JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

"Study of Formulation and Development of Carbamazepine in Matrix Tablet for Polymorphism".

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Abstract:

The drug Carbamazepine, a dibenzazepine derivative, is used to treat a variety of disorders, including epilepsy, trigeminal neuralgia, and bipolar disorder. Carbamazepine is the most effective and affordable first-line medication for seizures. The biopharmaceutical classification system classifies Carbamazepine as BCS class II drug because of their strong membrane permeability and poor water solubility, which make dissolution the rate-limiting stage in the absorption process. By considering it formulation was designed and polymorphic alterations of the drug Carbamazepine are evaluated in its tablet dosage form. A differential scanning colorimetric study was carried out for a tablet formulation of Carbamazepine to identify the polymorphic changes in the drug. The basic goal of study to investigate the impact of Carbamazepine Matrix tablet design by utlizing lyophilization technique on the drug Carbamazepine for specific polymorphic modifications in designed tablet dose form.

Key words: Carbamazepine, Polymorphism, DSC, Lyophilization, Epilepsy, Tablet.

Introduction:

A chronic brain condition known as epilepsy can afflict people of any age. globally, 50 million people suffer from epilepsy. The 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 activities, movements, sensations, thoughts, and emotions. It regulates the body's automatic internal processes, including heart and lung function. The brain cells can communicate with each other 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 BCS class II drug. 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.

The lyophilized form of drug Carbamazepine is formulated in Matrix tablet by wet granulation was used to formulate the Carbamazepine tablet in order to enhance the drug's physic-chemical qualities. There are several different Carbamazepine formulations on the market, including pills with 100 mg or 200 mg of the drug, tablets with a controlled release (CR) of 200 mg or 400 mg of Carbamazepine liquid with a concentration of 100 mg per 5 mL. In unit operations in bulk manufacturing as well as in the large-scale production of dosage form formulations, polymorphism is a significant phenomenon lead to alter the performance of formulation. It can also have an impact on a variety of API properties, including tableting, solubility, stability, and even biopharmaceutical performance, including safety and efficacy as well as toxicity. Additionally, the physicochemical properties of these polymorphic API forms can also change or vary, including solubility and dissolution, chemical and physical stability, and hygroscopicity.

Therefore, given that the study of polymorphism was found to be important for the pharmaceutical process in the literature review as a whole, the current study topic was chosen to investigate the various polymorphic changes that occurred during the formulation and development of the drug Carbamazepine.

1. Experimental :

1.1 Material :

The pure drug Carbamazepine is procured from Aarti Distributers in Mumbai. The remaining reagents are used for Analytical Grade and other excipients and material utilized for work provided by Loba- Chem Pvt. Ltd, at Laboratories.

2.2.1 Methods:

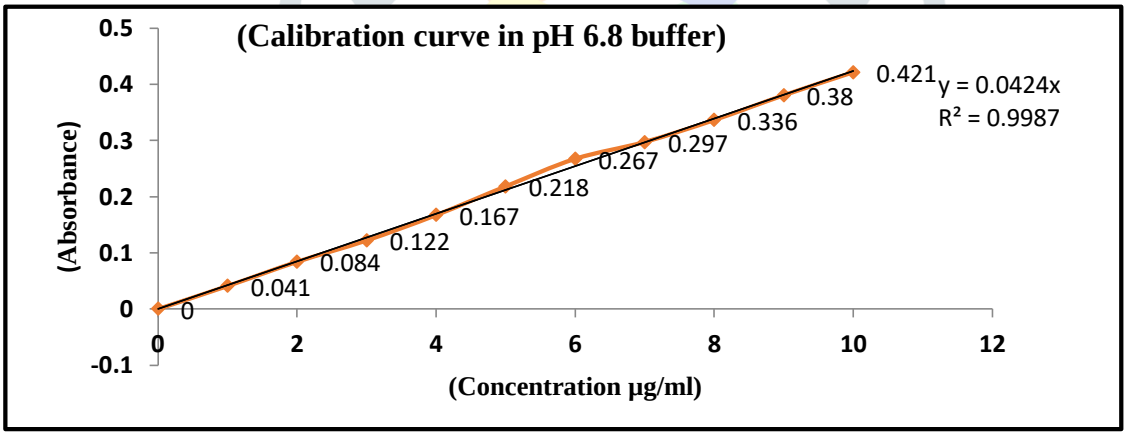
A) Preparation of Carbamazepine Standard Calibration Curve in Phosphate Buffer at pH 6.8:

