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Physicochemical Characterization of Raft-Forming Delivery Systems for Curcumin Formulated Using Polysaccharide Hydrogels

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***SUMMARY*. Raft-forming delivery systems incorporating curcumin solid dispersions were prepared based on hydrogels of alginate or pectin. The solid dispersion using a 10:1 ratio of polyvinylpyrrolidone K-30 to curcumin improved the solubility of the active. The raft-forming formulations were composed of a polysaccharide gelling polymer in combination with HPMC K4M as an addition polymer. All formulations formed a floating raft within 1 min of exposure to simulated gastric fluid (pH 1.2) and maintained buoyancy for more than 8 h. Raft formulations incorporated HPMC K4M provided more gradual and sustained release of up to 80 % of the curcumin load over a period of 8 h. Raft formulations based on either 1% w/v sodium alginate solution (low viscosity grade) 1% w/v sodium alginate solution (medium viscosity grade) or 2% w/v pectin solution incorporating 0.5% w/v HPMC K4M exhibited an acceptable viscosity, raft strength and resulted in release of 60-80% of the curcumin.**

RESUMEN. Se prepararon sistemas de liberación formadores de balsa que incorporan dispersiones sólidas de curcumina basadas en hidrogeles de alginato o pectina. La dispersión sólida usando una relación 10:1 de polivinilpirrolidona K-30 a curcumina mejoró la solubilidad del activo. Las formulaciones formadoras de balsa estaban compuestas por un polímero gelificante de polisacáridos en combinación con HPMC K4M como polímero de adición. Todas las formulaciones formaron una balsa flotante dentro del min de exposición al fluido gástrico simulado (pH 1.2) y mantuvieron la flotabilidad por más de 8 h. Las formulaciones en balsas que incorporaron HPMC K4M proporcionaron una liberación más gradual y sostenida de hasta el 80% de la carga de curcumina durante un período de 8 h. Formulaciones de balsa basadas en solución de alginato de sodio al 1% p/v (grado de viscosidad bajo) solución de alginato de sodio al 1% p/v (grado de viscosidad medio) o solución de pectina al 2% p/v que incorpora HPMC K4M al 0,5% p/v exhibieron una aceptable viscosidad, resistencia de la balsa y dio como resultado la liberación del 60-80% de la curcumina.

INTRODUCTION

Raft-forming systems have been widely exploited as the gastro-retentive drug delivery systems to prolong drug residence in the stomach, thereby extending the time for local action in the stomach and upper part of the small intestine [1,2]. Raft-forming systems are conventionally stored in liquid form at room temperature and transform to a gel on contact with gastric fluids. The gel networks float on the surface of gastric fluid and may also act as a barrier to prevent the reflux of gastric contents into esophagus. The advantages of raft forming systems include increasing the effectiveness of the local drug delivery to the stomach for treatment of peptic ulcers and eradication of *H. pylori,* reducing the frequency of administration and dosage dosing and improving patient compliance. Moreover, the process of raft preparation is relatively simple and easily scaled up for industrial manufacture. There are many gelation mechanisms of polymer such as the pH dependent gelation, the temperature dependent gelation and ionic cross linking gelation [3,4]. The natural polymers including sodium alginate, pectin and gellan gum are widely used to develop raft-forming system for oral drug delivery. Solutions of these polysaccharides undergo gelation by ionic cross linking [5-7] and form a layer or raft on contact with the acidic gastric fluid. The raft floats on the stom-

KEY WORDS: alginate, curcumin, pectin, raft forming systems, solid dispersion.

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ach content due to entrapment of carbon dioxide which is generated by inclusion of a gas-forming agent such as calcium carbonate, in the raft formulation, which makes the density of the system less than that of the gastric fluids. Incorporated drug gradually released from the raft and the residue is finally expelled from the stomach [3].

Curcumin, the active component of turmeric (*Curcuma longa* Linn.), has been proven to exhibit anti-inflammatory [8], wound healing [9,10], anti-oxidant and anti-peptic ulcer activity [11,12]. The stability of curcumin in acidic conditions is significantly higher than in alkaline conditions and the compound is therefore highly suitable for incorporation in raft-forming oral delivery systems [13]. Curcumin raft-forming systems have been shown previously to improve treatment of gastric ulcers in rat compared with curcumin suspensions [2]. Curcumin has also a good safety profile showing no toxicity after administration of high doses (3000 mg/day) for 3 months in humans [14]. However, the low aqueous solubility, and poor oral bioavailability of curcumin, combined with short gastric emptying times limit the efficacy of curcumin for peptic ulcer treatment. The aim of this study was to improve the aqueous solubility and oral bioavailability of curcumin by incorporating the compound as a solid dispersion in raft-forming systems based on the gel-forming polysaccharides, alginate and pectin. Alginate, a block copolymer consisting of β-D-mannuronic acid (M) and α-L-glucoronic acid (G), has been widely used because of the favorable biological properties such as biodegradability, biocompatibility and non-toxicity. Pectin, a linear polymer consisting mainly of D-galacturonic acid (GalA) units joined with α-(1-4) glycosidic linkage, has been utilized in a variety of drug delivery systems including tablet formulations and raft-forming systems. The developed formulations were characterized in terms of their floating properties, raft strength and *in vitro* drug release characteristics.

