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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLET OF PARACETAMOL AND CHLORPHENIRAMINE MALEATE

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Keywords:

Fast dissolving tablets, Paracetamol, Chlorpheniramine maleate, Superdisintegrants, Cross carmellose sodium, Direct compression method

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ABSTRACT: The aim of the present work was to formulate and evaluate Fast Dissolving Tablet (FDT) of a combined oral dosage form of Paracetamol (PCM) and Chlorpheniramine Maleate (CPM). Paracetamol is an antipyretic and Chlorpheniramine maleate is an antihistamine used to relieve symptoms of hay fever, allergy, and the common cold. Combining both the drugs can be used as pain-relieving and fever in cold and flu conditions. Three super disintegrating agents such as Cross Carmellose Sodium (CCS), Sodium Starch Glycollate (SSG) and Microcrystalline Cellulose (MCC) at different concentrations were used to enhance the disintegration and to improve the bioavailability of the drugs. By using the direct compression method, the FDT's were prepared and evaluated for hardness, weight variation, wetting time, friability, disintegration time, *in-vitro* dissolution study, Thermogravimetric Analysis (TGA), and stability studies. A new Spectrophotometric method was developed for simultaneous estimation of PCM and CPM in FDT. Among all six formulations, F2 with CCS 27% concentration found the best formulation. F2 resulted in best wetting time *i.e.* 26 sec, good water absorption ratio *i.e.* 81%, fastest disintegration time *i.e.* 20 sec and faster drug release within 25 min. No changes in drug release upon storage on different temperature and humidity was estimated in stability studies. The results showed that croscarmellose sodium as the superdisintegrants was ideal. The result indicates that FDT of a combined oral dosage form of PCM and CPM can be successfully explored and employed in the therapy of pain and fever in cold and flu conditions.

INTRODUCTION: Fast dissolving tablets are a solid dosage form containing a therapeutic substance or active ingredient that generally disintegrates rapidly within a few seconds. The Fast Dissolving Drug Delivery System (FDDDS) has been developed as an alternative to the conventional dosage form.

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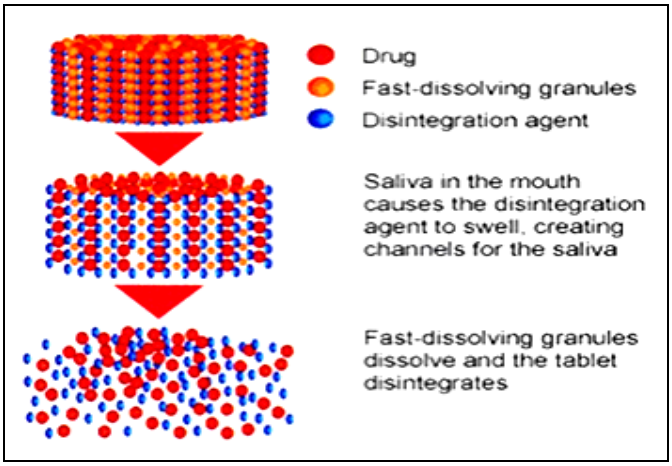

FIG. 1: MECHANISM OF DISINTEGRATION OF GRANULES OF FDT'S

These tablets are intended to break down or deteriorate quickly in the spit for the most part under 60 sec [1].

The FDT's can be obtained with various techniques such as direct compression, wet granulation, compression molding, volatilization, and freeze-drying. They include several mechanisms, such as the use of a large amount of hydrophilic disintegrating agents that allow the dosage form to rapidly disintegrate [2].

Paracetamol or Acetaminophen is a broadly utilized over-the-counter pain-relieving (torment reliever) and antipyretic (fever reducer) widely used. It is usually used for the relief of migraines and other minor pains. In combination with opioid analgesics, paracetamol can also be used in the treatment of more intense pain, for example, postoperative pain [3].

Chlorpheniramine is an antihistamine used to relieve symptoms of allergy and the common cold. These symptoms are rash, watery eyes. Irritated eyes/nose /throat/skin, hake runny nose sneezing. This medicine works by blocking a specific natural substance (histamine) produced by the body during an infection.

Paracetamol is quickly absorbed after an oral dose with a bioavailability of about 45%. A peak plasma concentration occurs within 2 to 4 h and its plasma half-life is about 4 h after an oral dose, Whereas Chlorpheniramine Maleate is quickly absorbed after an oral dose with a bioavailability of about 25%. Peak plasma concentration occurs within 5 to 8 h and its plasma half-life is about 13 h after an oral dose. In the management of fever as well as cough & cold flu both are given in doses 500 mg for paracetamol and Chlorpheniramine Maleate is given in a dose of 4 mg two times a day.

The aim of the proposed work was to formulate and characterize FDT's of Paracetamol and Chlorpheniramine Maleate for quick dissolution of the drug and absorption, which can provide a rapid onset of action in the treatment of fever, as well as cough & cold flu in patients.

The combined dosage form of two or more drugs has proven useful in multiple therapies because it offers better patient compliance compared to a single drug. The fixed-dose combination containing the antipyretic agent and the antihistaminic agent to treat fever as well as cough & cold flu. [3]

MATERIALS AND METHODS:

Materials: Paracetamol and Chlorpheniramine Maleate were obtained as a gift sample by Modern Laboratories Pvt. Ltd., Indore (M.P.). The institute provided other excipients. All reagents and chemicals were of analytical quality.

