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# Development and *In-Vitro* Evaluation of a Novel Bilayered Floating Tablets of Capecitabine and Ondansetron

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**ABSTRACT**

The prepared blend for IR layer tablets and SR layer tablets also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, and friability. The optimized formulation F8 in IR formulations contains an average thickness of 2.4mm, an average hardness of 3.4 kg/cm$^2$, an average weight of 149mg, friability of 0.43%. The optimized formulation F7 in SR formulations contains an average thickness of 2.3mm, average hardness of 7.3 kg/cm$^2$, and friability of 0.41%. The F7 formulation which releases the capecitabine in a sustained manner in 1$^{st}$ hour releases 25.5% but the remaining drug release was sustained up to 12 hours and the ondansetron immediate release F7 formulation showed 96 % drug release within 30 min. With the data of kinetic analysis, the F7 formulation showed the best linearity in Higuchi's Equation plot indicating that the release of the drug from the matrix tablet follows Non-Fickian diffusion.

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## INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles, and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility, and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipment choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in drug discovery such as genomics. Injections generally are not favored for use by patients unless facilitated by sophisticated auto-injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generated predominantly chemical entities with low molecular weights. [1-5]

### Multilayer tablets

Multilayer tablets are tablets made by compressing several different granulations fed into a die in succession, one on top of another, in the layer. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for 2 or 3 layers. More is possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes.

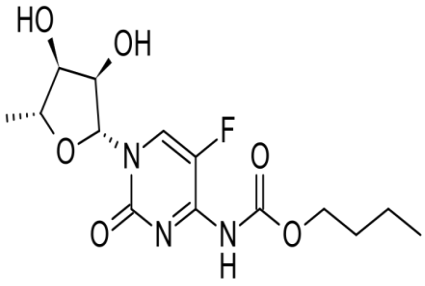
**Advantages of Multilayer tablets:** Incompatible substances can be separated by formulating them in separate layers as a two-layer tablet or separating the two layers by a third layer of an inert substance as a barrier between the two**.** Two-layer tablets may be designed for sustained release –one layer for the immediate release of the drug and the second layer for extended release, thus maintaining a prolonged blood level. Layers may be colored differently to identify the product. [6-10]

**The goals of designing bilayer tablets:** Controlling the delivery rate of either single or two different APIs. To separate incompatible APIs from each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property). For the administration of fixed-dose combinations of drugs, Prolonging the drug product life cycle**,** buccal /mucoadhesive delivery systems, and manufacturing novel drug delivery systems such as chewing devices and floating tablets for gastro-retentive drug delivery

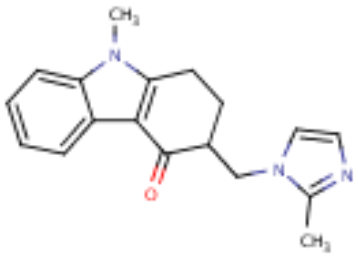
systems. To adapt the total surface area available for the API layer either by sandwiching with one or two inactive layers to achieve swellable/erodible barriers for controlled release. Bi-layer tablet is suitable for the sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablets in which one layer is immediate release as the initial dose and the second layer is maintenance dose. One layer is formulated to obtain the immediate release of the drug, to reach a high serum concentration in a short period. The second layer is a controlled release, which is designed to maintain an effective plasma level for a prolonged period. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at a steady state as the drug is released from the sustaining layer. [11-15]

**Advantages of bilayer tablets dosage form:** Bilayer tablets can be designed in such a manner as to modify release as either of the layers can be kept as extended and the other as an immediate release. Bi-layer tablet is suitable for preventing direct contact between two drugs and thus maximizing the efficacy of the combination of two drugs. Separation of incompatible components. Prospective use of single entity feed granules. Greatest chemical and microbial stability overall oral dosage form. Objectionable odor and bitter taste can be masked by the coating technique. Bilayer execution with optional single - layer conversion kit. Low cost compared to all other dosage forms. Offer the greatest precision and least content uniformity. Easy to swallow with the least hang-up problems. Flexible concept. Suitable for large-scale production. Lighter and compact. [15-20]

The main aim of the present investigation is to prepare and evaluate the bilayered floating tablets with a combination of Capecitabine and Ondansetron drugs.




**Capacitabine**




**Ondansetron**

## MATERIALS AND METHODS

### Preformulation studies:

### Preparation of linearity plot of Ondansetron in 0.1N HCl

**Preparation of 0.1N Hcl:** Take 8.5ml of HCl in distilled water and makeup to 1000ml with distilled Water to get 0.1N HCl.

**Determination of λ max of Ondansetron in 0.1N HCl:** Ondansetron was dissolved in0.1N HCl and the $\lambda_{max}$ was obtained at 310nm against the blank primary stock solution concentration of Ondansetron1000µg/ml was prepared. All measurements were made at room temperature.

**Standard Stock solution:**100 mg of Ondansetron was dissolved in 100 ml 0.1N HCl to give a concentration of (1000 µg/ml).

**Scanning:** From the stock solution 100µg/ml was prepared in 0.1N HCl and a UV scan was taken between 200 to 400 nm. The absorption maximum was found to be 310 nm and was used for further analytical studies. [21-25]

**Calibration curve of Ondansetron in 0.1N HCl** The standard solutions was prepared by proper dilutions of the primary stock solution with absolute 0.1N HCl to obtain working standards in the concentration range of 5-15µg/ml of a pure sample of Ondansetron. The concentration of Ondansetron present in the microspheres was obtained from the calibration curve.

### Construction of Standard Graph of Capacetabine (0.1 N HCl)

**Preparation of stock solution:** Accurately weighed amount of 100 mg was transferred into a 100ml volumetric flask. A few ml of water was added to dissolve the drug and the volume was made up to 100 mL with 0.1 N HCl. The resulting solution had a concentration of 1mg/ml which was labeled as ‘stock’.

**Preparation of working standard solution:** From this stock, solution 10ml was taken and diluted to 100 mL with 0.1 N HCl which has given the solution a concentration of 100 mcg/mL.

**Preparation of serial dilutions for standard calibration curve:** Necessary dilutions were made by using this second solution to give the different concentrations of Capacetabine(0-60mcg/mL) solutions. The absorbances of the above solutions were recorded at λthe $_{max}$ (303nm) of the drug using a double-beam UV-Visible spectrophotometer. The standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

**Construction of Standard Graph of Capacetabine (pH6.8 buffer)**

**Preparation of stock solution:** Accurately weighed amount of 100 mg was transferred into a 100ml volumetric flask. A few ml of water was added to dissolve the drug and the volume was made up to 100 mL with pH6.8 buffer. The resulting solution had a concentration of 1mg/ml which was labeled as 'stock'.

