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FORMULATION, EVALUATION AND OPTIMIZATION OF ORODISPERSIBLE TABLETS OF DILTIAZEM HYDROCHLORIDE 30 MG

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ABSTRACT

The concept of Mouth Dissolve Drug Dilivery System emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate or dissolve to release a drug as soon as they come in contact with saliva in oral carvity, thus obviating the need for water during administration, an attribute that makes them highly attractive for pediatric and geriatric patients. Difficulty in swallowing conventional tablets and capsules (Oral solid dosage form) in common among all age groups especially on elderly and dysphasic patients. Elderly patients may find the administration of the conventional oral dosage forms difficult as they regularly require medicines to maintain healthy life. Children may also have difficulty in ingesting because of their under developed muscular nervous system. The problem of swallowing tablets is also evident in travelling patients who may not have ready access to water. Aforementioned problems can be resolved by means of Mouth Dissolving Tablets. Some tablets are designed to dissolve in saliva within few seconds, and are true fast- dissolving tablets .Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed as fast disintegrating tablets, as they may take about to disintegrate completely. The most common preferred route is oral rout of administration. Today oro-dispersible tablet from novel drug delivery system gain importance from patient. Which is administer to the patient to control the attack of angina or hypertension, but for immediate control, Oro-dispersible tablet is oral solid dosage form in which the tablet gets dispersed in oral cavity in absence of water. Various manufacture are formulated this formulation by various method. The most importance thing in this formulation are masking of taste of drugs. Generally oro-dispersible tablet are prepared by direct compression method. Dry granulation, wet granulation, Spry drying is the various methods for preparation of oro-dispersible tablet. Oro-dispersible tablet generally contains filler, glidant, anti-adherent super disintegrate, sweetener and resins. Evaluation parameter includes hardness, friability, wetting time, moisture uptake, disintegration test, and dissolution test. Wetting time, Disintegration time, and Dissolution test is directly proportional to the hydrophobic ingredient added for lubrication, anti-adherent, Glidant action. These hydrophobic ingredient are Magnesium Stearate. To oppose the action of magnesium stearate, hydrophilic additives are incorporated viz Sodium lauryl sulphate, Cross carmillose sodium, sodium starch glycol ate are added.

KEYWORDS: Oro-dispersible tablet, wetting time, Dissolution test.

INTRODUCTION

Quality are built in the pharmaceutical formulation by design the formulation. The total quality in the product are known as Total Quality Management. To gain this goal of optimized quality product, the knowledge obtained from pharmaceutical development studies and manufacturing provides the scientific background. Although it is based on different pharmaceutical studies, but it has its aim that it minimizes the end product testing and Increases the chances of regulatory acceptance by different pharmaceutical governing bodies. The aim and objective of the present study is to develop and evaluate oro dispersible tablet of Diltiazem Hydrochloride and enhance the onset of action of Diltiazem Hydrochloride and also to study the influence of excipients on the physical characteristics of the tablets by applying two

level three factor factorial designs Diltiazem Hydrochloride as model drug which is used in the treatment of the Hypertension, Angina Pectoris, cardiac arrhythmia. The study of this formulation to select the best possible excipient combination of semi synthetic & natural and artificial additives to development of formulation. Super disintegrants viz Cross carmillose sodium are added to formulate the dispersible tablets and other Additives, diluents and disintegrants used. Finally the effect of the additives or various excipients ratio and super disintegrants on various properties of the tablet were also determined.

