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DOMPERIDONE-EXCIPIENT COMPATIBILITY STUDIES FOR ADVANCED DRUG DELIVERY SYSTEMS DEVELOPMENT

Mahmoud Mahyoob Alburyhi*, Abdalwali Ahmed Saif and Maged Alwan Noman

Professor Dr. of Pharmaceutics and Industrial Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.

***Corresponding Author: Prof. Dr. Mahmoud Mahyoob Alburyhi**
Professor Dr. of Pharmaceutics and Industrial Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.

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ABSTRACT
Domperidone functions by blocking peripheral dopamine receptors, resulting in its gastroprokinetic effects. It enhances gastric peristalsis and promotes coordination between the stomach and duodenum, aiding in the emptying of gastric contents. Additionally, the anti-emetic properties of domperidone stem from its ability to block dopamine (D2) receptors at the chemoreceptor trigger zone (CTZ). The main objective of the present study was to the preformulation studies were performed to know the development of formulation and evaluation of Domperidone Orodispersible Tablets to improve the bioavailability of Domperidone. In the present study that the compatibility was assessed by, FTIR spectroscopy, and melting point apparatus, precompression parameters and powder flow properties. Results showed that physical mixtures of Domperidone and various excipients as mannitol, lactose and avicel PH 102 as diluents, and sodium starch glycolate, croscarmellose sodium, and crospovidone as superdisintegrants and sodium lauryl sulfate as wetting agent were evaluated for preformulation studies parameters. It was concluded that the drug Domperidone was found to be compatible with various excipients which were selected for the formulation development of the Domperidone ODTs. 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: Domperidone, Compatibility, Excipients, Development, Preformulation, Formulation, Anti-emetic agents.

INTRODUCTION

Preformulation Studies[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.

In the present study, it was proposed to Domperidone-excipient compatibility studies of 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., with commonly different excipients using for formulation development of Orodispersible tablets ODTs.

MATERIALS AND METHODS

Materials used in this study as shown in Table 1.

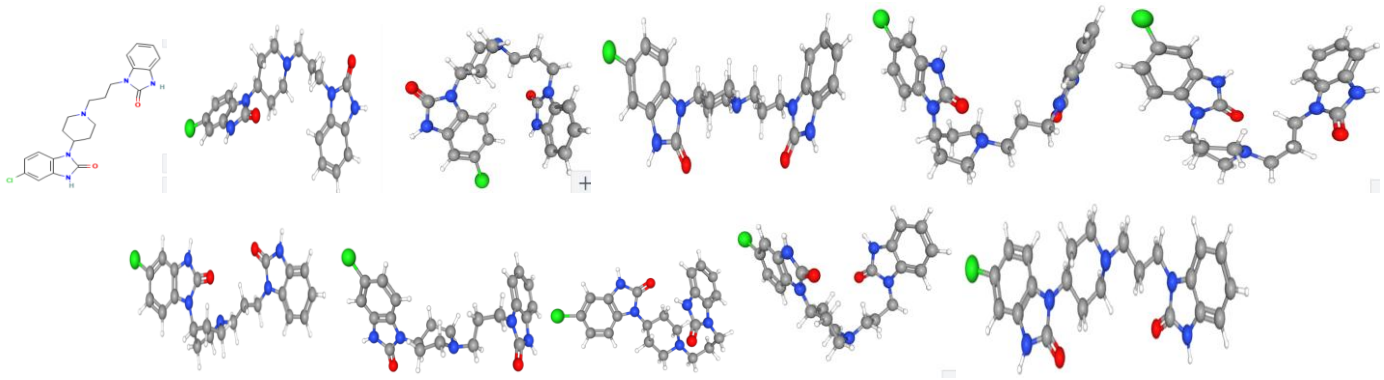
Table 1: Materials.

No	Materials	Function
1	**Domperidone**	Domperidone is the active pharmaceutical ingredient (API) used in medications to treat nausea, vomiting, and other gastrointestinal disorders. It functions by increasing the movement of the stomach and intestines, thereby relieving symptoms.
2	**Sodium Saccharin**	Sodium Saccharin is an artificial sweetener used to provide a sweet taste for drug.
3	**Croscarmellose Sodium**	Croscarmellose Sodium is a disintegrant, which means it helps tablets and capsules to break apart and dissolve quickly.
4	**Mannitol**	Mannitol is a sugar alcohol, it serves as a bulking agent, sweetener, and stabilizer.
5	**Crospovidone**	Crospovidone is another disintegrant, it assists in the rapid breakdown and dissolution of tablets.
6	**Avicel-102**	also known as microcrystalline cellulose (MCC-102), is a commonly used excipient that acts as a binder and filler in tablet formulations. It helps to provide structural integrity to tablets
7	**Sodium Starch Glycolate**	Sodium Starch Glycolate (SSG) is another disintegrant used to facilitate the disintegration and dissolution of tablets.
8	**Mg Stearate**	Magnesium Stearate is a lubricant, it helps to prevent sticking of the tablet mixture to the equipment during manufacturing and aids in the release of the tablet from molds.
9	**Aspartame**	Aspartame is an artificial sweetener used to provides a sweet taste.
10	**Aerosil-200**	Aerosil-200, also known as colloidal silicon dioxide (CSD), is used as a flow agent and anticaking agent in powdered formulations. It prevents clumping and improves flow characteristics.
11	**Sucralose**	Sucralose is an artificial sweetener used to provides a sweet taste.
12	**Lactose**	Lactose is a sugar found in milk; it is used as a binding agent in tablets.
13	**Sodium bicarbonate**	Sodium Bicarbonate (NaCO3), also known as baking soda, It can help adjust pH, create effervescence, aid disintegration, and potentially mask taste.
14	**Talc**	Talc is a lubricant and diluent, it enhances the powder mixture's flow properties and facilitating easy swallowing of tablets
15	**Na Lauryl Sulfate**	It is a surfactant, and plays a role in wetting and dispersing the tablet ingredients upon contact with saliva.
16	**Tween 80**	Also known as Polysorbate 80, it is a solubilizing agent and emulsifier.
17	**Poly Ethylene Glycol 6000**	It is a hydrophilic polymer that acts as a binder, holding the tablet ingredients together. It also provides lubrication
18	**Poloxmer**	Used as detergent , surfactant, and stabilizer.
19	**Lemon Flavor**	Lemon flavor is used to enhance the taste of tablets
Note: "All previous materials were gift from (Modern/ Global Pharmaceutical Industry Company-Yemen).		

Evaluation of Drug-Excipient Compatibility Studies Methods [34-138]

Table 2: Domperidone Data.

