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# The Study of Polymorphism in Pharmaceutical Operating Processes: Granulation Technique for Carbamazepine Tablets

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**Abstract:-** Epilepsy, trigeminal neuralgia, and bipolar disorder are just a few of the conditions that are treated with Carbamazepine, a Dibenzazepine derivative. First-line treatment for seizures that has exceptional efficacy and is inexpensive is Carbamazepine (CBZ). Due to their high membrane permeability and low water solubility, which make dissolution the rate-limiting step in the absorption process, they are categorised as BCS class II substances by the Biopharmaceutical Classification System. The polymorphic alterations of the drug Carbamazepine are examined in its tablet dosage form by taking into consideration variations in the granulation process or method. To discover the polymorphic alterations in Carbamazepine, a DSC study was conducted for a tablet formulation. This study is set out to investigation to identify the effects of various granulation techniques on the drug Carbamazepine for distinct polymorphic alterations in tablet dosage form.

***Keywords:-*** *Carbamazepine, Polymorphism, DSC, Variations, Epilepsy, Tablet.*

## I. INTRODUCTION

In Human Kind any age group can be impacted by epilepsy, a chronic brain condition. Around 50 million people worldwide suffer from epilepsy. Greek term epilepsy translates as "to be overpowered, seized, or besieged." The propensity for seizures that a person has is simply referred to as having "epilepsy." The brain is a fragile and intricate organ. This organ directs and regulates all of our behaviours, gestures, feelings, thoughts, and emotions. It regulates the body's automatic internal processes, including heart and lung function. Brain cells communicate with one another using electric signals. On rare occasions, a seizure could be brought on by an abnormal electrical discharge from a group of cells.

According to the BCS classification system, Carbamazepine is a class II medication. Currently administered orally, Carbamazepine has a low water solubility (170 g/ml), requiring high and frequent doses to maintain therapeutic effect. This is important because it affects the slow and erratic GI system's slow and variable medicine absorption, which causes variable Carbamazepine bioavailability. It can also affect a wide range of API properties such as tableting, dissolving rate, solubility, stability, and even biopharmaceutical performance such as safety and efficacy as well as toxicity, as well as the physicochemical features of these polymorphic forms of API varies/changes such as dissolution and solubility[1].

Polymorphism is important physicochemical properties, and it brings major polymorphic changes in drug,in unit operations, bulk manufacturing as well as in manufacturing dosage forms on a large scale.

## II. EXPERIMENTAL

### *A. Material*

The Carbamazepine pure drug was procured from Aarti Distributers,Mumbai and all other ingredients were procured Loba-Chem Pvt. Ltd.

### *B. Methods*

a) Formulation and Development

The tablet's composition, which includes Carbamazepine, microcrystalline cellulose as a diluent, and magnesium stearate as a lubricant, was created to be hard and tough for the last dose. To improve medication compatibility and better understand the polymorphic changes that take place during the formation of Carbamazepine tablets, tablet formulation is created. Wet and Dry granulation was used to formulate the Carbamazepine tablet.

| Sr. No | Name of Ingredients | Quantity taken for each tablet (Set Formula) (mg) | Quantity taken for each tablet (Set Formula) (gm) | % Strength (w/w) |
|---|---|---|---|---|
| 1 | Carbamazepine | 100 | 0.1 | 33.33 |
| 2 | Starch | 4 | 0.004 | 1.33 |
| 3 | Magnesium Stearate | 1 | 0.001 | 65.33 |
| 4 | Microcrystalline Cellulose /Lactose | Q.S….. 300 | Q.S….. 0.3 | Q.S … 100 |

Table 1: Formulation of Carbamazepine Tablets

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b) Making Carbamazepine Tablets Through Dry and Wet Granulation:
According to the formulation table, the precise weights of all the constituents, including the medication and excipients, were recorded. After thoroughly combining all the materials, with the exception of the lubricant and disintegrant, the powder mixture was compressed into a slug. Following that, the slug was milled and sieved.

The next stage involved combining the granules with the disintegrant and lubricant before compressing them into tablets. All materials, including the medication and excipients, were correctly weighed for wet granulation in accordance with the formulation table. The ingredients, with the exception of the lubricant, were all well combined after which the starch paste was added. The damp mass was then made, wet screened, and then the damp mass was screened into granules.

The wet granulation process using hydroxypropyl methyl cellulose as the polymer in place of the diluent microcrystalline cellulose.

*C. Observations of Evaluations:*

a) Pre-Compression Parameters of Carbamazepine Tablets:

| Formulations | Angle of Repose | Loose of Bulk density (gm/ml) | Tapped Bulk Density (gm/ml) | Carr's Index | Hausner's Ratio |
|---|---|---|---|---|---|
| **A1** | 19.98 | 0.588 | 0.683 | 13.85 | 1.11608 |
| **A2** | 19.71 | 0.596 | 0.685 | 12.98 | 1.1492 |

Table 2: Preformulation Parameters of Powder Mixture :

