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RESEARCH PAPER

Pelletization of ibuprofen-phosphatidylcholine self-assembling nanoparticles

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ABSTRACT

Objective(s): Prescription of ibuprofen as a non-steroidal anti-inflammatory drug is limited by its gastrointestinal side effects and poor aqueous solubility. It was shown that phospholipid-association (PA) can lead to assembling assembly of the micellar form, thereby improving solubility of non-steroidal anti-inflammatory drugs solubility and reducing their gastrointestinal side effects.

Materials and Methods: Ibuprofen in PA form was prepared and its interaction, crystallinity, and particle size were evaluated. Conventional ibuprofen and PA pellets in different drug contents were prepared by extrusion-spheronization. The mMorphology, shape factors, mechanical strength, and drug content of pellets were investigated. The dissolution test also was conducted in an intestinal-simulated medium and a gastric-simulated medium.

Results: The results showed that PA micelles of ibuprofen were demonstrated to be formed, amorphous, and in an acceptable size range. Using a suitable composition of solid components and granulation fluid, pellets with desirable size, shape, and sphericity could be produced. All pellets have had plastic mechanical properties and the strength of formulations were decreased with increasing PA ratio. The PA-pellet formulation had faster drug release compared to conventional ibuprofen pellets, via increasing ibuprofen solubility by reducing crystallinity in solid state and micelle formation in dissolution media. Moreover, ibuprofen solubility in a gastric-simulated medium was decreased and might result in reduced gastrointestinal side effects.

Conclusion: Due to the demonstrated bioavailability advantages of PA-pellets, they can be considered for further studies.

Keywords: *Complex, Drug delivery, Gastrointestinal tract, NSAID, Phospholipid*

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INTRODUCTION

Ibuprofen, as a non-steroidal anti-inflammatory drug, is routinely prescribed with the aim of treating fever, inflammation, and pain through prostaglandin inhibition due to the inhibition of cyclooxygenase enzyme [1, 2]. According to the stimulation of synthesis of gastroprotective prostaglandins by cyclooxygenase enzymes, ibuprofen might reduce the production of gastroprotective prostaglandins which can lead to gastrointestinal toxicity [2]. In addition, ibuprofen is aqueous insoluble moiety as it is lipophilic [3].

Several methods have been applied in order to solve the mentioned problems. Preparation of NSAIDs complexes [4], solid dispersions [5] flurbiprofen (FLU, prodrugs [6), etc., has been demonstrated to be able to improve their bioavailability. In this study, association which can be considered as a potential system for improvement of drug bioavailability [7, 8], is applied to overcome challenges of ibuprofen bioavailability.

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Up to now, it has been demonstrated that many amphiphilic dimers in aqueous solution are able to assemble into nanoparticles without any surfactant, resulting in a considerable improvement compared to their parent drugs [9–11]. Amphiphilic molecules including phospholipids can make weak gel in particular condition. In specific pH or temperature, phospholipid tails can make strong interaction together and change rheological and lubrication properties by immobilization of phospholipid in 3D network [12,13]. This mechanism has been used to design and develop controlled release formulations [14]. The nanoparticles have properties such as small size and huge surface area which causes increase in absorption of poorly soluble chemicals through enhancement of dissolution rate [15] or lymphatic absorption [16].

It was revealed that in ibuprofen-phosphatidylcholine association (PA), ibuprofen carboxyl group is in the vicinity of phosphatidylcholine's choline and phosphate moiety. Preparation of PA led to increased amphiphilic characteristics and nanometric size particles which could be attributed to self-assembly of nanoparticles. The nanoparticles were able to reduce gastrointestinal toxicity of ibuprofen and improve its absorption rate [7]. Unfortunately, phospholipid-drug association is viscose, adhesive and semi-solid which might lead to difficulty in administeration. Phospholipid association is also challenging due to its crystal growth and physical instability. Solid dosage forms including tablet, granule, pellet and hard gelatin capsules are highly acceptable and palatable among patients [17, 18] low dose (content uniformity and are more stable than other pharmaceutical dosage forms. In solid dosage forms, the drug is mixed and diluted with solid excipients and may reduce their degradative physical and chemical instabilities such as hydrolysis, oxidation, crystal growth and etc. [19].

