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Formulation and evaluation of Ornidazole Co-crystalline Microspheres

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ABSTRACT: Background: Low aqueous solubility is a major problem with formulation development of new chemical entities and generic development. Among all newly discovered chemical entities, about 40 % are lipophilic and fail to reach the therapeutic range due to their poor water solubility. **Aim:** This study aims to improve the solubility of Ornidazole, an anti-protozoal drug with limited water solubility, by employing a two-step formulation strategy. **Method:** Primarily, co-crystals of Ornidazole were synthesized using solvent evaporation technique. Subsequently, the obtained co-crystals were encapsulated into microspheres using the ion gelation technique using polymers like HPMC and Guar gum. Various evaluation parameters like Particle size, percentage yield, drug content, entrapment efficiency, *in vitro* dissolution studies, and their release kinetics were also assessed, to obtain the controlled release of the Ornidazole. **Results:** The solubility of the poorly soluble drug was increased by preparing co-crystals by solvent evaporation using co-formers like PABA and benzoic acid so we can summarize that the co-crystals of the drug are formed by PABA are perfect rather than benzoic acid by performing tests like *in vitro* solubility and calculating the % yield. **Conclusion:** Drug: HPMC in 1:2 ratio has passed the evaluation tests, micromeritic properties, and *in vitro* dissolution studies and was optimized as the best formulation. This dual approach not only increases the solubility of Ornidazole but also provides controlled release properties, potentially improving its therapeutic profile.

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INTRODUCTION:

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The extent of the solubility of a substance in a specific solvent is generally measured as the concentration of the solute in a saturated solution, one in which no more solute can be dissolved at this point, and the two substances are said to be in equilibrium. It depends on the composition of the solute and solvent (including their pH and the presence of other dissolved substances) as well as on temperature and pressure. Solubility can often be explained in terms of

interactions between the particles (atoms, molecules, or ions) of the two substances, and of thermodynamic concepts such as enthalpy and entropy. Under certain conditions, the concentration of the solute can exceed its usual solubility limit. The result is a supersaturated solution The concept of solubility does not apply when there is an irreversible chemical reaction between two substances, such as the reaction of calcium hydroxide with hydrochloric acid [1].

Drug absorption from the GI tract can be limited due to a variety of factors like poor aqueous solubility and poor membrane permeability [2]. On administration of an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GIT to reach the systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing the solubility and dissolution rate of poorly water-soluble drugs. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability [2].

Solubility is not to be confused with the ability to dissolve or liquefy a substance, since this process may occur not only because of dissolution but also because of a chemical reaction. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for generic development. Among all newly discovered chemical entities, about 40 % of drugs are lipophilic and fail to reach therapeutic range due to their poor water solubility. Drugs with poor water solubility show slow dissolution rates, and incomplete absorption leading to low bioavailability [3].

Various techniques of particle size reduction, canonization, pH adjustment, solid dispersion, complexation, co-solvency, hydrotropic, sonocrystallization, supercritical fluid (SCF) process, solid dispersion, co-crystallization, etc have been adopted to improve solubility and dissolution rates of poorly water-soluble drugs which include as following [4].

A co-crystal is a crystalline material consisting of API and a co-former. Multiple component crystalline solids are formed when API and co-former are mixed in a stoichiometric ratio under ambient conditions [5]. Co-formers are most important for co-crystal formation and their structure dictates the structure of the co-crystal and also dictates its solubility. Examples are Benzoic acid, PABA, citric acid, urea, histidine, ascorbic acid, etc. They are prepared using various methods, such as the evaporative method, grinding method, antisolvent method, sslurry conversion method, and supercritical fluid technology [6].

The objective of the study is to enhance the solubility of a BCS Class II drug by co-crystallization and further convert them into microspheres to achieve prolonged drug release.

