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Development and Evaluation of Orodispersible Tablets of Diltiazem Hydrochloride

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ABSTRACT

The objective of this study was to formulate and evaluate dispersible tablets of diltiazem HCl using direct compression method for enhanced patient compliance. Oro dispersible tablets prepared by using super disintegrants such as croscarmellose sodium, crospovidone, sodium starch glycolate. It was observed that all the formulations were acceptable with reasonable limits of standard required for oro dispersible tablets. It was concluded that dispersible tablets with enhanced dissolution rate can be made using selected super disintegrants.

Keywords: Orally disintegrating tablet, Improved bioavailability, super disintegrants.

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INTRODUCTION

Oro dispersible drug delivery systems are extensively used to improve bioavailability and patient compliance. ODTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. Most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration owing to its several advantages and high patient compliance compared to many other routes. Many patient groups such as the elderly, children and patients who are mentally retarded, un co-operative, nauseated or on reduced liquid-intake/diets have difficulties swallowing these dosage forms.[1-5]

Pharmaceutical technologists have developed a novel oral dosage forms known as oro dispersible tablets which disintegrates rapidly in saliva usually in a matter of seconds without the need to take water.[6-11] Oro dispersible tablets are also called as mouth dissolving tablets, melt-in mouth tablets, fast dissolving tablets, rapimelts, quick dissolving tablets oro dispersible tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperse in the saliva. The faster the drug into solution, the quicker the absorption & onset of clinical effect. Some drugs are absorbed from the mouth, pharynx & esophagus as the saliva passes down into the stomach. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pre-gastric 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 tablet.[12-16]

Diltiazem is an Antianginal; calcium-channel blocker and is widely used in the management of Prinzmetal's variant angina, chronic stable angina, hypertension, atrial fibrillation or flutter. Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. Diltiazem undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. *In vitro* binding studies show diltiazem is 70% to 80% bound to plasma proteins. Single oral doses of 30 to 120 mg of diltiazem tablets result in detectable plasma levels within 30 to 60 minutes and peak plasma levels 2 to 4 hours after drug administration.[17,18]

The aim of the proposed work was to formulate and characterize mouth dissolving tablets of Diltiazem Hydrochloride for rapid dissolution of drug and absorption, which may produce rapid onset of action in the management of hypertension in elderly patients

MATERIALS AND METHOD

Materials:

Diltiazem hydrochloride was obtained as a gift sample from Balaji drugs gujrath, India Crospovidone, sodium starch glycolate, Ac-Di-Sol, and Microcrystalline cellulose were purchased from S.D Fine chemicals. All other chemicals and reagent were of analytical grade.

Preparation:

Various formulations of orally disintegrating tablets were developed for diltiazem HCl By direct compression method by using various super disintegrating agents like crospovidone, crosscarmellose sodium sodium starch glycolate and microcrystalline cellulose was used as a diluents, magnesium stearate was used as a lubricant. Sodium saccharine was used as a sweetening agent along with a flavouring agents. The tablets were compressed by using a flat faced 9 mm punch to get a oro-dispersible tablet.

Table:1 Formulations of Diltiazem hydrochloride containing different superdisintegrants

S.no	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Diltiazem HCl	60	60	60	60	60	60	60	60	60
2	Sodiumstarch glycolate	6	12	18	24	-	-	-	-	-
3	Croscarmellosesodium	-	-	-	-	6	12	18	24	-
4	Crospovidone	-	-	-	-	-	-	-	-	6
5	MCC	128	122	116	110	128	122	116	110	128
6	Magnesium stearate	2	2	2	2	2	2	2	2	2
7	Sodium saccharine	4	4	4	4	4	4	4	4	4

Table:2 Formulations of Diltiazem hydrochloride containing different superdisintegrants

S.no	Ingredients	F10	F11	F12	F13	F14	F15	F16	F17	F18
1	Diltiazem HCl	60	60	60	60	60	60	60	60	60
2	Sodiumstarchglycolate	-	-	-	30	6	-	-	6	30
3	Croscarmellose sodium	-	-	-	6	30	6	30	-	-
4	Crospovidone	12	18	24	-	-	30	6	30	6
5	MCC	122	116	110	98	98	98	98	98	98
6	Magnesium stearate	2	2	2	2	2	2	2	2	2
7	Sodium saccharine	4	4	4	4	4	4	4	4	4

Evaluation of Mouth dissolving tablets:

Thickness

Ten tablets were selected randomly from each batch and thickness was measured by using Verniercalipers.[19,20,21]

Weight Variation

Twenty tablets were selected randomly from the lot and weighed individually to check for weight variation. Weight variation specification as per I.P. is shown in table.[22]

Table 3: Weight variation specification as per I.P. is shown in table

Average Weight of Tablet	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

Hardness

Tablets were selected at randomly from each formulation and hardness was checked by using Monsanto Hardness Tester.[23,24,25]

