Research Article

Design and Evaluation of Novel Sustained-Release Floating Microspheres for Oral Delivery of Ciprofloxacin Hydrochloride

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Abstract

Background: Ciprofloxacin (CIP) is a broad-spectrum antibiotic, used to treat various bacterial infections. Administration of conventional oral dosage forms of CIP is associated with multiple challenges such as short residence time of the drug in the gastrointestinal tract which could reduce bioavailability and effectiveness of the drug. This study aimed to design and develop novel floating microspheres for the sustained release of CIP in the stomach over 24 hours after oral administration, besides evaluating the effect of different variables on the characteristics of developed microspheres.

Methods: Microspheres were developed by the solvent-evaporation method utilizing cellulose acetate and polyvinyl alcohol, then characterized for physicochemical properties including bulk density, buoyancy, and entrapment efficacy. The drug-excipient compatibility was evaluated by Fourier-transform infrared spectroscopy and the Scanning electron microscopy was used to observe the morphology of microspheres. The effects of the drug to polymer ratio, polymer concentration, and the pace of stirring through the preparation process, on the size and release rate were also evaluated.

Results: Morphology analysis indicated round-shape microspheres with a mean particle size between 66-344 μm. The polydispersity index of prepared formulations was determined to be in the range of 0.129 to 0.230. It was observed that at higher polymer concentrations the drug release rate from microspheres decreased while the mean particle size increased. Increasing the drug to polymer ratio and decreasing the stirring speed increased the mean particle size. All formulations showed more than 70% cumulative drug release in the prolonged period of 24 h while remaining buoyant in the meantime. The formulations followed Higuchi and Korsmeyer-Peppas kinetics and release the drug by diffusion mechanism.

Conclusion: Based on the results obtained from *in vitro* release study besides floating properties, the prepared microspheres could be considered suitable for enhanced sustained-release of CIP following the oral administration.

Introduction

While oral administration of drugs is always considered as the most convenient and compliant route of administration,[1,2] it faced challenges including the poor bioavailability of drugs resulting from the rapid passage of the dosage form through the gastrointestinal tract (GIT) or the high hydrophobicity of the drug substance.[3,4] The contact time of the drug with the gastric mucosa greatly affects the drug absorption from the GIT. Hence, the longer residence time of a dosage form in the stomach could be advantageous in delivering drugs.

The gastro-retentive drug delivery systems including mucoadhesive, high-density, expandable, and floating systems are promising novel delivery systems with prolonged release of drugs. Floating delivery systems are capable of enhancing drug delivery by floating on the gastric fluids due to the lower density.[5-8] These systems have a wide range of advantages such as reducing the mucosal irritation due to controlled release, enhancing the drug delivery during specific conditions like diarrhea, and having a potential for prolonged or delayed drug delivery.[9] In an experimental study conducted by Sheikh *et al.*[10], a floating hydrogel-based delivery system of moxifloxacin was developed that exhibited advantageous properties including increased residence time in the stomach of animal model. Gunda *et al.*[11] has also developed multiple floating formulations for delivery of moxifloxacin and reported a prolonged release profile for these formulations.

Microspheres are drug carriers majorly composed of polymers with particle sizes ranged between 1-1000 μm. These systems have the advantages of prolonging drug delivery, enhancing drug absorption, and protecting the drug molecules from gastric fluids.[12] Application of floating microspheres could result in higher bioavailability, lower dose size, reduced dosing frequency, and stronger therapeutic effects due to the increased residence time.[13-15]

Ciprofloxacin hydrochloride (Mw=331.346 g/mol) (CIP) is an antibacterial agent belonging to the fluoroquinolones administrated for the treatment of various infections including respiratory, gastrointestinal, urinary tract, skin, and bone infections. This drug was reported to have an almost 70% bioavailability[16] and an increased water-solubility in acidic conditions up to 25 mg/mL in 0.1 N HCl compared to 1.35 mg/mL at neutral pH.[17] CIP is categorized in Biopharmaceutics Classification System (BCS) as class II/IV. Due to the poor permeability besides poor solubility in neutral pH, it can be classified as class IV while higher solubility in acidic pH, can led to classify this drug as class II.[18] As mentioned before, CIP absorption is greatly increased in acidic conditions; hence this drug has a narrow absorption window limited to the proximal area of GIT. As a result, prolonging the residence time of the drug in the stomach could enhance the water solubility and consequently absorption of CIP.[19-21]