MATERIALS AND METHODS:

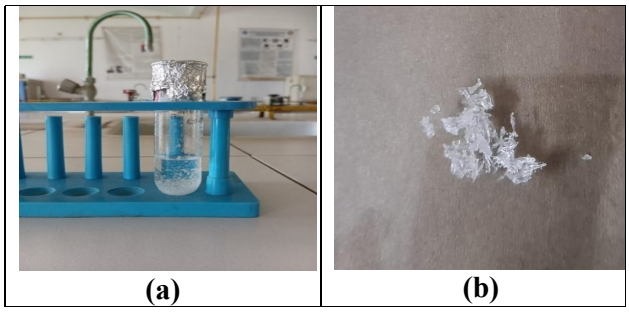
All the materials used in the present dissertation work are of pharma grade. Ornidazole was obtained as a gift from Yarrow Chem, Mumbai. Para amino benzoic acid (PABA) from Finar Chemicals Ahmedabad, Gujarat, HPMC K100, and Guar gum from Otto Chemicals Mumbai. Sodium alginate from Fischer Scientific India Private Ltd Powai, Maharashtra, and Methanol from Changshu Hongsheng Fine Chemical Co, China.

Preparation of Ornidazole cocrystalline (CCs):

The CCs containing Ornidazole were prepared by the Solvent Evaporation technique. This method involves dissolving drugs and co-formers in suitable solvents. Then solution of the co-former was added drop by drop to the solution of the drug and it was set aside until the solvent was completely evaporated and the precipitation of solids was formed. The co-formers used are PABA and Benzoic acid. The amount of drug and co-former were taken based on the molar ratios [6,7].

Table 1. Ratios of drug to co-former for preparation of CCs.

Molar ratios	Drug (g)	PABA (g)	Benzoic acid (g)
1:1	0.5g	0.326	0.378



(a) (b)

Fig 1. Preparation of CCs a) Solution left for solvent evaporation b) Synthesized drug-loaded CCs.

Preparation of Microspheres:

The CCs that exhibited the highest solubility were further formulated using the ion gelation technique. In this method, calculated amount of polymer was taken in a beaker and water was added until it formed a smooth

paste. Then 0.785 g of the co-crystallized drug was added to the above mixture and a small quantity of water until it dissolved completely. Finally, the required amount of sodium alginate was added to the above solution. About 1 % w/v calcium chloride solution was prepared and the above drug-polymer mixture into it with the help of a syringe. Then the calcium chloride solution was through filter paper, and the microspheres dried under air until solid particles were obtained [7,8].

Table 2. Formulation of Ornidazole CCs Microsphere.

Materials (g)	F1	F2	F3	F4
Drug	0.785	0.785	0.785	0.785
Sodium Alginate	1	1	1	1
HPMC	0.01	0.02	-	-
Guar Gum	-	-	0.01	0.02
Calcium chloride	10	10	10	10

Evaluation of Microspheres:

Micromeritic properties [8,9]**:**

The angle of repose (θ):

The flow characterization of the microspheres was assessed by determining the angle of repose. The angle of Repose is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. A sufficient quantity of the microspheres was passed through a funnel whose tip was placed at a height of 2.5 cm until it formed a heap. The height and the radius(r) of the heap were measured. The angle of repose was calculated using the formula.

Angle of Repose (θ) = $\tan^{-1}(h/r)$ …..(1)

Bulk density:

Accurately weighed microspheres were transferred into a 50ml measuring cylinder, and the volume occupied by the powder was noted. The bulk density was calculated in gm /ml by the following formula.

Bulk Density (ρ_O) = M/V_O ……(2)

M = Mass of the powder and V_O = Volume of the powder.

Carr's Index:

Based on the apparent bulk density and the tapped density, the percentage compression of the powder was determined by the following formula.

Carr's Index = [(TD-BD)/TD] …….(3)

Haushner's Ratio:

Hausner's ratio is an indirect index of ease of measuring the powder flow. It is calculated by the following formula.

Hausner's Ratio = TD/BD …..(4)

Haussner's ratio <1.25 indicates better flow properties.

Particle size analysis:

Microspheres were separated into different size fractions by sieving for 10 mins using a mechanical shaker containing standard sieves of sieve numbers #14, #18, #20, #25, and #30. The particle size distribution of the microspheres for all the formulations was determined and the mean particle size of the microspheres was calculated using the following formula [10].

$$MPS = \frac{\Sigma \text{ MPS of the fraction} \times WF}{\Sigma WF} \quad \text{…..(4)}$$

MPS - Mean particle size, WF – Weight Fraction

Yield:

The percentage yield was calculated by using the formula.

