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DESIGNING AND PHARMACEUTICAL EVALUATION OF FAST DISSOLVING TABLET OF FEXOFENADINE USING COPROCESSED SUPERDISINTEGRANTS

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ABSTRACT: Among various novel drug delivery systems fast dissolving tablets have attracted great attention in recent years due to their ability to release the drug content gradually. Therefore the demand for this dosage form has been increased since last few years especially in patients with swallowing difficulties as this dosage form provides advantage of being swallowed without water. The objective of this research study was to prepare and evaluate fast dissolving tablet of Fexofenadine for acting as a suitable approach to the treatment of allergy together with improved efficacy and reduced dosing frequency. The tablets were prepared by direct compression technique after incorporating superdisintegrants (Ac-di-sol, Sodium starch Glycolate and Crospovidone) in concentrations (1-4%). For preliminary studies twelve (F1-F12) formulations were prepared. Optimization technique was employed to predict the best formulation of all combinations prepared. Pre and Post compression characterization was done on tablets. Then co processed superdisintegrants were used for formulation of tablets showing superior properties. In investigation 3^2 full factorial design was employed to investigate the combined effect of two formulation variables that is SSG and CP. Total nine formulations (FDT1-FDT9) were prepared according to factorial design with 30 seconds disintegration and 0.5% friability. The optimized formulation was evaluated for content uniformity and *in vitro* drug release showing more than 90% release in five minutes and followed first order kinetics. The short term stability studies was performed for three months at 45^0C and 75% RH, no significant changes in percent friability and *in vitro* disintegration time were observed. The shelf life of the formulation was predicted more than one year (372 days).

INTRODUCTION: For the past two decades, there has been enhanced demand for more patient compliant dosage form. As a result, the demand for their technologies is been increasing 3 fold annually.

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Since the development cost of a new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reducing dosing frequency to minimize side effects.

The oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. The most popular solid dosage forms

being tablet and capsule, one important drawback of these dosage forms is the difficulty to swallow by elderly persons because of their hand tremors and dysphasia. Swallowing problems are also common in young individuals because of their under developed muscular system. To fulfill these medical needs, the pharmaceutical technologist have devoted considerable effort to develop a novel type of dosage form for oral administration, the Fast Dissolving Tablet (FDT), tablet that disintegrates and dissolves rapidly in saliva without need of water [1].

USFDA defines FDT as 'A solid dosage form containing medicinal substance or active ingredient which disintegrates and dissolves rapidly usually within a matter of seconds when placed upon the tongue' the disintegration time ranging from several seconds to about a minute [1].

Hence, to enhance the patient compliance in allergy Fast Dissolving Tablets, of an existing drug Fexofenadine with an improved efficacy and bioavailability together with reducing dosing frequency were prepared to minimize side effect by using direct compression technique. Fexofenadine was chosen as a model H_1 antihistaminic drug for the present study.

It is water-soluble drug and as it is not available in any such dosage form, its formulation into fast dissolving tablet form would render it to release rapidly and thereby resulting in rapid absorption without any lag time [2].

MATERIALS AND METHODS:

Materials: Fexofenadine was obtained as a gift sample from (Cipla, Baddi, India), Ac-di-sol, Sodium starch Glycolate, Avicel PH 102 and Crospovidone were purchased from (Signet chemicals, Mumbai, India) Isopropyl alcohol, Sodium phosphate and Sodium Hydroxide were purchased from (E. Merck, India Ltd, Mumbai, India), Dextrose and Magnesium stearate were purchased from (Loba Chem Mumbai, India).

Methods:

Preparation of Fexofenadine tablets: For preliminary studies initially twelve formulations (F1-F12) were prepared with varied concentrations of superdisintegrants (1-4% w/w) to assess their efficiency and to achieve rapid disintegration using direct compression method. Formulation composition is depicted in **Table 1** all the ingredients were passed through sieve no. 60 and were co-grounded in a glass pestle motor [3-5]. The mixed blends before compression were evaluated for mass volume relationship (bulk density, tapped density, Hausner's ratio, compressibility index) and flow properties (angle of repose). All these parameters were evaluated by established methods refer (3-5). The mixed blends were than compressed using single punch tablet machine (Cadmach Ahmadabad) and were evaluated for quality control parameters like thickness, hardness, friability, disintegration time, dispersion time and wetting time.

TABLE 1: FORMULATION OF DRUG FREE TABLETS WITH SUPERDISINTEGRANTS

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Fexofenadine	150	150	150	150	150	150	150	150	150	150	150	150
Sodium Starch Glycollate	1	2	3	4	-	-	-	-	-	-	-	-
Crosspovidone	-	-	-	-	1	2	3	4	-	-	-	-
Ac-Di-Sol	-	-	-	-	-	-	-	-	1	2	3	4
Avicel PH102	50	50	50	50	50	50	50	50	50	50	50	50
Dextrose	37.5	35	32.5	30	37.5	35	32.5	30	37.5	35	32.5	30
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5

Thickness: The thickness of the tablets was recorded using micrometer (Mityato, Japan).

Hardness [6]: Hardness of the tablets was determined using Pfizer Hardness tester.

Friability [7-8]: Friability was determined using Roche Friabilator Six tablets from each batch were examined for friability using Riche Roche Friabilator, Mumbai and the equipment was run for 4 min at 25 revolutions per minute. The tablets were taken out, de dusted and reweighed.

Weight variation [9]: The weight variation test would be satisfactory method of determining the drug content uniformity. As per USP, twenty tablets were taken and weighted individually, calculating the average weight, and comparing the individual tablet weights to the average. The average weight of one tablet was calculated.

Wetting time [10-12]: Wetting time of the tablets was measured using a piece of tissue paper (12 cm X 10.75 cm) folded twice, placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer (pH 6.8). A tablet was put on the paper, and the time for the complete wetting was measured. **Figure 1** shows wetting property.

