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# Formulation, development and *invitro* evaluation of sustained release matrix tablets of capecitabine

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## ABSTRACT

The aim of the present study was to develop sustained release formulation of Capecitabine to maintain constant therapeutic levels of the drug for over 12 hrs. HPMC-K 100M, Sodium Carboxy Methyl Cellulose, Grewia gum, Almond gum were employed as polymers. The tablets were prepared by direct compression method. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (C5) showed better and desired drug release pattern i.e., 99.9% in 12 hours. It contains the HPMC-K 100 M 1:1 as sustained release material. It followed peppas release kinetics mechanism.

**Keywords:** Capecitabine, HPMC-K 100 M, Sodium Carboxy Methyl Cellulose, Grewia gum, Almond gum, Sustained release system and Direct compression method.

## INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body[1]. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action[2, 3]. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect[4]. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use[5, 6].

The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ[7, 8].

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and

- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed[9].

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

## *Rationale for extended release dosage forms*

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen[10,11]. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose . However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Fig.1).

The sustained plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well[12].

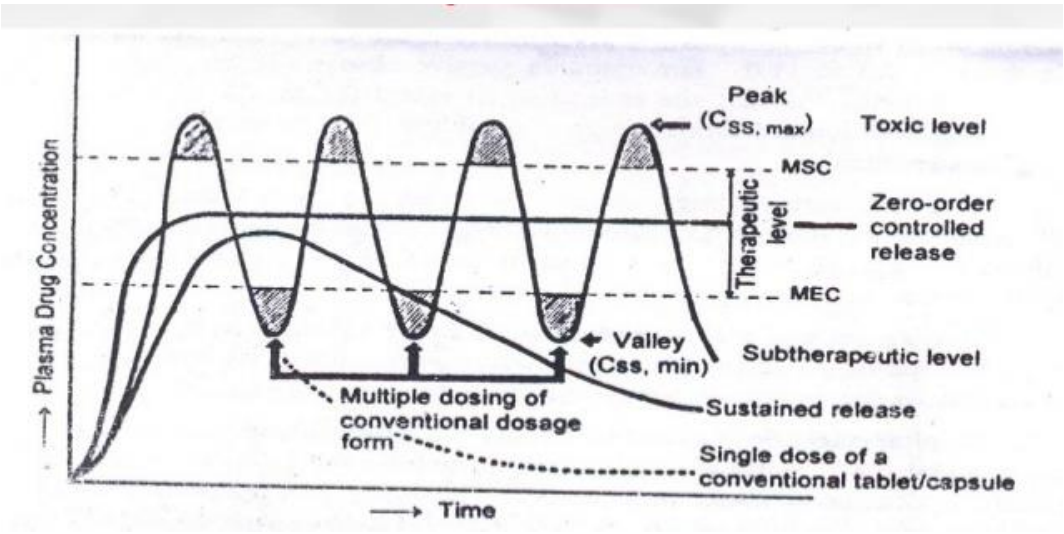


**Fig 1: Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.**

## *AIM AND OBJECTIVES*

The aim of the present work is to formulate and evaluate the Capecitabine Sustained release tablets using various polymers such as HPMC-K 100 M, Sodium Carboxy Methyl Cellulose, Grewia gum and Almond gum.

- ➢ The objective of this present study is to reduce the dosing frequency of Capecitabine so prepared Sustained release dosage form for prolong its duration of action, and reduced side effects.
- ➢ The present work is aimed at preparing and evaluating sustained-release (SR) matrix tablets of Capecitabine using different polymers.
- ➢ To study the effect of nature of the polymer and drug: polymer ratio on the rate of drug release.

- To evaluate pre and post compression evaluation parameters
- To perform Drug and Excipient compatibility studies (FTIR)
- To optimize the formula.

## MATERIALS AND METHODS

### *Formulation development of Sustained release Tablets*

All the formulations were prepared by direct compression method. The compositions of different formulations are given in Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Capecitabine.

