FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF CAPECITABINE USING DIFFERENT HYDROPHYLIC POLYMERS

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ABSTRACT

The objective of this work was to formulate and evaluate the sustained release matrix tablets of Capecitabine - an anti cancer drug used in the treatment of metastatic breast cancer and colorectal cancers by using various hydrophilic polymers such as Xanthan gum, Carbopol and hydroxy propyl methyl cellulose K 100 [HPMC K 100] as cost-effective, nontoxic, easily available, with suitable hydrophilic matrix systems. Matrix tablets of Capecitabine were prepared by wet granulation method. Granules were evaluated for pre compression parameters such as bulk density, tapped density were found within limits. Angle of repose showed that the blend was freely flowing and Carr’s index was in 11.29 ± 0.324 to 14.53 ± 0.926 showing that the powered blend were having good compressibility. The prepared tablets were evaluated for various post compression parameters such as hardness, friability, uniformity of weight were showed good physical properties by satisfying with the limits. The uniformity of drug content was found to be 99.63 ± 0.65% to 99.08 ± 0.28% indicating that the drug content was uniform in all batches. The dissolution test was performed in the phosphate buffer media (pH 6.8) up to 24 hours. Among the different formulations prepared, formulation no. 2 with HPMC K 100 10%, Xanthan gum 10% has the % drug release 98.44% up to 24 hours was found to be satisfactory compare to other formulations. Overall, the safety and patient compliance was improved as well as the efficacy of the drug; this was achieved by reducing the frequency of drug administration and better control of drug plasma levels.
INTRODUCTION
The main goal of therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage forms is an important element in achieving this goal. The terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose are sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms.[1-3]

The oral conventional types of drug delivery systems are known to provide a prompt release of the drug. Therefore to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This results in a significant fluctuation in drug levels often with a subtherapeutic and or toxic levels and wastage of drug. Recently several technical advancements have resulted in the development of new systems of drug delivery having better control of the rate of drug absorption, sustaining the duration of therapeutic action and targeting the delivery of drug to a tissue [4, 5].

![A Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations](image)

The term controlled/extended release implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and a known mechanism of release. This means that the release of drug ingredient(s) from a controlled release drug delivery system proceeds at a rate that is not only predictable kinetically but also reproducible from one unit to another. In other words, the system attempts to control drug concentration in the target tissue. [6, 7]

Sustained release drug delivery system consists of mainly two parts: an immediate dose and a sustaining part. The immediately available dose is normally added to the sustaining part of the tablet or alternatively incorporated in the core of the tablet i.e., a portion (initial priming dose) of the drug i.e. released immediately in order to achieve the desired therapeutic response promptly. The remaining dose of the drug (maintenance dose) is then released slowly thereby resulting in therapeutic drug / tissue level, which is a prolonged. [8-11]

The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. [12-13]

Capecitabine is an orally administered chemotherapeutic agent used in the treatment of metastatic breast cancer and colorectal cancers. Capecitabine is a prodrug that is enzymatically converted to 5-Flourouracil in the tumour where it inhibits DNA synthesis and slows growth of tumour tissue. The dose of capecitabine is 1250mg/m2 twice daily orally for 2 weeks followed by a one week rest period in a 3-week cycle. [14-16]

The objective of the present work is to investigating the possibility of sustaining of Capecitabine Release from matrix tablet prepared by hydrophilic polymer and gums.

The specific objective of this research includes:
1. To overcome the main adverse effects associated with anticancer drugs such as GI disturbances due to their fast release in GIT.
2. Ensuring safety and improving patient compliance as well as the efficacy of the drug; this can be achieved by less frequent dosing and better control of drug plasma levels.
3. The formulation should exhibit superior processing properties and end-product performance such as an excellent compressing/hardness profile, low friability and no sticking issues.

