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DESIGN AND EVALUATION OF LOW COST DIRECTLY COMPRESSIBLE EXCIPIENTS

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ABSTRACT

Co-processed directly compressible excipients by wet granulation method were prepared using a native food grade corn-starch (Manibhadra Food Products, Hubli, Karnataka) along with mannitol, maltodextrin and dicalcium phosphate dihydrate in different ratios. The developed excipients were evaluated for hygroscopicity, Carr's index and Hausner's ratio in comparison with commercial variety of corn-starch (SD fine Chem. Mumbai), as the control. The hygroscopicity of the developed excipients was found to be in the range of 1-3%, Carr's index in the range of 5.17-38.0% and Hausner's ratio in the range of 1.09-1.71. Among all the twenty-one prepared excipients, ten were found to be promising based on the above parameters (Carr's index <15% and Hausner's ratio <1.18%).

KEYWORDS: Coprocessing; directly compressible excipients; mannitol; maltodextrin; dicalcium phosphate dihydrate.

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INTRODUCTION

Over the past hundred years tablet manufacturers have developed materials and processes that can produce compressed tablets containing a precise amount of an active pharmaceutical ingredient (API) at high speed and at relatively low cost. The developments in the fields of APIs, excipients and tableting machines during the past decades have made tablet manufacturing a science and the tablets the most commonly used dosage form[1,2]. The ease of manufacturing, convenience in administration, accurate dosing, and stability compared to oral liquids, tamper-proofness compared to capsules, safe compared to parenteral dosage forms makes it a popular and versatile dosage form. Experts in the art of tableting are aware with the basic art of tableting employing the three well known methods, i.e., wet granulation, roller compaction and direct compression [3-5].

Current usage of the term "direct compression" is used to define the process by which tablets are compressed directly from the powder blends of active ingredient and suitable excipients. No pre-treatment of the powder blends by wet or dry granulation is involved[5]. The simplicity of the direct compression process is apparent from a comparison of the steps involved in the manufacture of tablets by wet granulation, roller compaction and direct compression techniques. It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets[4]. The rest of the materials lack flow, cohesion or lubricating properties necessary for the production of tablets by direct compression. The use of directly compressible adjuvants may yield satisfactory tablets for such materials[3].

Advantages of direct compression over wet granulation include: 1) It is economic, since the direct compression requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost of tablets. 2) It is more suitable for moisture and heat sensitive drugs, since it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental effects. 3) Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulation[5]. 4) Disintegration or dissolution is the rate-limiting step in absorption in the case of tablets of poorly soluble drug prepared by wet granulation. The tablets prepared by direct compression disintegrate into drug particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution. 5) Due to fewer unit operations, the validation and documentation requirements are reduced. 6) Due to the absence of water in granulation, chance of microbial growth is minimal in tablets prepared by direct compression[6].

Directly compressible adjuvants can be prepared by various methods, viz., physical modification, crystallization, granulation/agglomeration, spray drying, co-processing, co-precipitation and dehydration. Co-processing is one of the most widely explored and commercially utilized methods for the preparation of directly compressible adjuvants. It is interesting because the products are physically modified in a special way without altering the chemical structure. A fixed and homogenous distribution for the components is achieved by embedding them within mini-granules. Segregation is diminished by adhesion of the actives on the porous particles making process validation and in-process control easy and reliable[7]. Hence, aim of the present investigation is to develop co-processed directly compressible excipients by wet granulation method using a native food grade corn-starch (Manibhadra Food products, Hubli, Karnataka) along with mannitol, maltodextrin and dicalcium phosphate dihydrate in different ratios. The developed excipients were evaluated for hygroscopicity, Carr's index and Hausner's ratio in comparison with commercial variety of corn-starch (SD Fine Chem., Mumbai), as the control.

MATERIALS AND METHODS

Maltodextrin was a generous gift from S.A.Pharmachem Pvt.Ltd,.Mumbai. Food grade corn starch (Manibhadra food products, Hubli) was purchased from the local market. Corn starch (laboratory grade) and D-mannitol were procured from SD Fine Chem, Mumbai. Dicalcium Phosphate dihydrate was obtained from E. Merck (India) Pvt. Ltd., .Mumbai. All other chemicals used were of analytical reagent grade.