Preformulation Study:

Determination of Solubility of Drugs in Different Solvents: The degree to which solute dissolves is called solubility, which is a homogeneous, chemical and physical mixtures of two/ more substances. The solubility of the drug (Paracetamol and Chlorpheniramine Maleate) has been tested in several solvents. A defined amount (10 mg) of the drug was dissolved in 10 ml of each solvent and studied at room temperature. Solubility has been observed with the UV method.

Precompression Parameters:

Flow Properties:

Angle of Repose: Angle of repose was estimated by the fixed funnel method. The frictional force in loose or granular powder was measured from the angle of repose. Angle of repose is the maximum possible angle between the surface of a pile of the granules/ powder and its horizontal plane. [4]

$$\text{Tan } \theta = h/r$$

Where, Θ = Angle of Repose, h = Height of Cone, r = Radius of Cone

TABLE 1: PARAMETERS FOR ANGLE OF R

Flow property	Angle of repose (°)
Excellent	<25
Good	25-30
Passable	30-40
Very poor	>40

Bulk Density: Bulk density refers to the measurement which describes a packing of powder/ granules. Bulk density is referred to the ratio of the mass of powder to the bulk volume and is expressed in g/ml or g/cm^3 although the international unit is kg/m^3 (1 g/ml = 1000 kg/m^3) because the measurements are made using cylinders. Bulk Density (ρb) was determined by using following equation [5].

$$\rho b = M / Vb$$

Where, ρb = Bulk density, M = Mass of the powder in g, Vb = Total volume of packing

Tapped Density: Tapped Density was determined by placing a particular amount of powder in a graduated cylinder and tapped it for a fixed unit (100 times). The powder bed reaches to its minimum volume [6].

$$\rho t = M / Vt$$

Where, ρt = Tapped density, M = Mass of the powder in g, Vt = Tapped volume of blend in cm^3

Carr's Index: Carr's index (Compressibility Index) is a measure of the tendency of the powder to be compressed. It was determined by bulk and tapped densities and was calculated using the following formula:

$$\text{Carr's Index} = \rho t - \rho b/\rho t * 100$$

Where, ρb = Bulk Density, ρt = Tapped Density

TABLE 2: PARAMETERS FOR CARR'S INDEX

Flow property	Carr's Index (%)
Excellent	5 – 15
Good	12 – 16
Fair to passable	18 – 21
Poor	23 – 35
Very poor	7-38
Very, very poor	>40

Hausner's Ratio: A flow property of powder mixture can be determined by Hausner's ratio. Hausner's ratio was calculated by the following formula: [7]

$$\text{Hausner's ratio} = \text{Tapped density} / \text{Bulk density}$$

Hausner's ratio >1.25 will be considered as poor flowability.

Calibration Curve of Drug: Measurement of spectra of Paracetamol and Chlorpheniramine Maleate by using UV-Visible 1600 Shimadzu double beam spectrophotometer and the solvent used for dilutions was 0.1 N NaOH for Paracetamol and Methanol for Chlorpheniramine Maleate.

Wavelength used for Drug: The standard solution of Paracetamol and Chlorpheniramine Maleate (10µg/ml) were scanned in the range between 200-400 nm and λ_{max} was determined. The λ_{max} obtained was taken for further estimation of absorbance.

Standard Stock Solution: For standard stock solution (1000 µg/ml), 100 mg of drug was taken and transferred to a volumetric flask and a sufficient solvent was added to produce 100 ml. For the second stock solution (100 µg/ml), 10 ml of the above stock solution was taken in a volumetric flask and diluted with 100 ml of the solvent.

Dilutions Preparation: From the standard second stock solution, five different dilutions of 2µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml were prepared.

Procedure: The measurement of the absorbance of different dilutions of standard and sample was done by using UV-Vis Spectrophotometer.

Melting Point: It was estimated by using the Melting Point apparatus. Firstly, fill the drug in the capillary tube. In the melting point apparatus place the capillary tube. Set the temperature at an adequate high point. The magnifying lens was used to observe the melting point.

Drug and Excipients Interaction: The compatibility of the drug and various excipients was studied by TLC (Thin Layer Chromatography) technique. For the interaction studies, Paracetamol and Chlorpheniramine Maleate both 10 mg was mixed thoroughly by mortar and pestle with excipients in the ratio of 1:5 respectively and placed in tightly closed vials. All the vials were stored at 40 ºC for 4 weeks. The samples were analyzed by physical observation and TLC.

Formulation of FDT's:

TABLE 3: FORMULA FOR FDT'S

S. no.	Ingredients (in mg)	F1	F2	F3	F4	F5	F6
1	Paracetamol (PCM)	325	325	325	325	325	325
2	Chlorpheniramine Maleate (CPM)	4	4	4	4	4	4
3	Cross Carmellose Sodium (CCS)	60	100	-	-	-	-
4	Microcrystalline Cellulose (MCC)	-	-	60	100	-	-

5	Sodium Starch Glycollate (SSG)	-	-	-	-	60	100
6	Mannitol	49.75	9.75	49.75	9.75	49.75	9.75
7	Citric Acid (0.5%)	2.25	2.25	2.25	2.25	2.25	2.25
8	Magnesium Stearate (1%)	4.5	4.5	4.5	4.5	4.5	4.55
9	Talc (1%)	4.5	4.5	4.5	4.5	4.5	4.5
	Total weight (in mg)	450	450	450	450	450	450

Method of Preparation of FDT's by Direct Compression Method: FDT's were prepared using a direct compression method of Paracetamol and Chlorpheniramine Maleate incorporating superdisintegrants (MCC, CCS and SSG). Six formulations were prepared using super-disintegrants in different concentrations, 22% and 27 % which was used to evaluate the effect of concentration on disintegration profile of the tablet.

