Available online on 15.03.2018 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

THE EFFECT OF A NOVEL HYDROPHILIC BIOPOLYMER DERIVED FROM *IPOMOEA BATATAS* TUBER AS A GRANULATING AGENT IN PARACETAMOL TABLET FORMULATION

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ABSTRACT

A novel hydrophilic biopolymer, *I-polygel* (IP) derived from the tubers of *Ipomoea batatas* was evaluated as a granulating agent (GA) at 2.50-5.50 % w/w in paracetamol tablets. The compatibility of IP with paracetamol was investigated using differential scanning calorimetry (DSC). The micromeritic properties of the granules prepared by wet granulation method were considered and later compressed into tablets with a 12.50 mm flat-faced punch fitted in a single punch tabletting machine. The organoleptic and mechanical properties, weight uniformity, disintegration time, dissolution profile, dissolution efficiency (DE) of the tablets were evaluated. Gelatin (GT) was employed as a standard GA. The DSC thermograms showed that paracetamol was compatible with IP. The flowability of the granules improved with increasing concentrations of up to 5.50 % w/w of the GAs with those of GT significantly better ($p<0.05$) than those of IP. Glossy, intact, odourless, round shaped tablets with range of tablet weight variations of 0.37 – 0.87 % were obtained for the respective batches, displaying improved mechanical and a corresponding decrease in friability properties as the concentrations of IP or GT increased, with GT contributing superior values at each concentration level ($p<0.05$). The tablets containing IP or GT disintegrated within 3.76 -7.62 and 10.89-20.92 min respectively. All the batches of tablets containing IP and that of 2.50 % w/w GT released up to 80.00 % of paracetamol within 30.00 min. Higher values of DE of 71.32-74.17 % was obtained within 2.50-4.00 % w/w of IP alone. Though tablets possessing acceptable mechanical properties were got from both IP and GT, but those with lower disintegration time (< 15.00 min) and higher DEs were attainable with IP mainly within the concentrations of 2.50-4.00 % w/w. This demonstrates that IP has better properties as a granulating agent than GT at the concentrations tested.

Keywords: Hydrophilic biopolymer, *I-polygel*, *Ipomoea batatas*, granulating agent, paracetamol, tablet.

Article Info: Received 18 Jan, 2018; Review Completed 3 March, 2018; Accepted 7 March, 2018; Available online 15 March, 2018

Cite this article as:

Ugoeze KC, Nwachukwu N, The effect of a novel hydrophilic biopolymer derived from *Ipomoea batatas* tuber as a granulating agent in paracetamol tablet formulation, Journal of Drug Delivery and Therapeutics. 2018; 8(2):112-117

DOI: http://dx.doi.org/10.22270/jddt.v8i2.1669

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INTRODUCTION

Tablets are solid dosage forms that contain an active pharmaceutical ingredient (API) and excipients in powder, crystalline or granular form with or without diluents which is manufactured either by moulding or compression process. They are extensively used due to their persistent benefits and acceptance[1]. Tablets are expected to deliver the API to the expected site of action in its active form in an amount that will be enough and at the correct rate to achieve the therapeutic expectations. The API content of the tablet needs to be stable in its physical and chemical state in order to ascertain its potency, safety over its shelf life. Its production is expected to be cost-effective and it should be acceptable to the patient[2]. The formula used in preparing a tablet contains several ingredients in

