FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF PROCHLORPERAZINE MALEATE USING COPROCESSING TECHNOLOGY

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Abstract:

The study evaluated two novel coprocessed excipients (with three methods) as disintegrants in a fast dissolving prochlorperazine maleate tablet formulation. The tablets produced were assessed for mechanical properties with the use of friability and tensile strength while the release properties were assessed with wetting time, water absorption ratio, disintegration time and dissolution profile. The results obtained showed that the methods of coprocessing and disintegrant incorporation influenced the activities of the disintegrants. The novel disintegrant enhanced the mechanical properties of the tablets containing them as shown by lower friability and higher tensile strength of the tablets. The result further showed that the rate and amount of water absorbed, type of disintegrant and the method of disintegrant incorporation influenced the total amount of prochlorperazine maleate released. The study concluded that the novel disintegrants will be effective in the formulation of fast dissolving prochlorperazine maleate tablets.

Keywords: coprocessing, lyophilization, microwave, solvent evaporation, dissolution, friability, disintegration time, water absorption ratio, wetting time.

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INTRODUCTION

Tablets are the most preferred oral dosage forms due to their numerous advantages, which includes: ease of manufacture and administration, high physical and chemical stability, high patient compliance, convenient packaging/storage and the ability to provide accurately measured dose of the drug[1-3]. However, its use in therapy is still associated with some challenges most especially among the geriatric and pediatric populations. Over the past two decades, fast disintegrating tablets (FDTs), a patient friendly dosage form, which disintegrates rapidly in the mouth upon contact with saliva, have gained increased importance, focus and patient acceptance because of their ability to addresses some of the challenges facing conventional tablets[4-6].

These FDTs obviate the need to swallow tablets thereby making drug usage more convenient for pediatric and geriatric patients who usually have compromised swallowing ability due to various physiological/psychological factors[7]. The convenience of administration without water also enables dosing on the goî, which facilitates patient adherence to the dosing regimen or administration[8]. Various methods such as lyophilization, molding, cotton candy, direct compression or tableting after granulation have been used in the manufacture of FDTs[6]. Coprocessed multifunctional excipients based on polyols, disintegrants and binders with improved physico-mechanical properties (e.g., pleasant mouth-feel, low hygroscopicity, better flow and compactability) have been used to conveniently manufacture FDTs with excellent disintegration properties without compromising the mechanical properties[8].

EXPERIMENTAL

Materials

The materials used were: Prochlorperazine maleate, Sodium starch glycolate, Crospovidone, Avicel pH 102, beta cyclodextrin (Combitic Global

Caplet, Sonipat), Lactose, Talc, Magnesium stearate (Lobachem, Mumbai)

Preparation of FDT

Fast dissolving tablets were organized by direct compression method because of their several advantages[9-11].

- Easiest way to manufacture tablets.
- High doses can be accommodated.
- Use of conventional equipment.
- Limited number of processing steps.
- Less disintegration time.

The tablets were prepared by using single punch tablet machine (Cadmach, Ahmedabad) to produce flat faced tablets weighing 100 mg each with a diameter of 5 mm. A minimum of 50 tablets were ready for each batch. Before compression tablet blends were measured for mass-volume relationship (Bulk density, Tapped density, Hausner's ratio, Compressibility index) and flow properties (Angle of repose).

Table 1: Preparation of Tablets with Superdisintegrants

Ingredients	F1	F2	F3	F4
Prochlorperazine maleate	10	10	10	10
Sodium Starch Glycolate	2	-	2	-
Crospovidone	-	2	-	2
Beta cyclodextrin	-	-	30	30
Avicel PH102	50	50	30	30
Lactose	28	28	18	18
Talc	5	5	5	5
Magnesium stearate	5	5	5	5

Pre compression Characterization

The quality of tablet, once formulated by rule, is generally expressed by the quality of physicochemical properties of blends. There are many formulations and process variables tangled in mixing steps and all these can affect the characteristics of blend produced. The description parameters for evaluating the flow property of mixed blends includes Bulk density, Tapped density, Hausner's ratio, Compressibility index and Angle of Repose.

Bulk density

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of powder (M) was determined[14-16]. The bulk density was proposed using the formula: $\rho_b = \frac{M}{V_b}$

Tapped density

The measuring cylinder containing a recognized mass of blend was tapped 100 times using density apparatus. The constant minimum volume (V_t) involved in the cylinder after tappings and the weight (M) of the blend was measured[14-16]. The tapped density (ρ_t) was designed using the formula: $\rho_t = \frac{M}{V_t}$

Compressibility index

The simplest way for measurement of flow of the powder is its compressibility, an indication of the luxury with which a material can be induced to flow[14-16]. It is uttered as compressibility index (I) which can be calculated as follows:

$$I = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

where, ρ_t = Tapped density; ρ_b = Bulk density

Hausner's Ratio

Hausner's ratio (HR) is an indirect index of affluence of powder flow. It is calculated by the following formula: $HR = \frac{\rho t}{\rho b}$ where, ρ_t is tapped density and ρ_b is bulk density.