MATERIALS AND METHODS

Materials

Curcuminoids extract (≥ 70% curcumin) was obtained from the Thai China flavours & fragrances industry Co., Ltd. (Bangkok, Thailand). Sodium alginate low viscosity grade (min. 45 cps, 1 % w/v at 25 °C) was purchased from Loba chemie PVT. Ltd. (Mumbai, India). Sodium alginate medium viscosity grade (≥ 2,000 cps, 2 % w/v at 25 °C) was provided by High Science Limited Partnership (Songkla, Thailand). Pectin low methoxy was a gift from CP Kelco ApS (Lille Skensved, Denmark). HPMC was a gift from the Dow Chemical Company (Michigan, USA). Polyvinylpyrrolidone (PVP) K30 was sourced from Vidhayasom Co., Ltd. (Bangkok, Thailand) and calcium carbonate from Loba Chemie PVT. Ltd. (Mumbai, India). Sodium bicarbonate was obtained from RCI Labscan (Bangkok, Thailand). All other reagents were of analytical grade.

Preparations of curcumin- PVP K30 solid dispersions

PVP K30 was selected as the hydrophilic polymer to prepare curcumin solid dispersions [15,16] using the solvent evaporation method. Curcumin and PVP K30 in the ratio of 1:3, 1:5, 1:8 and 1:10 by weight were added to acetone (50 mL) containing methanol until the PVP K30 component completely dissolved. The solvent was evaporated using a rotary evaporator at 40 °C and the curcumin/PVP dispersion residue was dried in a vacuum oven at room temperature overnight. The obtained samples were restricted to 0.05-0.25 mm particle size by sieving. The curcumin-PVP K30 solid dispersions (Cur-SD) were kept in air-tight containers at 25 °C and protected from light until used. The optimum ratio of curcumin and PVP K30 in the solid dispersion was determined by solubility testing in simulated gastric fluid (0.1 N hydrochloric acid pH 1.2) using a flask-shaking method [2,17]. Samples of the dissolution medium were collected at specific time intervals of 5, 10, 15, 30, 45, 60, 90, and 120 min and the curcumin content was determined by a UV Spectrophotometer (Spectronic Genesis 5, USA). The crystallinity of the curcumin- PVP K30 solid dispersions was also analysed using x-ray diffraction.

Formulation of raft-forming systems incorporating curcumin-PVP K30 solid dispersions

Raft-forming systems were prepared by dissolving 1 g of sodium bicarbonate in 40 mL of water and adding the gelling polymer (sodium alginate low viscosity (AL), sodium alginate medium viscosity (AM) or pectin (P)) with vigorous stirring. The weights of gelling polymer contained in each formulation are listed in Tables 1-3. Hydroxypropyl methylcellulose (HPMC) as the addition polymer was dissolved separately in 40 mL of water to produce solu-

Formulation	AL1	AL2	AL3	AL4	AL5	AL6
Sodium alginate low viscosity(g)	1.00	2.00	3.00	1.00	1.00	1.00
Sodium bicarbonate (g)	1.00	1.00	1.00	1.00	1.00	1.00
HPMC (g)	-	-	-	0.50	1.00	2.00
CaCO3 (g)	0.50	0.50	0.50	0.50	0.50	0.50
Curcumin solid dispersion (g)	0.55	0.55	0.55	0.55	0.55	0.55
q.s to (mL)	100.0	100.00	100.00	100.00	100.00	100.00
Floating lag time (s)	9	10	11	9	8	6
Duration of floating (h)	>8	>8	>8	>8	>8	>8
Viscosity of liquid prep. (cPs)	449.9 ± 42.4	659.9 ± 42.4	1970.0±14.1	849.9 ± 42.4	1260.0 ± 0.0	5099.0 ± 169.7
Raft strength (g)	1.5 ± 0.1	2.0 ± 0.0	4.3 ± 0.1	2.4 ± 0.1	2.9 ± 0.1	2.0 ± 0.0

Table 1. Composition of raft formulations containing sodium alginate low viscosity (AL).