Characterization of Domperidone



Domperidone Structure and 3D Conformer

Chemical Structure	6-chloro-3-[1-[3-(2-oxo-2H-benzimiazole-1-yl)propyl]piperidin-4-yl]-1H-benzimidazol-2one.	**Appearance**	Is white to off-white to solid.
Chemical Formula	$C_{22}H_{24}ClN_5O_2$	**Drug Solubility**	Soluble in DMSO. **Water solubility:** The drug substance has poor aqueous solubility in distilled water (0.134 mg/ml at 20 ±5° C) and 3.815 mg/ml in 0.1NHCL.
Molecular Weight	425.9 g/mol	**BCS**	Class-II Drug
Drug Action and Use	Domperidone functions by blocking peripheral dopamine receptors, resulting in its gastroprokinetic effects. It enhances gastric peristalsis and promotes coordination between the stomach and duodenum, aiding in the emptying of gastric contents. Additionally, the anti-emetic properties of domperidone stem from its ability to block dopamine (D2) receptors at the chemoreceptor trigger zone (CTZ). Domperidone does not cross the blood-brain barrier, making it suitable for concurrent use with levodopa. Domperidone is commonly used as an antiemetic and can effectively treat gastroparesis, pediatric acid reflux, and other gastrointestinal disorders. During pregnancy, it is used to manage nausea and vomiting, although the potential teratogenicity of dopamine antagonists is still under investigation. In cases of severe symptoms, such as hyperemesis gravidarum, hospital admission may be necessary. For lactating mothers, domperidone can increase milk production, but it must be used as prescribed, not exceeding a daily dose of 30 mg to avoid cardiac complications. Studies from various countries have shown no significant side effects in infants given a dose of 10 mg three times a day for lactation purposes.		
Domperidone Pharmacokinetics			
Drug Absorption	Domperidone is taken orally and reaches peak levels in the bloodstream within 30 minutes. However, only 15% of the drug is available for use due to first-pass metabolism.	**Drug Distribution**	Domperidone binds strongly to plasma proteins (91-93%) and is widely distributed throughout the body (5.71 L/Kg).
Drug Metabolism	Domperidone undergoes extensive metabolism in the liver, primarily through N-dealkylation and hydroxylation reactions catalyzed by cytochrome P 450 enzymes. The resulting metabolites are inactive.	**Drug Excretion**	Metabolites of Domperidone are excreted in both urine and feces. Approximately 66% of the drug is detected in the feces after oral administration. In healthy individuals, the elimination half-life is around 7.5 hours. However, in patients with significant renal impairment, the elimination half-life can extend up to 20 hours.
The Elimination Half-Life (T1/2)	The elimination half-life of Domperidone is approximately 7 hours.	**Availability**	Oral Tablets, Oral Suspensions, Oral Drops, Suppository.

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)	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
Lactose Anhydrous (Anhydrous Lactose)	O-b-D-Galactopyranosyl-(1!4)-b-D-glucopyranose]	Directly compressible tablet excipient, dry powder inhaler carrier, lyophilization aid, tablet and capsule diluent, tablet and capsule filler.	widely used in pharmaceutical formulations	Soluble in water	incompatible with strong oxidizers. When mixtures containing a hydrophobic leukotriene antagonist. -hydrolysis of the ester and amidine groups.	white to off-white crystalline particles or powder.
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.		
Aspartame	N-a-L-Aspartyl-L-phenylalanine 1-methyl ester	Sweetening agent. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.	The WHO has set an acceptable daily intake for aspartame at up to 40 mg/kg body-weight.	slightly soluble in ethanol (95%); sparingly soluble in water. At 20°C the solubility is 1% w/v at the isoelectric point (pH 5.2).	incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate.	Occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.
Sucralose (SucraPlus)	,6-Dichloro-1,6-dideoxy-b-D-fructofuranosyl-4-chloro-4-deoxya-D-galactopyranoside	Sweetening agent.	0.03–0.24%	Freely soluble in water.	---	Crystalline powder
Sodium Lauryl Sulfate	Dodecyl alcohol hydrogen sulfate, sodium salt, dodecyl sodium sulfate, dodecyl sulfate sodium salt, Elfan 240. C12H25NaO4S	Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.	10% 0.5–2.5% 1.0–2.0%	Freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and ether.	Incompatible with salts of polyvalent metal ions, such as aluminum, lead, tin or zinc	White or cream to pale yellow colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances
Talc	Altalc, E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Luzenac Pharma, magnesium hydrogen metasilicate. Mg6(Si2O5)4(OH)4.	Anticaking agent, glidant, diluent, lubricant.	1.0–10.0% 5.0–30.0%	Practically insoluble in dilute acids and alkalis, organic solvents, and water.	Incompatible with quaternary ammonium compounds.	is a very fine, white to grayish-white, crystalline powder.

According to Domperidone and excipients data as shown in Tables 2 and 3, it was selected that the different excipients to preformulation study with Domperidone 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**

Solubility Analysis

Solubility is defined as the number of grams of substance which will dissolve in 100 ml of solvent at a stated temperature. The solubility of drug was studied in different solvents such as methanol, acetate buffer, phosphate buffer, HCL by measuring how many parts of solvent is required for one part of solid. Then analyzed by spectrophotometer. Solubility specification of drugs as shown 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

Determination of λ Max for Domperidone

The standard solution of Domperidone was scanned in the range of 200-400 nm and the λ max was determined

Preparation of Working Solutions

Domperidone solubility test is performed in methanol, buffer phosphate pH6.8, acetate buffer pH4.5 and 0.1NHCl pH1.5.

Preparation of Phosphate Buffer pH 6.8

Dissolving 3.40g of potassium dihydrogen phosphate and 0.45g of hydroxide sodium (NaOH), then complete the volume to 500ml with purified water. Taken 200ml of buffer phosphate and then dissolving 10mg of active ingredient Domperidone and shake the volumetric flask by sonicator device. Let the volumetric flask sit undisturbed for several hours to allow any undissolved particles to settle. Filtration of solution that contains the active ingredient, then measure the solubility under UV spectrophotometer.

Preparation of Acetate Buffer pH 4.5

Dissolving 1.495g of sodium acetate trihydrate into 500ml Volumetric flask, add amount of water and add 7ml of 2N of acetate buffer, dilute to volume with purified water and mix. Taken 200ml of acetate buffer and then dissolving 10mg of active ingredient Domperidone and shake the volumetric flask by sonicator device. Let the volumetric flask sit undisturbed for several hours to allow any undissolved particles to settle. Filtration of solution that contains the active ingredient, then measure the solubility under UV spectrophotometer.

Preparation of 0.1N HCl

Taken 0.05ml of 0.1N HCl in volumetric flask and complete the volume with purified water to 500ml.Taken 200ml of buffer HCl and then dissolving 10mg of active ingredient Domperidone and shake the volumetric flask by sonicator device. Let the volumetric flask sit undisturbed for several hours to allow any undissolved particles to settle. Filtration of solution that contains the active ingredient, then measure the solubility under UV spectrophotometer.