addition to the API. There are various types of excipients such as filler or diluent, binder, lubricant, glidant, disintegrant, anti-adherent, colouring agent, flavouring agent, etc[2]. The use of excipients occupy a very important place in the production of tablets and other pharmaceutical dosage forms since they aid in the processing, safety, stability and performance of any dosage form[3,4] . In addition, excipients are needed to make a good quality tablet at the required tablet press speed. They help in the flow, compressibility and the ability of the tablet to eject from the tablet press without falling apart. They equally augment the hardness, disintegration, appearance, colour, taste and the overall performance of the tablets[5]. Tablets could be prepared by mixing the dry powdered ingredients together and compressing into tablets. This procedure is described as the direct compression (DC) method. The powders applicable for this method are expected to possess some qualities such as being able to blend together with the other ingredients and stay mixed. The blend is expected to flow, be compressible and eject from the tablet press without defects on the tablet and posses sufficient hardness and low friability to withstand the stress of handling and is expected to dissolve quickly to release its API content. When an excipient, especially filler does not possess the above qualities, it will not yield a good tablet since the tablet obtained through its use may be too friable. Such particles need to be homogenized and held firmly by using a pharmaceutical adhesive called a binder or granulating agent. When such excipient comes in contact with water or any suitable solvent, it forms a sticky solution referred to as a binding or granulating agent which when sprinkled unto the blended powders causes their aggregation. Such aggregated powders remain in dry clumps after the evaporation of its moisture content and could be milled into the required particle size in order to improve the flow, compressibility, etc. This procedure of preparing granules towards the production of tablets is known as the wet granulation method. There are different powders with divergent features; some may only require a very small amount of binder and some may require large amounts of a binder. Some powders need a level of extreme blending while adding a granulating fluid while some may not. However, the blending or wet massing achieved by applying a granulating agent could be likened to kneading dough when preparing bread. The resultant wet blend once screened through appropriate sieve size and dried at appropriate temperatures and the dried mass screened through necessary sieves gives rise to what is described as granules. A granulation is, therefore, the formation of small agglomerates called granules. The wet granulation method is very common. It takes much time and involved many processes. It is not very suitable for use with APIs that are unstable with moisture or heat. However, the final objective is to make good quality granules with good flowability and compressibility that can result in acceptable tablet uniformity of weight, thickness, hardness, low friability, devoid of defects and able to offer good disintegration and dissolution[1,2,5].

In this work, a novel hydrophilic biopolymer derived from *Ipomoea batatas* tubers (*I-polygel*) is applied as a granulating agent in paracetamol tablet production. Paracetamol is the choice of API because of its poor compressibility[6]. The processing and excipient functionality, as well as the evaluation of its suspending properties on sulphamethoxazole suspension of the novel hydrophilic biopolymer (*I-polygel*), derived from *Ipomoea batatas* tubers, have been documented[7, 8].

MATERIALS AND METHODS

Materials

The following materials were used as procured and included: sodium hydroxide, hydrochloric acid, corn starch, acetone (BDH, England), sodium hypochlorite (3.5 % w/v) (Multipro, Nigeria), ethanol (96 %), *n*-hexane, silica gel (JHD, China), paracetamol (Cipla, India) and lactose (Loba Chemie, India).

Methods

Preparation of a novel hydrophilic biopolymer derived from *Ipomoea batatas* tubers *(I-polygel)* (IP)

The method developed by Ugoeze *et al*[7] in the production of a novel hydrophilic biopolymer from *Ipomoea batatas* tubers was adopted with modification. A 500.00 g of the pulverized fibre obtained from *Ipomoea batatas* tubers was submerged in 3.50 % w/v of sodium hypochlorite and blended for 10.00 min. The wet mass was washed with distilled water until it was neutral to litmus. It was slurred in 96.00 % v/v ethanol for 5.00 min and dried at 60.00 ^{o} C in a hot air oven (Memmert, England) to constant weight and pulverized to 250.00 µm particle size using a stainless steel sieve (Retch, Germany). A 100.00 g of the powder was blended with 3.00 % w/v sodium hydroxide for 5.00 min and precipitated with acetone. The precipitated material was dried to constant weight in an air-tight desiccator loaded with silica gel and sized through 250.00 µm sieve to obtain *I–polygel*.

