

# Development of pellets: Preformulation studies and initial screening of excipients

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**Abstract**— The objective of the current study was to carefully examine some of the significant physicochemical characteristics of rifaximin for pellet manufacturing. Rifaximin underwent testing for its physicochemical qualities, including solubility, dissolution, melting point, assay development, excipient compatibility, etc. Based on the formed pellets' dissolution characteristics, a binder and disintegrant were selected. Good flow characteristics, excipient compatibility, solubility profile, melting point, entrapment efficiency, and release profile are the results of the preformulation research. We can infer from this work that 2% sodium carboxymethyl cellulose can be used as a binder, and 2.5% sodium starch glycolate can be used as a disintegrant, to create Rifaximin pellets.

**Keywords**— Preformulation; Pellets; Rifaximin; Sodium carboxymethyl cellulose, sodium starch glycolate

## I. INTRODUCTION

The active pharmaceutical ingredient (API) is contained in pellets, which are defined as small, spherical, free-flowing granules with a narrow size distribution and typically varying in diameter between 500 and 1500 micrometers. Pellets are used in pharmaceutical applications. To convey the suggested complete portion, these subunits are filled into a sachet or typified or compacted into a tablet. In the GIT, pellets are distributed freely. It illustrates the advantages of pellets over tablets by maximizing drug absorption, minimizing local irritant drug irritation of the mucosa, reducing variations in gastric emptying rates, and being simple to coat [1-5].

Pellets are also gaining popularity due to their technological and therapeutic advantages, including a favorable size-to-volume ratio, a spherical shape that makes them ideal for coating, the possibility of incorporating a high drug load, the widespread dispersion throughout the gastrointestinal tract, a lower risk of irritation to the gastric mucosa and dose dumping, and a larger surface area that makes them more vulnerable to colonic bacterial attack[6],[7].

Rifaximin (RFX)(C<sub>43</sub>H<sub>51</sub>N<sub>3</sub>O<sub>11</sub>) is a nonsystemic underlying simple of rifampin that restrains the combination of bacterial RNA by restricting to the b subunit of bacterial DNA subordinate RNA polymerase (Fig 1). As a result, it has long been considered an antibiotic, as evidenced by its apparent modulation of the gut microbiota. Travelers' diarrhea caused by noninvasive Escherichia coli strains can be treated with RFX, which also lowers the risk of overt hepatic encephalopathy recurrence [8-11].

Any dosage form development requires a preformulation study that focuses on the physicochemical characterization of the drug candidate to determine how the drug will perform in the dosage form. The fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder must be determined before these major dosage forms can be developed. Many of the subsequent events and strategies in formation development are determined by this information. The overall goal of preformulation testing is to gather data that can be used by the formulator to create mass-produced dosage forms that are stable and bioavailable. When a newly synthesized drug demonstrates sufficient pharmacologic promise in animal models to warrant human testing, preformulation takes place. The physicochemical properties of the new compound that have the potential to influence drug performance and the creation of an effective dosage form should be the primary focus of these studies. A thorough comprehension of these properties may ultimately support the need for molecular modification or justify formulation design [12],[13].

## II. MATERIALS AND METHODS

### Materials

Rifaximin was purchased from Swapnroop drugs and pharmaceuticals, Aurangabad, Microcrystalline cellulose, Sodium CMC, Sodium starch glycolate and Crosspovidone from Research- lab Fine Chemindustries, Mumbai and Glycerol from Loba Chemie Pvt. Ltd. All other chemicals used were of analytical grade.

### Drug Profile:

Rifaximin [8],[10],[14]

Chemical Name:

(2S,16Z,18E,20S,21S,22R,23R,24R,25S,26S,27S,28E)-5,6,21,23-Tetrahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-1,15-dioxo-1,2-dihydro-2,7-(epoxypentadeca-[1,11,13]trienimino)[1]benzofuro[4,5-e]pyrido[1,2-a]benzimidazol-25-yl-acetate.