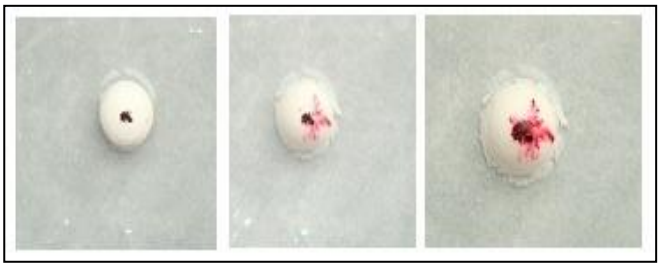


FIGURE 1: *IN VITRO* WETTING PROPERTY

***In vitro* dispersion time [13]:** *In vitro* dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of Sorenson's buffer (pH 6.8). Six tablets from each formulation were randomly selected and *in vitro* dispersion time was performed. **Figure 2** shows dispersion time.

FIGURE 2: *IN VITRO* DISPERSION PROPERTY

Disintegration test: Disintegration of fast disintegrating tablets is achieved in the mouth owing to the action of saliva, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* conditions. A modified 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 placed below the sieve. To determine disintegration time, 6 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve. Tablet was placed on the sieve and the whole 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 composite samples and the average value was determined [14]. **Figure 3** shows modified disintegration apparatus.

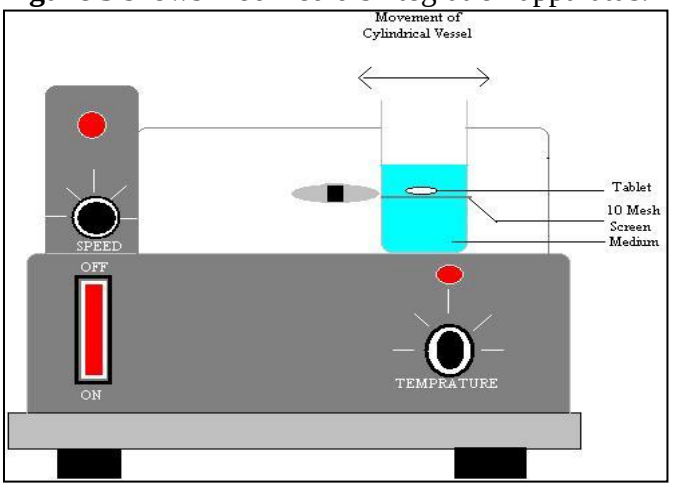


FIGURE 3: DISINTEGRATION TEST APPARATUS

Preparation of disintegrated blend (physical mixture and coprocessed superdisintegrant): The physical mixture of sodium starch Glycolate and Crosspovidone was prepared by mixing them together in glass pestle motor. The co-processed superdisintegrants were prepared as follows: blends of SSG and Crosspovidone in different ratio 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 maintained between 65-70^{o}C and stirring was continued till most of isopropyl alcohol evaporated. The wet coherent mass was sieved through sieve no 100 the wet powder was dried in a tray drier at 60^{0} for 20 minutes. The dried powder were sifted on 120 mesh sieve and stored in airtight container till further use. For the preliminary study and evaluation only physical mixture and co-processed superdisintegrants were prepared in 1:1 ratio. Rest of ratio was prepared for the factorial design batch. The prepared co processed superdisintegrants were evaluated for the mass volume relationship, swelling properties and flow properties [15].

Development of Combined Superdisintegrants tablet: The fast dissolving tablets were prepared by the combination of two disintegrants to check their influence on the pre and post compression characteristics of the tablets. These tablets were prepared as methods described earlier. Only the least concentration of the disintegrants was used in tablets to evaluate their combined effect. The blends and tablets were characterized as described earlier. The formulation of the tablet is tabulated in **Table 2.**

TABLE 2: FDT WITH PHYSICAL MIXTURE AND CO-PROCESSED SUPERDISINTEGRANTS

Formulation	F13 (Physical Mixture)	F14 (Co-Process)
Fexofenadine	150	150
Sodium starch Glycolate	2.5	2.5
Crosspovidone	2.5	2.5
Avicel PH 102	50	50
Dextrose	35	35
Talc	5	5
Mg. Stearate	5	5

Particle size analysis: The microscopic technique was used to test the particle size distribution of superdisintegrants and their blends. The slides of powder were prepared and observed under microscope. To test the swelling of superdisintegrants in water and Sorenson's buffer (pH 6.8, saliva pH), disintegrant powder were first dispersed in a small volume of liquid and the ultrasonicated for 10 minutes. The suspension transferred with a pipette to a small volume on the glass slide. The ratio of particle diameter in the dispersing medium to the dry powders were used as an intrinsic swelling capacity of super disintegrant in the test medium [16].

Mass- volume relationship and flow properties: For the mass-volume relationship bulk density (*ρb*), tapped density (*ρt*), Hausner's ratio (RH = ρt / ρb) and compressibility index (*Ic =100*(ρt – ρb) / ρb) were determined with the bulk/tapped densitometer.

