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Floating gellan gum-based *in situ* gels containing curcumin for specific delivery to the stomach

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Objectives: Curcumin has been used for several decades to treat gastric ulcers and other digestive disorders. To overcome the poor aqueous solubility and prolong the gastric residence time of curcumin, a novel floating gellan gum-based *in situ* gel with incorporated curcumin-PVP K-30 solid dispersions was developed.
Methods: The solvent evaporation method was used to prepare the curcumin-PVP K-30 solid dispersions. The *in situ* gelling systems, was composed of gellan gum as the base polymer, HPMC K4M as an added polymer, calcium carbonate and curcumin PVP K-30 solid dispersions. The developed formulations were evaluated for their floating abilities and drug release properties.
Results: The curcumin PVP K-30 solid dispersions (ratio 1:10) improved the curcumin solubility by approximately 4000 times higher than for curcumin powder. The X-ray diffraction study indicated that the curcumin solid dispersions were in an amorphous form. After incorporation of the solid dispersions into the *in situ* gelling systems, dark orange liquid preparations for oral use were obtained. The liquid floated within 5 to 7 s and its floating was maintained for more than 24 h in the test medium. The amount of curcumin released from the floating gel was between 50 to 80 % within 8 h depending on the polymer composition. The incorporation of HPMC K4M at concentrations of 1% and 2% w/v was found to retard the release of curcumin.
Conclusion: The floating gellan gum-based *in situ* gel incorporating curcumin as a solid dispersion was successfully developed. The selected formulation (G2) comprised 0.5 % w/v gellan gum, 0.5% w/v calcium carbonate, 0.25% w/v sodium citrate and a 0.55% w/v of curcumin solid dispersion. The results demonstrated that the newly formulated *in situ* gelling systems had the potential to be used for the stomach-specific drug delivery of a poorly water soluble substance such as curcumin.

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Introduction

The *in situ* gel forming systems are one of the most interesting systems in floating oral drug delivery. They have been designed to prolong the gastric residence time and control the rate of drug release which is useful for local gastric treatment. When the system comes in contact with the gastric fluid, a gel is formed and floats on the surface of the stomach contents. The drug then has a sustained release from the gel in the stomach[1]. The floating *in situ* gels have been shown to improve the efficacy of many compounds for example, they are far more effective in eradication of *H. pylori* using amoxicillin[2] and have superior efficacy in the treatment of chronic gastric ulcer by curcumin[3]. The main components of such systems are the gelling agents that form a gel in the acidic environment and an agent to generate gas that makes the system float. The incorporated drugs in this gel forming system should be acid stable and act locally in the stomach[1].

Curcumin, is a polyphenolic compound obtained from the rhizomes of turmeric (*Curcuma longa Linn*) that has antioxidant, antimicrobial, anti-inflammatory and anticarcinogenic activities[4] together with a good safety profile[5]. Studies of the effects of curcumin on acute and chronic gastric ulcers in rats have revealed that curcumin prevented gastric mucosal lesions and accelerated the healing of chronic gastric ulcers[6-8]. In addition, the study of alginate raft forming systems incorporating curcumin in solid dispersions has demonstrated a superior curative effect in chronic gastric ulcer compared to normal curcumin suspensions[3]. Gellan gum is an anionic polysaccharide secreted by some bacteria. Gellan gum is commonly used as a gel former, a thickening agent and stabilizer for the delivery of food and drugs. The gels are formed in the presence of a cation especially a divalent ion[9]. In this study, curcumin-PVP K-30 solid dispersions

were prepared and incorporated into the floating *in situ* gel systems. The obtained formulations were evaluated for their floating abilities and drug release.

Methods

Preparation of curcumin PVP K-30 solid dispersions: To prepare curcumin solid dispersions (SD), curcumin and PVP K-30 were weighed in the ratio of 1:10[10, 11] and dissolved in acetone (50 mL) with a minimum amount of methanol required to dissolve the PVP K-30 completely. The clear solution was then evaporated and dried in a vacuum oven[10]. The obtained curcumin solid dispersions were kept in tight containers at 25°C and protected from light until used. In addition, the solubility of curcumin- PVP K-30 solid dispersions was evaluated by a shake flask method and the crystallinity of the curcumin- PVP K-30 solid dispersions was studied by X-ray diffraction.

Preparation of the floating in situ gelling systems incorporating the curcumin solid dispersions: The compositions of the formulations are shown in Table 1. Gellan gum was dissolved in 40 mL of deionized water containing 0.25% (w/v) sodium citrate while HPMC K4M was separately dissolved in 40 mL of deionized water. After the polymer was completely dissolved, the HPMC K4M solution was added to the gellan gum solution. Then calcium carbonate and curcumin solid dispersions were added and stirred until thoroughly dispersed. The volume was adjusted to 100 mL with deionized water. The obtained formulations were kept in tight bottles and protected from light until used.