Pre-formulation studies

A pre-formulation study was carried out to investigate the compatibility of paracetamol with IP using a differential scanning calorimetry (DSC) equipment model STAR SW 12.10 (Mettler, USA). A pure sample of the paracetamol was loaded in the aluminum sample holder of the equipment and scanning was done by heating from 60.00-300.00 ˚C at 10.00 ˚C min^{-1} incremental adjustments under inert atmosphere flushed with nitrogen at the rate of 20 mL min^{-1}

Preparation of granules containing paracetamol powder

Three batches of granules containing 2.50, 4.00 and 5.50 % w/w respectively of *I-polygel* as a granulating agent were prepared by the wet granulation method. Gelatin (GT) B.P was used as a standard. Each batch contains 500.00 mg paracetamol B.P (83.33 % w/w), corn starch B.P (10.00 % w/w) as a disintegrant, magnesium stearate (0.50 % w/w) as a lubricant and lactose as a filler to target a tablet weight of 620.00 mg. A batch containing neither IP and GT nor any disintegrant served as a control. The respective ingredients were blended batch by batch, wet-massed and screened through a stainless

steel sieve (1.70 mm). The wet screened mass was dried to a constant weight in a hot-air oven at 60 ^{o} C and screened through another sieve (1.00 mm).

Properties of granules

The flow rate of the different batches of the granules was assessed according to the methods described by Carstensen and Chan[9] using 15.00 g of granules in each case. A funnel of 5.0 cm diameter and orifice of 1.00 mm diameter was used. The time taken for the complete discharge of 15.00 g of the granules from the funnel was noted and the flow rate was calculated from equation 4.

The bulk and tapped volumes of the granules were determined using a Stampfvolumeter (STAV 2003 JEF, Germany). The bulk and tapped densities were calculated from the corresponding values of the bulk and tapped volumes. The particle density was determined using *n*-hexane (a non-solvent) as a displacement fluid. The pycnometer was weighed empty (W), and was filled with *n*-hexane and reweighed (W_1). The weight of the *n*-hexane was determined by subtracting W from W_1. A 0.5 g quantity (W3) of (IP) was transferred into the pycnometer, was wiped of excess *n*-hexane and weighed (W_4)[10]. Replicate determinations were done and the bulk, tapped and particle densities respectively were calculated from equations 1-3.

$$Bulk\ density = weight\ of\ bulk\ granules / volume\ of\ granules \quad \ldots\ldots\ldots (1)$$

$$Tapped\ density = weight\ of\ granules / tapped\ volume\ of\ granules \quad \ldots\ldots (2)$$

$$Particle\ density = W2 \times W3 \div V(W3 - W4 + W2 + W) \quad \ldots\ldots\ldots\ldots\ldots (3)$$

Where,

V = 25.00ml (volume of pycnometer),

W= weight of empty pycnometer,

W_1= weight of pycnometer and *n*- hexane,

W_2 = the difference between the W & W_1,

W_3 = weight of sample powder,

W_4 = weight of sample + *n*-hexane + pycnometer.

The angle of repose was determined using the constant powder heap height method[10]. A clean glass funnel of 1.00 cm orifice diameter was clamped on a retort stand such that a constant perpendicular height of the tip of the funnel was 3.00 cm from a horizontal flat base spread with a clean graph sheet of paper. The 3.00 cm height serves as the height of the heap of the granules. Each batch of the granules was, in turn, poured into the funnel until the granule heap that was formed touched the funnel tip which stopped further outflow of the granules from the funnel orifice. The procedure was carried out in triplicate for each batch of granules. The angle of repose was calculated after replicate determinations using equation 5.

$$Flow\ Rate = \frac{weight\ of\ granules}{time\ of\ complete\ flow} \quad \ldots\ldots\ldots (4)$$

$$Angle\ of\ repose, \theta = tan^{-1}\ 2h/d \quad \ldots\ldots\ldots (5)$$

Where h = constant height of granules heap, d = diameter of granules heap

The derived parameters such as the Carr's index, Hausner's ratio and porosity were calculated using the following equations[11, 12]:

$$Carr's\ index = \frac{(Tapped\ density - Bulk\ density)}{Tapped\ density} \quad \ldots\ldots\ldots (6)$$

$$Porosity = 1 - \frac{Bulk\ density}{True\ density} \times 100 \quad \ldots\ldots\ldots (7)$$

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density} \quad \ldots\ldots\ldots (8)$$

Compression of tablets

The respective batches of the granules were compressed at a pressure of 4.50 kg and dwell time 30.00 s using a single punch tabletting machine (Cadmach single punch automatic tablet machine, model SSF3, India) fitted with a punch of diameter, 12.50 mm and a rounded lower punch curvature.