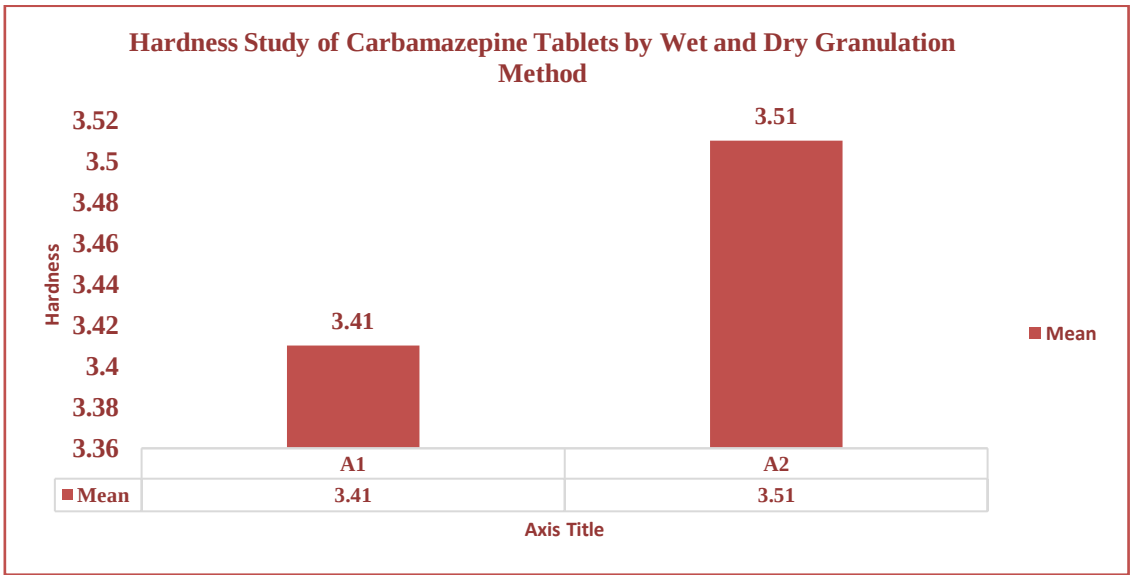
b) Flow Properties :
Determination of angle of repose, Carr's index and Hausner's ratio were used to characterize flow properties of powder which are used to prepare Conventional tablet of Carbamazepine by fixed funnel method . The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies.

*D. Post-Compresional Parameters of Carbamazepine Tablet:*

a) Hardness :
Tablets should be sufficiently hard to resist breaking during normal handling. The hardness of tablets was measured by Monsanto hardness tester, hardness was measured in terms of kg/cm$^2$.

| Formulations | Hardness (kg/cm$^2$) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | Mean | SD | SEM |
| A1 | 3.2 | 3.2 | 3.7 | 3.1 | 3.1 | 3.41 | ±0.444 | 0.27 |
| A2 | 3.2 | 3.5 | 3.0 | 3.3 | 3.3 | 3.51 | ±1.026 | 0.41 |

Table 3: Hardness of Carbamazepine Tablets




Graph 1: Hardness study of Carbamazepine Tablets by Wet and Dry Granulation Method.

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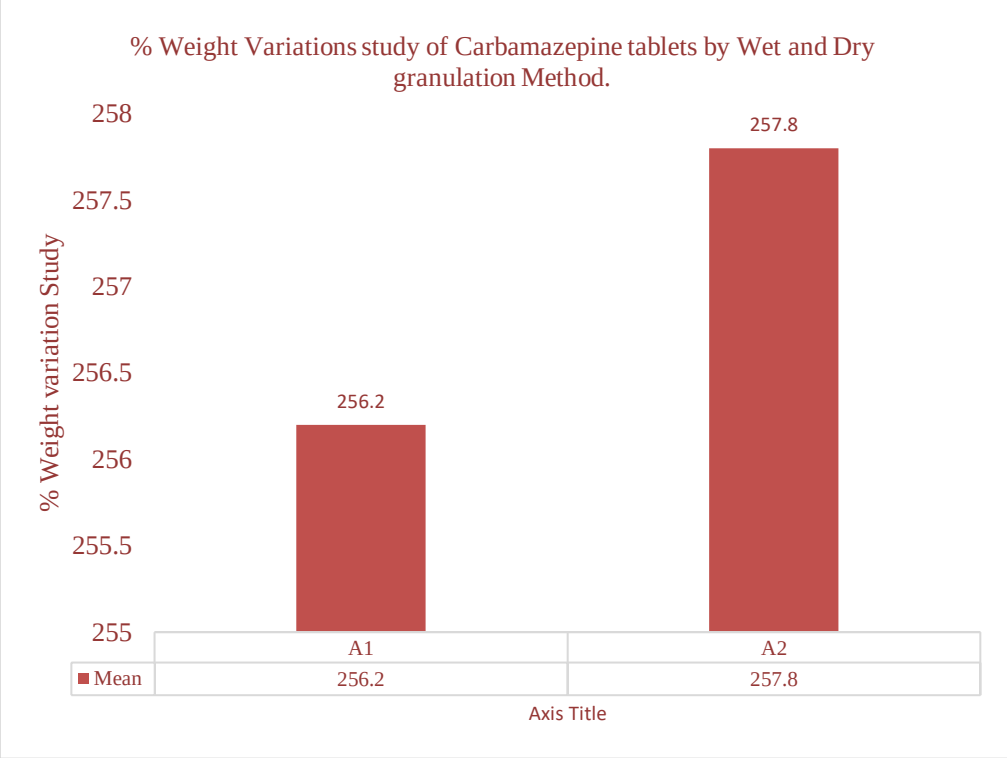
After compression, a tablet requires a certain amount of mechanical strength to withstand the shock of handling in the manufacture, packing, shipping and dispensing. The hardness of the tablet was found to be in the range of 3.41 to 3.55 kg/cm$^2$as shown in table. This ensures that tablets with good mechanical strength

b) % Weight Variation:
The weight of tablet were measured to ensure that a tablet contain the proper amount of drug. Weight variation test was performed as per IP 2007. Twenty tablets were selected randomly and weighed. Average weight of the tablet was determined,not more than the two of the individual weights deviate from the average weight by more than 5% percentage deviation.

| Formulation code | Mean | SD |
|---|---|---|
| A1 | 256.2 | ±1.356 |
| A2 | 257.8 | ±2.324 |