Paracetamol, Chlorpheniramine Maleate, Mannitol and Starch were mixed thoroughly in glass mortar using a pestle. Superdisintegrants were blended in the powder mixture to all formulation in the tablets accordingly and then finally citric acid, magnesium stearate and talcum were added. The blend was passed via sieve no. 40 twice. FDT's were formulated by using a 9.525 mm round biconvex punch of the single stock tablets compression machine.

Post Compression Studies:

Thickness: By using Vernier Caliper, the thickness of the FDT's was determined. Five tablets of each formulation type were used and the mean values were calculated [8].

Weight Variation: From each FDT's formulation, individually 20 FDT's were weighed using an electronic balance and the average weight of FDT's was calculated. Then the individual weight of tablets was compared with the mean value and the weight deviation was determined [9].

Hardness: Monsanto Hardness Tester was used to estimate Hardness by using 6 FDT's from every formulation [10].

Friability: Roche Friabilator was used to determine the friability of FDT's by using 20 tablets. 20 pre-weighed tablets were rotated for 4 min at 25 rpm. The tablets were weighed again after removal using a 60 mesh size screen and % weight loss was evaluated [11].

$$\% \text{ Friability} = (\text{Final weight} / \text{initial weight}) * 100$$

Wetting Time: The wetting time of FDT's was evaluated by taking a piece of paper that was folded twice and was kept in petridish with 5.5 cm diameter. 6 ml of water containing erythrosine a water-soluble dye is added to petridish. One FDT from each formulation was placed over the separate tissue paper. The time at which water reaches the tablet surface indicated as wetting time [12].

Water Absorption Ratio: A piece of tissue paper folded twice in a petridish was kept with 6 ml of water. One weighed FDT from each formulation was placed on the tissue paper and left to moisten completely and then weighed again. The water absorption ratio (R) was estimated by using the following equation [12].

$$R = 100 * (W_a - W_b) / W_a$$

Where, Wa = Weight of FDT after water absorption, W_b = Weight of FDT before water absorption.

Content Uniformity: The drug content of each formulation was evaluated using the U.V. spectro-photometer by the simultaneous equation method.

Preparation of Standard Solution: Firstly stock solutions (1000µg/ml) of both drugs were prepared individually. Stock solutions were then diluted with methanol to make a concentration between 5 to 30µg/ml for both drugs.

Preparation of Sample: FDT's were weighed and triturate to a fine powder. An exact powder was weighed equivalent to 325 mg of Paracetamol was transferred into a volumetric flask which was dissolved in 10 ml of methanol and then makes up the volume to 50 ml of distilled water and was sonicated for 15 min. Then the solution was filtered *via* Whatman filter paper and the amount of Paracetamol and Chlorpheniramine Maleate were evaluated.

Simultaneous Equation Method: The absorbance of all dilutions was recorded at evaluated wavelength λ_1 (for Paracetamol) and λ_2 (for

Chlorpheniramine Maleate) and absorptivity coefficients of both the drugs were determined.

$$C_x = (A_2ay_1\text{-}A_1ay2) / (ax_2ay_1) – (ax_1ay_2)$$
$$C_y = (A_1ax_1\text{-}A_2ax2) / (ax_2ay_1) – (ax_1ay_2)$$

Where,
A_1 = Absorbance of the sample solution at λ_1 nm, A_2 = Absorbance of the sample solution at λ_2 nm
ax_1 = Absorptivity of PCM at λ_1 nm, ax_2 = Absorptivity of PCM at λ_2 nm
ay_1 = Absorptivity of CPM at λ_1 nm, ay_2 = Absorptivity of CPM at λ_2 nm

***In-vitro* Disintegration Time:** Disintegration time was estimated in 900 ml buffer solution (pH 5.8) at temperature 37 ± 0.5 ºC without disc. The disintegration time of 6 FDT's from each formulation were recorded and the mean time was calculated [13, 18].

***In-vitro* Dissolution Studies:** The dissolution rate was reported by using USP Paddle Dissolution Apparatus Type II, in 900 ml of phosphate buffer pH 6.8 at 37.0 ± 0.5 °C temperature at 50 rpm. At a particular time interval, 5 ml sample solutions were taken out from the USP paddle dissolution apparatus and then the samples were replaced with the dissolution medium. The samples were then filtered and the drug content of PCM and CPM in each sample was analyzed after suitable dilution by Shimadzu UV-spectrophotometer at 248.7 nm and 261.9 nm respectively. Cumulative percentage (%) of drug release was then calculated [13, 18].

Thermogravimetric Analysis: TGA is a technique that helps to control the function of temperature or time when the sample is subject to a controlled temperature program at a controlled atmosphere. It is a technique in which when a material is heated, then its weight gets increases/decreases. TGA of PCM, CPM, and FDT was determined [14-15].

Stability Studies: The stability studies were performed as given in ICH guidelines for one month for accelerated study at 40 ± 2 ºC/ RH 75 ± 5%. The tablets were removed after 30 days and analyzed to determine the physical characterization and drug content. The FDT's were divided into three batches and kept under 3 different temperature *i.e.* at room temperature 25 ± 2 ºC/ RH 60 ± 5%, at accelerated temperature 40 ± 2 ºC/ RH 75 ± 5% and at cool temperature 4 ± 2 ºC/ RH 65±5% to time 30 days and 60 days respectively. Then each sample was withdrawn at a specific time and then the drug stability studies were performed [16-17].

RESULTS AND DISCUSSIONS:

Determination of Solubility: Solubility was evaluated using the following solvent.

