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DETERMINATION OF THE CONCENTRATION BLENDS OF SUPERDISINTEGRANT FOR FAST DISINTEGRATING TABLETS

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ABSTRACT

In this research work, different blends of superdisintegrants with different ratio in fixed concentration were taken and placebo tablets were formulated and evaluated with a view to optimize a formula and concentration blends of superdisintegrants for Fast Disintegrating Tablets (FDT). In this research work three superdisintegrants, viz. Crosscarmellose, Crospovidone and Sodium Starch Glycolate were used in different ratio (1:1, 1:2, 2:1) in fixed concentration of 4% w/w in combination in each batch. Six blends were prepared and 3 batches of tablets of each formulation code blend were formulated and evaluated for pre-compression parameters like Compressibility, Hausner's ratio, Bulk density, Tapped density and post-compression parameters like Hardness, Weight variation, Disintegration time, Dispersion time, Friability, Wetting time, Water absorption ratio. Based on results it revealed that the formulation code blend A3 which had Croscarmellose, Crosspovidone in ratio 1:2 (4%w/w) emerged as best blend of superdisintegrants for FDT formulation. To optimize the formula of A3 blend, Paracetamol FDT was formulated and evaluated using the concentration blend of A3; three batches were formulated and evaluated for all above parameters and *in-vitro* drug release (pH5.8 phosphate buffer) and disintegration time was found between 23-27 seconds and release was more than 80% in 30 minute. We can conclude that a good FDT can be formulated using the above A3 blend concentration.

INTRODUCTION: Oral route of administration still enjoys, as most preferred route because of its numerous advantages. The most popular oral dosage forms are tablets and capsules. However, one important drawback of these dosage forms is the need to swallow. Many patients express difficulty in swallowing tablets and hard gelatin capsules, resulting in non-compliance and ineffective therapy [1].

Recent advances in Novel Drug Delivery Systems (NDDS) aims to formulating a dosage form of drug molecules for convenient administration and to achieve better patient compliance. One such approach leads to development of fast dissolving/ disintegrating tablets [2-4].

Advantages of this drug delivery system include convenience of administration and accurate dosing as compared to liquids, easy portability, ability to provide advantages of liquid medication in the form of solid preparation, ideal for pediatric and geriatric patients and rapid dissolution/absorption of the drug, which may produce rapid onset of action. Some drugs are absorbed from mouth, pharynx and esophagus as the

saliva passes down into the stomach and in such cases bioavailability of the drug is increased: pre-gastric absorption can result in improved bioavailability and as result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

The need for delivering drugs to patients efficiently and with few side effects has prompted pharmaceutical companies to engage in the development of new drug delivery system. A solid dosage form that dissolves Oral disintegrates/Fast disintegrating tablets, rapidly in oral cavity, resulting in solution or suspension without the need of water is known as fast dissolving dosage form or mouth dissolving tablets [5]. When this type of tablet is placed into the mouth, the saliva will serve to rapidly dissolve the tablet. They are also known as oro-dissolving, rapid – dissolve orodispersible, melt in mouth, rapimelt, quick dissolving, fast melts and porous tablets.

Conventional oral dosage forms like tablets, capsules, oral suspension, syrups etc. are available in market but the major drawbacks with these are many patients find it difficult to swallow (Dysphagia) tablets and hard gelatin capsules. The difficulty experienced in particular by pediatrics and geriatrics patients [6]. Other groups that may experience problems include the mentally ill, developmentally disable and patients who are uncooperative and hence do not take their medicines as prescribed leading to patient noncompliance.

Disintegrating agents are substances routinely included in the tablet formulations to aid in the breakup of the compacted mass when it is put into a fluid environment. They promote moisture penetration and dispersion of the tablet matrix. In recent years, several newer agents have been developed known as "Superdisintegrants". These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrants, whereas if concentration of superdisintegrant is above critical concentration, the disintegration time remains almost constant or even increases [7, 8, 9].

The objective of this study was to achieve better concentration blends of superdisintegrants in minimum concentration which will give best FDT formulation, to formulate good tensile strength Paracetamol FDT by using the optimized blend to validate the formula of the blend, to study the effects of different superdisintegrants in combination on *in-vitro* drug release and disintegration time [10, 11].

MATERIALS AND METHOD: Crosscarmellose obtained from Fischer Scientific Lot No.5556 6901-1, Crospovidone obtained from S D fine Chem. Ltd. Batch No.1092/0209/1808/13, Sodium Starch Glycolate Central Drug House Lab. Lot No. 01105. Paracetamol was obtained from Shri Baalaji Medicare pvt.Ltd.

