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Research Article

# FORMULATION AND IN VITRO EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF ACALABRUTINIB

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## ABSTRACT

*Acalabrutinib has a short biological half-life of 0.6-2 hours and having less bioavailability which necessitates multiple daily dosing hence the present study was aimed to develop a controlled release formulation of Acalabrutinib to reduce the dose related side effects and to reduce the dosage regimen. The present research project aimed to develop a Control release oral formulation of anti-cancer drug Acalabrutinib, the present research comprising Acalabrutinib useful for the treatment of mantle cell Lymphoma. Polymers like HPMC K4M, HPMC K 15M and Carbopol 940 were used for controlling the drug release, and the polymers are mixed in a predetermined ratio. Totally 9 formulations were prepared and evaluated for pre-compression and post compression parameters, and all the results were found to be within the limits. From the drug and excipients compatibility studies (FT-IR) it was confirmed that the drug and excipients used weren't have any interactions. The in vitro dissolution studies revealed that the F9 formulation containing 30% of Carbopol 940 controls the drug release up to 24hours. So Carbopol 940 containing F9 formulation was considered to be suitable for the formulation of Acalabrutinib controlled release tablets at 30% concentration, and the drug release kinetics revealed that the F9 formulation shows super case transport mechanism.*

***KEYWORDS:*** *Acalabrutinib, HPMC K4M, HPMC K 15M and Carbopol 940, FT-IR.*

## INTRODUCTION

Oral route of drug administration is the ideal, convenient and preferred route. Conventional oral drug administration does not generally offer target specificity or rate-controlled release. In controlled release drug delivery systems (CRDDSs), an active therapeutic is incorporated in the network structure of the polymer in such a way that the drug is released in a predefined controlled manner. Prolonging gastric residence time (GRT) is the most important objective of CRDDSs as short GRT is the major hindrance in the development of CRDDSs. The prolonged residence time of the drug in the body is believed to prolong its duration of action [1].

The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period, an amount of the drug equivalent to the eliminated by the body [2]. A dose of the drug initially is released immediately after administration, which is usually equivalent to a single dose of the conventional drug formulation. After a certain period, a second single dose is released. In some preparation, a third single dose is released after a certain time has elapsed, following the second dose. The main advantage is that it provides the convenience of supplying additional dose(s) without the need of re-administration. It has disadvantage that the blood levels still exhibit the "Peak and valley" characteristic of conventional intermittent drug therapy.

**Drug Properties Relevant to Controlled-Release Formulations:**

The extent of fluctuation in drug concentration at steady state is determined by the relative magnitude of the elimination half – life and the dosing interval. If a drug is given at an interval equal to the elimination half-life, there is a two-fold difference between the maximum and minimum concentrations at steady state. Some drugs those have relatively high solubility at the low pH with short biological half-lie, are not suitable for conventional oral dosage formulations, because the high acid solubility property of drug results in rapid drug absorption and clearance, causing large and undesirable fluctuations in plasma concentration.

For drugs with short half-lives and with a clear relationship between concentration and response, it will be necessary to dose at regular, frequent intervals in order to maintain the concentration within the therapeutic range. Higher doses at less frequent intervals will result in higher peak concentrations with the possibility of toxicity. For some

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drugs with wide margins of safety, this approach may be satisfactory, e.g. amoxicillin has a half-life of approximately one hour, but a dosage frequency of 8 hours.

Acalabrutinib is a novel anti-cancer drug and a second generation Bruton's tyrosine kinase (BTK) inhibitor developed by Acerta Pharma. It is more potent and selective (fewer side-effects) than ibrutinib, the first-in-class BTK inhibitor, was used as a model drug to develop a controlled release formulation. Acalabrutinib has a short biological half-life of 0.6-2 hour and having less bioavailability which necessitates multiple daily dosing hence the present study was aimed to develop a controlled release formulation of Acalabrutinib to reduce the dose related side effects and to reduce the dosage regimen.

## MATERIALS AND METHODS

The materials used in present work, Acalabrutinib was procured from B.M.R. Chemicals, HPMC K4M, HPMC K15M and Carbopol 940 were procured from Strides Arcolab, Bangalore, Lactose, PVP K 30, Magnesium Stearate, Micro Crystalline cellulose were procured from Loba chemie pvt.ltd, Mumbai.

