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COMPATIBILITY STUDIES WITH PHARMACEUTICAL EXCIPIENTS OF SIMVASTATIN FOR THE DEVELOPMENT OF NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT

Simvastatin is a lipid lowering drug which is used to lower the risk of cardiovascular disease and manage abnormal lipid levels by inhibiting the endogenous production of cholesterol. Simvastatin is practically insoluble in water and undergoes extensive first-pass metabolism in the liver, thus the oral bioavailability is very low (5%). The main objective of this research is to develop Orodispersible tablets of Simvastatin to overcome the two mentioned problems. The main objective of the present study was to the preformulation studies were performed to know the physico-chemical and mechanical properties of Simvastatin for formulation development of Simvastatin ODTs. 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 drug-excipient compatibility studies were conducted to characterize the drug Simvastatin present in Orodispersible Tablets Delivery System ODTDS. Preformulation, formulation and evaluation of Simvastatin to avoid problems associated with conventional delivery system such as limited permeation, low dissolution and bioavailability and also to improve bioavailability and for the treatment of hyperlipidemia. 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 Simvastatin and various excipients as mannitol, microcrystalline cellulose 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 Simvastatin was found to be compatible with various excipients which were selected for the formulation development of the Simvastatin 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: Simvastatin, Compatibility, Excipients, Development, Preformulation, Formulation.

INTRODUCTION

Preformulation studies[1-140]

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 Simvastatin - 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.

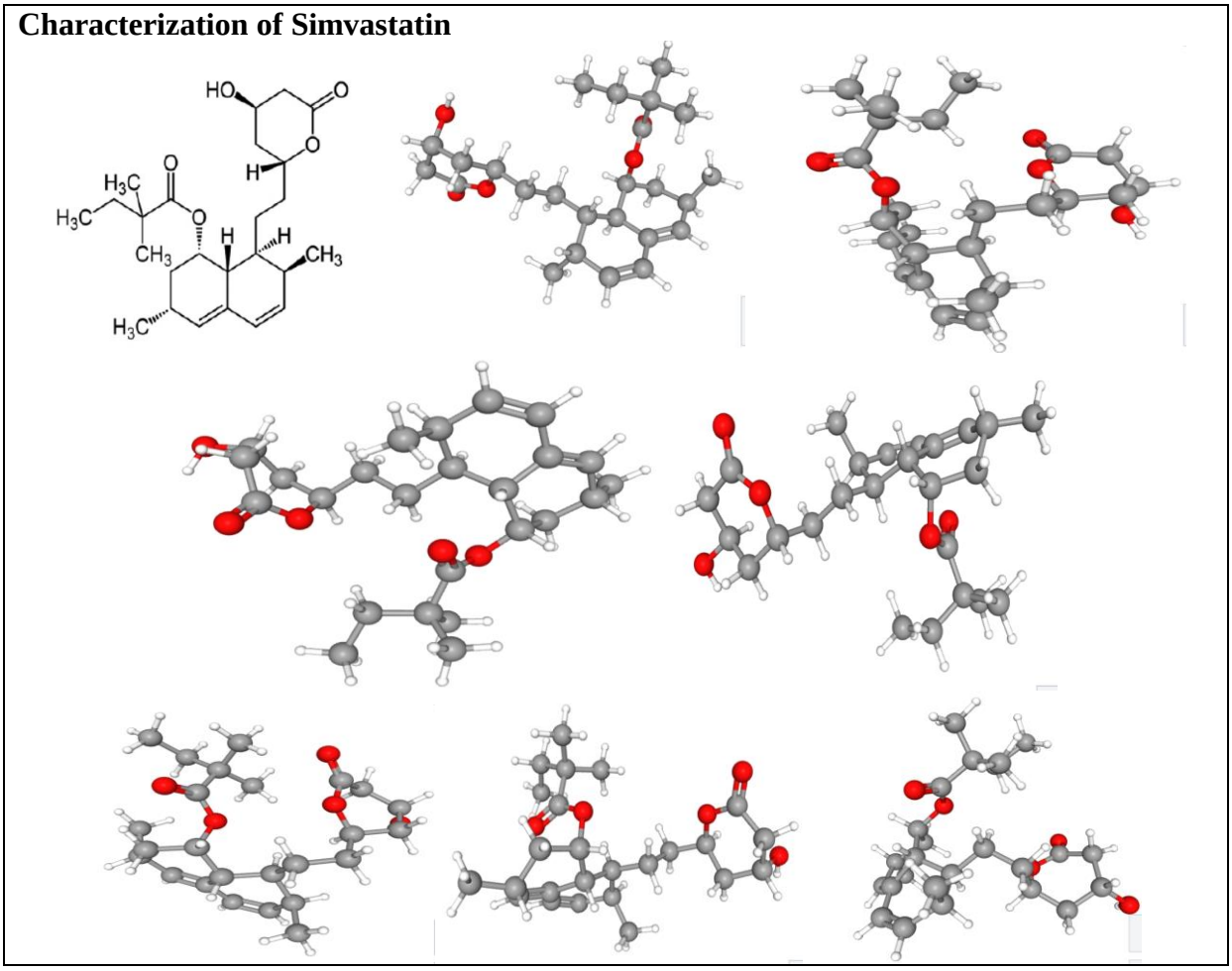
MATERIALS AND METHODS

Simvastatin was obtained as a gift from (BioPharm Pharmaceutical Industry Company-Yemen), While Sodium Starch Glycolate, Croscarmellose Sodium, Microcrystalline Cellulose, Crospovidone, Mannitol, Magnesium stearate, Sodium Saccharin, Aerosil, Beta-Cyclodextrin and Lactose were obtained as a gift from (Modern and Global Pharmaceutical Industry Company-Yemen).

Evaluation of drug-excipient compatibility studies methods[44-270]

Table 1: Simvastatin data.

Characterization of Simvastatin



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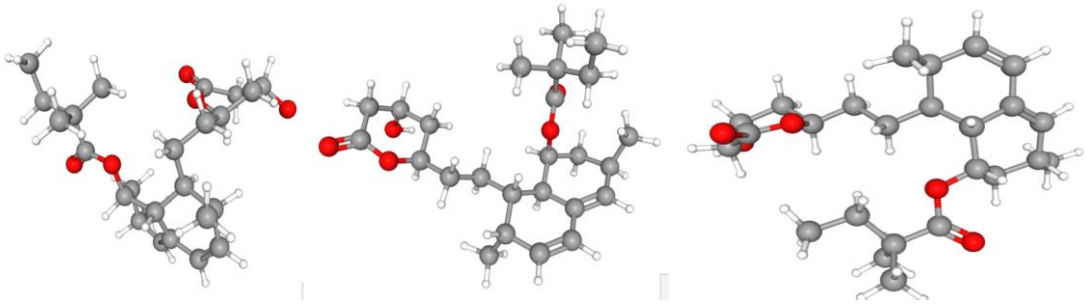
<tr><td colspan="4"> 
Simvastatin Structure and 3D Conformer</td></tr>
<tr><td>Chemical Structure</td><td>(1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl] ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoat</td><td>Appearance</td><td>Is white crystalline powder.</td></tr>
<tr><td>Chemical Formula</td><td>C25H38O5</td><td>Drug Solubility</td><td>Is soluble in organic solvent such as ethanol, DMSO, dithmethylformamide. In ehanol approximetly 20mg/ml</td></tr>
<tr><td>Molecular Weight</td><td>418.566 g/mol.</td><td>BCS</td><td>Class-II Drug</td></tr>
<tr><td>Drug Action and Use</td><td colspan="3">Simvastatin is indicated for the treatment of hyperlipidemia to reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C).
HMG-CoA reductase inhibitor; inhibits the rate-limiting step in cholesterol biosynthesis by competitively inhibiting HMG-CoA reductase**.**
Lower low-density lipoprotein, or LDL (bad) cholesterol and triglycerides in the body.
Increase high-density lipoprotein, or HDL (good) cholesterol.
Slow the development of heart disease and reduce the risk of stroke.</td></tr>
<tr><td colspan="4">Simvastatin Pharmacokinetics</td></tr>
<tr><td>Drug Absorption</td><td>Peak plasma concentration of Simvastatin was attained within 1.3 to 2.4 hours post-dose. While the recommended therapeutic dose range is 10 to 40 mg/day, there was no substantial deviation from linearity of AUC with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when Simvastatin was administered immediately before a test</td><td>Drug Distribution</td><td>Volume of distribution
Rat studies indicate that when radiolabeled Simvastatin was administered, Simvastatin-derived radioactivity crossed the blood-brain barrier.
Protein binding
Both Simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins.</td></tr>
</table>

	meal. Bioavailability: <5% Onset of action: >3 days Peak plasma time: 1.3-2.4 hr Maximum effect: 4-6 weeks.		
Drug Metabolism	Simvastatin undergoes extensive first-pass extraction in the liver, the target organ for the inhibition of HMG-CoA reductase and the primary site of action. Simvastatin is administered as the inactive lactone derivative that is then metabolically activated to its hydrolysis by nonspecific carboxyesterases in the intestinal wall, liver, and plasma. Oxidative metabolism in the liver is primarily mediated by CYP3A4 and CYP3A5, with the remaining metabolism occurring through CYP2C8 and CYP2C9. The major active metabolites of Simvastatin are β-hydroxyacid metabolite and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives. Polymorphisms in the CYP3A5 gene have been shown to affect the disposition of simvastatin and may provide a plausible explanation for interindividual variability of Simvastatin disposition and pharmacokinetics.	**Drug Excretion**	Route of elimination Excretion: Feces (60%); (Urine 13%)
The Elimination Half-Life (T1/2)	The elimination half-life is about 4.85 hours.	**Availability**	Tablet 5mg, 10mg, 20mg, 40mg, 80mg. Oral suspension 4mg/mL, 8mg/mL.

Table 2: 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
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	Practically insoluble in organic solvents, water. - hygroscopic but adsorbs large	Incompatible with diethylstilbestrol preparations.	A submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored,

			nontoxic and nonirritant excipient.	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.		odorless, tasteless, amorphous powder.
Saccharin Sodium	1,2-Benzisothiazolin-3-one 1,1-dioxide, sodium salt, Crystallose, E954, gendorf 450, sucaryl sodium	Sweetening agent. Saccharin can be used to mask some unpleasant taste characteristics or to enhance flavor systems. Its sweetening power is approximately 300–600 times that of sucrose.	0.02–0.5% w/w.	Readily dissolved by dilute ammonia solutions, alkali hydroxide solutions, or alkali carbonate solutions. 1 in 290 water.	Saccharin can react with large molecules. Saccharin sodium does not undergo Maillard browning.	White crystals or a white crystalline powder.

