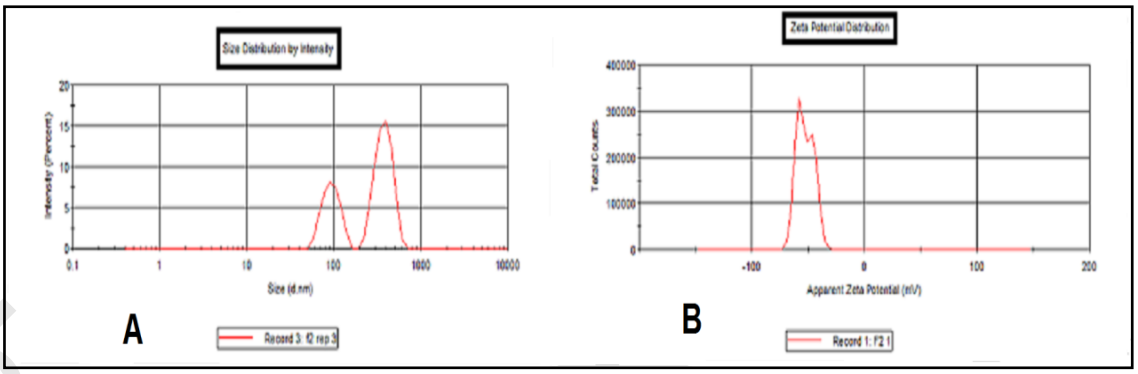

Figure 74: Particle size (A) and zeta potential (B) graphs for F1.

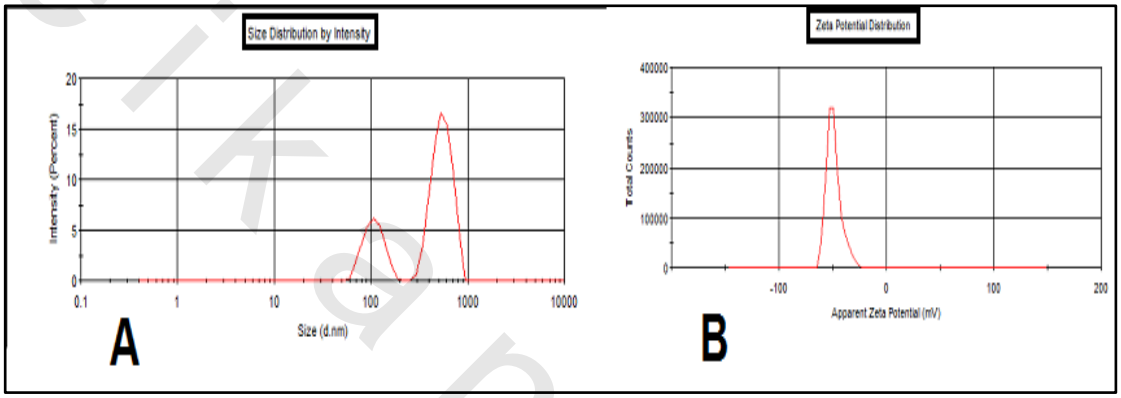

Figure 75: Particle size (A) and zeta potential (B) graphs for F2.

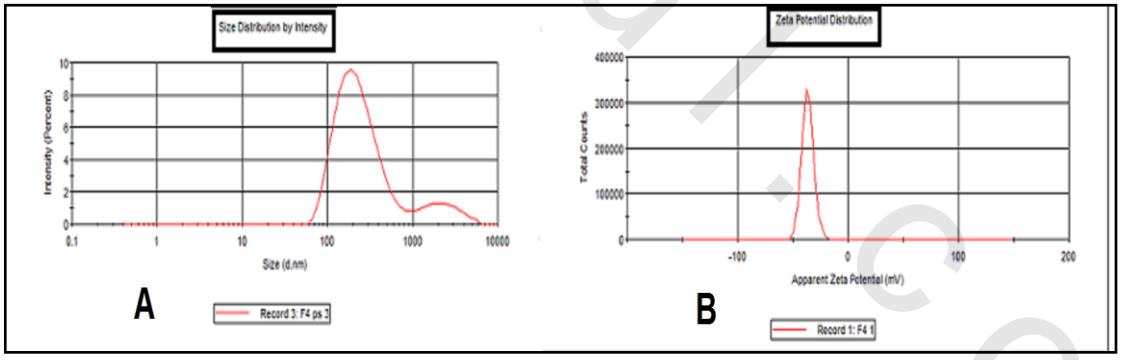

Figure 76: Particle size (A) and Zeta potential (B) graphs for F3.

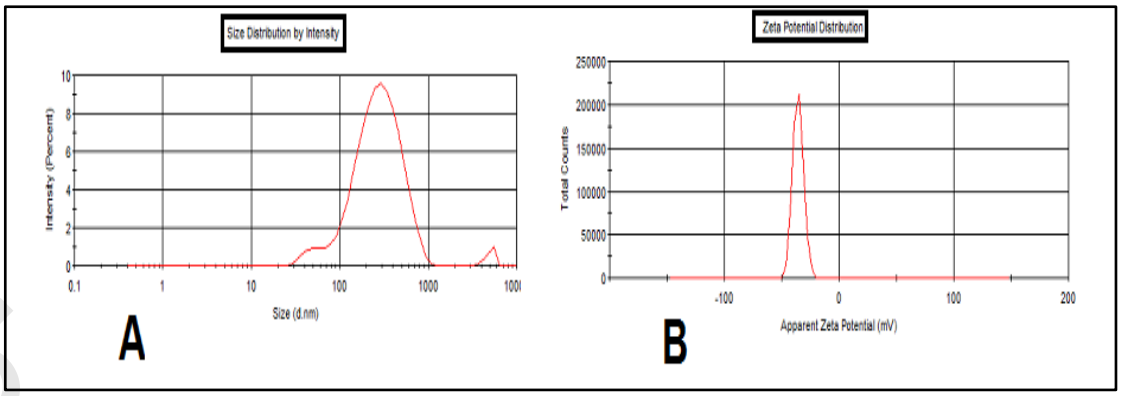

Figure 77: Particle size (A) and Zeta potential (B) graphs for F 4.

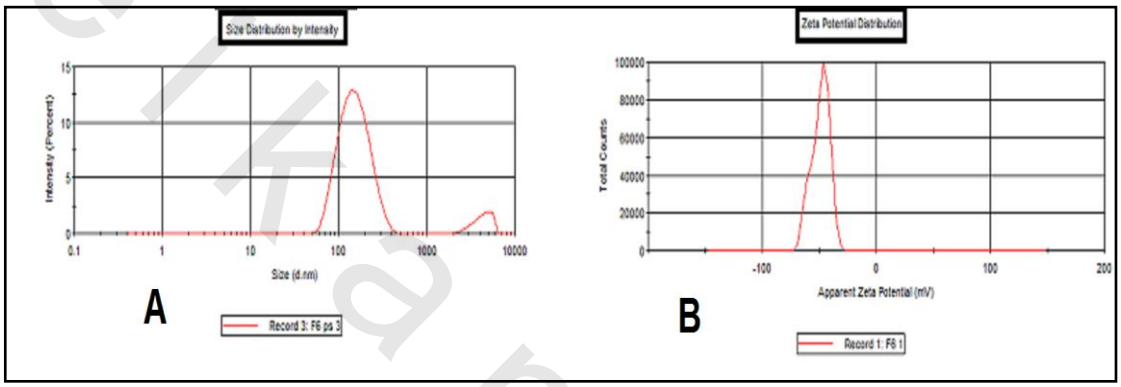

Figure 78: Particle size (A) and Zeta potential (B) graphs for F 5.

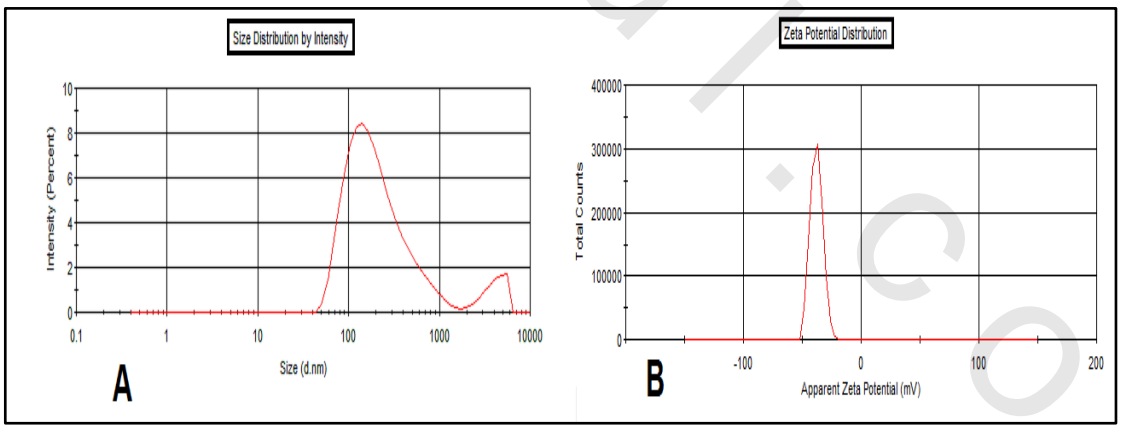

Figure 79: Particle size (A) and Zeta potential (B) graphs for F6.

