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Evaluation of Cetrizine Hydrochloride–Loaded Orally Disintegrating Tablets for Disintegration Time and Dissolution Studies

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ABSTRACT

This study demonstrates the effect of three different super disintegrants, sodium starch glycolate (SSG), Polyplasdone XL and croscarmellose sodium (CCS) alone as well as in combination of SSG and Polyplasdone XL at different ratio (25:75, 50:50 & 75:25) and also without disintegrants. Direct compression technique was used to prepare Cetrizine hydrochloride tablets. Tablets were prepared with 2, 3 and 4% level of disintegrant and compared with tablets without disintegrant. Tablets were compressed at the breaking force range of 60-80 N. Compressed tablets were evaluated for weight, thickness, breaking force, friability, disintegration and dissolution. Formulation made without disintegrant shows very slow dissolution rate when compared to formulation with disintegrant. Formulations made with different disintegrants alone and also in combination show 90% drug release at 15 min time point versus 30 min in case of formulation without disintegrant. Formulation with 3 and 4% disintegrant level, SSG and Polyplasdone XL combination in different ratios shows significantly higher percentage drug release in initial time point when compared to the formulation containing SSG alone as disintegrant. The dissolution profile of formulations made with combination of disintegrants in 3 and 4% level was found to be in the order of SSG:PPXL (25:75) > SSG:PPXL (50:50) > SSG:PPXL (75:25). From the results of this study it can be concluded that SSG and Polyplasdone XL used in combination could be an alternative approach to increase the dissolution of the tablets when compared to the formulation with SSG alone as disintegrant.

Keywords: Super disintegrants, Orally disintegrating tablets, Disintegration and dissolution

INTRODUTION

Disintegrants are single or mixture of substances added to the drug formulation that facilitate the breakup or disintegration of tablets or capsule content into smaller particles due to very large volume expansion in liquid media that breaks more rapidly with respect to the absence of disintegrant and promoting a more rapid release of the drug substance. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. Recently new materials termed as super-disintegrant have been developed to improve the disintegration processes. The disintegrants have the major function to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet. Higher the binding nature, the more effective must be the disintegrating agents in order to release its medication. Ideally, it should cause the tablet to disrupt, not only into the granules from which it was compressed but also into powder particles from which the granules were prepared. The ideal disintegrant should have the following properties.

1. Poor solubility
2. Poor gel formation

3. Good hydration capacity
4. Good molding and flow properties
5. No tendency to form complexes with the drugs

The mechanism by which the tablets are broken into small pieces and then produces a homogeneous suspension due to disintegrant is based on:

I. Capillary action e.g. starch [1-7].
II. High swellability e.g. Gums, celluloses [8-16].
III. Capillary action and high swellability. e.g. crosspovidones [16-19].
IV. Chemical reaction (Acid base reaction) e.g. sodium bicarbonate, sodium carbonate, potassium bicarbonate or calcium carbonate.

Factors affecting on disintegration capacity of a disintegrant are as follows:

1. Percentage of disintegrants present in the tablets.
2. Types of substances present in the tablets.
3. Combination of disintegrants.
4. Presence of surfactants.
5. Hardness of the tablets.
6. Nature of drug substances.
7. Mixing and screening.

There are three methods of incorporating disintegrating agents into the tablet viz. internal addition (intra-granular), external addition (extra granular) and partly internal & external.

The purpose of the study was to demonstrate the effect of two different super disintegrants combination blend like, sodium starch glycolate and Polyplasdone XL added in different ratios to a model formulation of Cetrizine hydrochloride tablets 10 mg in order to compare the dissolution performance of the formulations with formulation containing SSG alone as disintegrant.

In this study, tablets were formulated using Cetrizine hydrochloride by direct compression, with blend of SSG and Polyplasdone XL disintegrants in different ratios (Table 5) at 2, 3 and 4% level and also with SSG, Polyplasdone XL and croscarmellose sodium alone as disintegrant. The tablets were subsequently evaluated for disintegration time and dissolution.

