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Rajeshwar V
School of Pharmacy,
Anurag Group of Institutions,
Venkatapur (V), Ghatkesar (M),
Medchal, Telangana, India

Vasudha Bakshi
School of Pharmacy,
Anurag Group of Institutions,
Venkatapur (V), Ghatkesar (M),
Medchal, Telangana, India

Correspondence
Rajeshwar V
School of Pharmacy,
Anurag Group of Institutions,
Venkatapur (V), Ghatkesar (M),
Medchal, Telangana, India

Formulation development and evaluation of fast dissolving tablets of Diltiazem HCL

Rajeshwar V and Vasudha Bakshi

Abstract
The purpose of present study was to formulate the Fast Dissolving tablets of Diltiazem Hcl tablets to achieve faster disintegration in the oral cavity without water. To achieve this goal attempts were made to enhance dissolution rate along with faster disintegration using superdisintegrants like croscarmellose sodium, sodium starc, h glycolate and crospovidone. Diltiazem Hydrochloride is an anti-hypertensive agent was selected as the active pharmaceutical ingredient in the study. The fast dissolving tablets were prepared by direct compression method and evaluated for hardness, thickness, and friability of the tablets. The *in vitro* drug release studies were performed for different formulations and to optimize the best formulae based on the dissolution profiles. Fourier transform infrared spectroscopy studies revealed that there was no interaction between Diltiazem Hydrochloride and excipients.

Keywords: Diltiazem hydrochloride, fast dissolving tablet, Crsopvidone, croscarmellose sodium and FT-IR studies

1. Introduction
The oral route is considered most frequent, natural, preferred, uncomplicated, convenient, more flexible, safe due to its ease of administration, patient acceptance, flexibility in formulation, and cost effective manufacturing process. The most of the therapeutic agents are, generally effectual when the release is at a fairly constant rate or near the absorption sites. The absorption of drug produced results in required plasma concentrations leading to reduce side effects and optimum efficacy. Many patient groups, such as the elderly, children, mentally retarded, uncooperative or nauseated, have difficulty in swallowing conventional dosage forms, like tablets. Swallowing conventional tablets will be further hindered by conditions such as unavailability of water, allergic reactions and episodes of coughing [1]. These problems can be solved by developing rapidly disintegrating and dissolving tablet dosage forms for oral administration, because they dissolve in saliva and does not require water for swallowing. Upon ingestion, the saliva serves to rapidly dissolve the dosage form. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and oesophagus, as the saliva passes down in to the stomach. In these cases, the bioavailability of drugs is significantly greater than those observed from conventional dosage forms [2]. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to Pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets [3]. A wide range of drugs requiring quick onset of action are the promising candidates for this dosage form. These include neuroleptics, antidepressants [4], cardiovascular drugs, analgesics and so on.
Fast dissolving tablets (FDTs) can be prepared by different methods, such as direct compression, freeze-drying, spray drying, sublimation, wet granulation method. The basic approach for the development of FDTs is the use of superdisintegrants [5-8].

2. Materials and Methods
2.1 Materials Used
Diltiazem Hydrochloride was obtained as gift sample from Pharmatrain, Hyderabad. Croscarmellose sodium, crospovidone and sodium starch glycolate were obtained from SD Fine Chemicals, Mumbai, All other chemicals and reagents used were of high analytical grade.

2.2 Methods Used
Tablet manufacturing by direct compression has increased steadily over the years. It offers advantages over the other manufacturing processes for tablets, such as wet granulation and provides high efficiency, Direct Compression method is used for tablet preparation Each tablet containing 50 mg of Diltiazem Hydrochloride. The superdisintegrants were used in different proportions and in different combinations. All the ingredients were weighed accordingly specified in the formulation and mixed well except magnesium Stearate. Then the blend was passed through sieve no 60 which was used for the evaluation of flow properties. To the mixed blend of powder and excipients finally add magnesium stearate and then mixed for 5 min. The mixed blend was compressed with Eight station tablet punching machine using 7 mm flat punches with break line. Four punches in the sixteen station compressor are fixed with die cavity and remaining is fixed with dummy punches.