4.3.3. *In vitro* dissolution study

On applying the pharmacopeial dissolution system for CUR in 1% SLS, Results illustrated at Figure 80 revealed that all the formulations passed the pharmacopeial tolerance (i.e. Not less than 75% after 60 mins) over CUR powder. This indicates that the latter dissolution system is not segregating system towards self phospholipid dispersion formulations to explain the dissolution behavior of the formulations due to presence of high concentration of SLS.

In Figure 81, water medium was used as dissolution medium to differentiate and explain the difference among the dissolution patterns for CUR phosphoilipid dispersion formulations. In case of F 1, it was shown that the dissolution of CUR reached a plateau at maximum dissolution to reach 36% after 15 mins, this dissolution behavior may be attributed due to CUR solubilization in high concentration of Phosal® 53 MCT which in turns increase the its dissolution results. However, F 2 showed similar dissolution behavior to F1 indicating that reduction of Phosal®53 MCT and addition of 13.1% of hydrophilic surfactants are not sufficient to improve the dissolution behavior.

In case of F3, It was shown an enhancement in the dissolution behavior for CUR in aqueous medium to reach 66% after 15 mins due to high solubilizing power for 70.5% of hydrophilic surfactants. However addition of Miglyol™ 812 in F4, F5 and F6 at concentration 5%, 15% and 25% respectively lead to enhance the initial dissolution for CUR to reach 80% after 15 mins, this may be attributed due to presence of oil which in turns lead to formation of stabilized O/W emulsion during dispersion in water which prevents CUR aggregation and separation in the dispersion medium.

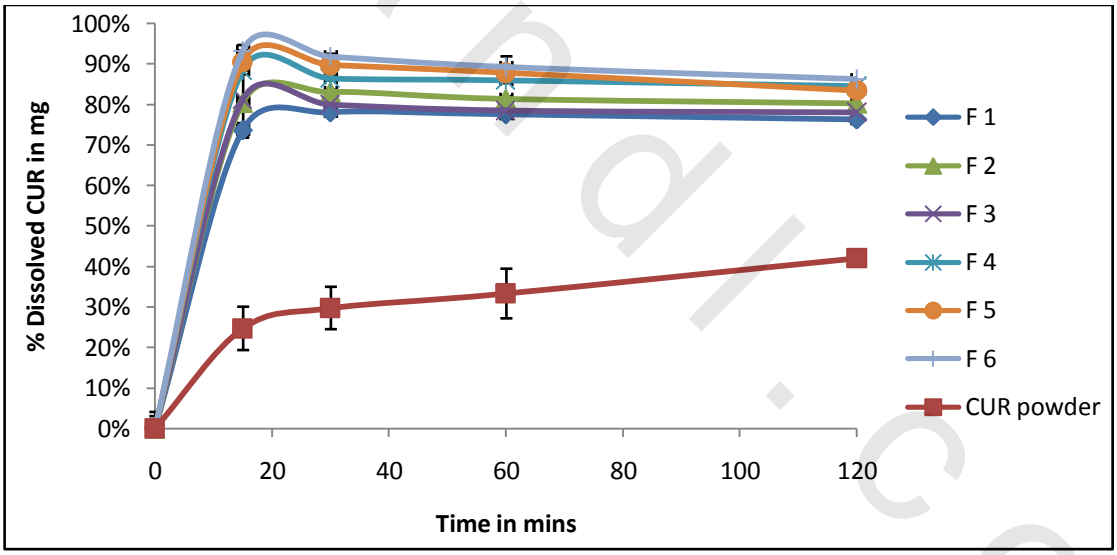

Figure 80: Comparative dissolution study among CUR SPND formulations in 1% SLS.

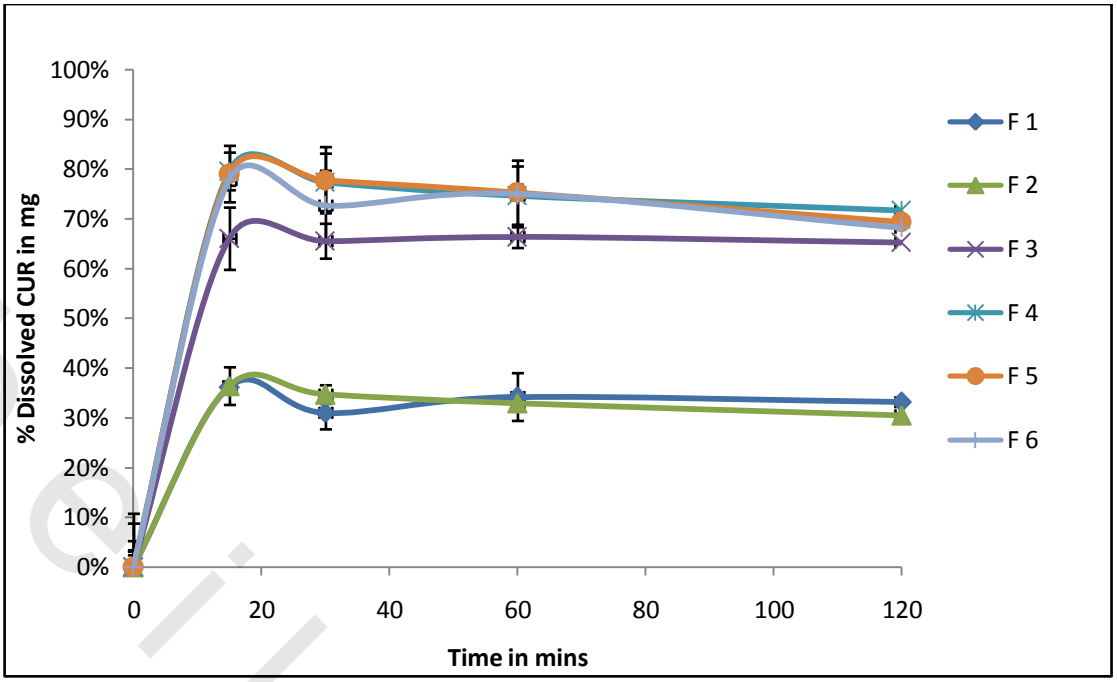

Figure 81: Comparative dissolution study among CUR SPND formulations in water.

4.3.4. Transmission electron microscope (TEM)

As shown in (Figure 82), TEM for F 1 revealed well formed, discrete vesicles. It was observed that the vesicles surrounded by a transparent layer (*pointed with arrows*) which may be attributed to a presence of phospholipid layer surrounding the formed vesicles while the inner part was seen to be dense and dark which may be attributed to solubilized CUR within PSL 53 MCT. These findings support our previous findings for increase the ZP values for such formulation compared to the others.

In F5, TEM photograph in (Figure 83), showed well formed vesicles. It was observed a presence of thin dark layer surrounding the vesicles (*pointed with arrows*) which may be due to presence of CUR solubilized in this layer which mainly composed of high concentration of surfactants while the inner part is transparent as for the presence of MCT oil which have a low solvent capacity towards CUR. And these findings support our suggestion about the effect of surfactants in decreasing the ZP value for such formulation.