To make a stock solution of carbamazepine, 100 mg of the drug was dissolved in 1000 ml of phosphate buffer, pH 6.8, while being shaken and sonicated for 30 minutes. To obtain standard stock solutions A of known concentration (100 g/ ml), the volume was brought up to the required level using the same solvent. Then, to create standard stock solution B with a specified concentration (10 g/ ml), 10 ml of solution from stock A was diluted with 100 ml of phosphate buffer pH 6.8. Then, using a phosphate buffer solution with a pH of 6.8, the proper dilution was carried out to create solutions containing 1 g/ ml, 2 g/ ml, 3 g/ ml, 4 g/ ml, and up to 10 g/ ml. Build and calibrate the calibration curve by focusing on the X-axis and absorbance and the Y-axis. The coefficient of correlation, slope, intercept, and percentage of relative standard deviation were calculated. The absorbance of Carbamazepine at various concentrations was given in table no. 2.[5]

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	1	0.041
3	2	0.084
4	3	0.122
5	4	0.167
6	5	0.218
7	6	0.267
8	7	0.297
9	8	0.336
10	9	0.380
11	10	0.421

Table 2 : Calibration curve for Carbamazepine in Phosphate Buffer pH 6.8

Calibration curve for Carbamazepine in Phosphate Buffer of pH 6.8



B) Melting Point Determination[14]:

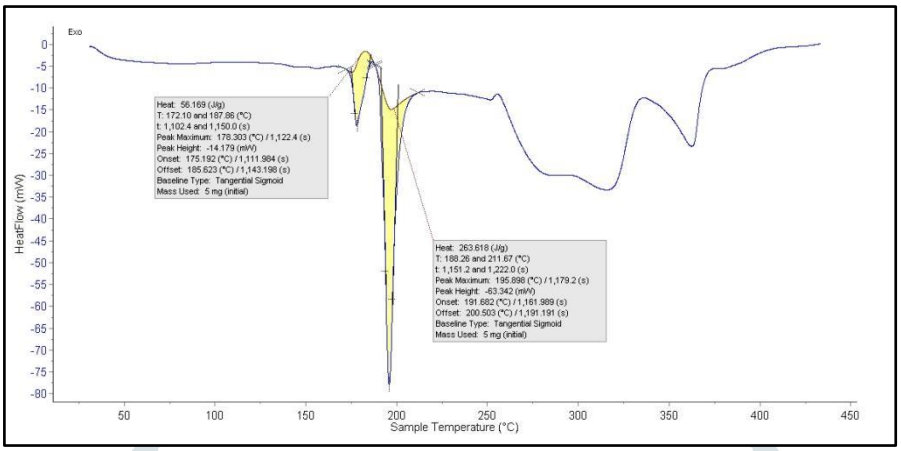
The melting point of drug was determined by capillary method using Thiel's tube. Precaution was taken to maintain the uniform heat to Thiel's tube containing capillary filled with drug[5].

Drug	Observed Melting point	Reported Melting point
Carbamazepine	191^{0}C	191-195^{0}C

Table 2 : Determination of Melting point

C) Differential Scanning Colorimetric Analysis of Carbamazepine:

The pure medication Carbamazepine was the subject of the DSC Study. For the 5mg sample, the DSC was observed between 0 and 450^{O}C. The thermogram was produced by heating the sample at a rate of 10^{O}C/min while it was in a crimped aluminium pan. With the aid of instrument software, data was examined.



Differential Scanning calorimetric Study of Pure drug Carbamazepine.