Table No.4: % Weight Variation Study of Carbamazepine Tablet




Graph 2: % Weight variation of Study of Carbamazepine Tablets

All the formulated A1 to A2 tablets shows 1.33%-2.36% weight variation was within the pharmacopoeial limits ±5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

c) Thickness:
The six tablets from each batch of formulation were collected and the diameter of the tablets was measured with the help of electronic VernierCaliper. The average thickness was calculated.

| **Formulation code** | **Thickness(mm)** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | Mean | SD | SEM |
| A1 | 6.4 | 6.5 | 6.4 | 6.5 | 6.7 | 6.3 | 6.46 | ±0.136 | 0.055 |
| A2 | 6.4 | 6.5 | 6.4 | 6.5 | 6.7 | 6.3 | 6.48 | ±0.147 | 0.060 |

Table 5: Thickness Study of Carbamazepine Tablets by Wet and Dry Granulation

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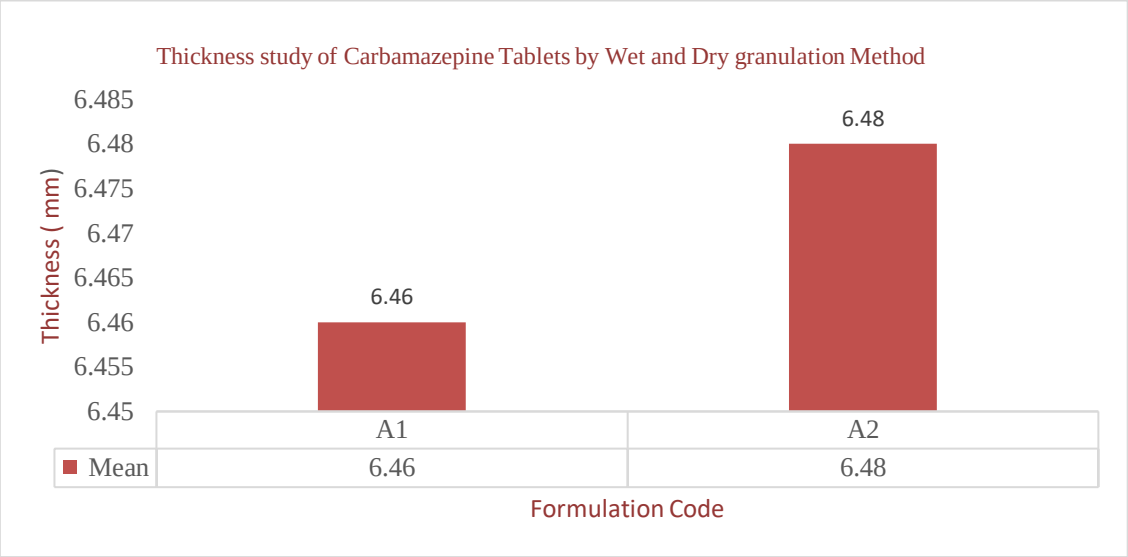


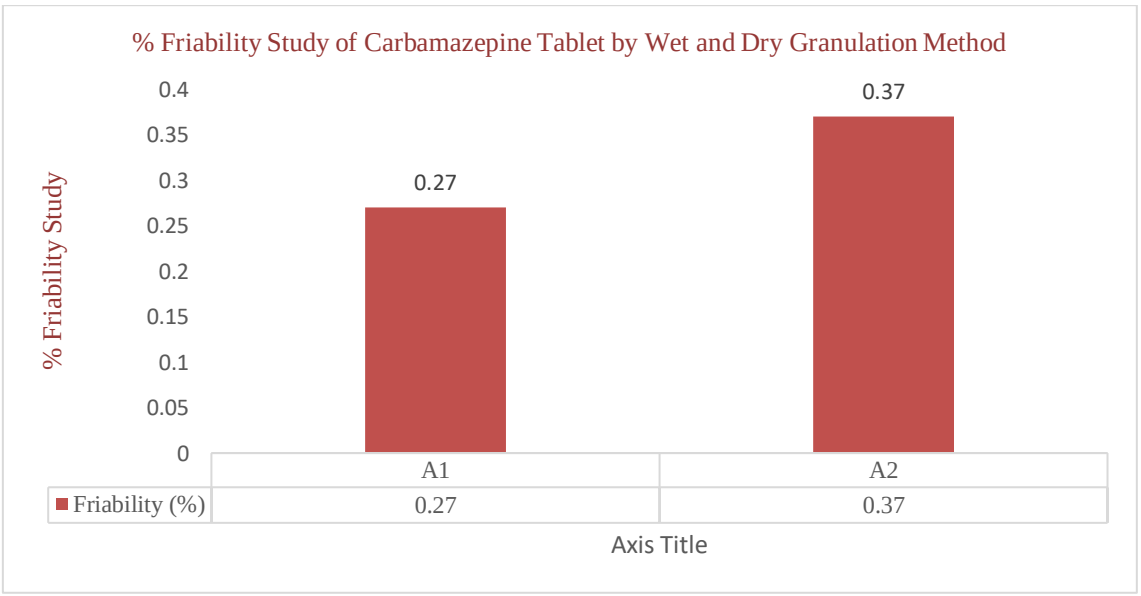

Graph 3: Thickness Study of Carbamazepine Tablet by wet and Dry granulation method.

