International Journal of Drug Delivery 4 (2012) 219-228
http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Development and characterization of solid lipid dispersion as delivery system for hydrophilic antihypertensive drug atenolol.

Eman Sadder El-Leithy[1], Mohamed Nasr[1*], and Raghda Abd el-Moneum[1]

***Corresponding author:**

Mohamed Nasr

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Helwan University, Helwan, 11790, Cairo, Egypt.

Abstract

Atenolol is a hydrophilic βblocker drug characterized by high solubility and low permeability which corresponds to BCS class III drug. The purpose of the study was to develop solid dispersion of atenolol with fatty excipients to modify the release and enhance intestinal permeability of the drug. The solid dispersions containing atenolol were prepared using lipophilic surfactants, saturated fatty acid, triglycerides and phospholipids by co-evaporation method. The obtained solid dispersions were characterized by differential scanning calorimetry, infrared spectroscopy, drug solubility, % yield, % encapsulation efficiency and in vitro drug release. The results of in vitro release studies indicated that drug release from the drug: phosphotidylcholine dispersion (1:1w/w) showed a sustained release in comparison with the pure atenolol and the other solid dispersions. The influence of phosphotidylcholine on drug intestinal permeation was further evaluated versus pure drug. The results of in vitro permeability revealed that drug-phosphotidylcholine solid dispersion significantly enhanced % permeation of atenolol in comparison with the pure drug. This could be attributed to higher lipophilicity acquired by incorporation of the drug within the solid lipid dispersion. On the basis of the result obtained, it was concluded that solid dispersion of atenolol with phosphotidylcholine is a good approach to modify the release and enhance permeability of water soluble drug. However, the influence of lipophilic solid dispersion on atenolol bioavailability needs further investigation..

Keywords: Atenolol, water soluble drug, lipophilic excipients, solid dispersion, sustained release, permeation.

.

Introduction

Most of drugs are often administered by oral route, whereas, their absorption is based on water solubility and membrane permeability. Drugs with high solubility and low permeability are classified according to Biopharmaceutics Classification System (BCS) as class III drugs [1]. The oral formulation of BSC class III drugs requires the addition of an absorption enhancer [2] and/or pharmaceutical means of drug delivery [3, 4]. Lipid-based formulations showed a great potential as attractive drug delivery systems that influence the absorption of active ingredients via various mechanisms, such as modifying the release of active ingredients, improving their bioavailability, changing the composition and hence the character of the intestinal environment, stimulating the lymphatic transport of active ingredients, interacting with enterocyte-based transport processes and reducing unwanted drug side effects [5]. Atenolol is a hydrophilic β-blocker free base with water solubility of 26.5 mg/ml at 37 ℃ and log p is 0.23 [6, 7]. It is commonly prescribed in treatment of cardiovascular diseases viz; hypertension, angina pectoris, arrhythmias and myocardial infarction [8]. Absorption upon oral administration is rapid but incomplete, leading to 50% - 60% systemic bioavailability due to its poor intestinal permeation [9]. Oral administration of conventional atenolol tablets exhibited fluctuation in plasma drug level and manifestation of its side effects, such as diarrhea, nausea, ischemic colitis, and mesenteric arterial thrombosis [10]. Many formulation approaches have been attempted to improve intestinal permeability and bioavailability of atenolol by controlling its release properties through hydrophilic matrices [11], osmotic pumps [12], transdermal drug delivery system [13], cyclodextrin-based film formulation intended for buccal delivery [14] and floating matrix tablets [15, 16]. The present study was developed to employ solid-

dispersion technique using fatty excipients to regulate the rapid release of atenolol and enhance its intestinal permeation. The drug was dispersed at the single-molecular level into fatty materials including; saturated fatty acids (lauric, palmetic and myristic acid), lipophilic surfactants (Span 60 and glycerol monostearate), triglycerides (Tristearin) and phospholipids (soybean phosphotidylcholine). The solid dispersions were evaluated by DSC, IR, solubility, % yield, and % encapsulation efficiency. *In vitro* drug release and *in vitro* permeability studies were carried out to evaluate the ability of lipophilic solid dispersions to regulate the drug release and permeation enhancement of water soluble drugs.

Materials and Methods

Materials

Atenolol was a gift sample from Cairo Pharma Co. (Egypt). Glycerol-monostearate was purchased from BDH Chemicals Ltd (Poole, England). Tristearin, myristic and palmetic acids were purchased from Fluka Chemicals (USA). Lauric acid was purchased from Sigma Aldrich. Soybean phosphotidylcholine with approximately 75% phosphotidylcholine content were purchased from Avanti Polar lipid Co. (USA). All other reagents were of analytical grade and were obtained from El-Nasr Pharmaceutical Co., Cairo, Egypt

Methods

Preparation of Solid Dispersions

Solid dispersions were prepared at ratio of drug: lipid carrier 1:1 (%w/w) by co-evaporation method described by Nokhodchi et al [17]. Accurately weighed amount of atenolol was dissolved in methanol. This alcoholic solution was poured into a solution of the lipoid substance in hexane/chloroform mixture at ratio 1:1 (v/v). The mixture was continuously stirred at room temperature till almost complete evaporation of solvents. The remaining solid residue was dried in an incubator (Refrigerated incubator FTC (90) E) at 40 ºC. All dispersions were pulverized with pestle and mortar and sieved (<250 µm) except those prepared with phospholipids that presented in a waxy state at room temperature. The samples were stored in a closed screw-capped glass vials away from the light and humidity until use.