Development of Directly Compressible Excipients

Directly compressible excipients were developed by co-processing technique, viz., wet granulation method. Corn starch, mannitol, dicalcium phosphate dihydrate and maltodextrin were used in different ratios according to the formulae given in Table 1. Method: All the ingredients were powdered separately in a dry, clean porcelain mortar, passed through #60 mesh sieve and mixed well in geometrical ratio. Granulating fluid is added to the powder mixture, small quantity at a time, while mixing thoroughly after each addition, until a coherent mass is formed. Then it is passed through # 44 mesh sieve and the wet granules were spread on a paper and dried in hot air oven at 55^{o}-60^{o} C (after 30 minutes air drying to remove residual alcohol). The dried granules were then passed through # 36 mesh sieve. Composition and formulation codes of various directly compressible excipients prepared are shown in **Table 1**.

Preparation of Starch Paste

Starch (6,10 or 14 g) was dispersed in 100 ml distilled water at ambient conditions and heated on a water bath for 80^{o} C for 15 min to obtain a gel of binder solution[8].

Evaluation of Directly Compressible Excipients[9]

Many factors influence the choice of the directly compressible adjuvant to be used in a tablet formulation. These factors vary from the primary properties of powder (particle size, shape, bulk density, solubility) and the characteristics needed for making compacts (compressibility and flowability) to factors affecting stability and pharmacopoeial acceptability. The prepared directly compressible adjuvants were evaluated for:

Bulk Density (D_b): It is the ratio of total mass of powder to the bulk volume of powder to the bulk volume powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/ml and is given by: $D_b = M / V_0$, Where, M is the mass of powder, V_0 is the bulk volume of the powder

Tapped Density (D_t): It is the ratio of total mass of powder to the tapped volume of powder. The volume (V_{500}) was measured by tapping the powder for 500 times. Then the tapping was done for additional 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2 %). If it is more than 2%, tapping is continued for 1250 times (for a total of 2500 times) and tapped volume (V_{2500}) was noted. It is expressed in g/ml and is given by: $D_t = M / V_t$, Where, M is the mass of powder, V_t is the tapped volume of the powder

Carr's Index (%): The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping a measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density. Carr's index = 100 x (Tapped density- Bulk density) / Tapped density

Hausner's Ratio: Hausner's ratio is the ratio of tapped density (calculated using V_{2500} ie, volume after 2500 tappings) to bulk density. Lower the value of Hausner's ratio better is the flow property and is calculated using the formula: Hausner's ratio = Tapped Density / Bulk Density.

Hygroscopicity: The % moisture absorption of all the developed excipients were determined under ambient temperature and humidity conditions by exposing an accurately weighted quantity (1g) for 48 hours to atmospheric conditions and determining the final weight (after exposure period). Hygroscopicity is calculated as % moisture absorption using the formula: Moisture absorption (% w/w) = 100 x (Final weight – Initial weight) /Initial weight

RESULTS AND DISCUSSION

Co-processed directly compressible excipients were prepared by wet granulation method using a local variety of food-grade corn-starch (Manibhadra Food products, Hubli, Karnataka) along with mannitol, maltodextrin and dicalcium phosphate dihydrate in different ratios. The developed excipients were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and hygroscopicity, in comparison with commercial variety of corn-starch (SD fine chem.), as the control. The results are shown in **Table 2**.

Bulk densities of the prepared excipients range from 0.37 to 0.75 g/ml, tapped densities from 0.44 to 1.28 g/ml. Carr's index 5-15 and 15-20 indicate excellent and good flowability, respectively; although a value greater than 21 indicates poor flow[9,10]. Lower the value of Hausner's ratio[9] better is the flow property. The powder with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively. The designed excipients have shown Carr's index in the range of 5.17-38.0% and Hausner's ratio in the range of 1.09-1.71. The hygroscopicity of the developed excipients was found to be in the range of 1-3%,

Among all the prepared twenty-one excipients, eight (four of maltodextrin-corn stach, two of DCP-corn starch, one of DCP-corn starch-maltodextrin and one of mannitol-corn starch combination) were found to be promising based on the above parameters (Carr's index <15% and Hausner's ratio <1.18%), as shown in **Table 3** and **Fig. 1.**

CONCLUSION

The developed promising low cost directly compressible excipients can be successfully exploited in the design and development of dispersible and orodispersible tablet formulations of various medicaments, and thus help in improving patient compliance, especially among the paediatric and geriatric categories with difficulties in swallowing solid oral dosage forms.