Formulation of Placebo Fast Disintegrating Tablet: The six different blends of superdisintegrants were taken (A1, A2, A3, B1, B2, B3, C1, C2, C3) which contains different ratio (1:1, 1:2, 2:1) of superdisintegrants Crosscarmellose, Crospovidone, Sodium Starch Glycolate and placebo tablets were formulated using Direct compression method [12]. The combination of different superdisintegrants and concentration was varying as shown in **Table 1**.

TABLE 1: COMPOSITION OF DIFFERENT BATCHES* OF PLACEBO FAST DISSOLVING TABLETS

Ingredients in mg/tab.	A1	A2	A3	B1	B2	B3	C1	C2	C3
Lactose Monohydrate	325	325	325	325	325	325	325	325	325
Croscarmellose	20	40	20	-	-	-	20	40	20
Crospovidone	20	20	40	20	40	20	-	-	-
Sodium starch glycolate	-	-	-	20	20	40	20	20	20
Microcrystalline cellulose (PH 101)	133	113	113	133	113	113	133	113	113
Magnesium stearate	2	2	2	2	2	2	2	2	2

* N=3 of each blend

The tablets were formulated by direct compression using 11.1mm tablet punch on Karnawati, Rimek, Minipress II. 3 batches of 30 tablets of each blend i.e. 27 batches were formulated and evaluated.

Pre-compression evaluation parameters for Placebo FDT: Prior to compression, blends of all batches were evaluated for their flow properties and compressibility parameters. Flow properties of blends were determined by bulk density, angle of repose. Compressibility index were determined by Hausner's ratio [13, 14]. Results are shown in **Table 2**.

TABLE 2: PRE-COMPRESSION EVALUATION RESULTS OF BLENDS

Blends	Compressibility index* (%)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Angle of repose (Degrees)
A1	22.73 ±1.06	0.4545	0.5882	1.29	31.42 ± 0.89
A2	23.82 ±2.04	0.4761	0.6250	1.31	29.72 ±1.23
A3	18.18 ±1.09	0.4545	0.5555	1.22	30.12 ± 1.24
B1	21.74 ±0.86	0.4347	0.5555	1.27	32.12 ± 1.42
B2	20.84 ± 1.52	0.4166	0.5263	1.26	30.12 ± 1.34
B3	21.74 ± 1.34	0.4347	0.5555	1.27	31.21 ± 1.14
C1	22.75 ± 1.85	0.4787	0.5880	1.23	32.12 ± 1.56
C2	23.70 ± 0.98	0.4882	0.6325	1.29	28.86 ±0.98
C3	22.69 ± 1.07	0.4378	0.5567	1.27	30.16 ± 1.12

N=3,*represents the value as mean ± SD. Post compression parameters of Placebo tablets for optimization

Post compression, the tablets of all 27 batches evaluated for hardness, weight variation, disintegration, wetting time, water absorption ratio, disintegration time and dispersion time.

After optimizing the blend having the best results by selecting that blend Paracetamol FDT was formulated for proving the ruggedness of formula, 3 batches were formulated and evaluated for the above same parameters in addition to that *in-vitro* drug release and drug content uniformity was evaluated.

Weight variation: The procedure described in United State Pharmacopoeia (USP-30) was employed to determine the weight variation of the tablets. Twenty tablets were randomly selected from each batch and weighed on an electronic balance and mean weight was taken. Each tablet was then weighed individually and standard deviation in weight was calculated for each batch [15].

Hardness: Five tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester. The mean values and standard deviation for each batch were calculated [16-18].

Friability: Friability indicates the ability of a tablet to withstand mechanical shocks while handling. Friability of the tablets were determined using Roche Friabilator and is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and placed into the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions and then the tablets were weight again (W_{final}). The loss in tablet weight due to abrasion or fracture was the measure of tablet friability. Percent friability (f) was calculated by using the following formula [19];

$$f = \frac{W_o - W_t}{W_o} \times 100\ \%$$

Where W_0 – Weight initial; W_t - Weight final

% friability of less than 1 % is considered acceptable.

Disintegration test: The disintegration time was determined by using USP Tablet disintegration test apparatus using 900 ml of distilled water without disk. The time in seconds taken for complete disintegration of the tablets until no mass remaining in the apparatus was measured [16-18].

