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The Disintegrant Property of a Hydrophilic Cellulose Polymer Derived from the Tubers of *Ipomoea batatas* in Paracetamol Tablet Formulation

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Authors' contributions

This research was carried out in collaboration between both the authors. Author UKC conceived the work. Both authors designed the study, wrote the protocol and interpreted the data. Both authors anchored the bench work and managed the literature search, performed the data and statistical analysis. Author UKC produced the initial draft. Both the authors read and approved the final manuscript.

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ABSTRACT

Aims: A new hydrophilic cellulose polymer (*I-hydrocel*) derived from the tubers of *Ipomoea batatas* was assessed as a tablet disintegrant in paracetamol tablet formulation in comparison with maize starch.
Methods: *I-hydrocel* was incorporated intragranularly at 5, 10 and 15% w/w to prepare granules containing paracetamol (80.65% w/w), gelatin (3.50% w/w) and lactose as a filler by wet granulation alongside those containing maize starch. The micromeritic evaluations of the granules were carried and later, they were lubricated with 0.5% w/w magnesium stearate and compressed at 4.50 kg into tablets using a single punch tablet press fitted with a 12.50 mm punch. The uniformity of

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weight/content and disintegration time tests for tablets were accomplished using the British Pharmacopoeia, BP methods. Tablet hardness, friability and tensile strength were also evaluated. A 30 min dissolution rate studies were conducted using the rotating paddle at 50 rpm (United States Pharmacopoeia, USP) in 900 ml of phosphate buffer (pH 5.8) at 37 ± 0.5°C. The absorbance of the respective samples were determined in an ultraviolet (UV) spectrophotometer at 245 nm.

Results: The granules were flowable and the tablets compressed from them complied with BP acceptable limit for uniformity of weight, drug content and disintegration time (≤ 15 min). However, tablets containing 5% w/w corn starch disintegrated significantly more quickly (P= 0.000) than those containing 5% w/w *I-Hydrocel* but at 10 and 15% w/w of *I-hydrocel* and maize starch, there was no significant difference (P= 0.296 and 0.543 respectively) in disintegration times of tablets. The tablets prepared with maize starch generally had higher values of hardness, tensile strength and hardness-friability-ratio (HFR) than those containing *I-hydrocel* (P = 0.000) while the friability obtained for the tablets from either disintegrant were less than 1%. In dissolution rate studies, all the batches of tablets containing either maize starch or *I-hydrocel* released their drug content above 80% and maximally within 15 min.

Conclusion: At 5% w/w, paracetamol tablets prepared with maize starch disintegrated earlier than those of *I-hydrocel* while at 10 and 15% w/w, there was no significant difference in disintegration time for both samples. Therefore, at 10 or 15% w/w, either maize starch or *I-hydrocel* could be used to achieve a similar disintegration outcome. However, the disintegration time obtained at 5, 10 and 15 % w/w of either disintegrant complied with BP specifications of ≤ 15 min for uncoated tablets.

Keywords: Hydrophilic cellulose polymer; Ipomoea batatas; disintegrant; paracetamol.

1. INTRODUCTION

The pharmaceutical industry sector has witnessed the development of several drug delivery systems, especially those targeting specific therapeutic sites. This notwithstanding, tablets, one of the oral solid dosage forms which up till now have been in existence since the 19th century, continue to be the most recurrent dosage form of choice for many. This continued acceptance includes the fact that the oral route is possibly the minimally disturbing approach of delivering medicinal products to achieve physiological impact in the human body since patients can afford to administer the medicine themselves. The tablet provides safe and suitable means of active pharmaceutical ingredients (API) usage with exceptional physiochemical strength in contrast to some other dosage forms making delivery of precise dose possible [1]. The methods used in the preparation of tablets include the direct compression, wet granulation, mass extrusion methods, etc. [2]. Tablets could be formulated as immediate or sustained release dosage. Most immediate release oral drug products, such as tablets or capsules, are formulated to release their active pharmaceutical ingredient (API) instantly when taken orally [3].

