IJBPAS, July, 2026, 15(7): 3128-3148

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

PASTILLATION -DRIVEN SOLUBILITY ENHANCEMENT OF RAMIPRIL: A NOVEL STRATEGY TO IMPROVE BIOAVAILABILITY AND MINIMIZE HYPERTENSIVE DRUG LOAD

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Received 10th June 2025; Revised 15th July 2025; Accepted 4th Oct. 2025; Available online 1st July 2026

https://doi.org/10.31032/IJBPAS/2026/15.7.10299

ABSTRACT

The primary objective of this study was to enhance the solubility of Ramipril using the pastillation technique. Improving the solubility of Ramipril is crucial for increasing its bioavailability and therapeutic efficacy. The study aimed to formulate and evaluate the pastilles of Ramipril and compare their solubility and dissolution profiles with that of the pure drug and marketed formulations. The pastillation technique was employed to enhance the solubility of Ramipril. Various batches of pastilles were prepared using different concentrations of excipients. The drug and excipient mixtures were heated, melted, and then cooled to form pastilles. PEG 6000 and gelucire 50/13 use as polymer for preparation of pastilles. The prepared pastilles were evaluated for their physicochemical properties, including solubility, drug content, and dissolution rate. Techniques such as Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and Scanning Electron Microscopy (SEM) were used to characterize the

pastilles and study the drug-excipient interactions. The study demonstrated that the pastillation technique significantly improved the solubility and dissolution rate of Ramipril. The optimized batch of pastilles showed a higher solubility and faster drug release compared to the pure drug and marketed formulations. FTIR, DSC, and SEM analyses confirmed the formation of a stable drug-excipient complex with no significant interactions that could affect the drug's stability. The drug release from the optimized pastilles followed a zero-order kinetics model, indicating a controlled and sustained release profile. The pastillation technique is an effective method for enhancing the solubility of Ramipril. The formulated pastilles showed improved solubility, higher drug content, and a better dissolution profile compared to the pure drug and marketed formulations. This technique can be potentially applied to other poorly soluble drugs to enhance their bioavailability and therapeutic efficacy.

Keywords: Bioavailability, Drug Release, DSC, FTIR, Pastillation Technique, Ramipril, SEM, Solubility Enhancement, Zero-order Kinetics

INTRODUCTION:

Oral administration is the most convenient and commonly employed root of drug delivery due to ease of administration, high patient compliance, cost effectiveness and flexibility of design of dosage form. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving pharmacological response. Poorly water-soluble drug often requires high doses in order to reach therapeutic plasma concentration. The poor solubility and low dissolution rate in an aqueous gastrointestinal fluid often cause insufficient bioavailability. Especially for BCS class II drug substance like Ramipril which is having poor aqueous solubility and poor oral bioavailability. The bioavailability can be enhanced by increasing the solubility and dissolution rate of the drug in gastrointestinal fluid. As for BCS class II drug rate limiting step is drug release from and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increase the bioavailability for BCS class II drugs. Pastillation is the process in which the solid dispersion using the drug and the polymer is made. Then this dispersion is placed in the glass syringe and then as the heat is applied by the heating coil then this hot molten mass is allowed to fall drop by drop on the metallic plate with cooling system. The over them the hot droplets solidify and form the pastilles. Pastilles are lipid-based formulation used to increase the solubility,

dissolution rate and bioavailability of BCS class-II drug. Lipid which melts and resolidifies are of good choice in pastillation process. These are the solid discrete unit made by pastillation process. Drug delivery using lipid-based formulation is emerging dosage form due to versatile structural appearance of lipid excipients this are considered as valuable alternative. The apparatus used for the pastillation is also known as droplet solidification apparatus **[1, 2]**.

MATERIAL AND METHOD:

A. Materials

Ramipril was procured from Unnati Pharmaceutical Pvt. Ltd. (India).

Polyethylene Glycol 6000 (PEG 6000) was obtained from Research–Lab Fine Chem Industries, Mumbai, India. Gelucire 50/13 was generously provided by Gattefossé.

B. Methods

Saturation solubility study

1. Ramipril

Saturation solubility was carried out to determine the saturation concentration of Ramipril in water. This study was conducted by the method proposed by Higuchi and Conors. Excess quantity (200mg) of drug was taken in screw capped tubes with fixed volume (20 ml) of deionized water. It was shaken at 100 rpm at 37 °C for 48hrs on orbital shaker for equilibrium. After 48 hrs, the samples were withdrawn and filtered through 0.22µm membrane filter. The filtrate was suitably diluted and analysed at 210 nm by using UV spectrophotometer **[3]**.

2. Physical mixture

Saturation solubility of drug with polymer mixture was done to select the polymer for pastillation. Mixture of drug and polymer showing highest solubility was selected for the preparation of pastilles. Excess quantity of physical mixture of drug and solubilizer in 1:1 ratio was taken in screw capped tubes with fixed volume (20 ml) of deionized water. It was shaken at 100 rpm at 37 0C for 48hrs on orbital shaker for equilibrium. After 48 hrs, the samples were withdrawn and filtered through 0.22µm membrane filter. The filtrate was suitably diluted and analyzed at 281 nm by using UV spectrophotometer **[3]**.

3. Preparation Method:

The formulation of Ramipril pastilles using the pastillation technique involves the following sequential steps:

a) **Preparation of Physical Mixture:** Ramipril, Polyethylene Glycol 6000 (PEG 6000), and Gelucire 50/13 are accurately weighed and mixed to form a homogeneous physical mixture. This mixture is then loaded into a pre-heated metallic syringe.

b) **Formation of Uniform Solid Dispersion:**
The metallic syringe is gently heated, allowing the components to melt and form a uniform molten mixture or solid dispersion. This ensures even distribution of the drug in the carrier system.

c) **Dispensing the Melt:**
Once a consistent melt is achieved, droplets are extruded from the syringe through its orifice. These droplets are carefully dropped onto a cooling surface.

d) **Solidification of Droplets:**
The hot droplets are allowed to cool and solidify on an ice plate or a cooled surface, which results in the formation of spherical or uniform-sized pastilles.

e) **Collection of Pastilles:**
The solidified pastilles are collected from the cooling surface for further evaluation and storage **[4]**.

4. Evaluation of pastilles: -

1) Solubility study

The solubility of Ramipril was assessed in various solvents, including distilled water, methanol and phosphate buffer pH 6.8 solutions. A saturated solution was prepared by adding an excess amount of Ramipril at room temperature. The vials containing the solution were then placed in an orbital shaker for 24 hours at 37°C. After reaching complete equilibration, the supernatant was carefully collected and filtered through a 0.45 μm membrane filter. The concentration of Ramipril in the filtered solution was determined using a UV-visible spectrophotometer **[5]**.

2) Compatibility study of drug with polymer:

FTIR Spectroscopy:

The FT-IR analysis is crucial for identifying the functional groups within the molecule's structure. To determine the drugs, FT-IR studies were conducted, allowing for the identification of functional groups present in the sample's structure. Samples of both the drug and drug-polymer mixture in (1:1) ratio were stored in amber-colored vials, sealed, and kept under 37°C conditions for 28 days. Subsequently, these samples were examined for any changes in the IR spectrum. Any variations observed compared to the initial spectrum could indicate interactions between the materials or degradation due to temperature fluctuations **[6]**.

