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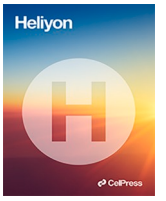

Research article

Development of raft-forming liquid formulations loaded with ginger extract-solid dispersion for treatment of gastric ulceration

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ABSTRACT

Raft-forming liquid formulations incorporating ginger extract solid dispersion (GE-SD) were developed to achieve prolonged delivery of 6-gingerol in the stomach and thus increase the effectiveness of gastric ulcer treatment. The solubility of 6-gingerol in 0.1 N HCl (pH 1.2) was maximized (15 mg/mL) by combining ginger extract with PVP K30 at 1:3 w/w ratio to produce a solid dispersion. The nature of GE-SD was confirmed by PXRD and FT-IR analysis. PXRD pattern showed miscibility of GE and PVP K30 in amorphous solid dispersion and the FT-IR spectra confirmed the formation of hydrogen bond between GE and PVP K30. GE-SD-loaded raft-forming liquids were prepared using sodium alginate as a gel former and HPMC as a release-controlling agent. The formulations exhibited rapid floating behavior in 0.1 N HCl (<30 s) and remained afloat on the surface over 8 h. The formed raft structures provided sufficient strength (>7.5 g) and allowed sustained release of more than 70 % of the 6-gingerol content over 8 h in 0.1 N HCl. Raft-forming formulations incorporating ginger extract demonstrated anti-inflammatory activity by inhibiting nitric oxide production in LPS-stimulated RAW 264.7 macrophage cells (IC_{50} = 5.13 ± 0.07 μg/mL). Exposure to the formulations also had a significant cytotoxic effect on AGS human gastric adenocarcinoma cells with an IC_{50} of 17.45 ± 0.29 μg/mL. In addition, the raft-forming formulations enhanced the migratory behavior of L929 mouse fibroblasts in the scratch wound model. Taken together, these findings reveal the benefits of gastro-retentive, GE-SD-loaded raft-forming liquid formulations for improving the treatment of gastric ulcers.

1. Introduction

Gastric ulcers are open sores that develop on the inside lining of the stomach. The risk factors inducing gastric ulcers are mainly the

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infection with *Helicobacter pylori* [1,2] and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are known to cause gastric ulcers by inhibition of the enzyme cyclooxygenase 1 (COX-1), which is involved in the production of prostaglandins. Complications of ulceration including gastric outlet obstruction, severe bleeding, and perforation can be potentially life threatening [3]. The conventional treatment for gastric ulcers includes proton pump inhibitors (PPIs), H_2 receptor antagonist, antacids or antibiotic therapy. However, adverse effects are common such as vitamin B_{12} deficiency, osteoporosis, cardiovascular events and thrombocytopenia [4]. The increasing prevalence of antibiotic-resistance has also led to increasing rates of failure of current therapies [5]. As a result, natural medicinal products have gained interest as alternative therapeutics for treatment of gastric ulcers.

Ginger has been widely used as a natural remedy for a variety of gastric ailments including constipation, dyspepsia, ulcerations and indigestion [6–8]. The major active compound found in the ginger rhizome is the phenolic 6-gingerol [9]. Ginger has been shown to display a wide range of pharmacological activities including antioxidant, anti-inflammatory [10,11], anti-cancer [12] and antibacterial behavior. 6-Gingerol exerts anti-inflammatory effect by inhibition of proinflammatory cytokine [10] and nitric oxide (NO) production, by down-regulating iNOS expression in a dose-dependent manner [11]. Gingerols have also been shown to inhibit *H. pylori* CagA+ expression associated with development of gastric ulcer and gastric cancer [12]. However, 6-gingerol has low oral bioavailability due to its limited aqueous solubility and short half-life (1.8 h) which restricts its clinical application [13,14]. Solid-dispersion (SD) technology offers a mean of enhancing the solubility of 6-gingerol by dispersion in a hydrophilic carrier matrix [15]. Polymers are typically used as the carrier, including polyvinylpyrrolidone (PVP) [16], polyethylene glycol (PEG) [17], Eudragit® EPO [18,19] and hydroxypropyl methylcellulose (HPMC) [20].

Floating drug delivery systems (FDDS) are considered one of the best options for achieving gastro-retentive behavior and prolonging drug release in the stomach to improve bioavailability [21]. Raft-forming systems, in particular, have received much attention for treating gastrointestinal infections and other disorders and have also formed strong barriers to hinder acid reflux [22]. A number of natural products have been formulated as FDDS and shown promise for treating gastric ulcers including curcumin [23], quercetin [16] and *Centella asiatica* extract [18]. Although gastro-retentive dosage forms of ginger extract have been developed for treatment of peptic ulcers based on floating beads [24] and expandable films [25], the raft-forming systems have not been reported to date. The important compositions of raft-forming formulations are hydrophilic polymer as a gel-forming substance, a crosslinking agent and a gas-generating agent. In this study, sodium alginate was used as a gelling agent because it could effectively form gel on contact with gastric fluids. The divalent calcium ions from calcium carbonate were employed as a crosslinking agent to enhance the gel strength. Sodium bicarbonate and calcium carbonate are used as the source of CO_2. Due to the trap of CO_2 in the cohesive gel layer, making this system less dense and float on the gastric fluids. The formulations also contained hydroxypropyl methylcellulose (HPMC) K4M as a drug release retardant due to a high degree of polymer chain entanglement which inhibited diffusion of drug from the raft [18,26,27].

This research describes the development of gastro-retentive, raft-forming liquid dosage form incorporating ginger extract-solid dispersions for treatment of gastric ulceration. The anti-inflammatory, cytotoxic, and wound healing activities of the formulations were evaluated using RAW 264.7 macrophage cell line, AGS gastric cancer cells, and L929 mouse fibroblasts, respectively.

2. Materials and methods

2.1. Materials

6-Gingerol (98 % purity) was obtained from Baoji Herbest Bio-Tech Co. Ltd (Shaanxi, China). Ginger extract (20 % gingerol content) was provided by Guangzhou Phytochem Sciences Inc. (Guangzhou, China). Polyvinylpyrrolidone K30 (PVP K30) was purchased from P.C. Drug Center Co., Ltd (Bangkok, Thailand). Eudragit® EPO (MW 150 kDa) was a gift from Evonik Industries AG (Darmstadt, Germany). Sodium alginate (medium viscosity, 2000 cps, 2 % w/w solution; 25 °C) was purchased from High Science Limited Partnership (Songkhla, Thailand). HPMC K4M was obtained from Rama Production Co. Ltd (Bangkok, Thailand). Calcium carbonate was purchased from LOBA Chemie Pvt. Ltd. (Mumbai, India). Sodium bicarbonate was supplied by RCI Labscan (Bangkok, Thailand).

AGS human gastric cancer cell line, mouse fibroblasts L929 cell line and RAW264.7 mouse macrophage cell line were obtained from the American Type Culture Collection (ATCC; Manassas, Virginia, USA). Penicillin-streptomycin, fetal bovine serum (FBS; 10 %), trypsin EDTA (0.25 %), and Kaighn's Modification of Ham's F-12 Medium (F12-K) were supplied by Gibco (Invitrogen, CA, USA). Dimethylsulfoxide (DMSO) was purchased from Amresco® (Solon, OH, USA). Phosphate-buffered saline (PBS), 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) reagent, indomethacin, Roswell Park Memorial Institute 1640 (RPMI-1640) medium, Dulbecco's modified Eagle's medium (DMEM), lipopolysaccharide (LPS), and Griess reagent were provided by Sigma Aldrich (Sigma Aldrich, Missouri, USA).