MATERIAL AND METHODS

Capecitabine was obtained as a gift sample and hydroxy propyl methylcellulose K100M, Xanthan gum, Carbopol, Povidone, Microcrystalline cellulose, lactose, talc, Magnesium Stearate from Celon laboratories Ltd, Hyderabad, India;

METHODOLOGY

Preformulation studies:

Preformulation can be defined as an investigation of physical and chemical properties of a drug substance alone. The overall objective of Preformulation studies is to generate information useful to the formulator in developing stable and bio available dosage forms.

- Organoleptic properties
- Solubility Studies

Organoleptic properties:

The organoleptic characters of the drug like colour, odour, taste and appearance play an important role in the identification of the sample and hence they should be recorded in descriptive terminology.

Solubility studies:

An excess of drug is suspended in 100ml of dissolution medium containing various concentrations of carriers in stopper flask and equilibrated by intermittent shaking for 72 hrs maintained at 37±2°C. The solution is filtered through whatman filter paper. A portion of filtrate is diluted suitably and analyzed by UV spectroscopy.

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour</td>
<td>White to light yellow</td>
</tr>
<tr>
<td>Odour</td>
<td>Odourless</td>
</tr>
<tr>
<td>Appearance</td>
<td>Powder</td>
</tr>
<tr>
<td>Melting point</td>
<td>116 -117 °C</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in water, Ethanol, 11.8 %, acetonitrile, &gt; 59 % dimethyl formamide, Marginally soluble in &gt; 40 %, methanol,</td>
</tr>
</tbody>
</table>

Analytical Method Development [17-23]

Construction of standard plot of drug in Acidic buffer:

Standard curve of drug was prepared in 0.1N HCl buffer.

Procedure:

1. Preparation of stock solution: An accurately weighed 100 mg of Capecitabine was dissolved in 0.1N HCl separately and make up the volume up to 100 ml in a volumetric flask (Stock Solution: I, 1000 µg/ml). This was sonicated for 5 minutes.
2. From this 10 ml of solution were pipette out and make up the volume up to 100 ml (Stock Solution: II, 100 µg / ml).
3. Then the aliquots were prepared, whose concentration ranging from 0 to 60µg/ml and the absorbance was measured at wavelength 303nm by using UV Spectrophotometer (Shimadzu, Model No: 2450) against the blank.

<table>
<thead>
<tr>
<th>Concentration Mcg/ml</th>
<th>Absorbance nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0.19</td>
</tr>
<tr>
<td>20</td>
<td>0.335</td>
</tr>
<tr>
<td>30</td>
<td>0.5</td>
</tr>
<tr>
<td>40</td>
<td>0.68</td>
</tr>
<tr>
<td>50</td>
<td>0.82</td>
</tr>
<tr>
<td>60</td>
<td>0.998</td>
</tr>
</tbody>
</table>
Construction of standard plot of drug in PH 6.8 Phosphate buffer:
Standard curve of drug was prepared in 6.8 phosphate buffer

Procedure:
1. Preparation of stock solution: An accurately weighed 100 mg of Capecitabine was dissolved in PH 6.8 phosphate buffer separately and make up the volume up to 100 ml in a volumetric flask (Stock Solution: I, 1000 µg/ml). This was sonicated for 5 minutes.
2. From this 10 ml of solution were pipette out and make up the volume up to 100 ml (Stock Solution: II, 100 µg / ml).
3. Then the aliquots were prepared, whose concentration ranging from 0 to 20µg/ml and the absorbance was measured at wavelength 303nm by using UV Spectrophotometer (Shimadzu, Model No: 2450) against the blank.