D) Formulation and Development :

The ingredients in the tablet, which also contain magnesium stearate as a lubricant and microcrystalline cellulose as a diluent, were chosen to make the final dose very hard and durable. Tablet formulation is developed to enhance drug compatibility and better comprehend the polymorphic changes that occur during the manufacture of Carbamazepine tablets. The Carbamazepine granule was formulated via wet granulation prior to compression of matrix tablet[5].

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	HPMC (Hydroy-propyl methyl cellulose).	Q.s….. 300	Q.s….. 0.3	Q.s … 100

Table 1 : Formulation of Carbamazepine Tablets.

1. Carbamazepine (Lyophilized Free Flowing Powder) Matrix Tablet Preparation through Wet Granulation[15]:

In this formulation, the pure medication Carbamazepine was dissolved in the solvent acetone further absorbent magnesium carbonate was considered to get final product. It was then freeze dried for two hours at -40°C by using lyophilizer. Subsequently, the freeze dried, drug's freely flowing powder are considered to compress Twenty tablets using the wet granulation process, with Carbamazepine being collected and

represented in the formula shown in Table No. 1 and Hydroxypropyl methyl cellulose being employed as a controlled release polymer[15].

A) Observations of Evaluations:

Formulations (n=6)	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

1 Pre-Compression Parameters of Carbamazepine Tablets:

n* indicate the number of tablets

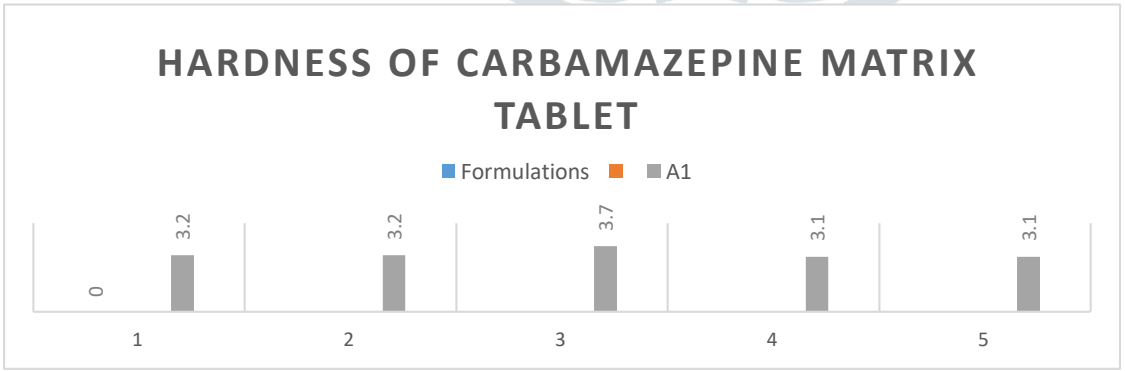
2. Carbamazepine Tablet Post-Compressional Parameters:

A) Hardness:

Tablets should be sufficiently hard to resist breaking during normal handling. The hardness of tablets 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

Table 2 : Hardness of Carbamazepine Matrix Tablets.



Graph 1 : Hardness study of Carbamazepine Matrix Tablet.

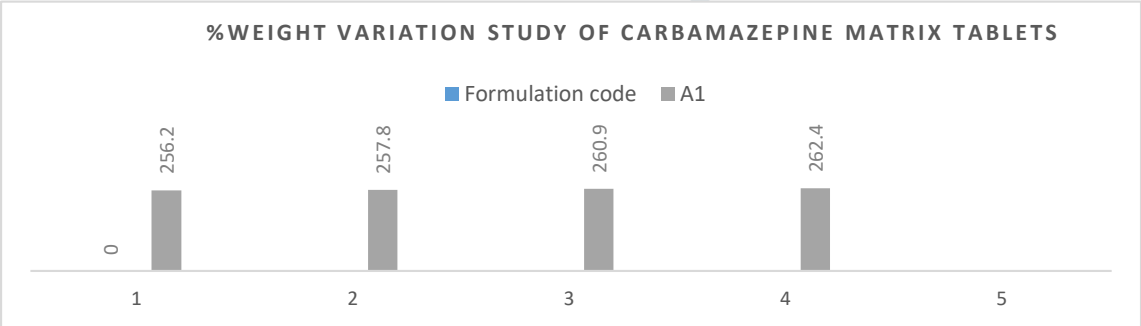
A tablet needs to have a particular degree of mechanical strength after compression in order to resist the shock of handling during production, packing, shipping, and dispensing. The tablet's hardness was determined to be between 3.1 and 3.7 kg/cm2, as stated in the table. This guarantees that tablets possess strong mechanical properties.