1. Experimental section

The materials, equipments, methodology and analytical methods used for preparation and analysis of Cetrizine hydrochloride tablets 10 mg were described in the following section.

MATERIALS

Materials used in this study were described below (Table 1).

Table 1: List of materials.

S.No	Ingredient	Grade	Manufacturer
1	Cetrizine dihydrochloride	Ph. Eur.	Vaikunth chemicals
3	Lactose monohydrate	Supertab11SD	Fonterra excipients
4	Crospovidone	Polyplasdone XL	ISP
5	Sodium starch glycolate	Type A	Roquette
6	Croscarmellose sodium	SD-711	FMC Biopolymer
7	Colloidal silicon di-oxide	Aerosil 200 PH	Degussa
8	Magnesium stearate	Vegetable origin	Ferro

Equipments

The following equipments and instruments were used for the preparation and evaluation of Cetrizine hydrochloride tablets (Tablet 2).

Table 2: List of equipments/instruments.

S.No	Equipments	Make/Model
1	Tablet press	Cadmach (Model: CMD4)
2	Double Cone blender 1.6 L	Erweka (Type: AR 402)
3	Disintegration tester	Erweka (Type: ZT 502)
4	Sieves	-
5	Tablet breaking force tester	Erweka (Model: TBH310)
6	Friabilator	Erweka (Model: TAR200)
7	Vernier caliper	-

8	Dissolution apparatus online	Varian (Model: VK7010)

Methodology

The procedure followed for this study was direct compression. Tablets composition, process involved and evaluation parameters were described below.

Tablet composition

Compositions of Cetrizine hydrochloride tablets with different disintegrant concentrations utilized for this study were mentioned in Table 3-6 and compositions of disintegrant mixtures studied were represented in Table 7.

Table 3: Tablet composition without disintegrate.

S.No	Ingredients	%w/w	mg/tablet
1	Cetrizine dihydrochloride	7.7	10
2	Lactose monohydrate	88.3	114.8
3	Colloidal silicon dioxide	2	2.6
4	Magnesium stearate	2	2.6
Total		**100**	**130**

Table 4: Tablet composition for 2% disintegrate mixture.

S.No	Ingredients	%w/w	mg/tablet
1	Cetrizine dihydrochloride	7.7	10.0
2	Lactose monohydrate	86.3	112.2
3	Disintegrant*	2.0	2.6
4	Colloidal silicon dioxide	2.0	2.6
5	Magnesium stearate	2.0	2.6
Total		**100.00**	**130.0**

*Disintegrants are SSG, PPXL, CCS and SSG/PPXL combinations (refer Table 7).

Table 5: Tablet composition for 3% disintegrant mixture.

S.No	Ingredients	%w/w	mg/tablet
1	Cetrizine dihydrochloride	7.7	10.0
2	Lactose monohydrate	85.3	110.9
3	Disintegrant*	3.0	3.9
4	Colloidal silicon dioxide	2.0	2.6
5	Magnesium stearate	2.0	2.6
Total		**100.00**	**130.0**

Table 6: Tablet composition for 4% disintegrant mixture.

S.No	Ingredients	%w/w	mg/tablet
1	Cetrizine dihydrochloride	7.7	10.0
2	Lactose monohydrate	84.3	109.6
3	Disintegrant*	4.0	5.2
4	Colloidal silicon dioxide	2.0	2.6
5	Magnesium stearate	2.0	2.6
Total		**100**	**130**

*Disintegrants are SSG, PPXL, CCS and SSG/PPXL combinations (refer Table 7).

Manufacturing procedure

All the formulations mentioned from Table 3 to Table 6 were manufactured by the following procedure.

1. Specified quantities of ingredients were dispensed as per the different composition.

2. Cetrizine hydrochloride, lactose, disintegrant and colloidal silicon di-oxide were sifted through # 30 mesh and loaded in to the double cone blender and blended for 15 min.

Pre-sifted magnesium stearate (# 40 mesh passed) was added to the step (ii) material and lubricated for 3 minutes.

Lubricated blend was compressed using 7.0 mm round standard concave punches.