During the literature review, similar studies that developed and evaluated the floating microspheres of CIP were investigated. Srinatha et al.[22] designed floating beads of CIP by blending alginate with different polymers and evaluate the in vitro release and kinetics profile of those formulations.In a clinical evaluation by Mostafavi et al.[20], the pharmacokinetic of floating tablets of CIP was evaluated in human participants.[20] In another study the effect of using various polymers was investigated on release profiles of floating tablets of CIP.[23] As it is obvious the main focus of these studies was on the evaluation of the effects of using different polymers on properties of floating formulations while in the present study the main aim was to investigate the impacts of changing variables such as the drug to polymer ratio, polymer concentration, and stirring speed on the release profile. Moreover, most of these studies were focused on the preparation of floating tablets while this study concentrated on designing microspheres that are more beneficial compared to tablets.

Polyvinyl alcohol (PVA) is a biodegradable, biocompatible, and synthetic polymer approved for food and drug industrials by Food and Drug Administration (FDA).[24] Cellulose acetate (CA) is also a biocompatible polymer with a natural base which is favorable for the preparation of oral formulations due to non-toxicity. Despite multiple beneficial advantages, these polymers have not been utilized for preparation of CIP-loaded floating systems in previous studies till now, to our knowledge.[25]

In this study, floating microspheres were designed and developed by PVA and CA polymers for sustained release of CIP following the oral administration. The formulations were characterized for morphological and physicochemical properties. The optimized formulations were subjected to in vitro release studies and the impacts of the drug to polymer ratio, polymer concentration, and the stirring speed on the release profile were investigated.

Material and Methods
Materials
Ciprofloxacin hydrochloride (CIP), Cellulose acetate (CA), and Polyvinyl alcohol (PVA) were purchased from Sigma–Aldrich Chemical (Sigma Aldrich Chemical Co, Steinheim, Germany). Dichloromethane (DCM) and HCL 12 N were obtained from Merck. All materials are of the analytical grades.

Preparation of Microspheres
As represented in Figure 1, floating microspheres in PVA solution were developed using the emulsification solvent-evaporation method. The components of each pre-formulation along with the stirring speed are shown in Table 1. First, four replicates of three different CA solutions (15 mL) with different concentrations (2%, 4%, and 6% w/v) were prepared by dissolving CA in DCM under continuous stirring for 12 h. Then CIP powder (at 1:20, 1:10, and 1:5 w/w drug to polymer ratio), was added to each CA solution until completely dissolved. The prepared drug-polymer mixture was added dropwise to 30 mL PVA (2% w/v) solution under magnetic stirring with different rates of stirring (900, 1700, and 2500 rpm) at room temperature for 24 h. After evaporation of the DCM, the mixture was centrifuged (Beckman Coulter, optima-L90K, USA) at 10000 rpm for 10 minutes and the separated microspheres were washed with distilled water three times. Twelve pre-formulations were developed and based on the formation of microspheres and visual appearance, six were selected as optimized formulations for further studies. Finally, the six prepared formulations were lyophilized using Christ freeze dryer (ALPHA 2-4 PLUS, Germany).

Characterization of microspheres
Fourier-Transform Infrared (FTIR) spectroscopy
To analyze the structure and possible interactions between components, the microspheres, and components were examined by the FTIR spectrometer (Shimadzu IR Prestige-21, Nakagyo-Ku, Japan). The KBr pellet method was used in which the samples were compressed with potassium bromide at 20 psi and the spectrum corresponding to each sample was recorded at 4000-400 cm^{-1} using the spectrophotometer.

