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The Use of Multifunctional Starch Based Coprocessed Excipients (Starac) in the Formulation of Metronidazole Tablets by Direct Compression

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ABSTRACT

The aim of this work was to use coprocessed particles of maize starch (MS) and acacia gum (Ac) (StarAc) as multifunctional excipients in the formulation of metronidazole tablets by direct compression (DC). Weighed quantities of MS and Ac at mixing ratios of 95:5 and 90:10 were used to form the coprocessed excipients; StarAc 955 and StarAc 9010 respectively. StarAc (955 & 9010) were evaluated for micromeritics and self-disintegrating properties as well as diluent/binder/disintegrant in the formulation of metronidazole tablets. The results of micromeritic properties revealed that the coprocessed excipients StarAc 955 and StarAc 9010 have good flow properties. The results of tablet properties showed that metronidazole tablets produced with StarAc 9010 were mechanically stronger (8.5Kgf) than those produced with StarAc 955 (5.5Kgf) but they have longer disintegration times (11.68 min) than StarAc 955 tablets (2.04 min) respectively. There was synergy of functionality improvement when StarAc 955 and StarAc 9010 were combined with Ludipress® and Avicel® PH 200. This study further revealed that StarAc 955 and StarAc 9010 possess self-disintegrating property and could be used as multifunctional excipients in the formulation of poorly compressible drug such as metronidazole into tablets by DC method.

KEYWORDS: Maize starch, Acacia gum, StarAc 955, StarAc 9010, Coprocessed excipients, Direct compression.

INTRODUCTION

The formulation of a tablet involves combining the active pharmaceutical ingredient (API) i.e. the "drug", with pharmacologically inactive ingredients called "excipients. Excipients aid in the manufacturing and performance of a dosage form, and serve different purposes as diluents, binder, disintegrant, glidant and lubricant. Thus, excipients can be called as the "functional components" of a formulation [1]. The oral route is the most common mode of administering drugs and among the oral dosage forms, tablets of various kind are the most common type of solid dosage form in contemporary use.

Tablets are produced by granulation compression or direct compression. Granulation compression is achieved both by wet or dry granulation, which involves many steps and it is labour intensive. Direct compression (DC) on the other hand involves few steps and is achieved by blending the API and other excipients and compressed. It is cost effective and efficient process. Direct compression is preferred method of tabletting, however, only few

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pharmaceutical excipients can function as DC excipients because of the essential properties of powder fluidity and compressibility [2, 3].

Direct compression process is directly influence by the properties of the excipients. The physico-mechanical properties of excipients that ensure good tabletting are good flowability, good compressibility, low or no moisture sensitivity and formation of good tablets even in high-speed tableting machinery with reduced dwell times [4,5]. The majority of excipients that are currently available cannot fulfil all these functionality requirements, thus creating the need for the development of new multifunctional excipients.

Coprocessing is a novel concept of processing two or more established excipients by some appropriate means to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients [6]. This allows production of high-functionality excipients to the formulator's advantage. The high functionality can be in terms of improved process ability such as flow properties, compressibility, content uniformity, dilution potential, and lubricant sensitivity, or improved performances such as disintegration and dissolution profile [7]. The major advantages of coprocessed excipients are the elimination of wet granulation production stages, avoidance of keeping and handling excipients, and the synergistic effect of having homogenous free flowing directly compressible formulation of the required excipients. Coprocessing of excipients cause them to interact at the subparticle level and lead to superior properties than single physical mixtures of their components [4].

Coprocessed excipients are introduced to fulfil the increasing demand of multifunctional excipients for direct compression tabletting [5]. Several of these excipients are commercially available e.g. Ludipress® (lactose, polyvinylpyrollidone and crosspovidone), Cellactose and Microlac (lactose and cellulose), StarLac (starch and lactose), Prosolv (microcrystalline cellulose and silicon dioxide), StarCap (maize starch and pregelatinized starch) etc. [3,4,5,8,9].

Native starches possess good compacting properties, but due to poor flowability and high lubricant sensitivity they are not suitable for use as DC binders [10]. The flowability of maize starch is very poor because of the small size of starch grain [11]. A directly compressible excipient should be free flowing. Many common manufacturing problems are attributed to incorrect powder flow, including non-uniformity in tablet weight, under or over dosage and inaccurate filling [8]. Therefore, agglomeration of starch particles by granulation or pregelatinization would improve the flow and tabletting properties of starches [12, 13].

