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FORMULATION AND IN-VITRO EVALUATION OF RAPIDLY ORO-DISPERSIBLE TABLETS USING HYDROCHLORTHIAZIDE

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ABSTRACT

The present study was aimed towards the formulation and *In- Vitro* evaluation of orodispersible tablets by direct compression technology using hydrochlorothiazide as a model drug. Fast disintegrating tablet of hydrochlorothiazide was formulated using different superdisintegrants like Croscarmellose sodium, sodium starch glycolate and Crospovidone. All the batches were prepared by direct compression method using the Cadmach Single punch tablet compression machine using flat punch. Disintegration time and drug release were taken as the basis to optimize the rapidly disintegrating tablet. Prepared tablets were evaluated for thickness, hardness, friability, uniformity of weight,disintegration time, wetting time and dissolution study. Crospovidone in the concentration of 9.6% gives fasted disintegration in 1.30 sec. and shows 98% drug release within 30 min. is selected as the optimized formulation. Optimized formulation was subjected to stability studies for thirty days which showed stability with regards to release pattern.

Key Words: Fast disintegrating tablet, Super disintegrants, direct compression, Hydrochlorothiazide.

INTRODUCTION

Pediatric and geriatric patients may have difficulties in swallowing or chewing pharmaceutical dosage forms for oral administration. Tablets that rapidly dissolve upon contact with saliva in the buccal cavity could present a solution to those problems and so there is an increased interest in fast dissolving dosage forms for buccal, sublingual and oral administration. Fast dissolving/ disintegrating tablet are perfect fit for these patients as these immediately release the active drug when placed on tongue by rapid disintegration/ dispersion, followed by dissolution of drug[1, 2].

Fast dissolving tablets are dosage form, which disintegrate in patient's mouth within a few seconds without the need of water, or chewing, providing best remedy for the patient suffering from dysphasia. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down the stomach. In such cases the bioavailability is greater than those observed for conventional dosage form. The advantages of mouth dissolving dosage form are increasingly being recognized in both industry and academia.

There growing importance was underlined recently when European Pharmacopoeia adopted the term "Orodispersible Tablet" as tablet that is to be placed in mouth where it disperses rapidly before swallowing [3, 4, 5].Hydrochlorothiazide is the diuretics of the benzothiadiazine group and has proved very important in the management of mild to moderate hypertension. It inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions. Hydrochlorothiazide is poorly water soluble drug having plasma half life of 6-8 hrs [6].

On the basis of these considerations, in the present study it was proposed to formulate an oral delivery device, in the form of rapidly disintegrating tablets by using direct compression technology, with the aim of reaching a high serum concentration in a short period of time. In this study, effort has been made to formulate fast disintegrating tablet of

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hydrochlorothiazide using three disintegrants,sodium starch glycolate, Crospovidone and Croscarmellose sodium.Effect of different concentration of disintegrants on disintegration time and drug release was studied.

MATERIALS AND METHODS

Hydrochlorothiazide was supplied by Granules india, Hyderabad. Sodium starch glycolate,cross and carmellose was obtained from the chemicka and biochemicka reagents, Mumbai. All the ingredients received were of pharmaceutical grade and were used as received. Other materials and solvents used were of analytical grade.

Table No: 01, Formulation

S.NO	INGREDIENTS	QUANTITY OF INGREDIENTS IN (mg)								
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1.	Hydrochlorothiazide	50	50	50	50	50	50	50	50	50
2.	Mannitol	60	60	60	60	60	60	60	60	60
3.	Avicel PH 101	107	103	99	107	103	99	107	103	99
4.	Sodium starch glycolate	16	20	24	-	-	-	-	-	-
5.	Crospovidone	-	-	-	16	20	24	-	-	-
6.	Croscarmellose sodium	-	-	-	-	-	-	16	20	24
7.	Aspartame	3	3	3	3	3	3	3	3	3
8.	Talc	12	12	12	12	12	12	12	12	12
9.	Magnesium stearate	2	2	2	2	2	2	2	2	2
10	Total	250	250	250	250	250	250	250	250	250

Preparation of tablet: Fast disintegrating tablets of hydrochlorothiazide was prepared according to Table-1. All the excipients without magnesium stearate,aspartame and aerosil were mixed uniformly followed by addition of magnesium stearate and aerosil. The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner ratio. After evaluation of powder blend the tablets were compressed with Cadmach single punch compression machine using flat faced punches.

Evaluation of tablet [7- 9]: All the tablets were evaluated for different parameters as thickness, hardness, friability, uniformity of weight, disintegration time, wetting time, drug content and in- vitro dissolution study.