Thickness of tablets were measured and found in the range of 6.46-6.48 mm. Uniform Thickness indicates uniform die fill, good flow properties, uniform pressure and uniform punch movement. It indicates thickness of the tablet is of 0.82-0.85 mm in thickness.

d) Friability :
Tablet hardness is not an absolute indicator of strength, since some formulation compressed into very hard tablet tend to cap on attrition losing their crown portion therefore another measure of tablet strengths, its friability is often measured. The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions at 25 rpm for 4 minute and then the tablets were reweighed. The percentage friability was calculated.

| Formulation Code | Initial Weight of 20 Tablets (mg) | Final Weight of 20 Tablets (mg) | Friability (%) |
|---|---|---|---|
| **A1** | 5.069 | 5.055 | 0.27 |
| **A2** | 5.112 | 5.093 | 0.37 |

Table 6: % Friability Study of Carbamazepine Tablets




Graph 4: % Friability Study of Carbamazepine Tablet by Wet and Dry granulation Method

The prepared tablets showed loss in weight in the range of 0.27 to 0.37%. The percent friability was less than 1% as

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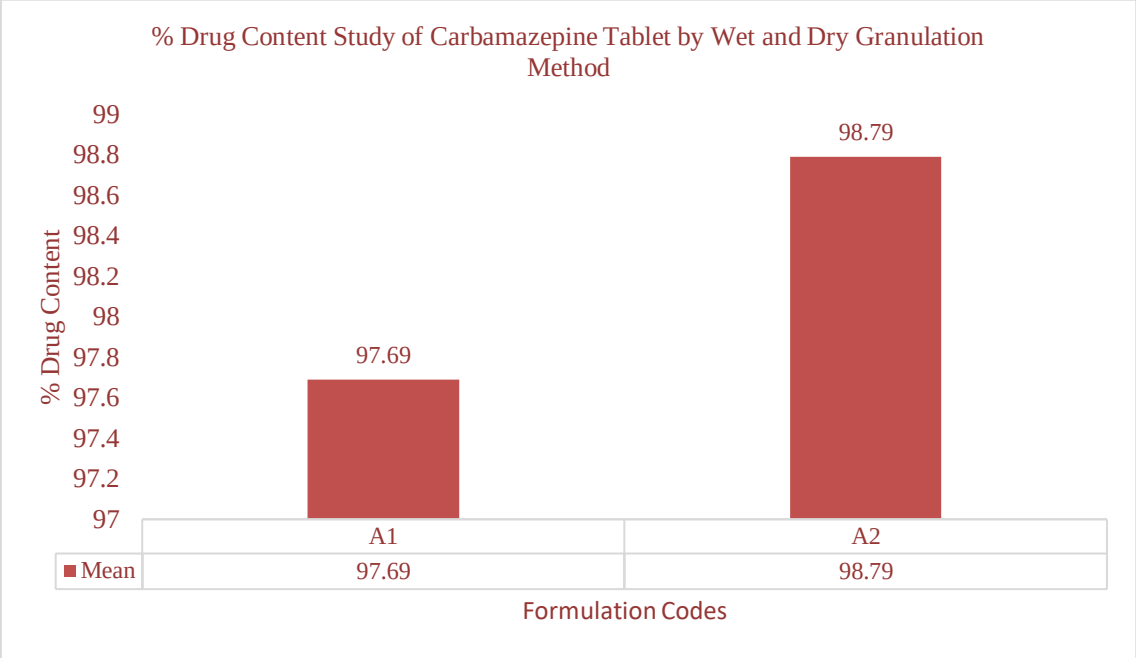
per official specification. This indicated that tablets of all formulations passed the friability test as per Pharmacopeial Standard and tablets were mechanically stable.

e) Drug Content:
The Six tablets of 300 mg from each formulation were taken in separate 100 ml volumetric flaks containing 1000 ml of pH 6.8 phosphate buffer and were kept for 24 hrs under constant stirring. The solutions were then filtered, diluted suitably and analyzed at 285 nm using UV spectrophotometer. The average of six tablets was taken as the content of drug in one tablet unit.

| Formulation Code | 1 | 2 | 3 | 4 | 5 | 6 | Mean | SD | SEM |
|---|---|---|---|---|---|---|---|---|---|
| A1 | 97.65 | 98.32 | 96.92 | 97.11 | 98.44 | 97.72 | 97.69 | ±0.40 | 0.35 |
| A2 | 98.75 | 98.42 | 98.85 | 99.22 | 97.65 | 99.85 | 98.79 | ±0.60 | 0.23 |

Table 7: % Drug Content Study of Carbamazepine Tablets

The percentage of drug content for A1 to A2 formulation was found to 97.26% to 98.97% of Carbamazepine, it complies with official specifications.




Graph 6: % Drug Content Study of Carbamazepine Tablet by wet and Dry Granulation Method

f) Drug Release Study of Formulations of Carbamazepine Tablets:

**I.** Drug Release of A1 Carbamazepine Tablets Formulated by Wet Granulation Method:

| Time (min) | Abs | Conc. (10µg/ml) | Conc. (µg/10ml) | Conc. (10 mg/10ml | Conc 10 mg/900ml | CDR | % CDR |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0.046 | 1.095 | 10.952 | 0.01 | 5.476 | 5.476 | 5.476 |
| 10 | 0.097 | 2.308 | 23.095 | 0.023 | 11.547 | 11.558 | 11.558 |
| 15 | 0.198 | 4.714 | 47.142 | 0.047 | 23.571 | 23.594 | 23.594 |
| 20 | 0.309 | 7.357 | 73.571 | 0.073 | 36.785 | 36.832 | 36.832 |
| 25 | 0.436 | 10.38 | 103.809 | 0.103 | 51.904 | 51.978 | 51.978 |
| 30 | 0.492 | 11.714 | 117.142 | 0.117 | 58.571 | 58.675 | 58.675 |
| 35 | 0.558 | 13.285 | 132.857 | 0.132 | 66.428 | 66.545 | 66.545 |