TABLE 4: SOLUBILITY OF THE DRUGS IN VARIOUS SOLVENTS

S. no.	Solvent	Solubility of Paracetamol	Solubility of Chlorpheniramine Maleate
1	0.1 N NaOH	Soluble	Soluble
2	PBS (pH6.8)	Soluble	Freely Soluble
3	Water	Very slightly soluble	Soluble
4	Methanol	Soluble	Soluble
5	Chloroform	Insoluble	Insoluble

Precompression Parameters:

Properties of Drug: Properties of the drug were determined. All the results were under the limit.

TABLE 5: PROPERTIES OF DRUG

Drug	Bulk density ρb = M / Vb	Tapped density ρt = M / Vt	Angle of repose Tan θ = h/r	Compressibility Index ρt - ρb/ρt *100	Hausner's ratio ρt / ρb
PCM	0.333 ± 0.006	0.502 ± 0.007	33.01 ± 0.005	1.50 ± 0.0024	31.34 ± 0.02
CPM	0.353 ± 0.003	0.566 ± 0.002	37.63 ± 0.012	1.60 ± 0.024	32.71 ± 0.04

*Values are represented as Mean ± S.D.

Calibration Curve: The λ_{max} for Paracetamol has been found to be 248.7 nm and λ_{max} for Chlorpheniramine Maleate has been found to be 261.9 nm. The calibration curve of Paracetamol and Chlorpheniramine Maleate was prepared, for both the drugs. Linear relationship was reported in the concentration of 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml. The correlation coefficient was found, which was within the limit.

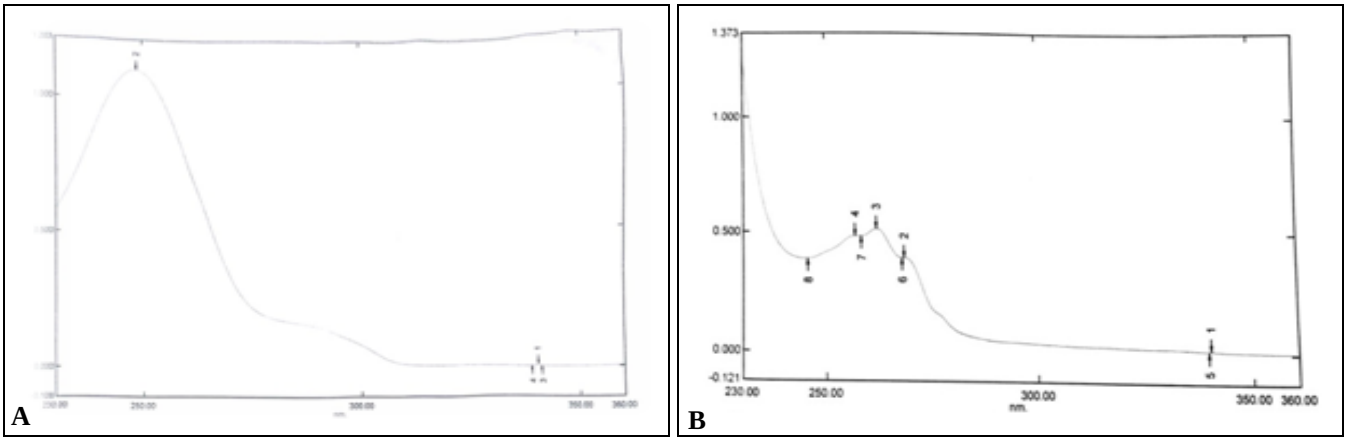

FIG. 2: UV SPECTRA OF (A) PARACETAMOL (B) CPM

TABLE 6: ABSORBANCE FOR CALIBRATION CURVE FOR PCM AND CPM

S. no.	Concentration (µg/ml)	Absorbance of PCM (at λ_{max} 248.7 nm)	Absorbance of CPM (at λ_{max} 261.9 nm)
1	0	0	0
2	2	0.239	0.195
3	4	0.388	0.371
4	6	0.578	0.542
5	8	0.688	0.691
6	10	0.859	0.843

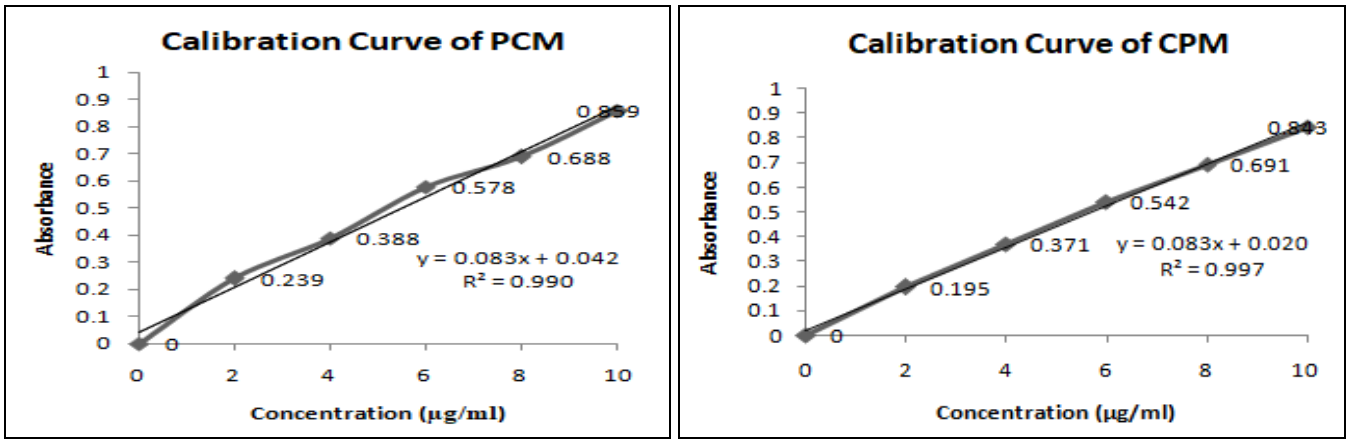

FIG. 3: CALIBRATION CURVE OF PCM AND CPM

Melting Point: Melting Point of Paracetamol has been found 170 ± 0.5 ºC and Melting Point of Chlorpheniramine Maleate has been found 132 ± 0.5 ºC.