2.3 Evaluation of Pre-Compressional Parameters [9].
2.3.1 Bulk density; Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder was determined.
Bulk density = M / V_b

2.3.2 Tapped density: The measuring cylinder containing a known mass of powder blend was tapped for a fixed number of times as per USP apparatus-11. The minimum volume occupied by the powder after tapping was measured.
Tapped density = weight/tapped volume

2.3.3 Compressibility index: Compressibility index is calculated as follows
Compressibility Index = Tapped density- Bulk density/ Tapped density*100
The value below 15% indicates a powder with good flow characteristics where as above 25% indicates poor flowability.

2.3.4 Haussner's ratio: It is an indirect index of ease of powder flow, it is calculated as follows.

Haussner's Ratio = Tapped density / Bulk density

2.3.5 Angle of Repose: Angle of repose was determined using funnel method. The blend was poured through funnel that can rise vertically until a maximum cone height (h) was obtained. Radius of the heap(r) was measured and angle of repose was calculated as follows.

$Ø = \tan^{-1} h/r \tan^{-1} h/r$

2.4 Evaluation of Post-Compressional Parameters [10, 11].
2.4.1 Weight variation: Twenty tablets from each formulation were selected randomly and average weight was determined. Individual tablets were then weighed and compared with average weight.

2.4.2 Hardness test: The force required to break a tablet in a diametric compression was determined by using Pfizer tablet hardness tester.

2.4.3 Friability: The weight of twenty tablets was noted and placed in the friabilator and then subjected to100 revolutions at 25 rpm. Tablets were dedusted using a soft muslin cloth and reweighed.

Percent friability = [initial weight – final weight / initial weight] × 100

2.5 Wetting time and Water absorption ratio
A piece of paper folded twice was kept in a petri dish (internal diameter 6cms) containing 6ml of purified water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was weighed. Water absorption ratio, R was determined using the following equation.

R = [Wa – Wb / Wb] × 100

where Wa, Wb are the weights of tablets before and after wetting.

2.5.1 *In vitro* dispersion time: Tablet was added to 10ml of distilled water at 37± 0.5˚C, time required for complete dispersion of tablet was measured.

2.5.2 Drug content uniformity: The drug content uniformity was determined by taking the powder equivalent to 10mg, then it was (n=3) dissolved in P^H6.8 phosphate. Required dilution (10µg/ml) was prepared and absorbance was taken against the blank at 206nm.

2.5.3 *In vitro* disintegration time: The disintegration was performed using an I.P 85 disintegration apparatus with distilled water at 37±0.5 ˚C.

2.6 Dissolution studies
Dissolution rate of Diltiazem HCl from all formulations was performed using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with paddle. The dissolution fluid was 900 ml of P^H6.8 phosphate buffer with a speed of 50 rpm and temperature of 37±0.5˚C were used in each test. 5 ml of sample was withdrawn at different time intervals (2.5, 5, 10, 15 & 20 mins) and fresh medium was replaced to maintain sink conditions. The samples are analyzed by using UV-Visible spectrophotometer at λ_{max} 205 nm. Dissolution studies were performed in triplicate.

3. Results and discussion
3.1 Results

Table 1: Formulation of oral disintegrating tablets of Diltiazem HCl

Ingredients (mg per tablet)	CCS1	CCS2	CCS3	SSG1	SSG2	SSG3	CP1	CP2	CP3
Diltiazem HCl	50	50	50	50	50	50	50	50	50
Lactose Anhydrous	80	80	80	80	80	80	80	80	80
CrosCarmellose Sodium	4.5	9	12	---	---	---	---	---	---
Sodium Starch Glycollate	---	---	---	4.5	6	12	---	---	---
Crospovidone	---	---	---	---	----	---	4.5	6	12
Sodium Sacharin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Orange flover	1	1	1	1	1	1	1	1	1
Aerosil	3	3	3	3	3	3	3	3	3
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight	200	200	200	200	200	200	200	200	200