Tablet properties

Tablets were evaluated for their organoleptic properties. The uniformity of weight was carried out using 20.00 tablets weighed on an electronic analytical balance (Mettler, USA). The hardness and thickness of 10.00 tablets per batch were determined using a diametrical digital tablet hardness tester (Veego, India). The friability of 10.00 tablets from each batch was determined in tablet friabilator (Erweka TAR 220, Germany) set to rotate at 25.00 revolutions per minute, (rpm) for 4.00 min. Using 6.00 tablets per batch, disintegration time was determined in a tablet disintegration apparatus (Erweka, ZT 122, Germany) containing 900.00 ml of 0.10 N hydrochloric acid maintained at 37 ± 1.00 °C [13].

The dissolution profiles were carried out in a dissolution apparatus (Erweka DT600, Germany) adopting the rotating paddle method in 900.00 ml of 0.10 N hydrochloric acid at 37 ±1.00^{o} C at a paddle speed of 50.00 rpm. A 5.00 ml of dissolution sample was withdrawn at predetermined intervals of 10.00, 20.00, 30.00, 40.00, 50.00, 60.00 min and replaced with the same volume of 0.10 N hydrochloric acid at the same temperature. The absorbance sampled solution was determined in a UV spectrophotometer (Jenway, model 6405, England) at a wavelength of 245nm. Replicate determinations were done. The T_{80} of each batch of tablets was determined. Dissolution efficiency was determined by calculating the area under the curve (AUC) between 0-30.00 min.

The tensile strength[14] of the tablets were calculated from the equation:

$$T = 2P/\pi dt \quad \ldots\ldots\ldots\ldots\ldots (9)$$

Where T = radial tensile strength, t = tablet thickness, d = tablet diameter.

Statistical analysis

Statistical analysis involving independent samples T-test or One-way ANOVA was performed using IBM SPSS

Statistics 20 software. Values were considered significant at $p < 0.05$

RESULT AND DISCUSSION

Pre-formulation study

The DSC thermograms obtained in the investigation of the compatibility of paracetamol powder with *I-polygel* (IP) are represented in Figures 1 and 2 and show the melting peaks of ≈169 and 170 ^{o}C respectively for pure paracetamol and a mixture of paracetamol and IP. Literature shows that pure paracetamol has a melting peak range of 169.00-171.00^{o}C [15, 16]. A melting peak of 170.00 ^{o}C obtained for paracetamol in its admixture with IP shows possible compatibility (Figure 2).

Table 1: Properties of granules

Parameter	*I-polygel* (IP)			Gelatin (GT)			Control
	Batches			Batches			
	2.50 %w/w	4.00 %w/w	5.50 %w/w	2.50 %w/w	4.00 %w/w	5.50 %w/w	
Flow rate (g/s)	9.62 ±0.57	11.24 ±0.52	13.85 ±0.39	9.71 ±0.91	11.93 ±0.24	14.60 ±0.24	7.53 ±0.46
Hausner's ratio	1.23 ±0.02	1.20 ±0.01	1.22 ±0.02	1.21 ±0.04	1.22 ±0.05	1.21 ±0.02	1.17 ±0.03
Carr's index	17.72 ±1.09	16.57 ±0.77	15.93 ±1.80	16.97 ±3.12	16.25 ±3.78	15.45 ±1.42	19.18 ±2.35
Angle of repose (deg.)	35.01 ±1.03	34.26 ±2.59	32.78 ±1.62	34.87 ±2.12	33.37 ±1.59	32.19 ±2.22	37.14 ±0.65
Bulk density(g/ml)	0.48 ±0.01	0.48 ±0.01	0.43 ±0.01	0.45 ±0.01	0.44 ±0.01	0.43 ±0.01	0.51 ±0.01
Tapped density(g/ml)	0.59 ±0.01	0.58 ±0.01	0.52 ±0.02	0.54 ±0.01	0.53 ±0.02	0.52 ±0.01	0.60 ±0.01
True density(g/ml)	1.22 ±0.12	1.28 ±0.03	1.29 ±0.05	1.17 ±0.02	1.18 ±0.02	1.17 ±0.02	1.27 ±0.05
Porosity (%)	60.25 ±3.79	62.45 ±0.72	67.06 ±0.67	61.60 ±1.18	62.87 ±0.90	63.19 ±1.19	59.79 ±2.26

