Research Article

FORMULATION AND *IN VITRO* EVALUATION OF RAPIDLY DISINTEGRATING TABLETS USING CAPTOPRIL AS A MODEL DRUG

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ABSTRACT

The present study was aimed towards the formulation and *in vitro* evaluation of rapidly disintegrating tablets by direct compression technology using Captopril as a model drug. Rapidly disintegrating tablet of Captopril was formulated using three Superdisintegrants in different concentrations i.e. 4%w/w, 8%w/w and 12%w/w and one disintegrants having concentration i.e. 2% w/w/, 4% w/w and 6% w/w like Croscarmellose sodium, Crospovidone, Sodium Starch Glycolate and Indion 414. All the batches were prepared by direct compression method using the Cadmach Single punch tablet compression machine using 8 mm flat punch. Disintegration time and drug release were taken as the basis to optimize the immediate release tablet. Prepared tablets were evaluated for thickness, hardness, friability, uniformity of weight, disintegration time, wetting time and dissolution study. Crospovidone in the concentration of 12 % gives fasted disintegration in 22 sec. and shows and 80% drug release in 10 min at gastric pH is selected as the optimized formulation. Selected formulation was subjected to stability studies for thirty days which showed stability with regards to release pattern.

Keywords: Rapidly disintegrating tablet; Superdisintegrants; Direct compression; Captopril.

INTRODUCTION

In the present scenario, there is an over increasing demand for more patient compliant dosage form. One important innovation in this direction is the development of rapid disintegrating oral dosage form that disintegrate rapidly before swallowing, upon contact with recipient tongue or buccal mucosa (with little amount of water or with saliva)[1, 2]. They have proved to be ideal for geriatric and pediatric population which have difficulty in swallowing or chewing pharmaceutical dosage forms, providing best remedy for the patient suffering from hand tremors and dysphasia[3], clinical condition where intake is limited and situation where water is not available. Particularly, patients often experience inconvenience in swallowing conventional tablet and for drug having high first pass metabolism[4].

Buccal disintegrating tablets require rapid disintegration and absorption of drug may produce rapid onset of action. Fast dissolving tablets are dosage form, which disintegrate in patient's mouth within a few seconds without the need of water, or chewing, some drugs are absorbed from the mucosal lining of mouth, pharynx and esophagus when they pass along with the saliva. This may help to enhance bioavailability of such drugs and pregastric absorption of drug can result in improved total bioavailability and consequently may require reduced dose. This can offer reduction in instances of unwanted side effects. 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. The advantages of mouth dissolving dosage form are increasingly being recognized in both industry and academia.[5]

Captopril is widely used antihypertensive drug but it is very bitter. Therefore, to provide this drug in a more accessible and patient compliant form and to overcome such problems, in the present study it was decided to mask the bitter taste and formulate into a rapid disintegrating tablet. The physicochemical properties of Captopril are water soluble drug having plasma half life of 2 hrs, make it suitable candidate to formulate buccal disintegrating tablets[6].

On the basis of these considerations, in this study, effort has been made to formulate rapidly disintegrating tablet of Captopril using four disintegrants, Croscarmellose sodium, Crospovidone, SSG and Indion 414 by using direct compression technology. Effect of different concentration of disintegrants on disintegration time and drug release was studied.

MATERIALS AND METHODS

Materials

Captopril, β-Cyclodextrin, Croscarmellose sodium, Crospovidone, Sodium Starch Glycolate, Indion 414 were supplied by Macleod's Pharmaceuticals Pvt. Ltd, Mumbai. All the ingredients received were of pharmaceutical grade and were used as received. Other materials and solvents used were of analytical grade.

Methods

Preparation of Taste Masked Inclusion Complex of Captopril: The bitter taste Captopril is masked by physical mixture method using β-cyclodextrin[6]. The required molar quantities of drug and β-cyclodextrin were weighed accurately and mixed together thoroughly in mortar with vigorous trituration for about 3 hrs. These mixtures were then passed through sieve no. 44 and finally were stored in airtight containers till further use. The drug: β-cyclodextrin ratio which produced taste masked complex was used for further studies[7].

