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NOVEL CO-PROCESSED SUPERDISINTEGRANTS IN THE DESIGN OF FAST DISSOLVING TABLETS

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ABSTRACT: In the present study, novel co-processed superdisintegrants were developed by solvent evaporation method using crospovidone and croscarmellose sodium in the different ratios (1:1, 1:2 & 1:3) for use in the fast dissolving tablet formulations. The developed excipients were evaluated for angle of repose, Carr's index and Hausner's ratio in comparison with physical mixture of superdisintegrants. The angle of repose of the developed excipients was found to be < 25°, Carr's index in the range of 10-15% and Hausner's ratio in the range of 1.11-1.14. Fast dissolving tablets of metoclopramide hydrochloride were prepared using the above co-processed superdisintegrants and evaluated for pre-compression and post-compression parameters. Based on *in vitro* dispersion time (approximately 23 sec), promising formulation CP_1 was tested for *in vitro* drug release pattern in pH 6.8 Phosphate buffer and short-term stability (at 40^0C/75% RH for 3 months), drug excipients interaction (IR spectroscopy) were studied. Among the designed formulations, the formulation (CP_1) containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and croscarmellose sodium) emerged as the overall best formulation ($t_{50\%}$ 2.4 min) based on drug release characteristics in pH 6.8 phosphate buffer compared to commercial conventional tablet formulation ($t_{50\%}$ 6 min). Short-term stability studies on promising formulation indicated that there were no significant changes in drug content and *in vitro* dispersion time ($p<0.05$).

Keywords: Co-processed superdisintegrants, metoclopramide hydrochloride, fast dissolving tablets, croscarmellose sodium, crospovidone.

INTRODUCTION

Major challenge for tablets and capsule manufacturing comes from the flow properties of the materials to be compressed. Most of the formulations (> 70%) contain excipients at higher concentration than active drug[1]. In recent years drug formulation scientists have recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately[2]. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability[3]. One such approach for improving the functionality of excipients is co-processing of two or more excipients.

Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual[4]. Co-processing excipients leads to the formulation of excipient granules with superior properties compared with physical mixtures of components or individual components[5]. The concept of formulating fast dissolving tablets (FDT) of metoclopramide hydrochloride (anti-emetic)[6] using co-processed superdisintegrants which increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by simple and cost effective (at low concentration of superdisintegrants) direct compression technique.

MATERIALS

Metoclopramide hydrochloride (MTH) was gift samples from Comed Chemicals Ltd, Baroda (India). Directly compressible mannitol (Pearlitol SD 200), microcrystalline cellulose (MCC, PH-102) and sodium stearyl fumerate (SSF) were generous gifts from Strides Arcolabss, Bangalore (India). All the other chemicals used were of analytical reagent grade.

METHODS

Preparation of Co-processed Superdisintegrants[7]

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and croscarmellose sodium (in the ratio of 1:1, 1:2 & 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 44-mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through # 44-mesh sieve and stored in airtight container till further use.

Preparation of fast dissolving tablets by direct compression method[8]

Fast dissolving tablets of MTH were prepared by direct compression. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150mg using 8mm round flat punches on 10-station rotary tablet machine (Clit).

Evaluation of fast dissolving tablets

Weight Variation[9]

Twenty tablets were selected randomly from each formulation and weighed individually using a Shimadzu digital balance (BL-220H). The individual weights were compared with the average weight for the weight variation.

Thickness variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a micrometer screw gauge.

Hardness and Friability

Hardness of the tablets was measured using the Monsanto Hardness Tester (Pharmalab, Ahmedabad, India). The friability of a sample of twenty tablets was measured using a USP type Roche friabilator (Pharmalab, Ahmedabad, India). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then dusted, reweighed and percentage weight loss (friability) was calculated.

Drug Content Uniformity[10]

For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 10 mg of MTH was extracted into distilled water and liquid was filtered (0.22 µm membrane filter disc (Millipore Corporation). The MTH content was determined by measuring the absorbance at 272.6 nm (using UV-vis spectrophotometer, Shimadzu 1700) after appropriate dilution with distilled water. The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

In Vitro Dispersion Time[11]

One tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5ºC and the time required for complete dispersion was determined.

Wetting Time and Water Absorption Ratio (R)[12]

Twice folded tissue paper was placed in a Petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation:

$R = 100 \times (w_a - w_b)/ w_b$

Where w_b and w_a were tablet weights before and after water absorption, respectively.