### *Procedure*

In the present work the Capecitabine tablets were prepared by direct compression method. The drug and the excipients were passed through 72# size mesh prior to the preparation of dosage form. The entire ingredients were weighed separately and mixed thoroughly for 10 minutes in double cone blender to ensure uniform mixing in geometric ratio. The tablets were prepared by direct compression technique using 12mm punch.

**Table 1: Formulation of Capecitabine release tablets**

| Ingredients(mg) | C1 | C2 | C3 | C4 | C5 | C6 | C7 | C8 | C9 | C10 | C11 | C12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Capecitabine | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| HPMC-K 100 M | 100 | - | - | - | 150 | - | - | - | 200 | - | - | - |
| Sodium Carboxy Methyl Cellulose | - | 100 | - | - | - | 150 | - | - | - | 200 | - | - |
| Grewia gum | - | - | 100 | - | - | - | 150 | - | - | - | 200 | - |
| Almond gum | - | - | - | 100 | - | - | - | 150 | - | - | - | 200 |
| MCC PH 102 | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| Sodium Stearyl Fumarate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Total Wt | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |

## RESULTS AND DISCUSSION

### *Standard Curve of Capecitabine in Phosphate buffer pH 6.8*

The scanning of the 10µg/ml solution of Capecitabine in the ultraviolet range (200-400nm) against 6.8 pH phosphate the maximum peak observed at the $\lambda_{max}$ as 305 nm. The standard concentrations of Capecitabine (10-50µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with $R^2$ value of 0.997, which suggests that it obeys the Beer-Lamberts law.

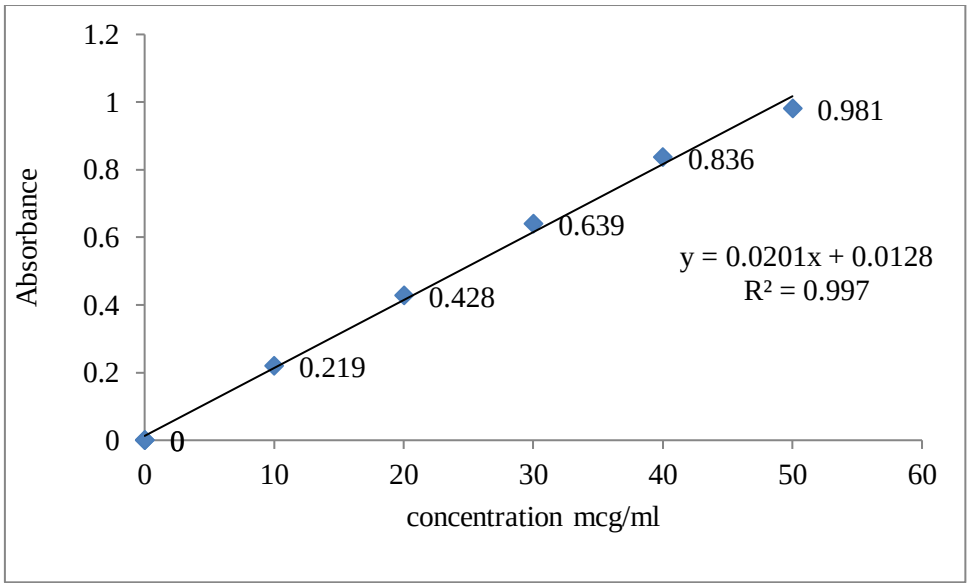


**Fig 2: Calibration of Capecitabine in Phosphate buffer pH 6.8**

### *EVALUATION PARAMETERS*

### *Pre-compression parameters*

**Table 2: Pre-compression parameters of powder blend**

| Formulation Code | Angle of Repose | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's index (%) | Hausner's Ratio |
|---|---|---|---|---|---|
| C1 | 25º.25 ±0.52 | 0.43 ±0.022 | 0.61 ±0.033 | 11.20 ±0.03 | 1.10 ±0.06 |