**Pre-formulation Studies:**

***Drug Excipient compatibility studies:***

There is always possibility for Drug-Excipient interaction, it is necessary to determine possible Drug-Excipient interaction. This will also indicate success of stability studies. The excipients were weighed and loaded into stability at 40℃/75% RH for 1 Month. Compatibility study with excipients was carried out by FTIR. The pure drug and its formulations along with excipients were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

**Formulation of Acalabrutinib controlled release matrix Tablets:**

1) ***Sifting:*** Acalabrutinib and remaining excipients were sifted through mesh# 40 and collected into a double poly bag.

2) ***Pre-Lubrication:*** Materials of step-1 were mixed for 10 minutes.

3) ***Sifting:*** Magnesium stearate is sifted through mesh#40 and added to the material of step2.

4) ***Lubrication:*** Final blend was mixed for 5 min and unloaded into double poly bag and taken for compression on a rotary tablet press.

5) ***Punch shape & Dimensions:*** Round, 8.5 mm

**Prepared Formulations:** [3-10]

Controlled release tablets of Acalabrutinib were prepared by direct compression method using variable concentrations of different polymers like HPMC K4M, HPMC K15M, Carbopol 940 and Polyvinylpyrollidine-K-30 as binder and lactose as diluents and MCC as a filler. As Acalabrutinib is poorly water-soluble drug lactose and MCC were used for increasing the solubility.

**Table No. 1: Tablet composition of different formulations of Acalabrutinib matrix tablets**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **Acalabrutinib** | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| **Lactose** | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| **HPMCK4M** | 60 | 90 | 120 | - | _ | _ | _ | _ | _ |
| **HPMCK15M** | _ | _ | _ | 60 | 90 | 120 | _ | _ | _ |
| **Carbopol 940** | _ | _ | _ | _ | _ | _ | 60 | 90 | 120 |
| **MCC** | 166 | 136 | 106 | 166 | 136 | 106 | 166 | 136 | 106 |
| **PVP K30** | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| **Talc** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Magnesium stearate** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Total (mg)** | **400** | **400** | **400** | **400** | **400** | **400** | **400** | **400** | **400** |

**Evaluation studies:**

**1) Pre-Compression Studies:**

Certain properties of powder have been evaluated to determine the suitability of blend for compression. As part of this evaluation powder properties such as Angle of Repose, Bulk density, Tapped density, Carr's compressibility index and Hausner's ratio were evaluated.

**a) Angle of repose**:

It is the angle formed by the horizontal base of the bench surface and edge of cone like pile of granules. Required amount of lubricated blend was weighed and then filled into a funnel connected to a burette stand with a white paper placed on the surface of bench. The blend was then allowed to flow from the funnel to the surface of the bench. A circle was drawn around the pile of blend formed, and the height of blend was measured using a ruler. Angle of repose was then calculated by using the below formula.

$$\theta = \tan^{-1}(h/r)$$

where,

θ = Angle of repose; h = height of pile; r = radius of Pile

**b) Bulk Density**:

It is the ratio of mass of the powder to its bulk volume. It is determined by taking a known amount of blend and is transferred into graduated measuring cylinder with the help of funnel and the volume occupied by the blend was noted. Bulk density of the powder is calculated by using below formula.

**Bulk Density (BD) = Mass of the powder / Volume occupied by the powder**

**c) Tapped Density**:

It is the ratio of mass of the powder to its tapped volume.

It is determined by taking a known quantity of blend and is transferred into graduated measuring cylinder and the cylinder is tapped for 1250 taps. The volume of blend occupied after 1250 tapings is noted.

**Tapped Density (TD) = Mass of the powder/ Tapped volume of the blend**

**d) Carr's Compressibility index:**

Compressibility is the ability of powder to decrease in volume under pressure. It is calculated by using the below formula.

**Carr's index = (Tapped density – Poured density) * 100 / Tapped density**

**e) Hausner's Ratio:**

It is indication of compressibility of powder. It is calculated by using below formula.