UV Visible Spectrophotometer

UV Scanning of Domperidone in Phosphate Buffer pH 6.8

The sample was scanned with UV-V spectrophotometer in the range 200 -800nm against phosphate buffer pH 6.8 as blank and the wavelength corresponding to maximum absorbance was noted.

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 Domperidone

The most common and most basic method of determination is the capillary method. Melting point of the Domperidone 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 Domperidone 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 Domperidone 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 in Room Condition

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

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

No	Component(s)	Amount(5mg:5mg)
1	Domperidone	1
2	Domperidone and Avicel PH 102	(1:1)
3	Domperidone and SSG	(1:1)
4	Domperidone and SLS	(1:1)
5	Domperidone and Crospovidone	(1:1)
6	Domperidone and Lactose	(1:1)
7	Domperidone and CCS	(1:1)
8	Domperidone and Mannitol	(1:1)
9	Domperidone and Mg.Stearate	(1:1)
10	Domperidone and Sucralose	(1:1)
11	Domperidone and Aerosil200	(1:1)
12	Domperidone and NaHCO3	(1:1)
13	Domperidone and Aspartame	(1:1)
14	Domperidone and Talc	(1:1)

Formulation of Domperidone Orodispersible Tablets

The Orodispersible tablets that contained a selected solid dispersion were prepared by direct compression method using a single punch tablet machine to produce round tablets with a biconvex surface, tablets were 100 mg in weight. 150 tablets were prepared for each formula batch as shown in Table 7. The formulations were developed by using superdisintegrants. The superdisintegrants (crospovidone, sodium starch glycolate, and croscarmellose sodium) were used in varied concentrations to develop the formulations. All the ingredients of the ten formulations are shown in Table 7. Each ingredient was passed through a sieve no.18 except mg stearate passed through sieve no.35, the ingredients were co-grounded in a glass pestle motor, then mixed geometrically. The prepared blends were evaluated for mass-volume relationship (bulk density, tapped density, hausner ratio, and compressibility index) and flow properties (Angle of Repose). The prepared blends were compressed using a rotary tablet compression machine of a punch size 6 mm concave punch to produce a convex faced tablet.

Mixing and Compression Processes: Mixing was performed geometrically, in which all excipients were accurately weighed then all of them with the exception of aerosil, magnesium stearate and vanilla flavor, were blended with specified quantity of Domperidone for 15minutes, while the other excipients were blended for 5 minutes and added to the former excipients. Then all formulae were passed through sieve no.18 to achieve particle size uniformity. Then each blend was subjected to powder properties examination and that will be shown in the evaluation of precompression parameters section. Finally, each mixture of each formulation has been compressed directly into tablets using rotary tablet compression machine of punch size 6 mm concave punch to prepare tablets weighing 100 mg.

Table 7: Composition of Domperidone Formulations ODTs.

Ingredients	Quantity Per Tablet (mg)									
	Formulation Code									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Domperidone	10	10	10	10	10	10	10	10	10	10
Croscarmellose Sodium	-	-	5	2.5	-	-	-	-	-	-
Mannitol	-	80.75	-	40.38	-	-	-	-	-	-
Crospovidone	5	-	-	2.5	7	7	7	7	7	7
Avicel-102 (MCC)	80.75	-	-	40.37	78.75	77.75	68.75	77.75	77.75	77
Sodium Starch Glycolate	-	5	-	-	-	-	-	-	-	-
Mg Stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Aspartame	-	-	-	-	-	-	-	-	-	-
Aerosil-200	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Sucralose	2	2	2	2	2	2	2	2	2	2
Lactose	-	-	80.75	-	-	-	-	-	-	-

Sodium Lauryl Sulfate	-	-	-	-	-	1	-	-	-	-
Tween 80	-	-	-	-	-	-	-	1	-	-
Poly Ethylene Glycol 6000	-	-	-	-	-	-	-	-	1	-
Poloxmer	-	-	-	-	-	-	-	-	-	1
Lemon Flavor	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75

Evaluation of Pre-Compression Parameters of Formulations

Bulk Density

Bulk density (ρb) was determined by placing pre sieved drug excipients mixture into a graduated cylinder and measuring the volume (Vb) and weight (M).

ρb = M/Vb.

Tapped Density

The measuring cylinder containing a known quantity of blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the drug excipients mixture was measured. The tapped density (ρt) was calculated using the following formula. ρt = M/Vt.

Angle of Repose

Angle of repose (**θ**) was determined using funnel method. The drug excipients mixture was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the pile (r) was measured and the angle of repose was calculated. **θ** = tan -1 (h/r). As shown in Table 6.

Carr's Index

Carr's Index or % compressibility is helpful to determine flow properties of powder mixtures, which is calculated as follows:

C = (ρt–ρb)/ρt X 100 Where, ρt - Tapped density, ρb - Untapped bulk density.

Hausner's Ratio

Hausner's ratio is an index of ease of powder flow; it is calculated by the following formula.

Hausner's ratio = ρt\ ρb Where, ρt - Tapped density ρb - Bulk density. As shown in Tables 8 and 9.

Table 8: Powder Flow Properties.

Description of Flow	Angle of Repose (θ)
Excellent	≤25
Very Good	25 – 30
Good	31 – 35
Fair	36 – 40
Passable (but flow aid might be needed)	41 – 45
Poor (agitation or vibration needed)	46 – 55
Very Poor	>56

Table 9: Powder Flow Properties.

Description of Flow	Carr's Index (%)	Hausner Ratio
Excellent	≤10	1.00 – 1.11
Good	11 – 15	1.12 – 1.18
Fair	16 – 20	1.19 – 1.25
Passable	21 – 25	1.26 – 1.34
Poor	26 – 31	1.35 – 1.45
Very Poor	32 – 39	1.46 – 1.59
Very, Very Poor	>40	>1.60

RESULTS AND DISCUSSION

Preformulation Studies

Solubility Analysis of Domperidone

Solubility in Acetate buffer (PH 4.5): 10mg/100ml of sample dissolved. Solubility in phosphate buffer (PH 6.8): 4mg/100ml of sample dissolved. The solubility of Domperidone was evaluated in three different buffer solutions with varying pH levels. The highest solubility was observed in the hydrochloride buffer with a pH of 1.5, where 25mg of Domperidone approximately fully dissolved in 100ml of HCl buffer however, Domperidone was found to be practically insoluble in the phosphate buffer with a pH of 6.8. These results indicate that the solubility of Domperidone is high soluble in HCl buffer.

Characterization of Domperidone by UV Spectroscopy

UV Scanning of Domperidone in Phosphate Buffer at pH 6.8

The concentration of 10mg of Domperidone solution was prepared in phosphate buffer pH 6.8 and was subjected to scanning under UV visible spectrophotometer, between the range 200-400nm.The λmax was found to be at λ_{max} of 286nm.