Pelletization is an agglomeration process which changes particles or powders of active pharmaceutical ingredients and excipients to free-flowing small spheres, called pellets. Pellets have a narrow size range between 0.5-2.0 mm. Pelletization can increase bulk density, define shape, improve hardness and friability and prevent segregation of co-agglomerated components (causing a content uniformity improvement) and dust formation (causing production process safety) [20]. Furthermore, pellet formulation can play an important role in improvement of bioavailability. In particular, pelletization can cause shorter absorption lag-time, fast stomach depletion, uniform dispersion in GIT, the less local drug concentration and reduced gastric side effects by dose dumping prevention [21–26] 6.5, 6.8 and 7.2. Pelletization has been demonstrated to be a promised technique for controlled release formulation of many drugs including ibuprofen [27–29].

In the present research, the feasibility of preparing pellets containing ibuprofen-phosphatidylcholine self-assembling nanoparticles is studied. The prepared pellets are evaluated by sieve analysis, drug content uniformity assessment, image analysis, mechanical tests, scanning electron microscopy and *in vitro dissolution studies.*

MATERIALS AND METHODS

Materials

Ibuprofen and Avicel® PH-101 (microcrystalline cellulose) were acquired from Darupakhsh Pharmaceutical Co. (Iran). Phospholipon® 90G (Soy-Phosphatidylcholine 95%) was provided by Lipoid (Germany), sodium dodecyl sulfate (SDS) and lactose were obtained from Merck (Germany). Fumed silica (Aerosil®) was bought from Evonik (Germany) and the rest of used chemicals were analytical grade.

Plain ibuprofen UV spectrum

To obtain UV spectrum of the applied plain ibuprofen powder, 5 mg of the powder was dispersed in 250 mL of distilled water and left stirring overnight to ensure complete dissolution. Next, UV absorbance of the prepared solution was recorded using a spectrophotometer at the range of 200- 400 nm (UV 1800, Shimadzu, Japan).

Preparation of drug-phospholipid association

According to our previous study [7], the best molar ratio for integration between ibuprofen and phosphatidylcholine with a view to improve ibuprofen solubility was selected. PA was prepared by "refluxing method". Briefly, ibuprofen with phosphatidylcholine in 1:0.5 molar ratio was refluxed in ethanol. After 5h, the association was dried under vacuum at 35-40 °C. The obtained association was kept in tightly closed container at argon (Ar) atmosphere before usage.

Association characterization

H-NMR

To confirm interaction between ibuprofen and phosphatidylcholine, H-NMR spectra of phosphatidylcholine and ibuprofen-phospholipid association (PA) was obtained by Bruker Avance III spectrophotometer (USA) at $CDCl_3$ as the solvent.

Differential scanning calorimetry (DSC)

Crystalline habit of ibuprofen and PA was investigated by differential scanning calorimetry (DSC). 3 mg of ibuprofen and PA were heated with the rate of 10 °C/min under nitrogen flow by DSC (Mettler Toledo, Switzerland). Thermogram of ibuprofen and PA was recorded from 35 – 230 °C.

Particle size analysis

average size and size distribution of particular form of PA was measured by dynamic light scattering (DLS). Briefly, 3 mg of PA was added to 50 mL of distilled water, HCl 0.1 N or phosphate buffer (pH 7.2) containing 0.2% SDS and stirred for 15 min at 100 rpm. Particle size of PA in the different media was detected by Zetasizer Nano (Malvern, UK).

Preparation of pellets

Conventional pellets (containing 10% ibuprofen) and phosphatidylcholine association (PA) pellets in four drug content (containing 20%, 30%, 40% and 50% of PA) were prepared by extrusion-spheronization. The PA has a semi-solid and sticky nature (to make a solid substance). It was mixed with Aerosil as an adsorbent. Other solid components (described in Table 2) were geometrically added and mixed for 15 min, and a satisfactory amount of water (Table 2) was slowly added to prepare wet mass with a proper consistency. The produced wet mass was subsequently extruded through a die with 1mm pore diameter by a screw extruder at 120 rpm (Dorsatech, Iran). Thereupon, the extrudates were spheronized by spheronizer (Dorsatech, Iran) with a rotated cross-hatch friction plate at 1000 rpm. The collected pellets were dried overnight at 35 °C in a conventional oven.