3) UV- Spectroscopy:

I. Determination of maximum absorbance (λmax) of by Ramipril using Phosphate buffer PH 6.8:

a. Preparation of Ramipril stock solution:

Stock solution was prepared by dissolving 10 mg Ramipril in 100 ml of volumetric flask using Phosphate buffer PH 6.8 to get stock solution of 100 µg/ml.

b. Determination of maximum absorbance of drug:

1ml stock solution (100 µg/ml) was pipetted out in 10 ml volumetric flask and make upthe volume by using Phosphate buffer PH 6.8 The UV spectra was scanned in between 200-400 nm. The λ max was recorded at 211 nm and it act as an analytical wavelength throughout the study.

c. Calibration curve of Ramipril:

From stock solution 2, 4, 6, 8 and 10 ml aliquots withdrawn and again diluted to 10 ml with Phosphate buffer PH 6.8. The absorbance was recorded at 211 nm using double beam UV- visible spectrophotometer.

II. Determination of maximum absorbance (λ max) of Ramipril in Methanol

a. Preparation of stock solution: -

Stock solution was prepared by dissolving 10 mg Ramipril in 100 ml of volumetric flask using methanol to get stock solution of 100 µg/ml.

b. Determination of maximum absorbance of drug: -

1 ml standard solution (100 µg/ml) was pipetted out in 10 ml volumetric flask and makeup the volume by using methanol. The UV spectra was scanned in between 200-400 nm. The λ max was recorded at 210 nm and it act as an analytical wavelength throughout the study.

c. Calibration curve in methanol: -

Aliquots of 1, 2, 4, 6, 8 and 10 ml were taken from the stock solution and each was diluted to 10 ml with methanol. The absorbance of these solutions was measured at 210 nm using a double-beam UV-visible spectrophotometer **[7]**.

1) Differential Scanning Calorimetric:

Differential scanning calorimetry (DSC) analyses were carried out on pure Ramipril, pure polymer, and pastilles containing the drug and polymer to understand the changes that occurred during pastille formation and to elucidate the phenomenon enhancing drug solubility. DSC studies were conducted using a DSC-60 Plus (SHIMADZU). After calibration with Indium and lead standards, samples weighing 3-5 mg were heated (in the range of 30-400°C, at a rate of 10°C/min) in crimped aluminum pans under a nitrogen atmosphere. The enthalpy of fusion and melting point was automatically calculated **[8]**.

5) **X-Ray Diffraction Studies**

XRD analyses were conducted on both the pure drug and the optimized pastilles to assess

changes in crystallinity resulting from the drug-polymer mixture. A comprehensive XRD study was performed using Philips analytical X-ray diffractometer (Model: PW3711, The Netherlands) **[9]**.

6) **Scanning electron microscopy (SEM) studies**

SEM studies were carried out on the pastilles that exhibited the most favorable outcomes in solubility and dissolution tests. These studies aimed to confirm any structural changes that occurred during pastille formation. Samples were prepared by mounting pastilles onto a brass stub using graphite glue and then coated with gold under vacuum before analysis. Images were captured at the required magnification, with an acceleration voltage of 10 kV, using a scanning electron microscope (FEI, Netherlands, Quanta 200).

7) **A Practical Yield-**

The percentage yield for various batches was determined by weighing all nine batches of pastilles formed. The calculation formula for percentage yield is expressed as:

% Yield = (Practical yield / Theoretical yield) × 100

Using this formula, the percentage yield for each batch was calculated, and the results are presented in the table below.

8) **Drug Content Analysis:**

To determine the quantity of drug incorporated in the Ramipril Pastilles, the drug was extracted by dissolving them in 100 ml of Phosphate buffer pH 6.8. The resulting solution was filtered through a 0.45µm membrane filter, and 1 ml was diluted into 10 ml of Phosphate buffer pH 6.8. Ramipril drug content was analyzed spectrophotometrically using a UV-Visible spectrophotometer a wavelength of 211 nm, with Phosphate buffer pH 6.8 serving as the blank **[10]**.

% Drug Content = (Wa/Wt) x 100

Where, Wa = Actual concentration of drug

Wt = Theoretical concentration of drug

9) **In Vitro Release Studies:**

The in vitro drug release of pastilles was conducted using a USP dissolution apparatus II (Electro Lab Dissolution Tester ETL11L, India), employing 900 mL of Phosphate buffer PH 6.8 as the dissolution medium. The apparatus operated at 50 rpm and maintained a temperature of 37 ± 0.5°C for 2 hours. At predetermined time intervals, 5 milliliters of aliquots were withdrawn, and sinked conditioned dissolution medium was added to maintain sink conditions. The samples were filtered through a 0.45 µm Whatman filter and analyzed using a UV-spectrophotometer at 211nm. Each experiment was performed in triplicate **[11]**.

10) Optimization Using DOE Software

Factorial design

Factorial design is a method used to simultaneously assess multiple factors in an

experiment. Treatments within factorial designs involve combinations of different levels of the factors being studied. This approach is valuable when exploring the impact of various factors and their interactions on experimental outcomes.

Factor: A factor represents an assigned variable, such as concentration, temperature, lubricating agent, drug treatment, or diet. Factors can be qualitative, indicated by names rather than numerical values, or quantitative, with numerical assignments.

Level: Levels refer to the specific values or designations assigned to each factor. For instance, levels of temperature could include 30ºC and 50ºC, while concentrations might be represented by 0.1 molar and 0.3 molar. In drug treatment studies, levels could be drug and placebo. Factorial experiments comprise all possible combinations of the levels of each factor.

Effect: The effect of a factor refers to the alteration in the response brought about by modifying the level(s) of that factor. For example, this could involve changes in viscosity resulting from adjustments in the concentration of viscosity enhancers **[12]**.

Mathematical and Statistical Analysis:

Table 1: Mathematical and Statistical Analysis

Factor name	Minimum level (mg)	Maximum level (mg)
Gelucire 50/13	350	600
PEG 6000	300	600

A 3^2 factorial design was utilized, focusing on the quantities of Gelucire 50/13 (A) and Polyethylene glycol 6000 (B), with maximum and minimum levels determined from **Table 1** (Maximum and minimum levels of two independent variables). Nine batches were prepared for both components using the factorial approach. ANOVA was conducted to assess the statistical significance of the independent variables and their interaction term. Polynomial equations were then derived to represent the responses. Design Expert (Version 7.0.0) facilitated the statistical and mathematical analyses **[13]**.