1. Compressed tablets were evaluated for different parameters like weight, breaking force, thickness, friability, disintegration and dissolution.

Assessment of tablets:

Tablets were collected and evaluated for the following parameters.

Tablet weight uniformity (20 individual tablets): Tablet weight uniformity was evaluated by measuring individual weight of 20 tablets.

Tablet breaking force and thickness: Breaking force of 20 tablets was determined using tablet breaking force tester. Thickness of 20 tablets was measured using digital vernier caliper.

Tablet friability: Tablets equivalent to 6.5 g was weighed and placed in the friabilator. Drum was rotated for 4 minutes (100 revolutions at the rate of 25 rpm), the tablets were de-dusted, reweighed and the % friability was determined using the below mentioned formula.

% Friability = $(W_1 – W_2 / W_1) \times 100$

Where,

W_1 – Initial weight of tablets before friability

W_2 – Final weight of tablets after the test

Disintegration test: Disintegration time of the tablets was determined in distilled water at 37 ± 0.5°C in DT apparatus for each batch of tablets.

Dissolution:

The dissolution test was carried out as per conditions specified for Cetrizine tablets in USFDA dissolution method database. Dissolution of 6 tablets is determined with the following parameters

Medium: de-aerated water;

Volume: 900 mL

Apparatus: USP apparatus 2(Paddle)

RPM: 50

Time points: 5, 10, 15, 20, 25, 30 and 45 min

Detector: UV maxima at about 231 nm

RESULTS AND DISCUSSION

Cetrizine hydrochloride tablets were prepared as per the formula mentioned in Table 3 to Table 6. Tablets were compressed at the breaking force range of 60-80 N. Physical data like weight, thickness, hardness, friability, disintegration and dissolution were generated for the formulation with different levels of disintegrant and compared with composition without disintegrant as given in Table 8. Compression was found to be good for all the above mentioned formulations. The physical parameters of different formulations were represented in Table 8.

The dissolution data of Cetrizine hydrochloride tablets was represented in Table 9 and depicted in Figures 1 to 6.

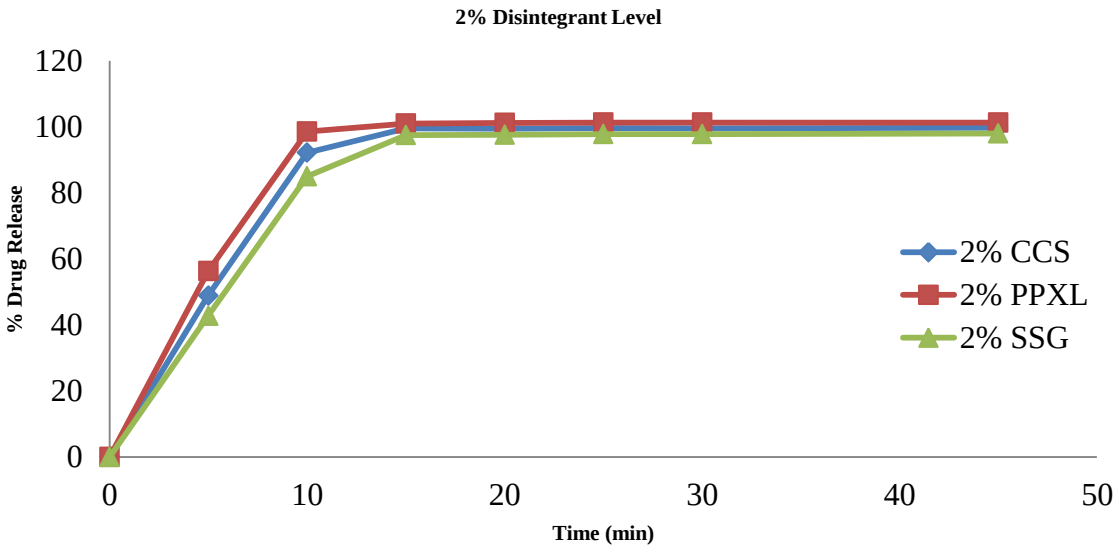

Figure 1: Dissolution profile of Cetrizine hydrochloride tablets 10 mg with 2% disintegrant concentration.