Differential Scanning Calorimetry (DSC)

Samples for DSC (3 mg) were weighed into aluminum pans (TA Instruments, Brussels, Belgium) and hermetically sealed. Runs were performed over a temperature range 20-200 ºC, at a constant rate of 10ºC/min under nitrogen purge (30 ml/min). Octadecane and indium standards were used to calibrate the DSC-7 calorimeter (Perkin-Elmer, Norwalk, CT).

Fourier Transform Infrared Spectroscopy (FT-IR).

FT-IR spectra were obtained on a Perkin-Elmer IR spectrometer (spectrum BX 100, Perkin-Elmer, USA). Samples were prepared in KBr discs (about 10 mg sample for 100 mg of dry KBr). The IR spectra were obtained in the spectral region 450–4000 cm-1.

Solubility Study

Solubility study was conducted to determine the effect of solid dispersion formulations on liposolubility of atenolol. An excess amount of the drug samples was dispersed in 5 ml of distilled water, phosphate buffer solution (pH = 7.4), and n-octanol in glass stoppered tubes, respectively. All the liquid samples were horizontally shaken (100 rpm) for 24 hrs in water bath shaker at 37 ºC. After reaching equilibrium, the samples were centrifuged (Hermle Z 200 A, Germany) at 3000 rpm for 5 min. Excess solid residue was filtered through 0.45 µm membrane filter. One ml sample of saturated solution was diluted with methanol and drug concentration was analyzed by UV spectrophotometer at 273 nm (Perkin Elmer, Lambda Ez 201, and USA).

% Yield, drug content and % Entrapment Efficiency determination

Percentage yield was determined by weighing the dried solid dispersion and calculated with respect to the weight of the initial components according to the following formula;

%Yield = [mass of solid dispersion/(mass of drug + mass of lipidic substances)]×100

Drug content was determined according to the procedure described by Hammady et al [18]. Ten milligrams of each solid dispersion were weighed in glass stoppered tubes and re-dispersed in 3 ml distilled water. The dispersion was then lysed with 1ml chloroform to allow for complete release for entrapped drug. Complete extraction of the drug was facilitated by shaking the tubes for 6 hrs in water bath shaker at 37 ºC. The samples were centrifuged at 6000 rpm for 5 min and then allowed to stand for complete separation of the two phases. The collected aqueous solutions were analyzed for determining drug concentration as previously described.
Drug concentration was also used for determining % encapsulation efficiency according to the following formula

% Encapsulation efficiency = (actual drug loading/ theoretical drug loading) ×100

In vitro Release Study

Drug dissolution was carried out by the paddle method, using USP XXIII dissolution assembly (Hanson Research Dissolution Tester, Chatsworth, USA). A weighed sample of the solid dispersion equivalent to 50 mg pure drug was placed in a tea bag. The tea bag tied with the paddle and immersed in 900 ml phosphate-

buffered saline (PBS) (pH 7.4) dissolution medium and rotated at 100 rpm at 37 ºC. Perfect sink condition prevailed during the dissolution test. Sample aliquots were withdrawn at appropriate intervals, assayed spectrophotometrically for drug concentration at 273 nm and replaced with equal volume of fresh buffer solution. All experiments were performed in triplicate samples.

In vitro Permeability Study

The study was conducted by using the intestinal tissue of a rabbit that allowed to be fasted over night. The duodenal part of the small intestine was isolated, divided into segment sacs and thoroughly flushed with cold Ringer's solution to remove lumen contents. The segment sacs were filled with the drug samples dispersed in 2 ml PBS (pH 7.4) and ligatures were placed at both ends. The tissues were hanged in organ baths filled with 30 ml PBS under continuous aeration and constant temp of 37 ºC. At predetermined time intervals, sample aliquots were withdrawn and replaced by fresh medium. The samples were analyzed for the drug concentration against blank [19].

Results and Discussion

Solid state characterization of solid-lipid dispersions

DSC thermograms

Thermal behaviors of the pure drug, lipid carriers and their solid dispersions were depicted in figure 1. Figure 1a, showed the DSC thermograms of atenolol, free fatty acids and atenolol-fatty acid dispersions. DSC thermogram of atenolol exhibited a sharp characteristic endothermic peak at 154.7 ºC, corresponding to its melting point [20], reflecting the crystalline state of the drug. DSC thermograms of myristic acid, lauric acid, and palmetic acid showed endothermic peaks at range of 48-66˚C. Drug-fatty acids dispersions showed a significant reduction in atenolol melting points to 124.9˚C, 122.8˚C and 128.9˚C, respectively. Figure 1b, presents the DSC thermograms of surfactants and atenolol-surfactant loaded dispersions. Atenolol-Span 60 loaded dispersion had a melting point at 155.5 ºC, revealing no remarkable interaction with atenolol (pure drug =154.7 ºC). However, glycerol monostearate dispersion showed a shift in the drug melting point to 131.8 ºC, indicating a possible interaction. Figure 1c, presented the DSC thermograms of tristearin, phospholipids and their drug loaded dispersions. Tristearin thermogram showed peak at 71.5 ºC whereas; its drug-loaded dispersion showed two characteristics peaks for both tristearin and drug at 72.8 ºC and 153.9 ºC, respectively. Comparing DSC thermograms of the phospholipids to its drug-loaded dispersion clearly revealed a complete disappearance of the two characteristic peaks of phospholipids previously appeared at 122.7 ºC and 178.8 ºC and a shift in the drug peak to 145.9 ºC (Figure 1c). Thermograms of atenolol in the solid dispersions of 1:1 and 1:2 w/w drug: (phospholipids/tristearin mixture, 1:1 w/w) were also given in Figure 1c. The two thermograms showed complete disappearance for the two peaks of phospholipids. However, the characteristic peaks of tristearin clearly appeared at 71.5 ºC and the drug at 143˚C. These results obviously revealed no drug-tristearin interaction and possible drug-phospholipids interaction.

