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MODE OF INCORPORATION OF SUPER DISINTERGRANTS AND THEIR EFFECTS ON THE PROPERTIES OF PARACETAMOL TABLETS

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ABSTRACT

Introduction: Super disintegrants are substances that are used to aid the breakdown of tablets so as to release their active medicament. In this research, crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG) were incorporated intragranularly, extragranularly, both intragranularly and extragranularly into paracetamol tablets so that their effects could be investigated.

Aim: The aim is to compare the effect of three super disintegrants on the tableting properties of paracetamol formulation by wet granulation.

Methods: Granules were prepared and they were characterized for particle size, angle of repose, bulk and tapped densities, Carr's index (CI), and Hausner's ratio (HR). Tablets were compressed from granules weighing 650mg with a single punch press using a 12mm flat faced punch and compressed at 57.5 MPa. The compressed tablets were stored at 75% RH/25 ^{0}C for 24 hours to allow for elastic recovery. Tablet properties such as weight variation, tablet thickness, crushing strength (CS), and disintegration time (DT), and *in vitro* drug release were evaluated.

Results: The results obtained revealed a good flow (with angle of repose < 30^0) for all the batches of granules, CI < 20%, and HR < 1.2 for all batches. All tablets had friability less than 1% which implies they passed the friability test. Tablets with intragranular addition of the super disintegrants had the highest crushing strength and longest disintegration time as compared to the other methods of addition. Tablets with the extragranular addition of super disintegrants had the highest value for Disintegration Efficiency Ratio (DER).

Conclusion: This shows that mode of incorporation of the disintegrant has an effect on the tablet properties. The extragranular addition of super disintegrants is the preferred mode of addition from the results obtained.

Keywords: Crospovidone (CP), Croscarmellose sodium (CCS), Sodium starch glycolate (SSG), super disintegrant, extragranular, intragranular, wet granulation.

INTRODUCTION

Amongst all the available dosage forms, tablets are the most widely used due to their ease and convenience of administration, relative stability compared to the liquid dosage forms and safety when compared to the parenteral dosage forms [1,2]. One very important quality that a tablet must possess is the ability to release the drug into the systemic circulation in a predictable manner [3]. The first step in the release of drug into circulation is the disintegration of the tablet that is facilitated by disintegrants. Disintegrants are substances that aid the

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 1 Issue 1 June, 2021 Page 48 - 57 ISSN: 2971_611X
APSB-05
APSBJournal

tablets break up into small particles when they come in contact with the gastro intestinal fluid which will increase the surface area and promote drug release [4]. A tablet is not useful until its active ingredient is made available for absorption as such the usefulness of disintegrants cannot be over emphasized [5]. A lot of mechanisms have been proposed to describe the action of disintegrants which include: swelling, porosity and capillary action (wicking), heat of wetting, chemical reactions, particle repulsive forces, deformation recovery, enzymatic reactions and gas release [4,6]. Disintegrants can be incorporated by three major ways: intra granularly, extra granularly or by a combination of both methods [7]. A number of materials have been used as disintegrants for pharmaceutical purposes such as starches, gums and celluloses. A class of new disintegrants referred to as super disintegrants are currently in use [8]. Super disintegrants are dispersed within the matrix of the dosage form, when they come in contact with fluid they swell very fast thereby causing a weakening of the structure of the dosage form and this will lead to disintegration [9]. They are effective even at low concentration and have high disintegration efficiency [10]. Some examples of super disintegrants are croscarmellose sodium, sodium starch glycolate and crospovidone [11]. In this study, three superdisintegrants, crospovidone, sodium starch glycolate and croscarmellose sodium were incorporated either intragranularly, extragranularly and partially intragranularly and partially extragranularly in tablet formulations and the tableting properties of crushing strength, disintegration time, friability, disintegration efficiency ratio (DER) and drug release were evaluated.

MATERIALS AND METHODS

MATERIALS

Paracetamol powder (Tiajin Bofa Pharmaceutical Co. Ltd), Lactose, Croscarmellose sodium, Sodium starch glycolate (DFE, Pharma, Klever Strase 187, D- 47574 Goch Germany), Acacia gum (Kerry Ingredients and Flavours Ltd Ireland) Crospovidone. All other materials were of analytical grade.