Friability Test

Pre-weighed sample of 20 tablets were placed in the Roche Friability tester, which was then operated for 100 revolutions. Tablets were dedusted and reweighed; tablets should not lose more than 1% of their initial weight.[26,27,28]

$$W_1\text{-}W_2/\ W1\times100$$

W_1 = Initial weight of tablet

W_2 = Final weight of tablet

***In vitro* Dispersion Time**

Tablet was added to 10 ml of buffer solution (pH 6.8) and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.[29]

Modified Disintegration Test

Many reports suggest that conventional DT apparatus may not give correct values of DT for MDTs. The amount of saliva available in the oral cavity is very limited (usually less than 6 ml) whereas the conventional DT apparatus uses a large amount of water with very rapid up and down movements. FDT is required to disintegrate in such small amount of saliva within a minute without chewing the tablet. In a simplest method to overcome this problem, 6 ml of phosphate buffer of pH 6.8 was taken in a 25 ml measuring cylinder. Temperature was maintained at 37±2°C. A FDT was put into it and time required for complete disintegration of the tablet was noted.[30]

Wetting time

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (6.5 cm internal diameter) containing 6 ml of phosphate buffer pH 6.8. A tablet was carefully placed on the surface of the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was measured as a wetting time.[31]

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish (10 cm diameter) containing 6 ml of phosphate buffer pH 6.8. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then reweighed. Water absorption ratio, R was determined using following equation.[32]

$$R = 100\ (Wa - Wb)/Wb$$

Where, Wa = weight of tablet after absorption &

Wb = weight of tablet before absorption.

Content of active ingredients

The drug content of the oro dispersible tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies with in the range of 95% to 101% of the standard amount Ten tablets were weighed and taken into a mortar and crushed into fine powder an accurately weighed portion of the powder equivalent to about 100mg of diltiazem HCl was transferred to a 100ml volumertric flask containing 50ml of 6.8 pH buffer solution. It was shaken by mechanical means for 1hr. Then the volume was made up to 100ml with 6.8 pH buffer and the mixture has filtered through a whattman filter paper from this resulted solution 1ml was taken, suitably diluted with 6.8pH buffer and absorbance was measured against blank at 236nm .

***In-vitro* dissolution**

In-vitro dissolution study of tablets was performed using USP 24 type II dissolution apparatus($37^0C \pm 0.5^0C$, 900 ml, 50 rpm) in phosphate buffer pH 6.8, and 5 ml Aliquots were taken out after every 2 min and the volume was replaced with 5 ml aliquots of fresh dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer. Cumulative percent drug release was calculated by using an equation obtained from a standard curve.[33]

RESULTS AND DISCUSSION:

Standard graph for Diltiazem HCl:

Standard graph of diltiazem HCl (Figure 1) has shown good linearity with R^2 value 0.999 in pH 6.8 buffer (Figure.1), which suggests that it obeys the "Beer-lambert's law"

