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Easy to Swallow "Instant" Jelly Formulations for Sustained Release Gliclazide Delivery

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ABSTRACT

It is a challenge to safely administer sustained release medicines to patients with dysphagia. Sustained release tablets must not be crushed and multiparticulates with large particle sizes cause grittiness reducing patient acceptability. The aim of this study was to develop "instant" jellies as delivery vehicles incorporating sustained release microparticles for patients with dysphagia. Dry powder mixtures containing gelling agents such as sodium alginate and calcium ions were hydrated in 20 mL of water and formed a jelly texture within 10 min. The "instant" jellies demonstrated comparable properites to commercial "read-to-eat" jellies in appearance, rheological/textural properties and *in vitro* swallowing performance in an artificial throat model. Gliclazide sustained release microparticles were produced by fluidized bed coating using Eudragit® NM 30 D and achieved 99% production yield and final coated particle size (D_{50}) of 198 ± 4.3 μm. Sustained gliclazide release was achieved over 15 h and the incorporation of the particles into the jellies significantly decreased the drug release rate. This novel drug delivery system offers a patient-centric solution to the long-standing challenge of administering sustained release medicines to patients with dysphagia and can potentially be used for paediatric patients.
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Introduction

The older population (aged 65 years or over) is the fastest growing subsection of the total population.[1] Older adults are more vulnerable to difficulties in swallowing (dysphagia) due to age-related diseases and the natural process of aging.[2] Dysphagia, together with other factors such as multi-morbidity, polypharmacy and cognitive impairments, brings significant challenge to medicine administration to older patients.[3] Solid oral dosage forms are often modified to facilitate swallowing by crushing tablets or opening capsules.[4,5] However, this can be hazardous due to changes in pharmacokinetics causing potential side effects or toxicity.[6]

Sustained release dosage forms can be beneficial for older patients in reducing dosing frequency and pill burden and thus improving medicine adherence compared to immediate release formulations.[7,8] However, sustained release dosage forms are often in the form of tablets that must not be crushed for administration due to potential toxicity.[6] Multiparticulate sustained release dosage forms, such as coated pellets or mini-tablets filled in capsules and to be sprinkled onto food, can be easier to swallow than tablets.[9] However, these 'sprinkles' were poorly accepted by older patients because of altered taste of food.[10] The large particle size of the multiparticulates (commonly in the range of 0.5—2.5 mm) can cause grittiness and reduce patient acceptability.[11,12] Small particles (<250 μm) would reduce grittiness but can creat problems in handling or require a delivery vehicle.

Jellies are considered to be highly palatable and acceptable to patients and have been used as medicine dosage forms; for example an oral immediate release jelly was marketed in Japan for Donepezil for the treatment of Alzeimer's disease to help patients with swallowing difficulties.[13] Conventional food jellies were hard and can stand freely on a plate; recently free-flowing granular jellies were developed as swallowing aids for children and adults to assist in tablet swallowing.[14,15] Both hard and granular jellies have demonstrated flow properties that can contribute to safe

swallowing by patients with dysphagia, indicating their suitability as medication aids for these patients.[16] Recent formulation developments also included commercial technologies which convert solid dosage forms such as tablets and pellets into semi-solid, gel-like dosage forms by adding water to aid swallowing.[17,18]

Gliclazide is a sulfonylurea for the treatment of Type 2 diabetes. Sustained release gliclazide (Diamicron SR) has been available for some years as tablets which must not be crushed for administration. No liquid or multiparticulate sustained release gliclazide formulation is currently available. Gliclazide is recommended to be used with caution in geriatric patients associated to the side effects of hypoglycaemia. Gliclazide 30 mg daily sustained release formulation is considered to be approximately equivalent in therapeutic effect to the standard immediate release formulation (80 mg, given in 2−3 divided doses), thereby affording a lower dose advantage, as well as the reduced frequency of dosing.[19] Sustained release gliclazide showed low incidence of hypoglycaemia even in the elderly (0.14%).[20] An "easy to swallow" non-solid sustained release gliclazide formulation would benefit patients with dysphagia who cannot swallow the sustained release tablet.

The aim of this study was to develop a powder composition that can be hydrated before administratin to form an "instant" jelly and to evaluate the feasibility of incorporating sustained release gliclazide microparticles into the jelly composition for administration to patients with dysphagia.

Materials and Methods

Materials

Sodium alginate (Protanol GP 1740), low acyl gellan gum (Kelcogel F) and guar gum were donated by FMC Biopolymer (UK), CP Kelco (UK) and B&V (Italy) respectively. Hydroxypropyl methylcellulose (HPMC, Methocel E5) and polyethylene oxide (Sentry Polyox WSR N10 LEO NF) was purchased from Colorcon, UK. Calcium chloride and citric acid were purchased from Fischer Scientific (UK), and dicalcium phosphate dihydrate was purchased from Sigma Aldrich, UK. Hartley's ready to eat jelly (containing gelling agents locust bean gum, xanthan gum and gellan gum) was manufactured by Hain Daniels Group (UK) and purchased from ASDA supermarket, UK. Ryukakusan jelly (agar based) was purchased from Ryukakusan, Japan.

Gliclazide was purchased from Sinobio Chemistry Co Ltd, China. Gliclazide sustained release 30 mg tablets (Diamicron) manufactured by Servier were ordered from AAH pharmaceuticals, UK. Microcrystalline cellulose microspheres (MCC, Cellets® 100) was obtained from Pharmatrans-Sanaq AG, Switzerland. Eudragit® NM 30 D (Poly(ethyl acrylate-*co*-methyl methacrylate) and Silicon dioxide (Aerosil 200 Pharma) were purchased from Evonik AG, Germany. Magnesium stearate was ordered from Acros Organics, Belgium. Talc was purchased from Imerys Talc, Italy.

Development of "Instant" Jellies

The term "instant" jelly was used in this study to differentiate from commercially available "ready-to-eat" jellies. It is a term usually used to describe the preparation of food jellies from dry powder mixtures involving heating and cooling. To ensure drug stability, the "instant" jellies prepared in this study eliminated the use of heating. Sodium alginate is known to form gels in the presence of calcium ions at room temperature,[21−23] which was utilised to form the "instant" jelly structure. Two types of jellies were developed mimicking the commercially available "ready-to-eat" jellies, a free-standing jelly (using Hartley's ready to eat jelly as reference comparator) and a granular, flowing jelly (similar to

Ryukakusan jelly, a swallowing aid for tablets). Free-standing jellies were developed by mixing sodium alginate (0.5 and 1% w/v) or sodium alginate mixed with another polymer (guar gum, polyethylene oxide, HPMC or low acyl gellan gum, 50:50) and dicalcium phosphate dihydrate (0.1−1% w/v) in 20 mL of deionised water using a spatula until no dry powder could be seen. Citric acid aqueous solution (1−10% w/v) was then added into the polymer suspension and stirred for 30 s. The resultant mixture was left to set at room temperature for 5 min.

