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# DESIGN AND DEVELOPMENT OF BILAYER TABLET OF ETORICOXIB AND ETODOLAC

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## Abstract

### Objective

The main goals of the current study were to improve patient compliance and develop a two-layer drug delivery system that would allow for drug release at a predetermined time following an initial release. This would allow for sustained drug release from the formulation during the effective treatment of arthritis. Increasing the bioavailability of etodolac and etoricoxib was the aim of the current investigation.

### Methods

An immediate release layer and a sustain release layer made up the two distinct components of the created Biayer drug delivery system. Crosspovidone was included in the immediate release layer together with the active component as a super disintegrant. Using the wet granulation process, the tablet was made. Kolloidon SR was used as a release-delaying polymer in the sustained release layer. Sustain release layer preparation was done using the direct compression method.

### Result

The developed formulations were assessed for their in vitro drug release profile, in vitro disintegration time, and physical properties.

### Conclusion

On the basis of these evaluation shown that optimized bilayer tablets formulation F5 showed 12 hrs drug release of Etodolac and F8 showed disintegration time is 36 sec for immediate release. The bilayer formulation by factorial showed compliance with treatment of Arthritis.

**Key Words:** Etodolac, Etoricoxib, Crosspovidone, Kolliodon SR, Bilayer Tablet

## Introduction

The oral route of drug administration stands out as the most significant and convenient method for delivering medications. However, the potential for sustained drug release over extended periods hasn't been fully tapped due to variations in absorption across different sections of the gastrointestinal tract (GIT). Consequently, only a handful of drug delivery systems have been developed to target specific regions of the GIT, such as the stomach, upper small intestine, or colon.

Worldwide, the two most prevalent conditions are joint pain (which includes back pain) and arthritis (which includes rheumatoid arthritis and osteoarthritis). Around 350 million episodes of arthritis-related knee pain occur worldwide each year, making it the second most feared condition after cardiovascular disease.

Encouraging patient convenience and compliance, the pharmaceutical industry has been more interested in the past ten years in developing a combination of two or more API in a single dosage form (bilayer tablet). When developing distinct drug release profiles (immediate release with extended release), bilayer tablets might be a major option to prevent chemical incompatibilities across API by physical separation. There are several major benefits of bilayer tablets. in reference to traditional monolayer tablets.

Bilayer tablets are a better option since one layer delivers the medication instantly, and the controlled release layer of the tablet keeps the drug's plasma level stable. The more recent and effective method for developing controlled release for emulation is the bilayer tablet, which is superior to the dosage forms that have been employed in the past. Bilayer tablets are useful for the sequential release of two medications in combination. They can also be used for sustained release, where one layer is used for immediate release as the inceptive dose and the second layer is used as the maintenance dose.

## Materials and methods

Etodolac was obtained from A.R. Life science Pvt. Ltd. Etoricoxib was obtained from Assurgen pharma pvt. Ltd. Avicel 101 as a diluent obtained from Patel chem. Specialist Ahemdabad, Filler lactose, starch also Binder PVP K 30 obtained from S.D. Fine chemicals Ahemdabad, Polymer Koloidn SR was obtained from global life science pvt, ltd. Superdisintigrant Crosspovidone was obtained from Vasa pharma chem.. Ahemdabad. Talc and Magnesium Stearate as a glidant and lubricant was obtained from Patel chemicals, Ahemdabad and Gangotri inorganics, pvt, ltd. Ahemdabad.

## Method of Preparation of Bilayer Tablets

The preliminary trials for polymer selection involved preparing tablets using different matrix-forming agents via wet granulation technique. In these preparation two layer were selected. 1) Immediate release layer and 2) Sustained release layer. In these preparation first of all Blends comprising the drug, diluents, and sustained release polymer were thoroughly mixed after passing through a 40# sieve. Then its bind using the binder like PVP k 30 solution. After completion of granulation process the bulk were dried and its passed through sieve no.22#. Talc and magnesium stearate were then added as glidant and lubricant, respectively. The blend was compressed using a bilayer tablet compress machine.

**Table 1 Formulation Table of Trial Batches of Immediate release layer tablets**

| Ingredients (mg) | TF1 | TF2 | TF3 | TF4 | TF5 | TF6 | TF7 | TF8 | TF9 |
|---|---|---|---|---|---|---|---|---|---|
| Etoricoxib | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| MCC 101 | 51 | 46 | 41 | 51 | 46 | 41 | 51 | 46 | 41 |
| Lactose | 115 | 115 | 115 | 115 | 115 | 115 | 115 | 115 | 115 |
| Starch | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| SSG | 5 | 10 | 15 | - | - | - | - | - | - |
| CCS | - | - | - | 5 | 10 | 15 | - | - | - |
| Crosspovidone | - | - | - | - | - | - | 5 | 10 | 15 |
| MagnesiumStearate | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Talc | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Aerosil | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Total (mg) | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

**Table 2 Formulation Table of Trial Batches of Sustained release layer tablets**

| Ingredients (mg) | TS1 | TS2 | TS3 | TS4 | TS5 | TS6 | TS7 | TS8 | TS9 |
|---|---|---|---|---|---|---|---|---|---|
| Etodolac | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |
| MCC 101 | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| Lactose | 50 | 40 | 30 | 50 | 40 | 30 | 50 | 40 | 30 |
| PVP K 30 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Ethyl cellulose | 50 | 60 | 70 | - | - | - | - | - | - |
| Kolloidon SR | - | - | - | 50 | 60 | 70 | - | - | - |
| HPMC K4M | - | - | - | - | - | - | 50 | 60 | 70 |
| Magnesium Stearate | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Talc | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Total (mg) | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 |

**Table 3 Layout of Factorial Design of Immediate release layer**

| $3^2$ Full Factorial Designs | | |
|---|---|---|
| **Batch No.** | **X1 Amount of Lactose** | **X2 Superdisintigrant Crosspovidone** |
| FIR1 | -1 | -1 |
| FIR2 | -1 | 0 |
| FIR3 | -1 | +1 |
| FIR4 | 0 | -1 |
| FIR5 | 0 | 0 |
| FIR6 | 0 | +1 |
| FIR7 | +1 | -1 |
| FIR8 | +1 | 0 |
| FIR9 | +1 | +1 |

| Translation of coded level in actual limit | | | |
|---|---|---|---|
| **Independent variables** | **Real Value** | | |
| | **Low(-1)** | **Medium(0)** | **High(+1)** |
| **Amount of lactose (mg) X1** | 110 | 115 | 120 |
| **Superdisintigrant crosspovidone (mg) X2** | 7.5 | 12.5 | 17.5 |

- ***Input variables***
  - ✓ X1-Amount of Lactose in (mg)
  - ✓ X2-Crosspovidone dosage (mg)
- ***Output variables***
  - ✓ Y1- % Drug release at 1 hour
  - ✓ Y1- Disintegration time

**Table 4 Layout of Factorial Design of Sustained release layer**

| $3^2$ Full Factorial Designs | | |
|---|---|---|
| **Batch No.** | **X1 Amount of PVP K 30** | **X2 Amount of Kolloidon SR** |
| FSR1 | -1 | -1 |
| FSR2 | -1 | 0 |
| FSR3 | -1 | +1 |
| FSR4 | 0 | -1 |
| FSR5 | 0 | 0 |
| FSR6 | 0 | +1 |
| FSR7 | +1 | -1 |
| FSR8 | +1 | 0 |

| | | |
|---|---|---|
| FSR9 | +1 | +1 |

| Translation of coded level in actual limit | | | |
|---|---|---|---|
| **Independent variables** | **Real Value** | | |
| | **Low(-1)** | **Medium(0)** | **High(+1)** |
| Amount of PVP K 30 X1(%) | 2 | 2.5 | 3 |
| Amount of X2 Kolloidon SR X2 (%) | 8 | 10 | 12 |

- ***Independent variables***
  - ✓ $X_1$-Amount of PVP K 30 (%)
  - ✓ $X_2$-Amount of Kolloidin SR (%)
- ***Dependent variables***
  - ✓ Y1- % Drug release at 1 hour
  - ✓ Y1- Hardness

**Table 5 Formulation Table of Factorial Batches of Immediate release layer tablets**

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Etoricoxib | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| MCC 101 | 53.5 | 48.5 | 43.5 | 48.5 | 43.5 | 38.5 | 43.5 | 38.5 | 33.5 |
| Lactose | 110 | 110 | 110 | 115 | 115 | 115 | 120 | 120 | 120 |
| Starch | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Crosspovidone | 7.5 | 12.5 | 17.5 | 7.5 | 12.5 | 17.5 | 7.5 | 12.5 | 17.5 |
| Magnesium Stearate | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Talc | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Aerosil | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Total (mg) | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| Etoricoxib | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |

**Table 6 Formulation Table of Factorial Batches of Sustained release layer tablets**

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Etodolac | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |
| MCC 101 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| Lactose | 62 | 50 | 38 | 59 | 47 | 35 | 56 | 44 | 32 |
| PVP K 30 | 12 | 12 | 12 | 15 | 15 | 15 | 18 | 18 | 18 |
| KolloidonSR | 48 | 60 | 72 | 48 | 60 | 72 | 48 | 60 | 72 |
| Magnsiumstearate | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Talc | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Total (mg) | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 |
| Etodolac | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |
| MCC 101 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |

# Methodology

## Preformulation

### Characterization of API: -

**Organoleptic property:**
This involves documenting the drug's hue and scent using precise language. and record the same in results and discussion chapter.

**Flow Property:**
The study examined the flow characteristics of API/powder blends. To determine bulk density, 10 grams of powder were carefully poured into a 50-milliliter measuring cylinder without compaction, and the volume of the powder was recorded. After tapping the powder 100 times, the volume was measured to obtain the desired tapped density. The powder mixtures' Carr's index (CI) & Hausner ratio (HR) were calculated using the measurements of powder densities.

**Melting point:**
The Melting Point Testing Apparatus: technique was incorporated into the device to determine the drug's (API) melting point.

Using a modern melting point apparatus, the following steps are needed to measure melting point:

- make sure the sample is completely dry and powdered
- put the sample in a capillary tube
- insert the capillary tube to the melting point apparatus
- quickly heat the sample to a predetermined temperature
- slow down the rate of temperature increase to see when the sample melts
- view the melting point through a viewing eyepiece
- digitally record the melting point.

**Drug Excipient Compatibility Study**
FTIR investigations were conducted to evaluate the compatibility between excipients and the drug. Samples of the pure drug and physical mixtures of excipients with the drug were analyzed using FTIR to assess their compatibility. The distinctive peaks corresponding to various functional groups were compared with established standard peaks to determine any discrepancies.

**Calibration Curve**
**Preparation of Standard Calibration Curve of Etoricoxib**
**Principle**: The Etoricoxib exhibits peak absorbance at 233 nm in 0.1 N HCl (1.2 pH).
**Instrument used**: UV - Vis 1700 Spectroscopy by Shimadzu, UV Spectrophotometer, Japan.
**Procedure:**

- Preparation of standard solution : 100 mg of etoricoxib was precisely measured and dissolved in a small volume of 0.1 N HCl (pH 1.2) in a 100 ml volumetric flask. The solution was then diluted with 0.1 N HCl (pH 1.2) to achieve a concentration of 100 0µg/ml (SS-I). From this solution, 10 ml was withdrawn and further diluted to 100 ml to obtain a concentration of 100 µg/ml (SS-II).
- Preparation of working standard solutions: Aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml and 1 ml from SS-II were pipetted into 10 ml volumetric flasks. The volume was adjusted with 0.1 N HCl (pH 1.2) to achieve final concentrations of 2, 4, 6, 8, and 10 µg/ml, respectively. The absorbance of each concentration was measured at 233 nm.
- A solution containing Etoricoxib (10 µg/mL) from SS-II was scanned in the UV region to identify the wavelength.
- λmax: 233 nm
- Beer's range: 2-10µg/ml.

**Preparation of Standard Calibration Curve of Etodolac**

**Principle**: The Etodolac exhibits peak absorbance at 276 nm in Phosphate buffer solution (6.8 pH).

**Instrument used**: UV - Vis 1700 Spectroscopy by Shimadzu, UV Spectrophotometer, Japan.

**Procedure:**

- Preparation of standard solution : 100 mg of Etodolac was precisely measured and dissolved in a small volume of Phosphate buffer (pH 6.8) in a 100 ml volumetric flask. The solution was then diluted with Phosphate buffer (pH 6.8) to achieve a concentration of 1000 µg/ml (SS-I). From this solution, 10 ml was withdrawn and further diluted to 100 ml to obtain a concentration of 100 µg/ml (SS-II).
- Preparation of working standard solutions: Aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml and 1 ml from SS-II were pipetted into 10 ml volumetric flasks. The volume was adjusted with Phosphate buffer (pH 6.8) to achieve final concentrations of 2, 4, 6, 8, and 10 µg/ml, respectively. The absorbance of each concentration was measured at 276 nm.
- A solution containing Etodolac (10 µg/mL) from SS-II was scanned in the UV region to identify the wavelength.
- λmax: 276 nm
- Beer's range: 2-10 µg/ml.

**Evaluation Parameters of Tablets**

**(A) Pre compression Parameters: -**

**Bulk Density**:

Computed using the formula that follows.

**Bulk density = Weight of powder / Bulk volume**

**Tapped Density**

Computed using the formula that follows

**Tapped density = Weight of powder / Tapped volume**

**Compressibility Index (CI):**

Computed using the formula that follows

**Carr's Compressibility index (%) = {(TD- BD) / TD} X 100.**

**Table 7 Scale of flow ability by Compressibility index**

| C.I. | Category | Hausner's Ratio |
|---|---|---|
| <10 | Excellent | 1.00–1.110 |
| 11 – 15 | Good | 1.12–1.180 |
| 16 – 20 | Fair | 1.19–1.250 |
| 21 – 25 | Passable | 1.26–1.340 |
| 26 – 31 | Poor | 1.35–1.450 |
| 32 – 37 | Very poor | 1.46–1.590 |
| >38 | Very very poor | >1.600 |

**Hausner's Ratio:**

The formula below can be used to compute this.

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

**(B) Post Compression Parameters**

**Weight Variation**

An electric digital balance was used to weigh twenty tablets of each formulation, and the average weight was determined.

**Table 8 IP/BP/USP limit of weight variation test.**

| IP/BP Average weight of tablet (mg) | % Deviation | USP Average weight of tablet (mg) |
|---|---|---|
| 130 or less | 10.0 | 80 or less |
| From 130 to 324 | 7.5 | From 80 to 250 |
| More than 324 | 5.0 | More than 250 |

**Hardness**

Hardness was assessed by diametrically compressing six tablets from each batch using a Monsanto hardness tester, and average values were subsequently computed.

**Friability**

Friability, which indicates tablet strength, was assessed using a Roche-type friabilator following this procedure: After twenty tablets were weighed precisely, they were put into the tumbling device, which turned at a speed of twenty-five revolutions per minute, lowering the tablets every six inches. The tablets were tumbling for four minutes, and a percentage of weight loss was computed by reweighing the tablets.

**% loss = initial wt.-final wt. / initial wt. × 100**

**Thickness**

Using vernier callipers, the thickness of the buccal tablets was measured. A random selection of ten tablets was made from each batch. and their thickness was individually assessed. The average thickness was then calculated from the recorded measurements.

**Assay**

Ten tablets were individually weighed and then pulverized. Next, an amount of powder equivalent to one tablet was weighed, and the drug was extracted in 0.1 N HCl, and Phosphate buffer $P^H$ 6.8.The resulting solution was filtered through a 0.45 µm membrane. After appropriate dilution, the absorbance was measured using a Shimadzu UV-1700 UV/Vis double-beam spectrophotometer.

