Formulation and Evaluation of Diltiazem Hydrochloride Ip 60 mg Immediate Release Tablet

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Abstract—Diltiazem Hydrochloride, a benzothiazepine calcium channel blocker, is widely used in the management of hypertension, angina pectoris, and cardiac arrhythmias due to its potent vasodilatory and cardio depressant actions.
The development of an Immediate Release (IR) tablet of Diltiazem HCl 60 mg requires a comprehensive understanding of its physicochemical properties, excipient compatibility, and formulation behaviour to ensure rapid disintegration and optimal bioavailability.
As a highly water-soluble BCS Class I drug, Diltiazem HCl lends itself well to IR formulations; however, challenges such as moisture sensitivity, poor flowability, and compression characteristics demand a carefully optimized manufacturing approach.
This review critically evaluates the formulation strategies, including the selection of suitable diluents, binders, disintegrants, and lubricants, along with the influence of granulation techniques on tablet quality.
It further discusses key pre-compression and post-compression parameters—such as flow properties, hardness, friability, drug content, and dissolution profile—that determine the overall performance of the dosage form.
Emphasis is placed on achieving rapid drug release, complying with pharmacopeial standards, and ensuring stability under ICH-recommended conditions. Overall, this article provides a detailed scientific overview of the formulation and evaluation of Diltiazem Hydrochloride IP 60 mg Immediate Release tablets, highlighting critical factors that contribute to a safe, stable, and therapeutically effective oral dosage form for cardiovascular disease management.

Index Terms—Diltiazem Hydrochloride, Immediate Release Tablet, Calcium Channel Blocker, Tablet Formulation, Dissolution, Disintegration, Quality Evaluation, Wet Granulation.

I. Introduction

Diltiazem Hydrochloride is a well-established therapeutic agent belonging to the benzothiazepine class of calcium channel blockers. It functions by inhibiting the influx of calcium ions through L-type calcium channels in cardiac and vascular smooth muscle, resulting in reduced myocardial contractility, decreased peripheral vascular resistance, and improved coronary blood flow. Because of its unique pharmacodynamic profile, Diltiazem Hydrochloride is extensively prescribed for the management of cardiovascular disorders such as hypertension, supraventricular tachycardia, atrial fibrillation, and chronic stable angina.

The drug's rapid onset of action and short half-life make it highly suitable for formulation into immediate release (IR) tablets, particularly for patients requiring quick symptomatic relief and flexible dose adjustment .Immediate Release tablets deliver the drug rapidly after oral administration, ensuring prompt absorption

and fast therapeutic response. Diltiazem Hydrochloride, being a BCS Class I drug (high solubility and high permeability), is ideal for IR formulations, as it dissolves readily in the gastrointestinal tract and displays efficient absorption.

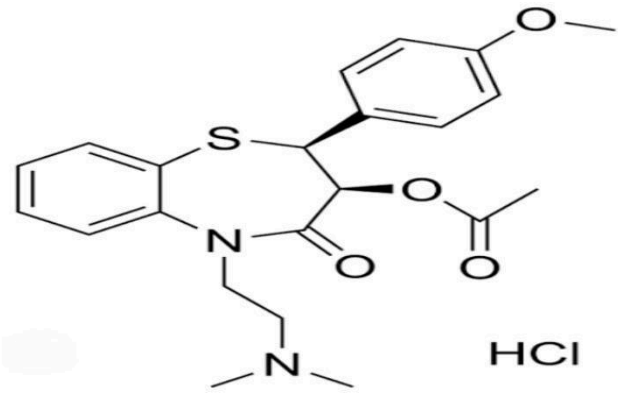
However, achieving a stable and high-quality IR tablet dosage form is not straightforward. The drug exhibits certain formulation challenges, including hygroscopic nature, sensitivity to moisture and light, poor flowability, and moderate compressibility, all of which influence its manufacturability and performance.

Therefore, a scientifically sound formulation approach is essential to overcome these limitations .Developing a Diltiazem HCl 60 mg IR tablet requires careful selection of excipients such as diluents, binders, disintegrants, glidants, and lubricants, which collectively influence tablet hardness, friability, disintegration, and ultimately, dissolution. Commonly used excipients include microcrystalline cellulose for compressibility, PVP K30 as a binder, and croscarmellose sodium or sodium strach glycolate as super disintegrants to accelerate tablet breakup. The choice between direct compression and wet granulation is also critical; although direct compression is simple and cost-effective, wet granulation is often preferred for this drug due to improved flow and content uniformity. Equally important are the preformulation studies, which provide essential insights into the drug's physicochemical characteristics—such as solubility, pH stability, melting point, and drug–excipient compatibility. These studies serve as the scientific foundation for selecting appropriate formulation strategies and manufacturing processes. Post-formulation, the IR tablet must comply with quality control parameters specified by pharmacopoeias (IP, USP), including hardness, thickness, friability, weight variation, assay, disintegration time, and dissolution profile. For an IR tablet of Diltiazem HCl, achieving rapid disintegration and ≥80% drug release within 30 minutes is crucial for ensuring therapeutic efficiency .Furthermore, stability studies conducted under ICH-recommended conditions ensure that the final product maintains its quality, potency, and safety throughout.

Stability concerns such as moisture uptake, colour change, or degradation must be thoroughly assessed and controlled Through appropriate formulation techniques and packaging materials .the formulation and evaluation of Diltiazem Hydrochloride IP 60 mg Immediate Release tablets represent a multidisciplinary process involving detailed preformulation analysis, rational excipient selection, optimized granulation technology, and stringent quality testing. This review provides an in-depth exploration of these aspects, aiming to offer a comprehensive understanding of the scientific and technical considerations necessary for developing a robust, stable, and therapeutically effective IR tablet for cardiovascular disease management.

Diltiazem Overview Chart :

Category	Detail
Other Name	Diltiazem Hydrochloride , brand name Tiazac Cardizem
Chemical Formula	$C_{22}H_{26}N_2O_4S \cdot HCl$
Mechanism of Action	Block L-type calcium channel in heart and blood vessel
Molecular weight	450.98g/mol
Dosage(adults)	60 mg to 120mg twice daily
Dosage(Children)	Generally not recommended for use in children
Side effect	Headache ,dizziness and swelling fatigue ,constipation etc.
Precautions	Avoid alcohol; do not exceed max dose use continuously with liver condition sun sensitivity ,liver disease
Forms Available	Immediate release tablet ,extended release capsule/ tablet ,Intravenous formulation .



DILTIAZEM HYDROCHLORIDE

Diltiazem hydrochloride is a calcium channel blocker (CCB) commonly used in the treatment of cardiovascular disorders such as hypertension, angina pectoris, and certain cardiac arrhythmias (e.g.. supraventricular tachycardia, atrial fibrillation). It acts by inhibiting the influx of calcium ions into vascular smooth muscle and cardiac tissue, leading to vasodilation and reduced cardiac workload. Diltiazem, also known as Calcium channel blocker .it also classified as a antianginal and antiarrhythmic medication

Diltiazem ia a prescription -only medication that must be prescribed by a doctor or other qualified healthcare professional.

