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FORMULATION AND EVALUATION OF DILTIAZEM HCl FAST DISSOLVING TABLETS USING DIFFERENT CO-PROCESSED EXCIPIENTS BY DIRECT COMPRESSION METHOD

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Keywords:

Fast dissolving tablets, Diltiazem HCl, Co-processed excipients, Direct compression method

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ABSTRACT: The aim of present work was to prepare Diltiazem HCl Fast Dissolving tablets by Direct compression method because of their convenience in administration and suitability for patients having dysphagia using Co-processed excipients-Disintequik MCC25, Disintequik MCC, Lubritose MCC, Lubritose SD, Lubritose AN, NF Fast flow Lactose Monohydrate modified spray dried. The Prepared powdered blend and tablets were evaluated for Pre compression parameters such as Angle of repose, Bulk density, Tapped density, Compressibility index, Hausners ratio and Post compression parameters such as weight variation, thickness, hardness, disintegration time, content uniformity, *in-vitro* dissolution studies and stability studies. All the parameters were within the limits. IR and DSC study showed that drug and excipients were compatible with each other. Twelve formulations were prepared by direct compression method in which F10 was the best formulation using Disintequik MCC25 at a concentration of 4% as it was disintegrated with in 30 sec and drug release was 99.88% over a period of 15 min. The wetting time and disintegration time decreases considerably with the increase in co-processed excipients.

INTRODUCTION: US FDA defined fast dissolving or disintegrating tablets (FDT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Fast disintegrating tablets (FDT) are also known as 'Fast Dissolving', 'Mouth Dissolving', 'Rapid Dissolving', 'Quick Dissolving', 'Orally Disintegrating', 'Rapid melt', Oro Dispersible', 'Porous Tablets'.

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Salient Features of Fast Dissolving Tablets:

- Ease of administration to patients who refuse to swallow tablets such as pediatric, geriatric and psychiatric patients
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have access to water.
- Rapid dissolution and absorption of drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach; in such cases bioavailability of drug is increased.
- Pre-gastric absorption can result in improved bioavailability.

MATERIAL AND METHODS:

Equipment: Bruker Alpha FTIR Spectrophotometer; Shimadzu U.V Spectrophotometer; Tablet Compression machine, USP type II Dissolution apparatus; Mansanto hardness tester, vernier calipers, Sonicator, Roche friabilator.

Chemicals and Reagents: Diltiazem Hydrochloride, pH 6.8 Phosphate buffer, Disintequik MCC25, Disintequik MCC, Lubritose MCC, Lubritose SD, Lubritose AN, NF Fast flo lactose monohydrate modified spray dried, Magnesium stearate as lubricant, Mannitol was used as diluent, Talc as a glidant.

Preparation of Diltiazem HCl fast dissolving tablets: Diltiazem HCl Fast dissolving tablets are prepared for F1 to F12 batches by using different concentration (mentioned in **Table 1**) of co-processed excipients like Disintequik MCC 25, Disintequik MCC, Lactose monohydrate NF spray dried, Lubritose anhydrous AN, Lubritose MCC, Lubritose SD by direct compression method. Keeping total weight (100mg) of tablet constant in all the formulations. All the ingredients are passed through sieve no. 40 to ensure better mixing. All ingredients were mixed in motar and pestle then magnesium stearate and talc were added. The resulting mixture is compressed into tablet and then tablets were evaluated.

TABLE 1: FORMULATION OF 100MG DILTIAZEM HYDROCHLORIDE FAST DISSOLVING TABLETS

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ingredients (taken in mg)												
Diltiazem Hydrochloride	60	60	60	60	60	60	60	60	60	60	60	60
Lubritose MCC	2	4	-	-	-	-	-	-	-	-	-	-
Disintequik MCC	-	-	2	4	-	-	-	-	-	-	-	-
Lubritose AN	-	-	-	-	2	4	-	-	-	-	-	-
Lubritose SD	-	-	-	-	-	-	2	4	-	-	-	-
Disintequik MCC 25	-	-	-	-	-	-	-	-	2	4	-	-
NF Fast Flo Lactose Monohydrate Modified Spray Dried	-	-	-	-	-	-	-	-	-	-	2	4
Mannitol	32	30	35	33	35	33	35	33	32	30	35	33
Magnesium Stearate	3	3	-	-	-	-	-	-	3	3	-	-
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total	100	100	100	100	100	100	100	100	100	100	100	100

Analytical methods:

Preparation of pH 6.8 phosphate buffer: Dissolve 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml.