Pharmacological profile:

Rifaximin is a semi synthetic, rifamycin-based non-systemic antibiotic, meaning that very little of the drug will pass the gastrointestinal wall into the circulation as is common for other types of orally administered antibiotics. Rifaximin acts by inhibiting RNA synthesis in susceptible bacteria by binding to the beta-subunit of bacterial deoxyribonucleic acid (DNA)-dependent ribonucleic acid (RNA) polymerase enzyme. Rifaximin's minimal oral systemic availability is consistent with its low intestinal permeability and low aqueous solubility (Biopharmaceutics Classification System [BCS] IV Classification); its oral

absorption is limited further by efflux transport by P-glycoprotein (P-gp). Animal studies demonstrate that 80% to 90% of orally administered rifaximin is concentrated in the gut with less than 0.2% in the liver and kidney, and less than 0.01% in other tissues.

#### **Methods**

##### **Identification of the drug**

The organoleptic characteristics of Rifaximin (RFX) and excipients like physical state, colour, appearance, odour, and melting point were assessed.

##### **Melting point**

It is one of the parameters to judge the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point. The melting point of the drug was performed by capillary method. In this, drug was filled in the capillary tube sealed at one end to a height of 3 mm from closed end and capillary was introduced into melting point apparatus. The temperature range at which drug melt was noted down.

##### **Usual solubility study in various solvents**

Solubility of the drug was determined by preparing supersaturated solution of Rifaximin in distilled water, 0.1N HCl (pH 1.2) and phosphate buffer (pH 6.8) at 37°C. The prepared solution was shaken for 24 hrs on linear motion shaker (RM8, Spectralab). The resulted solutions were observed for their visual clarity and evaluated quantitatively. The observed data has been depicted in the Table 1.

##### **pH determination**

This was done by shaking a 1% w/v dispersion of the sample in water for 5 min and the pH determination using a digital pH meter at room temperature (25°C). The data presented here is for triplicate determinations.

##### **Loss on drying of Rifaximin**

1gm sample was taken in pre weighed aluminium foil and put it in the oven for 3 hrs at 105°C. Then note the weight of the sample. The LOD is calculated using the following equation.

$$\text{LOD \%} = \frac{A-B}{A} \times 100$$

##### **Drug-excipient compatibility study by FT-IR Spectroscopy**

Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing many absorption band from which a wealth of information can be derived about the structure of an organic compound. The sample (drug and drug-polymer combinations) was scanned from 4000–400 cm<sup>-1</sup> using Jasco FTIR 4100.

##### **Determination of λ<sub>max</sub> and calibration curve of drug**

Accurately weighed RFX was dissolved and diluted with and PBS pH 6.8 to make stock solution (100 µg/ml). The diluted solution was scanned spectrophotometrically in the range of 200 nm – 400 nm for determination of λ<sub>max</sub>. The stock solution (100 µg/ml) was diluted with PBS pH 6.8 to make solutions of concentration of 2 to 20 µg/ml. The UV absorbances were recorded at λ<sub>max</sub> and equation for regression was obtained by plotting the graph of concentrations on X – axis vs. absorbances on Y – axis.

##### **X-ray diffraction**

X-Ray diffraction of the pure drug were performed using a D8 Advance diffractometer (Bruker-SPPU). equipped with a rotating target thermionic tube and a camera lens direction finder. The X-ray supply was Kα radiation from a copper target with black lead monochromator. The thermionic tube was operated at a possible of 50 kW and a current of 150 mA. The vary (2θ) of scans was from 5° to 50° at a speed of 2° per minute at increments of 0.1°.

##### **Selection of excipients & preparation of pellets [15],[16]**

A preliminary study was conducted to evaluate the pellets prepared from sodium carboxy methyl cellulose (SCMC) and glycerin as binder. Disintegrants tried including cross povidone (CP) and sodium starch glycollate (SSG). Microcrystalline cellulose (MCC) was selected as spheronizing aid based on the literature review. Rifaximin pellets were prepared by Extrusion spheronization technique. The drug and different excipients were mixed properly. SCMC and Glycerin in 0.5-1% w/v used as binder solutions was added in the powder mixture of drug and excipients to make a damp mass. The damp mass was passed through radial type extruder, using sieve screen size of 0.87 mm. Then extrudes were spheronized at appropriate speed and time. Final pellets were collected and dried at 70°C temperature.