Lower Hausner's ratio (<1.25) indicates improved flow properties than higher ones[17-19].

Angle of Repose

Angle of Repose was determined using funnel method. The blend was dispensed through a funnel that can be elevated vertically until a specified cone height (h) was achieved. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula[17-19]

$$\tan\theta = \frac{h}{r}; \qquad \text{Therefore; } \theta = \tan^{-1}\left(\frac{h}{r}\right)$$

where, θ is angle of repose; h is height of cone; r is radius of cone.

Table 4: Characterization of Tablets Blends

Formulation Codes	Constraints				
	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's Ratio	Compressibility Index (%)	Angle of Repose (°)
F1	0.398 ±0.021	0.426 ±0.019	1.075 ±0.025	7.009 ±1.233	28.22 ±1.432
F2	0.403 ±0.003	0.431 ±0.018	1.078 ±0.012	6.496 ±1.128	27.16 ±1.257
F3	0.415 ±0.015	0.436 ±0.012	1.055 ±0.007	5.275 ±1.229	24.16 ±1.122
F4	0.416 ±0.011	0.440 ±0.002	1.057 ±0.022	5.454 ±1.324	24.56 ±0.836

n=6, ±S.D

Post Compresion characterization

After compression of powder blends, the prepared tablets were evaluated for organoleptic features like color, odor, taste, diameter, thickness and physical characteristics like hardness, friability, disintegration time, wetting time, % drug release. The results are shown in Table 5.

General appearance

The general appearance of a tablet, its visual identification and over all 'elegance' is essential for consumer acceptance. This includes tablet's size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws etc[20].

Tablet thickness

Ten tablets were taken and their thickness was evaluated using micrometer (Mityato, Japan).

Weight variation

The weight variation test would be acceptable method of determining the drug content uniformity. As per USP[21], twenty tablets were taken and weighted individually, calculating the average weight, and comparing the distinct tablet weights to the average. The average weight of one tablet was calculated.

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in direction to break the tablet. The confrontation of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Pfizer Hardness Tester[20].

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Friability

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the collective effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Pre weighed sample of tablets was located in the friabilator and were subjected to 100 revolutions. Tablets were dedusted by means of a soft muslin cloth and reweighed. The friability (F %) is determined by the formula

$$F\% = \left(1 - \frac{Wo}{W}\right) X100$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test[13-16].

Wetting time

Wetting time of the tablets was measured by means of a piece of tissue paper (12 cm X 10.75 cm) folded twice, placed in a small petridish (ID = 6.5 cm) comprising of 6 ml of Sorenson's buffer (pH 6.8). A tablet was put on the paper, and the time for the whole wetting was measured[22-23].

Fig 1: *In vitro* Wetting Property

Disintegration test

Disintegration of fast disintegrating tablets is attained in the mouth due to the action of saliva, however amount of saliva in the mouth is restricted and no tablet disintegration test was found in USP and IP to simulate *in vivo* conditions[24]. A altered method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10 mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be located under the sieve (Figure 4.2). To determine disintegration time, 6 ml of water was placed inside the container in such way that 4 ml of the media was underneath the sieve and 2 ml above the sieve. Tablet was placed on the sieve and the entire assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the complex samples and the average value was determined[25].

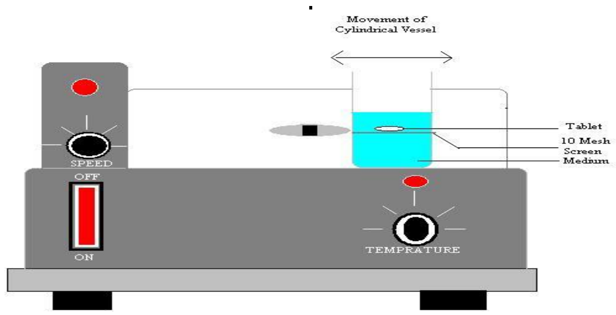

Fig 2: Disintegration Test Apparatus

In-vitro Release Study

The dissolution studies of new as well as conditioned FDT's were carried out using BP type II dissolution test apparatus[16]. The tablets were positioned in dissolution vessel containing 900 ml of 0.1 N HCl maintained at 37ºC ± 0.5 and stirred at 50 rpm. Samples (5 ml) were collected periodically at different time intervals (1, 2, 3, 4, 5 min) and substituted with fresh dissolution medium. The absorbance was determined spectrophotometrically at 284 nm. Dissolution contours were constructed as shown in Fig.4.8. Concentrations were calculated using calibration curves established in respective media. Taking into account, the loss of drug in aliquot replaced, the correction factor was used as shown in eq[25].