Olowosulu et al.,[14] reported studies on novel coprocessed excipients of maize starch and acacia gum (StarAc) for the first time. The coprocessed excipients were prepared using simple technique of co-drying aqueous mixtures of maize starch and acacia gum. The commercially available coprocessed excipients are mainly prepared by spray drying. The spray drying process is burdensome and a relatively expensive procedure [15]. The simple technique described in producing StarAc may be of advantage in manufacturing industries because of its potential cost-effectiveness. These new starch based products were shown to have good flowability and high tensile strength, as well as low lubricant sensitivity and a good disintegration potential which is suitable as direct compression excipients. StarAc excipients also, showed better tabletting performance than pregelatinized starch and the physical mixtures of the excipients in the same ratio of components as the coprocessed excipients [16]. This was attributed to increase in structural strength due to presence of acacia gum in the particle structure of StarAc. Acacia gum gathered together starch particles into larger, permanent aggregates, leading to improvement in their flowability and compactability as well as reduction in lubricant sensitivity of the excipient.

This paper reports the results of micromeritic and self-disintegrating properties of StarAc 955 and StarAc 9010 as well as their use as filler-binder-disintegrant in the formulation of directly compressed metronidazole tablet formulations. Metronidazole was chosen due to its poor compressibility and it therefore, required the addition of a filler/binder in order to produce tablets of acceptable quality.

RESULTS AND DISCUSSION

Micromeritic Properties of StarAc and Some Commercial DC Excipients

Comparative physical properties of StarAc 955 and StarAc 9010 and some commercial DC excipients namely; Ludipress® (LDP), a coprocessed excipient, Avicel® PH 200 (MCC 200), large particle size MCC intended for direct compression and Avicel® PH 101 (MCC 101) are shown in Table 2. The coprocessed excipients have higher bulk and tapped densities than the commercial DC excipients. This shows that the

coprocessed excipients would have better blending with active pharmaceutical ingredients than the other DC excipients [20]. The angle of repose of pharmaceutical powders range between 25 - 45°, the lower values indicate a better flow than the higher values [21]. Based on the angle of repose and flow rate, the flow properties of the excipients might be ranked in decreasing order as follows: StarAc 9010>StarAc 955>Ludipress>MCC PH 200>MCC 101. The Carr's index (CI) and Hausner's ratio (HR) are indirect measure of powder flow properties. Based on CI and HR the StarAc 9010 excipient had the best flow when compared with the other excipients. MCC 101 powder had the poorest flow judging from the values obtained from the flow indices.

Table 1: Tablet composition of various batches of tablet containing metronidazole as active pharmaceutical ingredient

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Metronidazole (mg)	200	200	200	200	200	200	200	200	200	200	200	200
StarAc 955 (mg)	418	-	-	-	-	444	-	-	209	209		-
StarAc 9010 (mg)	-	418	-	-	-	-	444	-	-	-	209	209
Ludipress (mg)	-	-	418	-	-	-	-	444	209	-	209	-
Avicel PH 200 (mg)	-	-	-	418	-	-	-	-	-	209	-	209
Avicel PH 101 (mg)	-	-	-	-	418	-	-	-	-	-	-	-
Corn starch (mg)	26	26	26	26	26	-	-	-	26	26	-	-
Talc (mg)	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate (mg)	3	3	3	3	3	3	3	3	3	3	3	3
Tablet weight (mg)	650	650	650	650	650	650	650	650	650	650	650	650

Table 2: Physical properties of StarAc and some commercial DC excipients

Physical Properties	PI	PII	PIII	PIV	PV
Bulk density	0.63	0.63	0.49	0.41	0.39
(g cm^{-3})	(0.02)[b]	(0.01)	(0.01)	(0.03)	(0.07)
Tapped density	0.77	0.75	0.59	0.48	0.50
(g cm^{-3})	(0.07)	(0.04)	(0.01)	(0.02)	(0.10)
Angle of Repose (°)	30.9°	30.2°	30.8°	31.2°	40.5°
	(1.23)	(0.84)	(2.11)	(2.39)	(1.23)
Flow rate (g sec^{-1})	9.31	10.2	8.44	5.05	0.83
	(0.49)	(0.52)	(0.45)	(0.18)	(0.03)
Carr's index (%)	18.18	14.9	17.51	14.63	23.00
	(1.47)	(5.62)	(1.96)	(2.51)	(0.11)
Hausner's ratio	1.22	1.19	1.21	1.21	1.28
	(0.08)	(0.05)	(0.03)	(0.07)	(0.08)