It is not available over the counter (OTC).

Diltiazem is used to treat serious condition such as high blood pressure (hypertension), Angina Pectoris (chest pain due to ischemia), Atrial fibrillation or Atrial flutter (for rate control)

Its available in various dosage forms such as immediate -release tablets, Extended-release capsules/tablets, Intravenous (IV) formulation for acute arrhythmias

Its common side effect like Headache, Dizziness, Fatigue, Edema, Bradycardia, Constipation, Flashing

. Diltiazem Hydrochloride is commonly formulated in immediate release and sustained release tablets depending on the therapeutic requirement. Immediate release tablets provide rapid onset of action and are useful in conditions requiring quick blood pressure control.

The direct compression method is often preferred for tablet formulation because it is simple, cost-effective, and provides better stability. However, proper selection of excipients is necessary to improve flowability, compressibility, and tablet hardness.

The formulation and evaluation of Diltiazem Hydrochloride tablets involve pre-compression studies such as angle of repose, bulk density, tapped density, and post-compression parameters like hardness, friability, weight variation, drug content, disintegration time, and dissolution study to ensure quality and effectiveness Diltiazem Hydrochloride is a calcium channel blocker mainly used for the treatment of hypertension, angina pectoris, and certain heart rhythm disorders. Immediate release tablets are designed to release the drug rapidly after administration to provide quick therapeutic action.

To improve the disintegration time, so-called disintegrants are used. The most accepted mechanisms of their action are wicking, swelling, deformation recovery, and particle repulsion. Together, these phenomena create a disintegrating force within the tablet matrix.

In the past, non-modified disintegrants were used to accelerate disintegration, such as starches, alginates, celluloses, pectin, and resins. Today, fast-working super disintegrants are chemically modified, typically by crosslinking the organic chains of polymeric molecules.

Three classes of super disintegrant are commonly used: Modified cellulose (Croscarmellose Sodium – Ac-Di-Sol®, Vivasol®), Crosslinked Polyvinyl Pyrrolidone (Crospovidone – Polyplasdone® XL-10), and Modified starch (Sodium Starch Glycolate – Primojel®, Explotab®).

The basic objective of this study was to produce immediate release tablets containing Diltiazem Hydrochloride by direct compression and to compare their properties, disintegration time, and dissolution profiles.

Diltiazem Hydrochloride was used as a model drug for immediate release tablets because of its primary indication in cardiovascular disorders where rapid onset of action is important. To achieve this goal, it is necessary to find suitable disintegrants having excellent compatibility and disintegrating properties.

❖ **Main key functions of Diltiazem Hydrochloride are :-**

1. **Antihypertensive**: Effective in reducing high blood pressure by relaxing blood vessels and improving blood flow.

2. **Antianginal**: Commonly used to prevent and control chest pain (angina) by improving oxygen supply to the heart muscles.

3. **Antiarrhythmic**: Helps in controlling abnormal heart rhythms by slowing electrical conduction in the heart.

4. It improves heart efficiency and reduces the workload on the heart.

- ❖ Mechanism of action :

1] Diltiazem Hydrochloride (Calcium Channel Blocker]

2] Blocks L-type calcium channels in cardiac and vascular smooth muscle.

3] Reduces calcium influx into cell Decreases myocardial contractility and heart rate.

4]Relaxes vascular smooth muscle (vasodilation Reduces blood pressure and myocardial oxygen demand Antianginal, Antihypertensive and Antiarrhythmic effect.

Concept of CGMP :-

Definition:-

1) The cGMP is defined as the regulations executed by the FDA that provides for systems will be to assure proper design, monitoring, and control of manufacturing processes and facilities.

2) The first WHO draft text on GMP was adopted in 1968.

3) GMP in India is prescribed under Schedule M in June 1988

4) In India Joint Commissioner (HQ) is authorized by Commissioner of State FDA, to sign and issue the certificate under the WHO GMP certification.

Objectives:-

The objectives of Current Good Manufacturing Practices (CGMP) are to ensure that products are consistently produced and controlled according to quality standards. CGMPs are enforced by regulatory authorities such as the FDA (in the U.S.) and serve as guidelines for manufacturing, testing, and quality assurance.

- **Key Objectives of CGMP:**

1) **Ensure Product Quality-**

To guarantee that pharmaceutical and other regulated products meet required quality standards for safety, efficacy, and purity.

2) **Minimize Risks-**

To reduce the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product alone.

3) **Compliance with Regulatory Requirements-**

To ensure manufacturing processes comply with national and international regulations, helping avoid legal issues and penalties.

4) **Consistent Production-**

To ensure that every batch of a product is produced consistently with the same quality attributes.

5) **Proper Documentation-**

To maintain detailed and accurate records of all manufacturing and quality control activities for traceability and accountability.

6) **Control of Manufacturing Processes-**

To establish and maintain validated processes that control critical manufacturing steps.

7) **Facility and Equipment Maintenance-**

To ensure the manufacturing environment and equipment are clean, maintained, and suitable for their intended use.

8) **Qualified Personnel-**

To employ properly trained and qualified personnel to handle all operations correctly and safely.

9) **Change Control and Continuous Improvement-**

To manage changes in procedures, equipment, or processes in a controlled manner and to continuously improve manufacturing practices.

❖ **<u>Following few basic principles are basis of GMP guidelines.</u>**

1. The production and distribution of the drugs must minimize any risk to their quality.
2. Manufacturing facilities must maintain a clean and hygienic manufacturing area, including laboratories and storage.
3. Manufacturing facility design, operating principles and environmental conditions must be controlled.
4. Manufacturing process must be clearly defined, validated, and controlled to ensure consistency and compliance with specifications
5. Any changes to the process must be evaluated, qualified, or validated as necessary.
6. Instructions and procedures must be written in clear and unmistakable language.
7. Operators should be trained to carry out the production and control of products as per approved procedures.
8. Records should be made during manufacture and quality control. Any deviations are examined documented.

9. The process should remain in a state of control throughout the product life cycle and it must be made when needed.

II. MATERIALS AND METHODS

Materials :

The following materials are commonly used in the formulation of Diltiazem Hydrochloride IP 60 mg Immediate Release Tablets:

- **Active Pharmaceutical Ingredient (API):**

  Diltiazem Hydrochloride IP

- **Excipients:**

  - **Diluents:** Microcrystalline Cellulose (MCC), Lactose Monohydrate
  - **Binder**: Polyvinylpyrrolidone (PVP K30)
  - **Disintegrants:** Croscarmellose Sodium (CCS), Sodium Starch Glycolate (SSG)
  - **Glidant:** Colloidal Silicon Dioxide (Aerosil 200)
  - **Lubricants:** Magnesium Stearate, Talc
  - **Solvents:** Purified Water (for binder solution)

All chemicals and ingredients used were of analytical or pharmaceutical grade, compliant with IP standards.