2.2. Preparation of ginger extract-solid dispersions (GE-SDs) and physical mixtures (GE-PMs)

Solid dispersions (SD) comprising ginger extract (GE) and hydrophilic polymers were prepared using solvent evaporation [23]. Briefly, 1 g of ginger extract was dissolved in 60 mL of ethanol, followed by addition of polyvinylpyrrolidone K30 (PVP K30) or Eudragit® EPO in various weight ratios (1:2, 1:3, 1:5 and 1:8 GE: polymer). The homogenous solution occurred after a continuous stirring. Then, ethanol was removed by a rotary evaporator (model Hei-VAP value digital, Heidolph Instruments GmbH, Schwa Bach, Germany) at 40 °C until the dry powder was obtained. The dried GE-SDs were pulverized using a mortar and pestle and passed through a 60-mesh (250 μm) sieve size. Ginger extract-physical mixtures (GE-PMs) were prepared at the same weight ratios by dry blending ginger extract and the hydrophilic polymers using a mortar and pestle. Both GE-SDs and GE-PMs were maintained at 4 °C in tight and

light-resistant bottles.

2.3. Characterization of ginger extract-solid dispersions and physical mixtures

2.3.1. 6-Gingerol content analysis

The amount of 6-gingerol in the formulations was detected by HPLC system (Agilent model 1260 series, CA, USA) as reported previously [25]. The content of 6-gingerol in each sample was measured using a Luna® C18 column: 250 mm × 4.6 mm, 5 μm particle size (Phenomenex, CA, USA) with wavelength detection at 282 nm. The mobile phase comprised methanol and 1 % acetic acid (75:25, v/v) at a flow rate of 1 mL/min. A standard curve of 6-gingerol was constructed by serial dilution of 6-gingerol solution to provide a series of concentrations in the range 5–200 μg/mL.

2.3.2. Solubility

The solubility of ginger extract alone, together with GE formulated as solid dispersions and physical mixtures was determined using a shake-flask method [23]. Briefly, 1 ml of 0.1 N hydrochloric acid (HCl), pH = 1.2 was added in to a vial before adding an excessive amount of ginger extract, GE-SD or GE-PM. Then, the mixture was agitated by a vortex (Vortex-Genie 250 Hz, Scientific Industries Inc., USA) for 10 min. Each vial were placed in a shaking water bath (SW22 Julabo, Seelbach, Germany) at 37 ± 0.1 °C and continuously agitated at 100 rpm. After 48 h, the samples were centrifuged at 6000 rpm for 20 min (Centurion PrO-Research K2015R, Centurion Scientific Ltd, UK) and the supernatant was filtered through a 0.45-μm membrane filter, prior to measurement of the 6-gingerol content by was HPLC (Section 2.3.1). Each experiment was performed in triplicate.

2.3.3. Powder X-ray diffraction (PXRD) studies

The crystallinity, of ginger extract, the hydrophilic polymers (PVP K30), GE-SDs and GE-PMs was measured using powder X-ray diffraction (Empyrean, PANalytical, Almelo, Netherlands). Spectra were obtained at 40 kV and 30 mA using a scan speed of 70.125 s/step at room temperature. Samples were scanned over a 2θ range of 5–90° using a step size of 0.026°.

2.3.4. Fourier transform infrared spectroscopy (FT-IR)

In order to observe the chemical interaction between PVP K30 and ginger extract of GE-SDs and GE-PMs, FT-IR spectroscopy was performed. The Vertex70 FT-IR spectrometer (Bruker, Ettlingen, Germany) equipped with a deuterated triglycine sulfate detector was used. Samples were prepared in the form of KBr pellets and spectra were recorded in the range 4000 to 440 cm^{-1}.

2.4. Preparation of GE-SD loaded raft-forming liquid formulations

GE-SD prepared using PVP K30 at a w/w ratio of 1:3 was used to prepare raft-forming liquid systems due to the higher solubility of 6-gingerol achieved compared with Eudragit® EPO. Raft-forming liquid formulations were produced by varying the concentration of sodium alginate (gelling agent) and HPMC K4M (release controlling agent) as listed in Table 1. Sodium bicarbonate and calcium carbonate were incorporated in the formulation at 1 % w/v concentration, as CO_2-generating agent and crosslinking agent, respectively. The weight GE-SD was fixed at 5 g. Sodium bicarbonate was first dissolved in 100 mL of deionized water, followed by dissolution of sodium alginate under continuous stirring. Calcium carbonate and GE-SD were dispersed in the resulting co-solution and the volume was adjusted to 100 mL with deionized water to obtain the finished raft-forming liquid formulation.

Table 1
Composition and physical characteristics of GE-SD loaded raft-forming liquid formulations.

Formulation	Composition (% w/v)		Raft strength (g)	Density (g/mL)	Viscosity (cPs)	Floating lag time (FLT) (s)
	Alginate	HPMC				
F1	1.0	–	16.6 ± 0.5	0.544 ± 0.011	1336 ± 49	10
F2	1.5	–	21.4 ± 0.3[a]	0.482 ± 0.012	2505 ± 29[a]	12
F3	2.0	–	24.5 ± 0.7[a]	0.443 ± 0.012	5855 ± 12[a]	15
F4	1.0	0.5	14.5 ± 0.6	0.542 ± 0.014	1480 ± 07	11
F5	1.0	1.0	12.0 ± 0.3[b]	0.526 ± 0.027	2797 ± 33[b]	14
F6	1.0	1.5	4.5 ± 0.1[b]	0.469 ± 0.015	4435 ± 07[b]	20
F7	1.5	0.5	18.9 ± 0.4	0.477 ± 0.010	4079 ± 42	12
F8	1.5	1.0	15.4 ± 0.6[c]	0.481 ± 0.022	5551 ± 14[c]	13
F9	1.5	1.5	10.8 ± 0.3[c]	0.465 ± 0.012	9347 ± 23[c]	20

Both $NaHCO_3$ and $CaCO_3$ content was fixed at 1 % w/v. The GE-SD content was fixed at 5 % w/v.
[a] Statistically significant at p values < 0.05 when compared with to F1 formulation.
[b] Statistically significant at p values < 0.05 when compared to F4 formulation.
[c] Statistically significant at p values < 0.05 when compared to F7 formulation.

2.5. Characterization of GE-SD-loaded raft-forming liquid formulations

2.5.1. Viscosity

The viscosity of the samples was determined by a Brookfield DV-III Rheometer with spindle no. 63 (LV3) at 25 ± 1 °C. The spindle was immersed in the test sample to measure the resistance to flow at the rotational speed of 10 rpm. Each sample was repeated in triplicate. The viscosity values were operated under Rheocalc 3.2 software. Rheology behavior was investigated and plotted at a speed ranging from 2.5 to 20 rpm against viscosity.

