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DROTAVERINE-EXCIPIENT COMPATIBILITY STUDIES FOR ADVANCED DRUG DELIVERY SYSTEMS DEVELOPMENT

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ABSTRACT

Drotaverine HCl is used as antispasmodic drug in the treatment of various spastic conditions such as gastrointestinal diseases, biliary dyskinesia, and vasomotor diseases associated with smooth muscle spasms. These spasms are painful and leave uncomfortable feeling. Drotaverine HCl needs about 15 minutes to start giving its effect, so to improve the drug onset of action and increase the drug release. 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. The main objective of the present study was to the preformulation studies were performed to know the physico-chemical and mechanical properties of Drotaverine Hydrochloride for formulation development of Drotaverine Hydrochloride ODTs. The drug-excipient compatibility studies were conducted to characterize the drug Drotaverine Hydrochloride present in Orodispersible Tablets Delivery System ODTDS. Preformulation, formulation and evaluation of Drotaverine Hydrochloride to avoid problems associated with conventional delivery system such as limited permeation, low dissolution and

bioavailability and also to improve bioavailability and as an antispasmodic agent. 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 Drotaverine Hydrochloride and various excipients as mannitol, microcrystalline cellulose as diluents, and sodium starch glycolate and croscarmellose sodium, as superdisintegrants were evaluated for preformulation studies parameters. It was concluded that the drug Drotaverine Hydrochloride was found to be compatible with various excipients which were selected for the formulation development of the Drotaverine Hydrochloride 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: Drotaverine Hydrochloride, Antispasmodic agent, Compatibility, Excipients, Development, Preformulation, Formulation.

INTRODUCTION

Compatibility Studies[1-200]

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.

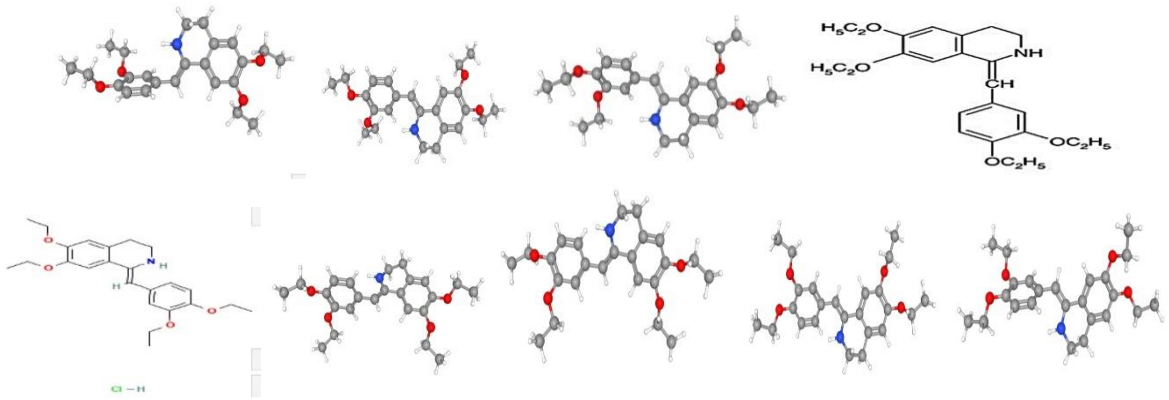
In the present study, it was proposed to drug-excipient compatibility studies of Drotaverine Hydrochloride, with commonly different excipients using for formulation development of Orodispersible tablets ODTs.

MATERIALS AND METHODS

Drotaverine Hydrochloride, Croscarmellose Sodium, Beta-Cyclodextrin, Sodium Starch Glycolate, Mannitol, Aerosil200, Stearic Acid, Magnesium Stearate, Microcrystalline Cellulose, Hydroxypropyl Cellulose (Klucel), Aspartame, Na Stearyl Fumarate, Talc, Lactose Anhydrous, Crospovidone, Sodium Saccharin, Mannitol, Sorbitol, Sodium Lauryl Sulfate, Sucralose, Menthol and Thymol were gift from (Global Pharmaceutical Industry Company-Yemen).

Evaluation of Drug-Excipient Compatibility Studies Methods[45-341]

Table 1: Drotaverine Hydrochloride Data.

Characterization of Drotaverine Hydrochloride			
			
Drotaverine Hydrochloride Structure and 3D Conformer			
Chemical Structure	(Z)1(3,4 diethoxybenzylidene) -6,7diethoxy1,2,3,4 tetrahydroisoquinoline.	**Appearance**	Drotaverine hydrochloride is light yellow or slightly greenish yellow crystalline powder, odourless and bitter taste
Chemical Formula	C24H31NO4. HCl	**Drug Solubility**	It is sparingly soluble in water, soluble in ethanol (96%),freely soluble in chloroform . Slightly soluble in acetone,practically insoluble in petroleum

			ether. melting point 211-213°C
Molecular Weight	433.97 g/mol	**BCS**	Class-II Drug
Drug Action and Use	Drotaverine is a selective inhibitor of phosphodiesterase 4 (PDE4), which is an enzyme responsible for the degradation of cyclic adenosine monophosphate (cAMP). Inhibition of PDE4 leads to elevated levels of cAMP, leading to smooth muscle relaxation. Drotaverine hydrochloride It is phosphodiesterase IV enzyme inhibitor and acts as an antispasmodic agent, specific for smooth muscle spasm and pain, used to reduce excessive labor pain. Drotaverine hydrochloride is an analogue of papaverine. It is phosphodiesterase IV enzyme inhibitor and acts as an antispasmodic agent. Analgesic : Compounds capable of relieving pain without the loss of consciousness. Parasympatholytics : Agents that inhibit the actions of the parasympathetic nervous system. The major group of drugs used therapeutically for this purpose is the muscarinic antagonists. Vasodilator Agents : Drugs used to cause dilation of the blood vessels.		
Pharmacokinetics of Drotaverine			
Drug Absorption	Drotaverine is not completely absorbed following oral administration and its bioavailability is highly variable. Following oral administration of a single 80 mg dose, the absolute bioavailability ranged between 24.5 and 91 % with a mean of 58.2 ± 18.2%. Mean Cmax was 292 ± 88 ng/mL. Mean AUC was 3251 ± 950 ng*h/mL. Mean Tmax was 1.9 ± 0.54 hours.	**Drug Distribution**	Volume of Distribution: Following oral administration of a single 80 mg dose, the mean volume of distribution was 193 ± 48 L. Following an intravenous dose of 80 mg, the mean volume of distribution was 195 ± 48 L.
Drug Metabolism	Drotaverine is reported to undergo extensive hepatic metabolism, which is its main route of elimination. It may also undergo biliary excretion to form conjugated metabolites. Proposed metabolic pathways and metabolites are based on limited animal studies: in rats, the major identified metabolites of drotaverine are 4'-desethyl-drotaverine, 6-desethyl-drotaverine, drotaveraldine, and 4'-desethyl-drotaveraldine, all	**Drug Excretion**	Route of Elimination: Drotaverine is mainly eliminated via hepatic metabolism. About 67% of the drug is found in feces and 20% of the drug was eliminated with urine. Clearance: Following oral administration of a single 80 mg dose, the mean renal clearance was 0.59 ± 0.18 mL/min. Following an intravenous dose of 80 mg, the mean renal clearance was 0.73 ± 0.29 mL/min.

	of which are glucuronidated in the bile. 4'- desethyl-drotaveraldine was the most predominant metabolite eliminated into the bile.		
The Elimination Half-Life (T1/2)	Following oral administration of a single 80 mg dose, the mean half-life was 9.11 ± 1.29 hours. Following an intravenous dose of 80 mg, the mean half-life 9.33 ± 1.02 hours.	**Availability**	Oral 40 mg, 80 mg tablets, a suspension, intravenous or intramuscular.