Methodology :

The Diltiazem Hydrochloride 60 mg Immediate Release tablets are generally prepared using the Wet Granulation Method, considered ideal due to better flow, compressibility, and uniform drug distribution. Below is the step-by-step methodology:

Preparation Method (Wet Granulation):

Step 1: Sifting

Accurately weighed Diltiazem HCl, lactose, and part of MCC are passed through a #40 mesh sieve.

Step 2: Dry Mixing

The sifted ingredients are blended thoroughly for 10–15 minutes to ensure proper drug distribution.

Step 3: Preparation of Binder Solution

PVP K30 is dissolved in a suitable volume of purified water to form a uniform binder solution.

Step 4: Wet Granulation

The binder solution is slowly added to the powder mixture with continuous mixing to form a cohesive wet mass.

Step 5: Granulation / Sieving

The wet mass is passed through a #12 or #16 mesh to produce uniform granules.

Step 6: Drying

The granules are dried in a tray dryer at 50–60°C until moisture content is below 2%.

Step 7: Sizing of Dried Granules

Dried granules are passed through #20 mesh to break oversized lumps.

Step 8: Lubrication

Aerosil, talc, and magnesium stearate are sieved (#60 mesh) and mixed with the dried granules for 3–5 minutes.

Step 9: Compression

Tablets are compressed using a rotary tablet compression machine equipped with 8 mm or 9 mm punches. Compression force is adjusted to achieve desired hardness (4–6 kg/cm²). Formulation Table: compare to other disintegrant. Due to its high interfacial Activity, it enhances the dissolution of poorly soluble drugs.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem Hydrochloride	60	60	60	60	60	60	60	60	60
Croscarmellose Sodium	3	6	9	-	-	-	-	-	-
Sodium Strach Glycolate	-	-	-	3	6	9	-	-	-
Microcrystalline cellulose	71	68	65	71	68	65	71	68	65
Mannitol	58	58	58	58	58	58	58	58	58
Orange Flavour	2	2	2	2	2	2	2	2	2

Formulation Table

Talc	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Total Weight (mg)	200	200	200	200	200	200	200	200	200

Evaluation of Diltiazem Hydrochloride 60 mg Immediate Release Tablets:

1. Pre-Compression Studies

Before tablet compression, the prepared granules are evaluated for physical properties to ensure good flow and compressibility.

2. Angle of Repose

Angle of repose was determined by measuring the height of the Cone of powder and Calculating the angle of repose - , from the prepared immediate release Diltiazem Hydrochloride

Tablets were characterized for their physicochemical properties, the methods are Discussed along with disintegration time and drug dissolution characteristics as The end of a funnel was Placed 2 cm above a flat base. The funnel was filled with The Powder , therefore after releasing the Powder out of the funnel the top of the resulting.

Cone Reached the end of the funnel. From the height of the cone (h) and the diameter at the base (d),

the angle of repose,(α) was determined:

Tan (α) =height /0.5×base

Where, Θ = is the angle of repose

H = is the height in (cm)

R = is the radius in (cm)

1 Determines the flowability of granules.

2 Method: Fixed funnel method

3 Acceptable range: 25°–30° indicates excellentflow; <35° acceptable.

3. Bulk Density

Bulk density measurements were carried out using flat –ground Measuring Cylinder with a volume of 250 ml .The cylinder was filled With the specified mass of powder mixture and Unsettled apparent Volume V0 was read to the nearest millilitre. After 10, 250, 500,1250 taps the corresponding volume was read to the nearest Millilitre.

- **Bulk density (P)= Weight of microcapsules(g)(M) ÷Bulk volume (ml) (V)**

- Volume occupied by powder before tapping.Formula:Bulk density =Weight of powder/Bulk volume.

4.True, bulk, and tapped density

The true densities of the powder mixtures were determined by Helium Picnometry . Three samples of each mixture were analyzed, each sample Was Read three times, and the overall means were calculated.

I] Tapped Density

Tapped density refers to the mass per unit volume of a powder when voids or Air gaps between particles are eliminated.

True/Tapped density (p_1)= Weight of microcapsules(g)(M)÷Tapped volume(ml)(V)

- Volumed after machinal tapping formula :

Tapped Density =weight of powder /bulk volume

5. Carr's Compressibility Index

Compressibility index was determined according to Carr'sindex: **Carr's index = (Tapped density)–(Bulk density) ÷ (Tapped density x 100** Indicates compressibility of granules.

Carr's Index = (Tapped density – Bulk density /Tapped density)

× 100

[1] 5–15% → Good flow

[2] 16–20% → Fair flow

6. Hausner Ratio

Flowability was defined according to Hausner ratio: **Hausner ratio = (Tapped density)/ (Bulk density)**

Flow of powder was measured using a standard funnel as Described in Ph. Into a dry Funnel, whose bottom opening has been blocked by suitable Means, a test sample was Introduced without compacting.

Hausner ratio = (Tapped density)/ (Bulk density)

Hausner ratio =Tapped density/Bulk density

[3] 1.00–1.25 → Good flow

7.Post-Compression Studies:

After compression, the tablets are evaluated to ensure quality, strength, and performance.

8.General Appearance

TABLE I. Shape, color, surface texture

TABLE II. No cracks, chips, or mottling.

9. Thickness and Diameter

Fig. 1. Measured using Vernier caliper.

Fig. 2. Ensures uniform size for packaging.

10. Hardness (Crushing Strength)

[1] Measures mechanical strength.

[2] Ideal range: 4–6 kg/cm².

11. Friability

- Using Roche friabilator (100 rotations).
- Tablets should not lose more than 1% weight.

12. Weight Variation

- 20 tablets weighed individually.
- Limits as per IP :o ±7.5% for tablets 130–324 mg.

13. Drug Content (Assay)

- Tablet should contain 95–105% of the label claim(60 mg).
- Method: UV spectrophotometer or HPLC.

14. Disintegration Time

- Tested using IP disintegration apparatus.

Immediate Release tablet:o Must disintegrate within 15 minutes in water at 37°C.

15. In vitro Dissolution Study

- Using USP Type II (paddle apparatus).
- Medium: 900 mL pH 6.8 phosphate buffer
- RPM: 50–75

- Requirements :o NLT 80% drug release within 30 minutes.

16. Stability Studies

Conducted as per ICe after mechanical tapping.