Standard graph for Diltiazem HCl

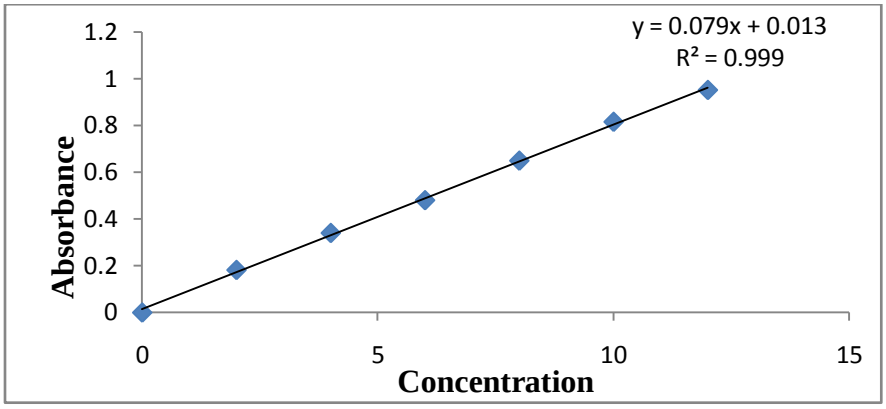

Figure 1 Standard graph for Diltiazem HCl

Table 4: Tablet blend evaluation tests for formulations F_1 to F_{18}

Formulation Code	Angle of Repose Θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio
F1	29.07±0.56	0.49±0.01	0.59±0.01	16.94±0.19	1.20±0.02
F2	27.67±0.35	0.46±0.02	0.58±0.01	20.68±0.44	1.26±0.01
F3	26.32±0.51	0.45±0.01	0.56±0.02	16.64±0.32	1.24±0.01
F4	23.52±0.36	0.44±0.02	0.54±0.01	18.51±0.81	1.22±0.02
F5	28.23±0.54	0.46±0.01	0.57±0.01	19.29±0.27	1.23±0.01
F6	26.93±0.29	0.44±0.01	0.56±0.01	21.42±0.68	1.27±0.01
F7	24.32±0.16	0.42±0.02	0.53±0.02	20.75±0.57	1.26±0.02
F8	21.91±0.40	0.40±0.01	0.52±0.01	23.07±0.73	1.30±0.01
F9	30.12±0.29	0.48±0.03	0.58±0.03	17.24±0.21	1.20±0.01
F10	29.62±0.58	0.47±0.01	0.56±0.02	16.07±0.18	1.19±0.02
F11	28.32±0.56	0.45±0.01	0.54±0.01	16.66±0.16	1.20±0.01
F12	27.29±0.36	0.44±0.01	0.52±0.01	15.38±0.28	1.28±0.01
F13	20.93±0.42	0.44±0.02	0.49±0.01	10.20±0.35	1.11±0.01
F14	20.28±0.39	0.40±0.01	0.51±0.01	21.56±0.45	1.27±0.02
F15	28.39±0.56	0.43±0.01	0.54±0.02	20.37±0.46	1.25±0.01
F16	26.32±0.28	0.42±0.01	0.51±0.01	17.64±0.32	1.21±0.01
F17	21.23±0.45	0.39±0.01	0.52±0.01	25.12±0.63	1.33±0.02
F18	25.32±0.31	0.43±0.02	0.55±0.02	21.81±0.47	1.31±0.01

Evaluation Blend:

Physical properties such as bulk density, tapped density, percent compressibility index, Hausner ratio, angle of repose were determined (Table 4) for the prepared tablet blend. For the tablet batches in which microcrystalline cellulose was used as diluents, the angle of repose was between 30º to 35 º,this indicated the passable flowability. This property may be attributed due to the presence of microcrystalline cellulose having filamentous particles as diluents. The tablet blend batches in which microcrystalline cellulose was used, angle of repose values were found to be 20º to 30º ,this indicated good flow properties of the tablet blend. This property may be attributed due to the spherical shape of the particles. The percent compressibility index and Hausner ratio were within the limits.

Table 5: Evaluation tests for Diltiazem HCl oral disintegration tablets

Formulation code	Thickness (mm)	Weight variation(mg)	Hardness ($kg/cm^{2)}$	Friability (%)	Disintegration time(sec)
F1	3.33±0.12	202.66±2.07	3.6±016	0.249±0.01	13.83±0.01
F2	3.46±0.04	199.33±1.52	3.3±0.09	0.277±0.03	13.79±0.13
F3	3.40±0.08	202.66±3.50	3.6±0.09	0.248±0.01	13.86±0.18
F4	3.46±0.04	200.66±1.52	3.6±0.16	0.343±0.07	12.08±0.14
F5	3.33±0.09	200.32±1.58	3.8±0.16	0.276±0.02	35.66±0.24
F6	3.43±0.12	201.33±2.15	3.2±0.21	0.252±0.01	30.02±0.63
F7	3.46±0.04	200.33±2.51	3.4±0.16	0.273±0.01	23.32±0.93
F8	3.43±0.09	199.33±1.52	3.0±0.27	0.315±0.01	20.31±0.82
F9	3.40±0.08	200.70±1.45	3.2±0.16	0.358±0.03	62.33±0.24
F10	3.43±0.09	201.25±1.92	3.0±0.16	0.413±0.04	51.33±0.49
F11	3.33±0.12	201.65±1.71	3.5±0.86	0.342±0.06	42.33±0.86
F12	3.46±0.04	200.30±1.87	3.6±0.87	0.267±0.01	56.33±0.05
F13	3.40±0.08	200.35±2.03	3.5±0.47	0.437±0.04	10.01±0.02
F14	3.33±0.09	200.85±2.05	3.4±0.83	0.324±0.02	12.08±0.14
F15	3.44±0.10	201.45±2.43	3.5±0.84	0.301±0.02	12.14±0.12
F16	3.20±0.08	201.90±2.70	3.4±0.41	0.253±0.01	13.79±0.13
F17	3.37±0.11	202.45±2.45	3.5±0.50	0.247±0.01	23.33±0.94
F18	3.43±0.09	202.66±2.07	3.5±0.65	0.367±0.02	20.31±0.82