Yield (%) = (ADC/TDC) × 100 ……(5)

ADC – Actual drug content, TDC – Theoretical drug content.

Drug Content:

About 100 mg of Ornidazole microspheres were taken, powdered, and transferred into a 100 ml volumetric flask. The volume was made up to the mark with 0.1M HCl and kept aside for 12 h with continuous stirring. The solution was then filtered through the filter paper and 1ml of the solution was diluted using 0.1M HCl and analyzed to obtain the drug content using a spectrophotometer at 320 nm. All the experimental units were analyzed in triplicate (n=3) [11].

Drug Encapsulation efficiency:

Drug encapsulation efficiency (DEE) was calculated using the following formula.

DEE = (ADC/TDC) × 100 …..(6)

Swelling Index (SI):

Microspheres (100 mg) were placed in a little excess of phosphate buffer (pH 7.4) and allowed to swell to constant weight. The microspheres were removed and blotted with filter paper, and their weight changes were measured at pre-determined time intervals (0, 1, 2, 3, 4, 5, 6 h) and the degree of swelling was then calculated from the formula [12].

SI = $(W_g - W_o)/W_o$ ….(7)

Where Wg= final weight, and Wo= initial weight of the formulation.

***In vitro* drug release studies**:

The drug release from CCs was carried out in a paddle type dissolution apparatus containing 900 ml of

dissolution medium maintained at a temperature of 37±0.5°C with a speed of 100 rpm throughout the experiment. An accurately weighed quantity of CCs equivalent to 5 mg of Ornidazole was added to the dissolution medium containing 900 ml of 0.1M HCl solution Samples were collected using a syringe fitted with a pre-filter at known intervals of time and replaced with a fresh dissolution medium maintained at the same temperature. The drug released from the samples at different time intervals was determined by measuring the absorbance at 320 nm by UV-Spectrophotometer [12,13].

RESULTS AND DISCUSSION:

The drug utilized in the present dissertation work is Ornidazole, an atypical antiprotozoal drug used in the treatment of amoebiasis belonging to BCS Class II. In the present study, the solubility of the drug was enhanced by the preparation of Co-crystals, which were later formulated into microspheres.

Identification of drug:

The drug substance was identified based on its organoleptic properties, melting point, and λ_{max} [14].

Organoleptic properties of the drug:

The organoleptic properties of ornidazole were observed as shown in following Table 2.

Table 3. Organoleptic properties of the drug.

Properties	Description
Appearance	Amorphous powder
Odor	Odourless
Color	White

Determination of melting point:

The melting point of ornidazole was observed to be at 87 °C by capillary method, which complies with the standard values mentioned in the monograph of the drug [15].

UV visible spectroscopy studies:

The spectra of Ornidazole were obtained at 320 nm by using a UV Visible Spectrophotometer [16].

Preparation of stock solution:

About 50 mg of the drug was taken into a volumetric flask, dissolved in 0.1M HCl and finally, volume was made up with distilled water to 50 ml whose concentration is1000 µg/m [17].

Preparation of working standard:

From the stock solution 10ml of the solution was taken into a 100 ml volumetric flask and the final volume was made up to the mark to obtain a working standard solution.

From the working standard 5, 10, 15, 20, and 25 µg/solutions were prepared, and their absorbance was observed at 320 nm in a UV-Spectrophotometer and the standard graph was plotted [18].

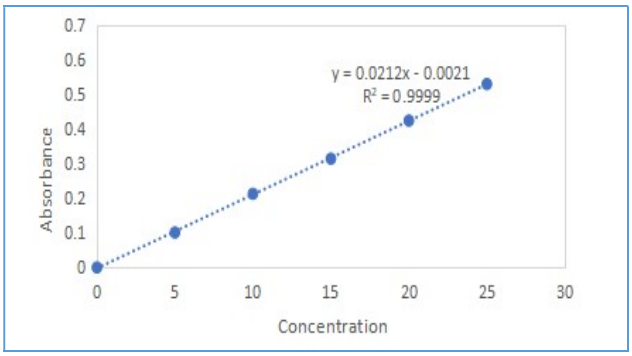


Fig 2. Standard graph of Ornidazole.