According to Simvastatin and excipients data as shown in Tables 1 & 2, it was selected that the different excipients to preformulation study with Simvastatin 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 Simvastatin was taken in a butter paper and viewed in well illuminated place. Taste and odor very less quantity of Simvastatin 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 analysis

Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in distilled water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. The bioavailability of drug is affected by various excipients in formulation. The approximate solubility of a compendial substance is indicated by one of the following descriptive terms. Solubility of Simvastatin in distilled water, methanol and ethanol 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

Preparation of working solution

Stock Solution prepared by using standard stock solution of Simvastatin was prepared by dissolving 10mg of Simvastatin in 10ml of 0.1N NaOH which gives 1000µg/ml. One ml of this stock solution was taken and was diluted up to 10ml by using 0.1N NaOH solvent to produce a concentration of 100µg/ml solution. From the above stock solution 1ml was transferred into 10ml volumetric flask and volume was made up to the mark with 0.1 N NaOH to make 10µg/ml.

Preparation of calibration curve solutions

UV scanning of simvastatin in 0.1N of NaOH: The sample was scanned with UV-V Spectrophotometer in the range 200-800nm against 0.1N NaOH as blank and the wavelength corresponding to maximum absorbance was noted which is its 238.

UV scanning of simvastatin in phosphate buffer(pH6.8): The sample was scanned with UV-V Spectrophotometer in the range 200-800nm against phosphate buffer 6.8 as blank and the wavelength corresponding to maximum absorbance was noted which is its 239.9 nm.

Calibration curve of simvastatin

Calibration curve of simvastatin in phosphate buffer pH6.8

Standard solutions of Simvastatin in the concentration range of 5 ug/ml to 65 ug/ml were prepared by transferring 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5 5.0, 5.5, 6.0, and 6.5 ml of Simvastatin stock solution (100 ppm) to a series of 13 volumetric flasks of 10 ml. The volume in each volumetric flask was made up with the solvent. The absorbance of the solutions was measured at the wavelength (λmax) 238.0 nm against Phosphate buffer pH 6.8 as blank and calibration curve was plotted.

Calibration curve of simvastatin in ethanol

The stock solution was prepared by taking accurately weighed 100 mg of Simvastatin in a 100 ml volumetric flask and dissolving it in ethanol and volume made up to the 100 ml mark. The concentration of the solution was 1000 µg/ml. From the stock solution, 1 ml was pipetted in a 10 ml volumetric flask and the volume was made up to mark with distilled water to obtain the concentration of 100 µg/ml. This was a working standard solution. from this solution, 0.5, 1, 1.5, 2, 2.5 and 3 ml were pipetted in separate 10 ml volumetric flasks and diluted up to mark with distilled water to get final concentrations of 5,10,15,20,25,30 µg/ml. The Samples were measured spectrophotometrically at λmax of a drug against ethanol as a blank. Absorbance values were plotted against concentrations of the drug to obtain a calibration curve.

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 simvastatin

Melting point of the Simvastatin 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 Simvastatin 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 Simvastatin 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 Simvastatin in room condition as shown in Table 5.

Infrared spectral study of samples after stored one month

Compatibility studies were performed by preparing blend of different excipients with drug and stored at 40°C ±2°C /75±5%RH for one month. The blend was evaluated after one month for changes like caking, liquefaction, discoloration and odor formation and by IR spectra. The drug excipient compatibility studies as shown in Table 5.

Table 5: Samples of Simvastatin and Different excipients for compatibility studies.

No	Component(s)	Amount(5mg:5mg)
1	Simvastatin	1
2	Simvastatin and Microcrystalline Cellulose	(1:1)
3	Simvastatin and Beta-Cyclodextrin	(1:1)
4	Simvastatin and Crospovidone	(1:1)
5	Simvastatin and Lactose	(1:1)
6	Simvastatin and Saccharin Sodium	(1:1)
7	Simvastatin and CCS	(1:1)
8	Simvastatin and SSG	(1:1)
9	Simvastatin and Mannitol	(1:1)
10	Simvastatin and Mg. Stearate	(1:1)
11	Simvastatin and Aerosil	(1:1)
12	Simvastatin and PEG	(1:1)
13	Simvastatin and CaPO4(H2O)	(1:1)

Preparation of simvastatin formulations

The compressed tablets were evaluated for various tablet properties. Compatibility studies were carried out between Simvastatin and commonly used tablet excipients in the performulation stage. Formulations (F1- F7) each tablet containing 5mg Simvastatin were prepared by using different ingredients. Various batches of tablet formulations prepared are shown in Table 6. Optimum combination was worked out based on powder blend properties and disintegration time of the tablets.

Table 6: Composition of orodispersible tablets simvastatin formulations.

Ingredients	Quantity Per Tablet (mg)						
	Formulation Code						
	F1	F2	F3	F4	F5	F6	F7
Simvastatin	5	5	5	5	5	5	5
Mannitol	120	136	133	133	139	69	43.6
Microcrystalline Cellulose	___	___	___	___	___	69	32.7

Lactose	___	___	___	___	___	___	32.7
Croscarmellose Sodium	30	24	____	___	___	___	14
Crospovidone	___	___	20	28	___	___	20
Sodium Starch Glycolate	___	___	____	___	18	26	25
Beta-Cyclodextrin	5	5	5	5	5	5	5
Aerosil	8	8	8	8	8	8	8
Sodium Saccharin	31	26	28	20	24	16	12
Magnesium Stearate	1	1	1	1	1	2	2

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 7 & 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 simvastatin

Organoleptic properties such as color, odor and taste of the Simvastatin raw material were assessed. The color of Simvastatin was presented to be white. The odor was observed be odorless and the taste was found to be bitter as shown in Table 9.

Table 9: Organoleptic properties of simvastatin.

Tests	Observations
Color	White Crystalline Powder
Odor	Odorless
Taste	Bitter

Solubility analysis

Solubility studies of Simvastatin was found to be sparingly soluble in water and soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF) as shown in Table 10.

Table 10: Solubility analysis of simvastatin.

Raw Material API	Solubility
Simvastatin	Sparingly soluble in water
	Soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF)

Characterization of Simvastatin by UV Spectroscopy

Wavelength of Simvastatin by UV scanning in 0.1N NaOH show in Figure 1, The result show that wavelength of Simvastatin is 238 nm.

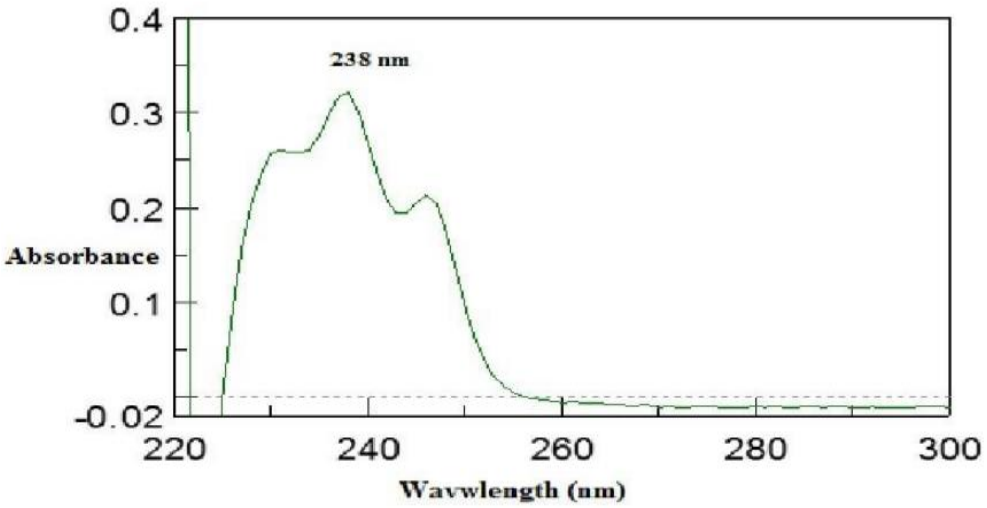


Fig. 1: UV Scanning of Simvastatin in 0.1N of NaOH.

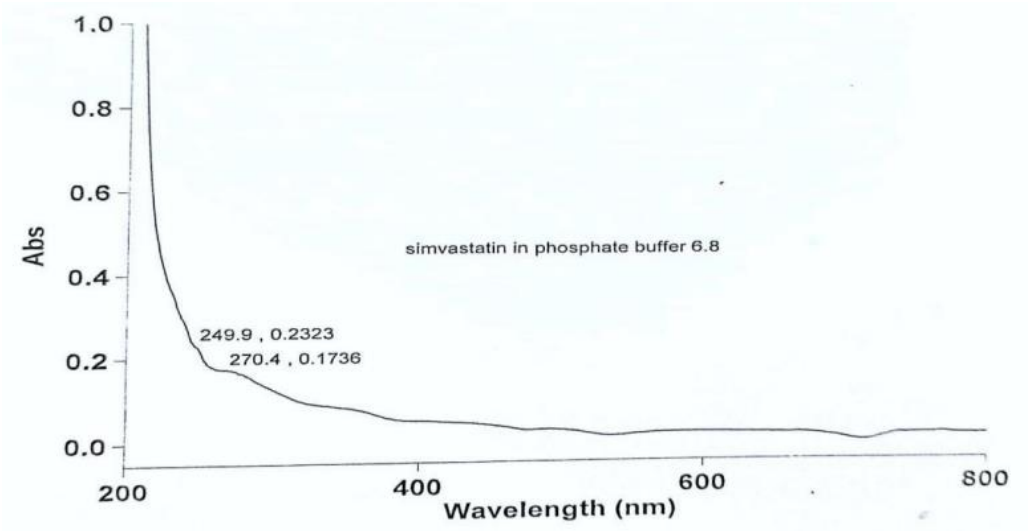


Fig. 2: UV Scanning of Simvastatin in Phosphate Buffer (pH 6.8).

Wave length of Simvastatin by UV scanning in phosphate buffer (pH 6.8)**.** The result show that wavelength of Simvastatin is 238nm as shown in Figure 2.

Calibration curve of simvastatin

The calibration curve of Simvastatin was prepared in two solutions, the first in phosphate buffer pH 6.8 and in ethanol as shown in Tables 11 & 12. The calibration curve of Simvastatin was prepared in phosphate buffer pH 6.8 and in ethanol. The plot of different

concentrations of simvastatin versus absorbance was found linear at 238 nm in both calibrations. The absorbance at different concentrations is shown in Tables 11 & 12 and Figures 3&4 the slope and correlation coefficient values of ethanol calibration were found 0.022 and 0.996 respectively. The intercept on Y-axis was found 0.012.

Table 11: Calibration Curve of Simvastatin in Phosphate Buffer (pH 6.8).