In Vitro Drug Release Study[13]

In vitro dissolution studies of the promising fast dissolving tablets of MTH, control and commercial conventional tablet formulations were performed according to USP XXIII Type-II dissolution apparatus (Electrolab, model TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5ºC as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals (2, 4, 6, 8, 10, 15&30 min) and replaced immediately with equal volume of fresh medium. The samples were filtered through 0.22 µm membrane filter disc and analyzed for drug content by measuring the absorbance at 272.4 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates of three.

Stability Studies

The tablets of the promising formulation CP1 were subjected to accelerated stability studies, by storing in amber colored rubber stopper glass vials at 40ºC/75% RH over a period of 3 months. At intervals of 1 month, the tablets were visually examined for any

physical changes and evaluated for changes in drug content and *in vitro* dispersion time. Drug-excipient interactions were ruled out by FT-IR spectroscopic studies on the samples stored at the above conditions.

RESULTS AND DISCUSSION

Co-processed superdisintegrants were prepared by solvent evaporation using crospovidone and croscarmellose sodium in different ratios (1:1, 1:2. & 1:3). The co-processed superdisintegrants were evaluated for their flow and compression properties in comparison with physical mixture of superdisintegrants. The angle of repose of co-processed superdisintegrants was found to be $<25^{o}$ which indicate excellent flow in comparison to physical mixture of superdisintegrants ($>30^{o}$) due to granule formation, Carr's index in the range of 10-15% and Hausner's ratio in the range of 1.10-1.14 (Table 2).

Fast dissolving tablets of MTH were prepared using above co-processed superdisintegrants and physical mixture of superdisintegrants. Directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance mouth feel. A total of six formulations and control formulation CP_0 (without superdisintegrant) were designed. As the blends were free flowing (angle of repose $<30^{0}$ and Carr's index <15% Table 3), tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specification i.e., below 7.5%. Drug content was found to be in the range of 99 to 101%, which is within acceptable limits. Hardness of the tablets was found to be in the range of 2.86-3.16 kg/cm^2. Friability below 1% was an indication of good mechanical resistance of the tablets. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 45-85% and 30-105 sec respectively. Among all the designed formulations, formulation, CP_1 was found to be promising and displayed an *in vitro* dispersion time of 23 sec, which facilitates their faster dispersion in the mouth.

Overall, the formulation CP_1 containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and croscarmellose sodium) was found to be promising and has shown an *in vitro* dispersion time of 23 sec, wetting time of 30 sec and water absorption ratio of 85% when compared to the formulation PM_1 containing 4% w/w of Physical mixture of superdisintegrant (1:1 mixture of crospovidone and croscarmellose sodium) which shows 35 sec, 38 sec, 75% and control formulation (CPO) which shows 99 sec, 105 sec and 45% values respectively for the above parameters (Table 4).

In vitro dissolution studies on the promising formulation CP_1, control (CP_0) and commercial conventional formulations (CCF) were carried out in pH 6.8 phosphate buffer, and the various dissolution parameter values viz., percent drug dissolved in 5 min, 10 min and 15 min (D_5, D_{10} and D_{15}), dissolution efficiency at 10 min (DE_{10} min), $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are shown in Table 5 and dissolution profile depicted in fig. 1.. This data reveals that overall, the formulation CP_1 has shown nearly two and a half fold faster drug release ($t_{50\%}$ 2.4 min) when compared to the commercial conventional tablet formulation of MTH ($t_{50\%}$ 6 min).

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of CP_1 showed all the characteristic peaks of MTH pure drug, thus confirming that no interaction of drug occurred with the components of the formulation. Short-term stability studies of the above formulations indicated that there are no significant changes in drug content and *in vitro* dispersion time at the end of 3 months period ($p<0.05$).

CONCLUSION

Co-processed superdisitegrants consisting of crospovidone and croscarmellose sodium exhibited good flow and compression characteristics. MTH tablets containing co-processed superdisintegrants exhibited quick disintegration and improved drug dissolution. It can be concluded from the present work that co-processed superdisintegrants of crospovidone and croscarmellose are superior to physical mixture of crospovidone and croscarmellose used in MTH fast dissolving tablets.