Preparation of Paracetamol Granules

Paracetamol granules were prepared by wet granulation according to the formula given in Table 1 described by [12,13]. A powder mixture consisting of paracetamol powder, lactose and crospovidone was prepared in a mortar with the aid of a pestle. A binder solution of acacia was incorporated into the powder mixture to obtain a wet mass. Wet screening was carried out by passing the wet mass through a 1.6 mm sieve. The resulting granules were dried in the oven at 40 ºC for 30 minutes. The dried granules were then passed through a 1mm sieve and dried further in the oven at 40 ºC for 1 hour. The entire process was repeated omitting the addition of the super disintegrants intragranularly and also using half the amount of the super disintegrant used.

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 1 Issue 1 June, 2021 Page 48 - 57 ISSN: 2971_611X
APSB-05
APSBJournal

Table 1: Granule Formula for each batch

	Quantity per Tablet (mg)								
Ingredients	1a	1b	1c	2a	2b	2c	3a	3b	3c
PCM 77%	500.50	500.50	500.50	500.50	500.50	500.50	500.50	500.50	500.50
Lactose 6%	39.00	39.00	39.00	39.00	39.00	39.00	39.00	39.00	39.00
Acacia 10%	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00
CP 5%	32.50	32.50	32.50	-	-	-	-	-	-
CC 5%	-	-	-	32.50	32.50	32.50	-	-	-
SSG 5%	-	-	-	-	-	-	32.50	32.50	32.50

Key: PCM = Paracetamol, CP = Crospovidone, CCS = Croscarmellose Sodium, SSG = Sodium starch Glycolate

Angle of Repose

Angle of repose was obtained using the fixed funnel method [12]. A clean funnel was clamped on a retort stand to a height of 10cm from the table top. The outlet of the funnel was plugged. Ten grams of the granules was poured into the funnel. The tip-plug was removed, and the granules were allowed to freely flow to form a conical heap. The height and the radius were measured, and the angle of repose determined using the equation below. A mean of three measurements was obtained for each sample

$Tan\ \theta = h/r$……Equation 1

Where h is the height and r is the radius

Determination of Flow Rate

Flow rate was determined by pouring 10g of the granules into the Erweka flowability apparatus and allowed to flow freely through the orifice. The time taken for the granules to flow out was noted. This was repeated three times for each granule formulation and the average was taken as described by [12]. The flow rate was calculated with the equation below:

FR=W/t …… Equation 2

Where W is the weight in grams and t is the time in seconds

Bulk and Tapped Densities

Ten grams of the granules was weighed and poured gently through a short, stemmed glass funnel into a 100 ml measuring cylinder. The volume V_o was noted. The cylinder was tapped gently 50 times at constant rate on a hard table and the tapped volume V_{50} was noted. The bulk and tapped densities were obtained three times for the sample and a mean of each recorded as described by [12]. Bulk and tapped densities were calculated using the equation below:

$$BD = \frac{Weight\ of\ granules}{Bulk\ volume}$$ ……..Equation 3

$$TD = \frac{Weight\ of\ granules}{Tapped\ volume}$$ ……..Equation 4

Where BD= Bulk density, TD = Tapped density

Carr's Index

The difference between the tapped and bulk densities divided by the tapped density was calculated and ratio expressed as a percentage. This is represented in the equation below:

$$Carr's\ Index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density}\ X\ 100$$

…….. Equation 5

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 1 Issue 1 June, 2021 Page 48 - 57 ISSN: 2971_611X
APSB-05
APSBJournal

Hausner's ratio

This was determined by calculating the ratio of the tapped density to bulk density as seen in the equation below

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

Equation 6

Compression of the granules to Tablets

Each batch of granules was mixed with the extragranular excipients which consist of extra granular superdisintegrant, glidant and the lubricant. The tablets were compressed at 57.5 MPa using a 12 mm punch and die set in a Single Punch Tablet Press. Each tablet weighed 650 mg. After the compression of the tablets, they were stored for 24 hours to allow elastic recovery prior to evaluation of tablet properties.