Table 2: Pharmaceutical Excipients Data.

Nonproprietary Name	Chemical Name	Functional Category	Concentration%	Solubility	Incompatibilities	Notes
Beta-Cyclodextrin	β-Cyclodextrin: beta-cycloamylose; beta-dextrin; Cavamax W7 Pharma; cycloheptaamylose; cycloheptaglucan; cyclomaltoheptose; Kleptose. β -Cyclodextrin C42H70O35.	Solubilizing agent; stabilizing agent. cyclodextrins form water-soluble complexes with lipophilic drugs such as corticosteroids. They have been shown to increase the water solubility of the drug; to enhance drug absorption into the eye; to improve aqueous stability; and to reduce local irritation.	Cyclodextrins are starch derivatives and are mainly used in oral and parenteral pharmaceutical formulations. They are also used in topical and ophthalmic formulations. Cyclodextrins are also used in cosmetics and food products, and are generally regarded as essentially nontoxic and nonirritant materials.	β -cyclodextrin: soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 20°C, 1 in 20 at 50°C; practically insoluble in acetone, ethanol (95%), and methylene chloride.	The activity of some antimicrobial preservatives in aqueous solution can be reduced in the presence of hydroxypropyl- β -cyclodextrin.	Cyclodextrins occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste.
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	White or grayish-white powder.

					zinc.	
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)	Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460**.**	Adsorbent, suspending agent, tablet and capsule diluent; tablet disintegrant.	5–20% 20–90%	Practically insoluble in water.	Incompatible with strong oxidizing agents.	Crystalline powder.
Mannitol (Emprove)	Cordy epic acid; C*PharmMannidex; E421; Emprove; manna sugar; D-mannite; mannite; mannitolum; Mannogem; Pearlitol.	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
Sorbitol	C*PharmSorbidex; E420; 1,2,3,4,5,6- hexanehexol; Liponic 70-NC; Liponic 76- NC; Meritol; Neosorb; sorbite; D sorbitol; Sorbitol Instant;	Humectant; plasticizer; sweetening agent; tablet and capsule Diluent.	25–90%	Solubility of sorbitol 1 in 0.5 of water.	Sorbitol will form water-soluble chelates with many divalent and trivalent metal ions in	Occurs as an odorless, white or almost colorless, crystalline, hygroscopic

	Sorbogem. D-Glucitol.				strongly acidic and alkaline conditions.	powder.
(Klucel) Hydroxypropyl Cellulose	Cellulose, 2-hydroxypropyl ether	Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.	15–35% 2–6% 5%	Freely soluble in water below 38°C.	The compatibility of hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration.	white to slightly yellow-colored, odorless and tasteless 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	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.
Aerosil 200	Aerosil; Cab-O-Sil, Cab-OSil M-5P, colloidal silica, fumed silica,	Adsorbent; anticaking agent glidant; viscosity-	0.1–1.0% 2.0–10.0% widely used in	Practically insoluble in organic	Incompatible with diethylstilbestrol	A submicroscopic fumed silica

	fumed silicon dioxide, SAS, silica colloidalis anhydrica	increasing agent.	oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient.	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 the viscosity of a system.	preparations.	with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.
Stearic Acid	Cetylacetic acid; Crodacid; E570; Edenor; Emersol; Hystrene; Industrene; Kortacid 1895; Pearl Steric; Pristerene; stereophanic acid; Tegostearic. Octadecanoic acid	Emulsifying agent; solubilizing agent; tablet and capsule lubricant.	1–20% 1–3%	practically insoluble in water.	Stearic acid is incompatible with most metal hydroxides and may be incompatible with oxidizing agents	Is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder.
Sucralose (SucraPlus)	,6-Dichloro-1,6-dideoxy-b-D-fructofuranosyl-4-	Sweetening agent.	0.03–0.24%	Freely soluble in	---	Crystalline powder

	chloro-4-deoxya-D-galactopyranoside			water.		
Menthol	1RS,2RS,5RS) -(±)-5-Methyl-2-(1-methylethyl)cyclohexanol	Flavoring agent, therapeutic agent.	0.005–0.015 0.05–10.0	Very slightly soluble in glycerin, practically insoluble in water.	Incompatible with: butylchloral hydrate, camphor; chloral hydrate, chromium trioxide, b-naphthol, phenol, potassium permanganate, pyrogallol, resorcinol, and thymol.	A free-flowing or agglomerated crystalline powder.
Thymol	cido trimico; 3-p-cymenol; p-cymen-3-ol; Flavinol; 3- hydroxy-p-cymene; 3- hydroxy-1-methyl-4-isopropylbenzene; Intrasol; isopropyl cresol; m-thymol; timol.	Antioxidant; antiseptic; cooling agent; disinfectant; flavoring agent; skin penetrant; therapeutic agent.		Soluble 1 in 1000 of water.	Thymol is incompatible with iodine, alkalis, and oxidizing agents.	Occurs as colorless or often large translucent crystals, or as a white crystalline powder with a herbal odor (aromatic and thyme-like) and a pungent caustic taste.

According to Drotaverine Hydrochloride and excipients data as shown in Tables 1 and 2, it was selected that the different excipients to preformulation study with Drotaverine Hydrochloride in the present study, the equipments used as shown in Table 3.

Table 3: 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 Drotaverine Hydrochloride was taken in a butter paper and viewed in well illuminated place. Taste and odor very less quantity of Drotaverine 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 Drotaverine Hydrochloride in 0.1N HCl, phosphate buffer at pH 6.8 and acetate buffer at pH 4.5 was determined by using sonicator at room temperature. Solubility in 0.1N Hydrochloride: 40 mg of Drotaverine Hydrochloride is added into 100 ml of 0.1N HCl, then 100 ml of 0.1N HCl is added gradually. Solubility in phosphate buffer pH 6.8: 40 mg of Drotaverine HCl is added into 100 ml of 0 phosphate buffer, then 800 ml of phosphate buffer is added gradually. Solubility in acetate buffer pH 4.5: 40 mg of Drotaverine Hydrochloride is added into 100 ml of acetate buffer, then 300 ml of acetate buffer is added gradually. was determined by using sonicator at room temperature. Approximate solubility of drugs as per B.P was indicated in Table 4.

Table 4: 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 Drotaverine Hydrochloride

UV Scanning of Drotaverine in Hydrochloride Phosphate Buffer at pH 6.8, in Acetate Buffer at pH 4.5, and in 0.1 HCl

The absorbance spectra of Drotaverine Hydrochloride in phosphate buffer at pH 6.8, in acetate buffer at pH 4.5 and in 0.1 HCl were studied. A preliminary scanning of Drotaverine Hydrochloride in phosphate buffer, in acetate buffer at pH 4.5 and in 0.1 HCl to determine the ʎ max by screening a 5µg/ml solution of Drotaverine Hydrochloride in phosphate buffer these between 200- 800 nm, in acetate buffer and in 0.1 HCl these also between 200- 800 nm.