Table 3: Standard curve of drug in Phosphate Buffer PH 6.8

<table>
<thead>
<tr>
<th>Concentration Mcg/ml</th>
<th>Absorbance nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0.478</td>
</tr>
<tr>
<td>12</td>
<td>0.555</td>
</tr>
<tr>
<td>14</td>
<td>0.646</td>
</tr>
<tr>
<td>16</td>
<td>0.754</td>
</tr>
<tr>
<td>18</td>
<td>0.825</td>
</tr>
<tr>
<td>20</td>
<td>0.922</td>
</tr>
</tbody>
</table>

y = 0.0164x + 0.0105
R² = 0.9991

Figure 2: Standard graph of capecitabine using 0.1N HCl

y = 0.046x + 0.0055
R² = 0.9992

Figure 3: Standard graph of capecitabine using Phosphate Buffer PH 6.8
FORMULATION AND DEVELOPMENT OF SUSTAINED RELEASE MATRIX TABLETS:
Design of formula and composition

The design of tablets involved various compromises on the part of the formulator, to produce desired product properties. It involves the correct selection and balance of excipients materials for active ingredients to achieve the desired response.

Formulation:

Table 3: Composition of Capecitabine sustained release tablets (mg)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
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<tr>
<td>Lactose</td>
<td>100</td>
<td>120</td>
<td>130</td>
<td>135</td>
<td>130</td>
<td>120</td>
<td>100</td>
<td>120</td>
<td>130</td>
</tr>
<tr>
<td>HPMC K 100</td>
<td>20</td>
<td>10</td>
<td>5</td>
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<td>10</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Carbapol</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Xanthan Gum</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Povidone K 25</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
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<tr>
<td>Water</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
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</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>90</td>
<td>90</td>
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<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Magnesium Stearate</td>
<td>4</td>
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<td>4</td>
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<td>4</td>
<td>4</td>
<td>4</td>
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</tr>
<tr>
<td>Total Weight in mg</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

PREPARATION OF GRANULES [5]:

Procedure:

Weighed all the ingredients like Capecitabine and HPMC-K100, Carbapol, Xanthan Gum, Povidone K 25, Micro crystalline cellulose pH 101, Talc and Magnesium Stearate accordingly to the formula. Dissolve providone K-25 in Water by slow addition. Avoid lump formation during addition of providone K-25 stir to dissolve and to form a homogenous clear solution. Mix the ingredients in rotating mixture granulator (RMG) for 25 minutes. Granulate the ingredients with proper addition of binder should be slow to effect granulation. Add extra amount of Binder, if required and recorded the same. Use chopper such that not lumps are formed during granulation. Airs dry the wet mass in fluidized bed dryer for 15 minutes for applying the initial drying. Received the dry granules through the sifter fitted with 20#.Mill the retained granules through a mill fitted with 2 mm screen. Dry the semidried granules in Fluidized Bed Dryer at temperature of 50°C of the outlet temperature gauge to suitably achieve on LOD of 1%. Record the temperature (periodically).Sifted the dried granules through 16#.The ingredients are passed through the sieve no 30 # and Pre-blended the received and a milled granule is double cone blender, alongwith sifted excipients. Except purified Talc and Magnesium Stearate, Sift to through 40# and blend it in to the blender and mix it for 8 minutes. Add the sifted lubricant purified Talc magnesium stearate into the previously prepared granules and mix uniformity.

EVALUATION OF GRANULES [5]:

Angle of Repose The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

\[ \tan \theta = \frac{h}{r} \]

Where,
- \( h \) and \( r \) are the height and radius of the powder cone,
- \( \theta \) is the angle of repose.
**Bulk density:**
A quantity of 20g of powder from each formula, previously lightly shaken to break any agglomerates formed is introduced into a graduated cylinder. The initial volume and weight were noted. Ratio of weight of the sample to the volume it occupied was calculated

\[
\text{Bulk density} = \frac{\text{weight of the powder}}{\text{volume of the packing}}
\]

**Tapped density:**
Weighed granules were transferred to a graduated cylinder and were placed on the tap density apparatus. It was operated for a fixed number of taps (500). Repeat the tapping on additional 750 times until no further change in volume was noted the tapped volume was measured. The tapped density is calculated by the following formula

\[
\text{Tapped density} = \frac{\text{weight of the powder}}{\text{Tapped volume of the pack}}
\]

**Hausner’s Ratio:**
It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr’s index.

\[
\text{Hausner’s Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

**Compressibility index:**
Compressibility index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, less the compressibility of a material, the more flowable it is.

\[
\% \text{ Compressibility} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100
\]

**PREPARATION OF TABLETS:**

**Compression:**
After preparation of granules by wet granulation technique the granules are compressed into tablets on a 8-station rotary tableting machine.