Table 6: Evaluation tests for diltiazem HCl oral disintegration tablets

Formulation Code	Wetting time(sec)	Water absorption ratio	Content of active ingredients
F1	26.66±0.24	84.64±0.34	98.85±0.19
F2	25.66±0.05	92.04±0.53	99.56±0.17
F3	27.66±0.24	99.34±0.99	99.51±0.13
F4	19.33±0.05	97.68±0.03	100.48±0.32
F5	34.33±1.41	84.64±0.34	98.76±0.06
F6	26.62±0.06	82.64±0.21	99.54±0.35
F7	21.11±0.52	83.75±0.20	99.73±0.02
F8	19.32±0.02	88.80±0.15	100.15±0.33
F9	54.40±0.79	72.80±0.35	98.14±0.12
F10	48.81±0.10	75.43±0.60	99.02±0.19
F11	44.41±0.01	79.50±0.32	98.91±0.15
F12	53.21±0.72	84.64±0.21	99.86±0.18
F13	20.40±0.15	99.34±1.99	99.92±0.22
F14	25.66±0.05	92.04±2.53	98.92±0.19
F15	29.4±0.48	88.80±0.15	100.34±0.20
F16	29.1±0.05	83.75±0.20	99.77±0.83
F17	34.7±0.45	84.64±0.34	98.85±0.28
F18	35.0±0.35	82.64±0.21	97.72±0.32

Average of three determination ± standard deviation

Water absorption ratio of diltiazem HCl oral disintegrating tablets containing various disintegrants (F1-F18)

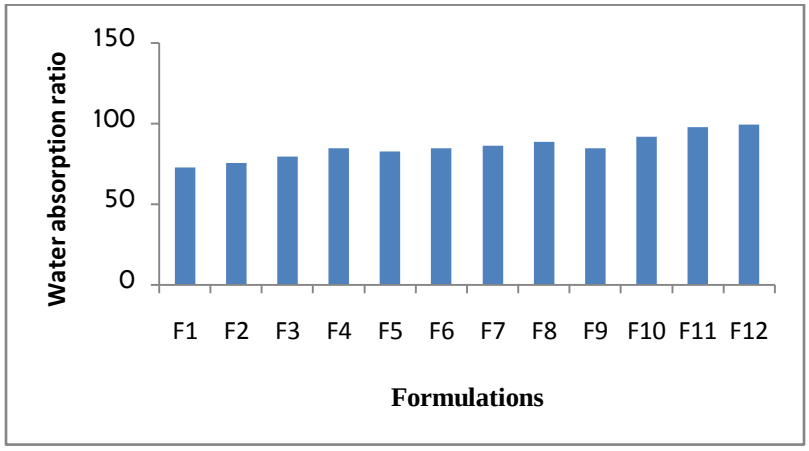

Figure: 2 Water absorption ratio of diltiazem HCl oral disintegrating tablets containing various disintegrants (F1 to F12)

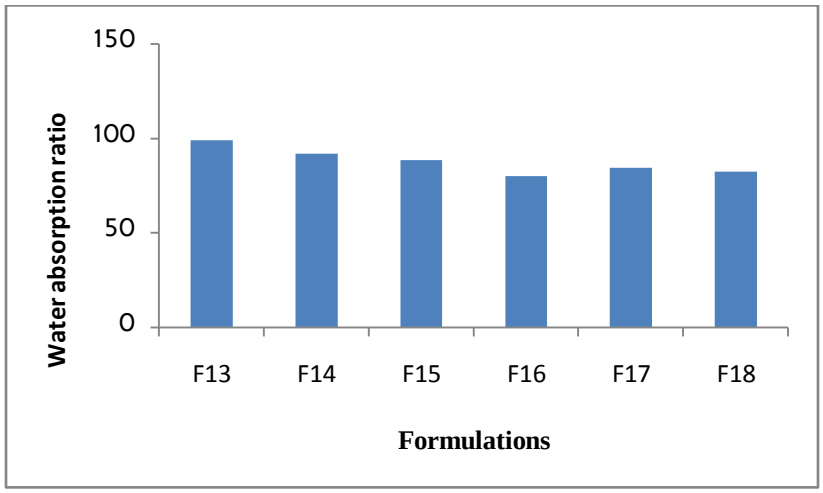

Figure: 3 Water absorption ratio of diltiazem HCl oral disintegrating tablets containing various disintegrants (F13 to F18)

Evaluation tests for Diltiazem HCl ODT's.

The diltiazem HCl orally disintegrating tablets were evaluated for hardness, friability, thickness, weight variation and content uniformity for all batches and the results (Table 5 & 6) were found to be within the acceptable limits.

All the formulations were found to pass the weight variation test. Content of diltiazem HCl from all the formulations was found to be in the range of 97% to 100%. The hardness was constantly maintained between 3-4 kg/cm^2 during compression. Friability for all the formulations was less than 0.5% which is in the acceptable limits indicated that formulations have good mechanical strength.

The *In-vitro* disintegration test was carried out for all prepared formulations. Tablet disintegration was effected by the wicking and swelling nature of the disintegrants. From the results the formulations in which crospovidone was present showed less disintegration time when compared with other superdisintegrants because it has excellent wicking nature, crospovidone finer particle size distribution improves mixing and minimizes changes in swelling properties on the tablet surface resulting from atmospheric humidity, so it swells only to a very less extent.