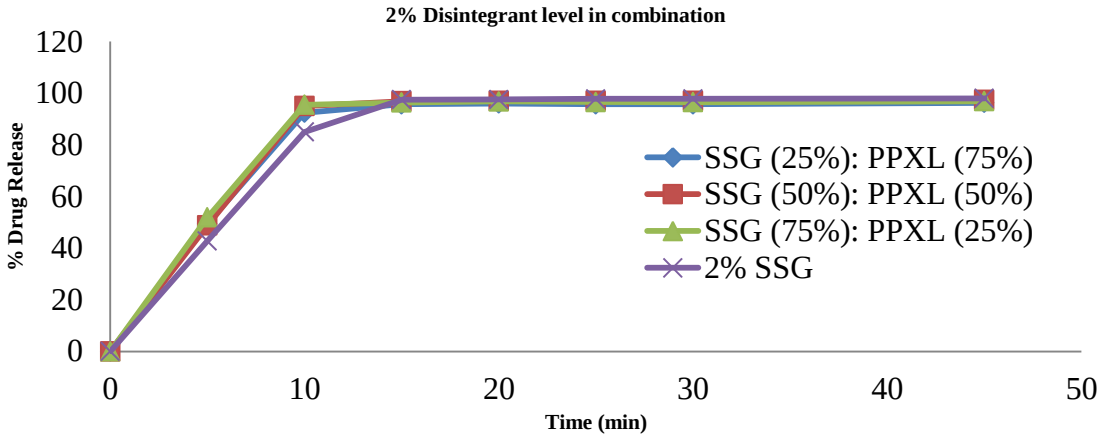

Figure 2: Dissolution profile of Cetrizine hydrochloride tablets 10 mg with 2% disintegrant concentration in combination.

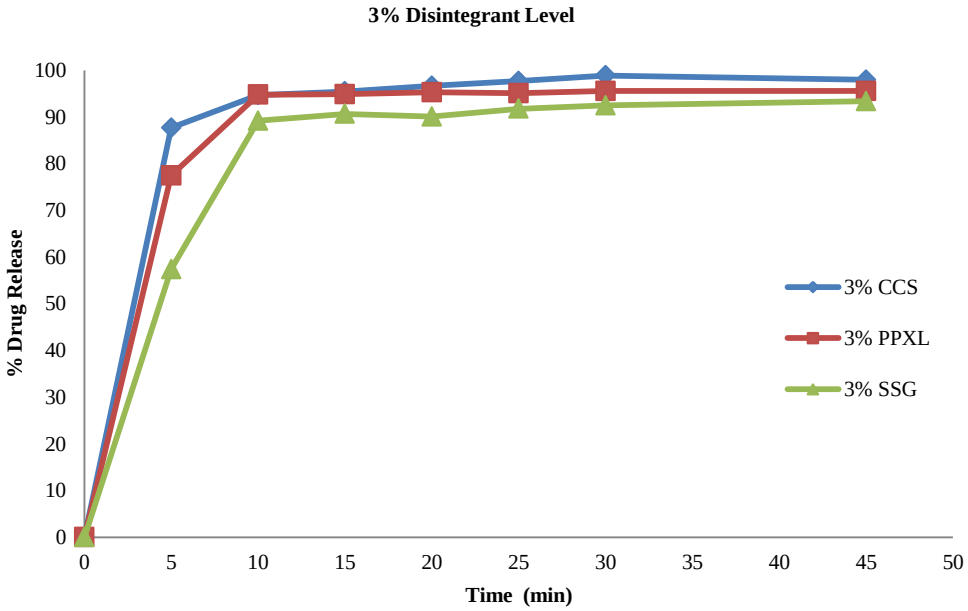

Figure 3: Dissolution profile of Cetrizine hydrochloride tablets 10 mg with 3% disintegrant concentration.

