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METRONIDAZOLE-EXCIPIENT COMPATIBILITY STUDIES FOR MEDICATED CHEWING GUM DELIVERY SYSTEMS DEVELOPMENT

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ABSTRACT

Metronidazole is an antibiotic used to treat various bacterial and parasitic infections. Metronidazole has been proved to be efficacious in treating: acute ulcerative gingivitis, pericoronitis, certain infections, some cases of osteomyelitis and infected socket. The drug may be of use in cases of chronic progressive periodontitis where anaerobes are implicated as pathogens. The main objective of the present study was to the preformulation studies were performed to know the physico-chemical and mechanical properties of Metronidazole for formulation development of Metronidazole Medicated Chewing Gum (MCG). The drug-excipient compatibility studies were conducted to characterize the drug Metronidazole Medicated Chewing Gum (MCG): A Modern Oral Drug Delivery System. Preformulation, formulation and evaluation of Metronidazole to avoid problems associated with conventional delivery system such as limited permeation, low release and bioavailability and also to improve bioavailability and providing more effective and convenient treatment methods. The compatibility was assessed by, FTIR spectroscopy, and melting point apparatus, precompression parameters and powder flow properties. Results showed that physical mixtures of Metronidazole and various excipients such as Mannitol, MCC, CMC, Acacia gum, Xanthan gum, etc, were evaluated for preformulation studies parameters. It was concluded that the drug Metronidazole was found to be compatible with various excipients which were selected for the formulation development of the Metronidazole MCG Delivery systems. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

KEYWORDS: Metronidazole, Compatibility, Medicated Chewing Gum, Development, Preformulation, MCG Delivery systems.

INTRODUCTION

Compatibility Studies of Medicated Chewing Gum Delivery systems[1-100]

Preformulation is essentials of pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance. Prior to the development of any dosage form new drug, it is essential that certain fundamental physical and chemical properties of drug powder are determined. This information may dictate many of subsequent event and approaches in formulation development. The safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

One of the objectives of this study is to development of drug delivery systems by building scientific pharmaceutical research information depend on formulation scientists to join the knowledge and experience as well as experimental and practical results of this study with regard to information in previous studies, and approved references. It was found to be that the most important concepts and basics of preformulation studies such as definitions, methods, conclusion, idea, and types of pharmaceutical analysis techniques using in evaluation of preformulation studies parameters, in this study that we focused on developing drug delivery systems and linking the formulation development to establish the basics of pharmaceutical research in studying the drug-excipient compatibility, dug with various excipients, which is important for the safety, effectiveness, quality, formulation, stability, bioavailability, and pharmacokinetics of the drug etc.

Determination of physical chemical properties of API

substance with the goal of developing a new drug which is safe stable and efficacious, each API, has intrinsic chemical and physical properties that were considered prior to the development of pharmaceutical formulation, the purpose of preformulation study is to generate useful information for the formulator in the development of stable and bioavailable dosage form, inappropriate preformulation study results in poor stability of active ingredients increase the overall cost of development and increased development time, preformulation studies help to fortify the pharmaceutical scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, enhance public safety standards, improve product quality, promote the implementation of new technologies, aids policy development and regulatory decision making and after compiling all data it is transferred to the development pharmacist and for the day work on formulation of dosage form.

Preformulation Study Objectives: To establish the Physico-chemical parameters of a new API entity, determine its kinetics and stability, establish its compatibility with common excipients, it provides insights into how drug products should be processed and stored to ensure their quality, estimate problem may arise during formulation that is stability problem poor *in-vivo* dissolution, poor bioavailability, to interpret BCS classification of drugs and its significance and develop optimal drug delivery system.

Drug-Excipient Compatibility Study: The primary objective of this investigation was to identify a stable storage condition for API in solid state and identification of compatible excipients for its formulation. Incompatibilities are major concerns in formulation development. Selection of the proper excipient during preformulation studies is of prime importance.

Dosage Forms: DF contain API and pharmaceutical excipients, which are intended to generate an ideal formulation and manufacturability of pharmaceutical products, thereby enabling a much safer and more effective administration. Pharmaceutical excipients are ideally inactive and have no impact on the stability or therapeutic effect of the active ingredient. On the other hand, there are studies that have presented that some pharmaceutical excipients are just allegedly described as inactive ingredient. Some pharmaceutical excipients have the capacity to affect API, efficacy by affecting its pharmacokinetics. Excipients can affect the physical and chemical form of pharmaceuticals by several factors such as hydrogen bond interaction, polymorphic conversion, and others. Accordingly, drug-excipient compatibility should be conducted so as to determine any drug-excipient interactions that may obstruct the stability, bioavailability, and manufacturability of pharmaceutical dosage forms.

Importance of Drug-Excipient Compatibility

Studies of active pharmaceutical ingredient (API)-excipient compatibility represent an important study in the preformulation stage of the development of new dosage forms, stability of the dosage form can be maximized, any physical or chemical interaction between API, and excipient can affect bioavailability and stability of drug, it helps to avoid the surprise problem, by performing drug excipient compatibility studies (DECS) we can know the possible reaction before formulating final dosage form, DECS data is essential for IND (investigational new drug) submission, and now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

The potential physical and chemical interactions between an API, and the excipients can affect the chemical nature, the stability and bioavailability of the former and, consequently, its therapeutic efficacy and safety, solid dosage forms are generally less stable than their API components and despite the importance of API-excipient compatibility testing, there is no universally accepted protocol to assess such interactions.

Pharmaceutical Excipients: Excipients are additive substances used to improve the bulkiness, disintegration, dissolution rate, and bioavailability of a formulation etc. Different dosage forms like powders, granules, capsules, tablets, oral liquids, injectable products, implants, eye products, nasal products, inhalers, topical creams, ointments, gels, transdermal patches and suppositories etc, contains different types of excipients. To make it acceptable and compatible various pharmaceutical excipients are added in pharmaceutical dosage form for their direct therapeutic action, manufacturing process, to protect, support or enhance stability, for bioavailability or patient compliance. These must be physiologically and chemically stable, must not have any incompatibility with the API, and must meet the standards of regulatory requirements.

Evaluation of Drug-Excipient Compatibility

The compatibility study of API and excipients is important to predict the stability of the API, in the final pharmaceutical product. It's the first time that API was compatible with excipients promoted physical and chemical compatibility studies was achieved by thermal and non-thermal methods. As a part of preformulation study, a compatibility study of API with the other excipients was carried out using physical blends in analytical techniques for the evaluation of drug-excipient interactions. The most commonly used pharmaceutical analytical techniques include, thermal techniques such as Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), Isothermal Microcalorimetry (IMC) and Hot stage microscopy (HSM) etc, and non-thermal techniques such as UV-Visible Spectrophotometric (UV), Infrared, Near-Infrared and Raman Spectroscopy (FT-IR), (NIR), Powder *X*-Ray Diffraction (PXRD), Solid-State Nuclear

Magnetic Resonance Spectroscopy (ssNMR), Microscopic techniques: Scanning Electron Microscopy (SEM), Chromatographic techniques: Thin Layer Chromatography (TLC), and High-Performance Liquid Chromatography (HPLC) etc.

Preformulation Parameters: According to dosage form of API, mainly solid state, particle size, shape, pKa, pH determination, common ion effect, temperature, partition coefficient, solubility studies, dissolution rate, melting point, powder flow properties, crystallinity, polymorphism, hygroscopicity, stability study and drug-excipient compatibility etc. While other dosage forms according to important of preformulation parameters used in study before start in development of formulation.

Drug-excipient compatibility and formulation stability is not depended on API only but also its affected by excipient. Excipient play important role in dosage form but side by side it also increases compatibility problem so proper selection of excipient is very important in development of formulation. Incompatibility can be result mainly in any of following changes: Changes in organoleptic properties, changes in dissolution performance, decrease in potency, and increase in degradation rate etc.

Drug excipient physicochemical characterization is a systematic approach towards design of therapeutically active and stable dosage forms. The rapid advancements in novel drug delivery systems development have led to an interest by formulation scientists in the role and functionality of the excipients.

Different types of active substances can be incorporated into the gum base because it is a convenient novel drug delivery system. Chewing gum was approved as a Pharmaceutical dosage form in 1991, by the commission of the European Council. According to European Pharmacopoeia, and guidelines, medicated chewing gums are defined as solid single-dose preparations with a base consisting mainly of gum that is intended to be chewed but not to swallow.

In the present study, it was proposed to drug-excipient compatibility studies of Metronidazole, with commonly different excipients using for formulation development of Metronidazole Medicated Chewing Gum (MCG): A Modern Oral Drug Delivery System.

MATERIALS AND METHODS

As shwon in Table 1.

Table 1: List of Materials.