***In Vitro* Dissolution Studies**

Using USP apparatus II, the dissolution profile was investigated while the dissolution medium (900 ml of 0.1N HCl) was kept at 37°C ± 0.5°C at 50 rpm. Each batch of pills had six that were put into separate baskets with the HCl solution within. Over the course of 30 min , 10 ml samples were taken out every 5

minute. A filter was applied to these samples. These solutions' absorbance was determined using a UV spectrophotometer.

***In Vitro* Dissolution Studies**

Using USP apparatus II, the dissolution profile was investigated while the dissolution medium (900 ml of phosphate buffer $P^H$ 6.8) was kept at 37°C ± 0.5°C at 50 rpm. Each batch of pills had six that were put into separate baskets with the phosphate buffer $P^H$ 6.8 solution within. Over the course of 12 hours, 10 ml samples were taken out every hour. A filter was applied to these samples. These solutions' absorbance was determined using a UV spectrophotometer.

**Drug Release Kinetic Study**

The zero order, first order, Korshmer and Papps, and Higuchi equation models were among them. Plotting the obtained data using the following models allowed us to study the release kinetics: Higuchi's model (Equation 3), which shows the cumulative percentage of drug released against the square root of time; zero order, which represents cumulative drug release over time (Equation 1); and first order, which shows the log cumulative percentage of remaining drug versus time (Equation 2). Drugs dissolved from pharmaceutical formulations that release the drug gradually without disaggregation are described by zero order kinetics.

$$Q_1 = Q_0 + K_0 t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots 1$$

$Q_0$ is the starting concentration of drug in solution, $Q_1$ is the amount of drug dissolved at time t, and $K_0$ is the zero-order rate constant, given in concentration units over time. Hours of time are represented by the variable t. A concentration versus time plot graphed would connect the axes' origin and produce a straight line with a slope equal to $K_0$.First order model has been used to describe absorption and elimination of drugs. The following equation express this model.

$$\text{Log } Q_1 = \text{Log} Q_0 + (K_1 t / 2.303) \ldots\ldots\ldots\ldots\ldots\ldots 2$$

where $Q_0$ is the starting drug concentration in the solution, $K_1$ is the first order release constant, and $Q_1$ is the amount of drug released in time t. This will result in a linear graph showing the decimal logarithm of the amount of dug that has been released over time.

In order to investigate the release of pharmaceuticals that are water soluble and low solubility when incorporated into semi-solid or solid matrices, Higuchi created a number of models. Giving rise to the following expression.

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

where t is the time in hours, Q is the amount of drug released at time t, and KH is the Higuchi dissolution constant reflecting the system's design characteristics. Therefore, the reciprocal of the square root of time and the medication release rate are proportionate. According to Higuchi, drug release is a diffusion mechanism that is time-dependent and based on Fick's law, square root.

Mechanism of Drug Release : Data from the dissolution research were plotted in Korsmeyer Peppa's equation as log cumulative percentage of drug released vs. log time in order to assess the mechanism of drug release from tablets. The exponent n was then determined by calculating the slope of the straight line.

$$F = (M_t / M) = K_m t^n \ldots\ldots\ldots\ldots\ldots\ldots 4$$

where $K_m$ is a constant dependent on the geometry of the dosage form, 'n' is the slope of the linear plot, Mt is the drug release at time t, F is the fraction of drug release at time t, and M is the total amount of medication in the dosage form. The releasing mechanism is indicated by the value of n.

When the exponent value n is equal to 0.5 in Fickian diffusion, and when it is between 0.5 and 1.0 in non-Fickian diffusion, it is considered abnormal. When the exponent value is n=1, it denotes a standard zero-order release or Case-II Transport.

### Stability Study

For a month, the optimised batch of floating tablets was subjected to accelerated stability testing in a humidity chamber with a temperature of 40°C and a relative humidity of 75%. The best batch of tablets were evaluated for appearance, drug content, floating qualities, and in vitro drug release characteristics before being wrapped in aluminium foil pouches.

## Results & discussion

### Preformulation Study of Etoricoxib drug

**Table 9 API properties**

| Sr. No. | Characteristic Properties | | Observation/Result |
|---|---|---|---|
| 1 | **Organoleptic Characteristics** | Colour of API | It is White colour crystalline Powder |
| | | Odour of API | It is Odourless powder |
| 2 | **Flow Properties** | Bulk density of API (g /ml) | 0.836 ± 0.01 |
| | | Tapped density of API (g /ml) | 1.253 ± 0.01 |
| | | Carr's index (%) of API | 33.28 ± 0.02 |
| | | Hausner's ratio of API | 1.49 ± 0.01 |
| | | Angle of repose (θ°) of API | 38.6 ± 0.2 |
| 3 | **Solubility** | It is soluble in organic solvents. Practically insoluble in water. | |
| 4 | **Melting Point** | 135-136 °C | |

### Standard Calibration Curve of Etoricoxib

The standard calibration curve was prepared in 0.1 N HCl (pH 1.2). The $\lambda_{max}$ found 233 nm. Please refer below figure for $\lambda_{max.}$

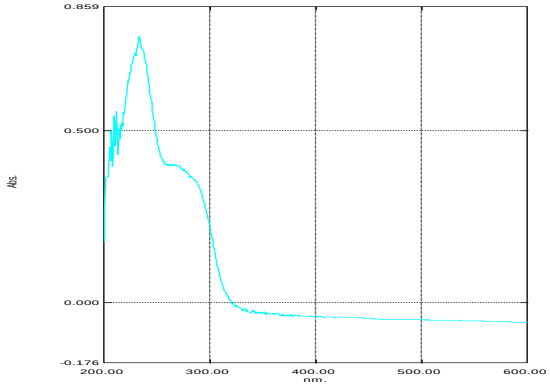



**Figure 0-1 $\lambda_{max}$ of Etoricoxib in 0.1 N HCl**

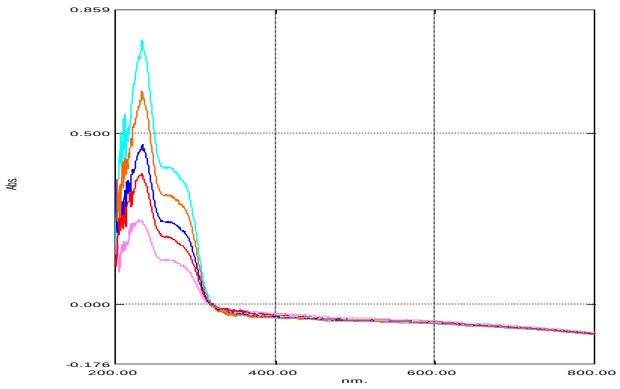



**Figure 2 Overlay plot of Etoricoxib in 0.1 N HCl**

**Table 10 Standard calibration curve Etoricoxib in 0.1 N HCl**

| Concentration (µg/ml) | Absorbance (Average) ± SD |
|---|---|
| 0.0 | 0.0 ±0.000 |
| 2 | 0.251 ± 0.002 |
| 4 | 0.379 ± 0.004 |
| 6 | 0.472 ± 0.003 |
| 8 | 0.626 ± 0.006 |
| 10 | 0.786 ± 0.002 |

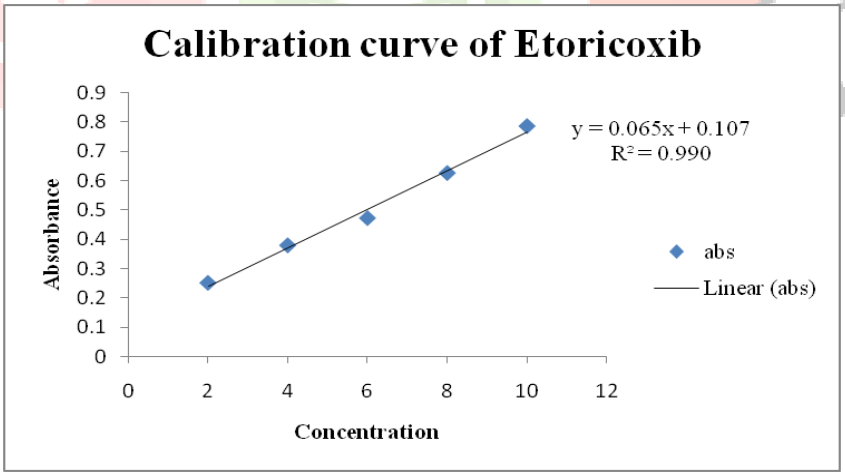



**Figure 3 Calibration curve of Etoricoxib in 0.1 N HCl**

**Drug- excipient compatibility studies**

The medication and some excipients were compatible, according to an FTIR investigation. There were no interactions of any type between the medication and the excipients. Please refer to figures.

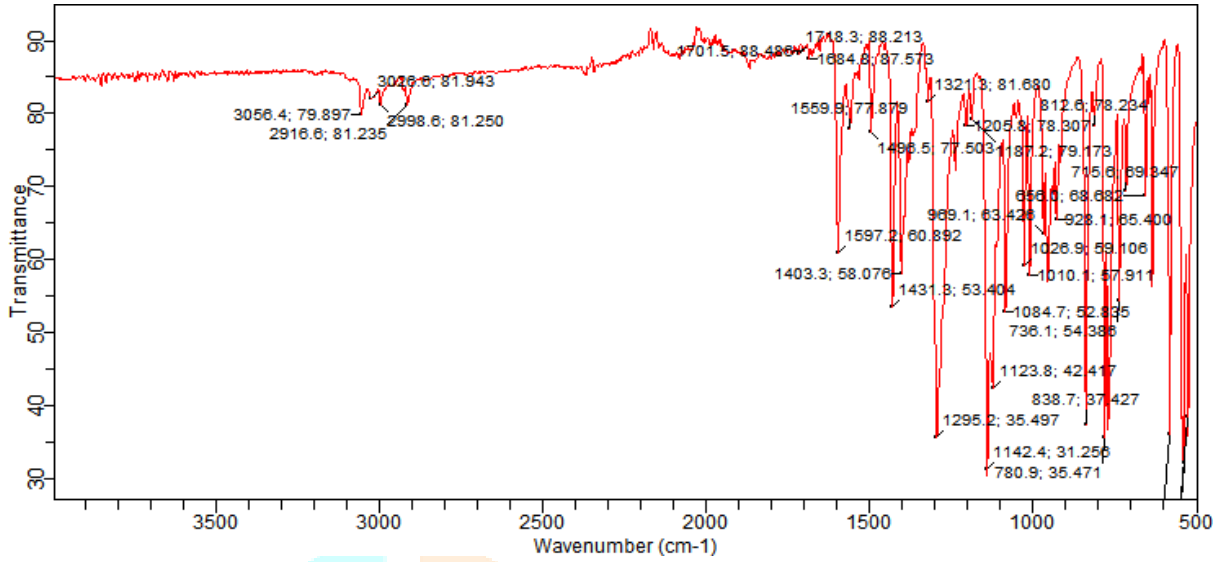



**Figure 4 FTIR spectra of Etoricoib**

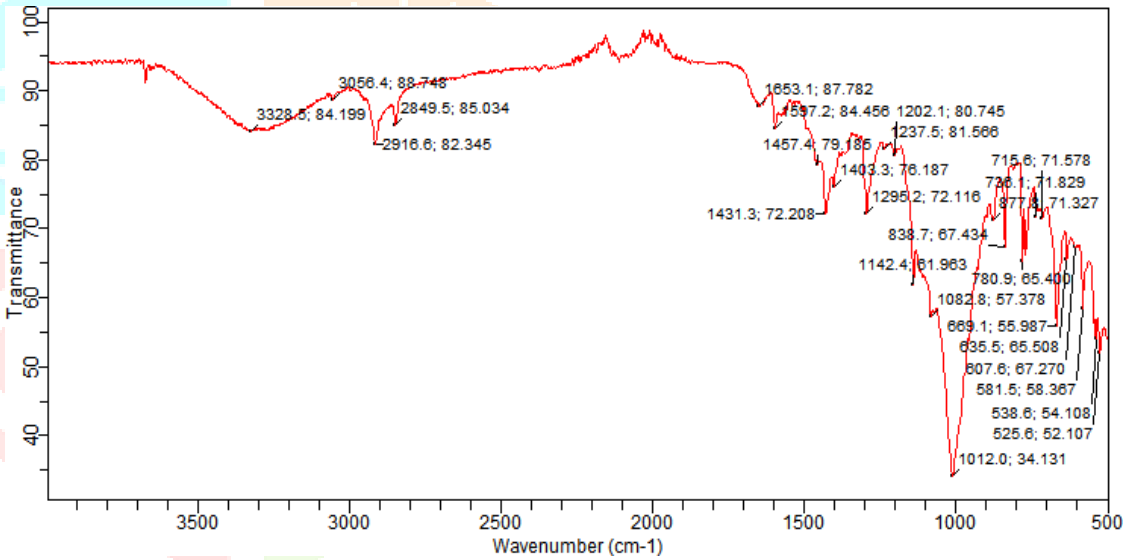



**Figure 5 FTIR of Physical Mixture of Optimized Formulation**

**Table 11 Interaction studies through IR spectroscopy**

| Stretching | Etoricoxib | Formulation |
|---|---|---|
| | Peak $cm^{-1}$ | Peak $cm^{-1}$ |
| C=N | 1597.2 | 1597.2 |
| S=O | 1431.3 | 1431.3 |
| C-Cl | 838.7 | 838.7 |

**Conclusion:** Based on the FTIR study findings presented above, it was concluded that there were no notable interactions observed between the drug and excipients. Therefore, the drug and other excipients are deemed compatible with each other.

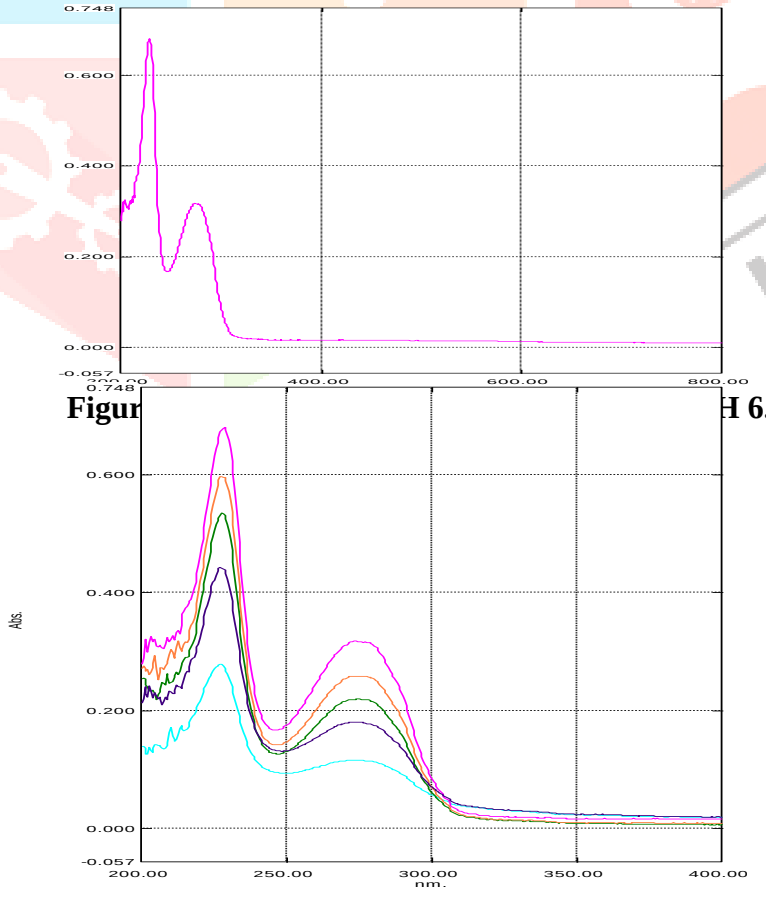
**Preformulation Study of Etodolac drug**

**Table 12 API properties**

| Sr. No. | Characteristic Properties | | Observation/Result |
|---|---|---|---|
| 1 | **Organoleptic Characteristics** | Colour of API | It is White to off white Powder |
| | | Odour of API | It is Odourless powder |
| 2 | **Flow Properties** | Bulk density of API (g /ml) | 0.315 ± 0.03 |
| | | Tapped density of API (g /ml) | 0.485 ± 0.01 |
| | | Carr's index (%) of API | 33.05 ± 0.03 |
| | | Hausner's ratio of API | 1.53 ± 0.01 |
| | | Angle of repose (θ°) of API | 34.5 ± 0.2 |
| 3 | **Solubility** | It is soluble in organic solvents. Practically insoluble in water. | |
| 4 | **Melting Point** | 145-148 °C | |

**Standard Calibration Curve of Etodolac**

The standard calibration curve was prepared in Phosphate buffer (pH 6.8). The $\lambda_{max}$ found 276 nm. Please refer below figure for $\lambda_{max}$.