Characterization of Captopril Inclusion Complexes

1. Drug Content Estimation: The quantities of drug complex powders equivalent to 12.5mg of Captopril were dissolved in Water (1:1). Appropriate dilutions were made and drug content of complex was calculated from UV absorbance value at 211nm.

2. Evaluation of Taste of Inclusion Complex: Taste of inclusion complex was checked by time intensity method. For this purpose six human volunteers were selected. In this method a sufficient quantity of sample was held in mouth for 10 seconds and volunteers were asked to evaluate the complex for taste. Bitterness levels were recorded immediately. Bitterness values are based on a 0-3 scale with. (3 being – strong bitter, 2 being – moderate bitter, 1 being – slight bitter, X being – threshold bitter, 0 being – tasteless).

These volunteers were instructed not to swallow the granules, which were placed on the tongue. They were instructed to thoroughly gargle their mouth with distilled water after the completion of test[1].

Preparation of Tablet

Rapidly disintegrating tablets of Captopril was prepared according to Table No 1. All the excipients without magnesium stearate and Aerosil were mixed uniformly followed by addition of magnesium stearate and Aerosil[6]. 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 8mm flat faced punches.

Table 1: Formulation of rapidly disintegrating tablet of Captopril

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Complex	49.5	49.5	49.5	49.5	49.5	49.5	49.5	49.5	49.5	49.5	49.5	49.5
Spray dried Mannitol	67.5	67.5	67.5	67.5	67.5	67.5	67.5	67.5	67.5	67.5	67.5	67.5
Avicel 102	21.75	15.75	9.75	21.75	15.75	9.75	21.75	15.75	9.75	21.75	15.75	9.75
Crospovidone	6	12	18	-	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	6	12	18	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	6	12	18	-	-	-
Indion 414	-	-	-	-	-	-	-	-	-	3	6	9
Aspartame	3	3	3	3	3	3	3	3	3	3	3	3
Strawberry	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Aerosil	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Mg. stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Total weight	150	150	150	150	150	150	150	150	150	150	150	150

Table 2: Evaluation of blend properties of Captopril rapidly disintegrating tablets

Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose	Carr's index	Hausner ratio
F1	0.425±0.02	0.515±0.05	28.85±0.01	17.48%	1.21
F2	0.435±0.02	0.522±0.02	29.67±0.02	16.67%	1.20
F3	0.430±0.01	0.524±0.02	31.06±0.01	17.94%	1.22
F4	0.415±0.03	0.532±0.05	32.08±0.01	21.99%	1.28
F5	0.435±0.04	0.525±0.04	28.45±0.02	17.14%	1.20
F6	0.432±0.04	0.540±0.04	29.67±0.01	20.00%	1.25
F7	0.430±0.04	0.522±0.05	31.06±0.04	17.62%	1.21
F8	0.435±0.03	0.520±0.02	32.08±0.02	16.35%	1.19
F9	0.415±0.03	0.532±0.05	28.78±0.03	21.99%	1.28
F10	0.432±0.04	0.540±0.04	30.12±0.03	17.62%	1.21
F11	0.430±0.04	0.522±0.05	28.25±0.04	16.35%	1.19
F12	0.415±0.03	0.532±0.05	29.02±0.02	21.99%	1.28