No	Concentration µg/ml	Absorbance
1	5	0.0840
2	10	0.1687
3	15	0.2465
4	20	0.3253
5	25	0.4150
6	30	0.4951
7	35	0.5843
8	40	0.6687
9	45	0.7496
10	50	0.8382
11	55	0.9343
12	60	0.9902
13	65	1.1030

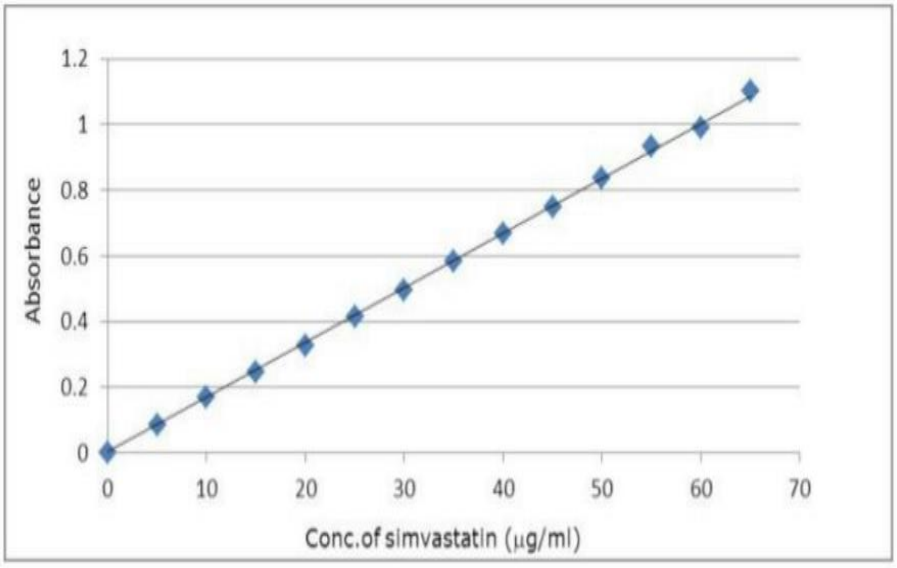


Fig. 3: Standard Calibration Curve of Simvastatin in Phosphate Buffer (pH 6.8).

Table 12: Calibration curve of simvastatin in ethanol.

No	Concentration (ug/ml)	Absorbance
1	5	0.001
2	10	0.09
3	15	0.21
4	20	0.33
5	25	0.42
6	30	0.55

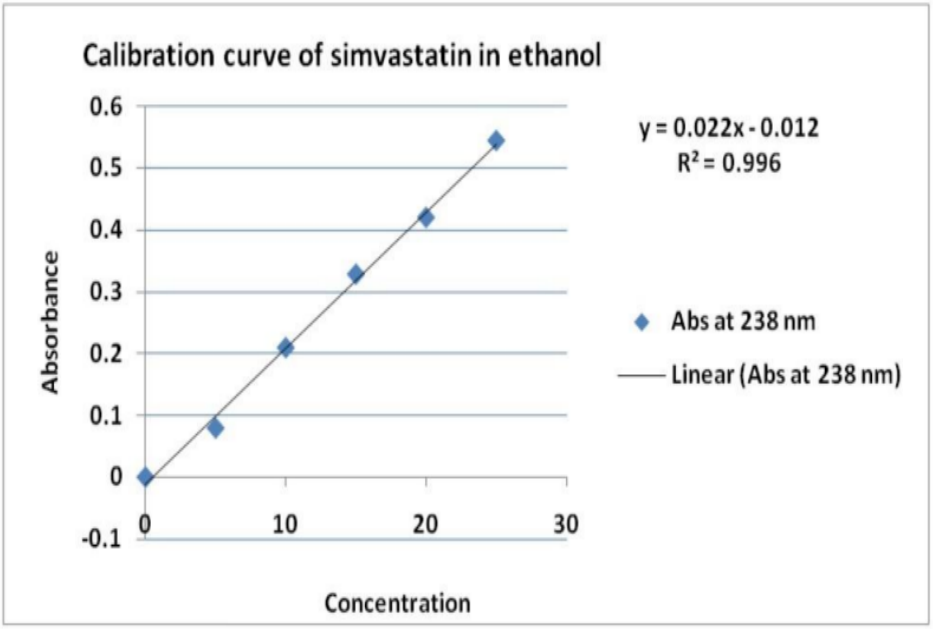


Fig. 4: Standard calibration curve of simvastatin in ethanol.

Melting point determination of simvastatin

Melting point of pure Simvastatin was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Simvastatin by repeated tapings. The capillary tube was placed in a 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 melting was recorded. The melting point range of Simvastatin was identical to reference melting point stated in BP (137-138°C). The sample started to melt at 137°C, and turned into liquid at 139 °C, indicating that the sample used is pure as shown in Table 13.

Table 13: Results of melting point of simvastatin.

Test	Temp Rang Analyzed (Melting)	Results
Test I Simvastatin	(137-138 °C)	137 °C
Test II Simvastatin	(137-138 °C)	137 °C

Characterization of Simvastatin by FTIR

FTIR spectrum studies indicated that major functional groups present in Simvastatin show characteristic peaks in IR spectrum. Figures (5) 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 Simvastatin. 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. The blend was evaluated after one month for changes like caking, liquefaction, discoloration and odor formation and by IR spectra the drug excipient compatibility studies were shown in Table 14.

Table 14: Study of infrared spectral assignment after one month.

No	Drug and Excipient	Ratio	Color	Aggregation	Odor
1	Simvastatin	1	White Crystalline Powder	No aggregate	Odorless
2	Simvastatin + Croscarmellose Sodium	1:1	White	No Aggregate	Odorless
3	Simvastatin + Sodium Starch Glycolate	1:1	Slightly Yellow	Slightly Aggregate	Odorless
4	Simvastatin + Microcrystalline Cellulose	1:1	White	No Aggregate	Odorless
5	Simvastatin + Crospovidone	1:1	White	No Aggregate	Odorless
6	Simvastatin + Mannitol	1:1	White	No Aggregate	Odorless
7	Simvastatin + Mg Stearate	1:1	Slightly Yellow	Slightly Aggregate	Odorless
8	Simvastatin + Sodium Saccharin	1:1	White	No Aggregate	Odorless
9	Simvastatin + Aerosil	1:1	White	No Aggregate	Odorless
10	Simvastatin + Beta-Cyclodextrin	1:1	White	No Aggregate	Odorless

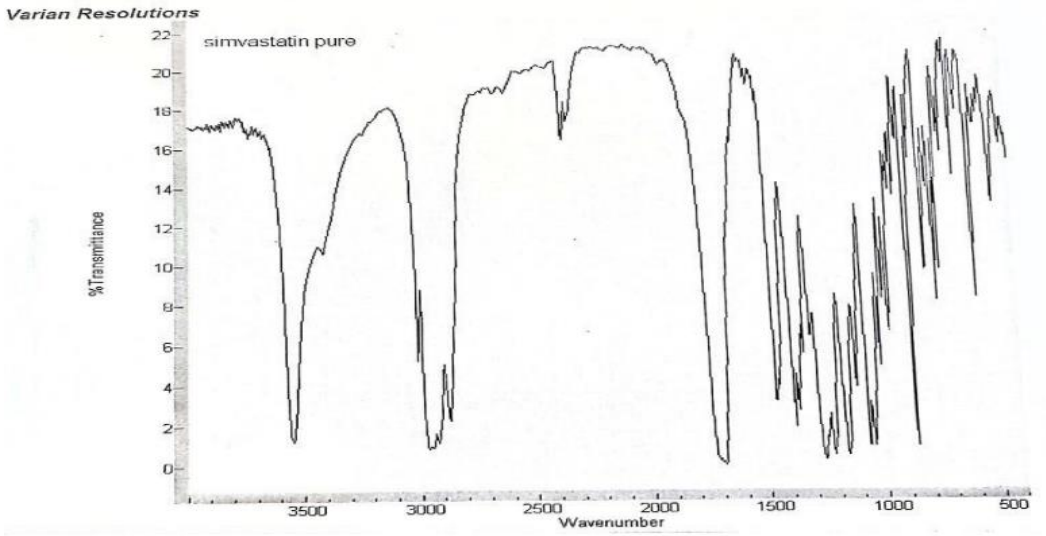


Fig. 5: FTIR Spectrum of Pure Simvastatin.