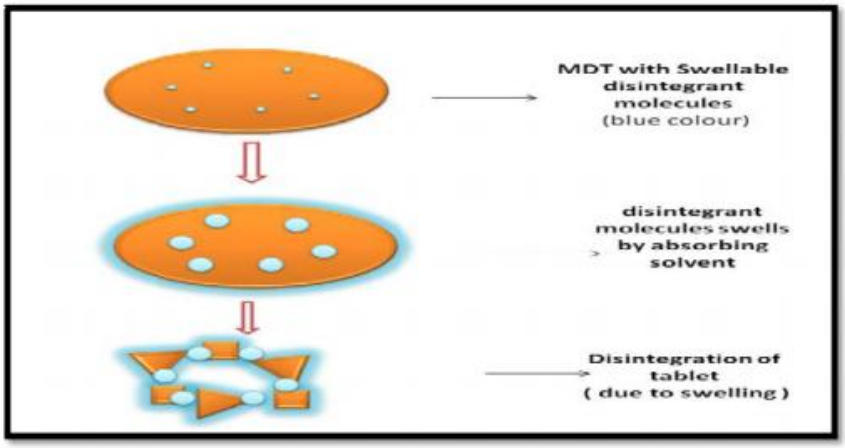
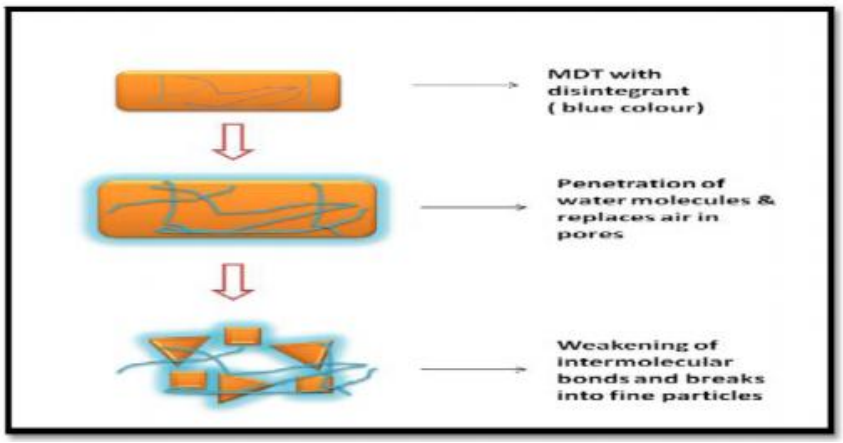


Figure 1: Swelling Mechanism of a Disintegrant



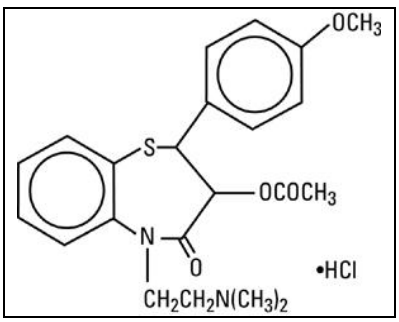
Swallowing machinism

2. MATERIAL AND METHOD

2.1 API Structure Characterization

Molecular formula: $C_{22}H_{26}N_2O_4S$• HCl
Molecular weight: 451.0
Melting point:
State/Form: Powder form
Category: Anti- arrythmic drug. Calcium chennal blocker.

Description: Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98.
Storage conditions: Store protected from light.
Solubility: It is soulube in water alcohol and methenol.
Therapeutic dosage: 30mg to 120mg



Structure and IUPAC Name of Diltiazem Hydrochloride

Diltiazem Hydrochloride is *s*-2,3,4,5-tetrahydro-5-(2-dimethy laminoethyl)-2-(4-methoxyphenyl) -4-oxobenzo[*b*] thiazepin-3-yl acetate monohydrochloride.