Preparation of Calibration Curve of Diltiazem HCl in pH 6.8 phosphate buffer: 100mg of Diltiazem HCl was weighed accurately and dissolved in pH 6.8 phosphate buffer, which resulted in 1000 µg/ml. Then from the stock solution 100 µg/ml solution was prepared from this 2, 4, 6, 8, 10 µg/ml were prepared.

The absorbance of the above dilutions were measured using UV-spectrophotometer at 236nm using 6.8 pH phosphate buffer as blank. The conc. of corresponding absorbance was given below table. standard curve was plotted by taking concentration on x-axis and absorbance on y-axis.

Preformulation studies:

Drug-Excipient Compatibility study (FTIR): The study was designed to determine compatibility of drug with different co-processed excipients. Completely dried KBR and samples (drug and excipients) taken in 9:1 ratio and grinded for proper mixing. Sample was filled into the holes of stainless steel disk and sandwiched in the hydraulic press until pressure reaches 20,000 psi. After few seconds, pressure was released and pellet was collected. Then the pellet was inserted into the sample holder and run for the spectrum. FTIR spectra of pure drug and excipients separately done to determine the compatibility. FTIR spectra of drug and excipients were obtained on alpha-Bruker FTIR (Tokyo, Japan). The spectra were scanned over the wave number range of4000-400 cm^{-1}.

X-Ray Diffraction studies (XRD): X-ray powder diffraction (XRD) is a rapid analytical technique

primarily used for phase identification of a crystalline material and can provide information on unit cell dimensions. The analyzed material is finely ground, homogenized, and average bulk composition is determined.

Differential Scanning Calorimetry: DSC is a thermoanalytical technique carried to know compatability between drug and excipient.

In which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. All the samples were run at a scanning rate of 10 ºC/min from 50-350 ºC.

Evaluation of mixed powder blend of drug and excipients:

Angle of Repose (θ): Angle of repose was determined by the fixed funnel and free standing cone method. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.

Formula: $\tan \theta = (h/r)$

$\theta = \tan^{-1} (h/r)$

Where ' h' is the height of the cone

'r' is the radius of the cone.

Different ranges of flowability in terms of angle of repose was shown in **Table 4**.

Bulk density (g/ml): The bulk density of Precompressional blend was determined by three tap method. Weighed quantity of Precompressional blend was transferred into 100ml graduated cylinder and the cylinder was dropped onto a hard wooden surface 3times from a height of 2.5cm at an interval of 2sec.

Bulk density = weight of the sample/bulk volume of the sample

Tapped density (g/ml): The weighed quantity of dry Precompressional blend was taken in a graduated cylinder and the cylinder was allowed to tap for 100 times onto a hard wooden surface from a height of 2.5cm.

Tapped density = weight of the sample/Tapped volume of the sample

Carr's Index or Compressibility: It is directly related to flow rate, cohesiveness and particle size.

Carr's index = Tapped density-Bulk density/ Tapped density

Hausner's Ratio: It is the ratio of tapped density to bulk density and was related to interparticle friction.

Hausner's ratio = Tapped density/Bulk density.

Porosity (%): Ratio of total volume of void spaces to the bulk volume of material is referred to as porosity. It was calculated by using the formula:

Percentage porosity = 100 [1 – Vt/ Vb]

Where, Vt = true volume of powder

Vb = bulk volume of powder

Evaluation of Tablets:

Weight variation test: To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

Thickness: The thickness of the tablets was determined using a Micrometer screw gauge. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm.

Hardness: It was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured.

Friability: Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability. A sample of preweighed 6 tablets was placed in Roche friabilator which was then operated for 100 revolutions *i.e.* 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1% in weight is generally considered acceptable.

Wetting Time: A piece of tissue paper folded twice containing amaranth powder on the upper surface was placed in a small Petri dish (ID =6.5 cm) containing 6 ml of pH 6.8 Phosphate buffer, a tablet was put on the paper and the time required

for formation of pink color was measured as wetting time. The study was performed in triplicate.

Drug Content Uniformity: Five tablets were weighed and crushed with pestle in a motar. The fine powder was weighed to get a100mg (equivalent to 60mg Diltiazem HCl) and transferred to 250 ml conical flask containing 100 ml of 6.8 pH phosphate buffer stirred for 45 min in an sonicator then the solution was filtered and it was analyzed by UV spectrophotometrically at 236 nm and drug content was determined.