TABLE 1 Formulations of MTH FDT Prepared by Direct Compression Method

Ingredient (mg)	Formulation code						
	CP_0	PM_1	PM_2	PM_3	CP_1	CP_2	CP_3
Metoclopramide HCL	10	10	10	10	10	10	10
Superdisintegrants (CP+CCS)	-	6	6	6	6	6	6
Aspartame	3	3	3	3	3	3	3
Sodium stearyl fumarate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3	3	3
Pine apple Flavour	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Microcrystalline cellulose (Avicel PH-102)	30	30	30	30	30	30	30
Mannitol (Pearlitol SD 200)	101	95	95	95	95	95	95
Total Weight	150	150	150	150	150	150	150

PM - Physical Mixture of crospovidone and croscarmellose sodium in different Ratios (1:1, 1:2, 1:3), CP -Co-processed Superdisintegrants of crospovidone and croscarmellose sodium in different Ratios (1:1, 1:2, 1:3), CPo-Control formulation (without superdisintegrants), CP – Crospovidone, CCS – Croscarmellose sodium

TABLE 2 Pre-compression Parameters of Co-processed Superdisintegrants and Physical Mixture of Superdisintegrants

Parameters	Formulation code					
	PM_1	PM_2	PM_3	CP_1	CP_2	CP_3
Bulk density (g/cc)	0.39	0.36	0.41	0.21	0.22	0.27
Tapped density (g/cc)	0.45	0.42	0.48	0.24	0.25	0.30
Angle of repose (degree)	31	30	35	24	25	23
Carr's index (percent)	13	15	14	12	12	10
Hausner's Ratio	1.15	1.16	1.17	1.14	1.13	1.11

TABLE 3 Pre-compression Parameters of MTH FDT Formulations Prepared by Direct Compression Method

Parameters	Formulation code						
	CP_0	PM_1	PM_2	PM_3	CP_1	CP_2	CP_3
Bulk density (g/cc)	0.57	0.53	0.53	0.55	0.50	0.52	0.51
Tapped density (g/cc)	0.60	0.60	0.62	0.62	0.56	0.58	0.58
Angle of repose (degree)	31.25	29.02	30.1	29.20	28.43	28.72	28.87
Carr's index (percent)	17	13	13	12	12	11.53	13
Hausner's Ratio	1.05	1.13	1.13	1.12	1.12	1.11	1.13

TABLE 4 Evaluation of MTH FDT Formulations

Parameters	Formulation code						
	CP_0	**PM_1**	**PM_2**	**PM_3**	**CP_1**	**CP_2**	**CP_3**
Hardness (kg/cm^2)* ±SD	2.86±0.05	2.9±0.1	2.93±1.4	3.06±0.05	3.03±0.05	3.13±0.05	3.16±0.05
Friability (%)	0.49	0.43	0.51	0.31	0.40	0.36	0.38
Thickness* (mm)	2.15±0.04	2.19±0.05	2.11±0.05	2.17±0.01	2.10±0.05	2.13±0.01	2.22±0.01
In vitro dispersion time (s)* ±SD	99±2	35.33±1.52	40.33±0.57	43.66±1.52	23±2	32.33±2.51	37±2.0
Wetting time (s)* ±SDs	105±4.93	38.66±1.52	41±1	49.33±1.5	30±0.5	35.33±1.52	40.66±1.15
Water absorption ratio (%)* ±SD	45±1	75.33±1.15	72.66±1.52	65±1	85±1	75±2.08	70.66±0.57
Percent drug content (%)* ±SD	99.28±1.52	99.30±1.01	100±1.57	101±2.02	99.87±0.07	101±1.09	99.45±2
Weight variation (%)	145-158 mg (IP limits ± 7.5%)						

* Average of 3 determinations

TABLE 5 *IN Vitro* Dissolution Parameters in pH 6.8 Phosphate Buffer

Parameters	Formulation code						
	D_5	**D_{10}**	**D_{15}**	**$t_{50\%}$**	**$t_{70\%}$**	**$t_{90\%}$**	**DE_{10min}**
CP_0	26%	53.43%	62.81%	9.30 min	12.50 min	>30 min	27.02%
CCF	40%	72%	81.77%	6 min	9.5 min	29 min	39.0%
PM_1	70%	80.86%	87.46%	3.48 min	5 min	16 min	61.39%
CP_1	76.5%	90.63%	99.27%	2.40 min	3.48 min	9.48 min	64.80%

CP_0 is control formulation, CP_1 is promising fast dissolving tablet formulation, PM_1 is formulation containing physical mixture of superdisintegrants in 1:1 ratio, CCF is conventional commercial tablet formulation, D_5 is percent drug released in 5 min, D_{10} is percent drug release in 10 min, D_{15} is percent drug release in 15 min, DE_{10min} is dissolution efficiency at 10 min, $t_{50\%}$ is time for 50% drug dissolution, $t_{70\%}$ is time for 70% drug dissolution, $t_{90\%}$ is time for 90% drug dissolution