Table 2: Design trial batches of pastilles

RUN	Gelucire 50/13 (mg)	PEG 6000 (mg)	Ramipril (mg)
1	475	450	10
2	600	300	10
3	475	300	10
4	475	600	10
5	600	600	10
6	350	450	10
7	600	450	10
8	350	600	10
9	350	300	10

RESULTS AND DISCUSSION

1) Solubility studies

Table 3 presents the solubility data of Ramipril in various solvents. The solubility is measured in mg/ml. Methanol also demonstrates high solubility with a value of 40 mg/ml. Phosphate buffer with a pH of 6.8 shows a lower solubility of 0.10 mg/ml. Distilled water has the least solubility for Ramipril, measured at 0.05 mg/ml. Methanol are the most effective solvents for dissolving Ramipril. In contrast, distilled water is the least effective. This information is crucial for formulation development, particularly in enhancing the drug's bioavailability.

Table 3: Solubility Studies

Sr. No.	Solvents	Solubility (mg/ml)
1	Distilled water	0.05 mg/mL
2	Phosphate Buffer (pH 6.8)	0.10 mg/mL
3	Methanol	40 mg/mL

2) Identification of Drug and Polymer

UV Spectroscopic Analysis.

1. **Determination of λ max of Ramipril in Phosphate buffer pH 6.8**

   A Phosphate buffer pH 6.8 was freshly prepared to dissolve pure Ramipril drug at a concentration of 100µg/ml. Subsequently, the solution was analyzed using a UV-visible spectrophotometer over the wavelength range of 200-400nm.

2. **Standard calibration curve in Methanol**

In Methanol, a standard calibration curve for Ramipril was established. The drug exhibited its maximum absorption at a wavelength of 210 nm. The resulting straight line in Methanol displayed a regression coefficient of 0.9986, indicating excellent linearity within the concentration range of 01-10 µg/ml. The derived equation is = 0.0946x+0.0744

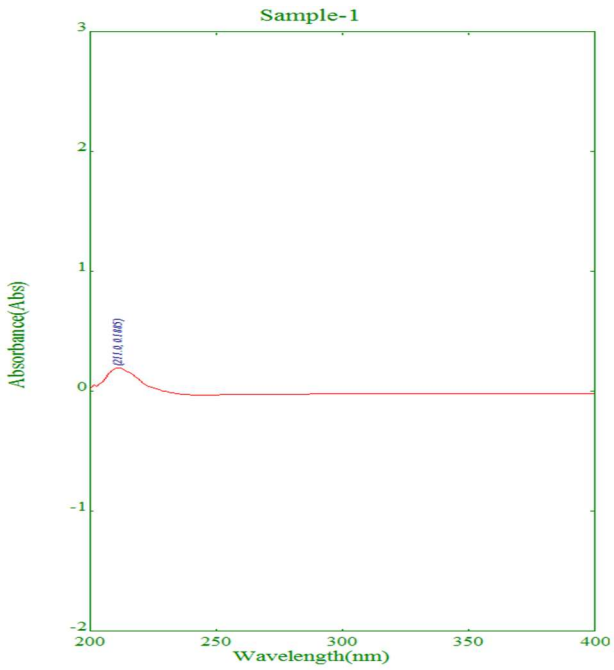

Figure 1: UV Spectra of Ramipril in Methanol

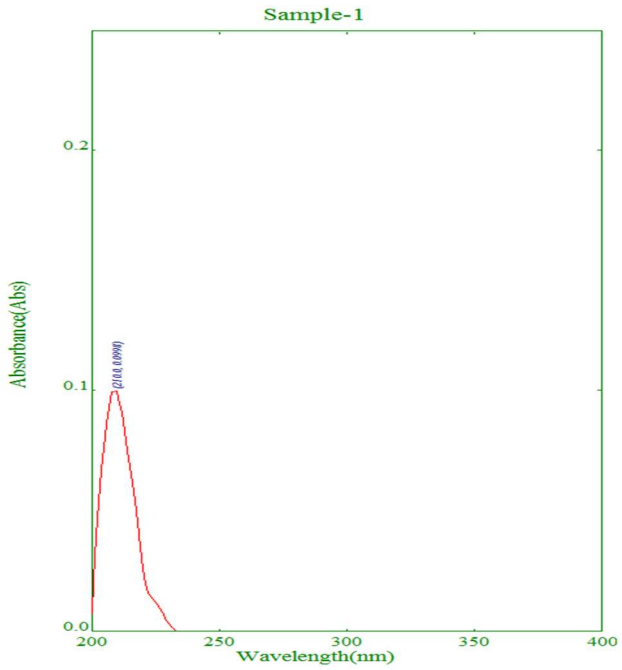

Figure 2: UV Spectra of Ramipril in Phosphate buffer pH 6.8

3) Fourier transforms infrared spectroscopy (FT-IR) analysis

The FT-IR spectra of Ramipril were taken and analyzed between 4000cm^{-1}-400cm^{-}

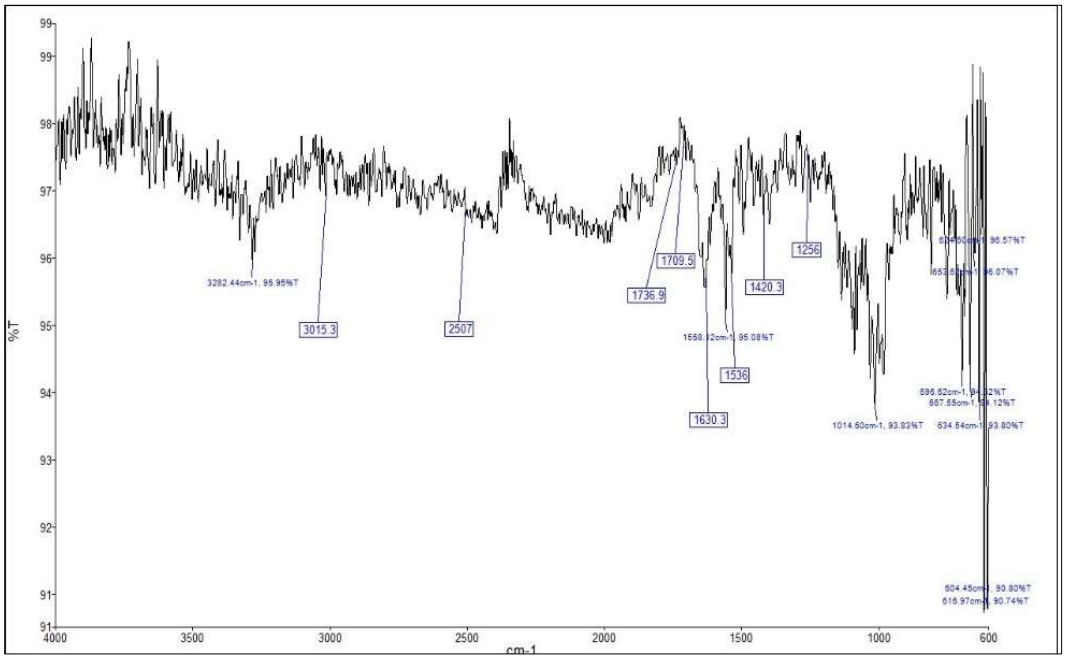

Figure 3: FT-IR of pure Ramipril

Table 4: FT-IR Frequencies for pure Ramipril

Functional groups(Pure Drug)	Observed ranges (cm^{-1})	Standard ranges (cm^{-1})
Amide I Band		
C=O	**1630.3**	**1630-1690**
N-H	**1536**	**1530-1550**
C-N	**1256**	**1200-1300**
Carboxyl group		
C=O	**1709.5**	**1700-1725**
O-H	**3282.44**	**2500-3300**
Aryl group		
C-H	**3015.3**	**3000-3100**
Ester group		
C-O	**1014.60**	**1000-1300**