Calibration Curve of Drotaverine Hydrochloride

The standard calibration curve graph was obtained by preparing aliquots of standard solution of Drotaverine in phosphate buffer (pH 6.8) and the absorbance at 239.6 nm was measured after suitable dilution using UV/Visible spectrophotometer.

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 Drotaverine Hydrochloride

Melting Point: Melting point of the Drotaverine Hydrochloride 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 Drotaverine Hydrochloride 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 5. 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 Drotaverine Hydrochloride 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 Drotaverine Hydrochloride in room condition as shown in Table 5.

Table 5: Samples of Drotaverine Hydrochloride and Different Excipients for Compatibility Studies.

No	Component(s)	Amount(5mg:5mg)
1	Drotaverine HCl	1
2	Drotaverine HCl and MCC	(1:1)
3	Drotaverine HCl and SSG	(1:1)
4	Drotaverine HCl and SLS	(1:1)
5	Drotaverine HCl and Crospovidone	(1:1)
6	Drotaverine HCl and Talc	(1:1)
7	Drotaverine HCl and Menthol	(1:1)
8	Drotaverine HCl and Thymol	(1:1)
9	Drotaverine HCl and Sucralose	(1:1)
10	Drotaverine HCl and Saccharin Sodium	(1:1)
11	Drotaverine HCl and Aspartame	(1:1)
12	Drotaverine HCl and CCS	(1:1)
13	Drotaverine HCl and Mannitol	(1:1)
14	Drotaverine HCl and Mg. Stearate	(1:1)
15	Drotaverine HCl and Stearic Acid	(1:1)
16	Drotaverine HCl and Aerosil	(1:1)
17	Drotaverine HCl and Klucel	(1:1)
18	Drotaverine HCl and Na Stearyl Fumarate	(1:1)
19	Drotaverine HCl and PEG	(1:1)
20	Drotaverine HCl and Beta Cyclodextrin	(1:1)
21	Drotaverine HCl and Sorbitol	(1:1)

Preparation of Drotaverine Hydrochloride Formulations

The ingredients were shown in Table 6 were passed through sieve no. 18 except Mg stearate passed through sieve no 35 and were co-grounded in a glass pestle motor. These blends were evaluated for mass-volume relationship (Bulk Density, Tapped Density, Hauser's Ratio, and Compressibility Index) and flow properties. The mixed blend of excipients was compressed using rotary tablet compression machine of punch size 6.25mm (champer diameter 7mm) to produce convex faced tablets.

Table 6: Composition of Drotaverine Hydrochloride Formulations ODTs.

Ingredients	Quantity Per Tablet(mg)										
	Formulation Code										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Drotaverine Hydrochloride	40	40	40	40	40	40	40	40	40	40	40
Beta-Cyclodextrin	---	---	---	---	40	40	40	60	---	60	40
Mannitol	146.40	146.40	126.40	144.244	102.844	104.844	43.797	64.50	69.90	49.50	62
Microcrystalline Cellulose	---	---	---	---	---	---	69	25	50	25	30

Croscarmellose Sodium	8	8	8	8	8	8	2	8	8	8	5
Sodium Starch Glycolate	---	---	---	2	4	2	3	---	---	---	---
(Klucel) Hydroxypropyl Cellulose	2	2	2	2	2	2	---	---	---	---	---
Aerosil 200	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5
Stearic Acid	---	---	20	---	---	---	---	---	29.6	15	19.5
Magnesium Stearate	1	1	1	0.75	0.75	0.75	0.7	1	1	1	1
Aspartame	1	1	1	1	1	1	---	---	---	---	1
Sucralose	---	---	---	1	1	1	1	1	1	1	1
Menthol	0.6	0.6	0.6	0.006	0.003	0.003	0.003	---	---	---	---
Thymol	0.6	0.6	0.6	0.6	0.003	0.003	---	---	---	---	---

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).

$$\rho b = M/Vb.$$

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. $\rho t = M/Vt$.

Carr's Index

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

$C = (\rho t – \rho b)/\rho t \times 100$ 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 7and 8.

Table 7: 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 8: 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

Characterization of Drotaverine Hydrochloride

The organoleptic properties like color, odor and taste of the API were evaluated. The color of Drotaverine Hydrochloride was found to be pale yellow crystalline solid; no characteristic odor was observed in the study and the taste was found to be bitter. Drotaverine Hydrochloride showed similar color, taste and odor as per IP specification.

Physical Identification of Drotaverine Hydrochloride

Drotaverine Hydrochloride is pale yellow crystalline.

Solubility Test

The solubility profile of Drotaverine Hydrochloride was present in Table 9.

Table 9: Solubility Analysis of Drotaverine Hydrochloride (API).

Raw Material (API)	Solubility
Drotaverine Hydrochloride	Sparingly Soluble in Water
	Soluble in Ethanol (96%)
	Freely Soluble in Chloroform
	Slightly Soluble in Acetone
	Practically Insoluble in Petroleum Ether

Characterization of Drotaverine Hydrochloride by UV Spectroscopy

The solubility studies of drug (API) revealed that Drotaverine Hydrochloride was sparingly soluble in water, soluble in ethanol (96%), freely soluble in chloroform, slightly soluble in acetone, and practically insoluble in petroleum ether. The result show that maximum wavelength of Drotaverine Hydrochloride is 239.6 nm in phosphate buffer pH6.8, 242.4 nm in acetate buffer pH 4.5, and 243.1 nm in 0.1NHCl as shown in Figures. 1-3.

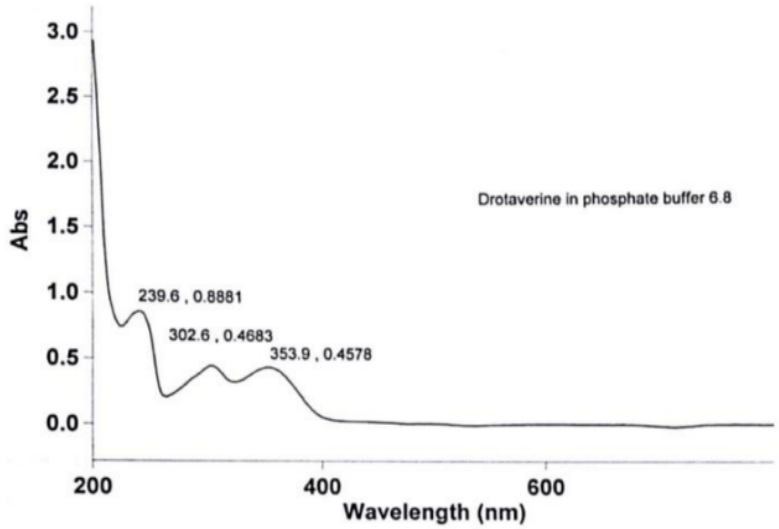


Fig. 1: UV Scanning of Drotaverine Hydrochloride in Phosphate Buffer (pH 6.8).