2.5.2. Density of formed raft structures

The density (g/mL) of rafts formed by the liquid formulations was measured following the method of Wannasarit et al. [18]. The 75 mL of 0.1 N HCl solution was added into a 100 mL measuring cylinder and weighed as W_i. The liquid formulation (10 mL) was introduced into the cylinder. and allowed to form a raft gel. After 10 min, the final weight of the cylinder and content volume were measured as W_r and V_r, respectively. The raft density (D) was calculated using Eq. (1) [16].

$$D = \frac{Wr - Wi}{Vr} \quad (1)$$

2.5.3. Raft strength

Raft strength was investigated using a texture analyzer (TA-XT plus, Haslemere, UK). Raft forming liquid samples (20 mL) were carefully added into 150 mL of 0.1 N HCl solution containing in 250 mL glass beaker and maintained at 37 °C. The formulations were allowed to form a raft gel around an L-shaped stainless-steel probe located at the center of the beaker. The wire probe was subsequently connected to the loading arm of the texture analyzer and pulled vertically upwards at a rate of 5 mm/s. The maximum recorded load (g) was assigned as the raft strength [28].

2.5.4. Floating and buoyancy characteristics

The buoyancy of liquid formulations was investigated as described previously [18]. Raft-forming liquid formulations (20 mL) were injected into 150 mL of 0.1 N hydrochloric acid maintained at 37 °C. The time required for the formed raft structures to float to the surface (floating lag time) and the residence time on the surface (duration of floating) were recorded. Each test was repeated in triplicate.

2.5.5. Release behavior of raft-forming formulations

The release pattern of 6-gingerol from raft-forming formulations was tested by using a USP 30 rotating paddle dissolution apparatus at a temperature of 37 ± 0.5 °C and speed of 50 rpm as previously described [18]. The dissolution medium consisted of 200 mL of 0.1 N hydrochloric acid (pH 1.2). Ten mL of each formulation were injected into the dissolution medium by syringe. Samples (5 mL) were withdrawn at 30, 60, 120, 180, 240, 300, 360, 420 and 480 min and replenished with an equivalent volume of fresh dissolution medium. The samples were filtered through a membrane filter (0.45-μm, VertiPureTM PVDF(HL), Vertical Chromatography Co., ltd., Bangkok, Thailand) before the analysis of 6-gingerol content using HPLC as mentioned in section 2.3.1. All experiments were conducted in triplicate. The data were presented as the mean value ± S.D. and release profiles were plotted as % cumulative 6-gingerol release against time.

2.6. Cell culture

Murine macrophage (RAW 264.7) cells were cultured in RPMI 1640 medium supplemented with components of 10 % fetal bovine serum (FBS) and 1 % penicillin-streptomycin (pen-strep) at 37 °C in a humidified 5 % CO_2 atmosphere. Human gastric adenocarcinoma (AGS) cells were grown in Kaighn's Modification of Ham's F-12 (F12–K) medium supplemented with 10 % FBS and 100 unit/mL of 1 % pen-strep. Whereas mouse fibroblasts (L929 cells) were raised in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10 % FBS and 1 % of pen-strep under the same conditions as RAW 264.7 cells. The media were removed and new media were added every two days until they reached 90–100 % confluence.

2.7. Cytotoxicity assay

The cytotoxicity of raft-forming formulations was investigated by the MTT reduction assay in conjunction with RAW 264.7 cells and L929 fibroblasts. In brief, RAW 264.7 and L929 cells were seeded in 96 well plates at a density of 1×10^5 and 1×10^4 cells/well, respectively, and incubated at 37 °C under a humidified atmosphere in 5 % CO_2 overnight. The cells were subsequently exposed for 24 h to increasing concentrations (1.25, 2.5, 5, and 10 μg/mL, equivalent concentration of 6-gingerol) of ginger extract, 6-gingerol, GE-SD, blank formulation and GE-SD-loaded raft-forming liquid formulation, respectively. Following incubation, the culture media were replaced by 0.5 mg/mL MTT solution and cells were incubated for a further 3 h. After removing the MTT solution, DMSO (100 μL) was added to dissolve the formazan crystals. Cell viability was determined by measuring the absorbance at 570 nm on a microplate spectrophotometer (Biotek PowerWave X, Santa Clara, CA, USA) and reported as a percentage of the control (cell culture medium) value. Results were obtained from tests carried out on triplicate samples.

The anti-proliferative activity of GE-SD based raft-forming liquid formulations against AGS cells was measured as described above,

but using a seeding density of 2×10^4 cells/well.

2.8. Investigation of anti-inflammatory activity

The anti-inflammatory activity of ginger extract, 6-gingerol, GE-SD, blank and GE-SD-loaded raft-forming liquid formulation was investigated by measuring their effect on nitric oxide production by LPS-induced RAW 264.7 cells. RAW 264.7 macrophages were seeded at a density of 1×10^5 cells/well in 96 well plates and grown overnight. The culture media were removed and replaced by culture media or test samples in which the cells were incubated to increasing concentrations (1.25, 2.5, 5, 10 μg/mL) with and without LPS (100 ng/mL). After 24 h incubation, the nitrite-containing media were transferred into new 96 well plates and mixed with Griess reagent at the volume 100 μL: 100 μL (ratio 1:1). The nitrite content of the media was measured by recording the UV absorbance at 570 nm and the percentage inhibition of nitric oxide production (anti-inflammatory activity) was calculated by applying formula given below (Eq. (2)) [29].

$$\%\ \text{Inhibition} = \frac{\text{Acontrol} - \text{Asample}}{\text{Acontrol}} \times 100 \tag{2}$$

where $A_{control}$ is the absorbance of media derived from cells exposed to with LPS alone; A_{sample} is the absorbance of media derived from cells exposed to the test sample and LPS. The NSAID, indomethacin, served as the positive control. Results were obtained from tests carried out on triplicate samples and anti-inflammatory activity was expressed as IC_{50} values.

2.9. Assay of wound healing potential

The wound healing potential of 6-gingerol, GE-SD, blank, raft-forming formulation and GE-SD-loaded raft-forming formulation was assessed using L929 fibroblasts in the scratch wound assay. Cells were seeded into 12 well plates and allowed to reach 100 % confluence at 37 °C under a humidified atmosphere in 5 % CO_2. After 24 h of starvation with DMEM containing 2 %, the cell monolayer was disrupted by scratching with a sterile 1000 μL pipette tip and immediately washed twice with PBS to remove cell debris. The cell monolayers were subsequently exposed to ginger extract, 6-gingerol, GE-SD, blank, and GE-SD-loaded raft-forming formulation respectively, of concentration equivalent to 5 μg/mL of 6-gingerol. Wound closure was monitored using an inverted microscope (EVOS XL Core, Thermo Fisher Scientific, Waltham, MA, USA) at 0, 48 and 72 h post exposure and analyzed using ImageJ software. The percentage wound closure was calculated using the following equation (Eq. 3) [30].

$$\%\ \text{wound closure} = \frac{A_{xh}}{A0h}\ \text{x}\ 100 \tag{3}$$

where A_{xh} is the wound closure area at x h; A_{0h} is the wound closure area at 0 h. Media containing 2 % FBS used as a control. Results were obtained from tests carried out on triplicate samples.

2.10. Statistical analysis

Data were reported as mean ± standard deviation (S.D.). Statistical analysis was carried out using Student's t-test and one-way analysis of variance (ANOVA). The differences between groups were considered statistically significant at $p < 0.05$.