Formulation	AM1	AM2	AM3	AM4	AM5	AM6
Sodium alginate medium viscosity (g)	1.00	2.00	3.00	1.00	1.00	1.00
Sodium bicarbonate (g)	1.00	1.00	1.00	1.00	1.00	1.00
HPMC (g)	-	-	-	0.50	1.00	2.00
CaCO3 (g)	0.50	0.50	0.50	0.50	0.50	0.50
Curcumin solid dispersion (g)	0.55	0.55	0.55	0.55	0.55	0.55
q.s to (mL)	100.0	100.0	100.0	100.0	100.0	100.0
Floating lag time (s)	10	12	13	10	9	8
Duration of floating (h)	>8	>8	>8	>8	>8	>8
Viscosity of liquid prep. (cPs)	599.0 ± 0.0	3059.0 ± 0.0	11937.0 ± 169.7	959.9 ± 42.4	2339.5 ± 84.1	6419.0 ± 339.4
Raft strength (g)	13.5 ± 1.0	21.2 ± 1.0	25.4 ± 0.8	10.7 ± 0.2	6.5 ± 0.7	4.6 ± 0.4

Table 2. Composition of raft formulations containing sodium alginate medium viscosity (AM).

Formulation	P1	P2	P3	P4	P5	P6
Pectin (g)	1.00	2.00	3.00	2.00	2.00	2.00
Sodium bicarbonate (g)	1.00	1.00	1.00	1.00	1.00	1.00
HPMC (g)	-	-	-	0.50	1.00	2.00
CaCO3 (g)	0.50	0.50	0.50	0.50	0.50	0.50
Curcumin solid dispersion (g)	0.55	0.55	0.55	0.55	0.55	0.55
q.s to (mL)	100.0	100.0	100.0	100.0	100.0	100.0
Floating lag time (s)	10	12	14	12	10	8
Duration of floating (h)	>8	>8	>8	>8	>8	>8
Viscosity of liquid prep. (cPs)	299.9 ± 0.0	359.9 ± 0.0	509.9 ± 42.4	899.8 ± 0.0	1200.0 ± 84.9	4145.5 ± 178.9
Raft strength (g)	2.0 ± 0.1	3.7 ± 0.3	6.4 ± 0.4	5.6 ± 0.2	6.6 ± 0.1	4.6 ± 0.3

Table 3. Composition of raft formulations containing pectin (P).

tions of concentration 0.5, 1, and 2% w/v, respectively, and added to the solution of gel-forming polymer and sodium bicarbonate. Raft-forming systems were also prepared from solutions of the gel-forming polymer without the addition of HPMC. In this case the main gelling polymer was dissolved in 80 mL of water. Calcium carbonate (0.5 g) and curcumin-PVP K30 solid dispersions (0.55 g) at the optimized ratio (1:10 by weight) were added and stirred until thoroughly dispersed. The volume was adjusted to 100 mL with water and the prepared formulations were stored in tight containers with light protection until used.

Viscosity measurements

The viscosity of raft-forming liquid preparations was measured using a Brookfield Viscometer (DV-III ultra, MA, USA) with spindle 64 at a temperature of 25 ± 1 °C. Viscosity measurements were obtained for triplicate samples of each formulation.

Gel forming behavior of liquid raft preparations

The gel forming capacity of the raft formulations was determined by slowly adding 1 mL samples to a test tube containing 5 mL of simulated gastric fluid (SGF, 0.1 N hydrochloric acid, pH 1.2) equilibrated at 37 °C. Gel forming behavior was assessed by visual examination [18]. The gel forming behavior of selected raft formulations was also examined in media of pH 2 (0.01 N hydrochloric acid) and pH 3 (0.001 N hydrochloric acid).

Floating behavior of curcumin-loaded raft formulations

SGF (150 mL) was introduced into a 250 mL glass beaker and maintained at a temperature of 37 °C. A 20 mL sample of liquid raft preparation, equivalent to the maximum expected dose, was added to the SGF medium. The time taken for the formulation to emerge at the SGF surface (floating lag time) and the time the raft floated on the surface (duration of floating) were recorded.

Raft strength measurements

Raft strength was measured using a texture analyzer (TA-XT plus, Stable micro system, Haslemere, UK). SGF (150 mL) was introduced into a 250 mL glass beaker and maintained at 37°C An L-shaped, stainless steel wire probe (20 × 90 mm) was suspended in the center of the beaker with the lower third immersed in SGF. A sample of liquid raft formulation (20 mL) was added to the SGF medium using a syringe. After 30 min of raft development, the beaker was placed on the table of a texture analyzer and the wire probe was pulled vertically up through the raft at a rate of 5 mm/s. The maximum applied force (g) was recorded [19].