Particle size analysis
Using a digital microscope (Dino-Lite, AM4013MZTL), the image of microspheres in each formulation was recorded and the size of the prepared microspheres was measured using ImageJ software. An average of 100 microspheres was recorded. To calculate the polydispersity index (PDI) which estimates the distribution of particle
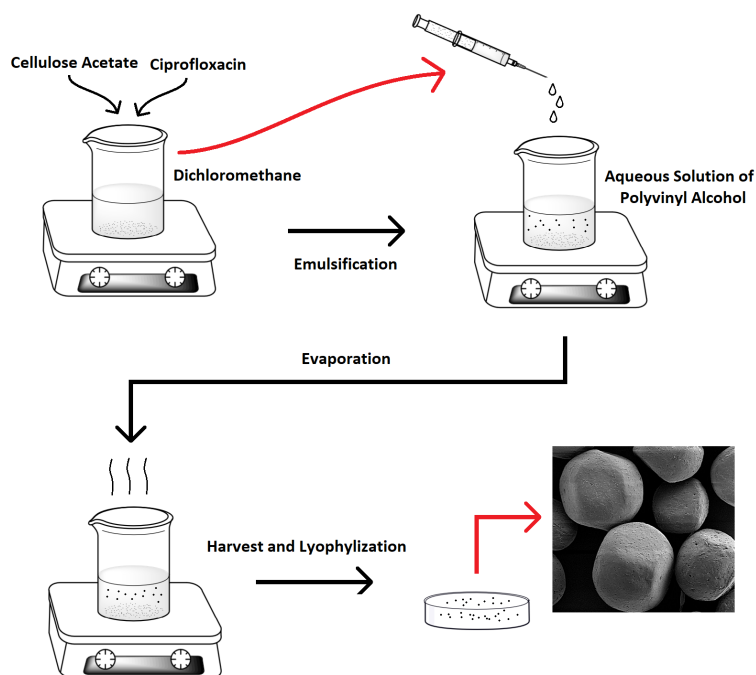
Figure 1. Schematic diagram of emulsification solvent-evaporation method for preparation of microspheres.

sizes, the standard formula (Eq. 1) was used in which the SD stands for the standard deviation of particle diameter and 2a is the mean particle diameter.

$$PDI = \frac{SD}{2a} \qquad \text{Eq. (1)}$$

Morphology characterization by Scanning Electron Microscopy (SEM)
To characterize the surface morphology of the prepared microspheres, the formulations were coated with gold under vacuum conditions and then observed by the scanning electron microscope (KYKY, EM-6200, China) at 12 kV accelerating voltage. The SEM images were taken at different magnifications.

Bulk density
The bulk density which is described as the mass of particles to total occupying volume was measured for each formulation. By transferring a determined number of microspheres to a measuring cylinder and tapping them three times consecutively the final volume was measured and the bulk density was estimated using the standard formula (Eq. 2).

$$\%Buoyancy = \frac{mass\ of\ the\ microspheres\ that\ remain\ floating}{total\ mass\ of\ the\ microspheres} \qquad \text{Eq. (2)}$$

Buoyancy percentage
A dissolution device was filled with 900 ml HCL (0.1 N) containing Tween 80 (0.02% v/v), then 0.1 g of Microspheres were distributed on the surface of the solution. Using the paddle rotating method, the solution was agitated at 100 rpm for 12 hours. The microspheres that remain floating on the surface were separated and weighed after drying. The % buoyancy of microspheres was measured by the

following formula (Eq. 3):

$$Drug\ entrapment(\%) = \frac{Mass\ of\ measured\ drug\ in\ microsphere}{Mass\ of\ drug\ used\ to\ prepare\ the\ formulation} \times 100 \qquad \text{Eq. (3)}$$

Entrapment efficiency (EE%)
The EE% was measured for all formulations using Eq. 4. Microspheres were initially dissolved in the minimum amount of DCM for complete decomposition of the microspheres. A volume of 20 mL of HCl 0.1 N was added and stirred for 1 h. the mixture was allowed to phase separation and a 1 mL sample of the aqueous phase was withdrawn. The ultraviolet-visible (UV) absorption of samples at 276 nm (λ_{max} of CIP) was measured after suitable dilution using a UV spectrophotometer (UV-Mini 1240, Shimadzu, China). The drug content was estimated using the regression equation obtained by the construction of the calibration curve.

$$Bulk\ density(\frac{g}{cm_3}) = \frac{Wheight\ of\ granules}{Apparent\ volume} \qquad \text{Eq. (4)}$$