| | | | | | |
|---|---|---|---|---|---|
| C2 | 24 °.16 ±0.68 | 0.54 ± 0.051 | 0.64 ±0.013 | 11.21 ±0.21 | 1.14 ±0.051 |
| C3 | 28 °.38 ± 0.56 | 0.47 ± 0.08 | 0.54 ± 0.01 | 12.96 ± 0.42 | 1.14 ± 0.031 |
| C4 | 28 °.53 ± 0.57 | 0.48 ± 0.06 | 0.56 ± 0.08 | 14.28 ± 0.47 | 1.16 ± 0.032 |
| C5 | 25 °.41 ±0.65 | 0.52 ±0.091 | 0.59 ±0.064 | 14.21 ±0.17 | 1.25 ±0.022 |
| C6 | 26 °.08 ± 0.51 | 0.55 ± 0.011 | 0.62 ± 0.06 | 11.29 ± 0.35 | 1.12 ± 0.023 |
| C7 | 26 °.43 ±0.62 | 0.56 ± 0.07 | 0.63 ± 0.012 | 11.11 ± 0.12 | 1.12 ± 0.056 |
| C8 | 25 °.46 ± 0.57 | 0.55 ± 0.08 | 0.62 ± 0.011 | 11.29 ± 0.57 | 1.12 ± 0.015 |
| C9 | 25 °.15 ± 0.58 | 0.49 ± 0.01 | 0.56 ± 0.08 | 12.5 ± 0.21 | 1.14 ± 0.012 |
| C10 | 28 °.01 ± 0.63 | 0.53 ± 0.09 | 0.61 ± 0.071 | 13.1 ± 0.15 | 1.15 ± 0.021 |
| C11 | 26 °.12 ± 0.1 | 0.44 ± 0.03 | 0.50± 0.061 | 12 ± 0.58 | 1.13 ± 0.012 |
| C12 | 27 °.26 ± 0.56 | 0.52 ± 0.055 | 0.59 ± 0.08 | 11.86 ± 0.57 | 1.13 ± 0.026 |

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 25 to 30; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.44±0.03 to 0.56 ± 0.07 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.50± 0.061to 0.63 ± 0.012 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 11.11 to 14.28 which showed that the powder has good flow properties. All the formulations were showed the hausner ratio ranging from 0 to 1.25 indicating the powder has good flow properties.

## *Post Compression Parameters For tablets*

**Table 3: Post Compression Parameters of Tablets**

| Formulation codes | Weight variation (mg) | Hardness (kg/cm2) | Friability (%loss) | Thickness (mm) | Drug content |
|---|---|---|---|---|---|
| C1 | 501.5 ± 0.25 | 4.8±0.04 | 0.51±0.04 | 5.6±0.03 | 102.3 ± 0.21 |
| C2 | 501.53 ± 0.34 | 4.5 ± 0.02 | 0.561±0.03 | 5.2 ±0.02 | 99.50 ± 0.22 |
| C3 | 498.25± 1.15 | 4.7±0.01 | 0.45±0.02 | 5.3 ±0.05 | 97.2 ± 0.19 |
| C4 | 502.15 ± 1.31 | 4.7±0.05 | 0.54±0.07 | 5.6±0.04 | 99.3 ± 0.13 |
| C5 | 499. 23±0.25 | 4.6±0.09 | 0.48±0.08 | 5.6 ±0.09 | 104.3 ± 012 |
| C6 | 503.26 ± 1.25 | 4.7±0.01 | 0.45±0.02 | 5.4±0.05 | 98.2 ± 0.19 |
| C7 | 499.5 ± 0.95 | 4.8±0.07 | 0.51±0.04 | 5.3 ±0.03 | 102.3 ± 0.28 |
| C8 | 502.5 ± 0.86 | 4.7±0.04 | 0.55±0.07 | 5.3 ±0.05 | 98.3 ± 0.20 |
| C9 | 501.36 ± 1.17 | 4.7±0.04 | 0.56±0.04 | 5.7±0.08 | 100.8 ± 0.17 |
| C10 | 499.95 ± 1.72 | 4.8±0.01 | 0.45±0.05 | 5.4 ±0.05 | 98.8 ± 0.14 |
| C11 | 502.26 ± 0.81 | 4.5±0.01 | 0.55±0.02 | 5.6±0.06 | 98.2 ± 0.15 |
| C12 | 500.25 ± 2.02 | 4.8±0.03 | 0.52±0.03 | 5.7±0.04 | 103.5 ± 0.14 |