Drug Content Uniformity: Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 0.15 g of Paracetamol, add 50 ml of 0.1M sodium hydroxide, dilute with 100 ml of water, shake for 15 minutes and add sufficient water to produce 200.0 ml. Mix, filter and dilute 10.0 ml of the filtrate to 100.0 ml with water. To 10.0 ml of the resulting solution add 10 ml of 0.1M sodium hydroxide, dilute to 100.0 ml with water and mix. Measure the absorbance of the resulting solution at the maximum at about 257 nm. Calculate the content of $C_8H_9NO_2$ taking 715 as the value of A (1%, 1 cm) at the maximum at about 257 nm [20].

Acceptance Limits: Paracetamol tablets contain not less than 90.0% and not more than 110.0% of labeled amount of paracetamol [20].

Wetting Time: The wetting time and capillarity of the oral dispersible tablets were measured by a conventional method. The tablet was placed in a petridish of 6.5 cm diameter containing 10 ml water at room temperature and the times for complete wetting of tablets were recorded [16].

Water Absorption Ratio: A piece of tissue paper folded twice was placed in a small petridish containing 6ml of distilled water. A tablet was put on the paper and the time required for complete wetting of the tablet was measured. The wetting tablet was then weighed. Water absorption ratio "R" was determined using the equation as follows [17]:

$$R = 100 \times (wa - wb)/ wb$$

Where, Wa is Weight of tablet after water absorption; Wb is Weight of tablet before water absorption.

***In-vitro* Drug Release Studies:** The *in-vitro* drug release studies of Paracetamol from tablets were carried out using USP dissolution test apparatus type-II (Paddle type), using 900 ml of phosphate buffer (PH 5.8) as the medium and rotating the paddle at 50 rpm for 30 minutes at 37 ± 0.5°C. In this test 8 tablets from each batch was used for the studies. At specified time i.e. 0, 5, 10, 15, 20, 25, 30 minutes withdrawn a suitable volume of the sample and filter promptly through a membrane filter disc with an average pore diameter not greater than 1.0 mm.

The absorbance of the resulting solution was measured at the maximum 243 nm [21].

RESULTS AND DISCUSSION: The Placebo tablets of all 27 batches were evaluated for the post compression parameters for optimizing the blend for formulation fast disintegrating tablets. A3 blend had shown the best results the disintegration time was 22 seconds, hardness was good, friability, weight variation was well within the acceptance criteria, So this blend A3 which had Croscarmellose, Crospovidone at 4% w/w in 1:2 ratio was consider as the best concentration blend for the formulation of superdisintegrants.

From the data of **Table 3**, it was concluded that A3 blend concentration was best among all the tablets of which had shown hardness 4.5Kg/cm^2, friability of 0.86% and weight variation is less than 5% which is well within the acceptance criteria given by USP-30, dispersion time was 22 seconds, wetting time was 42 seconds. So, it was considered as optimized blend of superdisintegrants and Paracetamol tablets were formulated and evaluated by using same formula and method. Three batches of Paracetamol FDT were evaluated.

TABLE 3: RESULTS OF POST COMPRESSION EVALUATION PARAMETERS OF PLACEBO TABLETS

Formulation code**	Wetting time (Sec.)*	Parameter					
		Absorption ratio (%)	Disintegration time (Sec.)	Dispersion time (Sec.)	Hardness* Kg/cm^2	Friability %	Weight variation
A1	36 ± 1.20	96.2	33.00 ±2.50	31.00± 1.30	4.5± 0.17	0.86	500.7± 0.8
A2	38 ± 0.90	98.2	35.00 ± 2.18	34.00± 1.18	4.6± 0.25	0.43	500.2± 1.3
A3	42 ± 0.92	98.6	24.00 ± 0.83	22.00±1.08	4.5± 0.75	0.76	498.0± 0.9
B1	55 ± 1.30	87.7	42.33 ± 1.69	44.11 ±0.90	4.7± 0.23	0.92	500.0± 1.2
B2	56± 2.35	98.0	29.00 ± 0.82	34.00±1.79	5.00±0.8	0.95	505.2± 1.8
B3	55± 2.70	91.8	37.00 ± 1.29	36.00±2.18	4.5± 0.35	0.86	499.0± 1.9
C1	57 ± 2.20	95.9	51.00 ± 3.00	54.00±1.08	5.2± 0.25	0.78	502.2± 1.2
C2	52 ± 1.20	99.7	52.33 ± 2.05	49.85±1.98	4.5± 0.18	0.69	500.0± 1.4

*N=6 Values represent as mean ± SD, **N=20 Values represent as mean ± SD

The compatibility studies for Paracetamol and other excipients were done at three different conditions 40°c / 75% RH, 25°C / 60% RH, 55°c for 15 days, visual evaluation was done no significant changes were observed and IR studies were also done data shown in **Fig. 1-7**.