2.2 Diltiazem Hydrochloride and Excipients studies (Six months).

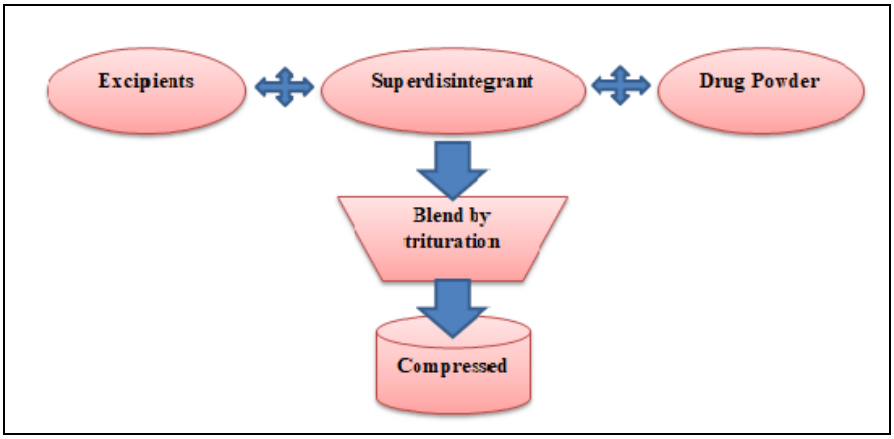
S. No.	Drug+ Excipients	Duration (months)	Result
1	Diltiazem Hydrochloride + Starch DC	6 Months	Stable
2	Diltiazem Hydrochloride + Mannitol	6 Months	Stable
3	Diltiazem Hydrochloride + Lactose	6 Months	Stable
4	Diltiazem Hydrochloride + Aspartame	6 Months	Stable
5	Diltiazem Hydrochloride + Talcum	6 Months	Stable
6	Diltiazem Hydrochloride + Magnesium Stearate	6 Months	Stable
7	Diltiazem Hydrochloride + Cross carmillose sod.	6 Months	Stable
8	Diltiazem Hydrochloride + Sod Starch Glycolate	6 Months	Stable
9	Diltiazem Hydrochloride + Methyl Paraben	6 Months	Stable
10	Diltiazem Hydrochloride + Propyl Paraben	6 Months	Stable
11	Diltiazem Hydrochloride + Sodium Lauryl Sulphate	6 Months	Stable

2.3 MATERIAL: Material and their use with obtained sources

Sr. No.	Material	Uses of Ingredients	Sources
1	Diltiazem Hydrochloride	Active Pharmaceutical Ingredients	Pacific India.Dhana, Village: Baghbania, Nalagardh solan H.P.
2	Starch DC	Diluents	Pacific India. A Pharmacutical Exporter, Villalge: Dhana, Baghbania. Nalagarh. Solan. Himachal Pradesh
3	Lactose	Diluents	
4	Mannitol	Sweetener	
5	Aspartame	Sweetener	
6	Talcum	Glidant	
7	Magnesium Stearate	Antiadhrants	
8	CCS	Super disintegrants	
9	SSG	Lubricants	
10	Methyl Paraben	Preservative	
11	Propyl Paraben	Preservative	
12	Sodium Lauryl Sulphate	Disintegrants	

2.4 Preparation of Diltiazem Hydrochloride 30 mg tablet by direct compression method. Formulation table.

Sr. No.	Ingredients	C1(mg)	C2(mg)	C3(mg)	C4(mg)	C5(mg)
1	Diltiazem Hydrochloride	30	30	30	30	30
2	Starch DC	120	123	126	129	132
3	Lactose	95	95	95	95	95
4	Mannitol	90	90	90	90	90
5	Aspartame	18	18	18	18	18
6	Talcum	15	15	15	15	15
7	Mag. Stearate	15	15	15	15	15
8	CCS	20	17	14	11	8
9	SSG	12	12	12	12	12
10	Methyl Paraben	4	4	4	4	4
11	Propyl Paraben	1	1	1	1	1
12	SLS	10	10	10	10	10
	Total weight	430 mg	430 mg	430 mg	430 mg	430 mg



All the ingredients viz active ingredients, additives were passed through 60 # sieve separately, Magnesium stearate & Talc through 40 #. Then the ingredients were weighed and mixed in double dilution order or Geometric mixing and tablets were compressed with 9 mm sizes biconvex round punch to get tablet using Rimeck double rotary Compression Machine.

3. Post compression Parameters

3.1 Thickness of compressed tablet

The thickness of the compress tablets of Diltiazem Hydrochloride 30 mg was determined using a Digital Vernier calliper. Ten tablets from each type of formulation were used and average values were calculated. It is expressed in mm.

3.2 Hardness

The resistance of tablets during passing through hopper, Blister Cartooning, breakage, under conditions of storage, transportation and Handling before usage are directly proportional to its hardness. For each formulation, the hardness of 6 tablets was determined using the Pfizer Hardener Tester and 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 in Monsanto tester and in case of Pfizer directly force applied until the tablet breakdown in the pieces. The reading the both cases at this point was noted.