Sieve analysis and pellets yield

All obtained pellets were sieved through two standard sieves (1180 µm and 500µm) and shaken for 10 min on a sieve shaker (Retsch-Germany. The pellets remaining between 1180 µm and 500µm sieve were weighted and their ratio was considered as yield of pelletization.

Drug content uniformity

To determine the drug content of the pellet formulations, pellet samples (n=3) equivalent to 5 mg ibuprofen were weighted and added to 50mL ethanol in a volumetric flask and stirred for 30 min on magnetic stirrer. Each sample was suitably diluted and the drug content of samples determined spectrophotometrically at 222 nm (UV 1800, Shimadzu, Japan).

Image analysis

To investigate the shape factors of pellets, stereomicroscopic images (magnification ×8) (Micros, Austria) of forty pellets from each formulation were taken on a black background under cold light, by a video camera (Sony, Japan). Digitized images were analyzed by ImageJ software (ImageJ for Java, Version 1.46r), d_{min} (shortest Feret diameter), *d* max (longest Feret diameter), A (the pellets projection area) and Pm (the pellet perimeter) were obtained, then the aspect ratio and circularity of pellets were calculated:

$$\text{Aspect ratio} = \frac{d_{max}}{d_{min}}$$

$$\text{Circularity} = \frac{4\pi A}{p_m{}^2}$$

Mechanical tests

The crushing strength (the force needed to break the brittle pellets) or yield stress (the force needed to deform the plastic pellets) and elastic modulus of 25 pellets (500-1180µm size range) were tested by Material Testing Machine (Hounsfield, UK). The speed of upper mobile platen fitted with a 1kN load cell was set at 1mm/min. The recorded data from mechanical test device were processed by a computer system (QMAT, Hounsfield, UK) attached to the apparatus, then force-displacement graph of each pellet formulation was drawn.

Scanning lectron microscopy (SEM)

To analyze surface morphological properties of the pellets, scanning electron microscopy (SEM) studies were carried out. The 30% PA pellets, as the optimized formulation (before and after dissolution in gastric or intestinal media), were mounted on an aluminum stub and coated by thin layer of gold under argon atmosphere. Afterwards, the samples were investigated by a SEM (TESCAN FESEM MIRA3, England). The images were recorded at 100×, 350× and 800× magnification.

In vitro dissolution study

Dissolution was conducted on pellets equivalent to 50mg ibuprofen by a USP Method 1 (rotating basket) at 100rpm in HCl 0.1 N as simulated gastric media, and simulated intestinal medium (phosphate buffer pH 7.2 ± 0.02 with 0.2% SDS), at 37 °C. Samples (1.5 ml) were withdrawn at different intervals and equal volume of fresh medium was added to maintain sink condition. For detection of total drug release, samples were diluted by ethanol to break the micelles and release the enclosed drug [7]. On the other hand, to evaluate the dissolved drug release (as the micellar drug is not absorbable in stomach), samples were filtered by ultra-filter (Amicon® ultra 10k device) at ×7000 g to separate the dissolved drug from micelles. All samples were assayed by UV-Vis spectrophotometer (UV 1800, Shimadzu, Japan) at wavelength 222nm.

RESULTS

Plain ibuprofen UV spectrum

In order to obtain the maximum absorbance peak of the used sample of ibuprofen, its spectrum was demonstrated in Fig. 1. The sample λ_{max} was calculated to be 222 nm and the following analyzes were performed at this wavelength. There is no interaction between ibuprofen and phospholipid or other ingredients of pellets and dissolution media.

Association characterization

H-NMR

According to H-NMR spectra of phosphatidylcholine and PA (Fig. 2), choline signals of phospholipid were changed after complexation. δ = 3.37 ppm (a: CH_2-CH2-N+-**(CH3)3**), 3.81 ppm (b: CH2-**CH2**-N+-$(CH_3)_3$), 4.29 ppm (c: **CH2**- CH2-N^+-$(CH_3)_3$) signals which represented choline moiety of phosphatidylcholine were shifted to 2.98 ppm (a), 3.51 ppm (b), 4.23 δ ppm

