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RESEARCH ARTICLE

Formulation and *In vitro* Evaluation of Sublingual Tablets of Ranolazine

Sandhya Jyothi R*[1], Gayatri Ramya Munagala[2], Madhuri D[3]

[1] *Student, Department of Pharmaceutics, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur Pin code-522510, Andhra Pradesh, India*
[2] *Associate Professor, Department of Pharmaceutics, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur Pin code-522510, Andhra Pradesh, India*

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Abstract:
The aim of this study was to create and assess Sublingual tablets of Ranolazine, an effective drug for treating Angina pectoris. The method involved utilizing super disintegrants through direct compression to develop these tablets, offering advantages such as rapid onset of action and bypassing the liver. Sublingual drug delivery provides an effective and convenient approach to managing Angina. Ranolazine underwent characterization based on its physicochemical properties, including melting point, solubility, UV, and FTIR studies. Croscarmellose sodium served as the super disintegrant, while HPC, HPMC, and Starch were employed as tablet binders, and microcrystalline cellulose as tablet diluents. Ten formulations (F1-F10) underwent preparation and evaluation. The tablets exhibited hardness ranging from 4.0 to 5.8 kg/cm^2, friability between 0.21 and 0.46%, weight variations, disintegration time spanning from 10 to 24 seconds, and in-vitro drug release varying from 61.82 to 96.79%. Among the formulations, F1, utilizing HPC as a binder, emerged as the best formulation based on its drug release characteristics. In conclusion, this study demonstrated that the inclusion of superdisintegrants enhanced the solubility and in-vitro release of Ranolazine.

Keywords: Sublingual tablets; Ranolazine; Angina pectoris; Croscarmellose sodium; Binders.

1. Introduction

Oral administration, a common route for drug delivery, involves taking substances through the mouth, often chosen for systemic effects. However, the sublingual route has gained attention due to its potential for immediate pharmacological effects, bypassing first-pass metabolism. Sublingual glands, also known as salivary glands, contribute to drug delivery, offering advantages like rapid absorption and maintaining oral hygiene. Factors affecting sublingual absorption include drug lipophilicity, solubility in salivary secretion, saliva pH, binding to oral mucosa, oral epithelium thickness, and oil-to-water partition coefficient. Advantages of sublingual administration include rapid onset, bypassing the liver, enhanced patient compliance, and reduced side effects. Despite these benefits, sublingual administration has drawbacks, such as interference with daily activities, unsuitability for sustained drug delivery, and limitations on patient cooperation. Different dosage forms like tablets, films, and sprays are utilized, each with its own preparation methods and advantages. Angina pectoris is a symptom resulting from an oxygen supply-demand imbalance, often treated by increasing blood flow to the heart. Ranolazine, a piperazine derivative, serves as a novel antianginal agent for chronic stable angina pectoris. Administered as extended-release tablets, ranolazine's mechanism of action is not fully understood, but it proves effective without significant changes in blood pressure or heart rate. The drug's pharmacokinetics involve metabolism by cytochrome P450 enzymes and exhibit suitability for patients with moderate hepatic impairment. In renal insufficiency, ranolazine concentrations increase, but food intake has no significant effect on its bioavailability. The main objective of this study is to develop and evaluate sublingual tablets of Ranolazine for the treatment of Angina pectoris

2. Materials and methods

2.1. Materials

Ranolazine was obtained as a complimentary sample from Zydus Cadila, Ahmedabad, India. Microcrystalline cellulose, Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose, Magnesium stearate, and Talc were acquired from Loba Chemie Pvt. Ltd., Mumbai, India. Croscarmellose Sodium was sourced from Ozone International, India, while Methanol and starch were purchased from Thermo Fisher Scientific India Pvt. Ltd, Mumbai.

* Corresponding author: Sandhya Jyothi R

2.2. Preformulation studies

2.2.1. Organoleptic properties

A small amount of the drug sample was placed in a watch glass and examined for its physical characteristics, including color and odor, through visual observation.

