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IMPROVEMENT OF THE PROPERTIES OF TABLETS BY SUPERDISINTEGRANTS PREPARED BY WET GRANULATION METHOD

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Abstract:

The objective of the present investigation was to study the influence of Superdisintegrants like sodium starch glycolate (SSG), croscarmelose sodium (CCS), crospovidone (CP), Physical mixture of Superdisintegrants and Co process superdisintegrants as dissolution enhancer on *in-vitro* dissolution in a model formulation and their different mode of incorporation like intragranular, extra granular and equal distribution between these two. Among the superdisintegrant croscarmelose sodium showed comparatively faster disintegrations time than sodium starch glycolate and crospovidone.The results indicated that Coprocess superdisintegrant was effective in improving the dissolution of the drugs used in the study and generally intragranular mode of addition seemed to be the best mode of incorporation.

Keywords: Superdisintegrant, Co process Superdisintegrant, Physical mixture of Superdisintegrant, Mode of addition, Wet granulation, Acetaminophen tablet.

Introduction:

Despite increasing interest in controlled-release drug delivery systems, the most common tablets that are intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastro-intestinal tract still remains the dosage form of choice. An important variable in any tablet system is the rate at which the drug substance dissolves and for many solid dosage forms, disintegration precedes drug dissolution.

Hence, the proper choice of disintegrants and its consistency of performance are of critical importance to the formulation development of such tablets[1]. Superdisintegrants generally improve disintegration efficiency compared to traditional disintegrants. They are generally used at low levels in solid dosage forms; typically 1–10 % of mass relative to the total mass of the dosage unit. Superdisintegrant such as croscarmelose sodium, sodium starch glycolate and crospovidone are now frequently used in tablet formulations to improve the rate and extent of tablet disintegration thereby increasing the rate of drug dissolution[2, 3, 4]. Wet granulation is one of the frequently used techniques to prepare blends that are compressed into tablets. The disintegrants can be incorporated in the blend before granulation, referred to as intragranular addition (IG), or after granulation, referred to as extragranular addition (EG), or it can be distributed both intra and extragranularly. Many reports are available in the literature where superdisintegrants in wet granulated tablets were incorporated either in intragranularly, extragranularly or it can be distributed both intra and extragranularly[5, 6, 7, 8, 9]. The purpose of the present study is to compare the effect of mode of addition of different superdisintegrants, Coprocess superdisintegrants and Physical mixture of superdisintegrants and evaluate their effect on dissolution and disintegration of model drugs (Acetaminophen).

Materials and Methods: Acetaminophen (Granules India Ltd., Hyderabad), Microcrystalline Cellulose, PVP-K30, Sodium Starch Glycolate(Primojel), Croscarmelose Sodium (Primellose), Crospovidone, Magnesium Stearate, Potassium dihydrogen phosphate, Sodium hydroxide, Isopropyl alcohol (Karnataka Antibiotics & Pharmaceuticals Ltd.Bangalore).All reagents were of Analytical Grade.

Methods:

Preparation of Co processed superdisintegrant:

A blend of crospovidone and Sodium Starch Glycolate/ croscarmelose sodium is added to isopropyl alcohol. The contents of the beaker were stirred on a magnetic stirrer. The temperature was maintained between 65ºC to 70ºC and stirring is continued till most of isopropyl alcohol evaporated. The wet coherent mass was granulated through 60-mesh sieve. The wet granules were dried in a tray dryer at 60ºC for 20 minutes. The dried granules were sifted on 60-mesh sieve and stored in airtight container till further use.

Preparation of tablets:

The tablets were prepared by wet granulation with binder like PVP K30. Purified water was used as the granulating fluid, to form the wet mass of formulation. The granulating fluid was added from a graduated measuring cylinder while the powder blend (Acetaminophen, MCC, and PVP K30) was mixed in a large poly bag to obtain the desirable consistency of the mass. The superdisintegrants like SSG, CCS, and Crospovidone, Physical mixture of Crospovidone and SSG (3:1) or Co process Superdisintegrant were mixed along with powder blend or with the lubricant or equal distribution between two phases, depending on their mode of administration. The wetted mass was then granulated by passing through a 2mm mesh screen. The granules were dried in a hot-air oven at 50ºC for 1h. The moisture content was determined with a moisture analyzer. The dried granules (moisture 2-4%) were passed through a 1mm mesh screen. At the end, MCC and lubricant magnesium stearate were added and mixed for 5 minutes. Tablets of 603 mg were made in a 16 stage rotary tableting machine. In each batch 200 no. of tablets were formulated. (Table No-1, 2 and 3).