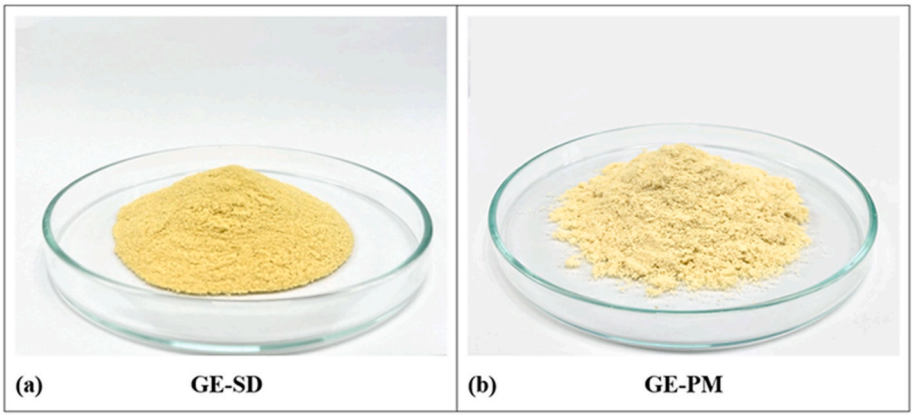

Fig. 1. The appearance of 1:3 w/w ginger extract solid dispersion (a) and 1:3 ginger extract physical mixture (b) prepared using PVP K30 as the hydrophilic carrier polymer.

3. Results and discussion

3.1. Characterization of ginger extract-solid dispersions (GE-SDs) and physical mixtures (GE-PMs)

Ginger extract-solid dispersions (GE-SDs) of yellow coloration were successfully prepared by dissolving ginger extract and hydrophilic polymer in ethanol, followed by solvent evaporation, whereas physical mixtures (GE-PMs) were prepared at the same weight ratios by dry blending (Fig. 1a and b). GE-SDs of weight ratios of 1:2, 1:3, 1:5 and 1:8 were prepared using bothPVP K30 and Eudragit® EPO.

3.2. Solubility of GE-solid dispersions

Solid dispersion techniques have been used extensively to increase the solubility and bioavailability of hydrophobic drug compounds [16–20,25,31,32]. The 6-gingerol component of ginger extract was previously reported to be poorly soluble, with values lower than 1 mg/mL [25]. In the present study, the solubility was measured as 0.41 mg/mL in 0.1 N hydrochloric acid (pH 1.2) and only minor improvements to 0.9 mg/mL were obtained by formulation of GE-PMs. In contrast, 6-gingerol solubility increased significantly by forming solid dispersions with PVP K30. The maximum solubility (15 mg/mL) was observed at 1:3 wt ratio corresponding to an increase of around 36 folds compared with GE (Fig. 2).

The enhanced solubility may be attributed to improved wetting of the compound. However, the solubility of 6-gingerol in GE-SDs decreased at weight ratios greater than 1:3. This behavior may be described by steric hindrance interactions arising between 6-gingerol and the PVP K30 polymer at high polymer loading [33], which incommode fluid uptake and wetting [34]. Similar pattern was reported previously for solid dispersion of *Centella asiatica* extract [18] and chebulinic acid [35]. The highest solubility (3 mg/mL) was obtained for 6-gingerol in GE-SDs prepared using Eudragit® EPO at weight ratio 1:2 (Fig. 3). Consequently, GE-SD prepared using of PVP K30 at a weight ratio 1:3 was selected for production of raft-forming liquid formulations.

3.3. Powder X-ray diffraction studies

X-ray diffraction patterns of PVP K30 did not display diffraction peaks corresponding to a crystalline phase while ginger extract presented strong crystalline peaks at (2θ) angles of 9.0, 10.7,12.5, 19.5 and 20.9 (Fig. 4). The physical mixture of ginger extract and PVP K30 resulted in crystallinity peaks around 9.0 and 12.5 (2θ) but of less intensity, designating an absence of strong interactions between the two substances [25]. In contrast, the diffractograms of GE-SD were similar to those of PVP K30, indicating the conversion of ginger extract from the crystalline to amorphous form. Crystallization inhibition may be due to the bond formation between ginger extract and the PVP K30 polymer [31]. The results were also confirmed by FT-IR spectra and the improvement of 6-gingerol solubility. Similar results have been reported for atorvastatin-PVP K30 [32], quercetin-PVP K30 [16], and curcumin-Eudragit® EPO solid dispersions [19].

3.4. Fourier transform infrared spectroscopy studies

FT-IR spectra were used to identify intermolecular interactions between ginger extract and PVP K30, in solid dispersions and physical mixtures, respectively (Fig. 5). The FT-IR spectrum of PVP K30 showed the major absorption band at 1661.16 cm^{-1} assigned to the stretching vibration of the carbonyl group (C=O) together with bands at around 2956.11 cm^{-1} represented the C–H stretch. Ginger extract showed a broad peak at 3412.55 cm^{-1} assigned to O–H stretching of hydroxyl groups of phenolic compounds. Moreover, the dominant peaks at 1701.51 cm^{-1} and 1100.86 cm^{-1} correspond to C = O stretching and C–O stretching, respectively.

The FT-IR spectra of 1:3 GE-SD showed the shift of the broad band from 3412.55 cm^{-1} to 3435.31 cm^{-1}. Additionally, the distinct peak at 1600 cm^{-1} and 1200 cm^{-1} were also disappeared. Moreover, the absorption band of the carbonyl group of PVP K30 was shifted

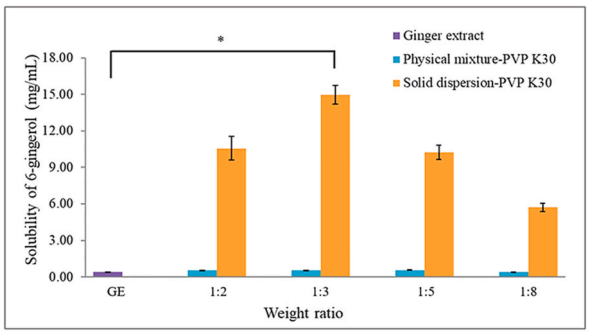

Fig. 2. The solubility of 6-gingerol in unformulated ginger extract (GE), ginger extract solid dispersion (GE-SD) and physical mixture (GE-PM) in 0.1 N HCl at 37 °C. PVP K30 used as the hydrophilic carrier polymer. *p values < 0.05; statistically significant difference compared to the solubility of GE.

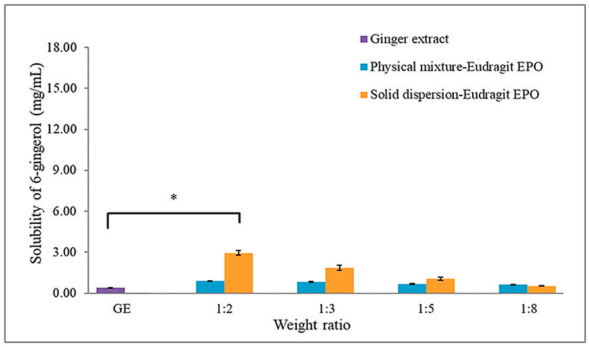

Fig. 3. The solubility of 6-gingerol in unformulated ginger extract (GE), ginger extract solid dispersion (GE-SD) and physical mixture (GE-PM) in 0.1 N HCl at 37 °C. Eudragit® EPO used as the hydrophilic carrier polymer. A statistically significant difference compared to the solubility of GE when p values < 0.05*.