**Preparation of working standard solution:** From this stock, solution 10ml was taken and diluted to 100 mL with pH6.8 buffer which has given the solution a concentration of 100 mcg/mL.[26-30]

**Preparation of serial dilutions for standard calibration curve:** Necessary dilutions were made by using this second solution to give the different concentrations of capecitabine (0-20mcg/mL) solutions. The absorbances of the above solutions were recorded at λthe $_{max}$ (303nm) of the drug using a double-beam UV-Visible spectrophotometer. The standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

**Drug – Excipient Compatibility Study:**

**FTIR Studies:** FTIR studies were performed on the drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wavenumbers 4000 and 400 $cm^{-1}$.

**Formulation development:** Pharmaceutical development studies have to be carried out to select the right dosage form and a stable formulation. These studies give a detailed description of all the steps involved in the process of formulation development. Such details are intended towards identifying critical parameters involved in the process, which have to be controlled to give reliable and reproducible quality products.

**Formulation of Bilayer Matrix Tablet (Sustained Release Layer):** The bilayer tablet was prepared by direct compression method. As shown in the Table powder mixtures of Capacetabine, microcrystalline cellulose, polymers, and binder were dry blended for 20 min

followed by the addition of Magnesium Stearate and Talc. The mixtures were then further blended for 10 min., 400mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with a 12mm punch and die to obtain the tablet. [31-35]

**Composition of the sustained release layer**

**Table No 1: Formulation table for the sustained release layer**

| Ingredients | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ | $F_9$ | $F_{10}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| **Capecitabine (mg)** | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| **HPMC K4M(%)** | 10 | -- | -- | -- | -- | -- | 5 | -- | -- | -- |
| **HPMC K100M(%)** | -- | 10 | -- | -- | 15 | 20 | 15 | 15 | 15 | 20 |
| **HPMC E15 (%)** | -- | -- | 10 | -- | -- | -- | -- | 5 | -- | -- |
| **EC(%)** | -- | -- | -- | 10 | -- | -- | -- | -- | 5 | 5 |
| **PVP K30 (%)** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Talc (%)** | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| **Magnesium stearate(%)** | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| **MCC(mg)** | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| **The total weight (mg)** | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |

MCC- Microcrystalline cellulose, EC – Ethylcellulose, PVP- Poly vinyl pyrrolidine, HPMC – Hydroxy Propyl methylcellulose.

**Direct compression for immediate layer:** All the ingredients were passed through a sieve and mixed in a motor and pestle for 30min for uniform mixing. The addition of ingredients was done geometrically. Then the ondansetron layer was compressed using an 8mm round punch.

**Composition of the immediate release layer**

**Table no: 2 Formulation table for the immediate release layer**

| Ingredients (mg) | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ | $F_9$ |
|---|---|---|---|---|---|---|---|---|---|
| **Ondansetron** | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| **HPC (%)** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **SSG(%)** | 5 | -- | -- | -- | -- | -- | -- | -- | -- |
| **CCS(%)** | -- | 5 | -- | 7.5 | 10 | 12.5 | 10 | 10 | 10 |
| **CP(%)** | -- | -- | 5 | -- | -- | -- | -- | -- | -- |
| **Lactose monohydrate** | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| **Magnesium stearate(%)** | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| **Talc (%)** | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| **SLS(%)** | -- | -- | -- | -- | -- | -- | 0.5 | 1 | 1.5 |
| **Total weight** | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |

CP- crospovidone, CCS: Cross carmellose sodium, SSG: Sodium starch glycolate, HPC- Hydroxy Propyl cellulose SLS – Sodium lauryl sulfate.

**Bilayered tablet punch:** After the batch was optimized in both the immediate release layer ( F8) and sustained release layer (F7). The optimized batch in both was compressed by using the same ingredients.

**Evaluation of Precompression Blend**

**Flow Properties:**

**The angle of Repose:** The flow property was determined by measuring the Angle of Repose. To determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free-standing surface of a powder heap and the horizontal.

$$\text{Angle of repose} = \tan^{-1}(h/r)$$

where,

h = height of a pile (2 cm)

r = radius of pile base.

**Procedure:** 20gms of the sample was taken, the sample was passed through the funnel slowly to form a heap, the height of the powder heap formed was measured, the circumference formed was drawn with a pencil on the graph paper, the radius was measured and the angle of repose was determined. This was repeated three times for a sample.

**Bulk density:** Bulk density is the ratio of a given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of a known mass of powder sample that has been passed through the screen into a graduated cylinder or through volume measuring apparatus into the cup.

$$\text{Bulk density} = M / V_0$$

Where M= mass of the powder;

$V_0$=bulk volume of the powder.

**Limits:**

It has been stated that bulk density values less than 1.2 g/cm3 indicate good packing and values greater than 1.5 g/cm3 indicate poor packing.

**Tapped density:**

A known quantity of powder was transferred to a graduated cylinder and volume $V_0$ was noted. The cylinder was fixed to a density determination apparatus and tapped 500 times than the reading was observed. The density is achieved mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume readings were taken until little further volume changes are observed.

$$\text{Tap density} = M / Vr$$

Where M = mass of the powder,

Vr = final tapping volume of the powder.

**Compressibility index and Hausner ratio:** The compressibility index and Hausner ratio may be calculated using measured values of bulk density and tapped density as follows:

Compressibility index = 100 × tapped density / bulk density

Hausner ratio = tapped density / bulk density

Flow properties and corresponding Angle of repose, Compressibility index and Hausner ratio:

**Table no 3: Acceptance criteria of flow properties**

| **Flow properties** | **Angle of repose(θ)** | **Compressibility Index (%)** | **Hausner ratio** |
|---|---|---|---|
| Excellent | 25-30 | <10 | 1.00-1.11 |
| Good | 31-35 | 11-15 | 1.12-1.18 |
| Fair | 36-40 | 16-20 | 1.19-1.25 |
| Agreeable | 41-45 | 21-25 | 1.26-1.34 |
| Poor | 46-55 | 26-31 | 1.35-1.45 |
| Very Poor | 56-65 | 32-37 | 1.46-1.59 |
| Very very Poor | > 66 | >38 | >1.6 |

**Evaluation of tablets:**

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability and invitro-dissolution characters.

**1. Physical Appearance**: The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odour, taste etc.

**2. Size & Shape:** It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

**3. Weight variation test:** This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests.. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets.