3.3 Friability Test

Friability Test is generally used the measure of tablet strength. Roche Friability tester was used for testing the friability using. In This test subjects a number of compressed tablets to the combined effect of shock abrasion by utilizing a circular plastic chamber which revolves at a speed of 25 revolution per minutes for 4 minutes i.e. 100 rpm, dropping the compressed tablets of Diltiazem Hydrochloride to a distance of 6 inches in each revolution. A sample of weighed 6 compressed tablets of was placed in Roche friability chamber which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then de-dusted, and broken tablet are removed and reweighed. A loss of less than 1 % in weight in generally considered acceptable according to Pharmacopeia. Percentage friability (% F) was calculated as follows:

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

3.4 Weight variation test

As per the limitation of Pharmacopeia to find out weight variation test, 20 tablets of each type of formulation were weighed individually using single pan balance or an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

Specifications for tablets as per Indian Pharmacopeia. 1996.

S. No.	Percentage Deviation	Average Weight of Tablet (mg)
1	10	80 mg or less
2	7.5	More than 80 mg but less that 250 mg
3	5	250 or more

3.5. Uniformity of drug content

Five tablets of each compression formulation are weighed and crushed in mortar Pastel and powder, or crushed equivalent to 30 mg of Diltiazem Hydrochloride was weighed and dissolved in 100 ml of 0.1N Hydrochloric acid (pH 1.2). This was the stock solution from which 0.2 ml sample was withdrawn and diluted to 10 ml with 0.1N Hydrochloric acid. The absorbance was measured at wavelength 237.5 nm using double beam Ultra Violet Visible spectro photometer. Content uniformity of the drug was calculated using formula.

% Purity of the Drug = 10 C (Au / As) -------

Where, C = Concentration,

Au and As=Absorbance's obtained from unknown preparation and standard Preparation.

3.6. Wetting time

This method is applied to calculate tablet wetting time. A piece of tissue paper or absorbent folded twice was placed in a small Glass Petri dish having the diameter 6.5 cm, containing 10 ml of water. Compressed tablet was placed on the paper, and the time record or note for complete wetting. Three trials for each batch were performed and standard deviation are calculated

3.7. In vitro disintegration time

The process of breakdown or convert the tablet into pieces or into smaller particles is called as disintegration. The in vitro Disintegration time of a tablet was determined using disintegration test apparatus as per Indian Pharmacopeia specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using distilled water maintained at 37° ± 2°C which is similar to body temperature. The assembly should be raised and lowered between 30 cycles per minute in the 0.1 N HCL or Distilled water maintained at 37° ± 2°C. The time in seconds taken for complete disintegration of the tablet.

In this disintegration test if the tablet are adhere to the 10 # sieve then continue the test till all tablet are completely disintegrated.

3.8. In vitro dissolution test

Rate of dissolution are studied by using USP type-II apparatus having 50 rpm, using 900ml of 0.1 N Hydrochloric acid as dissolution solvent. Temperature of the dissolution medium was maintained at 37 ± 0.5°C. The sample of dissolution medium was withdrawn at every 5 min interval and first filtered. The absorbance of filtered solution was measured by using Ultra Violet spectrophotometric method at 237.5 nm and concentration of the drug was determined from standard calibration curve.

In vitro drug release studies details:

- Dissolution test apparatus
- 0.1 N HCL as Dissolution medium
- 900 ml Dissolution medium volume
- 37 ± 0.5°C as std. Temperature
- 50 rpm Speed of basket paddle
- 5 min sampling intervals
- 10 ml volume Sample withdraw
- 237.5 nm Absorbance measured

4. RESULT AND DISCUSSION

4.1 Pre compression Parameter and studies

S. No.	Formulation code	Angle of Repose	Bulk density (weight/ml)	Taped Density (weight/ml)	Flow Time (100 gm)
1	C1	32.32±0.70	0.43±0.02	0.50±0.04	32 sec.
2	C2	29.70±0.58	0.42±0.03	0.48±0.02	26 sec
3	C3	28.86±0.67	0.44±0.03	0.47±0.04	25 sec.
4	C4	28.44±0.45	0.43±0.02	0.46±0.02	28 sec.
5	C5	25.40±0.65	0.43±0.03	0.48±0.02	27 sec.