In vitro release study
To observe the *in vitro* release of drug from floating microspheres, a diffusion setup was assembled. A specific amount of each optimized formulation containing an equal amount of drug was filled in a dialysis bag tied at both ends, then was immersed into a receptor medium containing 20 mL HCl (0.1 N) and kept at 37 °C under continuous stirring (100 rpm). Samples were withdrawn at regular time intervals and were replaced with the same amount of fresh medium to maintain the sink condition. The UV absorption of samples at 276 nm was measured after suitable dilution using the UV spectrophotometer.
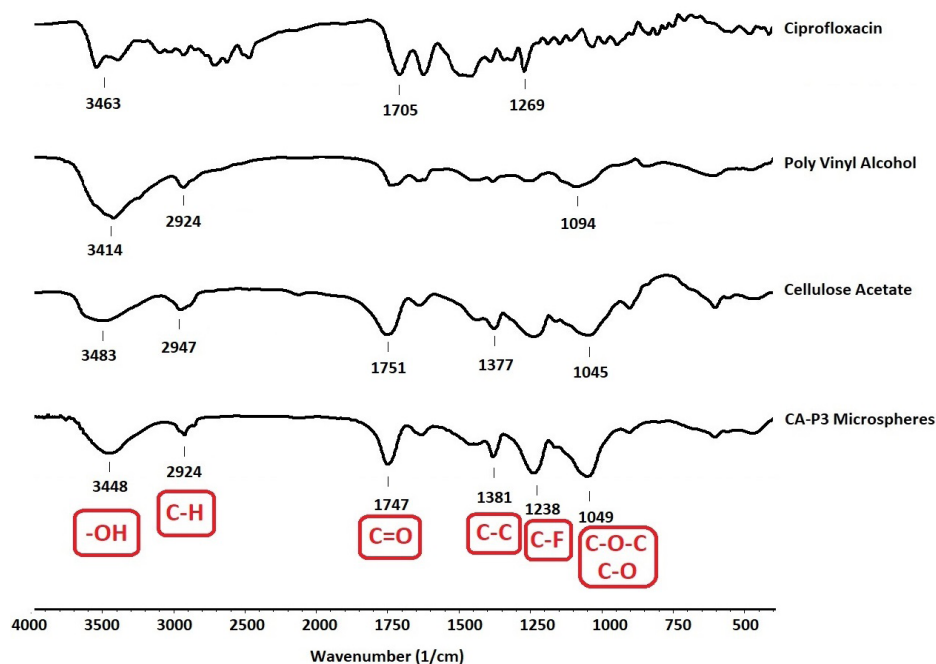
Figure 2. FTIR spectra of microspheres, drug (CIP), and polymers (PVA, and CA).

The drug content was calculated using the regression equation obtained by the constructed calibration curve.

Release mechanism and kinetics

The mechanism of drug release from formulations was predicted by fitting release data in various equations elucidating each kinetical model of zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell. The model obtained the highest correlation coefficient was chosen as the best-fitted release model.

Results and Discussion
Preparation of microspheres

Among twelve prepared pre-formulations, microspheres were successfully developed in six formulations. In the initial visual analysis, the prepared formulations showed a suitable round shape appearance with good stability and were subjected to further physicochemical tests.