Infrared Spectroscopy

The IR analysis was performed to complement the results obtained from thermal analysis. The IR spectra for atenolol and its solid dispersions were given in Figure 2. Figure 2a, showed the IR spectra of atenolol, free fatty acids and their drug-loaded dispersions. The bands of hydroxyl and amine groups were assigned at range of 3174-3355 cm^{-1}, aliphatic C-H groups at range of 2867-2963 cm^{-1} and the band of C=O amide group at 1642 cm^{-1}, these values corresponding to the characteristics IR of atenolol. The IR spectra of free fatty acids (myristic, lauric and palmetic) identified characteristics absorption bands of C=O group at 1701 cm^{-1} and C-H aliphatic groups at range 2850-2916. IR spectra of atenolol-free fatty acid loaded dispersions showed a shift in the characteristic carbonyl group (C=O) of free fatty acids to 1662 $cm^{-1}$and disappearance of the characteristic C=O amide group of pure drug. This result was in agreement with their DSC thermograms (Figure 1a) and was attributed to the possible interaction through H-bond formation between hydroxyl group of pure drug and free fatty acids carbonyl group.

The IR spectra of the drug, surfactants (Span 60 and glycerol monostearate) and their drug loaded dispersions were presented in Figure 2b. Span 60 and glycerol monostearate IR spectra identified the characteristics ester C=O group at 1735 $cm^{-1}$and C-H aliphatic groups at range 2851-2920 cm^{-1}. IR spectra of their drug loaded dispersions showed a decrease in the intensity of ester C=O peaks. Figure 2c demonstrated the IR spectra of the drug, tristearin, phospholipids and their drug-loaded dispersions. Tristearin had a characteristic absorption band at 1735 $cm^{-1}$for the C=O ester group and C-H aliphatic groups at range (2854-2920 cm^{-1}). The IR spectrum of tristearin-drug loaded dispersion was not superimposed with that of pure drug or tristearin. However, there was an appearance to C=O ester group of tristearin at 1735 $cm^{-1}$and slight shift of the drug C=O amide group to 1635 cm^{-1}. This result was also in agreement with their DSC thermograms that showed characteristic peak of tristearin at 71.5 ºC, and drug at 154. ºC Figure 2c, showed the characteristic absorption bands of phospholipids spectrum; phosphoryl group o-p=o at 1234 cm^{-1}, C-H aliphatic groups at range 2854-2929 cm^{-1} and ester C=O group at 1739 cm^{-1}. Spectrum of drug-phospholipids loaded dispersion (1:1 w/w) showed a slight shift for the phosphoryl group towards a lower frequency (1242 cm^{-1}), which attributed to H-bond formation between phosphoryl and drug hydroxyl groups (Figure 2c). Such interaction was in accordance with the disappearance of phospholipids peaks and shift of the drug peak in DSC thermogram (Figure 1c). IR spectra for the drug dispersion in phospholipids/tristearin carriers' mixture at ratios 1:1 and 1:2 w/w were also presented at Figure 2c. The results clearly revealed slight shift in both phosphoryl group of phospholipids from 1234 cm^{-1} to 1242 cm^{-1} and in carbonyl amide group of the drug from

1642 cm^{-1} to 1635 cm^{-1}. Based on the results of DSC thermograms and IR spectra of atenolol solid dispersions with different types of lipophilic carries, it was concluded that both free fatty acids and phospholipids showed a remarkable tendency to interact with the pure drug.

Solubility Study

Saturated solubility and partition coefficient (Log p) of pure atenolol and its loaded dispersions in different solvents were given in Table1. The solubility of atenolol was 21.5±0.95 and 0.3±0.015 mg/ml in distilled water and n-octanol, respectively with very low partition coefficient (Log p= -1.88), reflecting its typical hydrophilic properties [21]. All samples of atenolol-loaded dispersion showed a remarkable decrease in aqueous solubility in comparison to pure atenolol. The drug partitioning into n-octanol was increased by about 35-46.80% in case of the solid dispersion with free fatty acids while lipophilic surfactants increased Log P by 50% comparing to pure drug. In addition, drug: phospholipids dispersions showed an obvious increase in Log P values in comparison with that of pure drug. The decrease in the aqueous solubility of drug-loaded dispersions with free fatty acids was attributed to the hydrophobic nature of these fatty acids and nature of their molecular structure. All fatty acids decreased both drug wettability and dissolution. The ability of lipophilic surfactants to increase Log P by about 50% comparing to that of pure drug was related to arrangement of surfactant hydrophilic groups towards drug core and formation of a protective hydrophobic sheath that cause partial masking of the drug hydrophilic properties. Phospholipids/tristearin' mixtures greatly improved the drug lipophilicity over each polymeric carrier.

This pronounced effect on increasing log P values were related to the possible formation of monolayer spherical shell of phospholipids surrounding the drug, which increased the drug partitioning into the more oily phase (tristearin). Thus, upon addition of these drug-loaded dispersions into n-octanol, the lipid particles enclosing the hydrophilic drug were freely dissolved [22].