Table 8: Drug Release Study of A1 Carbamazepine Tablet by Wet Granulation Method

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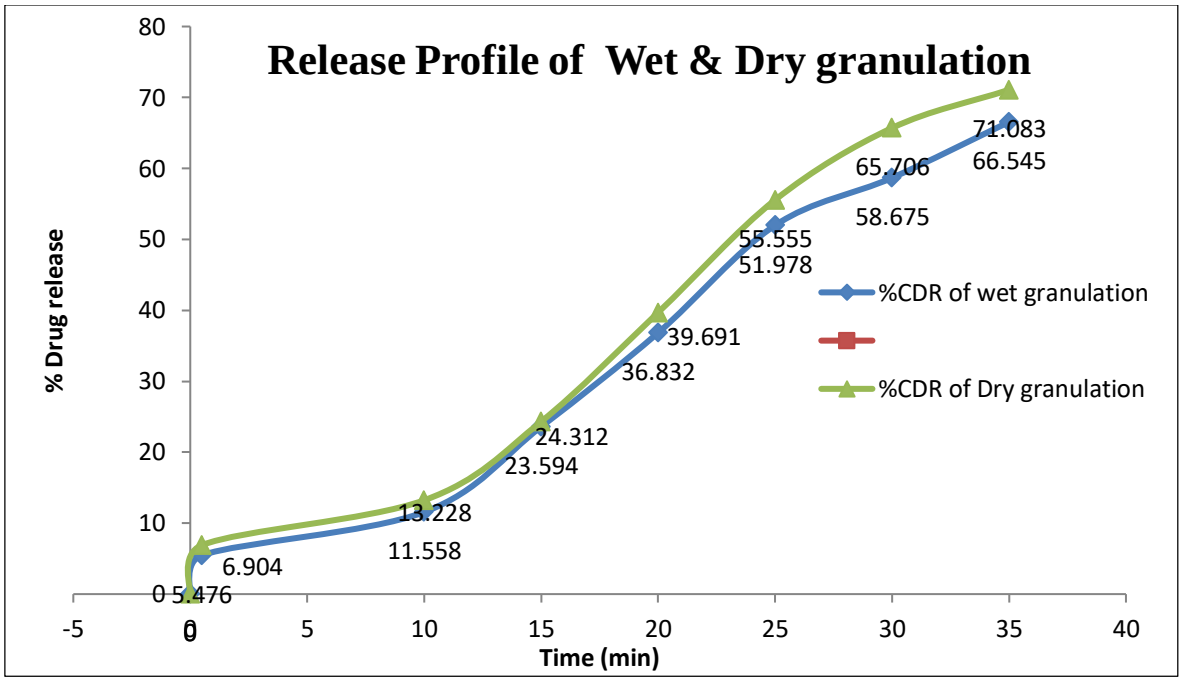
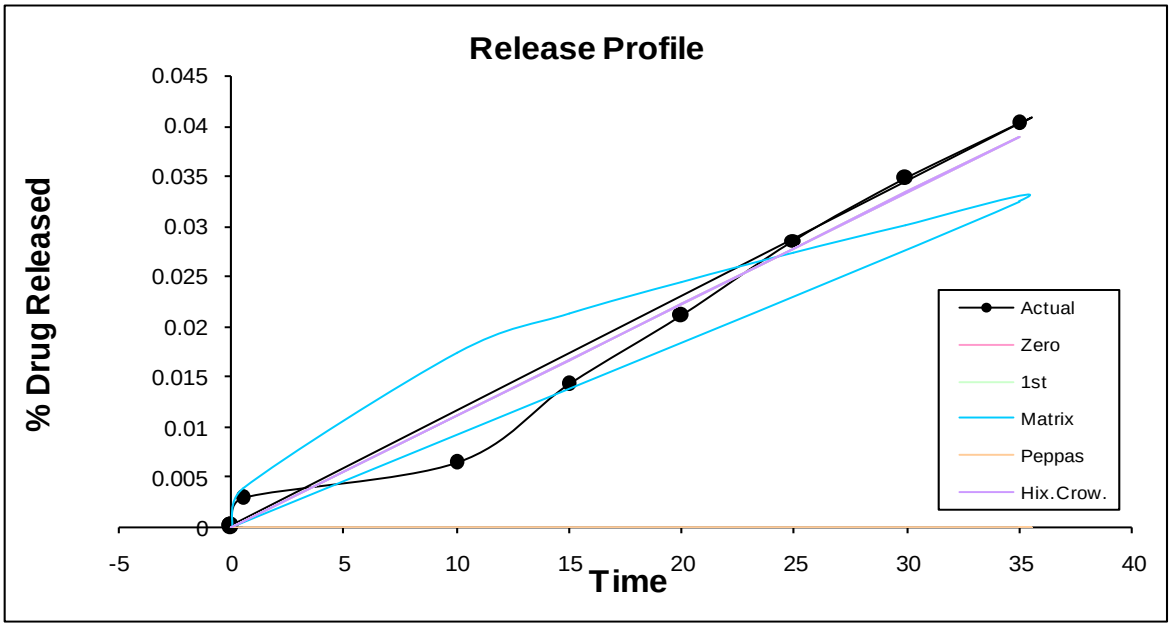
**II. Drug Release of A2 Carbamazepine Tablet Formulatedby Dry Granulation Method :**

| Times (Min) | Abs | Conc. (10µg/ml) | Conc. (µg/10ml) | Conc. (mg/10ml) | Conc. (mg/900ml) | CDR | % CDR |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.5 | 0.058 | 1.38 | 13.809 | 0.0138 | 6.904 | 6.904 | 6.904 |
| 10 | 0.111 | 2.642 | 26.428 | 0.026 | 13.214 | 13.228 | 13.228 |
| 15 | 0.204 | 4.857 | 48.571 | 0.048 | 24.285 | 24.312 | 24.312 |
| 20 | 0.333 | 7.928 | 79.285 | 0.079 | 39.642 | 39.691 | 39.691 |
| 25 | 0.466 | 11.095 | 110.952 | 0.11 | 55.476 | 55.555 | 55.555 |
| 30 | 0.551 | 13.119 | 131.19 | 0.131 | 65.595 | 65.706 | 65.706 |
| 35 | 0.596 | 14.19 | 141.904 | 0.141 | 70.952 | 71.083 | 71.083 |

