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Optimization of Ritonavir Preformulation: Techniques and Approaches for Enhancing Drug Formulation

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Excipients are essential for creating a stable, safe, and effective dosage form. A natural polymer called Lapidium Sativum lyophilized powder was used to create a co-processed excipient. Drug excipient compatibility was examined using a range of approaches, including DSC, infrared (FT-IR) Fourier transform spectroscopy, particle X-ray diffraction, after first drug identification and preformulation process development. The preformulation research aims to provide an elegant, simple, and cost-effective approach for determining Ritonavir in bulk dosage forms, as well as an in-vitro study. Ritonavir absorbs at 290 nm. Curves for calibration are displayed across specified wavelengths, and they were determined to be straight between 5 and 30 mcg/ml. The recovery experiments demonstrated the suggested methods accuracy, and the findings were validated in accordance with ICH recommendations. Precision and accuracy investigations were conducted, and good findings were obtained. The validity of Ritonavir was confirmed by DSC and FITR spectra. Ritonavir concentrations in bulk and blood plasma were determined using a UV spectrophotometric technique. Research were conducted into the level of saturation solubility, micromeritical characteristics, temperature of melting, pH, the humidity, and equilibrium profile. The UV method was continuous from 5 to 50 μg/mL. The small % CV values for intra-day and inter-day variations indicated the proposed technique's resilience. A very high regression coefficient value of 0.999 indicated the robustness of the approach. The physicochemical evaluation of the medication indicated RIT's appropriateness for the oral route. In brief, pharmaceutical preformulation investigations were conducted to ensure the successful creation of coprocessed excipients for safe and effective formulation development.

Keywords: Calibration; Differential Scanning Calorimetry (DSC); Preformulation; Retonavir; Spectroscopy.

Ritonavir inhibits the HIV-1 and HIV-2 proteases by peptidomimetic mechanisms. Inhibition of HIV protease prevents the enzyme from digesting the precursor of the gag-pol polyprotein, which causes the development of immature HIV particles that are not infectious. Ritonavir is a white to light brown powder with a sharp metallic taste. Antiretroviral medication with HIV protease inhibitor.

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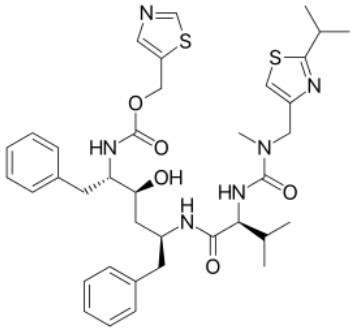

Mol. wt - 720.9 g/mol, Mol For - $C_{37}H_{48}N_6O_5S_2$,
Half Life: 3-5 hours[1]

Preformulation is a group of research that examine a novel drug candidate's physicochemical characteristics and how they might affect dosage form development and therapeutic performance. Preformulation study is to determine the kinetic rate profile, compatability with other components, and physicochemical parameters of novel medicinal substances in order to create a dose form that is elegant, stable, effective, and safe. Extensive characterisation of a medicine is required to properly understand its characteristics. The data produced from the preformulation research gives reasonable evidence for developing a safe and efficient formulation. This knowledge could potentially be beneficial for product development or to demonstrate the need for chemical modification. Therefore, throughout the current work, preliminary formulation tests were conducted on Ritonavir (RIT) to test its suitable for oral dosage form. RIT is a peripherally acting dopaminergic D2 receptor inhibitor with a high initial metabolism after consumption. The RIT in mass and plasma form were determined using an ultraviolet (UV) spectrophotometric methodology. The liquid chromatography approach, accordingly. Absolute dissolution, micromeritical properties, temperature of melting, pH levels, the humidity, and stabilisation pattern were studied. The ultra violet (UV) method was proportional in the region of 5-30 µg/mL. The small % CV values for variations indicated the proposed method's resilience. The technique's resilience was proved by an exceptionally high coefficient of variance (0.999).

Results from the psychometric testing on the medicine demonstrated that RIT is suitable for consumption through the mouth. Furthermore, the medication proved to be stable under a variety of situations. The conventional preformulation investigation necessitates drug characterisation in both solid as well as liquid forms. Preformulation can assist reduce costs for efficient Pharmacological growth of the medication. Curative effect of a pharmacological item designed for oral administration is mostly dependent on gastrointestinal absorption. However, in order to be absorbed, a drug ingredient must be solubilized.

