**RESEARCH ARTICLE**

# Solubility Enhancement of Poorly Water-Soluble Drug Ritonavir using Polyvinylpyrrolidone and Chitosan-based Platform Technique

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## ABSTRACT

The antiviral medication ritonavir (RTV) belongs to the biopharmaceutics classification system (BCS) class II drug category and is known for its high permeability and poor solubility. Therefore, the prime objective of this research was to increase the rate of dissolution and improve the solubility of RTV using a polymer system. Solid dispersions consisting of binary polymer components i.e., chitosan (CH) and polyvinylpyrrolidone (PVP) were prepared using microwave microwave-assisted physical mixing technique and optimization of solid dispersion was performed with 32 factorial designs. Dispersions were analyzed for their physicochemical characteristics by the use of X-ray diffraction (XRD), differential scanning calorimetry (DSC), and fourier transform infrared spectroscopy (FTIR). The polymeric dispersions prepared were evaluated for the release of RTV throughout 1 h in 0.1N sodium chloride in a USP class II dissolving device. The phase solubility study demonstrated a considerable improvement in the saturation solubility of RTV when CH and PVP K30 were present either individually or in combination. Virtual interaction studies between the drug and polymers revealed physical interactions driven by van der Waals and hydrophobic forces between RTV and excipients. Carbonyl, amine, and hydroxyl groups, among others, were probably present in both RTV and CH, which allowed for these interactions to take place. There was no discernible interaction between the RTV and the polymers included in the FTIR research. The dispersion strategies have improved the dissolving rate, according to the *in-vitro* drug release investigation. A formulation including a polymeric dispersion of the optimal concentration of PVP and chitosan may efficiently boost the release of RTV, according to the *in-vitro* release profile.

**Keywords:** Solubility, Solid dispersion, Amorphous, Dissolution, BCS class II.

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## INTRODUCTION

Drug molecule solubility affects the rate of *in-vitro* dissolution, which in turn affects the rate of absorption and bioavailability *in-vivo*. As a result, a drug's solubility is crucial to its ability to achieve its therapeutic goals. The ideal concentration of a medicine in the bloodstream and its pharmacological effect are both dictated by its solubility.[1] Poorly soluble medications may lead to several restrictions, including the requirement for large doses, increased frequency of administration, and increased adverse reactions.[2] Despite having strong therapeutic efficacy, the majority of recently identified chemical compounds possess a low solubility in water and poor bioavailability, which results in inadequate absorption in the gastrointestinal tracts.[3,4]

The rate-limiting stage for drug absorption into the bloodstream is the pace at which poorly soluble medicines dissolve in GI fluids. Thus, if one wants to increase their bioavailability, it is necessary to enhance the dissolving rate and solubility of these drugs.[5] Increasing the rate of disintegration and drug release of insoluble medicines increases drug bioavailability as a result of improved drug solubility.[6] As a result, several formulation techniques such as nanoformulation, solid dispersion, micellization, size reduction, and others are utilized to intensify the therapeutic efficiency of drugs that are not very soluble in water.[7,8]

Amorphous formulations are frequently favored among these because they frequently produce greater solubility in a highly concentrated liquid and dissolving rate relative to the crystalline counterpart.[9] As the number of Food and Drug Administration (FDA) approved medications has rapidly increased in the past few years, solid dispersion has since established itself as a method for the creation of drugs that are not readily soluble.[10] A wide variety of processes, including solvent casting, freeze-drying, hot-melt extrusion, electrospinning, wet milling, and spray drying, can be used

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to create solid dispersion.[11] Nevertheless, the scientific community has only occasionally examined the use of microwave technology in order to make these drugs more bioavailable in the body, as well as more soluble in laboratory settings and more effective in therapeutic applications.[12,13] MW heating differs from conventional heating in that heat is first sent to the material's surface before moving within. Within the material, heat is generated and then distributed throughout the whole volume at a constant pace in the MW process.[14,15]

Ritonavir (RTV), a frequently used HIV-1-specific protease inhibitor medicine is classified as a class II BCS agent, with poor water solubility and low and unpredictable oral bioavailability.[16,17] To boost their bioavailability and dissolving rate, they must therefore become more soluble. One of the most effective methods for use in significantly enhancing RTV solubility among the several tactics documented is the use of pharmaceuticals in solid dispersions, which may include amorphous medicine. So, in this research, an effort has been made to increase the rate at which RTV dissolves utilizing solvent-free microwave irradiation.

## MATERIAL AND METHODS

A free sample of ritonavir was provided by Lupin Research Park in Pune. The chitosan was provided by Mahatani Chitosan Pvt. Ltd. as a complimentary sample. Ahmedabad. Acetone and methanol were procured from a chemical supplier. Every single chemical that was used was of an analytical grade.

### Pre-formulation Studies

*Solubility*

The solubility of RTV was established in 0.1 N HCl, distilled water, acetone, ethanol, and methanol as per the standard procedure and reported.

*Phase solubility studies*

Phase solubility tests were conducted to investigate the solubility behavior of RTV in the presence of polyvinylpyrrolidone (PVP) polymer by Higuchi and Connors. In this study, extra RTV was dissolved to 10 mL of distilled water containing different concentrations of PVP polymer, either alone or in combination with chitosan (CH). The test tubes containing the binary and tertiary suspensions were mixed on a Bio Technics India mechanical shaker set at 100 rpm for 48 hours at ambient temperature. The supernatant, which contained the dissolved RTV, was carefully collected. A blank solution was used for UV analysis to evaluate the RTV content after the filtered samples were appropriately diluted.[16,18]

### Formulation Studies

*Preparation of polymer platform of RTV using experimental design*

The formulation design of RTV polymer dispersion (Table 1) was done with the help of the trial version of the Design Expert 12 program. In the design process, two independent variables were selected: the concentration of CH and the concentration of PVP. These variables were denoted as X1 and X2, respectively, and two dependable responses were evaluated for each batch: Y1 represents concentration in and Y2 represents drug release.[19-21]

**Table 1:** Formulation batches of ritonavir

| *Batches* | *Drug 0.5 M (gm)* | *PVP 1 M (gm)* | *Chitosan 1 mM (mg)* |
|---|---|---|---|
| R1 | 3.65 | 0.2 | 40 |
| R2 | 3.65 | 0.2 | 80 |
| R3 | 3.65 | 0.2 | 120 |
| R4 | 3.65 | 0.4 | 40 |
| R5 | 3.65 | 0.4 | 80 |
| R6 | 3.65 | 0.4 | 120 |
| R7 | 3.65 | 0.8 | 40 |
| R8 | 3.65 | 0.8 | 80 |
| R9 | 3.65 | 0.8 | 120 |

*Radiation-based polymeric platform drug delivery system*

RTV drug-polymer platforms were prepared to utilize a microwave-assisted dry grinding technique. The predetermined amounts of the required ingredients were accurately weighed and ground using a mortar and pestle for approximately 20 minutes. After that, the ingredients were placed in a microwave (Panasonic, 230V-50Hz-1250W) set to a power of 600 W with two intervals of 3 minutes each.[22]

### Characterization of Ritonavir Formulation

*Micromeretic studies*

Micromeretic properties of RTV and RTV-based solid dispersions were determined using previously reported methods.