Table 9: Drug Release Study of A2 Carbamazepine Tablet by Dry Granulation Method




Graph 6: Release Profile for A1 Formulation of Carbamazepine Tablet by Dry and Wet Granulation Method




Graph 6: Model Fitting for A1 Formulation of Carbamazepine Tablet by Wet granulation Method

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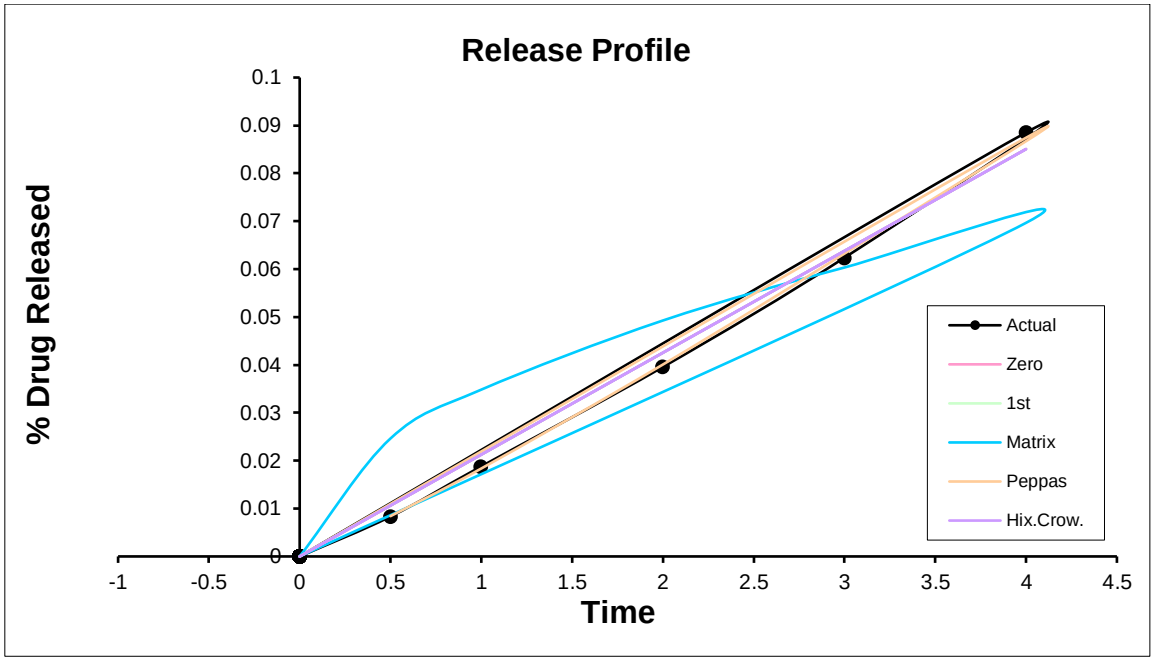


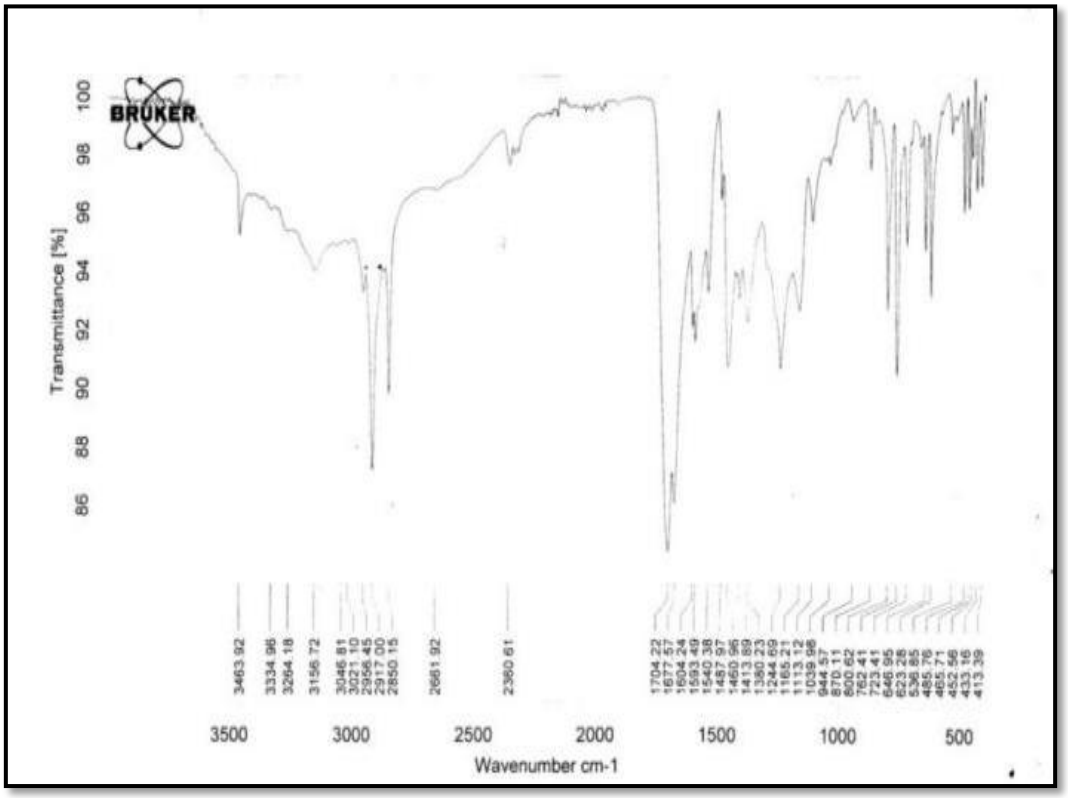

Graph 7: Model Fitting for A2 Formulation of Carbamazepine Tablet by Dry granulation Method

## III. KINETIC STUDY:

Best release kinetics fitting model to all formulation represent.A1 and A2 best fitted in to zero order mathematical model which shows non fickian.