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Table 1: Composition of Co-Processed Excipients

Sl. No.	Code	Corn starch % w/w	Mannitol % w/w	DCP* % w/w	Maltodextrin % w/w	Granulation fluid used
1	MDC_1	-	100	-	-	90% Alcohol
2	MDC_2	25	75	-	-	90% Alcohol
3	MDC_3	50	50	-	-	90% Alcohol
4	$CPDC_1$	25	-	75	-	90% Alcohol
5	$CPDC_2$	50	-	50	-	90% Alcohol
6	$MDDC_1$	50	-	-	50	90% Alcohol
7	$MDDC_2$	75	-	-	25	90% Alcohol
8	MDC_{1a}	-	100	-	-	70% Alcohol
9	MDC_{2a}	25	75	-	-	70% Alcohol
10	MDC_{3a}	50	50	-	-	70% Alcohol
11	$CPDC_{1a}$	25	-	70	5	70% Alcohol
12	$CPDC_{2a}$	50	-	45	5	70% Alcohol
13	$MDDC_{1a}$	50	-	-	50	70% Alcohol
14	$MDDC_{2a}$	75	-	-	25	70% Alcohol
15	MDC_{1b}	-	100	-	-	Starch paste
16	MDC_{2b}	25	75	-	-	Starch paste
17	MDC_{3b}	50	50	-	-	Starch paste
18	$CPDC_{1b}$	25	-	75	-	Starch paste
19	$CPDC_{2b}$	50	-	50	-	Starch paste
20	$^{**}MDC_0$	50	50	-	-	Starch paste
21	$^{**}CPDC_0$	50	-	50	-	Starch paste

* Dicalcium phosphate dehydrate,

** Control formulations prepared using commercial corn starch (Sd Fine Chem, Mumbai)

Table 2: Evaluation of Co-Processed Excipients

Sl.No	Sample code	Sample mass (gms)	Bulk volume (ml)	Tapped volume (V_{500})	Tapped volume (V_{2500})	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's ratio	Hygro-scopicity (%)
1	MDC_1	5	10.0	7.3	7.1	0.50	0.70	26.4	1.40	3
2	MDC_2	5	10.0	6.6	5.9	0.50	0.84	34.6	1.68	2
3	MDC_3	5	9.9	6.2	5.9	0.50	0.84	37.5	1.68	3
4	$CPDC_1$	5	6.6	4.1	3.9	0.75	1.28	38.0	1.70	1
5	$CPDC_2$	5	6.9	4.7	4.4	0.72	1.13	32.0	1.56	1
6	*$MDDC_1$	5	11.5	10.2	10.0	0.43	0.50	12.24	1.16	2
7	*$MDDC_2$	5	13.6	11.8	11.2	0.36	0.44	14.28	1.22	2
8	MDC_{1a}	5	9.6	8.4	8.1	0.52	0.59	11.86	1.13	3
9	MDC_{2a}	5	11.6	8.5	7.9	0.43	0.58	26.0	1.34	2
10	MDC_{3a}	5	11.2	9.3	8.7	0.45	0.54	16.0	1.20	3
11	*$CPDC_{1a}$	5	9.1	8.6	8.3	0.55	0.58	5.17	1.05	1
12	$CPDC_{2a}$	5	13.8	10.4	10.0	0.37	0.48	22.9	1.28	1
13	*$MDDC_{1a}$	5	8.0	7.2	7.0	0.62	0.71	13.16	1.14	2
14	*$MDDC_{2a}$	5	10.0	8.6	8.3	0.50	0.58	13.79	1.16	2
15	MDC_{1b}	5	11.2	9.4	9.2	0.45	0.54	15.09	1.20	3
16	MDC_{2b}	5	13.0	10.8	10.3	0.38	0.48	17.39	1.26	3
17	*MDC_{3b}	5	13.8	12.0	11.4	0.36	0.44	14.28	1.22	3
18	*$CPDC_{1b}$	5	10.8	10.0	9.6	0.46	0.52	8.0	1.13	1
19	*$CPDC_{2b}$	5	13.2	11.4	10.8	0.38	0.46	11.62	1.21	1
20	*MDC_0	5	13.0	10.2	10.7	0.38	0.46	17.39	1.21	2
21	*$CPDC_0$	5	11.6	11.0	9.9	0.43	0.50	12.24	1.16	1