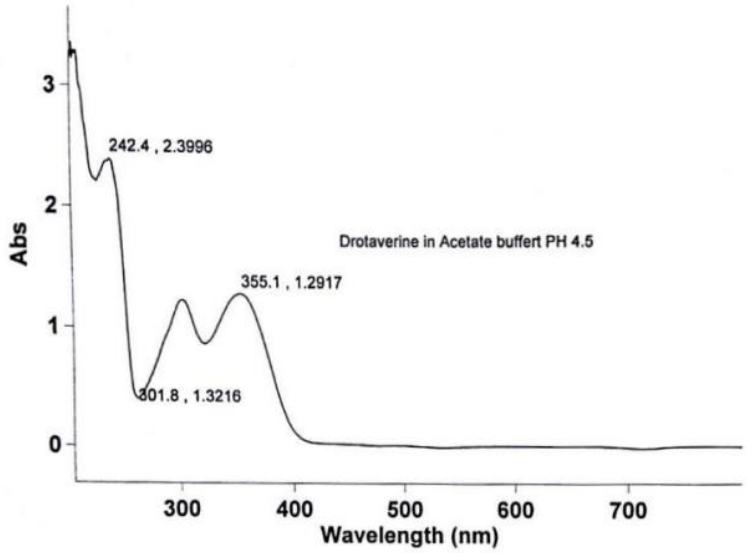


Fig. 2: UV Scanning of Drotaverine Hydrochloride in Acetate Buffer (pH 4.5).

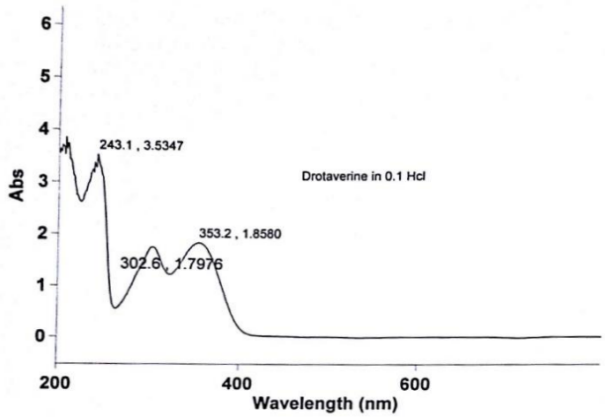


Fig. 3: UV Scanning of Drotaverine Hydrochloride in 0.1N HCl.

Melting Point Determination of Drotaverine Hydrochloride

Melting point of Drotaverine Hydrochloride was observed to be 212.7℃. Reported melting point of Drotaverine Hydrochloride is (211-213 °C). The melting point range of Drotaverine Hydrochloride was identical to reference melting point stated in BP (211-213 °C).The sample started to melt at 112.7C°, and turned into liquid at 212.7 °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 Drotaverine Hydrochloride.

Test	Temp Rang Analyzed (Melting)	Results
Drotaverine Hydrochloride	(211-213 °C)	212.7 °C

Characterization of Drotaverine Hydrochloride 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 Drotaverine Hydrochloride, thus conforming that no interaction of drug occurred with the components of the formulation excipients as shown in Figures (4-24).

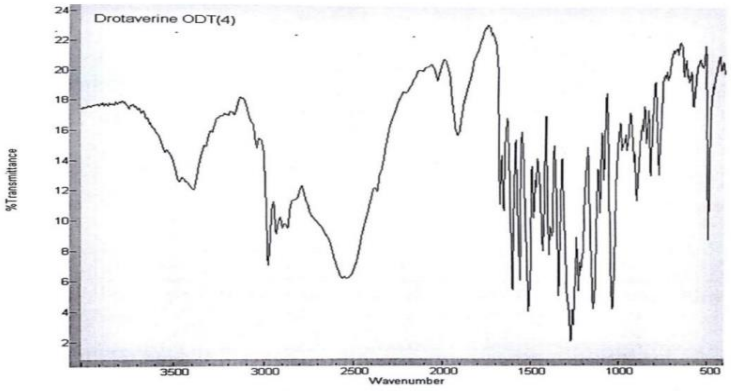


Fig. 4: FTIR Spectrum of Drotaverine Hydrochloride.

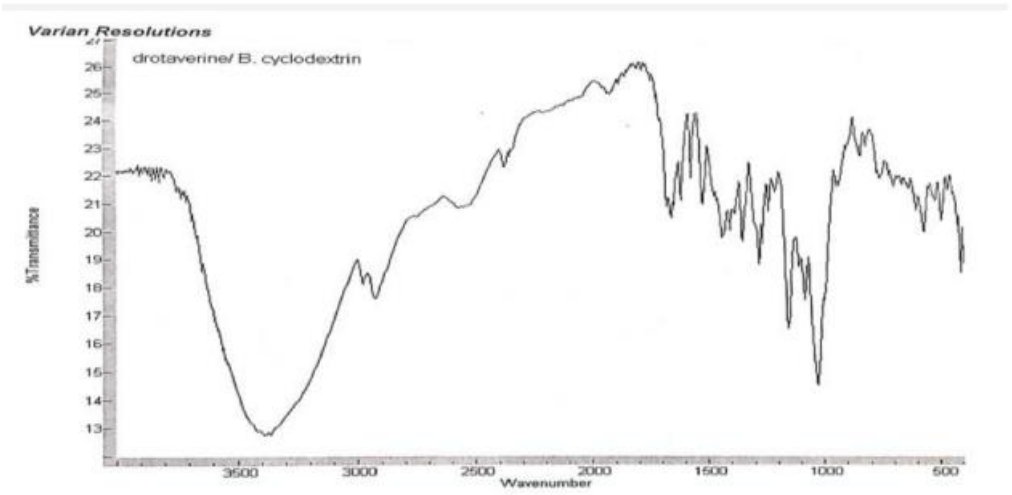


Fig. 5: FTIR Spectrum of Drotaverine Hydrochloride with Beta-Cyclodextrin.

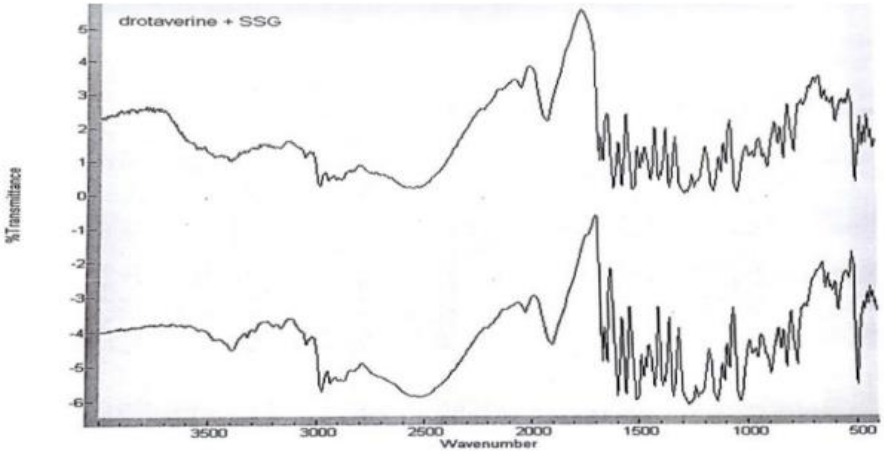


Fig. 6: FTIR Spectrum of Drotaverine Hydrochloride with SSG.