Table 2: Evaluation of flow properties of the blend

Formulations	Bulk Density (g/cc)	Tapped Density(g/cc)	Hausner ratio	Compressibility index (%)	Angle of repose	Bulk Density (g/cc)
CCS1	0.464	0.574	1.23	19.1	29.47	0.464
CCS2	0.423	0.501	1.16	15.5	27.63	0.423
CCS3	0.456	0.542	1.22	15.8	25.54	0.456
SSG1	0.467	0.559	1.25	16.4	26.23	0.467
SSG2	0.485	0.593	1.10	18.2	27.21	0.485
SSG3	0.460	0.556	1.21	17.2	30.38	0.460
CP1	0.478	0.575	1.24	16.8	28.46	0.478
CP2	0.450	0.554	1.28	18.7	25.71	0.450
CP3	0.442	0.537	1.27	17.6	31.82	0.442

Table 3: Quality control tests for the Fast Dissolving tablets of Diltiazem Hcl

Formulations*	Avarage Weight*	Hardness* Kg/cm^2	Friability* (%)	Wetting time*	Water Absorption Ratio*
CCS1	149±0.12	3.6±0.11	0.25±0.16	15±0.23	39±0.14
CCS2	150±0.21	3.6±0.24	0.23±0.17	12±0.47	28±0.15
CCS3	151.3±1.8	3.5±0.49	0.26±0.17	10±0.35	34±0.24
SSG1	149.5±0.25	3.9±0.11	0.24±0.16	19±0.32	38±0.16
SSG2	148.9±0.54	3.8±0.14	0.28±0.19	16±0.49	40±0.14
SSG3	150±0.01	3.9±0.17	0.32±0.24	14±0.28	38±0.18
CP1	149±0.19	3.9±0.21	0.27±0.21	25±0.16	42±0.19
CP2	148±0.71	3.7±0.15	0.29±0.27	20±0.25	44±0.28
CP3	150±0.76	3.7±0.17	0.24±0.15	17±0.51	47±0.14

* Data represent mean ±SD (n=3)

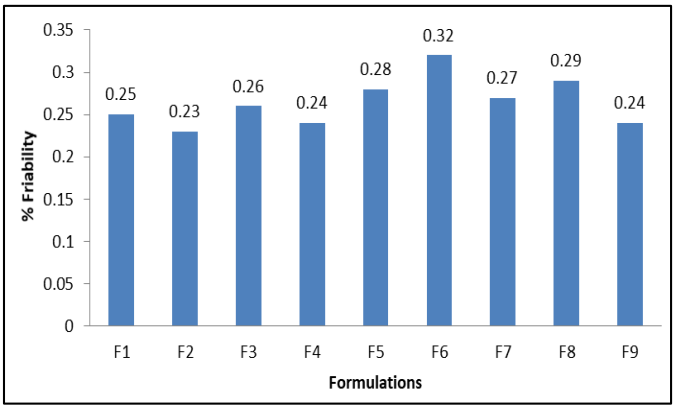

Fig 1: Bar graph comparison friability for all formulations

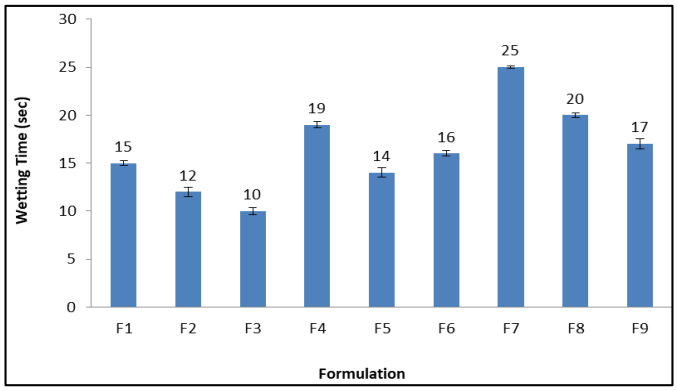

Fig 2: Bar graph comparison between wetting time for all formulations

Table 4: Quality control tests for the Fast Dissolving tablets of Diltiazem HCL

Formulations*	Disintegration time * (sec)	Drug content* (%)	Percentage Drug Dissolved After 10 min*.	*In vitro* Dispersion time* (s)
CCS1	19±0.54	102.21±0.73	89.24±0.42	17±0.79
CCS2	16±0.63	98.97±0.12	91.21±0.31	15±0.82
CCS3	12±0.48	99.58±0.53	97.24±0.86	11±0.64
SSG1	28±0.57	97.25±0.62	87.24±0.68	23±0.63
SSG2	23±0.72	98.21±0.54	91.25±0.45	19±0.71
SSG3	18±0.41	98.56±0.41	91.35±0.76	16±0.92
CP1	34±0.68	94.95±0.25	84.91±0.13	28±0.87
CP2	26±0.43	96.78±0.61	88.24±0.95	21±0.83
CP3	22±0.60	98.8±0.32	95.42±0.42	19±0.75