The angle of repose was determined using funnel method. The blend was poured through a glass funnel that can be raised vertically until a specified cone height (h) was obtained. Radius of the conical pile (r) was measured and angle of repose (θ) was calculated using the formula [17-21];

$$\tan \theta = h/r$$

Preparation of fast dissolving tablets (Factorial design batches): The raw materials were passed through a no. 100 screen prior to mixing. Fexofenadine, SSG, Crospovidone, microcrystalline cellulose and lactose were mixed using a glass mortar and pestle. The blends were lubricated with 2% w/w talc and 2% w/w magnesium stearate. The blends ready for compression were converted into tablets using a single-punch tablet machine (Cadmach, Ahmadabad, India). The composition of factorial design batches is shown in **Table 3.**

TABLE 3: FORMULATION OF FACTORIAL DESIGN BATCHES

Ingredients	FDT1	FDT2	FDT3	FDT4	FDT5	FDT6	FDT7	FDT8	FDT9
Fexofenadine	150	150	150	150	150	150	150	150	150
SSG	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5
Crosspovidone	2.5	5	7.5	2.5	5	7.5	2.5	5	7.5
Avicel PH 102	50	50	50	50	50	50	50	50	50
Dextrose	35	32.5	30	32.5	30	27.5	30	27.5	25
Talc	5	5	5	5	5	5	5	5	5
Mg. Stearate	5	5	5	5	5	5	5	5	5

Development of Optimized Fast Dissolving Tablet: After application of full factorial design and with help of polynomial terms the optimized tablet was produced which have targeted to the disintegration time 30 s and 0.5% percent friability. The optimized fast dissolving tablet was prepared with the best amount of co-processed superdisintegrants suggested by the software. The prepared tablets were evaluated for its physiochemical properties. Composition of optimized formulation is given in **Table 4.**

TABLE 4: DEVELOPMENT OF OPTIMIZED FORMULATION

Formulation	OPT
Fexofenadine	150.00
Sodium Starch Glycolate	5.20
Crospovidone	6.45
Avicel PH 102	50.00
Dextrose	28.35
Talc	5.00

Scanning Electron Microscopy: Finally to investigate the morphology of SSG, Crospovidone and prepared Coprocessed superdisintegrants, scanning electron micrographs were taken using (JOEL, JSM-35, CF) scanning electron microscope; where the samples were previously sputter coated with gold [22].

Full Factorial design: To know the actual amount of 2 superdisintegrants for the desirable property of fast dissolving tablets a 3^2 randomized full factorial design was used. In this design 2 factors were evaluated, each at 3 levels and experimental trials are performed at all 9 possible combinations [23-24]. The amount of SSG (X_1) and the amount of Crosspovidone (X_2) was selected as independent variables. The disintegration time and percentage friability were selected as dependent variables.

Optimization of Fast Dissolving Tablet: After application of full factorial design and with help of polynomial terms the optimized tablet was produced which have targeted to the disintegration time 30 s and 0.5% percent friability. The optimization was done with the help of software Design Expert 7.1.6. The optimized amount of the co-processed SSG and Crosspovidone was incorporated in the tablet formulation (OPT) which was also used as the check point of the regression analysis model. The response surface prediction plots were formulated with the help of the software.

Content uniformity: Ten randomly selected tablets were weighed and average weight was calculated, the tablets were powdered in a glass mortar pestle. The weight equivalent to 150 mg Fexofenadine was weighed. The weighed amount was dissolved in 100 ml of Sorenson's buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml from this solution was diluted appropriately with Sorenson's buffer (pH 6.8) in separate volumetric flask. The content in each formulation was determined spectrophotometrically at 259 nm.

***In vitro* dissolution study:** *In vitro* dissolution study for optimized tablet and marketed tablet were carried out using USP paddle method at 50 rpm in 900 ml of Sorenson's buffer (pH 6.8) as dissolution media, maintained at 37±0.5^o. 5 ml of aliquot was withdrawn at the specified time intervals (1 minute), filtered through whatmann filter paper and assayed spectrophotometrically at 259 nm. An equal volume of fresh medium, pre warmed at 37^o, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the study.

Stability studies: The optimized fast dissolving tablets of Fexofenadine were packed in wide mouth air tight glass container and stored at (45±1^{o}C and 75±5% RH) for a period of 3 months. The tablets were withdrawn after a period of 15 days and analyzed for physical characterization and drug content spectrophotometrically at 259 nm.

RESULTS AND DISCUSSION: In this present research work Fast dissolving tablets of Fexofenadine were successfully formulated by direct compression technique. In preliminary investigation twelve formulations were prepared (F1-F12) with varied concentrations of superdisintegrant and tablet blends were evaluated for flow properties. The powder blends of all formulations indicated good flow characteristics shown in **Table 5** and after compression the tablets were evaluated for thickness, hardness, friability, in vitro wetting time, *in vitro* dispersion time and disintegration time. The results are indicated in **Table 6.**

TABLE 5: CHARACTERIZATION OF TABLETS BLENDS

Formulation Codes	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's Ratio	Compressibility Index (%)	Angle of Repose (°)
F1	0.371 ±0.012	0.395 ±0.013	1.071 ±0.012	6.604 ±1.330	23.34 ±1.363
F2	0.408 ±0.015	0.436 ±0.012	1.065 ±0.024	5.621 ±1.233	25.19 ±1.221
F3	0.383 ±0.023	0.405 ±0.021	1.048 ±0.013	4.556 ±1.422	27.35 ±1.007
F4	0.387 ±0.004	0.421 ±0.002	1.059 ±0.015	5.623 ±1.221	24.44 ±1.126
F5	0.406 ±0.013	0.427 ±0.005	1.073 ±0.010	6.792 ±1.012	25.99 ±1.096
F6	0.403 ±0.025	0.433 ±0.006	1.065 ±0.003	6.076 ±1.231	23.56 ±1.132
F7	0.409 ±0.034	0.436 ±0.014	1.069 ±0.006	6.422 ±1.086	26.59 ±1.165
F8	0.384 ±0.013	0.405 ±0.017	1.057 ±0.016	5.432 ±1.097	26.32 ±1.136
F9	0.396 ±0.017	0.424 ±0.023	1.082 ±0.027	7.601 ±1.242	25.22 ±1.432
F10	0.405 ±0.006	0.429 ±0.023	1.095 ±0.010	8.756 ±1.134	23.59 ±1.243
F11	0.399 ±0.023	0.417 ±0.012	1.059 ±0.015	5.594 ±1.123	25.62 ±0.968
F12	0.402 ±0.005	0.422 ±0.007	1.067 ±0.023	6.294 ±1.324	23.54 ±0.847