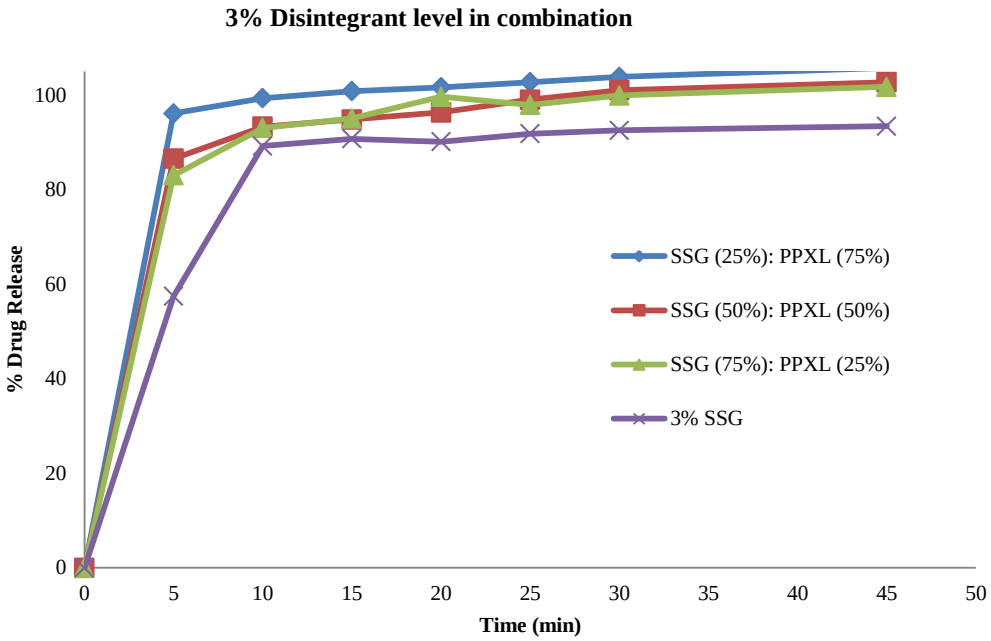

Figure 4: Dissolution profile of Cetrizine hydrochloride tablets 10 mg with 3% disintegrant concentration in combination.

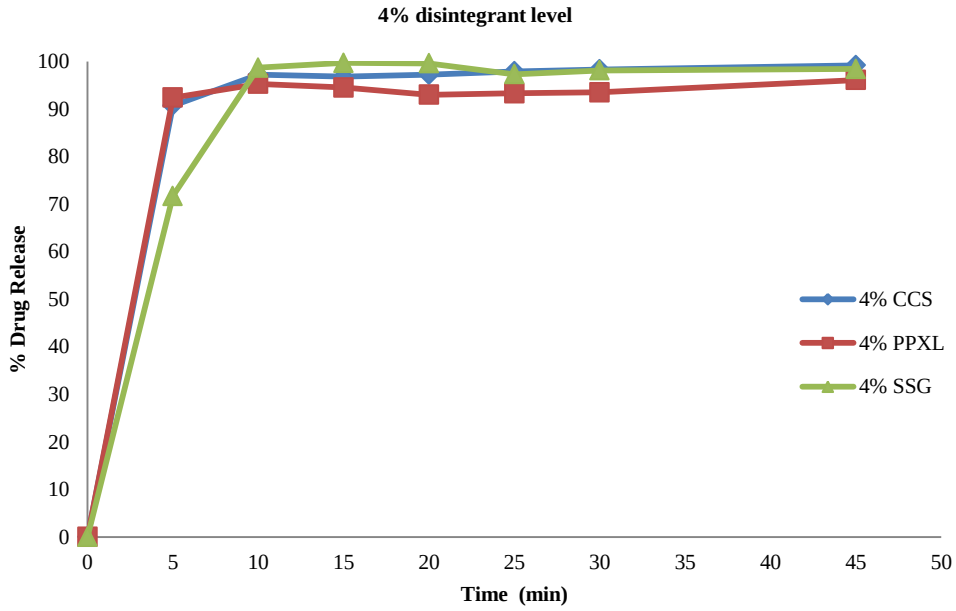

Figure 5: Dissolution profile of Cetrizine hydrochloride tablets 10 mg with 4% disintegrant concentration.