Granular jellies were developed by adding sodium alginate (0.5−2% w/v) or sodium alginate mixed with another polymer (guar gum or low acyl gellan gum, 50:50) in 10 mL of deionised water and mixing using a spatula until no dry powder could be seen. A low concentration calcium chloride aqueous solution (0.1−0.3% w/v, 10 mL) was added to the polymer suspension and continuously mixed for 30 s.

Evaluation of "Instant" Jellies

Visual Inspection of Jelly Formation

The jelly mixtures resultant from Section Development of "Instant" Jellies were assessed using the following criteria:

- Appearance and texture: These were developed by visual inspection of the commercial jellies. For free-standing jelly (Hartley's jelly), the criteria included being easily cut with a spatula, being firm enough that the angles produced by cutting retained its shape and quivering or being wobbly when it was held on a spatula.[24] For granular jellies (Ryukakusan jelly), it contained large gel-like granules throughout the mixture and flowed when the container was inverted. Each developed jelly formulation was given a "yes" or "no" answer indicating whether or not the above criteria were met.
- Jelly formation time: This was the time for the primary structure of the mixture to be stabilised (no change in appearance was observed after this time). For free-standing jellies, this time was the additional time needed after the 5 min setting time.
- Volume of residual water: Water that was not incorporated into the structure of the mixture was poured out and the volume was measured.

Following the visual inspection one free-standing jelly composition (Jelly 1) and two granular jelly compositions (Jelly 2 and 3) were selected and subjected to further evaluation.

Rheological and Textural Characterisation of the Jellies

A TA 1500 EX controlled−stress rheometer (TA instruments) was used to obtain oscillatory viscoelastic data. Measurements were carried out at 25 °C using parallel plate geometry (40 mm diameter) for oscillatory stress sweep (torque 0.01−10,000 micro N.m at a frequency of 10 rad/s) and frequency sweep (0.1−100 rad/s) tests.

Textural characteristics were evaluated using a texture analyser (TA.XT. Plus, Stable Microsystems, United Kingdom). Two tests were conducted: gel strength test for free-standing jellies and back extrusion test for granular jellies. The gel strength was measured by depressing a standard 4 mm cylindrical (P/0.5) probe (Stable Microsystems, United Kingdom) into a spherical jelly sample cut into 4.5 cm diameter and 2 cm height. The back extrusion test was conducted using an extrusion disc (35 mm) positioned centrally over the container holding 100 mL of jelly sample and the disc penetrated the sample to a depth of 20 mm at a 0.5 mm/s test speed. The maximum force (g) used to reach this depth was the measurement of firmness. The maximum negative force, when the probe was drawn up at a speed of 0.5 mm/s, was the indication of cohesiveness. Surface adhesion was determined by lowering the

Table 1
Processing Parameters for Drug Loading and Polymer Coating.

Processing conditions	Drug layering	Sustained release coating
Nozzle size (mm)	0.5	0.5
Inlet air temperature (°C)	70−80	30−32
Product temperature (°C)	40−45	18−20
Atomization pressure (bar)	2.0	1.5
Fluidisation air velocity (m³/hr)	18 ± 0.5	18 ± 0.5
Spray rate (g/min)	1.5−2.0	1.1−2.0

disc at a speed of 0.5 mm/s towards the sample; the disc was then held on the surface of the sample for 30 s and pulled away at 2 mm/s. The force (g) for withdrawal of the disc from the sample indicated surface adhesion (adhesiveness). All measurements were carried out at room temperature in triplicates.

In Vitro Processing of the Jellies

An *in vitro* swallowing simulator − "Cambridge Throat" − was used to evaluated the *in vitro* processing behaviour of the "instant" jellies.[25−28] Detailed descriptions of the use of the *in vitro* model for testing jellies were reported by Patel et al. 2019.[16] In brief, the test sample (5 mL) was held within a 25 mm wide dialysis tube attached to the curved top of the model. Jelly 1 (free-standing jelly) was manually fragmented into 4 mm pieces before putting into the sample tube. By releasing a pin, a roller with an attached weight (190 g) moved the bolus through the tubing. The roller movement ended just before the area of the model representing the epiglottis. An iPhone camera (6S, Apple, USA) was used to capture images of the test sample flowing through the throat model at 30 frames per second. The *in vitro*-oral transit time (OTT) and bolus length (BL) of the test sample at area of the model representing the pharynx and larynx juncture were calculated from the images.[16] *In vitro*-OTT was calculated as the time taken by the roller to reach an angle of 120° as reported by Mowlavi et al., 2016.[27] ImageJ (Fiji) image processing software was used to calculate BL by capturing the first image in which the bolus front reached the pharynx and larynx juncture. BL was measured as the length of the bolus from front to tail.[16]

Evaluation of "Instant" Jellies as Delivery Vehicle for Sustained Release Gliclazide Microparticles

Determination of Gliclazide Solubilities

The solubility profile of gliclazide was determined in liquid vehicles at pH 1−13 at room temperature using serial dilutions of 0.1 M HCl (pH 1−7) and 1 M NaOH (pH 8−13) aqueous solutions. Excess quantity of gliclazide was added into the liquid vehicle and shaken for 72 h in a roller shaker (Roller Mixer SRT9, Stuart Equipment, UK). The pH value of the liquid was measured using a pH probe (WTW inoLab, WTW GmbH, Germany) before and immediately after gliclazide addition and after 24 h. The pH was adjusted to the desired level using 1 M HCl or 1 M NaOH solutions if necessary. Samples (2 mL) were taken and centrifuged (MiniSpin Plus, Eppendorf AG, Hamburg) at 14,500 rpm for 15 min and 1 mL or 0.1 mL aliquot of the supernatant was diluted using pH 7.4 (0.05 M) phosphate buffer. Gliclazide concentration was determined using UV-

spectrophotometer (T80; PG Instruments Ltd., UK) at wavelength 226 nm. Measurements were made in triplicate.

Preparation of Gliclazide Sustained Release Microparticles

Gliclazide was layered onto MCC cores (Cellets® 100, 100 g) using a Wurster fluidized bed coater (Mini-Glatt, Glatt GmbH, Germany). Gliclazide was milled for 2 h using a mini ball mill (160 g batch size with 60 × 10 mm, 19 × 20 mm and 24 × 10 mm mini balls at 450 rpm) (Copley Scientific, UK) and suspended (10% w/w) in an aquous vehicle containing HPMC (1% w/w) and talc (1.9% w/w). The drug layering process followed parameters shown in Table 1 until 50% drug loading weight gain was reached.

The gliclazide layered Cellets (100 g) were coated using an Eudragit® NM 30 D aqueous dispersion in a Wurster fluidized bed coater (Mini-Glatt, Glatt GmbH, Germany). The polymer dispersion was prepared by suspending talc in water using a magnetic stirrer, followed by homogenisation at 10,000 rpm for 20 min (L4RT, Silverson, UK). The talc suspension was added to the Eudragit® NM 30 D dispersion and stirred using a magnetic stirrer. The coating process was conducted using parameters shown in Table 1 until 16, 20, 25 and 60% coating levels (CL)/weight gains were reached. Magnesium stearate was added every 15 min (0.1 g for each addition) into the fluidized bed coater through an external feeding port following the method reported by Mohylyuk et al. 2020.[29] Silicon dioxide was added into the coating chamber before the coated microparticles were discharged to separate the free flowing particles from the particles stuck in the coating chamber. The collected particles were cured in an oven at 40 °C for 24 h. The percentage yield was calculated based on the coated particles that were free flowing without agglomeration.[29] Particle size measurements of the coated microparticles were made using a laser diffraction particle sizer (Sympatec HELOS/RODOS, Sympatec GmbH, Germany). The average particle size was described as D_{50} (by volume). Surface images of coated microparticles were taken using scanning electron microscopy (SEM) after the application of 25 nm gold coating (Phenom ProX, Lambda Photometrics, UK).