**Hausner's ratio= Tapped density/Bulk density**

**Table No. 2: Flow properties and corresponding angle of repose**

| Flow Properties | Angle of repose |
|---|---|
| **Excellent** | 25-30 |
| **Good** | 31-35 |
| **Fair (aid not needed)** | 36-40 |
| **Passable (may hang up)** | 41-45 |
| **Poor (must agitate, vibrate)** | 46-55 |
| **Very poor** | 56-65 |
| **Very, very poor** | > 66 |

**Table No. 3: Compressibility index and Hausner's ratio**

| Compressibility Index | Flow Properties | Hausner's ratio |
|---|---|---|
| **<10** | Excellent | 1.00-1.11 |
| **11-15** | Good | 1.12-1.18 |
| **16-20** | Fair (aid not needed) | 1.19-1.25 |
| **21-25** | Passable (may hang up) | 1.26-1.34 |
| **26-31** | Poor (must agitate, vibrate) | 1.35-1.45 |
| **32-37** | Very poor | 1.46-1.59 |
| **>38** | Very, very poor | >1.6 |

**2) Post-compression studies:**

The formulated Acalabrutinib controlled release matrix tablets were evaluated for Average weight, Thickness, Friability, Drug content uniformity and in vitro dissolution studies.

**a) Average weight of tablets:**

20 tablets were taken and weighed individually. Average weight of 20 tablet is calculated and compared with individual tablet weight. NMT 2 tablets are outside the percentage limit and no tablet differs by more than two times the percentage limit.

**b) Friability:**

Tablets equivalent to 6.5 g was weighed and loaded into friability equipment for 4 minutes, 100 revolutions. Tablets were collected, dedusted and weighed and the weight was recorded. Friability is calculated by using the below formula

**Percentage Friability = W1 – W2/W1 × 100**

Where, W1 = weight of tablets before testing
W2 = weight of tablets after testing.

**c) Content uniformity:**

Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in different buffers, the drug content was determined using a UV/Visible Spectrophotometer at 236nm (PG Instruments).

**d) In-Vitro dissolution studies:**

The release rate of Acalabrutinib from tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of pH 1.2, for first 2 hours and followed by phosphate buffer (pH 6.8; 900 mL) for remaining hours at 37.5±0.5$^0$C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus for 24 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with respected dissolution medium.

Absorbance of these solutions was measured at 236nm using a UV-Visible Spectrophotometer (PG Instruments).

**Table No. 4: Weight variation limits**

| Average weight of tablets (IP/BP) | Limit | Average weight of tablets (USP) |
|---|---|---|
| **80 mg or less** | ± 10% | 130 mg or less |
| **80-250 mg** | ± 7.5% | 130-324 mg |
| **>250 mg** | ± 5% | >324 mg |

## RESULTS AND DISCUSSIONS

**1. Drug-excipient compatibility studies:**

FT-IR studies revealed that the drug and excipients used weren't have any interactions.

**2. Pre-Compression studies:**

The compressibility values of the powders were below 25% and hence they exhibit good flow characteristics. The angles of repose of the powders were in the range of $25^0$ to $29^0$, which indicate a good flow property of the powders. Hausner's ratio was found to be <1.25, indicates that the Acalabrutinib have god flow property.

**3. Post Compression Studies:**

The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 8.24±0.22 to 9.20±0.54 Kg/cm$^2$. It was within the range of monograph specification.

Thicknesses of the tablets were found to be in the range of 4.00±0.22 to 4.52±0.36mm. The friability of the tablets was found to be less than 1% and it was within the range of standard specification. The drug content for all the batches were found to be in the range of 88.26±0.54 to 96.64±0.94%.