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's Ratio	Carr's index	Angle of repose (^{0})
F_1	0.312± 0.14	0.400± 0.14	1.28± 0.11	22 ± 2.32	29º.06'± 0.04
F_2	0.326± 0.11	0.442± 0.33	1.35 ± 0.63	18± 0.11	27º.67'± 0.11
F_3	0.322 ± 0.63	0.450± 0.04	1.39±0.36	28±0.36	26º.85'± 0.24
F_4	0.294± 0.33	0.312± 0.11	1.06± 0.14	5± 0.04	27º.78' ± 0.63
F_5	0.303 ± 2.32	0.322±0.36	1.06± 0.33	5.9± 0.33	26º.08'±'0.36
F_6	0.310± 0.04	0.333 ± 2.32	1.07 ± 0.63	6± 0.24	25º.08'± 0.14
F_7	0.290 ± 0.63	0.320± 0.11	1.10± 0.14	9± 0.14	28º.67'± 0.11
F_8	0.285± 0.11	0.326 ± 0.63	1.0 ± 2.32	12.5± 0.24	27º.55' ± 0.63
F_9	0.306±0.36	0.357± 0.14	1.16± 0.11	14.2 ± 0.63	27º.08±'0.36

Table No. 2: Evaluation of blend properties of fast disintegrating tablet.

Thickness: Thickness of tablets was determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness: For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability: Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. after revolution the tablets were dusted and weighed.Uniformityof weight: Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Disintegration test: Disintegration test was carried out on the Disintegration apparatus (Veego, 2D). Tablets were placed in the dissolution medium 0.1 N HCl.

Wetting time: The wetting time of tablets was measured using a simple procedure. A piece of tissue paper folded twice was placed in a small petri-dish containing 10 ml of distilled water. A tablet having amaranth powder on the upper surface was placed on the filter paper. Time required to develop red color on the upper surface of tablet was recorded as wetting time.

Dissolution Studies:The release rate of hydrochlorothiazide from fast dissolving tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCL, at 37 ± 0.5 C and 100 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus every 2 min. for 30 min, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper no. 41. Absorbance of these solutions was measured at 273 nm using UVspectrophotometer Shimadzu 1700.

Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

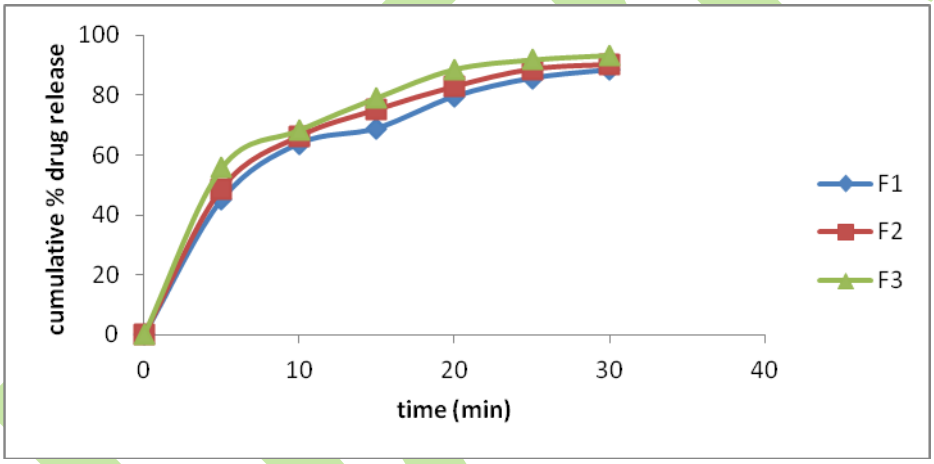

Figure 1: Dissolution profile of formulation F1,F2,F3

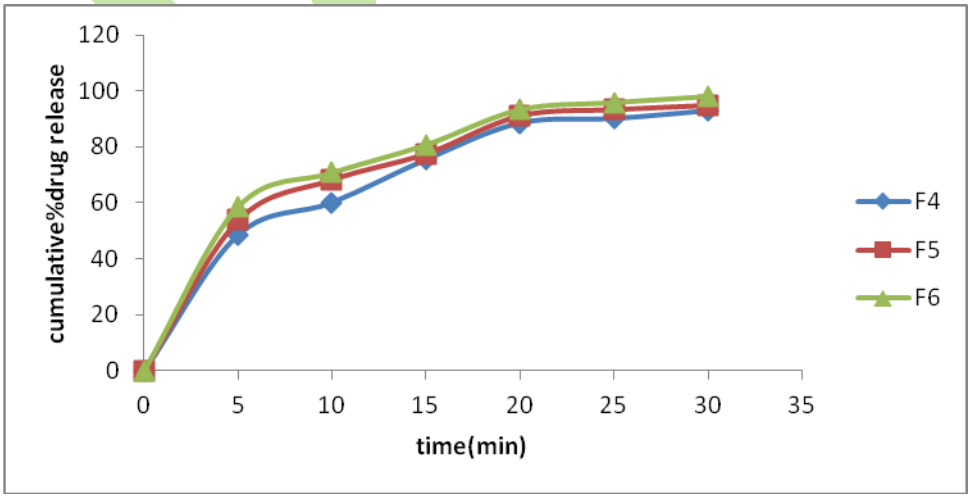

Figure 2: Dissolution profile of Formulation F4,F5,F6

Comparative Cumulative drug release of F3, F6, F9 with marketed formulation

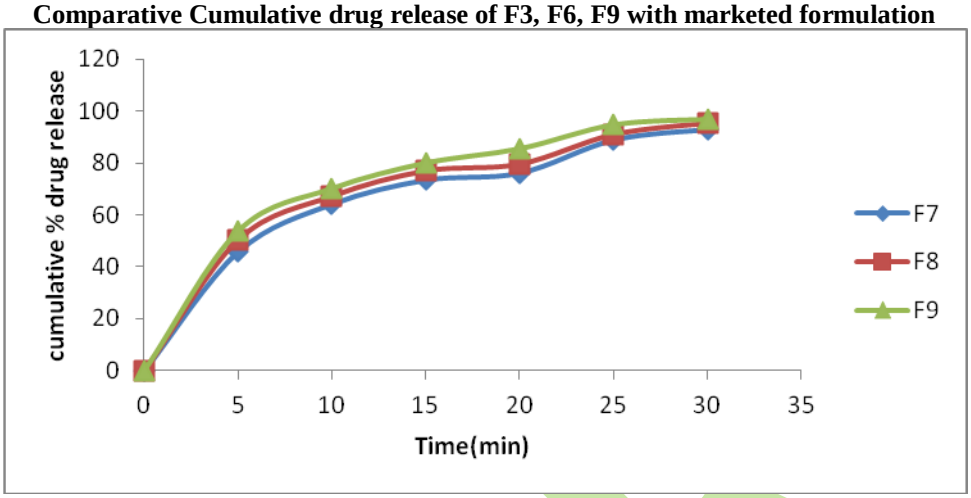

Figure 3: Dissolution profiles of Formulation F7,F8,F9

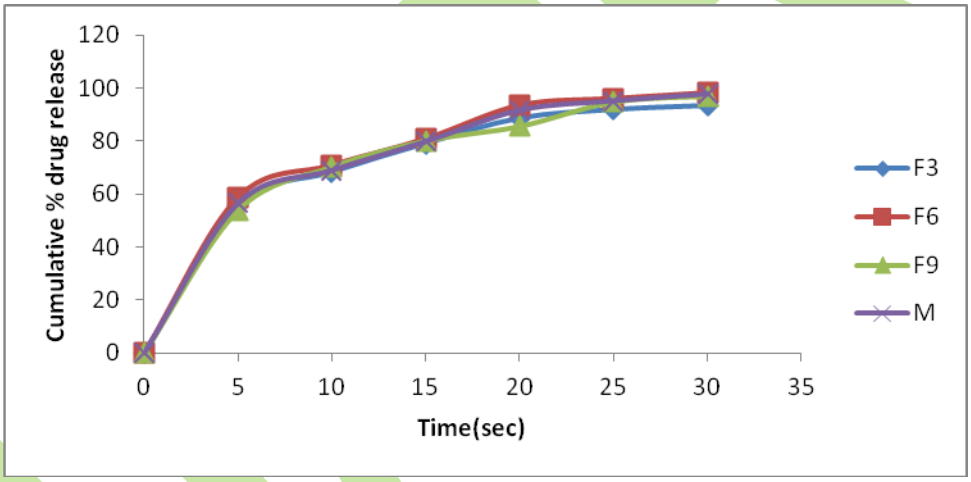

Figure 4: Comparative Cumulative drug release of F3, F6, F9 with marketed formulation

Accelerated stability studies: stability studies were carried out on optimized formulation. The tablets were stored at 40± 2 C/75 ± 5 % RH for duration of one month. After an interval of one month samples were withdrawn and tested for various physical tests and drug release study.

RESULT AND DISCUSSION

Evaluation of blend properties:For each designed formulation, blend of drug and excipients was prepared and evaluated for micromeritic properties shown in Table-2. Bulk density was found to be between 0.290±0.63-0.326±0.11 gm/cm3and tapped densities between 0.312±0.11and 0.450±0.04 gm/cm for all 3 formulations.Angle of repose was found to be in the range of 25.08^{o} to 29.06^{o}. Hausner ratio was found below 1.39. All the formulation shows the good blend properties for direct compression and hence tablets were prepared by using direct compression technology.