**Figur** **H 6.8)**

**Figure 7 Overlay plot of Etodolac in Phosphate buffer (pH 6.8)**

**Table 13 Standard calibration curve Etodolac in Phosphate buffer (pH 6.8)**

| Concentration (µg/ml) | Absorbance (Average) ± SD |
|---|---|
| 0.0 | 0.0 ±0.000 |
| 2 | 0.116 ± 0.004 |
| 4 | 0.183 ± 0.004 |
| 6 | 0.221 ± 0.003 |
| 8 | 0.263 ± 0.004 |
| 10 | 0.315 ± 0.002 |

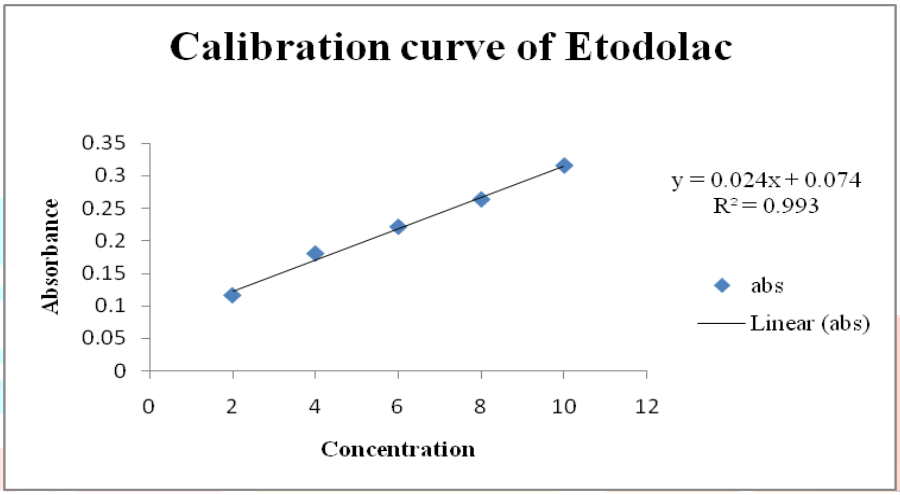



**Figure 8 Calibration curve of Etodolac in Phosphate buffer P$^{H}$ 6.8**

## Drug- excipient compatibility studies

The medication and some excipients were compatible, according to an FTIR investigation. There were no interactions of any type between the medication an the excipients. Please refer to figures.

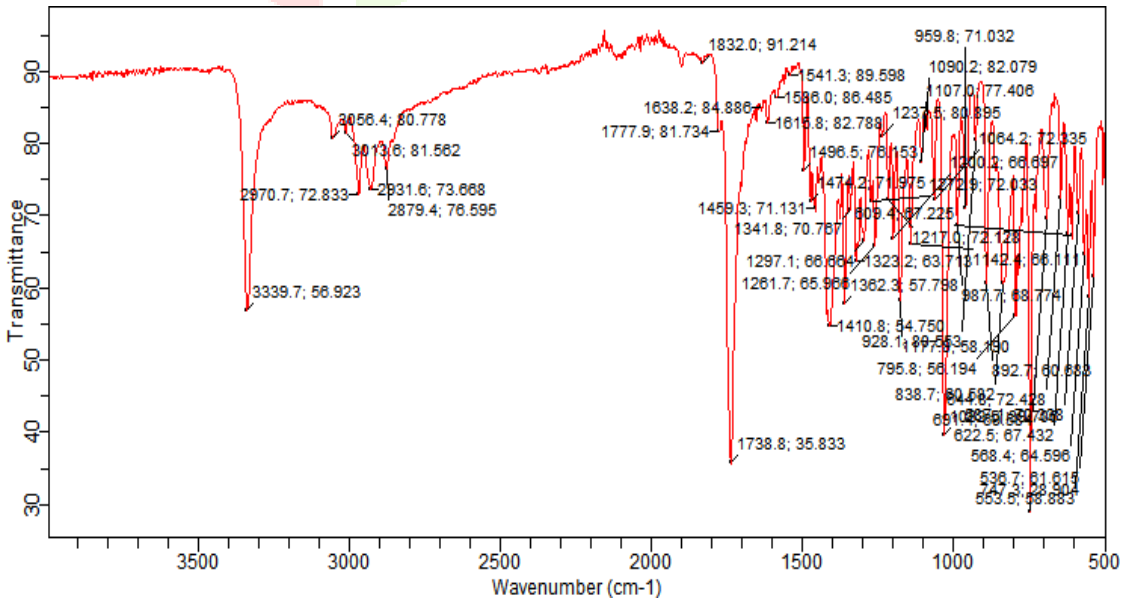



Figure 9 FTIR spectra of Etodolac

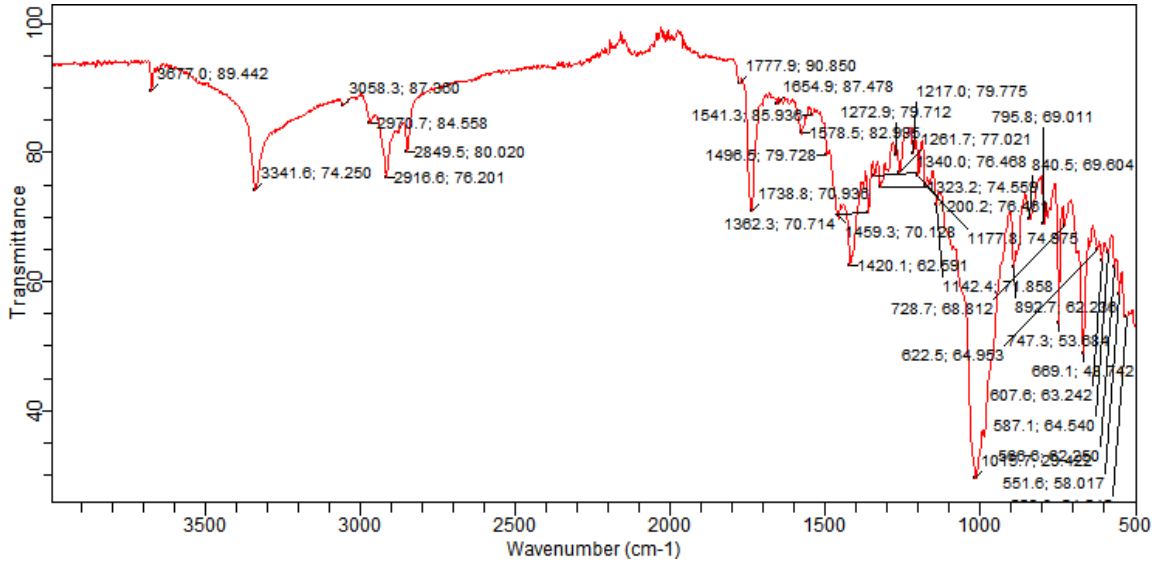



**Figure 10 FTIR of Physical Mixture of Optimized Formulation**

**Table 14 Interaction studies through IR spectroscopy**

| Stretching | Tapentadol HCl | Formulation |
|---|---|---|
| | Peak $cm^{-1}$ | Peak $cm^{-1}$ |
| C=C | 1738.8 | 1738.8 |
| H-C-H | 1362.3 | 1362.3 |
| C-O | 1142.4 | 1142.4 |
| N-H | 3339.7 | 3341.6 |
| C-H | 3056.4 | 3058.3 |
| C=C | 1738.8 | 1738.8 |

**Conclusion:** Based on the FTIR study findings presented above, it was concluded that there were no notable interactions observed between the drug and excipients. Therefore, the drug and other excipients are deemed compatible with each other.

**Pre compression Parameters of Trial Batches**

**Table 15 Result of Pre compression parameters of Trial Batches of Immediate release**

| Batch | Bulk density (g/ml)(n=3) | Tapped density (g/ml)(n=3) | Carr's index (%) (n=3) | Hausner's ratio (n=3) | Angle of repose (θ°) (n=3) |
|---|---|---|---|---|---|
| **TF1** | 0.50 ± 0.03 | 0.59 ± 0.03 | 12.25 ± 0.04 | 1.18 ± 0.02 | 32.4º ± 1.2 |
| **TF2** | 0.54 ± 0.04 | 0.61 ± 0.02 | 11.47 ± 0.02 | 1.12 ± 0.04 | 31.2º ± 2.3 |
| **TF3** | 0.45 ± 0.03 | 0.52 ± 0.04 | 13.46 ± 0.03 | 1.15 ± 0.02 | 33.1º ± 2.5 |
| **TF4** | 0.52 ± 0.10 | 0.59 ± 0.05 | 11.86 ± 0.05 | 1.13 ± 0.03 | 34.4º ± 3.1 |
| **TF5** | 0.48 ± 0.05 | 0.54 ± 0.03 | 12.72 ± 0.05 | 1.12 ± 0.04 | 30.2º ± 1.9 |
| **TF6** | 0.56 ± 0.10 | 0.63 ± 0.04 | 11.11 ± 0.03 | 1.12 ± 0.05 | 31.3º ± 2.4 |
| **TF7** | 0.51 ± 0.02 | 0.59 ± 0.03 | 13.55 ± 0.06 | 1.15 ± 0.06 | 34.4º ± 2.3 |
| **TF8** | 0.50 ± 0.04 | 0.57 ± 0.02 | 12.85 ± 0.03 | 1.14 ± 0.04 | 31.6º ± 1.3 |
| **TF9** | 0.54 ± 0.03 | 0.62 ± 0.05 | 12.90 ± 0.02 | 1.14 ± 0.06 | 30.3º ± 2.3 |

It can be concluded from the flow property data above that the blended flow is of a good nature and handles compression smoothly.

**Table 16 Results of pre compression parameters of Trial Batches of Sustained release**

| Batch | Bulk density (g/ml)(n=3) | Tapped density (g/ml)(n=3) | Carr's index (%) (n=3) | Hausner's ratio (n=3) | Angle of repose (θ°) (n=3) |
|---|---|---|---|---|---|
| **TSR1** | 0.52 ± 0.05 | 0.60 ± 0.03 | 13.33 ± 0.05 | 1.15 ± 0.03 | 34.2º ± 2.4 |
| **TSR2** | 0.57 ± 0.03 | 0.66 ± 0.05 | 13.63 ± 0.03 | 1.15 ± 0.02 | 33.5º ± 1.5 |
| **TSR3** | 0.51 ± 0.10 | 0.57 ± 0.03 | 10.52 ± 0.03 | 1.11 ± 0.04 | 32.1º ± 1.3 |
| **TSR4** | 0.54 ± 0.03 | 0.61 ± 0.04 | 11.47 ± 0.02 | 1.12 ± 0.03 | 34.5º ± 3.1 |
| **TSR5** | 0.55 ± 0.02 | 0.62 ± 0.05 | 11.29 ± 0.05 | 1.13 ± 0.04 | 33.1º ± 1.5 |
| **TSR6** | 0.56 ± 0.04 | 0.64 ± 0.02 | 12.53 ± 0.06 | 1.14 ± 0.03 | 30.2º ± 2.4 |
| **TSR7** | 0.52 ± 0.03 | 0.59 ± 0.04 | 11.8 ± 0.03 | 1.14 ± 0.05 | 34.2º ± 2.1 |
| **TSR8** | 0.54 ± 0.10 | 0.61 ± 0.02 | 11.47 ± 0.05 | 1.12 ± 0.04 | 33.7º ± 1.3 |
| **TSR9** | 0.57 ± 0.03 | 0.65 ± 0.05 | 12.30 ± 0.02 | 1.14 ± 0.06 | 32.2º ± 2.3 |

**Table 17 Results of post compression parameters of Trial Batches of Immediate release**

| Formulation Code | Weight variation (mg) (n=20) | Thickness (mm) (n=3) | Hardness ($kg/cm^2$) (n=3) | Friability % | Drug content % (n=3) | Disintegration time |
|---|---|---|---|---|---|---|
| **TIR1** | 250.13±0.05 | 3.74±0.01 | 4.53±0.17 | 0.62±0.04 | 98.72±0.02 | 126 sec |
| **TIR2** | 250.25±0.04 | 3.93±0.05 | 5.25±0.12 | 0.78±0.07 | 96.96±0.01 | 109 sec |
| **TIR3** | 248.88±0.26 | 3.49±0.03 | 5.0±0.13 | 0.57±0.03 | 97.44±0.05 | 90 sec |
| **TIR4** | 250.25±0.35 | 3.63±0.03 | 5.48±0.16 | 0.68±0.07 | 95.68±0.04 | 120 sec |
| **TIR5** | 250.28±0.04 | 3.57±0.04 | 4.85±0.13 | 0.59±0.06 | 97.61±0.02 | 96 sec |
| **TIR6** | 250.87±0.34 | 4.35±0.07 | 5.50±0.15 | 0.61±0.09 | 98.80±0.03 | 83 sec |
| **TIR7** | 249.99±0.23 | 3.23±0.09 | 4.94±0.17 | 0.59±0.06 | 96.91±0.03 | 92 sec |
| **TIR8** | 251.65±0.26 | 3.14±0.06 | 5.33±0.11 | 0.69±0.05 | 93.73±0.03 | 74 sec |
| **TIR9** | 250.22±0.16 | 3.56±0.03 | 5.30±0.13 | 0.54±0.02 | 98.12±0.03 | 40 sec |

**Table 18 Results of post compression parameters of Trial Batches of Sustained release**

| Formulation Code | Weight variation (mg) (n=20) | Thickness (mm) (n=3) | Hardness ($kg/cm^2$) (n=3) | Friability % | Drug content % (n=3) |
|---|---|---|---|---|---|
| **TSR1** | 600.80±0.02 | 5.50±0.03 | 5.57±0.12 | 0.48±0.05 | 97.47±0.02 |
| **TSR2** | 600.25±0.04 | 5.59±0.01 | 5.30±0.15 | 0.60±0.02 | 96.45±0.01 |
| **TSR3** | 600.47±0.22 | 5.63±0.04 | 6.00±0.13 | 0.57±0.07 | 97.58±0.05 |
| **TSR4** | 600.30±0.5 | 6.22±0.03 | 5.49±0.12 | 0.59±0.03 | 99.28±0.04 |
| **TSR5** | 600.50±0.04 | 5.57±0.04 | 5.89±0.15 | 0.63±0.06 | 98.82±0.02 |
| **TSR6** | 600.72±0.2 | 5.70±0.05 | 5.50±0.15 | 0.54±0.04 | 97.35±0.03 |
| **TSR7** | 600.99±0.23 | 5.53±0.07 | 6.2±0.13 | 0.60±0.06 | 96.91±0.03 |

| | | | | | |
|---|---|---|---|---|---|
| **TSR8** | 600.65±0.26 | 5.50±0.02 | 5.30±0.11 | 0.63±0.02 | 97.53±0.03 |
| **TSR9** | 600.22±0.16 | 5.56±0.03 | 5.00±0.13 | 0.59±0.05 | 98.42±0.03 |