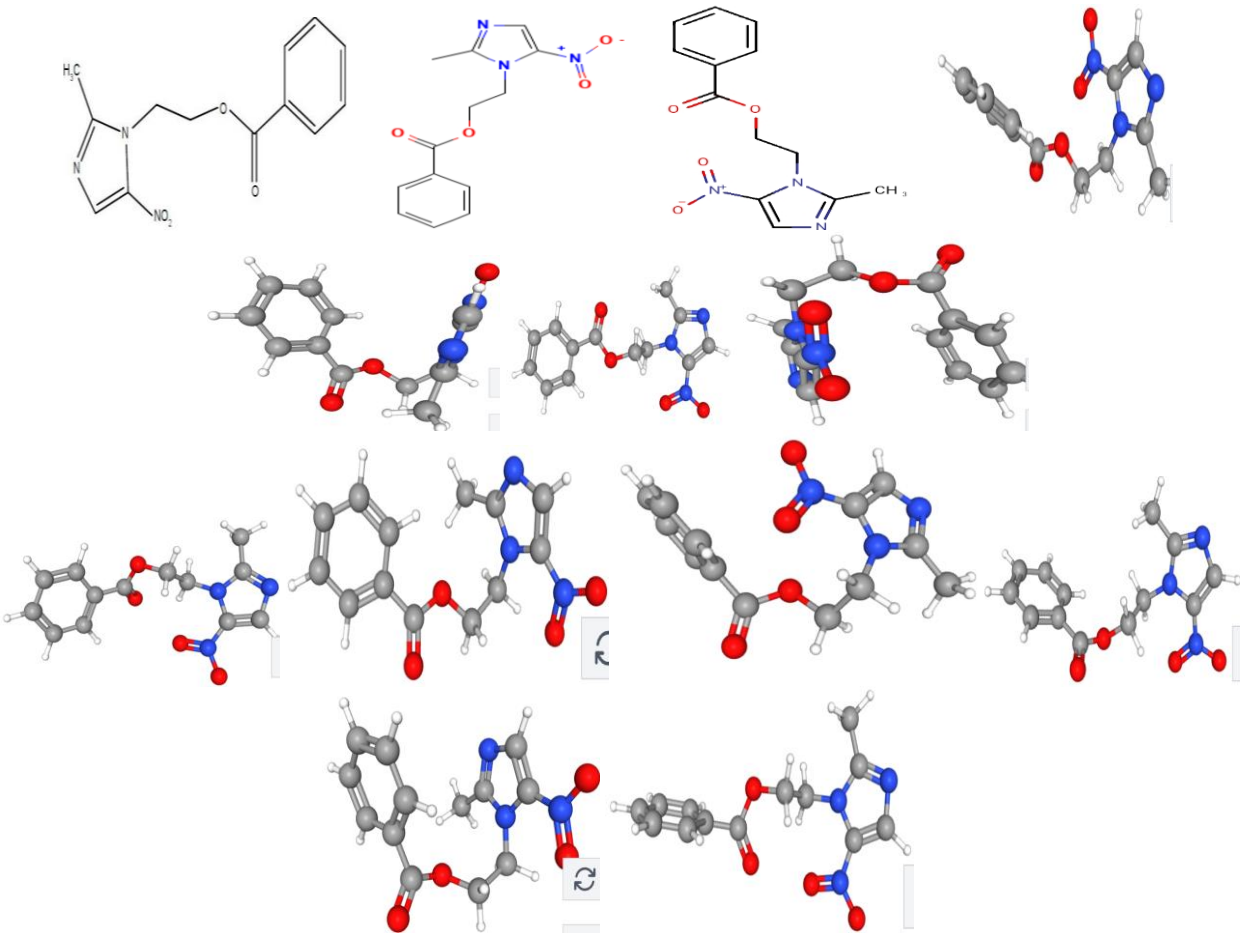
NO	Name of Materials
1	Metronidazole Benzoate
2	Acacia gum HPLC- MUMBAI
3	Xanthan Gum
4	PEG 6000
5	Povidone 30
6	Natural Gum
7	Masticatory Gum Base
8	Bees Wax
9	Aspartame
10	Sodium Saccharine
11	Sucralose
12	Mannitol
13	Sorbitol
14	Glycerol
15	Mint. Powder
16	Strawberry Liquid
17	Orange Liquid
18	Calcium Carbonate
19	Talc
20	CMC
21	MCC
22	Magnesium Stearate
23	Aerosil 200
24	Sodium Stearyl Fumarate
25	Ascorbic Acid
26	Stearic Acid
27	Beta Cyclodextrin
28	Potassium Dihydrogen Phosphate
29	Palm Oil

30	Ethanol 99.9%
31	Glacial Acetic Acid
32	Acetonitrile
33	Phosphate Buffer
Most of the materials a gift sample by Global Pharmaceutical Industry Company- Sana'a, Yemen. Phosphate buffer a gift sample by Shiba Pharmaceutical Industry Company- Sana'a, Yemen. Acacia gum HPLC- MUMBAI, Natural gum, Masticatory gum base and Ethanol were purchase from the local market.	

Evaluation of Drug-Excipient Compatibility Studies Methods[20-142]

Table 2: Metronidazole Data.

Characterization of Metronidazole



Metronidazole Structure and 3D Conformer

Chemical Structure	2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl benzoate]	**Appearance**	Typically appears as a white to off-white crystalline powder.
Molecular Formula	C13H13N3O4	**Solubility**	Soluble in organic solvents such as ethanol and propylene glycol. Slightly soluble in water.
Molecular Weight	275.26 g/mol	**BCS**	Class-I Drug
Action and Use	Metronidazole crosses the membrane of the cell target by passive diffusion; then, its nitro group is reduced to nitro radicals by ferredoxin or flavodoxin. The selectivity of metronidazole for anaerobic or microaerophilic microorganisms is due to the redox potential of their electron transport components, which are responsible for nitro group re-duction and generate toxic metabolites. These metabolites such as N-(2-hydroxyethyl) oxamic acid and acetamide can react with DNA and form adducts with guanosine. Metronidazole is an antibiotic used to treat various bacterial and parasitic infections. Metronidazole has been proved to be efficacious in treating: acute ulcerative gingivitis, pericoronitis, certain infections, some cases of osteomyelitis and infected socket. The drug		

	may be of use in cases of chronic progressive periodontitis where anaerobes are implicated as pathogens.		
Pharmacokinetics of Metronidazole			
Drug Absorption	In patients treated with Metronidazole injection using a dosage regimen of 15 mg/kg loading dose followed six hours later by 7.5 mg/kg every six hours, the average peak steady-state concentrations (Cmax) and trough (Cmin) were 25 mcg/mL and 18 mcg/mL, respectively. Plasma concentrations of Metronidazole are proportional to the administered dose. An eight-hour intravenous infusion of 100 mg to 4,000 mg of metronidazole benzoate in normal subjects showed a linear relationship between dose and peak plasma concentration.	**Drug Distribution**	Less than 20% of the circulating Metronidazole is bound to plasma proteins. Metronidazole appears in cerebrospinal fluid, saliva and breast milk in concentrations similar to those found in plasma.
Drug Metabolism	The metabolites of Metronidazole result primarily from side-chain oxidation [1-(βhydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2 methyl-5-nitroimidazole-1-ylacetic acid] and glucuronide conjugation. Both the parent compound and the hydroxyl metabolite possess in vitro antimicrobial activity.	**Drug Excretion**	The major route of elimination of Metronidazole and its metabolites is via the urine (60 to 80% of the dose), with approximately 20% of the amount excreted appearing as unchanged Metronidazole. Renal clearance of Metronidazole is approximately 10 mL/min/1.73 m2**.** Fecal excretion accounts for 6 to 15% of the dose. Renal Impairment: Decreased renal function does not alter the single-dose pharmacokinetics of Metronidazole.
The Elimination Half-Life (T1/2)	The average elimination half-life of Metronidazole in healthy subjects is 8 hours.	**Availability**	Oral Tablets- Oral Suspensions- Vaginal Suppostory- IV Infusion- Topical Gel, Creams.

Table 3: Pharmaceutical Excipients Data.

Nonproprietary Name	Chemical Name	Functional Category	Concentration %	Solubility	Incompatibilities	Notes
Croscarmellose Sodium (Ac-Di-Sol)	Cellulose, carboxymethyl ether, sodium salt, crosslinked	Tablet and capsule disintegrant.	0.5-5% 10-25%	Insoluble in water	Incompatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.	White or grayish-white powder
Sodium Starch Glycolate (Explotab)	Sodium carboxymethyl starch	Tablet and capsule disintegrant.	2–8%	Gives a translucent suspension in water	Incompatible with ascorbic acid.	Very hygroscopic
Microcrystalline Cellulose (Avicel PH)	Cellulose	Adsorbent, suspending agent, tablet and capsule diluent; tablet disintegrant.	5–20% 20–90%	Practically insoluble in water	Incompatible with strong oxidizing agents.	Crystalline powder

Crospovidone (PVPP)	1-Ethenyl-2-pyrrolidinone homopolymer	Tablet disintegrant.	2–5%	Practically insoluble in water	Compatible with most organic and inorganic pharmaceutical ingredients.	Hygroscopic powder
Mannitol (Emprove)	Mannitol	Diluent, plasticizer, sweetening agent, tablet and capsule diluent, therapeutic agent, tonicity agent.	10–90%	Freely soluble in water	Incompatible with may be salted out by potassium chloride or sodium chloride. Sodium cephapirin. xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.	Crystalline powder
Magnesium Stearate (magnesium salt)	Octadecanoic acid magnesium salt	Tablet and capsule lubricant.	0.25 - 5.0%	Practically insoluble in water	Incompatible with strong acids, alkalis, and iron salts.	Greasy
Aspartame	3-Amino-N-(a carboxyphenethyl) succinamic acid N-methyl ester; 3-Amino-N- (a methoxycarbonylphenethyl) succinamic acid;	Sweetening agent.			incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate.	
Talc	Altalc, E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Luzenac Pharma, magnesium hydrogen metasilicate.	Anticaking agent; glidant, diluent, lubricant.			Incompatible with quaternary ammonium compounds.	
Aerosil	Aerosil; Cab-O-Sil, Cab-OSil M-5P, colloidal silica, fumed silica, fumed silicon dioxide, SAS, silica colloidalis anhydrica	Adsorbent; anticaking agent glidant; viscosity-increasing agent	0.1–1.0% 2.0–10.0% widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient.	Practically insoluble in organic solvents, water. - hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing	Incompatible with diethylstilbestrol preparations.	A submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

				the viscosity of a system.		
Saccharin Sodium	1,2-Benzisothiazolin-3-one 1,1-dioxide, sodium salt, Crystallose, E954, gendorf 450, sucaryl sodium	Sweetening agent.			Saccharin sodium does not undergo Maillard browning.	
PVP K30	E1201, Kollidon, Plasdone, polyvidone, polyvinylpyrrolidone, PVP;1vinyl-2-pyrrolidinone polymer.	Disintegrant, tablet binder.	2.0–5.0	Greater than 10% solubility in water, methanol, PG….	compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals.	White to yellowish-white amorphous powder.
Sodium Lauryl Sulfate	Dodecyl alcohol hydrogen sulfate, sodium salt, dodecyl sodium sulfate, dodecyl sulfate sodium salt, Elfan 240	Detergent; lubricant; wetting agent.			incompatible with salts of polyvalent metalions, such as aluminum, lead, tin or zinc	

According to Metronidazole and excipients data as shown in Tables 2 and 3, it was selected that the different excipients to preformulation study with Metronidazole in the present study, the equipments used as shown in Table 4.

Table 4: The Equipment's Used.