B) The FT-IR spectra of **Physical Mixture** was taken and analyzed between 4000cm^{-1}-400cm^{-}

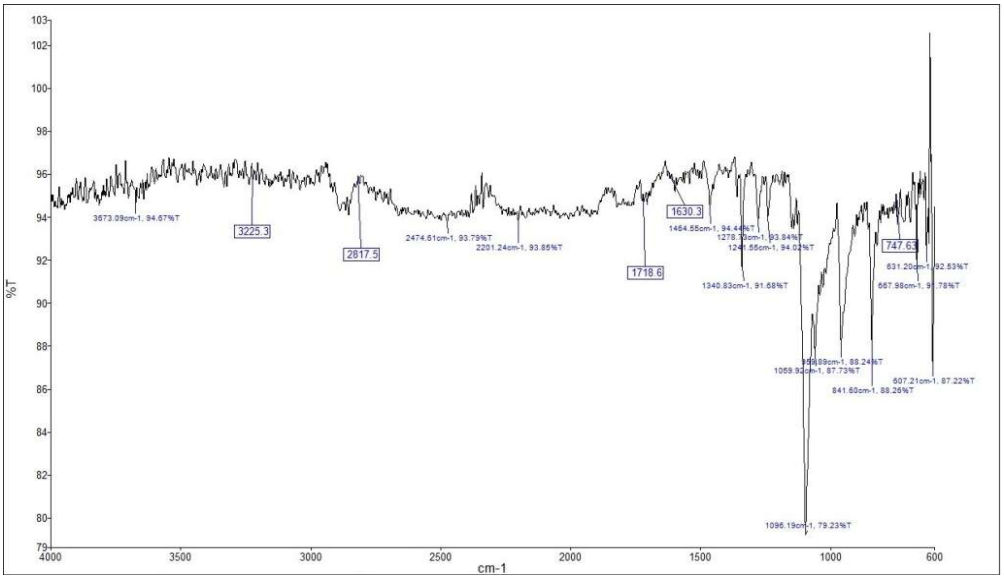

Figure 4: FT-IR spectra of Physical Mixture

Table 5: FT-IR Frequencies for physical mixture

Functional groups (Physical Mixture)	Observed ranges (cm−1)	Standard ranges (cm−1)
Amide		
C-N	**1278.73**	**1200-1300**
Carboxyl group		
C=O	**1718.6**	**1700-1725**
O-H	**2817.5**	**2500-3300**
Aryl group		
C-H	**747.63**	**675-900**
Ester group		
C-O	**1096.19**	**1000-1300**

4) Practical Yield: The percentage yield for various batches was determined by weighing all nine batches of pastilles formed. The calculation formula for percentage yield is expressed as:

% Yield = (Practical yield / Theoretical yield) × 100.

Table 6: Percentage yield

Sr. no.	Batch	Yield%
1.	B1	96.97%
2.	B2	96.82%
3.	B3	95.60%
4.	B4	97.45%
5.	B5	97.80%
6.	B6	97.58%
7.	B7	98.35%
8.	B8	98.07%
9.	B9	96.55%

5) Drug content analysis

Table 7: Drug content values of different batches of pastilles

Sr. no.	Batch	Drug content (%)
1.	B1	97.12
2.	B2	98.03
3.	B3	98.09
4.	B4	97.15
5.	B5	98.93
6.	B6	97.19
7.	B7	98.32
8.	B8	97.40
9.	B9	98.61

The drug content of all the batches shows good results which represent the batches contain efficient amount of drug. The maximum drug content was observed for batch B5 98.93 %

6) In Vitro Drug Release:

Table 8: In vitro dissolution of Ramipril pastilles B1-B9

Time (Min)	B1	B2	B3	B4	B5	B6	B7	B8	B9
0	0	0	0	0	0	0	0	0	0
5	6.02±0.10	6.12±0.33	6.19±0.25	5.73±0.13	7.23±0.14	5.24±0.14	6.55±0.13	7.09±0.12	7.16±0.14
10	10.13±0.12	11.24±0.16	12.22±0.15	11.38±0.19	13.47±0.29	10.02±0.13	11.45±0.19	13.07±0.15	13.22±0.16
15	15.22±0.16	15.12±0.13	15.34±0.18	14.08±0.14	19.03±0.10	14.23±0.12	14.48±0.34	16.78±0.18	17.14±0.12
25	23.28±0.18	24.77±0.19	25.08±0.12	23.11±0.34	27.09±0.11	24.47±0.18	24.66±0.18	26.13±0.27	26.34±0.23
35	37.21±0.12	38.18±0.23	37.22±0.12	37.08±0.23	41.19±0.34	36.88±0.16	38.56±0.15	39.44±0.23	39.88±0.16
45	58.18±0.34	58.25±0.12	58.34±0.23	57.78±0.16	50.34±0.12	57.82±0.14	59.23±0.19	59.54±0.18	50.03±0.14
60	69.23±0.23	69.77±0.34	70.22±0.32	68.67±0.18	72.64±0.12	68.88±0.13	70.45±0.12	71.86±0.34	72.23±0.13
75	77.12±0.16	77.52±0.13	77.67±0.15	76.67±0.32	79.13±0.36	76.73±0.14	78.23±0.13	78.67±0.15	79.02±0.23
90	83.25±0.18	84.05±0.25	84.41±0.16	80.33±0.19	86.19±0.12	83.02±0.12	83.65±0.32	85.37±0.18	85.88±0.13
105	89.18±0.10	90.12±0.32	89.45±0.13	88.32±0.16	90.78±0.23	88.45±0.18	89.64±0.35	89.82±0.12	90.45±0.16
120	96.32±0.13	97.12±0.18	97.32±0.32	96.39±0.12	98.76±0.14	96.55±0.19	97.54±0.13	97.72±0.19	97.84±0.14