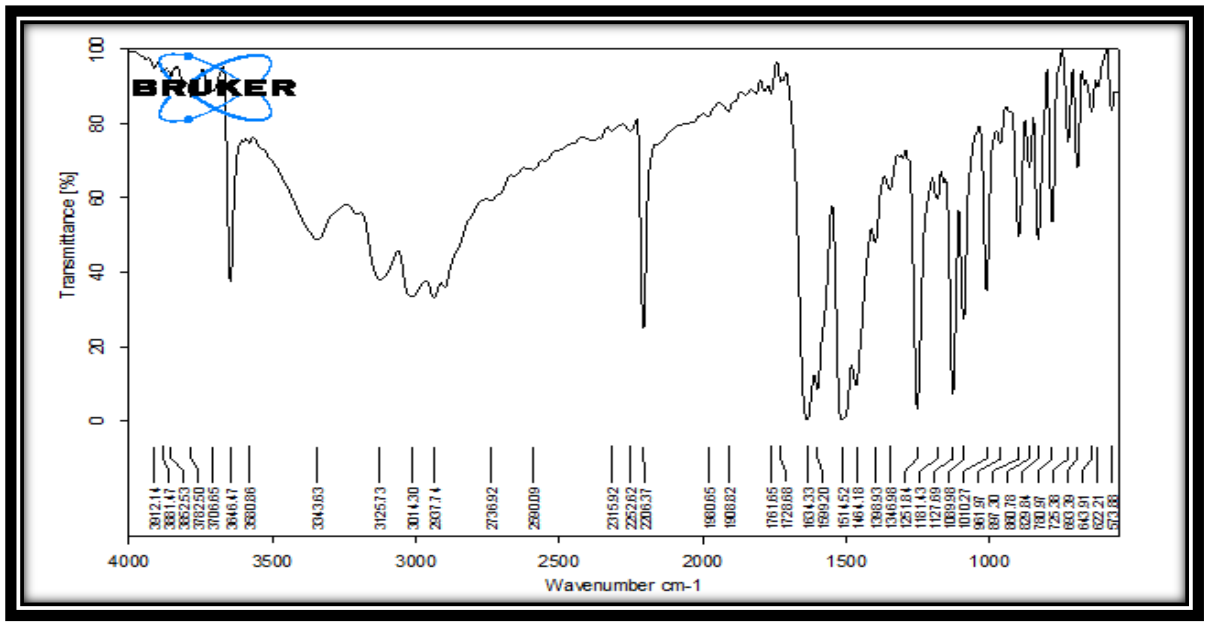


**Fig. 1: IR Spectra of Acalabrutinib pure**

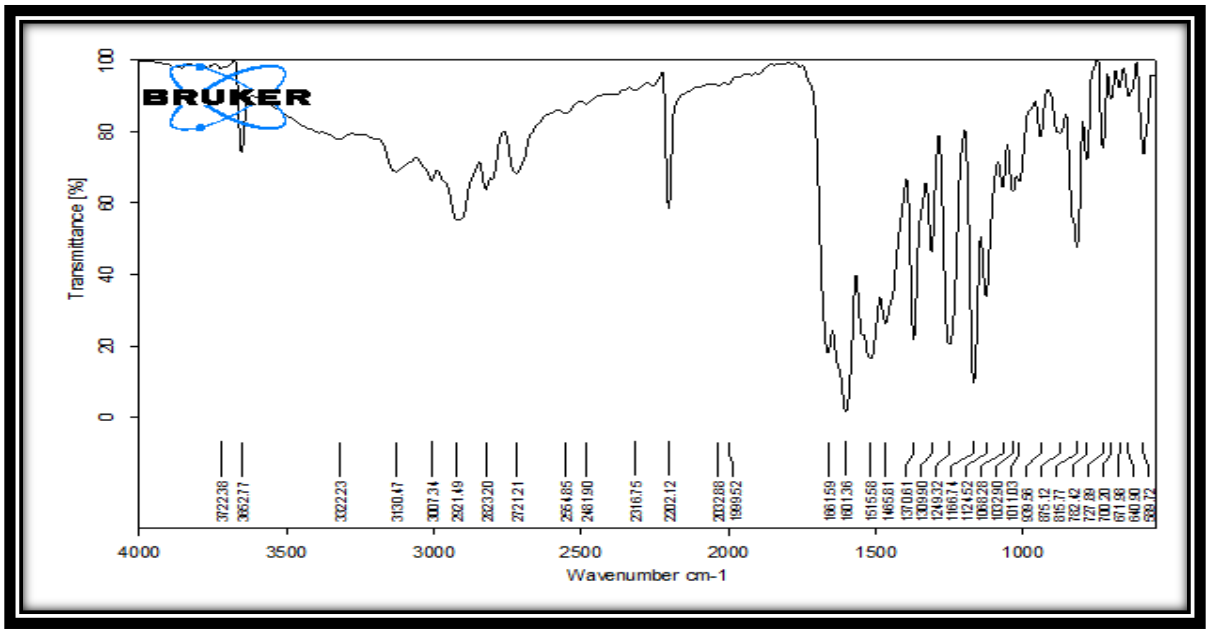


**Fig. 2: IR Spectra of Acalabrutinib pure and Excipients**

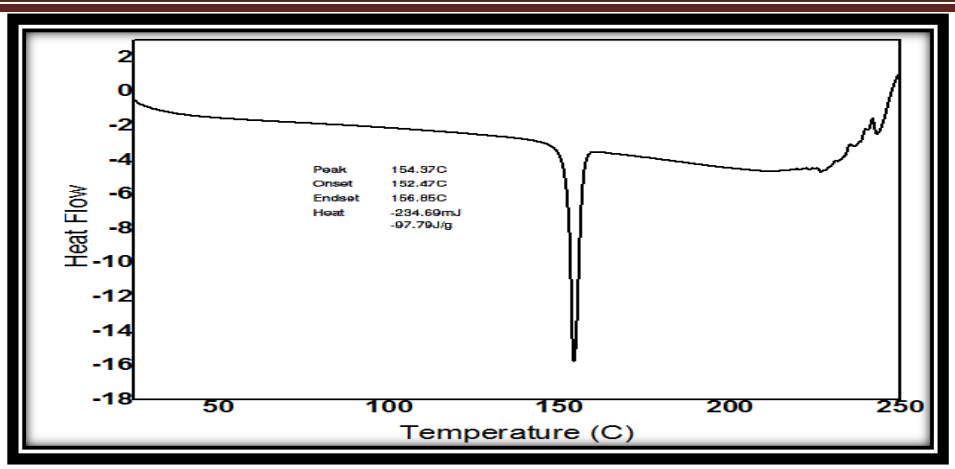


**Fig. 3: Acalabrutinib Pure DSC**

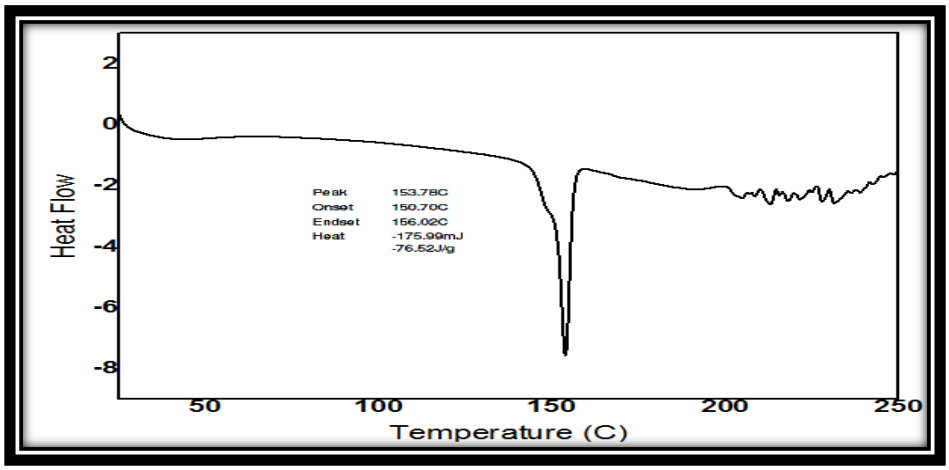


**Fig. 4: Acalabrutinib Pure and Excipients DSC**

**Table No. 5: Pre-Compression Parameters of Acalabrutinib controlled release matrix Tablets**

| FC | Angle of Repose | Bulk density | Tapped density | Hausner's ratio | Carr's index |
|---|---|---|---|---|---|
| **F1** | 26.21±0.24 | 0.282±0.44 | 0.324±0.36 | 1.14±0.22 | 12.96±0.54 |
| **F2** | 29.84±0.36 | 0.270±0.16 | 0.316±0.24 | 1.17±0.54 | 14.55±0.26 |
| **F3** | 26.96±0.28 | 0.266±0.84 | 0.327±0.21 | 1.22±0.26 | 18.65±0.33 |
| **F4** | 28.85±0.52 | 0.270±0.26 | 0.330±0.22 | 1.22±0.87 | 18.18±0.20 |
| **F5** | 26.46±0.65 | 0.264±0.22 | 0.325±0.18 | 1.20±0.62 | 18.76±0.14 |
| **F6** | 28.64±0.24 | 0.268±0.14 | 0.334±0.54 | 1.24±0.48 | 19.76±0.02 |
| **F7** | 27.64±0.10 | 0.252±0.02 | 0.320±0.26 | 1.26±0.34 | 21.25±0.54 |
| **F8** | 25.85±0.24 | 0.268±0.97 | 0.330±0.24 | 1.23±0.22 | 18.78±0.62 |
| **F9** | 26.54±0.89 | 0.266±0.24 | 0.320±0.52 | 1.20±0.04 | 16.87±0.10 |