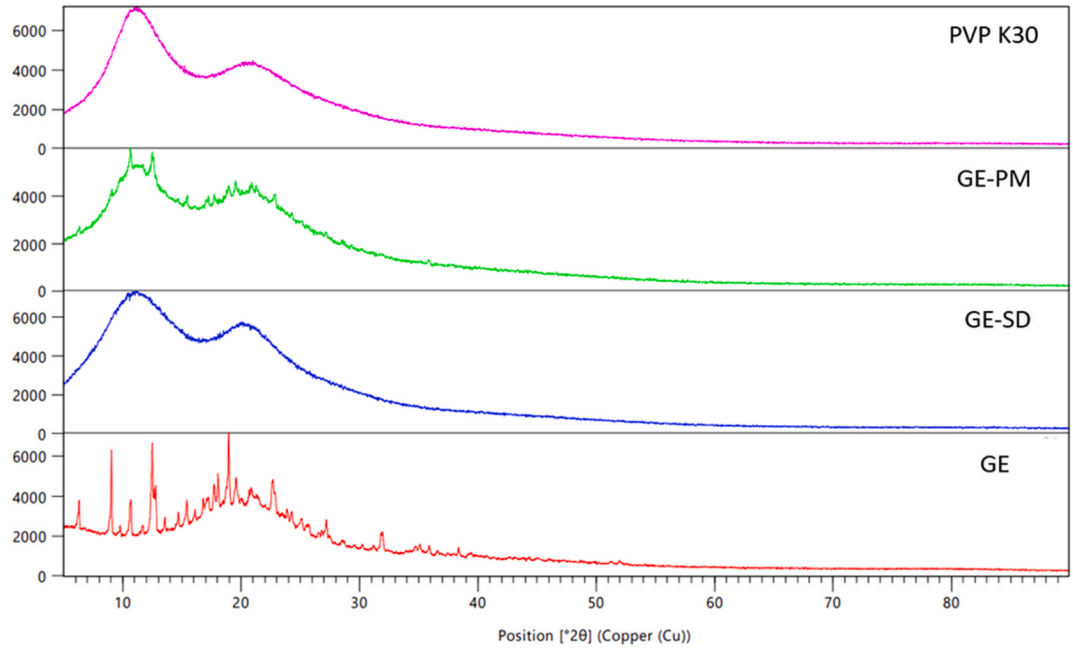

Fig. 4. Powder X-ray diffraction spectra of ginger extract, PVP K30, ginger extract solid dispersions (GE-SD) and physical mixtures (GE-PM).

to 1659.33 cm^{-1} suggesting interaction with the hydroxyl group of ginger extract [2,31], which may explain interference with the process of crystallization of ginger extract.

3.5. Physicochemical characterization of GE-SD loaded raft-forming formulations

3.5.1. Viscosity

The viscosity of oral liquid dosage form plays an essential role in dose administration and patient acceptance [36]. The viscosity values of raft-forming formulations containing only the alginate gelling agent increased by over three times on raising the concentration from 1 to 2 % w/v (Table 1). The incorporation of HPMC K4M in the liquid formulation as a release-controlling agent also resulted in significant increases in viscosity. For example, the combination of HPMC at 0.5 and 1.5 % w/v concentration with alginate (1 % w/v) raised the viscosity from 1480 to 4435 cPs (F4, F5, F6). This behavior is explained by the higher resistance to flow caused by polymer chain entanglement [18]. The viscosity of all formulations decreased with an increase in rheometer spindle speed (Fig. 6), indicating non-Newtonian pseudoplastic or shear-thinning flow behavior [37].

3.5.2. Raft density and floating lag time

The density and floatability in 0.1 N HCl (pH 1.2) of raft structures formed by GE-SD loaded formulations are listed in Table 1. The density of raft structures ranged between 0.47 and 0.54 g/mL and thus floated in 0.1 N HCl which has a density close to that of water

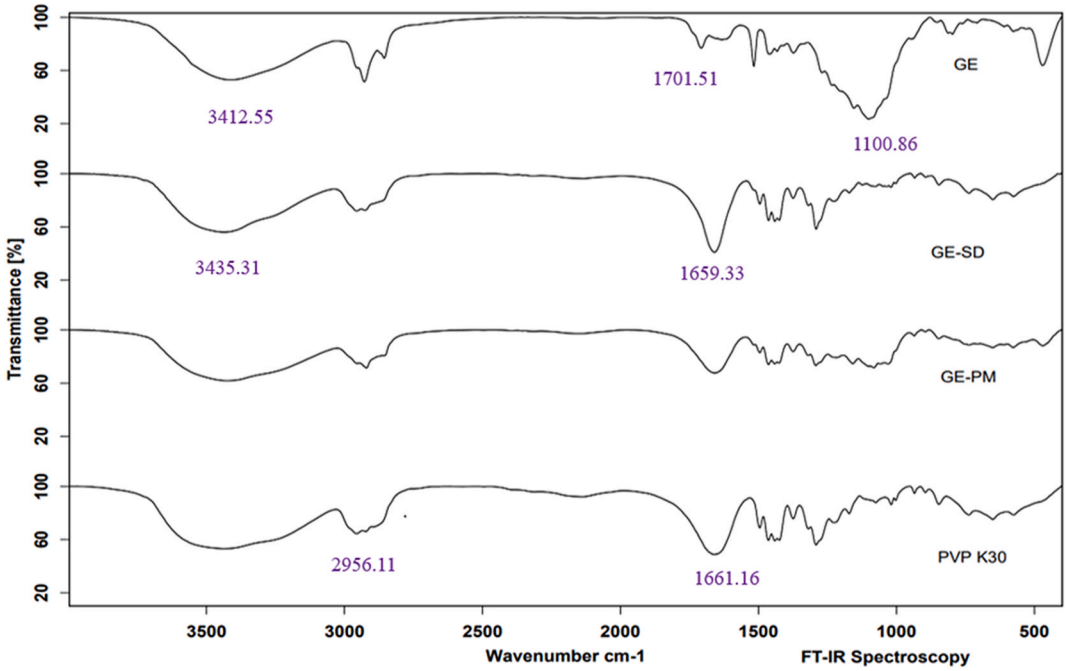

Fig. 5. FTIR spectra of ginger extract, PVP K30, ginger extract solid dispersions (GE-SD) and physical mixtures (GE-PM).