For such formulations, the tablets have to disintegrate or break up into smaller fragments to enable the release of its API to go into solution. It is the dissolved API that will be bioavailable for therapeutic action.

The process of disintegration opposes the binding forces which hold the particles that made up the tablets when it is compressed [4]. To improve dissolution and hence bioavailability of any medicinal product from immediate-release tablets, disintegration is one of the significant processes [5,6]. The disintegrants are added to a tablet or capsule formulation to help in the break-up of the tablet when it is in contact with a liquid. They are employed in immediate release solid dosage forms such as tablets or capsules to increase dissolution and hence bioavailability of any drug [7-10].

Tablet disintegration may occur by swelling, porosity/capillary (wicking), deformation, etc. The disintegrants that yield their action through swelling when in contact with water overcome the adhesiveness of other ingredients in the tablet, causing the compacted mass to crumble. However, those that do not swell are thought to have the mechanism of working through porosity and capillary action [11,12]

Starch has remained one of the foremost and most commonly used disintegrant. Maize or potato starch when included at concentrations of 5 – 10% is found to be effective in tablet disintegration. In addition to starch, other disintegrants include pregelatinised starch

(Starch 1500, with effective use at concentrations of 5 -10% w/w), and microcrystalline cellulose (Avicel (R), 10-20% w/w), etc. [13].

In this work, a new hydrophilic cellulose polymer (*I-hydrocel*) (IH) derived from the tuber of *Ipomoea batatas* was investigated as a tablet disintegrant and was compared with a natural product, maize starch (MS). The processing and the characterization of *I-hydrocel* have been documented, described as a hydrophilic cellulose polymeric powder being tasteless, off-white, smooth and odourless. It is insoluble in organic solvents but disperses and swells rapidly in contact with water with a high swelling, hydration and moisture adsorption capacities [14]. *I-hydroce*l has been applied as a filler-disintegrant in piroxicam orally dispersible tablets (ODTs) in comparison with microcrystalline cellulose (MCC) (avicel® PH 101) and lactose where tablets possessing higher mechanical strength and higher dissolution efficiency, DE were obtained with *I-hydrocel* compared to avicel PH 101 and lactose thus enhancing the solubility of piroxicam which is noted for its poor water solubility [15]. The ability of *I-hydrocel* to enhance high solubility in a known poorly-water soluble drug like piroxicam has led to its investigation as a disintegrant in paracetamol immediate release solid dosage form. Paracetamol is a poorly compressible as well as poorly water-soluble drug [16].

2. MATERIALS AND METHODS

2.1 Materials

Magnesium stearate (BDH, England), lactose (SureChem, UK), ethanol (96%), hydrochloric acid (HCl) (JHD, China), gelatin, maize starch (BDH, England), sodium hypochlorite, 3.5% w/v (Multipro, Nigeria), n-hexane (JHD, China), paracetamol (Cipla, India). *I-hydrocel* was processed in the Department of Pharmaceutics and Pharmaceutical Technology Laboratory, Faculty of Pharmaceutical of Sciences, University of Port Harcourt, Port Harcourt, Nigeria.

2.2 Methods

2.2.1 Preparation of a novel hydrophilic polymer (*I-hydrocel*)

This was prepared using the procedure documented by Ugoeze, et al. [14]. The peeled tubers of *Ipomoea batatas* was milled. The starch content was filtered to obtain the fibre which was dried at 60°C and pulverised. A 500 g of the powdered fibre was submerged in 3.50% w/v of sodium hypochlorite and mixed for 10 min. This was washed with distilled water to a neutral pH. It was then slurried in 96% ethanol for 5 min, dried at 60°C in a hot air oven. The dry mass was pulverised and passed through 250 µm size stainless steel sieve. The powder was stored in an amber coloured class container for further studies.