These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

**Method:** Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

**Table no 4: Limits for Tablet Weight variation test:**

| **Average weight of tablet (mg)** | **% Difference allowed** |
|---|---|
| 130 or less | 10 % |
| From 130 to 324 | 7.5 % |
| > 324 | 5 % |

**Friability**: Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

**Method**: A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ friability} = (W_1\text{-}W_2) / W_1 \text{ X } 100$$

$W_1$ = Weight of tablets before test

$W_2$ = Weight of tablets after test

**Thickness:** The thickness of the tablets was measured by vernier calipers. It is expressed in **mm**.

**Hardness:** Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by Monsanto hardness tester. The tablets from each batch were used for hardness studies and results are expressed in **Kg/cm$^2$**.

**Dissolution studies**

**In vitro Dissolution Studies for sustained release layer of Capacetabine** In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 8hr, at 50 rpm, 0.1 N HCl was used as a dissolution medium for first 2 hours and 6.8 pH phosphate buffer for next 12hours. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 303nm.

**Kinetic Analysis of Dissolution Data** To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannouet al., 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t \qquad (1)$$

where, $K_0$ is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC_0 - K_1 t / 2.303 \quad (2)$$

Where, $C_0$ is the initial concentration of drug and $K_1$ is first order constant.

$$Q = K_H t^{1/2} \quad (3)$$

Where, $K_H$ is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \quad (4)$$

Where, $Q_t$is the amount of drug remained in time t, $Q_0$ is the initial amount of the drug in tablet and $K_{HC}$ is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data.

Cumulative % drug release vs. time (Zero order kinetic model);

Log cumulative of % drug remaining vs. time (First order kinetic model);

Cumulative % drug release vs. square root of time (Higuchi model);

And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

**Mechanism of drug release:** Korsmeyeret al (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \quad (5)$$

where $M_t$ / M∞ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table16, for the cylindrical shaped matrices.Case-II generally refers to the erosion of the polymeric chain and

anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Peppas, 1985).

**Table no 5. Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape**

| Diffusion exponent (n) | Overall solute diffusion mechanism |
|---|---|
| 0.45 | Fickian diffusion |
| 0.45 < n < 0.89 | Anomalous (non-Fickian) diffusion |
| 0.89 | Case-II transport |
| n > 0.89 | Super case-II transport |

**In vitro Dissolution Studies for immediate release layer of Ondansetron** In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 1 hr, at 50 rpm, 0.1 N HCl was used as a dissolution medium. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 310nm.

**Dissolution study of capacetabine and ondansetron from bilayer tablet:** The release kinetic of optimized Capacetabine and Ondansetron from bilayer tablet was studied by conducting dissolution studies. Dissolution tests performed using USP Type II dissolution apparatus and 900ml of 0.1N HCL at 37± $0.5^0$ C at 50rpm for 2hrs. 5ml of sample were withdrawn at the intervals of every 60min, sampling was carried out and everytime replaced with fresh 5ml of buffer. After 2hrs, the 0.1N HCL buffer was replaced with 6.8pH phosphate buffer. The absorbance of solution was recorded at 304nm and 310nm using buffer as blank. The result was calculated as Percentage drug release of Capacetabine and Ondansetron.[36-41]

## RESULTS AND DISCUSSION

### Preparation of standard calibration curve of Ondansetron:

**Table No 6. Standard calibration curve of Ondansetron in 0.1N HCl**

| S.No | Concentration | Absorbance at 310nm |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 5 | 0.181 |
| 3 | 7.5 | 0.282 |
| 4 | 10 | 0.365 |
| 5 | 12.5 | 0.452 |
| 6 | 15 | 0.545 |

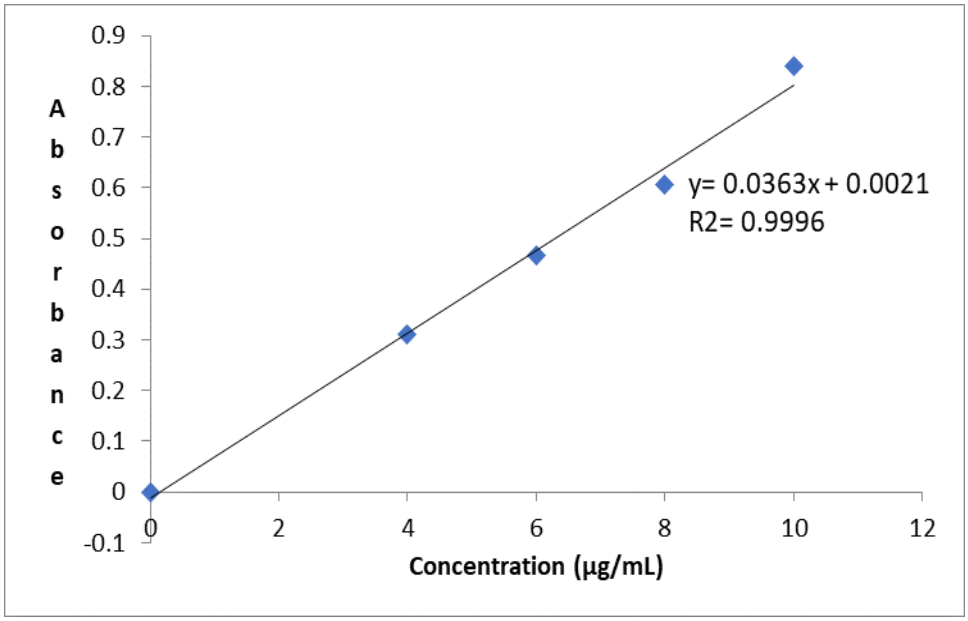



**Fig. 1- Calibration curve of Ondansetron in 0.1N HCl**

### Standard Graph of Capacetabine (0.1 N HCl):

The standard graph of capacetabinehas shown good linearity with $R^2$ values 0.9991 in 0.1 N HCl and which suggests that it obeys the “Beer-Lambert’s law”.

**Table No 7**

| Concentration | Absorbance at 303nm |
|---|---|
| 0 | 0 |
| 10 | 0.19 |
| 20 | 0.335 |
| 30 | 0.50 |
| 40 | 0.68 |
| 50 | 0.82 |
| 60 | 0.998 |