Characterization of microspheres
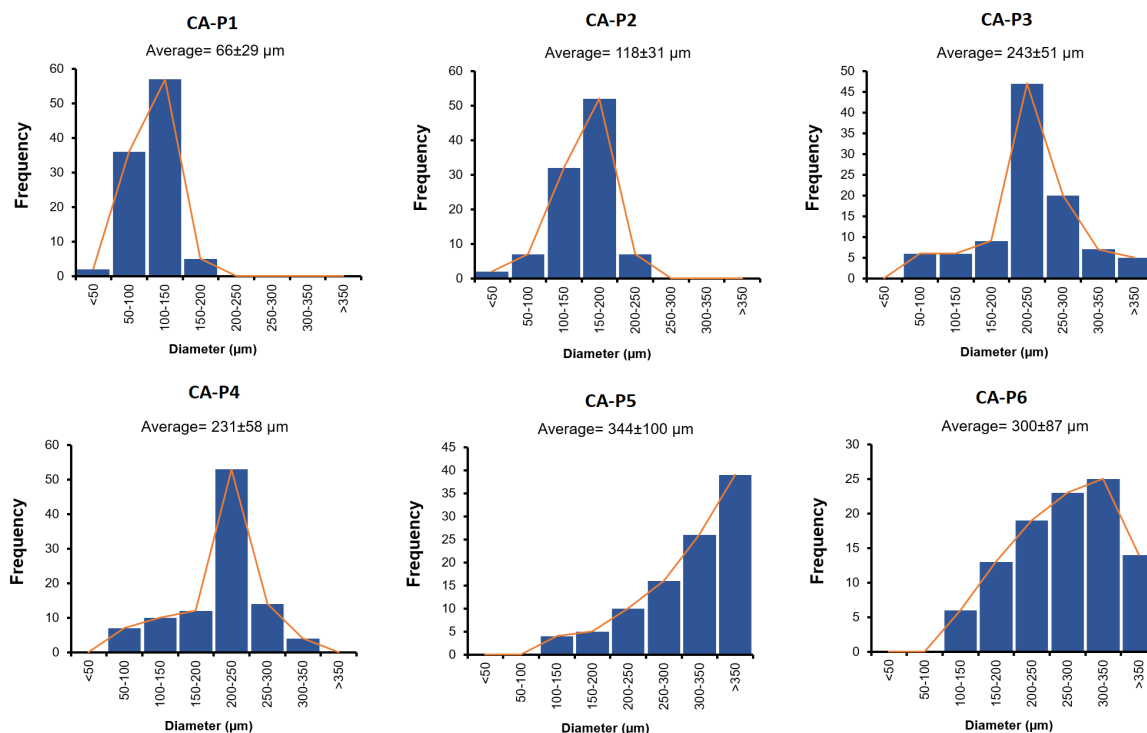#### Fourier-Transform Infrared (FTIR) spectroscopy

The FTIR spectra recorded for CIP, CA, PVA, and prepared microspheres (CA-P3 formulation) are represented in Figure 2. The characteristic peaks of drug and polymers were detected in the spectrum obtained for the microsphere. The peaks at 2900-3500 cm^{-1} were assigned to the OH groups of both PVA,[26] CA,[27] and CIP.[28] There is a peak at 2924 cm^{-1} which is attributed to the asymmetrical -CH$_2$ in CA[27] and PVA.[26] The peaks merged at 1747 cm^{-1} are related to the C=O group stretching of CIP[28] and stretching vibration of the carbonyl group of CA.[27] The peak at 1381 cm^{-1} is attributed to symmetrical C-CH3 of CA.[27] There is a characteristic peak at 1238 cm^{-1} which is related to the C-F bands stretching in CIP.[28] Also, the C-O-C stretching

vibration of CA[27] and C-O stretching of PVA[26] appears as a merged peak at 1049 cm^{-1}.

The only interaction which was expected to take place between drug and polymers was hydrogen bonding. Hydrogen bonding leads to a massive shift of the involved groups toward lower frequency and significant broadening of the -OH peak with a decreased intensity. None of the above is detectable in the FTIR spectrum of formulation compared to the pure drug; hence it could be concluded that no significant interaction occurred between drug and polymers. A similar study reported that no interaction occurred between drug and polymers, with similar shifts in wavenumber as this study.[29]

Particle size analysis

Figure 3 compared the histogram of size distribution in each formulation and the mean particle size and PDI of each formulation are shown in Table 2. To evaluate the effect of increased polymer concentrations on the particle size of microspheres, the concentration of CA was increased in a fixed drug-polymer ratio; it was observed that the mean diameter of microspheres is increased at higher polymer concentrations. The reason behind this increased size is the increased interfacial tension, resulted from a higher amount of polymer molecules. This higher interfacial tension inhibits the droplets to be separated and form smaller particles.[30] Moreover, an increase in the stirring speed at fixed polymer concentrations resulted in decreased droplet size which seems to be due to the disability of the lower speeds to break the large droplets into smaller droplets and also the reduced shear stress.[30,31] Increasing the drug-polymer ratio enhanced the mean particle size.[32]

CA-P1
Average= 66±29 µm

CA-P2
Average= 118±31 µm

CA-P3
Average= 243±51 µm

CA-P4
Average= 231±58 µm

CA-P5
Average= 344±100 µm

CA-P6
Average= 300±87 µm

Figure 3. The histograms of the size distribution for different microsphere formulations.