The mechanism involved in cross carmellose sodium & sodium starch glycolate is when it comes in contact with water it swells to a large extent to disintegrate the tablet. also it has fibrous nature that allows intra-particulate as well as extra particulate wicking of water at low concentration levels. The probable reason for delayed disintegration time of cross carmellose sodium & sodium starch glycolate might be due to their tendency to gel more than crospovidone.

***In vitro* Release profile of Diltiazem hydrochloride tablets containing Sodium starch glycolate**

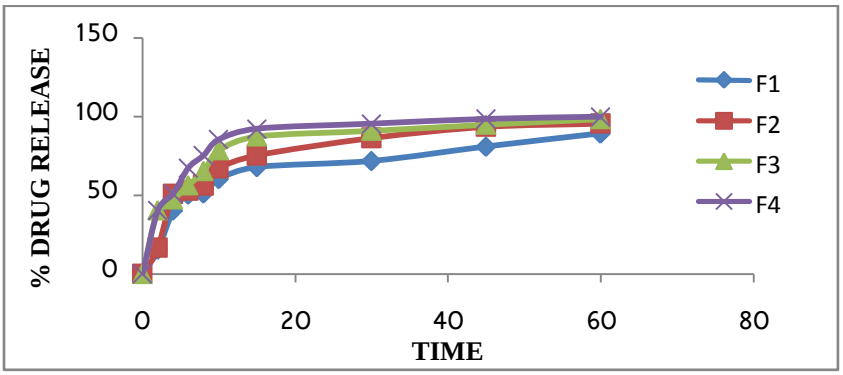

Figure 4*: In vitro* Release profile of Diltiazem hydrochloride tablets containing Sodium starch glycolate

***In vitro* Release profile of Diltiazem hydrochloride tablets containing Crosscarmellose sodium**

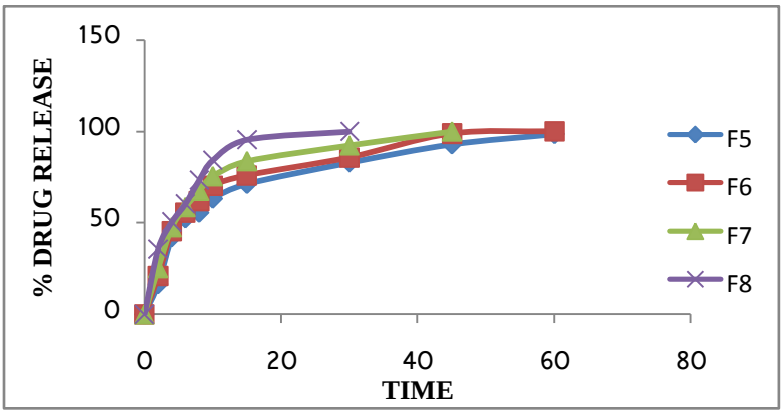

Figure 5: *In vitro* Release profile of Diltiazem hydrochloride tablets containing Crosscarmellose sodium

In vitro **Release profile of Diltiazem hydrochloride containing crospovidone**

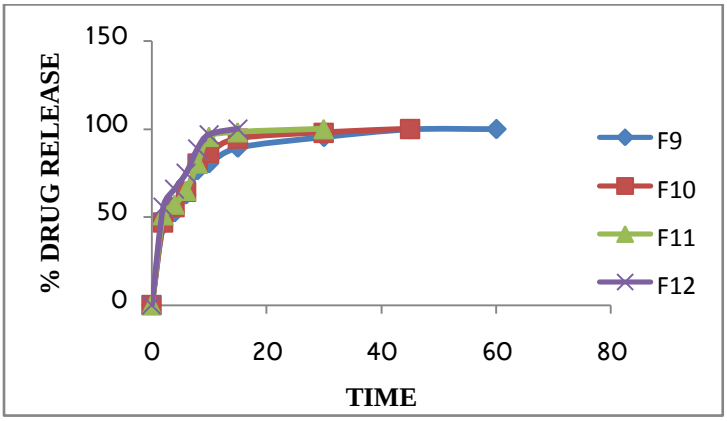

Figure 6: *In vitro* Release profile of Diltiazem hydrochloride containing Crospovidone

In vitro **Release profile of Diltiazem hydrochloride containing crospovidone and crosscarmillose**