* Data represent mean ±SD (n=3)

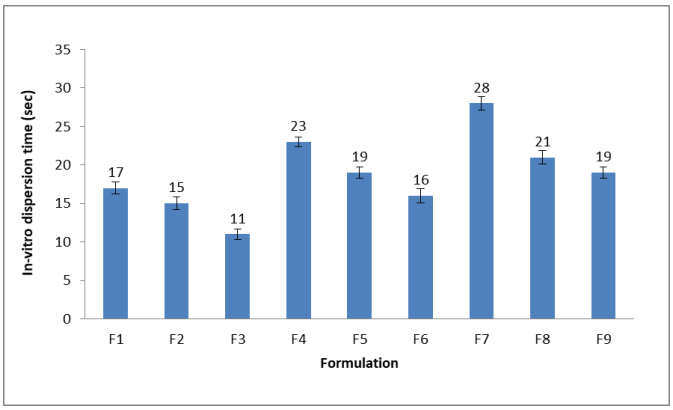

Fig 3: Bar graph comparison between In-vitro dispersion time for all formulations

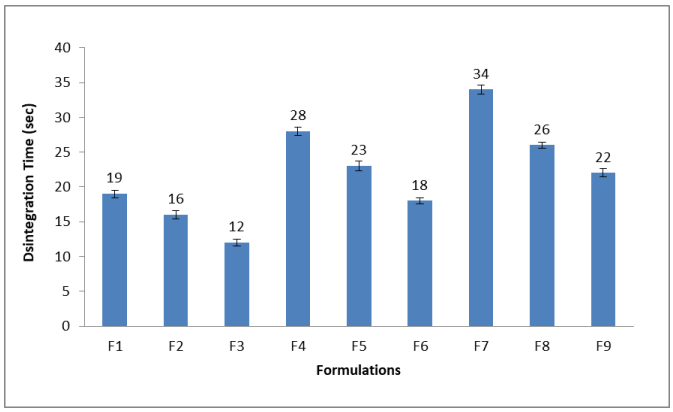

Fig 4: Bar graph comparison between Disintegration time for formulations

Table 5: Dissolution profile of the Fast Dissolving tablets of Diltiazem HCl with Croscarmellose Sodium

Formulations	0	2.5	5	10	15	20
CCS1	0	37.6±0.26	60.24±0.35	79.25±0.92	91.25±0.24	98.47±0.31
CCS2	0	41.25±0.12	62.25±0.95	81.54±0.7	89.350.89	97.28±0.71
CCS3	0	50.24±0.21	71.26±0.31	85.45±0.12	91.78±0.21	99.12±0.11
SSG1	0	44.2±3.16	59.21±0.24	78.4±0.12	89.9±0.1	95.24±0.21
SSG2	0	43.21±0.14	60.21±0.1	75.26±0.21	88.7±0.31	96.25±0.14
SSG3	0	43.8±2.3	69.35±0.35	78.98±0.26	91.36±0.32	94.27±0.12
CP1	0	39.8±1.26	67.2±0.54	79.28±0.11	90.4±0.12	93.14±0.78
CP2	0	41.6±0.51	68.5±0.32	75.9±0.64	88.6±0.85	95.7±0.74
CP3	0	43.7±2.5	60.35±0.12	75.44±0.46	88.69±1.3	97.25±0.2

* Data represent mean ±SD (n=3)

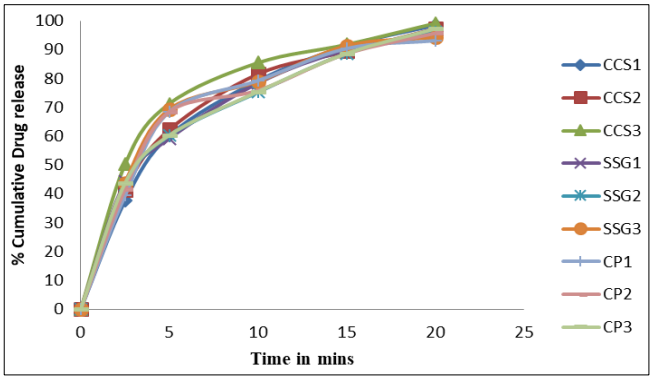

Fig 5: Comparison of dissolution profiles of Diltiazem HCl with all superdisintegrants