% Yield, Drug Content and Entrapment Efficiency (%EE)

Table 2 showed that %yield of all solid dispersions was in range 70-86%, indicating reproducibility and efficiency of the method of preparation. A sticky and tacky mass was obtained with Span 60, glycerol monostearate and phospholipids solid dispersions causing their poor handling and bad flowability. Solid dispersions along with the other lipophilic carriers showed good flow properties. Entrapment efficiency was expressed as percentage of the total amount of drug initially used. The drug-fatty acid dispersions showed the lowest %EE (51.50-57.50%). The drug-surfactant loaded dispersions showed an increase in %EE reaching 63.3 and 68% for Span 60 and glycerol monostearate, respectively. %EE of the drug within phospholipids, tristearin or phospholipids/tristearin carriers' mixtures at ratios 1:1 and 1:2 %w/w was 82.6 %, 78, 86.6% and 79% respectively. The results of %EE was clearly revealed a good relationship between the molecular structures of the lipophilic carriers and the higher %EE for the drug. The lowest %EE resulted with free fatty acids was related to their linear saturated hydrocarbon molecular structure that decreases the tendency of H-bonding sufficient to entrap the drug. The increase in % EE obtained with tristearin and phospholipids were attributed to increase molecular structure branching and molecule flexibility to bend and rotate for enclosing the drug within its structure by H- bonds. Another explanation for the higher entrapment of a hydrophilic drug within phospholipid was given by Kawaguchi et al [23]; the authors attributed the high %EE to the amphiphilic nature of phospholipids which have both hydrophilic and hydrophobic regions arranged in cylindrical molecular shape producing closed vesicles to include water soluble as well as oil soluble drugs. The results also demonstrated the influence of drug to lipid carrier ratio on % EE. Increase drug to phospholipids ratio (3:1w/w) lead to low %EE. However, increasing the phospholipids content (drug: phospholipids at ratio 2:1 and 1:1 w/w) raised the %EE by providing more space to incorporate the drug and increased the ability of phospholipids to enclose the drug molecules. Increment of lipid content also reduces the escaping of the drug into external phase, which accounts for an increase in % EE [24].

In- Vitro Drug Release Study

Dissolution profiles of atenolol comparing to its solid dispersions in phosphate buffer (pH 7.4) were shown in Figure 3. The pure drug showed a complete release within the first two hours, while a complete release of the drug from its solid dispersion with free fatty acids (figure 3a) were recorded after 3, 4 and 6 hours for lauric acid, palmetic acid and myristic acid solid dispersions, respectively. Figure 6b revealed similarity in release profiles of pure drug comparing to its solid dispersions with Span 60 and glycerol monostearate. There was a complete leakage of the drug from its solid dispersions into the aqueous medium within the first two hours.

A sustained release of atenolol was achieved with the solid dispersions of atenolol: phospholipids (1:1 w/w) and atenolol: (phospholipids/tristearin mixture) at ratio 1:2 w/w. (figure 3c). Both solid dispersions showed remarkable decrease in % drug released with disappearance of the burst effect. Drug release from the drug: phospholipids dispersion (1:1w/w) showed a controlled drug release, starting with 18%, 29% and 35% drug released during first three hours, respectively and extended to reach 80% after 8 hours. However, drug release from drug: (phospholipids /tristearin carriers' mixture) solid dispersion at ratio 1:2 was 25%, 33% and 37% during the first three hours, respectively and reached 50%

Table 1. Solubility and partition coefficient (Log P) of Atenolol and its lipophilic solid dispersions

Sample	Solubility in water (mg/ml)	Solubility in n-octanol (mg/ml)	Partitioning in n-octanol/ water	Log P
Atenolol	21.5± 0.95	0.3±0.015	0.01	-1.88
Atenolol:Lauric acid (1:1 w/w)	3.6±0.06	0.27±0.01	0.06	-1.22
Atenolol:Palmetic acid (1:1 w/w)	3.4±0.33	0.34± 0.03	0.10	-1.0
Atenolol:Myristic acid (1:1 w/w)	3.2±0.3	0.29±0.015	0.09	-1.04
Atenolol:Span 60 (1:1 w/w)	4.5 ±0.3	0.53±0.03	0.11	-0.95
Atenolol:Glycerol monostearate(1:1w/w)	4.67±0.3	0.53±0.03	0.11	-0.95
Atenolol: Phospholipids* (1:1 w/w)	3.7±0.22	0.23±0.017	0.06	-1.22
Atenolol: Phospholipids(2:1 w/w)	15.8±0.3	1.2±0.033	0.07	-1.12
Atenolol: Phospholipids (3:1 w/w)	19.5± 0.3	0.95±0.033	0.04	-1.34
Atenolol:Tristearin (1:1 w/w)	6.2±0.5	0.45±0.036	0.07	-1.13
Atenolol:(Phospholipids+Tristearin)(1: 1w/w)	4.6±0.3	0.63±0.033	0.14	-0.85
Atenolol:(Phospholipids+Tristearin) (2:1w/w)	4.0± 0.3	0.6±0.033	0.15	-0.82

*Phospholipids = (Soya bean phosphotidylcholine)

Table 2. % yield, % drug content and % entrapment efficiency (%EE) of atenolol- lipophilic solid dispersion