Drug and Excipients Interaction Study:
Paracetamol and Excipients:

TABLE 7: PARACETAMOL (PCM) AND EXCIPIENTS INTERACTION BY TLC

S. no.	Drug	Initial	After 4 Weeks	Observation
1	PCM	R_f= 0.37	R_f= 0.38	No interaction was found
2	PCM + Mannitol	R_f= 0.42	R_f= 0.48	No interaction was found
3	PCM + Starch	R_f= 0.46	R_f= 0.48	No interaction was found
4	PCM + Citric Acid	R_f= 0.51	R_f= 0.53	No interaction was found
5	PCM + CCS	R_f= 0.44	R_f= 0.45	No interaction was found
6	PCM + SSG	R_f= 0.45	R_f= 0.46	No interaction was found
7	PCM + MCC	R_f= 0.39	R_f= 0.41	No interaction was found
8	PCM + Talc	R_f= 0.42	R_f= 0.44	No interaction was found
9	PCM + Mg. stearate	R_f= 0.41	R_f= 0.42	No interaction was found
10	PCM + All excipients	R_f= 0.55	R_f= 0.54	No interaction was found

Chlorpheniramine Maleate and Excipients:

TABLE 8: CHLORPHENIRAMINE MALEATE (CPM) AND EXCIPIENTS INTERACTION BY TLC

S. no.	Drug	Initial	After 4 Weeks	Observation
1	CPM	R_f= 0.53	R_f= 0.56	No interaction was found
2	CPM + Mannitol	R_f= 0.53	R_f= 0.54	No interaction was found
3	CPM + Starch	R_f= 0.59	R_f= 0.60	No interaction was found
4	CPM + Citric Acid	R_f= 0.52	R_f= 0.54	No interaction was found
5	CPM + CCS	R_f= 0.54	R_f= 0.55	No interaction was found
6	CPM + SSG	R_f= 0.60	R_f= 0.62	No interaction was found
7	CPM + MCC	R_f= 0.53	R_f= 0.54	No interaction was found
8	CPM + Talc	R_f= 0.62	R_f= 0.66	No interaction was found
9	CPM + Mg. Stearate	R_f= 0.64	R_f= 0.65	No interaction was found
10	CPM + All Excipients	R_f= 0.60	R_f= 0.63	No interaction was found

Precompression Parameter of Powder Blend: Each formulation's powder blend of drug and excipients were prepared and evaluated by various parameters. Bulk density has been found in the range between 0.52 to 0.59 g/ml, and tapped density has been found between 0.63 to 0.70 g/ml. Using the above data compressibility index and Hausner's ratio was calculated. The powder blend of all six formulations has a compressibility index between the range 11% to 15% and Hausner's ratio for all six formulations was <1.25 which shows good flowability.

TABLE 9: PRECOMPRESSION PARAMETER OF POWDER BLEND

Formulations	Bulk Density(g/ml) ρb = M / Vb	Tapped Density(g/ml) ρt = M / Vt	Angle of Repose (°) Tan θ = h/r	Carr's Index (%) ρt - ρb/ρt *100	Hausner's Ratio ρt / ρb
F1	0.57 ± 0.02	0.70 ± 0.01	24.54 ± 0.22	14 ± 0.14	1.22 ± 0.01
F2	0.58 ± 0.01	0.69 ± 0.00	25.28 ± 0.18	15 ± 0.13	1.18 ± 0.02
F3	0.59 ± 0.21	0.67 ± 0.01	26.34 ± 0.28	11 ± 0.08	1.13 ± 0.01
F4	0.52 ± 0.03	0.63 ± 0.02	27.21 ± 0.21	15 ± 0.05	1.21 ± 0.02
F5	0.56 ± 0.02	0.64 ± 0.01	26.32 ± 0.24	12 ± 0.11	1.14 ± 0.02
F6	0.54 ± 0.02	0.64 ± 0.01	25.65 ± 0.26	15 ± 0.04	1.18 ± 0.01

*Values are represented as Mean ± S.D.