Curcumin release behavior from raft formulations

The release behavior of curcumin from the various raft formulations containing curcumin/PVP solid dispersions was studied in SGF at 37± 0.5 °C using a USP 30 rotating paddle apparatus and a rotation speed of 50 rpm. Individual samples of raft-forming liquid preparations (20 mL) were added to 900 mL of SGF. Samples of release medium (5mL) were withdrawn at time intervals of 30 and 60 min and then hourly for the following 7 h and replaced with fresh medium. The concentration of curcumin in the release media was measured using UV Spectrophotometry (Spectronic Genesis 5, USA) at a wavelength 425 nm by comparison with a standard curve constructed using a series dilution of curcumin in SGF over the concentration range 1 to 5 µg/mL. Testing was carried out in triplicate for each formulation, and data was reported as mean ± S.D. A plot of cumulative curcumin release (%) against time was constructed to illustrate the drug release profiles. Testing was also performed using 450 mL of SGF for selected raft formulations to evaluate the effect of medium volume on curcumin release behavior.

RESULTS AND DISCUSSION

Preparation of curcumin PVP solid dispersions

Curcumin:PVP solid dispersions of w/w ratio 1:3, 1:5, 1:8, and 1:10 were obtained as orange powders with a particle size range of 0.05-0.25 mm. The solubility of curcumin in SGF obtained using the solid dispersions was found to increase from 2.1 to 13.9 mg/mL as the content of PVP increased (Fig. 1a) and was 600-3000 times higher than the solubility of curcumin (3.5 µg/mL) in (SGF) 20,21. The dissolution profiles of curcumin solid dispersions in SGF illustrated in (Fig. 1b) revealed that around 70-80% of the curcumin content was rapidly released in around 20 minutes from 1:8 and 1:10 curcum-