*Fourier transformation-infrared spectroscopy*

A technology developed by BRUKER, ECO, ATR, and ALPHA in Germany, known as fourier transform-infrared (FTIR) spectroscopy, was used for the physicochemical characterization. FTIR analysis was conducted for formulated solid dispersion and physical mixture of drug with excipients. After placing the samples directly on a pan, they underwent 24 scans in the spectral region of 600 to 4000 $cm^{-1}$.[23]

*Differential scanning calorimetry*

The TA Instruments, SDT Q600 USA, differential scanning calorimetry analyzer was used to conduct the measurements. During the course of the experiment, a sample of five milligrams was heated in a nitrogen atmosphere at a rate of 200°C/minute.[15,24]

*Powder X-ray diffractometry*

Using a BRUKER-D2 PHA-SER X-ray diffractometer with a Cu tube anode and a time interval of 10-90/2 hours, the X-ray diffraction patterns were found for several substances, including physical mixes, pure medicine RTV, polymer CH, PVP, and formulation batches. Here are the operating data: The generator's current is 10 milliamperes and its voltage is 30 kilovolts.[25]

*Nuclear magnetic resonance study*

Solid-state NMR (SSNMR), which provides access to precise information on molecular structure, is another helpful technique for characterizing amorphous dispersions.[26] NMR spectra of RTV and formulations of RTV were determined.

*Percentage drug content estimation*

An RTV (20 mg) solid dispersion was added to a 25 mL volumetric flask. Using a mechanical stirrer set to 100 rpm for 48 hours, 10 cc of methanol was added and stirred well. Whatman filter paper no. 41 was utilized to filter it after equilibrium. The drug content was analyzed spectrophotometrically at 288 nm using the following formula after the solution was appropriately diluted with methanol.[27]

$$\% \text{ drug content} = \frac{\text{actual drug content in methanol}}{\text{theoretical equivalent drug taken}} \times 100$$

*In-vitro dissolution study*

The *in-vitro* dissolution test was conducted using a LABINDIA Dissolution test equipment, DS 8000, a paddle-type dissolution apparatus of the USP Type II. To finish the dissolving process, 900 mL of 0.1 N hydrochloric acid was poured to each dissolving vessel. The paddle was set to spin at 50 rpm and a temperature of 37 ± 0.5°C was maintained. It was then spectrophotometrically examined using a UV-vis spectrophotometer operating at 288 nm on the dissolved samples.[28-30]

*Stability study*

The experiment was conducted in a REMI SC 16S stability chamber set at 40°C and 75% relative humidity. The duration of the trial was three months. Samples were evaluated for drug content using UV spectroscopy for the study of the interaction between RTV with polymers using IR spectroscopy.[7,21]

## RESULT AND DISCUSSION

### Pre-Formulation Studies of Model Drug RTV

*Solubility studies in different pH conditions*

The solubility studies of RTV, an antiviral drug with low aqueous solubility due to its nonpolar nature, were conducted in various pH conditions, including water. RTV is classified as a practically insoluble drug in water, falling under BCS class II. Table 2 demonstrates that RTV exhibits very low solubility in all tested media, including water. However, the solubility profile was found to be influenced by pH, showing a decrease in solubility as the pH increases. This observation indicates that RTV has a lower solubility in alkaline as well as acidic conditions.

**Table 2:** Solubility studies of RTV in different solvents

| *pH* | *Concentration (µg/mL)* |
|---|---|
| 0.1N HCl (pH 1.2) | 11.34 |
| DD water | 6.20 |
| Phosphate buffer (pH 7.4) | 7.45 |

*Phase solubility studies of RTV*

Saturation solubility experiments were performed on RTV in distilled water, using a rotary shaker at 100 rpm. RTV, classified as practically insoluble, showed a solubility of 7.3 µg/mL in distilled water. Adding the hydrophilic polymer CH increased solubility to 41.3 µg/mL, likely due to enhanced hydrophilic interactions. Introducing PVP further increased solubility to 145.96 µg/mL, potentially through improved drug-polymer interactions. Notably, the ternary phase system with RTV, CH, and PVP displayed the highest solubility of 365.48 µg/mL, suggesting a synergistic effect between the two polymers. These findings demonstrate that both CH and PVP can enhance RTV solubility, with the ternary system showing the greatest improvement. Increasing the concentration of PVP improved saturation solubility in CH-containing formulations relative to CH-free ones (Figure 1).

The addition of CH and PVP to RTV in distilled water increased solubility due to their physical interactions with the drug. CH improved wettability and hydrophilic interactions, while PVP enhanced solubility and formulation stability. Furthermore, ternary complexes with varying amounts of CH and PVP enhanced solubility further (Table 3). Increasing amounts of CH, and PVP, combined to provide a considerable improvement in solubility. These findings demonstrate the potential of CH and PVP.

*Virtual interactions study*

Virtual physical interaction between RTV- CH was analyzed by V-Life MDS 4.6 software as shown in Figure 2.

The CH polymer platform, when combined with PVP, serves as a framework to enhance the solubility. The interactions between CH and RTV were characterized by 169 van der Waals interactions and 86 hydrophobic interactions, indicating the strength of these interactions. The strength of the interactions was determined based on the interatomic distances observed between the atoms involved. Van der Waals interactions were identified when interatomic distances ranged from 2 to 3.8 Å, while hydrophobic interactions were observed when distances ranged from 1.9 to 4.5 Å.