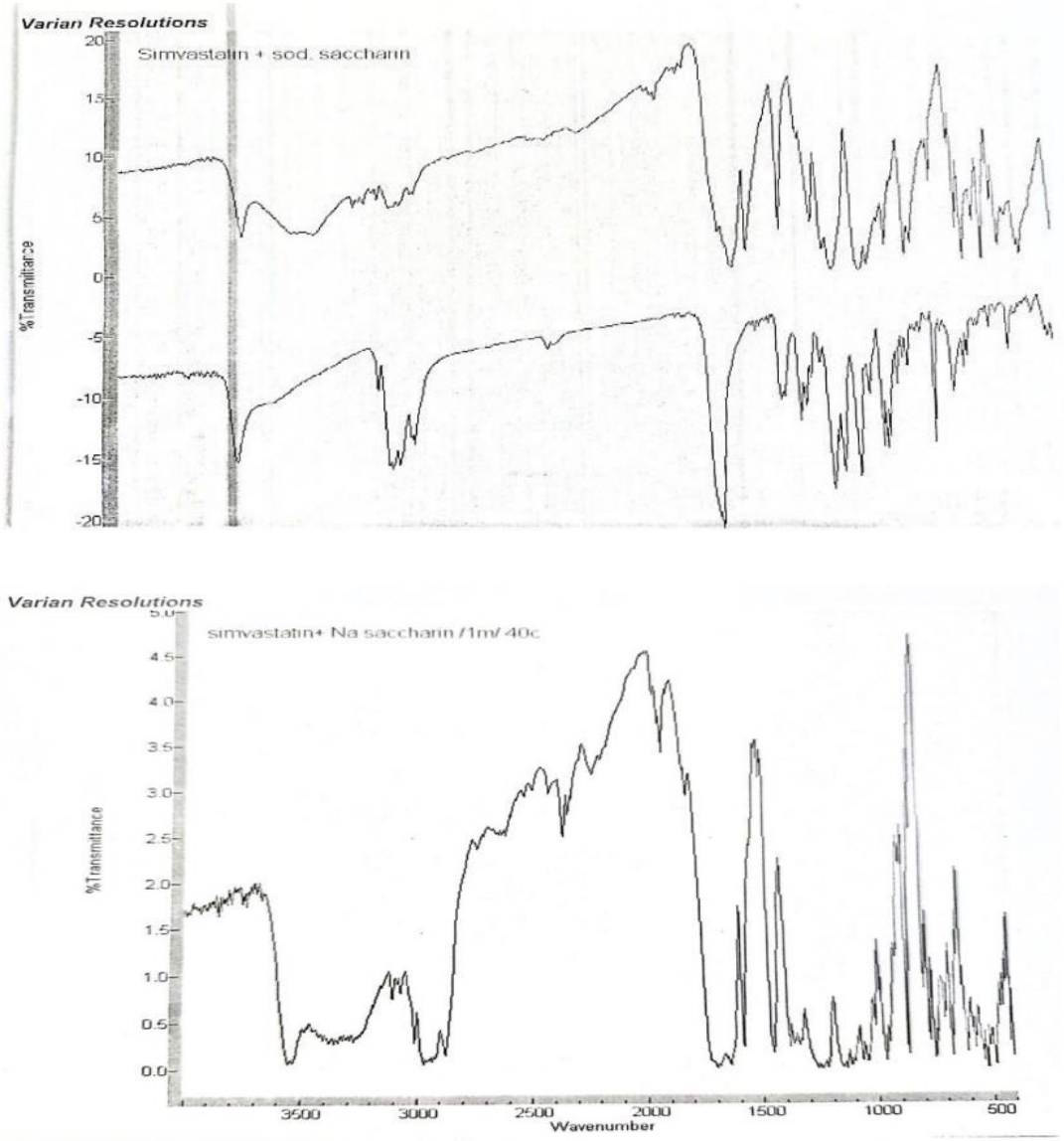
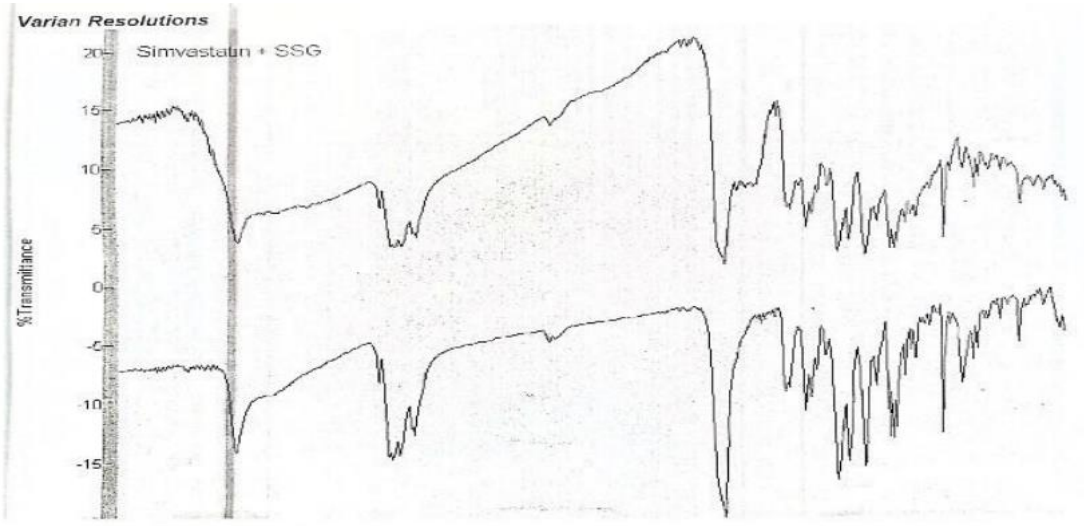


Fig. 6: FTIR Spectrum of Physical Mixture Fresh and Stored of Simvastatin and Sodium Saccharin.



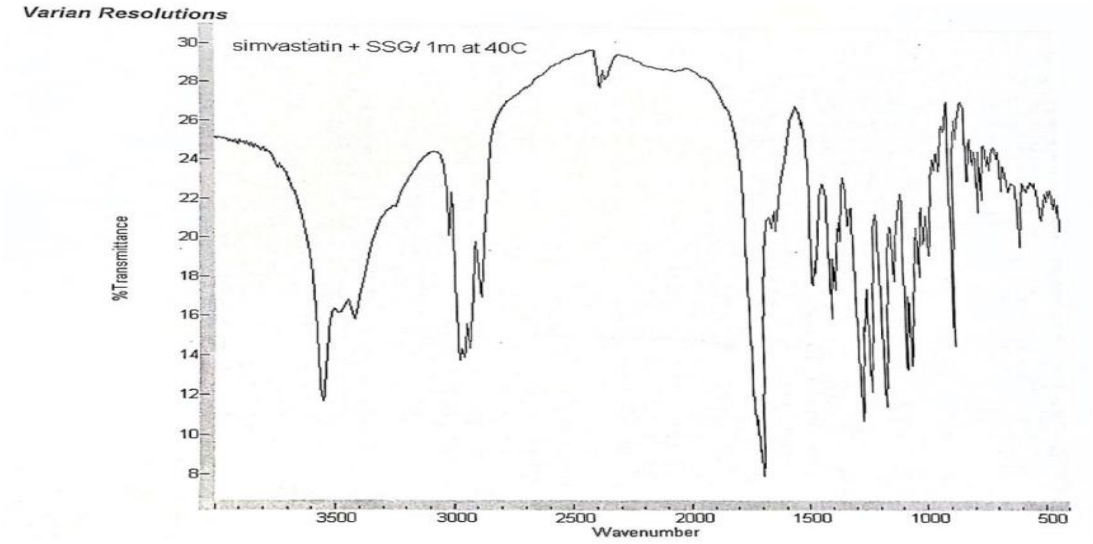


Fig. 7: FTIR Spectrum of Physical Mixture Fresh and Stored of Simvastatin and SSG.

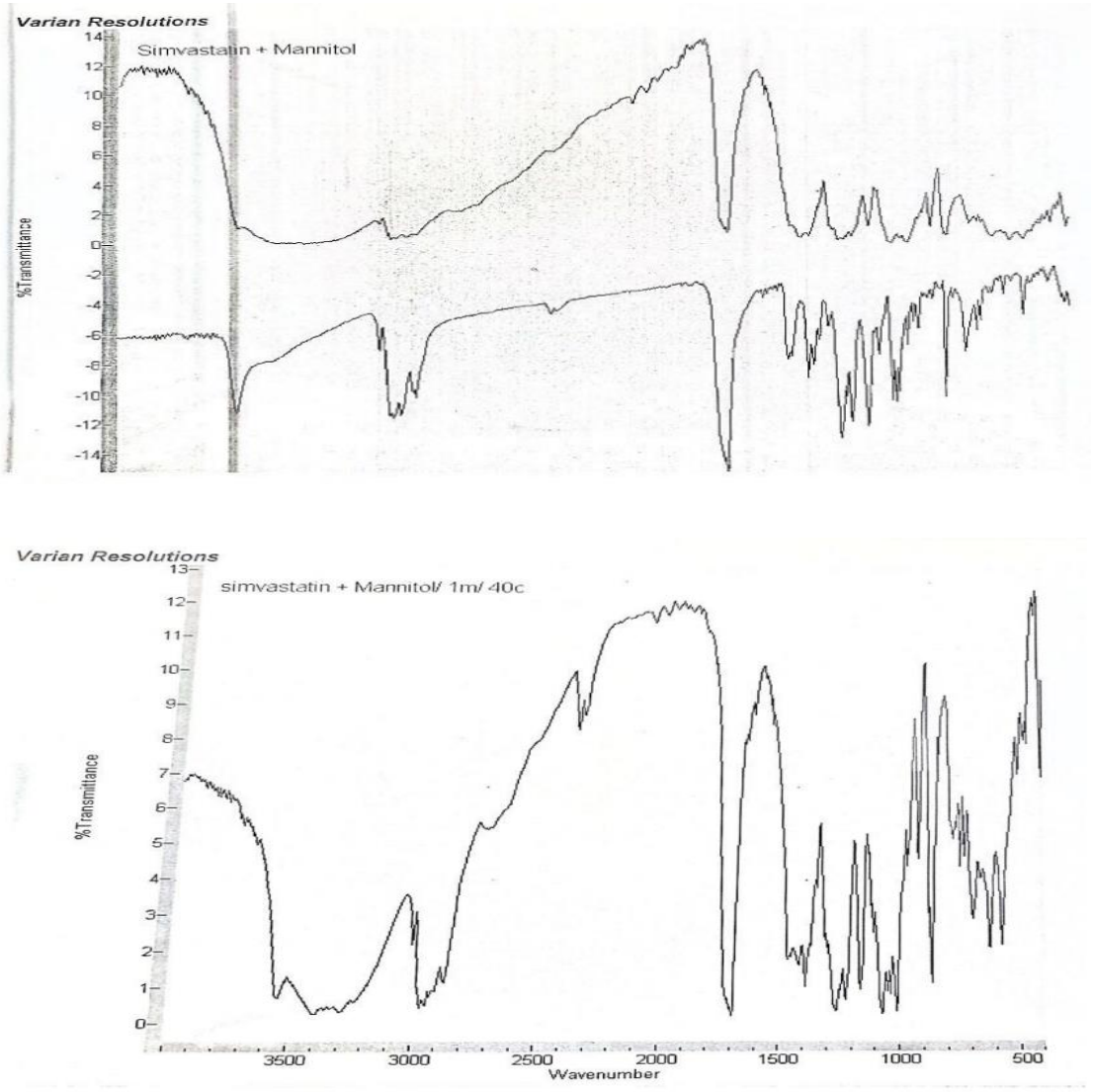


Fig. 8: FTIR Spectrum of Physical Mixture Fresh and Stored of Simvastatin and Mannitol.

