RESEARCH PAPER

Development And Investigation Of Porous Starch Based Formulation Of Ranolazine For Enhancement Of Solubility

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Abstract

Biopharmaceutics classification system (bcs) class ii drugs are characterized by low aqueous solubility and high permeability, which poses significant challenges in achieving optimal bioavailability. This study focuses on the development and evaluation of a porous starch-based formulation to enhance the solubility and bioavailability of a ranolazine. Porous starch, owing to its high surface area and porous network, were utilized as a carrier for drug loading via solvent evaporation and adsorption techniques. The prepared formulations were characterized using differential scanning calorimetry (dsc), fourier-transform infrared spectroscopy (ftir), and x-ray diffraction (xrd) to evaluate drug-excipient interactions, crystallinity, and surface morphology. In-vitro dissolution studies demonstrated a significant improvement in the solubility and dissolution rate of the drug from the porous starch matrix compared to the pure drug. The results suggest that porous starch is a promising carrier for the delivery of poorly water-soluble drugs and can serve as an effective strategy for enhancing oral drug absorption.

Keywords: Porous Starch, Factorial Design, Ranolazine, Sd'S.

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1. Introduction

The oral route is the most preferred and widely accepted method for drug administration owing to its convenience, non-invasiveness, cost-effectiveness, and high level of patient compliance. However, the effectiveness of oral drug delivery is often compromised by poor aqueous solubility of drug molecules, which in turn limits their bioavailability. Approximately 40% of new chemical entities (NCEs) exhibit poor water solubility, posing significant challenges during formulation development [1].

According to the Biopharmaceutics Classification System (BCS), drugs are categorized into four classes based on their solubility and intestinal permeability. BCS Class II drugs are characterized by low solubility and high permeability, meaning their rate-limiting step for absorption is dissolution rather than permeation [2]. Enhancing the solubility and dissolution rate of these drugs is critical to improving their oral bioavailability and therapeutic effectiveness. Numerous formulation strategies such as micronization, solid dispersions, cyclodextrin inclusion complexes, lipid-based systems, and nanoparticulate delivery have been developed to address solubility issues [3]. However, many of these approaches face limitations in scalability, stability, or excipient compatibility.

In recent years, porous carriers have emerged as promising materials for enhancing drug solubility due to their high surface area, large pore volume, and ability to accommodate drug molecules within their porous structure. These carriers can facilitate faster wetting and dissolution of drugs by reducing crystallinity and improving dispersion at the molecular level [4]. Among various porous materials investigated, porous starch has shown potential as a biocompatible and biodegradable carrier for drug delivery.

Porous starch is a modified form of native starch that possesses a sponge-like structure created through enzymatic, chemical, or physical treatments. This structure allows for high adsorption capacity and controlled drug release. The inherent hydrophilic nature of starch improves wettability, while the porous architecture enhances surface contact between the drug and dissolution medium, promoting rapid dissolution [5]. Additionally, starch is an FDA-approved excipient with a long history of safe use in pharmaceuticals, making it suitable for industrial application.

Studies have demonstrated the utility of porous starch in improving the solubility of poorly water-soluble drugs such as ibuprofen, ketoprofen, and fenofibrate [6]. These improvements are often attributed to a combination of mechanisms including increased

surface area, reduction in crystallinity, and transformation into an amorphous form when loaded into the starch matrix [7]. Despite these promising results, further research is required to systematically investigate the physicochemical interactions between BCS Class II drugs and porous starch, as well as the impact on in vivo performance.

This study aims to develop and evaluate a porous starch-based formulation for a model BCS Class II drug to enhance its solubility and bioavailability. The research focuses on optimizing drug loading into porous starch, characterizing the resulting formulation through various analytical techniques, and assessing its dissolution behavior and pharmacokinetic performance. The findings from this study are expected to provide insights into the feasibility of using porous starch as a versatile carrier in solubility enhancement strategies, with potential applications in commercial drug development.

2. Materials and Methods

2.1 Material:

Ranolazine was received as a gift sample from Sun Pharma Industries, Ltd. Plain Starch was received from Loba Chemie, Mumbai, India. All the other chemicals and reagents used were of analytical grade.