Table 1. Components of each formulation.

Formulation	PVA (%w/v)	CA Concentration (%w/v)	Drug: Polymer ratio	Stirring Speed (rpm)
A	2	2	01:20	900
B	2	2	01:10	1700
C*	2	2	01:05	2500
D	2	2	01:10	2500
E	2	4	01:20	900
F	2	4	01:10	1700
G*	2	4	01:05	2500
H*	2	4	01:10	2500
I	2	6	01:20	900
J*	2	6	01:10	1700
K*	2	6	01:05	2500
L*	2	6	01:10	2500

* The optimized pre-formulations chosen for further studies entitled as follows: CA-P1 (C), CA-P2 (H), CA-P3 (G), CA-P4 (L), CA-P5 (K), CA-P6 (J)

Table 2. Size, PDI, bulk density, Buoyancy, and EE% of formulations (mean ± SD, n = 3).

Formulation	Mean particle size (µm)	PDI	Bulk density (g/cm³)	Buoyancy (%)	Entrapment Efficacy (%)
CA-P1	66.38 ± 29.87	0.230	0.892 ± 0.054	64.0 ± 1.8	60.01 ± 0.33
CA-P2	118.22 ± 31.13	0.132	0.833 ± 0.076	69.8 ± 2.5	62.21 ± 0.66
CA-P3	243.40 ± 51.01	0.184	0.735 ± 0.090	77.5 ± 3.0	61.01 ± 1.12
CA-P4	231.36 ± 58.68	0.219	0.781 ± 0.100	74.0 ± 2.9	65.11 ± 2.56
CA-P5	344.94 ± 100.40	0.138	0.619 ± 0.064	85.7 ± 3.5	64.02 ± 1.23
CA-P6	300.68 ± 87.50	0.129	0.694 ± 0.075	78.4 ± 1.5	70.03 ± 1.01

Morphology

The surface morphology of prepared microspheres was characterized by SEM imaging as represented in Figure 4.

Based on the SEM images the developed microspheres had a smooth surface in a spherical shape. There were small distinct pores on the prepared microspheres which were
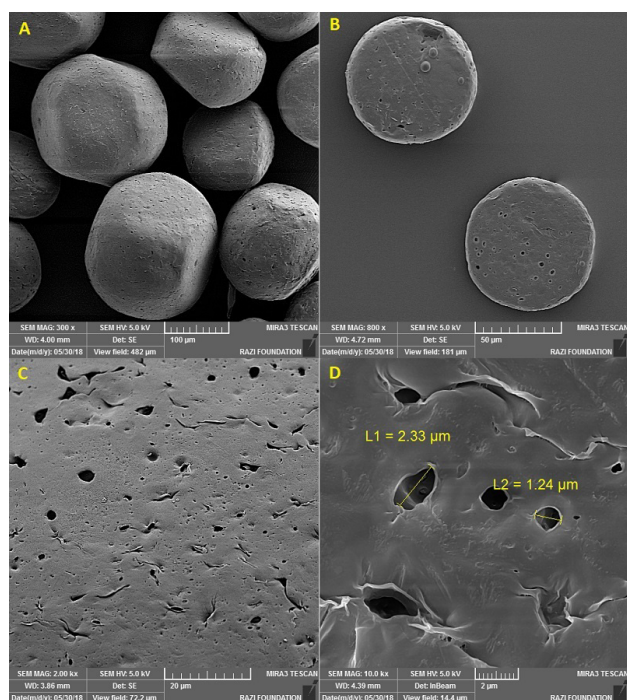
Figure 4. SEM images of A, B: CA-P3 microspheres, C, D: pores on the surface of microspheres with different magnifications.

considered to be responsible for the sustained release of the drug. The reason behind the formation of these pores was considered to be the gradual evaporation of solvent from the microdroplets.[33]