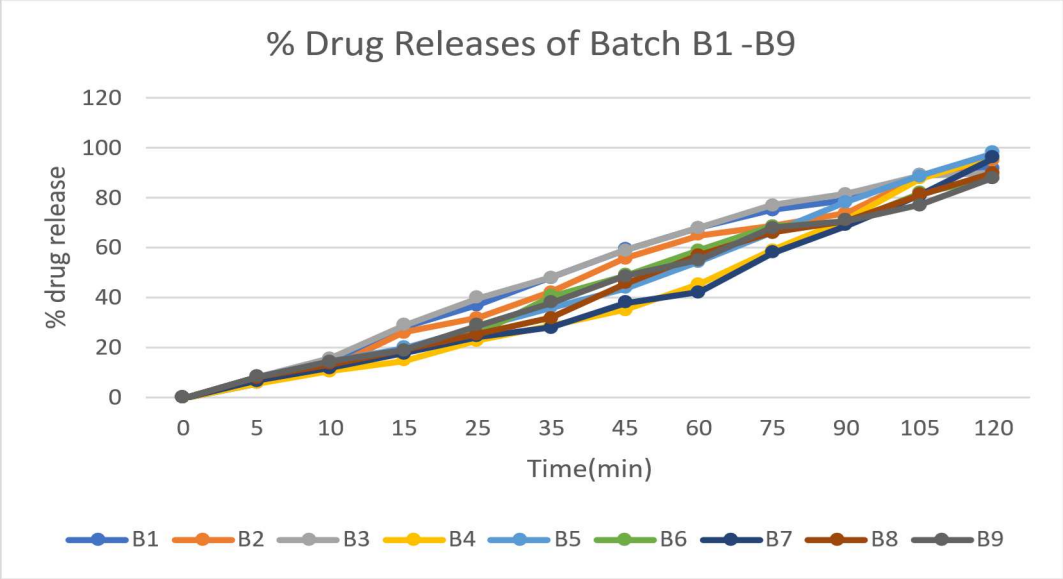

Figure 5: Graphical representation of drug release profile of batches B1-B9

7) Drug Release Kinetic Model

On the basis of *In vitro* release profile, B5 was considered as an optimized and drug release kinetics was performed.

Table 9: Drug Release Kinetic

Time (min)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remainining	log time	log Cumu % drug released
0	0	100	0.000	2.000	0.000	0.000
5	7.23	92.77	2.236	1.967	0.698	0.859
10	13.47	86.53	3.162	1.937	1.000	1.129
15	19.03	80.97	3.873	1.908	1.176	1.279
25	27.09	72.91	50.00	1.862	1.397	1.432
35	41.19	58.81	59.16	1.769	1.544	1.614
45	50.34	49.66	6.708	1.696	1.653	1.701
60	72.64	27.36	7.746	1.437	1.778	1.861
75	79.13	20.87	8.660	1.319	1.875	1.898
90	86.19	13.81	9.487	1.140	1.954	1.935
105	90.78	9.22	10.247	0.964	2.021	1.957
120	98.76	1.24	10.954	0.093	2.079	1.994

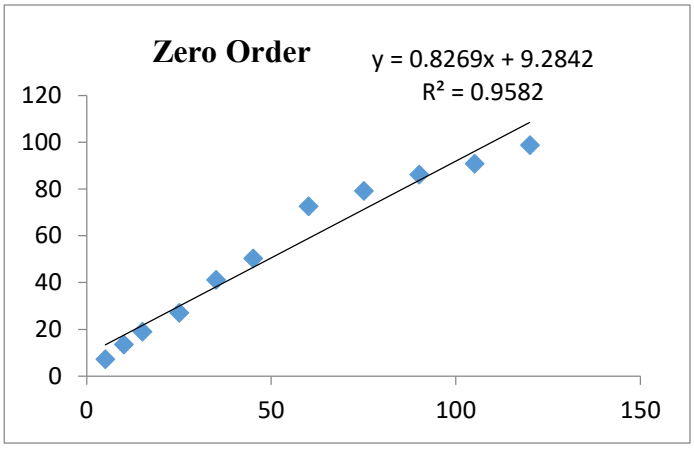

Figure 6: Zero order kinetic plot

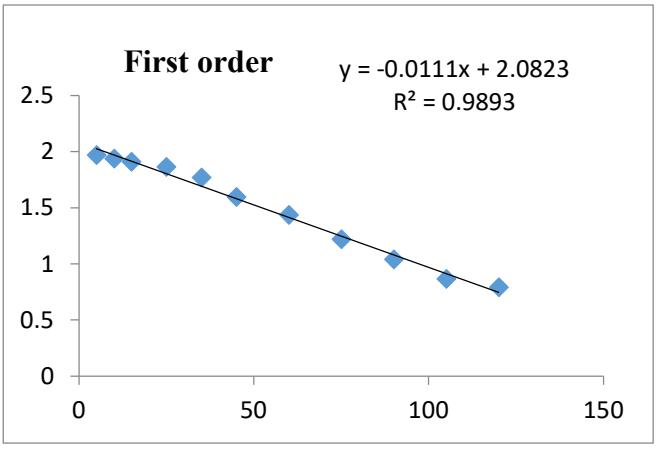

Figure 7: First order plot

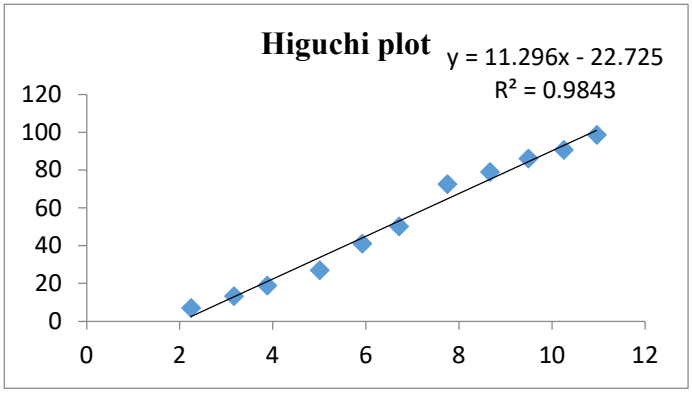

Figure 8: Higuchi plot

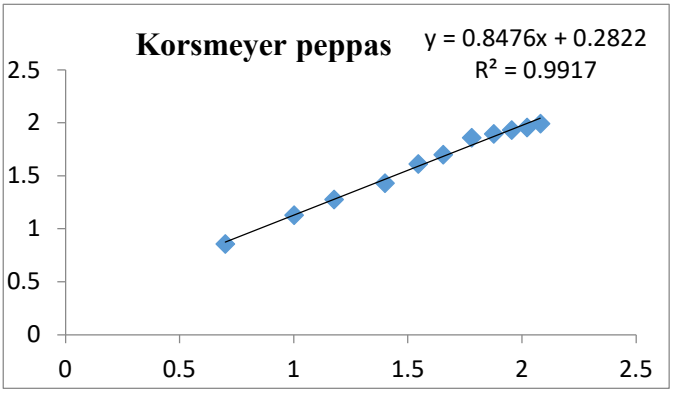

Figure 9: Korsmeyer Peppas plot

Table 10: Model fitting of optimized batch of Ramipril pastilles

Run	Zero order	First order	Higuchi model	Korsmeyers peppas model
R^2	0.9582	0.9893	0.9843	0.9917

- From the R^2 value it was concluded that the drug releases profile of optimizes batch followed zero order kinetics & release pattern respectively. The zero order release kinetics independent on the concentration of drug in the dosage form. In the zero order kinetics profile the drug is released initially and then, the drug is distributed through the body and elimination of the drug occurs following zero order kinetics.

