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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 sodium starch glycolate in 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^{o}, Carr's index in the range of 10-15% and Hausner's ratio in the range of 1.13-1.16. 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 19 sec), promising formulation CP_1 was tested for *in vitro* drug release pattern in pH 6.8 Phosphate buffer, short-term stability (at 40^{0}C/75% RH for 3 months) and drug excipient interaction (IR spectroscopy). Among the designed formulations, the formulation (CP_1) containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and sodium starch glycolate) emerged as the overall best formulation ($t_{50\%}$ 1.30 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 ($p<0.05$).

KEY WORDS

co-processed superdisintegrants, metoclopramide hydrochloride, fast dissolving tablets, sodium starch glycolate, crospovidone.

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INTRODUCTION

Solid oral dosage forms, especially tablets, remain one of the most popular because of advantages like patient convenience, ease of storage and dispensing, dose accuracy and easy manufacturability. Major challenge for tablets 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]. Excipients with improved functionality can be obtained by developing new chemical excipients, new grade of existing materials and new combination of existing materials[4]. New combinations of existing excipients are an interesting option for improving excipient functionality because all formulations contain multiple excipients. 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[5]. Co-processing excipients lead to the formulation of excipient granules with superior properties, compared with physical mixtures of components or individual components, like improved flow properties, improved compressibility, better dilution potential, fill weight uniformity, and reduced lubricant sensitivity[6]. Several co-processed superdisintegrants are commercially available: Ludipress (lactose monohydrate, polyvinylpyrrolidone and crospovidone), Starlac (lactose and maize starch), Starcap 1500 (corn starch and pregelatinized starch), Ran Explo-C (microcrystalline cellulose, silica and crospovidone), Ran Explo-S (microcrystalline cellulose, silica and sodium starch glycolate), PanExcea MH300G (microcrystalline cellulose, hydroxy propyl methyl cellulose and crospovidone)[7].

The widely used superdisintegrants are crospovidone, croscarmellose sodium and sodium starch glycolate. In the present investigation, the preparation and evaluation of fast dissolving tablets by using co-processed superdisintegrants containing crospovidone and sodium starch glycolate was studied. The reasons for selection of crospovidone are high capillary activity, pronounced hydration capacity and little tendency to form gels[8]. Sodium starch glycolate was chosen because of its high swelling capacity[9]. The concept of formulating fast dissolving tablets (FDT) of metoclopramide hydrochloride (anti-emetic)[10] using co-processed superdisintegrants helps to increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by simple and cost effective 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

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other chemicals used were of analytical reagent grade.

METHODS

Preparation of Co-processed Superdisintegrants[11]

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and sodium starch glycolate (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.

Table 1

Formulations of MTH FDT Prepared by Direct Compression Method

Ingredients (mg/tab)	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+SSG)	-	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

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PM - Physical Mixture of crospovidone and sodium starch glycolate in different ratios (1:1, 1:2, 1:3), CP - Co-processed Superdisintegrants of crospovidone and sodium starch glycolate in different ratios (1:1, 1:2, 1:3), CPo - Control formulation (without superdisintegrants), CP – Crospovidone, SSG – sodium starch glycolate

Preparation of fast dissolving tablets by direct compression method[12]

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 MTH fast dissolving tablets

1). Weight Variation[13]

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.

2). Thickness variation

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

3). 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 Roche friabilator (Pharmalab, Ahmedabad, India). Pre-weighed tablets were placed in the plastic chamber of 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.

4). Drug Content Uniformity[14]

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.

5). *In Vitro* Dispersion Time[15]

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.

6). Wetting Time and Water Absorption Ratio (R)[16]

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

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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.

7). *In Vitro* Drug Release Study[17]

In vitro dissolution studies of the promising fast dissolving tablets of MTH, formulation containing 1:1 physical mixture of crospovidone and sodium starch glycolate (PM_1), 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.

8). Stability Studies

The tablets of the promising formulation CP_1 were subjected to accelerated stability studies, by storing in amber colored rubber stoppered 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 sodium starch glycolate 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 1.13-1.16 (Table 2).

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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)	0.35	0.47	0.40	0.24	0.26	0.31
Tapped density (g/cc)	0.41	0.55	0.45	0.27	0.30	0.36
Angle of repose (degree)	29.14	27.50	25.11	24.44	23.31	22.83
Carr's index (percent)	14.63	14.54	13.04	14.81	13.33	13.88
Hausner's Ratio	1.17	1.17	1.15	1.13	1.15	1.16

Fast dissolving tablets of MTH were prepared using above co-processed superdisintegrants and physical mixtures 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 2.85-3.20 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 45-87% and 23-105 sec respectively. Among all the designed formulations, formulation CP_1 was found to be promising and

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displayed an *in vitro* dispersion time of 19 sec, which facilitates its faster dispersion in the mouth.