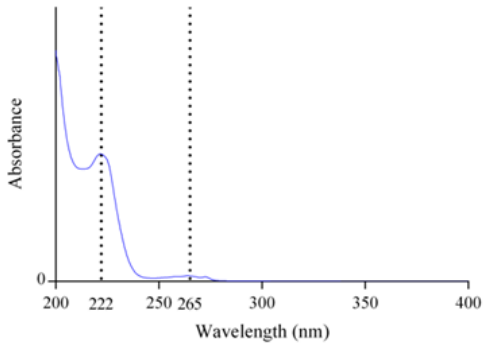

Fig. 1. UV spectrum of plain ibuprofen

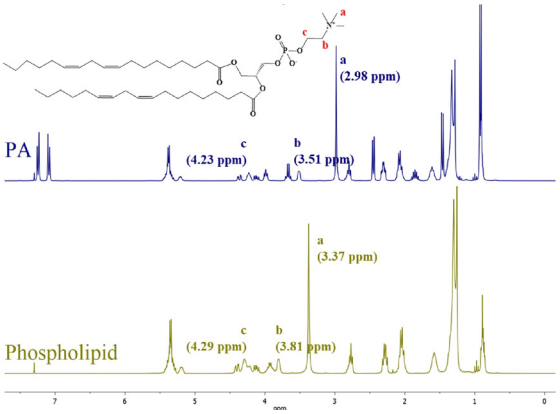

Fig. 2. H-NMR spectra of ibuprofen-phospholipid association (PA) and phospholipid

(c) in the association and it means the formation of a bond (hydrogen bond) between ibuprofen and the choline group of phosphatidylcholine.

Differential scanning calorimetry

In order to analyze PA physical structure, Ibuprofen and PA DSC thermograms were obtained. Ibuprofen thermogram demonstrated an endometrial peak at 77 °C, which was disappeared after association with phospholipid (Fig. 3).

Particle size analysis

To obtain size distribution of PA after hydration, DLS study was used. The average size and Zeta potential of PA nanoparticles in distilled water, simulated intestinal medium and HCl 0.1 N was reported in Table 1.

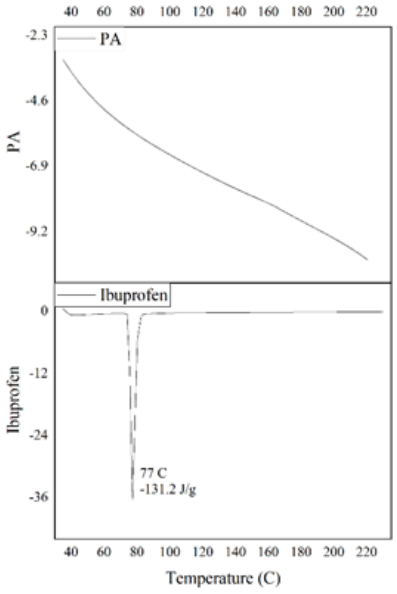

Fig. 3. DSC diagram of ibuprofen and ibuprofen-phospholipid association (PA)

Table 1. Particle size and Zeta potential of the nanoparticles in different media

Medium	Particle size (nm)	Zeta potential (mV)
HCl 0.1 N	285.6 ± 41.4	-23.2 ± 7.8
Buffer 7.2 pH + SDS	197.7 ± 34.8	-31.2 ± 5.9
Distilled water	230.7 ± 64.5	-28.6 ± 9.4

Sieve analysis and pellets yield

Spheronization time and yield of different formulation of the prepared pellets were determined (Table 2). Formation of desirable 50% PA pellets was not possible, due to extensive sticky feature of the extruded mass.

Drug content uniformity

To investigate content uniformity and drug distribution in mixing process, drug content of three different batches of each formulation were evaluated spectrophotometrically. The content of ibuprofen in conventional pellets, 20% PA pellets, 30% PA pellets and 40% PA pellets were obtained 99.03 ± 3.92, 100.17 ± 5.33, 98.75 ± 6.74, 99.53 ± 5.27 respectively.

Image analysis

The shape factors (aspect ratio and circularity) were calculated for 20% PA, 30% PA, 40% PA and conventional pellets (Table 3).

Mechanical analysis

Mechanical factors (yield stress and elastic modulus) of 20% PA, 30% PA, 40% PA and conventional pellets were detected (Table 4). Phosphatidylcholine association of ibuprofen caused pellets to show plastic characteristics and they were not crushed under stress (Fig. 4-a), compared to the conventional ibuprofen pellets which demonstrated brittle behavior with no yield point (Fig. 4-b).