B) % Weight Variation:

The weight of tablet is 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[10].

Formulation code	Mean	SD
A1	256.2	±1.356

Table 3 : Weight variation study of Carbamazepine Matrix tablets.

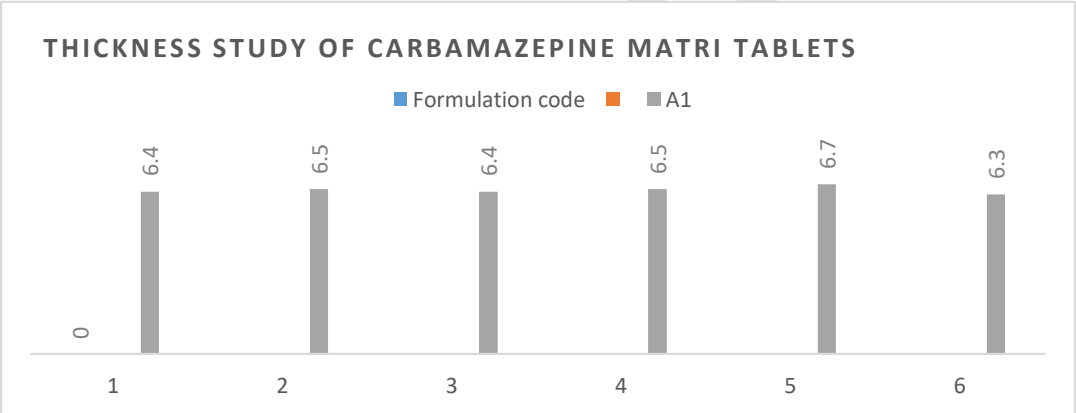


Graph 2 : % Weight variation study of Carbamazepine Matrix tablets.

All of the A1 formulation pills had weight variations between 1.33% and 2.36% that were within the pharmacopoeial range +5% of the weight. All of the tablets had consistent weights with small standard deviation values.

C) Thickness:

The six tablets from each batch of the formulation were gathered, and an electronic Vernier Caliper was used to measure the tablets' diameter. The typical thickness was determined[10].



Graph 3 : Thickness Study of Carbamazepine Tablets.

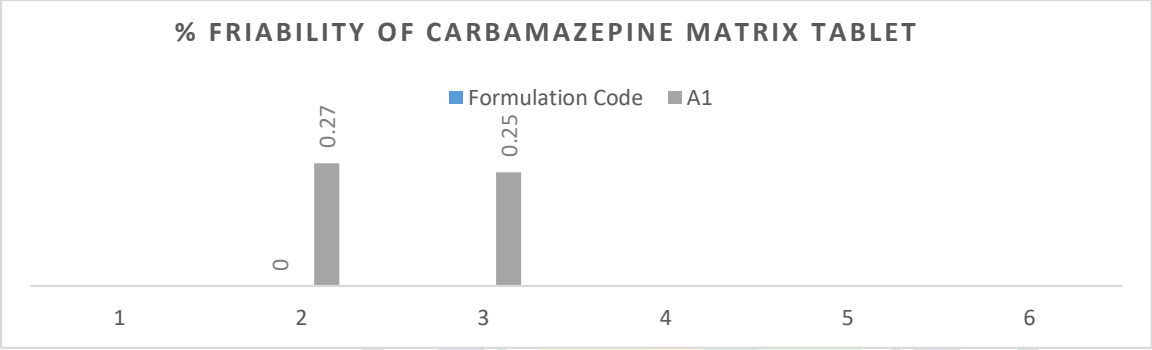
The thickness of the tablets was measured and was determined to be between 6.46 and 6.48 mm. Good flow characteristics, uniform pressure, and uniform punch movement are all indicators of uniform thickness. It states that the tablet was between 0.8 and 0.85 mm for its thickness.