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)	0.45	0.4681	0.4631	0.47	0.46	0.465	0.47
Tapped density (g/cc)	0.53	0.54	0.54	0.55	0.54	0.53	0.55
Angle of repose (degree)	31.25	28.91	29.45	29.15	29.15	29.30	28.05
Carr's index (percent)	15	14.59	14.81	14.54	14.81	12.96	14.54
Hausner's Ratio	1.17	1.14	1.17	1.17	1.17	1.15	1.17

Overall, the formulation CP_1 containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and sodium starch glycolate) was found to be promising and has shown an *in vitro* dispersion time of 19 sec, wetting time of 23 sec and water absorption ratio of 87% when compared to the formulation PM_1 containing 4% w/w of physical mixture of superdisintegrants (1:1 mixture of crospovidone and sodium starch glycolate) which shows 30 sec, 32 sec and 66% values respectively and control formulation (CP_O) which shows 99 sec, 105 sec and 45% values respectively for the above parameters (Table 4).

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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	3.1±0.11	2.9±0.1	3.2±0.05	3.2±0.05	2.85±0.05	3.16±0.15
Friability (%)	0.49	0.62	0.78	0.57	0.61	0.55	0.54
Thickness* (mm)±SD	2.15±0.04	2.14±0.12	2.16±0.06	2.12±0.02	2.09±0.01	2.22±0.04	2.13±0.02
In vitro dispersion time (sec)* ±SD	99±2.0	30±2.0	48.66±1.52	57.66±2.51	19.66±1.52	34±1.0	45.33±1.52
Wetting time (sec)* ±SD	105±4.93	32.66±1.52	56.66±2.08	64±1.0	23±1.0	38.66±1.52	51±1.0
Water absorption ratio (%)* ±SD	45±1.0	66.66±3.2	62.22±3.8	55.55±3.85	87±3.4	64.46±2.9	62±1.0
Percent drug content ±SD	99.28±1.52	99.45±1.01	101±1.57	100±2.02	99.57±0.07	100±1.09	99.85±2.0
Weight variation (%)	142-159 mg (IP limits ± 7.5%)						

** Average of 3 determinations*

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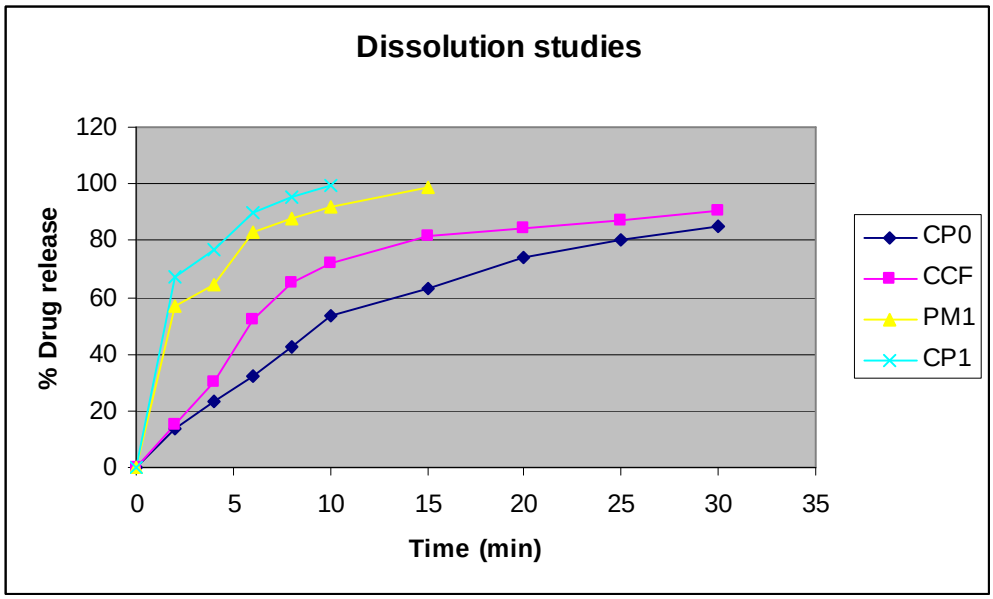
In vitro dissolution studies on the promising formulation CP_1, PM_1, control (CP_0) and commercial conventional formulations (CCF) were carried out in pH 6.8 phosphate buffer, and the various dissolution parameter values viz., percent drug dissolved in 5 min, 10 min and 15 min (D_5, D_{10} and D_{15}), 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 graph 1. This data reveals that overall, the formulation CP_1 has shown nearly four fold faster drug release ($t_{50\%}$ 1.30 min) when compared to the commercial conventional tablet formulation of MTH ($t_{50\%}$ 6 min).

Graph 1

Dissolution studies of the formulation



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

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Table 5

***Invitro* Dissolution Parameters in pH 6.8 Phosphate Buffer**

Formulation code	Parameters						
	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%	72.0%	81.77%	6 min	9.5 min	29 min	39.0%
PM_1	73%	91.5%	99.05%	1.48min	4.42min	9.24min	65.0%
CP_1	83%	99.10%	-	1.30min	2.36min	6.18min	75.0%

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

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 formulations. 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 superdisintegrants consisting of crospovidone and sodium starch glycolate exhibit good flow and compression characteristics. MTH tablets containing co-processed superdisintegrants exhibit quick disintegration and improved drug dissolution. It can be concluded from the present work that co-processed superdisintegrants of crospovidone and sodium starch glycolate are superior to physical mixtures of crospovidone and

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sodium starch glycolate used in MTH fast dissolving tablets.

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