## *In Vitro Drug Release Studies*

The formulations prepared with different polymers by direct compression method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1N HCl for 2 hours and 6.8 pH phosphate buffers for remaining hours as a dissolution medium.

**Table 4: Dissolution Data of Capecitabine Tablets Prepared with 1:0.5 (Drug : polymer) Ratios of polymers like HPMC-K 100 M (C1), Sodium Carboxy Methyl Cellulose (C2), Grewia gum(C3), Almond gum (C4).**

| TIME (hr) | CUMULATIVE PERCENT OF DRUG RELEASED | | | |
|---|---|---|---|---|
| | C1 | C2 | C3 | C4 |
| **0** | 0 | 0 | 0 | 0 |
| **1** | 28.4±1.35 | 29.6±0.98 | 31.4±1.12 | 22.6±0.99 |
| **2** | 36.3±1.25 | 39.9±1.87 | 46.6±2.41 | 28.8±1.01 |
| **3** | 46.6±1.05 | 47.6±0.82 | 59.9±1.05 | 35.6±1.37 |
| **4** | 57.5±1.10 | 59.6±1.37 | 68.6±1.34 | 57.3±0.55 |
| **5** | 64.6±1.35 | 67.1±0.91 | 79.8±0.05 | 66.8±0.94 |
| **6** | 76.3±1.16 | 78.6±1.56 | 88.3±1.54 | 77.6±1.24 |
| **7** | 84.2±1.24 | 90.6±0.81 | 99.5±0.75 | 85.8±1.82 |
| **8** | 95.7±1.09 | 99.4±1.29 | | 93.4±0.98 |
| **10** | 99.8±1.37 | | | 100.1±0.64 |

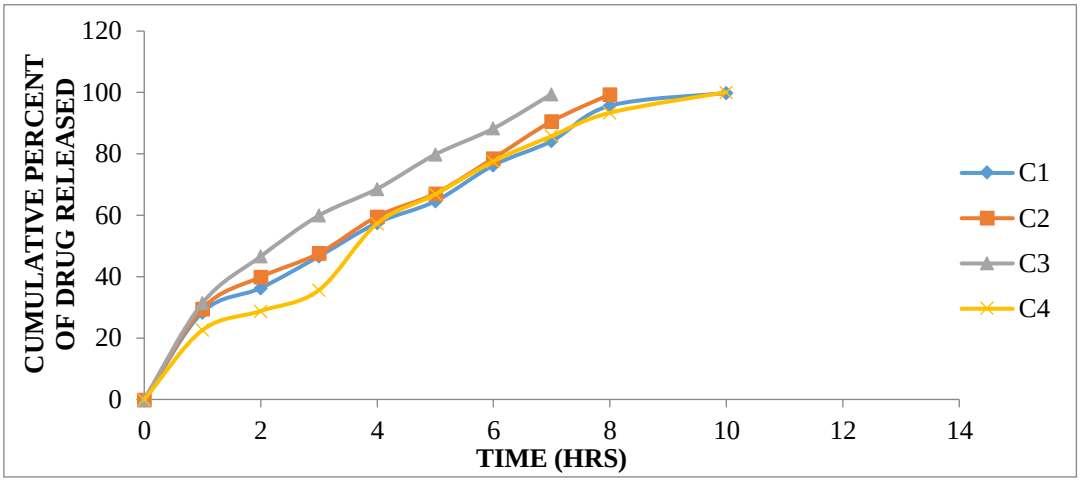


**Fig 3: Dissolution study of Capecitabine Sustained tablets (C1 to C4)**

**Table 5: Dissolution Data of Capecitabine Tablets Prepared with (Drug : polymer) Ratios of polymers like HPMC-K 100 M (C5), Sodium Carboxy Methyl Cellulose (C6), Grewia gum(C7), Almond gum (C8).**