8) Differential Scanning Calorimetry:

DSC thermogram of Ramipril

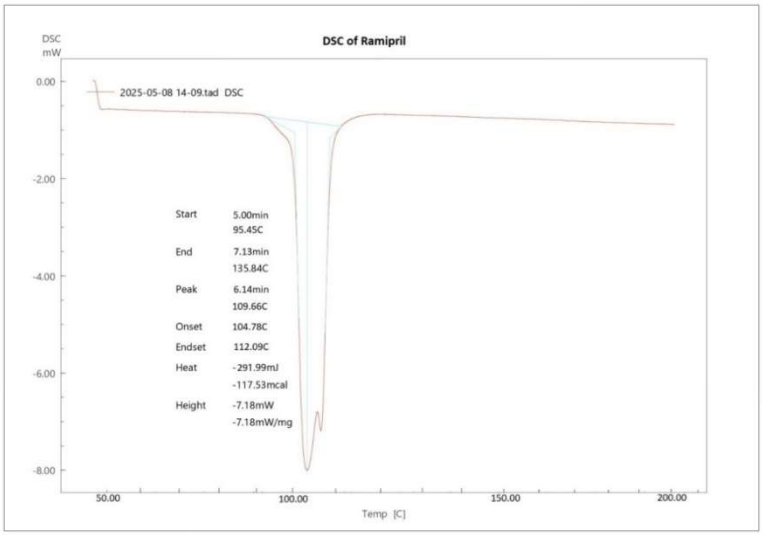

Figure 10: DSC thermo gram of Ramipril

The DSC curve for Ramipril exhibits a sharp peak at 109.66°C, which aligns with the reported melting point, indicating no observed deviation. This consistency suggests that the drug remains in its pure form.

DSC thermo gram of pastilles

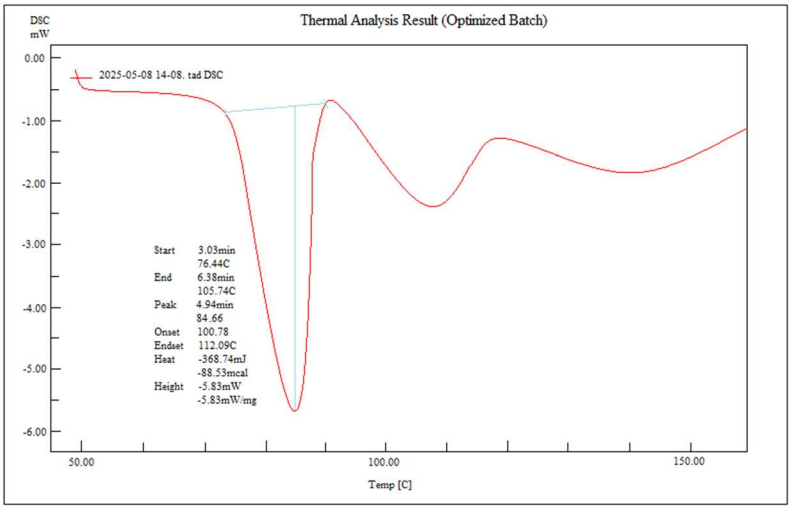

Figure 11: DSC curve for Ramipril pastilles

The DSC curve for Ramipril pastilles showed a broad peak at 84.66 °C. This decrease in melting point is attributed to the effect of the polymer in the pastilles. The broad peak in the DSC thermogram of the Ramipril pastilles may indicate a change in the drug's form from crystalline to amorphous.

9) Scanning Electron Microscopy (SEM)

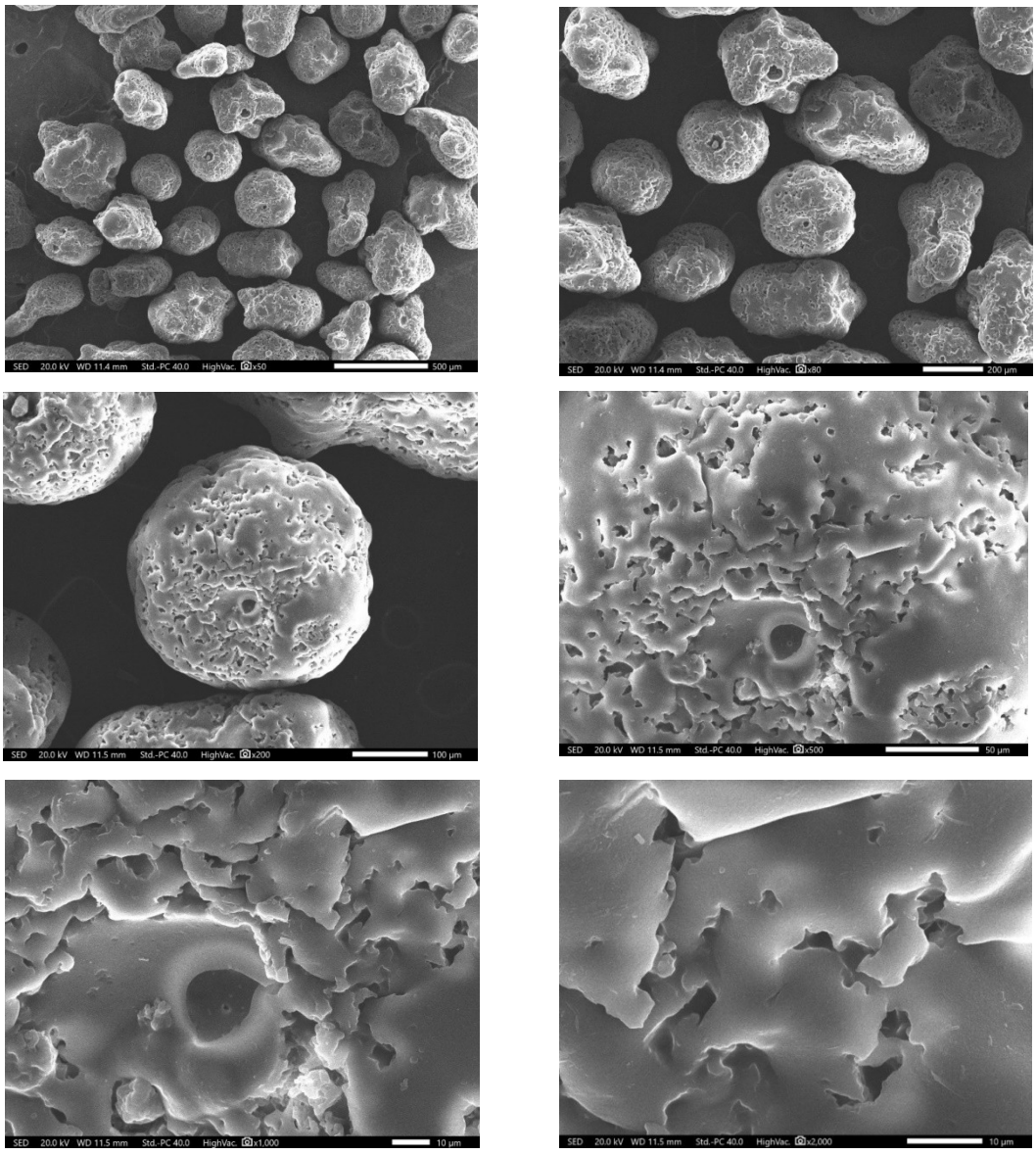

Figure 12: SEM image of Ramipril pastilles

The scanning electron microscopy SEM is done to check the physical appearance and shape of the Ramipril pastilles and according to the SEM result the images shows that the shape of Ramipril is spherical in the shape.