**In Vitro Drug Release Study**

**Preliminary Trials**

**Table 19 Drug release of Trial Batches of Immediate release**

| Time(min) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 0±0.0 | 0±0.0 | 0±0.0 | 0±0.0 | 0±0.0 | 0±0.0 | 0±0.0 | 0±0.0 | 0±0.0 |
| **5** | 15.1± 4.5 | 20.4± 3.1 | 23.8± 4.2 | 20.9± 3.0 | 28.4± 2.8 | 31.2± 3.6 | 25.6± 2.8 | 32.4± 1.9 | 39.5 ±3.6 |
| **10** | 22.0 ±2.9 | 37.9± 2.8 | 41.2± 3.3 | 27.5± 2.8 | 38.3± 2.4 | 44.8± 2.8 | 32.7± 2.4 | 47.5± 1.6 | 51.6 ±2.8 |
| **15** | 37.4 ±3.4 | 45.5± 2.6 | 47.8± 2.5 | 41.1± 2.1 | 50.7± 2.2 | 57.3± 2.4 | 46.2± 2.3 | 59.6± 1.3 | 67.3 ±2.4 |
| **20** | 49.3 ±2.7 | 59.6± 2.4 | 61.4± 2.3 | 53.5± 1.9 | 65.9± 1.9 | 69.6± 2.1 | 59.9± 2.1 | 71.4± 1.4 | 83.6 ±2.3 |
| **25** | 62.2 ±2.3 | 68.3± 2.3 | 74.3± 2.0 | 64.3± 1.4 | 76.6± 1.5 | 79.1± 2.0 | 70.4± 2.6 | 83.5± 1.1 | 90.4 ±1.8 |
| **30** | 70.1 ± 2.5 | 80.9 ±2.1 | 88.9± 1.6 | 76.4± 1.2 | 85.4± 1.2 | 91.7± 1.5 | 83.7± 1.5 | 90.3± 1.0 | 98.8 ±1.4 |

**Table 20 Drug release of Trial Batches of Sustained release**

| Time(hour) | TSR1 | TSR2 | TSR3 | TSR4 | TSR5 | TSR6 | TSR7 | TSR8 | TSR9 |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 37.5± 4.4 | 32.1± 2.5 | 29.5± 4.2 | 35.4± 4.3 | 30.1 ±3.8 | 24.2± 4.2 | 30.5± 4.0 | 26.7± 3.6 | 20.6± 3.0 |
| **2** | 40.6 ±3.6 | 39.2± 3.6 | 36.8± 3.6 | 39.5± 4.1 | 36.3± 3.4 | 31.7± 4.1 | 42.1± 4.2 | 33.4± 3.5 | 25.3± 2.6 |
| **3** | 47.1± 2.1 | 44.9± 1.5 | 46.2± 3.2 | 48.2± 3.7 | 45.4± 3.1 | 40.7± 3.7 | 49.4± 3.7 | 39.7± 3.1 | 31.5± 2.4 |
| **4** | 58.4± 1.2 | 56.6± 1.7 | 53.0± 2.9 | 56.9± 3.5 | 51.7± 2.7 | 45.1± 3.2 | 53.7± 3.4 | 44.1± 2.8 | 38.4± 2.1 |
| **5** | 63.6± 1.7 | 60.7± 1.2 | 59.4± 2.7 | 60.2± 2.6 | 59.6± 2.4 | 52.8± 3.4 | 58.3± 2.3 | 51.6± 2.6 | 46.8± 2.6 |
| **6** | 72.5± 2.0 | 68.6± 1.5 | 62.7± 1.8 | 65.3± 2.3 | 61.7± 2.1 | 59.3± 2.3 | 63.6± 2.2 | 58.3± 2.5 | 50.1± 2.4 |
| **7** | 86.2± 1.9 | 82.6± 2.1 | 71.1± 2.4 | 73.2± 3.2 | 69.8± 2.5 | 68.1± 2.4 | 70.4± 2.4 | 63.9± 2.4 | 57.5± 2.4 |
| **8** | 91.0± 1.5 | 89.3± 1.6 | 74.2± 1.5 | 81.5± 2.9 | 77.4± 1.6 | 72.5± 2.6 | 74.5± 2.5 | 69.4± 2.3 | 63.6± 2.9 |
| **9** | 97.7± 2.2 | 93.0± 1.5 | 80.6± 1.7 | 91.6± 2.1 | 82.2± 1.4 | 79.4± 2.4 | 78.4± 2.8 | 73.2± 1.8 | 67.3± 1.8 |
| **10** | 99.2± 2.1 | 95.5± 1.7 | 84.5± 1.4 | 96.4± 1.4 | 87.9± 1.3 | 83.8± 2.1 | 82.8± 1.4 | 79.7± 1.6 | 73.4± 1.2 |
| **11** | - | 98.6± 1.1 | 87.4± 2.4 | 99.5± 1.1 | 92.6± 1.3 | 93.3± 1.5 | 87.9± 1.3 | 82.4± 1.3 | 77.3± 1.4 |
| **12** | - | - | 91.1± 2.6 | - | 98.4± 1.2 | 95.6± 1.2 | 93.5± 1.1 | 87.1± 1.1 | 84.8± 1.2 |

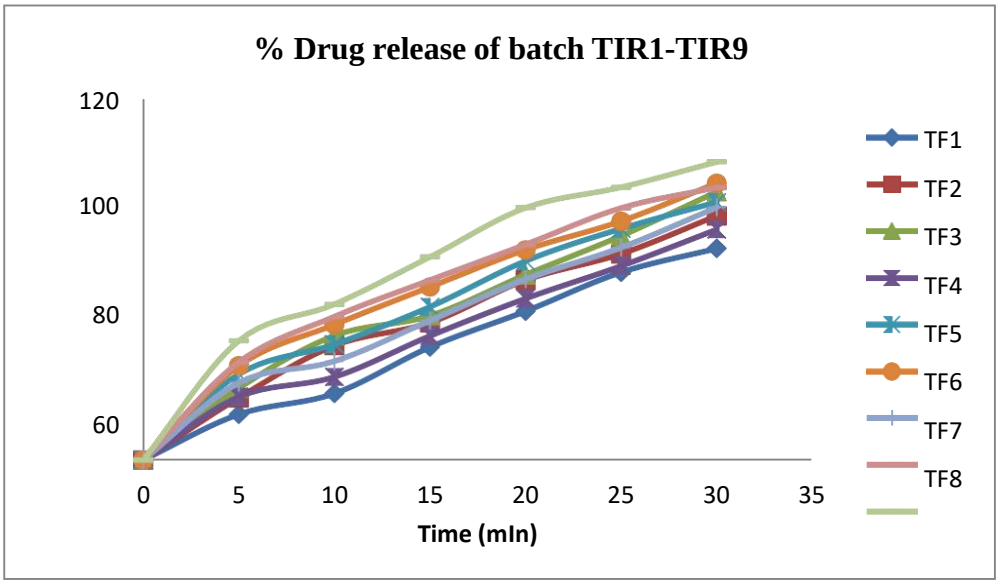



**Figure 11 Drug release of Batch T1-T9of Trial Batches of immediate release**

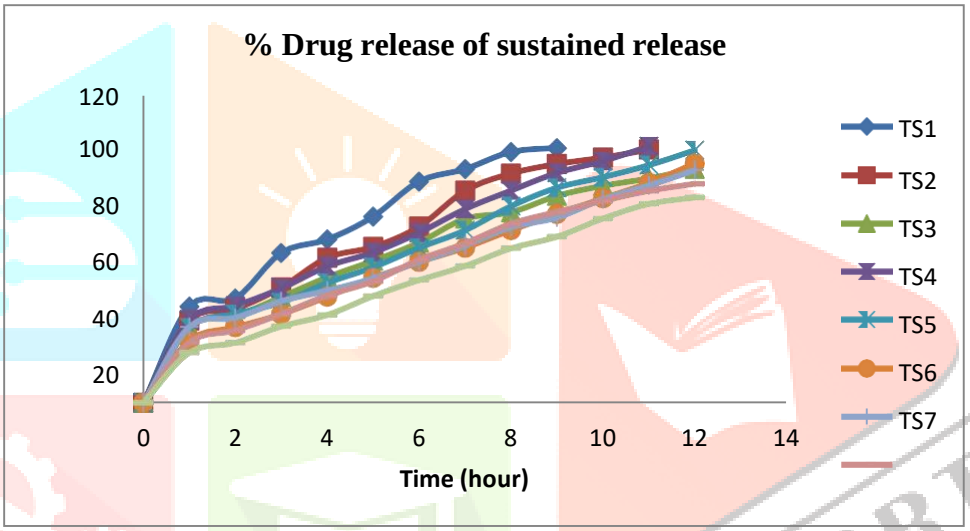



**Figure 12 Drug release of Batch T1-T9 of Trial Batches of sustained release**

**Evaluation of factorial batches**

Powder blend of factorial batches F1-F9 checked for pre-compression parameters. Observed results are mentioned in following table 6.9. From the below table it concluded that the all batches have a good flow properties.

**Table 21 Results of Pre compression parameters of factorial batches of immediate release**

| Formulation Code | Bulk den-sity (g/ml) (n=3) | Tapped density (g/ml) (n=3) | % Carr's index (n=3) | Hausner's ratio (n=3) | Angle of repose |
|---|---|---|---|---|---|
| **FIR1** | 0.50 ± 0.02 | 0.59 ± 0.02 | 15.25 ± 0.02 | 1.18 ± 0.02 | 32.4±0.04 |
| **FIR2** | 0.45 ± 0.04 | 0.52 ± 0.05 | 13.46 ± 0.06 | 1.15 ± 0.07 | 34.2±0.03 |
| **FIR3** | 0.52 ± 0.05 | 0.59 ± 0.03 | 11.86 ± 0.02 | 1.12 ± 0.08 | 30.1±.002 |
| **FIR4** | 0.54 ± 0.02 | 0.62 ± 0.03 | 12.90 ± 0.04 | 1.14 ± 0.05 | 32.4±0.03 |
| **FIR5** | 0.55 ± 0.03 | 0.62 ± 0.05 | 11.29 ± 0.05 | 1.12 ± 0.06 | 33.6±0.02 |

| | | | | | |
|---|---|---|---|---|---|
| **FIR6** | 0.56 ± 0.05 | 0.63 ± 0.04 | 11.11 ± 0.08 | 1.12 ± 0.04 | 31.3±0.02 |
| **FIR7** | 0.52 ± 0.04 | 0.59 ± 0.06 | 11.86 ± 0.07 | 1.13± 0.08 | 31.7±0.03 |
| **FIR8** | 0.56 ± 0.06 | 0.63 ± 0.04 | 11.11 ± 0.05 | 1.12± 0.02 | 30.0±0.04 |
| **FIR9** | 0.53 ± 0.05 | 0.61 ± 0.04 | 13.11 ± 0.04 | 1.15± 0.06 | 31.2±001 |

**Table 22 Results of Pre compression parameters of factorial batches of sustained release**

| Formulation Code | Bulk den- sity (g/ml) (n=3) | Tapped density (g/ml) (n=3) | % Carr's index (n=3) | Hausner's ratio (n=3) | Angle of repose |
|---|---|---|---|---|---|
| **FSR1** | 0.52 ± 0.03 | 0.59 ± 0.03 | 11.86 ± 0.04 | 1.13 ± 0.02 | 32.2±0.02 |
| **FSR2** | 0.54 ± 0.02 | 0.61 ± 0.05 | 11.47 ± 0.02 | 1.12 ± 0.07 | 32.5±0.02 |
| **FSR3** | 0.57 ± 0.04 | 0.65 ± 0.02 | 12.30 ± 0.05 | 1.14 ± 0.08 | 31.1±.004 |
| **FSR4** | 0.54 ± 0.05 | 0.61 ± 0.04 | 11.47 ± 0.04 | 1.12 ± 0.05 | 32.3±0.03 |
| **FSR5** | 0.53 ± 0.02 | 0.62 ± 0.05 | 14.51 ± 0.03 | 1.16 ± 0.06 | 30.3±0.02 |
| **FSR6** | 0.56 ± 0.03 | 0.64 ± 0.03 | 12.5 ± 0.06 | 1.14 ± 0.04 | 32.1±0.04 |
| **FSR7** | 0.51 ± 0.04 | 0.59 ± 0.05 | 13.55 ± 0.05 | 1.15± 0.08 | 31.4±0.05 |
| **FSR8** | 0.55 ± 0.02 | 0.63 ± 0.06 | 12.69 ± 0.07 | 1.14± 0.02 | 31.2±0.03 |
| **FSR9** | 0.52 ± 0.04 | 0.59 ± 0.03 | 11.86 ± 0.03 | 1.13± 0.06 | 30.7±002 |

**Table 23 Results of Post compression parameters of factorial batches of immediate release**

| Formula-tion Code | Weight variation (mg) (n=20) | Thick-ness (mm) (n=3) | Hard- ness ($kg/cm^2$) (n=3) | Friabil-ity % | Drug content %(n=3) | Disinte-gration Time (Sec) |
|---|---|---|---|---|---|---|
| **FIR1** | 249.21 ±0.19 | 3.72±0.05 | 5.60±0.10 | 0.66±0.01 | 97.25 ±0.05 | 120sec |
| **FIR2** | 251.13 ±0.28 | 3.36±0.09 | 5.29±0.15 | 0.62±0.02 | 97.10 ±0.04 | 109 sec |
| **FIR3** | 252.15 ±0.36 | 3.45±0.08 | 5.30±0.09 | 0.59±0.06 | 98.45 ±0.03 | 103 sec |
| **FIR4** | 249.36 ±0.39 | 4.15±0.05 | 4.78±0.13 | 0.63±0.02 | 98.14 ±0.04 | 92 sec |
| **FIR5** | 250.54 ±0.45 | 3.49±0.07 | 5.10±0.19 | 0.58±0.08 | 97.65 ±0.07 | 83 sec |
| **FIR6** | 251.12 ±0.29 | 4.30±0.08 | 4.85±0.12 | 0.62±0.03 | 99.42 ±0.02 | 70 sec |
| **FIR7** | 249.99 ±0.36 | 3.15±0.03 | 5.15±0.11 | 0.61±0.01 | 98.41 ±0.04 | 58 sec |
| **FIR8** | 250.46 ±0.42 | 3.45±0.05 | 5.57±0.13 | 0.56±0.03 | 98.36 ±0.05 | 36 sec |

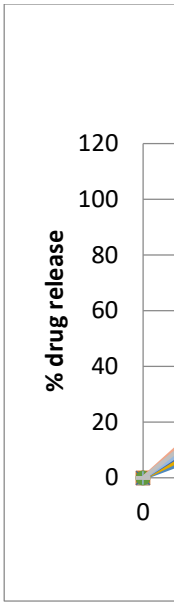
| | | | | | | |
|---|---|---|---|---|---|---|
| **FIR9** | 251.42 ±0.28 | 3.89±0.06 | 5.50±0.18 | 0.58±0.05 | 96.25 ±0.06 | 48 sec |

**Table 24 Results of post compression parameters of factorial batches of sustained release**

| Formulation code | Weight variation (mg) (n = 3) | Thickness (mm) (n = 3) | Hardness ( kg/cm$^2$) n = 3) | Friability % (n = 3) | Drug Content % (n = 3) |
|---|---|---|---|---|---|
| **FSR 1** | 599.25 ±0.13 | 5.23±0.03 | 5.20±0.10 | 0.64±0.03 | 97.38 ±0.02 |
| **FSR 2** | 600.15 ±0.26 | 5.39±0.04 | 5.34±0.15 | 0.62±0.02 | 98.47 ±0.04 |
| **FSR 3** | 601.12 ±0.39 | 5.85±0.05 | 5.82±0.09 | 0.66 ±0.04 | 97.57 ±0.03 |
| **FSR 4** | 599.39 ±0.26 | 5.65±0.02 | 6.32±0.13 | 0.55±0.06 | 99.14 ±0.01 |
| **FSR 5** | 600.54 ±0.36 | 5.15±0.04 | 5.32±0.19 | 0.58±0.03 | 98.74 ±0.03 |
| **FSR 6** | 600.11 ±0.20 | 5.53±0.07 | 5.85±0.12 | 0.62±0.05 | 98.34 ±0.02 |
| **FSR 7** | 601.76 ±0.25 | 5.36.±0.03 | 5.52±0.11 | 0.59±0.02 | 98.12 ±0.03 |
| **FSR 8** | 599.59 ±0.58 | 6.25±0.05 | 5.57±0.13 | 0.57±0.04 | 97.16 ±0.02 |
| **FSR 9** | 601.42 ±0.28 | 5.37±0.06 | 5.50±0.18 | 0.64±0.06 | 98.42 ±0.02 |

**Drug release**

Drug release of factorial batches was performed to check the impact of the amount of polymer and efferent agent. Based on results it found that the amount of polymer change the release profile of the tablets. The actual impact was checked by using factorial design. The comparative plot was shown in below figure.