Drug loading capacity of the microparticles was measured by crushing 3.95 g coated microparticles (equivalent to 0.8 g theoretical gliclazide content). The powdered particles were added to 200 mL of acetonitrile and shaken for 1 h, followed by filtration. Ten millilitre of the filtrate was diluted to 200 mL using a mixture of acetonitrile:water (2:3 v/v). The gliclazide concentration in the resultant solution was analysed using high pressure liquid chromatography (HPLC, UK). A Synergi Fusion-RP column (size 250 × 4 mm, Phenomenex, UK) was used with a flow rate of 0.9 mL/min at ambient temperature. A 20 μL injection volume was used with a detection wavelength of 235 nm. Mobile phase was prepared using trimethylamine, trifluoroacetic acid, acetonitrile and water (0.1:0.1:45:55 v/v). The drug loading capacity and encapsulation efficiency were calculated as below:.

$$Loading\ capacity,\ \% = \frac{drug\ content\ in\ coated\ microparticles,\ mg}{weight\ of\ coated\ microparticles,\ mg} \times 100 \tag{1}$$

$$Encapsulation\ efficiency,\ \% = \frac{measured\ drug\ content\ in\ coated\ microparticles,\ mg}{theoretical\ drug\ content\ in\ coated\ microparticles,\ mg} \times 100 \tag{2}$$

Incorporating Sustained Release Gliclazide Microparticles into the Jellies

Microparticles were incorporated into the jellies (Jelly 1, 2 and 3) by mixing the required quantity (142 mg, equivalent to 30 mg gliclazide) of the particles with the polymers (sodium alginate or polymer mixture) and the jellies were subsequently prepared using the methods described in Section Development of "Instant" Jellies.

In Vitro *Dissolution Tests of Sustained Release Gliclazide Microparticles With and Without Incorporation into Jellies*

All dissolution tests were conducted in triplicate using USP II apparatus with a paddle speed of 100 or 200 rpm (DIS 6000, Copley Scientific, UK). The dissolution tests were performed in 900 mL of pH 7.4 phosphate buffer (0.05 M) for 14 h at 37 °C. Gliclazide release was determined using a UV-spectrophotometer (PG Instruments Ltd., UK) at wavelength 226 nm. Samples tested included the commercial gliclazide SR 30 mg tablet (Diamicron, Servier, UK), the coated sustained release gliclazide microparticles (equivalent to 30 mg gliclazide) at varying coating levels (CL16, CL20, CL25, and CL60) and coated gliclazide microparticles at CL20 and CL25 incorporated into the "instant" jellies (Jelly 1, 2 and 3). The dissolution of Jelly 1 incorporating the microparticles was tested in two ways - as whole jelly and fragmented to 4 mm pieces. The completion of drug release after each dissolution test was checked by extending the dissolution run time for additional 6 h at 200 rpm paddle speed and subsequently measuring the drug concentration by UV at 226 nm.

Dissolution testing was also conducted using placebo jellies (without the incorporation of the sustained release microparticles). The pH change of the dissolution media during dissolution testing of placebo jellies was measured using an ELIT PH2011 pH electrode (NICO2000 Ltd, UK.) and recorded using a 6-channel pH monitor (NICO2000 Ltd, UK).

Drug release in biorelevant media was conducted in pH 7.4 phosphate buffer containing FeSSIF powder (56 g FeSSIFF powder, Biorelevant.com Ltd, UK, per 5 L of buffer solution). Samples from dissolution vessels were withdrawn, without media replacement, using an auto-sampler (Vankel 8000, LabX, Canada) and the drug concentration was determined using HPLC as described in Section Preparation of Gliclazide Sustained Release Microparticles.

Data Analysis

The similarity factor (f_2) between different dissolution profiles was calculated using Equation (3).[30]

$$f_2 = 50 \times log\left(\left[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right) \quad (3)$$

where n corresponds to the number of time points and R_t corresponds to drug release of the reference profile at time t, and T_t corresponds to drug release of the test product at time t. The closeness of the dissolution profile was indicated when f_2 was between 50 and 100.

Prism Graphpad (version 7.0) was used to assess normality of dissolution profiles using the Shapiro-Wilk test; normal distribution was rejected ($p < 0.05$). The Mann-Whitney U test was applied to compare significant differences between dissolution profiles and significance differences were accepted when $p \leq 0.05$. The Shapiro-Wilk test was used to assess normality of the texture analysis data of jellies and normal distribution was accepted. The unpaired T-test was applied to compare significant differences between texture profiles of jellies with and without microparticles.

Results

Development and Evaluation of "Instant" Jellies

Visual Inspection of Jelly Formation

Table 2 shows the visual inspection results of free-standing jelly formation using sodium alginate, dicalcium phosphate dihydrate and citric acid. Generally, increasing the concentrations of the polymer, the calcium salt or citric acid increased jelly formation time. The composition of sodium alginate (0.5% w/v), dicalcium phosphate dihydrate (0.4% w/v) and citric acid (2% w/v) met the appearance and texture criteria in comparison to Hartley's ready-to-eat jelly and showed relatively low volume of residue water (6 mL); however the jelly formation time (11 min) was longer than the requirement (less than 10 min) in the criteria. Mixing sodium alginate in this composition with guar gum (50:50, w/w) reduced jelly formation time to 6 min and the volume of residue water to 3 mL and this was selected as Jelly 1. Preliminary trials showed that mixing sodium alginate solution with low concentration calcium chloride solution resulted in jelly structure similar to the granular Ryukakusan's jelly (data not shown). Table 3 shows visual inspection results of granular jelly formation at different sodium alginate and calcium chloride concentrations. The composition of Jelly 2 (sodium alginate at 2% w/v and calcium chloride at 0.3% w/v) showed the closest resemblance in appearance and texture in

Table 2
Visual Inspection of Jelly Formation for Free-Standing Jellies.

Sodium alginate (% w/v)	Dicalcium phosphate dihydrate (% w/v)	Citric acid (% w/v)	Second gelling agent[a]	Whether or not meeting appearance and texture criteria	Jelly formation time (min)	Residual water (mL)
0.5	0.5	1	–	✗	13	4
0.5	0.5	2	–	✓	12	7
0.5	0.5	5	–	✓	17	8
0.5	0.5	10	–	✗	18	8
0.5	0.1	2	–	✗	9	8
0.5	0.2	2	–	✗	10	8
0.5	0.4	2	–	✓	11	6
0.5	1	1	–	✗	11	5
1	0.5	1	–	✓	19	4
0.5[b]	0.4[b]	2[b]	Guar gum[b]	✓	6	3
0.5	0.4	2	Polyethylene oxide	✓	8	7
0.5	0.4	2	HPMC	✓	9	7
0.5	0.4	2	Low-acyl gellan gum	✓	6	9

[a] Second gelling agent:sodium alginate (w:w) at 50:50.
[b] Composition of Jelly 1.