Formula:

- Tapped density =Weight of powder/Tapped volume

SOP handling:-

Standard Operating Procedure

- SOP is the written step by step instrument that how to Perform the activities to complete the task. All concern persons are required to follow these steps. SOP are the application in all type of industries, Rules & Regulation, Government Laws & Organization to running the own business. SOPs defines the essential steps, their sequences, and the precautions essential to formally repeat a quality performance.
- Pharmaceutical Standards Operating Procedure (SOP) is a tested, verified, approved, and documented way of executing operations that form the pharmaceutical industries basis. It Provides step by step guidance for the personnel to perform a specific process.
- A Standard Operation Procedure is written in document. That lists the routine tasks necessary to maintain the calibre of the inquiry.

Equipment and Instrument Handling

1)Weighing Balance :-

Procedure For Handling Digital Weighing Balance

1. Plug in to ensure the power supply.
2. Switch ON the main power supply and instrument mains.
3. Make sure the weighing pan is free of particles.
4. Ensure that the initial weights that is displaying is ZERO.
5. Place the weighing vessel, Weigh boat, or weighing paper on the balance pan.
6. Press on the TARE button so the display reads ZERO.
7. Using a spatula or sampling tool, transfer the substance being measured into the weighing vessel placed on the balance pan.
8. Record the mass of the object as displayed.
9. Do not exceed the limit of precision of the instruments. This is a major reason for error in measurement.
10. After use SWITCH OFF the balance.

2) DoubleConeBlender:-

Procedure For Handling Double Cone Blender

1. Ensure that the lid and safety pin lock are properly assembled from one side.
2. Adjust the angle of the blender with the help of a moving wheel to a required position for convenience in loading of materials.
3. Load all the materials from the containers into the blender.
4. After loading the materials, close the lid of the blender.
5. Put the safety pin on the lid and fit it properly.
6. Switch ‘ON’ the equipment and start the mixing as per the time specified.
7. When the mixing is completed, switch off the equipment.
8. Adjust the position of the blender at the required angle for convenience in unloading the material
9. Unlock the safety pin and remove the lid from the blender.
10. Unload the mixed materials in cleaned polythene lined SS containers and label it appropriately.

3) SieveApparatus :-

Procedure For Handling Sieve Apparatus

1. Select the sieves with mesh sizes that are to be used and stack them together beginning with a pan at the bottom.
2. Then the finest sieve followed by increasing coarser sieves with the coarsest on top.
3. Place stack of sieves in the shaker with the bottom pan resting on the cradle platform.
4. Cover the top sieve so that the stack can be easily secured in the shaker.
5. Secure the stack with the sieve hold-down bar on the stack and screw the nuts on the vertical support rods firmly against the holder.
6. Adjust and tighten the nuts at the top of the vertical support rods according to the weight of the material in the sieves.
7. The greater the weight of the load, the tighter the nuts should be.
8. Start the motor and observe the initial sieving action to see if the sieves are fastened securely, readjust and tighten the nuts if necessary.
9. Set the built-in timer for the desired shake time and turn the machine on.
10. The machine will stop when the timer has expired.

4)Tablet compression Machine :-

Procedure For Handling Tablet Compression Machine.

1.Change the status of area & equipment and ensure that dully filled and signed status label is affixed on the equipment as per SOP for Status Labelling.

2.Release the pressure before cleaning the machine.

3.Switch ‘’OFF’’ electrical supply, remove all adhering powder on the machine with the help of vacuum dust extraction pipe.

4.Use Compressed Air gun to remove dust from inner area.

5.Remove the hopper, feed frame, Tablet chutes, extraction points, granule scraper, Studs and kept them in a SS trolley cover with polybag & take it to washing area through unclean equipment room.

6.Clean the machine parts thoroughly with sufficient potable water by using with nylon scrubber & finally rinse with Purified water followed by drying with compressed air.

7.Remove the upper punches, lower punches and dies carefully, clean them thoroughly with 70% IPA & store them in punches & dies cabinet as per SOP for Punches and Dies

8.Remove the following parts from the machine & clean them with 70 % IPA & dry with lint free cloth.

Clean the upper cams with 70 % IPA & dry with lint free cloth.

5) Friability Tester :-

Procedure For Handling Friability Tester

1. Ensure that the instrument is clean & dust free.
2. Weigh accurately the number of tablets & carry out the procedure as described in the monograph.
3. Open the apparatus from the removable side of the drum.
4. Transfer the tablets in it & close the drum.
5. Switch on the apparatus & count the resolutions as specified in the monograph.
6. The tablets are tumbled at each term of the drum by a curved projection that extends from the middle of the drum to the outer wall.
7. Rotate the drum 100 times & remove the tablets.
8. Remove any loose dust/broken tablets & weigh.
9. Switch off the apparatus after the use.

6) Disintegration Test Apparatus :-

Procedure For Handling Disintegration Test Apparatus

1. Ensure that the instrument is clean & free from dust.
2. Ensure that the all the switches & knobs are off & in normal position.
3. Switch on the main switch & then put ON/OFF switch at the rare panel to on position.
4. Suspended the basket rack assembly in the 1000ml beaker containing the specified liquid medium.
5. Switch on the heater-thermostat & adjust the temperature of the liquid bath at 37 +/- 20◦c
6. Now add the no. of samples (tablets/capsules) as specified in the monograph, in the cylindrical holes provided in the basket/rack assembly.
7. Close with disc where applicable & specified in the monograph. Start the oscillation by putting its switch at on position.

The oscillations can be set as required with the help of thermostatic control knob & switch off the apparatus after the use|

EXIPIENT COMPATIBILITY STUDY:-

The drug-excipients compatibility study is the preliminary step in the development of Solid Dosage form of a drug substances and it is defined as an investigation of physico Chemical Propertiesol drag substance alone and when combined with excipients.

To perform a drug–excipient compatibility study using DSC (Differential Scanning Calorimetry), the thermal behavior of diltiazem is compared with its mixtures (1:1 w/w) with each excipient. This analysis helps determine physical or chemical interactions, especially melting point shifts, disappearance of drug peaks, or formation of new peaks.

DSC-Based Drug–Excipient Compatibility Study

- **Drug:** Diltiazem Hydrochloride **Excipients:-**
- **Diluents:** Microcrystalline Cellulose (MCC), Lactose Monohydrate
- **Binder:** Polyvinylpyrrolidone (PVP K30)
- **Disintegrants:** Croscarmellose Sodium (CCS), Sodium Starch Glycolate (SSG)
- **Glidant:** Colloidal Silicon Dioxide (Aerosil 200)
- **Lubricants:** Magnesium Stearate, Talc o Solvents: Purified Water (for binder solution)

- **Objective**

To determine the thermal compatibility of Diltiazem with selected excipients by analyzing changes in melting endotherm, enthalpy, or appearance of new thermal events.