Table 3. Shape factors of different pellet formulations

Formulation	Aspect ratio	Circularity
Conventional Pellet	1.24	0.93
20% PA[a] Pellet	1.31	0.92
30% PA Pellet	1.35	0.92
40% PA Pellet	1.47	0.94

aIbuprofen-phosphatidylcholine association

Table 4. Mechanical factors of different pellet formulations

Formulation	Yield stress (N)	Elastic modulus (MPa)
Conventional Pellet	34.12 (± 4.01) [b]	166.5 (± 23.5)
20% PA[a] Pellet	3.13 (± 0.77)	82.75 (± 4.43)
30% PA Pellet	3.02 (± 0.54)	51.67 (± 4.10)
40% PA Pellet	1.25 (± 0.72)	28.39 (± 1.64)

a Ibuprofen-phosphatidylcholine association
b Conventional pellet has brittle behavior, so crushing strength was reported

Scanning electron microscopy

SEM images demonstrated that the prepared pellets were spherical and uniform in shape confirming the results obtained by image analysis (Fig. 5). Before dissolution (Fig. 5-A_{1-3}), 30% PA pellets showed spherical shape with intact and rough surface. The particles of microcrystalline cellulose or lactose were seen on the surface of the

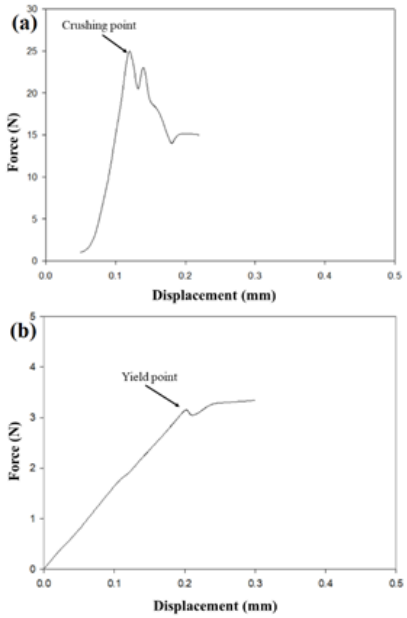

Fig. 4. Force – displacement diagram of (a) 20% PA pellets and (b) conventional pellets

Table 2. Composition, spheronization time, and yield of different formulations of pellets

Formulation	-	Aerosil	Avicel	Lactose	Water	Spheronization time	500-1180 µm pellet yield
Conventional Pellet	%10 Ib[b]	%2	%68	%20	%105	3 min	%80
20% PA[a] Pellet	%20 PA	%2	%63	%15	%40	2 min	%87
30% PA Pellet	%30 PA	%2	%58	%10	%35	2 min	%96
40% PA Pellet	%40 PA	%2	%53	%5	%30	1.5 min	%83
50% PA Pellet	%50 PA	%2	%43	%5	%5	1 min	%0

a Ibuprofen-phosphatidylcholine association
b Pure ibuprofen

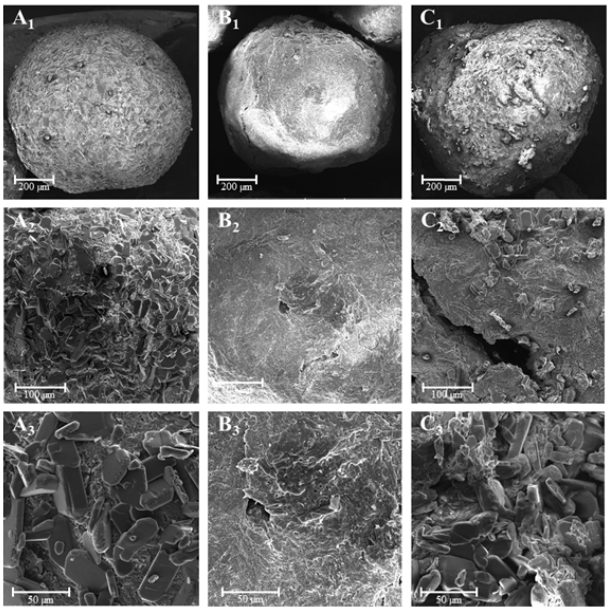

Fig. 5. Scanning electron microscopic images of 30% PA pellets before (A1-3) and after dissolution in simulated gastric (B1-3) and intestinal (C1-3) simulated media

pellets. After dissolution in simulated gastric media (Fig. 5-B_{1-3}), pellets retained their shape but their surface was changed to a smooth appearance.