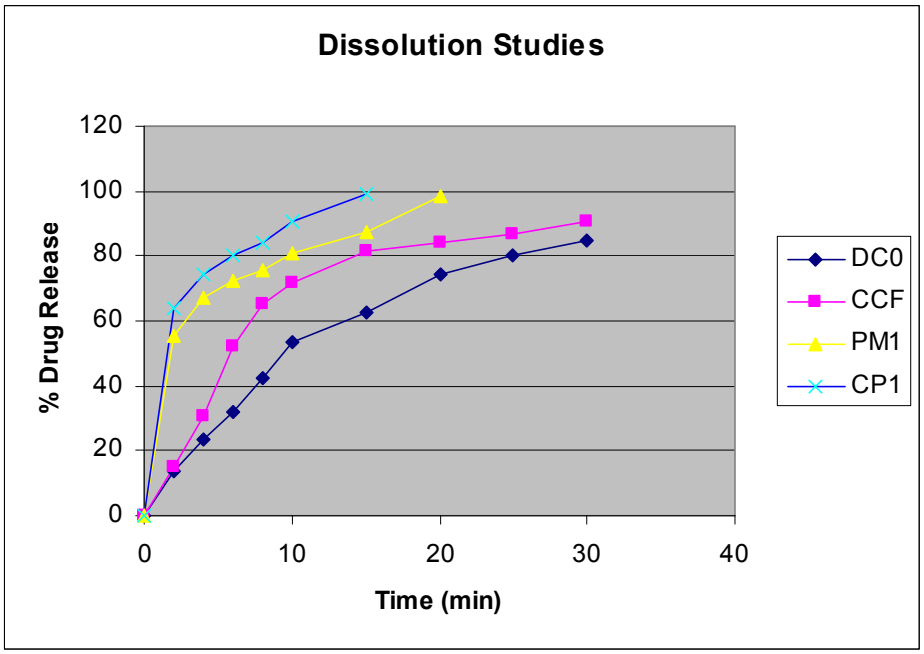

FIGURE 1 Dissolution rate profiles of (–♦–) control formulation (–■–) conventional commercial formulation (–▲–) formulation containing 1:1 physical mixture of crospovidone and croscarmellose sodium (--×--) promising formulation in pH 6.8 phosphate buffer

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REFERENCES

1. York P. Crystal engineering and particle design for the powder compaction process. Drug Dev Ind Pharm. 1992; 18(6, 7):677-721.
2. Block LH et al. Co-processed excipients. Pharmacopeial forum. 2009; 35(4):1026-8.
3. Avachat A, Ahire VJ. Characterization and evaluation of spray dried co-processed excipients and their application in solid dosage forms. Indian J Pharm Sci 2007; 69(1):85-90.
4. Reimerdes D. The near future of tablet excipients. Manuf chem. 1993; 64:14-5.
5. Jacob S, Shirwaikar AA, Joseph A, Srinivasan KK. . Novel co-processed excipients of mannitol and microcrystalline cellulose for preparing fast dissolving tablets of Glipizide. Indian J Pharm Sci 2007; 69(5):633-9.
6. Sweetman SC, editor. Martindale: The Complete Drug Reference. 33rd ed. Pharmaceutical Press, London 2002; p1235-7.
7. Gohel MC et al. Preparation and Assessment of Novel Co-processed Superdisintegrant Consisting of Crospovidone and Sodium Starch Glycolate: A Technical Note. AAPSPharmSciTech. 2007;8(1):Article 9:p.E1-E7
8. Kuchekar BS, Badhan AC, Mahajan HS. Mouth dissolving tablets of salbutamol sulphate: A novel drug delivery system. Indian Drugs.2004; 41:592-8.
9. Bankar GS, Anderson NR. Tablets. In: Lachman L, Lieberman HA, Kanig JL, editor. The theory and practice of industrial pharmacy. 3rd ed. Mumbai: Varghese Publishing House; 1987. p. 293-9.
10. Indian Pharmcopoeia: New Delhi: Controller of Publication, Government of India; 1996. p. 735-6.
11. Bi YX, Sunada H, Yonezawa Y, Danjo K. Evaluation of rapidly disintegrating tablets by direct compression method. Drug Develop Ind Pharm 1999;25: 571-81.
12. Chaudhari PD, Chaudhari SP, Kohle SR, Dave KV, More DM. formulation and evaluation of fast dissolving tablets of famotidine. Indian Drug 2005;42: 641-9.
13. Bhagwati ST, Hiremath SN, Sreenivas SA. Comparative evaluation of disintegrants by formulating cefixime dispersible tablets. Indian J Pharm Edu Res 2005; 39:194-7.