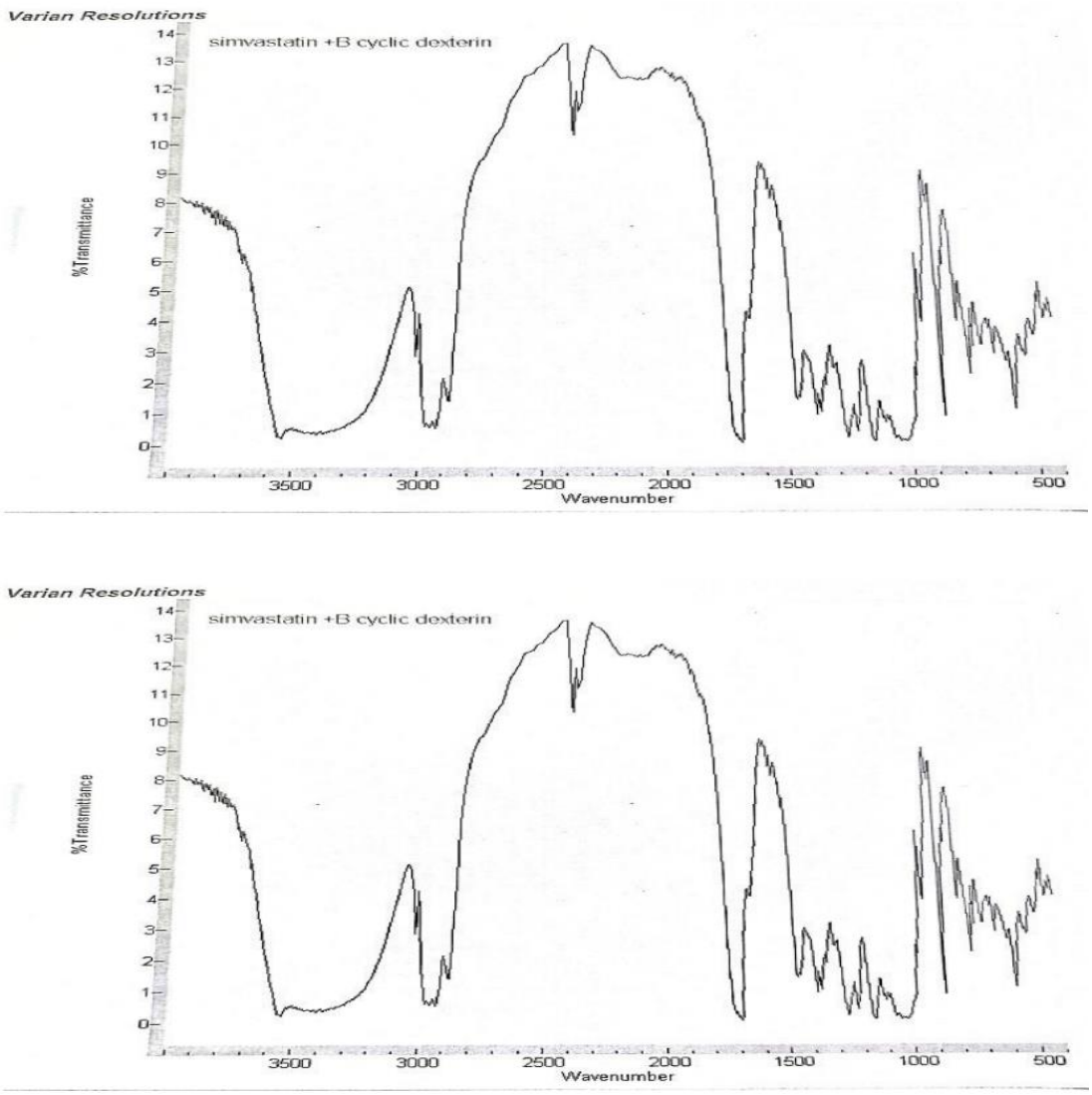
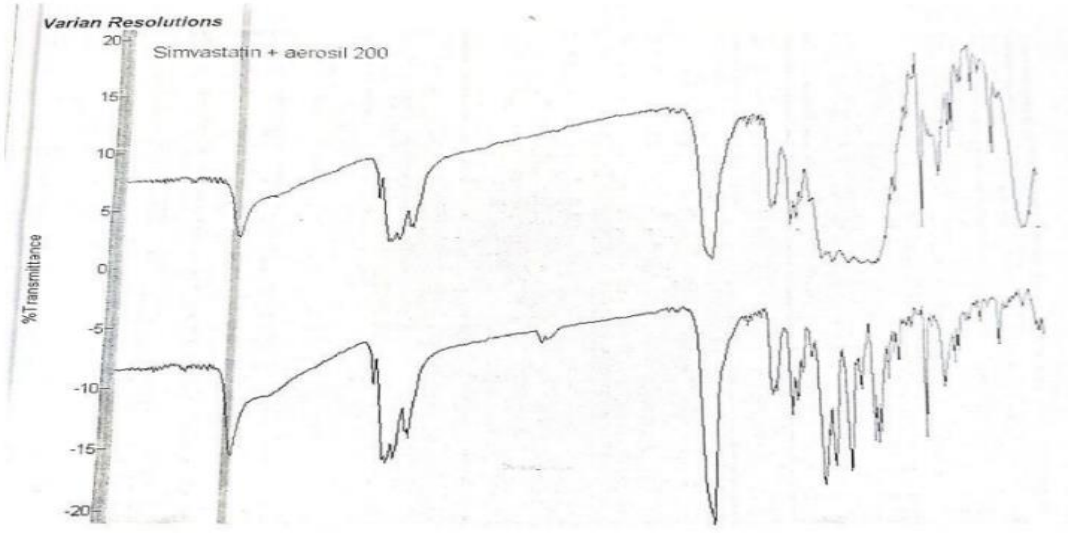


Fig. 9: FTIR Spectrum of Physical Mixture Fresh and Stored of Simvastatin and Beta-Cyclodextrin.



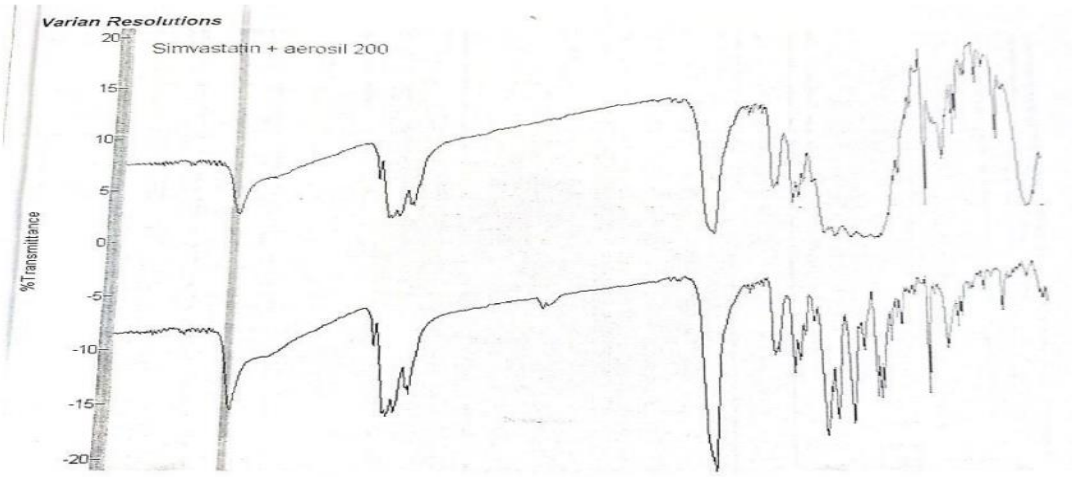
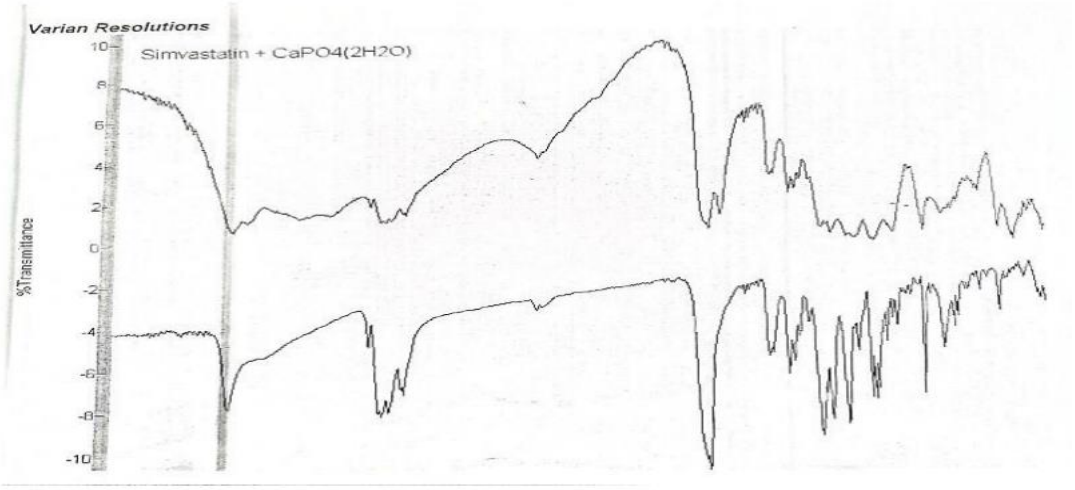


Fig. 10: FTIR Spectrum of Physical Mixture Fresh and Stored of Simvastatin and Aerosil.



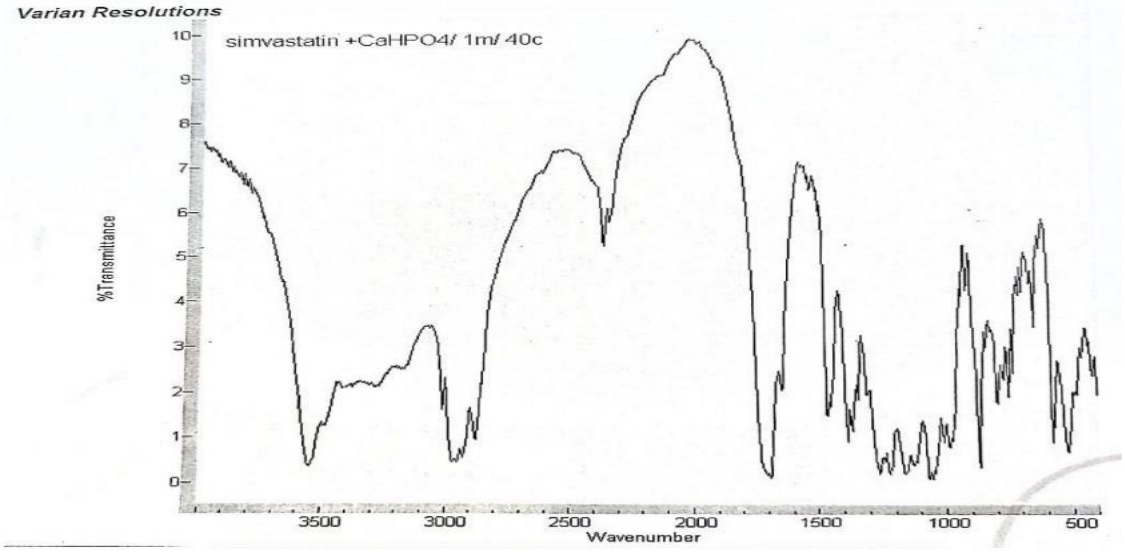


Fig. 11: FTIR Spectrum of Physical Mixture Fresh and Stored of Simvastatin and CaPO4 (H2O).