Methodology

- **Sample Preparation**

Each mixture: 1:1 ratio of Diltiazem Hydrochloride and excipient

Samples: Diltiazem Hydrochloride alone with each excipient

Instrument: DSC with N_2 purge Heating rate:
10°C/min

Temperature range: 25–300°C

- **Expected Observation**

Pure Diltiazem hydrochloride : Sharp endothermic peak at ~213°C (melting point)

Compatible: Minor shift or no change in peak

Incompatible: Peak disappears, broadens, or new peaks appear.

Below is the DSC-based compatibility study of Diltiazem Hydrochloride with commonly used excipients of immediate-release tablets.

The blue bars represent the DSC peak temperatures.

The red line indicates enthalpy change.

Noticeable temperature depression or major enthalpy reduction indicates possible interactions.

Hypothetical DSC Peak Data

Sample	Peak temperature (.c)	Enthalpy (J/G)	Interpretation
Diltiazem HCl (Pure Drug)	213.2	135	Baseline control
Microcrystalline Cellulose (MCC PH 102)	212.5	130	Slight shift ,likely compatible
Lactose Monohydrate	212.8	128	Small decrease compatible
Croscarmellose Sodium	211.9	132	Minor shift Compatible
PEG 4000	208.5	95	Slight depression - possible interaction
Sodium strach gylcolate (scg)	212.0	133	Stable compatible
Magnesium stearate	205.0	80	Major shift
Talc	212.7	134	No significant change , compatible
Aerosil 200	213.0	133	Stable compatible

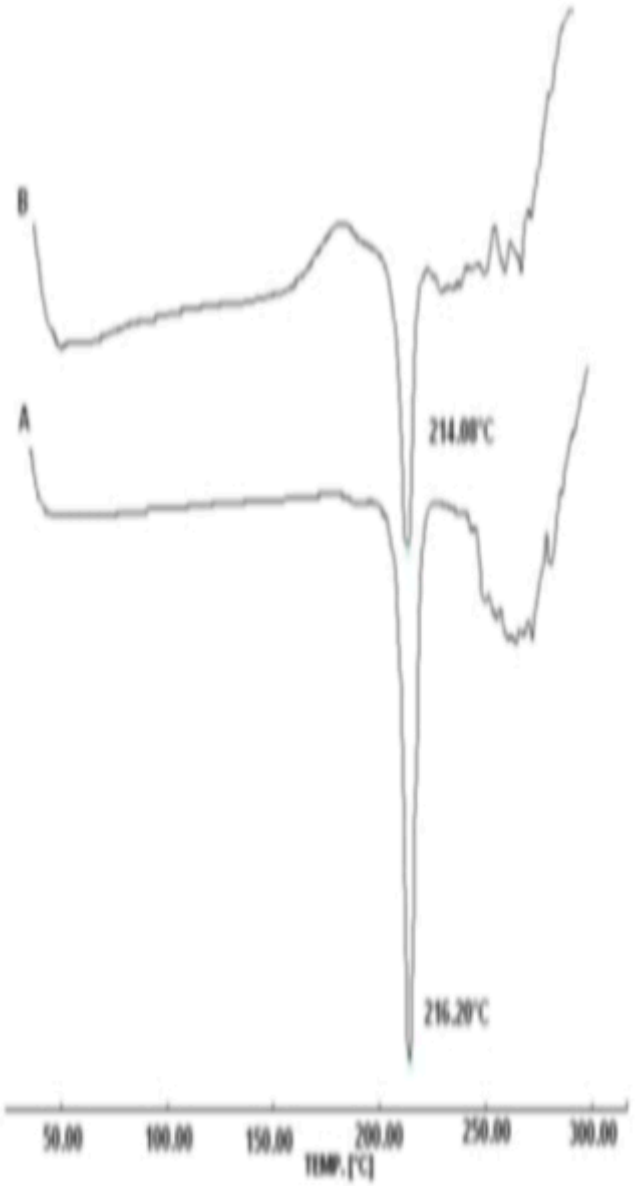


Figure 5: Overlain DSC of A) pure drug Diltiazem hydrochloride and B) optimized formulation F3

Fig:1. Graphical representation of Excipient Compatibility study(DSC)

ROLE OF INGREDIENTS

INGREDIENTS	ROLE OF INGREDIENT
Diltiazem Hydrochloride	API
Microcrystalline cellulose	Diluent compressibility
Lactose Monohydrate	Diluent
PVP K30	Binder
Croscarmellose sodium	Super disintergration
Sodium Starch Glycolate	Super disintergration
Mg Stearate	Lubricant
Aerosil 200	Glidant

PREFORMULATION OF STUDIES

A. Introduction : It is defined as the phase of research and development in which pre-formulation studies characterize physical and chemical properties of a drug molecule in order to develop safe, effective and stable dosage form.

In pre-formulation studies, physicochemical properties of drug molecules are characterized either alone or in combination with excipients. The meaning of pre-formulation refers to the steps to be undertaken before formulation.

Pre-formulation includes determination of physical chemical properties of drug substance with the goal of developing a new drug which is safe stable and efficacious. Each drug has intrinsic chemical and physical properties that were considered prior to the development of pharmaceutical formulation the purpose of pre-formulation study is to generate useful information for the formulator in the development of stable and bioavailable dosage form.

Inappropriate pre-formulation study results in poor stability of active ingredients increase the overall cost of development and increased development time.

After compiling all data it is transferred to the development pharmacist and for the day work on formulation of dosage form.

B. Objectives:

To establish the Physicochemical parameters of a new drug entity

To determine its kinetics and stability

- It provides insights into how drug products should be processed and stored to ensure their quality
- To estimate problem may arise during formulation that is stability problem poor in Vivo dissolution and poor bioavailability
- To develop optimal drug delivery system.

1. Goals.

1.To establish physicochemical parameter of candidate drug molecule.

2.To determine the Kinetic rate profile of drug substance.

3.To establish the compatibility of candidate drug molecule with common excipients

4.To choose the correct form of drug substances .

2.Physicochemical Characteristics of Diltiazem Hydrochloride Drug.

a. **Common Name:** Diltiazem Hydrochloride

b. **Chemical Name:**

(2S,3S)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3-dihydro1,5-benzothiazepin-3-yl] acetate;hydrochloride.