Bulk density
The calculated bulk density of each formulation is demonstrated in Table 2. Due to the presence of pores in the surface and polymeric matrix of microspheres which resulted in decreased density, they have the ability to float on gastric fluids which aid them for longer residence in the GIT and had a prolonged effect.[34,35] All formulations had bulk densities ranging from 0.619 to 0.892 g/cm³ which is considered suitable for a floating formulation. Similar results were reported by Srinatha et al.[22] detected 0.8-1.0 g/cm³ density for floating microspheres of ciprofloxacin. It was claimed in the mentioned study that microspheres with a density less than gastric fluid (1.004 g/cm³) could be considered suitable for floating. CA-P5 which had the largest particle size showed the least bulk density of 0.619 g/cm³ while the CA-P1 which had the smallest particle size showed the highest bulk density of 0.892 g/cm³. Based on these findings it could be concluded that increasing the particle size resulted in a decrease in the bulk density which is considered to occur because of increased intra-particulate space.[36]

Buoyancy percentage
Buoyancy Percentage is one of the parameters which is a key parameter affecting the drug release from a floating formulation.[37,38] The values of buoyancy percentage which is shown in Table 2, were in the range of 64 to 85.7% considered suitable for a floating formulation. In a

similar study, 46-70% buoyancy was considered suitable for the floating microspheres.[39] The highest buoyancy percentage measured for the microspheres belonged to CA-P5 while CA-P1 had the least buoyancy percentage. These results confirmed that lower particle size is related to higher buoyancy percentage and consequently enhanced floatability.[36]

Entrapment efficiency (EE%)
Table 2 compared the EE% of formulations. The measured EE% for all formulations was in the acceptable range of 60 to 70%. In a similar study, focused on designing floating microspheres of verapamil hydrochloride, EE was measured to be almost 65-85% that was considered suitable.[39] EE% could be affected by the method of preparation. The emulsification solvent-evaporation method is one of the most promising methods for achieving an acceptable EE%.[40] The CA-P6 with 6% w/v CA showed the highest value for EE% comparing to other formulations which had lower levels of CA and formulation CA-P1 with 2 % w/v CA showed the lowest EE%. Using T-test against test value of 55%, (SPSS 25.0) the EE% was significantly related to the concentration of the polymeric solution and it was generally higher for the formulations with higher polymer concentrations ($p<0.05$).

In vitro release study
Figure 5 demonstrated the cumulative percentage release of the drug in 24 hours from different formulations. In vitro release studies of CIP showed that all formulations could release the drug in 24 h. The mechanism behind drug release from microspheres is that the gastric fluids permeated into the microspheres from the pores on the surface of them and release the dissolved drug. The cumulative percentage of released drug with a fixed drug-polymer ratio could significantly decrease with an increase in polymer concentration. The CA-P3 and CA-P5 formulation showed an enhanced drug release of 86.04 ± 0.03% and 84.49 ± 5.36% compared to CA-P2 and CA-P4 with 82.04 ± 0.08% and 68.48 ± 0.01% drug release, in 24 h, respectively. On the other hand, among the three formulations of CA-P1,
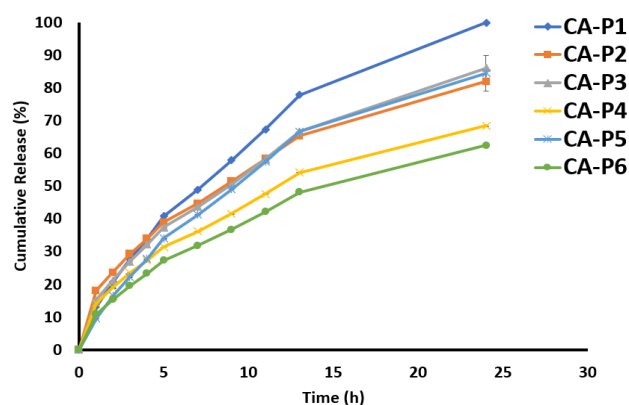
Figure 5. In vitro release of ciprofloxacin from different microspheres in 20 mL HCl (0.1 N) at 37 °C under continuous stirring (100 rpm).

Table 3. The regression coefficient of formulations obtained by fitting the formulations in different kinetical models.