2.2.2 Preparation of granules containing paracetamol

Table 1 represents the percentages of the respective ingredients used in the formulation of paracetamol tablets for the study of the disintegrant properties of *I-hydrocel.* Using the wet granulation method, three batches of granules were prepared with *I-hydrocel* (IH) as a disintegrant in concentrations of 5, 10 and 15% w/w respectively, added intragranularly. Each batch contains, paracetamol (80.65% w/w), gelatin (3.5% w/w, a binder), magnesium stearate (0.5% w/w, a lubricant) and lactose (a filler). Similar batches of granules were prepared with maize starch (MS) for comparison. A homogenised blend of paracetamol, lactose and IH (or MS as appropriate) was wet massed in an aqueous slurry of gelatin. Wet and dry screening stages were carried out with a stainless steel sieves 10 (1.70 mm) and 16 (1.00 mm) (Retch, Germany) respectively. Each drying procedure was carried out in an oven (Memmert, England) at 60°C for 30 min. The granules were packaged in airtight amber coloured glass containers stored in desiccators packed with silica gel as desiccants for further studies.

Table 1. Formula for preparation of paracetamol tablets

Ingredient	I-hydrocel			Maize starch		
	Batch/ Concentration (% w/w)			Batch/ Concentration (% w/w)		
	5.00	10.00	15.00	5.00	10.00	15.00
PCM	80.65	80.65	80.65	80.65	80.65	80.65
Gelatin	3.50	3.50	3.50	3.50	3.50	3.50
Mag.stearate	0.50	0.50	0.50	0.50	0.50	0.50
Lactose	10.35	5.35	0.35	10.35	5.35	0.35

2.2.3 Evaluation of the properties of the granules

2.2.3.1 Bulk, tapped and particle densities

A 20.0 g quantity of the granules was employed in the determination of bulk and tapped densities using Stampfvolumeter (STAV 2003JEF, Germany) [17,18].

The particle density was determined by displacement method using a 25 ml pycnometer and n-hexane as a non-solvent [19]. The empty pycnometer was weighed (W) and later, filled with n-hexane, wiping excess fluid, it was reweighed (W1). The difference between this and W was calculated as W2. A 0.5 g quantity of the granules, in turn, was weighed (W3) and carefully transferred into the pycnometer. The superfluous fluid was dabbed with a soft clean towel and the pycnometer was weighed again (W4). Three determinations were carried out and the average was used to determine the particle density, *Pt* (g/ml).

The bulk, tapped and particle densities of the respective samples were calculated from equations 1, 2 and 3 below respectively after three replicate determinations:

$$\text{Bulk density} = \text{Weight of Powder}/\text{Bulk volume} \quad (1)$$

$$\text{Tapped Density} = \text{Weight of Powder}/\text{Tapped volume} \quad (2)$$

$$\text{Particle Density, } \rho t = w2 \times w3/v(w3 - w4 + w2 + w) \quad (3)$$

Where:

v is the volume of pycnometer, 25 ml,
W = weight of empty pycnometer,
W1 = weight of pycnometer and n- hexane,
W2= the difference between the W and W1
W3= weight of *granules,*
W4= weight of *granules* + n- hexane + pycnometer.

2.2.3.2 Determination of flow properties

The flow rate of the granules was determined using the funnel method [20]. The angle of repose was determined using the modified method reported by Jones and Pilpel [21]. The angle of repose, θ was calculated after three replicate determinations from equation 4 below:

$$\theta = \tan^{-1}\frac{2h}{d} \quad (4)$$

Where,

h = the height of the heap, d = base diameter of the heap.

Hausner's ratio (HR) [22] of the granules was obtained as:

$$HR = Tapped\ density/Bulk\ density \quad (5)$$

Compressibility Index (CI) [23] of the granules was calculated from equation 6 below:

$$Carr's\ index = (Tapped\ density - Bulk\ density) \div Tapped\ density \times 100 \quad (6)$$

Porosity (ρ) of the granules was determined from the expression in equation 7 below:

$$\rho = \left(1 - \frac{\text{Bulk density}}{\text{True density}}\right) \times 100 \quad (7)$$

2.2.4 Compression of tablets

The respective batches of the granules were lubricated with 0.5 % w/w of magnesium stearate and compressed at a pressure of about 4.0 - 4.5 kgF using a single punch tableting machine (Cadmach single punch automatic tablet machine, model SSF3, India) fitted with a punch of diameter,12.5mm and a rounded lower punch curvature.