After dissolution in pH 7.2 in the presence of surfactant (Fig. 5-C_{1-3}), Most pellets retained their shapes but their surface porosity was increased.

In vitro dissolution studies

In order to better understanding the release mechanism of ibuprofen from the PA pellets, the micellar released drug and the dissolved drug were determined separately. Total released amount of ibuprofen (in both dissolved and micellar form) from PA pellets was significantly more than the conventional pellets, as micelles of PA were dissolved more rapidly in medium compared to plain ibuprofen due to more amorphicity, improved wettability and increased surface area caused by their particle size. Since the micellar drug is not absorbable in stomach, dissolution profile of absorbable dissolved form of ibuprofen in the medium was also investigated (Fig. 6-top). There was not any significant difference in release pattern of the dissolved drug from 20% PA pellets

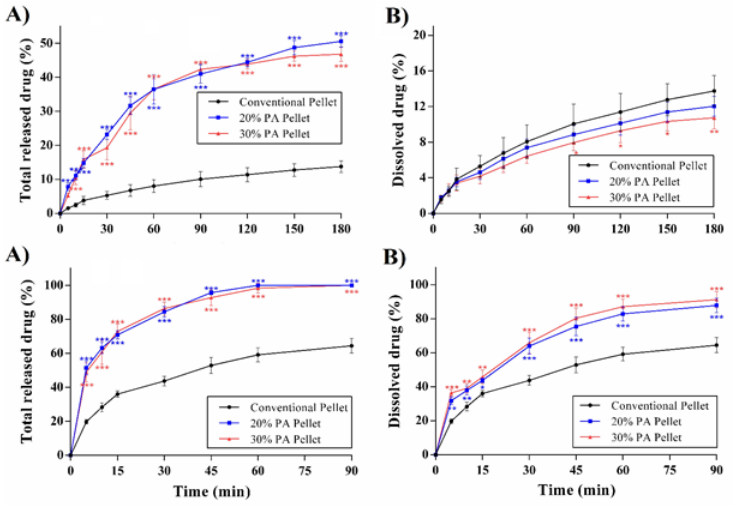

Fig. 6. Dissolution study of total released (A) and dissolved (B) ibuprofen from conventional, 20% PA and 30% PA pellets in (top) HCl pH 1.2 and (bottom) phosphate buffer pH 7.2 and 0.2% SDS. Values are mean ± SD of released drug percent (n = 6). *P< 0.05, **P< 0.01, ***P< 0.001 as compared to pure ibuprofen (two-way ANOVA test)

and conventional pellets, but the release from 30% PA pellets was less than conventional pellets after 90 min.

In simulated intestinal medium, total amount of released ibuprofen from PA pellets was enhanced and reached to 100% compared to the plain ibuprofen pellets (60%) (Fig. 6-bottom). According to the dissolution profiles, although the release of the dissolved form of ibuprofen from PA pellets was significantly more than the conventional pellets (Fig. 6-B), the amounts of dissolved form of the drug was lower than the total released drug, so that it just was released by 90% after 90 min.

DISCUSSION

The displacement of these characteristic peaks indicates the presence of an electrophilic group in neighboring of choline group. Changes of choline proton signals confirmed the interaction between carboxyl group of ibuprofen and choline moiety of phosphatidylcholine during association [7]. In addition, as the endothermic peak at 77 °C in ibuprofen DSC thermogram was caused by ibuprofen crystals melting, it was concluded that disappearing of the peak in PA DSC thermogram was due to the fact that the crystalline behavior of ibuprofen was changed during the reaction with phosphatidylcholine and the drug was at amorphous form in the association. Furthermore, particle size analysis demonstrated that the PA can be used as self-assembling nanoparticle drug delivery system in distilled water and dissolution media to create nanoparticles with small size and large surface area that increase the solubility and dissolution rate of ibuprofen. The PA in acidic environment has created the coarsest particles, which indicated the low tendency of the PA in gastric media to create particulate forms. But in intestinal medium (alkaline environment containing surfactants and emulsifiers), it is easily dispersed into small particle.

