

# Formulation and Evaluation of Dispersible 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 wet granulation method for enhanced patient compliance. Dispersible Tablets prepared using Superdisintegrants such as Croscarmellose Sodium (Ac-Di-Sol) and Sodium Starch Glycolate. Formulations were evaluated for the standard of Dispersible Tablets. It was observed that all the formulations were acceptable with reasonable limits of standard required for Dispersible Tablets. The study reveals that Superdisintegrants used were effective in low concentration. It was concluded that Dispersible Tablets of Dispersible Tablets with enhanced dissolution rate can be made using selected Superdisintegrants.

**Keywords:** Dispersible tablets; Diltiazem; Croscarmellose Sodium (Ac-Di-Sol) and Sodium Starch Glycolate.

## INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as "Dispersible Tablets". Dispersible Tablets are also known as quick dissolves, fast melts, fast dissolving, fast disintegrating, rapid-dissolve, or orally dissolving tablets. Their characteristic advantages such

as administration, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market.<sup>1</sup>

Despite increasing interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). The proper choice of

Superdisintegrants and its consistency of performance are of critical importance to the formulation development of such tablets. In more recent years, increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in water and to be swallowed.<sup>2</sup>

Over a decade, the demand for development of dispersible tablets has enormously increased as it has significant impact on the patient compliance. Dispersible tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphasia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. DTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population.

## EXPERIMENTAL DESIGN

### Materials

Diltiazem hydrochloride was obtained as a gift sample from S. N. Institute of Pharmacy, Pusad. Ac-Di-Sol, Sodium starch glycolate and microcrystalline cellulose were obtained as gift sample from Signet Chemicals Ltd, Mumbai. All other chemicals and reagent were of analytical grade.

### Method

#### Preparation of Diltiazem HCL Dispersible tablet

Compositions of Five different formulations of Diltiazem HCL tablets were prepared. All ingredients were passed through sieve no. 120, and then weighed accurately and mixed thoroughly (except magnesium stearate). Tablets were prepared by wet granulation method. Granules were prepared by passing the wet mass through sieve no. 40.

Prepared granules were dried in hot air oven at 45° C. Dried granules were sized through sieve no. 40 placed over sieve no. 60, lubricated with magnesium stearate. Tablets were made by multi tooling lab scale punching machine (Karnavati) at slow speed and high compression pressure to avoid capping.

FT-IR absorption spectrum of pure drug sample was recorded by KBr dispersion technique over the range of 400 to 4000  $\text{cm}^{-1}$ . From the FT-IR spectra of the pure drug and the combination spectra of drug with the excipients, it was observed that all the characteristic peaks of Diltiazem HCL i.e. peaks for C-H stretch, N-H stretch and C-O stretch were present in the pure drug as well as in combination spectra. Before tablet preparation, the mixture blend subjected for compatibility studies (IR), and pre-compression parameters like angle of repose, bulk density, tapped density, Hausner's ratio, and compressibility index.

#### Flow properties of blend<sup>3,4,5,6</sup>

The characterization of mixed blend done for the flow property of powder that are bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose.