**EVALUATION OF TABLETS [5]:**

**Weight variation test:**
Take 20 tablets and weighed individually using electronic balance. The average weight is calculated. Percent weight variation was calculated as follows. The tablet pass the U.S.P. test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

\[
\% \text{ Weight variation} = \frac{(W_H - W_I) \times 100}{W_A}
\]

Where,

- \(W_H\) = Highest weight in mg.
- \(W_L\) = Lowest weight in mg.
- \(A\) = Average weight of tablet in mg.

\[
\% \text{ Maximum positive deviation} = \frac{(W_H - A)}{A} \times 100
\]
\[
\% \text{ Minimum negative deviation} = \frac{(W_L - A)}{A} \times 100
\]

**Thickness:**
Tablet thickness was measured by Vernier calipers or by other device. Tablet thickness should be controlled within a ± 7.5% variation of standard value.

**Hardness:**
Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. It was determined by placing the tablet between the anvils only one of which is movable, driven by electricity. It presses the tablet at constant load till the tablet breaks. It was recorded in kp (1kp= 1 kg).
**Note:** From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

**Friability:**
Friability was determined in Electro lab Friabilator. From each batch, ten tablets were accurately weighed and the initial weight was noted. They were placed in the apparatus and subjected to 100 revolutions at speed of 25 rpm. When the drum stopped, tablets were taken and dedusted and final weight was taken.

\[
\% \text{ Friability} = \frac{(W_1 - W_2) \times 100}{W_1}
\]

Where,
- \(W_1\) = Initial weight of the 20 tablets.
- \(W_2\) = Final weight of the 20 tablets after testing.

Acceptance criteria: The friability value should be less than 1.0%.

**Drug Content Uniformity:**
The tablets were crushed in a mortar to get fine powder. Weight of powder equivalent to 100 mg was placed in volumetric flask. 20 methanol was added and sonicated for 15 minutes to dissolve completely. Then volume was adjusted to 100 ml with same media. Then filter the solution through 0.45 µm filter and suitable dilutions were prepared with pH 6.8 phosphate buffer. Same procedure was followed for the preparation of standard by taking 100 of pure drug. These solutions were analyzed by recording the absorbance at 303 nm by using UV-Visible spectrophotometer.

The drug content was calculated from the following formula

\[
\text{Drug content} = \frac{\text{Amount of drug in each tablet}}{\text{Label claim}} \times 100
\]

Where, amount of drug in each tablet was calculated as:

\[
\text{Amount} = \frac{\text{Absorbance}_{\text{test}} \times \text{dilution}_{\text{std}} \times \text{drug purity} \times \text{avg. wt}}{\text{Absorbance}_{\text{std}} \times \text{dilution}_{\text{test}} \times 100}
\]

**IN-VITRO DRUG RELEASE CHARACTERISTICS**
Drug release was assessed by using USP dissolution test apparatus type I (Basket). 900 ml of dissolution medium maintained at 37±0.5°C was used. Basket was rotated at 50 rpm for 24 hrs. An aliquot (10ml of samples) were withdrawn at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 hours time intervals, replacing the same amount with the pre warmed fresh medium. The samples withdrawn were filtered and the amount of drug dissolved was analyzed by a UV-Visible spectrophotometer (Shimadzu UV) at 303 nm.