A significant number of new chemical molecules and classical compounds are discovered to be weakly water soluble in nature. To improve medication delivery, pharmaceutical researchers must address the matter of poor water solubility. Ritonavir is a BCS-class 4 medication with a moderate solubility and penetration profile. In the current study, ritonavir, a popular antiviral medicine, was chosen as a possibility. Preformulation can help to reduce the product cost for successful medicinal formulation advancement.[2,3]

MATERIAL AND METHODS

Ritonavir (RIT) is supplied from Zhejiang Pharmaceutical Co. Ltd. in China. the alcohol methanol was acquired via M/s Finar Limited of Ahmedabad, India. The research facility produced a buffer with phosphate pH 6.8 and twice distilled water for testing. Preparation is an essential step in the manufacturing and creation of medicinal products to ensure the most suitable form of administration and excipients. In the medication preformulation research, certain variables were tested:

Analytical Preformulation

Estimation of Substance in Bulk Ritonavir was quantified in bulk using the UV spectroscopic technique described below8. Equipment A UV spectrophotometric study was carried out using a twin beam UV spectrophotometer with Quartz cells measure 1 cm. The instruments setting were modified to provide a spectrum with around 80% full-scale levels. Each band was recorded in threefold. For every subsequent examination, the cell was filled with new fluid.[4]

Developing a Phosphate Buffer with a pH value of 6.8

Mix 28.8 g for of Di-sodium hydrogen phosphate with 11.45 g of potassium hydroxide phosphate in the correct amount of water to generate 1000 mL. The UV spectrophotometer was used to detect the ultraviolet absorption of a 10 g/ml concentration in a buffer with phosphate (pH levels as = 6.8) between 200 and 400 nm. RIT has limited water solubility (BCS Class II). To create the stock solution, 100mg of RIT was properly weighed and fully dissolved in 5 ml of methanol. To generate a 1000 µg/ml solution, appropriate solvents were gently added to the dissolved RIT to prevent deposition. To create a 100 µg/ml solution, 10 ml of the original solution had been reduced to 100 ml.(97.98) A stock solution of RIT at 100mg/100ml was produced in 0.1N HCl. To obtain a 100 µg/ml solution, 1 ml of the generated stock solution was diluted to 10 ml. The same procedure was followed for phosphate buffer at pH 6.8. To achieve dilutions of 5-30 µg/ml, aliquots were obtained from the stock solutions and diluted with the appropriate solvent. The measurements were made in duplicate and monitored for three days to check for intra as well as interday changes. Design of a calibration graph A calibration curve was constructed using values between 5 and 30 µg/ml. Each solution's absorbance was calculated at a wavelength of 290 nm. At 290 nm wavelength, absorbance versus concentration was graphed to construct the Ritonavir calibration curve. Three copies of the test were taken.[5,6]

Physical and chemical characteristics and Micromeritical Preliminary formulation Maximum Solubility Research

Ritonavir has been mixed abundantly in a fresh and dry volumetric vessel then scattered in 50 mL of filtered liquid. The combination of ingredients was effectively agitated, then the total solution volume was lowered to 100 ml before shaken for approximately ten minutes using an inverted mixer orbit spinner (CIS-24 Remi, India). The solution was set aside for 15 minutes before a 5 ml sample was taken out from the remainder of the solution and examined using a conventional chemical technique. The method was performed again using several solvents (Methanol, Ethanol, Phosphate buffer pH 6.8).[7]

Melting Point

The M.P. was obtained using the capillary fusion method in melting point equipment. The capillary was sealed at one end and it is filled with small quantity of Ritonavir, then flipped and placed in the melting point instrument.[8]

The pH level at 1% RIT liquid

A pH meter that was digital was employed to monitor the pH of a 10% RIT solution (10mg/100mL).[9]