Table no-1: Formulation batches.

Sl.No	INGRIDENTS	Batch Code							
		F1	F3	F4	F5	F6	F7	F8	F9
1	Acetaminophen	500	500	500	500	500	500	500	500
2	MCC	46	46	46	46	46	46	46	46
3	PVP K30	30	30	30	30	30	30	30	30
4	SSG	18	18	---	---	---	---	---	---
5	CCS	---	---	18	18	18	---	---	---
6	Crospovidone	---	---	---	---	---	18	18	18
7	Mg. Stearate	09	09	09	09	09	09	09	09
8	TOTAL(mg)	603	603	603	603	603	603	603	603

Table no-2: Formulation Batches

SL.NO.	INGRIDENTS	BATCH CODE					
		F10	F11	F12	F13	F14	F15
1	Acetaminophen	500	500	500	500	500	500
2	MCC	46	46	46	46	46	46
3	PVP K30	30	30	30	30	30	30
4	Physical mixture superdisintegrant	18	18	18	---	---	---
5	Co-process Superdisintegrant	---	---	---	18	18	18
6	Mg. Stearate	9	9	9	9	9	9
7	TOTAL(mg)	603	603	603	603	603	603

Table no-3: Formulation design.

Formulation No.	Superdisintegrants	Mode of Addition	
		IG	EG
F1	SSG	9	9
F2	SSG	18	0
F3	SSG	0	18
F4	CCS	9	9
F5	CCS	18	0
F6	CCS	0	18
F7	Crospovidone	9	9
F8	Crospovidone	18	0
F9	Crospovidone	0	18
F10	Physical Mixture of Superdisintegrant	9	9
F11	Physical Mixture of Superdisintegrant	18	0
F12	Physical Mixture of Superdisintegrant	0	18
F13	Coprocess Superdisintegrant	9	9
F14	Coprocess Superdisintegrant	18	0
F15	Coprocess Superdisintegrant	0	18

EVALUATION OF DRUG LOADED GRANULES:

The angle of repose[10] of granules was determined by funnel method. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

Bulk densities[11] of all types of granules were determined by pouring gently some amount of sample through a glass funnel into a 10ml graduated cylinder. The volumes occupied by the sample were recorded. Bulk density was calculated

$$\text{Bulk density (g/ml)} = \frac{\text{weight of sample in gms}}{\text{volume occupied by the smaple}}$$

Tapped densities[11] of all types of granules were determined by pouring gently some amount of sample through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained (300 taps). Volume occupied by the sample after tapping were recorded and tapped density was calculated.

$$\text{Tapped density (g/ml)} = \frac{\text{weight of sample in gms}}{\text{volume occupied by the smaple}}$$

% compressibility was determined by the Carr's compressibility index[23].

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

EVALUATION OF TABLETS:

Prepared Acetaminophen tablets were evaluated for Weight variation**,** hardness, friability & content uniformity were determined using reported procedure[12].

Hardness and Friability determination

The hardness of the prepared tablets were determined 24 hours after compression using Monsanto hardness tester (Rupa Industries, India).Ten tablets were tested for hardness from each batch.Pre-weighed 20 tablets

were placed in a plastic chambered Friabilator (Electrolab) attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed and percentage mass loss (friability) was calculated.

Disintegration time

The disintegration times of six randomly selected tablets from each tablet batch were evaluated in purified water at 37±1°C using disintegration apparatus. The time for each tablet to completely disintegrate and pass into solution was noted and the mean value was calculated.