n=6,±SD

TABLE 6: POST-COMPRESSION CHARACTERIZATION

F. Codes	Thickness (mm)	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Wetting Time (s)	Dispersion Time (s)	Disintegration Time (s)
F1	5.436±0.012	253.667±2.082	3.6±0.152	0.612±0.042	74±4.01	112±1.52	98±1.52
F2	5.421±0.015	249.333±1.528	3.2±0.187	0.626±0.038	66±2.51	102±2.93	84±2.93
F3	5.414±0.011	251.000±2.646	3.3±0.165	0.665±0.057	54±3.21	90±2.04	63±2.04
F4	5.425±0.011	253.332±1.528	3.4±0.170	0.690±0.048	39±2.08	81±2.08	51±2.08
F5	5.437±0.009	251.00±2.646	3.1±0.178	0.608±0.028	62±2.21	107±3.01	87±3.01
F6	5.412±0.011	249.667±2.082	3.3±0.095	0.602±0.031	58±1.98	95±1.51	76±1.51
F7	5.445±0.008	252.667±1.528	3.4±0.165	0.579±0.041	41±2.31	79±1.98	59±1.98
F8	5.425±0.017	258.00±2.646	3.6±0.187	0.547±0.052	32±1.52	73±2.02	42±2.02
F9	5.431±0.014	248.333±1.528	3.2±0.179	0.679±0.036	87±4.93	121±4.01	106±4.01
F10	5.408±0.012	249.333±2.517	2.9±0.134	0.725±0.053	75±3.87	109±3.21	89±3.21
F11	5.421±0.018	253.667±2.887	3.2±0.178	0.748±0.056	58±2.65	88±2.22	70±2.22
F12	5.396±0.013	249.00±2.517	2.9±0.126	0.773±0.058	48±1.85	78±1.89	62±1.89

n=6, ±SD

In preliminary investigation, water, ethyl alcohol, dichloromethane and isopropyl alcohol were used for co processing of the Superdisintegrants. Water was ruled out for further experiment because gel formation occurs due to the presence of starch in sodium starch glycolate. Dichloromethane was omitted because of floating of crosspovidone and sedimentation of sodium starch glycolate. Sodium starch glycolate was sparingly soluble in ethyl alcohol. Isopropyl alcohol was selected considering the absence of gel formation and phase separation.

Particle size and swelling: The volume median diameters of superdisintegrants in different media were determined is given in **Figure 4.** A significant reduction in swelling capacity was also observed in physical mixture as well as coprocessed superdisintegrants in Sorenson's buffer (pH 6.8).

The strong decrease in swelling capacity of chemically modified starch may attribute to the converting of the carboxymethyl sodium moieties to its free acid form in acidic medium. Since the acid medium form has less hydration capacity than its salt form, the liquid holding capacity of the disintegrant particle reduces after deionization in the slightly acidic medium[5]. Therefore, the total degree of substitution and the ratio of basic to acidic substituent's were potential factors determining the extent of influence of medium pH on the swelling properties of disintegrants and blends particles. Unlike the other superdisintegrant, there was no apparent change in the swelling capability of the nonionic polymer crosspovidone in both media. The results clears that the physical mixing and coprocessing gives better swelling than used alone due to their combined effect.