* Promising co-processed excipients

Table 3: Promising Directly Compressible Excipients Based On the Carr's Index And Hausner's Ratio

Sl. No.	Code	Corn starch %w/w	Mannitol w/w%	DCP %w/w	Maltodextrin %w/w	Granulation fluid used	Carr's Index (%)	Hausner's ratio
1	$MDDC_1$	50	-	-	50	90% alcohol	12.24	1.16
2	$MDDC_2$	75	-	-	25	90% alcohol	14.28	1.22
3	$CPDC_{1a}$	25	-	70	5	70% alcohol	5.17	1.05
4	$MDDC_{1a}$	50	-	-	50	70% alcohol	13.16	1.14
5	$MDDC_{2a}$	75	-	-	25	70% alcohol	13.79	1.16
6	MDC_{3b}	50	50	-	-	Starch paste	14.28	1.22
7	$CPDC_{1b}$	25	-	75	-	Starch paste	8.0	1.13
8	$CPDC_{2b}$	50	-	50	-	Starch paste	11.62	1.21
9	*$CPDC_o$	50	-	50	-	Starch paste	12.24	1.16
10	*MDC_0	50	50	-	-	Starch paste	15.5	1.21

* Control formulations prepared using commercial corn starch (Sd Fine Chem, Mumbai)

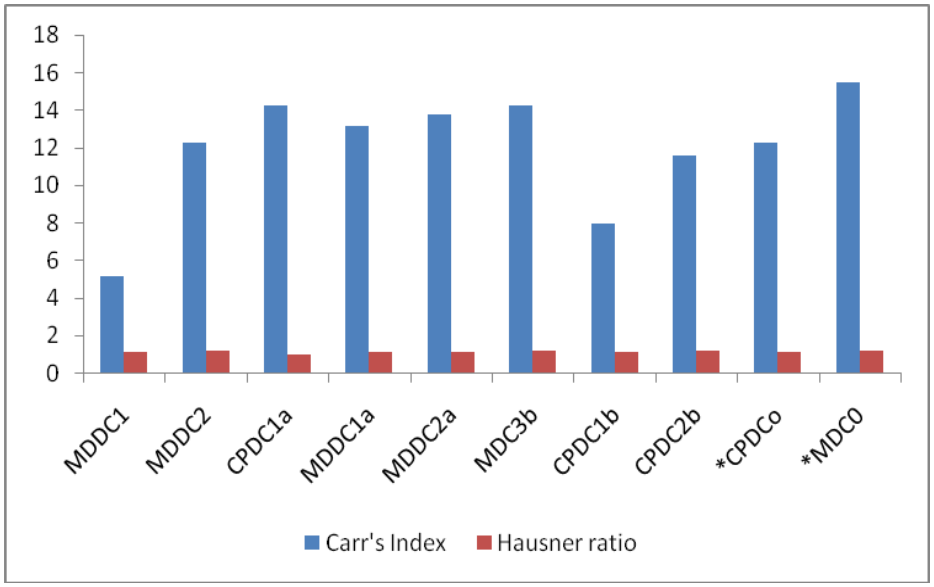

Fig. 1: Comparison of Carr's Index (%) and Hausner ratios of promising co-processed excipients.
[*Control formulations prepared using commercial corn starch (SD Fine Chem, Mumbai)]

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