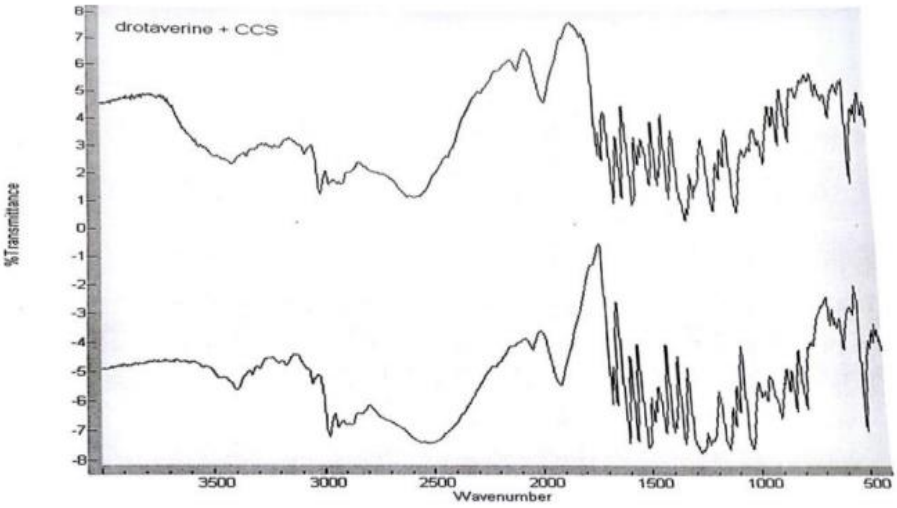


Fig. 7: FTIR Spectrum of Drotaverine Hydrochloride with CCS.

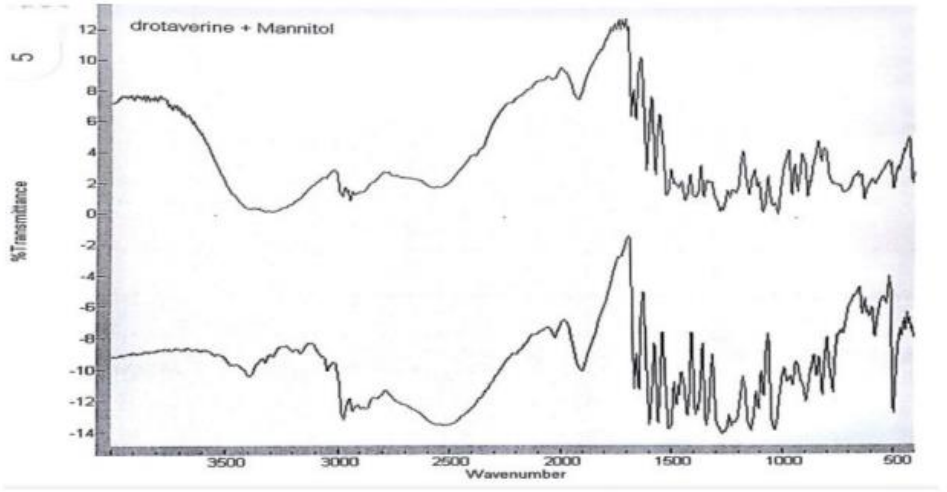


Fig. 8: FTIR Spectrum of Drotaverine Hydrochloride with Mannitol.

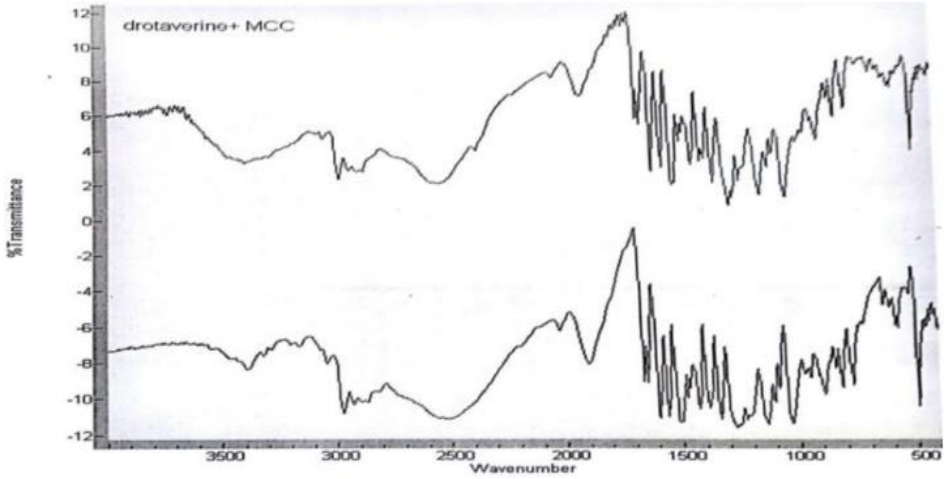


Fig. 9: FTIR Spectrum of Drotaverine Hydrochloride with MCC.

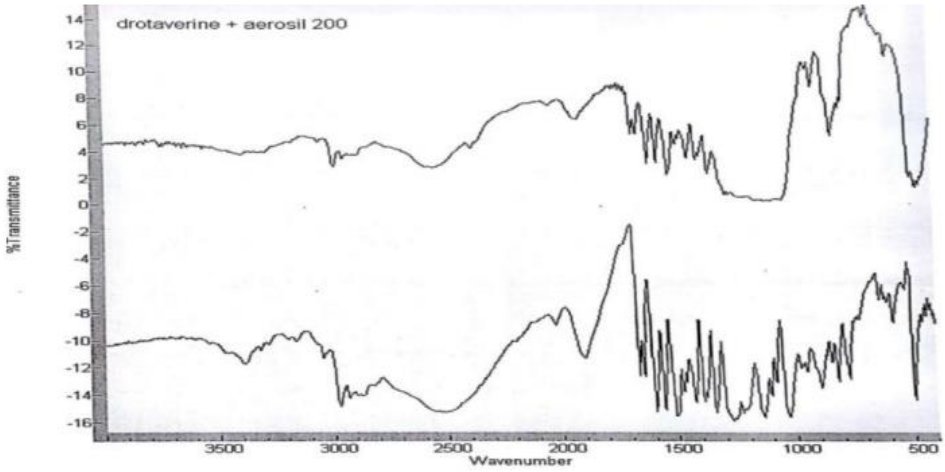


Fig. 10: FTIR Spectrum of Drotaverine Hydrochloride with Aerosil.

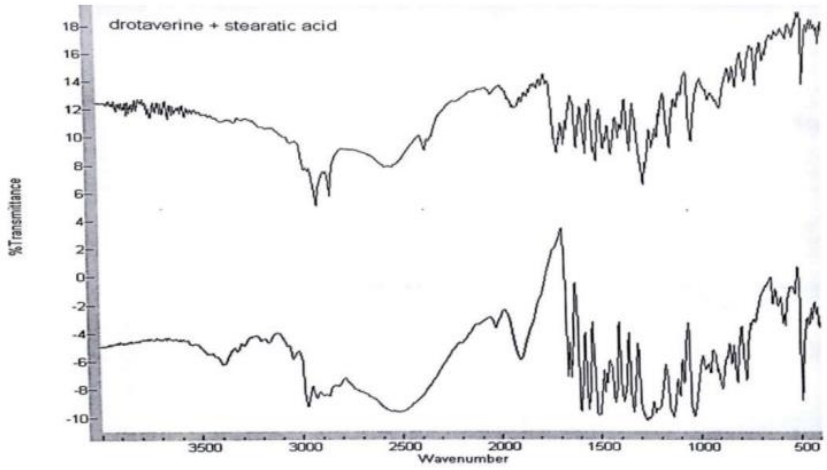


Fig. 11: FTIR Spectrum of Drotaverine Hydrochloride with Stearic acid.