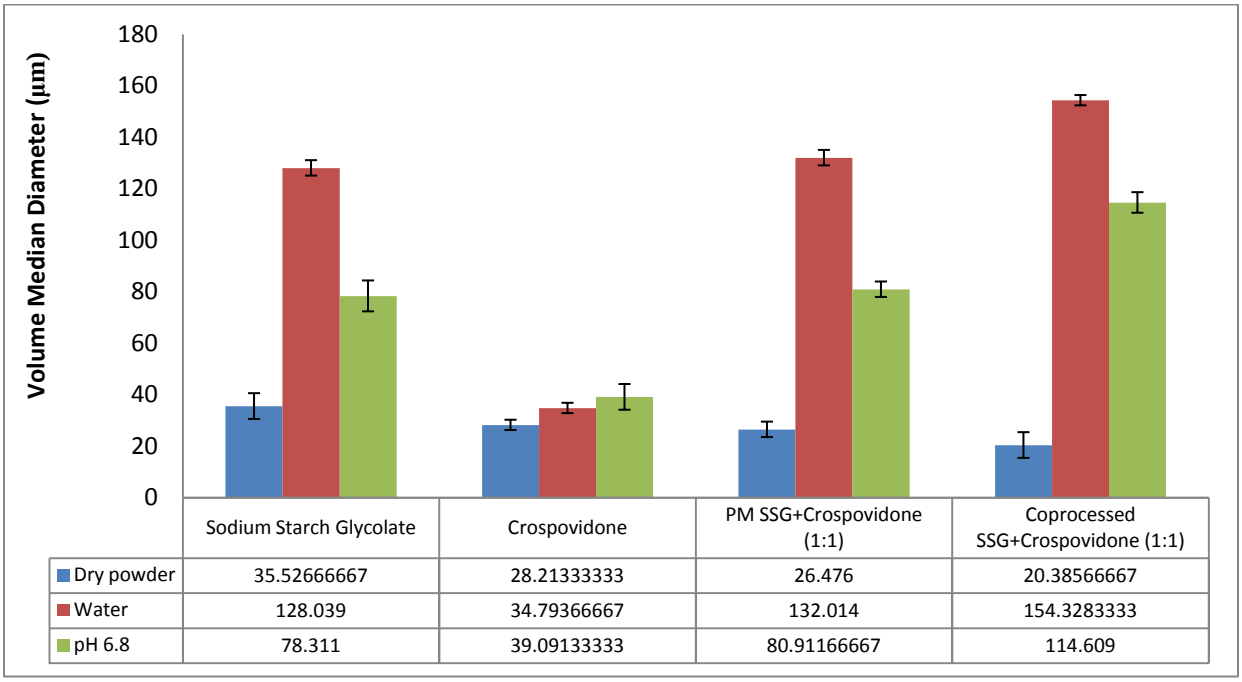


FIGURE 4: PARTICLE SIZE ANALYSIS

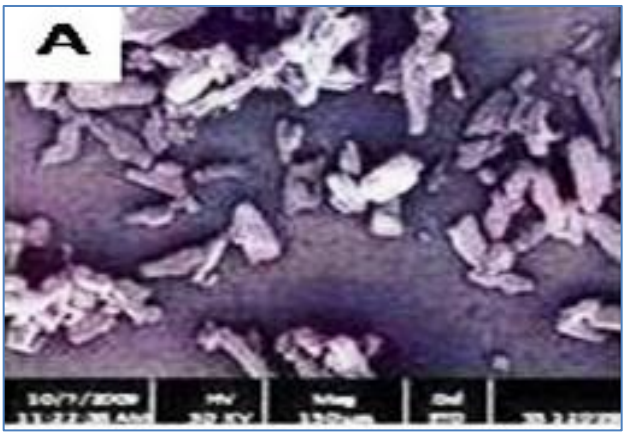
Table 7 reports the bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose for all studied batches. According to literature data, powder having a compressibility index between 5 to 16% is suitable for producing tablets, and those with a Hausner's ratio below 1.25 are exhibited good flowability. Only co-processed superdisintegrant batch was fallen in the limit/range. On the evaluation of superdisintegrant angle of repose of the physical mixture and coprocessed disintegrants (1:1) was found to be 37.83^{o} and 22.42^{o} respectively. According to literature, good flow (angle of repose between 20^{o} and 35^{o}) was shown by co-processed superdisintegrants.

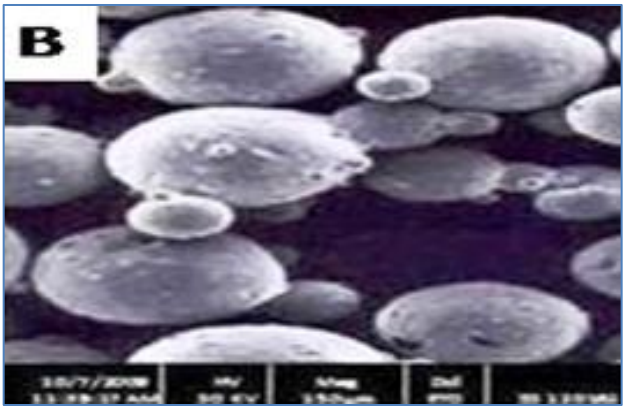
Therefore, it was concluded that particle size distribution and shape of the excipients would be kept the same to avoid the tabletting problem that is dependent on the flow of powder from hopper to die cavity.

TABLE 7: EVALUATION OF SUPERDISINTEGRANT

Batch	Ratio	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's Ratio	Compressibility Index (%)	Angle of Repose (^{0})
SSG	-	0.759±0.005	0.945±0.004	1.250±0.004	20.029±0.234	36.18±0.174
Crosspovidone	-	1.244±0.020	1.858±0.015	1.494±0.034	33.039±1.519	44.02±1.010
Physical Mixture (SSG + Crosspovidone)	1:1	0.891±0.008	1.157±0.040	1.299±0.039	22.946±2.268	37.83±1.714
Coprocessed (SSG + Crosspovidone)	1:1	0.624±0.002	0.700±0.004	1.122±0.004	10.856±0.332	22.42±0.626

n=6, ±SD





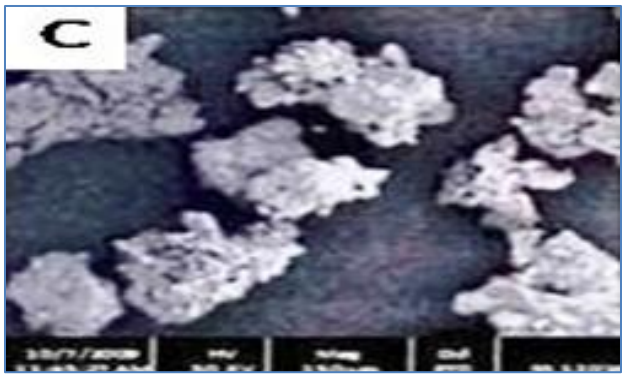


FIGURE 5: SCANNING ELECTRON MICROGRAPHS AT SAME MAGNIFICENCE

A. Crosspovidone; **B.** Sodium Starch Glycolate; **C.** Coprocessed Sodium Starch Glycolate + Crosspovidone

The co-processed superdisintegrants in different ratios of sodium starch glycolate and crosspovidone (1:1, 1:2; 1:3, 2:1, 2:3, 3:1 and 3:2) were prepared for the development of optimization batches. The results shown in **Table 8** indicate that concentration-dependent disintegration was observed in batches prepared using co-processed SSG and Crosspovidone.

TABLE 8: 3^2 FULL FACTORIAL DESIGN LAYOUT

Batch Codes	Variable Levels in Coded Form		Disintegration Time	% Friability
	X_1	X_2	DT (s)	F (%)
FDT1	-1	-1	62	0.534
FDT2	-1	0	55	0.486
FDT3	-1	1	41	0.349
FDT4	0	-1	48	0.562
FDT5	0	0	36	0.528
FDT6	0	1	28	0.487
FDT7	1	-1	29	0.602
FDT8	1	0	18	0.551
FDT9	1	1	7	0.487
OPT	0.08	0.58	30	0.499

Coded values	Actual Values (mg)	
	X_1	X_2
-1	2.5	2.5
0	5	5
1	7.5	7.5

A. X_1 indicates amount of SSG (mg); X_2, amount of Crosspovidone (mg); DT, disintegration time; and F, friability. PCP used as checks point and optimized batch. (n=6)

Factorial Design: The amount of SSG (X_1) and the amount of crosspovidone (X_2) was selected as independent variables. The disintegration time and percentage friability were selected as dependent variables. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed.