Identification of λ_{max} of the drug:

The drug was dissolved in 0.1M HCl solution and scanned in a UV-Spectrophotometer between the range of 400 to 200nm. The absorption maxima (λ_{max}) were identified at 320 nm [19].

Solubility of the drug:

The solubility of Ornidazole was observed in various solvents and it was identified that it is insoluble in water but soluble in ethanol, methanol, and acetone [20].

Pre-formulation studies:

It is the first step in the rational development of the dosage form of the drug. It can be defined as an investigation of various physical and chemical properties of a drug substance and its compatibility with the excipients. It is a phase of research and development process, carried out to develop a safe and effective dosage form [21].

Fourier Transform Infrared Spectroscopy (FTIR):

The FTIR results have shown that the spectrum of Ornidazole characteristic bands at 2517.13 cm^{-1} shows C-H stretching, bands 1410.81cm^{-1} shows N=O stretching, band 1364.90 cm^{-1} shows C-O stretching and band 828.60 cm^{-1} shows C-C stretching [22].

The FTIR results have shown that the spectrum of PABA characteristic bands at 3755 cm^{-1} shows N-H stretching, bands 1667 cm^{-1} shows C-H stretching, band

1601.20 cm^{-1} shows C-C stretching and band 1173.14 cm^{-1} shows C-O stretching [23].

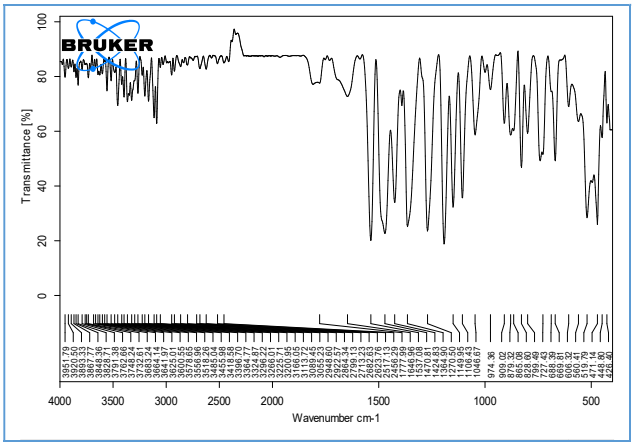


Fig 3. FTIR of Ornidazole.

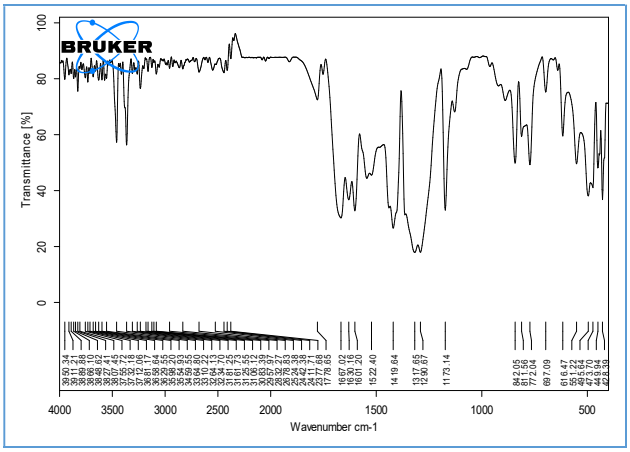
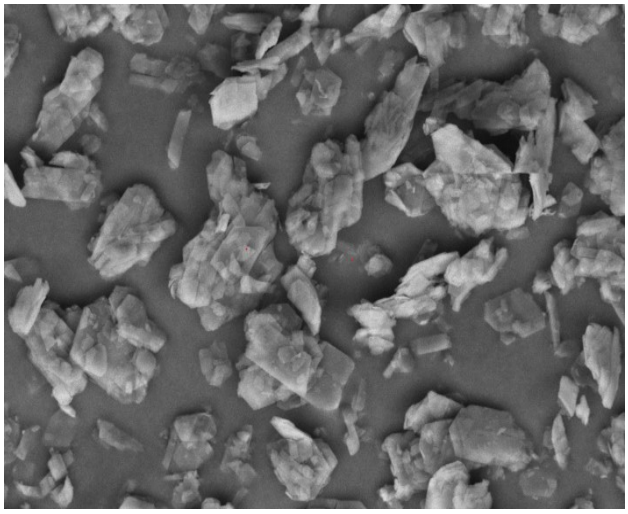