### Formulation Studies of Model Drug RTV

*Fourier-transform infrared spectrometry*

The pharmacological spectrum of RTV showed distinctive peaks during fourier-transform infrared (FTIR) analysis. The peaks that were observed consist of an amide group stretching at 3359 $cm^{-1}$, an ester linkage peak at 1716 $cm^{-1}$, and aromatic

**Table 3:** Solubility data of ritonavir

| *Batch* | *Conc. of PVP K30 (mM)* | *Amt. of PVP K30/10 mL* | *Solubility* |
|---|---|---|---|
| RP1 | 0 | 0 | 7.3 |
| RP2 | 0.1 | 40 | 52.7 |
| RP3 | 0.2 | 80 | 115.3 |
| RP4 | 0.3 | 120 | 170.3 |
| RP5 | 0.4 | 160 | 358.7 |

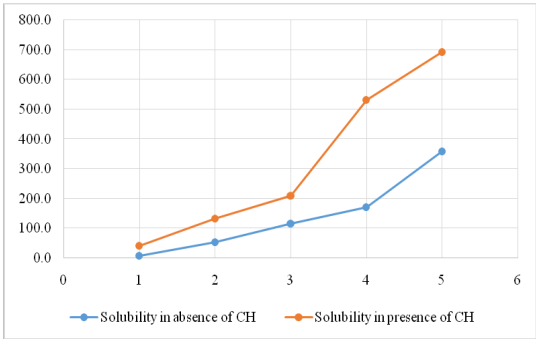


**Figure 1:** Comparative solubility studies

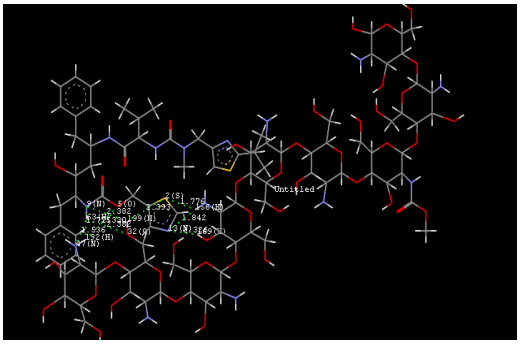

**Figure 2:** Virtual physical interaction between RTV- CH

carbon -C═C- stretching peaks at 1650 and 1525 $cm^{-1}$. When a combination of RTV, PVP, and CH was examined, the FTIR spectra displayed a compounded pharmacological spectrum, PVP, and CH. This finding demonstrated that the medicine did not interact with the additives and remained unchanged. Significant changes were observed in the spectra of polymer dispersion, indicating interactions between the drug and the carrier (PVP and CH). Intermolecular hydrogen bonding was observed, as evidenced by the shifting of the peak corresponding to the NH group of RTV from 3359 $cm^{-1}$ to the range of 3311 to 3315 $cm^{-1}$ in all formulation batches of the ternary mixture. The presence of secondary hydrogen bonding, as seen by a large and robust absorption peak at 1140 $cm^{-1}$, was absent in the pure drug spectra. An aliphatic aldehydic group's distinctive C-H stretching band and C◇O stretching band were shown by the significant absorption peaks at 1763 and 2800 $cm^{-1}$, respectively. The spectra of the medication in its crystalline form did not include these bands. The medication and polymers were found to interact with each other via the production of aldehydic groups and hydrogen bonding. FTIR spectra of RTV and different batches are illustrated in Figure 3.

*Differential scanning calorimetry*

Differential scanning calorimetry (DSC) scans of pure drug RTV and various formulations were recorded (Figure 4). DSC of formulations prepared by the microwave-assisted technique suggested the formation of a monotectic system. A significant change in delta H from 153.4 to 5.8 J/g in formulation batches of RTV indicated an interaction between the polymer and drug. The endothermic peak at 125.66° in the DSC thermogram of pure RTV corresponds to its melting point and has an integral

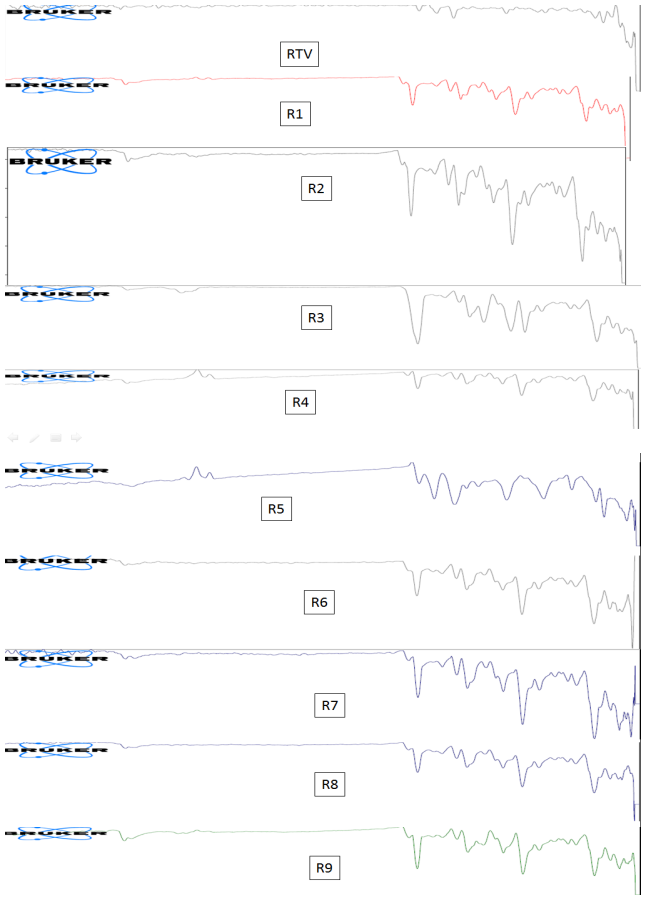


**Figure 3:** FTIR spectra of RTV and formulation batches

enthalpy of 153.4 J. The findings point to the possibility of a eutectic solid dispersion, in which the medicine exists as very small crystals embedded in a polymer matrix.

*X-ray diffraction*

The polymorphic transformation occurring during the preparation of a drug delivery system for RTV was investigated using X-ray diffraction (XRD). XRD measurements were performed on pure RTV drug and a polymeric dispersion was prepared using a microwave-assisted technique. In the XRD spectrum of the RTV, sharp and intense crystalline peaks were observed at 2θ values of 6.92° and 35.66°. In contrast, the formulation dispersion exhibited less intense and broadened peaks compared to the drug, indicating a transformation of the drug into an amorphous structure. Specifically, the formulation prepared using microwave treatment displayed a distinct broad peak characteristic of amorphous and highly disordered materials. Although the peaks corresponding to RTV were less intense in the formulation dispersion, they were still observable, indicating the presence of some crystalline portion of the drug in all formulations (R1 to R9). This suggests that the solid dispersions had a eutectic nature, with the drug dispersed on the carrier matrix. XRD analysis confirmed the occurrence of a polymorphic transformation during the preparation of the drug delivery system for RTV. The formulation dispersions exhibited reduced intensity and