Paracetamol FDT were formulated by direct compression method, 3 batches were formulated and evaluated (**Table 4 & 5**).

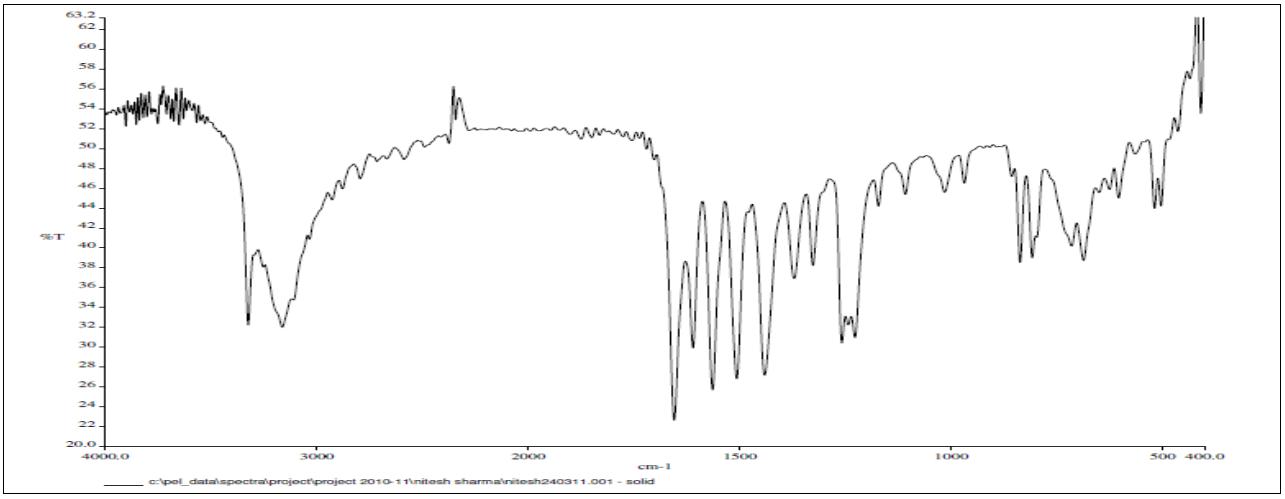

FIG. 1: IR SPECTRA OF PARACETAMOL (PCM)