No	Equipment's
1	Fourier Transform Infrared Spectrophotometer
2	UV/VIS Spectrophotometer
3	Melting Point Tester
4	Moisture Tester
5	Density Tester
6	pH Meter
7	Ultra-sonic
8	Accelerate Stability Study Chamber
9	Electronic Balance

Determination of The Organoleptic Properties

The organoleptic properties like color, odor and taste of the API was evaluated. Color a small quantity of Metronidazole was taken in a butter paper and viewed in well illuminated place. Taste and odor very less quantity of Metronidazole was used to assess the taste with the help of tongue as well as smelled to get odor. The organoleptic properties of the API substance were assessed.

Solubility Test: Solubility of Metronidazole in distilled water and methanol was determined by using Sonicator at room temperature. Approximate solubility of drugs as per B.P was indicated in Table 5.

Table 5: Solubility Specification of Drugs.

Solubility	Approximate Volume of Solvent in ml per gm of Solute
Excellent	Less than 1
Very soluble	1 to 10
Freely soluble	10 to 30
Soluble	30 to 100
Sparingly soluble	30 to 100
Slightly soluble	1000 to 10000
Very slightly soluble	1000 to 10000
Practically insoluble/ Insoluble	More than 10000

UV-Visible Spectrophotometric Method

UV Scanning of Metronidazole benzoate in 50% Methanol

The absorption spectra of Metronedazole in 50% methanol with 50% distilled water was subjected to scanning under UV visible spectrophotometer, between the range 200- 400nm.

Determination of λ Max for Metronidazole

The standard solution of Metronidazole was scanned in

the range of 200-400 nm and the λ max was determined.

UV scanning of Metronidazole in Phosphate Buffer at pH 6.8

The absorption spectra of Metronidazole in phosphate buffer at pH 6.8 were studied. A preliminary scanning of Metronidazole in phosphate buffer to determine the ʎ max by screening a 5µg/ml solution of Metronidazole in phosphate buffer these between 200- 400 nm.

Preparation of Calibration curve Solutions

Preparation of Phosphate buffer (pH 6.8): 0.896g of NaOH and 6.804g of KH2PO4 dissolved in sufficient quantity of water, complete volume to 1000 ml with distilled water and mixed well by sonication.

Calibration Curve

50 mg of Metronidazole was weighed accurately and dissolved in 50 ml of phosphate buffer (pH 6.8) in a 50 ml of volumetric flask to obtain a stock solution. aliquots of 1 ml, 5 ml, 10 ml, 15 ml, 20 ml and 25ml were taken and transferred to 100ml volumetric flask and volume was made up to 100 ml phosphate buffer (pH,6.8). The absorbance of these solutions was measured at 318 nm against a blank of phosphate buffer. The calibration curve was plotted between concentration and absorbance.

Calibration Curve of Metronidazole

The standard calibration curve graph was obtained by preparing aliquots of standard solution of Metronidazole in phosphate buffer (pH 6.8) and the absorbance at 318nm was measured after suitable dilution using UV/Visible spectrophotometer.

Appropriate aliquots were pipette out from standard stock solution into the series of volumetric flask and the volume was made up to the mark with concentration range 1-25 µg/ml of Metronidazole. Solutions of different concentrations were analyzed 318 nm against blank solution and absorbance were recorded. The calibration curve was plotted between concentration and absorbance.

Preformulation Studies

Preformulation studies are initiated to define the physical and chemical properties of the agent. The key goals of preformulation studies are to ensure the delivery of drug product with acceptable stability, bioavailability, and manufacturability.

Melting Point Determination of Metronidazole

Melting Point: Melting point of the Metronidazole was determined by capillary method; one sided closed capillary filled with drug and put into the Melting Point Apparatus. Temperature was noted at which solid drug changed into liquid.

Drug-Excipient Compatibility Studies

A physical mixture including Metronidazole and excipient was created in a 1:1 ratio, and it was subjected to analytical techniques such as FTIR spectroscopy. FTIR, of both pure drug and physical mixes were obtained, and the spectra of the both drug and mixture of excipient with drug were compared to look for any incompatibilities.

FTIR Spectroscopy Study

FTIR study KBr-disc method was used to record the FTIR spectra and KBr pellets were made in 1:100 ratio of sample and KBr. FTIR spectra was recorded using FTIR spectrum in a range of 4000-400cm^{-1}. Different functional groups of test compound for distinctive vibrational frequencies are identified using FTIR spectroscopy. FTIR spectra were used for the investigation of interaction in the physical mixture of API and excipient through shifting of peaks to lower or higher wavenumbers and appearance or disappearance of characteristic peaks of functional groups for pure API in physical mixture. FTIR spectroscopic study was performed to check the compatibility between API, and different excipients in amount (5mg:5mg) as ratio (1:1) as shown in Table 6. The FTIR spectra of a API alone and API with excipients were obtained by KBr method and compared with the standard FTIR spectrum of the pure API. Infrared spectrophotometer is not only used for determining the compatibility of excipients with the APIs, but also for API identification.

Preparation of IR Samples

The sample was determined by the disc method. Triturate 5mg of the substance to be examined with 300-400 mg of finely powdered and dried potassium bromide R or potassium chloride R. Each excipient was mix with Metronidazole equally then of potassium bromide is added to the mixture. Carefully grind the mixture, spread it uniformly in a suitable die, and submit it to a pressure of about 800 MPa (8 t·cm^{-2}). Then the tablets were inserted to the device and the Infrared spectra was recorded at mild-infrared light in wavenumber range of 4000 cm^{-1} to 400 cm^{-1}. After that the spectra were compared with the reference.

Infrared Spectral Study of Samples

Compatibility studies were performed by preparing blend of different excipients with Metronidazole in room condition as shown in Table 6.

Table 6: Samples of Metronedazole and Different Excipients for Compatibility Studies.

No	Component(s)	Amount(5mg:5mg)
1.	Metronedazole benzoate	1
2.	Metronedazole benzoate with Masticatory Gum Base	1:1
3.	Metronedazole benzoate with Natural Gum	1:1
4.	Metronedazole benzoate with Bees Wax	1:1
5.	Metronedazole benzoate with Sucralose	1:1
6.	Metronedazole benzoate with Aspartame	1:1
7.	Metronedazole benzoate with Mint Powder	1:1
8.	Metronedazole benzoate with Aerosol 200	1:1
9.	Metronedazole benzoate with Mg Stearate	1:1
10.	Metronedazole benzoate with Mannitol	1:1
11.	Metronedazole benzoate with CMC	1:1
12.	Metronedazole benzoate with PEG 6000	1:1
13.	Metronedazole benzoate with Acacia	1:1
14.	Metronedazole benzoate with Calcium Carbonate	1:1
15.	Metronedazole benzoate with Xanthan Gum	1:1
16.	Metronedazole benzoate with Talc	1:1
17.	Metronedazole benzoate with Sodium Saccharine	1:1
18.	Metronedazole benzoate with MCC	1:1
19.	Metronedazole benzoate with Povidone 30	1:1
20.	Metronedazole benzoate with BCD	1:1
21.	Metronedazole benzoate with Ascorbic Acid	1:1
22.	Metronedazole benzoate with Potassium Dihydrogen Phosphate	1:1

RESULTS AND DISCUSSION

Preformulation Tests

Organoleptic Properties

The organoleptic properties of Metronidazole benzoate as shown in Table 7.

Table 7: Organoleptic Properties of Metronidazole Benzoate.

Tests	Specification	Observation
Color	White or slightly yellowish crystalline powder	White powder
Taste	Unpleasant or sharp metallic	Unpleasant or sharp metallic
Odor	Characteristic	Characteristic

The organoleptic properties like color, odor and taste of the API were evaluated. The color of Metronidazole benzoate was found to be a white crystalline powder, Un pleasant or sharp metallic odor was observed in the study and the taste was found to be characteristic. Metronidazole benzoate showed similar color, taste and odor as per IP specification.

Solubility Test

It was determined as procedure were shown in Table 8.

Table 8: Solubility Analysis of Metronidazole Benzoate.

Material	Test	Specification	Observation
Metronidazole Benzoate	**Solubility**	Practically insoluble in water, freely soluble in methylene chloride, soluble in glacial acetic acid with acetonitrile, soluble in acetone, slightly soluble in alcohol	slightly soluble in methanol, soluble in glacial acetic acid with acetonitrile, freely soluble in methylene chloride

The solubility studies of drug revealed that Metronidazole benzoate is Practically insoluble in water, freely soluble in methylene chloride, methanol, glacial acetic acid and acetonitrile, soluble in acetone, slightly soluble in alcohol.

Evaluation of Pre-Compression Parameters

Metronidazole benzoate was measured using UV scanning at a wavelength of 318 nm. This measurement is considered selective because the scan on the placebo at the baseline shows no peaks. Thus, the selectivity of the method is confirmed. As shown in Figure 1.

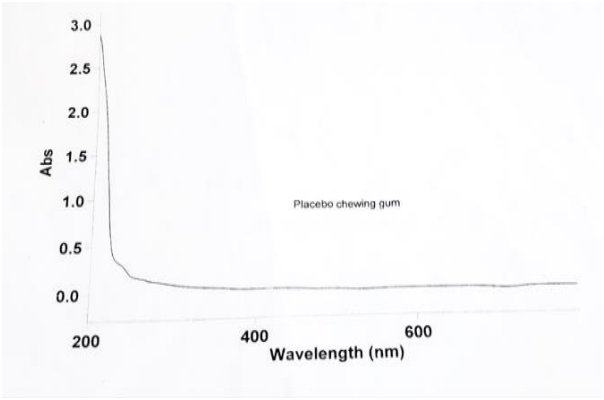


Fig. 1: Placebo Chewing Gum.

Characterization of Metronidazole by UV Spectroscopy

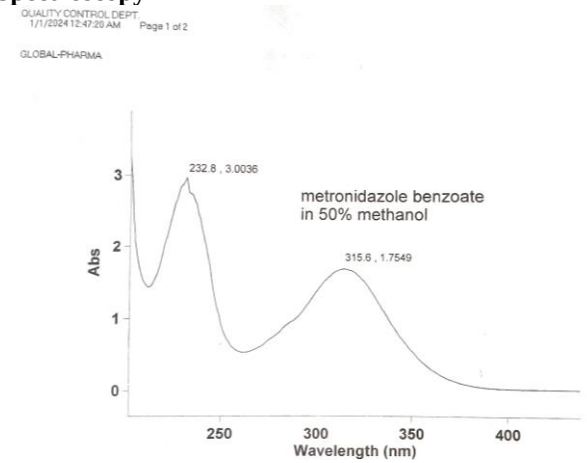


Fig. 2: UV Scanning of Metronidazole in 50% Methanol.