The amount of required water to produce extrudable wet mass depends on different variables such as amount and characteristics of drug or excipients. Water plays two important roles in pelletization process. It can bind powder excipient together and also plasticize materials to easily pass through the extruder and well-formed during spheronization stage [30, 31]there is an increase in the apparent water content necessary to form good spheres above a critical solubility between 350 and 400 gl-1. Copyright (C. Containing more PA, caused pellet formulations to require less water in order to attain the desired consistency for extrusion, it can be attributed to the viscose and oily feature of the PA which leads to binding effect. The maximum amount of PA loading was 40% because by increasing the amount of PA, oily feature of the association will be overcome and pelletization will not be possible. Increasing the amount of Aerosil as an adsorbent (which led to decrease in Avicel amount) in the formulation is not suitable to reduce this adhesive and viscose feature of PA due to negative effect on extrudability and also dissolution of pellets. 30% PA pellets demonstrated the most optimum size dispersion, as 96% of the pellets were in desired diameter range (500-1180 µm).

Drug content uniformity study results showed that despite the high viscosity of PA, it was mixed suitably with other excipients to achieve a uniform distribution of ibuprofen in pellet structure during extrusion and spheronization process.

Analysis of the pellets' images demonstrated that addition of PA did not affect circularity of the ibuprofen pellets, which is supported by previous studies on pelletization of nisoldipine and indomethacin phosphatidylcholine association (29, 32]. In addition, circularity had little variation from 1, indicating that all the formulated pellets have spherical shape. However, aspect ratio was demonstrated to be increased with addition of PA amount in the pellets which could be related to its sticky nature.

According to mechanical analysis, 40% PA pellet showed the most plastic behavior and did not demonstrate an acceptable yield stress; therefore, it was excluded from the further analysis. To sum up, the sticky feature of PA resulted in more plastic mass which can lead to production of pellets with lower elastic modulus and yield stress.

Scanning electron microscopy demonstrated that after 30% PA dissolution test in acidic medium, the exposed particles were washed or dissolved and a smooth surface was appeared which was supposed to be related to the amorphous drug-phospholipid matrix (The amorphous nature of the PA matrix was confirmed by DSC results.). It was predicted that at gastric medium, lipid matrix had surrounded the pellets surface and increased medium viscosity which was assumed to be able to reduce ibuprofen release ratio. Furthermore, it was assumed that the high percentage of microcrystalline cellulose in the formulation

maintained the pellet integration, while dissolution of lactose in the formulation caused pore formation in the pellets and increased the drug dissolution rate.

In vitro dissolution studies demonstrated that in simulated gastric media PA pellets released ibuprofen mostly in particulate form. Exposure of PA to an aqueous medium, resulted in production of self-assembling nanoparticles. Although ibuprofen PA can solubilize the drug as particulate form, it does not increase the dissolved fraction of the drug in simulated gastric medium, thus, most of the drug was dispersed in the stomach in a protected form which was not freely absorbable and was less irritant to the gastric mucosa [33]. Furthermore, the dispersed nanoparticular drug could make the dissolution and absorption of drug easier upon entering the intestine.

At the end of the dissolution study in simulated intestinal media, all the ibuprofen molecules were dispersed, while most of the dispersed molecules were in free drug form. However there was still a fraction of drug in micellar form, since the micelles also could be absorbed through intestinal mucosa, we could assume that the drugs were totally dissolved in simulated intestinal media [34, 35].

According to our observations, the PA pellets were intact and were only surrounded by lipid matrix in the gastric medium, while they were mostly shrunk and cracked after dissolution test in the intestinal medium.

CONCLUSION

The pellets containing 20%-50% PA were prepared by extrusion-spheronization technique. 20% and 30% PA pellets demonstrated desirable size, morphological and mechanical properties. In addition, PA pellets compared to the conventional pellets showed the self-assembly of micelles, resulted in increased dissolution rate in intestinal-simulated medium and less irritation in gastric-simulated medium, which could lead to improved absorption and decreased risk of gastrointestinal irritation. The designed formulation of 30% PA can be considered as the optimum formulation due to its mechanical and morphological characteristics, and dissolution profiles of ibuprofen compared to other studied PA formulations. To summarize, this work shows the feasibility of preparing desirable pellets containing ibuprofen-phospholipid association with improved dissolution characteristics which can be filled as hard gelatin capsules.

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CONFLICTS OF INTEREST

The authors declared no conflict of interest in the manuscript.

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