**Calculation**
Calculate the % release of Capecitabine per tablet by using the formula:

\[
\frac{\text{Test absorbance} \times \text{Standard weight (mg)} \times \text{Sample dilutions} \times 900 \times \text{Standard purity}}{\text{Standard absorbance} \times 100 \times \text{Test dilutions} \times \text{Label claim}}
\]

**FTIR STUDIES [24]**

**Procedure:**
Weighed amount of drug (1 mg) was mixed with 99 mg of spectroscopic grade potassium bromide (dried at 40-50°C). The mixture was taken and compressed under 7-ton pressure in a hydraulic press of Shimadzu 8400 series FTIR instrument to form a transparent pellet. The pellet was scanned in the IR range from 500 to 3500cm\(^{-1}\) in IR spectrophotometer. FTIR of Capecitabine, drug with other excipients and polymers like Xanthan gum 10 % and HPMC K100 10 % was selected as best formulation used for the study.
RESULTS AND DISCUSSION

Evaluation Of Granules

Table 4: Pre Compression Parameters

<table>
<thead>
<tr>
<th>Code</th>
<th>Angle of repose (ϴ)</th>
<th>Bulk Density (gm/cm³)</th>
<th>Tapped Density (gm/cm³)</th>
<th>Hausner’s ratio</th>
<th>Carr’s index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>25.12±0.98</td>
<td>0.646±0.006</td>
<td>0.735±0.009</td>
<td>1.137±0.003</td>
<td>12.09±0.233</td>
</tr>
<tr>
<td>F2</td>
<td>24.78±.82</td>
<td>0.617±0.004</td>
<td>0.722±0.003</td>
<td>1.170±0.013</td>
<td>14.53±0.926</td>
</tr>
<tr>
<td>F3</td>
<td>26.89±0.80</td>
<td>0.634±0.005</td>
<td>0.720±0.008</td>
<td>1.136±0.022</td>
<td>11.99±1.739</td>
</tr>
<tr>
<td>F4</td>
<td>27.21±0.72</td>
<td>0.645±0.005</td>
<td>0.742±0.005</td>
<td>1.150±0.001</td>
<td>13.24±0.169</td>
</tr>
<tr>
<td>F5</td>
<td>25.62±0.53</td>
<td>0.652±0.012</td>
<td>0.740±0.003</td>
<td>1.134±0.021</td>
<td>11.89±0.562</td>
</tr>
<tr>
<td>F6</td>
<td>27.89±0.92</td>
<td>0.669±0.024</td>
<td>0.757±0.002</td>
<td>1.131±0.019</td>
<td>11.62±0.327</td>
</tr>
<tr>
<td>F7</td>
<td>26.58±0.94</td>
<td>0.654±0.011</td>
<td>0.728±0.003</td>
<td>1.130±0.009</td>
<td>12.16±1.202</td>
</tr>
<tr>
<td>F8</td>
<td>27.226±0.69</td>
<td>0.669±0.002</td>
<td>0.788±0.006</td>
<td>1.127±0.002</td>
<td>11.29±0.324</td>
</tr>
<tr>
<td>F9</td>
<td>26.32±0.72</td>
<td>0.660±0.002</td>
<td>0.750±0.011</td>
<td>1.135±0.001</td>
<td>11.93±0.084</td>
</tr>
</tbody>
</table>

The pre compression parameters of the entire formulations blend were conducted for angle of repose, bulk density, tapped density, compressibility index hausner’s ratio. The angle of repose gives important information about the flow properties of the powder mixture. The powder flow depends on three general areas: the physical properties of the particle (e.g., size, shape, compressibility), and the processing environment (e.g., storage, humidity). The angle of repose <30 indicates free flowing material and >40 poor flow. Values for angle of repose were found in the range of 29.327±0.76 showing that blend is free flowing. The values for carr’s index was in between 11.29±0.324 to 14.53±0.926 indicating that all batches of powder blends were having good compressibility. Hausner’s ratio was within the limits 1.138(<1.25).