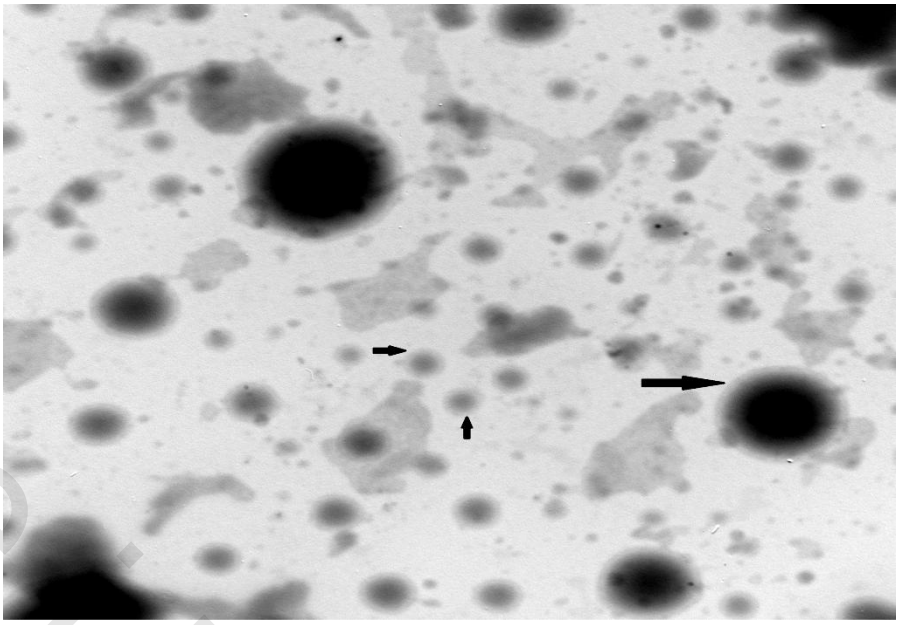

Figure 82: Transmission electron microscopic photograph of F1 with 20-folds dilution in distilled water

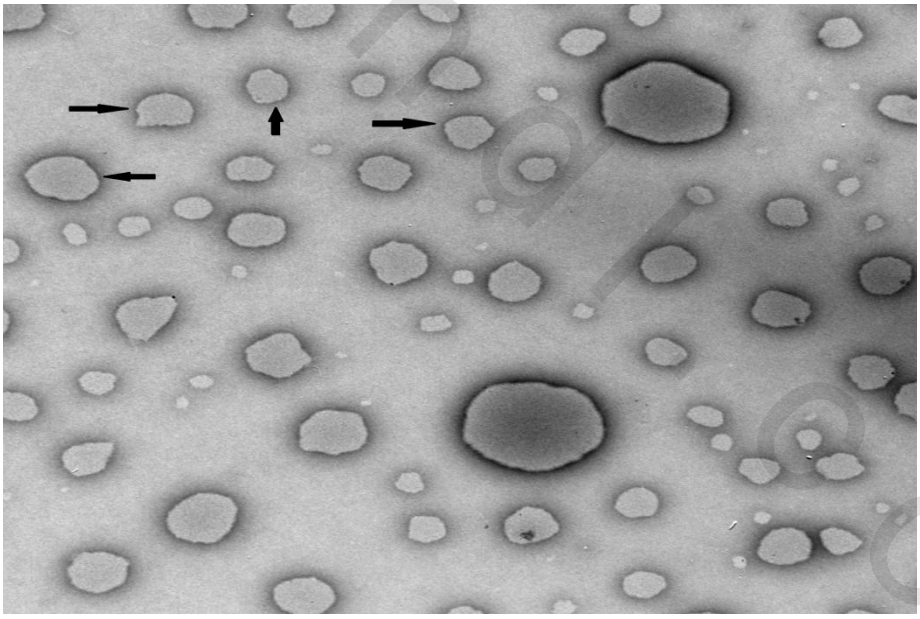

Figure 83: Transmission electron microscopic photograph of F 5 with 20-folds dilution in distilled water.

4.3.5. *In vivo* absorption study

This experiment was taken place to study the in-vivo absorption of CUR through GIT by analyzing the CUR content after an hour because CUR and its metabolites could detected easily and measured at this time as reported by Marczylo *et al* [130] . Three different successive stages represent the absorption pathway through GIT; lumen of GIT which represents the remaining of unabsorbed CUR, mucosal cells of the intestine represents the amount of CUR found at the mucosal cell of the intestine (i.e. unpermeated CUR) and plasma of the blood represents the amount of CUR permeated through the GIT.

Selected formulations; F1 and F5 were used in this experiment comparable to CUR powder suspended in 1% Methyl cellulose.

- ***Lumen of GIT:*** As shown in (Figure 84), it was observed that the amount of CUR remained unabsorbed in decreasing order is CUR suspension > F 5 > F 1 with values 3.16, 2.29 and 1.4 mg respectively.
  It is concluded that suspension form of CUR unable to be absorbed through GIT due to its poor aqueous solubility in contrast to CUR from F1 and F 5 which is predicted to be highly absorbed through GIT.

- ***Mucosal cells of GIT:*** As shown in (Figure 85), results revealed that the amount of CUR found at the mucosal cells in decreasing order; CUR suspension > F5 > F1 with values 3.3, 1 and 0.57 respectively.
  These results indicate that CUR passes through GIT in case of F1 and F 5 being found to be in low amounts while in case of CUR suspension it is found to be in high concentration and this result line with those explained by Marczylo *et al* [130] which may be attributed to the presence of CUR attached strongly on outer surface of the mucosa being a lipophilic molecule and its disability to partition through the intestinal cell to be permeated due its poor water solubility.

- ***Blood plasma:*** A calibration curve for CUR in plasma was held with a linear equation: y= 60956 x with R^2 value = 0.9 as shown in (Figure 86).
  Results revealed the absence of CUR in the blood plasma after administration of CUR suspension and this result support our previous results which confirm the poor permeability for CUR suspension through the GIT.
  CUR was found in the blood plasma after using F1 and F5 with different values as illustrated in (Figure 87). In case of F 1, CUR value reached to1.6 µg/ml while it reached to 0.6µg/ml in F5. This difference in CUR value between the two formulas may be attributed to a difference in a metabolism process for CUR in such formulations.

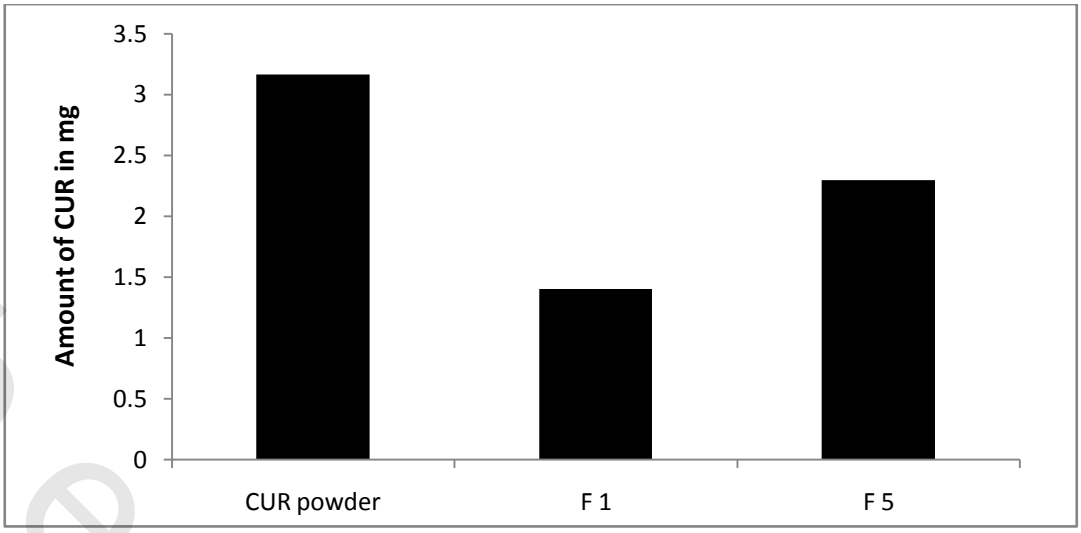

Figure 84: CUR content in the lumen of GIT.

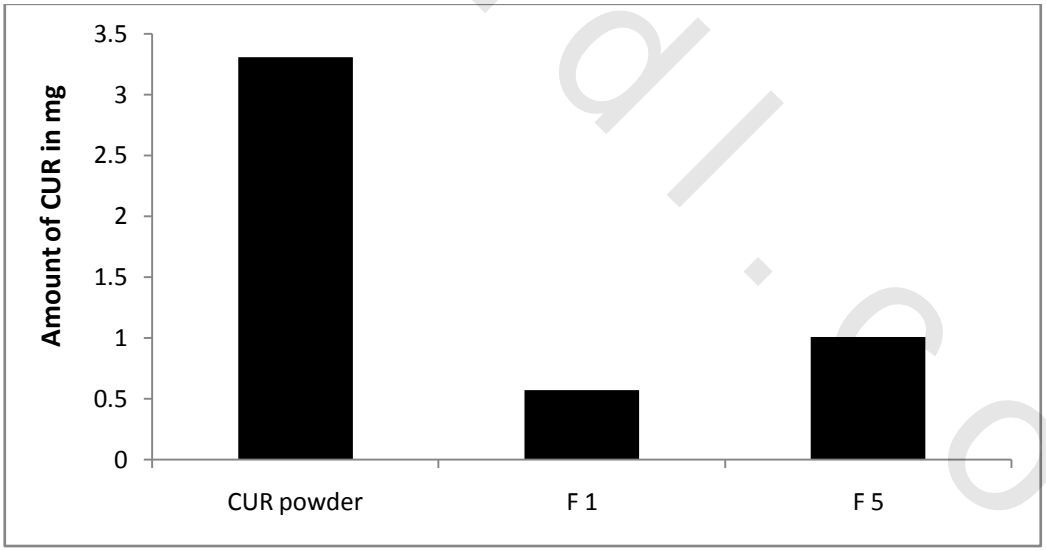

Figure 85: CUR content at the intestinal mucosal cells.