**Table No. 6: Post Compression Parameters of Acalabrutinib controlled release matrix Tablets**

| FC | Avg.Wt (mg) | Thickness (mm) | Hardness (kg/cm²) | Friability (%) | Drug Content (%) |
|---|---|---|---|---|---|
| **F1** | 401.28±1.54 | 4.12±1.26 | 8.54±0.04 | 0.22±0.48 | 92.14±0.98 |
| **F2** | 400.02±0.26 | 4.02±0.58 | 8.92±0.12 | 0.16±0.02 | 91.54±0.46 |
| **F3** | 398.56±0.54 | 4.22±0.68 | 9.12±0.25 | 0.54±0.16 | 90.26±0.84 |
| **F4** | 400.28±0.11 | 4.28±0.84 | 8.26±0.36 | 0.28±0.48 | 93.64±0.38 |
| **F5** | 399.64±0.28 | 4.10±0.12 | 8.54±0.98 | 0.10±0.25 | 92.41±0.78 |
| **F6** | 402.14±0.36 | 4.02±0.69 | 9.20±0.54 | 0.46±0.66 | 88.26±0.54 |
| **F7** | 400.01±0.28 | 4.00±0.22 | 8.86±0.87 | 0.29±0.22 | 90.14±0.69 |
| **F8** | 399.87±0.54 | 4.52±0.36 | 8.24±0.22 | 0.84±0.48 | 95.12±0.89 |
| **F9** | 398.54±0.08 | 4.26±0.14 | 8.26±0.69 | 0.12±0.25 | 96.64±0.94 |

**4. In vitro drug release studies:**

From the in vitro drug release studies of Acalabrutinib controlled release tablets using HPMC K4M, HPMC K15M and Carbopol 940 in three different polymer ratios using lactose as a diluent, MCC as a filler and PVP K30 as binder.