Melting Point Determination of Domperidone

Melting point of pure Domperidone was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Domperidone by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath. The rise in temperature was viewed through screen. The temperature at which the drug started d melting was recorded. The melting point range of Domperidone was identical to reference melting point stated in MP (242-244°C). The sample started to melt at 242°C, and turned into liquid at 244°C, indicating that the sample used is pure. That reading has stated in melting point tester.as shown in Table 10.

Table 10: Results of Melting Point of Domperidone.

Test	Temp Rang Analyzed (Melting)	Results
Test I Domperidone	(242-244°C)	242 °C
Test II Domperidone	(242-244°C)	242°C

Characterization of Domperidone by FTIR

FTIR spectrum studies indicated that major functional groups present in Domperidone show characteristic peaks in IR spectrum. Figures (1) to (15) show peaks observed at different wave numbers and the functional group associated with these peaks for drug and drug with different excipients. The major peaks are identical to functional group of Domperidone. Hence, it was confirmed that there was compatibility between drug and various excipients, thus conforming that no interaction of drug occurred with the components of the formulation excipients.

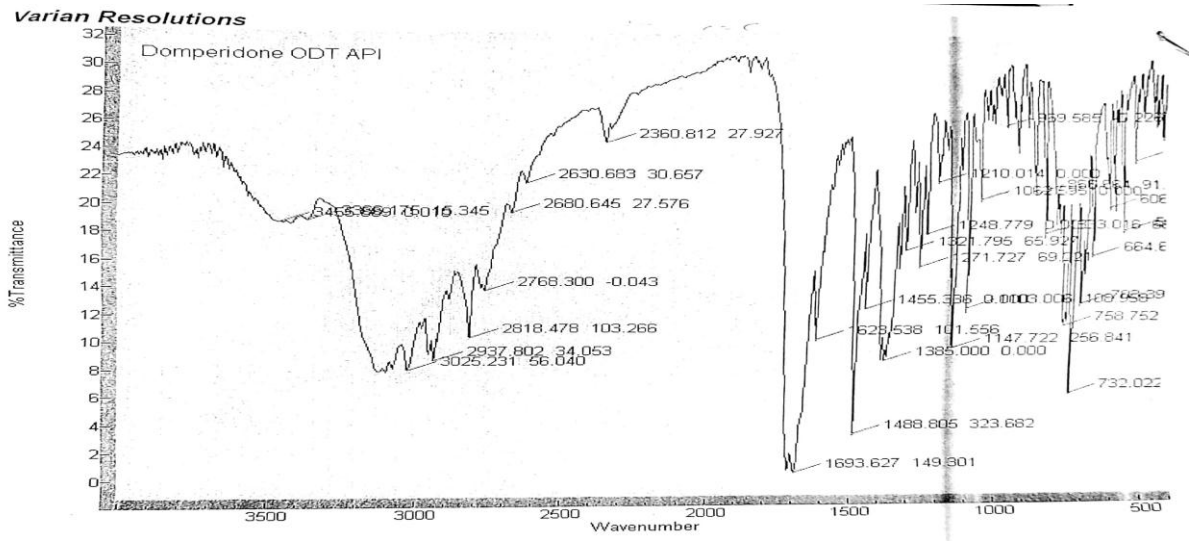


Fig. 1: FTIR Spectrum of Pure Domperidone.

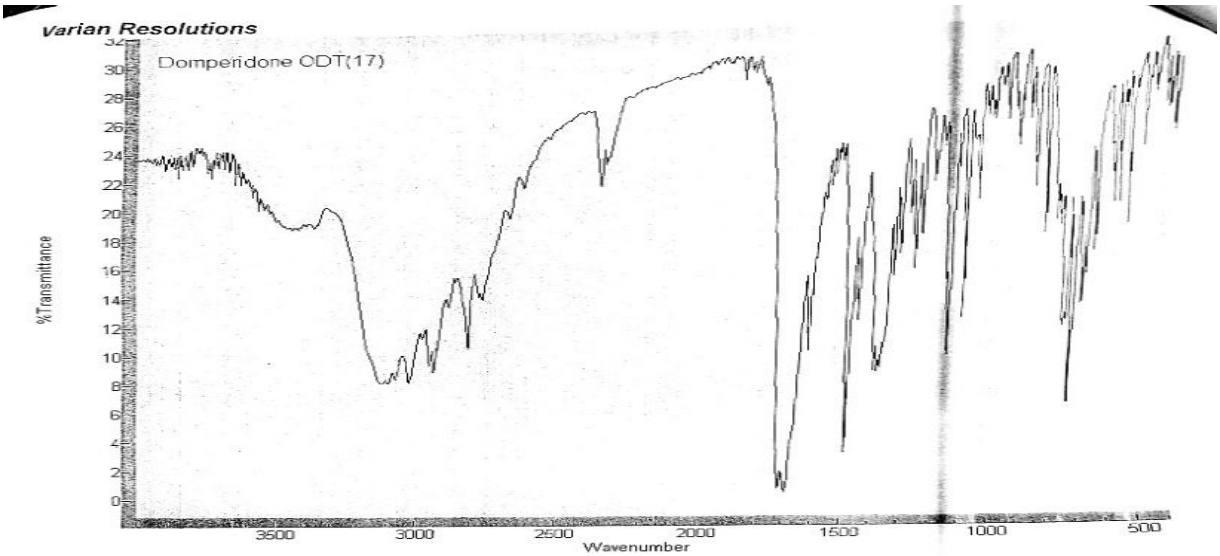


Fig. 2: FTIR Spectrum of Domperidone ODTs.

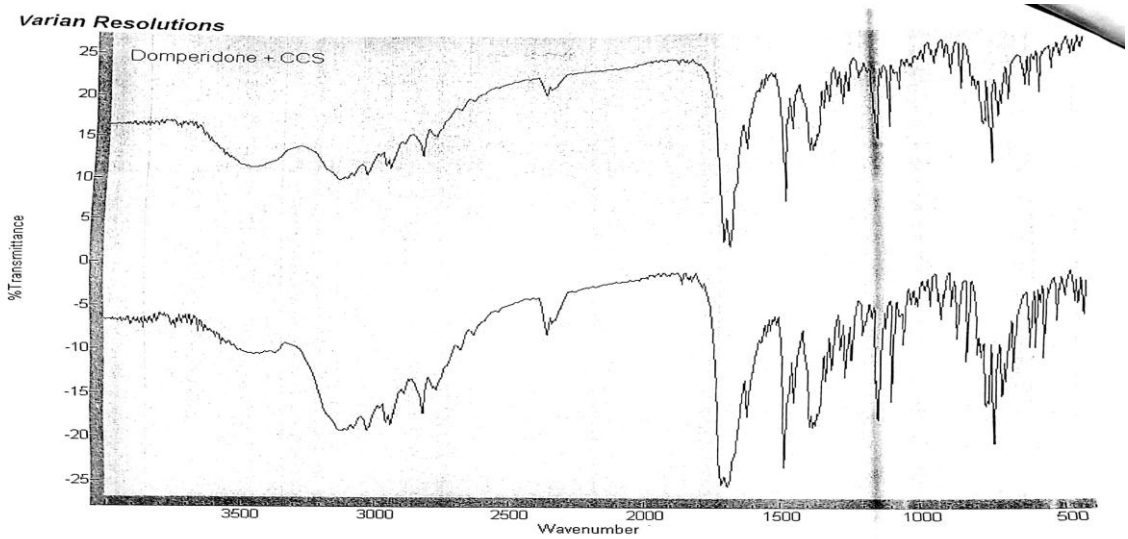


Fig. 3: FTIR Spectrum of Physical Mixture Domperidone and CCS.