2.2.2. Determination of melting point

The melting point, the temperature at which a solid transforms into a liquid, was assessed for Ranolazine using the capillary tube method. This involved sealing one end of a capillary tube, placing a small drug sample inside, and determining the melting temperature using a thermometer in a melting apparatus

2.2.3. Solubility studies

Ranolazine drug solubility investigations were conducted with various solvents. In these experiments, a small amount of the drug sample was dissolved in 1ml of different solvents in a test tube. The drug and solvent were stirred using a vortex mixer until the drug completely dissolved in the specific solvent.

2.2.4. Construction of calibration curve

A 100mg quantity of Ranolazine was accurately weighed and dissolved in methanol in a 100 ml volumetric flask, creating a solution with a concentration of 1000µg/ml. Subsequently, working stock solutions of 500µg/ml and 100µg/ml were derived by pipetting 50ml and 20ml, respectively, from the stock solution and diluting in 100ml volumetric flasks. UV scanning of the 100µg/ml solution revealed a maximum absorbance at 273nm. For the calibration curve, working solutions spanning concentrations of 20 to 140µg/ml were prepared from the stock solution, and their absorbance at 273nm was measured. A graph plotting concentration against absorbance was then constructed.

2.2.5. Drug excipient incompatibility studies using Fourier transform infrared (FTIR) analysis

The physico-chemical compatibility between Ranolazine and polymers used in the research were carried out by subjecting to IR spectral studies using Fourier transform infrared spectrophotometer, Bruker. The sample was prepared by mixing the drug with all the excipients

2.3. Preparation of Ranolazine sublingual tablets

Ranolazine sublingual tablets were formulated using the direct compression method, incorporating various excipients such as HPMC, HPC, Starch, croscarmellose sodium, magnesium stearate, Talc, and Microcrystalline cellulose. Precise quantities of polymer and MCC were geometrically mixed in a mortar for each batch. Ranolazine was then added and lightly blended with a pestle, followed by the uniform addition of the required amount of croscarmellose sodium. The resulting powder was sieved through a no. 40 sieve and mixed for 3 minutes. Subsequently, magnesium stearate was added for a few minutes, followed by the addition of talc and an additional 2-minute mixing period. The final mixture, equivalent to 680 mg, was compressed into tablets. The composition of tablets is shown in Table 1.

Table 1. Formulation showing composition of various formulations of Ranolazine sublingual tablets

Ingredients	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8 (mg)**	**F9 (mg)**	**F10 (mg)**
Ranolazine	500	500	500	500	500	500	500	500	500	500
Croscarmellose Sodium	25	22.5	20	2.5	15	25	17.5	15	20	2.5
Microcrystalline Cellulose	100	105	110	122.5	110	100	115	120	125	145
HPC	27.5	25	22.5	-	-	-	-	-	-	-
Starch	-	-	-	25	27.5	29.5	-	-	-	-
HPMC	-	-	-	-	-	-	27.5	17.5	12.5	10
Magnesium Stearate	2.5	5	7.5	15	9	5	7.5	10	15	17.5
Talc	25	22.5	20	15	18.5	20.5	12.5	17.5	7.5	5
Total weight	680	680	680	680	680	680	680	680	680	680

2.4. Determination of flow properties

2.4.1. Bulk density

1g of accurately weighed valsartan was placed in a10ml measuring cylinder. Volume occupied by the drug was noted after tapping of cylinder for 3 times onto a hard surface. The bulk density was calculated using the following equation. The values expressed in gm/cc^3.

$$\text{Bulk density} = \frac{\text{weight of powder}}{\text{volume of powder}}$$

2.4.2. Tapped density

Accurately weighed 1g of drug was placed in 10ml measuring cylinder. The cylinder was dropped onto a hard surface 100 times from a height of 1 inch. The final volume was recorded and the tapped density was calculated by the following equation. The values are expressed in gm/cc^3.

$$\text{Tapped density} = \frac{\text{weight of sample}}{\text{tapped volume of sample}}$$

2.4.3. Carr's compressibility index

The Carr's index is frequently used as an indication of the Flowability of a powder. Flow property of blend depends upon compressibility index. A value less than 15 is indicated as excellent flow. It is calculated by the formula.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{tapped density}} * 100$$