Disintegration Time: Disintegration time is the time required for a tablet to break into granules of specified size (or smaller), under carefully specified test conditions. Six tablets were placed in each of the tubes and run the apparatus using phosphate buffer 6.8 pH which is maintained at 37±2 ºC. The time required for complete passage of tablet fragments through the sieve #10 was considered as the disintegration time of the tablet.

***In-vitro* dissolution Studies:** The release rate of Diltiazem HCl tablets was determined using USP Dissolution type II testing apparatus (paddle type). One tablet was placed in each of the six dissolution flasks containing 900 ml of dissolution medium previously maintained at 37 ± 0.5ºC and at 50 rpm. After completion of each specified time interval, aliquots of 5ml was withdrawn from the dissolution media and the samples were replaced with fresh dissolution medium. After filtration and samples are diluted and absorbance was noted at 236 nm using UV visible spectrophotometer and percentage of drug release was calculated.

RESULTS AND DISCUSSSION:

UV Absorbance Maxima of Diltiazem HCl: Standard calibration curve obeyed Beer`s law in the concentration range of 2-10 µg/ml and the value of regression coefficient was found to be 0.99948 which showed a linear relationship between concentration and absorbance as shown in the **Fig.1**

FTIR Compatibility studies FTIR spectra of Diltiazem HCl alone and with Co-processed excipients Disintequik MCC25, Disintequik MCC, Monohydrate NF spray dried, Lubritose MCC, Lubritose SD, Lubritose AN, Magnesium Stearate, Mannitol, Talc was done. Hence there was No Interaction between Diltazem HCl and Excipients.

XRD: The X- RAY diffraction studies of Diltiazem HCl show a characteristic sharp intensity peak at 2θ values of 10.1˚, 19˚, 22˚, which reflected the crystalline nature of drug. Both the formulations showed diffraction peaks at respective 2θ values of pure Diltiazem HCl although their relative intensities were reduced or there was a slight shift in their peaks, suggesting reduced degree of crystallinity of drug in Optimized formulation.

DSC: Melting point of Diltiazem HCl was found to be 216˚C and optimized formulation melting point was found to be 214˚C.

Concentration	Absorbance
2	0.054
4	0.101
6	0.154
8	0.206
10	0.256

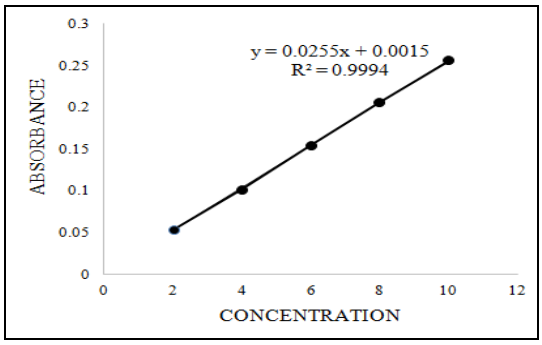


FIG. 1: CONCENTRATION VS ABSORBANCE

Micromeritic Properties of Powder Blend: The powder mixtures of all the batches (F1-F12) were evaluated for Bulk density, Tapped density, Carr's index, Porosity, Hausners ratio, Angle of repose and showed in the **Table 6**. Bulk density ranged from 0.45 to 0.52g/ml, Tapped density ranged from 0.55 to 0.69 g/ml, Angle of repose ranged from 18^0 17' to 20^0 42', Hausners ratio ranged from 1.12 to 1.25 %. All these results indicated that the powder mixture possess Good flow property and compressibility index.

***In vitro* Drug Release Studies:** *In vitro* dissolution studies were performed in pH 6.8 Phosphate buffer. The dissolution results showed gradient increase with the increase in the concentration of the coprocessed excipients. Among all the formulations F10 was found to show best results with 99.88%

release and it is more suitable for Fast dissolving tablets by direct compression technique.

Stability studies: The results of stability was given in **Table 5**. After analysis it was found that there was no substantial changes in all parameter of optimized batch F10. The results revealed the product is stable for the period of one month at 40ºC±2ºC/RH75±5%.