2.2 Methods:

2.2.1 Modification of Starch Using Microwave irradiation

With minimal changes, porous starch was made as previously reported [8]. 20 mL of room temperature distilled water was mixed thoroughly with 5 grams of starch. The boiling point was reached in 30 milliliters of distilled water. Subsequently, the boiling water was mixed rapidly with starch dispersion. In order to create a translucent gel, the temperature was gradually lowered to room temperature while stirring continuously. In order to bring the gel into equilibrium, it was kept in excess water at 8°C for the entire night. Next, the gel was exposed to ethanol as a solvent exchange. In order to keep the gel's porous structure intact, it was equilibrated and kept in ethanol for 48 hours at 8°C. The gel was microwave-irradiated to dry it after it reached the equilibrium state. Before being used again, the dried material was ground and vacuum-sealed. Also known as porous starch, this substance is widely used.

2.2.2 Preparation of SD's from Porous Satrch

The SD's were prepared by homogenous mixing of accurately weighed amount of individual drug with Porous Starch (PS). In this case the weight to weight (W/W) ratio of drug with Porous Starch (PS) was taken from 0.5 to 2.5 keeping amount of mixture constant. To this mixture 1-3 mL of water was added for each gram of starch to make homogenous slurry. The fixed amount of slurry 5gm was taken in glass beaker and irradiated with microwave radiation at power 640 with continuous stirring SD's were grounded in mortar and pestle to obtain the size of 8 to 25 µm.

2.2.3 Optimization of SD's:

Porous Starch

3^2 Full Factorial Design

For the present work 3^2 full factorial design was selected. It has been summarized in Table. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations as reflected in the table.

The two independent variables selected were

Table 1: Factors and their levels

Variables	Code	Factor
Independent	X1	Drug : Porous Starch ratio
	X2	Concentration of water
Dependent	Y1	Solubility
	Y2	Dissolution

Table 2: Details of the nine formulations in the 3 2 factorial design

Formulation code	Coded Values			
	X_1	%	X_2	%
F1	-1	0.5	-1	1
F2	0	1.5	-1	1
F3	+1	2.5	-1	1
F4	-1	0.5	0	2
F5	0	1.5	0	2
F6	+1	2.5	0	2
F7	-1	0.5	+1	3
F8	0	1.5	+1	3
F9	+1	2.5	+1	3

2.2.4 Saturation solubility determination

The Shake flask method was used for the determination of the solubility of prepared solid dispersions. The excessive quantity of prepared SDs was added in a glass stoppered flask containing 25 ml of solvent and flasks were shaken for 24 h at 37±0.5 °C. After 24 h, the solution was filtered, diluted appropriately and absorbance was taken at the λmax of a drug. Analysis of each sample was carried out in triplicate. The Change in solubility value was compared with pure drug solubility. [9-11]

2.2.5 *In vitro* dissolution studies

The *in vitro* Dissolution data was obtained by using USP Type II (Paddle type) dissolution apparatus with a rotating speed of 100 rpm and the media used was 900 ml phosphate buffer pH 6.8 maintained at 37±0.5 °C. Sample equivalent to 40 mg added in dissolution media. At specific time intervals i.e. after every 10 min, a 5 ml sample was pipetted, and an equal amount of fresh media was added. Pipetted samples were filtered, diluted, and analyzed by UV spectrophotometer at λmax of drug [9-12]. Analysis of each sample was carried out in triplicate.

2.2.6 Entrapment efficiency (%)

SD equivalent to 20 mg was dissolved in 10 ml methanol and further volume was made up of phosphate buffer 7.5 up to 100 ml and a further 1 ml diluted up to 10 ml (20 ppm solution). Absorbance at 296 nm of all the trials was taken and the amount of TLM was determined, which was further compared with theoretical absorbance from the linearity plot of standard.

2.3 Characterization

2.3.1 Differential scanning calorimeter (DSC)

DSC was carried out on DSC Q10 V9.9 Build 303. Purified indium (99.99%) was used to calibrate the instrument. Models (5 mg) were sealed in an aluminum pan with a flat bottom (Shimadzu DSC-60, Japan). This pan was put into the DSC device and scanned at a rate of 10 °C/min between 30° and 300 °C. With a flow rate of 10 ml/min, nitrogen was utilised as a carrier gas to completely reverse the oxidative and pyrolytic effects [13-15].

2.3.2 Fourier-transform infrared spectroscopy (FT-IR) studies

FT-IR can be used to characterise potential interactions between API and carrier in the solid state. The FT-IR was obtained using an FT-IR Spectrophotometer (The FT-IR of the inclusion complexes was performed on (FT-IR Bruker Shimadzu, Japan) and a dried sample of pure TLM, PEG 4000, PVP K 25, physical mixing, and SD-formulation. The observed peaks are identified for the functional group [16].