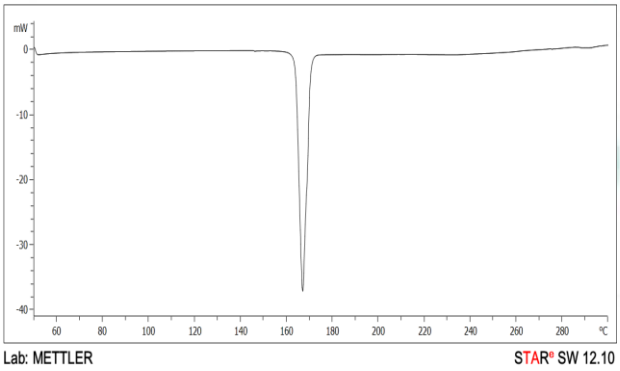

Figure 1: DSC thermogram of paracetamol B.P

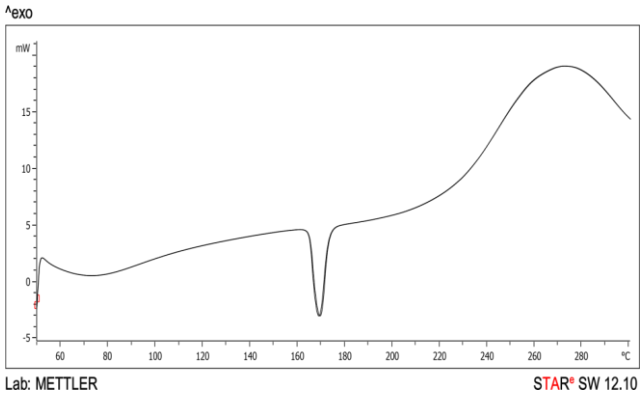

Figure 2: DSC thermogram of a blend of *I-polygel* and paracetamol

Properties of granules

The properties of the granules are shown in Table 1. The results of the flow rate, the angle of repose, Hausner's ratio and Carr's index[11, 12] shows that the granules flowability improved as the concentration of granulating agent increased, with the granules prepared from GT exhibiting a higher flowability than those of the IP ($p < 0.05$). There was a notable difference in the corresponding values of the respective bulk and tapped densities ($p < 0.05$). This and the values for porosities may imply that the granules are compressible.

Evaluation of tablets

The tablet properties are shown in Table 2. A glossy, intact, odourless, round shaped and slightly bitter tablets were obtained from both granulating agents. The variation in weights of all the batches of the tablets was in the range of 0.37 – 0.87% which is less than 5.0 % specified in the British Pharmacopeia[13] (for the tablets weighing more than 250 mg). The mechanical properties of the tablets obtained across the batches show a consistent increase in the hardness, tensile strength, hardness friability ratio (HFR) and a decreasing order of friability as the concentration of each of the granulating agent increased, with the tablets containing GT showing higher mechanical strength. This could be summarized as follows: GT-5.50 % w/w > GT-4.00 % w/w > GT-2.50% w/w > IP-5.50%w > IP-4.00%w/w > IP-2.50%

w/w > Control). The disintegration time of the various batches can also be concisely presented as follows: Control < IP-2.50% w/w (3.76 min) < IP-4.00 w/w (5.85 min) < 5.50% w/w (7.61min) < GT-2.50% w/w (10.89 min) < GT-4.00% w/w (18.54 min) < G-5.50% w/w (20.92 min). The British Pharmacopoeia[13] specifies minimum disintegration time of 15.00 min for uncoated tablets.