Table 3
Visual Inspection of Jelly Formation for Granular Jellies.

Sodium alginate (% w/v)	Calcium chloride (% w/v)	Second gelling agent[a]	Whether or not meeting appearance and texture criteria	Jelly formation time (min)
0.5	0.1	–	✕	3
1	0.1	–	✕	4
2	0.1	–	✕	7
0.5	0.2	–	✕	3
1	0.2	–	✕	7
2	0.2	–	✕	10
0.5	0.3	–	✕	2
1	0.3	–	✕	2
2[b]	0.3[b]	–	✓	3
2	0.15	Guar gum	✕	5
0.5[c]	0.15[c]	Low-acyl gellan gum[c]	✓	3

[a] Second gelling agent:sodium alginate (w:w) at 50:50.
[b] Composition of Jelly 2.
[c] Composition of Jelly 3.

comparison to the Ryukakusan's jelly and short jelly formation time (3 min). Reducing the sodium alginate and calcium chloride concentration and mixing with low-acyl gellan gum obtained similar jelly appearance, texture and jelly formation time (3 min) (Jelly 3). There was no residual water in any of the granular jellies. Fig. 1 shows images of Jelly 1, 2 and 3, and the commercial reference comparators.

Rheological and Textural Characteristics of the Jellies

The representative oscillatory frequency sweeps are shown in Fig. 2 for Hartley's jelly, Ryukakusan's jelly and Jellies 1, 2 and 3. All of the jellies showed the same characteristic features: G' dominance over G'' and a decline in complex viscosity η^* over the frequency range. A greater magnitude of G' was observed for Jelly 1 and Jelly 2 compared to their respective commercial reference products Hartley's jelly and Ryukakusan's jelly. Jelly 3 showed a similar magnitude of G' and G'' modulus compared to Ryukakusan's jelly.

Similar gel strength was demonstrated by Jelly 1 (11.1 g $\pm$ 0.4 g) in comparison to Hartley's jelly (13.36 g $\pm$ 1.47 g). The firmness, cohesiveness and adhesiveness of granular jellies in comparision to Ryukakusan's jelly are shown in Table 4. Jelly 2 showed much higher firmness but lower cohesiveness than Ryukakusan's jelly

and Jelly 3 demonstrated similar textural properties as the Ryukakusan's jelly.

In Vitro Swallowing Process of the Jellies

Fig. 3 shows the images of the jellies in the *in vitro* swallowing simulator at the time when the sample reached the pharynx and larynx juncture. The *in vitro*-OTT and BL of the "instant" jellies were comparable to those of the commercial jellies (Hartley's and Ryukakusan jellies) reported previously.[16]

Evaluation of "Instant" Jellies as Delivery Vehicles for Sustained Release Microparticles

Gliclazide Solubility

Gliclazide showed pH-dependent aqueous solubility with low solubility at pH values below 6, slowly increasing solubility at pH values 6–8 and rapid increasing above pH 8 (Fig. 4).

Preparation of Gliclazide Sustained-Release Microparticles

Successful drug layering and polymer coating processes were achieved for the gliclazide microparticles. The yields for polymer coatings at CL16, CL20, CL25 and CL 60 were 98.4, 99.3, 99.0 and 98.7% respectively. A representative SEM image of coated microparticles at CL25 is shown in Fig. 5. The D_{50} values of Cellets® 100
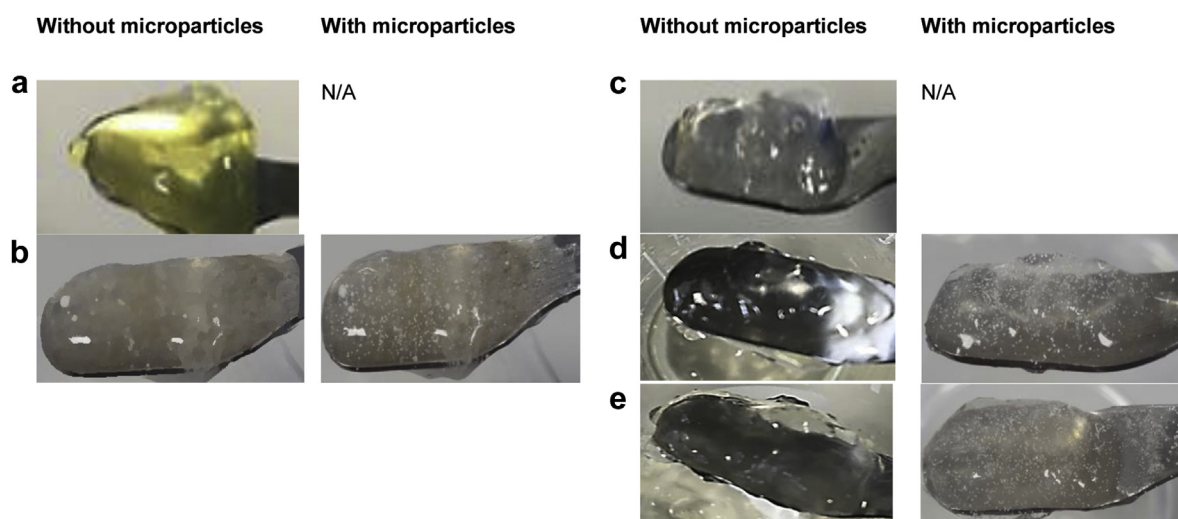
Fig. 1. Images of a) Hartley's jelly, b) Jelly 1, c) Ryukakusan jelly, d) Jelly 2 and e) Jelly 3 with and without coated microparticles.
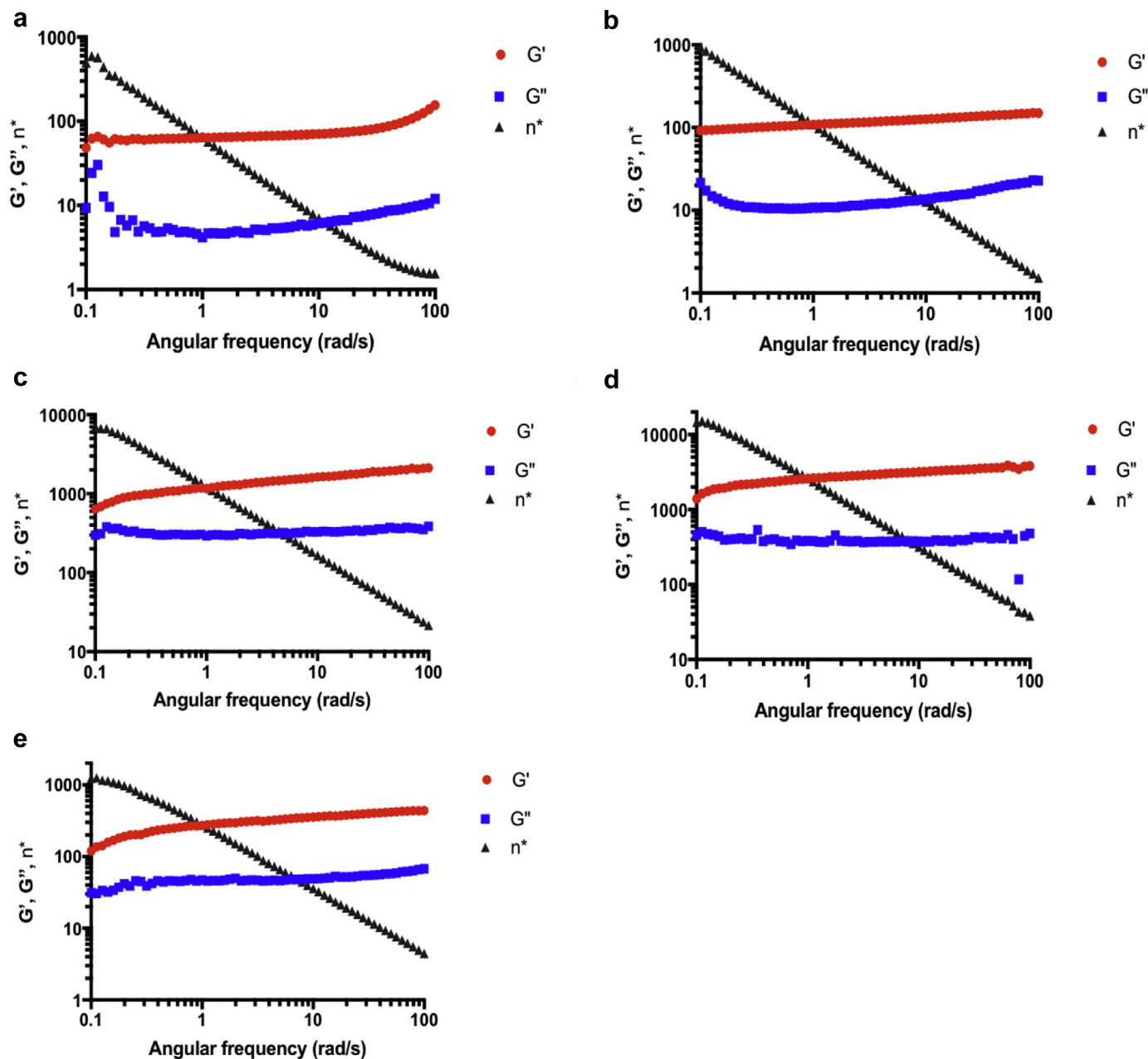
Fig. 2. Frequency dependence of G′ and G″ for a) Hartley's, b) Ryukakusan jelly c) Jelly 1, d) Jelly 2 and e) Jelly 3.