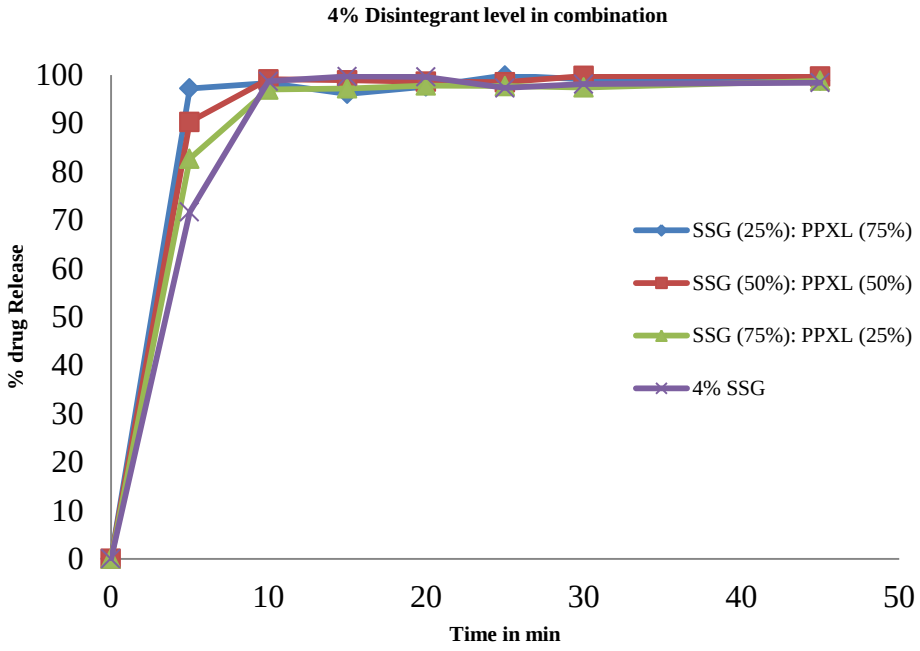

Figure 6: Dissolution profile of Cetrizine hydrochloride tablets 10 mg with 4% disintegrant concentration in combination.

Formulation made without disintegrant shows higher disintegration time (19 minutes) in comparison to formulations with different disintegrant. Increase in level of Polyplasdone XL and sodium starch glycolate concentration in formulation shows gradual decrease in disintegration time whereas for croscarmellose sodium, disintegration time was found to be similar in case of 3 and 4%.

Formulation made without disintegrant shows very slow dissolution rate when compared to formulation with disintegrant. Formulation made with different disintegrants alone and also in combination shows 90% drug release at 15 min time point where as 30 min in case of formulation without disintegrant. Irrespective of the disintegrants, increased concentration of disintegrant increases the percentage drug release. At initial time point, formulation made with Polyplasdone XL alone as disintegrant shows higher percentage drug release in all concentrations when compared to the formulation containing sodium starch glycolate alone as disintegrant. At 2% disintegrant concentration, SSG and Polyplasdone XL used alone and in combination do not show significant difference in dissolution profile at initial time points. Formulations with 3% and 4% disintegrant level, SSG and Polyplasdone XL combination in different ratios shows significantly higher percentage drug release at initial time point when compared to the formulation containing SSG alone as disintegrant.

The dissolution profile of formulations made with combination of disintegrants at 3% and 4% level were found to be in the order of SSG:PPXL (25:75)>SSG:PPXL (50:50)>SSG:PPXL (75:25). Above results clearly indicates that, SSG used in combination with Polyplasdone XL promotes the dissolution rate of drugs when compared to formulation with SSG alone. Higher dissolution rate in case of combination disintegrant may be due to bursting effect of Polyplasdone XL which helps in overcoming the retarding effect of swellable SSG.