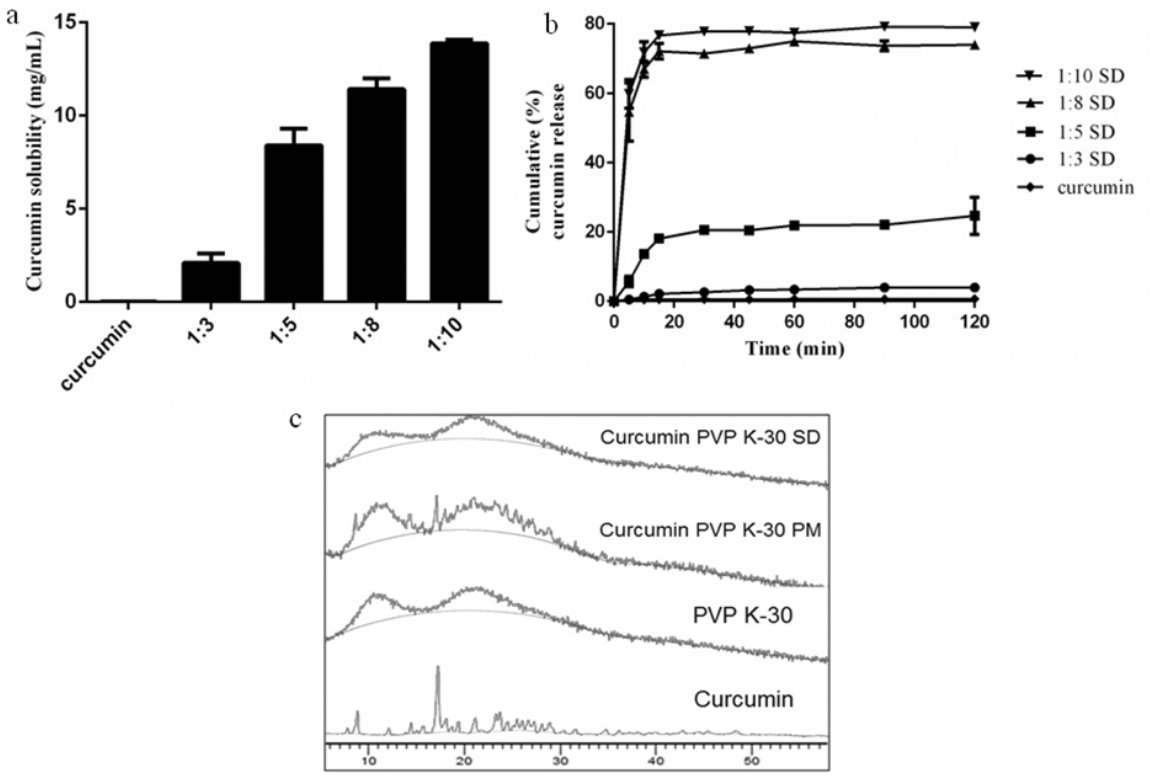

Figure 1. **a**) Solubility of curcumin solid dispersions (SD) in 0.1 N hydrochloric acid (pH 1.2). Bars represent mean ± SD (n = 3). **b**) Dissolution profile of curcumin and solid dispersions (SD) in 0.1 N hydrochloric acid (pH 1.2). Graph presents mean ± SD (n = 3). **c**) Powder X-ray diffractograms of curcumin:PVP K-30, curcumin physical mixtures and curcumin solid dispersions.

in:PVP solid dispersions compared with less than 1% for the native curcumin powder. The hydrophobicity and poor wetting properties resulted in the curcumin powder floating on the surface of the dissolution medium, whereas the particles of solid dispersion was easily wetted and exposed to the dissolution medium. The 1:3 curcumin:PVP solid dispersions resulted in limited cumulative release of curcumin of 4% w/w in 2 h). The solid dispersions of curcumin and PVP at a weight ratio of 1:10 were selected for further studies. The improvement of the dissolution behavior of curcumin using solid dispersions is also attributed to the inhibition effect of PVP K-30 on crystallization of curcumin which has been reported previously [22]. The amorphous form shows higher solubility than the crystalline form. The amorphous state of curcumin in curcumin:PVP K30 solid dispersions prepared in the current study was confirmed by X-ray diffraction (Fig. 1c). No characteristic crystalline peaks were evident in the diffractogram of curcumin: PVP solid dispersions.

Formulation of raft-forming systems incorporating curcumin-PVP solid dispersions

The raft-forming systems incorporated curcumin solid dispersions in low viscosity sodium alginate solution (AL), medium viscosity sodium alginate solution (AM) or pectin solution (P) respectively as gelling component and HPMC K4M was added as the addition polymer. Calcium carbonate was added in the formulation as the crosslinking agent. Dark orange liquid formulations resulted, which immediately transformed to a gel on contact with SGF and floated on the surface, forming a raft. The raft was expected to sustain curcumin release for treatment of various gastric conditions and act as a physical barrier to prevent back flow of gastric contents into the esophagus.

Viscosity measurements

The viscosity of liquid raft-forming systems is important for pouring from the package and for administration. Although exact values of viscosi-

ty are not recommended, studies of antacid preparation mention a preferred aqueous suspension having a viscosity of about 100 to 1000 cPs at 25 °C [23]. The rheological properties of all formulations exhibited pseudoplastic flow or a shear thinning behavior; where the viscosity was inversely proportional to the rotation speed (data not shown). The viscosity of liquid raft-forming formulations is displayed in Tables 1-3. The viscosity of the formulations increased with increasing concentration of the gel-forming polymer. Preparations containing medium viscosity alginate solution were highly viscous (599.0 ± 0.0 at 1% w/v) compared with those based on low viscosity alginate solution (449.9 ± 42.4 at 1% w/v) while use of pectin solution showed the lowest viscosity (299.9 ± 0.0 at 1% w/v). Six raft-forming formulations (AL1, AL2, AM1, P1, P2 and P3) resulted in a viscosity less than 1000 cPs [24] (Tables 1-3). The addition of HPMC K4M from 0.5 g to 2 g increased the viscosity of the raft formulation. Therefore the content of HPMC K4M was restricted to 0.5 g to maintain the viscosity of the formulation at a value less than 1000 cPs.

Gel forming behavior of liquid raft preparations and raft floating behavior

The raft-forming systems gelled and floated following contact with SGF due to exposure to calcium ions and the generation of carbon dioxide respectively. The gel was formed by ionic interaction between alginate or pectin and calcium ions [25,26]. Entrapment of carbon dioxide in the gel network resulted in flotation of the gel. The liquid formulations firstly sank to the bottom of the SGF medium, then floated forming a raft on the surface of the medium (Fig. 2).

The time taken for the formulations to float (lag time) and the duration of floating are shown in Tables 1-3. All formulations floated within 15 s of adding to SGF and stayed afloat for more than 8 h. The concentration of gelling polymer and affected the floating behavior. The lag time tended to increase slightly by one to three seconds when the weight of gelling polymer in the formulation increased (Tables 1-3), which may be explained simply by the time required to reduce the density of the gel below that of the SGF medium. In contrast, the floating lag time decreased slightly by one to three seconds when the content of HPMC increased. The hydrophilic polymer is commonly used in swelling-controlled drug delivery systems [27] and the good swelling tendency on contact with SGF results in a rapid reduction in gel density.