Maximum absorbance of Metronidazole benzoate in 50% methanol was determined by scanning the Metronidazole solution from 200-400 nm. The maximum absorbance was found at 318nm. As shown in Figure 2.

Calibration Curve of Metronidazole

Table 9: Calibration Curve of Metronidazole in Phosphate Buffer pH (6.8).

S.No	Concentration µg/ml	Absorbance
1	1	0.0273
2	5	0.1626
3	10	0.3300
4	15	0.4926
5	20	0.6583
6	25	0.821

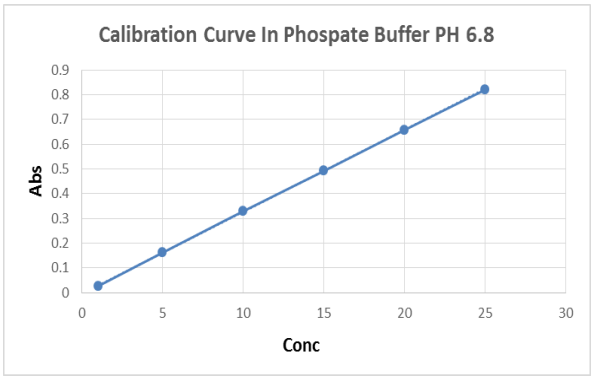


Fig. 3: Standard Calibration Curve of Metronidazole Benzoate in Phosphate Buffer (pH 6.8).

The calibration curve of metronidazole benzoate was prepared in mixture (0.1% glacial acetic acid/acetonitrile) 60%: 40%. The plot of different concentrations of metronidazole benzoate versus absorbance was found linear at 318 nm in calibrations. The absorbance at different concentrations as shown in table 9. The regression equation for metronidazole benzoate was obtained by plotting absorbance (a) versus concentration of metronidazole benzoate (c). The data of standard curve was linearly regressed. The linear regression equation was y = 0.033c - 0.0032. The regression coefficient (r2 = 0.99) was very much significant. The calibration curve was shown in figure 3.

Melting Point Determination of Metronidazole Benzoate

Melting point of Metronidazole Benzoate was observed to be 101.5℃. Reported melting point of Metronidazole Benzoate is (99-102°C). The melting point range of Metronidazole Benzoate was identical to reference melting point stated in BP (99-102°C).The sample started to melt at 101.5C°, and turned into liquid at 101.5°C, as shwon in Table 10, indicating that the sample used is pure. That reading has stated in melting point apparatus.

Table 10: Results of Melting Point of Metronidazole Benzoate.

Test	Temp Rang Analyzed (Melting)	Results
Test I Metronidazole Benzoate	(99-102°C)	101.5°C
Test II Metronidazole Benzoate	(99102°C)	101.5 °C

Characterization of Metronidazole by FTIR

FT-IR spectral studies indicated that the drug is compatible with all the excipients. The FT-IR spectrum of physical mixture showed all the characteristic peaks of

Metronidazole, thus conforming that no interaction of drug occurred with the components of the formulation excipients as shown in Figures (4-25).

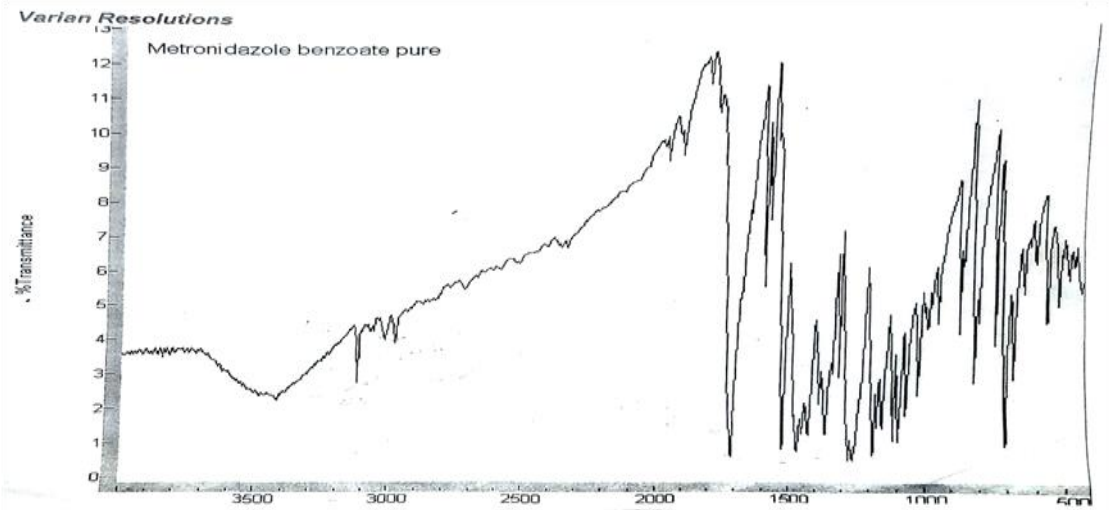


Fig. 4: FTIR Spectrum of Metronidazole Benzoate.

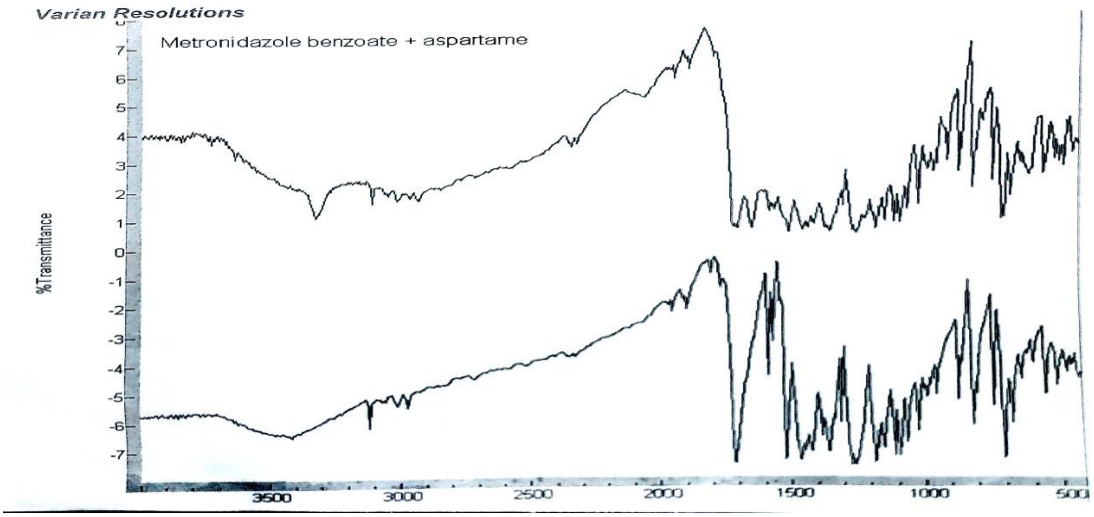


Fig. 5: FTIR Spectrum of Metronidazole Benzoate with Aspartame.

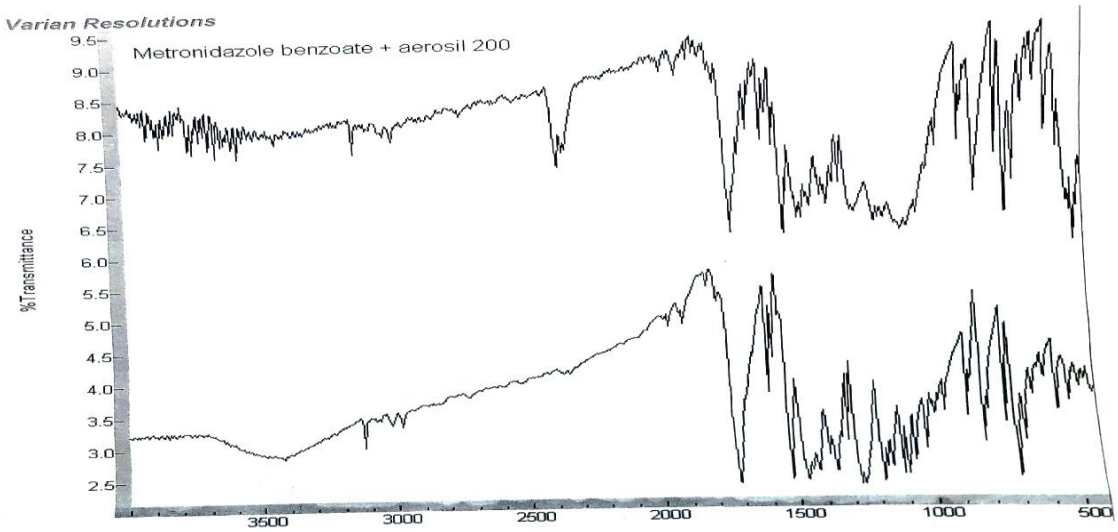


Fig. 6: FTIR Spectrum of Metronidazole Benzoate with Aerosil 200.