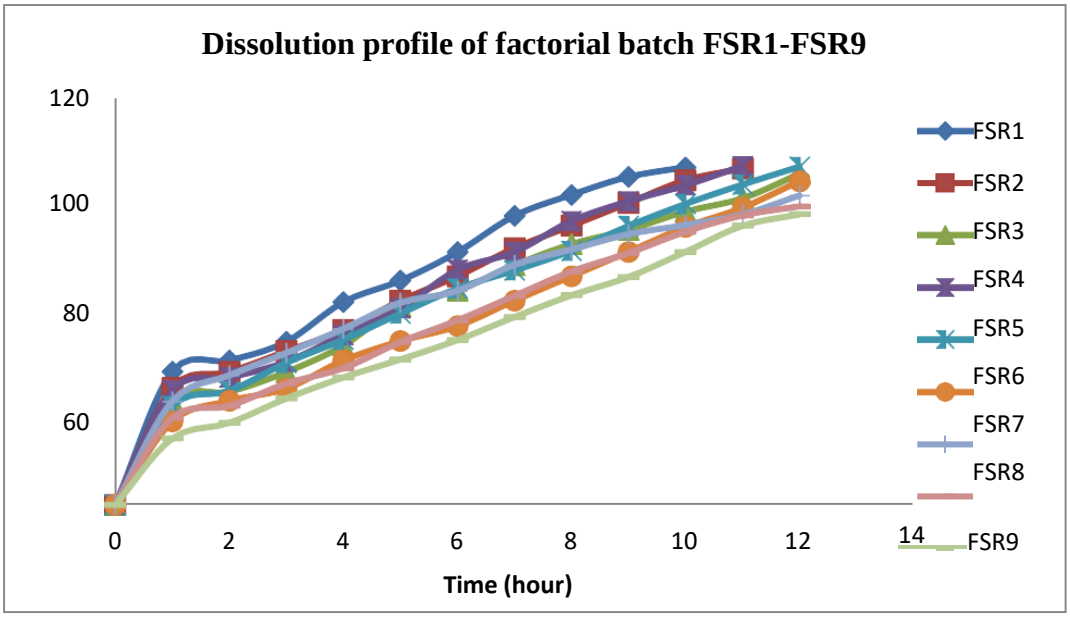



| Time (min) | FIR1 | FIR2 | FIR3 | FIR4 | FIR5 | FIR6 | FIR7 | FIR8 | FIR9 |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 0±0.00 | 0±0.00 | 0±0.00 | 0±0.00 | 0±0.00 | 0±0.00 | 0±0.00 | 0±0.00 | 0±0.00 |
| **5** | 12.1±3.4 | 16.6±3.2 | 21.4±3.2 | 15.8±3.4 | 20.1±2.8 | 25.5±2.5 | 21.6±2.8 | 29.3±2.6 | 26.1±1.6 |
| **10** | 33.4±3.6 | 38.7±3.0 | 42.6±3.1 | 37.2±3.1 | 43.3±2.7 | 49.2±2.1 | 46.3±2.4 | 48.7±2.3 | 45.4±1.2 |
| **15** | 48.9±3.1 | 53.6±2.8 | 57.1±2.5 | 52.9±2.9 | 58.8±2.5 | 61.6±1.9 | 60.5±2.2 | 63.4±1.8 | 58.7±1.4 |
| **20** | 56.6±2.7 | 68.2±2.6 | 74.5±2.2 | 58.3±2.5 | 72.6±2.1 | 79.2±1.6 | 66.7±1.8 | 81.9±1.3 | 79.7±0.7 |
| **25** | 63.1±2.5 | 72.4±2.2 | 80.6±1.9 | 66.4±1.6 | 80.5±1.4 | 87.4±1.2 | 78.3±1.5 | 92.4±0.8 | 90.4±0.5 |
| **30** | 74.4±2.1 | 80.8±1.9 | 85.3±1.7 | 80.6±1.3 | 84.9±1.3 | 91.6±0.7 | 87.5±1.7 | 98.5±0.4 | 94.8±0.2 |

**Figure 13 Drug release profile of TIR1-TIR9**

**Table 25 drug release profile of sustained release layer**

| Time (hour) | FSR1 | FSR2 | FSR3 | FSR4 | FSR5 | FSR6 | FSR7 | FSR8 | FSR9 |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 39.3±4.6 | 34.5±4.3 | 30.1±3.8 | 33.8±4.8 | 29.1±4.3 | 24.6±4.6 | 30.5±4.1 | 25.7±3.9 | 19.6±4.8 |
| **2** | 42.6±4.3 | 39.2±4.1 | 33.4±3.5 | 37.5±4.4 | 33.6±4.1 | 30.7±4.0 | 38.2±3.9 | 29.2±3.6 | 24.2±4.4 |
| **3** | 48.1±4.1 | 45.3±3.8 | 39.2±3.1 | 42.2±4.1 | 41.9±3.8 | 34.3±3.8 | 44.8±3.7 | 35.8±3.4 | 31.4±4.1 |
| **4** | 59.8±3.9 | 51.6±3.6 | 47.0±2.9 | 50.1±3.8 | 48.7±3.7 | 42.6±3.6 | 51.9±3.2 | 40.3±3.1 | 37.6±3.8 |
| **5** | 66.1±3.6 | 60.2±3.0 | 58.6±2.8 | 57.9±3.6 | 56.4±3.4 | 48.3±3.5 | 59.6±2.8 | 48.0±2.9 | 42.9±3.5 |
| **6** | 74.5±3.1 | 67.4±2.8 | 63.2±2.5 | 69.3±3.2 | 63.8±3.2 | 52.7±3.1 | 63.1±2.7 | 54.4±2.6 | 48.6±3.2 |
| **7** | 85.2±3.0 | 75.7±2.6 | 70.7±2.1 | 74.5±2.5 | 69.1±2.9 | 60.2±2.8 | 70.8±2.4 | 61.6±2.4 | 55.4±3.1 |
| **8** | 91.4±2.7 | 82.3±2.5 | 76.9±1.8 | 83.7±2.5 | 74.9±2.5 | 67.4±2.5 | 75.3±2.1 | 68.8±2.7 | 61.8±2.9 |
| **9** | 96.7±2.1 | 89.0±1.9 | 81.1±1.6 | 89.5±2.4 | 82.2±1.6 | 74.6±2.0 | 79.8±1.7 | 74.2±2.2 | 67.2±2.6 |
| **10** | 99.5±0.2 | 95.7±1.5 | 86.5±1.5 | 94.2±1.3 | 88.7±1.4 | 81.9±1.7 | 82.5±1.5 | 80.5±2.5 | 74.6±2.4 |
| **11** | - | 99.1±0.3 | 90.4±1.5 | 99.9±0.03 | 94.4±0.8 | 87.6±1.4 | 85.6±1.4 | 85.3±3.5 | 82.3±2.7 |
| **12** | - | - | 95.2±1.3 | - | 97.2±0.5 | 94.4±1.1 | 91.2±1.7 | 88.0±3.0 | 85.7±2.8 |




**Drug Release Kinetic Study**

In vitro drug release study data was fitted in kinetic models and results obtained were shown in below table 6.13. Formulation was best fitted with **Korsmeyer Peppas** model and mechanism of drug release was found to be Non-Fickian type of diffusion.

**Table 26 Drug Release Kinetic Study of factorial batches FIR1-FIR9**

| FORMULATIONS | ZERO ORDER | FIRST ORDER | HIGUCHI MODEL | KORS PEPAS |
|---|---|---|---|---|
| **FIR1** | 0.952 | 0.803 | 0.987 | 0.954 |
| **FIR2** | 0.944 | 0.823 | 0.985 | 0.967 |
| **FIR3** | 0.944 | 0.850 | 0.982 | 0.978 |
| **FIR4** | 0.957 | 0.831 | 0.983 | 0.965 |
| **FIR5** | 0.939 | 0.827 | 0.983 | 0.970 |
| **FIR6** | 0.947 | 0.855 | 0.984 | 0.979 |
| **FIR7** | 0.951 | 0.832 | 0.985 | 0.966 |
| **FIR8** | 0.973 | 0.909 | 0.993 | 0.995 |
| **FIR9** | 0.968 | 0.904 | 0.986 | 0.991 |

**Table 27 Drug Release Kinetic Study of factorial batches FSR1-FSR9**

| FORMULATIONS | ZERO ORDER | FIRST ORDER | HIGUCHI MODEL | KORS PEPAS |
|---|---|---|---|---|
| **FSR1** | 0.992 | 0.988 | 0.977 | 0.977 |
| **FSR2** | 0.996 | 0.997 | 0.979 | 0.978 |
| **FSR3** | 0.989 | 0.979 | 0.982 | 0.981 |
| **FSR4** | 0.987 | 0.991 | 0.968 | 0.966 |
| **FSR5** | 0.996 | 0.977 | 0.996 | 0.997 |
| **FSR6** | 0.991 | 0.984 | 0.980 | 0.976 |
| **FSR7** | 0.993 | 0.981 | 0.991 | 0.992 |

| | | | | |
|---|---|---|---|---|
| **FSR8** | 0.996 | 0.993 | 0.981 | 0.985 |
| **FSR9** | 0.866 | 0.632 | 0.911 | 0.776 |

**Analysis of factorial design for immediate release**

The obtained results were compiled for analysis using factorial design. The factors and responses tabulated in software than analysis was done using below table.

**Table 28 Factorial design analysis table of immediate release**

| Batch | Lactose (mg) | Crosspovidone (mg) | Disintegration time (sec) | % drug release |
|---|---|---|---|---|
| **FIR1** | 110 | 7.5 | 120 | 74.4 |
| **FIR2** | 110 | 12.5 | 109 | 80.8 |
| **FIR3** | 110 | 17.5 | 103 | 85.3 |
| **FIR4** | 115 | 7.5 | 92 | 80.6 |
| **FIR5** | 115 | 12.5 | 83 | 84.9 |
| **FIR6** | 115 | 17.5 | 70 | 91.6 |
| **FIR7** | 120 | 7.5 | 58 | 87.5 |
| **FIR8** | 120 | 12.5 | 33 | 98.5 |
| **FIR9** | 120 | 17.5 | 48 | 94.8 |

**ANOVA for Quadratic model**
**Response 1: Disintegration time**

**Table 29 ANOVA of response 1 for immediate release**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 6511.36 | 5 | 1302.27 | 25.12 | 0.0118 | Significant |
| A-lactose | 6016.67 | 1 | 6016.67 | 116.06 | 0.0017 | |
| B-crosspovidone | 400.17 | 1 | 400.17 | 7.72 | 0.0691 | |
| AB | 12.25 | 1 | 12.25 | 0.2363 | 0.6602 | |
| $A^2$ | 14.22 | 1 | 14.22 | 0.2743 | 0.6367 | |
| $B^2$ | 68.06 | 1 | 68.06 | 1.31 | 0.3350 | |
| **Residual** | 155.53 | 3 | 51.84 | | | |
| **Cor Total** | 6666.89 | 8 | | | | |

Factor coding is **coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 25.12 implies the model is significant. There is only a 1.18%chance that an F-value this large could occur due to noise.

**P-values** Model terms are considered significant when P-values are less than 0.0500. A is a significant model term in this instance. The model features are not significant if the value is

bigger than 0.1000. Model reduction could make your model better if it has a large number of unimportant model terms (apart from those needed to maintain hierarchy).

**Coefficients in Terms of Coded Factors**

**Table 30 Coefficient factor of response 1 for immediate release layer**

| Factor | Coefficient Estimate | df | Standard Error | 95% CI Low | 95% CI High | VIF |
|---|---|---|---|---|---|---|
| Intercept | 77.78 | 1 | 5.37 | 60.70 | 94.86 | |
| A-lactose | -31.67 | 1 | 2.94 | -41.02 | -22.31 | 1.0000 |
| B-crosspovidone | -8.17 | 1 | 2.94 | -17.52 | 1.19 | 1.0000 |
| AB | 1.75 | 1 | 3.60 | -9.71 | 13.21 | 1.0000 |
| $A^2$ | -2.67 | 1 | 5.09 | -18.87 | 13.54 | 1.0000 |
| $B^2$ | 5.83 | 1 | 5.09 | -10.37 | 22.04 | 1.0000 |

**Polynomial Equation :-** $Y1 = 77.78 - 31.67X_1 - 8.17X_2 + 1.75X_{12} - 2.67X1^2 + 5.83X2^2$

When all other factors are maintained constant, the coefficient estimate shows the expected change as a result for each unit change in parameter value. The total average response of all the runs is the intercept in an orthogonal design. Based on the factor parameters, the coefficients are adjustments around that average. VIFs are 1 when the factors are orthogonal; VIFs larger than 1 denote multi-colinearity; the higher the VIF, the more severe the factor correlation. VIFs of fewer than 10 are generally acceptable.