and the coated microparticles at CL16, CL20, CL25 and CL60 were 160 ± 2.1, 173 ± 3.6, 185 ± 2.4, 198 ± 4.3 and 208 ± 6.7 μm. The drug loading capacity and encoproation efficiency of the microparticles at CL25 were 20.2% and 95.8% respectively.

Table 4
Textural Properties (Firmness, Cohesiveness and Adhesiveness) of Granular Jellies.

Product	Firmness (g)	Cohesiveness (g)	Adhesiveness (g)
Ryukakusan's jelly	32.7 ± 0.2	14.9 ± 0.03	8.2 ± 0.3
Jelly 2	238.7 ± 22.9	5.3 ± 0.09	13.3 ± 1.29
Jelly 3	28.9 ± 1.4	14.2 ± 2.7	6.7 ± 0.1
Jelly 2 with microparticles	206.1 ± 10.7	4.4 ± 0.8	11.4 ± 1.6
Jelly 3 with microparticles	22.4 ± 4.3	10.3 ± 0.9	6.1 ± 0.4

Incorporating Sustained Release Gliclazide Microparticles into the Jellies

There was no change in colour or visual appearance of jellies once the microparticles were added to the jellies (Fig. 1) and the jelly formation times remained the same. No gliclazide was detected in the residue water (3 mL) of Jelly 1. The gel strength of Jelly 1 did not change significantly after incorporation of the microparticles (10.7 g $\pm$ 0.2 g). Similarly, no significant change was noted for the texture properties of Jellies 2 and 3 after incorporation of the microparticles (Table 3).

In Vitro *Dissolution Tests of Sustained Release Gliclazide Microparticles With and Without Incorporation into Jellies*

Fig. 6 shows gliclazide release profiles from coated microparticles at coating levels CL16, CL20, CL25 and CL60 in comparison to
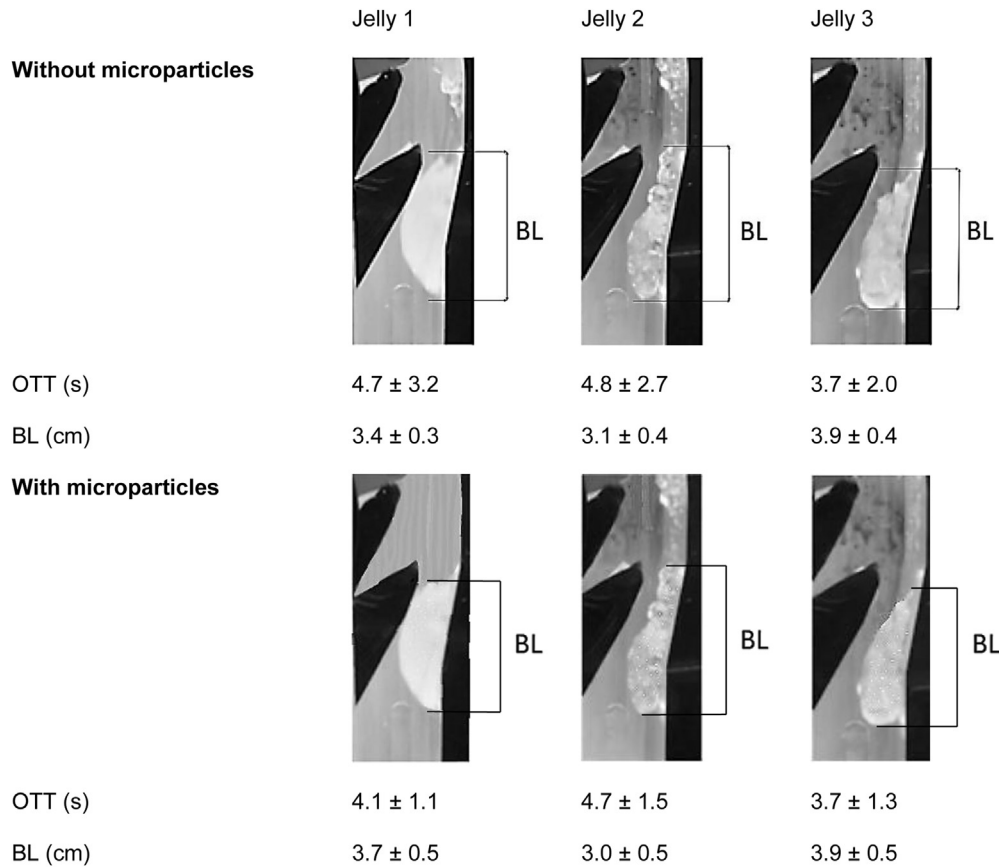
	Jelly 1	Jelly 2	Jelly 3
Without microparticles			
OTT (s)	4.7 ± 3.2	4.8 ± 2.7	3.7 ± 2.0
BL (cm)	3.4 ± 0.3	3.1 ± 0.4	3.9 ± 0.4
With microparticles			
OTT (s)	4.1 ± 1.1	4.7 ± 1.5	3.7 ± 1.3
BL (cm)	3.7 ± 0.5	3.0 ± 0.5	3.9 ± 0.5