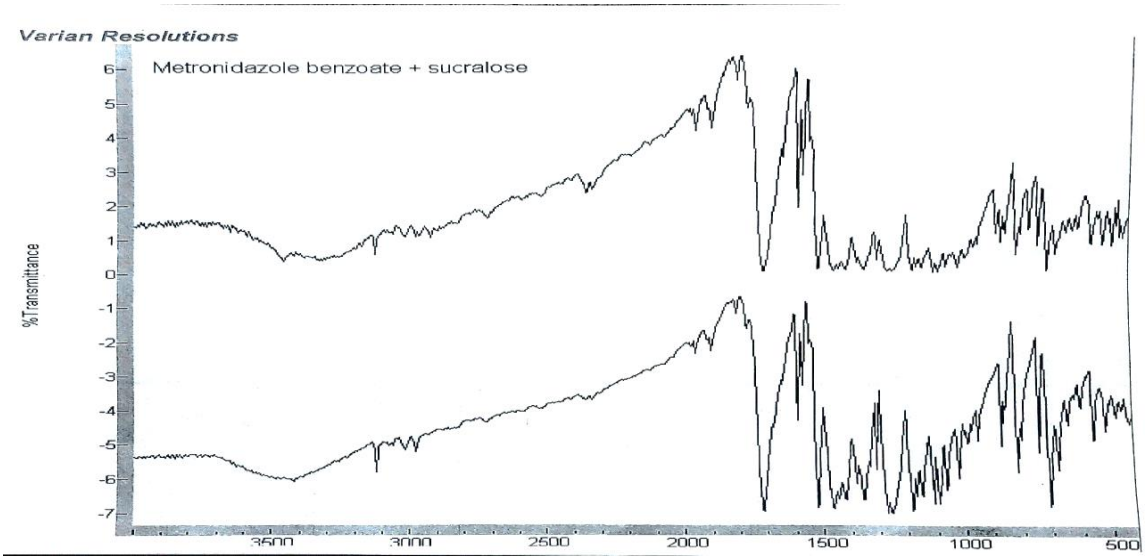


Fig. 7: FTIR Spectrum of Metronidazole Benzoate with Sucralose.

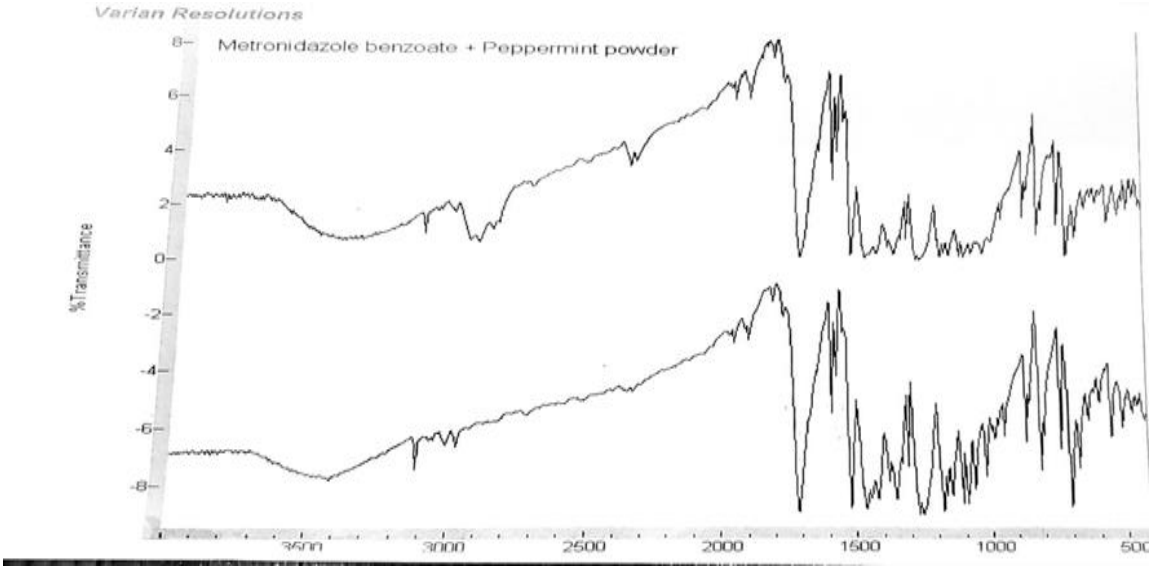


Fig. 8: FTIR Spectrum of Metronidazole Benzoate with Peppermint Powder.

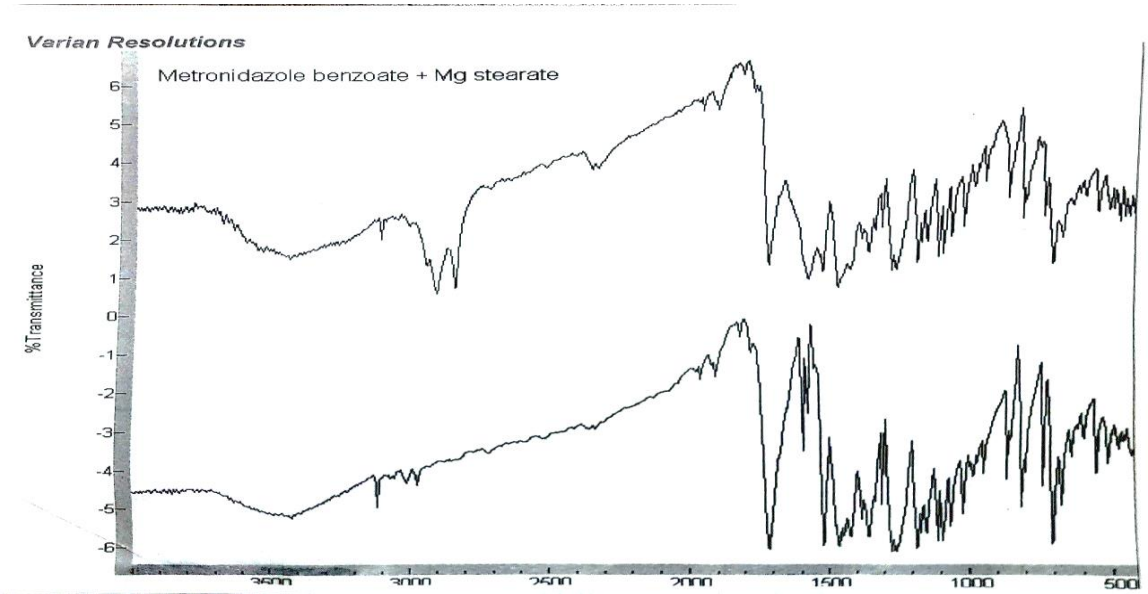


Fig. 9: FTIR Spectrum of Metronidazole Benzoate with Mg Stearate.

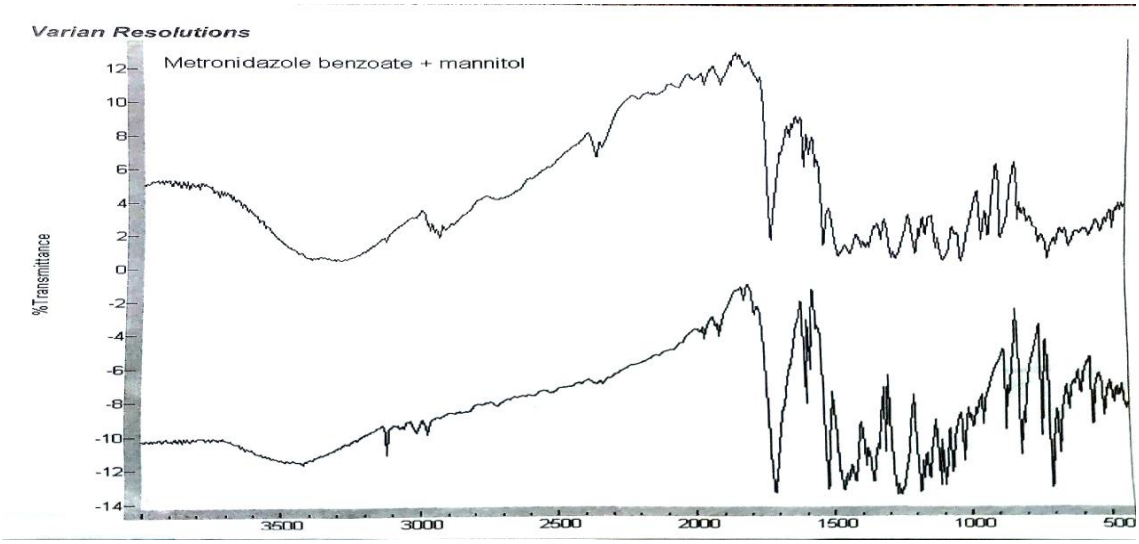


Fig. 10: FTIR Spectrum of Metronidazole Benzoate with Mannitol.

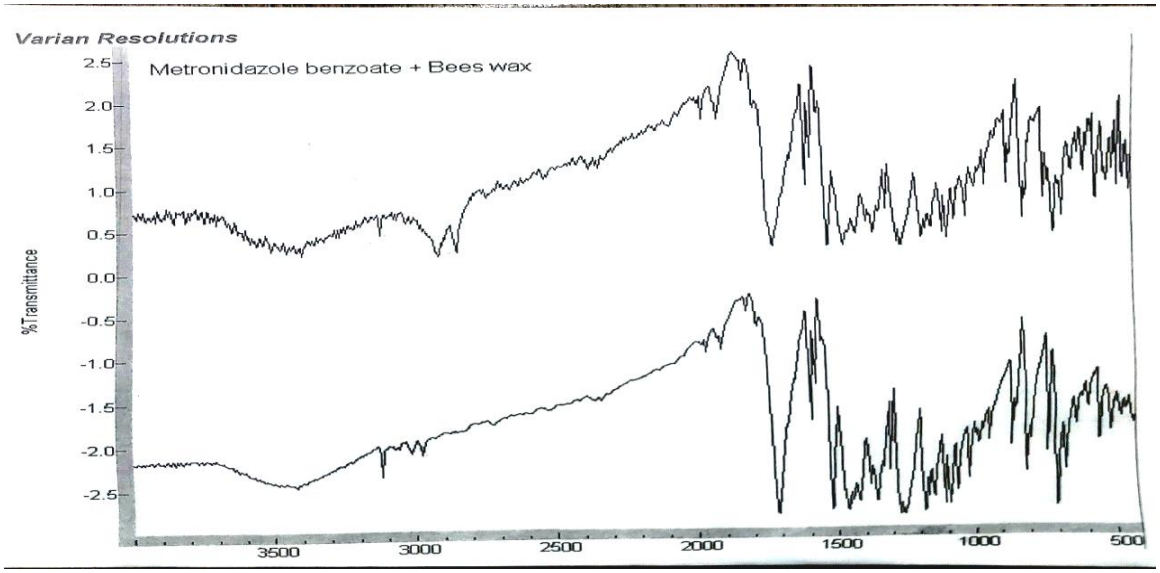


Fig. 11: FTIR Spectrum of Metronidazole Benzoate with Bees Wax.