2.2.5 Evaluation of tablet properties

The tablet properties were evaluated using the methods outlined in the British Pharmacopoeia [24].

2.2.5.1 Organoleptic properties

Tablets were examined for colour, odour, shape, taste and texture.

2.2.5.2 Uniformity of weight

The uniformity of tablet weight was studied by weighing singly 20 tablets that were randomly selected from each batch using an analytical balance (Mettler, Germany).

2.2.5.3 Hardness

The hardness of ten tablets randomly selected was tested individually using a diametrical digital tablet hardness tester (Veego, India).

2.2.5.4 Friability

The friability of 10 tablets from each batch was determined in a tablet friabilator (Erweka TAR 220, Germany). This test was done three times.

2.2.5.5 Disintegration time

A total of 6 tablets per batch was utilised to study the disintegration time using a tablet disintegration apparatus (Erweka, ZT 122, Germany) in 900 ml of 0.1 N HCl maintained at 37 ± 1°C. Determinations were done thrice.

2.2.5.6 Dissolution rate studies

The dissolution rate studies were carried out in a dissolution apparatus (Erweka DT600, Germany). The rotating paddle method (Apparatus 2) [17,24], paddle speed, 50 rpm in 900 ml of phosphate buffer (pH 5.8) maintained at 37 ± 0.5°C for a dissolution duration of 30 min. A 5 ml of dissolution sample was withdrawn at predetermined intervals of 5, 10, 15, 20, 25 and 30 min, replacing with the same volume of plain dissolution medium at the same temperature. The absorbance of each sample was determined in an ultraviolet (UV) spectrophotometer (Jenway, model 6405, England) at a wavelength of 245 nm. Determinations were done in triplicates.

2.2.5.7 Thickness

A micrometer screw gauge was used to individually measure the thickness of 10 tablets that were randomly selected.

2.2.5.8 Tensile strength

The tensile strength [25] of the tablets was calculated from equation 8 below:

$$T = 2P/\pi dt \quad (8)$$

Where,

T = radial tensile strength, *P* = tablet hardness, *t* = tablet thickness, *d* = tablet diameter.

2.2.6 Statistical analysis

All the statistical analysis involving the mean, standard deviation and one-way ANOVA was computed with IBM SPSS Statistics 20 software.

3. RESULTS AND DISCUSSION

3.1 Granules Properties

The properties of the granules prepared with either IH or MS as disintegrant are shown in Table 2. The results of the porosity, bulk and tapped densities show that the granules generally are compressible. Also, flow properties such as the flow rate, angle of repose, Carr's index and the Hausner's ratio showed that the granules have good flow properties [22,23]. The flowability of the granules may have led to the result obtained for uniformity of tablet weight and drug content as shown in Table 3.

3.2 Tablet Properties

3.2.1 Uniformity of weight

The properties of the tablets are presented in Table 3. Intact and glossy tablets were obtained. The uniformity of weight of the respective batches of the tablets was within acceptable range. The British Pharmacopeia [24] allows a limit of 5% maximum variation in tablet weight for tablets weighing more than 324 mg. In all the tablet batches studied, the variation in weight falls within the range of 0.39 - 2.79%.