| TIME (hr) | CUMULATIVE PERCENT OF DRUG RELEASED | | | |
|---|---|---|---|---|
| | C5 | C6 | C7 | C8 |
| **0** | 0 | 0 | 0 | 0 |
| **1** | 19.7±0.79 | 24.2±1.08 | 27.9±1.29 | 16.8±1.87 |
| **2** | 29.2±0.95 | 33.3±0.56 | 41.6±1.05 | 22.7±1.98 |
| **3** | 42.1±1.37 | 42.6±1.60 | 48.2±1.82 | 30.5±1.05 |
| **4** | 53.4±0.86 | 54.3±0.81 | 60.4±0.36 | 49.1±0.82 |
| **5** | 61.9±1.54 | 61.8±1.82 | 66.8±1.33 | 61.7±0.79 |
| **6** | 70.6±1.92 | 72.6±0.97 | 78.6±2.19 | 68.8±1.34 |
| **7** | 76.8±0.87 | 81.8±0.36 | 87.3±0.34 | 73.4±1.08 |
| **8** | 81.6±1.06 | 94.2±0.54 | 98.7±0.22 | 81.1±1.34 |
| **10** | 97.3±0.88 | 99.1±0.81 | | 98.2±0.79 |
| **12** | 99.9±1.07 | | | |

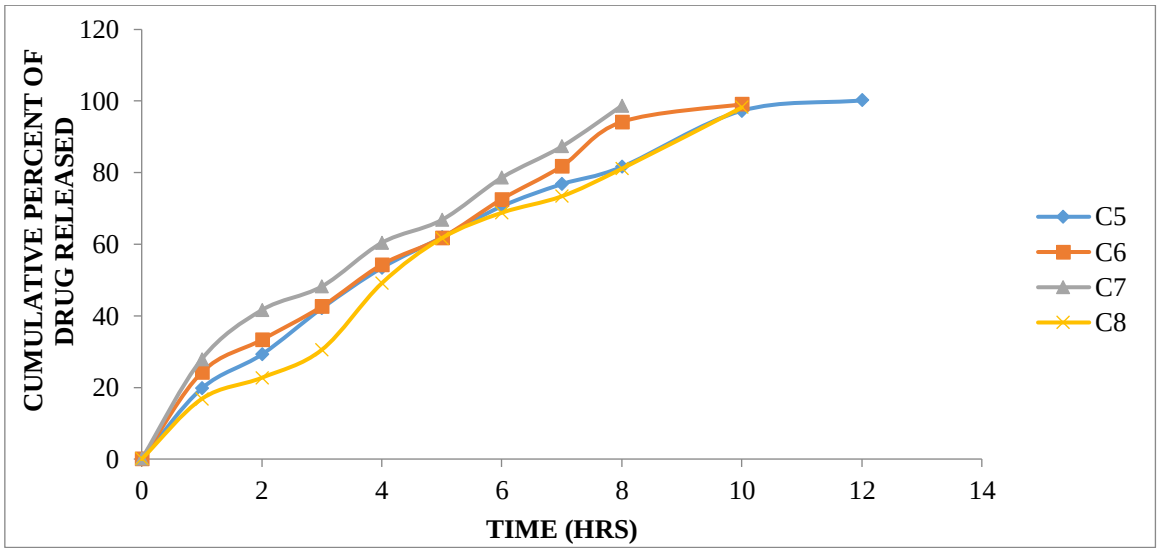


**Fig 4: Dissolution study of Capecitabine (C5 to C8)**

**Table 6: Dissolution Data of Capecitabine Tablets Prepared with (Drug : polymer) Ratios of polymers like HPMC-K 100 M (C9), Sodium Carboxy Methyl Cellulose (C10), Grewia gum(C11), Almond gum (C12).**