Tablet Formulations:

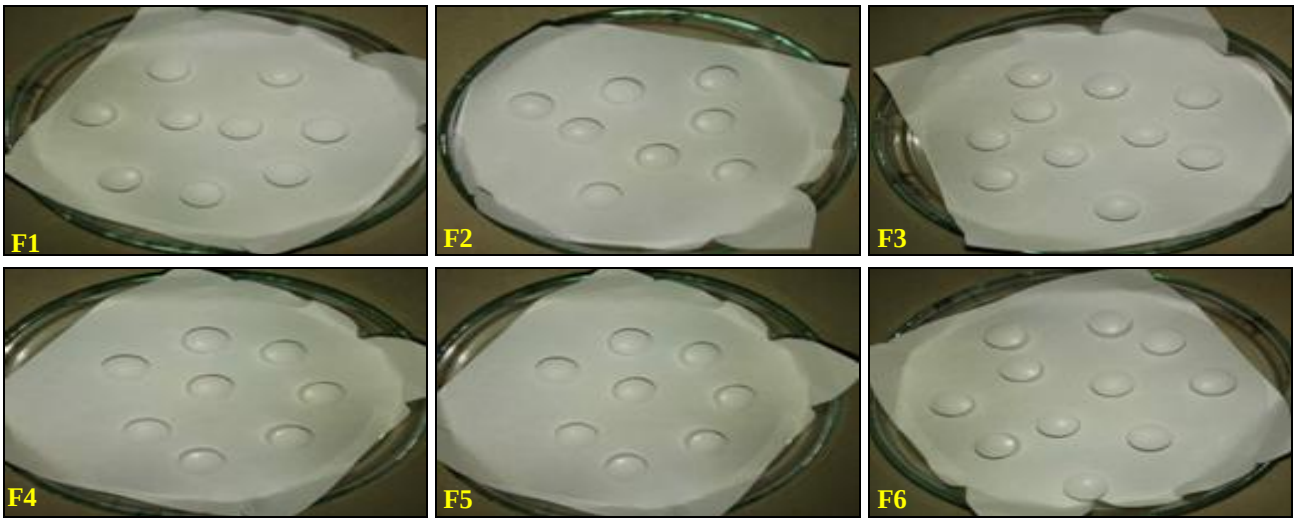

FIG. 4: FAST DISSOLVING TABLETS

Post Compression Parameter:

Evaluation of Tablet: Evaluation of post-compression parameter was performed. Hardness has been found within a range of 2.0 to 4.0 kg/cm^2 for all formulations indicate good mechanical strength. The thickness of all six formulations has been found within the range of 5.39 to 5.56 mm. All formulations have the friability values are less

than 1%. All six formulations have passed the weight variation test as the % weight variation. Water Absorption Ratio of all six formulations was found between 51 to 81%. Wetting Time has been found between 26 to 42 sec. Disintegration time has been found to be 20-32 sec. All the evaluation parameters meet the IP limit.

Wetting Time:

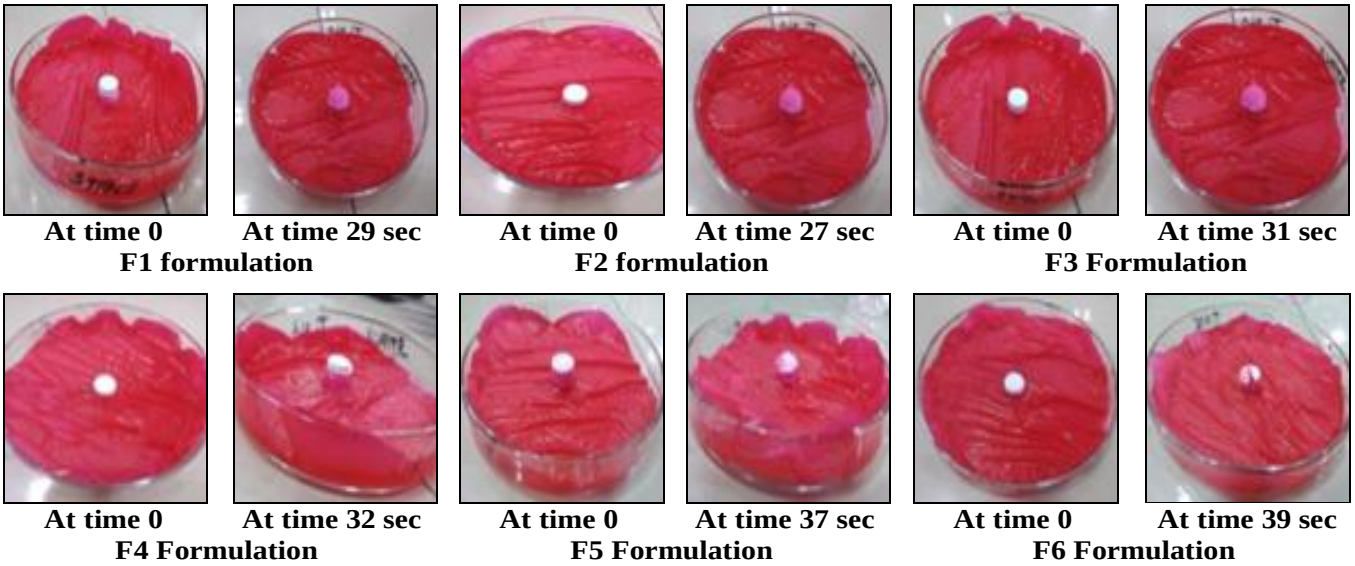

FIG. 5: WETTING TIME OF ALL FORMULATIONS

TABLE 10: POST COMPRESSION PARAMETER-I

Formulations	Thickness (mm ± SD) (n=5)	Hardness (kg/cm^2 ± SD) (n=5)	Weight variation (Avg. wt. ± % SD) (n=20)	Friability (%)
F1	5.49 ± 0.20	2.3 ± 0.27	460 ± 0.52	0.68
F2	5.49 ± 0.16	2.6 ± 0.41	442 ± 0.35	0.70
F3	5.46 ± 0.16	2.0 ± 0.27	447 ± 0.74	0.71
F4	5.39 ± 0.15	3.0 ± 0.49	449 ± 0.37	0.70
F5	5.56 ± 0.30	3.9 ± 0.27	451 ± 0.49	0.73
F6	5.54 ± 0.21	4.0 ± 0.41	448 ± 0.32	0.78

*Values are represented as Mean ± S.D.