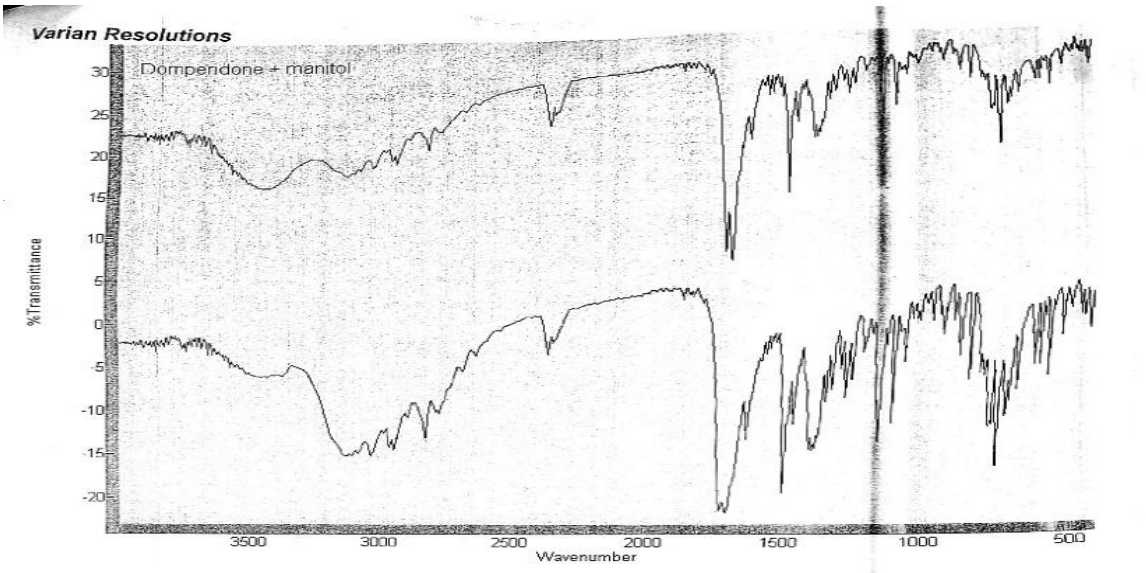


Fig. 4: FTIR Spectrum of Physical Mixture Domperidone and Mannitol.

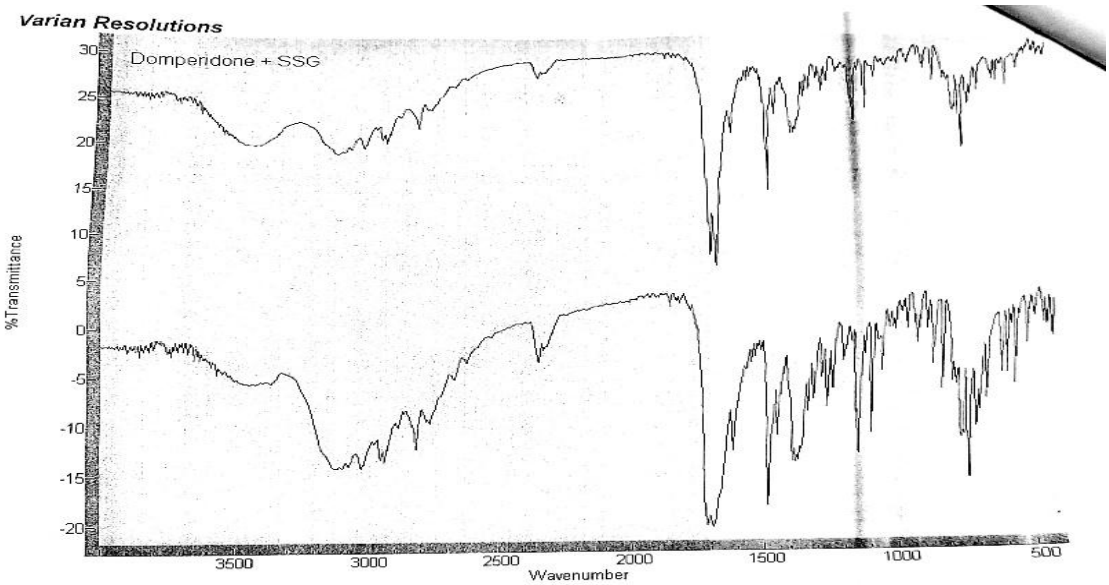


Fig. 5: FTIR Spectrum of Physical Mixture Domperidone and SSG.

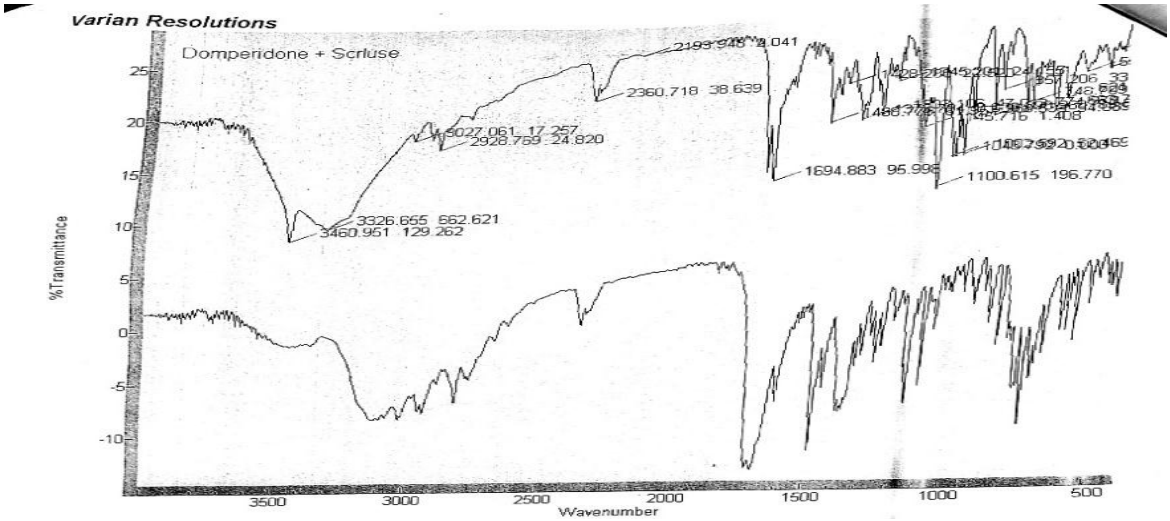


Fig. 6: FTIR Spectrum of Physical Mixture Domperidone and Sucralose.