Table 2. Properties of paracetamol granules

Ingredient	I-hydrocel (IH)			Maize starch (MS)		
	Batch			Batch		
	5%w/w	10%w/w	15%w/w	5%w/w	10%w/w	15%w/w
Flow rate (g/s)	7.59±0.66	9.69±0.45	10.88±0.61	10.15±0.88	9.45±0.66	9.85±0.72
Angle of repose (deg.)	35.17±0.18	36.87±0.10	34.94±0.19	33.94±1.54	34.43±0.25	34.66±0.11
Bulk density (g/ml)	0.36±0.02	0.37±0.01	0.38±0.03	0.36±0.01	0.37±0.01	0.39±0.01
Tapped density(g/ml)	0.38±0.01	0.42±0.01	0.44±0.02	0.43±0.01	0.44±0.01	0.45±0.01
True density (g/ml)	1.02±0.18	1.06±0.22	1.19±0.02	1.00±0.28	1.06±0.10	1.16±0.13
Porosity (%)	64.71±0.01	65.09±0.01	68.07±0.02	64.00±0.02	65.09±0.01	66.64±0.02
Hausner's ratio	1.06±0.02	1.14±0.01	1.16±0.01	1.18±0.02	1.19±0.02	1.15±0.02
Carr's index (%)	5.26±0.68	11.91±0.72	13.64±2.44	16.27±1.39	15.91±1.38	13.33±1.48

3.2.2 Total drug content /assay

Considering the results of the total drug content uniformity, the values obtained for the respective batches prepared with IH or MS are within the ranges of 100.46 -102.72% and 101.78 -102.76 % of paracetamol content. The British Pharmacopoeia states that the preparation conforms to the test if each individual content is between 85% and 115% of the average content. It also specifies that the preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75% to 125% of the average content. The tablets in the batches of tablets prepared with either IH or MS conformed to the BP specification [24].

3.2.3 Hardness

The hardness of the tablets are shown in Table 3. There was a general increment in the tablet hardness as the concentration of the disintegrant increased in the tablet formulations containing both disintegrants. Tablets containing MS were harder than those containing IH at all concentrations except at 10% w/w. All the batches met with acceptable range of hardness of ≥ 4 kgF except tablets containing IH at 5% w/w which had a value of 3.31 ± 0.91 kgF.

3.2.4 Friability

Generally tablet friability is a necessary assessment tool for abrasion in tablets. The USP permits a maximum tablet friability of 1.0% for uncoated tablets formulated for immediate release [17,26]. In this study, the values of tablet friability obtained across the batches of tablets prepared with IH or MS were less than 1.0% which implies compliance, Statistically, there was no significant difference in the friability between the tablets containing 5% w/w IH and 5% w/w MS, 15% w/w IH and 10% w/w MS, 15% IH and 15% w/w MS (P = 0.000).

3.2.5 Disintegration time

The respective batches of tablets prepared with either IH or MS disintegrated in less than 15 min. The British Pharmacopoeia [24] specifies a maximum disintegration time of 15 min for immediate release tablets. In as much as all the batches of tablets prepared with either of the disintegrants passed the disintegration time test as specified in the BP, at 5% w/w tablets prepared with MS disintegrated in a shorter time than those containing IH (P = 0.000). However, there was no significant difference in the disintegration time for the tablets prepared with either IH or MS at 10 and 15% w/w (P = 0.296 and 0.543 respectively).

3.2.6 Tensile strength/hardness-friability-ratio

The tensile strength and hardness-friability-ratio (HFR) of the tablets prepared with MS exhibited higher mechanical strength than those containing IH at all the concentrations studied (P = 0.000).

3.2.7 Dissolution rate studies

Fig. 1 represents the dissolution profile for the different batches of tablets containing either IH or MS. The USP [17] specifies that not less than 80% of the labelled amount of paracetamol is expected to dissolve in 30 min *in vitro*. Each batch of tablets prepared with either IH or MS at every concentration released maximally above 80% of its paracetamol content at 30 min. The maximal dissolution of paracetamol from the tablets prepared with either of IH or MS may be due to their ability to disintegrate in very short time brought about by their hydrophilic properties. The grains of starches in the