Table 3: Evaluation of Captopril rapidly disintegrating tablets

Formulation	Hardness (Kg/cm2)	Thickness (mm) (Mean ± S.D)	Weight Variation (mg)	Friability (% w/w loss)	Content Uniformity (%)	D.T. (In Vitro) (sec.)	Tablet wetting Time (sec)
F1	3.5	2.360 ± 0.061	Complies	0.5253	100.06±0.241	142.33± 1.15	171.5 ± 2.18
F2	3.0	2.745 ± 0.023	Complies	0.4900	98.38 ± 0.199	111 ± 1.00	166.2 ± 2.15
F3	3.5	2.506 ± 0.026	Complies	0.5000	96.36 ± 0.158	88.66 ± 0.57	82.0 ± 2.47
F4	3.5	2.006 ± 0.037	Complies	0.3947	98.92 ± 0.137	107 ± 1.15	54.4 ± 1.18
F5	3.0	2.628 ± 0.032	Complies	0.4304	101.66 ±0.209	95.33 ± 1.15	43.2 ± 1.15
F6	3.0	2.745 ± 0.011	Complies	0.500	102.04 ± 0.88	22.33 ± 2.51	32.0 ± 1.12
F7	3.0	2.745 ± 0.015	Complies	0.4545	100.01 ± 0.90	137.3 ± 0.57	93.1 ± 1.09
F8	3.0	2.745 ± 0.02	Complies	0.4635	98.59 ± 0.581	105 ± 1.73	79.3 ± 1.27
F9	3.0	2.745 ± 0.015	Complies	0.5300	101.36 ±0.58	78.33 ± 0.57	67.0 ± 2.15
F10	3.5	2.506 ± 0.011	Complies	0.5400	97.81 ± 0.446	162.33± 0.57	174.8 ± 1.90
F11	3.0	2.628 ± 0.032	Complies	0.4362	99.47 ± 0.487	117.33±1.00	123.3 ± 2.17
F12	3.0	2.745 ± 0.037	Complies	0.5000	98.69 ± 0.493	91.33 ± 0.57	94.2 ± 1.16

(± = *standard deviation.)*

Evaluation of Tablet

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 (table 3).

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 6 tablets was determined using the Monsanto hardness tester (Cadmach).

Friability: Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated, after revolution the tablets were dusted and weighed.

Uniformity of weight: Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.[7,8,9]

Disintegration test: The *in vitro* disintegration studies were carried out using Digital Tablet Disintegration Test Apparatus (Veego). One tablet was placed in each of the six tubes of the basket assembly and disk was added to each tube. This assembly was then suspended in one-liter beaker containing water maintained at 37±2 ^{0}C. The basket was then moved up and down through a distance of 5 to 6 cm. at a frequency of 28 to 32 cycles per minutes. The time required for complete disintegration of the tablet was recorded[10].

Wetting time: A piece of tissue paper (10 cm) folded twice was placed in a small Petri dish (6.5 cm), to simulate the tongue condition. 10 ml of water containing methylene blue, a water soluble dye, was added to the Petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time.

Dissolution Studies: The release rate of Captopril from rapid disintegrating tablets was determined using IP Dissolution Test Apparatus Type II (basket type). Tablets were placed in a dry basket at the beginning of each test. Lower the basket in the dissolution medium and apparatus was run at 50 rpm, The dissolution test was performed using 900 ml of 0.1 M HCL, at 37± 0.5^{0}C and 50 rpm. Ten-milliliter aliquots were withdrawn at time intervals of five minute. This was maintained at same temperature, was added to the bulk. The samples were filtered through Whatman filter paper no. 41. Absorbance of these solutions was measured at 211 nm using UV spectrophotometer Shimadzu 1700. Cumulative percentage drug release was calculated using an equation obtained from a standard curve [11].

Accelerated stability studies: stability studies were carried out on optimized formulation F6. The tablets were stored at 40 ± 2^0 C/75 ± 5 % RH for duration of one month. After an interval of thirty days each samples were withdrawn and tested for various physical tests and drug release study.

RESULTS AND DISCUSSION

The result shows that drug: β-cyclodextrin in the ratio of 1:3 has better as compared to the other. Inclusion complex prepared by physical mixture method showed nearly 100% drug content. Also, sensory evaluation for taste by panel of 06 healthy volunteers confirmed the tasteless characteristics of the inclusion complex as none of the subject felt any bitter taste even after keeping in mouth for 10 sec. Hence this technique of taste- masking using β-cyclodextrin was found to be effective in masking the bitter taste of drug. The prepared inclusion complexes were found to be tasteless, so they were compressed into rapidly disintegrating tablet

Evaluation of Blend Properties

Bulk densities of various formulations were found in between 0.430-0.435 g/cm^3. The angle of repose values varied from 28 to 32. CI values varied from 16% to 21%. From these values it was evident that all these blends had excellent flow properties.