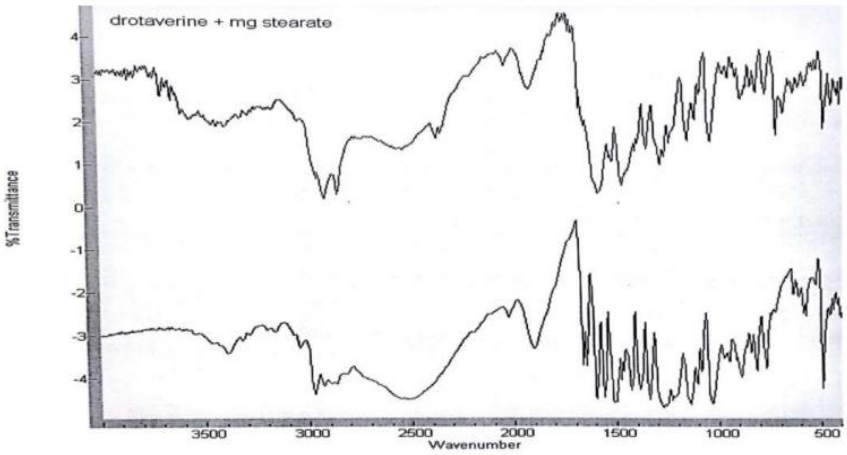


Fig. 12: FTIR Spectrum of Drotaverine Hydrochloride with Magnesium Stearate.

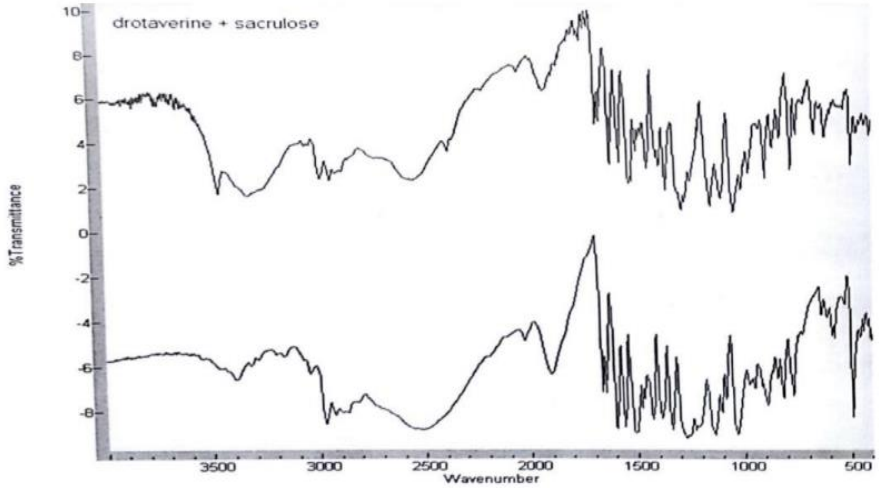


Fig. 13: FTIR Spectrum of Drotaverine Hydrochloride with Sucralose.

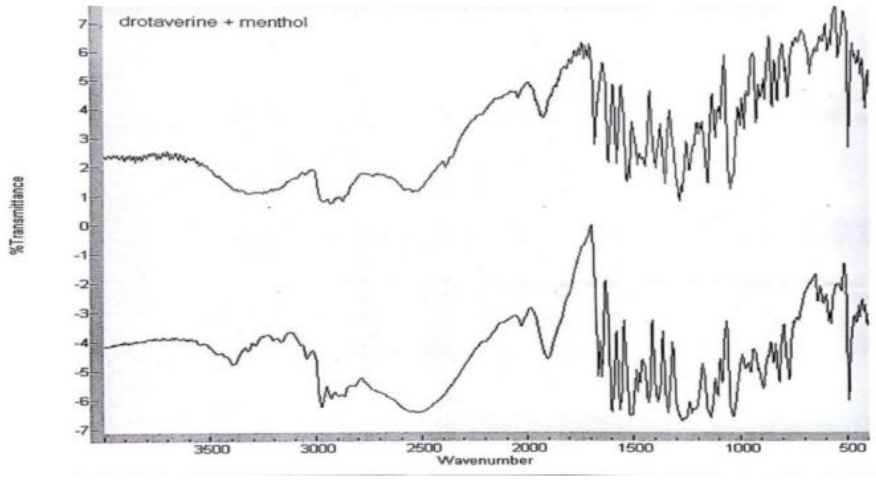


Fig. 14: FTIR Spectrum of Drotaverine Hydrochloride with Menthol.

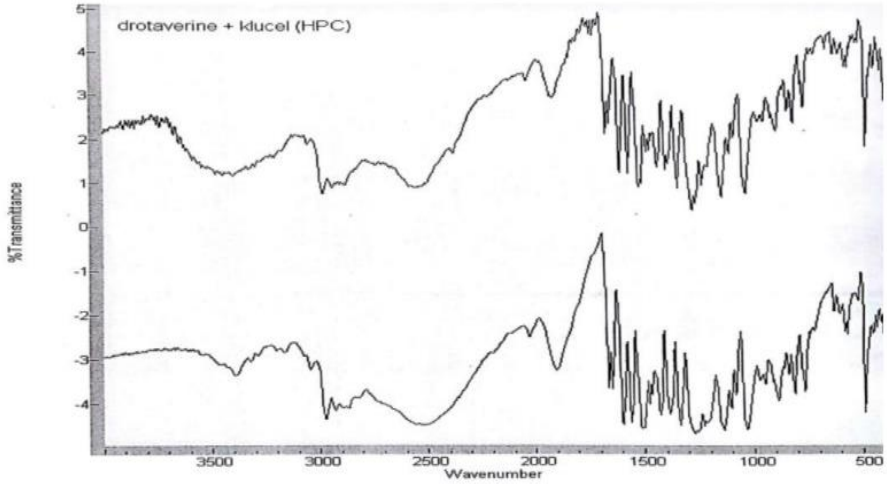


Fig. 15: FTIR Spectrum of Drotaverine Hydrochloride with Klucel (HPC).

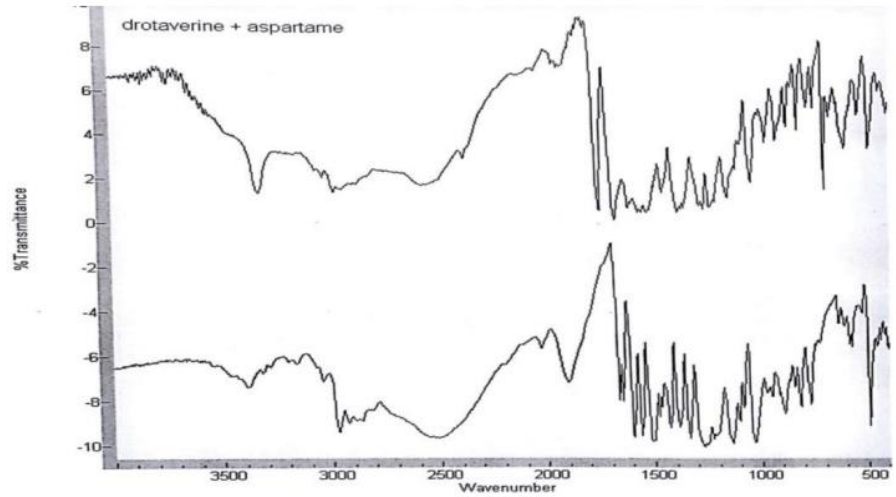


Fig. 16: FTIR Spectrum of Drotaverine Hydrochloride with Aspartame.