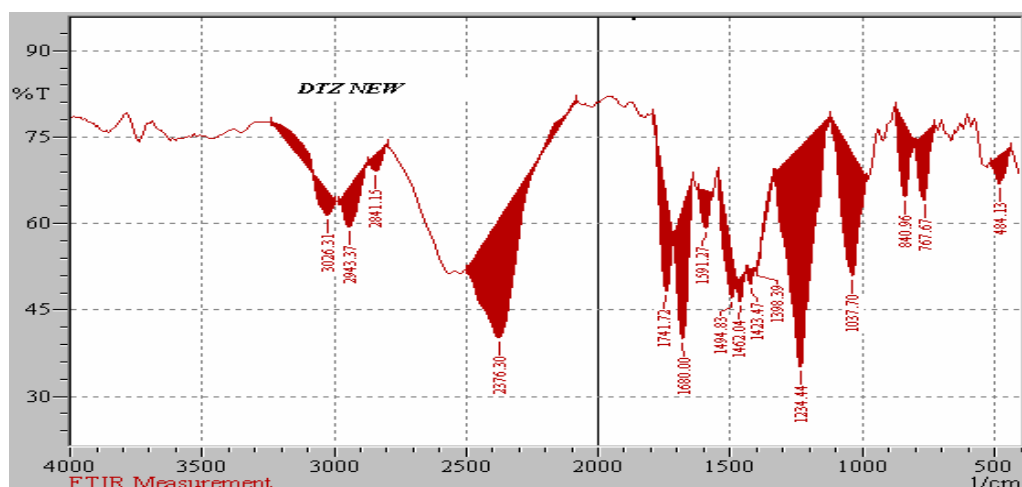


Figure No. 1. IR Spectra of Diltiazem HCL

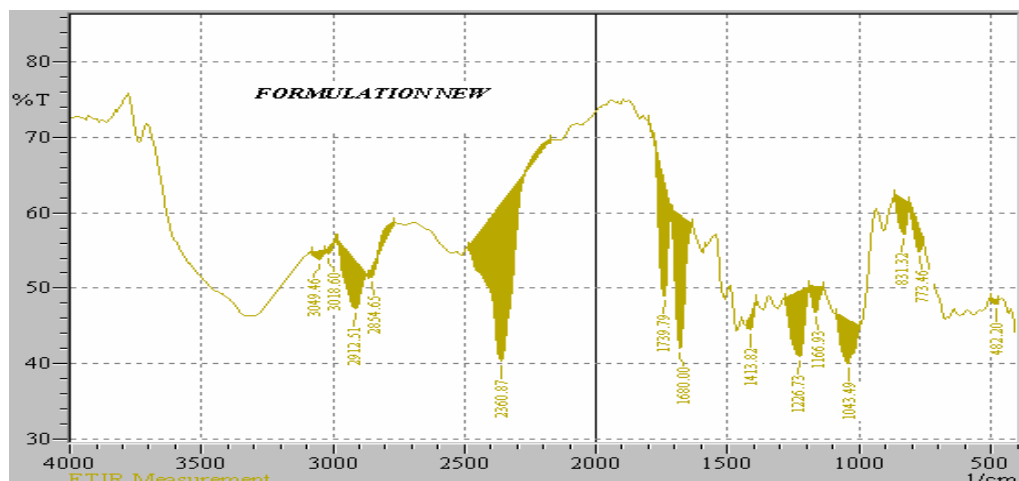


Figure No.2 IR Spectra of Physical mixture

Table No.1 Composition of Dispersible Tablets of Diltiazem HCL with Corresponding Formulations

Formulation Code	Ingredients Per Tablet (mg)					
	Diltiazem HCL	Ac-di-sol	Sodium Starch Glycolate	Avicel pH 102	Mg. stearate	Aspartame
A1	60	16	16	103.5	2.5	2
A2	60	08	08	119.5	2.5	2
A3	60	16	08	111.5	2.5	2
A4	60	08	16	111.5	2.5	2
A0	60	-	-	135.5	2.5	2

**EVALUATION OF TABLETS:**

The tablets from all the batches were evaluated for different parameters as follows:

**Appearance**<sup>7</sup>

Tablets were evaluated for organoleptic properties.

**Thickness**<sup>8,9</sup>

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

**Weight Variation**<sup>7,9,10</sup>

Twenty tablets were selected and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

**Hardness**<sup>7,9,10</sup>

Tablets were selected at random from each formulation and hardness was checked using Monsanto Hardness Tester.

**Friability**<sup>7,9</sup>

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

**Content of Active Ingredient:**<sup>7,11</sup>

Drug content of all the batches was determined. For this purpose six tablets were weighed and crushed with pestle in a small glass mortar. The fine powder was weighed to get 200 mg (equivalent to 60 mg of Diltiazem HCL), and transferred to 250 ml conical flask containing 100 ml of Distilled water stirred for 45 min in ultra sonicator. Solution was filtered and the filtrates obtained were analyzed UV spectrophotometrically and drug content was determined.