Among the all 9 trails F1-F3 trails were formulated using HPMC K 4M in three different ratios like 15%, 22.5% and 30%, the drug release was decreased with increase in the polymer concentration. F1 formulation containing 15% of HPMC K4 M shows 98.63% of drug release at the end of 8hours, while F2 formulation containing 22.5% of HPMC K4 M shows 99.08% of drug release at the end of 12hours, whereas F3 formulation containing 30% of HPMC K4 M shows 99.62% of drug release at the end of 16hours, Among all the three formulations of HPMC K 4M none of the formulations didn't controlled the drug release for 24hours even at 30% concentration. So further formulations were prepared using HPMC K15M.

Then F4-F6 trails were formulated using HPMC K 15M in three different ratios like 15%, 22.5% and 30%, the drug release was decreased with increase in the polymer concentration. F4 formulation containing 15% of HPMC K15 M shows 96.28% of drug release at the end of 10hours, while F5 formulation containing 22.5% of HPMC K15 M shows 98.34% of drug release at the end of 14hours, whereas F6 formulation containing 30% of HPMC K15 M shows 96.01% of drug release at the end of 20hours, Among all the three formulations of HPMC K 15M none of the formulations didn't controlled the drug release for 24hours even at 30% concentration. So further formulations were prepared using Carbopol 940.