The dissolution profile for the batches of tablets prepared with either IP or GT is presented in Figure 3. The USP 2007, 30th ed.[17] specifies that not less than 80.00 % of the labelled amount of paracetamol is expected to dissolve in 30.00 min *in vitro*. Figure 4 shows the respective amounts of paracetamol released at 30.00 min for the tablets prepared with IP or GT. Lower concentrations of granulating agents resulted in a higher amount of drug release across IP and GT. Figure 5 is a representation of the specific time for the attainment of T_{80} by each batch of tablets. The highest amount of paracetamol (89.49 %) was released in the least time (21.00 min) with IP at 2.50 % w/w when compared with other concentrations of GT ($p<0.05$) did this batch have better properties than other batches? In a summary, T_{80} occurred as follows: IP-2.5 % w/w (21.00 min) < IP-4.00 % w/w (27.00 min) < IP-5.50% w/w (29.00 min) < GT-2.50 % w/w (58.00 min). Tablets containing GT-4.00% w/w and GT-5.50%w/w failed to attain T_{80} after 60.00 min. These results show that the mucilage of IP is a better granulating agent when compared to GT in their ability to release the drug content. This is further shown from the values of dissolution efficiency (DE) obtained as follows: IP- 2.50 % w/w (74.17 %) > IP-4.00 % w/w (71.32 %) > IP-5.50 % w/w (58.02 %) > GT-2.50 % w/w (54.12 %) > GT-4.00 % w/w (54.02 %) > GT-5.50 % w/w (51.34 %) ($p<0.05$).

Table 2: Tablet properties

Parameter	*I-polygel* Batches			Gelatin Batches			Control
	2.50 %w/w	4.00 %w/w	5.50 %w/w	2.50 %w/w	4.00 %w/w	5.50 %w/w	
Weight (mg)	614.60±2.06	622.30 ±7.20	616.55 ±1.30	614.80±2.10	617.35 ±3.20	623.05 ±4.20	623.90 ±2.50
Thickness (mm)	4.55 ±0.06	4.71 ±0.15	4.61 ±0.36	4.56 ±0.09	4.68 ±0.08	4.77 ±0.04	4.30 ±0.39
Hardness (kgf)	4.93 ±0.46	8.79 ±0.95	11.19 ±1.01	8.84 ±1.01	10.58 ±0.92	11.55 ±1.31	3.87 ±0.68
Friability (%)	0.36 ±0.002	0.32 ±0.01	0.27 ±0.03	0.30 ±0.004	0.29 ±0.08	0.24 ±0.05	5.31 ±0.15
Disintegration (min)	3.76 ±0.51	5.85 ±0.64	7.61 ±1.13	10.89 ±0.84	18.54 ±0.94	20.92 ±1.41	0.56 ±0.29
Tensile strength (N/m^2)	54.92 ±0.1	94.38 ±0.60	127.80 ±0.28	98.30 ±0.28	117.93 ±0.11	128.96 ±0.1	43.03 ±0.1
*HFR	13.69 ±0.12	27.47 ±0.13	44.44 ±0.10	29.47 ±0.11	36.48 ±0.12	48.13 ±0.10	0.73 ±0.13

*HFR: Hardness Friability Ratio.