All the formulation shows the good blend properties for direct compression and hence tablets were prepared by using direct compression technology.

Evaluation of Rapidly Disintegrating Tablet

Tablet Thickness: Thickness values for of all tablets were in the range of 2.006 ± 0.037 to 2.745 ± 0.023 mm.

Uniformity of Weight: Weight variation values for prepared tablets were found within the specifications of I.P Limit.

Hardness: The hardness was uniformly maintained and it was found to be within 3-3.5 Kg/cm^2.

Friability: Percent friability was less than 1% in the entire formulations and the values obtained lies within 0.394 to 0.525.

Disintegration test: Tablets from each batch show immediate disintegration. Disintegration time decreases with increase in concentration of the superdisintegrants. Disintegration time was given in Table No.3. Among the four disintegrants used, Crospovidone showed the highest efficiency in this regard followed by Sodium Starch Glycolate, Croscarmellose sodium and Indion 414. This is due to the rapid uptake of water from the medium, swelling and burst effect. In case of Crospovidone as the concentration increases the disintegration time decrease up to certain concentration i.e. up to 12%, the probable reason may be high gelling tendency of Sodium Starch Glycolate, Croscarmellose sodium than Crospovidone which causes swelling of tablet mass leading to slow disintegration.

Wetting time: The wetting time of all the formulations were found to be in the range of 32.0 ± 1.12 – 174.8 ± 1.90 sec. The wetting time was rapid in Crospovidone followed by Croscarmellose sodium, Sodium Starch Glycolate, Indion 414. Here also it was observed that as the concentration of disintegrants increased the time taken for wetting was reduced.

Percentage drug content: The percentage drug content of all the tablets were found to be between 96.36 ± 0.158 to 102.04 ± 0.88, which was within the acceptable limits.

Effect of Disintegrants on Release of Captopril

Dissolution profile of the formulations F1, F2 and F3 is shown in (Figure No 1)**.** As the concentration of Croscarmellose sodium increased there was decrease in the disintegration time and increase in dissolution of drug. They have recorded 80% drug release within 25min, 20min and 15min. respectively.

Dissolution profile of the formulations F4, F5 and F6 is as shown in (Figure No. 2). Formulations F4, F5 and F6 which contained increasing concentrations of Crospovidone i.e. 4%w/w, 8%w/w and 12%w/w have recorded 80% drug dissolution within 20min, 20min and 10min. respectively. From drug release it was observed that increase in concentration of Crospovidone increases the drug release up to 12% concentration in the tablet Therefore formulation F6 having disintegrant Crospovidone in the concentration of 12% was selected as the optimized formulation.

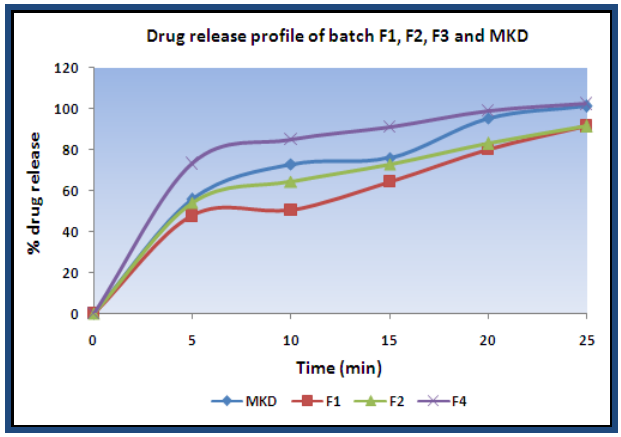

Figure 1: Dissolution profile of batches F1, F2, F3 and MKD containing Croscarmellose sodium