Content Uniformity

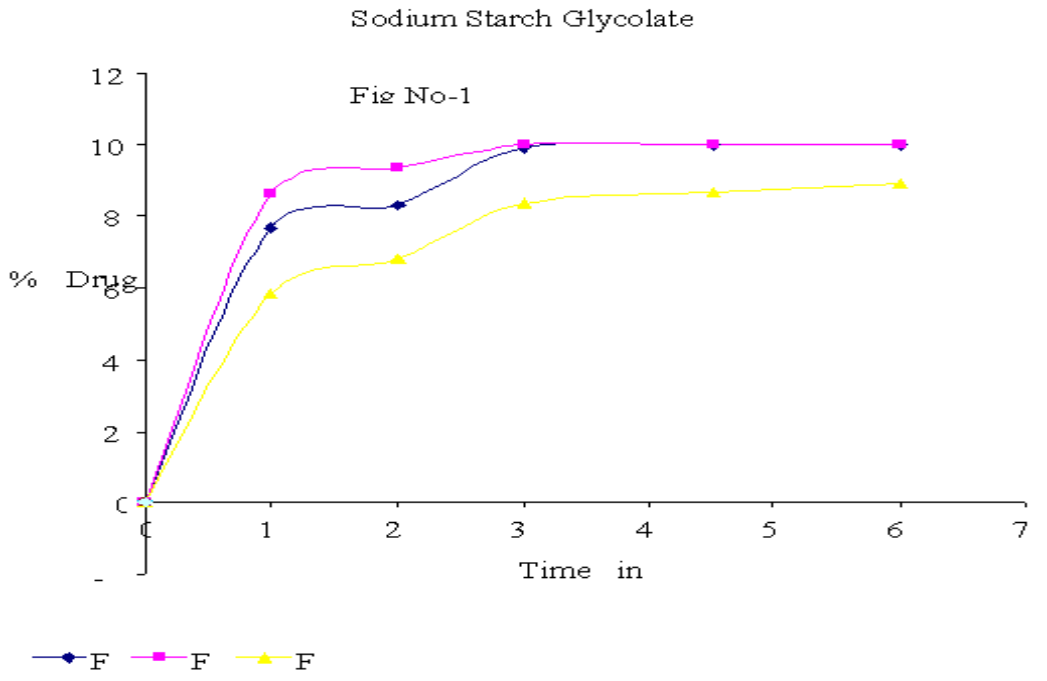
The prepared tablet formulations were assayed for drug content.20 tablets were weighed accurately and powdered. Powder equivalent to 0.15g of Acetaminophen was taken in a 200ml volumetric flask. To this 50ml of 0.1M NaOH was added and then diluted with 100ml of water. This content was shaken for 15 minutes and sufficient water was added to make up the volume. Then this solution was mixed and filtered by using of what-man filter paper. From this 10ml of filtrate was taken in a 100ml volumetric flask and diluted up to 100ml with water. 10ml of this solution and 10ml of 0.1M NaOH were taken in a 100ml volumetric flask and sufficient water was added to make up the volume. The resulting solution was mixed thoroughly and the absorbance of the resulting solution was taken at maximum at about 257nm spectrophotometerically. Then the content of Acetaminophen was calculated by taking 715 as the specific absorbance at 257nm.