2.4.4. Hausner's ratio

Hausner's ratio is an indication of the compressibility of a powder. The Hausner's ratio is frequently used as an indication of the Flowability of a powder. A value less than 1is indicated as excellent flow .It is calculated by the formula.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} * 100$$

2.4.5. Angle of repose (θ)

The sample powder was allowed to flow from the funnel, so the height of the pile just touched the tip of the funnel. Funnel was adjusted in such a way that the stem of the funnel lies 2.5cm above the horizontal surface. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of 3 diameters. A value less than 20 is indicated as excellent flow. The angle of repose is calculated by using this formula:

$$\theta = \tan^{-1} h/r$$

Where, θ is angle of repose,
h is the height of the pile,
r is the radius of the pile.

2.5. Evaluation of sublingual tablets

2.5.1. Thickness

From each formulation one tablet was taken and individual tablet thickness was measured by using Vernier caliper.

2.5.2. Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each formulation one tablet was taken and measured for hardness.

2.5.3. Weight variation test

To study weight variation individual weights (W_1) of 3 tablets from each formulation were noted using electronic balance .Their average weight (W_A) was calculated. Percent weight variation was calculated as follows .Average weights of the tablets along with standard deviation values were calculated.

$$\%\text{weight variation} = (W_A - W_1) \times 100 / W_A$$

2.5.4. Friability

From each batch 3 tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator).Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating .The tablets were then taken after 100 Rotations, deducted and reweighed .The friability was calculated as the percentage Weight loss.

$$\%\text{Friability} = (W_1 - W_2) \times 100 / W_1$$

Where, W_1=initial weight of the 3 tablets, W_2=Final weight of the 3 tablets after testing.

Disintegration time

The disintegration time of the tablets was determined as for Indian pharmacopoeia. The test was carried out using USP XXII disintegration apparatus. 0.1 N Hcl was used as a disintegrating medium at 37+/- 0.5°C. The required to obtain complete Disintegration of all the tablets was noted.

2.5.5. Drug Content

Five Tablets were weighed and powdered in a motor. Accurately weighed tablet powder samples equivalent to 500mg of Ranolazine was transferred to a 100 ml volumetric flask and the Ranolazine was extracted into 75ml methanol. The solution was suitably diluted with 0.1N HCL and the absorbance was measured at 273nm.The estimations were carried out in triplicate

2.5.6. In vitro drug release study

Drug release was assessed by using dissolution apparatus USP type II (paddle Method).The Invitro release ranolazine tablets was studied in 900 ml of 0.1 normal Hcl for 2 hr at 37+/- 0.5°C at 100 rpm. Aliquot 5 ml sample was withdrawn at specific time intervals and replaced with the same volume of fresh dissolution medium. The absorbents values were analyzed by UV visible spectrophotometer at 273 nm.

2.5.7. Drug release kinetics

Following the in-vitro dissolution study, the obtained data was subjected to fitting into various experimental models. The Zero-Order Model, commonly used for assessing drug release from modified dosage forms, is expressed by the equation Qt = Q0 + Kat, where Qt represents the amount of drug dissolved at time t, Q0 is the initial amount of drug in the solution, and Ka is the zero-order release constant in terms of concentration per unit time. The First Order Model, applied to describe drug release from porous matrices containing water-soluble drugs, is expressed by the equation Log C = Log C0 – Kt/2.303, where C0 is the initial concentration of the drug, Kt is the first-order rate constant, and C is the concentration of the drug after time t. The Higuchi Model, the first mathematical model used to describe drug release from matrix tablets, is represented by the equation Ft = Q = A √D (2Cs)* Cst, where Q is the amount of drug release in time t per unit area A, C is the initial drug concentration, CS is the drug solubility in the matrix system, and D is the diffusivity of drug molecules in the matrix substance. The Korsemeyer-Peppas Model, characterizing drug release from polymeric systems, is expressed by the equation Mt/M = Ktn, where Mt/M represents the fraction of drug release at time t, K is the release rate constant, and n is the release exponent characterizing different release mechanisms for various geometrical-shaped matrices