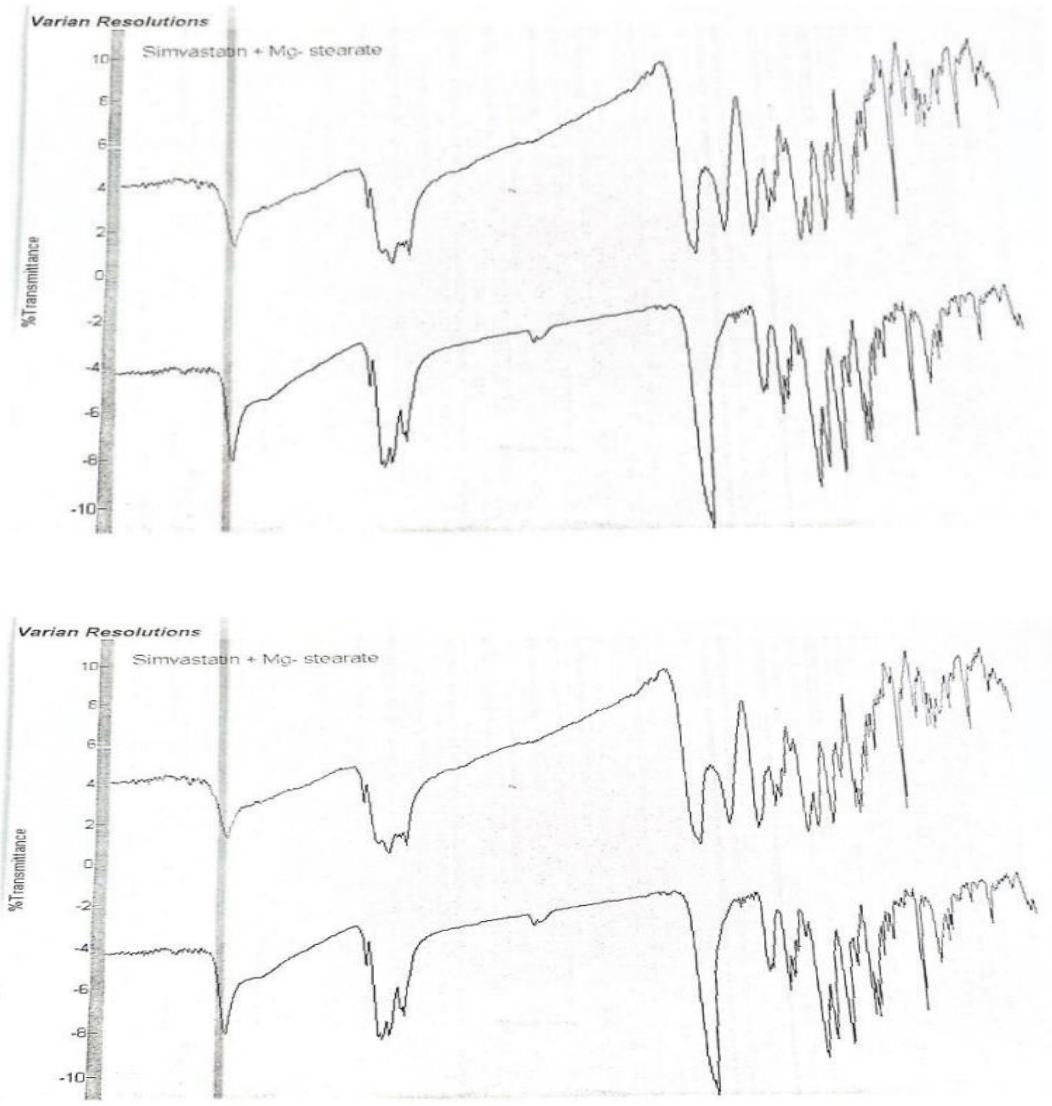
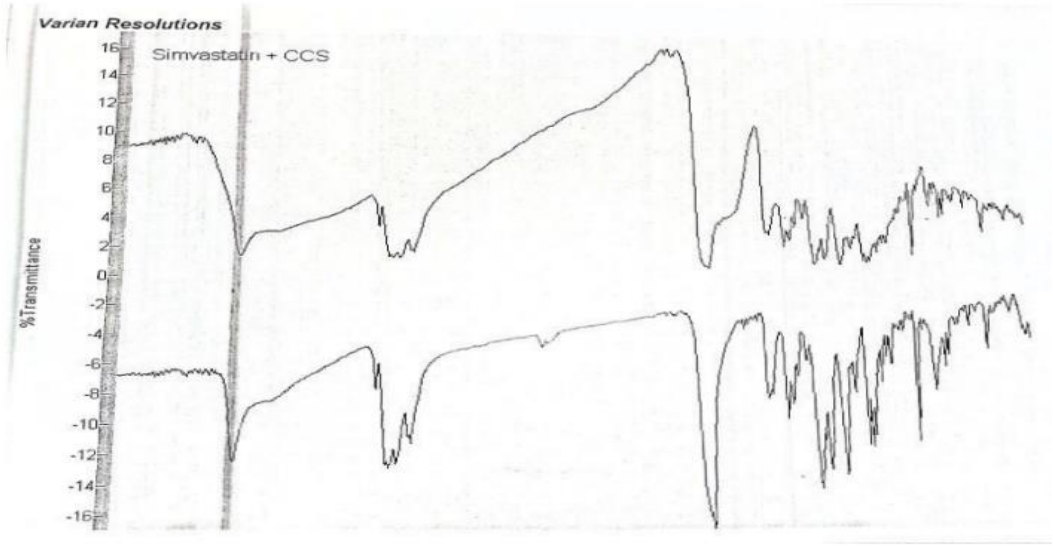


Fig. 12: FTIR Spectrum of Physical Mixture Fresh and Stored of Simvastatin and Magnesium Stearate.



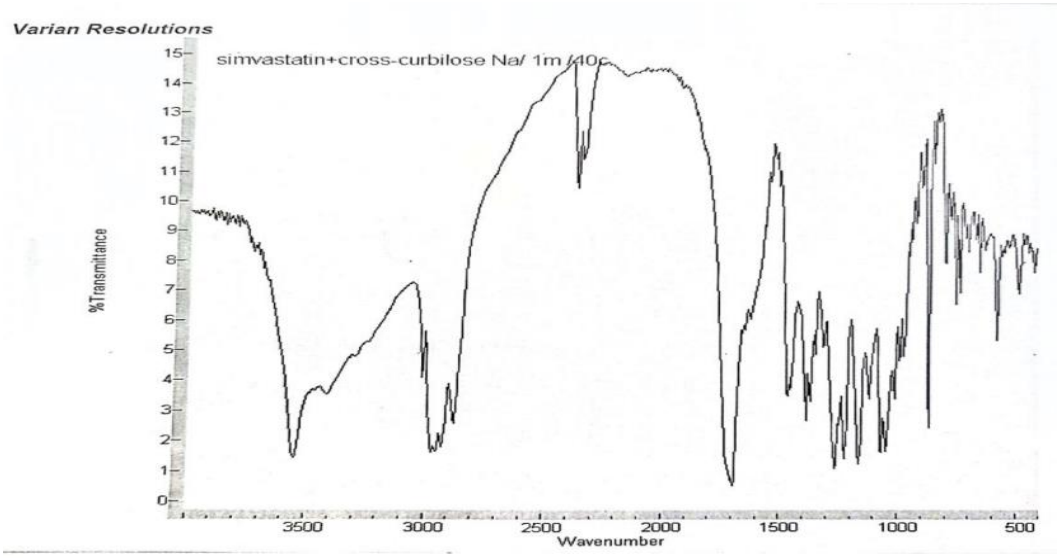


Fig. 13: FTIR Spectrum of Physical Mixture Fresh and Stored of Simvastatin and CCS.

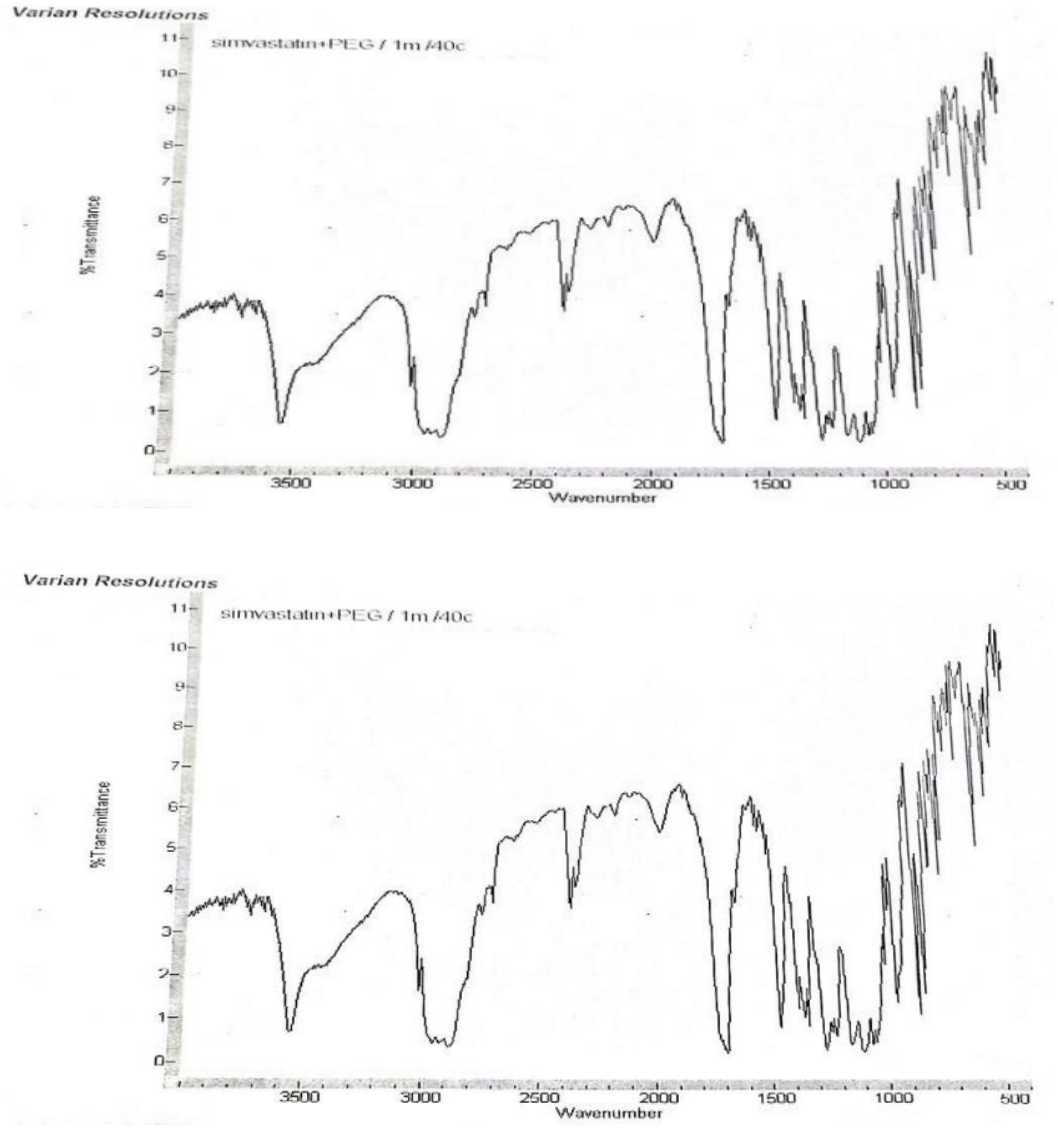


Fig. 14: FTIR Spectrum of Physical Mixture Fresh and Stored of Simvastatin and PEG.