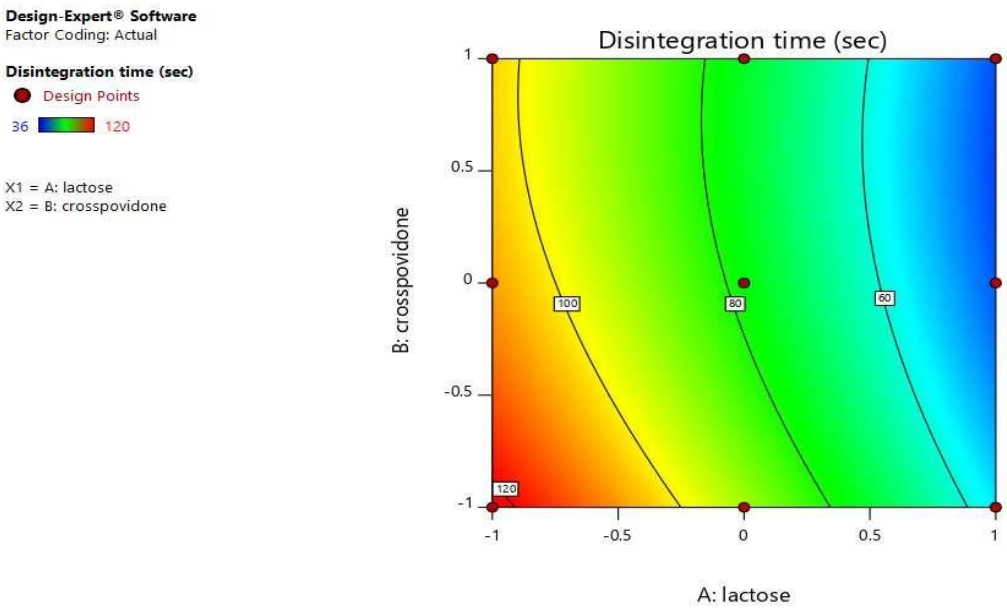



**Figure 15 Counter plot of disintegration time**

fi

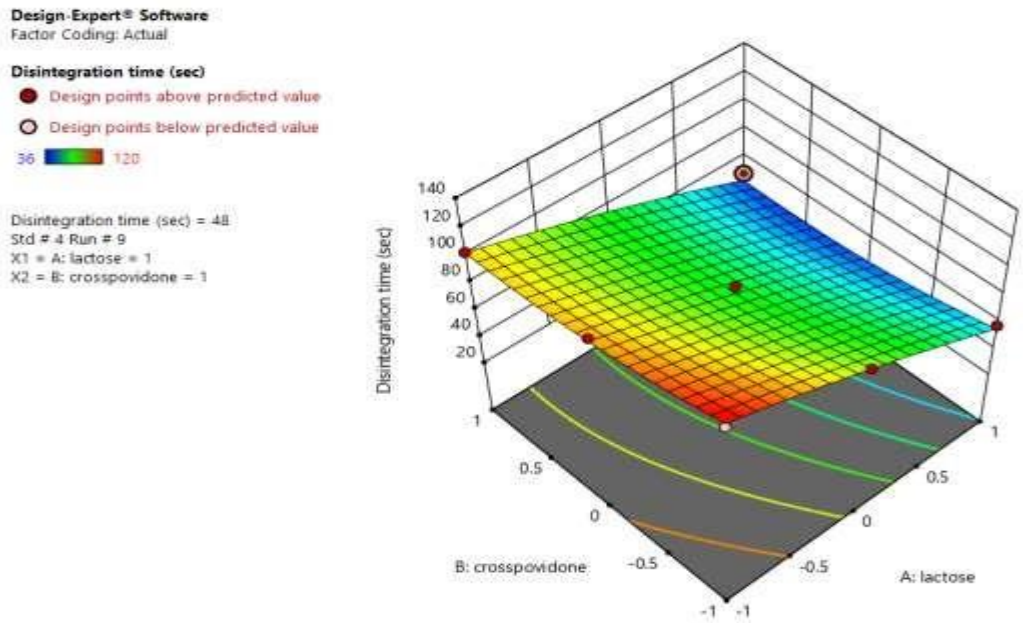



**Figure 16 Surface Plot of Disintegration Time**

## ANOVA for Quadratic model

## Response 2: %drug release

**Table 31 ANOVA data of response 2 for immediate release layer**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 430.03 | 5 | 86.01 | 9.36 | 0.0475 | Significant |
| A-lactose | 270.68 | 1 | 270.68 | 29.45 | 0.0123 | |
| B-crosspovidone | 142.11 | 1 | 142.11 | 15.46 | 0.0293 | |
| AB | 3.24 | 1 | 3.24 | 0.3525 | 0.5945 | |
| $A^2$ | 2.80 | 1 | 2.80 | 0.3047 | 0.6194 | |
| $B^2$ | 11.20 | 1 | 11.20 | 1.22 | 0.3502 | |
| **Residual** | 27.58 | 3 | 9.19 | | | |
| **Cor Total** | 457.61 | 8 | | | | |

Factor coding is **coded**.

Sum of squares is **Type III – Partial** The **Model F-value** of 9.36 implies the model is significant. There is only a 4.75% chance that an F-value this large could occur due tonoise.

**P-values** less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are notsignificant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

### Coefficients in Terms of Coded Factors

**Table 32 Coefficient data of response 2 for immediate release layer**

| Factor | Coefficient Estimate | df | Standard Error | 95% CI Low | 95% CI High | VIF |
|---|---|---|---|---|---|---|
| Intercept | 87.28 | 1 | 2.26 | 80.09 | 94.47 | |
| A-lactose | 6.72 | 1 | 1.24 | 2.78 | 10.66 | 1.0000 |
| B-crosspovidone | 4.87 | 1 | 1.24 | 0.9275 | 8.81 | 1.0000 |

| | | | | | | |
|---|---|---|---|---|---|---|
| AB | -0.9000 | 1 | 1.52 | -5.72 | 3.92 | 1.0000 |
| $A^2$ | 1.18 | 1 | 2.14 | -5.64 | 8.01 | 1.0000 |
| $B^2$ | -2.37 | 1 | 2.14 | -9.19 | 4.46 | 1.0000 |

**Polynomial Equation**

$$Y2 = 87.82 + 6.72X_1 + 4.87X_2 - 0.9000X_{12} + 1.18X1^2 - 2.37X2^2$$

The coefficient estimate, assuming that all other factors remain constant, shows the anticipated change in response for each unit change in factor value. In an orthogonal design, the intercept represents the mean response of all the runs combined. The factor settings' adjustments around that average are represented by the coefficients. VIFs of one indicate orthogonality; those of larger than one suggest multi-colinearity; the higher the VIF, the more severe the factor correlation. VIFs under 10 are generally considered tolerable.

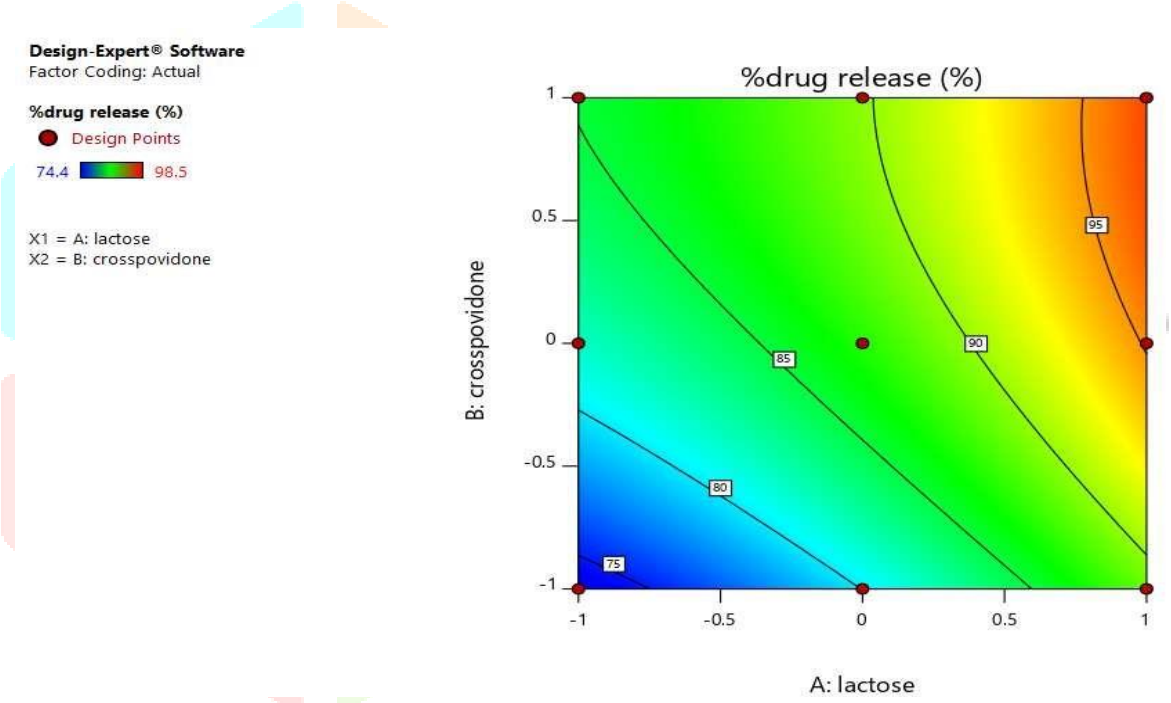



**Figure 17 Counter plot of % drug release**

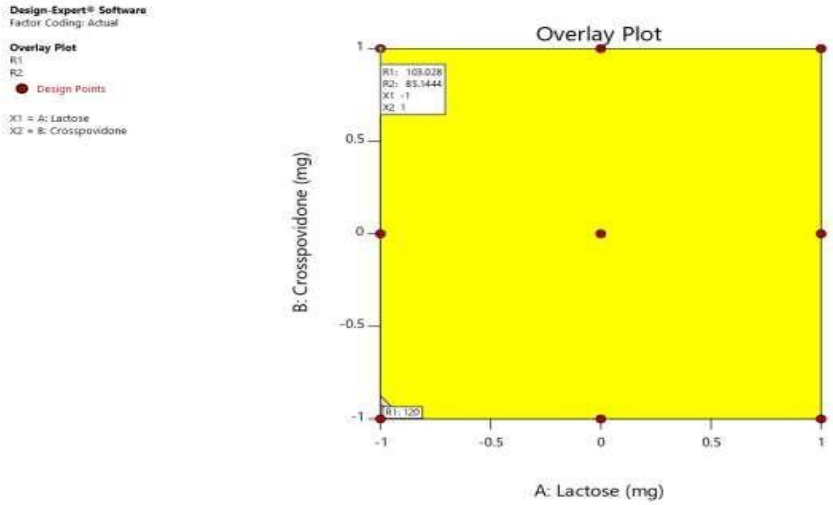



**Figure 20 Check point batch for immediate releas**

## Analysis of factorial design for sustained release

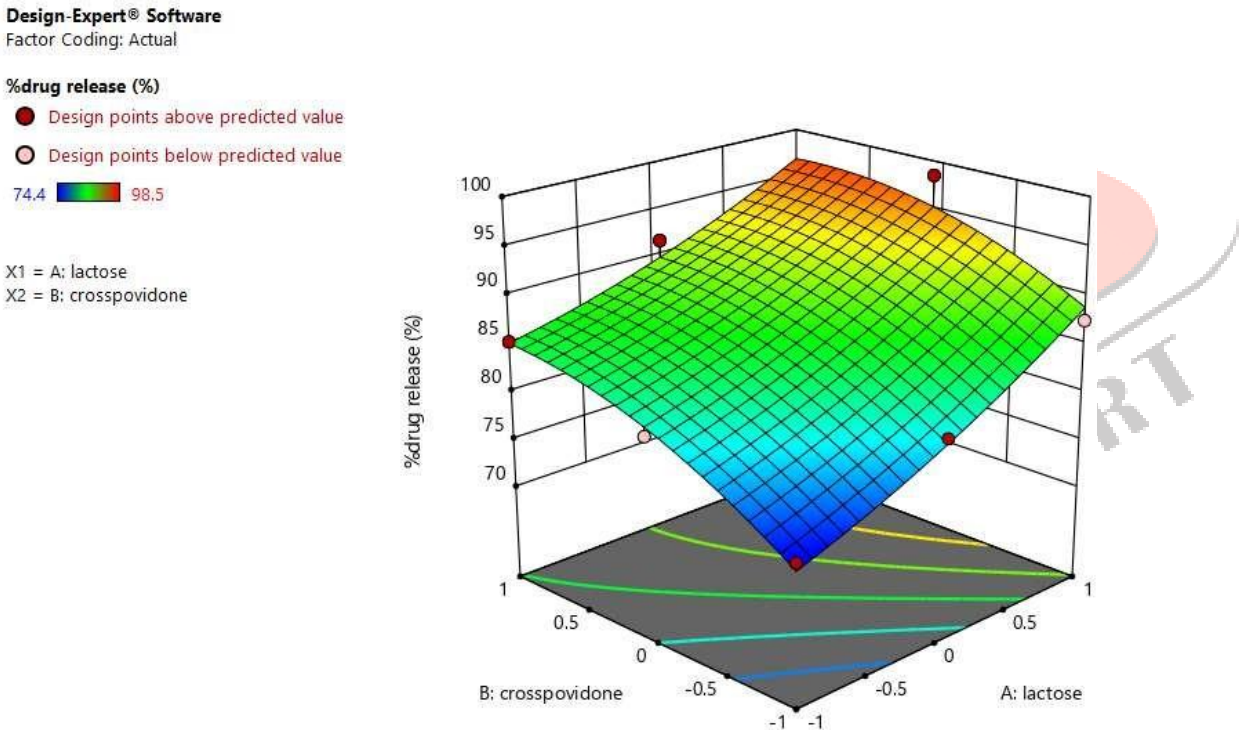



**Figure 18 surface plot of % drug release**

Utilizing data fitting in design expert software, the design is analyzed.

**Table 33 Factorial design analysis table of sustained release**

| Batch | PVP K 30 (%) | Kolloidon SR (%) | Hardness ($kg/cm^2$) | % drug release At 1 hour |
|---|---|---|---|---|
| FSR1 | 2 | 8 | 5.5 | 39.3 |
| FSR2 | 2 | 10 | 5.7 | 34.5 |
| FSR3 | 2 | 12 | 5.8 | 30.7 |
| FSR4 | 2.5 | 8 | 5.5 | 33.8 |
| FSR5 | 2.5 | 10 | 5.9 | 29.1 |
| FSR6 | 2.5 | 12 | 6.0 | 24.6 |
| FSR7 | 3 | 8 | 5.9 | 30.5 |
| FSR8 | 3 | 10 | 6.0 | 25.7 |
| FSR9 | 3 | 12 | 6.3 | 19.6 |

**ANOVA for Quadratic model**
**Response 1: Hardness**

**Table 34 ANOVA model of response 1 for sustained release**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 2.07 | 5 | 0.4132 | 68.70 | 0.0027 | significant |
| A-PVP K 30 | 1.82 | 1 | 1.82 | 301.75 | 0.0004 | |
| B-Kolloidon SR | 0.0241 | 1 | 0.0241 | 4.00 | 0.1393 | |
| AB | 0.0484 | 1 | 0.0484 | 8.05 | 0.0658 | |
| $A^2$ | 0.0601 | 1 | 0.0601 | 9.99 | 0.0508 | |
| $B^2$ | 0.1184 | 1 | 0.1184 | 19.69 | 0.0213 | |
| **Residual** | 0.0180 | 3 | 0.0060 | | | |
| **Cor Total** | 2.08 | 8 | | | | |

Factor coding is **coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 68.70 implies the model is significant. There is only a 0.27%chance that an F-value this large could occur due to noise.

**P-values** less than 0.0500 indicate model terms are significant. In this case A, $B^2$ are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those requiredto support hierarchy), model reduction may improve your model.

**Fit Statistics**

| | | | |
|---|---|---|---|
| **Std. Dev.** | 0.0776 | **$R^2$** | 0.9913 |
| **Mean** | 5.06 | **Adjusted $R^2$** | 0.9769 |
| **C.V. %** | 1.53 | **Predicted $R^2$** | 0.9018 |
| | | **Adeq Precision** | 23.9511 |

The **Predicted R²** of 0.9018 is in reasonable agreement with the **Adjusted R²** of 0.9769; i.e. the difference is less than 0.2.

Adeq Precision calculates the ratio of signal to noise. Ideally, the ratio should be higher than 4. With a ratio of 23.951, you have a sufficient signal. The design space can be navigated using this concept..