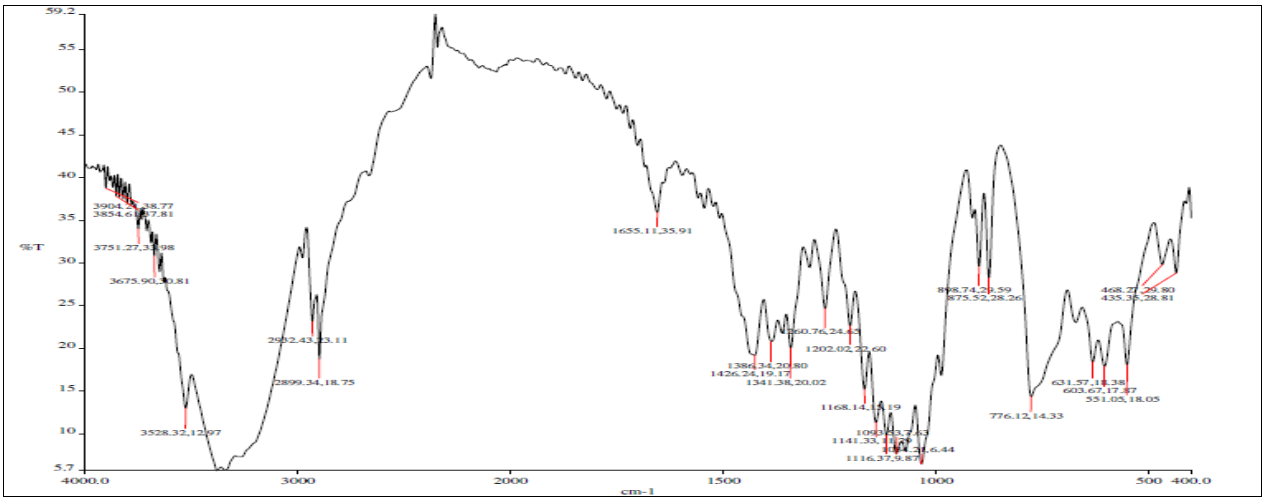

FIG. 2: IR SPECTRA OF PARACETAMOL + LACTOSE

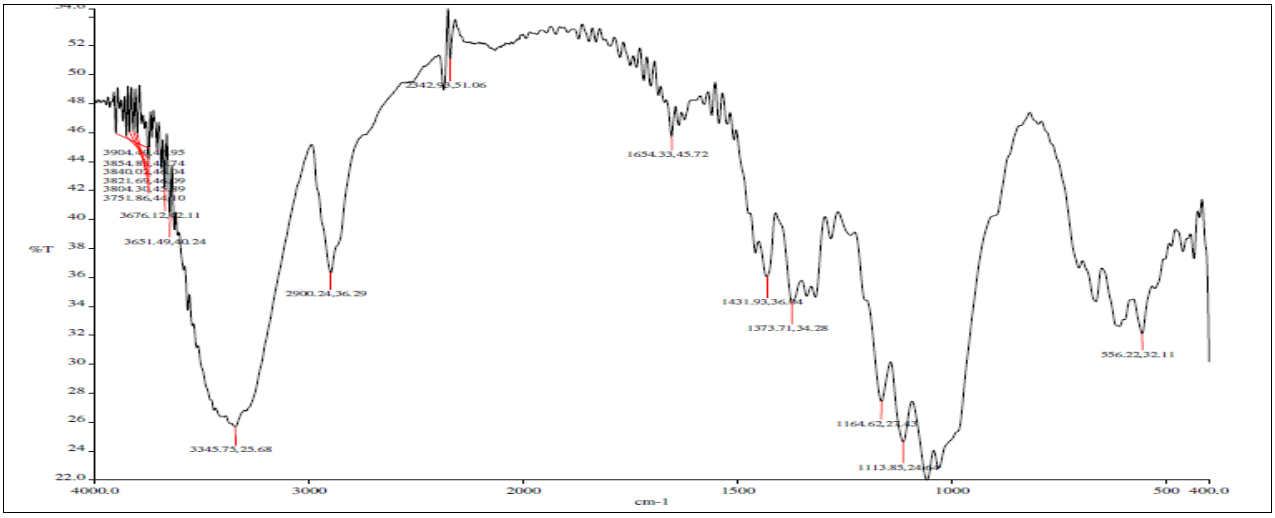

FIG. 3: IR SPECTRA OF PARACETAMOL + MICROCRYSTALLINE CELLULOSE

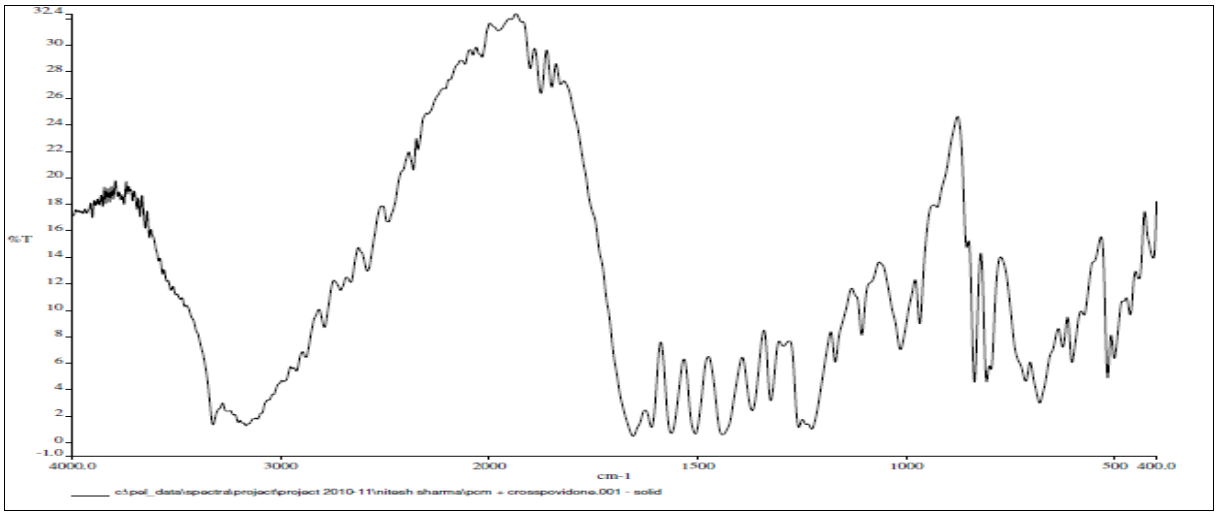

FIG. 4: IR SPECTRA OF PARACETAMOL + CROSSPOVIDONE

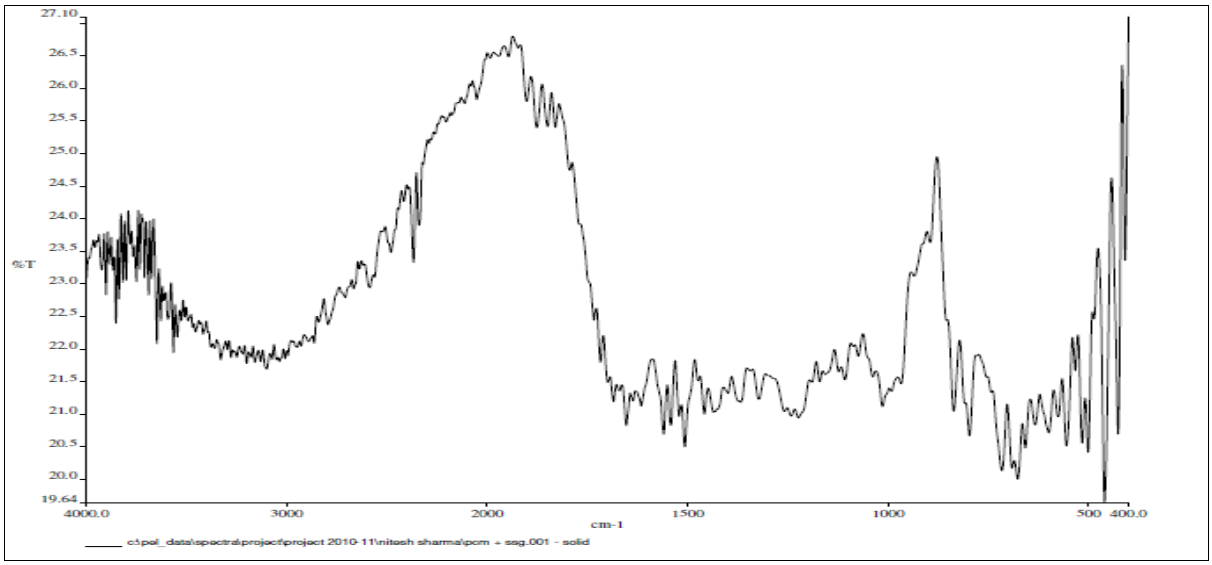

FIG. 5: IR SPECTRA OF PARACETAMOL + SODIUM STARCH GLYCOLATE

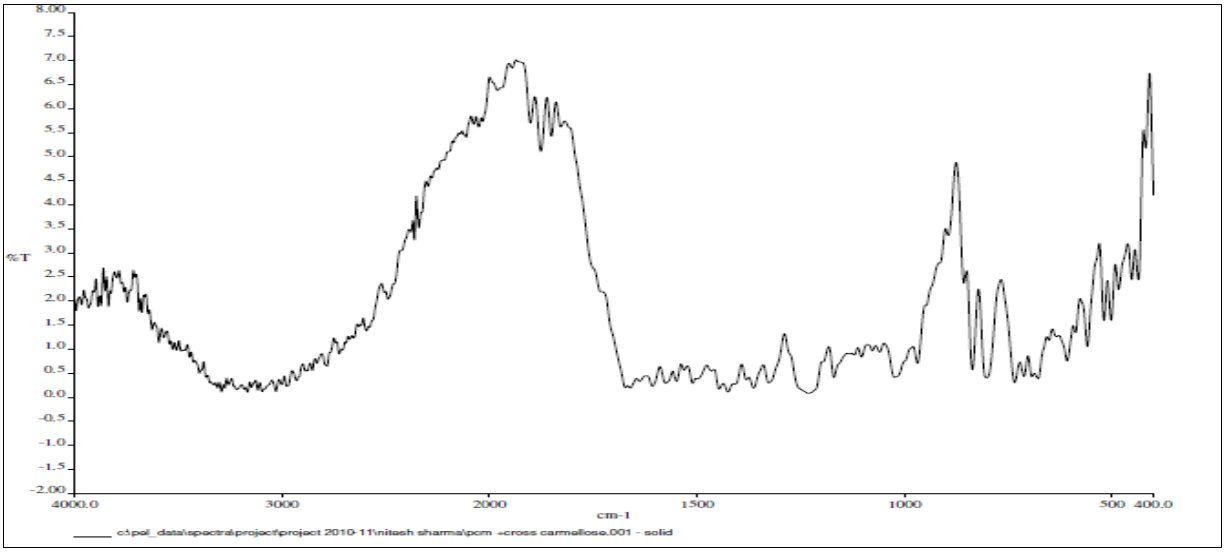

FIG. 6: IR SPECTRA OF PARACETAMOL + CROSCARMELLOSE

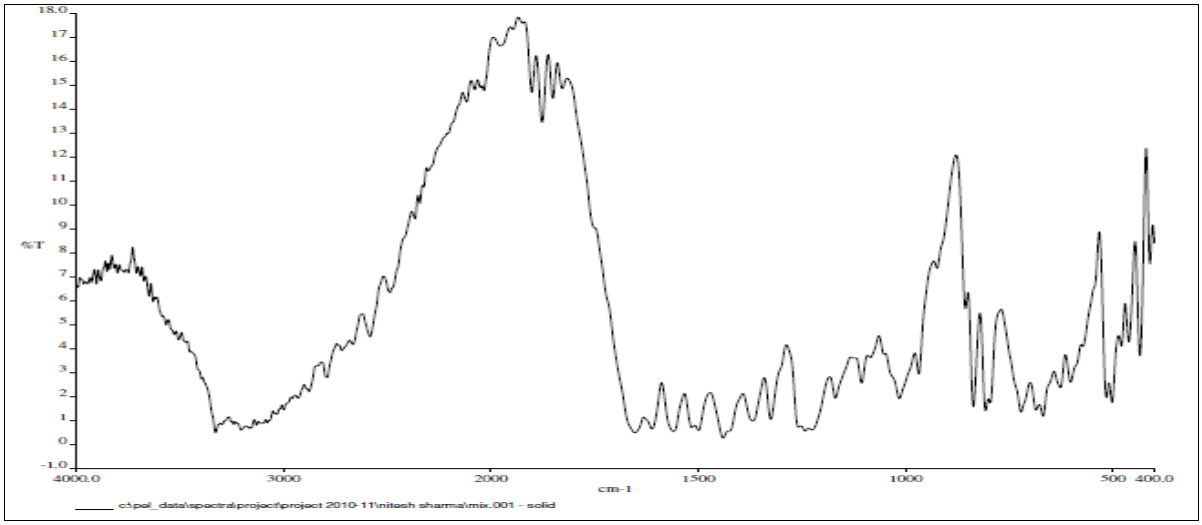