| TIME (hr) | CUMULATIVE PERCENT OF DRUG RELEASED | | | |
|---|---|---|---|---|
| | C9 | C10 | C11 | C12 |
| **0** | 0 | 0 | 0 | 0 |
| **1** | 17.2±0.58 | 18.7±0.95 | 15.6±1.55 | 11.9±1.79 |
| **2** | 22.6±1.05 | 28.6±1.26 | 26.8±0.69 | 17.6±0.36 |
| **3** | 33.8±0.72 | 39.6±0.78 | 33.9±0.87 | 26.3±1.57 |
| **4** | 44.3±1.36 | 51.2±1.87 | 49.8±0.79 | 33.3±1.16 |
| **5** | 52.8±0.29 | 57.8±0.34 | 52.5±1.06 | 41.8±0.28 |
| **6** | 65.9±1.00 | 64.6±1.97 | 62.1±0.33 | 58.2±1.09 |
| **7** | 73.3±0.35 | 76.8±0.39 | 70.6±1.09 | 68.3±0.28 |
| **8** | 79.7±1.01 | 85.8±1.27 | 79.5±1.28 | 78.8±1.34 |
| **10** | 90.5±1.41 | 90.9±0.98 | 88.6±0.80 | 81.9±0.33 |
| **12** | 99.1±1.87 | 93.1±1.33 | 90.3±0.27 | 88.9±1.05 |

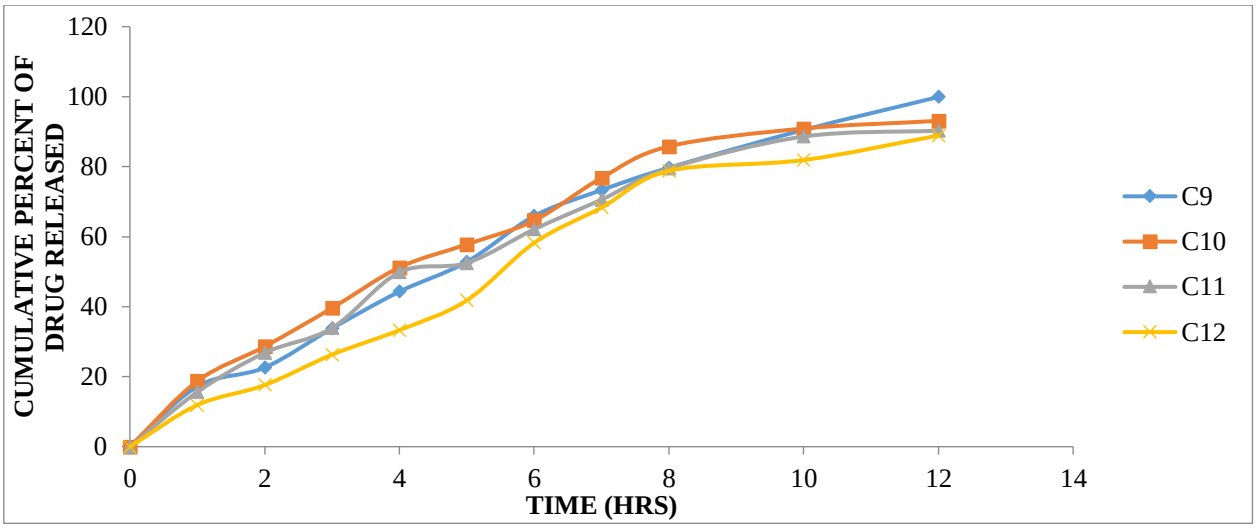


**Fig 5: Dissolution study of Capecitabine (C9 to C12)**

### *Application of Release Rate Kinetics to Dissolution Data*

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Capecitabine release from Sustained tablets. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms and the results were shown in below table it follows the zero order kinetics