TABLE 2: STABILITY STUDIES OF OPTIMIZED FORMULATION

Study	Storage Condition	Duration
Long term	25±2°C,RH 60±5%	12 months
Intermediate	30±2°C, RH 65±5%	6 months
Accelerated temperature	40±2°C, RH 75±5%	6 months

TABLE 3: LIMITS FOR WEIGHT VARIATION ACC TO IP

Average Tablet Weight (mg)	Percentage Deviation (%)
Up to 80 mg	5
> 80mg,<250 mg	7.5
250mg or more	10

TABLE 4: RELATIONSHIP BETWEEN ANGLE OF REPOSE AND FLOW PROPERTY

Angle of repose (degrees)	Flow property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

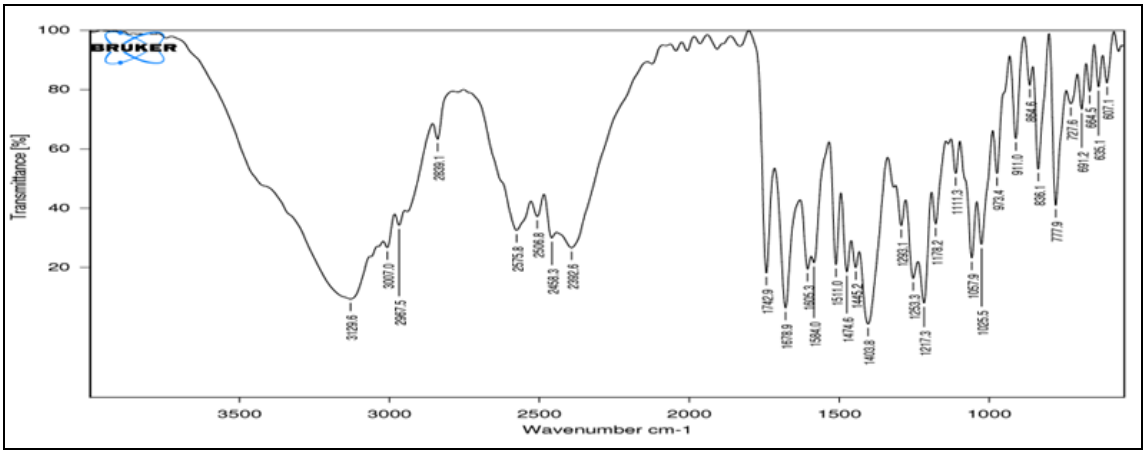


FIG. 2: FTIR SPECTRA OF DILTIAZEM HCl

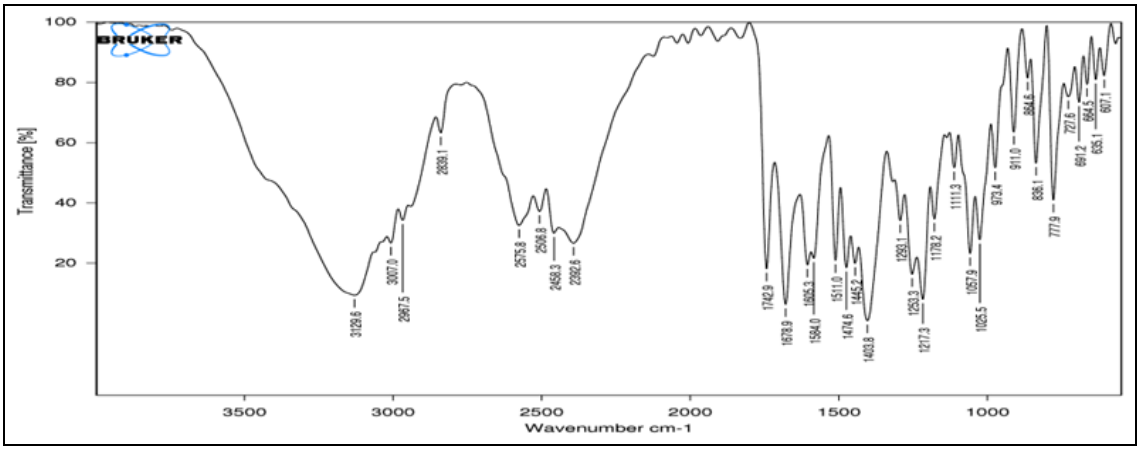