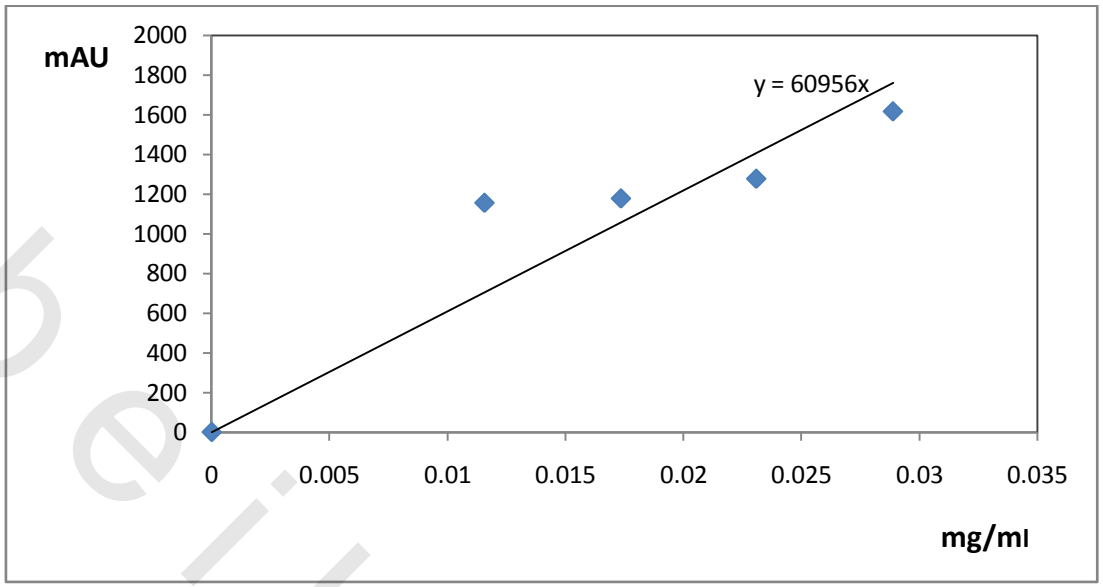

Figure 86: Calibration curve for CUR in the rat blood plasma.

Being exposed to extensive metabolism, it is observed new peaks at different retention times differ from CUR peak (Figure 88) which may be referred to metabolic products for CUR. The ratio between CUR and its metabolites was 7.2:1 in case of F1 shown in as shown in (Figure 89) while 1:10.4 in case of F5 in (Figure 90).
Upon out previous discussion, F1 is nominated to be the best formula to deliver CUR as a parent compound to the systematic circulation over F5.

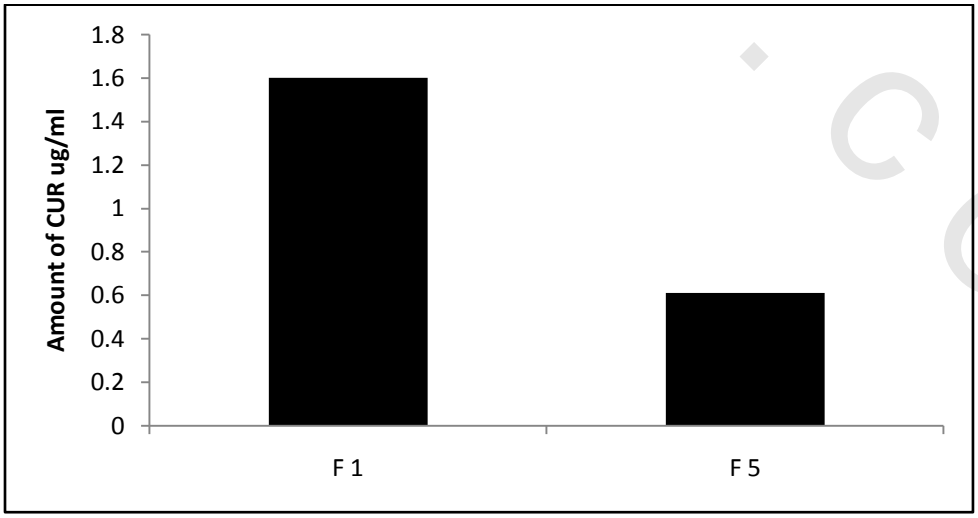

Figure 87: CUR content in the blood plasma of rats.

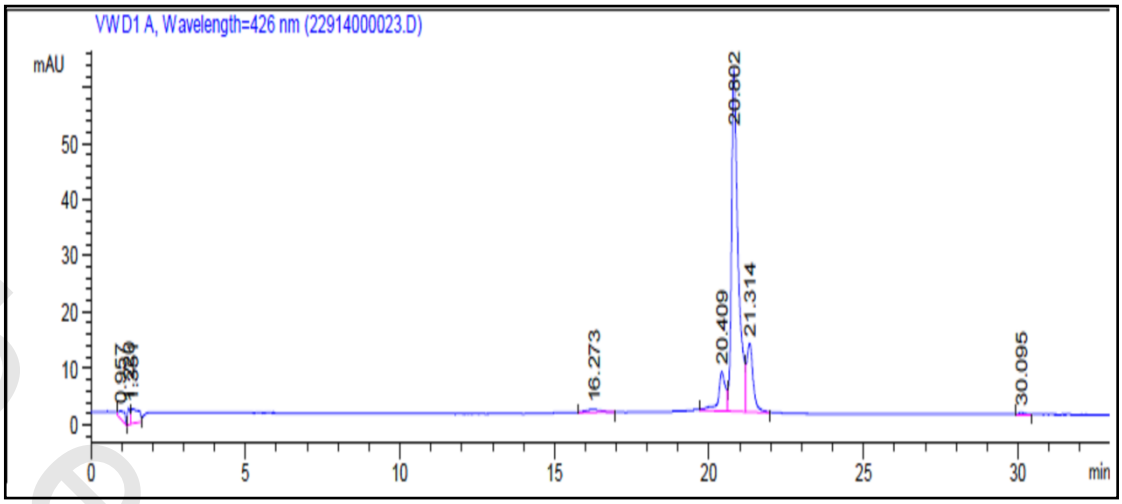

Figure 88: HPLC chromatogram for pure CUR in the blood plasma.