Table 2. Tablet Formular with the Incorporation of Extragranular Excipients

	Quantity per Tablet (mg)								
Ingredients	**1a**	**1b**	**1c**	**2a**	**2b**	**2c**	**3a**	**3b**	**3c**
PCM 77%	500.50	500.50	500.50	500.50	500.50	500.50	500.50	500.50	500.50
Lactose 6%	39.00	39.00	39.00	39.00	39.00	39.00	39.00	39.00	39.00
Acacia 10%	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00
CP 5%	32.50	32.50	32.50	-	-	-	-	-	-
CCS 5%	-	-	-	32.50	32.50	32.50	-	-	-
SSG 5%	-	-	-	-	-	-	32.50	32.50	32.50
Talc 1%	6.50	6.50	6.50	6.50	6.50	6.50	6.50	6.50	6.50
MST 1%	6.50	6.50	6.50	6.50	6.50	6.50	6.50	6.50	6.50

Key: 1a = intragranular addition of crospovidone, 1b = extragranular addition of crospovidone 1c = partly intragranular and partly extragranular addition of crospovidone, 2a = intragranular addition of croscarmellose sodium, 2b = extragranular addition of croscarmellose sodium, 2c = partly intragranular and partly extragranular addition of croscarmellose sodium, 3a = intragranular addition of sodium starch glycolate, 3b = extragranular addition of sodium starch glycolate, 3c = partly intragranular and partly extragranular addition of sodium starch glycolate, CP = Crospovidone, CCS = Croscarmellose sodium, SSG = Sodium starch glycolate, MST = Magnesium stearate

Uniformity of Weight Test

The uniformity of weight of each tablet formulation was determined using twenty randomly selected tablets according to the British Pharmacopoeia method [12].

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 1 Issue 1 June, 2021 Page 48 - 57 ISSN: 2971_611X
APSB-05
APSBJournal

Measurement of thickness and diameter of the tablets

The thickness and diameter of five tablets selected at random from each batch was determined using a digital vernier caliper [12].

Mechanical strength of tablets

A Monsanto tablet hardness tester was employed to determine the mechanical strength of the tablets. The average force required to crush five Tablets from each batch was obtained and recorded [12].

Friability testing of tablets

To evaluate the degree of friability of the tablets from each batch, five tablets were randomly selected, dusted and weighed. The tablets were placed in a Roche friabilator and subjected to its tumbling actions at 25 revolutions per minute for four minutes. Afterwards, the tablets were once again dusted and reweighed to determine the percentage loss in weight as seen in the equation below

$$\%\ Friability = \frac{Initial\ weight - final\ weight}{Initial\ weight}\ X\ 100$$

……Equation 7

Disintegration Time

Six tablets from each batch were utilized for disintegration studies in distilled water at 37˚C using an Erweka disintegration apparatus. The time taken for the tablets to disintegrate and pass through the mesh was noted and the average disintegration time of the six tablets per batch was noted [12].

Disintegration Efficiency Ratio (DER)

The disintegrant efficiency ratio (DER) was calculated using the relationship

$$DER = \frac{CS/FR}{DT}$$ …… Equation 8

Where CS = Crushing strength, FR = Friability and DT = disintegration time

Dissolution Studies

Dissolution studies were carried out using Erweka Dissolution apparatus (Type DT6, GmbH, Heusenstamm, Germany) under sink conditions. Each tablet was placed in 900 ml 0.1N HCl at 37˚C and a rotating speed of 50 rpm. In all the batches, 5 ml of the sample was withdrawn at time intervals of 5,10,15, 30, 45 and 60 min and replaced with an equal volume of 0.1N HCl after each withdrawal to maintain sink conditions. The withdrawn samples were filtered and assayed spectrophotometrically at 245 nm using the UV spectrophotometer (UV – 1800 Spectrophotometer, Shimadzu Corporation, USA).

RESULTS

Physical Properties of the Paracetamol Granules

Table 3 displays the physical properties of the paracetamol granules prepared for all the batches. The mean granule size (MGS) ranged from 275.6 – 367.1 µm for the formulations containing the superdisintegrants as intragranular disintegrants, the MGS ranged from 352.4 – 368.3 µm for the formulations that contained the superdisintegrants as extragranular disintegrants and the MGS ranged from 293.9 – 382.8 µm for the formulations that contained the superdisintegrants as partially intragranular and partially extragranular. The formulations that contained the superdisintegrants as intragranular disintegrants had a lower MGS as compared to the others.