$$C_i = Ai + \frac{Vs}{Vt}\sum_{i=1}^{n-1} Ai \left(\frac{Vt}{Vt - Vs}\right) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots$$

Table 5: Post-Compression Characterization

F. Codes	Parameters						
	Thickness (mm)	Weight (mg)	Hardness (kg/cm²)	Friability (%)	Wetting Time (s)	Disintegration Time (s)	Drug Release (%)
F1	2.112 ±0.022	99.140 ±0.639	2.7 ±0.150	0.663 ±0.010	47 ±4.06	71 ±2.86	9.04 ±0.114
F2	2.067 ±0.124	98.456 ±0.718	3.2 ±0.147	0.578 ±0.018	70 ±2.71	91 ±1.59	14.03 ±0.048
F3	2.110 ±0.106	99.514 ±0.621	3.4 ±0.058	0.651 ±0.013	49 ±2.21	73 ±1.78	61.10 ±0.436
F4	2.294 ±0.082	99.982 ±0.833	2.8 ±0.169	0.553 ±0.002	70 ±1.32	92 ±2.13	63.20 ±0.188

n=6, ±SD

Preparation of physical mixture and co-processed superdisintegrants

Mixture of numerous concentration of superdisintegrants were prepared bestowing to factorial design batches. The physical mixture of SSG and crospovidone was organized by mixing them together in glass pestle motor. The co-processed superdisintegrant was prepared as follows:

1) **Solvent Evaporation Technology**:

Blends of sodium starch glycollate and crospovidone in diverse proportion, total weight of 10 g were added to 50 ml of isopropyl alcohol. The contents of beaker were stirred on a Magnetic stirrer. The temperature was kept between 65-70⁰ and stirring was continual till utmost of ethyl alcohol evaporated. The wet coherent mass was sieved through sieve no.100 the wet powder was dried in a tray drier at 60⁰ for 20 minutes. The dried powder were sifted on 120 mesh sieve and stored in airtight container.

2) **Microwave Technology:**

Blends of SSG and crospovidone in different ratio, total weight of 10 g were added to 50 ml of isopropyl alcohol. The beaker was situated inside microwave oven. The temperature was sustained between 65-70⁰ and heating was unremitting till most of ethyl alcohol evaporated.

3) **Lyophilized Technology**:

The Blends of SSG and CP in diverse ratio, total weight of 10 g were added to 50 ml of water. Resulting solution was taken into round bottom flask and frozen for 2 hours followed with condenser temperature of -77.5⁰C.When complete freezing was achieved RBF's were removed from freezing chamber, vaccum was Pragmatic and sample were bare to lyophilization for 4 hours with vaccum of 0.02 mbar. Complete sublimation of water transpired and dried mass remained in RBF. Dried powder was detached from freeze dryer and placed in desiccator. Wet coherent mass was sieved through sieve no.100 the wet powder was dried in a tray drier at 60⁰ for 20 minutes. The dried powder was sifted on 120 mesh sieve and stored in airtight container till additional use.

Development of fast dissolving tablets with physical mixture and coprocessed superdisintegrants

The superdisintegrants (Sodium Starch Glycolate and Crospovidone) coprocessed by solvent evaporation, microwave and lyophilization techniques were used to develop the tablets. All the ingredients were passed through sieve no. 60 and were co-grounded in a glass pestle motor. The tablets were prepared by using single punch tablet machine (Cadmach, Ahmedabad) to produce flat faced tablets weighing 100 mg each with a diameter of 5 mm.

A minimum of 50 tablets were ready for each batch. Before compression tablet blends were measured for mass-volume relationship (Bulk density, Tapped density, Hausner's ratio, Compressibility index) and flow properties (Angle of repose).

After compression of powder blends, the prepared tablets were evaluated for organoleptic features like color, odor, taste, diameter, thickness and physical characteristics like hardness, friability, disintegration time, wetting time, % drug release. The results are shown in Table 6.