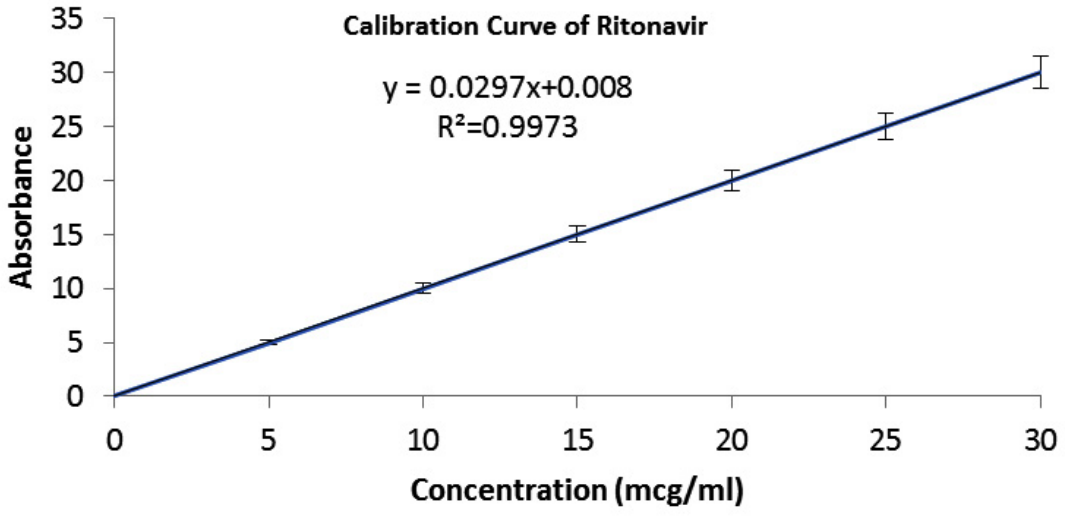

Fig. 1. Standard Calibration Curve of Ritonavir in 0.1 N HCl
Each value represents the mean ± standard deviation (n=3)

Hygroscopicity

Multiple specimens of 25 milligrams RIT were put in Mirrored dish cups and subjected to varying moisture levels in desiccants (already measured) a set timeframe. The quantity of Moist got soaked & evaluated by gravimetric measurement. Heterogeneous Phase Equilibrium Study. RIT were accurately measured and disseminated in water after evaporation. The liquid was disclosed to different circumstances for a certain amount of time and its RIT content was monitored on a regular basis. The drug's stability in the The existence of sunlight, air, humidity, pH values, and strength of ions was also assessed.[10]

Differential Scanning Calorimetry (DSC)[11]

The DSC examination was carried out with a Netsch DSC 204. The specimens were warmed in a wide aluminum pan at a rate of 100 per minute in a temparature that varied from 30 to 3000 degrees Celsius with a nitrogen supply of 40 millilitres per minute.

Fourier Transform Infrared (FTIR) Spectroscopy

Using a Shimadzu FTIR Model 8400-S spectrometer, the FTIR data were collected. The spectra were captured using an infrared disc with a The measurement frequency is between 400 and 4000 cm-1 & a spatial resolution of 1 cm-1, using a specimen dispersion in potassium bromide (2 mg sample in 200 mg KBr).[12]

Micromeritical Properties

Particle size and placement were assessed using a A regulated laser. The total density and degree of tension were computed using conventional density equipment and the fixed funnel technique, correspondingly. The Carr's Index (%) and Hausner's ratio were evaluated by equations :

Carr's Index (%) = TBD-LBD/TBD × 100. Hausner's ratio equals TBD/LBD.[13]

RESULT AND DISCUSSION

Analytical Techniques considering their relevance in pharmaceutical analysis, spectrophotometry technologies for drug determination have seen significant advancement in recent years. The standard calibration curves were created using the experimental data. The examination of regression revealed a very excellent association (r2=0.997 in phosphate buffer and 0.9973 in methanol).

The approach's efficiency was assessed by estimating RIT recoveries using the conventional addition technique at each of the three levels (80%,

Table 1. Preliminary formulation variables for RIT

Parameters	Description	Results Ritonavir
Organoleptic Properties	Display	White Crystallized Flour
	Smell	Characteristics
	Taste	Bitter
Saturation Solubility	D. W. (mg/L)	48.23±1.19
pH solubility profile	pH is 1.2 buffer (mg/L)	97.12±4.29
	pH 4.5 buffer (mg/L)	11.51±5.23
	pH 6.8 buffer (mg/L)	31.5±2.56
	pH 7.4 buffer (mg/L)	87.54±1.23
Partition Coefficient	Octanol /Water	3.37
Melting Point	°C	129-133
Micrometrical Properties	Average particle size	319.27 ± 21.18
	Bulk density	0.527 ± 0.15
	Tapped density	0.637 ±0.01
	Carr's density	17.54385965
	Hausner's ratio	1.2
Assay(Purity)	%	100.01±3.25
Intrinsic Dissolution Rate (IDR)	mg/min/cm^2	0.0087±0.0001