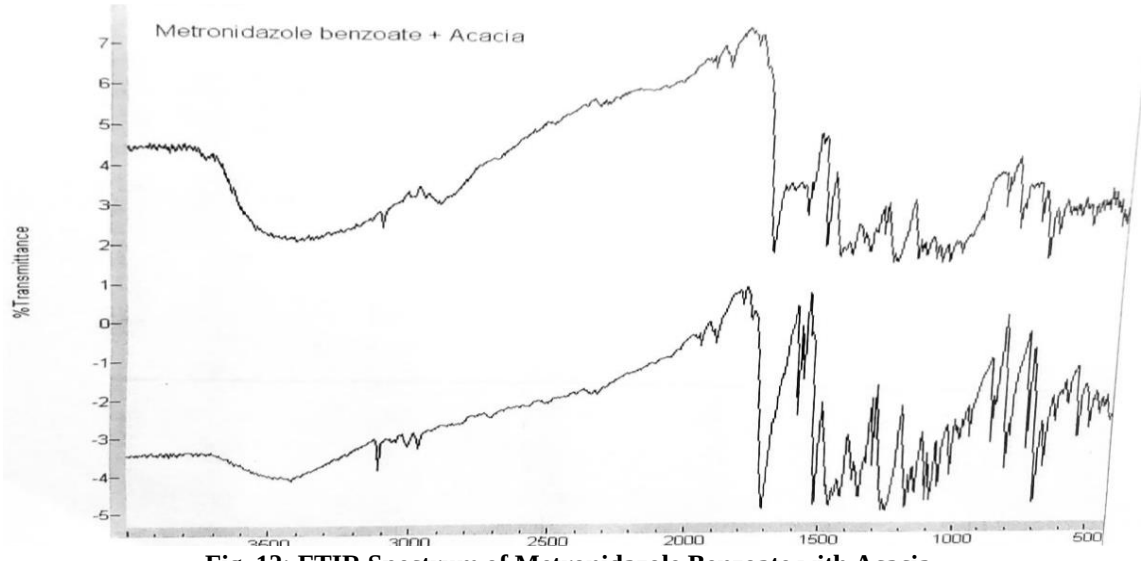


Fig. 12: FTIR Spectrum of Metronidazole Benzoate with Acacia.

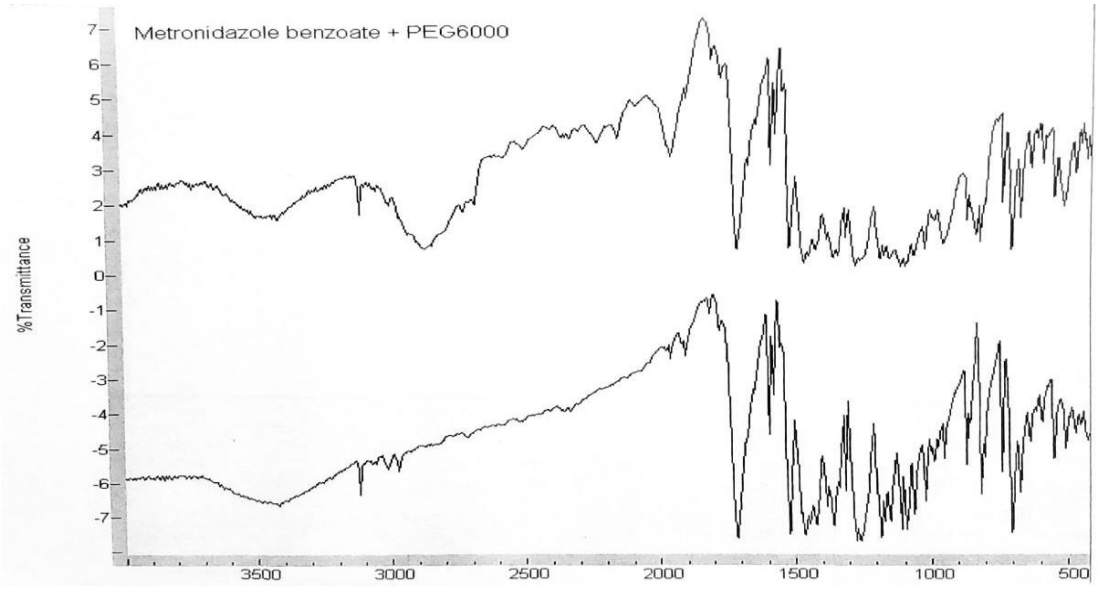


Fig. 13: FTIR Spectrum of Metronidazole Benzoate with PEG6000.

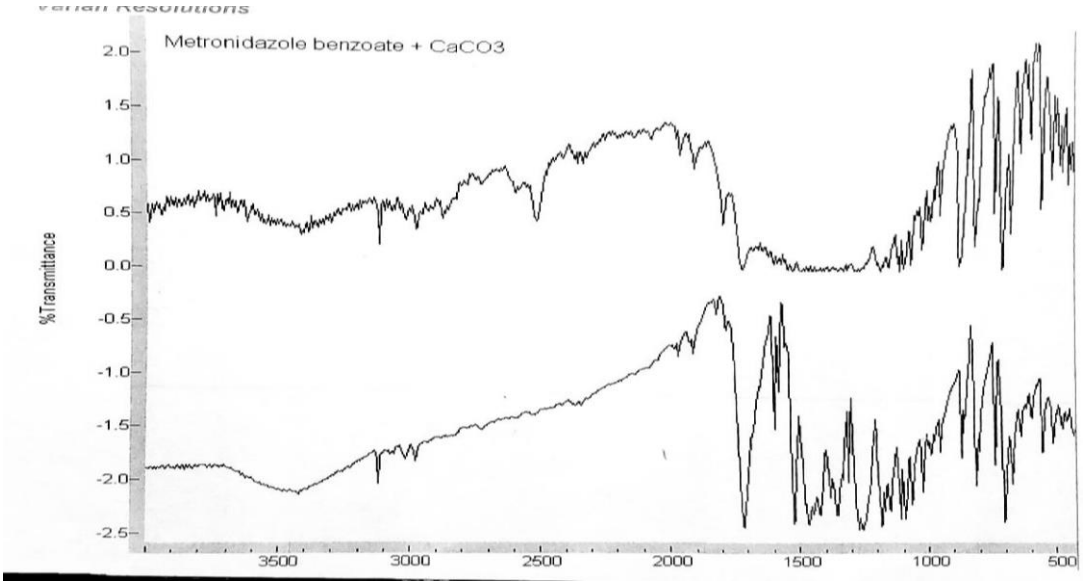


Fig. 14: FTIR Spectrum of Metronidazole Benzoate with CaCO3.

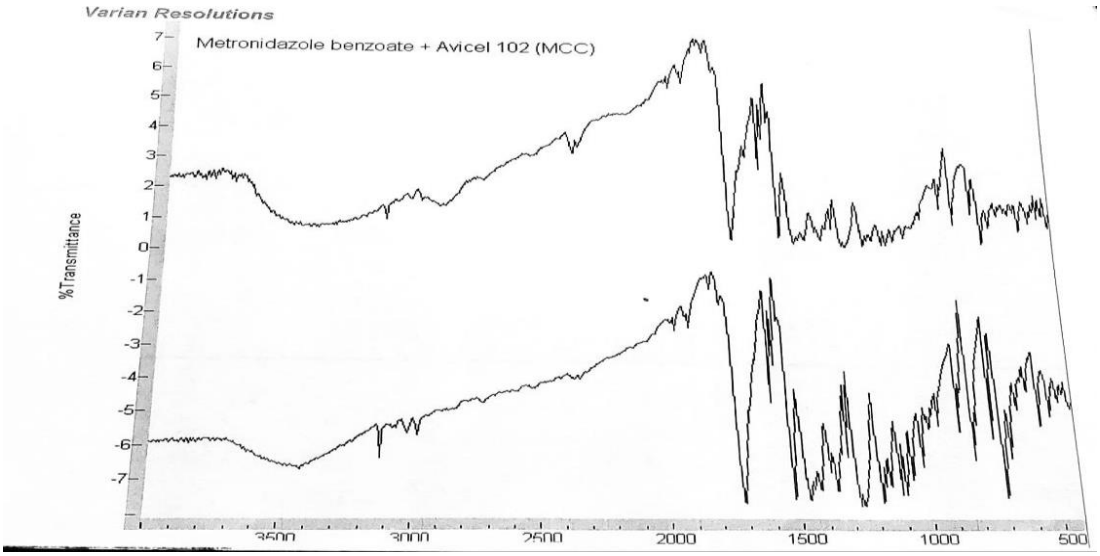


Fig. 15: FTIR Spectrum of Metronidazole Benzoate with MCC.

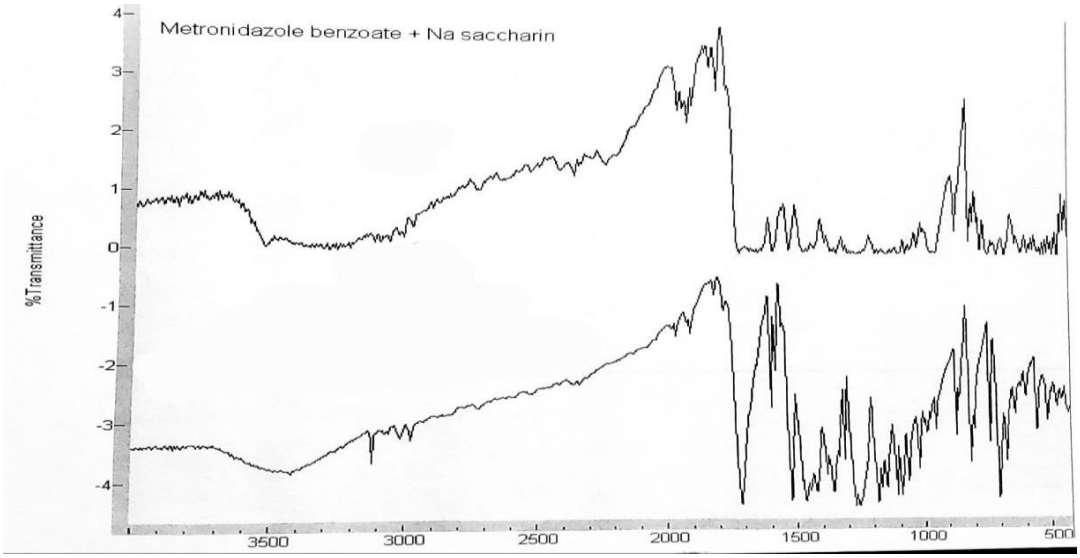


Fig. 16: FTIR Spectrum of Metronidazole Benzoate with Na Saccharin.