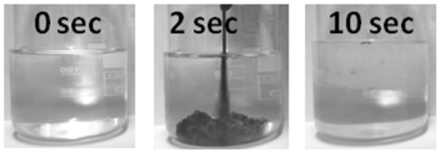

Figure 2. Floating behavior in 0.1 N hydrochloric acid (pH 1.2) of raftforming systems incorporating curcumin-PVP K 30 solid dispersions in alginate (AM4).

Raft strength measurements

Raft-type drug delivery systems are designed to prolong residence time in the stomach and must therefore withstand the peristaltic motion of gastric contents. The raft strength measured as the maximum applied force (g) required to pull a wire probe through the gelled raft. Gel formation results from electrostatic interaction between the calcium ions liberated from the calcium carbonate component of the formulation and the gelling polymer (alginate or pectin). A higher content of the main gelling polymer provides stronger raft structures due to an increase of raft density. For example, rafts formed from liquid formulations containing 1 g medium viscosity alginate exhibited a strength of 13.5 ± 1.0 g compared with 21.2 ± 1.0g for rafts formed from liquids containing 2 g medium viscosity alginate (Tables 1-3). The highest strength (25.4 ± 0.8 g) was measured for rafts prepared using medium viscosity sodium alginate compared with 4.3 ± 0.1 g for rafts produced using low viscosity sodium alginate. The longer polymer chains of the higher molecular weight material provide more functional groups (*e.g.* carboxylic group and hydroxyl group) for interaction with calcium ions to form the classic 'egg box structure' of alginate hydrogels, resulting in improved physical properties of the resultant gels [24]. The raft strengths of all formulations (Tables 1-3) were between 1.5 and 25.5g which were similar to the values of 1.1 to16.5 g reported for antacid commercial products [19]. The addition of HPMC decreased the strength of rafts prepared suggesting that an excessive amount of HPMC disturbs the hydrogel structure.

***In vitro* dissolution studies of raft forming systems incorporating curcumin solid dispersions**

The *in vitro* dissolution profiles in SGF of curcumin: PVP solid dispersions and the devel-

oped raft forming systems incorporating curcumin-PVP solid dispersions are shown in Figs. 3 and 4. Curcumin:PVP solid dispersions resulted in rapid release of around 80% of the curcumin content in 15 min. The pectin formulations showed high 'burst' release of curcumin of 60-80% in 1 h and the release profile then plateaued (Fig. 3c). Rafts prepared using 1, 2