##### **Micromeritics Study**

From the viewpoints of both physical stability and pharmacologic response, successful formulation of many dosage forms depends on the particle size. For achieving the necessary flow properties and proper mixing of granules and powders, control of particle size is essential especially in the manufacture of tablets and capsules. Therefore, bulk density, tapped density, Hausner's ratio and angle of repose for drug and pellets were studied.

##### **Friability test**

Roche Friabilator was used for evaluating the pellet formulations. Prior to and following the test, the weights of the formulations were accurately recorded, and the friability ratios were calculated. The results were expressed in terms of the percentage of weight lost during the process.

##### **In vitro drug release study:**

The in vitro dissolution study of preliminary batches TB1 to TB6 was done in USP type-I apparatus using pH 6.8 phosphate buffer at 37°C±0.5°C and 100rpm. The measurement of % drug release was carried out by UV-Visible spectroscopy method at 445 nm.

### III.RESULTS AND DISCUSSION

The observations for organoleptic properties are shown in table and figure 1.

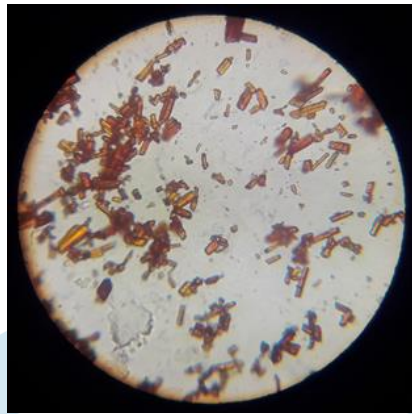


Figure1: Microscopic view of Rifaximin crystals

Table 1: Physical Properties of Rifaximin

Parameters	Results
<b>Description</b>	The drug is reddish orange crystalline powder
<b>Solubility</b>	
Distilled water	Practically insoluble (0.01mg/ml)
0.1 N HCl	Slightly soluble (4.56mg/ml)
Phosphate buffer pH 6.8	Slightly soluble (3.22mg/ml)
Saturation Solubility	0.0736±0.053 mg/ml
<b>pH of 1% (w/v) of Rifaximin at 25°C</b>	6.9
<b>Loss on drying</b>	0.0272% w/w
<b>Bulk density</b>	0.32gm/ml
<b>Tapped density</b>	0.42g/ml
<b>Compressibility index</b>	19.91%
<b>Angle of repose</b>	22.93°
<b>Melting point</b>	189°C-191°C

The UV analytical method for the Rifaximin was developed at 445 nm. Lambert's law was obeyed in the concentration range of 2-20 µg/ml.