Evaluation of fast disintegrating tablet:

a) Weight variation

All the formulated (F1 to F9) tablets were passed weight variation test as the % weight variation was within the IP limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values. The prepared formulation complies with the weight variation test.

b) Thickness

The maximum thickness of the formulation was found to be 2.78mm. The minimum thickness of the formulation was found to be 2.65mm. The average thickness of the all formulation was found to be 2.71mm.

c) Hardness

The hardness of the tablet was found to be 3.1 to 4.3 Kg/cm^2.

d) Friability test

The maximum friability of the formulation was found to be 0.63%. The minimum friability of the formulation was found to be 0.42%. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

e) Drug content

The maximum drug content for the all formulation was found to be 100.51% and minimum % drug content from the all formulation was found to be 97.14%. The results were within the limit specified by the IP.

e) In vitro Disintegration test

In vitro Disintegration time was found to be in the range 25 to 65 sec. From all formulations, F6 (10 % Cross Povidone) has minimum disintegration time. Formulations containing sodium starch glycolate has taken more time for disintegration because of its gelling properties.

f) Wetting Time

Wetting Time was found to be in the range 30 to 88 sec. From all formulations, F6 (10% Cross Povidone) has minimum wetting time.

g) In vitro drug release

All the 9 formulations were subjected to in vitro dissolution studies by using 0.1N HCl (pH 1.2). Dissolution data shows that formulation F6 shows improved dissolution as compared to other formulations.

Effect of disintegrants on release of Hydrochlorothiazide: Dissolution profile of the formulations F3, F6, F9, MARKETED is shown in Figure-4. As the concentration of Crospovidone increased there was decrease in the disintegration time and increase in dissolution of drug.

98% drug was released from the all the formulations .From drug release it was observed that increase in concentration of Crospovidone increases the drug release upto 9.6% concentration in the tablet, but further increase in the concentration of Crospovidone does not show any increase in the dissolution rate.

93-97% drug were released from the all the formulation F7, F8, F9 in 30 minutes respectively. From drug release it was observed that increase in concentration of Croscarmellose sodium increases the drug release. Therefore formulation F6 having disintegrant Crospovidone in the concentration of 9.6% was selected as the optimized formulation.

88-93% drug were released from all the formulation F1, F2, F3 in 30 minutes. From drug release it was observed that increase in concentration of sodium starch glycolate increases the drug release.

Dissolution profile of the formulations containing both the disintegrants was compared with the marketed formulation of hydrochlorothiazide. Marketed formulation of hydrochlorothiazide releases 97.7% drug in 30 minutes. Stability studies showed that there was no significant change in hardness, friability, drug content, and dissolution profile of formulation F6. The formulation was stable under accelerated conditions of temperature and humidity.

Formulation	Weight variation(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)	%drug release
F_1	249.1 ± 0.12	2.65±0.02	3.3± 0.12	0.61± 0.06	65± 0.54	88.4
F_2	248.8 ±1.12	2.78±0.01	3.4± 0.21	0.58± 0.12	58 ± 0.02	90.1
F_3	247.3 ± 0.54	2.74±0.01	3.7± 0.23	0.52± 0.11	37± 0.14	93.3
F_4	248.2 ± 0.63	2.68±0.02	3.1± 0.08	0.45± 0.04	34± 0.25	92.9
F_5	247.6 ± 0.87	2.72±0.01	4.1± 0.14	0.59± 0.12	39± 0.14	94.9
F_6	247.2 ± 0.36	2.73±0.02	3.5± 0.18	0.68± 0.02	25 ± 0.01	98.1
F7	247.6 ± 0.74	2.72±0.03	4.3± 0.22	0.42± 0.04	50 ± 0.36	93.1
F8	248.3 ± 0.52	2.73±0.01	3.1± 0.18	0.54± 0.08	45 ± 0.14	95.1
F9	248.5 ± 0.14	2.71±0.01	2.7± 0.16	0.63± 0.12	37 ± 0.14	96.9

Table No. 3: Evaluation of physical properties of fast disintegrating tablet

CONCLUSION

Thus from above results it can be concluded that the Crospovidone is having better disintegrant property than that of Croscarmellose sodium and sodium starch glycolate and lower concentration of Crospovidone i.e. 9.6% gives better disintegration and dissolution profile. Stability study shows that that there was no significant change in hardness, friability, drug content, a dissolution profile of the selected formulation. Thus Crospovidone can be successfully used in the formulation of fast disintegrating tablets.

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