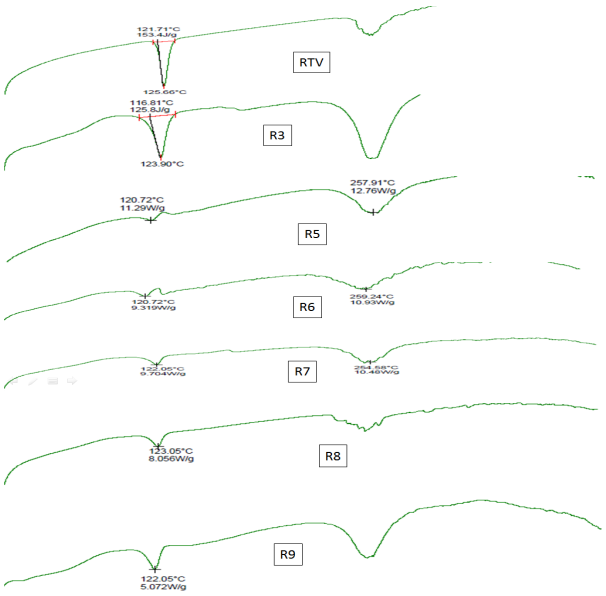


**Figure 4:** DSC thermogram of RTV and formulation batches

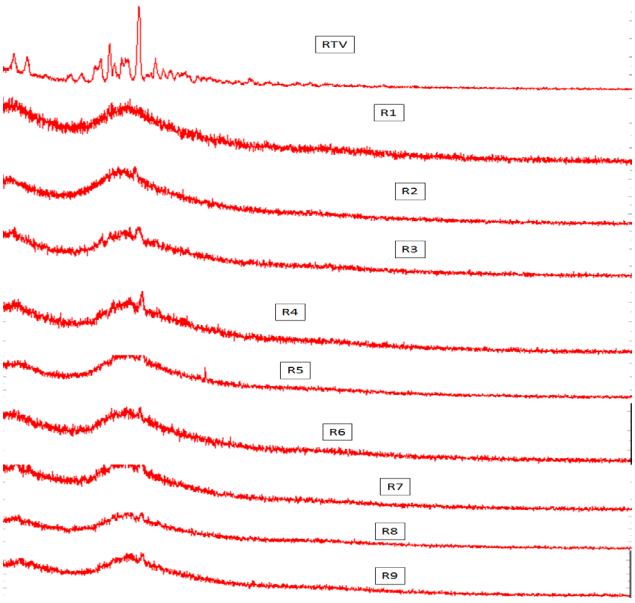


**Figure 5:** XRD spectra RTV and formulation batches

broadened peaks. However, traces of the crystalline drug were still present in the dispersions, indicating a eutectic nature of the solid dispersions with ultrafine drug crystals dispersed on the carrier matrix. Detailed results are shown in Figure 5.

*Saturation solubility*

Saturation solubility of RTV and different formulations was obtained as follows.

When optimizing formulation batches using design expert software, it is one of the variable elements. Increasing the concentration of CH and PVP improved solubility in distilled water and dissolving media (Figure 6A). Compared to pure medication RTV, the formulation batches exhibited a greater saturation solubility of RTV. Furthermore, an increase in the concentration of hydrophilic polymer PVP enhances the

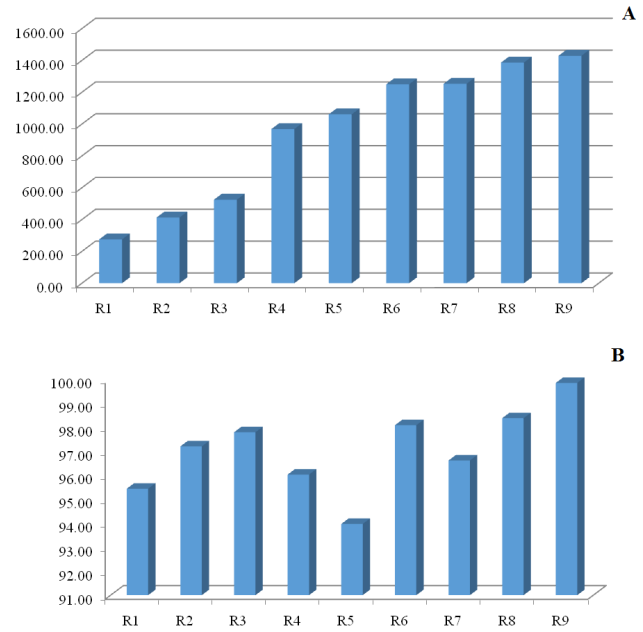


**Figure 6:** (A) Saturation solubility of formulation batches and (B) Drug content of all formulated batches

saturation solubility, but the effect was observed to be modest after a certain level of concentration of polymer PVP and chitosan. The concentration of PVP was found to be directly proportional to the enhancement of the solubility of a drug.

*NMR study*

NMR study demonstrated the miscibility of the drug due to the use of a polymer platform (Figure 7).

*Drug content*

According to Figure 6B, the optimization batches R6 and R8 had drug percentage contents ranging from 93.97 to 99.85%, and saturation solubility values of 150 and 178.33 µg/mL, respectively. During the batch production process, there was little medication loss. Therefore, there was relatively little variance in the drug content. When compared to pure medication RTV, the saturation solubility of R6 and R8 was almost ten times higher.

*Dissolution study*

We compared the dissolving profile of pure RTV with the percentage cumulative drug release for each batch. The stable crystalline form of RTV resulted in a drug release of 25.89% only after 150 minutes (Figure 8). But since the formulation contains the hydrophilic polymer chitosan and PVP, which physically interact with one another, a higher drug release was observed for RTV in the formulation. The R8 batch exhibited the maximum drug release among all the batches tested.

The coefficient of regression analysis was performed to determine the release pattern of different batches (Table 4). Results showed that all batches, except for R2, R5, and R8, exhibited a release pattern consistent with the Higuchi model. The results showed that the medication, RTV, was primarily released through a diffusion process from the complex formed by microwave radiation. The microwave