The angle of repose of all the formulations with the different mode of incorporation of superdisintegrants were less than 30 ^{0}C

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 1 Issue 1 June, 2021 Page 48 - 57 ISSN: 2971_611X
APSB-05
APSBJournal

which implies that all the batches had good flow properties irrespective of the mode of incorporation of the superdisintegrant. It must however be noted that the formulations that had the disintegrant incorporated intragranularly had the lowest angle of repose which implies a better flow. The bulk and tapped densities ranged from 0.37 – 0.58 g/mL across all the batches and the Hausner's ratio and Carr's index are consistent with the angle of repose.

For all the properties of the granules that were evaluated, it was observed that irrespective of the mode of incorporation of the disintegrants the results observed were similar.

Table 3: Physical Properties of Paracetamol Granules

Batches	1a	1b	1c	2a	2b	2c	3a	3b	3c
Mean Granule Size (µm)	357.10	368.30	382.20	275.60	332.30	293.90	289.60	352.40	327.70
Standard Deviation for Mean Granule size	357.10 (0.01)	368.30 (0.02)	382.20 (0.02)	275.60 (0.03)	332.30 (0.01)	293.90 (0.01)	289.60 (0.04)	352.40 (0.01)	327.70 (0.03)
Flow rate (g/s)	2.50 (0.02)	2.63 (0.01)	2.70 (0.01)	2.40 (0.00)	2.45 (0.03)	2.50 (0.02)	2.60 (0.03)	2.72 (0.01)	2.70 (0.00)
Angle of repose (^{0})	25.00 (0.02)	26.00 (0.01)	25.00 (0.01)	25.00 (0.02)	26.20 (0.03)	25.00 (0.01)	25.00 (0.04)	25.30 (0.02)	26.10 (0.01)
Bulk density (g/ml)	0.42 (0.01)	0.51 (0.01)	0.45 (0.03)	0.37 (0.01)	0.45 (0.01)	0.43 (0.02)	0.38 (0.00)	0.45 (0.01)	0.41 (0.02)
Tapped density (g.ml)	0.47 (0.03)	0.58 (0.01)	0.51 (0.01)	0.42 (0.02)	0.51 (0.01)	0.50 (0.02)	0.43 (0.02)	0.52 (0.01)	0.46 (0.01)
Carr's index %	11.00 (0.01)	12.00 (0.02)	12.00 (0.01)	12.00 (0.01)	12.00 (0.02)	14.00 (0.01)	12.00 (0.03)	13.00 (0.01)	11.00 (0.01)
Hausner's ratio	1.11 (0.01)	1.14 (0.01)	1.13 (0.04)	1.13 (0.02)	1.11 (0.03)	1.16 (0.01)	1.13 (0.02)	1.16 (0.01)	1.12 (0,01)

Key: 1a = intragranular addition of crospovidone
1b = extragranular addition of crospovidone
1c = partly intragranular and partly extragranular addition of crospovidone
2a = intragranular addition of croscarmellose sodium
2b = extragranular addition of croscarmellose sodium
2c = partly intragranular and partly extragranular addition of croscarmellose sodium
3a = intragranular addition of sodium starch glycolate
3b = extragranular addition of sodium starch glycolate
3c = partly intragranular and partly extragranular addition of sodium starch glycolate

Physical Properties of Paracetamol Tablets

The physical properties of the paracetamol tablets produced from the 9 batches are presented in Table 4. The mean weight of the tablets ranged from 640mg – 660mg for all the batches. The mean weight of the tablet, the thickness and the diameter of the tablets seemed to have a correlation as the tablet with the highest weight had the highest values for thickness and diameter.