C. Synonyms:

1.Diltiazem hydrochloridum

2.Diltiazem monohydrochloride

3.(2S,3S)-3-Acetyloxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl) 1,5benzothiazepin-4(5H)-one hydrochloride (IUPAC / chemical name)

4.Benzothiazepine calcium channel blocker (class-based synonym)✔ Brand / Trade Names (Common in many countries)

1.Cardizem

2.Dilzem

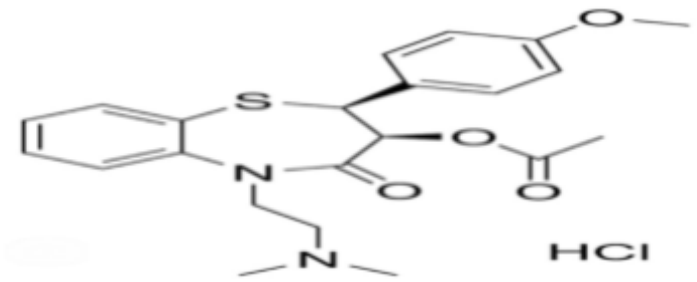
3.Dilt-CD

4.Tiazac

c. **Molecular Formula:**

$C_{22}H_{26}N_2O_4S \cdot HCl$

d. **Structural Formula:**



e. **Molecular Weight: 450.98 g/mol**

▯ Chemical and physical properties of Diltiazem Hydrochloride.

a. Description: White to off-white crystalline powder, odourless.
b. Melting point: 200-204 °C (decomposition}c. Solubility: Freely soluble in water, soluble in methanol, slightly soluble in ethanol (96%), practically insoluble in acetone and inether.
c. .Spectroscopy data: Infrared, ultraviolet, nuclear magnetic resonance, fluorescence and mass spectra have been reported
d. . Stability: Diltiazem Hydrochloride is stable under normal conditions. It is slightly hygroscopic and should be protected from light and moisture. Degradation may occur under strongly acidic or alkaline conditions and at elevated temperatures.
e. Dissociation constant: pKa= 7.7-8.1
f. Partition coefficient: log P (octanol: water, pH 7.4) -2.6-3.1

❖ EVALUATION TEST:-

1) ORGANOLEPTIC PROPERTIES.

Property	Description
1.Appearance	Crystalline powder
2.Colour	White
3.Odour	Odourless
4.Taste	Slightly better

Table.no. 4:Organoleptic Properties

2) DISSOLUTION TEST

Purpose: The dissolution test measures the rate and extent to which diltiazem hydrochloride is released from the tablet into solution. It's important for ensuring the tablet will deliver the drug properly in the body.The vessel is partially immersed in a suitable water-bath of any convenient size or heated by a suitable Device such as a heating jacket. The water-bath or heating device permits maintaining theTemperature inside the vessel at 37 ± 0.5 ºC during the test.

General Procedure:

1.Apparatus:

USP Apparatus 1 (Basket) or Apparatus 2 (Paddle).Most commonly, Apparatus 2 (Paddle) is used for diltiazem tablets.

2.Test Medium:

Usually 900 mL of phosphate buffer (pH 5.8) or 0.1N HCl (depending on pharmacopeia standards).
Temperature maintained at 37 ± 0.5°C (simulating body temperature).

3.Paddle Speed:

Commonly set at 50 rpm.

4.Sampling Times:

Samples typically taken at 5, 10, 15, 20, 30, and 45 minutes (as per requirement).

5.Sample Handling:

Withdraw a specific volume (e.g., 10 mL), replacing it with fresh medium.Filter and analyze the sample using UV spectrophotometry at λ = 243 nm or HPLC.

6.Acceptance Criteria:

Example (based on USP for immediate release): Q = 80% (amount dissolved) in 30 minutes.
(Q = quantity of active ingredient dissolved.)

Analysis

Measured the absorbance of each sample at λ_max = 243 nm using a UV-Vis Spectrophotometer. Calculated the concentration of diltiazem l in each sample using a previously Constructed calibration curve Determined the cumulative percentage of drug released (% CR) at each time point.

Important Notes:

If tablets don't meet dissolution at the first stage (Stage 1), additional testing stages may be needed (Stage 2 or Stage 3).Uniformity of dissolution is important: individual tablet results should not fall far from the average.

Observation Table:

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	8	10	15	13	14	18	9	8	7
10	15	18	28	22	25	35	20	18	12
15	28	30	45	38	40	52	35	32	25
30	45	48	68	55	60	75	50	47	40
45	65	68	85	74	80	90	70	66	60
60	82	84	95	89	92	97	83	81	72