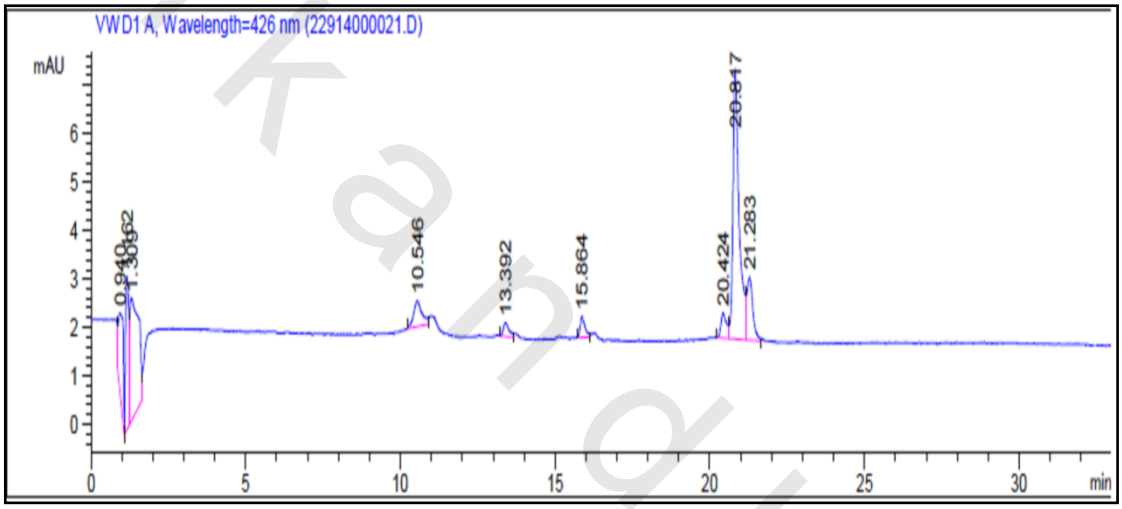

Figure 89 : HPLC chromatogram for CUR in blood plasma from F1

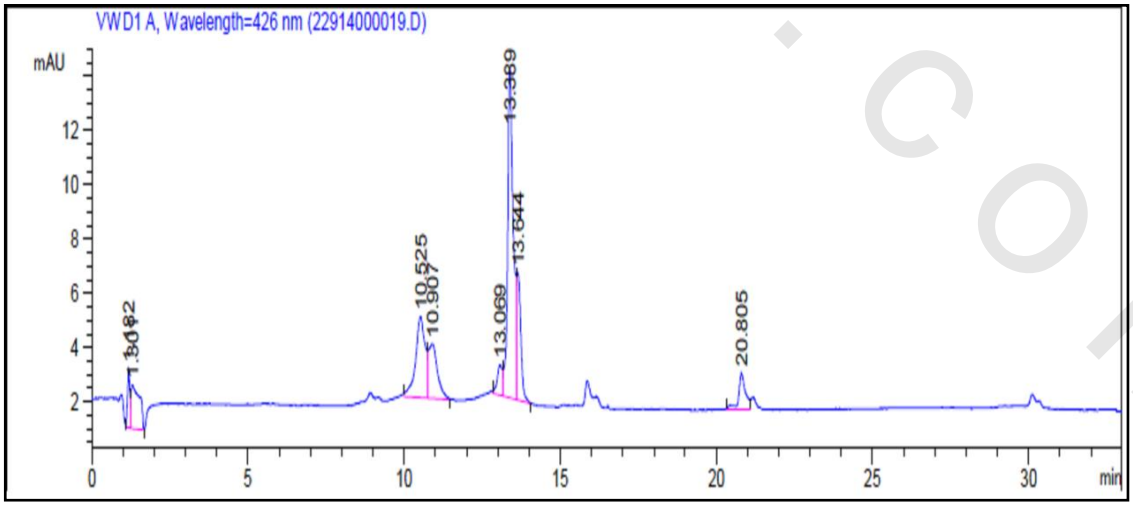

Figure 90 : HPLC chromatogram for CUR in blood plasma from F5.

From our previous findings, it is obvious that F1 formulation reduce the probability of CUR metabolism after oral administration in contrast to F 5 and this could be concluded from previous previewed HPLC charts. This may be attributed to the presence of CUR inside SPC formed vesicle as shown in (Figure 82) which in turns protects CUR from metabolism in F1 while CUR is present in a solubilized form at the surface surrounding the formed vesicles as shown in (Figure 83) in F5 which in turns increases its susceptibility to metabolism after oral administration. Although high oral administrated CUR dose (i.e. 340 mg/Kg), the sum of amount detected in the lumen, GIT and plasma of CUR or its metabolites is not equivalent to the initially administrated dose. Our studies could not explain the reason behind this result in addition most of research papers also could not explain these results [129, 130, 132, 158, 225]

4.3.6. Shelf stability study for CUR (SPND) formulations

4.3.6.1. Shelf stability study in tightly closed containers

4.3.6.1.1. *In vitro* dissolution study

In vitro dissolution study was conducted for F1 and F 5 which were stored in a tightly closed container. As shown in (Figure 92 and 94), dissolution pattern for both F1 and F5 wasn't change in both dissolution media (i.e. 1% SLS and water) upon storage for 3 months.

4.3.6.2. CUR (SPND) formulations in softgels

4.3.6.2.1. *In vitro* dissolution study

As shown in Figure 91, dissolution of CUR from F1 in 1% SLS and water was sharply reduced in comparison with its pattern at zero time to reach 26.3% after 180 min in 1% SLS and 2.96% in water. This decrease indicates that the solubilized system of CUR in Phosal® 53 MCT is affected by the soft gelatin capsule leading to CUR precipitation inside the soft gelatin capsule.

Similarly, dissolution pattern of F5 in 1% SLS and water is reduced to nearly 50% from its initial dissolution at zero time as shown in Figure 93. Also presence of such formulation in a softgel reduced its dissolution due to CUR precipitation inside the capsules.
The previously mentioned findings could be explained by F1 and F 6 dispersion in water and photographed by transmission electron microscope.

4.3.6.2.2. Transmission electron microscope (TEM)

For F1, It is observed in Figure 95 irregular empty transparent vesicles surrounded by numerous small dark spots which may be referred to CUR. This result supports our suggestions that CUR precipitates out its solubilized form leading to decrease its dissolution results. In figure 96, it is shown that the vesicles of F5 are changed if compared to its form at zero time shown in figure 83 to show small dark spots in the inner part of vesicles surrounded by a less dark layer. This darkness may be referred to CUR and it is may be explained that a part of CUR is precipitated while other part still in its solubilized form surrounding the vesicles.

Depending on previously mentioned results, it is concluded that soft gelatin capsule is inconvenient to be a dosage form containing F1 or F5 formulations. The reason may be due to possible interactions between shell contents and these formulations or water migration phenomena that may affect the stability of such formulations inside softgels. So further studies must be conducted to optimize softgel shell formulation to be capable of using as an oral dosage form to deliver such formulations to systematic circulation.

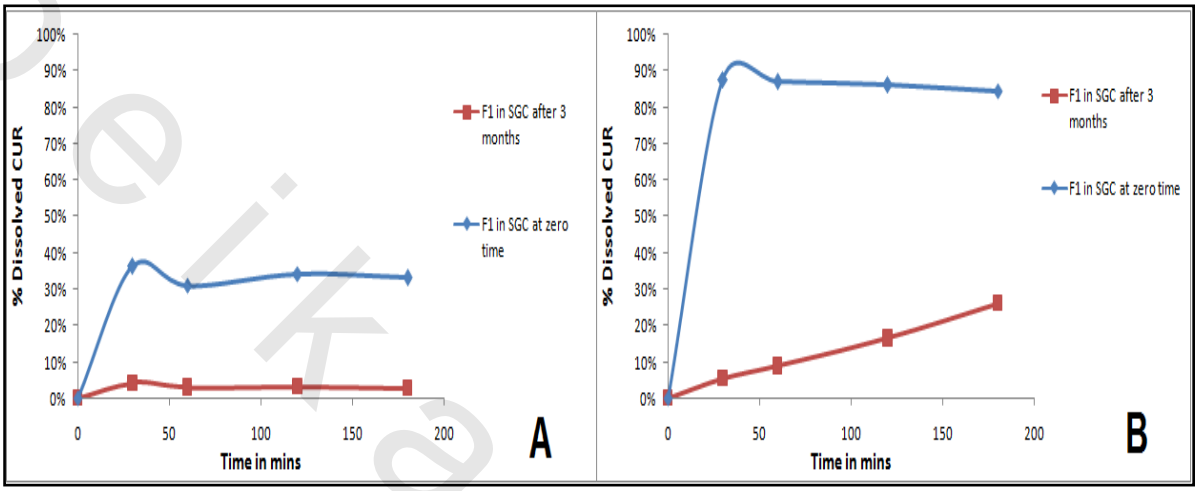

Figure 91: Dissolution pattern for F 1 in SGC in water (A) and 1% SLS (B).