For all the batches, tablets formulations with the intragranular disintegrants had the highest crushing strength, followed by the one with

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 1 Issue 1 June, 2021 Page 48 - 57 ISSN: 2971_611X
APSB-05
APSBJournal

the extragranular disintegrants and lastly the one with partial intragranular disintegrants and partial extragranular disintegrants. The batch of tablets that had the disintegrants incorporated intragranularly had the longest disintegration time which correlated with their crushing strength because they had the highest crushing strength, batches of tablets with partial intragranular disintegrants and partial extragranular disintegrants were the next and the batches with extragranular disintegrants had the shortest disintegration time. Tablet friability for all the batches was less than 1 % which implies all the batches of tablets passed the British Pharmacopeia requirements. The batch of the tablets that had the disintegrant incorporated partially intragranular and partially extragranular was selected for the dissolution studies. The time taken to release 50 % of the drug (T_{50}) ranged between 15.65minutes and 32.68 minutes. The batch 2c with had croscarmellose sodium as the disintegrant took the shortest time to release 50 % of the drug and it also took the shortest time to release 100 % of the drug (42.60min). Tablets that had the extra granular addition of disintegrants had the highest value for DER amongst all the batches of tablets formulated.

Table 4. Physical Properties of Paracetamol Tablets

Batches	Mean weight (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Friability (%)	DT (mins)	DER
1a	640 (0.72)	5.19 (0.07)	12.09 (0.01)	64.72 (0.02)	0.19	7.50 (0.02)	45.42
1b	650 (0.54)	5.21 (0.02	12.13 (0.01)	53.94 (0.01)	0.50	2.00 (0.01)	53.94
1c	650 (0.20)	5.25 (0.01)	12.14 (0.01)	29.42 (0.05)	0.79	5.00 (0.01)	7.45
2a	640 (0.26)	5.18 (0.04)	12.01 (0.02)	73.35 (0.02)	0.20	7.00 (0.03)	52.39
2b	660 (0.33)	5.28 (0.01)	12.06 (0.02)	60.80 (0.02)	0.50	2.00 (0.02)	60.80
2c	660 (0.35)	5.27 (0.08)	12.05 (0.01)	41.19(0.01)	0.65	6.00 (0.01)	10.56
3a	640 (0.30)	5.17 (0.12)	12.03 (0.04)	78.45 (0.02)	0.36	9.00 (0.01)	24.21
3b	650 (0.08)	5.18 (0.07)	12.02 (0.01)	63.74 (0.03)	0.60	3.00 (0.03)	35.41
3c	640 (0.14)	5.15 (0.01)	12.02 (0.04)	43.15 (0.01)	0.90	6.50 (0.02)	7.38

Key: DT = Disintegration time

Table 5: Dissolution Data

Batches	T_{50} (Mins)	T_{100} (Mins)
1c	30.95	48.52
2c	15.65	42.60
3c	32.68	57.80

Keys: 1c = cross povidone, 2c = cross carmellose sodium, 3c = sodium starch glycolate

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 1 Issue 1 June, 2021 Page 48 - 57 ISSN: 2971_611X
APSB-05
APSBJournal