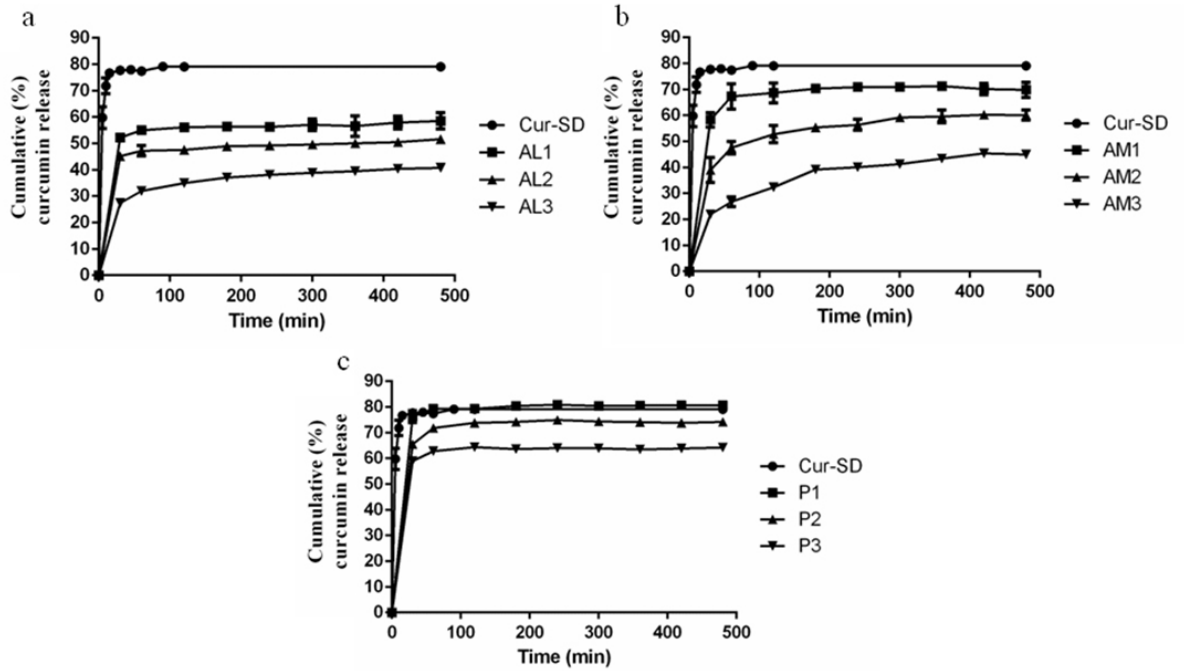

Figure 3. Effect of gelling polymer concentration on curcumin release from raft formulations in 0.1N HCl (pH 1.2). **a**) low viscosity sodium alginate (AL) **b**) medium viscosity sodium alginate (AM) and **c**) pectin (P). Bars represent mean ± S.D. (n = 3). AL, AM and P1, P2, P3 signify 1, 2, and 3 g of polymer concentration.

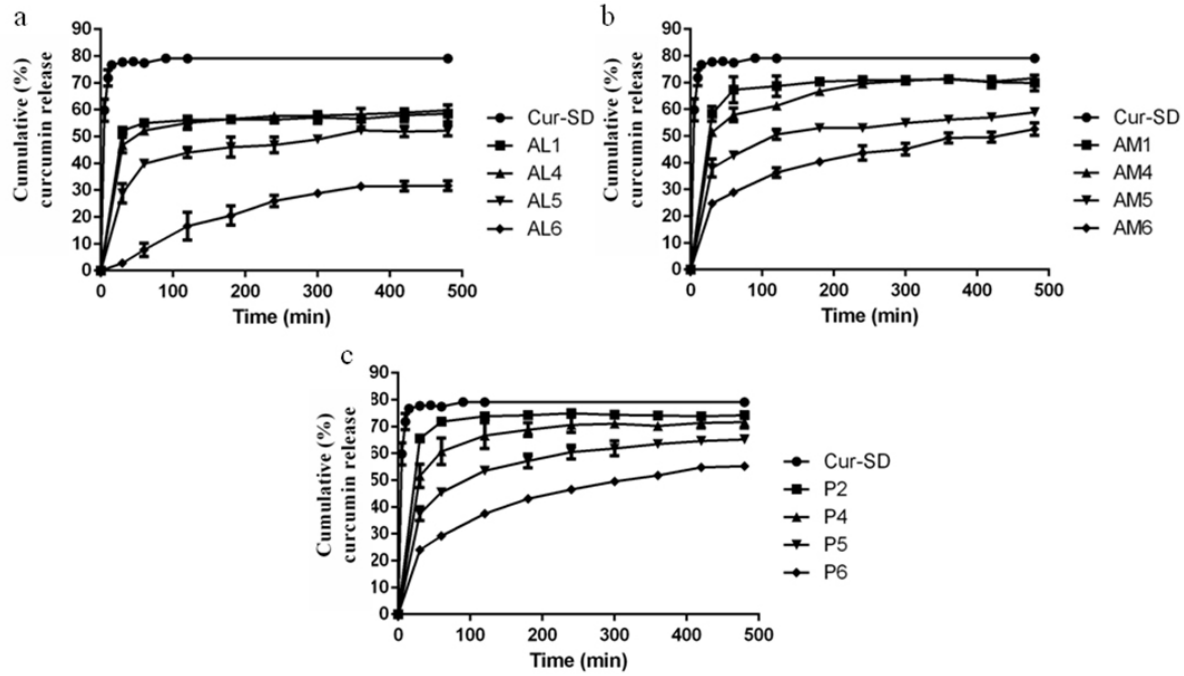

Figure 4. Effect of HPMC content on the release of curcumin from raft formulations in 0.1 N HCl (pH 1.2). Bars represent mean ± S.D. (n = 3) **a**) low viscosity sodium alginate (AL) **b**) medium viscosity sodium alginate (AM) and **c**) pectin (P). AL, AM and P 4, 5, 6 signify 0.5, 1, and 2 g HPMC addition.

and 3% of low viscosity alginate resulted in release of 30, 45 and 50% of the curcumin content in 60 minutes and limited further release of 40, 50, and 60% at 8h (Fig. 3a). Rafts prepared using 2 and 3 g of the medium viscosity alginate resulted in curcumin release of 45% and 25% after 60 mins but more gradual release up to 45 and 58% respectively in 8 h. The increasing polymer concentration increased the density of the polymer matrix and restricted molecular diffusion of curcumin. However, the dissolution profiles did not relate to the viscosity of the gelling polymer. The low viscosity sodium alginate formulations resulted in the lowest raft strength (Tables 1-3) and curcumin release in agreement with the study of Liew et al. which found that alginate viscosity did not correlate with drug release. The alginate properties including particles size and M/G ratio are the important factors modulating drug release [28].