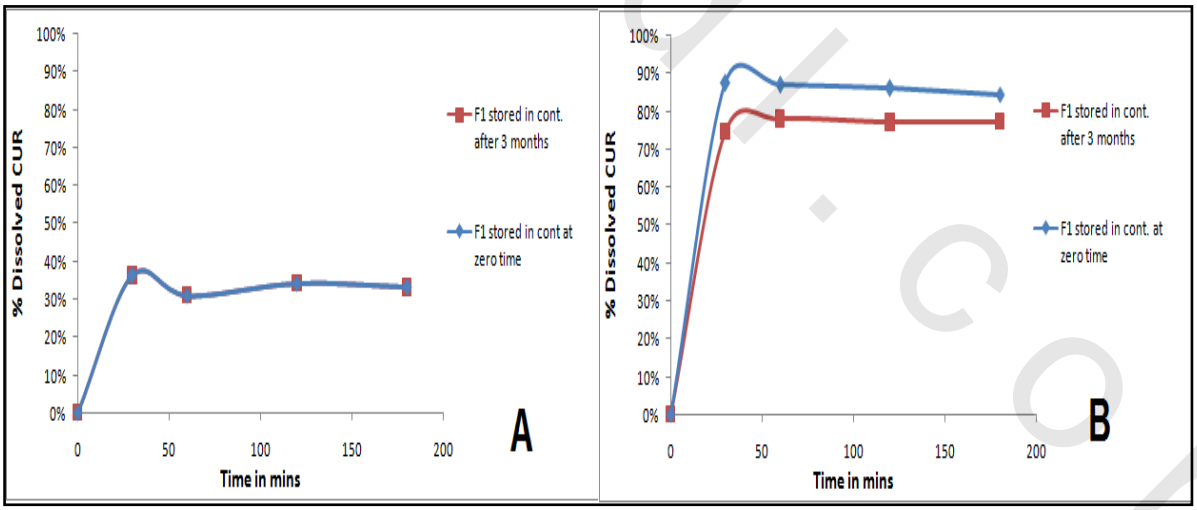

Figure 92: Dissolution pattern for F 1 stored in cont. in water (A) and 1% SLS (B).

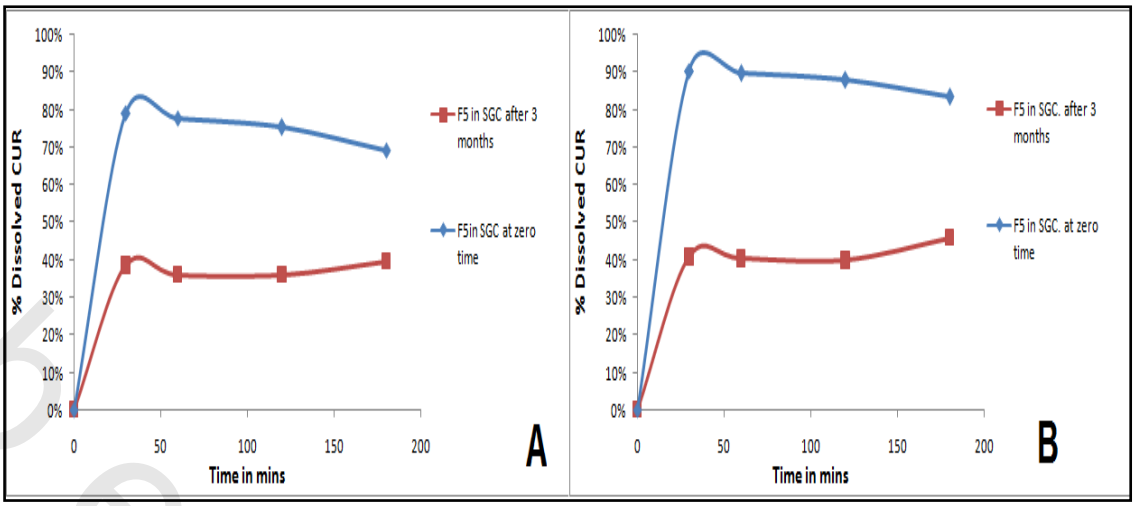

Figure 93: Dissolution pattern for F 5 in SGC in water (A) and 1% SLS (B).

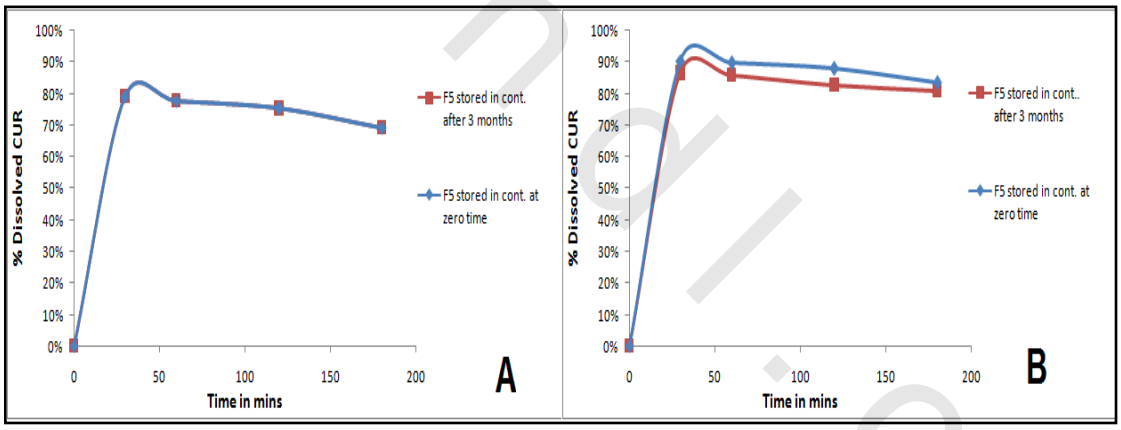

Figure 94: Dissolution pattern for F 5 stored in cont. in water (A) and 1% SLS (B).

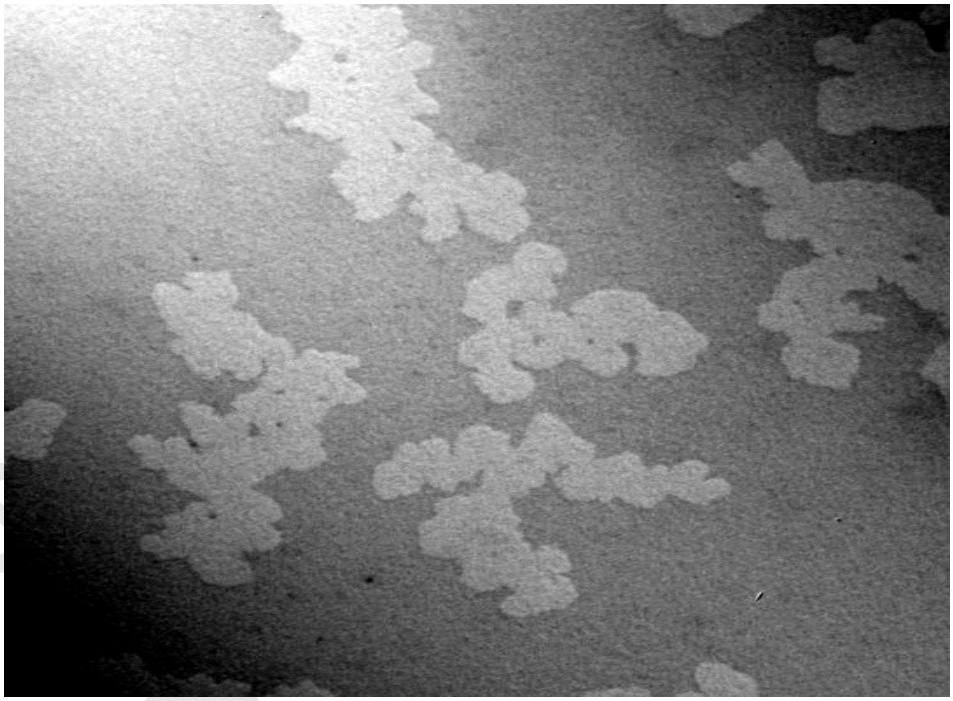

Figure 95: Transmission electron microscopic photograph of F1 with 20-folds dilution in distilled water.

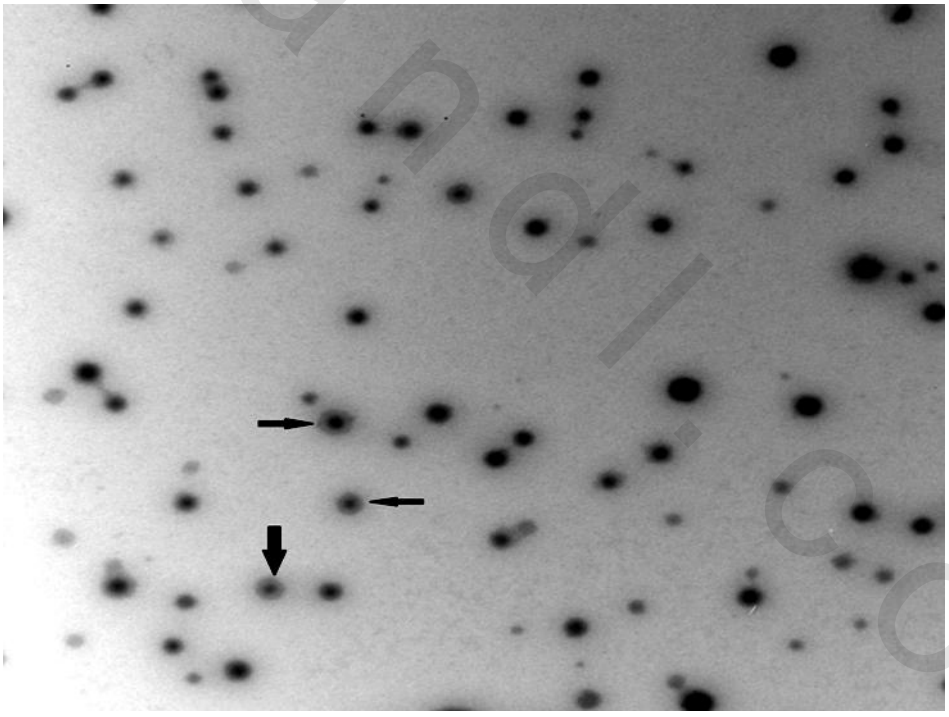

Figure 96: Transmission electron microscopic photograph of F5 with 20-folds dilution in distilled water.