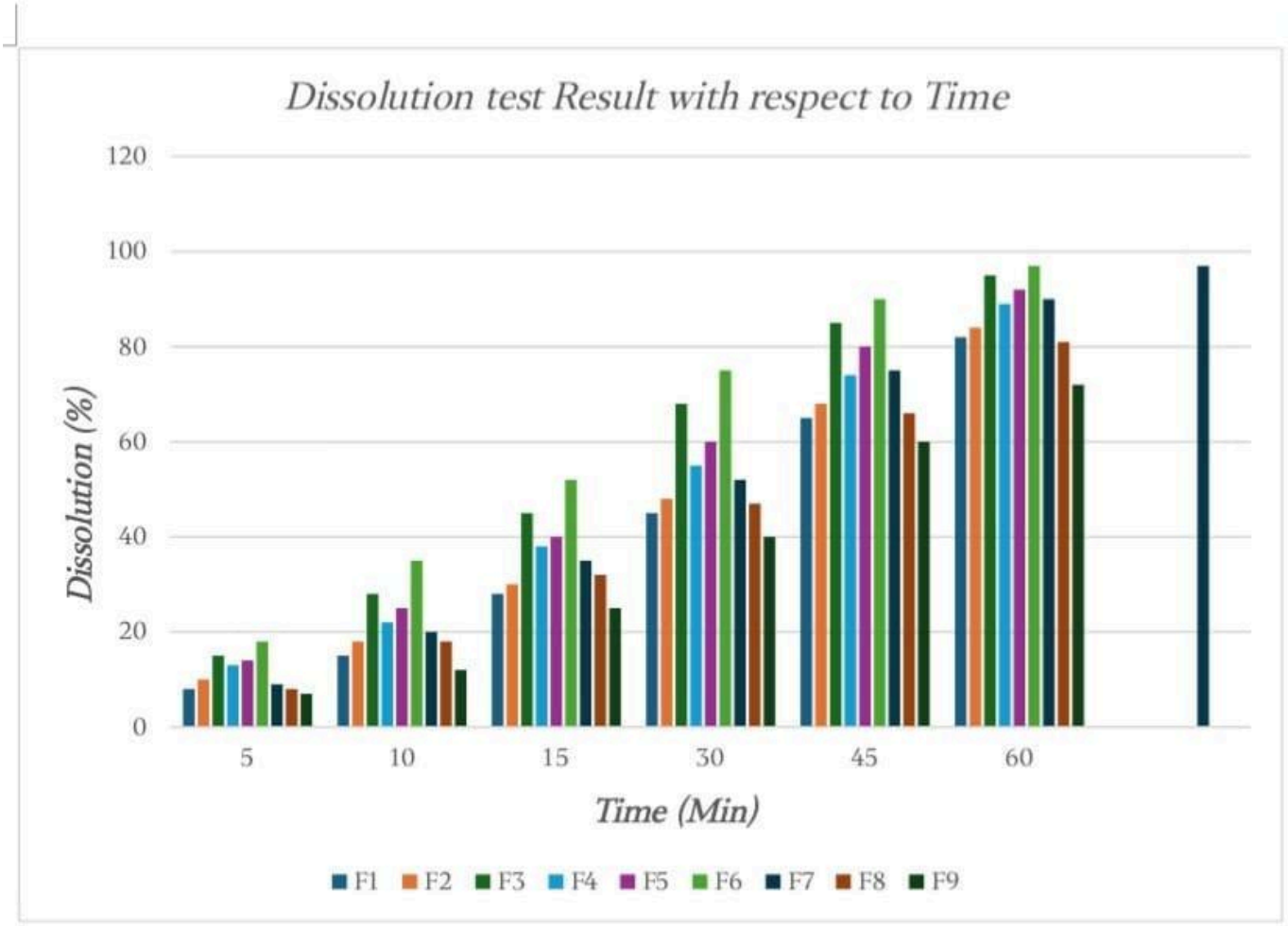


Fig 2. Graphical representation of dissolution test result

Disintegration Test

It is a laboratory test used to determine how quickly and completely a tablet or capsule breaks apart into smaller fragments in a specified liquid medium under standardized conditions. The purpose is to ensure that the dosage form releases the active ingredients properly for absorption in the body.It is commonly performed using a disintegration apparatus as described in pharmacopeias (like USP, IP, BP)

To carry out a disintegration test for tablets, we use a Basket which holds 1 to 6 tablets. This is Then raised and lowered into a beaker of water, which is Used to simulate conditions in the stomach at 3737 ± 0.5 ºC.

If the tablets , perforated plastic disks are placed on the top of the tablets To keep them under the

water level. The tablet disintegration Time is taken when no residue is left in the mesh.

Procedure:

Disintegration Test Apparatus was used to carry out the process.

The apparatus has one beaker containing basket rack with 6 tubes.

Apparatus setup:

• Fill each tube with distilled water at temperature 37°c.

• Place one tablet in each of the 6 tubes of the basket rack.

• Use a disc in each tube to ensure even pressure

• Suspend the basket in the beaker containing the medium.

Method:

Started the apparatus and observed the tablets Recorded the time when each tablet has

Disintegrated completely (no residue, except fragments of insoluble Coating).

As per BP/USP, all 6 tablets should disintegrate within 15 minutes (for uncoated tablets)

Result : Observation Table

Formula	Disintegration time
F1	6.2
F2	8.1
F3	5.5
F4	9.3
F5	6.8
F6	5.7
F7	5.9

Table no 6 ;Disintegration test result with respect to time

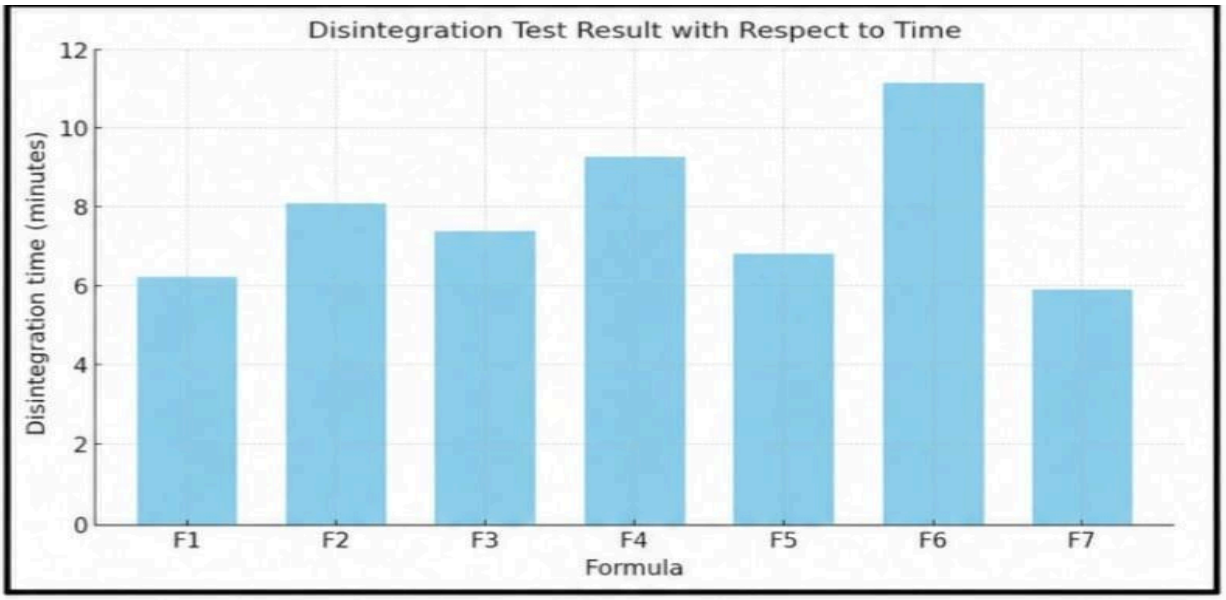


Fig.3: Graphical representation of Disintegration test result

4) WEIGHT VARIATION TEST.

Weight Variation Test checks the consistency of individual tablet or capsule weights in batch. A sample of units is weighed individually, and the average weight is calculated. Each unit's weight is compared to this average. If the variation falls within specified pharmacopeial limits (like USP, BP), the batch passes. It's mainly used for tablets and capsules to ensure uniformity and quality.

5) FRIABILITY TEST

Friability Test is done to measure how easily a tablet can break, chip, or crumble when handled —basically checking its mechanical strength. It's a key quality control test in tablet manufacturing.

The test is typically performed using a device called a friabilator (like a Roche Friabilator).

Procedure:

- Weigh a sample of tablets (usually around 6.5 grams or 10–20 tablets) — Initial Weight (W_0).
- Place them in the friabilator.
- Rotate the drum at 25 rpm for 4 minutes (100 revolutions total).
- Remove the tablets, dust them off, and weigh again — Final Weight (Wf).
- Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again.

The percentage friability was measured using the formula,

% F = {1-(Wo/W)} ×100

Initial weight – Final weight÷ initial Weight ×100

Where, % F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Friability test= Initial weight – Final weight÷ initial weight ×100

= 6500-6480÷ 6500 ×100

= 20 ÷ 983×100

=0.00307×100

Friability test =0.307%

6)HARDNESS TESTING

Formulation and development of diltiazem hydrochloride immediate release tablet

Tablet hardness is a measure of the force required to break a tablet in a test apparatus that places

The tablet under a tension. The hardness of a tablet plays a crucial role in its efficacy and overall

Performance,especially during packaging, shipping, and patient use.

The units of hardness testing are kilograms (kg), Newtons (N), or kiloponds (KP).