Fig. 3. Images of Jellies 1, 2 and 3 in the *in vitro* swallowing simulator at the juncture of the pharynx and larynx, with the oral transit time (OTT) and bolus length (BL).

Diamicron SR tablets in pH 7.4 phosphate buffer. Increasing the coating level decreased drug release rate from the microparticles and at CL25 the particles showed a f_2 value of 54.2 (p = 0.6653) in comparison to Diamicron, demonstrating equivalent drug release according to the Food and Drug Administration (FDA) guideline.[28] Drug release was complete at the end of the dissolution test from Diamicron and microparticles with coating levels of CL16, CL20 and CL25, but not from microparticles with CL60.
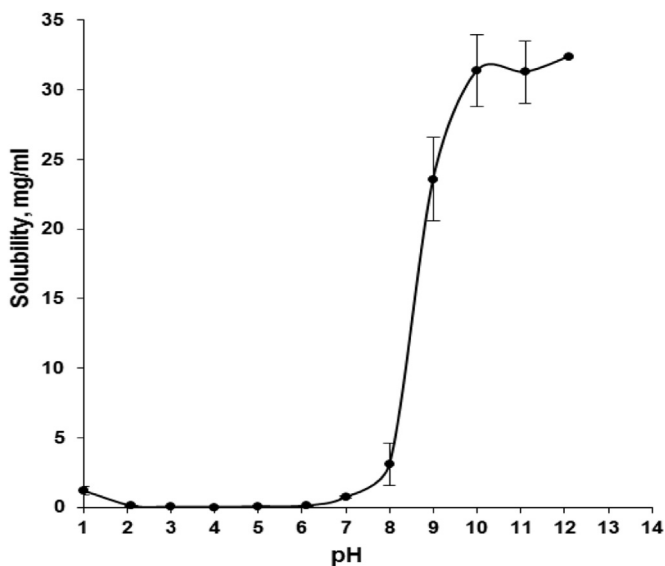

Fig. 4. Gliclazide pH-dependent solubility profile.
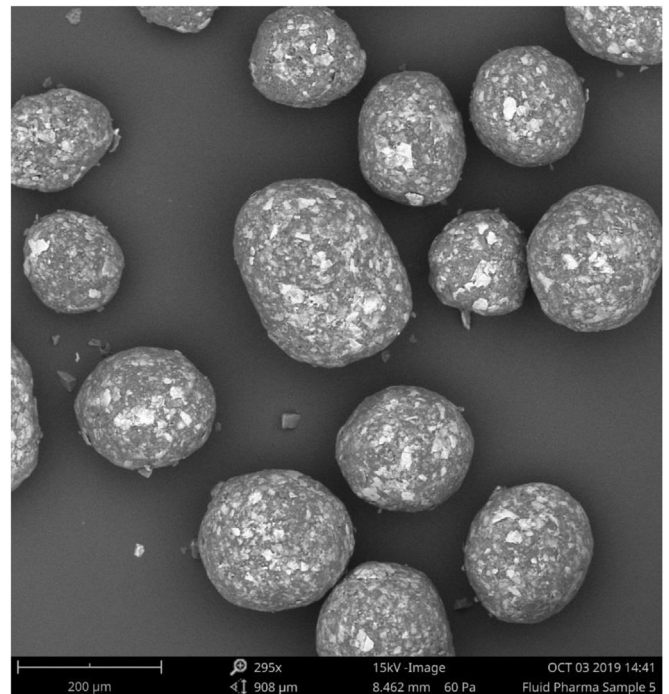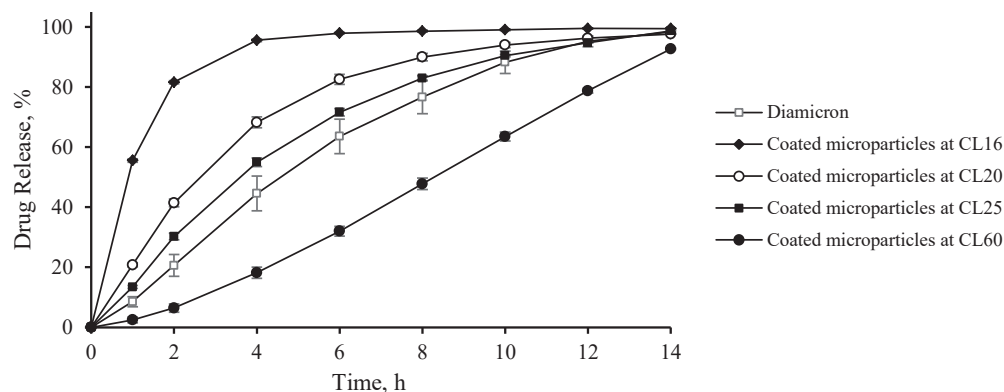

Fig. 5. SEM image of coated gliclazide sustained release microparticles at 25% coating level.
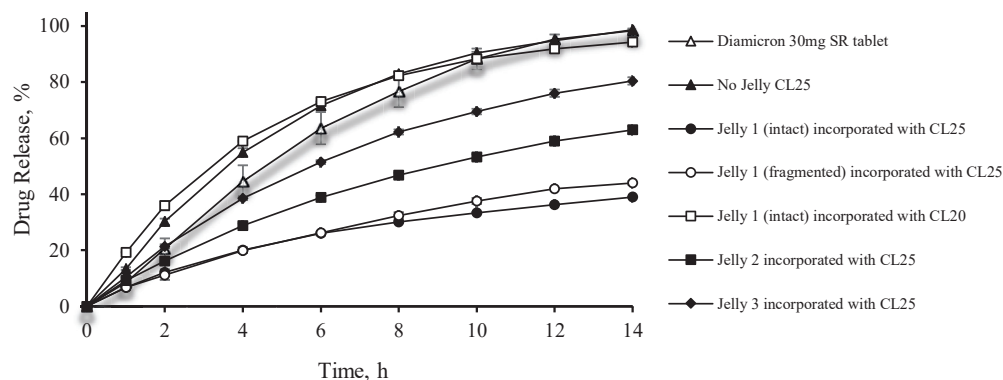
Fig. 6. Gliclazide release from coated microparticles at coating levels CL16, CL20, CL25 and CL60 and the commercial Diamicron SR tablets in phosphate buffer pH 7.4 (n = 3, mean ± SD). CL: coating level.