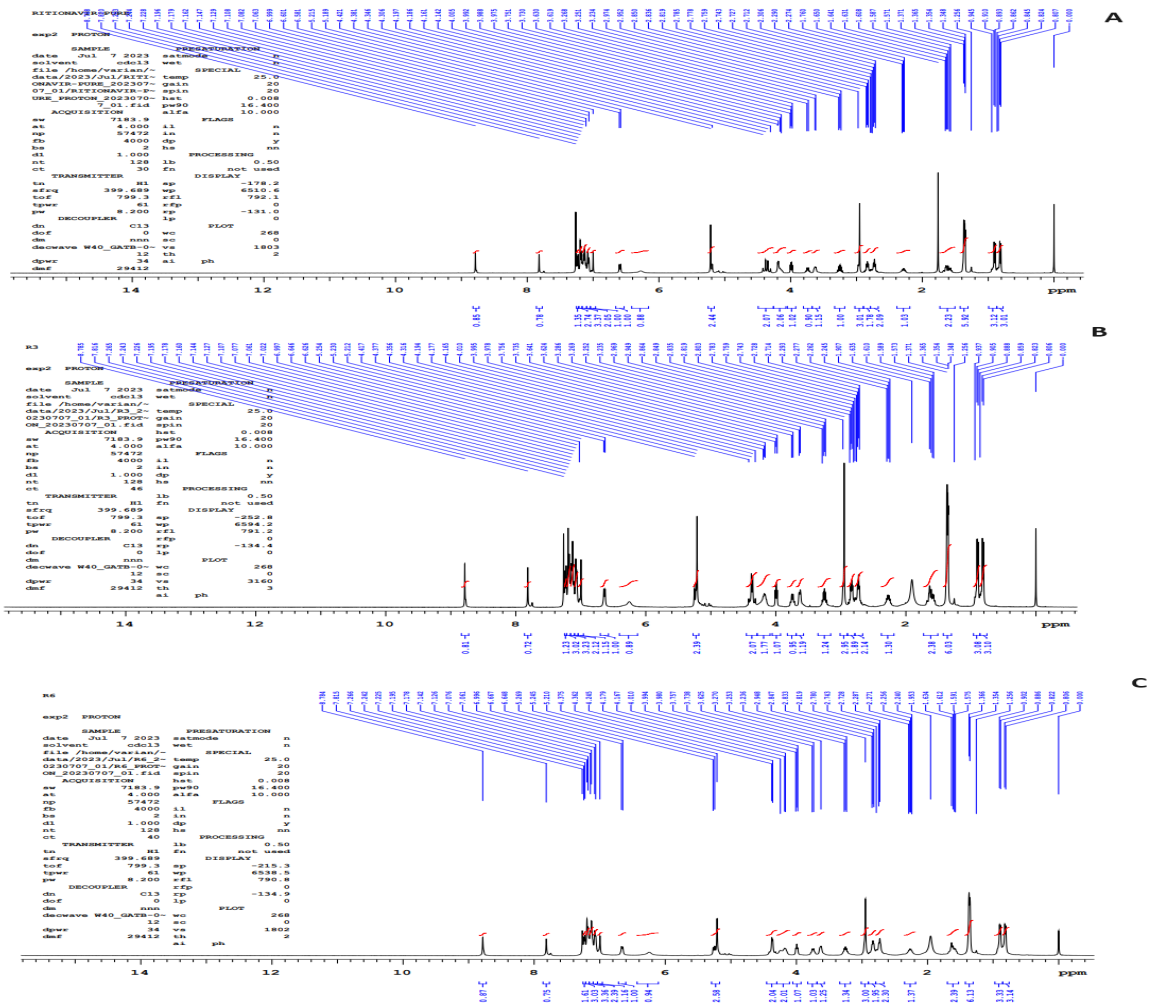


**Figure 7:** NMR spectra of (A) RTV (B) batch R3 and (C) batch R6

**Table 4:** Drug release kinetics of RTV

| | *R1* | *R2* | *R3* | *R4* | *R5* | *R6* | *R7* | *R8* | *R9* |
|---|---|---|---|---|---|---|---|---|---|
| First order | 0.916 | 0.9614 | 0.9744 | 0.8725 | 0.963 | 0.9879 | 0.9153 | 0.939 | 0.9913 |
| Korsmeyer P | 0.9484 | 0.9823 | 0.9699 | 0.9576 | 0.981 | 0.9687 | 0.9607 | 0.969 | 0.9571 |
| Zero-order | 0.8441 | 0.8951 | 0.8946 | 0.8062 | 0.8865 | 0.9274 | 0.8119 | 0.833 | 0.9165 |
| Higuchi | 0.9809 | 0.9783 | 0.9887 | 0.964 | 0.9742 | 0.9937 | 0.9711 | 0.9641 | 0.9993 |
| H. Crowell | 0.8934 | 0.9422 | 0.9558 | 0.8523 | 0.9414 | 0.979 | 0.8854 | 0.9091 | 0.9755 |

radiation created a polymeric matrix that entrapped RTV both externally and internally to the matrix. CH formed a matrix-type complex when in the solution base, contributing to the Higuchi-based drug release. The formulation containing both chitosan and PVP K30 exhibited the highest drug release when the concentration of PVP K30 was maximized. This combination of polymers facilitated better drug release through a combination of diffusion and erosion mechanisms.

Interestingly, batches R2, R5, and R8 deviated from the Higuchi model and instead followed the Korsmeyer-Peppas model at a medium concentration of CH. This deviation may be attributed to the specific formulation characteristics and the influence of chitosan concentration. The R8 batch, exhibiting the highest drug release, validated the optimized application of the Korsmeyer-Peppas model. Drug release kinetics are mentioned in Table 5 and model fitting is shown in Figures 9, 10, and 11.

Drug release kinetics of RTV and optimized batch were studied and drug release kinetics optimized based on coefficient of regression are shown in Table 5.

The rate of medication release is proportional to the concentration of PVP due to acting as a solubilizing agent,

facilitating the dispersion of RTV in a soluble form. However, the amount of CH significantly affects the release pattern. Pharmacological release from the prepared polymer platform formulation with increasing kinetics can be explained by the Higuchi model. When the particle size decreases and the drug is released from the formulation, the Hixon-Crowell model can explain the phenomenon. The coefficient of regression was higher in the Higuchi model for a medium concentration of CH and a high level of PVP in comparison with plain drug RTV, but it was lower in the Hixon Crowell and Korsmeyer Perppas model. The batch R8, which exhibited maximum drug release, followed the Higuchi model for drug release (Figure 12).

*Stability studies*

Accelerated stability experiments were conducted for 6 months on the chosen formulation in accordance with ICH recommendations. Once a month, we checked the optimized formulations for changes in how they looked, how much medicine they contained, and how they dissolved in the lab. The drug content and dissolving behavior of the chosen formulation were not significantly different from one another ($p > 0.05$), according to the findings. As shown in Figure 13, the optimized formulation had a medication percentage ranging from 94.56 to 94.585%. The existence of CH and PVP polymers at the ideal concentration may explain why the formulation is stable, as this demonstrates.