5. CONCLUSION

It is concluded the applicability of using a low cost a product containing 53% soybean phosphatidylcholine known as Phosal®53 MCT to optimize a nano delivery system to improve the systematic bioavailability for CUR. It was found that formulation of CUR to be solubilized in conduct the best way to deliver CUR as a parent compound into systematic circulation over other formulations which contain hydrophilic surfactants. Although good stability of such formulations upon storage in well closed containers, it shows a bad stability inside soft gelatin capsule due to possible interactions between shell contents and fill contents or due water migration phenomena. This issue may be improved in the future by further more studies to optimize the shell formulation to improve its ability to be filled with such viable formulations

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SUMMARY

Although softgel delivery system offered the advantage as a convenient way to deliver non-aqueous liquid or semi-solid matrix containing a dissolved or dispersed compound as a unit dose solid dosage form, little researchers focused on development of softgels containing novel lipid based drug delivery systems which were utilized to enhance oral bioavailability of poor water soluble drugs concerning its efficacy and its stability inside soft gelatin capsule. Also, few studies were applied on appropriation of softgels to deliver such delivery systems including its production capabilities and its stability.

This thesis focused on the application of different novel delivery systems on poorly water soluble drugs to improve their oral bioavailability and development of softgels containing these delivery systems. Among these delivery systems; application of lipid formulations according to lipid formulation classification system to improve the aqueous solubility of poor water soluble drug like etodolac and to study the effect of these formulations on physical stability of soft gelatin capsule. Also, application of phytosome technology was applied with viable herbal drug like curcumin to enhance its bioavailability in addition to using much lower cost phospholipid product known as Phosal® 53 MCT to develop a new delivery system for curcumin named as self phospholipid nano dispersion system and to develop soft gelatin capsules capable to be filled with these novel delivery systems of curcumin. The work in the current thesis was divided into two parts:

Part One

Etodolac Softgels: Feasibility Assessment and Considerations for Lipid-Based/hydrophilic Formulations of a highly hydrophobic drug.

This part endeavored to develop an oral dosage form expressed as soft gelatin capsule for etodolac formulated in lipid vehicle according to lipid formulation classification system and in hydrophilic vehicle as a different attempt to enhance the oral bioavailability of etodolac in addition to study the effect of these systems on the stability of soft gelatin capsules after encapsulation process. Etodolac was formulated with different lipid formulations composing of different concentrations of oils, hydrophobic surfactants, hydrophilic surfactants and co-solvents in addition to PEG 400 as a hydrophilic base which solubilize etodolac. Etodolac lipid formulations were screened through their in-vitro dissolution study by using the pharmacopeial official dissolution system for etodolac to reach the most appropriate formula which improved the dissolution characteristics for etodolac from its lipid formulation. In addition, the effect of such lipid/hydrophilic formulations on the stability of the soft gelatin capsules was conducted whenever this formula improved the dissolution of etodolac or not.

It was observed that Typy III_b which composed of oils, hydrophilic surfactants and co-solvents (i.e. PEG 400) a remarkable enhancement in the dissolution rate for etodolac even after accelerated and shelf stability study in addition to Type IV formulation which based mainly on hydrophilic surfactants. Also, hydrophilic based vehicle was shown to improve the dissolution behavior for etodolac too. In addition, soft gelatin capsules containing these systems showed good physical stability.

Part two

Optimization and development of vesicular delivery systems for curcumin encapsulated in soft gelatin capsule

This part focused on the development of novel delivery systems for curcumin being used as chemoprotetctive agent, anti-inflammatory, anti-oxidant and anti-cancer agent like colorectal cancer to enhance its oral bioavailability knowing that its bioavailability was only 1%. In addition to develop such delivery systems to be encapsulated in soft gelatin capsule for oral administration. This part divided into two chapters:

Chapter One

Preparation and evaluation of soft gelatin capsule containing curcumin-phospholipid complex.

The work in this chapter aimed to develop a locally made CUR-phospholipid complex by local technology with complete similarity to Meriva™. Complete characterization experiments was taken place on the locally prepared CUR-phospholipid complex where the molar ratio between CUR and phospholipid (i.e. LIPOID S 100) was 1:2 in comparison with Meriva™ including in-vitro dissolution studies, TEM photographs, SEM photographs, DSC, IR, TLC and ex-vivo studies showed a complete similarity between the two previously mentioned products.

In addition to previously mentioned work, curcumin-phospholipid complex was subjected to development into fill formulation as suspension by using its powder form where the CUR content was 100 mg/ unit dose and in a semi-solid form to be where the CUR content was 200 mg/unit dose encapsulated into soft gelatin capsules. As a result of screening tests among different formulations containing; oil, hydrophilic surfactants (i.e. KSL P 124, CRM EL) and co-solvents as PEG 400. F 13 formulation containing 40% CRM EL and a hydrophilic vehicle represented as PEG 400 showed that best dissolution results and the highest stability inside the soft gelatin capsule.

Chapter Two

Preparation and evaluation of curcumin phospholipid nano dispersion: As a novel delivery system to enhance curcumin systematic bioavailability

Another form of phospholipid represented in using PHOSAL® 53 MCT providing a liquefied form of phospholipid which encountered to be cheaper than Lipoid® S 100 was utilized as an approach to prepare a novel vesicular delivery system to enhance the solubility and permeability of CUR through the GIT namely as phospholipid nano dispersion (PND) to be encapsulated in a soft gelatin capsule as an oral dosage form. Throughout screening experiments held on many formulations containing different concentrations of Phosal® 53 MCT, hydrophilic surfactants and MCT oil, F1 and F6 were subjected to in-vivo absorption test for curcumin. Although F 1 showed the best performance in the in-vivo study to be subjected as oral soft gelatin capsule, it showed poor stability inside the gelatin capsules which open the door to further studies and researches to optimize the shell formulations to be fit for F 1 encapsulation as a soft gelatin capsule.

الملخص العربي

بالرغم من أهمية الكبسولات الجيلاتنية الرخوة كونها الخيار الأمثل لتوصيل الأدوية المعلقة او الذائبة في اوساط لامائية او شبه صلبة إلي الدورة الدموية، إلا انه يوجد القليل من الأبحاث العلمية المهتمة بتطوير كبسولات جيلاتينية رخوة تحتوي على انظمة حديثة لتوصيل الدواء وذلك بهدف تحسين الإتاحة الحيوية لهذه الأدوية داخل جسم الإنسان عند تناولها عن طريق الفم كما إنه لا توجد دراسات مستفيضة عن ثباتية مثل هذه الأنظمة داخل الكبسولات الرخوة و لا يوجد ايضا دراسات عن مدى التأثير المتبادل بين هذه الأنظمة المستحدثة و الكبسولات الجيلاتنية الرخوة. و لذلك يلاحظ عدم جدوى الدراسات المقدمة عن الأنظمة الحديثة كونها لا يتم تطويرها لتصبح في صورة جرعة دوائية يسهل تناولها ولاسيما عن طريق الفم.