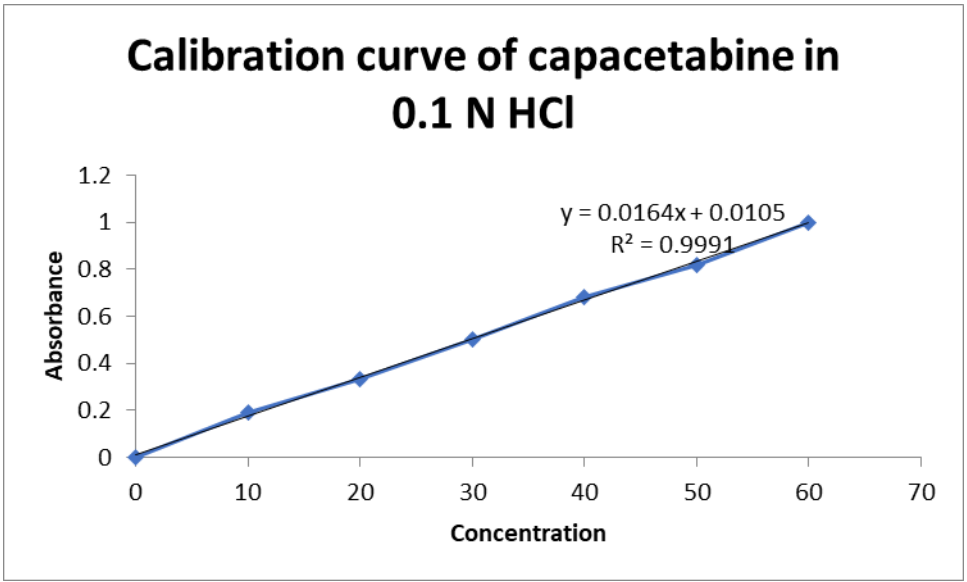



**Fig.2 calibration curve for Capacetabine in 0.1N HCl at 303nm**

**Standard Graph of Capacetabine in 6.8pH phosphate buffer:** The standard graph of Capacetabine has shown good linearity with $R^2$ values 0.9992 and, which suggests that it obeys the "Beer-Lambert's law".

**Table No-8**

| Concentration | Absorbance |
|---|---|
| 0 | 0 |
| 10 | 0.478 |
| 12 | 0.555 |
| 14 | 0.646 |
| 16 | 0.754 |
| 18 | 0.825 |
| 20 | 0.922 |