In vitro floating studies: 20 mL of the formulation was added to 150 mL of medium (0.1N hydrochloric acid; pH 1.2) in a 250 mL beaker. The temperature was maintained at 37 °C. The floating lag time; the time that the formulation took to emerge from the medium and the duration of the floating time; the time that the formulation consistently floated on the medium surface were measured[12].

Drug release studies: The drug release study used a USP 30 rotating paddle apparatus at 37± 0.5 ºC and a rotating speed of 50 rpm. 900 mL of 0.1N hydrochloric acid (pH 1.2) was the dissolution medium. 20 mL of the floating *in situ* gel was added into the dissolution medium. Samples (5 mL) were withdrawn and replaced with fresh medium after 30, 60, 120, 180, 240, 300, 360, 420 and 480 min. The amount of curcumin in the withdrawn samples was measured by a UV spectrophotometer at a wavelength of 425 nm. Each formulation was tested in triplicate. The data was reported as a mean value ± S.D. A plot of the cumulative % release of the curcumin against time was constructed to illustrate the drug release profiles.

Table 1. Composition of floating *in situ* gel incorporating the curcumin solid dispersions

Ingredient	%w/v							
	G1	G2	G3	G4	G5	G6	G7	G8
Gellan gum	0.25	0.5	1	0.25	0.5	1	0.5	0.5
HPMC K4M	-	-	-	0.5	0.5	0.5	1	2
Sodium citrate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Calcium carbonate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Curcumin PVP K-30 SD (ratio 1:10)*	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Water q.s. to	100	100	100	100	100	100	100	100
Floating lag time (sec)	5	5	5	6	6	6	7	7
Duration of Floating (h)	>24	>24	>24	>24	>24	>24	>24	>24

*curcumin PVP K-30 solid dispersion ratio 1:10 equivalent to 50 mg of curcumin

Results

Preparation of curcumin PVP K-30 solid dispersions: The curcumin PVP K-30 solid dispersions were orange powders with particle sizes between 0.05-0.25 mm after sieving. The solubility of the curcumin PVP K-30 solid dispersions (at the ratio 1:10 by weight) in 0.1N HCl (pH 1.2) was 13.88 ± 0.19 mg/mL which was much higher than the solubility of native curcumin (3.5 µg/mL) in simulated gastric fluid (SGF)[13]. The crystallinity of the curcumin PVP K-30 solid dispersions from the X-ray diffraction results is illustrated in Figure 1. The X-ray diffraction pattern of curcumin shows the characteristic peaks. While, there is no characteristic peak seen in the diffractogram of the curcumin PVP K-30 solid dispersions.

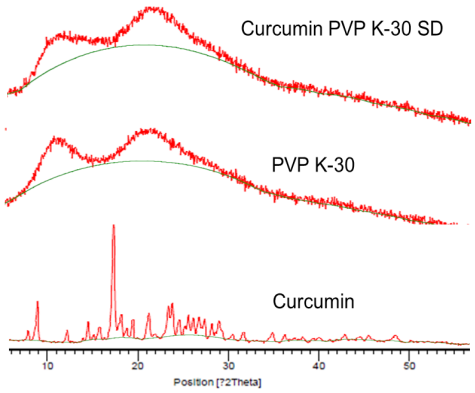

Figure 1. Powder X-ray diffractograms of curcumin, and solid dispersions (SD).

Preparation of the floating in situ gelling systems incorporating the curcumin solid dispersions: The obtained floating *in situ* gelling formulations were in liquid form. These systems could be easily swallowed and transformed to a gel when making contact with the acidic gastric fluid. Moreover, the floating gel was maintained on the surface of the acidic medium for a prolonged period to encourage a slow release of the drug into the stomach contents.

In vitro floating studies: The floating lag times and the duration of floating are presented in Table 1. All the formulations floated on the medium within less than 1 minute and maintained floating for up to 24 h. The addition of HPMC K4M increased the longer floating lag time.

Drug release studies: The release study of the floating *in situ* gelling systems is demonstrated in Figure 2. The drug release was between 50-80 % in an 8 h period. The data shows the effect of the composition of the formulation on the drug release profile. An increase of the gellan gum concentration obviously reduced the release rate of curcumin in both situations with and without the addition of HPMC K4M. The addition of 0.5 % HPMC K4M to the formulations had no significant effect on the release profile when compared to the formulations with gellan gum alone. However, at higher concentrations of HPMC K4M (1 and 2%) a slower drug release was clearly observed.