تقوم هذه الرسالة بإلقاء الضوء على تطوير انظمة دوائية حديثة لأدوية شحيحة الذوبان في الماء من اجل تحسين إتاحتها الحيوية داخل الجسم وتطوير كبسولات جيلاتينية رخوة مناسبة لها وذلك عن طرق دراسة مدى ثباتية مثل هذه الأنظمة داخل الكبسولة و كذلك مدى تأثير هذه الأنظمة على ثباتية الكبسولات الجيلاتينية الرخوة. من ضمن الأنظمة المستخدمه هو استخدام التركيبات التي تحتوي في تكوينها على دهون و ذلك حسب ما يعرف بنظام تصنيف صياغة الدهون (Lipid formulation classification system" LFCS") وذلك بإستخدام دواء الإيتودولاك كدواء نموذجي الذي يعرف بشحاحة ذوبانه في الماء. حيث يتم دراسة ثبانية النركيبة المناسبة التي قامت بدورها في تحسين ذوبان الإيتودولاك داخل الكبسولة الجيلاتنية كذلك دراسة تأثيرها والتركيبات الأخرى على الثبات الفيزيائي للكبسولة الجيلاتنينة الرخوة. كما تتناول الرسالة تطوير انظمة فيتوزمية حديثة محلية الصنع من اجل تحسين توصيل ادوية عشبية مثل الكوركومين الذي ثبت حديثا أهميته العلاجية في العديد من الأمراض ولاسيما حالات محددة من السرطان لتكافئ مثيلتها من المنتج الأجنبي و هو ما يعرف ب Meriva™ و كذلك تطويرها في صورة كبسولة جيلاتنينة رخوة. بالإضافة إلي استحداث نظام دوائي أخر لتوصيل الأدوية بإستخدام نوعية اخرى اقل سعرا من الفوسفوليبد النقي و هي PHOSAL® 53 MCT لتوصيل عقار الكوركمين إلي الدورة الدموية للإنسان. تتضمن هذه الرسالة إلي جزءين :

الجزء الأول

دراسة وتقييم جدوى استخدام الأوساط الدهنية و المحبة للماء على كبسولات جيلاتينية رخوة المحتوية على الإيتودولاك.

يتناول هذا الجزء من الرسالة دراسة تطوير كبسولات جيلاتينية رخوة تحتوي على مركب الإيتودولات في اوسط دهنية او محبة للماء و ذلك من اجل تحسين ذوبان المركب في الماء لزيادة امتصاصه عبر الأمعاء عند تناوله عن طريق الفم. كذلك دراسة التأثير المتبادل بين الأوساط السالف ذكرها و الكبسولة الجيلاتينية الرخوة بما يتضمنه ذلك من ثباتية الكبسولة و الأنظمة المستخدمه لهذا الغرض. وبعد عدة تجارب على الأوساط الدهنية المختلفة شملت إختبار الذوبان للتركيبات بإستخدام الإختبار المعتمد من دستور الأدوية الأمريكي للوصول إلي افضل تركيب يحسن من معدل ذوبان ال ETODOLAC وجد ان التصنيف الثالث من نظام تصنيف صياغة الدهون Type III_b المتكون من زيوت، مركبات ذات نشاط سطحي محبة للماء Hydrophilic surfactants، مركبات تساعد على الذوبان co-solvents متمثلة في البولي إيثيلين جليكول 400 يعد افضل الأوسطة الدهنية لتحسين ذوبان الإيتودولاك بجانب الوسيط المحب للماء المتمثل في البولي إيثيليم جليكول 400 . بالإضافة إلى نجاح تلك الأنظمة في عدم التاثير على الثبات الفيزيائي للكبسولة الجيلاتينية اثناء إجراء دراسات الثبات عليها.

الجزء الثاني

تطوير و تحسين كبسولات جيلاتينية رخوة تحتوى على انظمة دوائية متحوصلة لعشب الكوركمين.

يتناول هذا الجزء من الرسالة دراسة تطوير انظمة دوائية متحوصلة للكوركمين كونه عشب ذو اهمية علاجية بالغة كمضاد للأكسدة، مضاد للإلتهابات و مضاد لبعض انواع من مرض السرطان. فبالرغم من اهمية هذا العقار إلا ان إتاحته الحيوية داخل جسم الإنسان محدوده للغاية حيث لا يتعدى 1% و ذلك بسبب انه شحيح الذوبان في الماء، كذلك عدم ثباته الكيميائي في الأوساط المائية و تعرضه لعملية الأيض داخل الأمعاء و الكبد مما يترتب عليه تناوله بجرعات كبيرة تتعدى 4 جم يوميا . ومن هذا المنطلق تمت دراسة العديد من الأنظمة الدوائية الحديثة في محاولة للتغلب على هذه المشكلات و تخفيض الجرعة المتناولة منه مع زيادة فاعليته بالجسم. هذا الجزء ينقسم إلي فصلين:

الفصل الأول
تحضير و تقيم كبسولات جيلاتينية رخوة محتوية على معقد الكوركومين ــ الفوسفوليبيد

يتناول هذا الفصل تحضير معقد الكوركمين – الفوسفوليبيد محليا ومقارنته بمثيله الأجنبي المعرف ب Meriva™ لخفض التكلفة مما يتيح الفرصة لإنتاجه محليا بدلا من إستيراده وذلك لكي يتم تداوله بتكلفة مخفضة. وثبت التطابق التام بين المنتجين بعد إتمام الدراسات المختلفة عليهما حيث شملت الدراسات على مقارنة معدل ذوبان التركيبتين في اوساط متعددة و استخدام الميكروسكوب الإلكتروني النافذ ، و صور الميكروسكوب الإلكتروني الماسح ، المسح المسعري التباييني ، التحليل بواسطة الأشعة تحت الحمراء، كروماتوجرفيا الطبقة الرقيقة و معدل امتصاص التركيبتين بإستخدام EX-vivo study. اما هذا المعقد فقد تم تطويره لكي يعبأ بداخل كبسولة جيلاتينية رخوة في صورة معلق في وسط دهني او في صورته الأوليه كشبه صلب. ووجد ان استخدام هذا المعقد في صورته الأوليه يتيح الفرصة لزيادة تركيز الكوركمين إلى 200 مجم داخل الجرعة الواحدة في وجود البولي إيثيلين 400 و الكريموفور إي إل (F 13) بدلا من 100 مجم لكل كبسولة بالإضافة إلى ثباتية هذه الصورة داخل الكبسولة الجيلاتينية خلال دراسة الثبات.

الفصل الثاني
تحضير و تقييم تركيبات متناهية الصغر قابلة للإنتشار للكوركومين بإستخدام الفوسفوليبد السائل كإحدى الأنظمة المطورة لتوصيل الدواء.

يتناول هذا الفصل تحضير عدد من التركيبات المحتوية على تركيزات على الفوسفوليبد السائل الذي يعد اقل تكلفة من صورته النقيه_بالإضافة إلى بعض الزيوت و المركبات ذات نشاط سطحي محبة للماء. و تبين من خلال هذه الدراسة ان الصورة الذائبة للكوركومين مع الفوسفوليبيد السائل F1 تعد افضل التركيبات التي من شأنها توصيل الدواء إلى الدورة الدموية بصورة عالية وهذا ما تم التأكد منه عند إجراء بعض التجارب على الفئران بالإضافة إلى دراسة معدل الذوبان الخارجي In vitro dissolution study، صور الميكروسكوب الإلكتروني النافذ، و قياس حجم الجزئ و انتشاره حجم الجيزيئات ,معامل تعدد الجزيئات , جهد زيتا ،. فبالرغم من ثبات نجاح التركيبة السالفة الذكر إلا انها لم تحظي بثبات داخل الكبسولة الجيلاتينية و هذا يتطلب المزيد من الدراسات و الأبحاث من اجل الوصول إلى التركيبة المثلى للكبسولة الجيلاتنينة من اجل الحفاظ على ثبات مثل هذه التركيبات بداخلها.

لجنة الإشراف على الرسالة

أ.د. أســـامة يوسف عبد الله .....

أستاذ بقسم الصيدلانيات

كلية الصيدلة – جامعة الإسكندرية

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مدرس بقسم الصيدلانيات

كلية الصيدلة – جامعة الإسكندرية

تطوير الكبسولات الجيلاتينية الرخوة المحتوية على أدوية شحيحة الذوبان

مقدمة من

صيدلي/ إبراهيم عبد المحسن عبد القادر كميل

بكالريوس العلوم الصيدلية، 2009

للحصول على درجة

الماجستير في العلوم الصيدلية (صيدلانيات)

لجنة المناقشة و الحكم على الرسالة

أ.د صفاء صلاح الدين الجمل .....

أ.د. أسامة يوسف عبد الله .....

أ.د. سناء الجيزاوي .....

تطوير الكبسولات الجيلاتينية الرخوة المحتوية على أدوية شحيحة الذوبان.

رسالة علمية

مقدمة إلى الدراسات العليا بكلية الصيدلة-جامعة الإسكندرية

استيفاء للدراسات المقررة للحصول على درجة

الماجستير

في

العلوم الصيدلية (صيدلانيات)

مقدمة من

صيدلي/ إبراهيم عبد المحسن عبد القادر

بكالريوس العلوم الصيدلية، 2009

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