D) Friability:

Since some formulations compacted into particularly hard tablets have a tendency to cap on attrition and lose their crown portion, another measurement of tablet strengths, its friability, is frequently taken. Tablet hardness is not an absolute indicator of strength. The friability of the tablets was evaluated using the Roche friability test equipment. Twenty pre-weighed pills were put inside the device, which was then turned on for four minutes at a speed of 25 revolutions per minute. After that, the tablets were reweighed. Friability was calculated as a percentage.

Formulation Code	Initial Weight of 20 Tablets (mg)	Final Weight of 20 Tablets (mg)	Friability (%)
A1	5.069	5.055	0.27

Table 4 : % Friability study of Carbamazepine Tablet.



Graph 4: % Friability study of Carbamazepine Tablet.

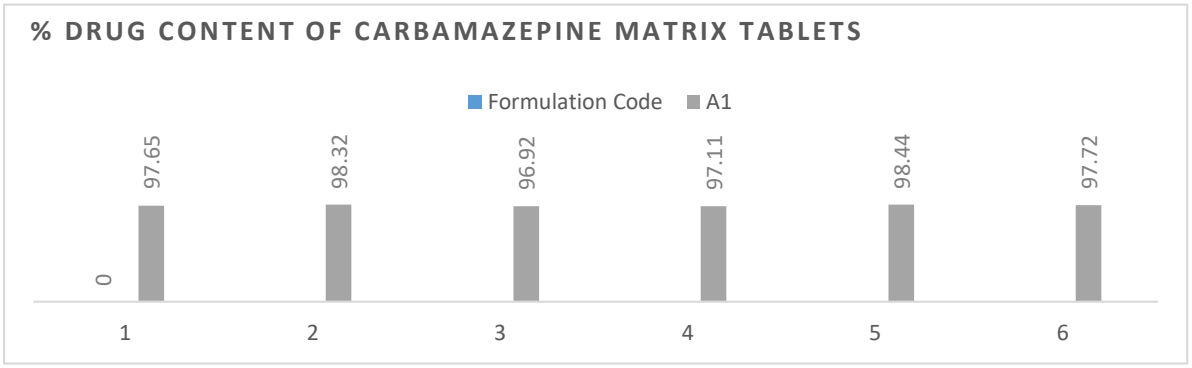
The produced pills demonstrated weight reduction ranging from 0.25 to 0.27%. As per the official specification, the percentage of friability was less than 1%. This demonstrated that all formulations of tablets passed the pharmacopeia standard's test for friability and mechanical stability.

E) Drug Content:

The six 300 mg tablets from each formulation were placed in individual volumetric flasks containing 100 ml of pH 6.8 phosphate buffer and stirred continuously for 24 hours. Following filtering and appropriate dilution, the solutions were examined at 285 nm with a UV spectrophotometer. As the amount of medication in one tablet unit, an average of six tablets was used.

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

Table 5 : % Drug content of Carbamazepine matrix Tablets.



Graph 5 : % Drug content of Carbamazepine matrix Tablets.

It was determined that the A1 formulation contained 97.26% to 98.97% of Carbamazepine, which complies with official standards.

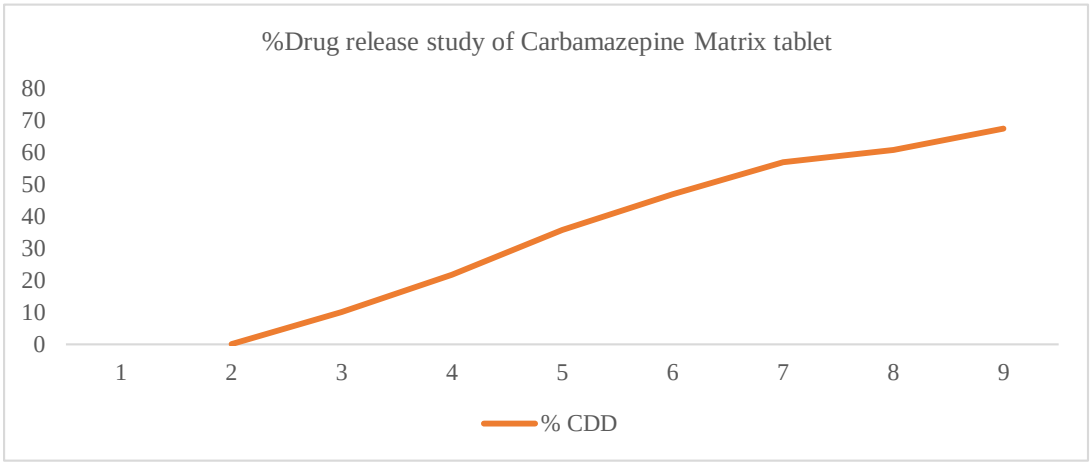
Drug Release of A1 Carbamazepine Matrix Tablet by Lyophilization Technique:

