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Formulation and Evaluation of Chlorpromazine Fast Dissolving Tablets Using Novel Co-Processed Superdisintegrants

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ABSTRACT

The present research work describes the preparation and evaluation of Fast dissolving tablets of Chlorpromazine Hydrochloride which were prepared by direct compression method using novel co-processed superdisintegrants. co-processed superdisintegrants were prepared by solvent evaporation using crospovidone and sodium starch glycolate in different ratios (1:1, 1:2. and 1:3). The developed co-processed superdisintegrants were evaluated for their flow and compression properties in comparison with the physical mixture of superdisintegrants**.** Fast dissolving tablets of chlorpromazine hydrochloride were prepared using all above co-processed superdisintegrants and physical mixtures of superdisintegrants and evaluated for pre-compression parameters such as bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio, and post-compression parameters such as hardness, friability, weight variation, *in-vitro* dispersion time, wetting time, water absorption ratio, drug content uniformity, *in-vitro* dissolution, drug-excipient interaction studies. From the result, it can be concluded that Fast dissolving tablets of Chlorpromazine Hydrochloride containing co-processed superdisintegrants exhibit quick disintegration and improved drug dissolution.

1. INTRODUCTION

Despite tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance[1]. Among the pharmaceutical dosage forms, conventional tablets are popular because of their special properties such as suitability to self-administration, improved stability, accurate dosing, ease of handling, versatility concerning to type and dose of the drug, and suitability to scale up[2].

Difficulty in swallowing (dysphagia) is common among all age groups, especially in the elderly, and is also seen in swallowing conventional tablets and capsules. This disorder is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head, and neck radiation therapy, and other neurological disorders, including cerebral palsy[3]. Drinking water plays an important role in the swallowing of oral dosage forms. Oftentimes people experience inconvenience in swallowing conventional dosage forms such as when water is not available[4]. These mentioned problems can be solved by developing rapidly disintegrating and fast dissolving tablet dosage forms for oral administration because they dissolve in saliva and do not require water for swallowing. The Administration is simple: the tablet is placed in the mouth, allowed to disperse or dissolve in the saliva, and then swallowed. To successfully deliver a drug into the body, the goal of any drug delivery system is to improve patient compliance, and mouth dissolving tablets are no exception. In addition to improving patient compliance, FDTs have been investigated for their potential in increasing the bioavailability of poorly water-soluble drugs through enhancing the dissolution profile of the drug. Moreover, pharmaceutical companies also have commercial reasons for formulating FDTs. As a drug reaches the end of its patent, the development and formulation of the drug into new dosage forms allows pharmaceutical companies to extend the patent life and market exclusivity. This allows pharmaceutical companies to attract new consumers through advertising and product promotion campaigns, and increase profits in the long term[5]. A fast disintegrating or dissolving system or tablet can be defined as a solid dosage form that can disintegrate or dissolve within a matter of seconds, in the oral cavity resulting in a solution or suspension without administration of water. The disintegration time for fast dissolving tablet varies from a few seconds to more than a minute depending on the formulation and the size of the tablet. FDTs are also called mouth dissolving tablets, melt in mouth tablets, rapid melts, porous tablets, orodispersible, quick-dissolving, or rapidly disintegrating tablets. United States Food and Drug Administration

(FDA) defined ODT as "A solid dosage form containing the medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue[6]. The bioavailability of some drugs may be increased due to absorption of drugs in the oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to the first-pass metabolism is reduced as compared to standard tablets[7].

Tablets and capsules are the most preferred dosage form of pharmaceutical scientists and clinicians because they can be accurately dosed and provide good patient compliance, they are easy for companies to manufacture, and they can be produced at a relatively low cost. Since, 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. One such approach for improving the functionality of excipients is the 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 an individual. Co-processing excipients leads to the formulation of excipients granules with superior properties compared with physical mixtures of components or individual components[8]. The concept of formulating fast dissolving tablets (FDT) using co-processed superdisintegrants increases the water uptake with the shortest wetting time and thereby decreases the disintegration time of the tablets by simple and cost-effective direct compression technique[9].