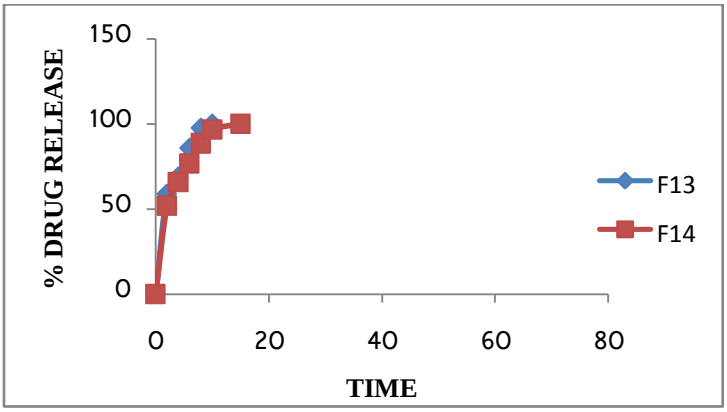

Figure 7: *In vitro* Release profile of Diltiazem hydrochloride containing crospovidone and crosscarmillose

In vitro **Release profile of Diltiazem hydrochloride containing crospovidone & sodium starch glycolate**

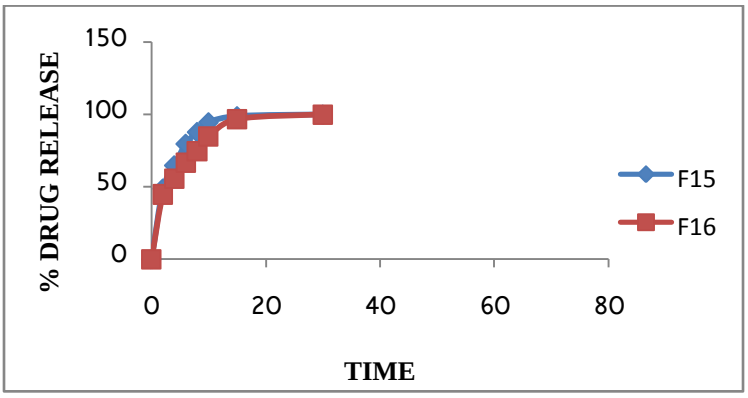

Figure 8: *In vitro* Release profile of Diltiazem hydrochloride containing crospovidone and sodium starch glycolate

***In vitro* Release profile of Diltiazem hydrochloride containing Crosscarmellose and sodium starch glycolate**

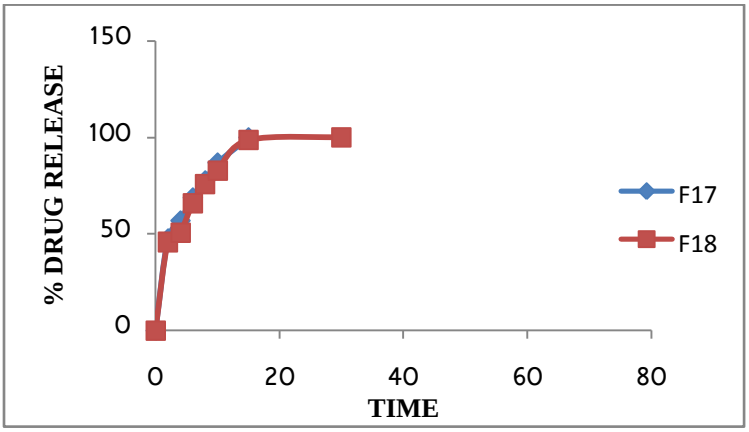

Figure 9: *In vitro* Release profile of Diltiazem hydrochloride containing Crosscarmellose and sodium starch glycolate

***In-vitro* drug release studies of diltiazem HCl oral disintegrating tablets containing different concentrations of super disintegrants are as follows.**

The maximum percent drug release for the formulations F1,F2,F3&F4 in which sodium starch glycolate was used were, at 60mins (89.37±0.41), (95.58±0.50), (98.60±0.44) and 100% respectively. By increasing the concentration of sodium starch glycolate, the drug release was increased.

The maximum percent drug release for the formulations F5 and F6 in which crosscarmellose sodium was used were, at 60mins (98.55±0.21) and 100% where as in formulation F7 and F8 maximum % drug release (100%) was observed as 45min and 30min respectively. By increasing the concentration of crosscarmellose, the drug release was increased.

The maximum percent drug release 100% for the formulations F9,F10,F11&F12 in which crospovidone sodium was used were, at 60mins, 45mins, 30mins and 15min respectively. By increasing the concentration of crospovidone, the drug release was increased.

The maximum percent drug release time for the formulations F13 and F14 in which combination of two different super disintegrations like crospovidone and crosscarmellose sodium was used were, at 10mins (100±0.22) and 15mins (100±0.42) respectively. By increasing the concentration of crospovidone, the drug release was increased.

The maximum drug release time for the formulations F15 and F16 in which combination of two different super disintegrations like crospovidone and sodium starch glycolate was used were, at 30mins (100±0.76) and 30mins(100±0.72) respectively. By increasing the concentration of crospovidone, the drug release was increased.