Time/abs	1	2	3	4	5	6	Mean	SD	SEM
0.5	0.061	0.099	0.111	0.113	0.077	0.043	0.084	±0.028	0.034
10	0.177	0.158	0.202	0.19	0.153	0.206	0.181	±0.022	0.073
15	0.278	0.333	0.209	0.379	0.369	0.232	0.3	±0.071	0.122
20	0.432	0.409	0.404	0.377	0.333	0.409	0.394	±0.034	0.16
25	0.501	0.532	0.444	0.478	0.49	0.423	0.478	±0.039	0.195
30	0.46	0.468	0.601	0.596	0.591	0.384	0.516	±0.091	0.21
35	0.531	0.565	0.666	0.501	0.555	0.572	0.565	±0.055	0.23

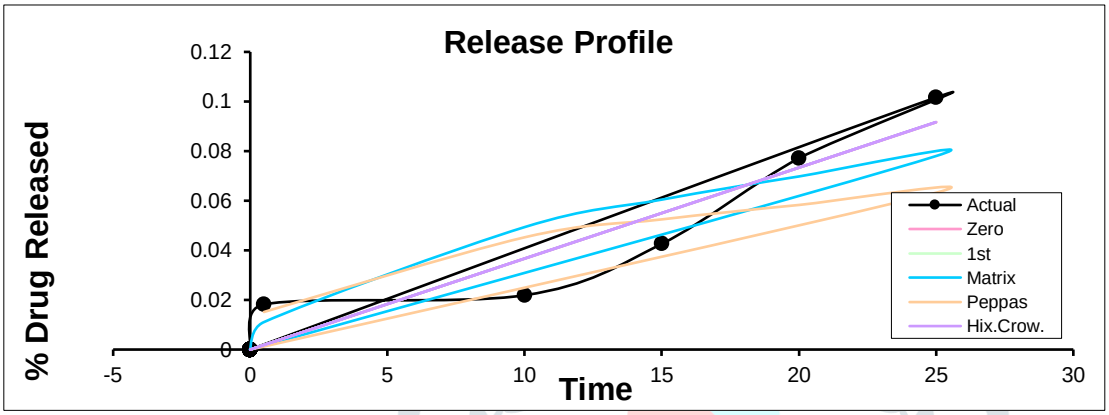
Table 6: Mean Absorbance A1 Lyophilized Carbamazepine Matrix Table

Times (hr)	Abs	Conc. (µg/ml)	Conc. (µg/10ml)	Conc. (mg/10ml)	Conc. mg/900ml	CDD	% CDD
0	0	0	0	0	0	0	
0.5	0.084	2	20	0.02	10	10	10
10	0.181	4.309	43.095	0.043	21.547	21.641	21.641
15	0.3	7.142	71.428	0.0714	35.714	35.757	35.757
20	0.394	9.38	93.809	0.0938	46.904	46.924	46.924
25	0.478	11.38	113.809	0.113	56.904	56.976	56.976
30	0.51	12.142	121.428	0.121	60.714	60.828	60.828
35	0.565	13.452	134.523	0.134	67.261	67.383	67.383