Observed that entrapping the crystalline drug in Pastilles was successfully achieved as no sign of crystalline structure is visible**.**

10) X-ray diffraction studies (XRD)

X-ray diffractometry was conducted for the pure drug, and for pastilles of ramipril. The diffractogram in **Figure 13** show some peaks

that appeared at 9.54, 14.66, 20.24, 21.18, 22.38, 29.0, 30.52, 36.72, etc. The peaks supported the crystalline nature of the drug The diffraction marks of the pastilles of ramipril showed only one high diffraction peak of 20.7. That peak appeared to be due to the crystal state of Gelucire 50/13, which was present in the pastilles of ramipril. The X-ray diffractogram of pastilles of ramipril showed an absence of any specific peak. This confirmed the complete conversion of the drug from its crystal sate to an amorphous state.

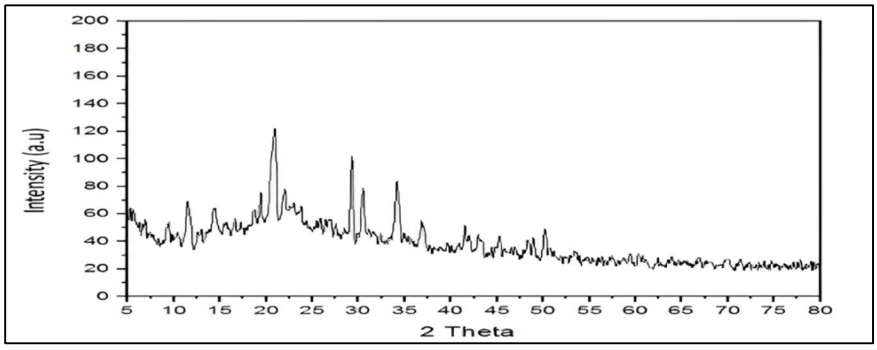

Figure 13: XRD of Ramipril

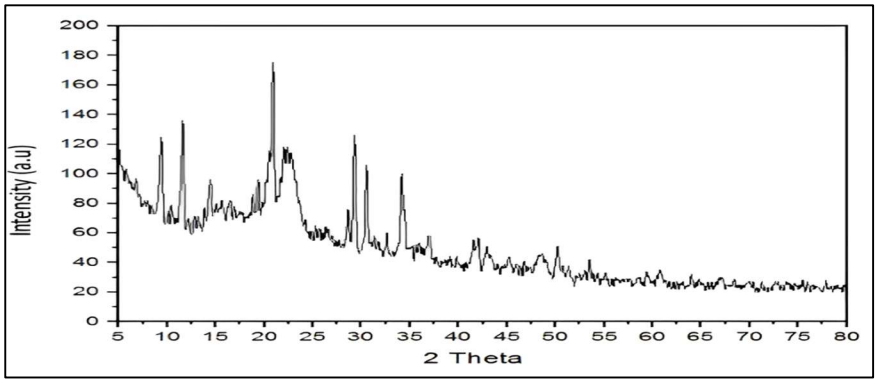

Figure 14: XRD of Optimized batch

11) Optimization of Pastilles By Design Of Experiment

A. Diagnostic case statistics of experimental matrix

1. Predicted Vs Actual graph of Drug release:

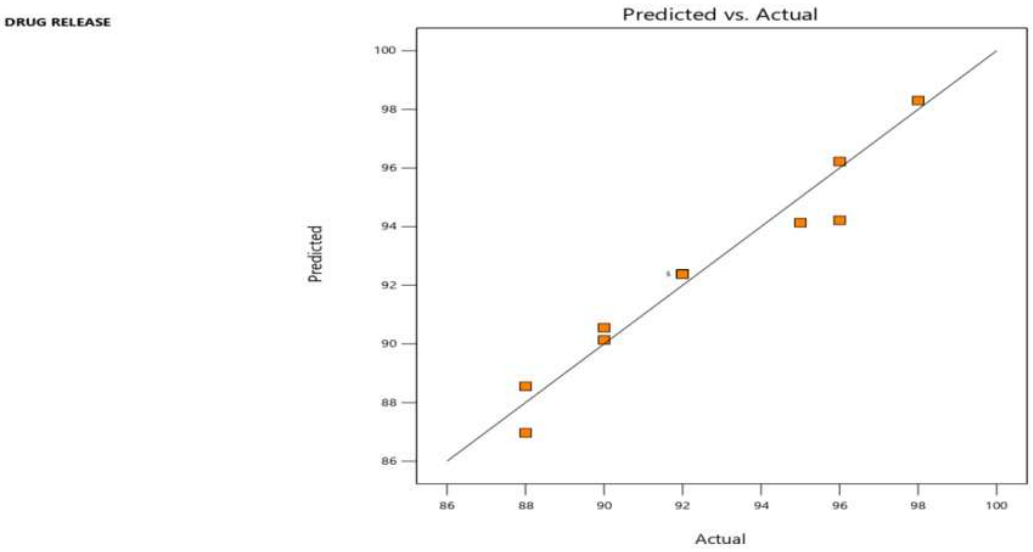

Figure 15: Predicted vs Actual plot obtained of drug release

2. Three dimensional graphical presentations 3-D surface:

3-D graph represent the increase in concentration Gelucire 50/13 and PEG 600 Increases Drug release. factor A, B having show Significant increase in Drug release of pastilles.

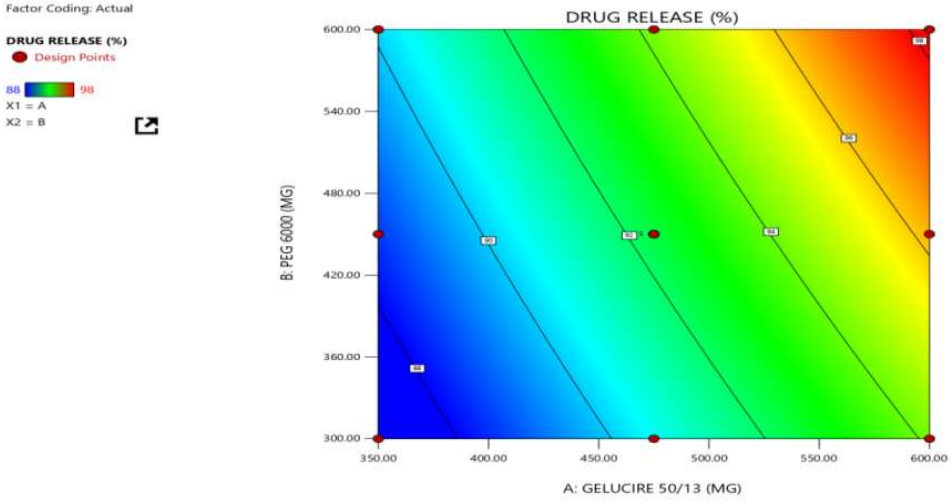

Figure 16: Counter plot obtained by D.O.E 7.0.0 related to the given data of drug