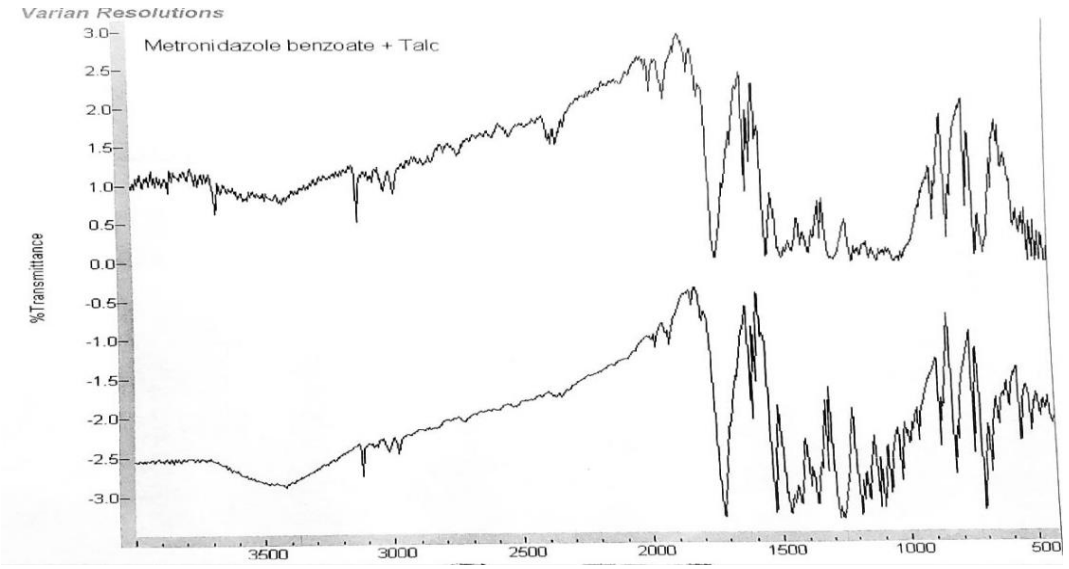


Fig. 17: FTIR Spectrum of Metronidazole Benzoate with Talc.

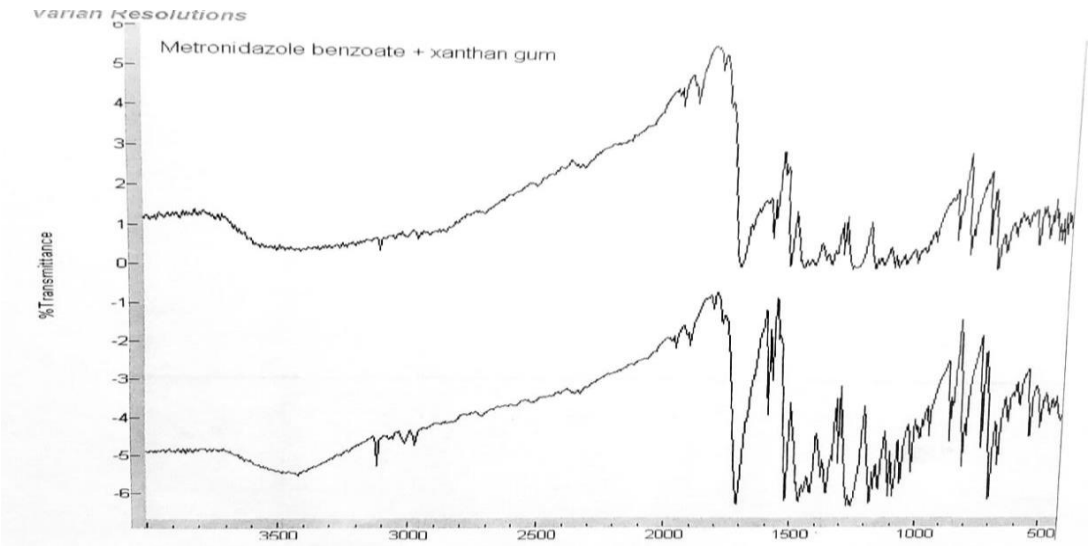


Fig. 18: FTIR Spectrum of Metronidazole Benzoate with Xanthan Gum.

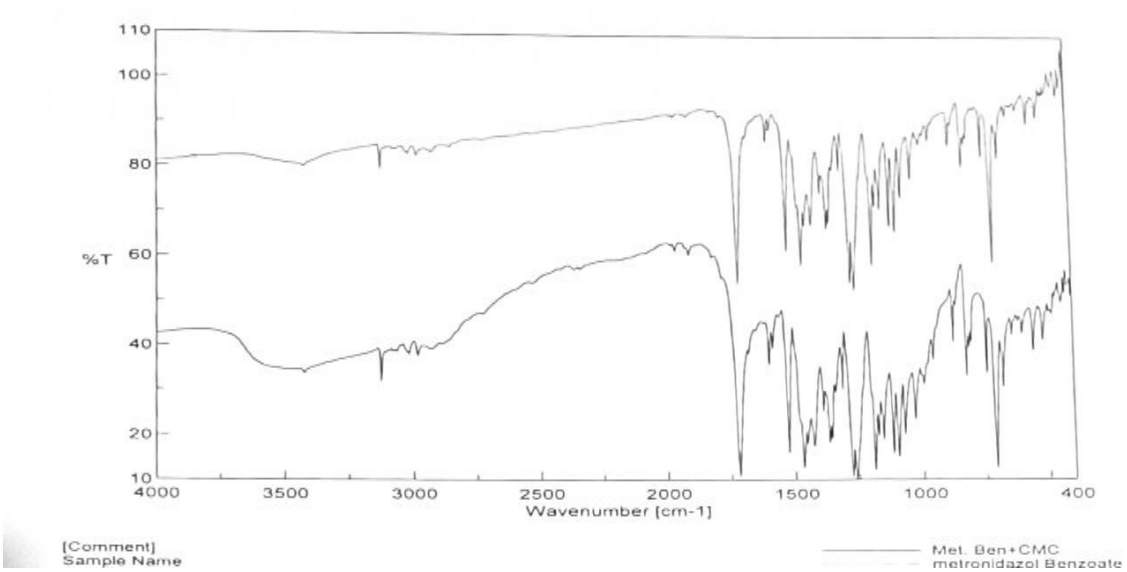


Fig. 19: FTIR Spectrum of Metronidazole Benzoate with CMC.

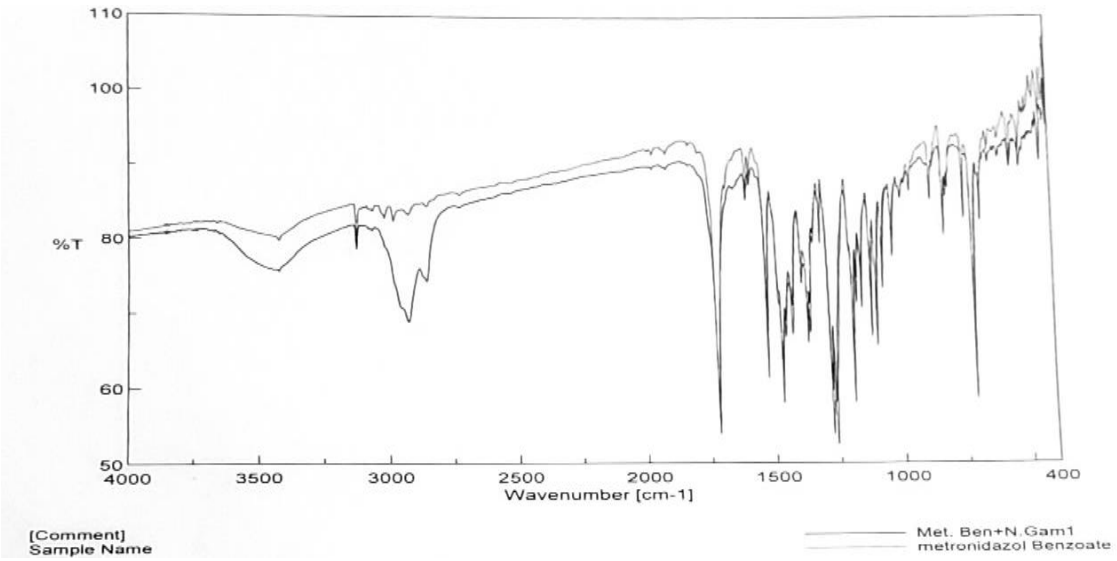


Fig. 20: FTIR Spectrum of Metronidazole Benzoate with Natural Gum.

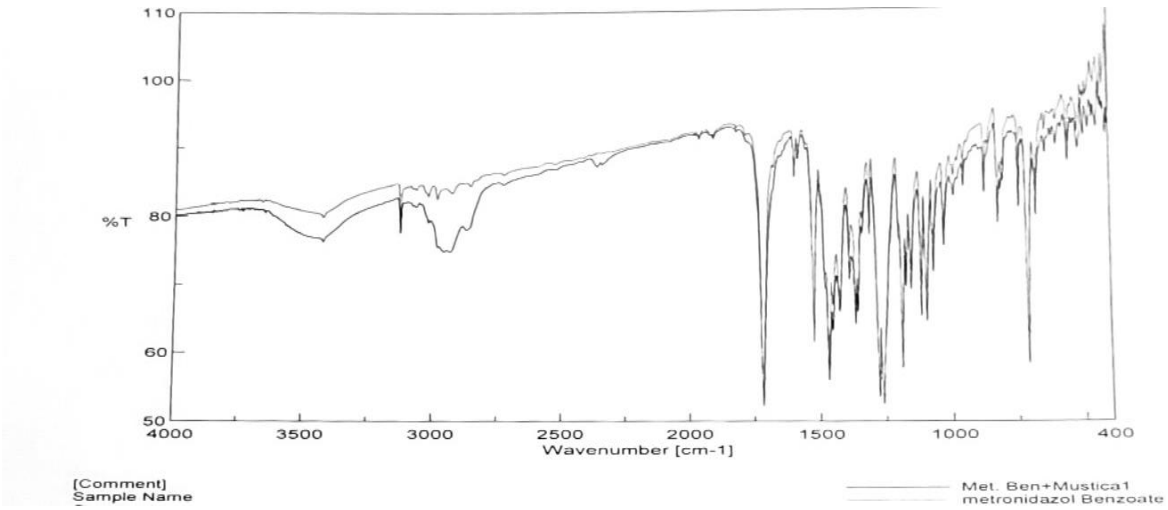


Fig. 21: FTIR Spectrum of Metronidazole Benzoate with Masticatory Gum Base.

