

DESIGN OF FAST DISSOLVING GRANISETRON HCL TABLETS USING NOVEL CO –PROCESSED SUPERDISINTEGRANTS

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ABSTRACT

In the present work, fast dissolving tablets of granisetron HCl were prepared using novel co-processed superdisintegrants consisting of crospovidone and sodium starchglycolate in the different ratios (1:1, 1:2 & 1:3). The developed superdisintegrants 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 granisetron 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 20 sec), promising formulation CP₁ was tested for *in vitro* drug release pattern in pH 6.8 Phosphate buffer and short-term stability (at 40°C/75% RH for 3 months), drug excipients interaction (IR spectroscopy) were studied. Among the designed formulations, the formulation (CP₁) containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and sodium starchglycolate) emerged as the overall best formulation ($t_{50\%}$ 2.0 min) based on drug release characteristics in pH 6.8 phosphate buffer compared to commercial conventional tablet formulation ($t_{50\%}$ >15 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, granisetron hydrochloride, fast dissolving tablets, sodium starchglycolate, 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 drug¹. 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 adequately². 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 ability³. 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 individual⁴. Co-processing excipients leads to the formulation of excipient granules with superior properties compared with physical mixtures of components or individual components⁵. The concept of formulating fast dissolving tablets (FDT) of granisetron 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

Granisetron hydrochloride (GSH) was gift samples from Natco Pharma Ltd, Hyderabad (India). Crospovidone (CP) and Sodium starchglycolate were gift samples from Wockhardt Research Centre, Aurangabad. 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 Superdisintegrants⁷

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and sodium starchglycolate (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 60° 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 method⁸

Fast dissolving tablets of GSH 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 Variation⁹

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 Uniformity¹⁰

For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 2.24 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 302 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 Time¹¹

One tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5°C 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 Study¹³

In vitro dissolution studies of the promising fast dissolving tablets of GSH, 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±0.5°C 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 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 302 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 40°C/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 starchglycolate 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° which indicate excellent flow in comparison to physical mixture of superdisintegrants (>30°) 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).

Table 1 Formulations of GSH FDT Prepared by Direct Compression Method

Ingredient (mg)	Formulation code						
	CP ₀	PM ₁	PM ₂	PM ₃	CP ₁	CP ₂	CP ₃
Granisetron HCL	2.24	2.24	2.24	2.24	2.24	2.24	2.24
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)	108.76	102.76	102.76	102.76	102.76	102.76	102.76
Total Weight	150	150	150	150	150	150	150

PM - Physical Mixture of crospovidone and sodium starchglycolate in different Ratios

(1:1, 1:2, 1:3), CP -Co-processed Superdisintegrants of crospovidone and sodium starchglycolate in different Ratios (1:1, 1:2, 1:3), CPo-Control formulation (without superdisintegrants), CP – Crospovidone, SSG – sodium starchglycolate.

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 (%)	13	15	14	12	12	10
Hausner's Ratio	1.15	1.16	1.17	1.14	1.13	1.11

Fast dissolving tablets of GSH 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 CP₀ (without superdisintegrant) were designed. As the blends were free flowing (angle of repose <30° 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 98 to 100%, which is within acceptable limits. Hardness of the tablets was found to be in the range of 2.9-3.20 kg/cm². 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 56-90% and 22-128 sec respectively. Among all the designed formulations,

formulation, CP₁ was found to be promising and displayed an *in vitro* dispersion time of 20 sec, which facilitates their faster dispersion in the mouth.

Table 3 Pre-compression Parameters of GSH 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	29	30	29	28	29	29
Carr's index (%)	17	13	13	12	12	12	13
Hausner's Ratio	1.05	1.13	1.13	1.12	1.12	1.11	1.13

Overall, the formulation CP₁ containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and sodium starchglycolate) was found to be promising and has shown an *in vitro* dispersion time of 20 sec, wetting time of 22 sec and water absorption ratio of 90% when compared to the formulation PM₁ containing 4% w/w of Physical mixture of superdisintegrant (1:1 mixture of crospovidone and sodium starchglycolate) which shows 32 sec, 33 sec, 76% and control formulation (CPO) which shows 125 sec, 128 sec and 57% values respectively for the above parameters (Table 4).