Sample	% Yield	% Drug content (Mean± S.D)	%EE (Mean ± S.D)
Atenolol:Lauric acid (1:1 w/w)	75	25.7 ±6.0	51.5 ±6.0
Atenolol:Palmetic acid (1:1 w/w)	72	27.2 ±3.8	54.5 ± 7.0
Atenolol:Myristic acid (1:1 w/w)	86	28.0 ±2.8	57.5 ±2.7
Atenolol:Span 60 (1:1 w/w)	70	35.0 ±3.5	68.0 ±5.6
Atenolol:Glycerol monostearate(1:1w/w)	70	31.50 ±3.5	63.0 ±6.0
Atenolol: Phospholipids (1:1 w/w)	75	41.30 ±3.0	82.6 ±5.0
Atenolol: Phospholipids(2:1 w/w)	70	62.0 ±0.42	92.5 ±0.7
Atenolol: Phospholipids (3:1 w/w)	80	60.0 ±0.6.0	80.0 ±1.0
Atenolol:Tristearin (1:1 w/w)	72	40.0 ±0.42	78.0 ±0.7
Atenolol:(Phospholipids+Tristearin)(1: 1w/w)	80	43.2 ±0.6	86.8 ±1.0
Atenolol:(Phospholipids+Tristearin) (2:1w/w)	80	39. 5 ± 3.0	79.0± 5.0

*Phospholipids = (Soya bean phosphotidylcholine)

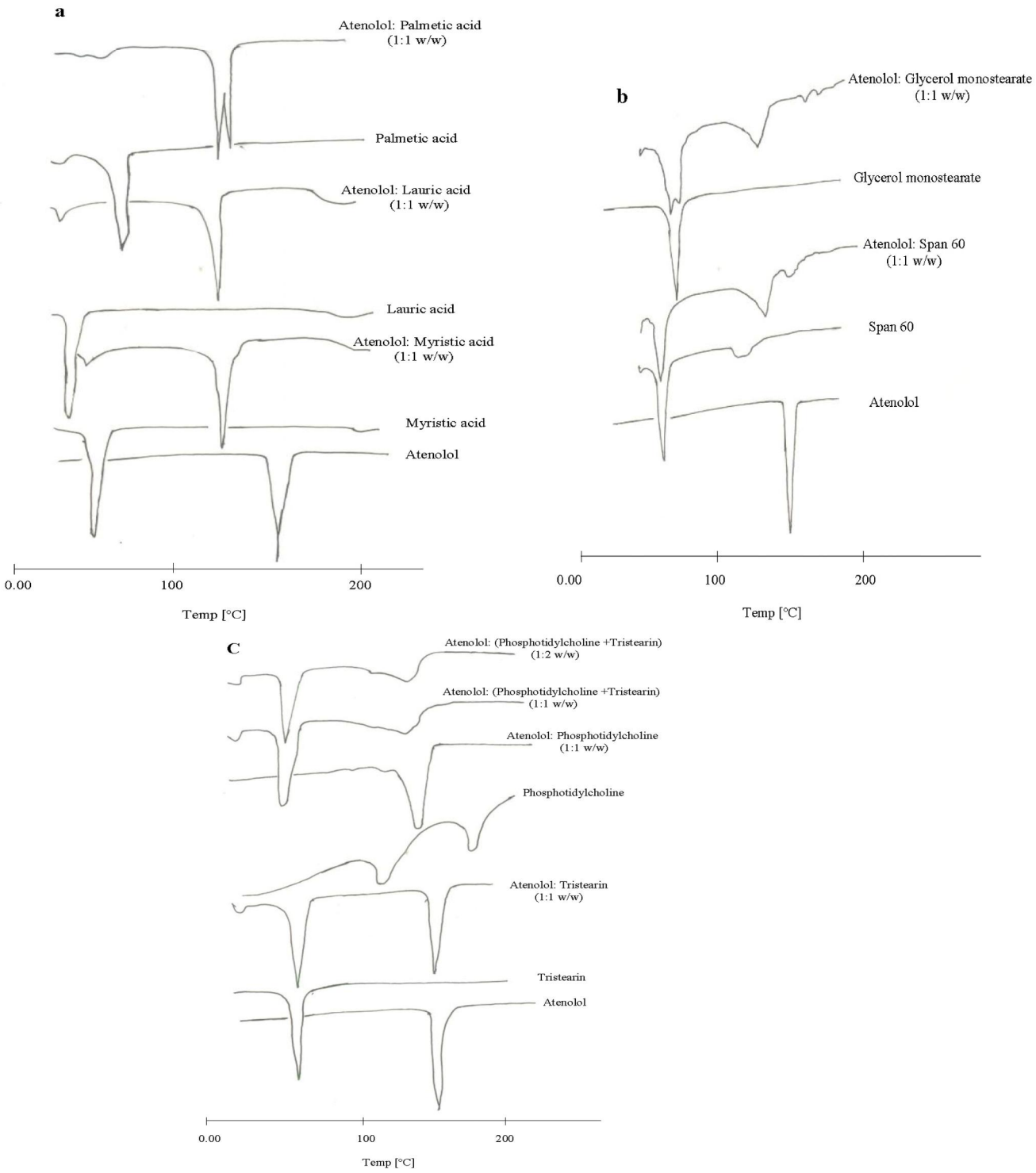

Figure 1. DSC thermograms of Atenolol- free fatty acids solid dispersions (a), Atenolol-surfactant solid dispersions (b) and Atenolol-phospholipids solid dispersion (c).