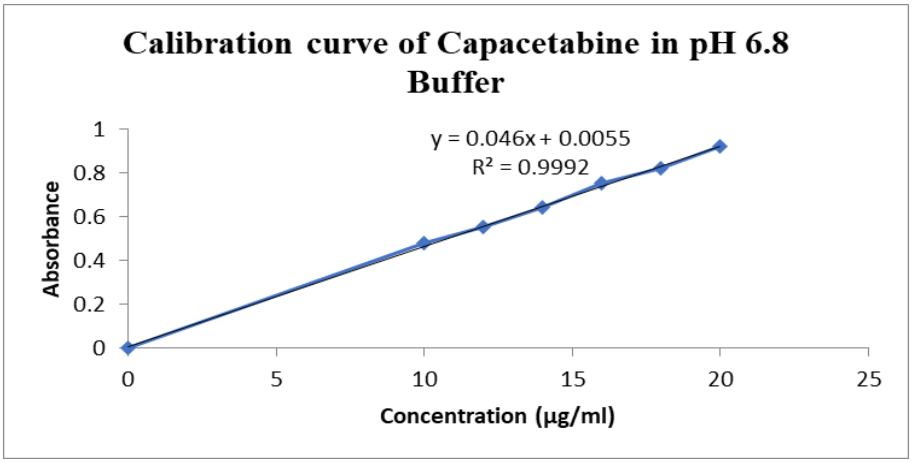



**Fig no 3 calibration curve for capacetabine in 6.8pH phosphate buffer at 304nm**

**Compatibility studies**

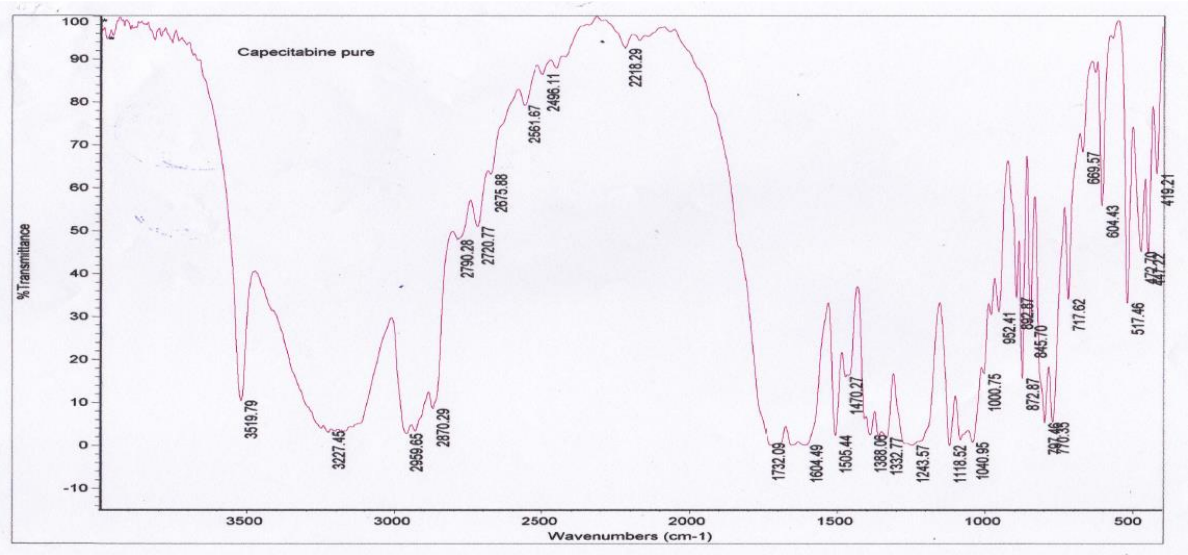



**Fig:4 FTIR spectra of Capecitabine pure drug**

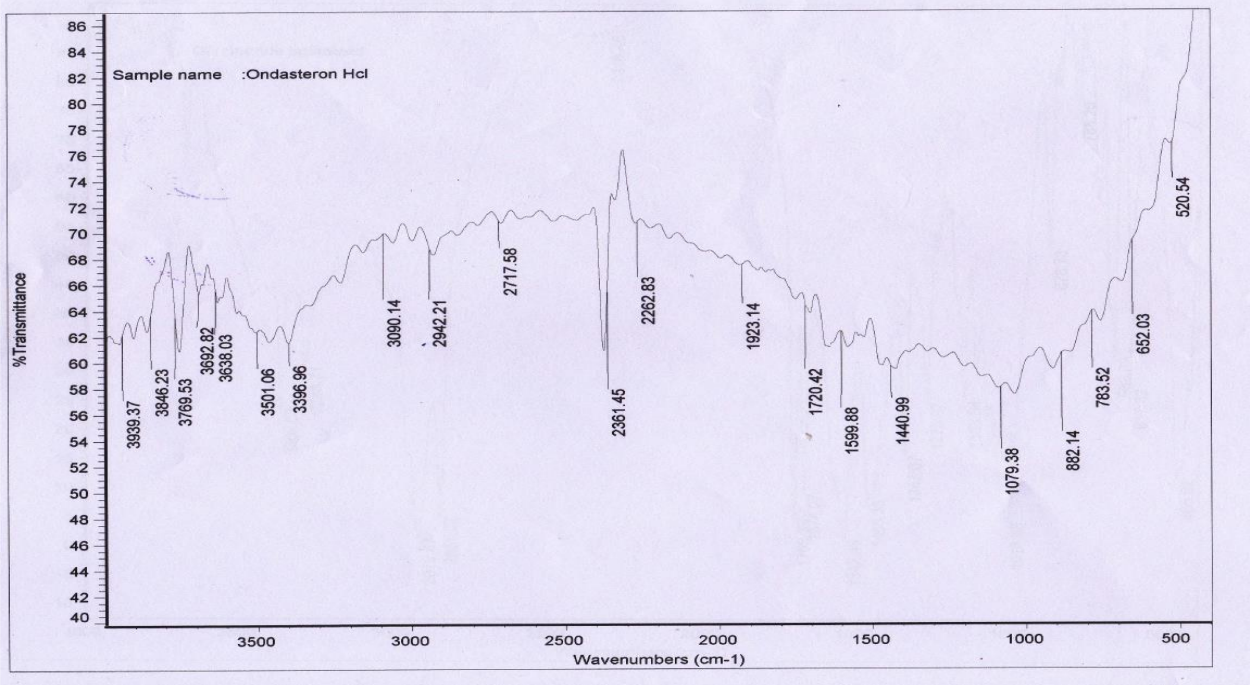



**Fig 5: FTIR spectra of Ondansetron pure drug**

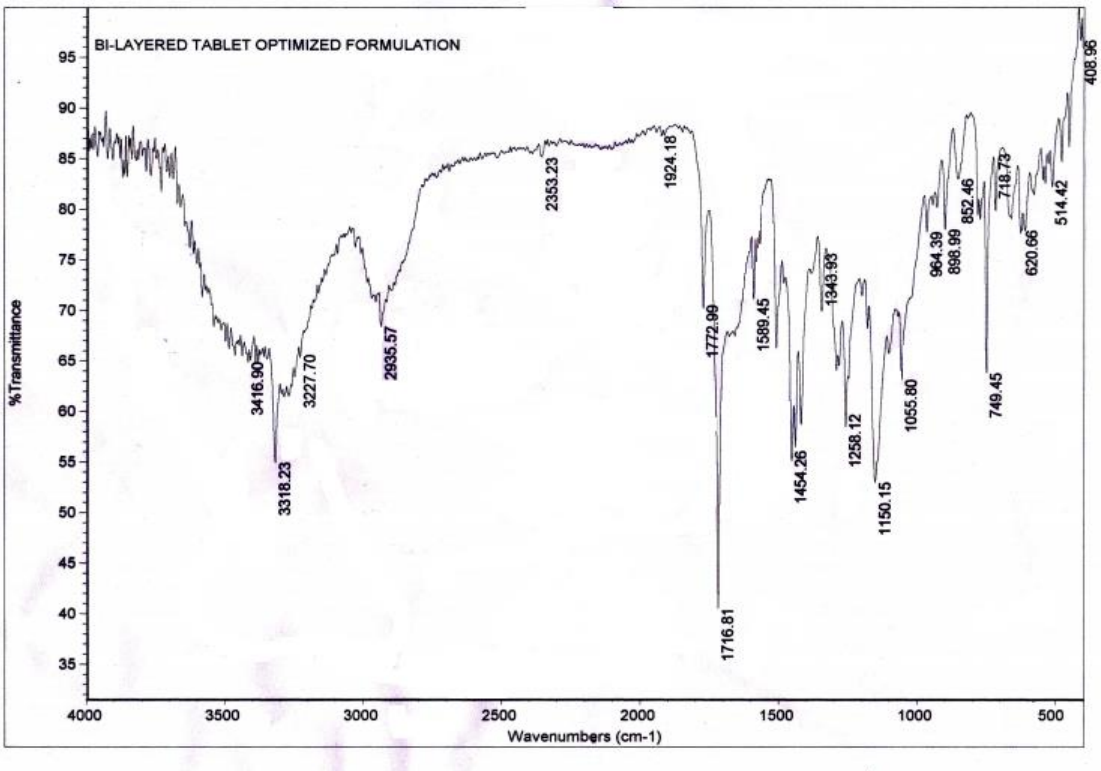



**Fig no 6: FTIR spectra of bilayered tablet**

**Table no 9 Evaluation of pre compression parameters for sustained release layer of capacetabine**

| Formulations | Angle of Repose (θ) | Loose Bulk Density (g/ml) | Tapped Bulk Density (g/ml) | %Compressibility | Hausner's ratio |
|---|---|---|---|---|---|
| **F1** | 25.40 ±0.090 | 0.34± 0.04 | 0.43 ± 0.04 | 20.93 ± 0.11 | 1.26 ± 0.08 |
| **F2** | 23.50 ± 0.12 | 0.39 ± 0.05 | 0.46 ± 0.03 | 15.21 ± 0.10 | 1.17 ± 0.02 |
| **F3** | 27.2±0.2 | 0.54±0.02 | 0.61±0.05 | 11.47±0.8 | 1.12±0.09 |
| **F4** | 24.9±0.14 | 0.58±0.03 | 0.66±0.05 | 12.12±0.05 | 1.13±0.05 |
| **F5** | 22.96 ± 0.12 | 0.41 ± 0.01 | 0.49 ± 0.01 | 16.32 ± 0.07 | 1.19 ± 0.02 |
| **F6** | 24.36 ± 0.12 | 0.37 ± 0.04 | 0.45 ± 0.07 | 17.77 ± 0.11 | 1.21 ± 0.06 |
| **F7** | 26.58±0.15 | 0.43±0.04 | 0.49 ± 0.04 | 12.24±0.6 | 1.13±0.04 |
| **F8** | 27.44±0.11 | 0.48±0.05 | 0.55 ± 0.1 | 12.72±0.4 | 1.14±0.02 |
| **F9** | 25.36±0.13 | 0.42±0.045 | 0.51 ± 0.04 | 17.64±0.8 | 1.21±0.08 |
| **F10** | 24.35±0.13 | 0.44±0.044 | 0.50± 0.01 | 12.09±0.1 | 1.13±0.06 |

From the above pre-compression parameters it was clear evidence that powdered blendhas excellent flow properties.