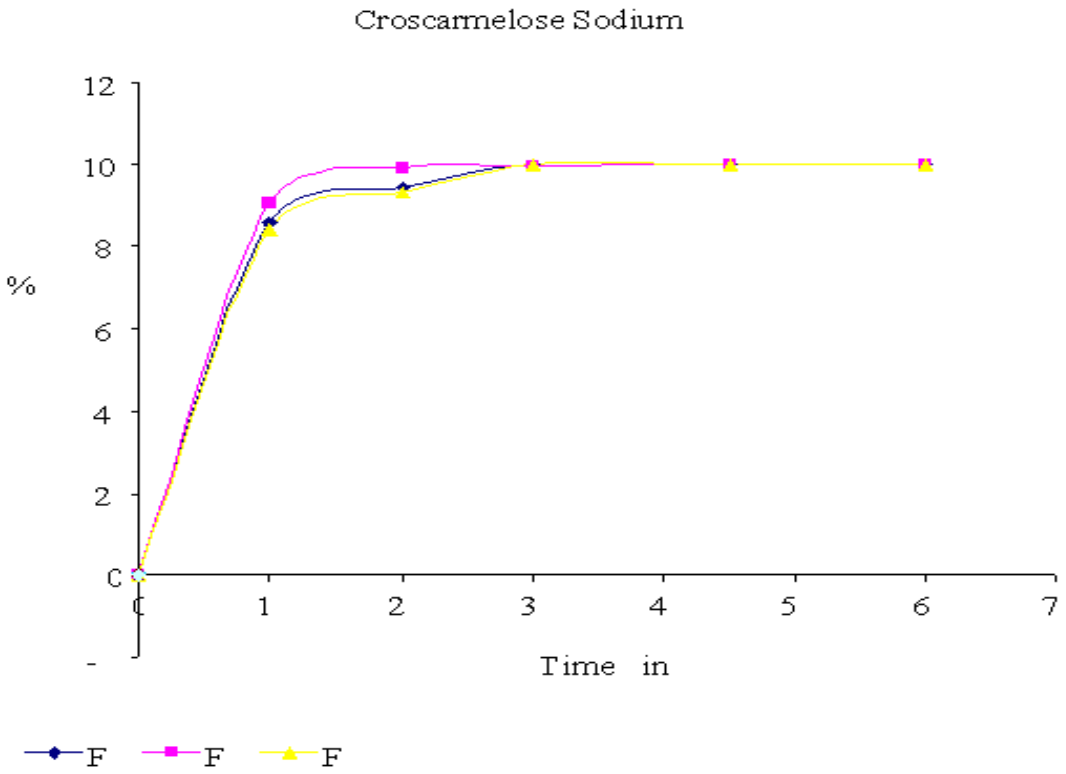
The drug-polymer interaction was studied by FTIR spectroscopy. (NEXUS 870 THERMONICOLET).

In Vitro Dissolution Studies

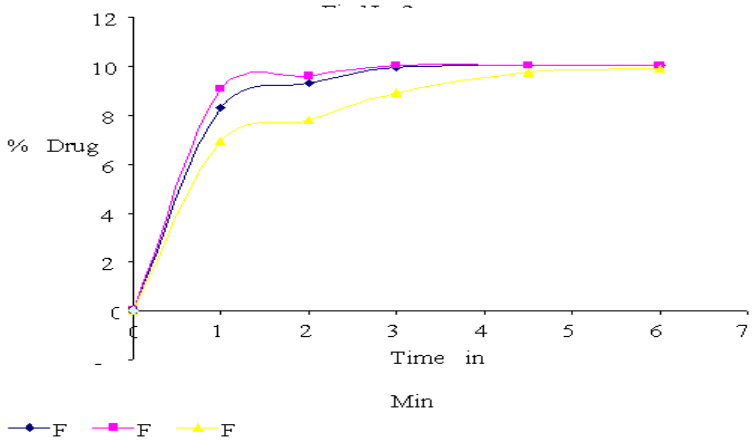
Drug release was evaluated by conventional *in-vitro* dissolution testing. The dissolution tests for tablets were performed by using eight stages USP Dissolution Tester. The medium was 900 ml of pH 5.8 phosphate buffer at 37°C ± 0.5° C. The paddles were rotated a 50 rpm. 2ml of sample was withdrawn at 10,20,30,45 and 60 minutes and replaced with the same volume of pH 5.8 phosphate buffer to maintain the perfect sink conditions. 0.1ml of sample was made up to 10 ml with pH 5.8 phosphate buffer and the absorbance was measured at wavelength of 243nm using a double beam UV spectrophotometer. The amount of drug release was calculated

by complying with the standard graph. Effects of mode of additions of superdisintegrants are represented by Fig no-1 to 8.