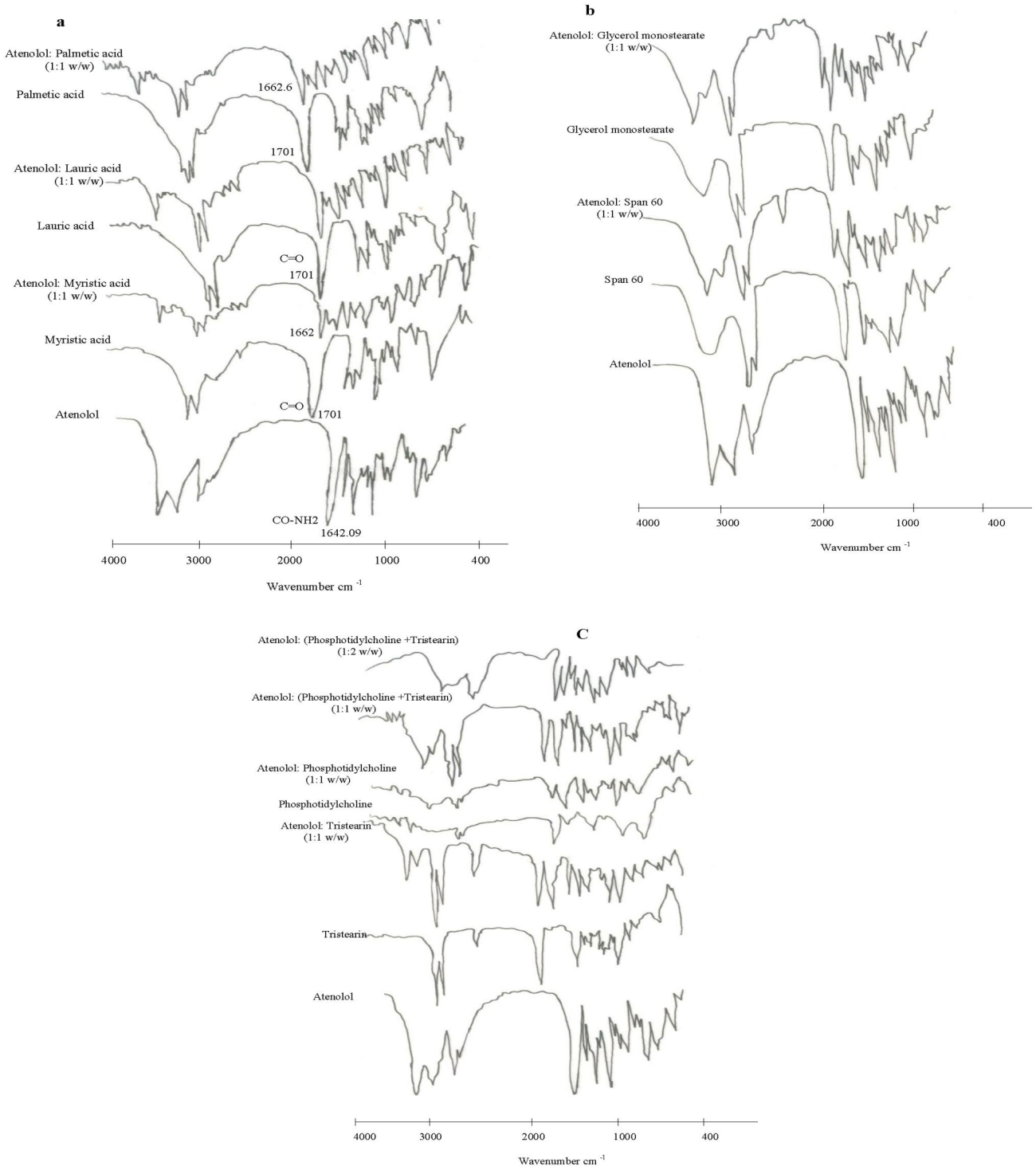

Figure 2. Infrared Spectra of Atenolol- free fatty acids solid dispersions (a), Atenolol-surfactant solid dispersions (b) and Atenolol- phospholipids solid dispersions (c).