2. EXPERIMENTAL

2.1 PHASE-I

2.1.1 Determination of λ_{max} in Distilled Water and 0.1N HCl solution

The UV spectrum was recorded in the wavelength range 200 - 400 nm.

2.1.2 Calibration curve of Chlorpromazine Hydrochloride in Distilled Water: -

Different aliquots were taken from stock solution (100 µg/ml) and diluted with distilled water to prepare series of concentrations in the range of 2 - 10 µg/ml.

2.1.3 Calibration curve of Chlorpromazine Hydrochloride in 0.1N HCl solution: -

Different aliquots were taken from a stock solution prepared by using 0.1N HCl and diluted with 0.1N HCl to prepare series of concentrations in the range of 2 - 10 µg/ml.

The absorbance was measured for each solution at λ_{max} of 254 nm using Shimadzu UV/visible 1700 spectrophotometer, a graph was plotted for absorbance versus concentration of Chlorpromazine Hydrochloride.

2.2 PHASE-II

2.2.1 PREFORMULATION STUDY

The following preformulation studies were performed for the drug and polymers; Melting point, Drug-excipient compatibility study by using FT-IR spectroscopy and Differential scanning calorimetry, Angle of repose, Bulk density, Tapped density, Compressibility index, Hausner's ratio.

2.3 PHASE-III

2.3.1 Preparation of co-processed superdisintegrants[10, 11]

The co-processed superdisintegrants were prepared by a solvent evaporation method. A blend of crospovidone and sodium starch glycolate (in the ratio of 1:1, 1:2, and 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 the ethanol evaporated. The wet coherent mass was granulated through the # 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 the # 44-mesh sieve and stored in an airtight container till further use.

2.3.2 Formulation of fast dissolving tablets of Chlorpromazine Hydrochloride by direct compression method[12]

Fast dissolving tablets of chlorpromazine hydrochloride were prepared by direct compression, using novel co-processed superdisintegrants consisting of crospovidone and sodium starch glycolate in the different ratios (1:1, 1:2, and 1:3) according to the formula given in Table No. 1 below.

Table No. 1: Composition of Chlorpromazine Hydrochloride Fast Dissolving Tablets

Ingredients (mg)	Formulation Codes						
	CP_0	**PM_1**	**PM_2**	**PM_3**	**CP_1**	**CP_2**	**CP_3**
Chlorpromazine Hydrochloride	10	10	10	10	10	10	10
Microcrystalline Cellulose	57	55	55	55	55	55	55
Mannitol	74	70	70	70	70	70	70
Crospovidone + Sodium starch glycolate	-	6	6	6	6	6	6
Aspartame	4	4	4	4	4	4	4
Talc	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2
Total Weight	150	150	150	150	150	150	150

All the ingredients were passed through the #60 mesh separately. The drug, co-processed superdisintegrants, Avicel PH 102 (directly compressible microcrystalline cellulose), mannitol, aspartame, and talc were weighed and mixed in geometrical order. Finally, magnesium stearate was added, mixed, and blended well with the initial mixture. The mixed blend of drug and excipients was compressed using a Cadmach single punch tablet punching machine to produce tablets weighing 150 mg each.

2.4 PHASE-IV

2.4.1 Evaluation of fast dissolving tablets of Chlorpromazine HCl

The following Post-compression parameters were evaluated for fast dissolving tablets of Chlorpromazine HCl**:**

Hardness, Thickness, Weight variation, Friability, Drug content uniformity, Wetting time, Water absorption ratio, *In-vitro* disintegration time.

3. RESULT AND DISCUSSION

In the present study, an attempt has been made to design and evaluate fast dissolving tablets of Chlorpromazine HCl by direct compression method using novel co-processed superdisintegrants.

3.1 PHASE-I

3.1.1 Determination of λ_{max}: -

λ_{max} of Chlorpromazine HCl was found to be 254 nm in distilled water and 0.1 N HCl.