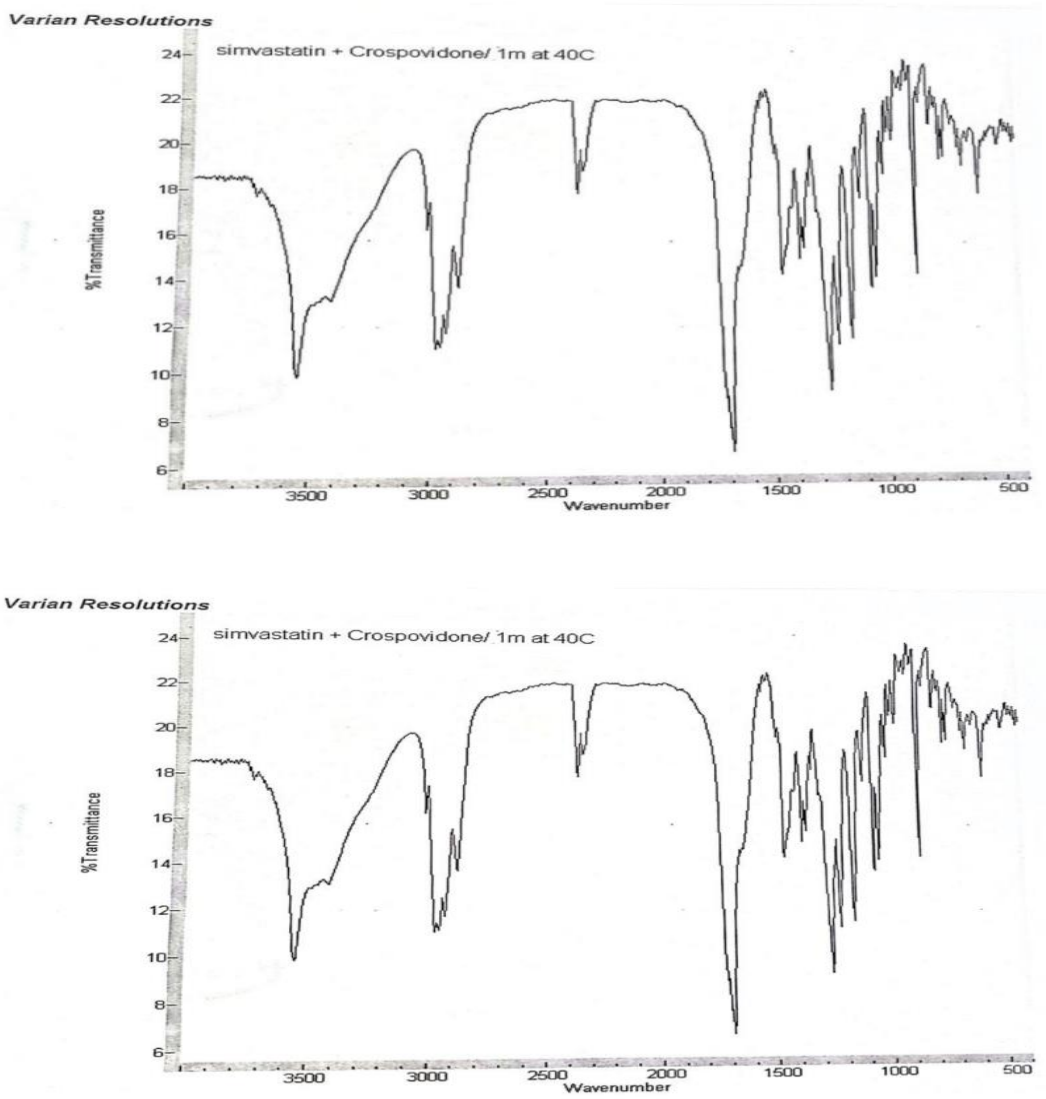


Fig. 15: FTIR Spectrum of Physical Mixture Fresh and Stored of Simvastatin and Crospovidone.

Micromeritic properties of simvastatin

The powder of Simvastatin 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 15.

Table 15: Micromeritic properties of simvastatin.

Raw Material (API)	Bulk Density (g/mL)	Taped Density (g/mL)	Compressibility Index	Hausner's Ratio	Angle of Repose
Simvastatin	0.14	0.16	16.8	2.28	48.54°

The angle of repose of Simvastatin was found to be 48.54° which indicates poor flow properties. The Hauser's ratio was presented to be 2.28 which indicates very poor flowability properties, The bulk density was found to be 0.14 g/ml to solve this problem by adding appropriate excipients to improve the flowability properties of Simvastatin.

CONCLUSION

The compatibility studies of physical mixtures of Simvastatin with different used excipients such as mannitol, and microcrystalline cellulose 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 Simvastatin formulations prepared were evaluated for precompression parameters and powder flow properties which were found to be within limits. It was concluded that the drug Simvastatin was found to be compatible with various excipients which were selected for the formulation development of the Simvastatin 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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REFERENCES

1. Santosh R, Kumar T, Yagnesh NS. Orodispersible Systems – an Alternative Approach for Enhanced Therapeutic Action. Indo American Journal of Pharmaceutical Research, 2018; 8(12).
2. Rahane RD, Rachh PR. A Review on Orodispersible Tablet. Journal of Drug Deliveryand Therapeutics, 2018; 8(5): 50-55.
3. Nagar P, et al. Orally Disintegrating Tablets: Formulation, Preparation Techniques and Evaluation. Journal of Applied Pharmaceutical Science, 2011; 01(04): 35-45.
4. Nehal SM, Garima G, Pramod KS. Fast Dissolving Tablets: Preparation, Characterization and Evaluation: an Overview. Int J Pharm Sci Rev Res, 2015; 31(2): 243-250.
5. Deshmukh H, Chandrashekhara S, Nagesh C, Murade A, Usgaunkar S. Superdisintegrants: a Recent Investigation and Current Approach. Asian J Pharm Tech, 2012; 2: 19-25.

6. Abha, Kaur LP. Superdisintegrations: an Arising Exemplar in Orodispersible Tablets. Int J Drug Res Technol, 2015; 5(1): 1-12.
7. Patil NC, Raja K. Formulation and Evaluation of Orodispersible Tablets of Metoclopramide Hydrochloride. Tamilnadu Dr.M.G.R. Medical University, 2012; 638-652.
8. Drug Information Handbook: a Comprehensive Resource for All Clinicians and Healthcare Professionals. American Pharmacist Association and Lexi-Comp, 2012; 21: S1620.
9. BNF. BMJ Group and Royal Pharmaceutical Society. September, 2022, 2023; S140-S141.
10. Preston CL. Stockley's Drug Interaction Pocket Companion. Pharmaceutical Press, 2015; 2: S119-S576.
11. Borse LB, Bendale AR, Borse SL, Naphade VD, Jadhav AG. Formulation and Evaluation of Mouth Dissolving Tablet Rivaroxaban and its Validation. Biosci Biotechnol Res Asia, 2022; 19(4): 943-954.
12. Stuart BH. Infrared Spectroscopy: Fundamentals and Applications. Wiley, 2004; 1: S168.
13. Bharate SS, Bharate SB, Bajaj AN. Interactions and Incompatibilities of Pharmaceutical Excipients with Active Pharmaceutical Ingredients: A Comprehensive Review. J Excip Food Chem, 2010; 1: 3-26.
14. Moyano MA, Broussalis AM, Segall A. Thermal Analysis of Lipoic Acid and Evaluation of the Compatibility with Excipients. J Therm Anal Cal, 2010; 99: 631-637.
15. Ceresole R, Han Y, Rosasco MA, Orelli LR, Segall AI. Drug-Excipient Compatibility Studies in Binary Mixtures of Avobenzone. J Cosmet Sci, 2013; 64: 317-328.
16. Chadha R, Bhandari S. Drug–Excipient Compatibility Screening—Role of Thermoanalytical and Spectroscopic Techniques. J Pharm Biomed Anal, 2014; 87: 82-97.
17. McDaid FM, Barker SA, Fitzpatrick S, Petts C, Craig DQM. Further Investigations into The Use of High Sensitivity Differential Scanning Calorimetry as A Means of Predicting Drug–Excipient Interactions. Int J Pharm, 2003; 252: 235-240.
18. O'Neill MA, Gaisford S. Application and Use of Isothermal Calorimetry in Pharmaceutical Development. Int J Pharm, 2011; 417: 83-93.
19. Ferraz Pinto M, Afonso de Moura E, Santos de Souza F, Oliveira Macêdo R. Thermal Compatibility Studies of Nitroimidazoles and Excipients. J Therm Anal Cal, 2010; 102: 323-329.

20. Oliveira Santos AF, Basilio Jr ID, Souza FS,Medeiros AFD, Ferraz Pinto M, de Santana DP. Application of Thermal Analysis of Binary Mixtures with Metformin. J Therm. Anal Cal, 2008; 93: 361-364.
21. Chou YP, Huang JY, Tseng JM, Cheng Y, Shu CM. Reaction Hazard Analysis for The Thermal Decomposition of Cumene Hydroperoxide in The Presence of Sodium Hydroxide. J Therm Anal Cal, 2008; 93: 275-280.
22. Sashima ES, Janowska G, Zaborski M, Vnuchkin AV. Compatibility of Fibroin/Chitosan and Fibroin/Cellulose Blends by Thermal Analysis. J Therm Anal Cal, 2007; 89: 887-891.
23. Medeiros AFD, Santos AFO, de Souza FS, Júnior IDB, Valdilânio J, Procópio JVV, de Santana DP, Macêdo RO. Thermal Studies of Preformulates of Metronidazole Obtained by Spray Drying Technique. J Therm Anal Cal, 2007; 89: 775-781.
24. Silva MAS, Kelmann RG, Foppa T, Cruz AP, Bertol CD Sartori T, Granada A, Carmignan F, Murakami FS. Thermoanalytical Study of Fluoxetine Hydrochloride. J Therm Anal Cal, 2007; 87: 463-467.
25. Lira AM, Araújo AAS, Basílio IDJ, Santos BLL, Santana DP, Macêdo RO. Compatibility Studies of Lapachol with Pharmaceutical Excipients for The Development of Topical Formulations. Thermochim Acta, 2007; 457: 1- 6.
26. Mura P, Furlanetto S, Cirri M, Maestrelli F, Marras AM, Pinzauti S. Optimization of Glibenclamide Tablet Composition Through the Combined Use of Differential Scanning Calorimetry and D-Optimal Mixture Experimental Design. J Pharm Biomed Anal, 2005; 37: 65-71.
27. Araújo AAS, Storpirtis S, Mercuri LP, Carvalho FMS, dos Santos Filho M, Matos JR. Thermal Analysis of The Antirretroviral zidovudine (AZT) and Evaluation of The Compatibility with Excipients Used in Solid Dosage Forms. Int J Pharm, 2003; 260: 303-314.
28. Matos APS, Costa JS, Boniatti J, Seiceira RC, Pitaluga Jr A, Oliveira DL, Visçosa AL, Holandino C. Compatibility Study Between Diazepam and Tablet Excipients. J Therm Anal Cal, 2017; 127: 1675-1682.
29. Liltorp K, Larsen TG, Willumsen B, Holm R. Solid State Compatibility Studies with Tablet Excipients Using Non Thermal Methods. J Pharm Biomed Anal, 2011; 55: 424-428.