3. Results and Discussion

3.1. Preformulation studies

In the pre-formulation studies, various organoleptic properties were assessed. The studies indicated that ranolazine is as an amorphous powder with a white to off-white solid color and an odorless nature. Flow properties of the active pharmaceutical ingredient (API), Ranolazine, were further examined, revealing an angle of repose of 30°, bulk density of 0.44 g/ml, tapped density of 0.49 g/ml, Carr's index of 10.20%, and Hausner's ratio of 1.11. Solubility studies were conducted using different solvents, demonstrating the drug's high solubility in methanol, acetonitrile, chloroform, acetone, dimethyl formamide, ethanol, isopropyl alcohol, dichloromethane, benzene, dimethyl sulfoxide, and glacial acetic acid. Additionally, solubility assessments in specific solutions such as 0.1N HCl, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer, and distilled water were conducted, indicating the highest solubility in 0.1N HCl (38.328 mg/ml) and the lowest solubility in distilled water (0.02 mg/ml). This information is crucial for understanding the drug's characteristics and optimizing its formulation for pharmaceutical use

3.2. Analytical studies

The calibration curve data indicates a consistent and proportional increase in absorbance as the concentration of Ranolazine escalates. This linear correlation is evident from the gradual rise in absorbance values from 0.145 at 20 µg/ml to 0.924 at 140 µg/ml.

The calibration curve graph in Figure 1 visually reinforces the linear trend observed in the tabulated data, providing a clear and concise representation of the drug's concentration-dependent absorbance behavior. This curve is crucial for accurate quantification of Ranolazine in subsequent analyses, enabling precise determination of its concentration based on absorbance measurements

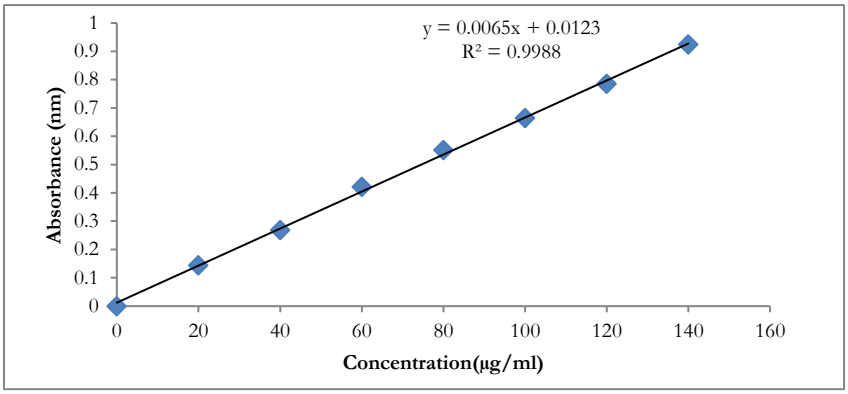

Figure 1: Calibration curve graph of Ranolazine

3.3. Drug Excipient Incompatibility studies using FTIR

The FTIR (Fourier Transform Infrared) results provide valuable insights into the functional groups and chemical interactions present in the Ranolazine and excipient mixture. The identified functional groups, including C=O stretching, N-H stretching, C-O stretching, O-H stretching, C=C stretching, and C-H stretching, are associated with specific ranges of wavenumbers. Upon analysis of the obtained peaks and their corresponding wavenumber ranges, it is evident that all peaks fall within their expected intervals. The C=O stretching falls between 2000 - 1670 cm^{-1}, N-H stretching between 3425 - 3140 cm^{-1}, C-O stretching between 1300 - 1000 cm^{-1}, O-H stretching between 3700 - 3500 cm^{-1}, C=C stretching between 1650-1450 cm^{-1}, and C-H stretching between 3000 - 2500 cm^{-1}. The fact that all observed peaks align with their designated ranges suggests that there is no significant shift or broadening of peaks (shown in Figure 2), indicating the absence of chemical interactions between Ranolazine and the excipients. This consistency in peak positions implies that the drug and excipients are compatible, and there is no evidence of drug-excipient incompatibility.