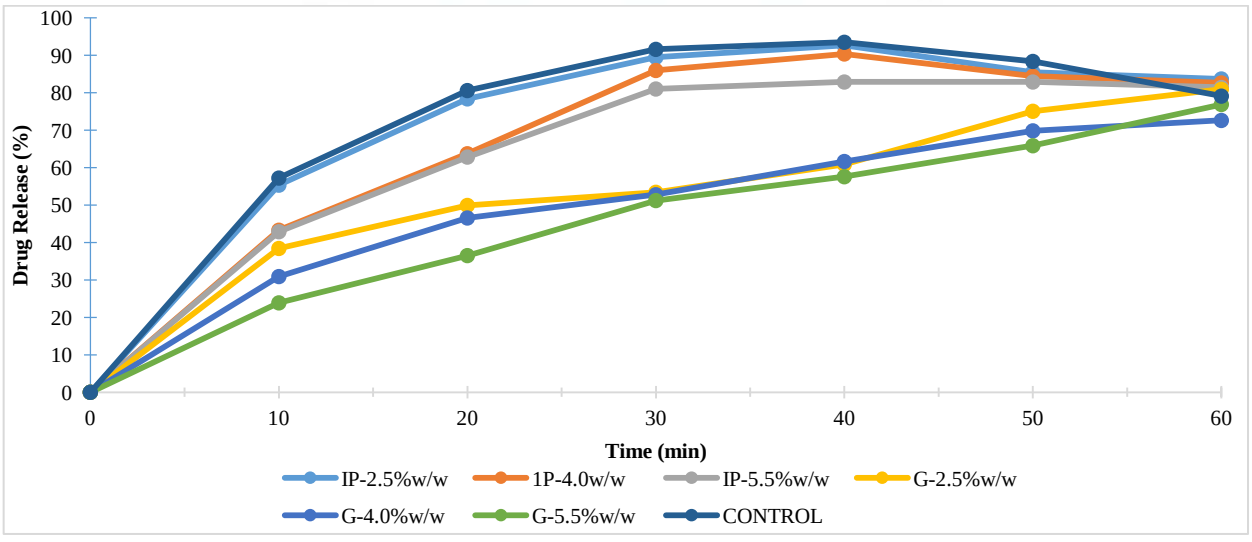

Figure 3: Dissolution profile for paracetamol tablets prepared with *I-polygel* and gelatin

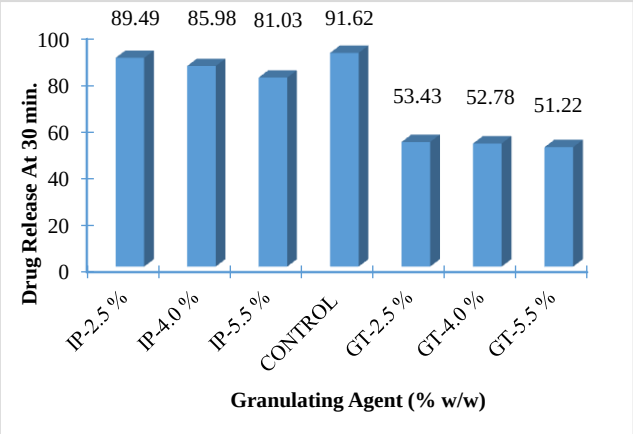

Figure 4: Amount of drug released at 30.00 min

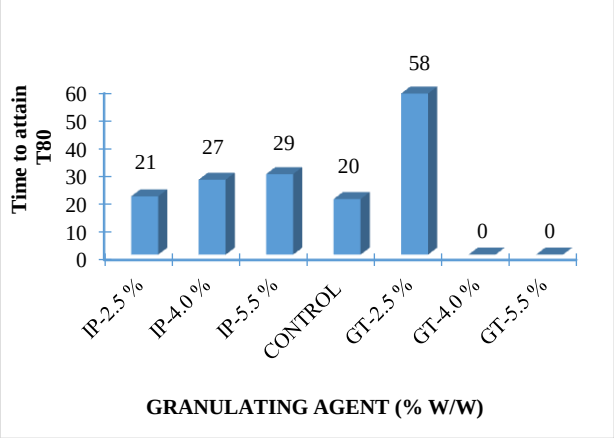

Figure 5: Time for the attainment of T_{80}.

CONCLUSIONS

A novel hydrophilic biopolymer (*I-polygel*) (IP) derived from the tubers of *Ipomoea batatas* has been evaluated as a granulating agent at 2.50, 4.00 and 5.50 % w/w in the production of paracetamol tablets using gelatin (GT) as a comparing standard. All the batches of granules were flowable and compressible, with the ones containing GT showing higher flowability. All the resulting tablets possessed acceptable mechanical strength; those containing GT were higher in values than those of IP which disintegrated in much less than 15.00 min and equally displaying higher dissolution efficiency for paracetamol when compared to GT. Therefore IP at the concentrations of 2.50 and 4.00 % w/w could serve as a better granulating agent than GT at similar concentrations.

Conflicts of interests

The authors have no conflict of interest in the publication of this research work.

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