**Tablet No 10 -Post Compression Parameters for Sustained Release Tablet**

| Formulations | Weight variation | *Hardness* | Thickness (mm) | Friability (%) |
|---|---|---|---|---|
| **F1** | 401 | 7.5 | 2.3 | 0.45 |
| **F2** | 400 | 7.3 | 2.5 | 0.48 |
| **F3** | 398 | 6.5 | 2.7 | 0.50 |
| **F4** | 400 | 7.6 | 2.3 | 0.52 |
| **F5** | 401 | 7.5 | 2.1 | 0.40 |
| **F6** | 399 | 7.5 | 2.4 | 0.49 |
| **F7** | 398 | 7.3 | 2.3 | 0.41 |
| **F8** | 402 | 7.4 | 2.0 | 0.43 |
| **F9** | 399 | 7.8 | 2.2 | 0.42 |
| **F10** | 400 | 7.9 | 2.8 | 0.47 |

**Invitro dissolution studies for sr tablets -**

**Dissolution study (sr tablets):**

**Acidic Stage:**

| | |
|---|---|
| Medium | : 0.1N HCL |
| Type of apparatus | : USP - II (paddle type) |
| RPM | : 50 |
| Volume | : 900ml |
| Temperature | : 37ºC± 0.5 |
| Time | : 2hrs |

**Buffer Stage:**

| | |
|---|---|
| Medium | : 6.8pH phosphate buffer |
| Type of apparatus | : USP - II (paddle type) |
| RPM | : 50 |
| Volume | : 900ml |
| Time | : 24hrs |

In vitro dissolution for SR tablets were done initially in 0.1N HCL for 2hrs and next in 6.8 phosphate buffer for 12hrs.

**Table 11 In-Vitro Drug Release Studies for SR tablets cumulative percentage drug release of sustained layer**

| Time(hrs) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dissolution medium 0.1N HCL** | | | | | | | | | | |
| 1 | 38.5 | 45.9 | 80.4 | 32.4 | 25.5 | 19.6 | 25.5 | 34.5 | 35.6 | 26.3 |
| 2 | 45.7 | 72.2 | 95.6 | 45.5 | 39.9 | 24.3 | 39.2 | 42.1 | 40 | 33.2 |
| **6.8pH phosphate buffer** | | | | | | | | | | |
| 3 | 53.8 | 80.7 | -- | 67.4 | 43.4 | 31.4 | 46.5 | 52.7 | 49.7 | 40.1 |
| 4 | 70.4 | 92.4 | -- | 72.6 | 59.4 | 45.9 | 55.2 | 60.3 | 53.9 | 45.6 |
| 5 | 84.9 | -- | -- | 85.4 | 78.2 | 57.3 | 68.5 | 72.4 | 63.8 | 55.2 |
| 6 | 93.6 | -- | -- | 95.8 | 94.2 | 80.7 | 75.9 | 78.3 | 70.4 | 63.8 |
| 8 | -- | -- | -- | -- | -- | 94.9 | 81.3 | 80.1 | 75.8 | 73.6 |
| 12 | -- | -- | -- | -- | -- | -- | 96.5 | -- | 84.9 | 80.4 |

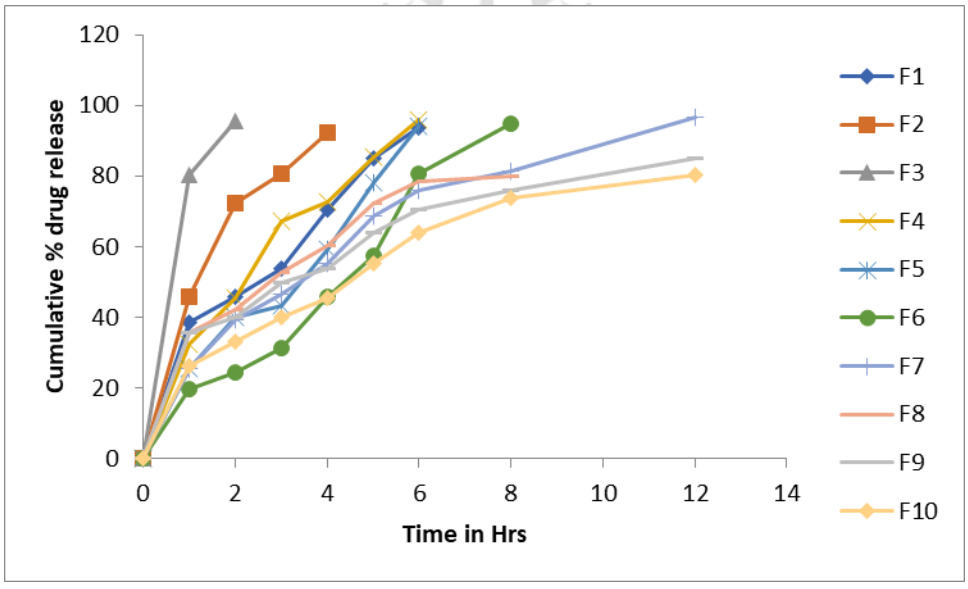



**Fig 7 - dissolution graph for sustained release formulations**

**Kinetic release models:**

**Table no 12 Release kinetics for F7 formulation for sustained release layer**

| | ZERO | FIRST | HIGUCHI | PEPPAS |
|---|---|---|---|---|
| | % CDR Vs T | Log % Remain Vs T | %CDR Vs √T | Log C Vs Log T |
| **Slope** | 7.526633663 | -0.114408924 | 29.17045474 | 1.212824992 |
| **Intercept** | 20.00089109 | 2.046966088 | -1.213900087 | 0.905575126 |
| **Correlation** | 0.936703553 | -0.983721127 | 0.994246713 | 0.753743671 |
| **R 2** | 0.877413546 | 0.967707256 | 0.988526526 | 0.568129522 |