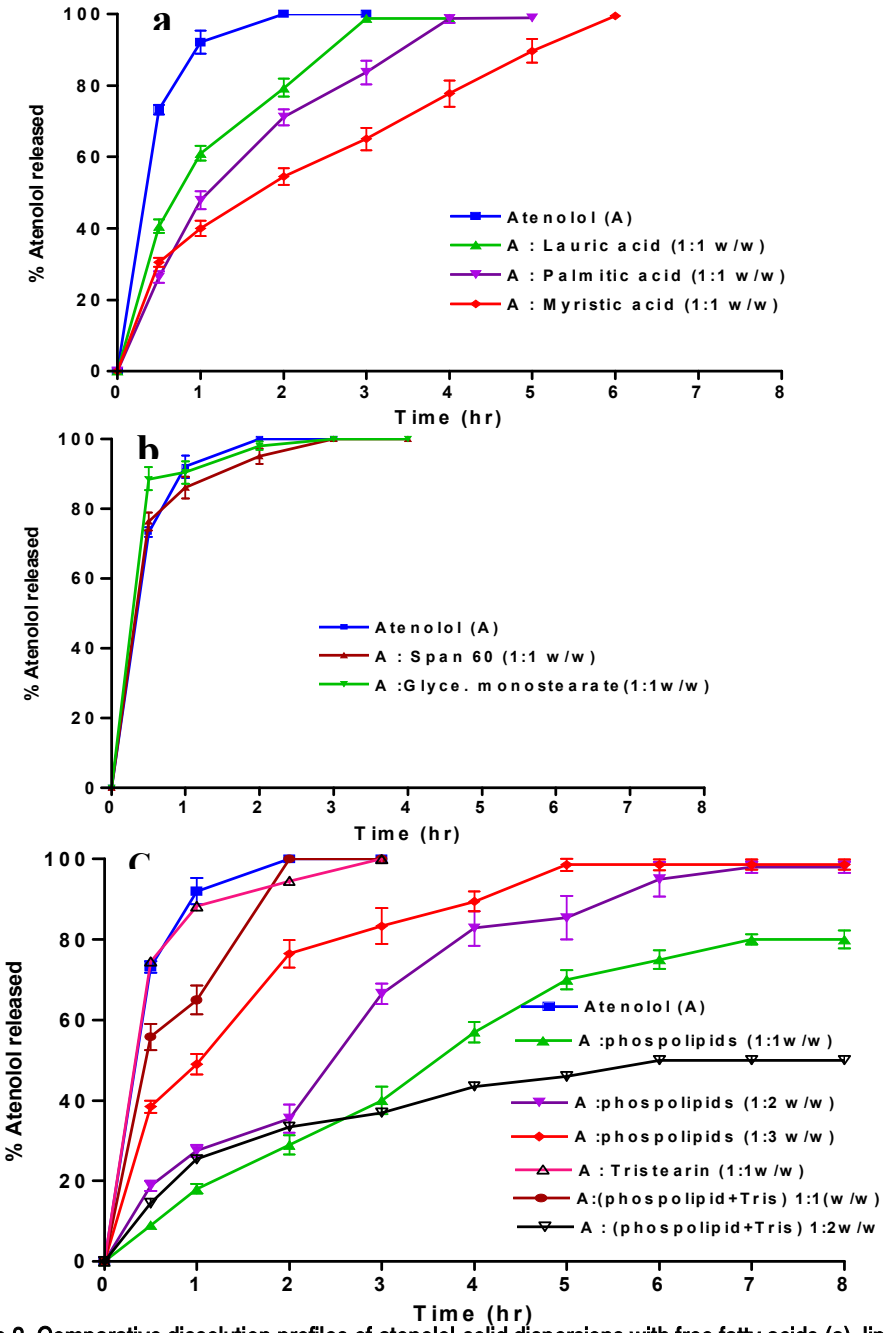

Figure 3. Comparative dissolution profiles of atenolol-solid dispersions with free fatty acids (a), lipophilic surfactants (b), phospholipids, Tristearin and their mixture (c). Each point refers to mean ± SD (n=3).

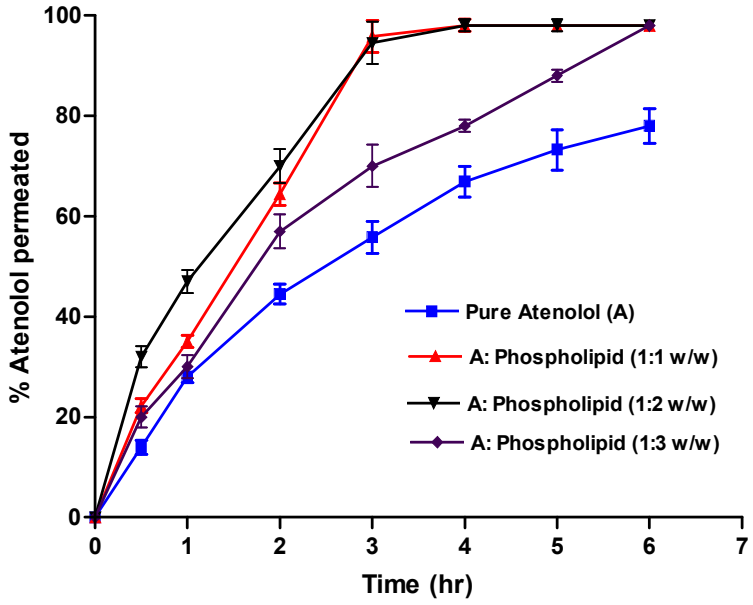

Figure 4. *In-vitro* permeation profiles of pure atenolol and atenolol dispersed with different ratios of phospholipids.

after 8 hours. Atenolol solid dispersion with phospholipids (1:1 w/w) showed the slowest release of atenolol than the other dispersions and provided sustained release for more eight hours.

In vitro Permeation study

In vitro permeation experiments were carried out for studying the effect of conjugating the hydrophilic drug (atenolol) to phospholipids and the effect of their relative concentrations to each other. The results demonstrated that phospholipids have a robust effect on improving the intestinal permeation of atenolol. It was also noted that % of permeated drug was highly dependent on phospholipids concentration. As the amount of phospholipids increased relative to that of drug, the % of permeated drug was also increased. There was no remarkable difference between the permeation results of drug: phospholipids dispersions at ratio 2:1 and 1:1. Both formulas allowed for 95% of drug to be permeated within 3 hours compared to 70% for drug: phospholipids dispersions at ratio 3:1 and 55% of pure drug (figure 4). These results showed the important role of phospholipids on improving the permeability of a hydrophilic drug that characterized by high aqueous solubility and low permeability through GIT membrane. The results of permeation were typically contrary to that of dissolution. The formula that showed lowest release profile allowed for the highest % of drug to be permeated.

Conclusions

On the basis of the results obtained, it was concluded that solid dispersion of atenolol with a lipophilic excipients such as phosphotidylcholine in the ratio of 1:1 w/w is a simple approach to sustained the drug release and enhance drug bioactivity and permeation through lipid barriers. However, the influence of lipophilic solid dispersion on atenolol bioavailability needs further investigation.