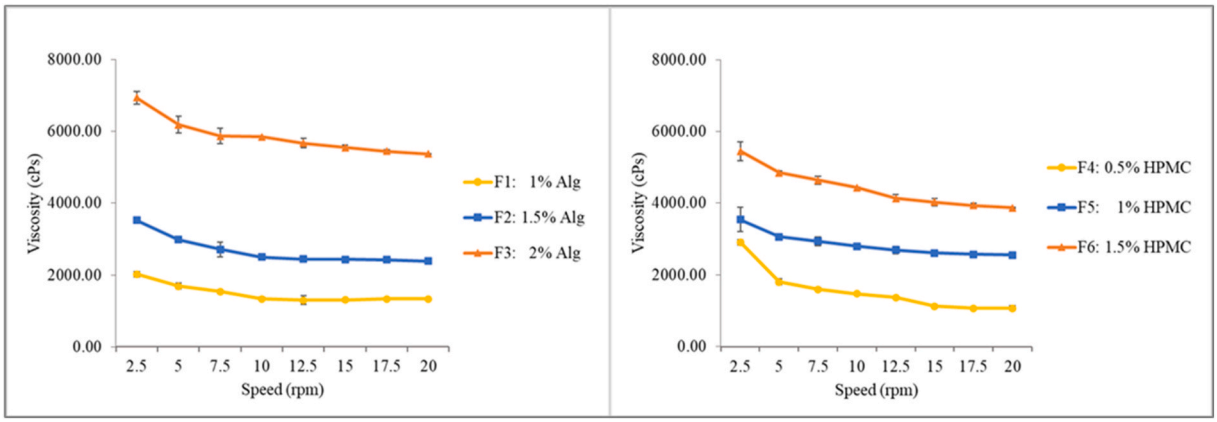

Fig. 6. Viscosity patterns of raft-forming liquid formulations. Data presented as mean ± S.D. (n = 3).

(1.00 g/mL) [38]. Upon contact with 0.1 N HCl solution, Ca^{2+} ions released by calcium carbonate in the liquid formulation interact with negatively charged sodium alginate, resulting in ionic crosslinks and formation of a hydrogel. At the same time, CO_2 generated after the reaction between sodium bicarbonate and acidic medium was entrapped within the gel network resulting in floatation (Fig. 7). All liquid formulations resulted in short floating lag times below 30s which is desirable for avoiding rapid clearance from the stomach [16,39]. The formed rafts also remained buoyant on the surface of 0.1 N HCl medium for over 8 h, which is advantageous for prolonging 6-gingerol release at the site of action in the stomach.

3.5.3. Raft strength

Raft strength in excess of 7.5 g is considered necessary for resisting breakdown by peristaltic movement along the gastrointestinal tract [40]. All raft forming liquid formulations resulted in structures exhibiting strength >7.5 g (Table 1), apart from F6, which featured high HPMC content of 1.5 % w/v. Raft strength was found to increase by around 50 % with increasing sodium alginate content in the formulation and in the absence of HPMC as a release rate controlling agent (Table 1, F1-3). Gelation of alginate results from crosslinking between Ca^{2+} cations and the alginate carboxylate groups [41]. Thus, increasing sodium alginate concentration is expected to increase the number of available Ca-binding sites, thereby raising the raft strength. When HPMC was included in the formulation as a release-controlling agent, raft strength tended to decrease by around 50 % with increasing HPMC concentration

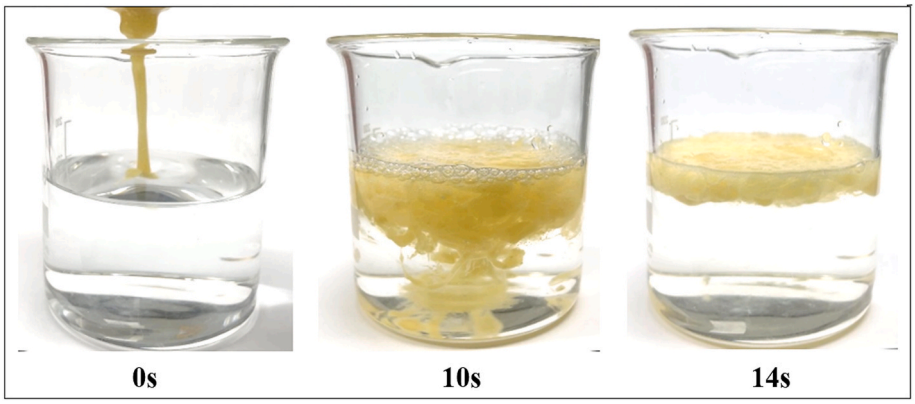

Fig. 7. Floatation behavior of raft-forming formulations containing GE-SD in 0.1 N HCl (pH 1.2). (F5; 1 % sodium alginate, 1 % HPMC K4M).

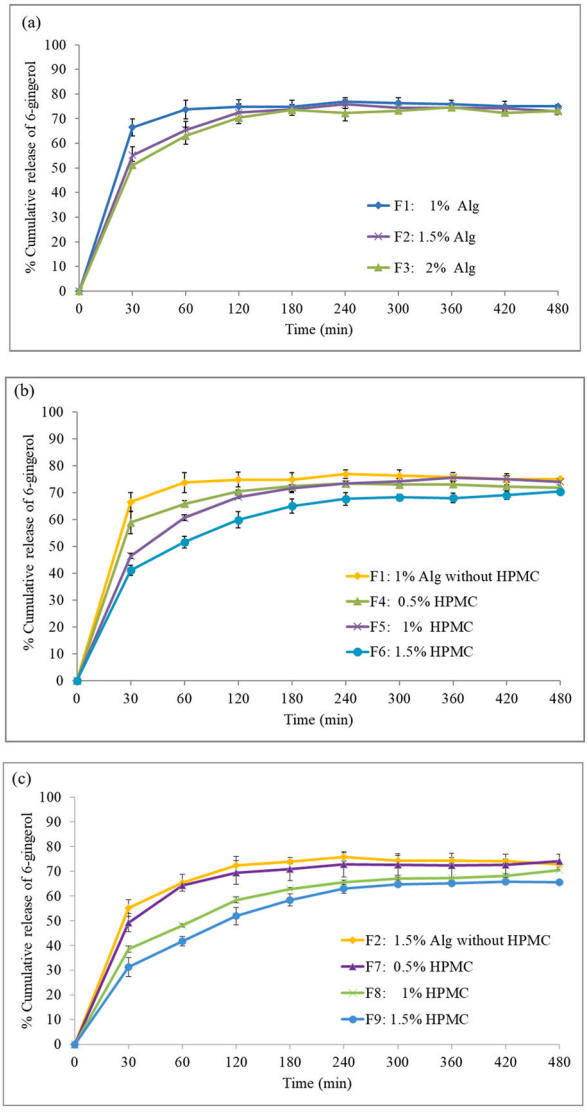

Fig. 8. Effect of a) sodium alginate content (1, 1.5 and 2 %w/v), b) 1 % sodium alginate and HPMC 0.5, 1.0 and 1.5 % w/v and c) 1.5 % sodium alginate and HPMC 0.5, 1.0 and 1.5 % w/v on the release profiles of 6-gingerol in 0.1 N HCl (pH 1.2) Data reported as mean ± SD (n = 3).

(Table 1, F4-6 and F7-9). This behavior may be due to competitive binding of HPMC with Ca^{2+} ions [16], or interference with gel continuity, leading to disruption of the hydrogel network. Similar behavior was reported by Nokhodchi and Tailor (2004) concerning the interaction between HPMC and aluminum cations during in-situ gelling of alginate formulations [42].

3.5.4. 6-Gingerol release from raft-forming formulations

The release behavior of 6-gingerol from the formulations in 0.1 HCl medium was generally similar, consisting of a gradual release phase over 3–4 h. Then, a plateau phase was observed for 8 h, with little further release occurring (Fig. 8). Delivery of around 70–75 % of the 6-gingerol content was achieved. Formulations prepared using 1 % alginate concentration in the absence of HPMC resulted in rapid, burst release of 70 % of the 6-gingerol content within 1 h (Fig. 8a). Increasing the sodium alginate concentration to 1.5 and 2 % w/v decreased burst release to 55 and 50 %, respectively, probably reflecting the restricted movement of 6-gingerol through a hydrogel exhibiting higher crosslink density.