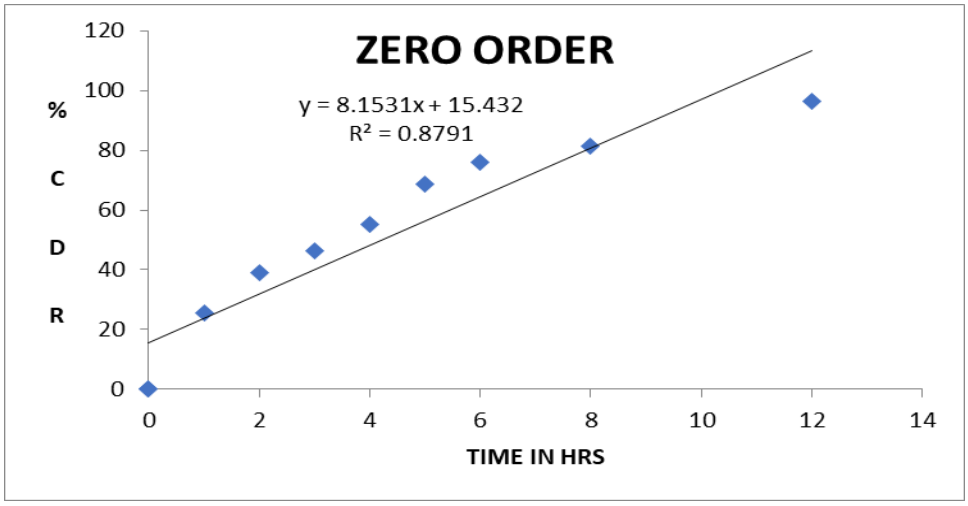



**Fig 8 - zero order release graph for F7 sustained release formulation**

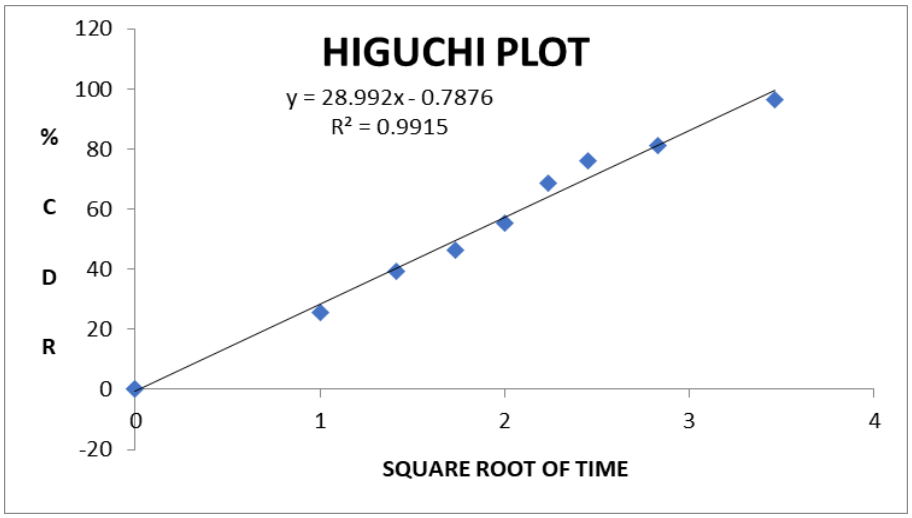



**Fig 9 - Higuchi model graph for F7 sustained release formulation**

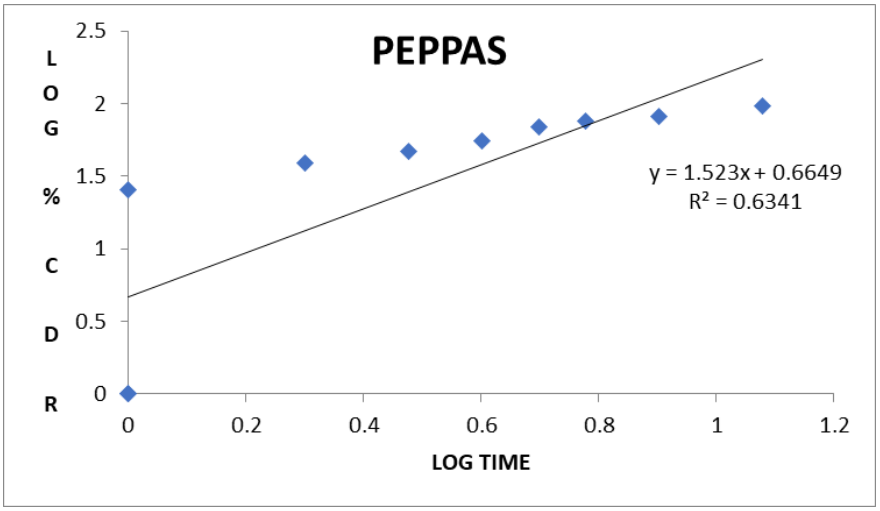



**Fig 10 - Peppas model for F7 sustained release formulation**


**Fig 11 NM- First order release graph for F7 sustained release formulation**

**Discussion for *in-vitro* release of capacetabine layer SR**

From the table, it was confirmed that the F1,F2, F3,F4,F5, F6 and F8 of SR layer does not fulfill the sustained release theory up to 12 hrs. And also from the table, it was also confirmed that the formulation made with combination of HPMC K100 and HPMC K4M (F7) showed maximum drug release up to 12hrs.

**Evaluation parameters for immediate release layer of Ondansetron**

**Pre compression parameters**

**Table No 13 precompression parameters of Ondansetron**

| Formulations | Angle of Repose (θ) | Loose Bulk Density (g/ml) | Tapped Bulk Density (g/ml) | %Compressibility | Hausner's ratio |
|---|---|---|---|---|---|
| **F1** | $23.9^0$ | 0.3 | 0.35 | 14.29 | 1.17 |
| **F2** | $24.2^0$ | 0.38 | 0.45 | 15.56 | 1.18 |
| **F3** | $27.2^0$ | 0.53 | 0.62 | 14.52 | 1.17 |
| **F4** | $25.5^0$ | 0.57 | 0.68 | 16.18 | 1.19 |
| **F5** | $23.8^0$ | 0.43 | 0.49 | 12.24 | 1.14 |
| **F6** | $24.1^0$ | 0.37 | 0.45 | 17.78 | 1.22 |
| **F7** | $29.4^0$ | 0.43 | 0.5 | 14.00 | 1.16 |
| **F8** | $22.10^0$ | 0.44 | 0.51 | 13.73 | 1.16 |
| **F9** | $26.4^0$ | 0.4 | 0.47 | 14.89 | 1.18 |

**From** the above pre-compression parameters it was clear evidence that drug and excipients has good flow properties and suitable for direct compression.

**Post compression evaluation parameters for immediate release formulation**

The results of the uniformity of weight, hardness, thickness and friability of the tablets are given in Table. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between147 to 152mg. The hardness of the tablets ranged from 3.1 to 3.6kg/cm$^2$ and the friability values were less than 0.5% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged fromto 2.1to 2.5mm. Thus, all the physical attributes of the prepared tablets were found be practically within control.