FIG. 3: FTIR SPECTRA OF DISINTEQUIK MCC 25

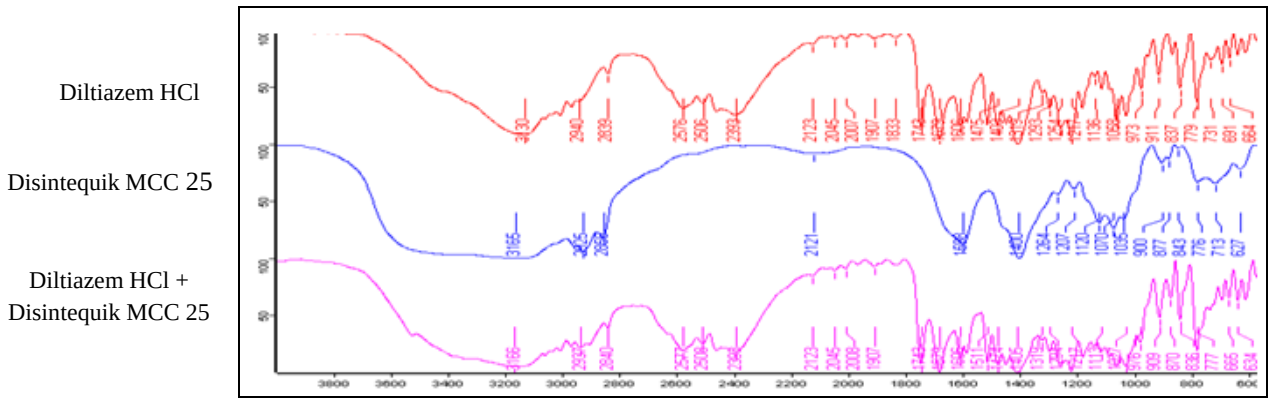


FIG. 4: COMPATIBILITY OF DILTIAZEM HCl AND DISINTEQUIK MCC 25

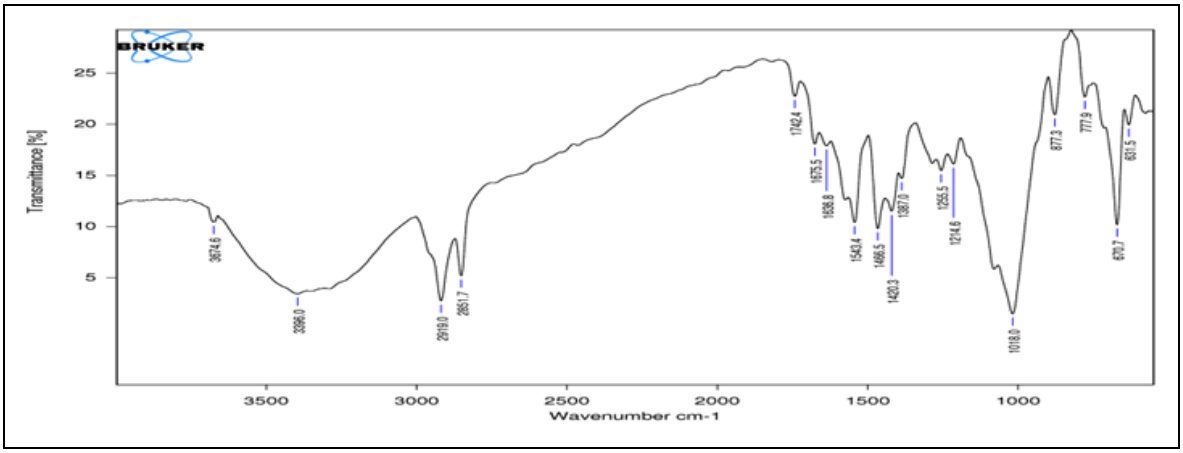


FIG. 5: FTIR SPECTRA OF DILTIAZEM HCl OPTIMIZED FORMULATION

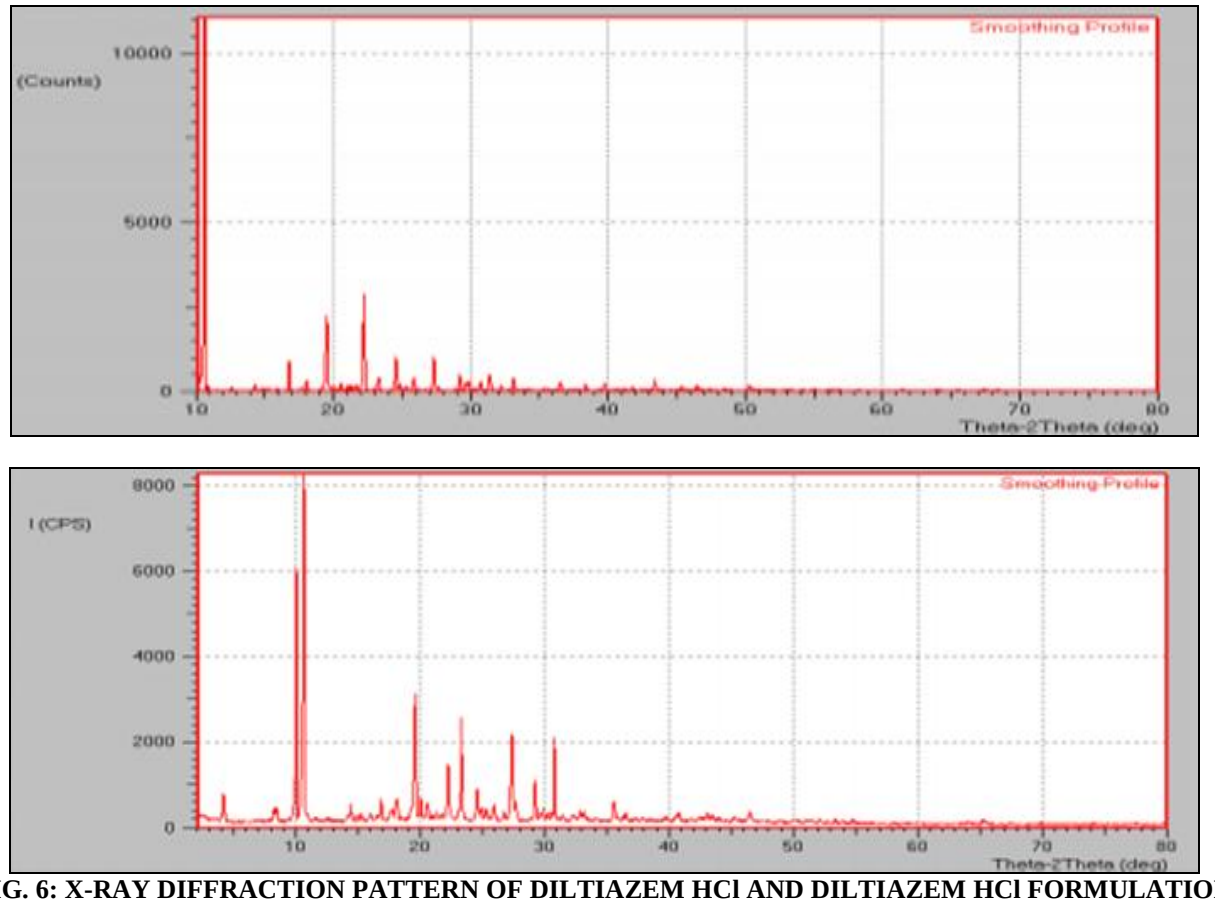
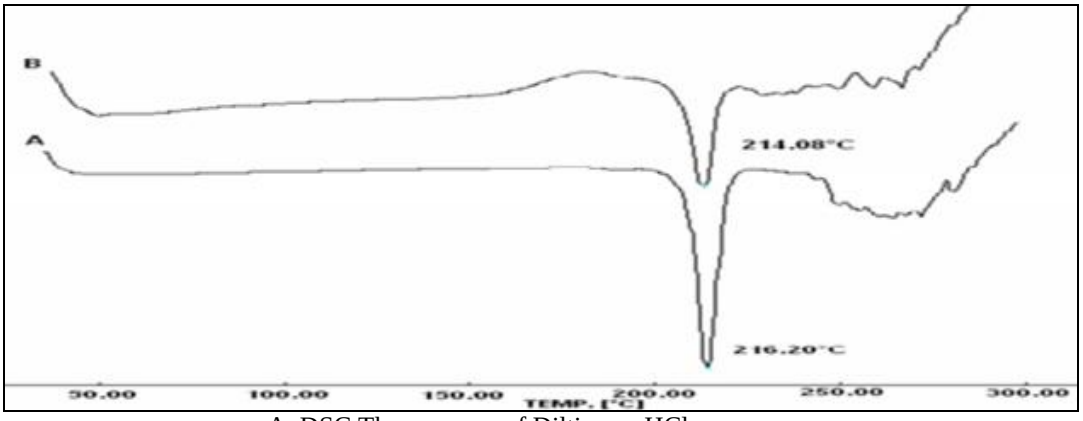