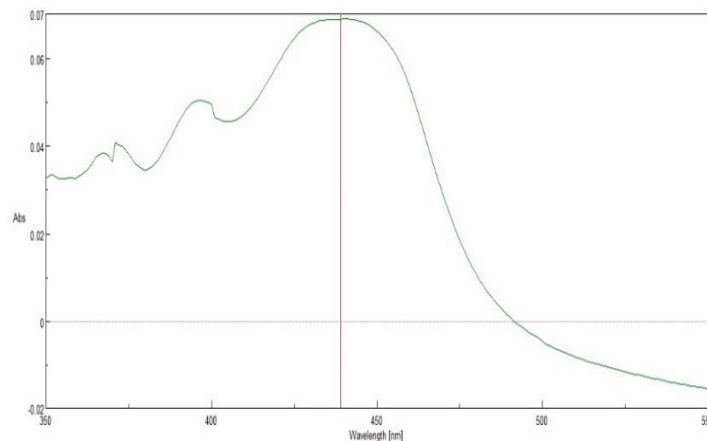


Figure 2: Absorption spectra of RFX in PBS pH 6.8

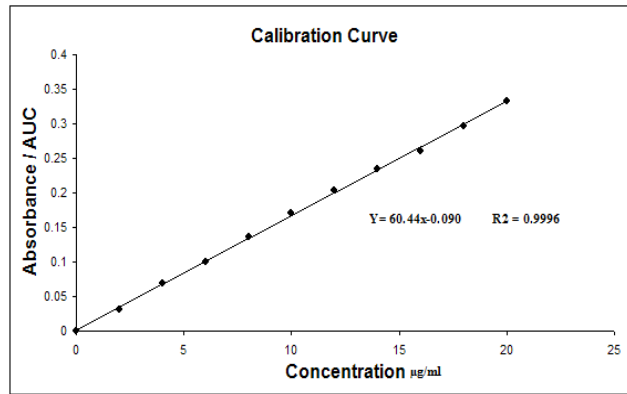


Figure 3: Calibration curve of RFX in PBS pH 6.8

The infra-red spectral analysis showed characteristic peaks of Rifaximin as shown in figure 4 and table 2.

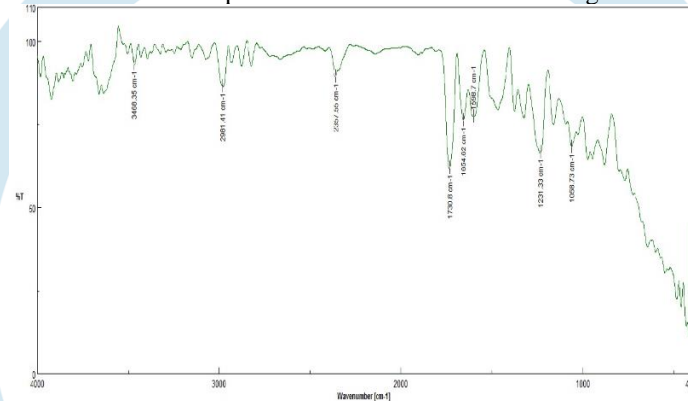


Figure 4: Infra-red spectral characteristics of Rifaximin (RFX)

Table 2: Interpretation of IR Spectra of Rifaximin (RFX)

S. No	Wave number (cm <sup>-1</sup> )	Interpretation
1	3468	-OH
2	2981	C-H Stretching
3	2357	C-C Stretching
4	1730	Carbonyl group
5	1654	Ester linkage

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic, or exothermic phase transformations). The thermogram of Rifaximin was obtained as given in Figure 5. The peak in the graph at 189.64°C confirms the melting point of Rifaximin.