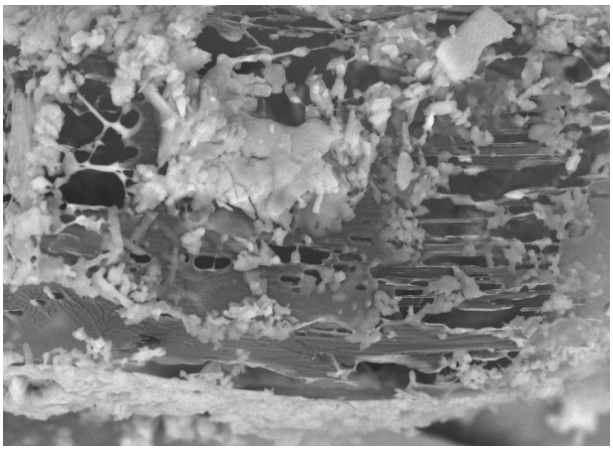
Fig 4. FTIR of PABA.

Scanning Electron Microscopy (SEM):

SEM photographs, to study the microscopic aspects of drugs and polymers illustrate them to be amorphous.



(A)



(B)

Fig 5 (A) SEM image of Pure drug Ornidazole (B) SEM image of PABA.

Percentage yield (% yield):

The percentage yield of the CCs was obtained by calculating accurately the initial weight of the raw materials and the final weight of the obtained CCs and substituting them in the following equation [24].

Tab 4. % Yield values of co-crystals.

Formulation	Practical yield	Theoretical yield	% Yield
PABA	0.685 g	0.785 g	87.2 %
Benzoic Acid	0.46 g	0.639 g	71.9 %

Drug Content:

The % drug content in Benzoic acid co-crystals was found to be 89.32 ±1.36 and PABA is 98.16±1.89 %.

Solubility:

Solubility studies were performed for the Pure drug and the prepared co-crystals to study the effect of co-crystallization on solubility [25].

Tab 5. Solubility studies of Co-crystals.

Time (min)	Pure drug	FC1	FC2
0	2.1±0.36	3.5±0.57	5.1±0.46
5	4.5±0.44	7.8±0.45	10.04±0.86
10	8.3±0.21	15.35±0.42	14.15±0.59
20	13.4±0.12	33.45±0.68	17.23±0.24
30	17.1±0.34	49.72±0.63	23.24±0.34
40	20.24±0.46	56.84±0.41	29.86±45
50	23.18±0.67	70.86±0.39	36.5±0.97
60	27.29±0.56	78.92±0.28	42.89±0.34

Each data represent Mean ± Standard deviation (n=3).

SEM studies of co-crystals:

SEM studies of the finished product show that the mixture of drug and co-former turned into crystal form by solvent evaporation method [26].

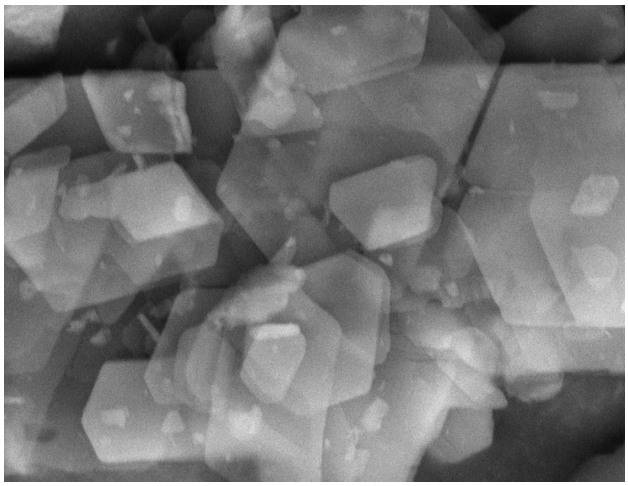


Fig 6. SEM imaging of Co-Crystals.

Micromeritic study of Microsphere:

The prepared Ornidazole microspheres are evaluated by the following tests [27,28].

Table 6. Micromeritic properties.