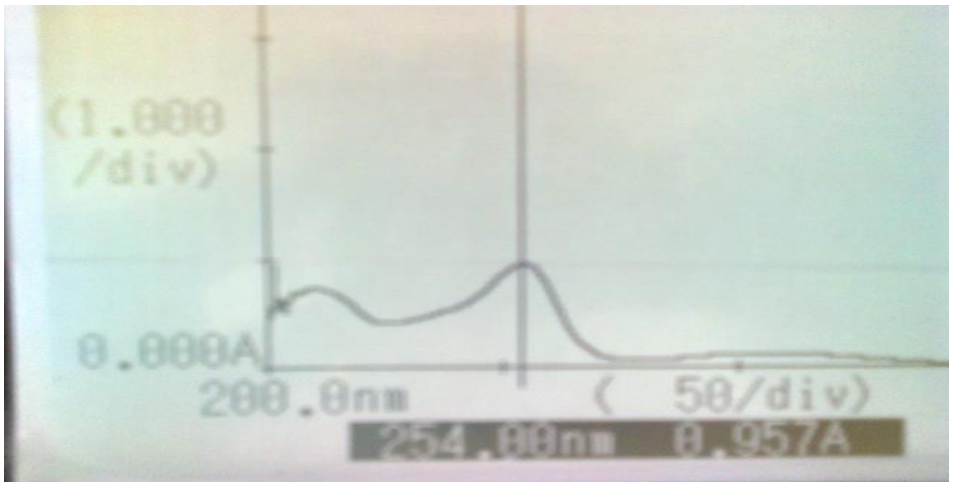

Figure No. 1: UV Spectrum of Chlorpromazine HCl in Distilled water

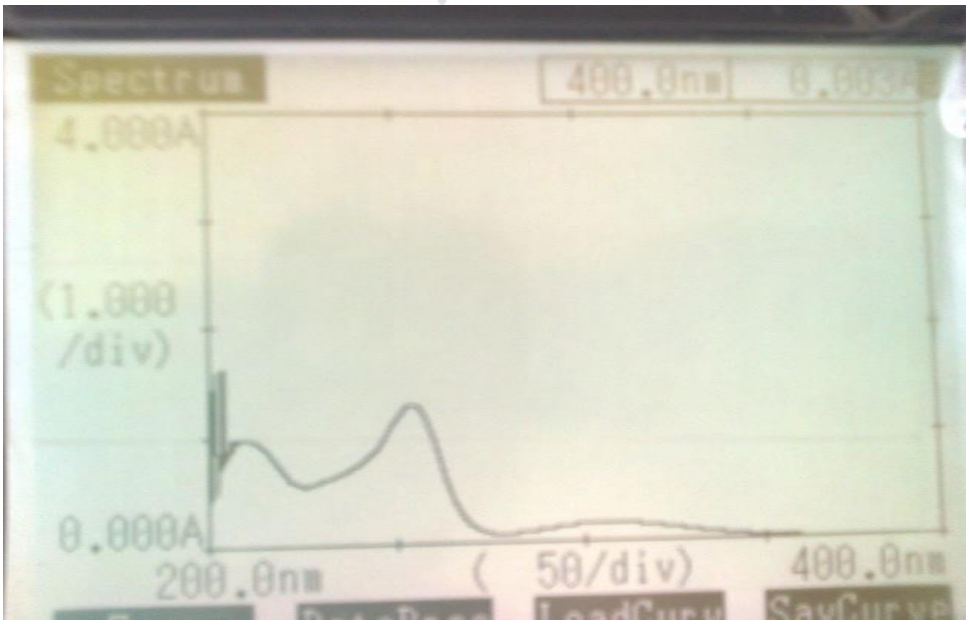

Figure No. 2: UV Spectrum of Chlorpromazine HCl in 0.1N HCl

3.1.2 Preparation of calibration curve of Chlorpromazine HCl in Distilled water and 0.1 N HCl

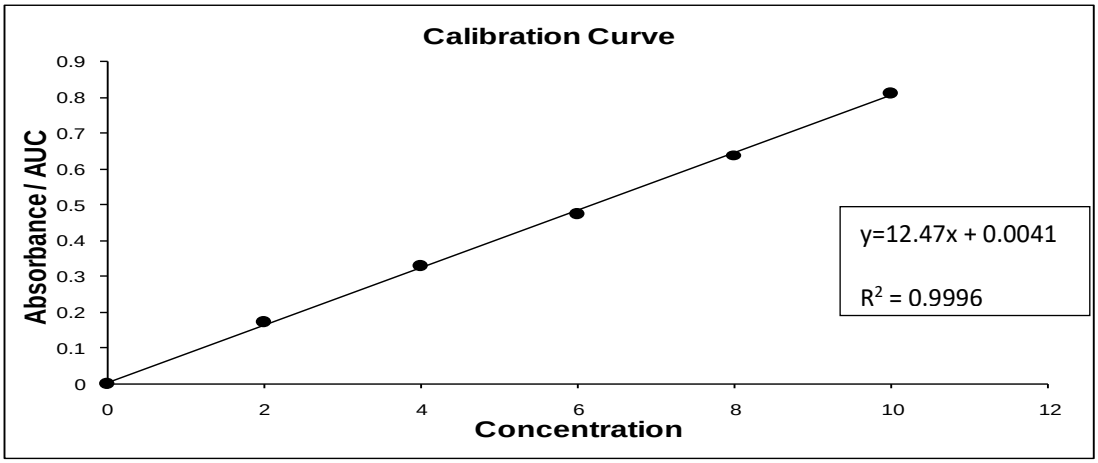

Figure No. 3: Standard graph of Chlorpromazine Hydrochloride in Distilled water.

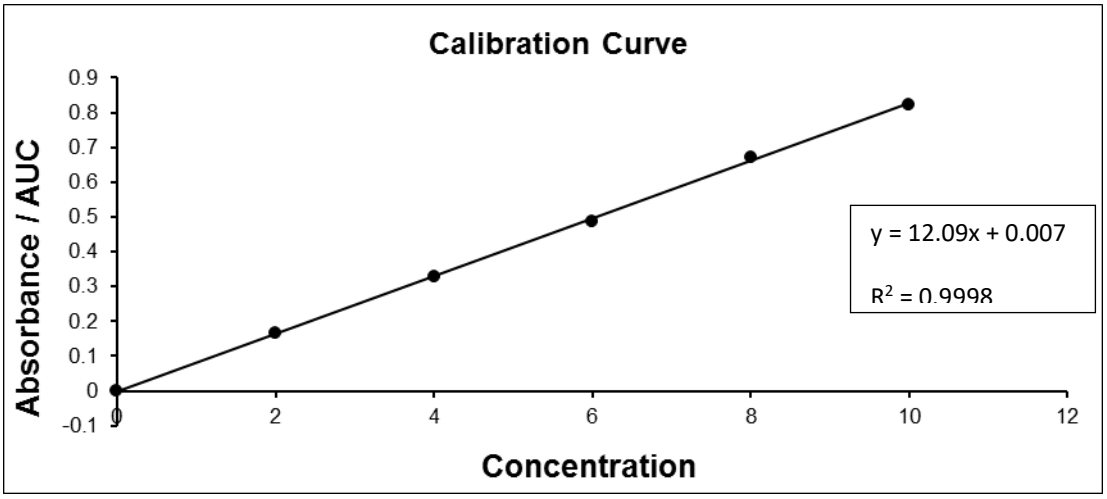

Figure No. 4: Standard graph of Chlorpromazine Hydrochloride in 0.1N HCl

3.2 PHASE-II: -

3.2.1 Melting point determinations

The Melting point of Chlorpromazine HCl was calculated by capillary method and it was found to be 180°C ± 0.59 (*n* = 3).

3.2.2 Drug–excipient compatibility studies: -

Drug–excipient compatibility studies were carried out using an FTIR spectrophotometer. The FTIR spectrum of pure drugs and the physical mixture of drugs and excipients were studied. In the present study, it has been observed that an FTIR spectrum of drug and polymers shows

that major frequencies of functional groups of the pure drug remain intact in granules containing different polymers; hence there is no chemical interaction between Chlorpromazine Hydrochloride and the excipients used in the study. No significant changes in peak pattern in IR spectra of pure drug and optimized formulation indicate that there is no interaction between pure drug and polymers.