TABLE 11: POST COMPRESSION PARAMETER-II

Formulations	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio (%)
F1	22 ± 1.00	28 ± 0.57	72 ± 2.05
F2	20 ± 1.52	26 ± 0.57	81 ± 1.52
F3	28 ± 0.57	31 ± 1.52	60 ± 0.37
F4	32 ± 1.15	32 ± 1.00	62 ± 2.08
F5	29 ± 0.57	39 ± 1.00	51 ± 1.01
F6	30 ± 1.00	42 ± 0.51	55 ± 0.57

*Values are represented as Mean ± S.D.

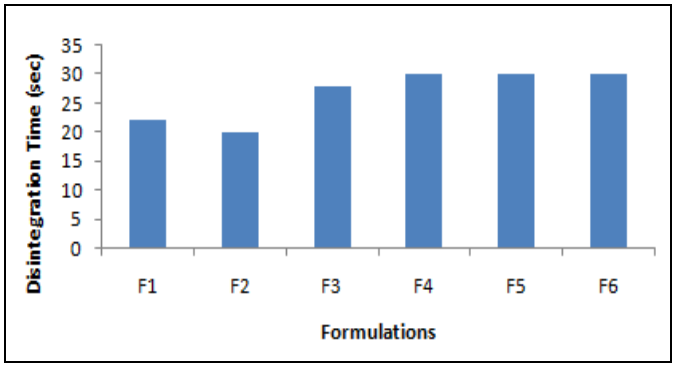

FIG. 6: DISINTEGRATION TIME OF ALL FORMULATIONS

Drug Content in Formulations: The drug content of all six formulations was estimated using a UV-visible spectrophotometer after appropriate dilution and filtration by using a simultaneous equation method and has been found within the IP limit.

TABLE 12: ABSORPTIVITY VALUE FOR PCM

Conc.	Absorbance at λ_1 (248.7 nm)	Absorptivity at λ_1 (248.7 nm)	Absorbance at λ_2 (261.9 nm)	Absorptivity at λ_2 (261.9 nm)
5µg/ml	0.886	0.1772	0.550	0.11
10µg/ml	1.292	0.1292	0.789	0.078
15µg/ml	1.922	0.1281	1.167	0.077
20µg/ml	2.566	0.1283	1.663	0.083
25µg/ml	2.706	0.1082	1.681	0.067
30µg/ml	2.905	0.096	1.790	0.059
	Absorptivity for $\lambda_1(ax_1)$ = 0.1534		Absorptivity for $\lambda_2(ax_2)$ = 0.094	

TABLE 13: ABSORPTIVITY VALUE FOR CPM

Conc.	Absorbance at λ_1 (248.7 nm)	Absorptivity at λ_1 (248.7 nm)	Absorbance at λ_2 (261.9 nm)	Absorptivity at λ_2 (261.9 nm)
5µg/ml	0.204	0.040	0.235	0.047
10µg/ml	0.407	0.040	0.519	0.051
15µg/ml	0.896	0.059	0.870	0.058
20µg/ml	1.049	0.052	0.901	0.045
25µg/ml	1.103	0.044	1.281	0.051
30µg/ml	1.201	0.040	1.512	0.050
	Absorptivity for $\lambda_1(ay_1)$= 0.055		Absorptivity for $\lambda_2(ay_2)$= 0.060	

TABLE 14: DRUG CONTENT IN FORMULATIONS

Formulation	PCM (%)	CPM (%)
F1	95.65	90.21
F2	98.83	95.13
F3	97.19	92.34
F4	98.03	93.67
F5	97.54	91.22
F6	96.81	90.91

In-vitro Dissolution Study:

TABLE 15: *IN-VITRO* RELEASE PROFILE OF COMBINATION OF DRUGS (IN %)

Time (min)	DRUG	F1	F2	F3	F4	F5	F6
0	PCM	0	0	0	0	0	0
	CPM	0	0	0	0	0	0
5	PCM	23	27	20	13	18	15
	CPM	27	30	25	18	22	20
10	PCM	34	37	29	20	25	22
	CPM	42	51	39	29	35	32
15	PCM	56	65	49	35	47	41
	CPM	61	72	54	38	50	45
20	PCM	68	89	62	41	57	49
	CPM	72	91	69	49	65	55
25	PCM	77	100	73	55	69	56
	CPM	86	100	80	65	72	69
30	PCM	99		95	79	90	86
	CPM	100		97	82	94	90

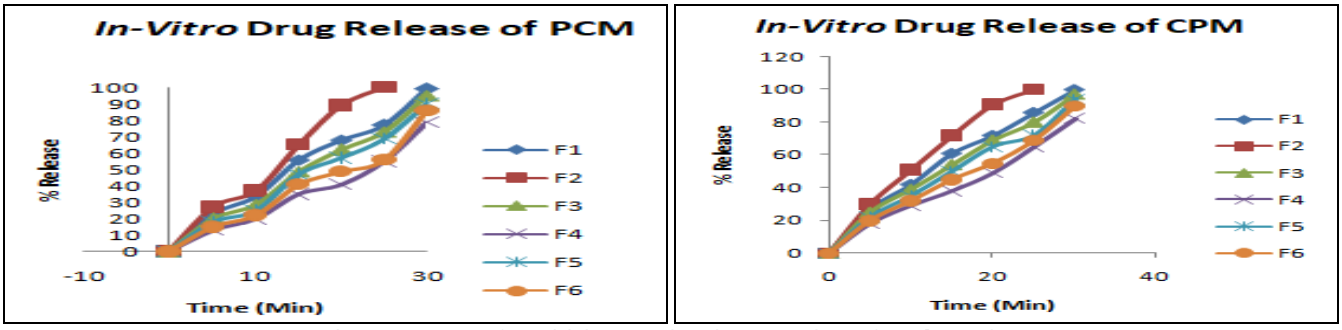

FIG. 7: *IN-VITRO* DISSOLUTION STUDY OF PCM AND CPM

Thermogravimetric Analysis (TGA):