Key: PI (StarAc 955), PII (StarAc 9010), PIII (Ludipress), PIV (MCC PH 200) and PV (MCC PH 101).
[b]Values in parentheses are standard deviations $n = 3$

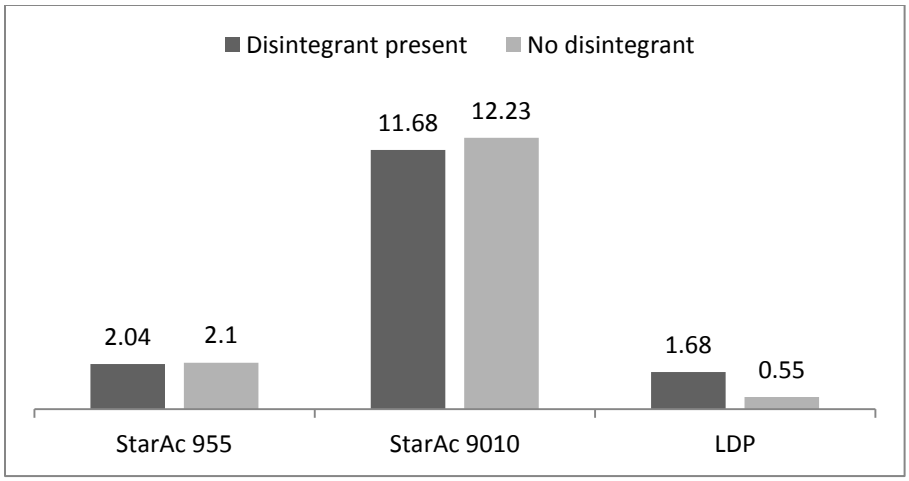

Fig. 1: Disintegration times of metronidazole tablet formulations with and without disintegrate

Table 3: Values of crushing strength (CS), friability (F), crushing strength-friability ratio (CSFR), CSFR/disintegration time (CSFR/DT) and tensile strength (TS) of metronidazole tablets formulated using the various excipients

Excipient	CS (Kgf)	F (%)	CSFR	CSFR/DT	TS (MNm^{-2})
F1	5.39 ± 0.00	1.84 ± 0.54	2.929	1.44	0.53
F2	8.33 ± 0.29	0.61 ± 0.03	13.66	1.17	0.90
F3	10.78 ± 2.00	0.79 ± 0.64	13.65	8.12	1.16
F4	12.74 ± 0.09	0.21 ± 0.39	60.67	15.21	1.36
F5	8.00 ± 0.71	2.2 ± 0.21	3.64	0.38	0.75
F6	5.88 ± 0.09	1.63 ± 0.39	3.61	1.72	0.63
F7	9.80 ± 0.00	0.55 ± 0.53	17.82	1.46	1.03
F8	9.11 ± 1.04	0.79 ± 0.17	11.54	20.98	0.98
F9	7.84 ± 0.00	0.87 ± 0.53	8.45	3.00	0.78
F10	11.07 ± 1.04	0.33 ± 0.17	36.92	34.19	1.18
F11	10.49 ± 1.04	0.61 ± 0.17	17.19	2.61	1.12
F12	12.25 ± 0.00	0.5 ± 0.03	24.50	6.48	1.30

F1 (StarAc 955), F2 (StarAc 9010), F3 (LDP), F4 (MCC 200), F5 (MCC 101), F6 (StarAc 955 No disintegrant), F7 (StarAc 9010 No disintegrant), F8 (LDP No disintegrant), F9 (StarAc 955:LDP), F10 (StarAc 955:MCC 200), F11 (StarAc 9010:LDP) and F12 (StarAc 9010:MCC 200)