*Micromeritic study*

In order to determine the powders' compressibility and flow characteristics, several micrometric parameters were measured. The angle of repose for the R8 batch showed a reduction from 45.90° (observed for RTV) to 29.70°, representing an improved flow property of the drug. The presence of chitosan and PVP K30 polymers in the physical mixture resulted in a slightly lower angle of repose compared to RTV alone. The Hausner's ratio and Carr's index of the R8 batch increased attributed to the microwave radiation treatment and the presence of hydrophilic polymers. This led to an enhancement in the compressibility

**Table 5:** Coefficient of regression of all mechanisms for optimized Batch

| *Reaction Kinetics* | *RTV* | *R8* |
|---|---|---|
| First Order | 0.891 | 0.991 |
| KorsmeyerPerppas | 0.953 | 0.951 |
| Zero Order | 0.882 | 0.914 |
| Higuchi | 0.899 | 0.998 |
| Hixon Crowell | 0.888 | 0.981 |

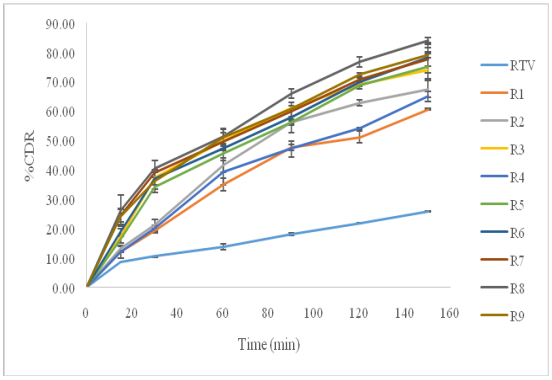


**Figure 8:** *In-vitro* dissolution studies of formulation batches

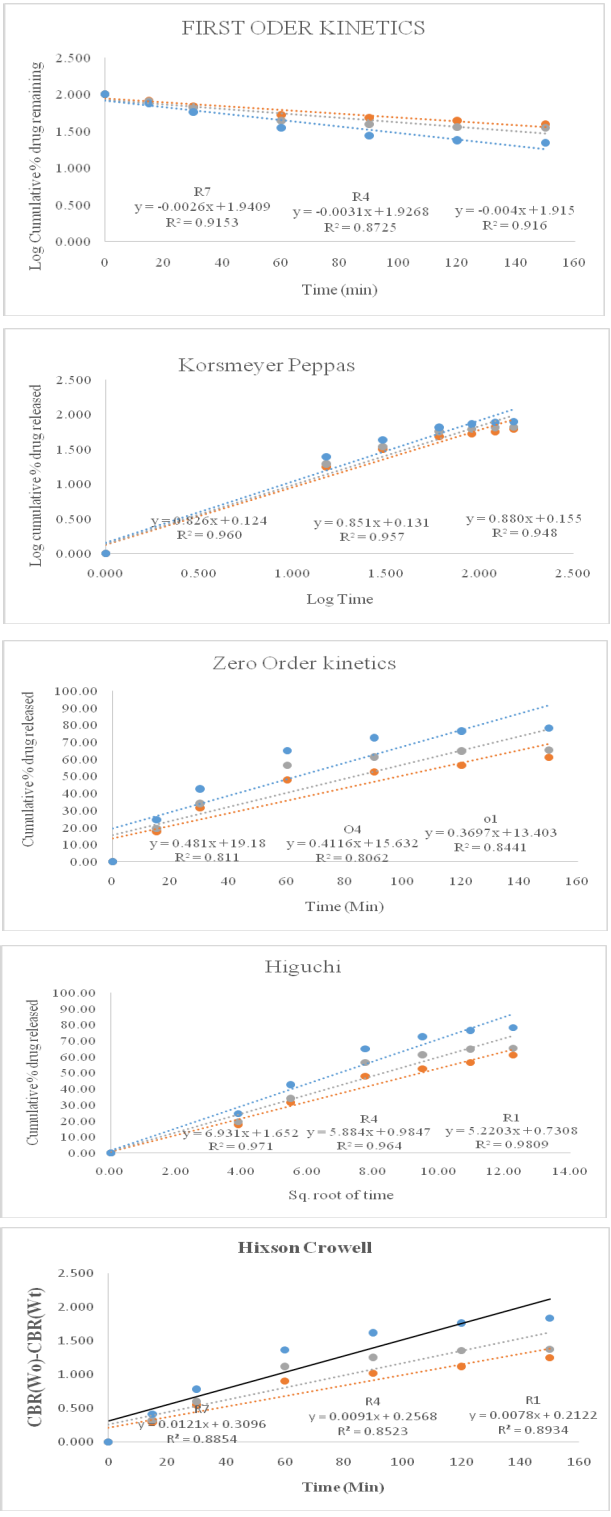


**Figure 9:** Release kinetics for R1, R4 and R7 batches

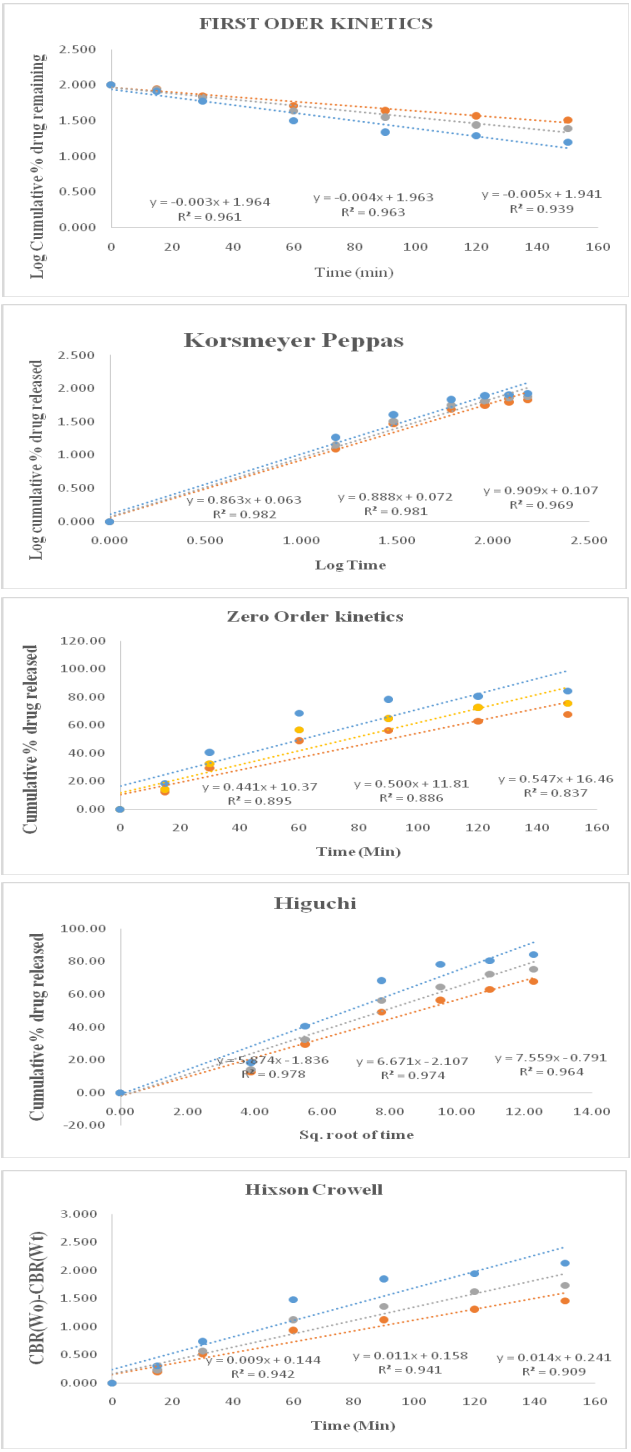