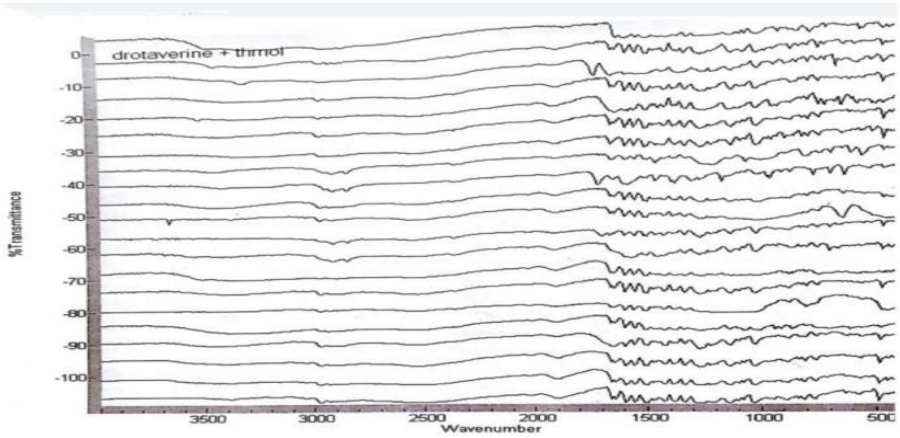


Fig. 17: FTIR Spectrum of Drotaverine Hydrochloride with Thymol.

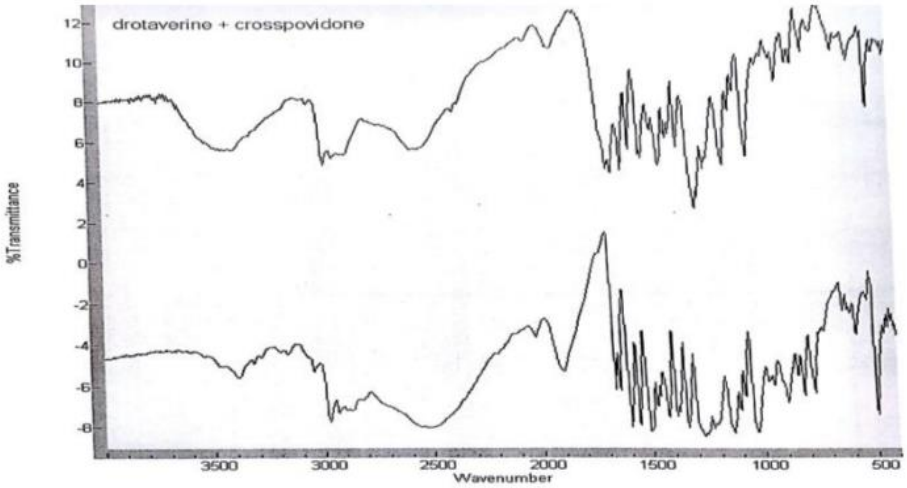


Fig. 18: FTIR Spectrum of Drotaverine Hydrochloride with Crospovidone.

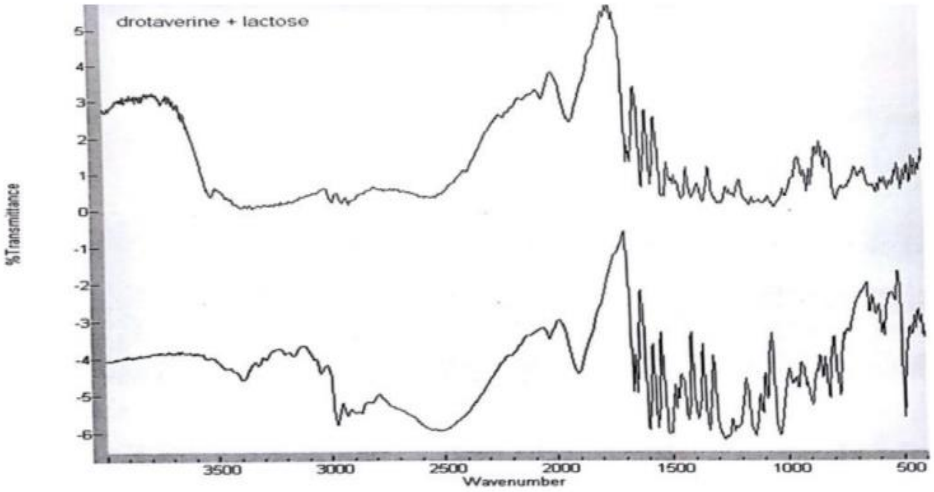


Fig. 19: FTIR Spectrum of Drotaverine Hydrochloride with Lactose.

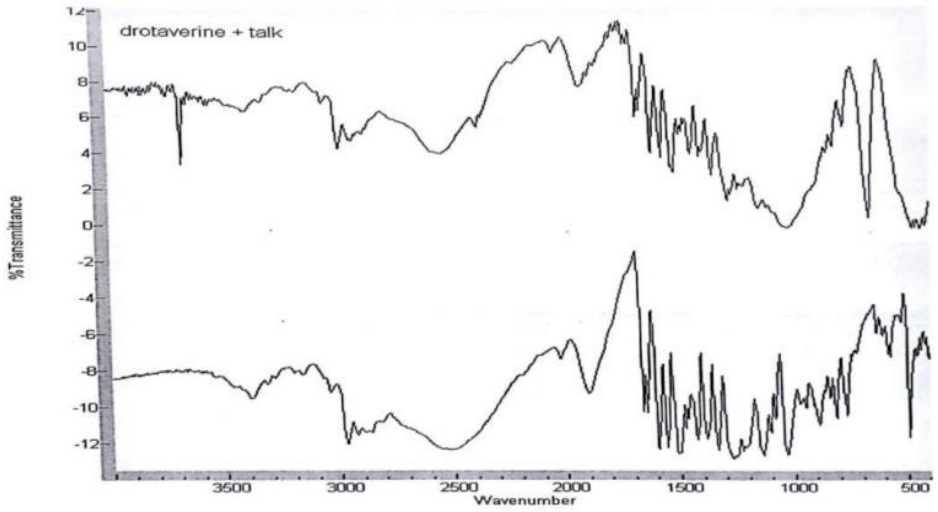


Fig. 16: FTIR Spectrum of Drotaverine Hydrochloride with Talc.

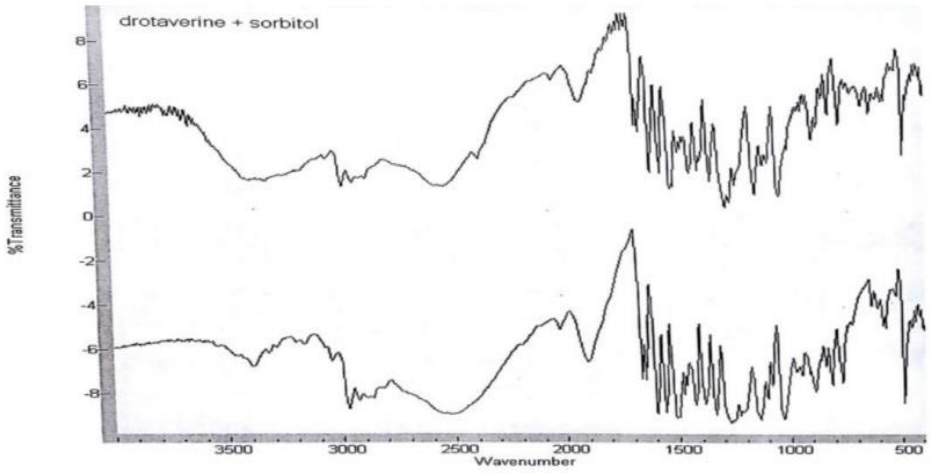


Fig. 20: FTIR Spectrum of Drotaverine Hydrochloride with Sorbitol.