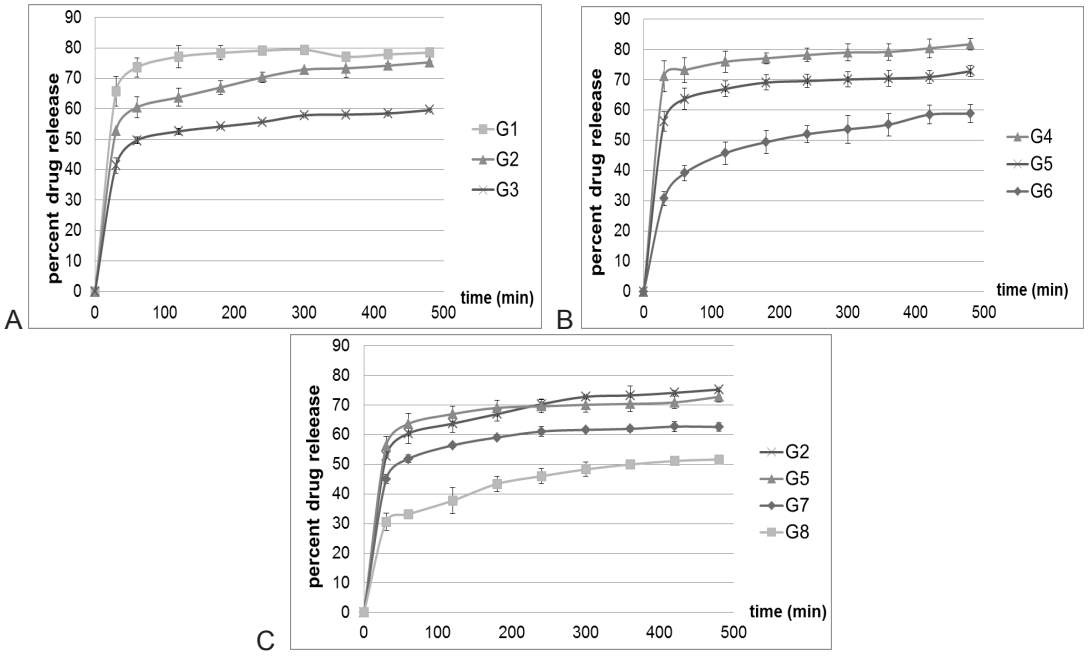

Figure 2. The *in vitro* drug release from the floating *in situ* gelling systems incorporating the curcumin solid dispersions. A) The effect of gellan gum concentration on the *in vitro* drug release. B) The effect of gellan gum on the *in vitro* drug release in the presence of 0.5% HPMC K4M. C) The effect of HPMC K4M on the *in vitro* drug release with 0.5% gellan gum. Bars represent mean values ± SD (n = 3).

Discussion

The solid dispersion technique has been widely used to improve the solubility of poorly water soluble compounds. The curcumin PVP-K30 solid dispersions (at a ratio of 1:10 by weight) improved the curcumin solubility in an acidic medium by up to 4000 times compared to the intact curcumin powder. The amorphous form of curcumin occurred in solid dispersions was confirmed by the X-ray diffractograms. The PVP-K30 might inhibit the growth of the curcumin molecule to form as a crystal[14].

The developed floating *in situ* gel formulation was composed of gellan gum as the main gelling polymer, calcium carbonate for generating calcium ions and the carbon dioxide bubble. The addition of the polymer HPMC K4M induced

swelling and produced a hydrogel to keep the drug in the gel network. The formulations rapidly formed a gel and floated in the medium. The floating gel occurred when calcium carbonate dissolved in the acidic fluid and released calcium ion; that interacted and formed a gel with the gellan gum; and carbon dioxide; was entrapped in the gel and made the systems float. The floating gel was maintained on the gastric fluid and a sustained release of curcumin occurred locally in the stomach. The higher gellan gum concentration produced a more dense matrix and the drug took a longer time to diffuse into the medium resulting in a slower drug release rate which was similar to results obtained in a previous study[2]. HPMC K4M at concentrations of 1% and 2% also slowed the release of curcumin because of its swelling and an increase in the gel thickness that acted as a barrier for drug release. Sermkaew *et al*. also reported that the higher the HPMC K4M concentration showed the slower of the drug release from the floating tablets[15]. The formulation with 0.5% gellan gum without HPMC K4M addition (G2) was selected as the most suitable formulation because it provided a sustained release of curcumin with a 75% release over an 8 h period. To identify the kinetic model of the selected formulations (G2), the release profile was analysed by linear regression analysis and the correlation coefficient (r^2) was calculated. The r^2 values for zero order, first order and Higuchi kinetics were 0.8638, 0.8301 and 0.9495 respectively. Therefore, the best fitting kinetic model for curcumin release from the floating *in situ* gel incorporating the curcumin solid dispersions was the Higuchi model (r^2 closest to 1) which meant that the curcumin was released by a diffusion mechanism from the gel network.

Conclusion

This study has involved the development and evaluation of a floating curcumin *in situ* gel systems for the specific delivery of curcumin to the stomach. The selected formulation contained 0.5 % w/v gellan gum, 0.5% w/v calcium carbonate, 0.25% w/v sodium citrate and 0.55% w/v curcumin solid dispersion. The liquid formulation rapidly formed a gel and floated in the acidic medium, and provided a sustained release of curcumin over an 8 h period. The novel floating gellan gum-based *in situ* gel system may provide a useful dosage form for the specific delivery of curcumin to the stomach.

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