**Table: Release kinetics data for optimized formulation (C5)**

| CUMULATIVE (%) RELEASE Q | TIME ( T ) | ROOT (T) | LOG( %) RELEASE | LOG ( T ) | LOG (%) REMAIN | RELEASE RATE (CUMULATIVE % RELEASE / t) | 1/CUM% RELEASE | PEPPAS log Q/100 | % Drug Remaining | Q01/3 | Qt1/3 | Q01/3-Qt1/3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | | | 2.000 | | | | 100 | 4.642 | 4.642 | 0.000 |
| 19.7 | 1 | 1.000 | 1.294 | 0.000 | 1.905 | 19.700 | 0.0508 | -0.706 | 80.3 | 4.642 | 4.314 | 0.327 |
| 29.2 | 2 | 1.414 | 1.465 | 0.301 | 1.850 | 14.600 | 0.0342 | -0.535 | 70.8 | 4.642 | 4.137 | 0.505 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 42.1 | 3 | 1.732 | 1.624 | 0.477 | 1.763 | 14.033 | 0.0238 | -0.376 | 57.9 | 4.642 | 3.869 | 0.773 |
| 53.4 | 4 | 2.000 | 1.728 | 0.602 | 1.668 | 13.350 | 0.0187 | -0.272 | 46.6 | 4.642 | 3.599 | 1.043 |
| 61.9 | 5 | 2.236 | 1.792 | 0.699 | 1.581 | 12.380 | 0.0162 | -0.208 | 38.1 | 4.642 | 3.365 | 1.277 |
| 70.6 | 6 | 2.449 | 1.849 | 0.778 | 1.468 | 11.767 | 0.0142 | -0.151 | 29.4 | 4.642 | 3.086 | 1.555 |
| 76.8 | 7 | 2.646 | 1.885 | 0.845 | 1.365 | 10.971 | 0.0130 | -0.115 | 23.2 | 4.642 | 2.852 | 1.790 |
| 81.6 | 8 | 2.828 | 1.912 | 0.903 | 1.265 | 10.200 | 0.0123 | -0.088 | 18.4 | 4.642 | 2.640 | 2.002 |
| 97.3 | 10 | 3.162 | 1.988 | 1.000 | 0.431 | 9.730 | 0.0103 | -0.012 | 2.7 | 4.642 | 1.392 | 3.249 |
| 99.9 | 12 | 3.464 | 2.000 | 1.079 | -1.000 | 8.325 | 0.0100 | 0.000 | 0.1 | 4.642 | 0.464 | 4.177 |