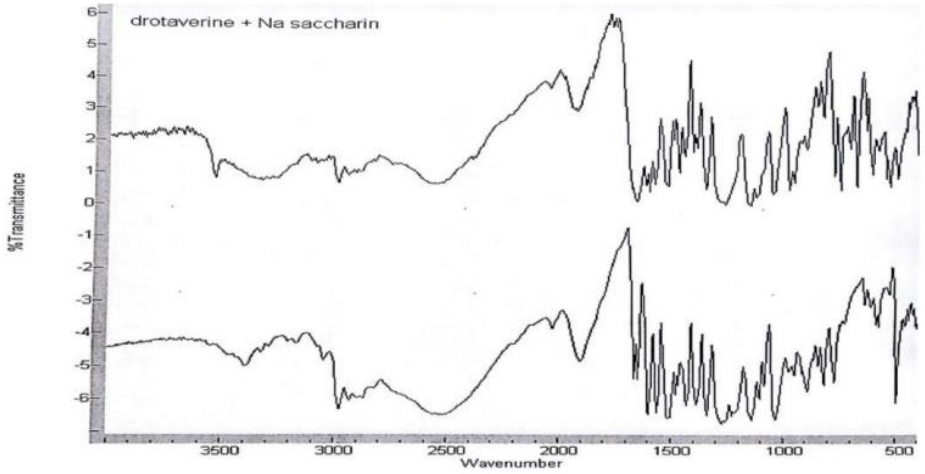


Fig. 21: FTIR Spectrum of Drotaverine Hydrochloride with Sodium Saccharin.

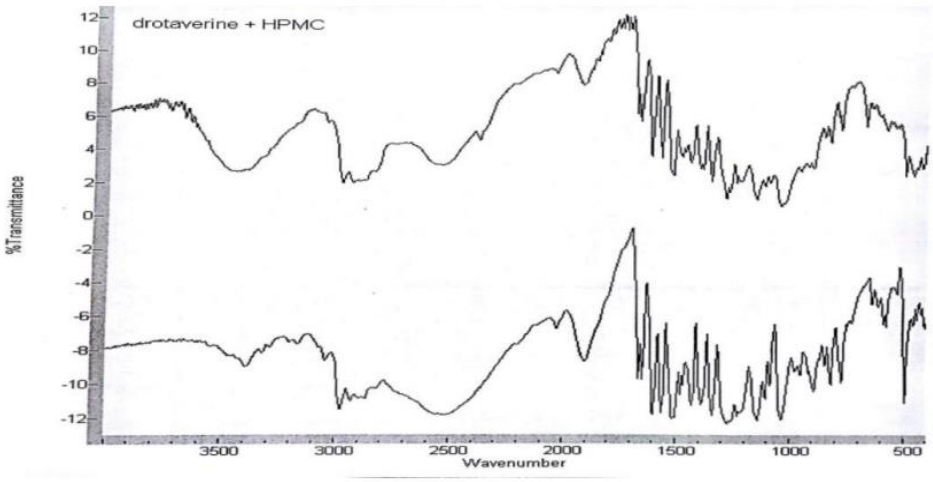


Fig. 22: FTIR Spectrum of Drotaverine Hydrochloride with HPC.

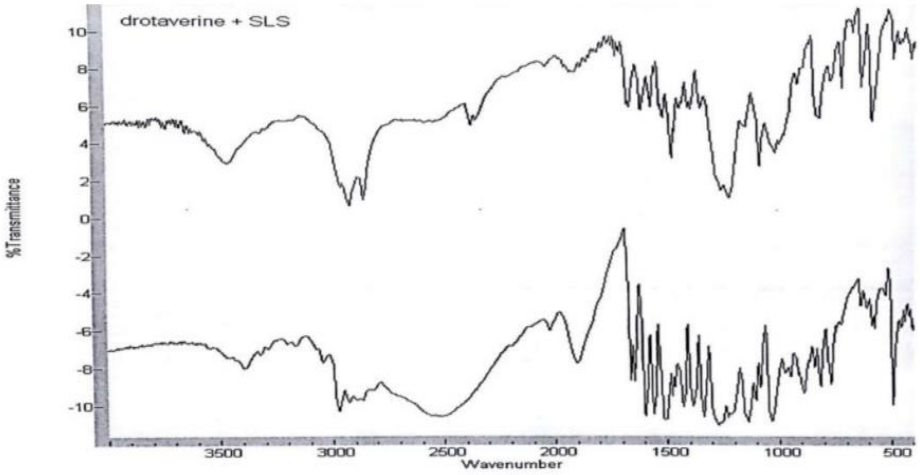


Fig. 23: FTIR Spectrum of Drotaverine Hydrochloride with SLS.

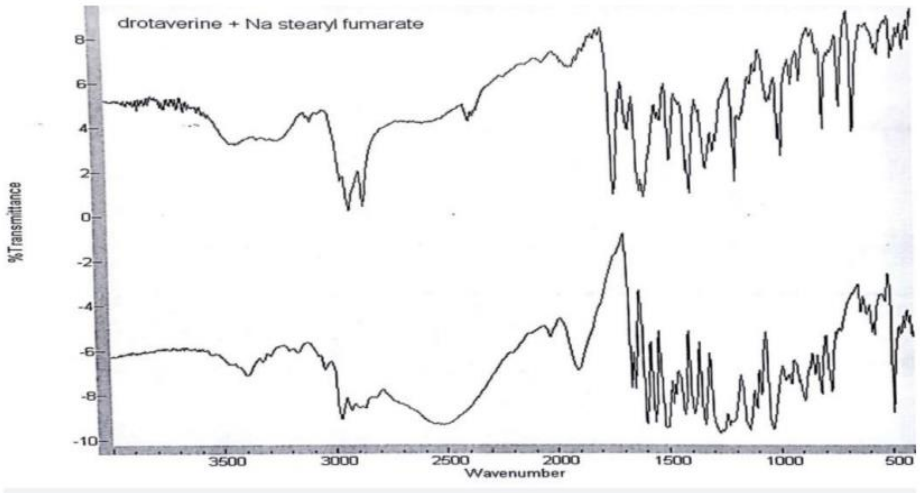


Fig. 24: FTIR Spectrum of Drotaverine Hydrochloride with Sodium Stearyl fumarate.

Micromeritic Properties of Drotaverine Hydrochloride

The powder of Drotaverine Hydrochloride was evaluated for the following parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The results were shown in Table 11.

Evaluation of Precompression Parameters

The powder blends were evaluated for the following parameters such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The results were shown in Table 11.

Table 11: Preformulation Parameters of Drotaverine Hydrochloride Powder Flow Properties.

Formulation code	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Compressibility Index (%)	Hausner's Ratio
F8	0.63	0.68	7.35	1.077
E9	0.52	0.59	11.86	1.14
F10	0.45	0.53	15.1	1.16
F11	0.49	0.60	19.4	1.24

The bulk density was found to be between 0.45 to 0.63 g/cm^3, the tapped density was found to be between 0.53 to 0.68 g/cm^3, the compressibility index was found in the range of 7.35 to 19.4 % and the Hausner's ratio lies between 1.077 to 1.24.

CONCLUSION

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