4.2 Post compression Parameter Studies.

Formulation code	Hardness (KG/cm2)	Friability (%)	Thickness (mm)	Diameter (mm)	Weight (mg)	Weight variation
C1	4.52	0.67	4.32	9.02	434	422 to 442 mg
C2	4.82	0.52	4.28	9.03	436	425 to 435 mg
C3	4.65	0.51	4.26	9.01	428	426 to 436 mg
C4	4.44	0.42	4.30	9.02	430	429 to 433 mg
C5	4.56	0.56	4.32	9.02	432	424 to 440 mg

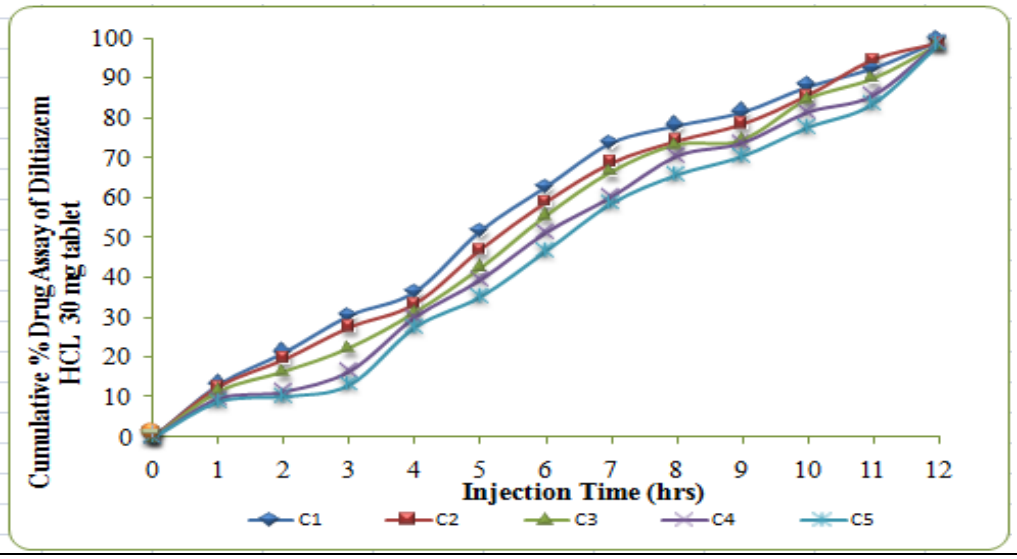
4.3 Post compression Studies

Formulation code	Assay of Drugs (%)	Water intake time (sec)	Disintegration time (sec)	Dissolution(%)
C1	99.32	16-20	9-11	94.85
C2	98.53	18-24	13-15	91.25
C3	98.42	20-26	16-17	85.45
C4	98.78	24-30	16-19	83.87
C5	98.51	26-34	19-21	79.25

5. GRAPHS

Time (hrs)	Cumulative % Drug assay of Diltiazem HCL tablet				
	C1	C2	C3	C4	C5
0	0	0	0	0	0
1	13.25	12.57	11.56	9.54	8.79
2	21.26	19.58	16.25	11.25	10.21
3	30.25	27.56	22.26	16.58	13.24
4	36.25	33.24	31.12	29.89	27.59
5	51.57	46.87	42.52	39.45	35.24
6	62.54	58.89	55.56	51.24	46.51
7	73.56	68.78	66.54	60.24	58.61
8	78.12	74.25	73.26	70.45	65.57
9	81.54	78.45	74.36	73.57	70.21
10	87.86	85.56	84.56	81.27	77.59
11	92.54	94.52	89.87	85.56	83.51
12	99.32	98.53	98.42	98.78	98.51