**Uniformity of Dispersion.**<sup>7,11</sup>

Two tablets were placed in 100 ml of water and stirred gently until completely dispersed. A smooth dispersion was obtained which passes through a sieve screen with a nominal mesh aperture of 710  $\mu$ m (sieve number 22).

**Wetting Volume**<sup>12</sup>

The tablet was placed in the center of the Petri dish and with the help of 5 ml pipette; distilled water was added drop wise on the tablet. The volume required to completely disintegrate the tablet was noted as the wetting volume.

**Wetting Time**<sup>9, 13</sup>

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (10 cm diameter) containing 10 ml of water. Containing Eosin, a water soluble dye, was added to Petri dish. A tablet was carefully placed on the surface of the tissue paper and allowed to wet completely. The time required for water to reach upper surface of the tablet was noted as a wetting time.

**Water Absorption Ratio**<sup>9, 14</sup>

A piece of tissue paper folded twice was placed in a small Petri dish (10 cm diameter) containing 6 ml of water. 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,

$$R = 100 (W_a - W_b) / W_b$$

Where, **W<sub>a</sub>** = weight of tablet after water absorption &  
**W<sub>b</sub>** = weight of tablet before water absorption.

**Dispersion Time**<sup>9, 13</sup>

Tablet was added to 10 ml of water and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and Dispersion time was performed.

**Disintegration Time**<sup>15</sup>

The disintegration time of tablet was measured in water (37°C) according to USP Disintegration test apparatus. Three trials for each batch were performed.