The maximum drug release time for the formulations F17 and F18 in which combination of two different super disintegrations like crosscarmellose sodium and sodium starch glycolate was used were, at 15mins (100±0.52) and 30mins (100±0.51) respectively. By increasing the concentration of crosscarmellose sodium, the drug release was increased.

The F13 formulation was considered as optimized formulation based on the *in-vitro* dissolution studies. Maximum percentage of drug release (100%), was observed at the end of 8mins.

From the FTIR studies for drug – excipients Compatability, it was observed that no physical incompatibility existed between the drug and excipients.

Table:7 Kinetics data:

Formulation code	First order kinetics	
	R^2	K_1
F1	0.1407	0.032
F2	0.3101	0.040
F3	0.9374	0.040
F4	0.8890	0.070
F5	0.2715	0.040
F6	0.8935	0.130
F7	0.8620	0.176
F8	0.9615	0.306
F9	0.9739	0.143
F10	0.9426	0.183
F11	0.9861	0.312
F12	0.8488	0.564
F13	0.7708	0.791
F14	0.8532	0.566
F15	0.9980	0.309
F16	0.9679	0.306
F17	0.7426	0.534
F18	0.9728	0.313

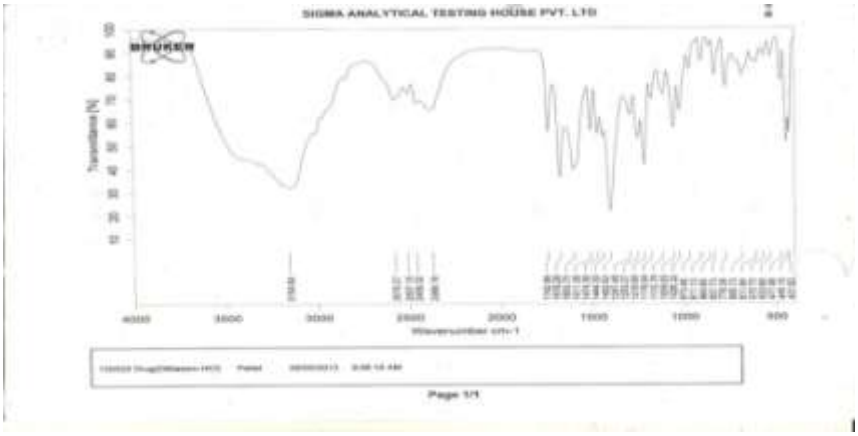

Figure 10: FTIR studies of Diltiazem HCl (Pure drug)