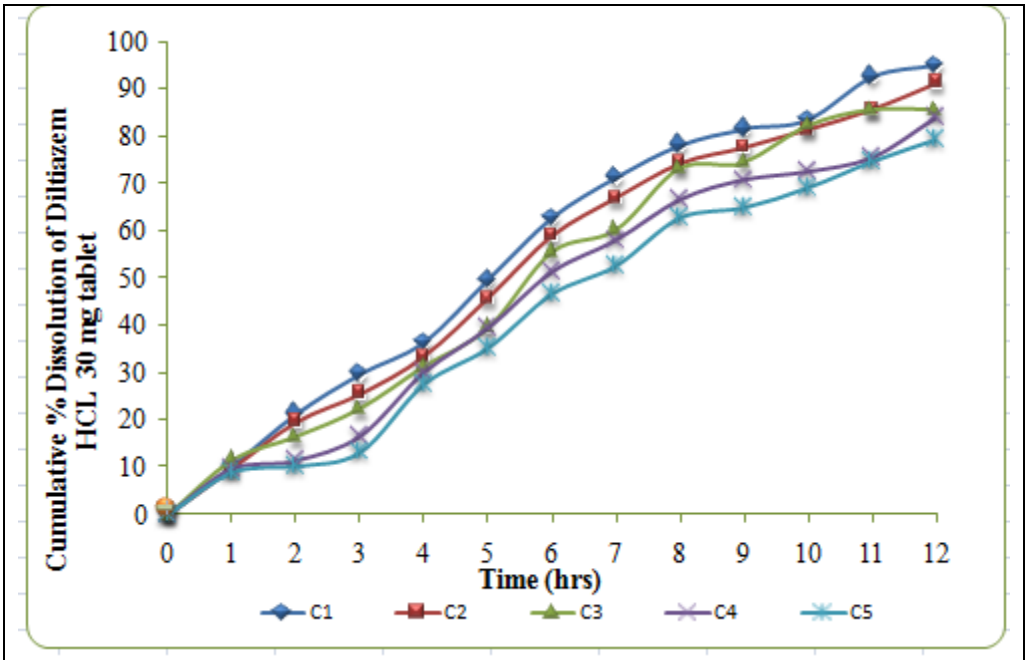
Assay data of Diltiazem Hydrochloride 30 mg ODT



Assay Graph of Diltiazem Hydrochloride 30 mg ODT.

Time (hrs)	Cumulative % Dissolution of Diltiazem HCL tablet				
	C1	C2	C3	C4	C5
0	0	0	0	0	0
1	10.25	9.57	11.56	9.54	8.79
2	21.26	19.58	16.25	11.25	10.21
3	29.58	25.57	22.26	16.58	13.24
4	36.25	33.24	31.12	29.89	27.59
5	49.57	45.67	39.51	39.45	35.24
6	62.54	58.89	55.56	51.24	46.51
7	71.25	66.87	60.24	57.84	52.51
8	78.12	74.25	73.26	66.57	62.57
9	81.54	77.51	74.36	70.54	64.85
10	83.25	81.27	82.24	72.51	68.91
11	92.54	85.57	85.51	75.52	74.51
12	94.85	91.25	85.45	83.87	79.25

Dissolution Data of Diltiazem Hydrochloride 30 mg ODT.



Dissolution Graph of Diltiazem Hydrochloride 30 mg ODT.

6. CONCLUSION

After the completion of this experiments the result obtained and we conclude that development of orodispersible Diltiazem Hydrochloride tablet 30 mg formulation by using super disintegrants i.e. Cross carmillose sodium are given the result of dissolution more than mentioned in the Pharmacopeia. Some result are mentioned below:

1. Active drug Diltiazem Hydrochloride with different excipient are stable viz Starch, Talcum, Mannitol, Lactose, Magnesium stearate, cross carmillose sodium and Starch DC Grade.
2. Fast Disintegrating Diltiazem Hydrochloride Tablets 30 mg were successfully prepared by direct compression method.
3. The flow property of the granules and uniformity of the compressed tablet are better as compare the granules prepared by weight of dry granulation method or by Slugging method.
4. The angle of repose of prepared granules are less than 30^{o} which show the good quality of granules.
5. The hardness of compressed tablet by direct compression method are found in the rage of 4.52 to 4.56 kg/cm^2.
6. The Thickness of the prepared tablets by direct compression methods was found between 4.26 mm. to 4.32 mm.
7. The Friability of the compressed tablet are within the range i.e. less than 1%. As the size of tablet are small.
8. The in vitro disintegration studies are found to be in 09 to 21 seconds. Formulation C1 showed in vitro disintegration time is 09-11 seconds.
9. On the basis of disintegration time formulation C1 which facilitate the faster disintegration in the mouth. The *in-vitro* percentage drug releases from fast dissolving tablets of Diltiazem Hydrochloride 30 mg prepared by direct compression method were found to be in the range of 99.32 %. Hence, finally it was concluded that the prepared oro dispersible tablets of Diltiazem Hydrochloride 30 mg tablet may prove to be potential candidate for effective fast disintegrating tablet dosage form.

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