CONCLUSION

Dissolution rate of tablets with Polyplasdone XL improves when concentration increased from 2% to 3% and 3% to 4%. Dissolution rate of tablets with sodium starch glycolate was significantly less when compared to the tablets with Polyplasdone XL at initial time points. Formulation having two

super disintegrants in combination shows higher percentage drug release at initial time points when compared to the formulation containing SSG as disintegrant. From the results of this study, it can be concluded that disintegrants such as SSG and Polyplasdone XL used in combination could provide better dissolution rate when compared to SSG alone. Thus it is recommended that combination of SSG and Polyplasdone XL could be a better replacement for the formulations containing SSG alone as disintegrant (Tables 7-9).

Table 7: Percentage composition of disintegrant mixture and ratio.

S.No	% Disintegrant	% SSG	% PPXL	% CCS
1.	0	0	0	0
2.	2	0	0	100
3.	2	0	100	0
4.	2	25	75	0
5.	2	50	50	0
6.	2	75	25	0
7.	2	100	0	0
8.	3	0	0	100
9.	3	0	100	0
10.	3	25	75	0
11.	3	50	50	0
12.	3	75	25	0
13.	3	100	0	0
14.	4	0	0	100
15.	4	0	100	0
16.	4	25	75	0
17.	4	50	50	0
18.	4	75	25	0
19.	4	100	0	0

Table 8: Physical parameters of Cetrizine hydrochloride tablets 10 mg with different disintegrant concentration.

S.No	Formulation	Avg. weight (mg)	Avg. Breaking force (N) with SD	Thickness range (mm)	Avg. DT (min) with SD
1	Without disintegrant	133.1	82.9 ± 9.5	3.22 – 3.28	19.3 ± 1.5
2% Level					
2	CCS alone	133.4	78.2 ± 7.3	3.25 – 3.30	4.6 ± 0.7
3	PPXL alone	131.8	84.9 ± 7.7	3.20 – 3.28	4.7 ± 1.1
4	SSG alone	131.7	76.3 ± 7.7	3.20 – 3.26	6.9 ± 0.8
5	SSG (25%):PPXL(75%)	133.9	83.0 ± 8.2	3.24 – 3.34	5.0 ± 0.9

6	SSG (50%):PPXL(50%)	133.1	81.3 ± 9.1	3.20 – 3.36	5.8 ± 1.2
7	SSG (75%):PPXL(25%)	133.1	71.4 ± 5.1	3.27 – 3.32	5.9 ± 0.9
3% Level					
8	CCS alone	133.4	63.7 ± 5.1	3.38 – 3.47	2.3 ± 0.6
9	PPXL alone	133.4	73.6 ± 9.3	3.20 – 3.28	3.7 ± 0.5
10	SSG alone	131.4	72.2 ± 10.4	3.30 – 3.34	4.8 ± 0.7
11	SSG (25%):PPXL(75%)	133.0	67.0 ± 8.2	3.30 – 3.39	2.9 ± 0.4
12	SSG (50%):PPXL(50%)	133.7	73.4 ± 6.4	3.31 – 3.42	3.4 ± 0.1
13	SSG (75%):PPXL(25%)	132.8	71.7 ± 7.5	3.35 – 3.40	3.4 ± 0.1
4% Level					
14	CCS alone	132.5	80.7 ± 11.9	3.30 – 3.38	2.3 ± 0.1
15	PPXL alone	132.0	74.6 ± 7.2	3.29 – 3.41	2.6 ± 0.3
16	SSG alone	132.0	75.0 ± 11.0	3.27 – 3.35	3.6 ± 0.4
17	SSG (25%):PPXL(75%)	131.5	58.4 ± 6.6	3.20 – 3.37	2.3 ± 0.4
18	SSG (50%):PPXL(50%)	131.9	64.0 ± 4.6	3.33 – 3.42	1.7 ± 0.3
19	SSG (75%):PPXL(25%)	133.4	69.6 ± 6.9	3.30 – 3.40	3.1 ± 0.6

Table 9: Dissolution profile of Cetrizine hydrochloride tablets 10 mg with different disintegrant concentration along with standard deviation.