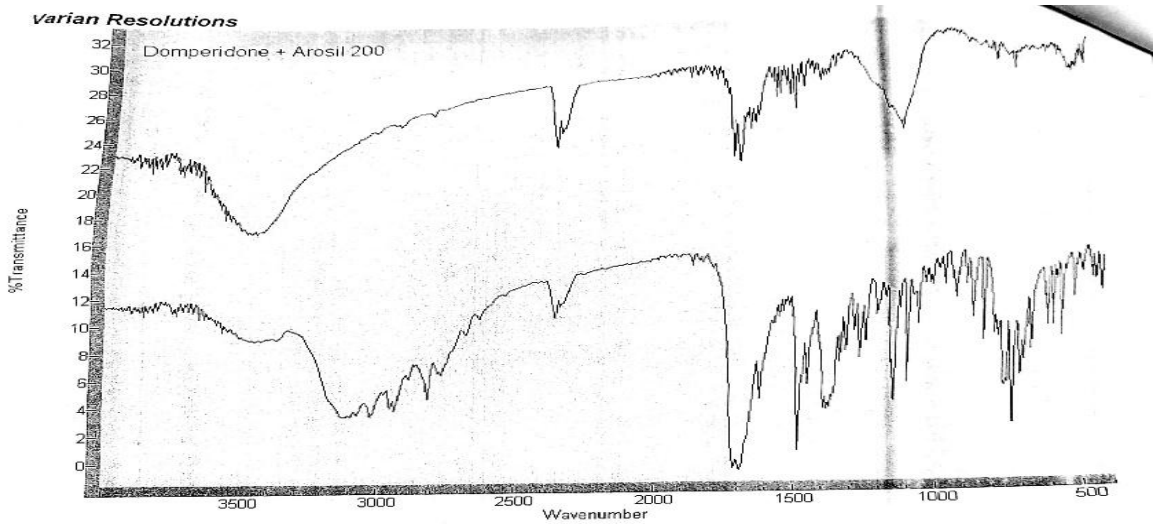


Fig. 7: FTIR Spectrum of Physical Mixture Domperidone and Aerosil 200.

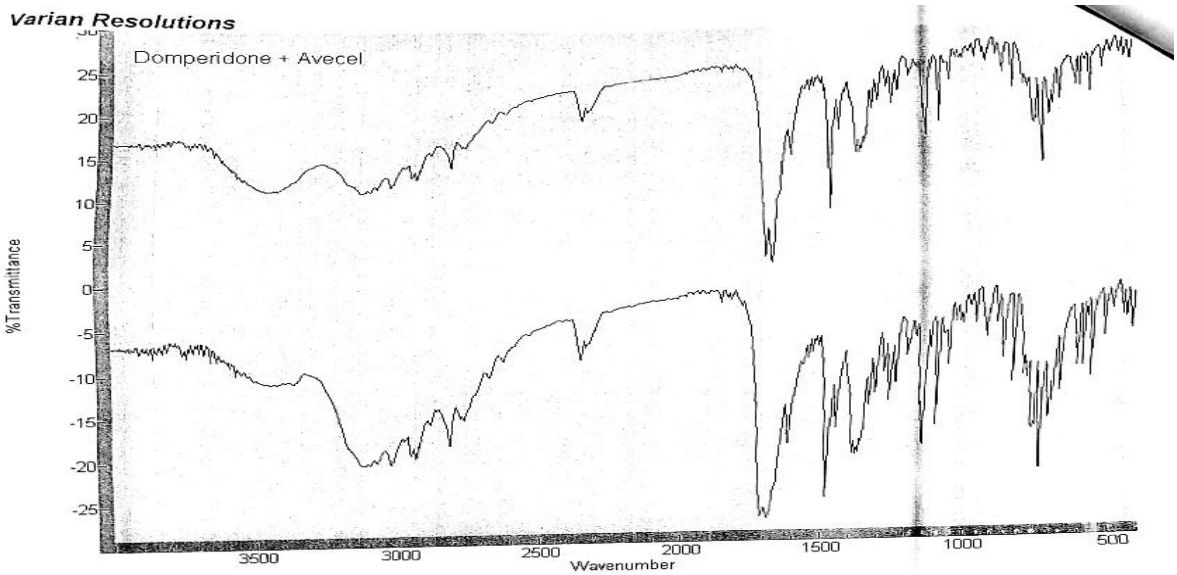


Fig. 8: FTIR Spectrum of Physical Mixture Domperidone and Avicel.

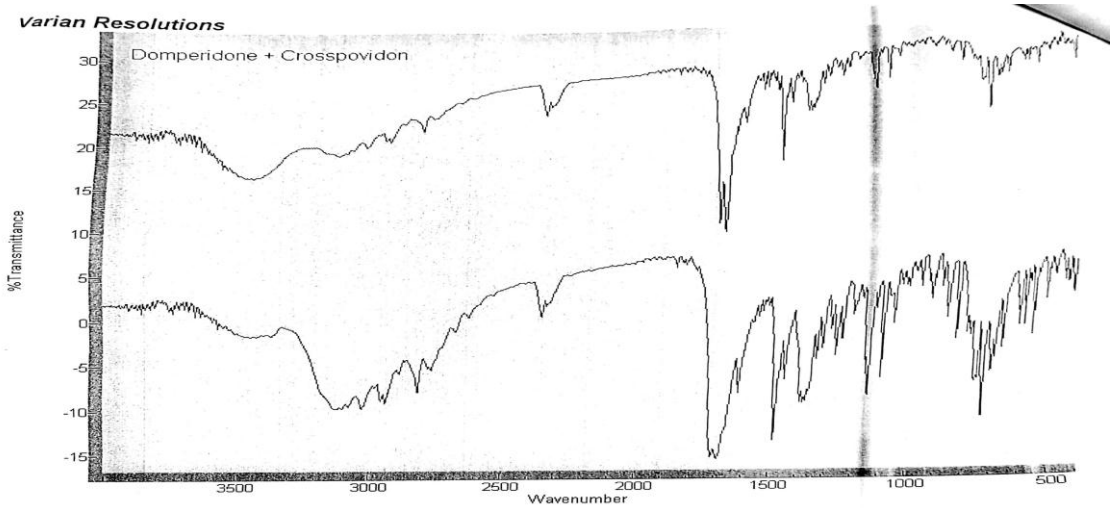


Fig. 9: FTIR Spectrum of Physical Mixture Domperidone and Crospovidone.