**Coefficients in Terms of Coded Factors**

**Table 35 Coefficient data of response 1 for sustained release**

| Factor | Coefficient Estimate | Df | Standard Error | 95% CI Low | 95% CI High | VIF |
|---|---|---|---|---|---|---|
| Intercept | 5.34 | 1 | 0.0578 | 5.16 | 5.53 | |
| A-PVP K 30 | 0.5500 | 1 | 0.0317 | 0.4492 | 0.6508 | 1.0000 |
| B-Kolloidon SR | 0.0633 | 1 | 0.0317 | -0.0374 | 0.1641 | 1.0000 |
| AB | -0.1100 | 1 | 0.0388 | -0.2334 | 0.0134 | 1.0000 |
| $A^2$ | -0.1733 | 1 | 0.0548 | -0.3479 | 0.0012 | 1.0000 |
| $B^2$ | -0.2433 | 1 | 0.0548 | -0.4179 | -0.0688 | 1.0000 |

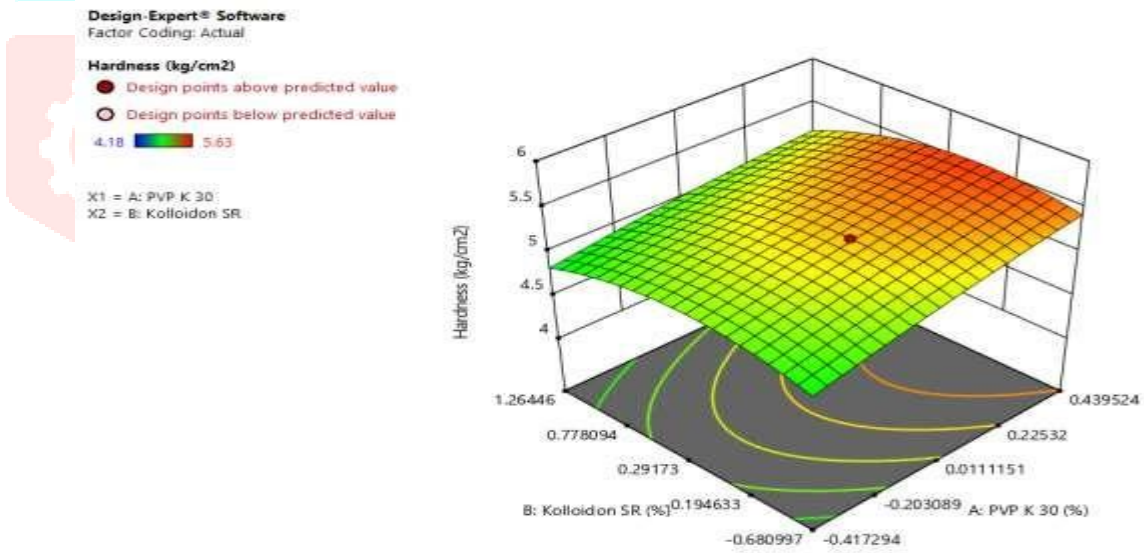



**Figure 21 Surface plot of Hardness**

**Polynomial Equation**

$$Y1 = 5.34 + 0.550X1 + 0.0633X2 - 0.1100X12 - 0.1733X1^2 - 0.2433X2^2$$

When all other factors are maintained constant, the coefficient estimate shows the expected change in response for each unit change in factor value. The total average response of all the runs is the intercept in an orthogonal design. Based on the factor parameters, the coefficients are adjustments around that average. VIFs are 1 when the factors are orthogonal; VIFs larger than 1 denote multi-colinearity; the higher

the VIF, the more severe the factor correlation. VIFs of fewer than 10 are generally acceptable.

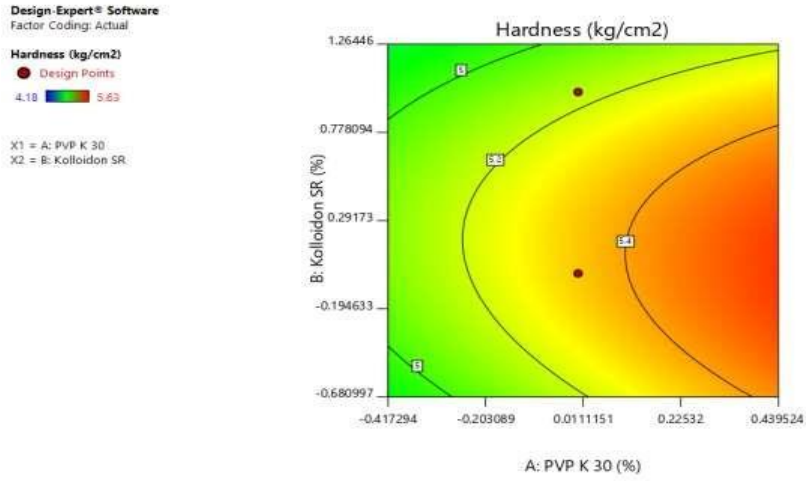



**Figure 20-1 Counter plot of Hardness**

**ANOVA for Quadratic model**

**Response 2: % drug release**

**Table 36 ANOVA model of response 2 for sustained release**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 211.79 | 5 | 42.36 | 67.12 | 0.0028 | Significant |
| A-PVP K 30 | 139.20 | 1 | 139.20 | 220.57 | 0.0007 | |
| B-Kolloidon SR | 39.01 | 1 | 39.01 | 61.82 | 0.0043 | |
| AB | 0.3600 | 1 | 0.3600 | 0.5704 | 0.5050 | |
| $A^2$ | 32.81 | 1 | 32.81 | 51.98 | 0.0055 | |
| $B^2$ | 0.4050 | 1 | 0.4050 | 0.6417 | 0.4817 | |
| **Residual** | 1.89 | 3 | 0.6311 | | | |
| **Cor Total** | 213.68 | 8 | | | | |

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 67.12 implies the model is significant. There is only a 0.28%chance that an F-value this large could occur due to noise.

**P-values** less than 0.0500 indicate model terms are significant. In this case A, B, $A^2$are significant model terms. Values greater than 0.1000 indicate the model terms arenot significant. If there are many insignificant model terms (not counting those re- quired to support hierarchy), model reduction may improve your model.

**Fit Statistics**

| | | | |
|---|---|---|---|
| **Std. Dev.** | 0.7944 | **$R^2$** | 0.9911 |
| **Mean** | 94.47 | **Adjusted $R^2$** | 0.9764 |
| **C.V. %** | 0.8410 | **Predicted $R^2$** | 0.8955 |
| | | **Adeq Precision** | 22.7140 |

The **Predicted $R^2$** of 0.8955 is in reasonable agreement with the **Adjusted $R^2$** of0.9764; i.e. the difference is less than 0.2.

**Adeq Precision** measures the signal to noise ratio. A ratio greater than 4 is desirable.Your ratio of 22.714 indicates an adequate signal. This model can be used to navigatethe design space.

**Coefficients in Terms of Coded Factors**

**Table 37 Coefficient data of response 2 for sustained release**

| Factor | Coefficient Estimate | Df | Standard Error | 95% CI Low | 95% CI High | VIF |
|---|---|---|---|---|---|---|
| Intercept | 97.47 | 1 | 0.5921 | 95.58 | 99.35 | |
| A-PVP K 30 | -4.82 | 1 | 0.3243 | -5.85 | -3.78 | 1.0000 |
| B-Kolloidon SR | -2.55 | 1 | 0.3243 | -3.58 | -1.52 | 1.0000 |
| AB | -0.3000 | 1 | 0.3972 | -1.56 | 0.9641 | 1.0000 |
| $A^2$ | -4.05 | 1 | 0.5617 | -5.84 | -2.26 | 1.0000 |
| $B^2$ | -0.4500 | 1 | 0.5617 | -2.24 | 1.34 | 1.0000 |

Polynomial Equation

$Y2 = 97.47 – 4.82X_1 – 2.55X_2 – 0.3000X_{12}$ $-4.05X1^2 – 0.4500X2^2$

The estimated coefficient of determination shows the anticipated shift in response for each unit change in factor value, assuming that all other factors remain constant. The average reaction over all runs in an orthogonal design is called the intercept. The factor settings determine how the coefficients are adjusted around that average. Orthogonal factors have VIFs of 1, while multi-colinearity is indicated by VIFs more than.1. The more severe the factor correlation, the higher the VIF. Tolerable VIFs are generally less than 10.

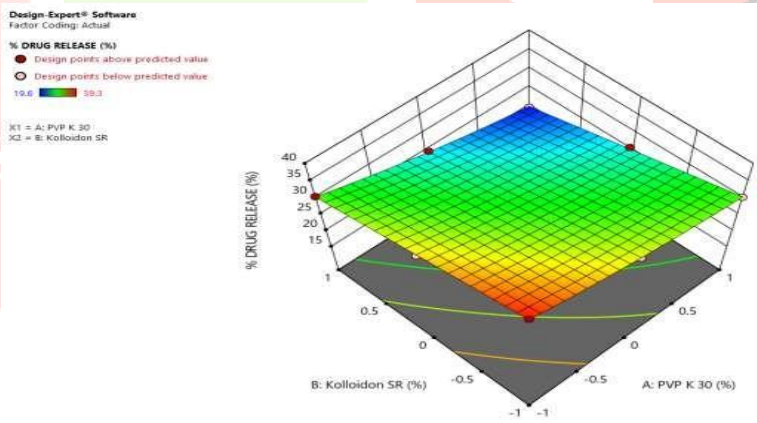


**Figure 23 Surface Plot of drug release**

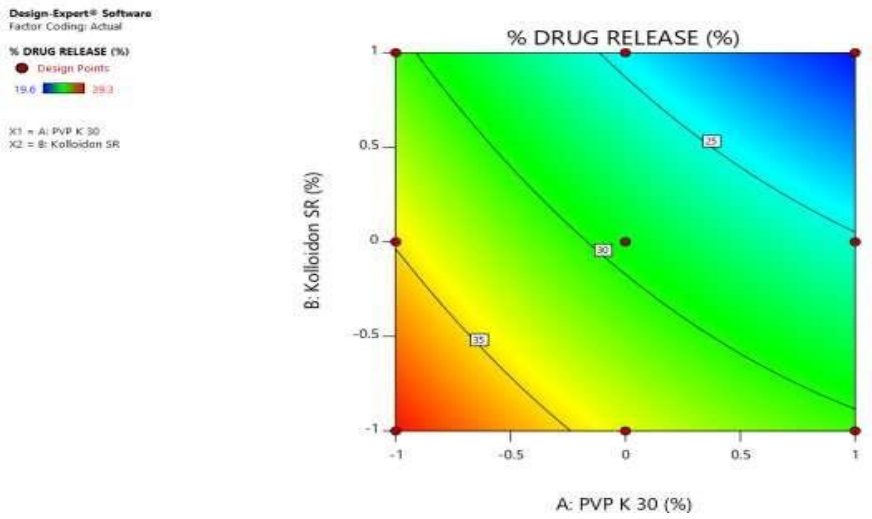



**Figure 24 Counter plot of drug release**

**Validation of Check Point Batch**

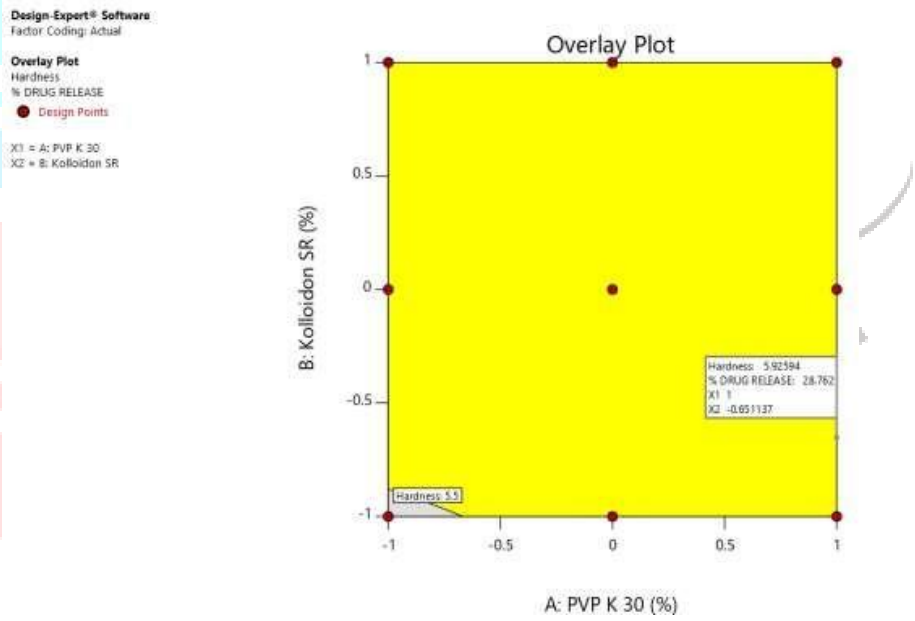



**Figure 25 Check point batch figure for sustained release**

**Table 38 Optomized batch formulation**

| Ingredient | FIR8 | Ingredient | FSR5 |
|---|---|---|---|
| Etoricoxib | 60 | Etodolac | 400 |
| MCC 101 | 38. | MCC 101 | 60 |
| Lactose | 120 | Lactose | 47 |
| Starch | 6 | PVP K 30 | 15 |
| Crosspovidone | 12.5 | Kolloidon SR | 60 |
| Magnesium Stearate | 4 | Magnesium Stearte | 8 |
| Talc | 6 | Talc | 10 |

| | | | |
|---|---|---|---|
| Aerosil | 3 | - | - |

**Table 39 Evaluation parameter of optimized batch**

| Bilayer Tablet | Hardness (kg/cm2) | Friability (%) | Disintegrationtime (sec) | % drug release | Assay (%) |
|---|---|---|---|---|---|
| Etoricoxib | 5.7 | 0.62 | 36 sec | 98.5 | 96.9 |
| Etodolac | | | | 97.2 | 97.5 |

**Table 40 Drug release data of optimized batch**

| Time (min) | % drug release of Etoricoxib | % drug release of Etodolac |
|---|---|---|
| 0 | 0 | 0.00 |
| 5 | 29.32 | 0.53 |
| 10 | 48.75 | 2.36 |
| 15 | 63.41 | 5.42 |
| 20 | 81.96 | 9.26 |
| 25 | 92.47 | 13.35 |
| 30 | 98.55 | 16.23 |
| 60 | - | 29.13 |
| 120 | - | 33.66 |
| 180 | - | 41.92 |
| 240 | - | 48.78 |
| 300 | - | 56.44 |
| 360 | - | 63.82 |
| 420 | - | 69.19 |
| 480 | - | 75.93 |
| 540 | - | 82.28 |
| 600 | - | 88.74 |
| 660 | - | 94.46 |
| 720 | - | 98.62 |