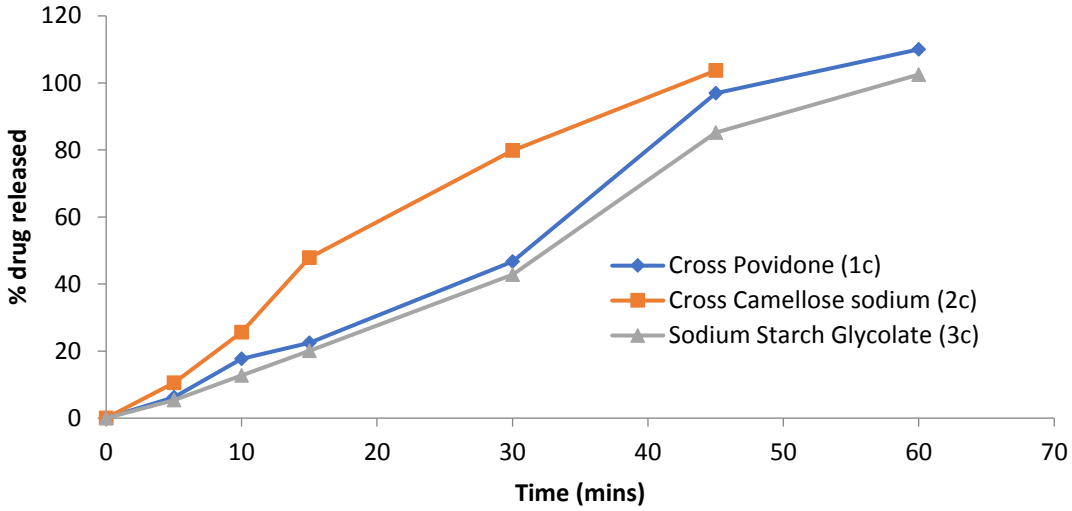

Figure 1: *Invitro* Release of Paracetamol Tablets

DISCUSSION

The results of this study show that the tablets that had the disintegrant incorporated intragranularly for the three super disintegrants used has the highest crushing strength and the ones that had partial intragranular and partial extragranular incorporation of the disintegrants had the lowest crushing strength across the batches. The higher crushing strength in the tablets that had the disintegrant incorporated intragranularly is consistent with the report of Odeku and Akinwade [12], and the report of Odeniyi and Ayorinde [3] who reported higher crushing strength for tablets that had sodium starch glycolate incorporated intragranularly. Crushing strength is an important property of a tablet because it gives an idea of how much of the stress the tablet can withstand during handling however care must be taken so as not to formulate a tablet that will not disintegrate to release its active constituents.

For all the batches of tablets formulated, the batch with the disintegrant incorporated extra granularly had the lowest disintegration time compared to the other two batches, this is consistent with the works of Adeoye and Alebiowu [13] and Odeku and Akinwande [12] who both reported faster disintegration time with the tablets produced with the extragranular disintegrants. This has been attributed to the fact that a large amount of the disintegrant comes in contact with the disintegration fluid which will result in absorption of large amounts of the fluid in a short while that will give rise to fast disintegration [11]. From the results, it was observed that tablets that had sodium starch glycolate had higher crushing strength and longer disintegration times when compared with the tablets that contained crosscarmellose sodium and crospovidone. This may be attributed to the different mechanisms by which these super disintegrants act. Crospovidone is said to disintergrate tablets faster [17] and it has been proposed to act by wicking, swelling and strain recovery [18]. Crosscarmellose sodium has the proposed mechanism of swelling, wicking and strain recovery while

sodium starch glycolate has the proposed mechanism of swelling [18–20]. Sodium starch glycolate is able to exhibit a very high degree of swelling due to its ability to carry out three dimensional swelling [20]. DER which is a measure of the balance between the mechanical and disintegrant properties of tablets, takes into the consideration the negative effects on disintegration time and weakness related to friability. Tablets with better balance have higher DER values [15,16]. It was observed that the tablets with the extragranular addition of the disintegrant had a higher DER for the three superdisintegrants used which implies that they had a better balance between the mechanical and disintegration properties, this finding is consistent with the report of Apeji *et al* [11].

Tablets that were formulated with sodium starch glycolate had higher crushing strength and longer disintegration times as compared to those formulated with crospovidone and croscarmellose sodium and this reflected in the results of the dissolution studies as tablets formulated with sodium starch glycolate had the longest dissolution time and tablets formulated with croscarmellose sodium had the shortest disintegration time and the shortest dissolution time.

CONCLUSION

In conclusion, the mode of incorporation of the super disintegrant has been seen to have effect on the properties of the tablets formulated. Tablets with Intragranular addition of the superdisintegrants had the highest crushing strength and longest disintegration time as compared to the other methods of addition. tablets with the extragranular addition of superdisintegrants had the highest value for Disintegration Efficiency Ratio (DER). From the results obtained in this experiment, the extragranular addition of super disintegrants had a better balance so it can be said to be the preferred mode of addition. It's therefore important to carefully select the method of incorporation of the superdisintegrant that will be used in any formulation so the formulator can get a balance of tableting properties.

Conflict of Interest: The authors have neither financial disclosure nor any other conflict of interests.

Credit Authorship Contribution Statement: OOA: Conceptualization, methodology, writing, supervision; DFD: Methodology, writing; AYE: Conceptualization, writing, review and editing
ASN: Writing, review and editing

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