The polynomial terms (X_1X_1 and X_2X_2) are included to investigate nonlinearity. The disintegration time and percentage friability for the 9 batches (FDT1 to FDT9) showed a wide variation (ie, 07 - 62 s and 0.349% - 0.602%, respectively). The data clearly indicate that the disintegration time and percentage friability values were strongly dependent on the selected independent variables. The fitted equation relating the responses disintegration time and percentage friability to the transformed factor are shown in **Table 9.**

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (ie, positive or negative). Table 10 shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors. The high values of correlation coefficient for disintegration time, 0.99538 and percentage friability, 0.997741 **(Table 10)** indicate a good fit.

TABLE 9: SUMMARY OF RESULTS OF REGRESSION ANALYSIS

Response (Full Model)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
Disintegration Time	37.66	-17.33	-10.50	-0.25	- 2.00	- 0.50
Percentage Friability	0.537	0.0451	-0.0625	0.017	-0.024	- 0.018

TABLE 10: CALCULATIONS FOR TESTING THE MODEL IN PORTIONS

For Disintegration Time						
	df	***SS***	***MS***	***F***	***Sign. F***	**R^2**
Regression	5	2472.917	494.5833	133.8722	0.001008	0.995538
Residual	3	11.08333	3.694444			
Total	8	2484				
For % Friability						
	df	***SS***	***MS***	***F***	***Sign. F***	**R^2**
Regression	5	0.038731	0.007746	9.037126	0.049823	0.997741
Residual	3	0.002571	0.000857			
Total	8	0.041302				

DF indicates: degrees of freedom; SS, sum of squares; MS, mean of squares; F, Fischer's ratio; R^2, regression coefficient.

Effect of Independent Variables on Dependent Variables: The results of multiple linear regression analysis reveal that, on increasing the concentration of either SSG or crosspovidone, a decrease in disintegration time is observed; both the coefficients b_1 and b_2 bear a negative sign. When higher percentage of SSG is used, higher water uptake swelling and deformation of the SSG take place, which gives internal pressure to tablet to disintegrate due the swelling of the disintegrant. The water uptake and subsequent disintegration were thus facilitated. It is obvious that in the presence of higher percentage of disintegrant crosspovidone, wicking is facilitated. An increase in the concentration of SSG leads to an increase in friability because the coefficient b_1 bears a positive sign. When a higher percentage of SSG was used, low compressible tablets were produced, which were mechanically weak. The increase in the concentration of crosspovidone results in decreased friability values because b_2 bears a positive sign. Crosspovidone was known to produce mechanically strong tablets. Results were shown in response surface plot for disintegration time and percent friability **(Figure 6-9)**