Table No. 2: Data obtained for FTIR spectra of Chlorpromazine Hydrochloride along with excipients

Group	Absorption peaks (cm^{-1})			
	Chlorpromazine HCl (Pure Drug)	Drug and Crospovidone	Drug and Sodium starch glycolate	Optimized formulation
C-Cl stretching	691.31	692	689.98	691.43
C-N stretching	1278.26	1280.42	1276.54	1279.62
C-S stretching	2387.84	2385.70	2387.72	2385.87
C=C stretching (aromatic)	1526.86	1529.66	1526.25	1531.67

From the FT-IR spectra, the interference was verified and found that chlorpromazine hydrochloride did not interfere with excipients.

Table No. 3: Pre-compression Parameters of Co-processed Superdisintegrants & Physical Mixture of Superdisintegrants

Parameters	Formulation Codes					
	PM_1	PM_2	PM_3	CP_1	CP_2	CP_3
Bulk density (gm/cc)	0.49	0.55	0.53	0.32	0.37	0.39
Tapped density (gm/cc)	0.57	0.64	0.62	0.36	0.42	0.45
The Angle of repose (degree)	29.28	29.13	28.96	24.23	23.41	23.88
Carr's index (%)	14.03	14.06	14.51	11.11	11.90	13.33
Hausner's ratio	1.16	1.16	1.16	1.12	1.13	1.15

Co-processed superdisintegrants were prepared by solvent evaporation using crospovidone and sodium starch glycolate in different ratios (1:1, 1:2, and 1:3). The developed co-processed superdisintegrants were evaluated for their flow and compression properties in comparison with the 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 a 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 1.11 - 1.16. co-processed superdisintegrants were found to be superior inflow and compression properties in comparison with the physical mixture of superdisintegrants as shown in Table No. 3.

Table No. 4: Pre-compression Parameters of Chlorpromazine HCl FDT Formulations Prepared by Direct Compression Method

Parameters	Formulation Codes						
	CP_0	**PM_1**	**PM_2**	**PM_3**	**CP_1**	**CP_2**	**CP_3**
Bulk density (gm/cc)	0.69	0.58	0.66	0.64	0.38	0.46	0.47
Tapped density (gm/cc)	0.81	0.68	0.77	0.75	0.43	0.53	0.54
The Angle of repose (degree)	32.84	29.91	29.58	29.21	28.05	28.63	27.97
Carr's index (%)	14.81	14.70	14.28	14.66	11.62	12.96	12.93
Hausner's ratio	1.17	1.17	1.16	1.17	1.13	1.15	1.14

Fast dissolving tablets of chlorpromazine hydrochloride were prepared using the above co-processed superdisintegrants and physical mixtures of superdisintegrants. Directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance the mouthfeel. A total of six formulations and control formulation CP0 (without superdisintegrant) were designed. These tablets were evaluated for pre-compression parameters such as bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio, and post-compression parameters such as hardness, friability, weight variation, *in-vitro* dispersion time, wetting time, water absorption ratio, and drug content uniformity.

3.3 PHASE IV: -

3.3.1 Evaluation of Tablet: -

Table No. 5: Post-compression Parameters of Chlorpromazine HCl FDT Formulations

Parameters	Formulation Codes						
	CP_0	**PM_1**	**PM_2**	**PM_3**	**CP_1**	**CP_2**	**CP_3**
Weight variation (mg) ± SD	150.28 ± 0.82	149.36 ± 1	150.35 ± 1.19	149.82 ± 0.50	150.01 ± 1.22	149.90 ± 1.14	149.76 ± 1.34
Hardness (kg/cm^2) ± SD	3.18 ± 0.11	3.11 ± 0.17	3.23 ± 0.21	3.55 ± 0.08	3.14 ± 0.15	3.22 ± 0.08	3.27 ± 0.16
Friability (%)	0.46	0.63	0.56	0.70	0.53	0.60	0.66
Thickness (mm) ± SD	3.5 ± 0.1	3.33 ± 0.15	3.4 ± 0.1	3.43 ± 0.23	3.53 ± 0.17	3.53 ± 0.18	3.43 ± 0.32
***In-vitro* dispersion time (sec) ± SD**	106.33 ± 2.08	39. ± 1	65 ± 2	70.33 ± 1.52	19.33 ± 1.51	41.66 ± 1.52	53 ± 2
Wetting time (sec) ± SD	124.66 ± 2.18	44.66 ± 3.51	69 ± 1	77 ± 2	26.33 ± 2.51	48 ± 2.64	56.33 ± 2.08
Water absorption ratio (%) ± SD	41.68 ± 0.38	65.69 ± 0.46	58.90 ± 1.12	55.42 ± 1.05	86.91 ± 1.98	64.47 ± 0.70	60.48 ± 0.40
Percent drug content (%) ± SD	96.12 ± 0.76	97.13 ± 0.29	96.76 ± 1.01	97.44 ± 1.07	99.95 ± 0.93	98.11 ± 1.12	98.46 ± 1