2.3.3 X-ray diffraction (XRD) analysis

A technique for examining the atomic or molecular structure of materials is XRD. It is non-destructive and works well with totally or partly crystalline materials. Holding the taster firmly in place while pressing the stage-up button with the other hand locks the sample into place on the instrument. According to the protocol, the slits in the "anti-scattering" and "detector" locations are checked. The doors then slowly and softly connect as they move together. After locking the doors, the computer expands "XRD commander" and, if necessary, increases power. An automatic save is done after the scan. After the task is complete, the taster is taken out and the enclosure's doors are shut. The XRD spectra of the pure TLM, PEG 4000, PVP K 25, PM and optimised formulation were recorded at room temperature using XRD (X'Pert XRD Powder type PW 30/40 panalytical, the Netherlands) with a voltage of 40 kV, 40 mA current and degree of crystallinity determined [17-20].

2.3.4 Stability studies

Stability study is the most crucial evaluation component for the creation of a pharmaceutically effective product. Any dosage form's potential capacity to continue meeting the necessary physical, chemical, toxicological, and therapeutic requirements is referred to as its stability. SD formulation was charged at accelerated stability condition as per ICH i.e. 40±2 °C/75±5% RH condition for up to 3 month in a stability chamber manufactured by Thermolab, and an assay of the formulation was determined [21-23].

3. Result and Discussion

3.1 Optimization of SD's

Entrapment efficiency study and solubility study of F1 to F9 shows that as there is increase in concentration of plain starch and concentration of water there are increase in entrapment efficiency study and solubility.

Table 3: Results for the optimization batches

Ingredient Formulation Code	Drug : Porous Starch ratio	Concentration of water	Entrapment Efficiency	Solubility
F1	0.5	1	46	0.078± 0.02
F2	1.5	1	59	0.112± 0.02
F3	2.5	1	68	0.166± 0.01
F4	0.5	2	57	0.298± 0.01
F5	1.5	2	62	0.402± 0.03
F6	2.5	2	71	0.568± 0.01
F7	0.5	3	69	0.754± 0.02

F8	1.5	3	82	0.828± 0.01
F9	2.5	3	94	0.902± 0.02

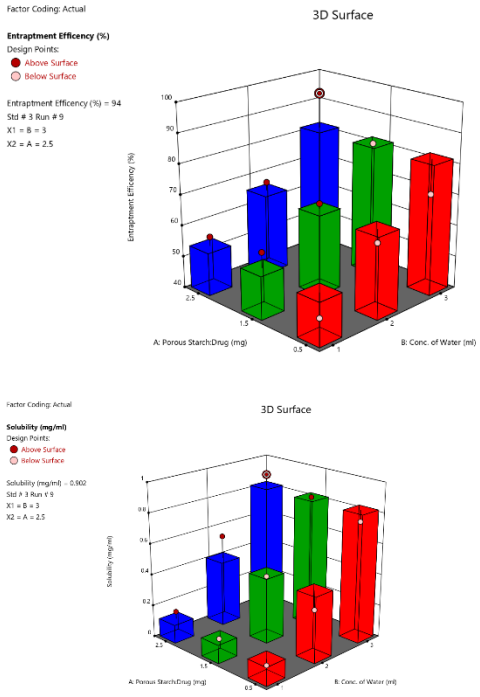

Figure 1: 3D Response Surface plot (Entraptment Efficiency & Solubility)

3.2 Saturation solubility determination

The SD formulation shows 8.0 fold rise in solubility as compared to pure drug. The results are as follows

Table 4: Solubility of Ranolazine SD's

Sr. No.	Batch	Solubility (mg/ml)	Increase in Solubility (folds)
1	Pure Drug	0.46	-
2	F1	0.72	1.56
3	F2	0.84	7.82
4	F3	1.11	2.41
5	F4	1.36	2.95
6	F5	1.48	3.21
7	F6	1.72	3.73
8	F7	1.99	4.32
9	F8	2.88	6.26
10	F9	3.68	8.00

3.3 *In vitro* dissolution studies

In vitro dissolution studies were determined for F1- F9 batches. Results are shown in table