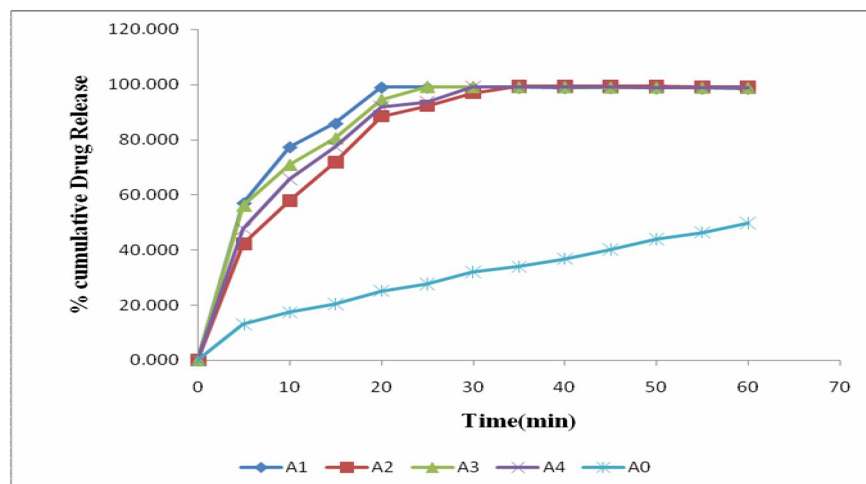
**In-vitro Dissolution:**<sup>16</sup>

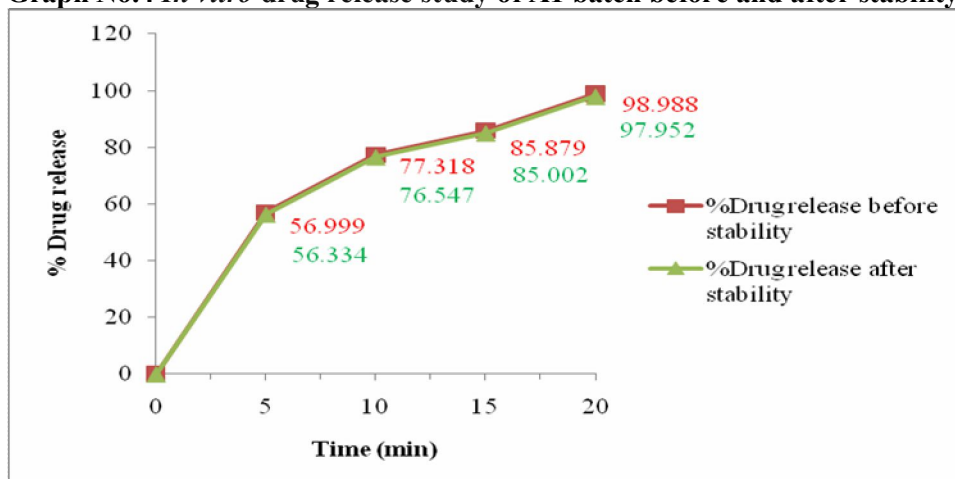
The in vitro dissolution study was performed in the USP apparatus type II Aliquot equal to 5 ml of dissolution medium was withdrawn at specific interval and replaced with fresh medium for maintaining sink condition. Sample was filtered and absorbance of filtered solutions determined by UV spectroscopy at 236 nm. Dissolution rate was studied for all formulations.

**Stability Study**<sup>8</sup>

In any rational design and evaluation of dosages forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal condition of temperature and humidity. However the studies will take a longer time and hence it would be convenient to carry out accelerated stability studies, were the product is stored under extreme condition of temperature and humidity. In the present study, stability studies were carried out on optimized formulation under the following condition for one month period as prescribed by ICH guidelines for accelerated study at  $40 \pm 2^\circ \text{C}$  and RH  $75\% \pm 5\%$ . The tablets were withdrawn after a period of 30 days and analyzed for physical characterization, dissolution and drug content.

**Graph No.3 In vitro drug release profile.**



**Graph No.4 In vitro drug release study of A1 batch before and after stability study****Table No.2 Evaluation of physical properties of tablet blends**

Formulation Code	Angle of Repose* ( $\theta^\circ$ )	Bulk Density* ( $\text{g/cm}^3$ )	Tapped Density* ( $\text{g/cm}^3$ )	Compressibility Index*	Hausner's Ratio*
Pure drug	$40.20 \pm 0.56$	$0.523 \pm 0.03$	$0.632 \pm 0.02$	$19.15 \pm 0.59$	$1.23 \pm 0.009$
A1	$25.70 \pm 1.31$	$0.453 \pm 0.01$	$0.511 \pm 0.01$	$11.33 \pm 0.30$	$1.12 \pm 0.003$
A2	$27.25 \pm 1.81$	$0.480 \pm 0.01$	$0.546 \pm 0.01$	$12.01 \pm 0.33$	$1.13 \pm 0.004$
A3	$25.51 \pm 1.17$	$0.429 \pm 0.02$	$0.490 \pm 0.01$	$12.40 \pm 1.81$	$1.14 \pm 0.02$
A4	$26.77 \pm 0.73$	$0.461 \pm 0.01$	$0.522 \pm 0.01$	$11.55 \pm 0.30$	$1.13 \pm 0.003$
A0	$26.42 \pm 1.15$	$0.447 \pm 0.03$	$0.512 \pm 0.02$	$12.84 \pm 1.51$	$1.14 \pm 0.02$

\*Average of three determinations

 $\pm$  Standard deviation.**Table No.3 Physical evaluation of tablet formulations.**

Formulation Code	Weight Variation* (mg)	Hardness* ( $\text{kg/cm}^2$ )	%Friability*	Thickness * (mm)
A1	$200.70 \pm 1.45$	$3.60 \pm 0.16$	$0.249 \pm 0.0001$	$3.43 \pm 0.09$
A2	$201.25 \pm 1.92$	$3.53 \pm 0.09$	$0.359 \pm 0.10$	$3.46 \pm 0.04$
A3	$201.65 \pm 1.71$	$3.66 \pm 0.09$	$0.248 \pm 0.0006$	$3.43 \pm 0.09$
A4	$200.30 \pm 1.87$	$3.60 \pm 0.16$	$0.277 \pm 0.03$	$3.43 \pm 0.09$
A0	$200.35 \pm 2.03$	$3.8 \pm 0.16$	$0.276 \pm 0.03$	$3.40 \pm 0.08$