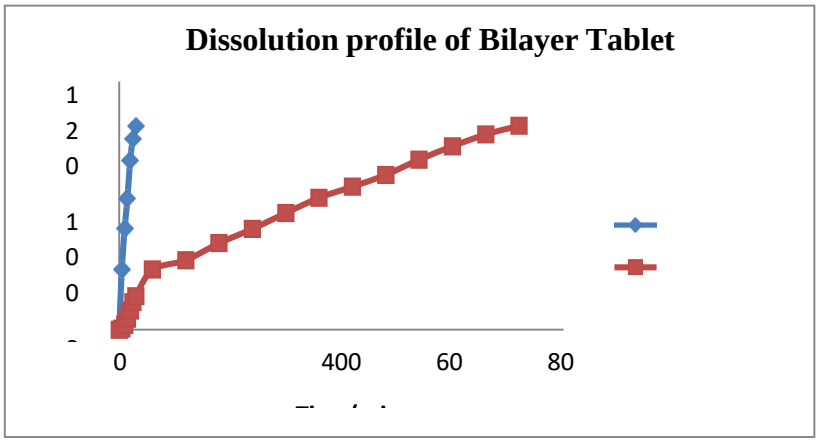
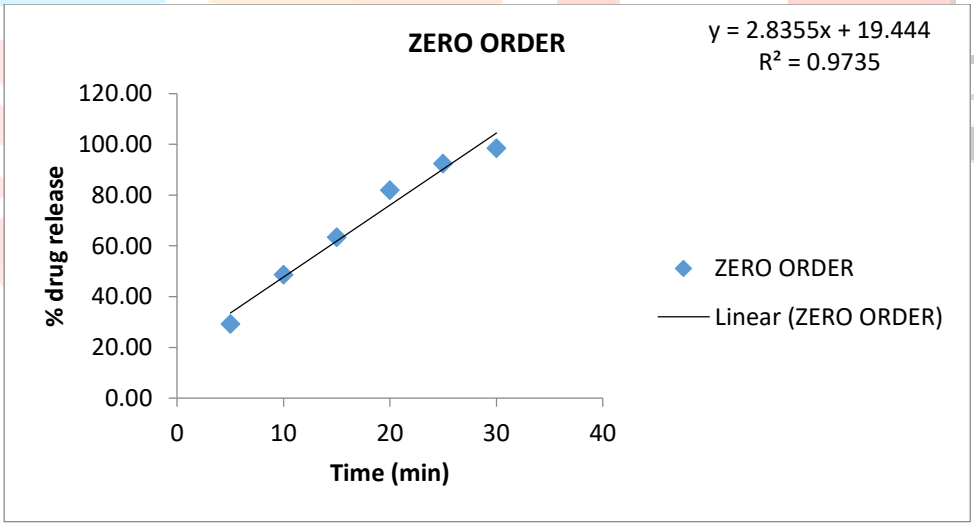



**Figure 26 Drug release profile of bilayer tablet batch**

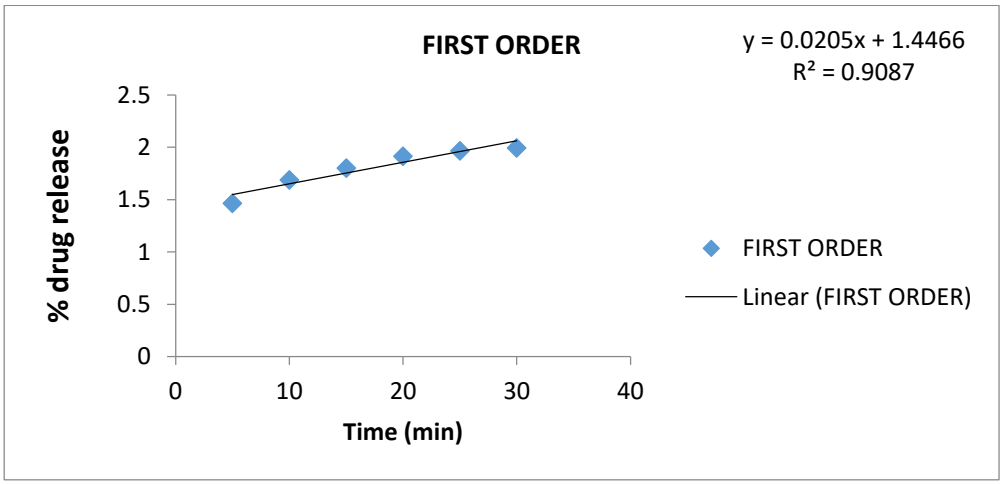
**Table 41 Kinetic release data of bilayer tablet**

| FORMULATIONS | ZERO ORDER | FIRST ORDER | HIGUCHI MODEL | KORS PEPAS |
|---|---|---|---|---|
| **Immediate release** | 0.973 | 0.908 | 0.992 | 0.994 |
| **Sustained release** | 0.997 | 0.978 | 0.996 | 0.997 |

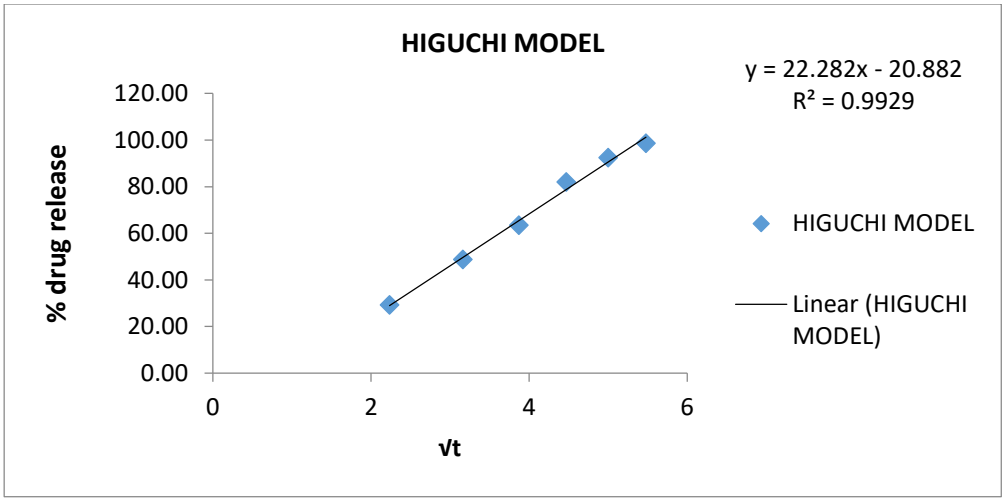
This optimized batch was selected and evaluated. The Prepared tablet were found satisfactory in physical as well as chemical evaluation. The tablet have uniform drug distribution hence drug content was found satisfactory. Diintegration time also found in acceptable limit. Drug release profile of immediate at 30 min found 98.5%. and in sustained release at 12 hours found 97.2%. Finally optimized batch was located for stability for 1 month.



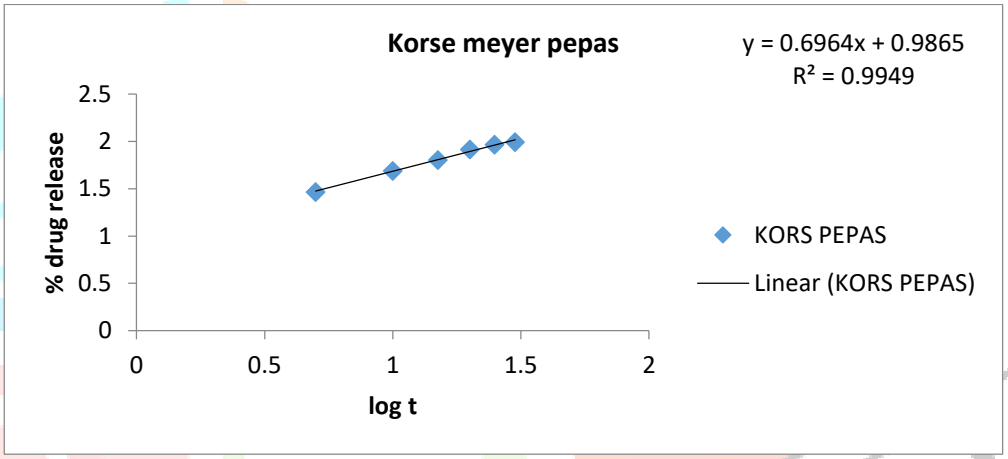

**[A]**



[B]

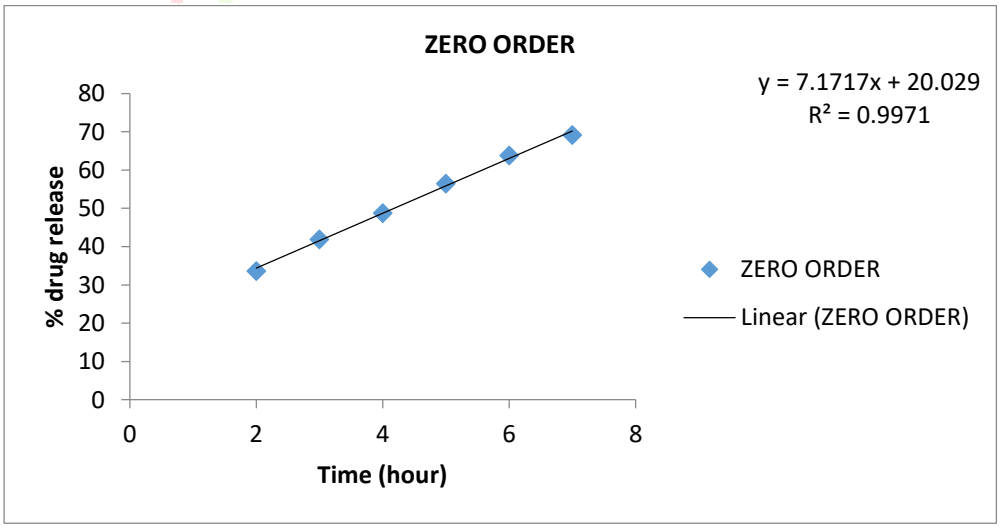



[C]

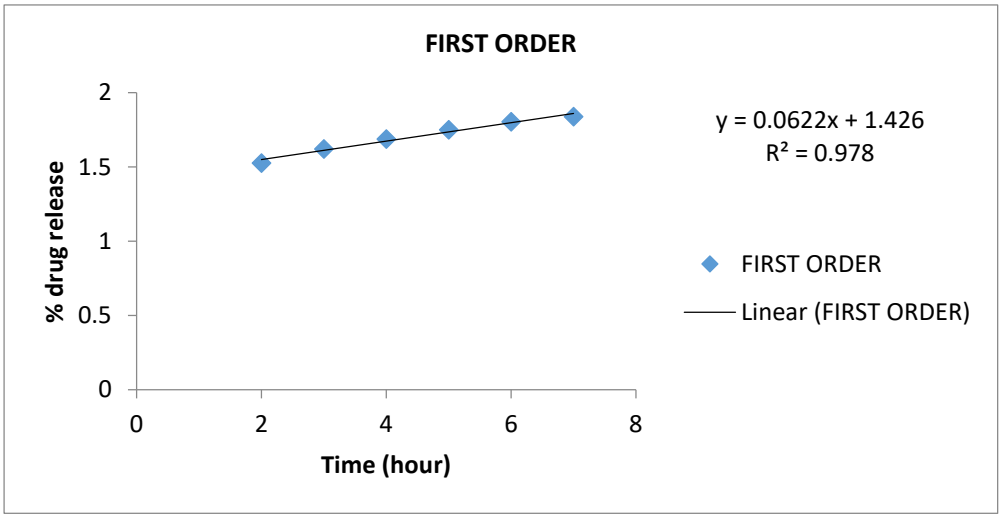



[D]

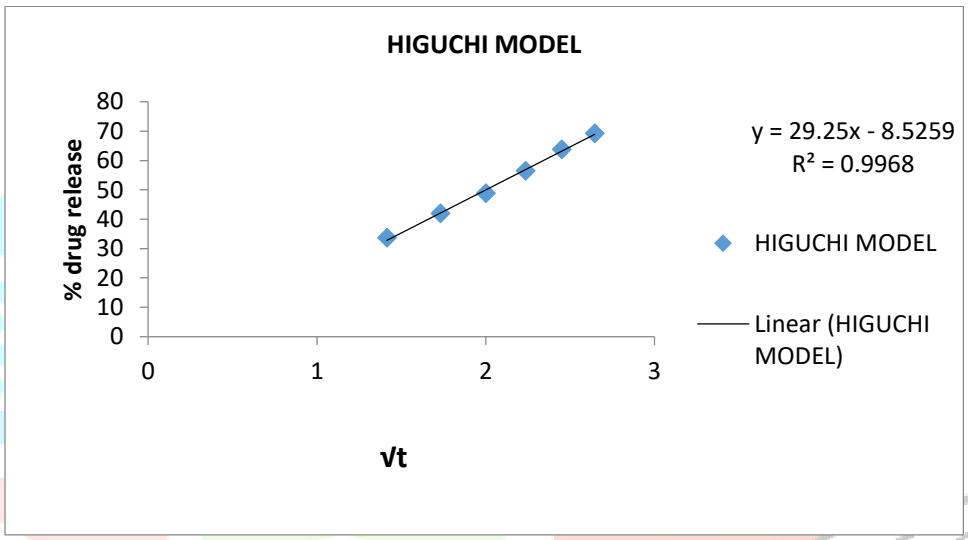
**Figure 27 Kinetic release of optimized batch of immediate release [A] Zero order [B] First order [C] Higuchi model [D] Kores meyer pepas model**



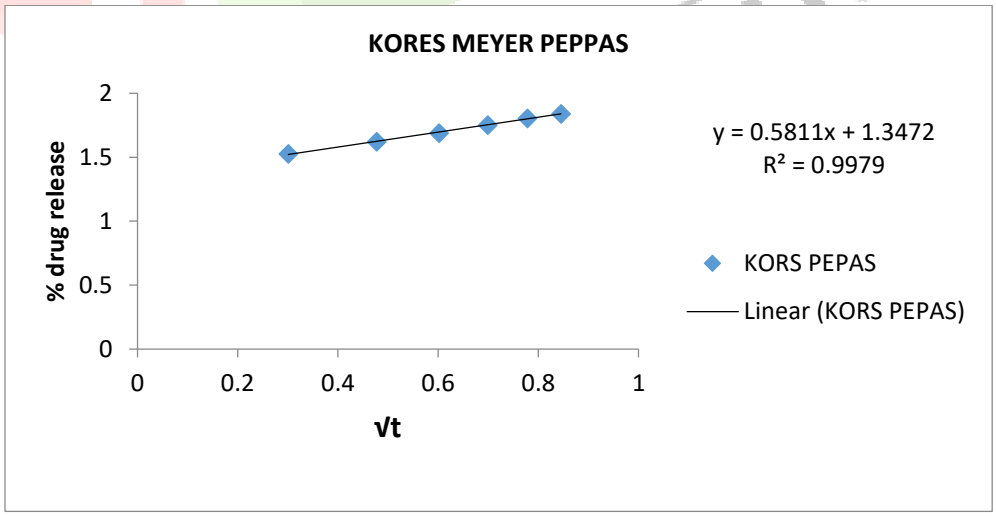

[A]




[B]




[C]




[D]

**Figure 28 Kinetic release of optimized batch of sustained release [A] Zero order [B] First order [C] Higuchi model [D] Kores meyer pepas model**

**Stability Study**

The optimized batch, O1, which exhibited superior results compared to other batches, was chosen for stability assessment. The stability study was conducted for one month under conditions of 40°C temperature and 75% relative humidity in a stability chamber. After the one-month duration, samples were withdrawn for analysis. The results indicated no alteration in the in-vitro drug release profile after 12 hours. Furthermore, the stability study demonstrated that the percentage drug content remained within the acceptable range. Additionally, there were no observable changes in the outer appearance of the tablets.

**Table 42 Results of stability study of batch**

| Parameter | | Initial | After 30 days |
|---|---|---|---|
| **Appearance** | | White to off white tablet | White to off white tablet |
| **Disintegration Time (sec)** | | 36 | 40 |
| **Hardness (kg/cm$^2$)** | | 5.7 | 5.6 |
| **Drug content** | **Etoricoxib** | 96.9 | 96.5 |
| | **Etodolac** | 97.6 | 97.5 |
| **% drug release** | **Etoricoxib** | 98.5 | 98.0 |
| | **Etodolac** | 97.2 | 96.9 |

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