Then F7-F9 trails were formulated using Carbopol 940 in three different ratios like 15%, 22.5% and 30%, the drug release was decreased with increase in the polymer concentration. F7 formulation containing 15% of Carbopol 940 shows 99.86% of drug release at the end of 12hours, while F8 formulation containing 22.5% of Carbopol 940 shows 98.62% of drug release at the end of 16hours, whereas F9 formulation containing 30% of Carbopol 940 shows 99.32% of drug release at the end of 24hours,

Among the all nine formulations F9 formulation containing 30% of Carbopol 940 controls the drug release up to 24hours. So Carbopol 940 was considered to be suitable for the formulation of Acalabrutinib controlled release tablets at 30% concentration. Based upon the viscosity of the polymers, drug release rate was found to be as Carbopol 940> HPMC K15M> HPMC K4M. So, the drug release kinetics were performed for the F9 formulation.

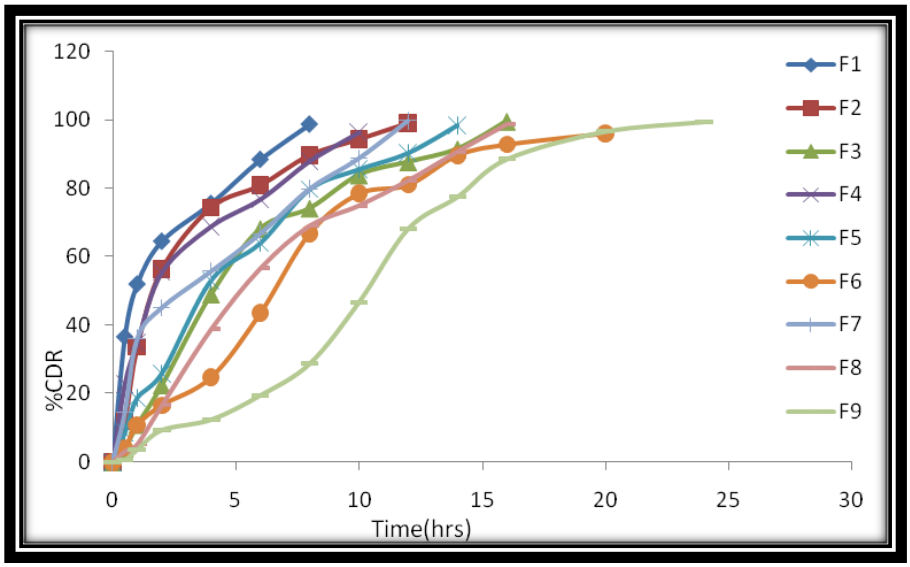


**Fig. 5: In-Vitro Drug Release Studies Of F1-F9 Formulations**

Optimized formulation F9 shows $R^2$ value 0.954. As its value nearer to the '1' it is conformed as it follows the Zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot. The 'n' value is 1.301 for the optimized formulation (F9) i.e., n value was > 0.89 this indicates super case transport.

**Table No. 7: Drug release kinetics of F9 Formulation:**

| | $R^2$ values | | | | n values |
|---|---|---|---|---|---|
| **Formulation** | **Zero order** | **First order** | **Higuchi** | **Korsmeyer - Peppas** | **Korsmeyer- Peppas (n)** |
| **F9** | 0.954 | 0.903 | 0.898 | 0.958 | 1.301 |

## CONCLUSION

In this study-controlled release matrix tablets of Acalabrutinib were prepared by Direct compression method, using HPMC K4M, HPMC K15M and Carbopol 940 polymers as retardants. The pre-compression and post compression evaluation studies shows that the values were found to be acceptable within the range. The drug-polymer ratio was found to influence the release of drug from the formulations.

Different parameters like hardness, friability, weight variation, drug content uniformity, in-vitro drug release was

evaluated. Among the all the nine formulations F9 formulation containing 30% of Carbopol 940 controls the drug release up to 24hours. So Carbopol 940 is suitable for the formulation of Acalabrutinib controlled release tablets at 30% concentration. Based on these results formulation F-9 was found to be the most promising formulations. The regression coefficient ($R^2$) of Optimized formulation F9 shows $R^2$ value 0.954. As its value is nearer to '1' it is conformed as it follows the Zero order release kinetics. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport. The F9 formulation shows n valve 1.301.

Thus, the aim of this study was achieved. Further preclinical and clinical studies are required to evaluate the efficacy of these formulations of Acalabrutinib.

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