\*Averages of three determination  $\pm$  Standard deviation**Table No.4 Evaluation of tablet formulations.**

Formulation Code	Wetting Time* (sec)	Wetting Volume* (ml)	Uniformity of Dispersion*	Content of Active Ingredients %
A1	$26.66 \pm 1.24$	$4.16 \pm 0.04$	Passes	100.78
A2	$46.33 \pm 1.69$	$4.83 \pm 0.04$	Passes	99.56
A3	$27.66 \pm 1.24$	$4.20 \pm 0.08$	Passes	100.48
A4	$28.66 \pm 0.47$	$4.40 \pm 0.08$	Passes	99.91
A0	More than 3 min	More than 5 ml	Passes	98.94

\*Averages of three determination  $\pm$  Standard deviation

**Table No.5 Evaluation of tablet formulations.**

Formulation Code	Water absorption Ratio* (%)	Dispersion Time* (sec)	Disintegration Time* (sec)
A1	114.63 ± 13.58	43.66 ± 4.18	35.66 ± 1.24
A2	92.04 ± 2.53	113.33 ± 13.52	56.33 ± 2.05
A3	99.34 ± 1.99	62.00 ± 11.43	37.66 ± 1.24
A4	97.68 ± 2.03	67.33 ± 3.85	39.66 ± 2.44
A0	--	More than 3 min	More than 3 min

\*Averages of three determination ± Standard deviation

## RESULT AND DISCUSSION

In the present investigation, FT-IR spectra of Diltiazem hydrochloride showed sharp characteristic peaks. All the above characteristic peaks appear in the spectra of Formulation at same wave number indicating no modification or interaction between the drug and excipients. FT-IR spectroscopy was used as means of studying drug excipient compatibility and confirmed undisturbed structure of Diltiazem, which indicate no drug-excipient interaction.

For each formulation blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. Bulk density was found in the range of **0.429-0.480 g/cm<sup>3</sup>** and tapped density between **0.490-0.546 g/cm<sup>3</sup>** as shown in **Table No. 2**. Using these two densities data compressibility index and hausner's ratio was calculated.

The powder blends of all the formulations had compressibility index between **11.33** and **12.84** which indicating good flowability of the powder blend. Hausner's ratio for all formulation was less than **1.14**, indicated good flowability. The compressibility-flowability correlation data indicated an excellent flowability of all powder blends, the good flowability of the blend was also evidenced with angle of repose which is between **25.51** and **26.77**. The results are shown in **Table No. 2**.

Diltiazem HCL dispersible tablets were prepared in five formulations with varying concentration of two superdisintegrants: Croscarmellose Sodium (Ac-Di-Sol) and Sodium starch glycolate and MCC (Avicel) was used as diluents. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using wet granulation technique. Tablets were obtained of uniform weight due to uniform die fill.

The data obtained of post-compression parameters such as thickness, hardness, friability, weight variation, amount of drug content, wetting time, wetting volume; water absorption ratio, dispersion time and disintegration time are shown in **Table No.3, 4, 5**.

The hardness was found to be in the range of **3.53 to 3.8 kg/cm<sup>2</sup>** for all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. Thickness of all formulations varied from **3.40 to 3.46 mm**. In all the formulations the friability values are less than 1% and meet the IP limits. Friability of the tablets was found below **0.248 - 0.359 %** indicating good mechanical resistance of tablets.

All the tablets passed weight variation test as the percentage weight variation was within the Pharmacopoeial limits. The weight of all the tablets was found to be uniform with low standard deviation values indicating efficient mixing of drug, disintegrants and excipients. The percentage drug contents of all the tablets were found between **98.94 % to 100.78 %** of Diltiazem, which was within the acceptable limits. All the batches pass the Uniformity of dispersion as per IP and the Dispersion time of all the batches tablet was within the range of **43.66-111.33 sec**.