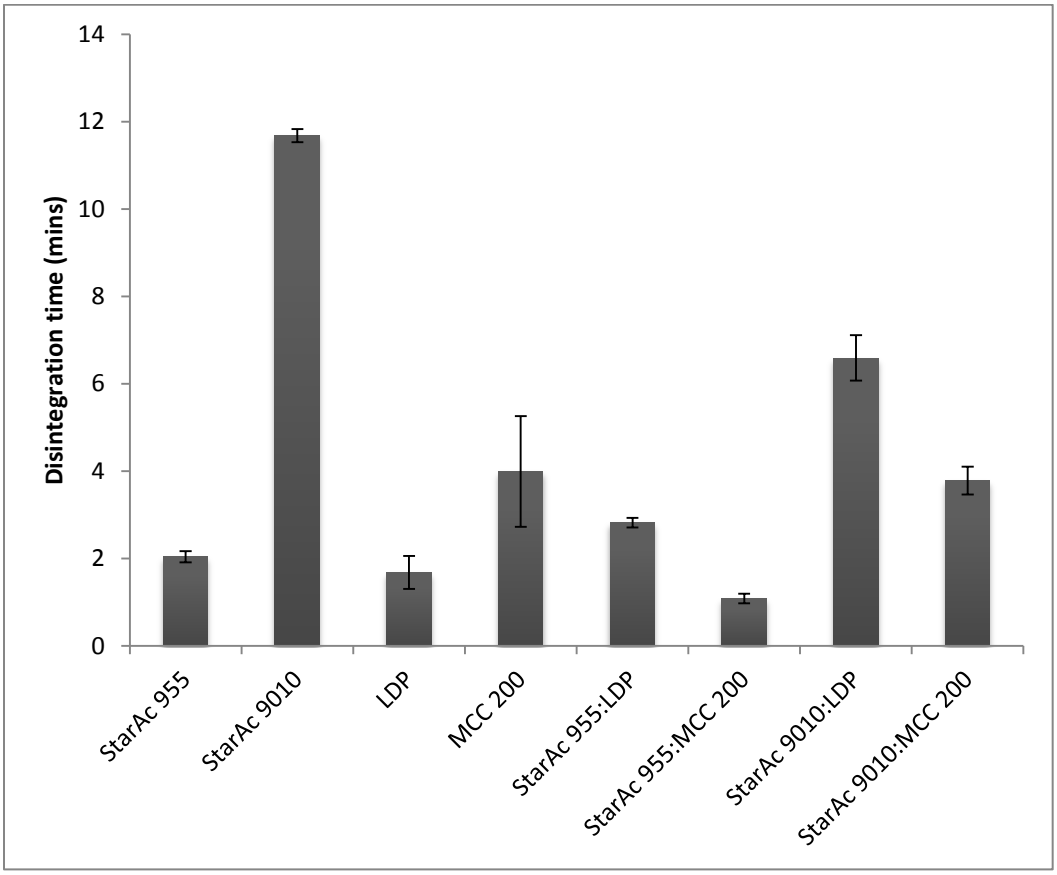

Fig. 2: Disintegration times of various metronidazole tablet formulations containing various excipients alone and in combination

Evaluation of the coprocessed excipient as filler-binder-disintegrant

The filler-binder-disintegrant properties of the coprocessed excipients were evaluated using the disintegration time and crushing strength friability/ disintegration time ratio (CSFR/DT) ratio to assess their disintegrant property [22,23]. The CSFR/DT ratio of a tablet formulation is an index of tablet quality which measures tablet strength (crushing strength) as well as the tablet weakness (friability), and simultaneously evaluates any negative effects of these parameters on disintegration time [22,23]. In general, higher values of the CSFR/DT ratio indicate a better balance between binding and disintegration properties. The filler-binder-disintegrant properties of the coprocessed excipients were investigated using Ludipress to provide basis for comparison. Ludipress has crospovidone (a superdisintegrant) in its particle structure as such it has self-disintegrating property.

The result of the disintegration times of metronidazole tablets formulated with and without disintegrant in their tablet formula are depicted in Fig. 1. The disintegration times of metronidazole tablets made with the excipients namely; StarAc 955, StarAc 9010 and LDP without disintegrants in the tablet formulae (F6-F9) are as follows: 2.10, 12.23 and 0.55 minutes respectively compared with those that contained disintegrants in their tablet formulae in the same order are as follows: 2.04, 11.68 and 1.68 min respectively. All the disintegration time values were within the official limits of 15 min. The presence of disintegrant in the metronidazole tablets did not significantly improved the disintegration time of the coprocessed excipients, especially the StarAc 9010 excipient.