Table 7: Drug Release Study of A1 Lyophilized Carbamazepine Matrix Tablet



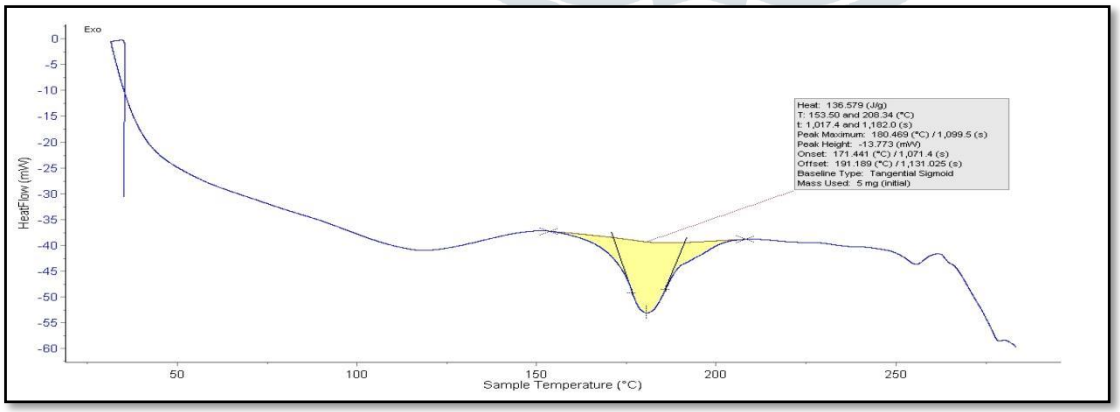
Graph 6 : Drug Release Study of A1 Lyophilized Carbamazepine Matrix Tablet



Graph 7: Model Fitting for A4 Formulation of Carbamazepine Lyophilized Matri Tablet.

The best release kinetics model that represents all formulations. The zero order mathematical models, which exhibit non-fickian relase of drug from matrix tablet of Carbamazepine, best fits the data in A1.

Differential scanning calorimetric study of Matrix tablets of Carbamazepine formulated by lyophilization technique:



Graph 8 : DSC of Carbamazepine Matrix Tablet by Lyophilization Method.

Result and Discussion:

The DSC Study of Carbamazepine tablet in the form of matrix tablet was done, and DSC Study was carried to identify the polymorphic changes in Carbamazepine drug during the steps involved in a formulation and development.[26]

The DSC of crushed matrix tablet of Carbamazepine is carried out from the temperature of 0 to 300^{O}C and it has been observed that the sharp endothermic peak at 180^{O}C indicate the drug and its excipients gets melt subsequently very broad exothermic peak with slight declined line is observed 200 to 250^{O}C indicate the drug evenly dispersed in a matrix of polymer(HPMC).Then followed by a small endothermic peak is observed at the temperature of 260^{O}C indicates the drug present in very little bit percentage in its amorphous form. From throughout the DSC Study of Carbamazepine matrix tablets it is found that there is no any major change in polymorphic form of Carbamazepine drug as shown in graph no 8[26].

Conclusion

The goal of this study was to find polymorphic variations in the drug Carbamazepine. The drug Carbamazepine is used as the first line of treatment for seizures. According to the Biopharmaceutical Classification System, Carbamazepine belongs to class II and has a high water permeability but a low water solubility. As a result, the rate-limiting step in the absorption of Carbamazepine is the dissolution process. Wet granulation was used to successfully produce the Carbamazepine matrix tablet employing excipients such as lactose, starch, microcrystalline cellulose, and the polymer hydroxypropylmethyl Cellulose (HPMC). Differential scanning calorimetry was used to characterize the Carbamazepine tablets (DSC). The lyophilization technology was used to formulate the Carbamazepine matrix tablet. Through this DSC study, it is revealed that a polymorphic change has not undergone in significantly.

Acknowledgement:

The Author wish to acknowledge the Head, Center of Innovation for Applied Science in Baramati, District of Pune, and the Head of the Center of Excellence in Dairy Technology in Malegaon (Kh) for providing the research facilities utilized for the successful completion and execution of the author's study work. One of the greatest thanks for the guidence of Dr. A.D Shinde for positivity and to make this work happen hopefully successful.

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