**Table: 14 Post compression parameters for immediate release tablets**

| Formulations | Average weight (mg) | *Hardness Kg/cm²* | Thickness (mm) | Friability (%) |
|---|---|---|---|---|
| **F1** | 149 | 3.4 | 2.1 | 0.29 |
| **F2** | 147 | 3.5 | 2.3 | 0.25 |
| **F3** | 150 | 3.1 | 2.5 | 0.30 |
| **F4** | 152 | 3.3 | 2.2 | 0.41 |
| **F5** | 150 | 3.6 | 2.4 | 0.52 |
| **F6** | 150 | 3.2 | 2.2 | 0.49 |
| **F7** | 148 | 3.1 | 2.5 | 0.44 |
| **F8** | 149 | 3.4 | 2.4 | 0.43 |
| **F9** | 150 | 3.3 | 2.3 | 0.42 |

**Table No 15 Dissolution for immediate release tablet of Ondansetron**

| Time in mins | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **5** | **25** | **22** | **14** | **22** | **36** | **31** | **40** | **65** | **48** |
| **10** | **37** | **38** | **26** | **42** | **57** | **59** | **67** | **70** | **63** |
| **15** | **45** | **49** | **40** | **56** | **65** | **65** | **79** | **84** | **80** |
| **30** | **50** | **56** | **54** | **63** | **72** | **72** | **86** | **96** | **94** |
| **45** | **48** | **72** | **63** | **78** | **88** | **86** | **94** | -- | -- |
| **60** | **62** | **80** | **75** | **89** | **93** | **95** | -- | -- | -- |

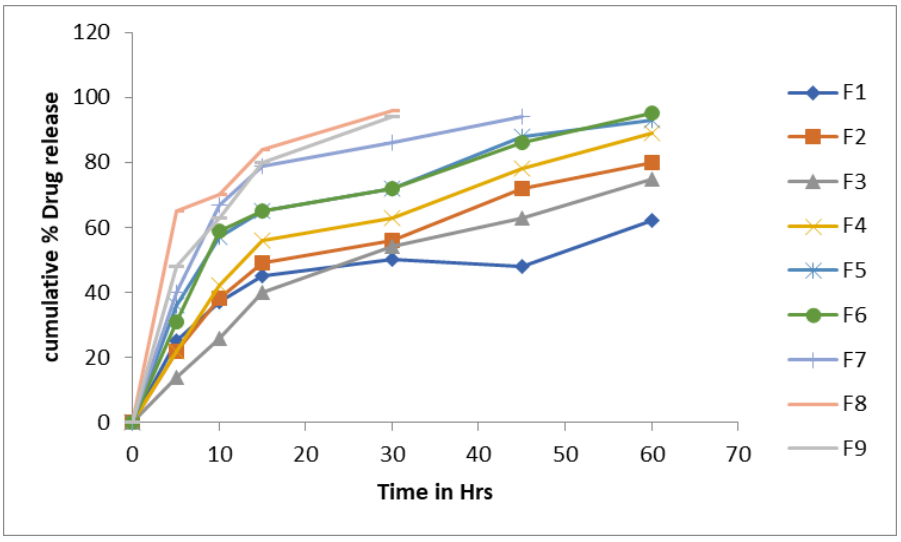



**Fig 12 Dissolution graph for formulations F1-F9**

**Bilayered tablet compression**

After the batch was optimized in both immediate release layer (F8) and sustained release layer (F7). The optimized batch in both was compressed by using same ingredients.

**Dissolution study (bilayered tablets):**

**Dissolution Medium for IR tablets**

**Acidic Stage:**

Medium : 0.1N HCL

Type of apparatus : USP - II (paddle type)

RPM : 50

Volume : 900ml

Temperature : 37ºC± 0.5

Time : 30min

In vitro dissolution for IR tablets were done in0.1N HCLfor 30 minutes.

**Dissolution Medium for SR tablets**

**Acidic Stage:**

Medium : 0.1N HCL

Type of apparatus : USP - II (paddle type)

RPM : 50

Volume : 900ml

Temperature : 37ºC± 0.5

Time : 2hrs

In vitro dissolution for SR tablets were done in6.8 pH for 12hrs.

**Tab: 16 Dissolution profile of bilayered tablet**

| S.NO | Sampling time | Percentage drug released (%) | |
|---|---|---|---|
| | | ONDANSETRON | CAPACETABINE |
| 1 | 15mins | 80.7 | 4.2 |
| 2 | 30 mins | 99.8 | 6.6 |
| 5 | 1hr | -- | 20.6 |
| 6 | 2hr | -- | 37.7 |
| 7 | 3hr | -- | 45.4 |
| 8 | 4hr | -- | 53.8 |
| 9 | 5hr | -- | 69.7 |
| 10 | 6hr | -- | 77.9 |
| 11 | 8hr | -- | 89.0 |
| 12 | 12hr | -- | 97.3 |

**Table 17 Stability data of optimized formulation**

| S.No | Time points (min) | Initial | Cumulative % Drug Release (mean ± SD) (n=3) | | | |
|---|---|---|---|---|---|---|
| | | | 25C/60%RH | | 40C/75%RH | |
| | | | 1st Month | 3rd Month | 1stMonth | 3rdMonth |
| 1 | 0.5 | 99.8 | 99.4 | 98.2 | 98.0 | 97.7 |
| 2 | **1** | **20.6** | 20.1 | 19.8 | 20.5 | 19.1 |
| 3 | **2** | **37.7** | 35.1 | 35.0 | 34.8 | 34.2 |
| 4 | **3** | **45.4** | 45.2 | 44.7 | 45.0 | 44.6 |
| 5 | **4** | **53.8** | 52.1 | 51.9 | 50.5 | 50.7 |
| 6 | **5** | **69.7** | 67.2 | 67.1 | 66.7 | 66.2 |
| 7 | **6** | **77.9** | 77.1 | 76.3 | 77.2 | 76.1 |
| 8 | **8** | **89.0** | 88.8 | 87.4 | 88.4 | 86.4 |
| 9 | Assay | 99.7 | 99.3 | 99.4 | 99.2 | 98.7 |

## CONCLUSION

The Bilayered tablets containing Capacetabine SR and Ondansetron IR were successfully prepared by direct compression method respectively. Various formulations were prepared and evaluated with an aim of presenting Capacetabine as sustained release and Ondansetron as immediate release for improving the patient's compliance. The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index. The prepared blend for IR layer tablets and SR layer tablets were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability.

The optimized formulation F8 in IR formulations contains the average thickness of 2.4mm, average hardness of 3.4 kg/cm$^2$, average weight of 149mg, friability of 0.43%. The optimized formulation F7 in SR formulations contains the average thickness of 2.3mm, average hardness of 7.3 kg/cm$^2$, friability of 0.41%. The F7 formulation which releases the capacetabine in sustained manner in 1$^{st}$ hour it releases 25.5% but the remaining drug release was sustained up to 12 hours and ondansetron immediate release F7 formulation showed 96 % drug release within 30 min. With the data of kinetic analysis, F7 formulation showed best linearity in Higuchi's Equation plot indicating that the release of drug from matrix tablet follows Non Fickian diffusion. The dissolution study was carried out for optimized bilayer tablet and it correlates with the drug release of individual release layer formulations.

Hence it may be summarized that the tablets prepared by direct compression method for sustained release layer and immediate release layer might be a perfect and effective formulation to prevent the side effects in treating cancer. Scale up studies of the optimized formulation, *In-vivo* studies, *In-vivo* and *In-vitro* correlation are recommended for further studies.

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