**Figure 10:** Release kinetics for R2, R5 and R8 batches

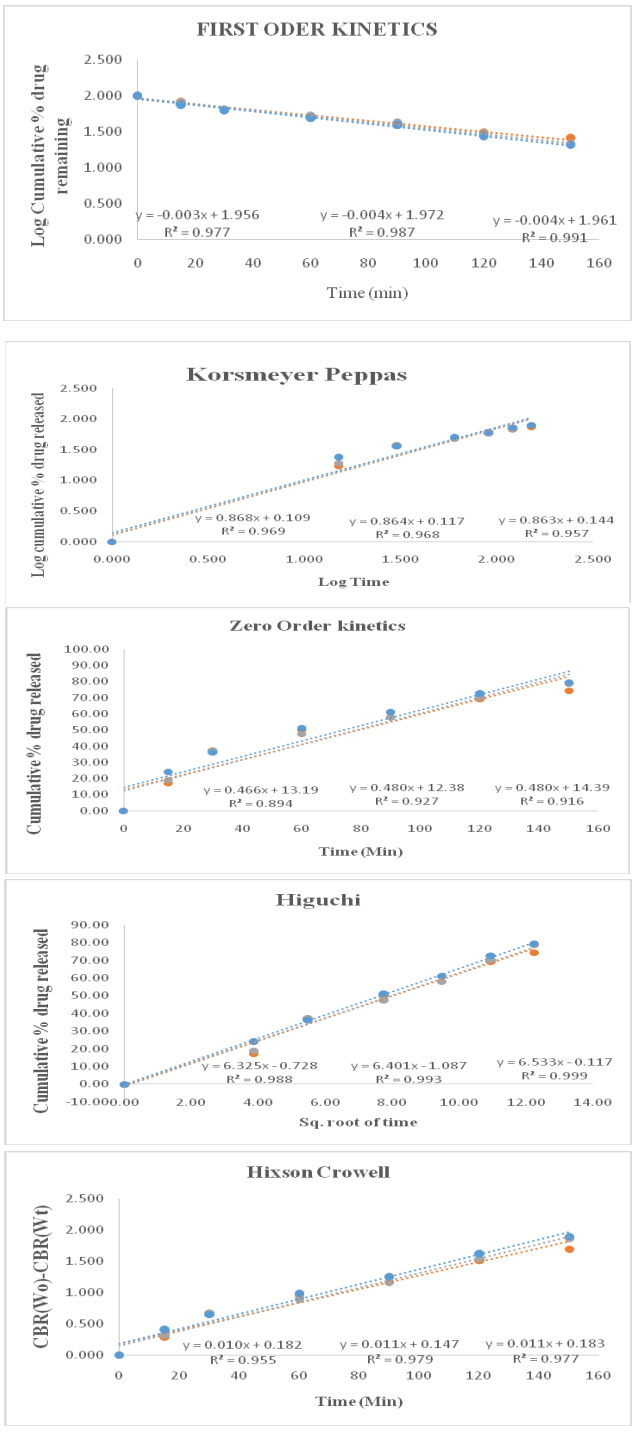


**Figure 11:** Release kinetics for R3, R6 and R9 batches

of the RTV powder. Overall, the formulated platform drug delivery system exhibited improved micromeritic properties, including enhanced flow property and compressibility of RTV.

The micrometric study demonstrated that the R8 batch of the formulated platform drug delivery system exhibited favorable flow properties and compressibility of RTV. The reduction in the angle of repose indicated improvements in the flowing behavior and compressibility of the drug powder (Figure 14).

## Factorial Analysis of Formulations

The F-value of 202.74 indicates that the quadratic model is the best-fitting model. Here, important model terms are X1, X2, and $X1^2$. Predicted $R^2$ and adjusted $R^2$ were found to be less than 0.2 apart. An acceptable signal was confirmed by an

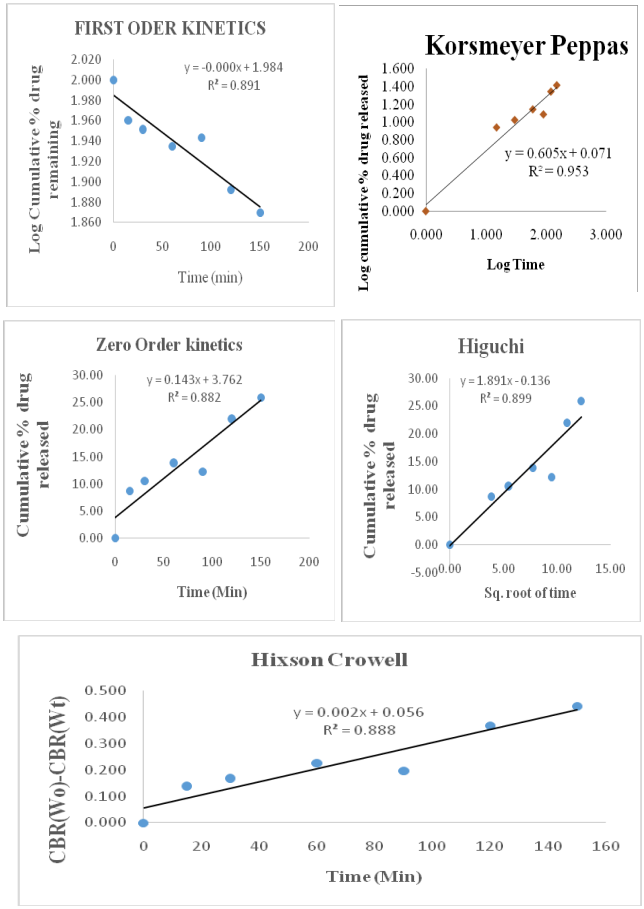


**Figure 12:** Mathematical models for RTV release

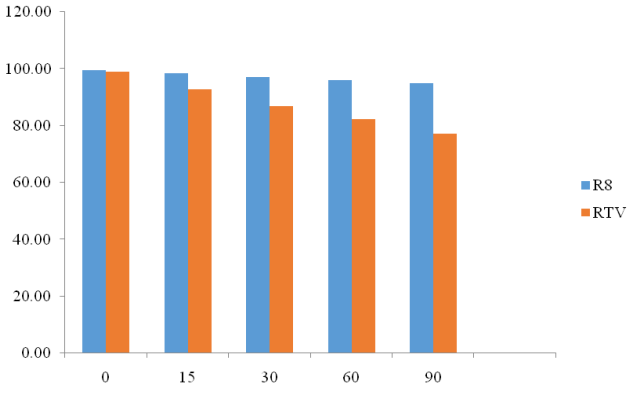


**Figure 13:** Stability study using drug content study of R8 and RTV

Adeq precision of 37.378, which may be utilized to explore the design space.