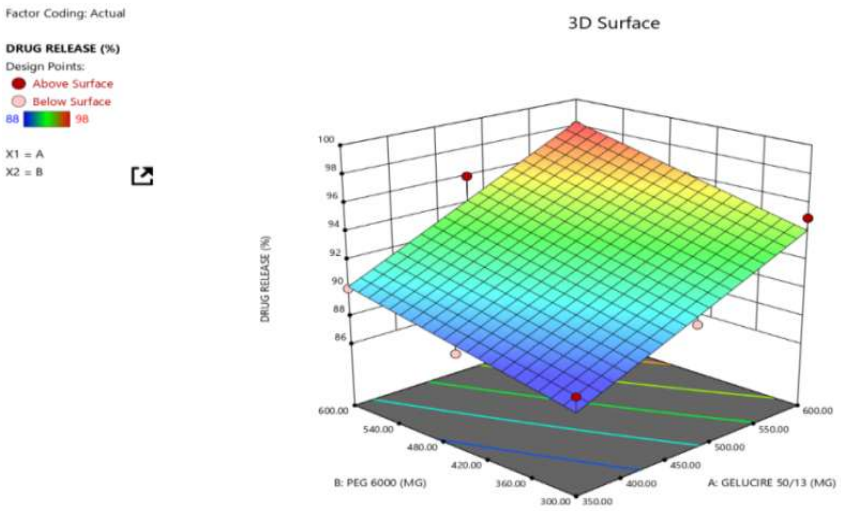

Figure 17: 3D surface plot obtained by D.O.E 7.0.0 related to the given data of drug release

B. Diagnostic case statistics of experimental matrix

1. Predicted Vs Actual graph of Drug content:

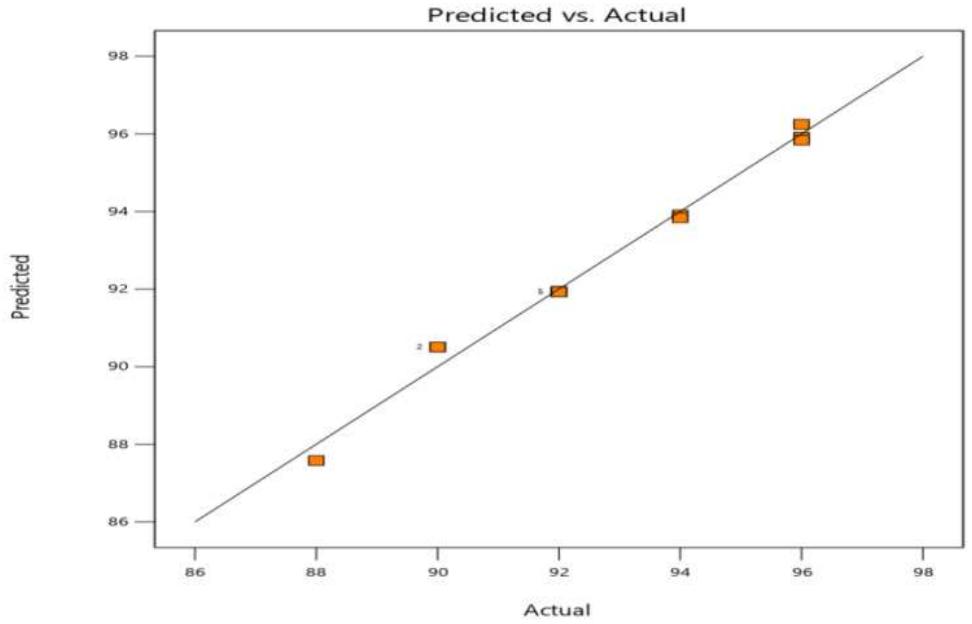

Figure 18: Predicted vs Actual plot of drug Content

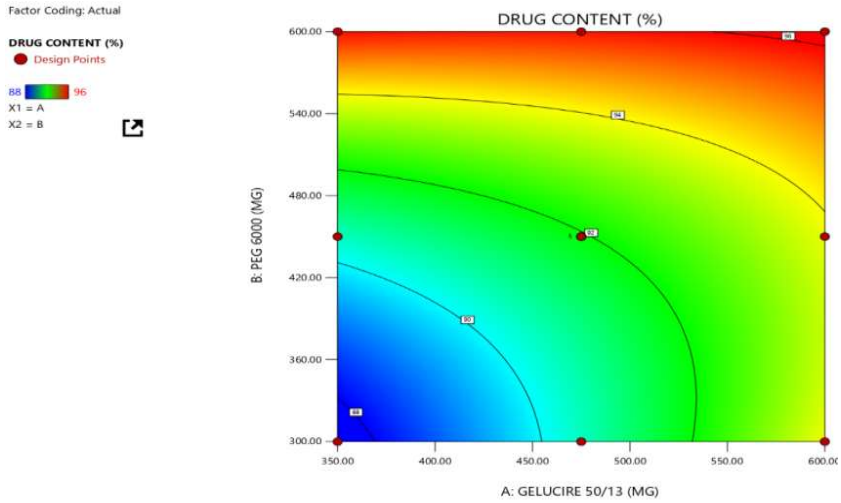

Figure 19: Counter plot obtained by D.O.E 7.0.0 related to the given data of drug release

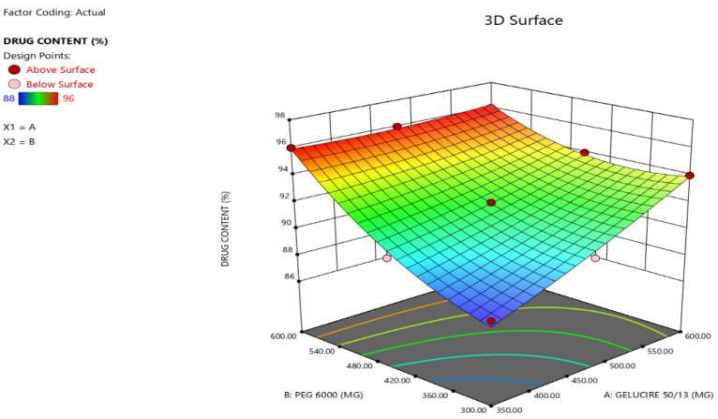

Figure 20: 3D surface plot obtained by D.O.E 7.0.0 related to the given data of drug release

12) Stability Studies

Table 11: Stability study of Optimized formulation

Time (day)	Colour	Shape	Drug content (%)	In vitro drug Release (%)
0	No Change	No Change	96.66± 0.22	98.02± 024
30	No Change	No Change	96.03± 0.26	98.06± 022
60	No Change	No Change	96.04± 0.24	98.30±0.18
90	No Change	No Change	95.98± 0.23	98.20±0.14

The Stability studies revealed no notable alterations in the color or shape of the pastilles under the specified parameters of elevated temperature and humidity. These findings indicate that the prepared formulations remained stable and was minimally affected by the conditions of increased humidity and temperature.

ACKNOWLEDGEMENT:

Authors are here by duly acknowledged the support of Principal and Management of Sandip Foundtion's, Sandip Institute of Pharmaceutical Sciences for providing the necessary facilities to conduct this research.

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