Table 5: *In vitro* dissolution study of Ranolazine SD's

Cumulative Drug Release (%) (±S.D.)									
Time (hr.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.6	10.7 ±0.01	12.23±0.02	25.43±0.02	28.34±0.22	27.24±0.05	26.43±0.04	30.43±0.02	32.33 ±0.02	30.43± 0.01
1	16.17±0.06	26.53±0.02	34.45±0.01	36.53±0.15	31.44±0.54	33.53± 0.53	34.43±0.02	42.22 ±0.02	37.33± 0.01
2	25.47±0.02	34.63±0.02	41.52±0.02	45.42±0.92	46.54±0.35	41.24±0.53	41.42±0.02	51.42 ±0.01	43.35± 0.03
3	33.09±0.01	41.68±0.03	44.55±0.03	51.42±0.42	56.35±0.55	45.54±0.54	46.22±0.04	55.33 ±0.01	51.74± 0.04
4	41.88±0.04	50.26±0.02	57.65±0.04	54.53±0.43	65.35±0.53	54.73±0.05	50.83±0.01	60.4 ±0.02	54.61± 0.05
5	47.17±0.01	56.75±0.04	63.24±0.05	65.63±0.25	74.55±0.43	61.24±0.22	55.33 ±0.02	64.33±0.05	60.54± 0.06
6	61.13±0.01	66.83±0.05	71.64±0.05	74.65±0.25	80.73±0.53	64.44±0.52	62.42±0.01	70.35 ±0.02	64.74± 0.09
12	75.98±0.02	71.43±0.04	80.67±0.03	81.53±0.25	87.56±0.03	74.53±0.57	77.33±0.01	72.42 ±0.02	74.84± 0.07
18	84.84±0.02	84.25±0.02	85.74±0.09	89.54±0.02	90.45±0.34	82.62±0.54	83.33±0.01	87.12 ±0.01	88.22± 0.02
24	89.20±0.02	90.60±0.04	92.43±0.12	93.60±0.24	94.4±0.05	95.3±0.1	95.8±0.01	96.2±0.004	98.9±0.03

From above results, it can be concluded that F9 batch shows % drug release 98.9%.

3.4 Entrapment efficiency (%)

Entrapment Efficiency were determined for F1- F9 batches. Results are shown in table

Table 6: Entrapment efficiency (%) of Ranolazine SD's

Ingredient Formulation Code	Drug : Porous Starch ratio	Concentration of water	Entrapment Efficiency
F1	0.5	1	46
F2	1.5	1	59
F3	2.5	1	68
F4	0.5	2	57
F5	1.5	2	62
F6	2.5	2	71
F7	0.5	3	69
F8	1.5	3	82
F9	2.5	3	94

From above results, it can be concluded that F9 batch shows highest entrapment efficiency 94%.

3.5 Differential scanning calorimeter (DSC)

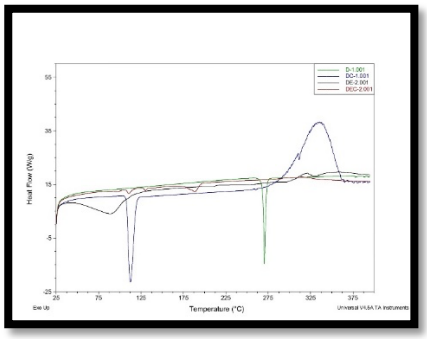

Figure 2: DSC Overlay of Optimized Formulation

From DSC graph it indicates shift in sharp peak of drug towards porous starch which ensures drug has been entrapped in porous starch**.**

3.6 Fourier-transform infrared spectroscopy (FT-IR) studies

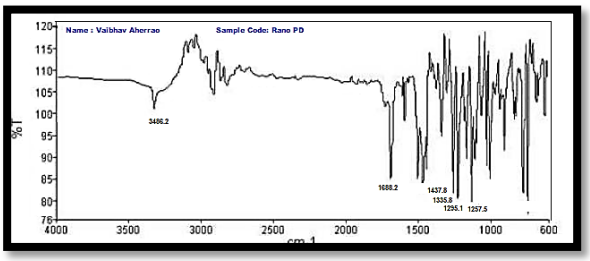

Figure 3: FTIR of ranolazine

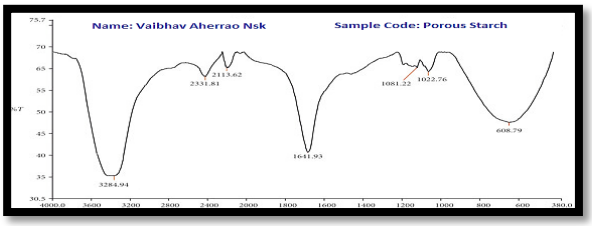

Figure 4: FTIR of Porous Starch

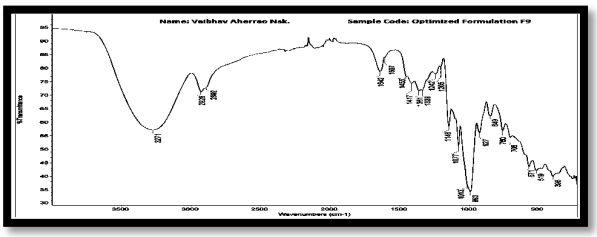

Figure 5: FTIR of Optimized Formulation

From FTIR spectra it indicates shift in sharp peak of drug towards spectra of porous starch which ensures drug has been entrapped in porous starch.