HPMC has been used extensively to control the rate of drug release from oral dosage forms by establishing a viscous gel medium to impede drug diffusion [43]. Its inclusion in floating tablets of pregabalin, for example, resulted in sustained release for 24 h in vitro [44]. The combination of 1 % w/v sodium alginate with 1.5 % w/v HPMC K4M (Fig. 8b, F1, F4-6) could help to prevent the burst release of 6-gingerol near 40 % in 30 min followed by a slow and continuous release up to 8 h. The combination of high concentrations of sodium alginate (1.5 %) and HPMC (1.5 %) resulted in a further decrement of burst release to 30 % (Fig. 8c), reflecting the high viscosity of the liquid formulation (9347 cPs, Table 1). These outcomes restricted the practical characteristics and pourability of liquid solutions, which would result in patient compliance.

Based on the release profile, viscosity, and raft strength, formulation F5, containing 1 % w/v sodium alginate as gelling polymer and 1 % w/v HPMC K4M as retard release polymer, was selected for biological assay.

3.6. Biological assay of raft-forming formulations incorporating GE-SD

3.6.1. Cytotoxicity

Macrophage cells play a vital role in the host immune response. In this work, we used RAW 264.7 macrophages to test the anti-inflammatory activity of raft-forming liquid formulations and employed L929 fibroblasts to test their wound healing potential. In lead up work, the cytotoxicity of 6-gingerol, ginger extract (GE), GE-SD, blank and GE-SD-loaded raft forming formulation towards RAW 264.7 and L929 cells was examined by the MTT assay after 24 h exposure to test samples containing increasing concentrations of 6-gingerol. The viability of RAW 264.7 macrophages was more than 90 % post treatment with all test samples and at all tested concentrations, indicating the absence of notable cytotoxicity in the range 1.25–10 μg/mL.

All test samples resulted in increasing cytotoxicity towards L929 cells in a concentration (dose) dependent manner (Fig. 9). GE and GE-SD-loaded raft-forming formulation resulted in the lowest cell viability (77 and 75 % respectively) at a concentration of 10 μg/mL 6-Gingerol resulted in 77 % cell viability at a concentration of 10 μg/mL compared with ginger extract (84 % cell viability), suggesting a small influence of other bioactive compounds present in ginger extract. Apart from 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol,

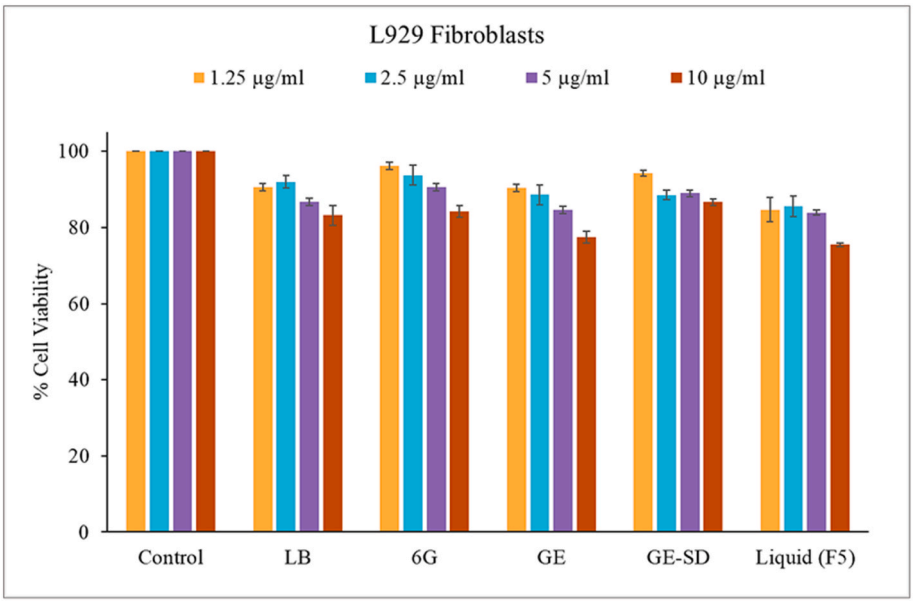

Fig. 9. Cell viability of L929 fibroblasts after 24h exposure to control (culture medium), blank raft forming liquid formulation (LB), 6-gingerol (6G), ginger extract (GE), GE-solid dispersion (GE-SD), and GE-SD-loaded raft forming liquid formulation (F5). Results are expressed as a percentage of the control. Data show mean ± SD of triplicate determinations.

paradol, zingerone, zingiberene, and phellandrene are abundant in ginger [45]. Accordingly, 5 μg/mL was selected as a suitable concentration for wound healing studies due to cell viability remained above 80 %.

3.6.2. Anti-inflammatory activity

Conventional anti-inflammatory drugs particularly NSAIDs, including aspirin, ibuprofen, and naproxen are known to increase the risk of developing peptic ulcers [46]. The bioactive compound 6-gingerol present in ginger has been repoted to inhibit the production of inflammatory cytokines, nitric oxide (NO) and TNF-α, as well as to reduce the expression of proteins involved in NF-κB signaling pathway [10,11,47]. Moreover, ginger may be beneficial for ameliorating aspirin-induced gastric ulceration [48].

Accordingly, we tested the anti-inflammatory activity of GE-SD-loaded raft forming liquid formulations by exposing lipopolysaccharide (LPS)-induced RAW 264.7 cells to increasing concentrations of test samples, equivalent to 6-gingerol, for 24 h. The raft-forming liquid formulation showed strong anti-inflammatory potential on the basis of its IC_{50} value for NO inhibition of 5.13 μg/mL, which was remarkably lower than that of indomethacin (32.47 μg/mL) (Table 2). Ginger extract and GE-SD expressed great anti-inflammatory activity with IC_{50} values of 6.46 μg/mL and 6.03 μg/mL against RAW 264.7 cells. The low anti-inflammatory activity of 6-gingerol (50.16 μg/mL) compared with GE, draws attention to the possible role of other bioactive compounds present in ginger. For example, Ballester et al. recently reported the anti-inflammatory activity of 6-shogaol [49]. Taken together, our findings on anti-inflammatory behavior indicated that GE-SD-loaded raft-forming liquid formulations offered a novel therapeutic strategy for treating gastric ulceration.

3.6.3. Wound healing activity

Apart from anti-inflammatory activity, the healing rate of ulcers is a commonly used criterion for evaluating the anti-peptic ulcer activity of drug compounds [50,51]. In the late stage of inflammation, fibroblasts are involved in tissue remodeling via cell migration, adhesion and collagen synthesis [52,53]. We thus applied the scratched wound assay based on L929 cell monolayers to explore the wound healing potential of 6-gingerol, GE, GE-SD, raft-forming formulation containing GE-SD, and blank formulation. Wound closure was found to increase over time (Table 3). At 72 h post-exposure (Fig. 10), GE-SD displayed the highest percentage of wound closure (84 %) compared with the control (45 %), followed by GE (77 %) and 6-gingerol (67 %). GE-SD-loaded raft-forming liquid formulation (58 %) revealed a higher percentage of wound closure than blank raft-forming liquid formulation (30 %).