Para-meter	F1	F2	F3	F4
Bulk Density	0.59± 0.06	0.59± 0.03	0.61± 0.04	0.58± 0.02
Tapped density	0.56± 0.03	0.62± 0.03	0.51± 0.01	0.056± 0.05
Angle of repose	25.5± 0.25	28.5± 0.28	26.2± 0.37	27.7± 0.53
Hausners ratio	1.12± 0.15	1.16± 0.11	1.13± 0.14	1.14± 0.11
Carr's Index	13.31± 0.12	11.60± 0.10	12.88± 0.13	14.92± 0.14

Each data represent Mean ± Standard deviation (n=3).

Table 7. Drug Encapsulation Efficiency, Drug Content of Indomethacin Microspheres.

FC	M1	M2	M3	M4
TDC (%)	100± 0.03	100± 0.02	100± 0.01	100± 0.02
EE	78.96± 0.33	76.54± 0.56	81.39± 0.41	84.22± 0.42
PDC (%)	79.74± 0.41	83.12± 0.38	80.90± 0.45	82.64± 0.67

Each data represent Mean ± Standard deviation (n=3). FC – Formulation code, TDC – Theoretical drug content, PDC – Practical Drug Content.

Table 8. Swelling index of the microspheres.

FC	1 h	2 h	3 h	4 h	5 h	6 h
	(%)					
F1	51±0.56	53±0.58	60±0.65	62±0.26	68±0.57	71±0.41
F2	53±0.38	54±0.34	58±0.39	60±0.53	64±0.74	68±0.67
F3	79±0.45	88±0.76	90±0.84	92±0.85	94±0.32	96±0.40
F4	78±0.65	82±0.21	88±0.19	90±0.31	92±0.43	94±0.68

Each data represent Mean ± Standard deviation (n=3).

Table 9. *In vitro* drug release studies.

Time	F1 (%)	F2 (%)	F3 (%)	F4 (%)
10 min	18.8±0.76	20.4±0.54	14.04±0.34	16.5±0.36
30 min	21.7±0.35	28.35±0.43	19.15±0.76	20.56±0.91
60 min	28.5±0.46	33.45±0.34	27.23±0.59	25.7±0.29
2 h	35.2±0.28	49.72±0.65	33.24±0.86	38.32±0.74
3 h	42.8±0.43	56.84±0.13	45.86±0.24	45.76±0.51
4 h	54.2±0.85	66.86±0.65	52.5±0.56	59.3±0.62
5 h	67.7±0.64	73.92±0.91	65.89±0.43	61.52±0.38
6 h	78.3±0.76	75.8±0.28	74.7±0.21	68.3±0.37
7 h	84.6±0.53	87.4±0.13	81.42±0.36	75.45±0.63
8 h	86.7±0.51	92.6±0.48	85.8±0.47	83.6±0.49

Each data represent Mean ± Standard deviation (n=3).

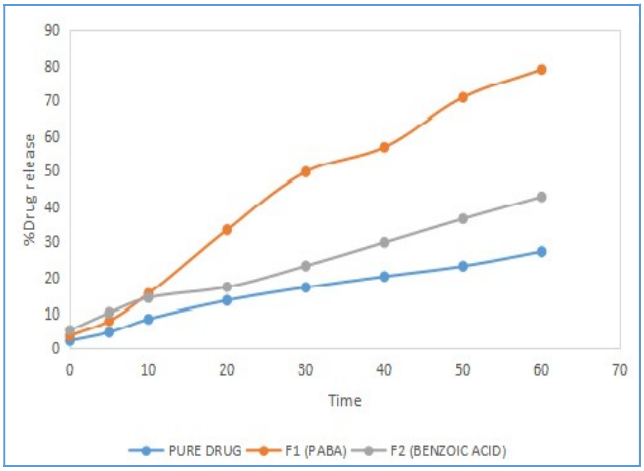


Fig 15. *In vitro* dissolution studies.