Table 4 Evaluation of GSH FDT Formulations

Parameters	Formulation code						
	CP ₀	PM ₁	PM ₂	PM ₃	CP ₁	CP ₂	CP ₃
Hardness (kg/cm ²)* ±SD	2.90±0.1	2.94±1.4	3.18±0.05	3.2±1.23	3.03±0.05	3.43±0.06	3.26±0.2
Friability (%)	0.42	0.50	0.53	0.43	0.38	0.46	0.35
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
<i>In vitro</i> dispersion time (s)* ±SD	125±2.24	32.09±1.62	37.79±2.16	41.46±1.64	20.32±1.10	31.16±2.31	35.09±1.62
Wetting time (s)* ±SDs	128±2.93	33.16±1.83	39.19±1.74	43.86±3.24	22.14±2.16	32.89±1.19	36.17±1.32
Water absorption ratio (%)* ±SD	56.79±1.38	76.18±1.73	73.14±2.16	69.23±1.73	90.45±1.29	85.20±1.05	83.15±1.34
Percent drug content (%)* ±SD	98.67±1.44	99.14±1.29	98.50±1.24	98.79±1.54	99.33±1.37	98.16±1.34	99.75±1.53
Weight variation (%)	143-155 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	11%	20.0%	25.0%	>15 min	>15 min	>15 min	10.64%
CCF	17%	32%	46%	>15 min	>15 min	>15 min	16.92%
PM ₁	47%	66%	82%	6 min	11.1 min	>15 min	43.5%
CP ₁	61%	92%	95%	2.0 min	7.1 min	11.4 min	58.0%

CP₀ is control formulation, CP₁ is promising fast dissolving tablet formulation, PM₁ is formulation containing physical mixture of superdisintegrants in 1:1 ratio, CCF is conventional commercial tablet formulation, D₅ is percent drug released in 5 min, D₁₀ is percent drug release in 10 min, D₁₅ 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

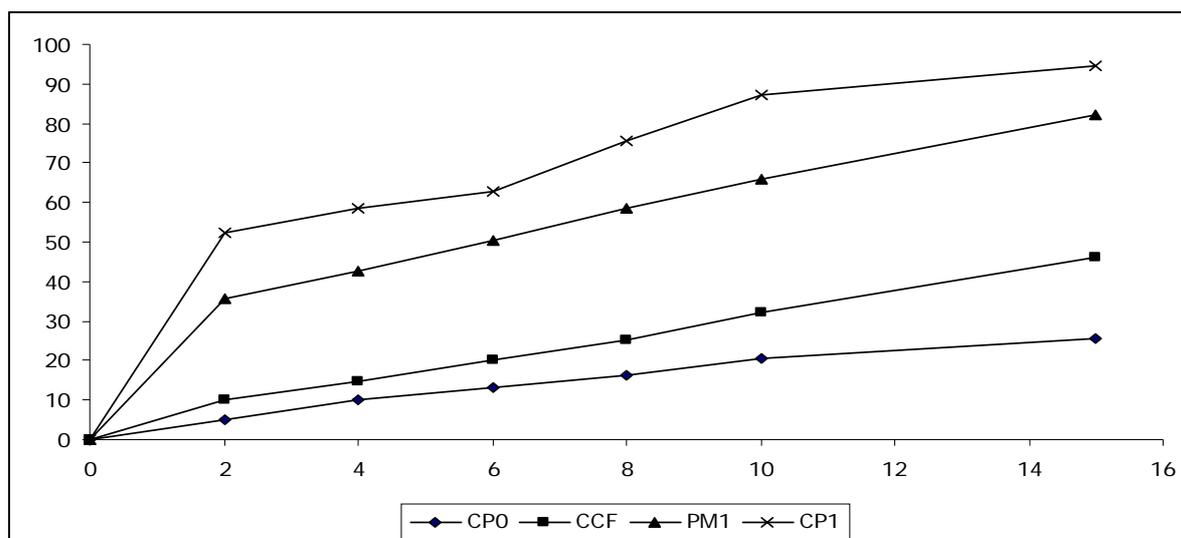


Figure 1 Dissolution rate profiles of (–◆–) control formulation (–■–) conventional commercial formulation (–▲–) formulation containing 1:1 physical mixture of crospovidone and sodium starchglycolate (–x–) promising formulation in pH 6.8 phosphate buffer

In vitro dissolution studies on the promising formulation CP₁, control (CP₀) 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 (D₅, D₁₀ and D₁₅), 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 CP₁ has shown more than seven fold faster drug release (t_{50%} 2.0 min) when compared to the commercial conventional tablet formulation of GSH (t_{50%} >15 min).

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of CP₁ showed all the characteristic peaks of GSH 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 superdisintegrants consisting of crospovidone and sodium starchglycolate exhibited good flow and compression characteristics. GSH 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 sodium starchglycolate are superior to physical mixture of crospovidone and sodium starchglycolate used in GSH fast dissolving tablets.

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