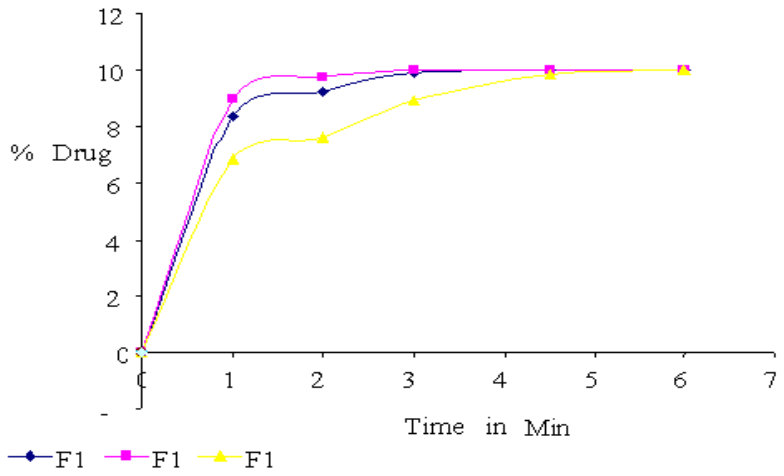




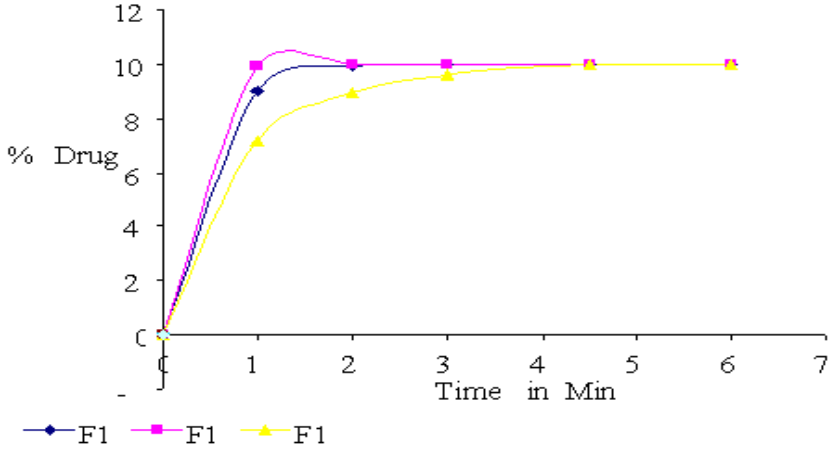
Crospovidone

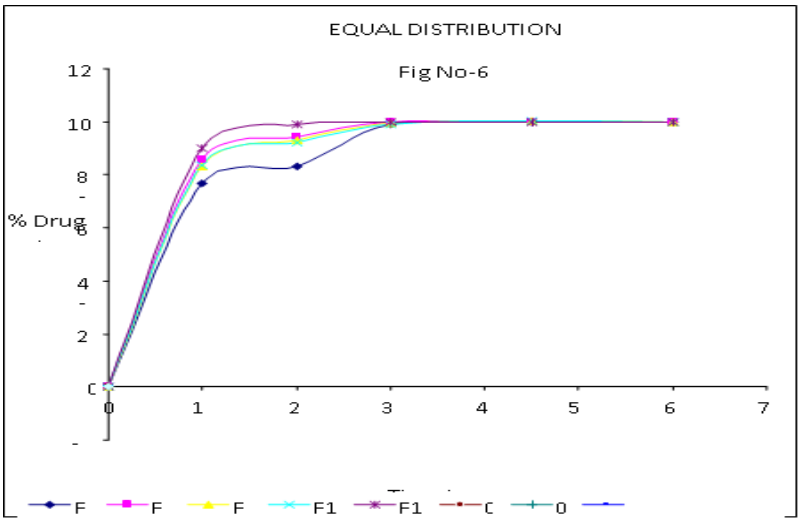


Physical Mixture of Superdisintegrants



Coprocess Superdisintegrant




EQUAL DISTRIBUTION
Fig No-6
% Drug
12
10
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6
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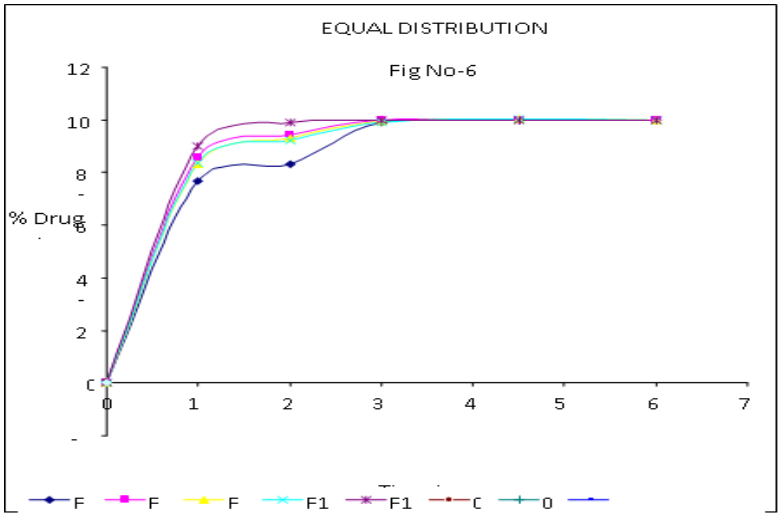
F1
F1
C
O


EQUAL DISTRIBUTION
Fig No-6
% Drug
12
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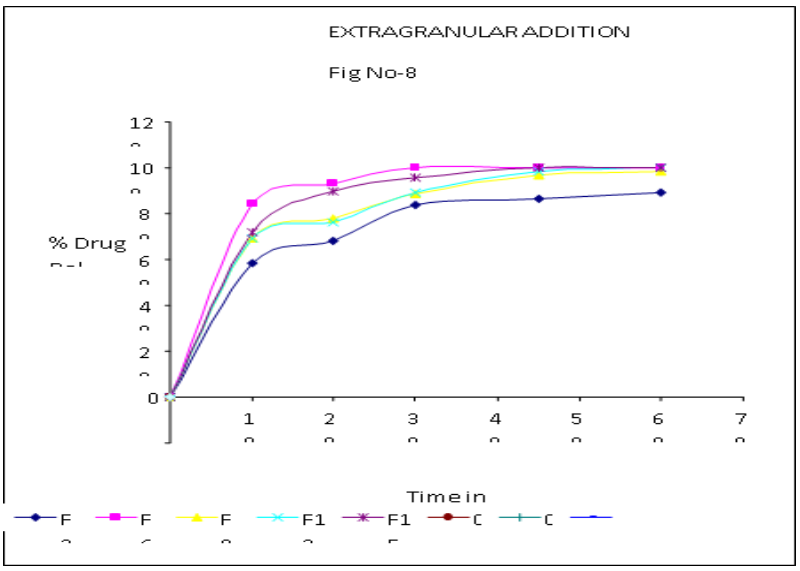
EXTRAGRANULAR ADDITION
Fig No-8
% Drug
12
10
8
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4
2
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1
2
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Time in
F
F
F
F1
F1
C
C

RESULTS AND DISCUSSION

The acetaminophen model formulations were prepared by using MCC as filler, PVP K30 as dry binder, Mg. Stearate as lubricant and glidant and D.M. water as granulating fluid. The superdisintegrant, physical mixture of superdisintegrants and Coprocess superdisintegrant were administered into the formulation by its different mode i.e. intragranular, extragranular and equal distribution in between these two. The characteristics of prepared granules were determined and the results were presented in table