Monsanto hardness tester provides quick readings of Hardness of Tablets and measures Hardness in Kg per sq

Observation table :-

Tablet	Hardness in kg per cm2
1	4.2Kg/cm2
2	4.6 Kg/cm2
3	5.0 Kg/cm2
4	4.4 Kg/cm2
5	4.8 Kg/cm2
6	4.5 Kg/cm2
7	4.9 Kg/cm2
8	4.3 Kg/cm2
9	4.7 Kg/cm2

III. CALIBRATION CURVE OF P10 UV SPECTROSCOPY

A calibration curve of diltiazem hydrochloride is used in analytical chemistry . to determine the concentration of diltiazem hydrochloride in a sample .typical using UV-

Visible spectrophotometry or High -Performance Liquid Chromatograpy (HPLC) Here a general overview.

1.UV-VIS Spectrophotometery method

Steps to Create the Calibration Curve:

1.Prepare Standard Solutions: Make a series of Diltiazem Hydrochloride solutions with known concentrations (e.g., 2, 4, 6, 8, 10 µg/mL).

2.Measure Absorbance: Use a UV-Vis spectrophotometer to measure absorbance at the λmax (usually around 237 nm).

3.Plot the Curve:

- **X-axis:** Concentration (µg/mL)
- **Y-axis:** Absorbance

4.Draw the Line of Best Fit: This should be a straight line if Beer-Lambert law is followed.

5.Equation: Often linear: A = εbc or in the form y = mx + c, where:

Y = absorbance,

X = concentration,

M = slope,

C = intercept.

***Result*:-**

Estimation of Diltiazem Hydrochloride in tablet dosage forms by UV spectrophotometric

Method was Carried out using UV visible spectrum of Diltiazem Hydrochloride . The standard and sample solution were prepared and the absorbance were recorded .

The absorption maxima was calculated successfully ,showing accurate analytical result for immediate release table formulation .

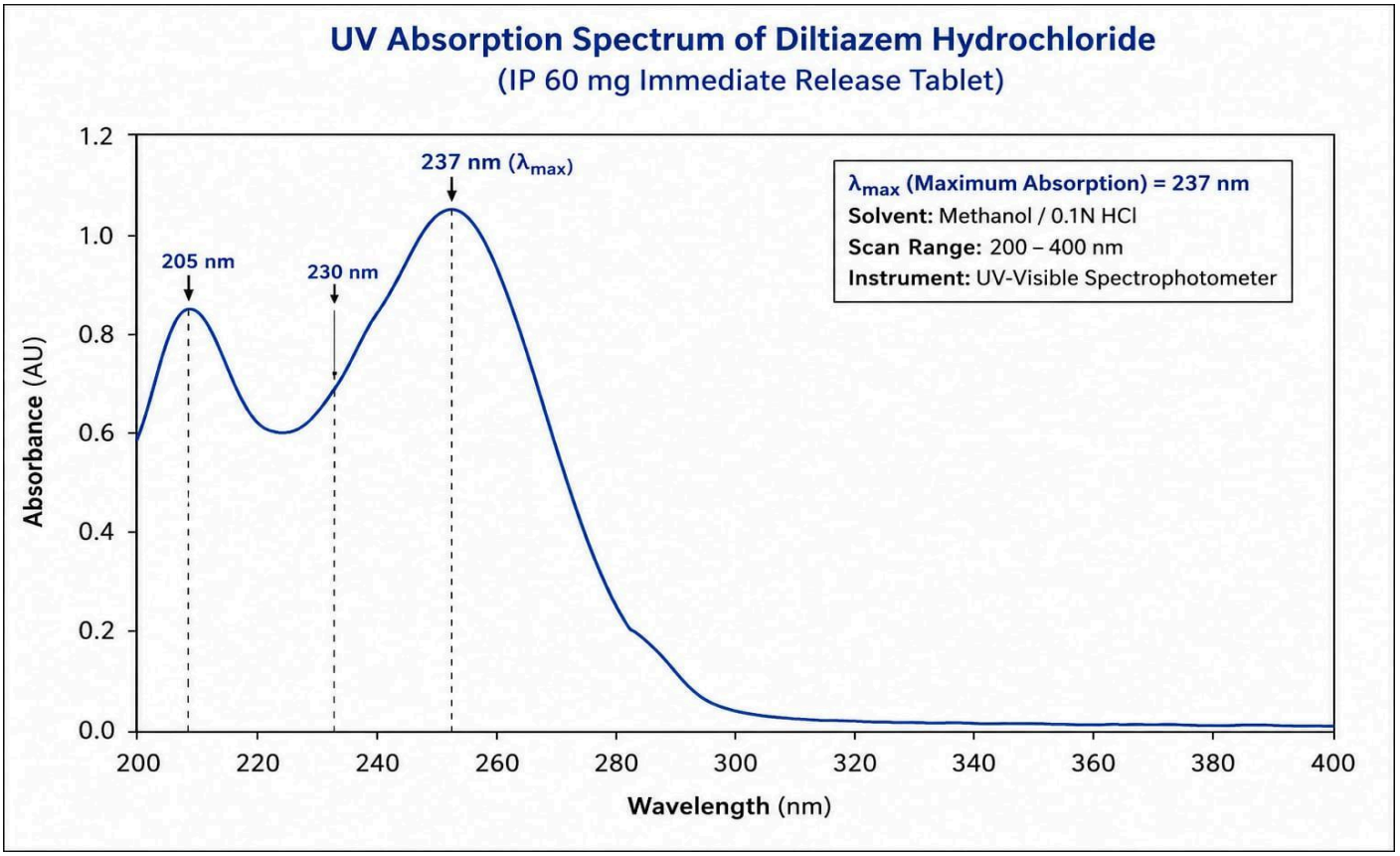


Fig 4; Graphical Representation of UV Spectroscopy result

IV. CONCLUSION

The formulation and evaluation of Diltiazem Hydrochloride IP 60 mg Immediate Release tablets demonstrate that a scientifically optimized combination of excipients and a wellcontrolled wet granulation process can successfully produce a stable, effective, and pharmaceutically elegant dosage form Pre-formulation studies provided essential insights into the drug's physicochemical characteristics and guided the rational selection of diluents, binders, and Super disintegrants. The prepared granules exhibited good flow and compressibility, ensuring uniform die filling and consistent tablet weight.Post-compression evaluation confirmed that the tablets met all pharmacopeial quality standards, including hardness, friability, drug content uniformity, disintegration time, and dissolution performance.

The rapid disintegration within a few minutes and achievement of more than 80% drug release within 30 minutes indicate excellent immediate-release characteristics, making the formulation suitable for rapid onset of therapeutic action. Furthermore, stability studies conducted under ICH conditions confirmed that the formulation remained physically and chemically stable, with no significant changes in drug content or dissolution

behaviour .Overall, the study concludes that Diltiazem Hydrochloride IP 60 mg Immediate Release tablets can be successfully developed using wet granulation and appropriate excipient selection. The formulation is robust, reproducible, and suitable for large-scale manufacturing, ensuring safe and effective delivery of Diltiazem for the management of cardio vascula disorder.

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