Formulation	Zero-Order	First-Order	Higuchi	Korsmeyer-Peppas	Hixson-Crowell
CA-P1	0.9843	0.9986	0.9972	0.9987	0.9963
CA-P2	0.9812	0.9956	0.9976	0.9961	0.9921
CA-P3	0.9804	0.9957	0.9976	0.9975	0.9920
CA-P4	0.9808	0.9927	0.9977	0.9968	0.9895
CA-P5	0.9846	0.9976	0.9969	0.9982	0.9948
CA-P6	0.9797	0.9911	0.9976	0.9978	0.9878

CA-P3, and CA-P5, with equal drug-polymer ratio, the CA-P1 formulation with the least particle size showed the most drug release of almost 100% in 24 h. A similar release profile was observed and reported in a previous study by Jelvehgari *et al.*[41] from theophylline-loaded floating microballoons prepared by CA butyrate and/or Eudragit RL 100 polymers. The reason behind the lower drug release in formulation with higher polymer concentration seemed to be the increased density of the polymeric matrix and increased diffusional path length. Also, the higher surface-to-volume ratio in the microspheres with a smaller size, prepared by lower polymer concentrations and higher stirring speed, could result in enhanced drug release.[31] Besides, the cumulative percentage release of the drug also increased with increasing drug-polymer ratio at fixed of the polymer concentration.[32]

Release mechanism and kinetics

The correlation coefficient of various fitted models is represented in Table 3. All formulations showed a high correlation to both Higuchi and Korsmeyer-Peppas with a negligible difference. CA-P2, CA-P3, and CA-P4 suggested Higuchi as the best-fitted model while CA-P1, CA-P5, and CA-P6 suggested Korsmeyer-Peppas as the best-fitted kinetical model. Korsmeyer-Peppas is a kinetical model for describing the mechanism of drug release from controlled-release polymeric matrices. This model is described by the following equation where M_t/M_∞ is a fraction of released drug at time t, K is release rate constant, and n stands for release exponent.

$$M_t / M_\infty = Kt^n \qquad \text{Eq. (5)}$$

When 0.5<n<1 the main mechanism behind drug release is the non-Fickian diffusion; hence CA-P1, CA-P5, and CA-P6 were released mostly by the diffusion phenomenon.[39]

The Higuchi model is described by Eq. 6 where Q is the amount of released drug at the time t, A is the contact area, C is the initial drug concentration, C_s is drug Solubility, D is diffusion coefficient, and K_H stands for Higuchi's rate constant.

$$Q = A\sqrt{(D(2C - C_s)C_s t)} = K_H \sqrt{t} \qquad \text{Eq. (6)}$$

This model also suggest diffusion as the dominant release mechanism of drug from the CA-P2, CA-P3, and CA-P4 formulations.[22]

Conclusion

To overcome the challenges of oral administration of ciprofloxacin which is an efficient anti-bacterial agent, floating microspheres were designed and prepared by the emulsification solvent-evaporation method using CA as a polymer matrix. The floating systems have the advantage of prolonged residence time in the gastrointestinal tract which could lead to enhanced drug release. Good floating properties were detected for all formulations due to the presence of pores on the surface of microspheres and low bulk density. The lowest concentration of polymer developed CA-P1 microspheres with the smallest particle size and lowest entrapment efficacy. It was observed that increasing the stirring speed and decreasing the polymer concentration could reduce the size of microspheres. Based on the results obtained from *in vitro* release studies, it was observed that CA-P1 formulation showed the highest cumulative release of 100% in 24 h. All formulations showed a 70-100% cumulative percentage of drug release in a prolonged period compared to conventional forms of the drug. Finally, it could be concluded that floating microspheres are suitable systems for sustained oral delivery of ciprofloxacin because of the increased residence time of the drug in its absorption window which is the proximal area of GIT allowing the drug to be completely absorbed and resulted in an enhanced bioavailability.

Author Contributions

Conceptualization, SM; Methodology, PSA and SM; Software, PSA; Validation, SM; Formal Analysis, SM and PSA; Investigation, PSA and SM; Resources, SM; Data Curation, SM and PSA; Writing – Original Draft Preparation, PSA; Writing – Review & Editing, SM; Visualization, SM and PSA; Supervision, SM; Project Administration, SM; Funding Acquisition, SM.

Conflict of Interest

The authors report no conflicts of interest.

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