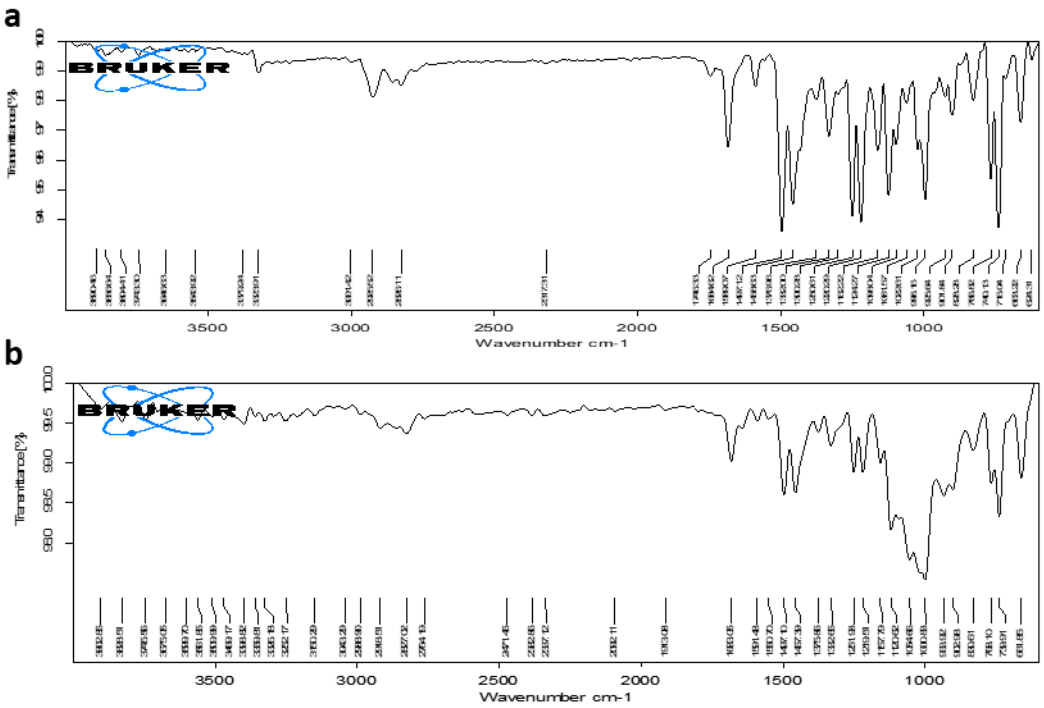

Figure 2. FTIR spectrum of a. Pure drug b. Drug + Excipients (1:1 mixture)

3.4. Precompression parameters

In the evaluation of various formulations of Ranolazine, the measured flow properties exhibited favorable characteristics. The angle of repose, representing the powder pile's maximum slope, ranges from 28 to 32 degrees, indicating a free-flowing nature with minimal cohesion. Carr's index, reflective of powder compressibility, ranges between 8% and 12%, demonstrating low compaction and excellent flow. Similarly, Hausner's ratio, indicating powder flowability, falls within the range of 1.05 to 1.15, suggesting low interparticle friction and efficient flow. These values collectively affirm that all formulations of Ranolazine possess good to excellent powder flow properties.

3.5. Post compression parameters

The results of post compression parameters presented in Table 2 provide a comprehensive overview of the characteristics of formulations F1 to F10 for Ranolazine. The hardness values, ranging from 4.0 to 5.8, reflect satisfactory tablet strength. Weight variation, within the range of 678 to 681 mg, indicates uniformity in tablet weight across all formulations. The friability, varying between 0.21% and 0.46%, falls within acceptable limits, highlighting the tablets' resistance to breakage during handling and transportation. The drug content, consistently uniform and ranging from 93.51% to 98.99%, ensures reliable and precise dosage delivery. Moreover, the disintegration time, spanning from 10 to 24 seconds across formulations, meets standard pharmaceutical expectations. Overall, the results suggest that the formulations (F1 to F10) exhibit desirable physical and chemical attributes, indicating their potential suitability for pharmaceutical use in terms of hardness, weight consistency, friability, drug content uniformity, and disintegration time.

