

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

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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 granules were carried and later, they were lubricated with 0.5 % w/w magnesium stearate and compressed at 4.50 kgF into tablets using a single punch tablet press fitted with a 12.50 mm punch. The uniformity of 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 compressible. Tablets with acceptable uniformity of weight and drug content were obtained which also disintegrated in less than 15 min. Though the tablets containing 5

% w/w maize starch disintegrated earlier than those of *I-hydrocel* ($P = 0.000$), there was no significant difference for the disintegration time between the tablets containing either *I-hydrocel* or maize starch at 10 and 15 % w/w ($P = 0.296$ and 0.543 respectively). While the friability obtained for the tablets from either disintegrant were less than 1%, the tablets prepared with maize starch generally had higher values of hardness, tensile strength and hardness-friability-ratio (HFR) than those containing *I-hydrocel* ($P = 0.000$). In dissolution rate studies, all the batches of tablets containing either maize starch or *I-hydrocel* released their drug content maximally and above 80 % at 15 min.

Conclusion: The tablets prepared with either *I-hydrocel* or maize starch disintegrated in less than 15 min, but at concentrations of 5 % w/w, paracetamol tablets prepared with maize starch disintegrated earlier than those of *I-hydrocel*. However, 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.

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].

An active pharmaceutical ingredient (API) contained in a solid dosage form has to go into solution in the gastro-intestinal fluid before it could be absorbed and become available in the physiological system. This will be attainable if the solid dosage form disintegrates. 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 process [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 been in use as a disintegrant. Maize starch or potato starch was known to cause tablet disintegration and is still in use in the concentrations 5 -10 %. In addition to starch, other disintegrants include pregelatinised starch (Starch 1500, with effective use at concentrations of 5 -10 % w/w), 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-hydrocel* 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. MATERIAL AND METHODS

2.1 Materials

The following materials were used as procured and includes 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 pulverized and passed through 250 µm size stainless steel sieve. The powder was stored in an amber coloured glass container for further studies.

2.2.2 Preparation of granules containing paracetamol

Table 1: Formula showing percentage composition of ingredients for the preparation of granules containing 500 mg of paracetamol using *I-hydrocel* or maize starch as a disintegrant (expected total tablet weight of 620 mg).

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

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 homogenized 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 (Mettmert, 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.

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 0.5g quantity of the granule, 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, P_t (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:

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

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

$$\text{Particle Density, } p_t = w_2 \times w_3 / v(w_3 - w_4 + w_2 + w) \dots\dots\dots (3)$$

Where: v is the volume of pycnometer, 25 ml, W = weight of empty pycnometer,

W_1 = weight of pycnometer and n- hexane, W_2 = the difference between the W and W_1

W_3 = weight of *granules*, W_4 = 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 Jones and Pilpel [21]. The angle of repose, θ was calculated after three replicate determinations from equation 4 below:

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

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

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

131 $HR = \text{Tapped density} / \text{Bulk density} \dots\dots\dots (5)$

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

133 $\text{Carr's index} = (\text{Tapped density} - \text{Bulk density}) \div \text{Tapped density} \times 100 \dots\dots (6)$

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

135 $\rho = \left(1 - \frac{\text{Bulk density}}{\text{True density}} \right) \times 100 \dots\dots\dots (7).$

136

137 **2.2.4 Compression of tablets**

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

142 **2.2.5 Evaluation of tablet properties**

143 The tablet properties were evaluated out using the methods outlined in the British Pharmacopoeia [24].
 144 Tablets were examined for colour, odour, shape, taste and texture. The uniformity of tablet weight was
 145 studied with 20 tablets (Mettler, Germany) while 10 tablets were used to evaluate for tablet hardness and
 146 thickness respectively using a diametrical digital tablet hardness tester (Veego, India). The friability of 10
 147 tablets from each batch was determined in tablet friabilator (Erweka TAR 220, Germany). A total of 6
 148 tablets per batch was utilised to study the disintegration time using a tablet disintegration apparatus
 149 (Erweka, ZT 122, Germany) in 900 ml of 0.1 N HCl maintained at 37 ± 1 °C. However, the dissolution rate
 150 studies were carried out in a dissolution apparatus (Erweka DT600, Germany). The rotating paddle
 151 method (Apparatus 2) [17, 24], paddle speed, 50 rpm in 900 ml of phosphate buffer (pH 5.8) maintained
 152 at 37 ± 0.5 °C for a dissolution duration of 30 min. A 5 ml of dissolution sample was withdrawn at
 153 predetermined intervals of 5, 10, 15, 20, 25 and 30 min, replacing with the same volume of plain
 154 dissolution medium at the same temperature. The absorbance of each sample was determined in an
 155 ultraviolet (UV) spectrophotometer (Jenway, model 6405, England) at a wavelength of 245 nm.