3.7 X-ray diffraction (XRD) analysis

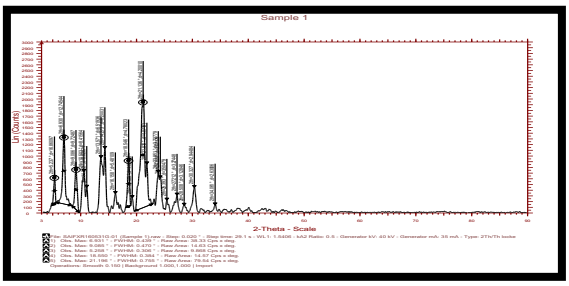

Figure 6: XRD of ranolazine

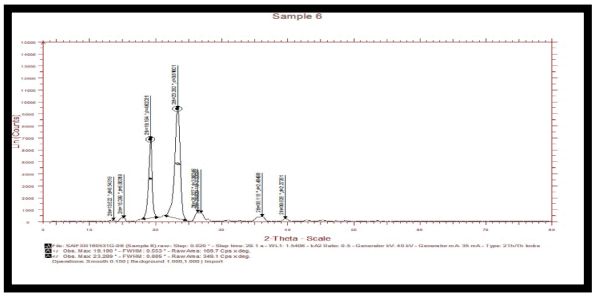

Figure 7: XRD of Porous Starch

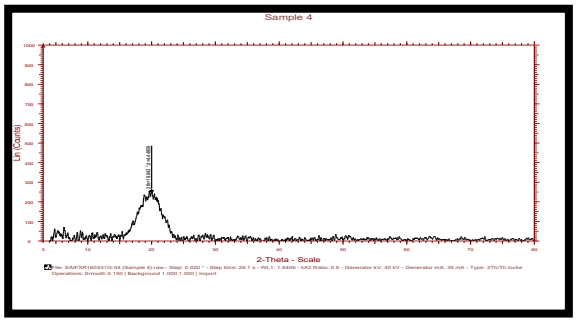

Figure 8: XRD of Optimized Formulation

From XRD it can be concluded that there is change in crystallinity of drug. In case of drug sharp peaks were seen which diminished in SD's. As sharp peak gets diminished there may be change in from of solids from crystalline to amorphous.

3.8 Stability studies

As per ICH guidelines, accelerated stability study of capsule containing Ranolazine SD's over a period of 6 months at a storage condition of 40°C±2°C/75% RH±5%RH (room temperature) and at 25°C±2°C/60%RH±5%RH (refrigerator temperature). The Ranolazine SD's were filled in cap vials packed in aluminium strips and stored for 6 months in stability chamber. The effect of duration on storage and storage condition on Entrapment Efficiency of the formulation was analysed at a time interval of 0 to 3months.

Effect on Entrapment Efficiency: As per ICH guidelines, accelerated stability study of capsule containing solid dispersion was carried out for Ranolazine SD's over a period of 6 months at a storage condition of 40°C±2°C/75%RH±5%RH (room

temperature) and at 25°C±2°C/60%RH±5%RH (refrigerator temperature) to find the effect on the Entrapment Efficiency. The Entrapment Efficiency was found to be more in case of Ranolazine SD's formulation kept at refrigerator temperature condition as the rate of drug leakage increased with increase in the temperature. But not much of a significant change was observed at the room and refrigerator temperature condition. This indicated that Ranolazine SD's were stable in presence of the excipients at this temperature and humidity. The results of the % Drug Entrapment Efficiency are as shown in table. The results indicate that the capsule containing solid dispersion was stable during accelerated stability conditions up to Six months.

Table 7: Effect on Entrapment Efficiency

Period in Months	40°C±2°C/75%RH ±5%RH (Room temperature)	25°C±2°C/60%RH ±5%RH (refrigerator temperature)
0	93.8	93.9
3	93.8	93.2
6	91.6	91.8

4. Conclusion

Solubility of Ranolazine was enhanced by 8 folds using porous starch. Optimization of formulation was successfully done by using full factorial design. The F9 batch shows more significant results as compared with pure drug. Conversion of crystalline to amorphous form of Ranolazine is confirmed by IR, DSC, PXRD and dissolution studies. The solubility and dissolution can be enhanced by solid dispersions of Ranolazine with porous starch. Stability study results confirm the absence of recrystallinity upon storage over a period of 6 months.

5. References

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