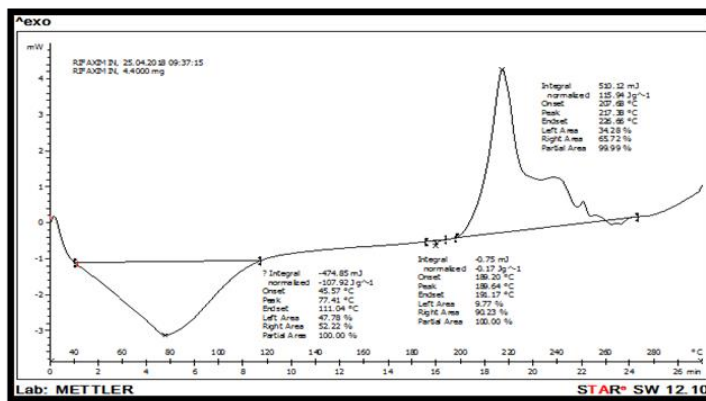


Figure5: DSC Graph of Rifaximin

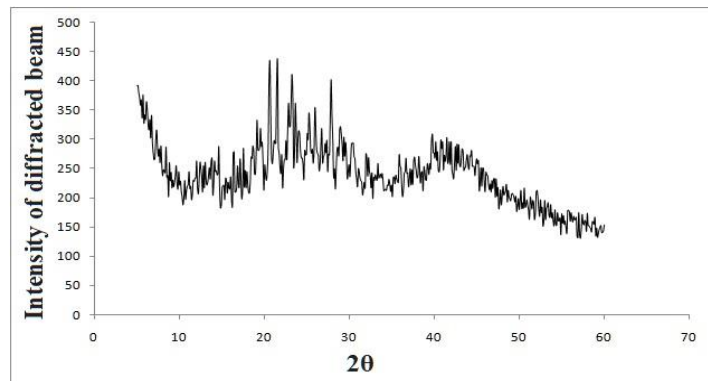


Figure 6: XRD of Rifaximin

The RFX sample exhibited various peaks at  $2\theta$  value of 20.63, 21.53, and 27.84 confirming the crystalline nature of drug. Table 3 and figure 7 shows the effect of different binders and disintegrants on pellets. At higher concentration (2%) of SCMC, a very thick mucilaginous binder was obtained, and a sticky dump mass was produced during binding stage, which was difficult to formulate into extrudes.

Table 3: Remarks of preliminary trial batches with different binder and disintegrant

Batch	Shape characteristics	Binding characteristics
TB1	Spheroid (even size)	Viscous enough
TB2	Dumbbell Shape	Mucilage (sticky dump mass formed)
TB3	Spheroid (uneven size)	High viscosity
TB4	Spheroid (uneven size)	High viscosity
TB5	Spheroid (uneven size)	High viscosity
TB6	Spheroid (uneven size)	High viscosity



Figure7: Rifaximin pellets (A) and its microscopic view (B, C)

Initially, the extrudes were produced which though got stuck to each other; but then when the mass force reduced the wet slippery mass kept rotating inside the extruder; preventing the further production of extrudes. By use of glycerin, spherical shape pellets were obtained but uneven size distributed due to high viscous for binding. Micromeritic studies of pellets showed better flow properties as compared to pure drug.

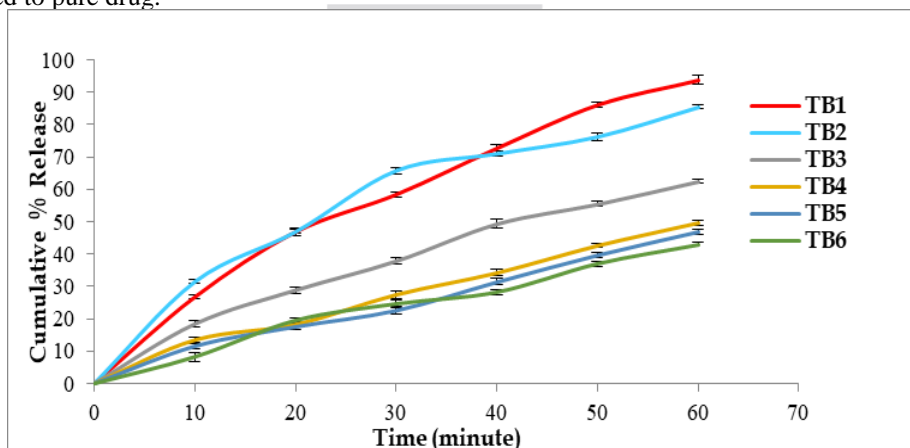


Figure 8: Invitro drug release of preliminary batches

In vitro dissolution study of the trial batch TB1 showed maximum (93.74%) drug release with 1% concentration of SCMC as binder and 2.5% concentration of SSG as disintegrant. Thus, SCMC and SSG were selected for formulation development.

#### IV. CONCLUSION

Studies conducted prior to formulation play a significant role in anticipating issues that may arise during formulation development. As a result, the extrusion-spheronization method was used to make trial batches of pellets and conducted preliminary research on Rifaximin in this work. Rifaximin's morphology, solubility, pH, micromeritic properties, and thermal property were evaluated as part of its physicochemical characterization. Good drug release was observed in the in vitro release profile of formulated pellets containing SSG as a disintegrant and SCMC as a binder. We concluded that the drug was suitable for pellet formulation selection based on this study's satisfactory results for all characterizations.

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