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

157 $T = 2P/\pi dt$ (8)

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

159 Statistical analysis

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

162 3. RESULTS AND DISCUSSION

164 3.1 Granule properties

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

171

172

173

174 Table 2: Properties of the granules

Ingredient	<i>I-hydrocel</i> (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

175

176 3.2 Tablet properties

177 The properties of the tablets are presented in Table 3. Intact and glossy tablets were obtained. The
 178 uniformity of weight of the respective batches of the tablets was within acceptable range. The British
 179 Pharmacopeia [24] allows a limit of 5 % maximum variation in tablet weight for tablets weighing more than
 180 324 mg. In all the tablet batches studied, the variation in weight falls within the range of 0.39 - 2.79%.
 181 Considering the results of the total drug content uniformity, the values obtained for the respective batches
 182 prepared with IH or MS are within the ranges of 100.46 -102.72 % and 101.78 -102.76 % of paracetamol
 183 content. The British Pharmacopoeia states that the preparation conforms to the test if each individual
 184 content is between 85 % and 115 % of the average content. It also specifies that the preparation fails to
 185 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].

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).

Considering tablet friability, a maximum tablet friability of 1.0 % is acceptable for uncoated tablets formulated for immediate release [17, 26]. Though, generally, the values of tablet friability obtained across the batches of tablets prepared with IH or MS were less than 1.0 %, statistically, there was no significant difference for 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 ($P = 0.000$).

Considering tablet hardness, tensile strength or hardness-friability-ratio (HFR), the tablets prepared with MS presented with higher mechanical strength than those containing IH at all the concentrations studied ($P = 0.000$).

Table 3: Tablet properties

Ingredient	<i>I-hydrocel</i>			<i>Maize starch</i>		
	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/m²)	37.22 ±0.15	95.69 ±0.21	106.68 ±0.67	56.36 ±1.75	67.43 ±0.14	123.48 ±0.17

Figure 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 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.

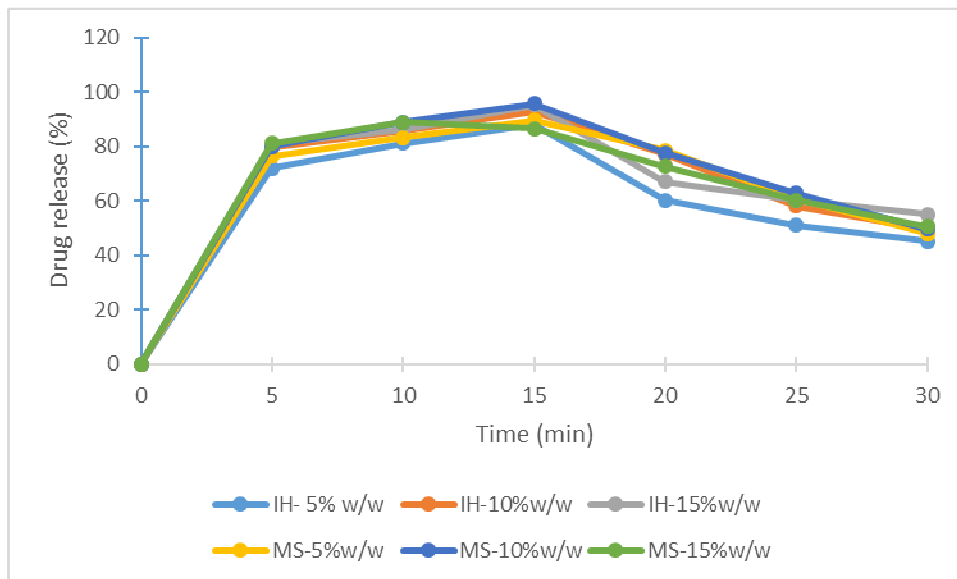


Figure 1: Dissolution profile for tablets prepared with various concentrations of I-hydrocel or maize starch

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 in comparison with the long existing tablet disintegrant, maize starch. Though all the batches of tablets prepared with either IH or MS disintegrated in less than 15 min, tablets prepared with only 5 % w/w of MS disintegrated in a shorter time than those of IH and statistically, there was no significant difference in the disintegration time for tablets prepared with 10-15 % w/w of either IH or MS. However, tablets prepared with MS demonstrated higher mechanical strength than those of IH. The general results indicated that early disintegration of paracetamol was obtained when 5 % w/w of MS was used compared to IH. However, at concentrations of 10 and 15 % w/w similar disintegration outcome was obtained. Therefore, at the concentration of 10 or 15 % w/w, *I-hydrocel* could serve as a substitute for maize starch.

235 **CONSENT**

236
237 It is not applicable

238 239 240 **ETHICAL APPROVAL**

241
242 It is not applicable

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