Table 3. Tablet properties

Ingredient	I-hydrocel			Maize starch		
	Batch			Batch		
	5 % w/w	10 % w/w	15 % w/w	5 % w/w	10 % w/w	15 % w/w
Tablet Weight (mg)	627.95±1.48	635.25±2.75	622.42±1.53	637.32±6.15	631.54±1.60	633.14±1.50
Drug Content (mg)	506.58±0.6	513.60±0.95	502.32±0.62	513.82±0.32	508.92±0.42	510.17±0.37
Disintegration(min)	9.92±0.07	4.92±0.07	3.41±0.44	7.64±0.59	4.60±0.40	3.22±0.24
Friability (%)	0.93±0.04	0.80±0.03	0.70±0.02	0.92±0.03	0.70±0.02	0.79±0.10
Hardness (kgF)	3.31±0.19	7.17±0.08	8.45±0.26	5.27±0.23	6.61±0.09	10.64±0.28
Thickness(mm)	4.61±0.03	3.83±0.06	4.11±0.10	4.99±0.11	5.01±0.39	4.47±0.12
Hardness Friability Ratio (HFR)	3.67±0.12	9.43±0.15	12.74±0.14	5.77±0.13	9.57±0.14	16.07±0.18
Tensile Strength (N/m^2)	37.22±0.15	95.69±0.21	106.68±0.67	56.36±1.75	67.43±0.14	123.48±0.17

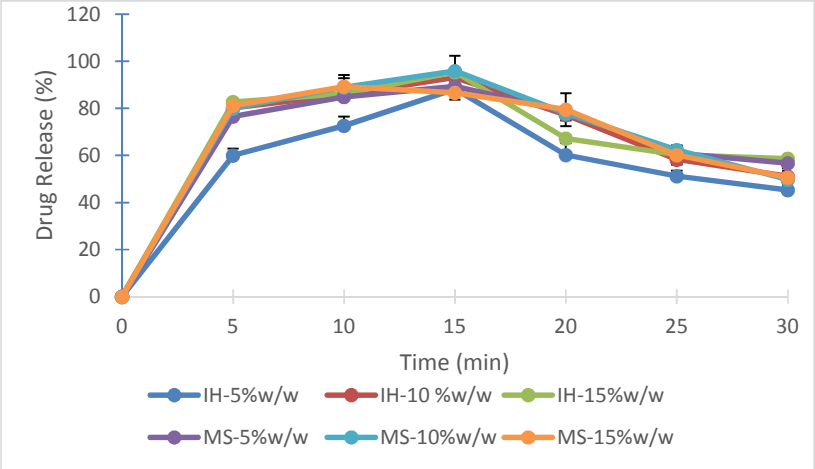

Fig. 1. Dissolution profile of paracetamol tablets containing I-hydrocel or maize starch

presence of water has been reported to exert pressure on the granules to force them apart [27, 28]. Shangraw et al. [29] reported that tablets of water-insoluble drugs comprising of starches disintegrated quicker than those of water-soluble drugs due to the reduced water absorption capability of the starches in the latter case.

4. CONCLUSION

The study evaluated the suitability of *I-hydrocel*, a new hydrophilic cellulose polymer derived from the tubers of *Ipomoea batatas* as a tablet disintegrant using maize starch as a comparing standard. The powders containing either of the disintegrants had similar flow, compressibility and densification behaviour. The tablets formed from them had minimal weight variation and good mechanical properties that is desirable for immediate release tablets and complied with BP set limits, even though the tablets containing MS were harder. Comparing the disintegration behaviours at different concentrations, it was found that at 5% w/w, paracetamol tablets containing MS disintegrated earlier than those containing IH. However, at 10 and 15% w/w, there was no significant difference in the disintegration times exhibited by both. The paracetamol tablets containing MS and IH at all the concentration tested in the study passed both the BP and USP disintegration time test for uncoated/ immediate release tablets which is stipulated as not more than 15 min. Based on these results, *I-hydrocel* as a disintegrant could be used as a substitute to corn starch at concentrations of 10 or 15% w/w.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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