EVALUATION OF TABLETS

Table 5: Post compression Parameters

<table>
<thead>
<tr>
<th>Code</th>
<th>Weight variation(mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Thickness(mm)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>400±0.82</td>
<td>3.42±0.32</td>
<td>0.32</td>
<td>3.93±0.14</td>
<td>97.07±0.02</td>
</tr>
<tr>
<td>F2</td>
<td>398±0.19</td>
<td>3.65±0.21</td>
<td>0.105</td>
<td>3.89±0.21</td>
<td>98.7±0.007</td>
</tr>
<tr>
<td>F3</td>
<td>400±0.53</td>
<td>4.01±0.42</td>
<td>0.117</td>
<td>3.92±0.16</td>
<td>97.7±0.008</td>
</tr>
<tr>
<td>F4</td>
<td>402±0.35</td>
<td>3.54±0.13</td>
<td>0.305</td>
<td>3.95±0.05</td>
<td>98.15±0.028</td>
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<tr>
<td>F5</td>
<td>401±0.45</td>
<td>3.97±0.14</td>
<td>0.104</td>
<td>3.9±0.02</td>
<td>98.67±0.32</td>
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<tr>
<td>F6</td>
<td>397±0.26</td>
<td>4.12±0.33</td>
<td>0.111</td>
<td>4.01±0.012</td>
<td>97.63±0.65</td>
</tr>
<tr>
<td>F7</td>
<td>400±0.76</td>
<td>3.76±0.25</td>
<td>0.214</td>
<td>3.96±0.07</td>
<td>98.75±0.86</td>
</tr>
<tr>
<td>F8</td>
<td>400±0.64</td>
<td>4.29±0.18</td>
<td>0.125</td>
<td>3.94±0.14</td>
<td>99.08±0.28</td>
</tr>
<tr>
<td>F9</td>
<td>400±0.12</td>
<td>3.87±0.09</td>
<td>0.287</td>
<td>3.81±0.02</td>
<td>98.43±0.07</td>
</tr>
</tbody>
</table>

The post compression parameters, weight variation was in the range of 397±0.26 to 402±0.35 mg for 400mg tablets, hardness of all formulations was found to be in the range of 3.42±0.032 to 4.29±0.18kg/cm², friability was found to be in the range of 0.104 – 0.32% and thickness values of the tablets of all the formulations was found to be in the range of 3.81±0.02 to 4.01±0.012. The batches showed good physical properties by satisfying the limits of weight variation, thickness, hardness, friability. The Drug content Uniformity i.e. Assay was performed for the prepared formulations and the obtained values for the dissolution trial batches were within the USP specifications 95-105% stating that the drug content was uniform in all the batches and no loss of drug has occurred. The assay values ranged from 97.63±0.65 to 99.08±0.28 %.
IN VITRO DISSOLUTION STUDIES:

Table 6: % Drug Release Data

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>21.52</td>
<td>24.08</td>
<td>25.5</td>
<td>19.08</td>
<td>16.97</td>
<td>17.26</td>
<td>13.2</td>
<td>12.6</td>
<td>11.6</td>
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<tr>
<td>4</td>
<td>30.16</td>
<td>32.45</td>
<td>33.16</td>
<td>28.01</td>
<td>23.42</td>
<td>25.08</td>
<td>21.8</td>
<td>18.7</td>
<td>16.2</td>
</tr>
<tr>
<td>6</td>
<td>38.08</td>
<td>39.66</td>
<td>41.85</td>
<td>33.12</td>
<td>30.83</td>
<td>32.4</td>
<td>27.4</td>
<td>23.1</td>
<td>21.5</td>
</tr>
<tr>
<td>8</td>
<td>43.2</td>
<td>45.47</td>
<td>49.7</td>
<td>41.31</td>
<td>39.85</td>
<td>40.67</td>
<td>32.3</td>
<td>29.8</td>
<td>28.3</td>
</tr>
<tr>
<td>10</td>
<td>49.45</td>
<td>54.17</td>
<td>57.23</td>
<td>47.01</td>
<td>42.43</td>
<td>44.63</td>
<td>37.8</td>
<td>34.6</td>
<td>35.6</td>
</tr>
<tr>
<td>12</td>
<td>56.81</td>
<td>60.41</td>
<td>64.25</td>
<td>52.51</td>
<td>46.36</td>
<td>49.7</td>
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<td>14</td>
<td>63.47</td>
<td>66.28</td>
<td>71.8</td>
<td>58.37</td>
<td>52.31</td>
<td>53.46</td>
<td>48.6</td>
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<tr>
<td>16</td>
<td>72.32</td>
<td>75.92</td>
<td>80.48</td>
<td>63.76</td>
<td>61.22</td>
<td>61.65</td>
<td>54.9</td>
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<tr>
<td>18</td>
<td>78.28</td>
<td>83.45</td>
<td>88.26</td>
<td>72.17</td>
<td>70.91</td>
<td>71.06</td>
<td>59.6</td>
<td>53.2</td>
<td>52.4</td>
</tr>
<tr>
<td>20</td>
<td>85.51</td>
<td>88.67</td>
<td>97.5</td>
<td>80.23</td>
<td>75.48</td>
<td>74.56</td>
<td>65.8</td>
<td>59.7</td>
<td>57.5</td>
</tr>
<tr>
<td>22</td>
<td>90.35</td>
<td>93.11</td>
<td>----</td>
<td>83.72</td>
<td>80.86</td>
<td>78.33</td>
<td>69.2</td>
<td>64.7</td>
<td>63.9</td>
</tr>
<tr>
<td>24</td>
<td>93.25</td>
<td>98.44</td>
<td>----</td>
<td>88.51</td>
<td>85.71</td>
<td>82.63</td>
<td>75.3</td>
<td>70.8</td>
<td>67.2</td>
</tr>
</tbody>
</table>

From the above results it can be observed that though the polymers HPMC, Xanthan gum has sustaining effect on the release of drug from the matrix tablet, but the increasing concentration of polymer on the formulation retards the release of Capecitabine from the tablet. The release of drug from all formulations F4 - F6 was less than 88% in 24 hours. The formulations F7 – F9 had a release of drug less than 75% in 24 hours. The formulation F1 releases the drug 93.25% in the given time and F3 releases 97.50% in 20hrs only. Whereas, the formulation F2 releases 98.44% drug up to 24 hrs respectively.

![Dissolution Graph](image_url)
FTIR DATA:

![Figure 4: FTIR spectra of Capecitabine Standard](image1)

![Figure 5: FTIR spectra of Capecitabine along with Excipients and Polymers like Xanthan Gum 10 % and HPMC K100 10 %](image2)

**CONCLUSION**

The sustained release matrix tablet of Capecitabine was prepared by wet granulation. Based on the drug release F2 formulation was selected as optimised when compared to all the 9 formulations. The results of dissolution studies indicated that the F2 formulation produced sustained effect with 98.44% of drug release over a period of 24hrs in comparison to other formulations. The polymers which have been used in the best formulation F2 containing HPMC K -100 and Xanthan gum. The release can be so well
controlled that it almost coincides the theoretical release pattern for the drug by proper adjustment of polymer ratio. It can be concluded that the polymer plays a major role in the design of sustained release matrix tablet. It was observed that the increasing concentration of polymers had a retarding effect on the drug release from the polymer matrices. The study reveals that the drug release increases with increasing polymer concentration up to certain concentration level, after that the release decreases with increase in polymer concentrations (HPMC and Xanthan gum). Hence it clearly manifests the necessity of combining different classes of polymers up to certain level of concentration to get an acceptable pharmacokinetic profile in the fluctuating in vivo environment. Hence the tablet designed possesses all the qualities of a sustained release formulation. It need for further study for sustained action. Therefore capecitabine can be given by this route for better bio-availability and can minimize side effects of drug.

ACKNOWLEDGEMENTS

In the first place we would like to record our gratitude to the Mr. Aravind. G, Sr. Manager of FR&D, CELON Laboratories Ltd., for extending his valuable support by providing excellent facilities and guidance. I would like to extend my thanks to my friends Sharath Chandra Seelam and Ruma Chandana, K, for their support and encouragement and valuable suggestions during the course of my dissertation work.

REFERENCES