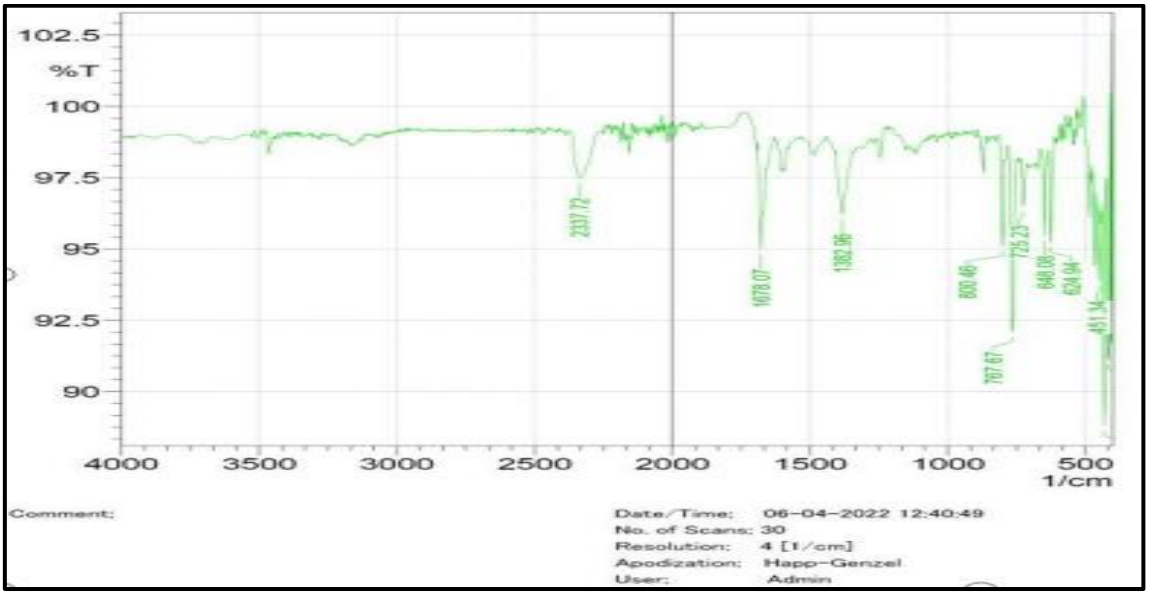
*A. FTIR Study of Formulation:*

- **FTIR Study of Carbamazepine Tablet Formulated by wet granulation Method:**




Graph 8: FTIR Spectrum of Carbamazepine Tablet by Wet Granulation Method

- **FTIR Study of Carbamazepine Tablet Formulated by Dry granulation Method :**

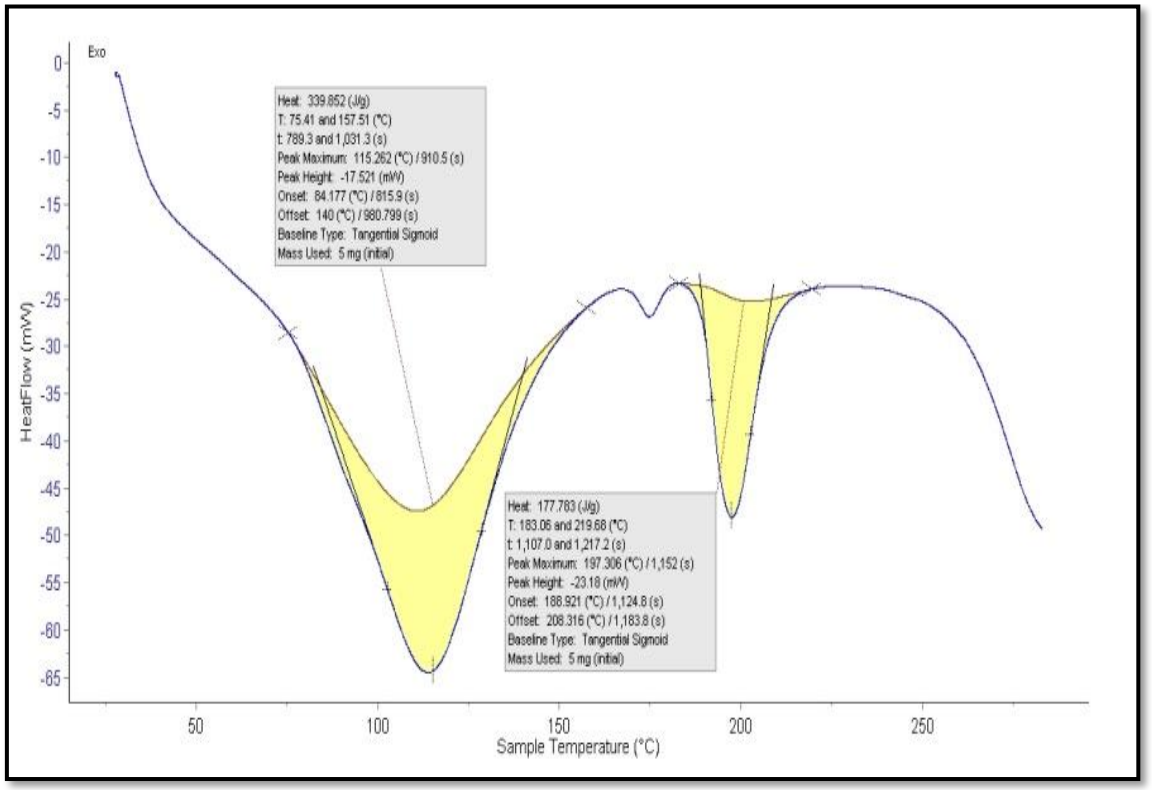



Graph 9: FTIR Spectrum of Carbamazepine Tablet by Dry Granulation Method

The FTIR spectrum of wet granulation method shows dominant characteristic peaks of Carbamazepine especially OH alcoholic Stretching O-H alkanes, C-H, C-O-C (ether)C=O carboxylic acid N at 3463.92, 3156.72, 2917.00, 1244.69 , 1704.22, 1165.21 respectively. The FTIR spectrum of dry granulation method shows dominant characteristic peaks of Carbamazepine especially OH alcoholic Stretching O-H alkanes, C-H, C-O-C (ether) C=O carboxylic acid C-N at 2307.72, 1678.07, 1382.96, 850.46 , 767.67, 725.23 respectively. The above spectrum indicated that physical changes not any chemical changes.

*B. Study of Polymorphic changes in drug Carbamazepine byusing Differential Scanning Calorimetric Analysis.*

- **DSC Study of Carbamazepine in Tablet Dosage form Formulated by Using Wet and Dry Granulation Method:**




Graph 10: DSC of Carbamazepine Tablet by Wet Granulation

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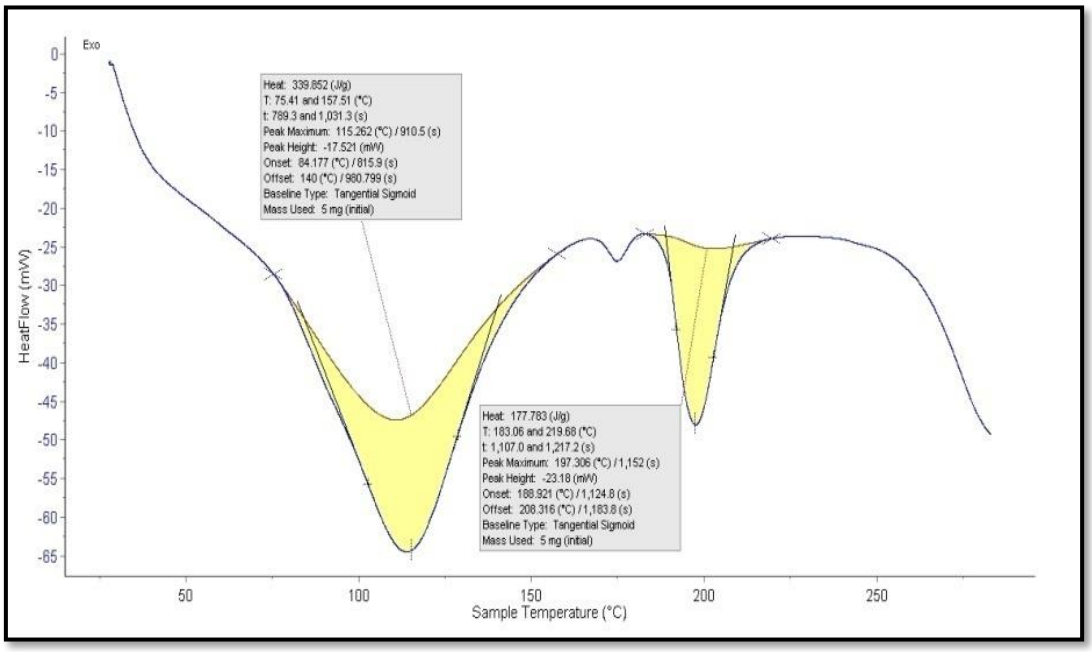


Graph 11: DSC of Carbamazepine Tablet by Dry Granulation

## IV. RESULT AND DISCUSSION

*A. Differential Scanning Calorimetric Analysis of Carbamazepine in Tablet Dosage form, formulated by using Wet and Dry Granulation Method :*

The polymorphic Change of Carbamazepine drug is studied for in its tablet dosage form by considering the variations in the granulation process in graph 10 and 11 ( Weight and Dry ). As far the DSC study recorded for the different thermogram to know the polymorphic changes happened in operating process utilizing the change in granulation technique. A sharp endothermic peak is observed at a temperature of 140°C in both granulation techniques. The drug and represented excipients melts at the specific temperature.

Then the next subsequent sharp endothermic peak is observed at 177.78°C and at 200°C for both granulation techniques is observed and indicate the drug present in its more percentage of amorphous polymorphic form. Followed by broad exothermic peak is observed from temperature range of 220°C to 280°C for both granulation technique indicates the drug present in less percentage in its crystalline polymorphic form. However the variations in granulation technique of Carbamazepine tablets never reflectpolymorphic changes even there is a change in granulation technique.

## V. CONCLUSION

This study was undertaken to identify polymorphic changes in the Carbamazepine drug. Characterization of Carbamazepine tablets was carried out using Differential Scanning Calorimetry (DSC). According to DSC study the variations in granulation technique of Carbamazepine tablets never reflects a polymorphic changes even there is a change in granulation technique.

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