Table 2: Determination of Evaluation parameters

Formulations	Hardness	Weight variation#	%Fraiability#	Drug content#	Disintegration Time (sec)
F1	4.0	680±0.90	0.25±0.07	95.14±0.57	10
F2	4.4	679±0.94	0.21±0.11	93.51±0.57	11
F3	4.7	680±0.92	0.24±0.15	95.00±0.42	12
F4	5.3	680±1.02	0.29±0.09	96.85±0.32	19
F5	5.5	680±1.12	0.37±0.44	95.79±0.27	20
F6	5.8	678±1.36	0.32±0.62	97.01±0.89	24
F7	4.9	680±1.22	0.42±0.53	96.15±0.42	17
F8	4.5	680±1.55	0.46±0.20	97.97±0.84	15
F9	5.0	680±1.52	0.28±0.32	98.99±0.42	19
F10	4.6	680±1.45	0.34±0.09	96.31±0.16	14

Mean ± SD (n = 3 observations)

3.6. *In vitro* drug release studies

The *in vitro* drug release studies for formulations F1 to F10 over a time course of 30 minutes reveal distinct release profiles. In the initial 5 minutes, formulations F1, F3, F6, F7, F8, and F9 exhibit notable drug release percentages, with F7 reaching 47.10%. By the 10th minute, F3, F6, F7, F8, and F9 continue to demonstrate accelerated drug release, surpassing 50%, with F9 achieving 77.88%. Subsequently, at the 15th minute, all formulations display substantial drug release, ranging from 62.63% to 82.70%, indicating a sustained release pattern. Formulations F3, F6, F7, F8, F9, and F10 maintain this trend, surpassing 88% drug release by the 25th minute, with F9 reaching 88.97% (Results are shown in Table 3). Overall, the cumulative drug release reaches a maximum of 96.79% by the 30th minute for F1, suggesting efficient drug dissolution. These results imply that formulations F3, F6, F7, F8, F9, and F10 exhibit promising in vitro drug release characteristics, indicating their potential suitability for controlled release formulations. The variations in release profiles among the formulations could be attributed to differences in the composition and ratios of excipients, demonstrating the importance of formulation design in influencing drug release kinetics.

Table 3. *In vitro* drug release profiles of all formulations

Time	% Cumulative Drug Release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
5	33.72	14.98	24.35	28.37	11.50	19.27	47.10	32.83	63.43	48.98
10	47.91	35.33	44.69	37.20	20.07	26.23	52.19	41.77	77.88	53.79
15	62.63	58.61	59.15	44.16	24.62	37.20	64.77	69.05	82.70	65.04
20	73.60	69.32	64.77	48.98	36.40	41.48	74.67	74.70	86.98	74.40
25	89.93	75.21	73.60	58.08	44.16	48.71	88.05	83.50	88.97	83.50
30	96.79	82.70	79.49	62.09	63.16	54.60	91.53	94.21	90.46	89.39

3.7. Drug release kinetics

The calculated R^2 values indicate that the first-order kinetics model better describes the drug release behavior for all formulations. The R^2 values for the first-order model range from 0.877 to 0.994, suggesting a high degree of correlation between the observed and predicted drug release. This implies that the drug release rates are proportional to the remaining drug concentration, characteristic of a first-order release process. The results are shown in Table 4.

Table 12. Drug release kinetics

S.No	Formulations	Zero order	First order
1.	F1	0.957	0.973
2.	F2	0.954	0.990
3.	F3	0.926	0.994
4.	F4	0.891	0.962
5.	F5	0.973	0.911
6.	F6	0.951	0.986
7.	F7	0.846	0.965
8.	F8	0.939	0.943
9.	F9	0.629	0.877
10.	F10	0.846	0.907

4. Conclusion

The current investigation involved the preparation of Ranolazine sublingual tablets using the direct compression method, employing Croscarmellose sodium as a super disintegrant, and varying concentrations of HPC, Starch, and HPMC as binders. Ten formulations were prepared, and the formulation F1 with HPC emerged as the best formulation, exhibiting a drug release of 96.97% and a disintegration time of 10 seconds. FTIR studies confirmed good compatibility between the drug and excipients, and solubility experiments revealed higher solubility in 0.1N HCl compared to other buffers. Preliminary evaluation of physical parameters demonstrated favorable results, and the drug release kinetics analysis favored first-order kinetics, indicating concentration-dependent release.

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