## *FTIR RESULTS*

### *Drug and Excipient Compatibility Studies*

### *FTIR study*

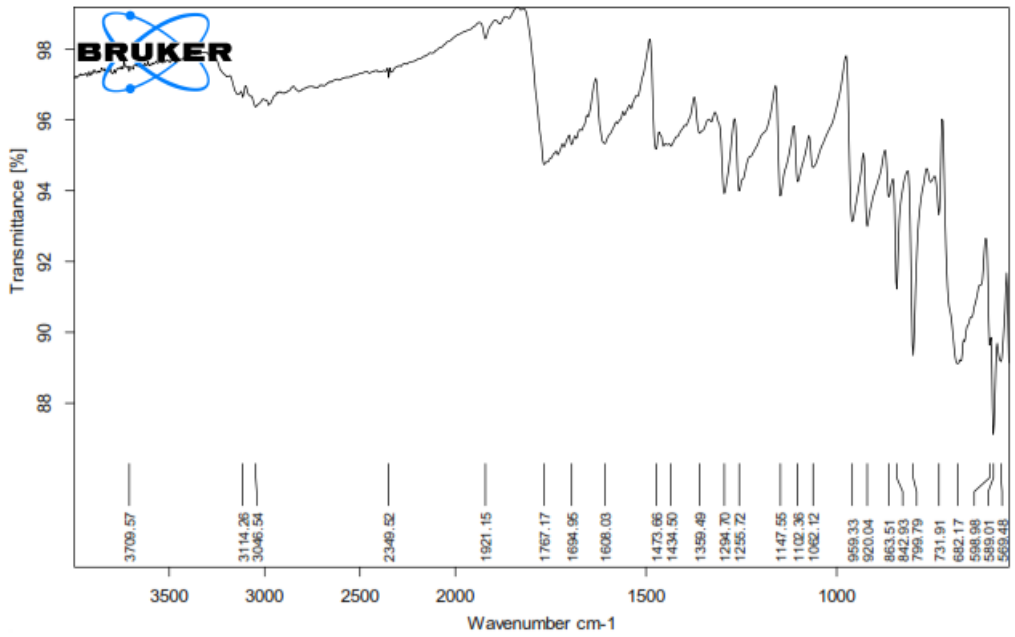


**Fig 6: FTIR GRAPH OF PURE DRUG**

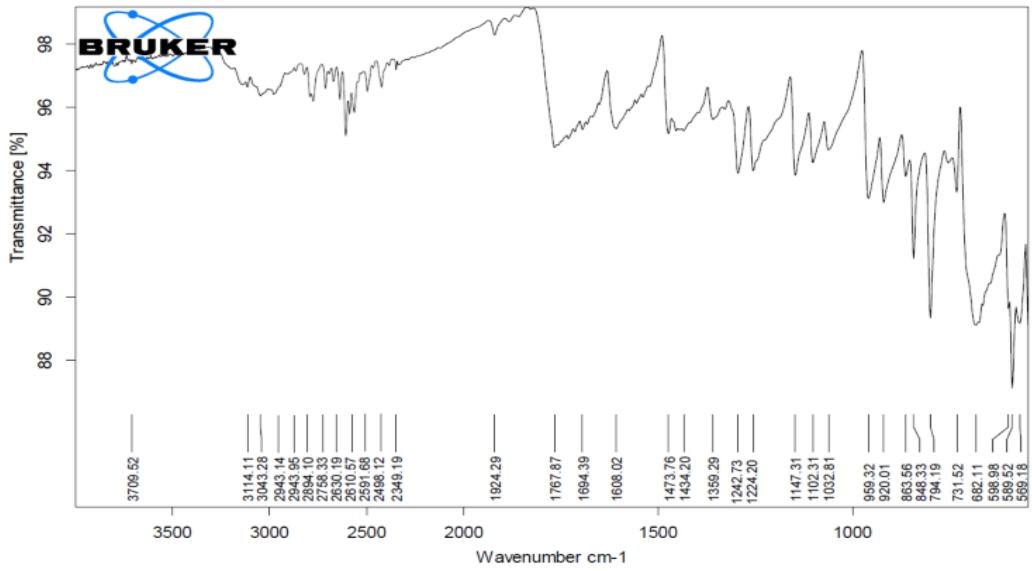


**Fig 7: FTIR GRAPH OF OPTIMISED FORMULATION**

From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

## CONCLUSION

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. Sustain release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration 2-3 times. The use of polymers in sustaining the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Sustain release can be achieved by using HPMC-K 200 M, Sodium Carboxy Methyl Cellulose, Grewia gum, Almond gum along with other excipients used were MCC as a direct compressible agent, talc and magnesium stearate as a glidant and lubricating agent respectively. Drug and excipients were subjected for compatibility study using FT-IR, which suggested that there was no interaction between drug and excipients. All the formulations were subjected for various pre-compression studies such as angle of repose, bulk density; tapped density, Carr's index, Haunser's ratio and results revealed that the powder mixtures showed good to acceptable flow and compressibility properties. All the formulations were subjected for various post-compression studies such as weight variation, hardness, thickness, friability, drug content and in-vitro dissolution studies were within the standard official specifications. The results of *in-vitro* dissolution study indicated that the drug release from formulation C5 showed 99.9% respectively at the end of 12 hours in sustain manner. The optimized formulation kinetic parameters were evaluated it follows the peppas release kinetics. The research study provided useful information for the formulation scientists on formulation, characterization during development of controlled drug delivery systems of Capecitabine using these polymers.

### *ACKNOWLEDGEMENT*

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