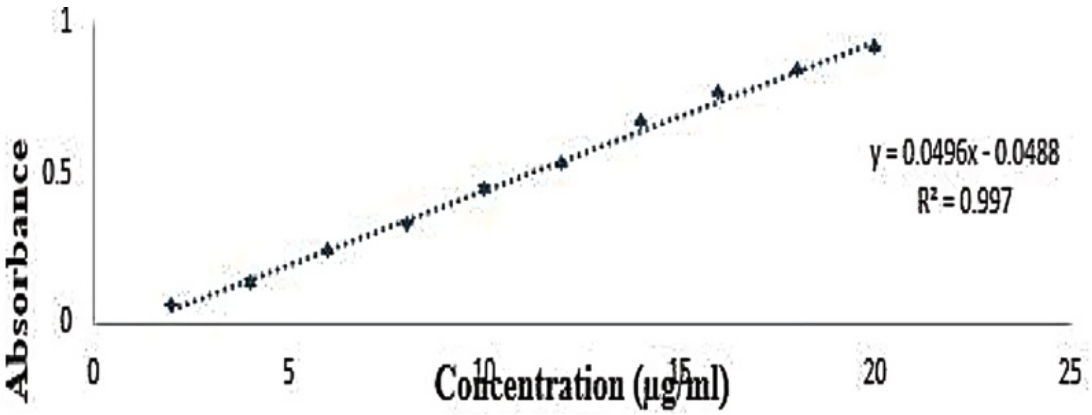

Fig. 2. Standard Calibration Curve of Ritonavir in Phosphate Buffer pH 6.8

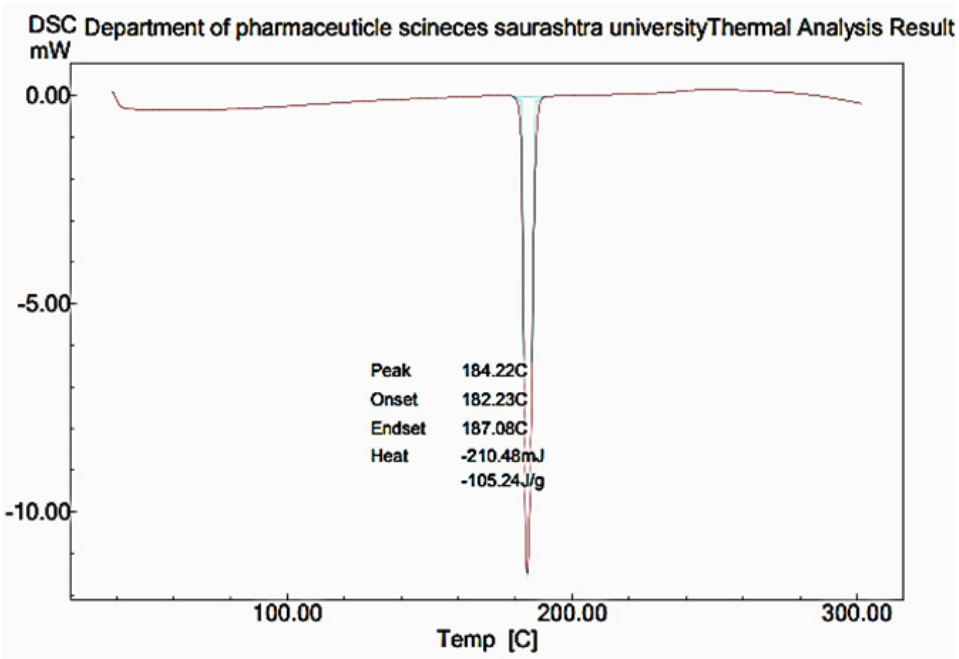

Fig. 3. DSC spectrum on pure Ritonavir

100%, and 120%). The mean % restoration was calculated. Intraday precision was assessed by analysing medicines at multiple concentrations (10, 20, and 30ìg/mL) at three separate times on the exact same day. Inter-day accuracy was measured in a similar manner, but the analysis was performed everyday for two days. The method's intraday consistency was established by analysing six specimens with the same dosage levels (10, 20, and 30ìg/mL).

To calculate the variance, each absorbance was measured and presented as a relative standard deviation. The method's specificity was assessed by comparing the UV spectra of blank samples in the presence and absence of excipients, scanning at 290nm, and checking for absorbance variations.[14,15]

Ritonavir's oral administration profile is determined by its organoleptic, solubility, and physicochemical qualities.

Figure 3 shows the DSC Thermogram of Ritonavir. Pure drug (RIT) had an endothermic peak at 184.22 °C.