Fig. 7 shows the effect of incorporation of the microparticles into the "instant" jellies on drug release from the coated microparticles. At coating level CL25, all three jellies reduced the drug release rate with Jelly 1 showing the biggest reduction and significant differences were noted between microparticles alone and after incorporation into Jelly 1 ($p \leq 0.0018$) and Jelly 2 ($p = 0.0425$). No significant difference was shown in drug release from microparticles alone and microparticles incorporated into Jelly 3 ($p = 0.0623$). Dissolution from microparticles in Jelly 1 as a whole jelly piece or fragmented into small pieces resulted in equivalent drug release profiles ($f_2 = 84.2$, $p = 0.2523$). Drug release was not complete at the end of the dissolution test from microparticles incorporated in Jelly 1, 2 and 3 at CL25. When incorporating microparticles at CL20 into Jelly 1, drug release profile was equivalent to Diamicron SR tablets ($f_2 = 59.7$, $p = 0.930$). Monitoring the pH changes during the dissolution of placebo jellies showed that the pH of the dissolution media decreased considerably for Jelly 1 from pH 7.4 to 7.0 whereas no changes in pH were observed for jellies 2 and 3 (Fig. 8). Increasing paddle speed from 100 to 200 rpm did not change the drug release rate from microparticle alone. When the microparticles were incorporated into all three jellies, drug release rates were slightly higher at 200 rpm paddle speed than that at 100 rpm; however, the differences were not significant ($p > 0.05$, Fig. 9). Drug release from coated microparticles alone and in combination with jellies were not significantly influenced by the use of biorelevant dissolution media with all release profiles in FeSSIF comparable to that in phosphate buffer and comparable to Diamicron SR tablets ($p > 0.05$, Fig. 10). However, drug release from microparticles incorporated in Jelly 3 was faster in biorelevant media than in phosphate buffer although the difference was not significant.

Discussion

To ensure adherence and therapeutic outcomes of a pharmaceutical product it is critical to consider patient acceptability.[31] Guidance issued by the European Medicines Agency (EMA) highlighted that acceptability must be an integral part of pharmaceutical formulation development, especially for products that are used in paediatric and geriatric populations.[32,33] Commonly used as food and desert and familiar to patients, gels and jellies are used as medication delivery vechicles to improve patient acceptability. Jellies are used in Japan as part of the dysphagia diet, as swallowing aids for tablets and capsules and as marketed medication dosage forms e.g. Donepezil jellies for the treatment of Alzeimer's disease.[13,14,34,35] Kluk & Sznitowska (2014) applied oral gels as media for administration of minitablets and pellets to paediatric patients.[12]

Jellies that are manufactured in a hydrated form (ready-to-eat) as pharmaceutical products contain a large proportion of water and are thus likely to cause stability issues for certain drugs. They also require antimicrobial preservatives. The concept of "instant" jellies that are in solid (powder) forms and could be hydrated before administration could mitigate these issues as medicine delivery vechicles. The common method to prepare a gel/jelly is by heating (typically to 70 °C) and cooling, resulting in a conformation change of the gelling agent from coil to helix forming a three-dimensional structure.[36] Heating causes instability of medicines and materials that gel at room temperature would be ideal to prepare the "instant" jellies without the need of increasing temperature. Sodium alginate is known to form gels by calcium induced cross-linking at room temperature.[21−23] In this study, calcium chloride

Fig. 7. Gliclazide release from coated microparticles and in combination with Jellies 1, 2 and 3 in pH 7.4 phosphate buffer (n = 3, mean ± SD). CL: coating level.
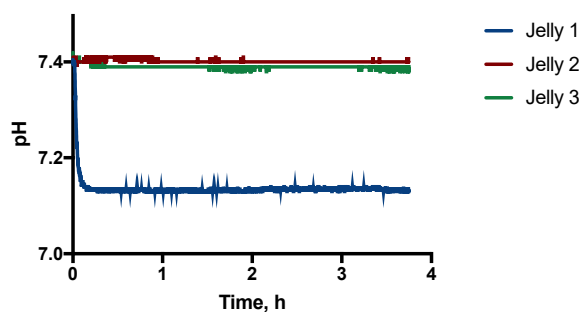
Fig. 8. The effect of placebo jelly dissolution on the pH level of pH 7.4 phosphate buffer.

solutions at low concentrations induced the formation of a free-flowing granular jelly structure when they were mixed with sodium alginate solution. This was the result of the unique gelation mechanism of sodium alginate when water soluble calcium salts were used. Water soluble salts such as calcium chloride interacted rapidly with sodium alginate, resulting in an inhomogeneous distribution of calcium ions. This led to the formation of a sharp gelling zone at the polymer-calcium interface and a decreased gel formation towards the center of the gel.[37] The granular structure of the free-flowing jellies was caused by this inhomogeneous gelation. As a result, it was problematic when calcium chloride solutions were used to form the homogeneous, hard and free-standing jellies (data not shown).

Dicalcium phosphate dihydrate is less soluble in cold water than calcium chloride. When it was mixed with sodium aliginate as powder and the mixture was hydrated by a citric acid solution, calcium ions were slowly released by ion-exchange with citric acid.[37,38] This facilitated in situ gelation of sodium alginate forming the homogeneous free-standing jelly texture. Calcium induced sodium alginate gels retained water through hydrogen bonds, and during gel contraction, water was released from the gel structure known as syneresis.[38] Addition of guar gum was able to reduce the volume of residual water, through controlling water migration during gel contraction because of guar gum's water binding properties.[39,40]

Jellies 1 and 2 showed a greater magnitude of G′ and G" on the frequency spectra of the rheology test, indicating a stronger gel-network compared to their respective commercial reference products. Jelly 2 also showed higher firmness in comparison to Ryuakusan's jelly. Jelly 3 showed comparable rheological and textural properties to Ryukakusan's jelly, likely because of its low sodium alginate concentration and the loosening of the gel

structure by low acyl gellan gum. All three jellies demonstrated in vitro swallowing behaviours in the artificial throat model similar to previously reported that of the commercial jellies and thickened fluids used in dysphagia patients.[16] These behaviours included slow in vitro oral transit and cohesive bolus movement, which were believed to be important for safe-swallowing by dysphagia patients, indicating their potential safe use by these patients.[16]

As previously reported, the fluid bed coating process successfully produced sustained release microparticles of sizes <200 μm with very low particle aggregation.[29] The small particle size is beneficial in improving patient acceptability. Oral grittiness (rough mouthfeel) increased with increasing particle size and particles below 263 μm showed low perception of grittiness when incorporated in HPMC gels.[11] It is the intention of future studies to assess acceptability of the delivery system in target patient groups.