The effect of incorporating HPMC in raft formulations on curcumin release was investigated by fixing the concentration of alginate solutions and pectin solutions at 1% and 2%, respectively (Tables 1-3). Raft formulations prepared without the addition of HPMC resulted in rapid release of curcumin during the first 60 min of exposure to SGF and the release profile plateaued (Fig. 4). HPMC reduces burst release of curcumin in the first hour and then gradual release up to 70% in AM4 and P4. The dissolution profiles in Fig. 4 clearly showed sustained release of curcumin from raft formulations containing HPMC and an immediate release profile for rafts containing only alginate or pectin as the gelling polymer. This might due to HPMC K4M can rapidly swell and form the thick hydrogel 29 when contact with medium. The effect of the concentration of the addition polymer (HPMC K4M) to drug release is illustrated in Fig. 4. The initial burst release of curcumin and the amount released over 8 h in SGF decreased with increasing content of HPMC (Fig. 4) which have also mentioned in the previous study showing the effect of HPMC K4M on drug release of THC floating tablets [30]. This behavior may be explained by swelling of the hydrogel which forms a thicker barrier to curcumin diffusion in the raft structure. The hydration of HPMC matrices and gel layer formation occurs and acts as a diffusion barrier that slows down further water uptake and in turn alters drug release rate [31].

Raft formulations containing curcumin:PVP solid dispersion and 0.5% w/v HPMC in 1% w/v low viscosity sodium alginate (AL4), 1% w/v medium viscosity sodium alginate (AM4) or 2% w/v pectin (P4) were selected for further study. The formulations provided high curcumin release in SGF of 60-70 % over a period of 8 h and showed acceptable viscosity of the raft-forming liquid preparation. The effect of SGF volume on curcumin release from raft formulations was evaluated since the volume of gastric contents in humans varies depending on the individual and the volume of the meal consumed [32]. The volume of the stomach contents in the fasted state is around 18-54 mL and increases to around 279-323 mL on drinking 300 mL of water [33]. When the selected formulations (AL4, AM4, P4) were tested in 450 mL and 900 mL of SGF, no differences were found in floating ability (the raft systems floated within 1 min) and dissolution profile (data not shown). However, it is recommended that at least 1 glass of water is taken before or after administration of the raft-forming liquid preparation to increase the gastric content volume and optimize flotation of the raft.

The pH of the gastric environment is highly acidic between 1.0 to 2.5 in the fasted state [34] and 4.3 to 5.4 in the fed state (during the meal) [35]. The gelation capacity of the selected raft-forming liquid preparations (AL4, AM4 and P4) was therefore investigated in acidic medium of pH 2 and pH 3 (0.01N and 0.001N hydrochloric acid), respectively. All formulations gelled at pH 1.2. The alginate gel which formed at pH 2 floated within 1 min but was thinner and weaker than that formed at pH 1.2. Gelation of alginate and pectin-based liquid preparations was not observed in acidic medium of pH 3, similar to a previous study [36]. However, the pectin-based raft preparation formed thicker and stronger gels than the alginate formulation in pH 2 medium, which may be explained by the temperature sensitive gelation behavior of pectin [37]. It is recommended that the developed raft-forming systems incorporating curcumin-PVP solid dispersions are administered in the fasted state or 1-4 h after meals when the pH in the stomach has decreased back to fasting state levels [33]. They should not be co-administered with antacid or acid suppressants. It is anticipated that the developed raft-forming systems incorporating curcumin solid dispersions will be highly suitable for treatment of gastric ulcers due to the lower pH of the stomach contents under such conditions [38].

CONCLUSION

Curcumin:PVP solid dispersions were incorporated in raft-forming formulations based on the gelling polysaccharides, alginate and pectin. All liquid preparations formed a floating raft in SGF within 1 min and the raft continued to float for over 8 h. Immediate release of around 50-70% of the curcumin content was obtained over 8 h by varying the content of medium viscosity alginate. Sustained and gradual release of around 70% of the curcumin content was obtained over 8h by incorporating HPMC in the medium viscosity alginate formulation. The developed formulations show significant promise as gastro-retentive drug delivery systems.

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