The distinctive absorption peaks of Ritonavir in FT-IR spectra, as illustrated in Figure

Table 2. Solid state stability study of RIT

No.	Influencing factors	Test Samples	Packaging material	Storage condition	Storage times (weeks)	Physiacal degra dation	Drug Contents
1	Moisture	Pure drug Substance	Open container	25°C/75 % R.H.	0 1	No No	98.99 ± 0.32 98.79 ± 0.29
2	Tempareture	Pure drug substances	50 mlGlass Container Withtwist-off Closure	70 °C	0 2 4	No No No	99 ± 0.74 100.43 ± 0.82 98.45 ± 0.45
3	Temperature+ Moisture	Purified Chemical material with consumed water. 25°C/75% humidity	50 milliliters bottle with a twist-off cap.	70 °C	0 2 4	No No No	99.24 ± 0.34 100.23 ± 0.11 99.31 ± 0.58
4	Oxidation	1%Aq.Sol. In 0.35 H2O2 Solution	25 mL crystal beaker with a glass cap.	50 °C	0 1 3	No No No	99.12 ± 0.63 100.66 ± 0.31 98.78 ± 0.38
5	Light	Pure Drug Substance	Open petridish	Xenon Lamp	24 hr 48 hr	No No	99.45 ± 0.33 101.34 ± 0.68

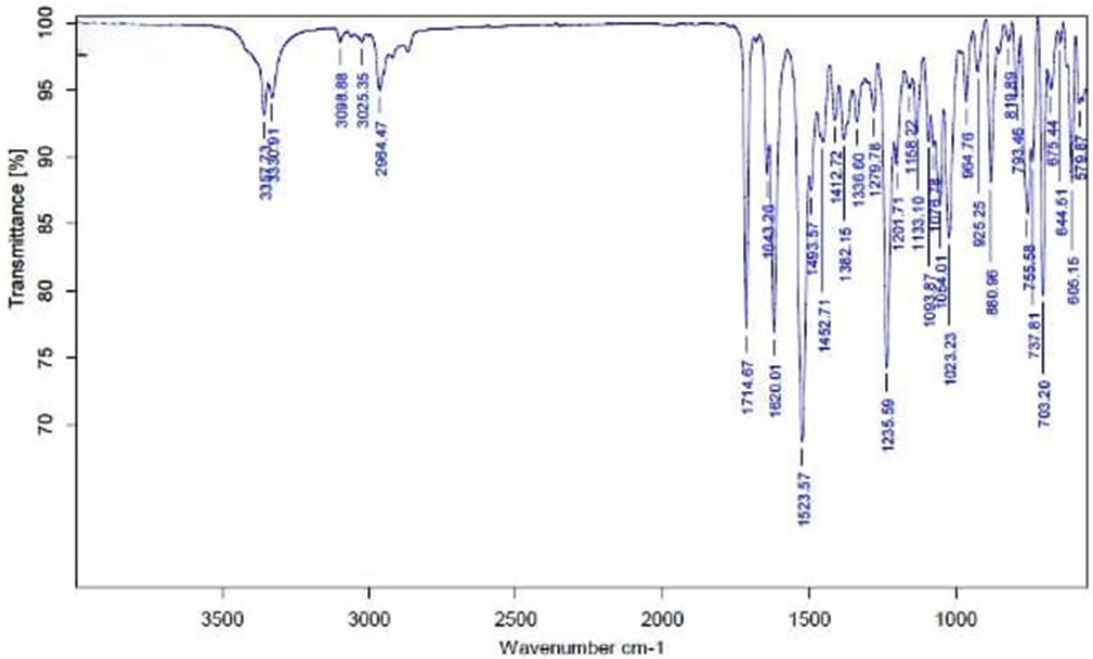

Fig. 4. FTIR Spectrum of Clear RIT

4, demonstrate a stable and clean pharmacological profile.

Furthermore, Ritonavir's stability was also evaluated under various degrees of humidity, daylight, burning, and the pH level conditions. The results of the durability investigation under preliminary formulation revealed that the drug's characteristics were stable under varied storage circumstances, as shown in the Table

CONCLUSION

The findings of the various preformulation studies show that RIT is appropriate for oral Preparation. The pH of RIT was discovered to be 6.5, indicating minimal irritation to the oral mucosa. The stability analysis conducted during preformulation indicated stable drug properties in both solid and aqueous states, validating the formulation's ultimate stability. In a nutshell, because to RIT's high first pass metabolism, it might be taken orally to increase bioavailability. This study additionally demonstrates that RIT can be administered as an oral spray.

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Conflict of Interest

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Authors Contribution

Pratiksha Prayag Nahar : Introduction, Result, Preliminary formulation variables for RIT, Conclusion and all remaining data.; Dinesh Prabhakar Patil : Materaial and Methods, Fourier Transform Infrared (FTIR) Spectroscopy, Preliminary formulation variables for RIT; Mahfoozur Rahman Malik: Developing a Phosphate Buffer with a pH value of 6.8, Calibration curve; Mitusha Devanand Chavan :Differential Scanning Calorimetry (DSC), Micromeritical Properties; Shekhar Dipak Jagtap : Solid state stability study of RIT

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