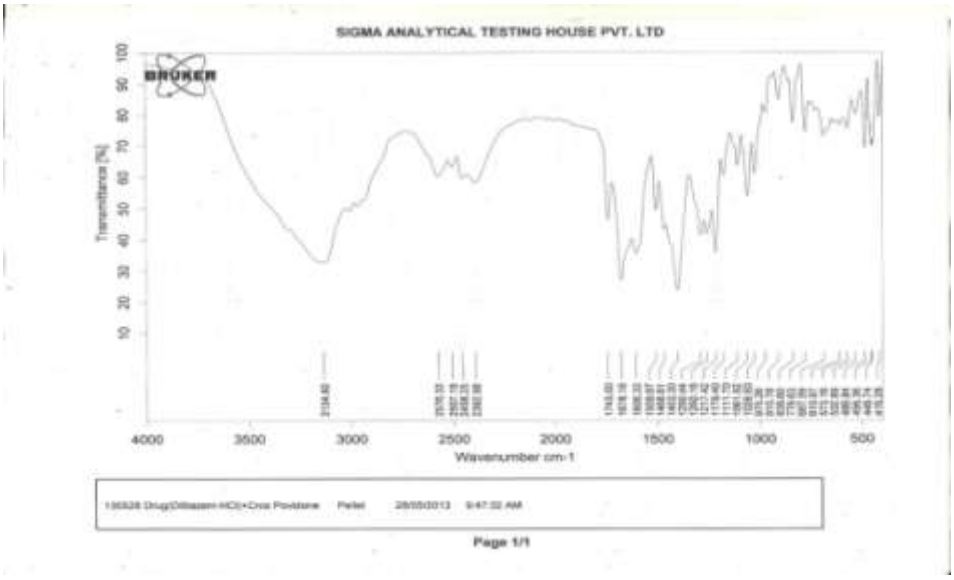

Figure 11: FTIR studies of diltiazem HCl and crospovidone

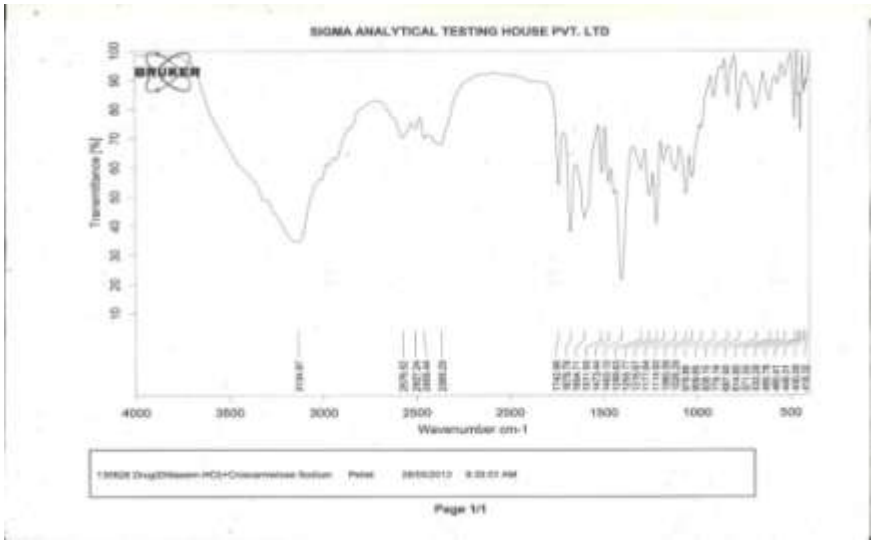

Figure 12: FTIR studies of diltiazem HCl and croscarmellose sodium

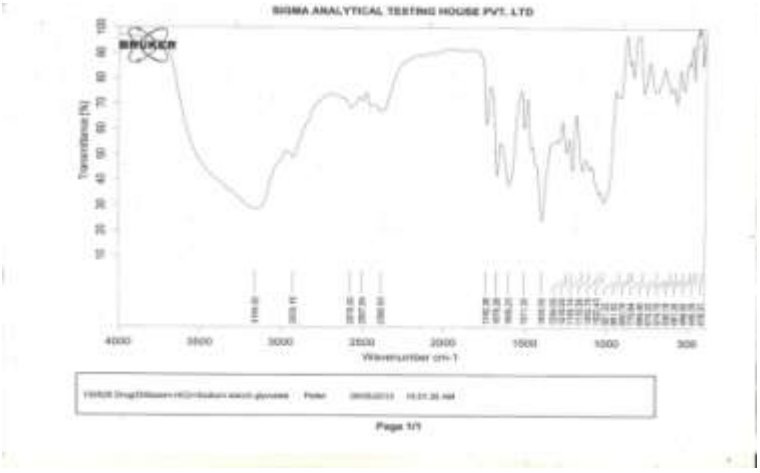

Figure 13: FTIR studies of diltiazem HCl and sodium starch glycolate

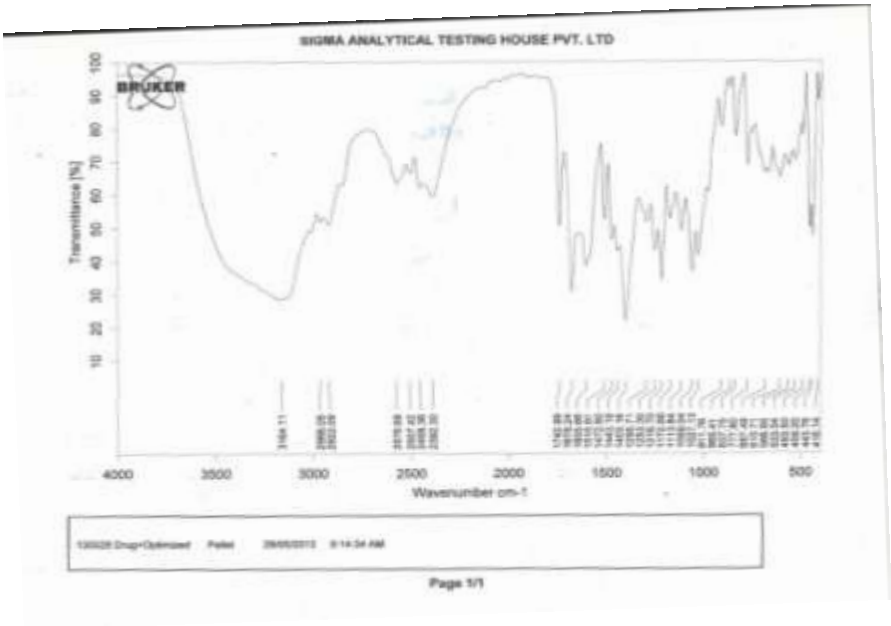

Figure 14: FTIR studies of diltiazem HCl and optimized formulation

CONCLUSION

Mouth dissolving tablets were prepared by, direct compression method. They are prepared by superdisintegrants addition method using Crospovidone, and Croscarmellose sodium, in different concentration like 6%,12%,18%,24. So, rapid absorption was improved, effective therapy & patient compliance. Mouth dissolving tablets can offer several biopharmaceutical advantages such as improved efficiency over conventional dosage forms. For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules.

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