No.4. All granules of different formulation showed angle of repose between 25º to 30º, indicating excellent flow. Compressibility index of all the formulations was found to be in the range of 7% to 20% and the packing factor value about 1.25, indicating excellent flow.

Table no-4: Evaluation Report of Granules.

BATCH NO.	ANGLE OF REPOSE (°)	BULK DENSITY (g /ml)	TAPPED DENSITY (g/ml)	HOUSNER RATIO	COMPRESI-BILITY (%)
F1	28	0.487	0.555	1.139	12.250
F2	30	0.487	0.588	1.207	17.176
F3	25	0.465	0.526	1.131	11.590
F4	27	0.425	0.526	1.237	19.201
F5	28	0.425	0.512	1.204	16.992
F6	29	0.444	0.540	1.216	17.777
F7	26	0.454	0.571	1.257	20.49
F8	27	0.465	0.571	1.227	18.564

F9	28	0.434	0.540	1.244	19.629
F10	27	0.454	0.540	1.189	15.925
F11	29	0.476	0.555	1.165	14.234
F12	26	0.434	0.526	1.211	17.490
F13	28	0.487	0.555	1.139	12.252
F14	25	0.500	0.540	1.080	07.407
F15	27	0.476	0.571	1.199	16.637

The tablets of different batches were subjected to various evaluation tests (Table No-5). The average tablet weight of all the formulation was within the specified limits. The friability tests of different batches were carried out and the result was found maximum up to 1.1%. The hardness was found to be 5-8Kg/cm² and among then the crospovidone and Coprocess superdisintegrant gave relatively higher hardness than other.