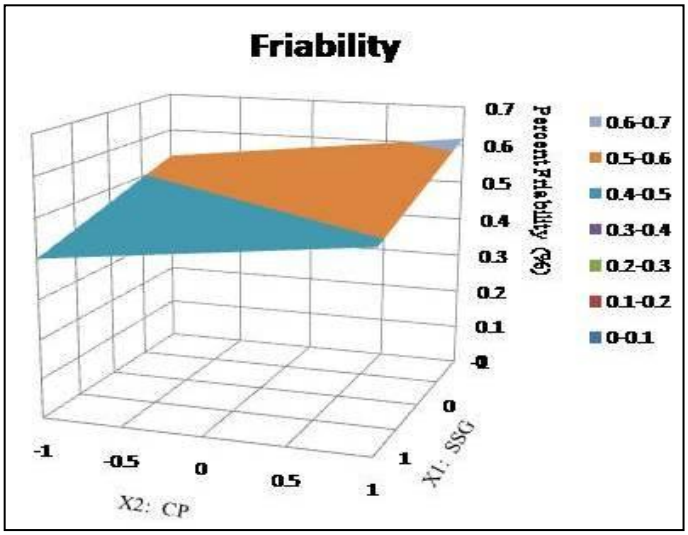


FIG. 6: RESPONSE SURFACE FOR DISINTEGRATION TIME

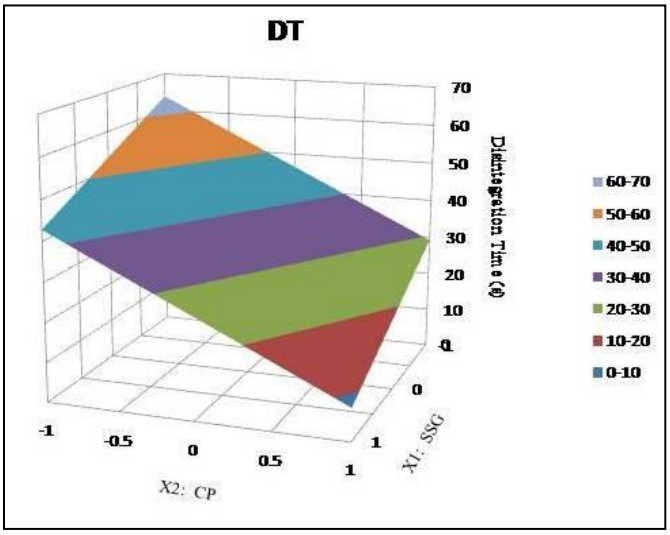


FIG. 7: RESPONSE SURFACE FOR PERCENT TIME FRIABILITY

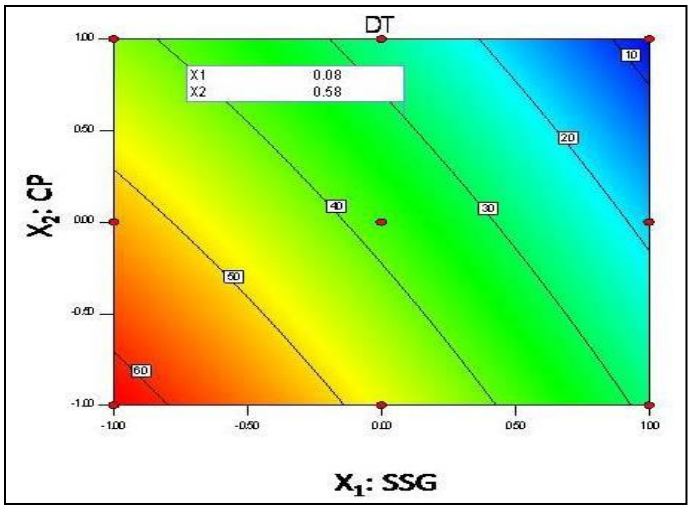


FIG. 8: CONTOUR PLOT FOR DISINTEGRATION TIME

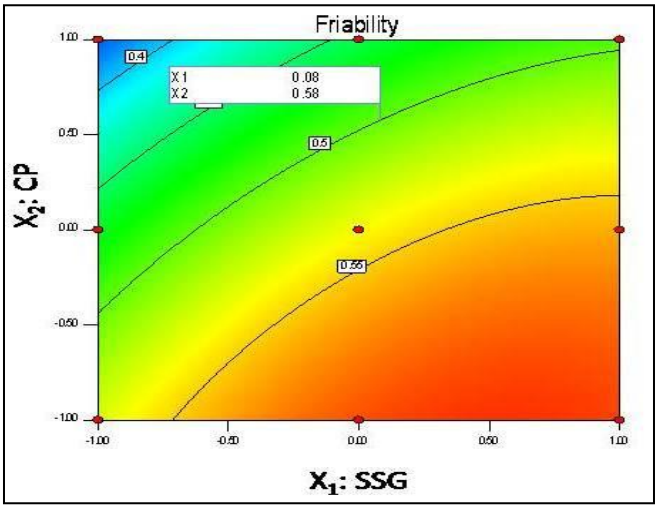


FIG. 9: CONTOUR PLOT FOR PERCENT FRIABILITY

The optimization of the fast dissolving tablet was decided to target disintegration time 30 second and percent friability is 0.5%. The optimized concentration was obtained by software as clears in the surface response prediction curves. Optimization results are shown in **Table 11 (Figure 10).** A checkpoint batch OPT was prepared at X_1 = 0.08 level and X_2 = 0.58 level. From the full model, it was expected that the friability value of the checkpoint batch should be 0.499, and the value of disintegration time should be 30.00 s. Table 11 indicates that the results were as expected. Thus, we can conclude that the statistical model was mathematically valid. The optimized formula was characterized for its blend properties and tablet characterization.

TABLE 11: OPTIMIZATION OF FAST DISSOLVING TABLET

Constraints				
Name	**Goal**	**Lower Limit**		**Upper Limit**
SSG	is in range	-1		1
Crospovidone	is in range	-1		1
DT (s)	is target = 30	7		62
Friability (%)	is target = 0.5	0.349		0.602
Solution				
SSG (X_1)	**Crospovidone (X_2)**	**DT (s)**	**Friability (%)**	**Desirability**
0.08	0.58	30	0.499	1.000

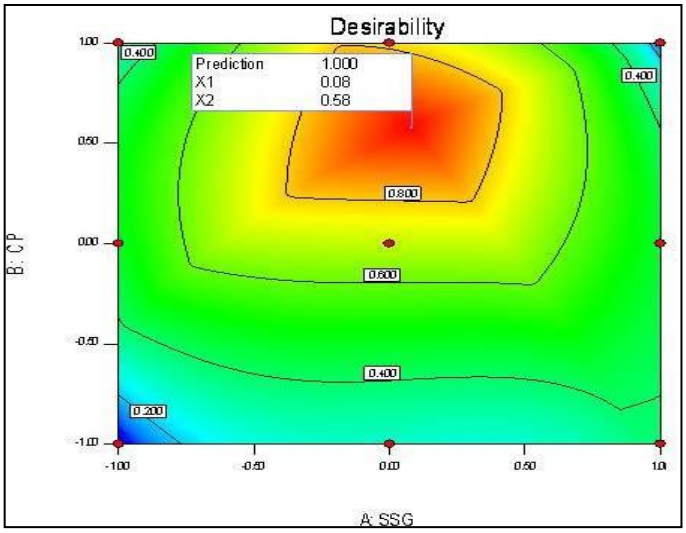


FIG. 10: RESPONSE SURFACE FOR OPTIMIZED FORMULATION

***In vitro* Drug Release Studies:** *In vitro* drug release experiments were performed at 37±0.5° in seven basket dissolution apparatus for the optimized formulation and conventional marketed tablet. The release data obtained were subjected to the kinetic treatment to know the type and order of drug release. The obtained data from *in-vitro* drug release study were tabulated and represented graphically as, Cumulative percentage drug released v/s Time (Zero order release kinetics) and Log cumulative percentage drug retained v/s Time (First order release kinetics).