4. Discussion

All the formulations prepared by direct compression method showed the angle of repose less than 34, which reveals good flow property. The bulk density and tapped density for all formulation (F1 – F9) varied from 0.442 - 0.485 gm/cm^3 and 0.501 - 0.593 gm/cm^3 respectively. The results of Carr's consolidate index or % compressibility index and Hausner's ratio for the entire formulation (F1 – F9) blend range from 15.5- 19.1 and 1.10-1.28 respectively, shows fair flow properties.

All the tablets show similar color, odour, taste and physical appearance. There is no impact of superdisintegrants in their organoleptic properties. By using the superdisintegrants, the hardness values ranged from 3.5±0.49 kg/cm^2 - 3.9±0.21 kg/cm^2 for formulations. The entire tablet passes weight variation test, as the average % weight variation was within the Pharmacopoeial limit - 7.5%. It was found to be 198±0.63 mg - 203±0.90 mg. The weight of all the tablets was found to be uniform with less deviation. The friability values were found to be within the limit (0.5 - 1%). The above evaluation parameter showed no significant difference between F1-F9 formulations. The experiment mimics the action of saliva in contact with the tablet to illustrate the water uptake and subsequent wetting of tablet. This shows the wetting process was very rapid in almost all formulations. This may be due to the ability of swelling followed by breaking and also capacity of water absorption and causes swelling.

By using superdisintegrants wetting time was found to be in the range of 10±0.35 - 25±0.16 sec. It shows crospovidone formulations take less wetting time comparing with that of crosscaramellose, sodium starch glycollate formulations. Water absorption ratio is important criteria for understanding the capacity of disintegrants. Tablet absorbs the water and loses its integrity. By using superdisintegrants water absorption ratio was found to be in the range of 34±0.24 - 47±0.14. The *in vitro* dispersion time is measured by time taken to uniform dispersion. By superdisintegrants *in vitro* dispersion time was found to be in the range of 11±0.64 - 28±0.87 sec. The result showed that and comparative profile. Disintegration test carried out in modified dissolution apparatus, Results shows the formulations with 3%, 5%, 7.5% of SSG having high disintegrating time as 34, 26, 22 sec. The disintegration time of CCS1, CCS2, CCS3 with 3%, 5%, 7.5% CP formulations is 19, 16, 12 sec respectively and is almost better than F4, F5, F6, F7, F8, F9 formulations and comparative profile. The concentration of the drug in all the formulations with superdisintegants was found to be 96±0.78 – 0102±0.73%. It was within the IP limits. The results of drug content of all batches are shown. Dissolution is carried out in USP apparatus type-2 apparatus at 50rpm in 900ml dissolution media (phosphate buffer pH 6.8) for 10 minutes. At the end of 10 minutes almost total amount of the drug is released (i.e. 96.96±0.54%), from the formulation prepared by the direct compression method with 7.5% croscarmalose sodium.

The FT-IR represents the peaks of the Diltiazem Hcl functional groups. These peaks were not affected, they were prominently observed in IR-spectra of Diltiazem Hcl along with superdisintegrants, simple disintegrants and other excipients. There was no difference in the position of the absorption bands, hence providing evidence for the absence of any chemical incompatibility between pure Drug with the excipients.

5. Conclusion

The above results suggest that the formulated Fast Dissolving tablets of Diltiazem Hcl exhibited good physical parameters and rapidly disintegrating without affecting the release profile and is very effective in case of elderly and pediatric patients. The overall results indicated that formulation with Croscarmallose Sodium (7.5%) had a higher edge compared to other formulations containing superdisintegrants. They satisfy all the criteria for oral disintegrating tablets. This direct compression process is simple, reproducible and robust to prepare Fast Dissolving tablets of Diltiazem Hcl.

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