FIG. 7: IR SPECTRA OF PARACETAMOL + LACTOSE MICROCRYSTALLINE CELLULOSE+ CROSSPOVIDONE + SODIUM STARCH GLYCOLATE + CROSCARMELLOSE

TABLE 4: PRE-COMPRESSION EVALUATION OF PARACETAMOL FDT A3 BLENDS

Blends	Compressibility index* (%)	Bulk density* (gm/cm^3)	Tapped density* (gm/cm^3)	Hausner's ratio*
A3-1	22.88 ± 0.98	0.4822 ±0.87	0.5567 ± 0.98	1.15 ± 1.18
A3-2	23.03 ± 1.08	0.5582± 0.90	0.6521 ±1.40	1.18 ±1.09
A3-3	23.89 ± 1.78	0.4671±1.08	0.6341 ± 1.32	1.32 ± 1.12

TABLE 5: POST COMPRESSION OF PARACETAMOL FDT

Parameters	Formulation code		
	A3-1	**A3-2**	**A3-3**
Hardness* Kg/cm^2	4.5 ± 1.03	4.7 ± 1.25	5.5 ± 1.08
Friability%	0.92	0.83	0.97
Weight variation*	498.0± 0.9	500.7± 1.45	500.8± 1.80
Wetting time (sec.)*	53 ± 0.87	59 ± 1.23	56 ± 0.98
Absorption ratio (%)	102	112	98
Disintegration time*	27 ± 0.97	25 ± 1.05	23 ± 0.87
Dispersion time(Sec.)	22.00 ±1.08	24.00 ±1.83	26.00 ±1.12

N=3,*represents the value as mean ± SD

Fig. 8 is the calibration curve for Paracetamol tablets; **Fig. 9, 10** shows the % drug release and its comparison.