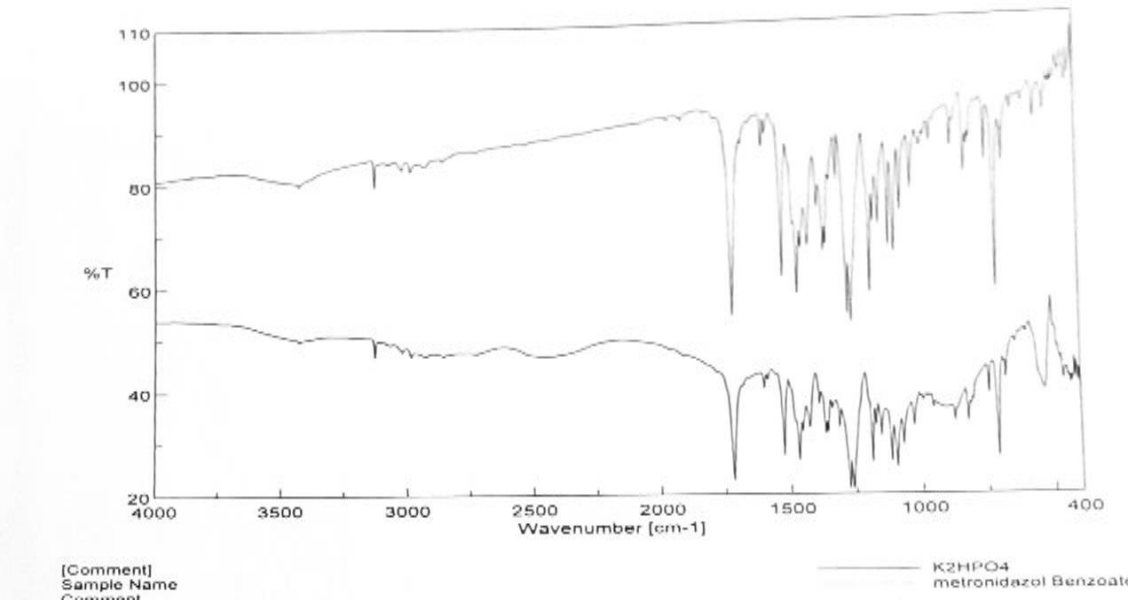


Fig.22: FTIR Spectrum of Metronidazole Benzoate with KH2PO4.

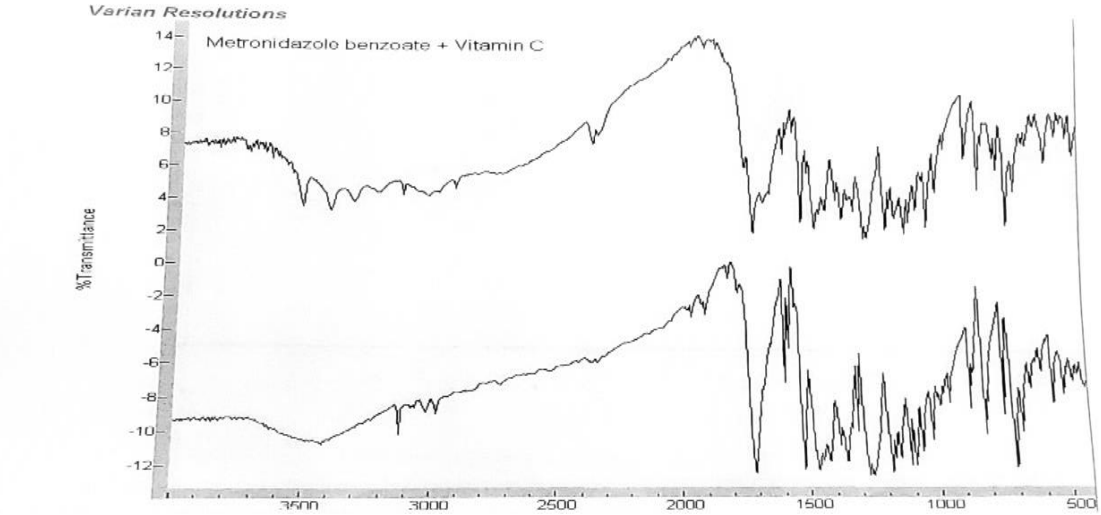


Fig. 23: FTIR Spectrum of Metronidazole Benzoate with Ascorbic Acid.

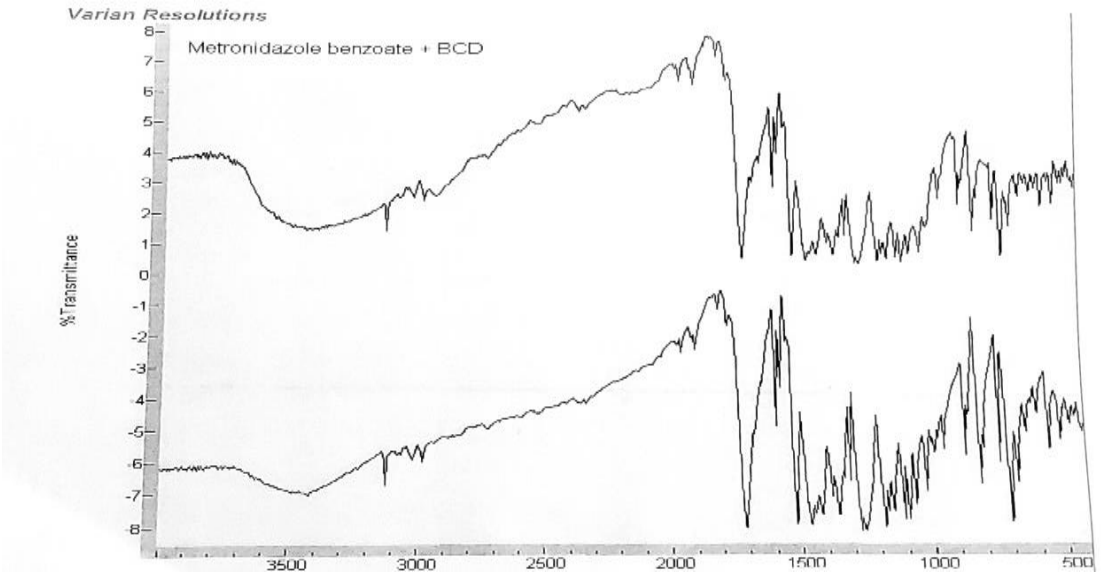


Fig. 24: FTIR Spectrum of Metronidazole Benzoate with BCD.

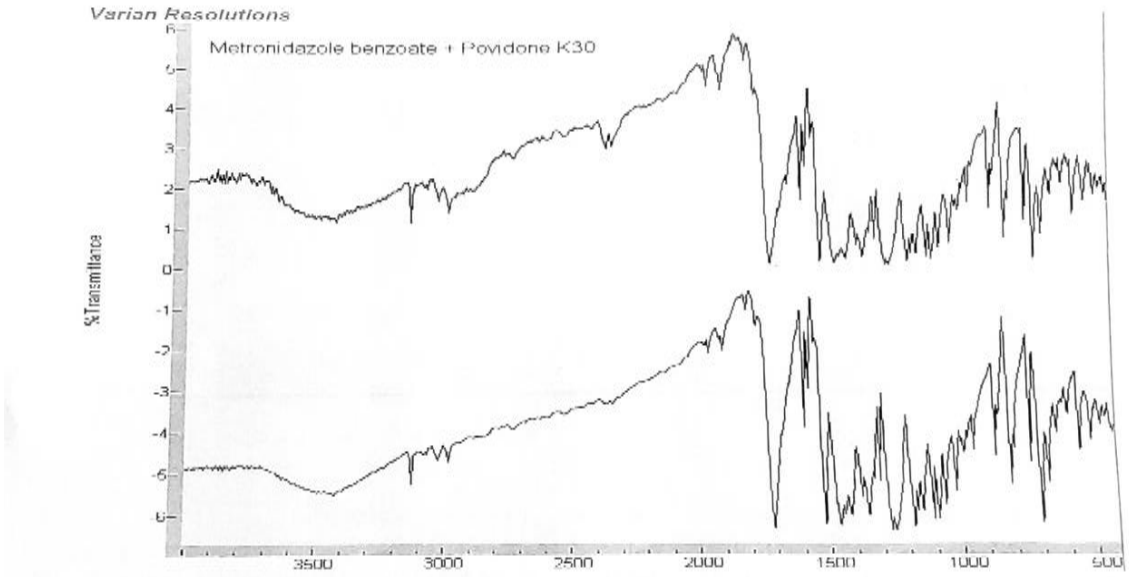


Fig. 25: FTIR Spectrum of Metronidazole Benzoate with Povidone k30.

FT-IR spectral studies indicated that the drug is compatible with all of the excipients. The FT-IR spectrum of physical mixture showed all the characteristic peaks of Metronidazole benzoate, thus conforming that no interaction of drug occurred with the components of the formulation.

CONCLUSION

The compatibility studies of physical mixtures of Metronidazole and various excipients such as Mannitol, MCC, CMC, Acacia gum, Xanthan gum, etc., were investigated by FTIR it was detected that there was no variation or minor deviation in the characteristic peaks in FTIR spectroscopy. The Metronidazole Medicated Chewing Gum (MCG) formulations prepared were evaluated for precompression parameters and powder flow properties which were found to be within limits. It was concluded that the drug Metronidazole was found to be compatible with various excipients which were selected for the formulation development of the Metronidazole Medicated Chewing Gum(MCG): A Modern Oral Drug Delivery System. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

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