In the current study, the jellies not only served as a deliver vehicle for the coated particles, they also reduced the gliclazide release rate from the dosage form. The jelly matrices provided an additional barrier for drug release which possibly occurred through a combination of drug diffusion through the jelly network and jelly erosion.[41] In phosphate buffer, ion-exchange occurred between sodium in the dissolution media and calcium in the jelly matrix, a process that loosened the structure of the gel network (un-cross-linking) and over time facilitated the erosion of the jellies.[41,42] Jelly 1 showed the strongest effect on drug release rate reduction in all three jellies, likely because of its highest calcium content forming strongest gel network structure and therefore slowest dissolution of the jelly matrix. It was previously reported that an increase in calcium concentration resulted in slower drug release from calcium alginate beads due to an enhanced structural network, reduced water intake and subsequently greater drug entrapment.[41-43] In addition, the dissolution of Jelly 1 decreased the pH level of the dissolution media which in turn decreases gliclazide solubility because of its pH-dependency. The reduction in drug release rate by the jellies can be utilised to reduce the coating level required to achieve the target drug release profile, as shown by the reduction of coating level from 25% to 20% by Jelly 1 to obtain similar drug release to Diamicorn SR tablets. It should be noted that these findings were based on dissolution tests in large media volume; further investigation is needed to understand the effect of jellies on drug release in more realistic dissolution conditions.

Drug release from the microparticle-in-jelly system showed relative robustness. Fragmentation of Jelly 1 to small pieces did not show an effect on drug release, indicating that drug release will not be influenced by chewing of the jelly. Furture study needs to demonstrate whether chewing can affect the structural integrity of the microparticles. Similarly, no significant effect was seen on drug
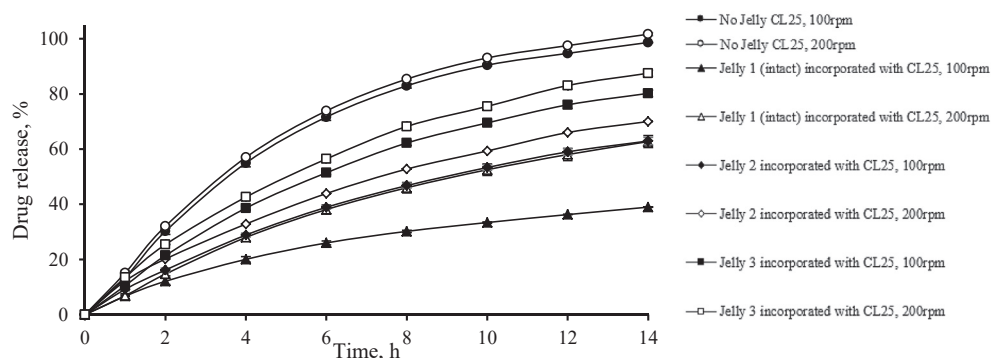

Fig. 9. Gliclazide release from coated microparticles at 25% coating level alone and in combination with Jellies 1, 2 and 3 in pH 7.4 phosphate buffer (n = 3, mean ± SD) at 100 and 200 rpm paddle speeds. CL: coating level.
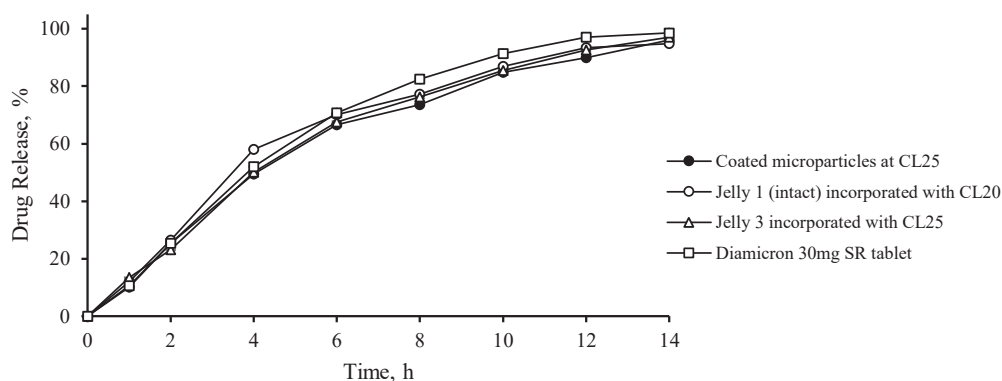
Fig. 10. Gliclazide release from coated microparticles and in combination with Jellies 1 and 3 in pH 7.4 FeSSIF phosphate buffer (n = 3, mean ± SD). CL: coating level.

release when higher paddle speed was used during dissolution, indicating low risk of changes in drug release due to variations in gastrointestinal movements. Drug release was not significantly affected by adding biorelevant (FeSSIF) powder in the dissolution media. It needs to be noted that the FeSSIF buffer was used at pH 7.4 to be comparable to that of the phosphate buffer. The results therefore only reflected the effect of the bile salts, lecithin and surfactants content in the FeSSIF powder on drug release. It is expected that the pH of the intestinal content would be lower in the fed state (pH 5.4–6.5) which could have an effect on drug release.[44]

Solid dosage forms that can be converted into semi-solids before administration offer both good stability and ease in swallowing and are commercially attractive for paediatric patients and patients with dysphagia. Recently a patented technology, the Parvulet™ Technology, was commercialised by Adare Pharmaceuticals, which is in the format of a solid dosage form such as tablet and can be converted into a gel-like semi-solid by addition of water to aid patients' swallowing.[17] Losan Pharma's Vismon® coating technology applies pellet coating which swells and creates a viscous and soft pellet pulp in the mouth to be swallowed.[18] The "instant" jellies incorporating coated microparticles reported in this study showed promises for sustained release drug delivery for patients who cannot swallow tablets. The rheological, textural and *in vitro* swallowing characteristics of the jellies demonstrated potential of easy and safe swallowing for patients with dysphagia. The synergetic effect of the jellies in controlling drug release provides benefits in reducing the coating level required to achieve desired drug release profiles. The findings are also useful for the development of sustained release dosage forms for paediatric patients.

Conclusions

A novel drug delivery platform was developed using calcium cross-linked alginate "instant" jellies as a vehicle for administration of sustained release microparticles. Two types of jellies were successfully produced that contained a dry powder mixture of sodium alginate, other gelling agents and calcium salts and can be hydrated rapidly before administration to form either a hard, free-standing jelly or a granular, flowing jelly. Both types of jellies demonstrated comparable properties to commercial "ready-to-eat" jellies with regards to appearance, rheological and textural properties. The "instant" jellies also showed 'safe' swallowing features with *in vitro* oral transit time and cohesive bolus flow similar to previously reported values for commercial jellies and commonly used thickened fluids for dysphagia patients. Sustained release gliclazide microparticles were successfully manufactured using fluidised bed

coating, with final particle size $D_{50} < 200 \mu m$, 99% production yield and adjustable drug release profiles that can be attuned to be comparable to the marketed gliclazide sustain release tablet. Incorporating the microparticles into the jellies did not significantly change the jelly appearance or structure. The jellies further reduced drug release rate from the coated particles depending on the jelly composition, offering a possibility of developing sustained release formulations incorporating microparticles in jellies with attunable drug release. The novel drug delivery system offers a promising solution for the long-standing challenge of administering sustained release medicines to paediatric patients and patients with dysphagia.

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