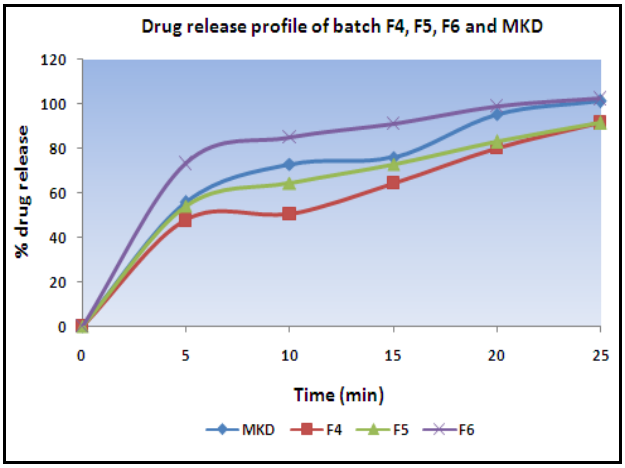

Figure 2: Dissolution profile of batches F4, F5, F6 and MKD containing Crospovidone

Formulations F7, F8 and F9 which contained increasing concentrations of Sodium starch glycolate i.e. 4%w/w, 8%w/w and 12%w/w respectively as shown in (Figure No.3). All of them have recorded 80% drug release within 25 min, 20min and 15min respectively

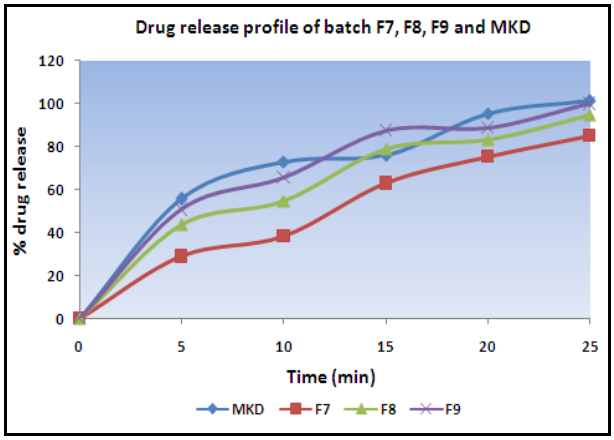

Figure 3: Dissolution profile of batches F7, F8, F9 and MKD containing Sodium starch glycolate

Formulations F10, F11 and F12 which contained increasing concentrations of Indion 414 i.e. 2%w/w, 4%w/w and 6%w/w respectively. All of them have recorded 80% drug release within 25 min, 20 min and 15 min respectively as shown in (Figure No. 4)

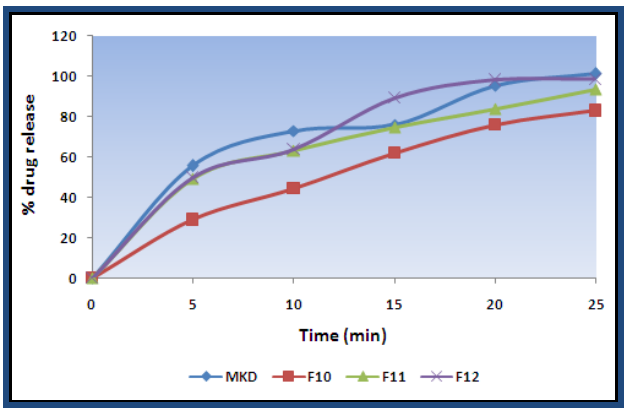

Figure 4: Dissolution profile of batches F10, F11, F12 and MKD containing Indion 414

Dissolution profile of the formulations containing both the disintegrants was compared with the marketed formulation of Captopril. The MKD tablet showed 80% drug release within 20 min.

The relative efficiency of these different superdisintegrants to improve the dissolution rate of tablets was in order,

Crospovidone > Sodium starch glycolate> croscarmellose sodium > Indion 414

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 different conditions of temperature and humidity.

CONCLUSION

Thus from above results it can be concluded that the Crospovidone is having better disintegrant property than that of Croscarmellose sodium and higher concentration of Crospovidone i.e. 12% gives better disintegration and dissolution profile. Stability study shows that that there was no significant change in hardness, friability, drug content and dissolution profile of the selected formulation. Thus Crospovidone can be successfully used in the formulation of rapidly disintegrating tablets.

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