As the blends were free-flowing (angle of repose < 30^0 and Carr's index < 15% Table No. 4), 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 96 to 100 %, which is within acceptable limits. The Hardness of the tablets was found to be in the range of 3-3.60 kg/cm^2. Friability below 1 % was an indication of good mechanical resistance of the tablets.

All values are expressed as mean ± SD.

3.4 PHASE V

3.4.1 *In-vitro* dissolution study: -

Table No. 6: Dissolution data of Chlorpromazine HCl in 0.1N HCl

Time (min)	Cumulative % Drug Release						
	CP_0	**PM_1**	**PM_2**	**PM_3**	**CP_1**	**CP_2**	**CP_3**
2	13.37±0.51	49.6 6± 0.54	37.85 ± 0.16	34.04 ± 0.33	65.7 8± 0.11	47.98±0.32	42.71 ± 0.49
4	23.28±0.43	73.63±0.54	54.46±0.33	50.99±0.54	85.11±0.27	70.60 ± 0.27	57.03 ± 0.35
6	32.24±0.41	85.10±0.86	71.19±0.22	67.30±0.56	96.57±0.38	80.30±0.38	75.03±0.38
8	42.58±0.49	91.26±0.44	82.09±0.23	78.44±0.17	99.67±0.10	87.42±0.38	84.62±0.53
10	50.44±0.66	94.56±0.44	88.42±0.33	86.02±0.55	-	93.45±0.33	92.60±0.61
12	57.17±0.66	98.31±0.16	93.62±0.22	90.41±0.28	-	98.25±0.22	95.82±0.50
14	64.73±0.61	99.70±0.16	96.67±0.33	94.45±0.79	-	99.64±0.21	98.30±0.45
18	73.28±0.62	-	98.79±0.21	97.79±0.41	-	-	99.74±0.18
22	78.94±0.74	-	99.88±0.09	98.76±0.30	-	-	-
26	84.99±0.79	-	-	-	-	-	-
30	91.32±0.58	-	-	-	-	-	-

All values are expressed as mean ± SD (n=3).