Table no-5: Evaluation Report of Tablets.

Batch No.	Wt. Avg. (mg)	Hardness (Kg/cm²)	Friability (%)	Disintegration Time (min)	Drug Content (%)
F1	605.20	6.17	0.584	2.06	102.46
F2	603.60	5.65	1.109	1.21	100.46
F3	598.75	5.48	0.630	3.28	97.88
F4	605.55	6.80	0.443	1.17	102.15

F5	603.70	6.00	0.750	1.08	100.59
F6	600.90	5.90	0.479	1.45	99.11
F7	603.40	7.20	0.443	1.42	101.12
F8	605.00	6.80	0.518	1.15	99.30
F9	603.65	7.00	0.674	3.02	100.13
F10	603.95	6.10	0.565	1.37	99.96
F11	604.10	5.80	1.069	1.19	98.71
F12	599.90	5.70	0.630	3.07	97.88
F13	603.85	7.80	0.479	1.12	99.84
F14	604.05	6.90	0.518	0.59	101.03
F15	602.10	7.80	0.514	2.58	100.14

Among superdisintegrants croscarmellose sodium showed comparatively faster disintegrations time than sodium starch glycolate and crospovidone. But overall Coprocess superdisintegrant showed faster disintegration than the simple physical mixture or with their individual components. Among the mode of addition of superdisintegrant, the intra granular administration gave the shortest disintegration time. In case of croscarmellose sodium; the mode of addition had little effect on disintegration time. Croscarmellose sodium and Sodium starch glycolate showed tremendous swelling before disintegration. Co processing of super disintegrants could lead to formation of superdisintegrant with superior properties compared with the simple physical mixture of their components or with their individual components. In the present study, the preparation and evaluation of coprocessdisintegrant containing crospovidone and sodium starch glycolate was explored.

Here different proportion of crospovidone and sodium starch glycolate had tried and the 1:3 ratios were found effective. One of the reasons for preparing the Coprocess superdisintegrant was to avoid the problem of segregation. The crospovidone disintegrate the tablets by wicking mechanism and sodium starch glycolate disintegrate the tablets by swelling mechanism. Both wicking and Swelling action of Coprocess superdisintegrant provide faster disintegration. All the formulations were subjected to in-vitro drug release study using USP standard eight stages paddle type dissolution tester in 900ml of PH 5.8 phosphate buffer as dissolution medium and at 50 rpm speed.

The result showed that formulations containing Coprocess superdisintegrant gave faster dissolution rate than other superdisintegrants. The formulation containing intra granular superdisintegrant showed faster dissolution than extra granular or equal distribution of superdisintegrants. So addition of superdisintegrants in intra granular mode leads to increase the average drug dissolution.

SUMMARY AND CONCLUSION

The coprocessed superdisintegrant proved to be superior to the physical blend of superdisintegrants and its individual components in terms of crushing strength, disintegration and drug dissolution. So the type of disintegrants impacts dissolution of a sparingly water soluble drug from a wet granulation tablet formulation. Among the mode of addition of superdisintegrants, the intragranular mode leads to dissolution enhancement. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. Disintegration remains a powerful influence and precursor for drug absorption. The development of fast dissolving or disintegrating tablets provides an opportunity to take an account of tablet disintegrants. Therefore, there is a huge potential for the evaluation of new Coprocess superdisintegrants, so as to formulate fast dissolving dosage form. Coprocess superdisintegrants offer new avenues and opportunities for formulation scientists as an additional option for improving the solubility of sparingly soluble drugs.

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