Water absorption ratio of all formulations was found between **92.04 and 114.63%**. This resulted in fast wetting of tablets of all formulations as reflected from wetting time ranging between **26.66-46.33 sec**. Wetting volume for all the batches was within the range of **4.16-4.83 ml**. The Dispersion time of all the batches tablet was within the range of **43.66-111.33 sec**, The results of wetting time and disintegration time of all the tablets were found to be within the prescribe limits and satisfy the criteria of Dispersible tablets.

It was observed that when Ac-Di-Sol is used as Superdisintegrants, the tablets disintegrate rapidly



within less time due to easy swelling ability of Ac-Di-Sol when compared to Sodium starch glycolate. Among the formulation tablets of batch A1 containing Ac-Di-Sol 16 mg was found to be the best as compare to other formulations as this formulation showed good hardness, low friability and least wetting time (**26.66 ± 1.24 sec.**) and disintegration time of (**35.66 ± 1.24sec.**), which is an ideal characteristic of an dispersible type tablet.

*In vitro* dispersion time is presented in **Table No.5**. All tablets disintegrated rapidly as per IP test especially when used at their optimum concentrations as reported in literature. The Disintegration time of all batches was within the range of **35.66-56.33 sec.**

Hence, the effect of superdisintegrants specifically at 4 and 8% level in dispersible tablet formulation on the *in vitro* dissolution was evaluated for functionality comparison. These levels included optimum concentrations of selected superdisintegrants to be used in formulations.

In the study, the relatively larger fragments generated by tablets containing sodium starch glycolate were not small enough to pass through the screen of the disintegration vessels. Accordingly a longer disintegration time and a larger variation were observed, especially when the sodium starch glycolate was used at the lower concentration.

Tablets formulated with Ac-Di-Sol can be seen to rapidly disintegrate into more or less uniform fine particles, while tablets formulated with sodium starch glycolate appeared to disintegrate much more slowly into more or less uniform coarser particles.

*In vitro* dissolution studies of the prepared DTs were performed in distilled water using USP apparatus Type –II (paddle). The drug release at the end of 20 minutes was found to be 98.988, 88.541, 94.467 and 91.918 % with Ac-Di-sol and SSG.

The percentage drug release of all the batches was found to be between **98.98 to 99.47%** this was within the acceptable limits. The cumulative percentage of the drug released for formulation batch A1 found by the dissolution test shows the better drug release of 98.988 % at the end of 20 minutes. Indicates good bioavailability of the drug from these formulations. Ac-Di-Sol when comes in contact with water gets inflated immediately burst out there by releasing the drug in the short duration of time. The tablets showed

not less than 85 % drug release in 20 minutes in distilled water. Comparative dissolution profile of all Batches (A0 to A4) is given in Graph No.3.

It was observed that as the concentration of superdisintegrants increased the drug release also increased. With reference to the type of superdisintegrants, the release rate was found to follow the order: **Ac-Di-sol > SSG.**

Stability study was carried out on optimized tablet formulation. Formulation was stored at 40°C ± 2°C / 75 ± 5 % RH for 30 days. Dissolution profile of optimized A1 batch before and after stability study was shown in **Figure No.4**. As there is no significant changes were found during study period. Thus the formulation was found to be stable.

## **CONCLUSIONS**

Overall, the results suggest that Dispersible tablets of Diltiazem hydrochloride containing superdisintegrants (crosscarmellose sodium and sodium starch glycolate) can be successfully formulated, the present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

It was observed that all formulations were acceptable with reasonable limits of standard required for dispersible tablets. The study reveals that Ac-Di-Sol and Sodium Starch Glycolate used as superdisintegrants were effective in low concentration. Among the formulations tablets of batch A1 containing Ac-Di-Sol showed superior micromeritic properties along with excellent *in vitro* disintegration time and drug release as compare to other formulations. It was concluded that superdisintegrants addition technique is a useful method for preparing dispersible tablets by wet granulation method.

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