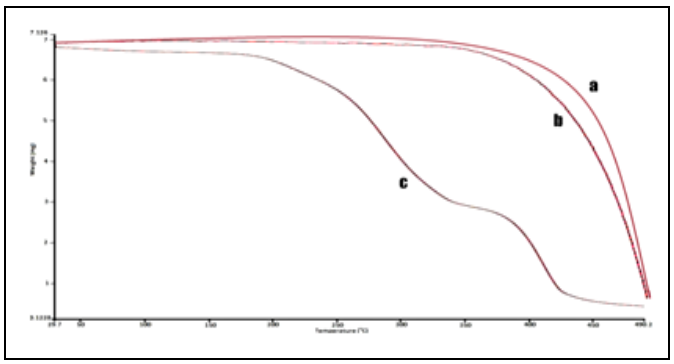

FIG. 8: TGA OF a) PURE DRUG PCM, b) PURE DRUG CPM, c) FORMULATED FDT'S

Stability Studies: According to the observation, it was reported that the sample stored at room temperature showed an acceptable release of the drug after a storage time of 30 and 60 days, i.e. 82.31 ± 0.81 and 79.45 ± 0.87 respectively for PCM and 80.91 ± 0.65 and 80.3 ± 0.94 respectively for CPM. While the samples show a decrease in % drug release when stored at cool and accelerated temperature. Hence, it was concluded that the suitable storage condition for FDT's is room temperature. All the evaluations were carried out in triplicate form and then the results were reported as Mean ± SD.

TABLE 16: STABILITY STUDY PROFILE

S. no.	Months (Days)	Stability conditions	Condition values	Release in 5 min (%) Formulation F2 PCM	CPM
1	30	Room temperature	(25±2°C/ 60±5% RH)	82.31 ± 0.81	80.91 ± 0.65
		Accelerated Temperature	(40±2°C/ 75±5% RH)	75.80 ± 0.61	74.18 ± 0.71
		Cool temperature	(4±2°C/ 65±5% RH)	79.70 ± 0.19	76.17 ± 0.12
2	60	Room temperature	(25±2°C/ 60 ±5% RH)	79.45 ± 0.87	80.30 ± 0.94
		Accelerated Temperature	(40 ± 2°C/ 75 ±5% RH)	70.80 ± 0.75	72.80 ± 0.77
		Cool temperature	(4 ±2°C/ 65 ±5% RH)	73.80 ± 0.75	74.90 ± 0.70

SUMMARY AND CONCLUSION: Around 1/3rd of the patients need quick therapeutic action of the drug, resulting in poor compliance with conventional drug therapy which leads to reduced overall therapy effectiveness. FDT's has been developed that offers the combined benefits of ease of dosing and cost-effectiveness of the dosage. This combination not only controls fever but also gives relief in cold, cough, flu and allergies.

The FDT's of Paracetamol and Chlorpheniramine Maleate was prepared successfully using direct compression. The tablets were estimated for weight variation, wetting time, friability, hardness, disintegration time, *in-vitro* dissolution study, TGA, and Stability Studies. A new spectro-photometric method was developed for the simultaneous estimation of Paracetamol and Chlorpheniramine Maleate in FDT.

Among all six formulations, promising formulation F2 with CCS 27% concentration was the best formulation. F2 resulted in good wetting time i.e. 26 sec, good water absorption ratio *i.e.* 81%, fastest disintegration time *i.e.* 20 sec and faster drug release within 25 min. Stability studies resulted that there is no change in drug release upon storage on different temperatures and humidity. The results concluded that CCS as the superdisintegrants was ideal. Effectiveness of disintegrants can be ordered as follows: Croscarmellose Sodium > Micro-crystalline Cellulose > Sodium Starch Glycollate.

By evaluating all the parameters of all six formulations, F2 formulation has been found in the best formulation. Various evaluation parameter for F2 formulation *i.e.* disintegration time, wetting time, water absorption ratio, *in-vitro* dissolution studies has been found to be 20 ± 1.52 sec, 26 ± 0.57 sec, 81 ± 1.52 %, within 25 min respectively & drug content has been found to be 98.83% for Paracetamol and 95.13% for Chlorpheniramine Maleate.

In the TGA graph of PCM, CPM and FDT (F2) resulted that the mass remained constant when there was an increase in temperature but it starts to decrease when it approached the melting point of drugs. The thermogram of FDT showed three endotherms which are probably the melting points of CPM at 135 ºC, PCM peak at 170 ºC, CCS at 205 ºC which revealed that excipients or moisture content have no adverse effect on formulations.

In stability studies, the sample stored at room temperature showed an acceptable release of the drug after a storage time of 30 and 60 days, *i.e.* 82.31 ± 0.81 and 79.45 ± 0.87 respectively for

PCM and 80.91 ± 0.65 and 80.3 ± 0.94 respectively for CPM. While the samples show a decrease in % drug release when stored at cool and accelerated temperature. Hence, it was concluded that the suitable storage condition for FDT's is room temperature.

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