The drug release was at the end of 5 minutes was more than 90% in optimized fast dissolving tablet whereas only 57.38% drug was released in marketed formulation. Results indicated that the plots of log cumulative % drug retained vs time of formulations were fairly linear as indicated by their high regression. Therefore, it was ascertained that the drug release from formulation could follow first order kinetics. The results of dissolution profile for the optimized formulation and marketed formulation are shown in **Table 12-13** and **Fig. 11-12.** The data for the fitted kinetic model is shown in **Table 14.**

TABLE 12: DISSOLUTION RELEASE PROFILE OF OPTIMIZED FAST DISSOLVING TABLET

Time (min)	Cumulative Mean Percent Drug Released ± S.D.	
	OPT	MKT
0	0.00	0.00
1	37.81±1.49	12.33±2.14
2	58.06±1.67	23.67±1.15
3	71.08±1.68	34.11±2.54
4	82.33±1.97	43.19±2.11
5	90.70±1.80	50.84±1.67
10	97.27±2.05	57.38±2.41

n=6, ±SD

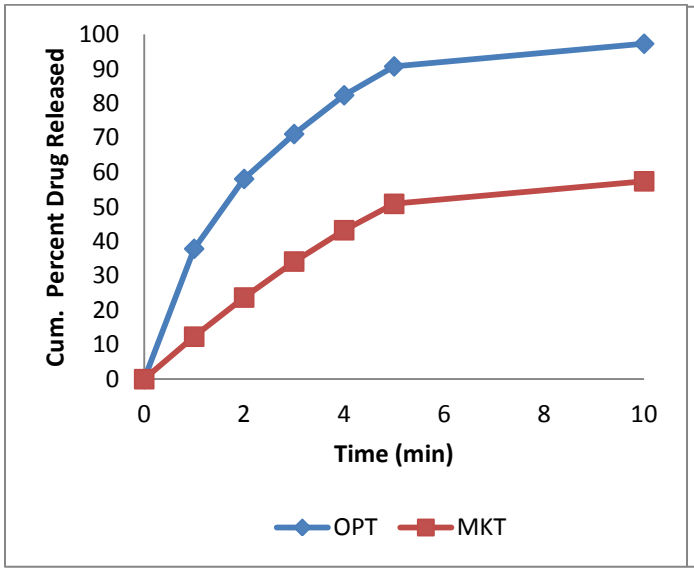


FIG. 11: COMPARISON OF ZERO ORDER RELEASE PROFILE

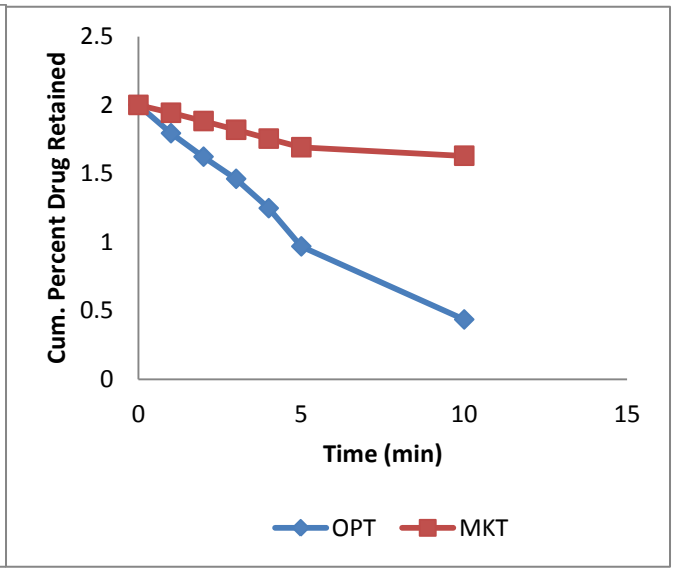


FIG. 12: COMPARISON OF FIRST ORDER RELEASE PROFILE

TABLE 13: DISSOLUTION RELEASE PROFILE OF OPTIMIZED FAST DISSOLVING TABLET

Time (min)	Log Cumulative Mean Percent Drug Retained ± S.D.	
	OPT	MKT
0	2±0.015	2±0.019
1	1.793721±0.024	1.942901±0.005
2	1.622594±0.018	1.882695±0.009
3	1.461148±0.011	1.81882±0.012
4	1.247155±0.016	1.754425±0.019
5	0.968639±0.004	1.691612±0.014
10	0.435632±0.008	1.629613±0.005

n=6, ±SD

TABLE 14: FIT OF VARIOUS KINETIC MODELS FOR TABLETS OF FEXOFENADINE

Formulation Code	Zero Order		First Order	
	R^2	K (mg/min)	R^2	K (min^{-1})
OPT	0.683	8.538	0.973	0.363
MKT	0.805	5.655	0.871	0.085

Temperature Dependent Stability Studies: The optimized fast dissolving tablets of Fexofenadine were packed in wide mouth air tight glass container and stored at (45 ± 1^{o} and $75\pm5\%$ RH) for a period of 3 months.

TABLE 15: EFFECT OF STORAGE CONDITION ON OPTIMIZED TABLET

Days	Temperature				
	Weight	Hardness	Friability	Disintegration Time (s)	Drug Content
0	250.024	3.2	0.488	31	98.35
15	249.335	3.2	0.491	31	98.32
30	249.116	3.1	0.505	29	98.15
45	248.995	3.1	0.512	29	98.13
60	248.714	3.1	0.516	29	98.10
75	248.612	3.1	0.529	29	98.10
90	248.364	3.0	0.536	29	98.07

CONCLUSION: In the present study fast dissolving tablets of Fexofenadine was optimized, prepared and evaluated. Fast dissolving tablets proved to be a potential carrier for the selected anti-histaminic drug (Fexofenadine) in terms of rapid and complete absorption in the body and for achieving therapeutic success. Co processing of excipients (Sodium starch Glycolate with Crosspovidone) could lead to superior properties compared with simple physical mixture of their components or with individual components.

By comparison with the experimental optimized preparation, the observed responses after performing experiment were in close agreement with the predicted values of the optimized formulation, thereby demonstrating the feasibility of the optimization procedure in development of fast dissolving tablets.

It can be concluded that by adopting a systematic formulation approach, an optimum point could be reached in the shortest time with minimum efforts. The fast dissolving tablets of anti-histaminic drug were found to be a better option in the each treatment of allergic conditions by providing fast onset of action and thus leading to patient convenience and compliance.

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