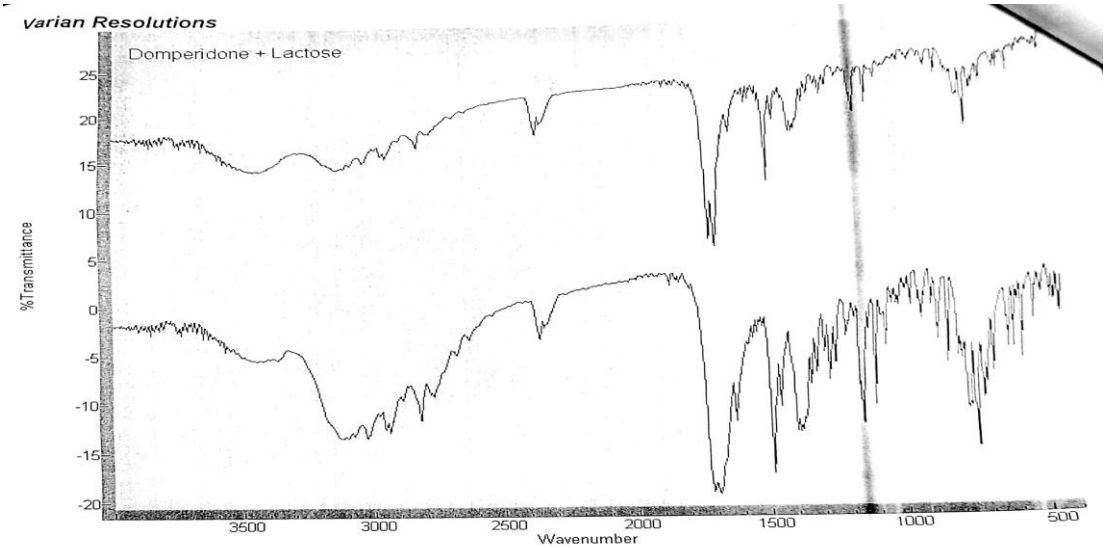


Fig. 10: FTIR Spectrum of Physical Mixture Domperidone and Lactose.

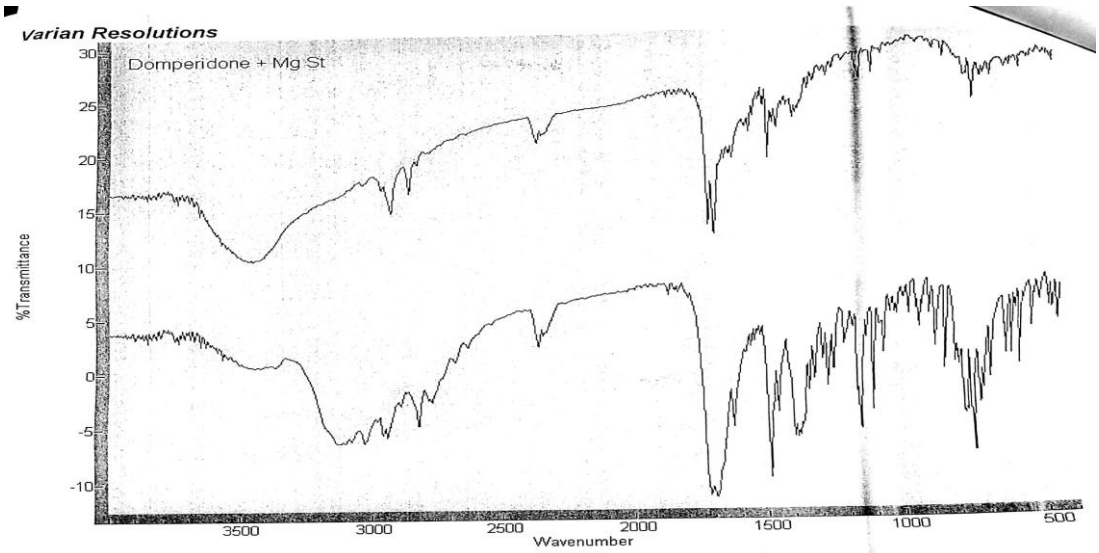


Fig. 11: FTIR Spectrum of Physical Mixture Domperidone and Mg Stearate.

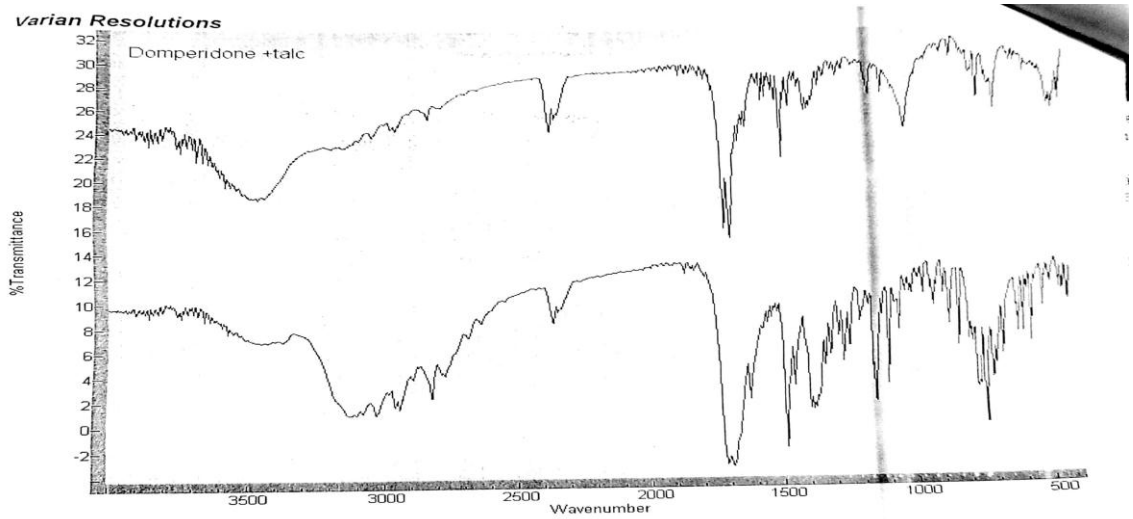


Fig. 12: FTIR Spectrum of Physical Mixture Domperidone and Talc.