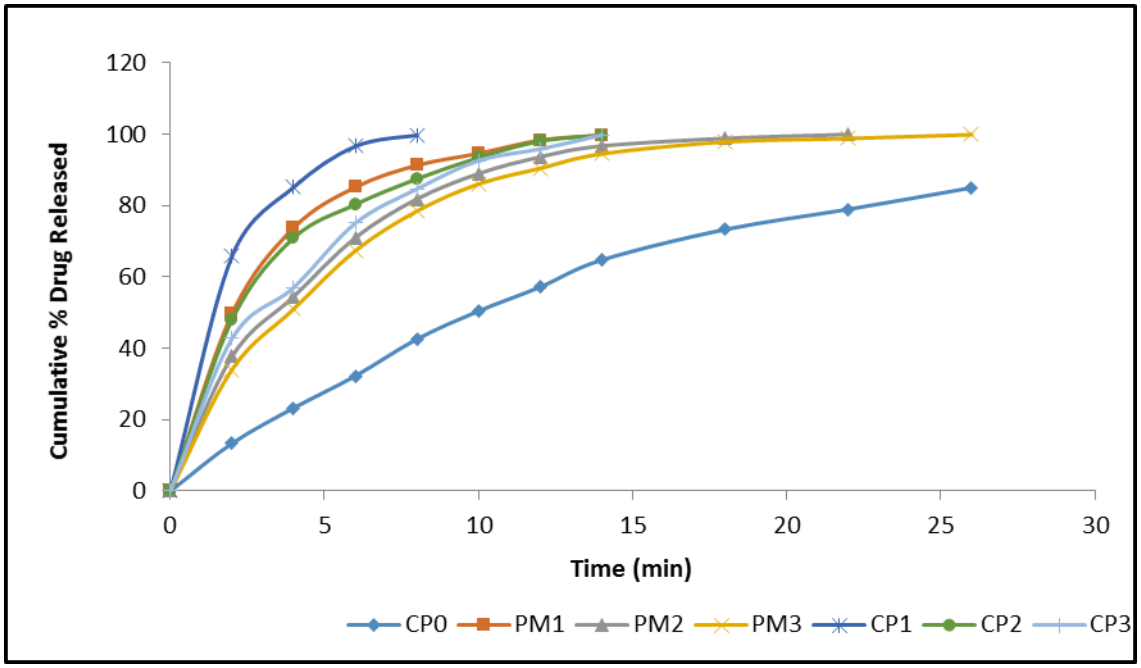

Figure No. 5: Dissolution studies of Chlorpromazine Hydrochloride FDT formulations.

Table No. 7: *In-vitro* Dissolution Parameters in 0.1N HCl

Formulation Code	Parameters					
	D_4	D_8	D_{12}	D_{18}	$t_{50\%}$	$t_{90\%}$
CP_0	23.28 %	42.58 %	57.17 %	73.28 %	10 min	>16 min
PM_1	73.63 %	91.66 %	98.31 %	-	2.01 min	7.88 min
CP_1	85.1 1%	99.67 %	-	-	1.50 min	4.65min

CP_0 is control formulation, CP_1 is promising fast dissolving tablet formulation, PM_1 is a formulation containing a physical mixture of superdisintegrants in 1:1 ratio, D_4 is percent drug released in 4 min, D_8 is percent drug release in 8 min, D_{12} is percent drug release in 12 min, D_{18} is percent drug release in 18 min. $t_{50\%}$ is time for 50 % drug dissolution, $t_{90\%}$ is time for 90 % drug dissolution.

In-vitro dissolution studies on the promising formulation CP_1, PM_1, CP_2, CP_3, PM_2, PM_3, and control formulation (CP_0) were carried out in 0.1N HCl. The various dissolution parameter values viz., percent drug dissolved in 4 min, 8 min and 12 min, 18 min (D_4, D_8, and D_{12}, D_{18}), $t_{50\%}$, and $t_{90\%}$ are shown in Table No.7 and dissolution profile depicted in Figure No. 5.

This dissolution data reveals that CP_1 has shown faster drug release (99.67 % within 8 min) in 0.1N HCl as compared to other batches of Chlorpromazine HCl FDT formulations and the

formulation CP_1 has shown nearly fivefold faster drug release ($t_{50\%}$ 1.50 min) when compared to CP_0 ($t_{50\%}$ 10 min).

4. CONCLUSION

In the present research work fast dissolving tablets of Chlorpromazine Hydrochloride were prepared by direct compression method using novel co-processed superdisintegrants. co-processed superdisintegrants were prepared by solvent evaporation using crospovidone and sodium starch glycolate in different ratios (1:1, 1:2. and 1:3) which are further used for the preparation of Fast dissolving tablets of chlorpromazine hydrochloride. Co-processed superdisintegrants consisting of crospovidone and sodium starch glycolate exhibit good flow and compression characteristics. Promising formulation CP_1 (containing co-processed superdisintegrants of crospovidone and sodium starch glycolate in ratio 1:1 released 99.67 % drug within 8 min as compared to other formulations of chlorpromazine hydrochloride and has shown nearly fivefold faster drug release as compared to CP_0. Fast dissolving tablets of Chlorpromazine Hydrochloride 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 sodium starch glycolate used in Chlorpromazine HCl fast-dissolving tablets.

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