FIG. 6: X-RAY DIFFRACTION PATTERN OF DILTIAZEM HCl AND DILTIAZEM HCl FORMULATION



A. DSC Thermogram of Diltiazem HCl

B. DSC Thermogram of Diltiazem HCl formulation

FIG. 7: DSC THERMOGRAM OF DILTIAZEM HCl AND DILTIAZEM HCl FORMULATION

TABLE 5: CUMULATIVE PERCENTAGE DRUG RELEASE OF DILTIAZEM HYDROCHLORIDE F1 TO F12

Time (min)	Cumulative percentage drug release (%)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
3	48.36± 0.12	55.42± 0.167	40.85± 0.13	41.25± 0.132	42.54± 0.145	50.23± 0.143	46.57± 0.103	51.52± 0.154	56.42± 0.165	41.66± 0.132	60.21± 0.123	66.26± 0.143
6	59.54± 0.166	62.57± 0.145	53.85± 0.143	56.54± 0.154	53.65± 0.142	61.25± 0.148	55.61± 0.99	60.52± 0.153	61.53± 0.17	68.91± 0.143	68.90± 0.135	70.19± 0.138
9	66.65± 0.112	76.24± 0.160	64.52± 0.124	78.18± 0.179	61.54± 0.138	72.40± 0.153	63.24± 0.108	68.70± 0.143	70.82± 0.143	85.48± 0.154	75.17± 0.165	82.83± 0.167
12	72.54± 0.151	82.76± 0.165	75.82± 0.18	94.45± 0.124	78.25± 0.179	84.50± 0.165	79.25± 0.198	74.50± 0.117	84.90± 0.132	96.45± 0.140	73.58± 0.122	88.65± 0.976
15	85.56± 0.166	90.02± 0.160	86.50± 0.172	99.40± 0.154	82.42± 0.154	92.52± 0.124	85.43± 0.132	80.53± 0.122	90.31± 0.154	99.88± 0.165	85.60± 0.182	92.54± 0.108

Values ± SD, n = 3

TABLE 6: EVALUATION PARAMETERS OF PRECOMPRESSIONAL POWDER BLEND

S.no	Formulation Code	Bulk Density (Gm/Ml)	Tapped Density (G/Ml)	Compressibilty Index (%)	Hausner's Ratio	Angle of Repose (°)
1	F1	0.50±0.041	0.63±0.028	20.00±0.65	1.25±0.42	18.17±0.52
2	F2	0.52±0.025	0.55±0.019	15.45±0.54	1.05±0.32	19.24±0.65
3	F3	0.45±0.027	0.62±0.032	18.18±0.43	1.22±0.41	20.42±0.61
4	F4	0.50±0.032	0.62±0.029	19.35±0.62	1.24±0.27	19.17±0.64
5	F5	0.46±0.026	0.55±0.028	16.36±0.8	1.19±0.36	20.24±0.66
6	F6	0.56±0.017	0.69±0.036	18.84±0.45	1.23±0.32	19.18±0.69
7	F7	0.53±0.028	0.59±0.034	12.02±0.32	1.11±0.36	18.24±0.58
8	F8	0.52±0.031	0.62±0.028	16.12±0.43	1.19±0.32	22.26±0.76
9	F9	0.50±0.028	0.62±0.037	19.35±0.65	1.25±0.29	20.34±0.61
10	F10	0.55±0.026	0.55±0.031	11.29±0.21	1.13±0.21	18.36±0.55
11	F11	0.45±0.019	0.56±0.035	19.64±0.62	1.12±0.34	20.36±0.65
12	F12	0.50±0.025	0.60±0.026	16.66±0.59	1.20±0.26	19.85±0.63

Values ± SD, n = 3

TABLE 7: EVALUATION PARAMETERS OF FORMULATED TABLETS

Formulation code / Parameters	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Content Uniformity (%)	Disintegration time(sec)	Wetting time (sec)
F1	3.95±0.18	4.01±0.01	0.12±0.002	99.92±0.02	30±0.52	26 ±0.45
F2	3.91±0.34	4.00±0.02	0.15±0.003	98.3±0.04	28±0.46	24±0.28
F3	3.70±0.28	4.01±0.01	0.14±0.004	99.90±0.01	24±0.42	20±0.42
F4	3.95±0.18	4.05±0.05	0.12±0.002	98.5±0.03	20±0.19	16±0.36
F5	3.71±0.24	4.05±0.05	0.10±0.001	98.9±0.02	30±0.28	26±0.67
F6	3.79±0.17	4.01±0.01	0.14±0.004	99.93±0.02	25±0.38	23±0.29