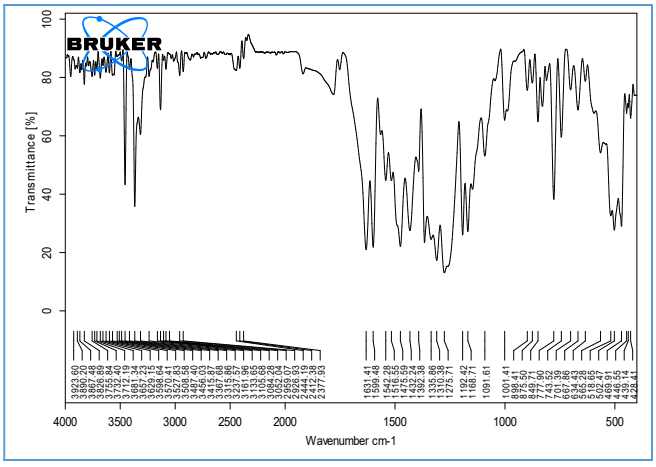


Fig 13. FTIR of co-crystals.

The peaks obtained in the spectra of Ornidazole co-crystals formulation with PABA, the peak at 3712 cm^{-1} can be attributed to N-H stretching, which is slightly shifted but still present. The co-crystal formulation peak, located at 3768.14 cm^{-1} indicates that the C-H stretching vibration with no significant interaction. The peak at 701.39 nm corresponds well to C-C stretching vibrations, and at 1631.41 cm^{-1} to C-O stretching vibrations, indicating no significant interaction. When the FTIR spectra of pure Ornidazole and its co-crystal formulation with PABA are compared, it can be seen that the drug's distinctive peaks have not changed much. The small changes that seen as typical of any formulation process and do not point to meaningful interaction. Consequently, the conclusion that there is no meaningful interaction between Ornidazole and PABA in the co-crystal formulation is supported by the FTIR results [29].

DISCUSSION:

The present study reports a novel approach to prepare microspheres of the anti-protozoal drug ornidazole by using polymers like Hydroxyl poly methylcellulose (HPMC) and Guar gum (GG) and to reduce the frequency of dose [30].

The microspheres of the ornidazole were prepared by the ion gelation technique by using polymers like HPMC and Guar gum [31]. Various evaluation parameters like Particle size, percentage yield, drug content, entrapment efficiency, *in vitro* dissolution studies, and their release kinetics were also assessed, to obtain the controlled release of the ornidazole [32].

The melting point of the ornidazole was assessed which complied with the IP standards thus indicating the purity of the obtained sample [33].

The solubility of the ornidazole was carried out and it was found that it is well soluble in Ethanol>methanol>acetone>water.

The flow properties of the ornidazole microcapsules were conducted and it was found that the 0.2 HPMC formulation has a better flow property when compared to the other three formulations. This was confirmed by performing micrometric studies like Bulk density, Tapped density, Angle of repose, Carr's index, and Hausner's ratio [34].

Entrapment efficiency was in the range of 70 to 79 %, the reason for the low encapsulation was that the drug tends to migrate into external media before it was completely encapsulated. The concentration of polymer also affects the encapsulation efficiency. The order of the entrapment efficiency is HPMC2>GG3>HPMC3>GG2>GG1>HPMC1. The amount of polymer affected the encapsulation efficiency as the amount of the polymer increased with the increase in the concentration of the polymer [33].

The swelling index of the ornidazole microspheres was increased with an increase in the polymer concentration. *In-vitro* release of the ornidazole microspheres was slow and the maximum of the percentage of the drug was released within the 12 h. Thus, synthetic polymers were found to be a better microencapsulating agent, and microspheres of ornidazole coated with HPMC as the polymer exhibited well-controlled release characteristics and were suitable as oral controlled release products [34].

CONCLUSION:

The solubility of the poorly soluble drug was increased by preparing co-crystals by solvent evaporation using co-formers like PABA and benzoic acid so we can summarize that the co-crystals of the drug are formed by PABA are perfect rather than benzoic acid by performing tests like in vitro solubility and calculating the % yield. We have concluded that the co-crystals have increased the solubility of poorly soluble drug i.e. ornidazole and converted them into microspheres using ion gelation technique by using two polymers HPMC and Guar gum in 1:1 and 1:2 ratios. Among them, the Drug: HPMC in 1:2 ratio has passed the evaluation tests, micrometric properties, and *in vitro* dissolution studies and was optimized as the best formulation.

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