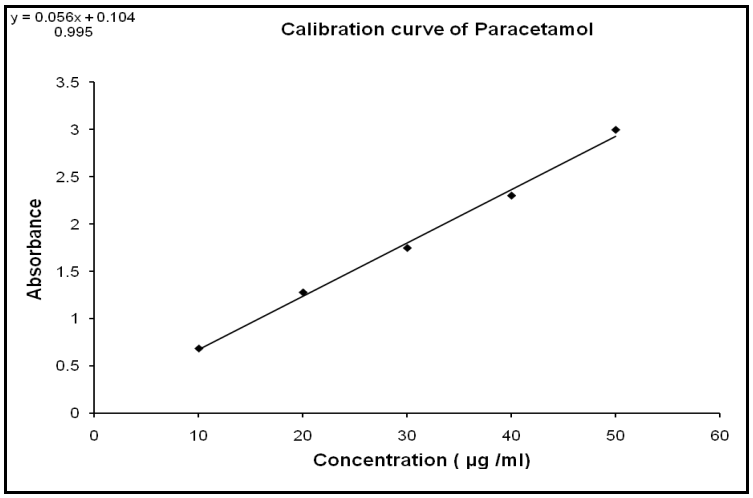

FIG 7.CALIBRATION CURVE OF PARACETAMOL TABLET

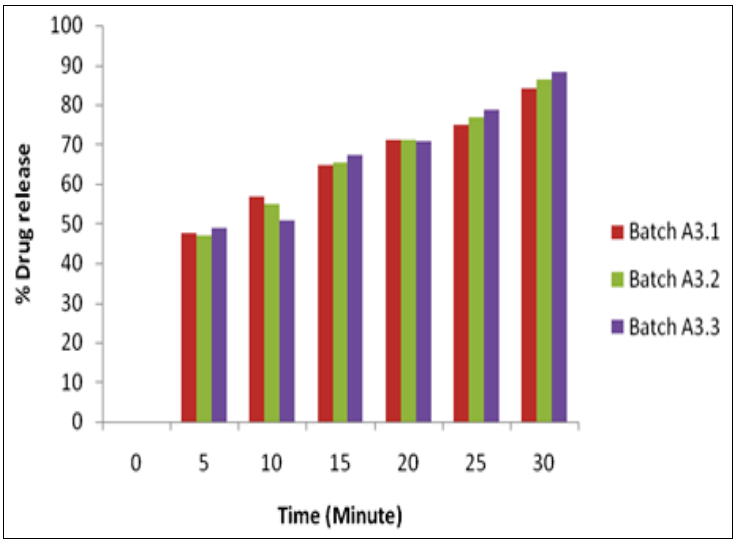

FIG.8 % DRUG RELEASE OF PARACETAMOL FDTs

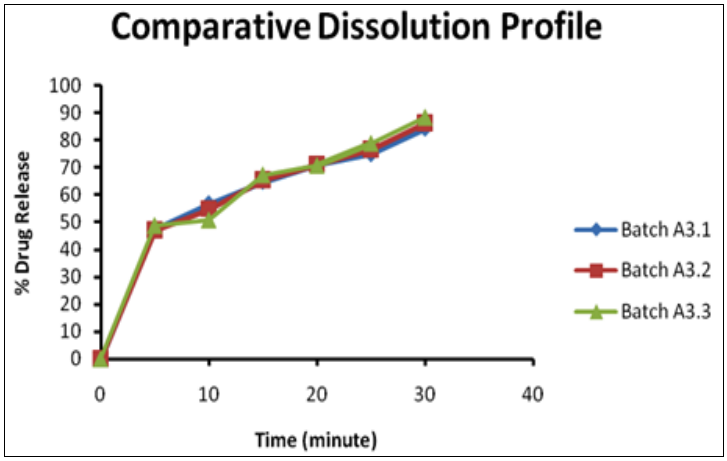

FIG. 4: COMPARISON OF RELEASE OF 3 BATCHES OF PARACETAMOL FDTs

CONCLUSION: It is concluded from the above study that 4%w/w Croscarmellose, Crosspovidone combination in 1:2 ratio is best and optimized blend for formulation of Fast disintegrating tablets. The tablet shows disintegration time less than 25 seconds of both placebo and Paracetamol, so it serves as the best formulation. This blend of superdisintegrants can be used for the formulation of fast disintegrating.

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