Although our results indicated the wound healing potential of 6-gingerol, the activity was lower than that of ginger extract, suggesting that multiple compounds present in ginger extract may be involved in targeting the various pathways involved in wound healing [51,54,55]. Our results support the findings of Khan et al. regarding the accelerated healing of burn wounds by ginger extract-loaded-hydrogel film [56].

The blank raft-forming formulation displayed lower activity than the control (culture media) suggesting that excipients in the liquid formulation would have an inhibitory effect on wound healing. However, the raft-forming liquid formulation containing ginger extract solid dispersion, resulted in a 30 % improvement in wound closure compared with the control, which renders it an interesting candidate for improving the healing rate of gastric ulcers.

3.6.4. Antiproliferative activity

Gastric cancer is a leading cause of death in upper-middle-income countries [57] with increased risk associated with gastric ulceration [58]. We investigated the anti-gastric cancer effect of 6-gingerol, GE, GE-SD, raft-forming formulation containing GE-SD and blank formulation by exposing samples of varying 6-gingerol concentrations to AGS human gastric cancer cells for 24h. The blank raft-forming formulation exhibited no anti-proliferative activity and 6-gingerol displayed low activity (IC_{50} value of 92 μg/mL). GE, GE-SD, and raft-forming liquid formulation containing GE-SD displayed similar higher activity with IC_{50} values around 17 μg/mL (Table 2). Our results support the study of Luo et al. who demonstrated that gingerol enhanced the cisplatin sensitivity of stomach cancer cells through inhibition of proliferation and invasion [59].

4. Conclusions

Gastro-retentive raft-forming systems incorporating solid dispersions of ginger extract and PVP K30 (GE-SD) were produced. The aqueous solubility of 6-gingerol present in the solid dispersions was enhanced due to its conversion to the amorphous form. Raft-forming liquid formulations containing GE-SD were prepared using sodium alginate and HPMC K4M, which floated in 0.1 N HCl medium within 30 s and gradually release of more than 70 % of the 6-gingerol content over 8 h with sufficient raft strength (>7.5 g). Anti-inflammatory activity of raft-forming formulation was demonstrated against RAW 264.7 macrophages with superior inhibition of NO production than indomethacin. Additionally, the formulation displayed good anti-proliferative activity towards AGS cells and was capable of wound healing in the scratch assay. These findings support the potential of GE-SD-loaded raft-forming liquids as gastro-retentive, controlled delivery devices for managing gastric ulceration.

Data availability statement

Data will be made available on request.

Table 2
Anti-inflammatory and cytotoxic activity of 6-gingerol, ginger extract, ginger extract solid dispersion and raft-forming liquid formulations.

Test sample	NO inhibition IC_{50} (μg/mL)	Cytotoxicity against AGS cells IC_{50} (μg/mL)
6-Gingerol	50.16 ± 0.82	91.97 ± 1.48
Ginger extract (GE)	6.46 ± 0.09 [a,b]	17.23 ± 0.48[c]
GE solid dispersion (GE-SD)	6.03 ± 0.15[a]	16.91 ± 0.25[c]
Raft-forming formulation (F5)	5.13 ± 0.07[a]	17.45 ± 0.29[c]
Blank raft-forming formulation	N.D.	N.D.
Indomethacin	32.47 ± 1.78	–

N.D. means not determined. Data represents mean ± S.D. of triplicate determinations (n = 3).
[a] p values < 0.05; statistically significant difference compared to NO inhibition of indomethacin.
[b] p values < 0.05; statistically significant difference compared to NO inhibition of 6-gingerol.
[c] p values < 0.05; statistically significant difference compared to cytotoxicity against AGS cells of 6-gingerol.

Table 3
Percentage wound closure in the scratch wound healing model based on L929 cell monolayers (5 μg/mL equivalent dose of 6-gingerol).

Test samples	% Wound closure (n = 3, mean ± S.D.)	
	48 h	72 h
Control: culture media	28.7 ± 0.4	44.7 ± 1.8
6-Gingerol	54.2 ± 1.0	67.2 ± 1.0[a]
Ginger extract (GE)	52.4 ± 2.9	76.6 ± 3.3[a]
Ginger extract solid dispersion (GE- SD)	67.5 ± 4.5	84.1 ± 3.6[a]
GE-SD loaded raft-forming liquid (F5)	35.3 ± 4.2	58.4 ± 1.3[a,b]
Blank raft-forming formulation	24.0 ± 0.6	30.1 ± 2.1

[a] p values < 0.05; statistically significant difference compared to % wound closure of control at 72 h.
[b] p values < 0.05; statistically significant difference compared to % wound closure of Blank raft-forming liquid at 72 h.

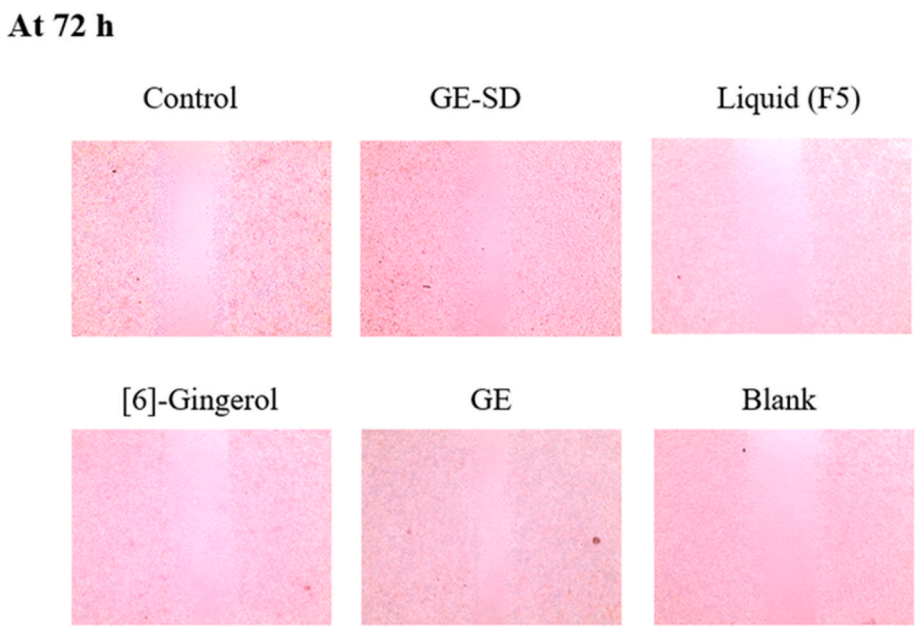

Fig. 10. Wound gap closure in scratch model based on L929 cell monolayers after exposure to test samples (5 μg/mL equivalent dose of 6-gingerol) and blank as control for 72 h.

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CRediT authorship contribution statement

Nattawipa Matchimabura: Writing – original draft, Methodology, Investigation, Data curation. **Rachanida Praparatana:** Writing – original draft, Methodology, Investigation, Data curation. **Ousanee Issarachot:** Writing – review & editing, Writing – original draft. **Kwunchit Oungbho:** Resources. **Ruedeekorn Wiwattanapatapee:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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