Conflict of Interest

There is no conflict of Interest

References

[1]. Koga K, Takarada N, Takada K. Nano-sized water-in-oil-in-water emulsion enhances intestinal absorption of calcein, a high solubility and low permeability Compound. Eur. J .Pharm. Biopharm. 2010, 74 (2), 223-32.

[2]. Wang S, Sun M, Ping Q. Enhancing effect of labrafac lipophile WL 1349 on oral bioavailability of hydroxysafflor yellow A in rats. Int. J. Pharm. 2008 Jun 24,358(1-2), 198-204.

[3]. Takada K. Oral delivery of hematopoietic factors: progress with gastrointestinal mucoadhesive

patches, microdevices, and other microfabrication technologies. Am. J. Drug Del. 2006, 4, 65–77.

[4]. Deshmukh DD, Ravis WR, Betageri GV. Improved delivery of cromolyn from oral proliposomal beads. Int .J. Pharm. 2008 24,358(1-2), 128-164.

[5]. Fricker G, Kromp T, Wendel A, Blume A, Zirkel J, Rebmann H, Setzer C, Quinkert RO, Martin F, Müller-Goymann C. Phospholipids and lipid-based formulations in oral drug delivery. Pharm. Res. 2010, 27(8), 1469-1555.

[6]. Ali O, Obaid R, Saify ZS, Ahmed SW. Biopharmaceutical evaluation of oral tablet Atenolol (100 and 50 mg) on local population. Pak. J. Pharm. Sci. 2005, 18(1), 25-32.

[7]. Milind P, Wagh J, Patel S. Biopharmaceutical Classification System: Scientific Basis for Bilayer Extensions Int. J.Pharm. Pharm.Sc. 2010, 2(1), 12-19.

[8]. Jug M, Beđrević-Lačan M, Bengez S. Novel cyclodextrin-based film formulation intended for buccal delivery of atenolol. Drug. Dev. Ind. Pharm. 2009 35(7), 796-807.

[9]. Wu F, Cheni P, Lee YJ, Long RR. Comparative Pharmacokinetics of Two Atenolol Products .Journal of Food and Drug Analysis.2003, 4-7.

[10]. Sastry SV, Reddy IK, Khan MA. Atenolol gastrointestinal therapeutic system: Optimization of formulation variables using response surface methodology. J. Control. Release. 1997, 45,121-130.

[11]. Singh B, Kaur S, Chakkal AN. Formulation and Optimization of Controlled Release Mucoadhesive Tablets of Atenolol Using Response Surface Methodology .AAPS. Pharm.Sci.Tech. 2006, 7(1), 3.

[12]. Vaithiyalingam SR, Sastry SV, Dehon RH, Reddy IK, Khan MA. Long- term stability characterization of a controlled release gastrointestinal therapeutic system coated with cellulose acetate pseudolatex. Pharmazie. 2001, 56, 66-69.

[13]. Kim J, Shin SC. Controlled release of atenolol from the ethylene-vinyl acetate matrix. Int. J. Pharm. 2004,273, 23-27.

[14]. Jug M, Beđrević-Lačan M, Bengez S. Novel cyclodextrin-based film formulation intended for buccal delivery of atenolol. Drug Dev. Ind. Pharm. 2009, 35(7), 796-807.

[15]. Kulkarni A, Bhatia M. Development and Evaluation of Regioselective Bilayer Floating Tablets of Atenolol and Lovastatin for Biphasic Release Profile. Iranian J. Pharma. Res. 2009, 8 (1), 15-25.

[16]. Srivastava AK, Wadhwa S, Ridhurkar D, Mishra B. Oral Sustained Delivery of Atenolol from floating Matrix Tablets—Formulation and in vitro Evaluation. Drug .Dev. Ind. Pharm. 2005, 31(4-5), 367-74.

[17]. Nokhodchi A, Talari R, Valizadeh H, Jalali MB. An investigation on the solid dispersions of chlordiazepoxide. Int. J. Bio. 2007, 3,211- 217.

[18]. Hammady T, El-Gindy A, Lejmi E, Dhanikula RS, Moreau P, Hildgen P. Characteristics and properties of nanospheres co-loaded with lipophilic and hydrophilic drug models. Int. J. Pharm. 2009, 18,369(1-2), 185-95.

[19]. Smith PL. Methods for evaluating intestinal permeability and metabolism in-vitro. Pharm. Biotechnol. 1996, 8, 13-34.

[20]. Rafael NP, Bruno RV, Ariane PC, Talize F, Fabio SM, Marcos AS. Thermo analytical Study of Atenolol and Commercial Tablets. Lat. Am. J. Pharm. 2007, 26, (3), 382-388.

[21]. Sharma P, Varma MV, Chawla HP, Panchagnula R. Relationship between lipophilicity of BCS class III and IV drugs and the functional activity of peroral absorption enhancers. Farmaco. 2005, 60(11-12), 870-873.

[22]. Wang T, Wang N, Hao A, He X, Li T, Deng Y. Lyophilization of water-in-oil emulsions to prepare phospholipid-based anhydrous reverse micelles for oral peptide delivery. Eur .J .Pharm. Sci. 2010, 18, 39(5), 373-382.

[23]. Kawaguchi E, Shimokawa K, Ishii F. Physicochemical properties of structured phosphotidylcholine in drug carrier lipid emulsions for drug delivery systems. Colloids Surf. B. Biointerfaces. 2008, 62(1), 130-135.

[24]. Robhash KS, Keon WK, Hoo-Kyun C. Preparation and characterization of solid lipid nanoparticles loaded with doxorubicin. Eur J .Pharm. Sci. 2009, 37, 508–513.

.