The relation between independent and dependent variables can be stated as follows,

$$\text{Concentration in} = +1095.79 + 475.97X1 + 117.78X2 - 18.44X1X2 - 213.05X1^2 - 3.48X2^2 \quad \text{Eq. 1}$$

Factor X1 and X2 exhibited positive effects on concentration in the formulation. The plot of predicted vs. actual and 3D surface response plots are shown in Figure 15A and 15B, respectively.

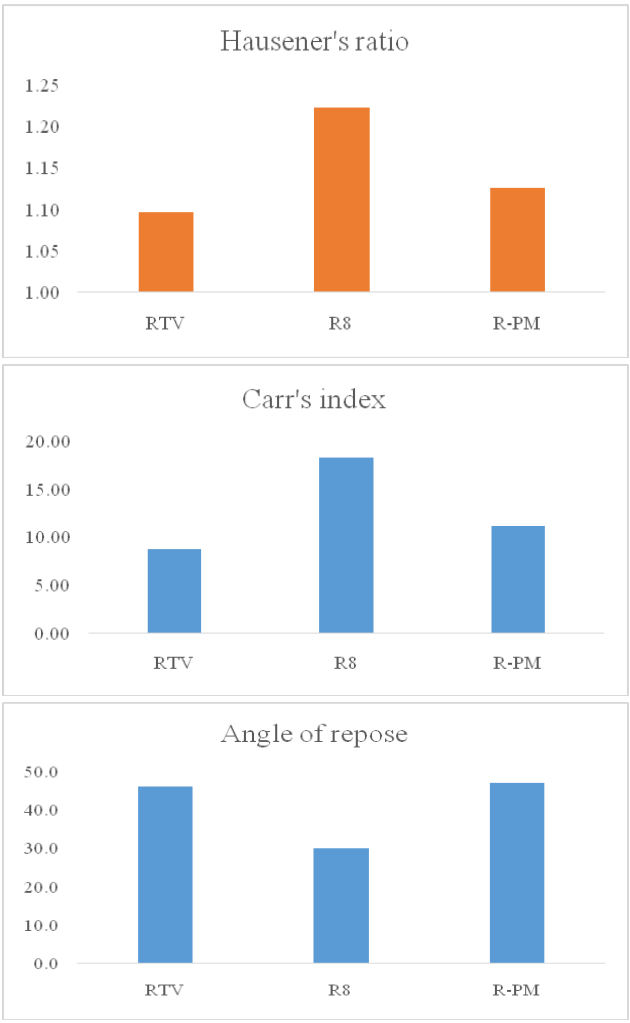


**Figure 14:** Micromeritics Properties of RTV, R8 and RPM batches

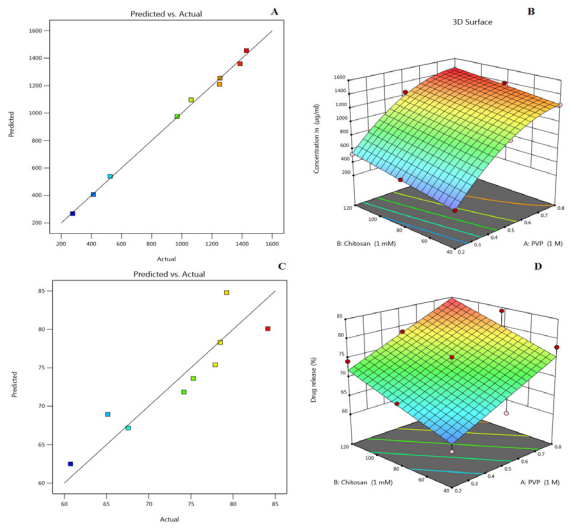


**Figure 15:** (A) Predicted vs. actual plot and (B) The impact of factors on Y1 is shown in a 3D response surface graphic. (C) Predicted vs. actual plot and (D) 3D response surface visualization of variable effects on Y2

There was a clear correlation between the two sets of data in the projected vs. reality figure. To examine the impact of independent factors on dependent variables, 2D and 3D response surface plots were created. Chitosan and PVP exhibited a positive effect on concentration.

*Effect of variables on drug release*

One linear model emerged as the most suitable. With an F-value of 14.52, we can say that our model has statistical significance. As one would anticipate, there is a discrepancy of more than 0.2 between the corrected $R^2$ of 0.7717 and the projected $R^2$ of 0.5454. With an Adeq precision ratio of 10.645, the signal is sufficiently strong. You may use this model to find your way around the design area. The plot of actual vs. predicted values of Y2 is shown in Figure 15C.

Drug release can be estimated using the following eqn,

Drug release= +73.63 +6.46A +4.69B Eq. 2

Chitosan and PVP exhibited positive effects on drug release. This is also confirmed by 3D response surface plot (Figure 15D)

## CONCLUSION

In conclusion, the hydrophilic polymer-based electromagnetic-assisted platform drug delivery system showed promising outcomes in addressing the solubility and permeability issues associated with RTV, a crystalline antiviral drug classified as BCS II. DSC and XRD analysis confirmed the transformation of RTV from its crystalline to its amorphous state. Microwave irradiation, in combination with CH and PVP, facilitated this polymorphic transformation, leading to an enhancement in dissolution profile and saturation solubility. Dissolution rate studies revealed that a specific formulation (R8 batch), containing the highest concentration of PVP and a medium concentration of CH, exhibited superior release properties compared to RTV alone. Overall, this study validates the successful application of the electromagnetic-assisted platform drug delivery system in addressing the solubility and micrometric challenges associated with BCS II drugs like RTV. The combination of microwave radiation and the incorporation of CH and PVP contributed to favorable drug release phenomena and improved micrometric properties. These findings highlight the potential of the radiation-based platform in enhancing the pharmaceutical and micrometric characteristics of BCS II drugs, with CH and PVP playing a key function in the polymorphic transformation and improved drug performance.

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