F7	3.70±0.28	4.00±0.02	0.11±0.001	98.6±0.03	24±0.56	22±0.27
F8	3.91±0.34	4.02±0.01	0.18±0.006	99.95±0.01	22±0.29	20±0.42
F9	3.95±0.18	4.05±0.05	0.12±0.002	99.2±0.03	26±0.57	24±0.48
F10	3.71±0.24	4.01±0.01	0.14±0.004	99.48±0.03	30±0.37	26±0.47
F11	3.79±0.17	4.02±0.01	0.17±0.005	99.67±0.02	26±0.42	22±0.29
F12	3.90±0.34	4.01±0.01	0.18±0.006	99.89±0.01	24±0.29	20±0.54

Values ± SD, n= 3

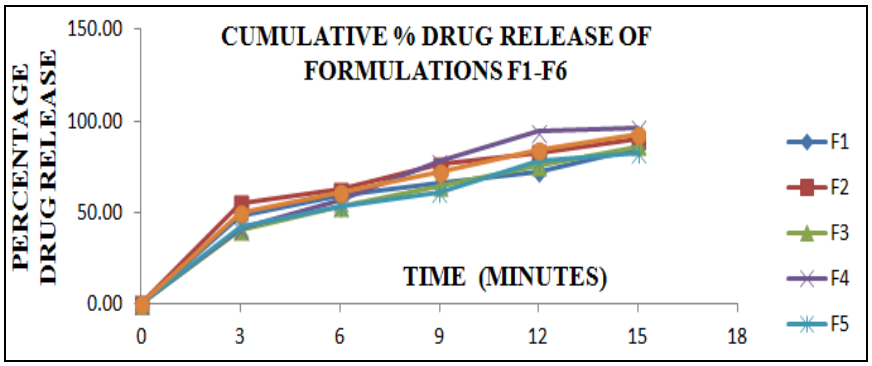


FIG. 8: CUMULATIVE PERCENTAGE DRUG RELEASE PROFILES OF DILTIAZEM HCl FAST DISSOLVING TABLET FORMULATIONS (F1-F6)

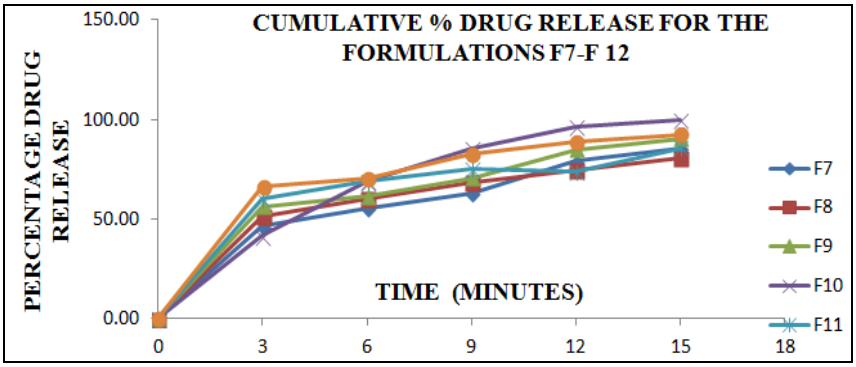


FIG. 9: CUMULATIVE PERCENTAGE DRUG RELEASE PROFILES OF DILTIAZEM HCl FAST DISSOLVING TABLETS FORMULATIONS (F7-F12)

CONCLUSION: Diltiazem HCl Fast Dissolving tablets were prepared by direct compression method using Disintequik MCC25, Disintequik MCC, Lactose monohydrate NF spray dried, Lubritose anhydrous AN, Lubritose MCC, Lubritose SD. The tablets disintegrated rapidly and had acceptable hardness and friability. In-vitro drug release from the tablets shows significantly improved drug dissolution. Hence it could be concluded that the Co-processed excipient based Diltiazem HCl Fast Dissolving tablets would be quite effective in providing quick onset of action without need for water for swallowing or administration.

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