Furthermore, the CSFR/DT ratio was used for the assessment of the disintegrant activity and strength of metronidazole tablets made with the various

excipients. There was a general increase in the CSFR/DT ratio for the excipients which did not contain disintegrant than those which contained disintegrant (Table 3). Metronidazole tablet formulations made with StarAc 955 and StarAc 9010 without added disintegrant in their tablet formulae had higher values of TS and CSFR than those with added disintegrant (4% corn starch) in their tablet formulae.

StarAc 955 and StarAc 9010 have high starch content and this may be responsible for their self-disintegrating properties. Expectedly, metronidazole tablets containing StarAc 9010 powder had longer disintegration time as well as lower CSFR/DT ratio than those containing StarAc 955 powder because of their higher acacia gum concentration.

Tabletting characteristics of binary mixtures of excipients

In order to study the effect of combination of coprocessed excipients (StarAc 955 & StarAc 9010) with other filler-binders, tablets were prepared with 1:1 mixtures of StarAc with LDP and MCC 200.

The mechanical properties of the metronidazole tablet formulations containing the excipients alone and in combination were assessed by crushing strength (CS) and friability (F) of the tablets. Furthermore, the crushing strength-friability ratio (CSFR) which, also provides a parameter for measuring tablet strength [23, 24, 25] and tensile strength (a measure of bond strength) were also used to assess the mechanical properties of the various tablet formulations. Generally the higher the CSFR value, the stronger the tablet. The CS, F, CSFR and TS values for various metronidazole tablet formulations made with the excipients are presented in Table 3.

The ranked order of CS and TS for the single excipients is as follows: MCC 200>LDP>StarAc 9010>StarAc 955. The rank order for the friability value for the excipients is as follows: MCC 200<StarAc 9010<LDP<StarAc 955.

The binary mixtures of the coprocessed excipients (StarAc 955 & StarAc 9010) with commercial DC excipients LDP and MCC 200 showed a marked improvement in their mechanical properties as compared with the coprocessed excipients. The values of CS, TS and CSFR of the binary mixtures were higher than those of StarAc 955 and StarAc 9010 alone. The combinations of the coprocessed excipients with MCC 200 were superior to the combination with LDP in terms of compact strength and friability values. The ranked order of CSFR is as follows StarAc 955:MCC 200>StarAc 9010:MCC 200>StarAc 9010:LDP>StarAc 955:LDP. This shows that for improved tabletting performance the coprocessed excipients are better combined with MCC PH 200. The coprocessed excipients and MCC 200 both deform plastically on application of pressure [16] and it does seem that this made their combinations with MCC 200 to be better than those with LDP which deforms by primarily by brittle fracture [26].

The disintegration times of various metronidazole tablet formulations made with various DC excipients alone and in combination are presented in Fig. 2. There was a marked reduction in the disintegration time of the combination of StarAc 9010 with LDP and MCC 200. Similarly, the combination of StarAc 955 with MCC 200 led to a reduction in disintegration time. A slight increase in disintegration time of StarAc 955 and LDP was observed. The histograms also showed that the combination of the coprocessed excipients (StarAc 955 & StarAc 9010) with MCC 200 exhibited lower values of disintegration time than the combination with LDP. Therefore, MCC 200 is a better excipient to combine with the coprocessed excipients where tablets with adequate bond strengths and effective tablet disintegration are required.

A synergy of functionality improvement was achieved, when the coprocessed excipients (StarAc 955 & StarAc 9010) were combined with commercially available DC excipient (LDP & MCC 200). The commercial DC excipients imparted higher compactibility on the combination, while the coprocessed excipients increase the disintegration efficiency of the combination because of their higher starch contents.

CONCLUSIONS

Coprocessing MS and Ac resulted in a considerable improvement in the functionality of starch as directly compressible excipients. Tablets produced with StarAc 9010 were mechanically stronger than those produced with StarAc 955 but had longer disintegration time. StarAc 955 and StarAc 9010 possess self-disintegrating property. There was synergy of functionality improvement when StarAc was combined with some commercial DC excipients,

especially combination with MCC PH 200. Therefore, StarAc 955 and StarAc 9010 excipients were found to be suitable in the formulation of robust metronidazole tablets by direct compression.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of this article.

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