Table 6: FDT with Physical Mixture and Coprocessed Superdisintegrants

Formulation	F5 *	F6+	F7#	F8^	F9*	F10+	F11#	F12^
Prochlorperazine Maleate	10	10	10	10	10	10	10	10
SSG	1	1	1	1	1	1	1	1
Crospovidone	1	1	1	1	1	1	1	1
Beta cyclodextrin	-	-	-	-	30	30	30	30
Avicel PH 102	50	50	50	50	30	30	30	30
Lactose	28	28	28	28	18	18	18	18
Talc	5	5	5	5	5	5	5	5
Mg. Stearte	5	5	5	5	5	5	5	5

n=6, ±SD * indicates physical mixture, + indicates solvent evaporation technique,

# indicates microwave technique, ^ indicates lyophilized technique

Table 7: Powder Blend evaluation of FDT with Physical Mixture and Coprocessed Superdisintegrants

Formulation	F5 *	F6+	F7#	F8^	F9*	F10+	F11#	F12^
Bulk Density (g/cc)	0.404 ±0.016	0.401 ±0.010	0.398 ±0.031	0.396 ±0.011	0.394 ±0.020	0.392 ±0.006	0.390 ±0.010	0.383 ±0.021
Tapped Density (g/cc)	0.438± 0.003	0.431 ±0.015	0.425 ±0.012	0.421 ±0.015	0.418 ±0.010	0.413 ±0.004	0.410 ±0.015	0.397 ±0.018
Hausner's Ratio	1.081± 0.008	1.074± 0.011	1.067 ±0.008	1.063 ±0.010	1.060 ±0.011	1.053 ±0.003	1.046 ±0.013	1.038 ±0.011
Compressibility Index (%)	7.762 ±1.014	6.960 ±1.327	6.352 ±1.084	5.938 ±1.229	5.741 ±1.119	5.084 ±1.218	4.878 ±1.092	4.526 ±1.426
Angle of Repose (°)	29.80 ±1.085	28.70 ±1.358	27.50 ±1.161	26.30 ±1.218	27.61 ±0.954	27.02 ±1.123	24.78 ±1.131	23.12 ±1.008

n=6, ±SD * indicates physical mixture, + indicates solvent evaporation technique,

# indicates microwave technique, ^ indicates lyophilized technique.

Table 8: Evaluation of FDT with Physical Mixture and Coprocessed Superdisintegrants

Formulation	F5 *	F6+	F7#	F8^	F9*	F10+	F11#	F12^
Thickness(mm)	2.451 ±0.056	2.326 ±0.126	2.301 ±0.071	2.310 ±0.092	2.146 ±0.120	2.581 ±0.014	2.402 ±0.102	2.315 ±0.016
Weight (mg)	99.421 ±0.261	100.562 ±1.453	97.675 ±0.608	98.987 ±0.323	98.961 ±0.327	97.684 ±0.519	98.988 ±0.884	100.018 ±1.021
Hardness (kg/cm^2)	2.9 ±0.104	3.0 ±0.103	2.9 ±0.098	2.8 ±0.204	2.9 ±0.206	3.0 ±0.076	2.8 ±0.271	2.9 ±0.128
Friability (%)	1.055 ±0.020	0.706 ±0.021	0.580 ±0.017	0.371 ±0.032	0.981 ±0.033	0.702 ±0.051	0.582 ±0.058	0.389 ±0.058
Wetting Time (s)	72 ±3.22	69 ±2.08	64 ±2.18	44 ±1.99	74 ±4.88	75 ±3.84	67 ±2.62	17 ±1.83
Disintegration Time (s)	100 ±2.25	92 ±1.24	90 ±2.78	39 ±2.75	101 ±2.44	98 ±2.23	90 ±1.19	36 ±2.82
Drug Release	18.6 ±0.018	22.82 ±0.351	26.19 ±0.432	32 ±0.711	69.21 ±0.159	75.80 ±0.350	82.8 ±0.255	90.5 ±0.131

n=6, ±SD * indicates physical mixture, + indicates solvent evaporation technique,

# indicates microwave technique, ^ indicates lyophilized technique.

CONCLUSION

From the results obtained from the study, it can be concluded that:

The method employed (solvent evaporation, microwave and lyophilization) in coprocessing excipients would affect the properties of the excipients and the effect they have on the formulations in which they are used.

The coprocessed disintegrants consisting of sodium starch glycolate and crospovidone, when used in the formulation tablets would enhance the mechanical properties of the resulting tablets.

The rate/amount of water intake into the tablets and wetting time and disintegration time would be limiting factors in early onset of drug dissolution and bioavailability.

Disintegrants coprocessed by lyophilization techniques would be effective disintegrants in the formulation of fast dissolving tablets of prochlorperazine maleate with disintegration times of less than 1 min without compromising the mechanical properties of the tablets.

Thus prochlorperazine maleate fast dissolving tablet produced from the disintegrants coprocessed by lyophilization technique provides better drug dissolution and bioavailability in cost effective manner.

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