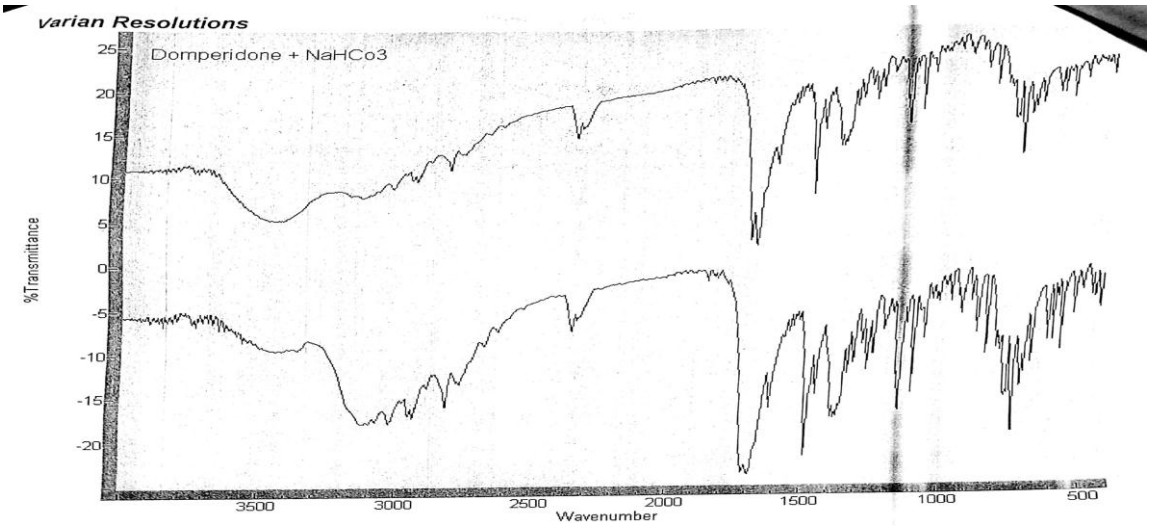


Fig. 13: FTIR Spectrum of Physical Mixture Domperidone and NaHCO3.

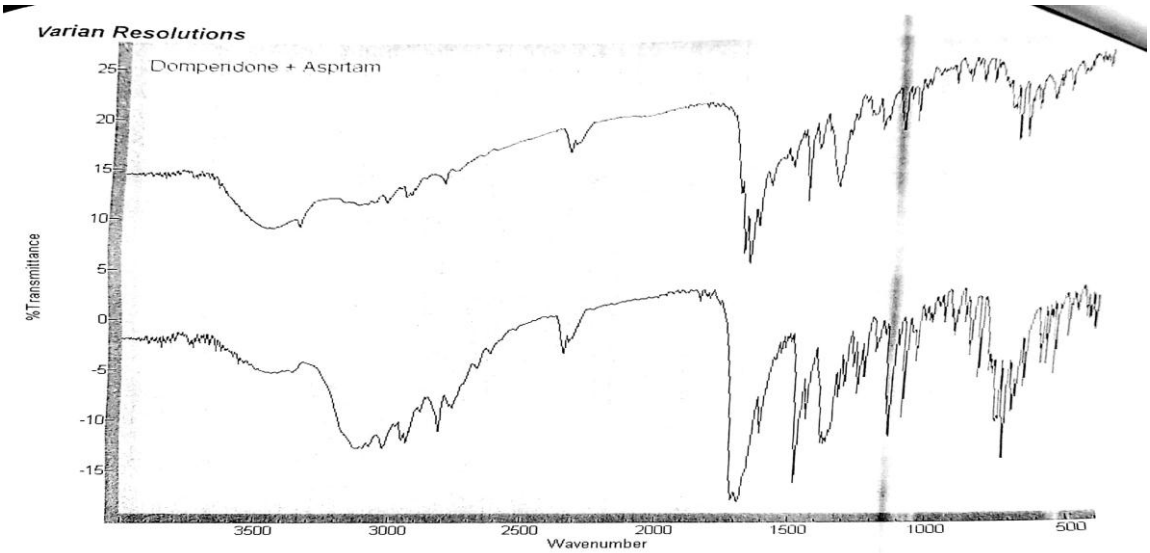


Fig. 14: FTIR Spectrum of Physical Mixture Domperidone and Aspartame.

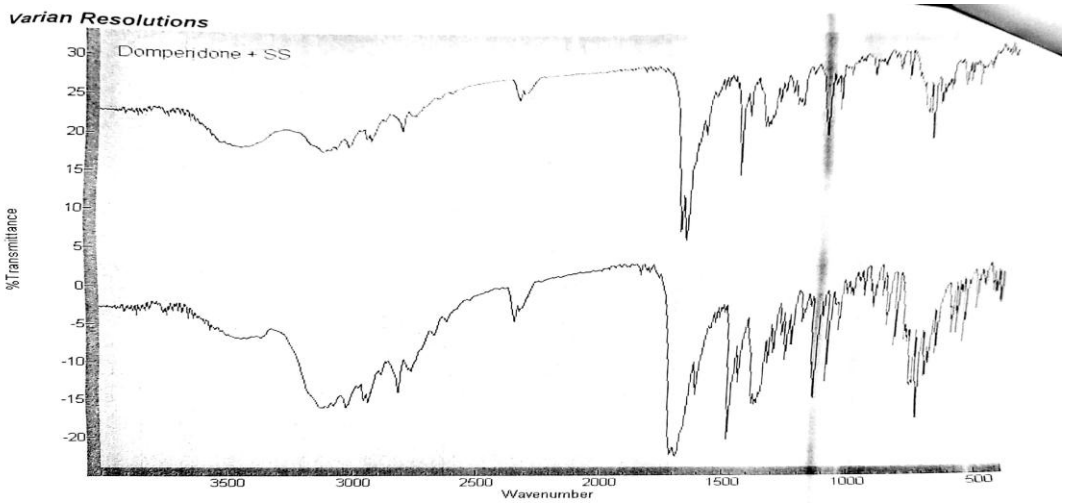


Fig. 15: FTIR Spectrum of Physical Mixture Domperidone and SLS.

Micrometric Properties of Domperidone

Table 11: Micrometric Properties of Domperidone.

Test of Powder Flowability	Results
Angle of Repose	31
Hausner Ratio	1.12
Compressibility Index	11

The powder being evaluated exhibits a moderate flowability, with an angle of repose of 31 degrees. It demonstrates relatively good flow properties and low compressibility, as indicated by a Hausner ratio of 1.12. The compressibility index of 11% suggests that the powder can be easily compacted under pressure, making it suitable for applications requiring good compressibility. However, further comparison with standard values or similar powders would provide a more comprehensive understanding of its performance characteristics as shown in Table 11.

CONCLUSION

The compatibility studies of physical mixtures of Domperidone with different used excipients such as mannitol, lactose and avicel PH 102 as diluents, and sodium starch glycolate, croscarmellose sodium, and crospovidone as superdisintegrants and sodium lauryl sulfate as wetting agent were investigated by FTIR it was detected that there was no variation or minor deviation in the characteristic peaks in FTIR spectroscopy. The Domperidone formulations prepared were evaluated for precompression parameters and powder flow properties which were found to be within limits. It was concluded that the drug Domperidone was found to be compatible with various excipients which were selected for the formulation development of the Domperidone ODTs. 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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