Time (min)	Without disintegrant	CCS	PPXL	SSG	SSG (25%): PPXL (75%)	SSG (50%): PPXL (50%)	SSG (75%): PPXL (25%)
	2% Level						
5	19.3 ± 0.5	48.9 ± 7.7	56.3 ± 5.8	42.8 ± 4.4	49.5 ± 3.6	48.8 ± 1.8	51.9 ± 2.6
10	27.7 ± 0.9	92.2 ± 4.5	98.6 ± 3.9	85.0 ± 3.9	92.4 ± 4.0	95.0 ± 0.7	95.5 ± 1.4
15	38.3 ± 3.5	99.5 ± 3.9	101.0 ± 5.1	97.5 ± 1.5	95.7 ± 2.4	96.9 ± 1.6	96.4 ± 0.7
20	62.0 ± 8.1	99.4 ± 4.1	101.2 ± 5.2	97.6 ± 1.5	96.0 ± 2.2	97.0 ± 1.6	96.8 ± 1.0
25	84.8 ± 6.6	99.6 ± 4.2	101.3 ± 5.2	97.8 ± 1.5	95.7 ± 2.3	97.1 ± 1.6	96.6 ± 0.9
30	99.8 ± 1.9	99.5 ± 4.1	101.3 ± 5.2	97.8 ± 1.5	95.7 ± 2.4	97.1 ± 1.6	96.5 ± 0.8
45	100.4 ± 1.8	99.7 ± 4.0	101.3 ± 5.2	98.0 ± 1.4	96.3 ± 2.3	97.4 ± 1.7	96.9 ± 0.7
	3% Level						
5	-	87.7 ± 4.6	77.5 ± 5.8	57.4 ± 6.1	96.1 ± 2.5	86.5 ± 4.0	83.0 ± 6.1
10	-	94.7 ± 5.1	94.8 ± 2.7	89.2 ± 1.6	99.3 ± 1.7	93.3 ± 2.3	93.0 ± 3.3
15	-	95.5 ± 5.1	94.9 ± 2.9	90.7 ± 2.9	100.8 ± 1.8	94.8 ± 2.4	95.0 ± 3.0
20	-	96.7 ± 4.6	95.3 ± 2.6	90.1 ± 2.1	101.6 ± 1.5	96.3 ± 2.2	99.6 ± 3.3
25	-	97.7 ± 4.9	95.1 ± 3.0	91.8 ± 3.7	102.7 ± 1.4	99.0 ± 1.8	97.9 ± 4.1
30	-	98.9 ± 4.1	95.6 ± 2.9	92.5 ± 3.5	103.8 ± 1.6	101.0 ± 1.9	99.9 ± 4.1
45	-	98.0 ± 4.9	95.6 ± 3.3	93.4 ± 2.6	105.7 ± 1.6	102.7 ± 2.6	101.7 ± 4.2
	4% Level						
5	-	90.7 ± 3.1	92.4 ± 2.6	71.7 ± 2.9	97.2 ± 4.1	90.3 ± 6.0	82.7 ± 7.1
10	-	97.2 ± 4.1	95.3 ± 4.9	98.7 ± 2.8	98.3 ± 3.9	99.1 ± 3.0	97.0 ± 4.2
15	-	96.8 ± 4.3	94.5 ± 3.8	99.7 ± 2.1	96.1 ± 2.7	98.9 ± 2.8	97.2 ± 4.3
20	-	97.2 ± 4.5	93.0 ± 2.9	99.6 ± 0.6	97.6 ± 2.8	98.6 ± 3.3	97.8 ± 4.0
25	-	97.9 ± 3.9	93.3 ± 3.1	97.3 ± 2.8	99.9 ± 0.3	98.5 ± 3.2	97.7 ± 4.5
30	-	98.3 ± 4.9	93.5 ± 3.1	98.1 ± 1.2	99.1 ± 2.1	99.8 ± 4.3	97.4 ± 4.2

45	-	99.2 ± 5.7	96.1 ± 6.7	98.4 ± 2.7	98.8 ± 3.4	99.7 ± 3.5	98.8 ± 3.7

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