30. Verma RK, Garg S. Selection of Excipients for Extended-Release Formulations of Glipizide Through Drug–Excipient Compatibility Testing. J Pharm Biomed Anal, 2005; 38: 633-644.
31. Verma RK, Garg S. Compatibility Studies between Isosorbide Mononitrate and Selected Excipients Used in The Development of Extended-Release Formulations. J Pharm Biomed Anal, 2004; 35: 449-458.
32. Silva LAD, Teixeira FV, Serpa RC, Esteves NL, dos Santos RR, Lima EM, da Cunha-Filho MSS, de Souza Araújo AA, Taveira SF, Marreto RN. Evaluation of Carvedilol Compatibility with Lipid Excipients for The Development of Lipid-Based Drug Delivery Systems. J Therm Anal Cal, 2016; 123: 2337-2344.
33. Veiga A, Oliveira PR, Bernardi LS, Mendes C, Silva MAS, Sangoi MS, Janissek PR, Murakami FS. Solid-State Compatibility Studies of A Drug Without Melting Point. J Therm Anal Cal, 2018; 131: 3201-3209.
34. Rus LM, Tomuta I, Iuga C, Maier C, Kacso I, Borodi G, Bratu I, Bojita M. Compatibility Studies of Indapamide/Pharmaceutical Excipients Used in Tablet Preformulation. Farmacia, 2012; 60: 92-101.
35. Tomassetti M, Catalani A, Rossi V, Vecchio S. Thermal Analysis Study of The Interactions between Acetaminophen and Excipients in Solid Dosage Forms and in Some Binary Mixtures. J Pharm Biomed Anal, 2005; 35: 949-955.
36. Ding T, Chen L, Zhai LH, Fu Y, Wang-Sun B. Compatibility Study of Rivaroxaban and Its Pharmaceutical Excipients. J Therm Anal Cal, 2017; 130: 1569-1573.
37. Raymond C. R, Sheskey PJ, Owen CS. Handbook of Pharmaceutical Excipients Fifth Edition Edited.
38. Shivangi S, Navneet V. Taste Masked Orodispersible Tablets. A highly patient Compliant Dosage Form. Asian J Pharm Clin Res, 2016; 9: 385-91.
39. Anupam R. Orodispersible Tablets: A Review. Asian J Pharm Clin Res, 2016; 9: 19-26.
40. Abdelbary G, Eouani C, Prinderre P, Joachim J, Reynier J, Piccerelle P. Determination of The Invitro Disintegration Profile of Rapidly Disintegrating Tablets and Correlation with Oral Disintegration. Int J Pharm, 2005; 292: 29–41.
41. Anusha P, Nirajana A, Mohammed S, Jilani S, Murali C, Harish G. Development and Evaluation of Drotaverine Taste Masked Tablets with Improved Dissolution Efficiency Using Soild Dispersion Technique. IJRPB, 2013; 1: 275–80.

42. Srikanth M, Uhumwangho M, Sunil S, Sreenivasa N, Ravi C, Ramana Murthy K. Design and Revaluation of Taste Masked Drotaverine HCl Orodispersible Tablets Using Polymethacrylate Polymers. Der Pharmacia Lett, 2010; 2: 223–31.
43. Narasimhulu et al. Formulation and Evaluation of Orodispersible Drotaverine Sublingual Tablets. Indo American Journal of Pharm Sciences, 2014; 1(06).
44. Rele RV, Ruparel DG. UV Spent to Photo Metric Estimation of Drotaverine Hydrochloride by Derivative Method in Pharmaceutical Dosage Form. International Journal of ChemTech Research, 2018; (10): 353-360.
45. Shirwaikar AC. Galan Fast Disintegrating Tablets of Famotidine by Dry Granulation Method. Ind J Pharm Sci, 2004; 66: 422-426.
46. Venkateswarlu B, et al. Formulation and Evaluation of Famotidine Fast Dissolving Tablets by Direct Compression Method. Indian Journal of Research in Pharmacy and Biotechnology, 2013; 9-10(609): 609-613.
47. Sunada H, Bi YX. Preparation, Evaluation and Optimization of Rapidly Disintegrating Tablets. Powder Technol, 2002; 188–198.
48. Pires SA, Mussel WN, Yoshida MI. Solid-State Characterization and Pharmaceutical Compatibility between Citalopram and Excipients Using Thermal and Non-Thermal Techniques. J Therm Anal Cal, 2017; 127: 535- 542.
49. Joshi BV, Patil VB, Pokharkar VB. Compatibility Studies between Carbamazepine and Tablet Excipients Using Thermal and Non-Thermal Methods. Drug Devel Ind Pharm, 2002; 28: 687–694.
50. Stulzer HK, Rodrigues PO, Cardoso TM, Matos JSR, Silva MAS. Compatibility Studies between Captopril and Pharmaceutical Excipients Used in Tablets Formulations. J Therm Anal Cal, 2008; 9: 323-328.
51. United State Pharmacopoeia. Famotidine Tablets, 2020 USP 43-NF 38.
52. https://go.drugbank.com/drugs/DB00641.
53. Raval VN. Formulation and Evaluation of Orodispersible Tablets of Famotidine Using Superdisintegrants. Indo American Journal of Pharmaceutical Research, 2011; (1): 42-50.
54. https://Pubchem.ncbi.nlm.nih.gov/compound/54454.
55. Reddy RA, Ramesh B. Kishan V. Drug-Excipient Interaction During Formulation Development In -Vitro and In -Vivo Evaluation of Gastroretentive Drug Delivery System for Nizatidine. Int J Pharm Sci Nanotech, 2013; 6: 2281-2293.
56. Prathyusha CH, Murthy TEGK. Compatibility Studies of Donepezil with Different Excipients by Using HPLC and FTIR. J Adv Pharm Tech Res, 2013; 3: 273-278.

57. Jangde R, Singh D. Compatibility Studies of Quercetin with Pharmaceutical Excipients used in The Development of Novel Formulation. Research J Pharm and Tech, 2014; 7: 1101-1105.
58. Shirwaikar AC. Galan Fast Disintegrating Tablets of Famotidine by Dry Granulation Method. Ind J Pharm Sci, 2004; 66: 422-426.
59. Venkateswarlu B, et al. Formulation and Evaluation of Famotidine Fast Dissolving Tablets by Direct Compression Method. Indian Journal of Research in Pharmacy and Biotechnology, 2013; 9-10(609): 609-613.
60. Tiwari SP, Vidyasagar G. Identification, Characterization, and Drug Excipient Compatibility of Diltiazem Hydrochloride by Physico-Chemical Techniques UK. J Pharm Bio Sci, 2014; 2: 49-53.
61. Gupta A, Kar HK. Solid State Compatibility Studies of Miconazole Using Thermal and Spectroscopic Methods. Adv Anal Chem, 2015; 5: 51-55.
62. Khan MI, Madni A, Ahmad S, Khan A, Rehman M, Mahmood MA. ATRFTIR Based Pre and Post Formulation Compatibility Studies for The Design of Niosomal Drug Delivery System Containing Nonionic Amphiphiles and Chondroprotective Drug. J Chem Soc Pak, 2015; 37: 527-534.
63. da Silva EP, Pereira MAV, de Barros Lima IP, Barros Lima NGP, Barboza EG, Aragã CFS, Gomes APB. Compatibility Study between Atorvastatin and Excipients Using DSC and FTIR. J Therm Anal Cal, 2016; 123: 933- 939.
64. Amir IM, Amir ME, Osama AA, Suzan A, Alaa IM. Investigation of Drug–Polymer Compatibility Using Chemometric-Assisted UV Spectrophotometry. Pharmaceutics., 2017; 9: 1-13.
65. Canbay HS, Doğantürk M. Application of Differential Scanning Calorimetry and Fourier Transform Infrared Spectroscopy to The Study of Metoprolol-Excipient and Lisinopril-Excipient Compatibility. Eurasian., J Anal Chem, 2018; 13: 1-7.
66. Monajjemzadeh F, Hassanzadeh D, Valizadeh H, Siahi-Shadbad MR, Mojarrad JS, Robertson TH, Roberts MS. Compatibility Studies of Acyclovir and Lactose in Physical Mixtures and Commercial Tablets. Eur J Pharm Biopharm, 2009; 73: 404-413.
67. Mura P, Manderioli A, Bramanti G, Furlanetto S, Pinzauti S. Utilization of Differential Scanning Calorimetry as A Screening Technique to Determine The Compatibility of ketoprofen with Excipients. Int J Pharm, 1995; 119: 71-79.
68. Malan CEP, de Villiers MM, Lötter AP. Application of Differential Scanning Calorimetry and High-Performance Liquid Chromatography to Determine the Effects of Mixture

Composition and Preparation During The Evaluation of Niclosamide-Excipient Compatibility. J Pharm Biomed Anal, 1997; 15: 549-557.

69. Daniel JSP, Veronez IP, Lopez Rodriguez L, Trevisan MG, García JS. Risperidone – Solid-State Characterization and Pharmaceutical Compatibility Using Thermal and Non-Thermal Techniques. Thermochim Acta, 2013; 568: 148-155.
70. Lima NGPB, Lima IP, Barros DMC, Oliveira TS, Raffin FN, de Lima e Moura TFA, Medeiros ACD, Gomes APB, Aragão CFS. Compatibility Studies of Trioxsalen with Excipients by DSC, DTA, and FTIR. J Therm Anal Cal, 2014; 115: 2311-2318.
71. Rosasco MA, Bonafede SL, Faudone SN, Segall AI. Compatibility Study Between Tobramycin and Pharmaceutical Excipients Using Differential Scanning Calorimetry, FT-IR, DRX and HPLC. J Therm Anal Cal, 2018; 134: 1929-1941.
72. Rojek B, Wesolowski M. Fourier Transform Infrared Spectroscopy Supported by Multivariate Statistics in Compatibility Study of Atenolol with Excipients. Vib Spectrosc, 2016; 86: 190–197.
73. Prasanna Kumar et al. An Overview on Preformulation Studies. Indo Am J Pharm Sci, 2015; 2(10).
74. Allen L, Ansel H. Pharmaceutical Dosage Forms and Drug Delivery Systems by Ansel (10th Edition). Lippincott Williams & Wilkins, Philadelphia, 2014.
75. Beringer P, Gupta PK, Felton L. Stability of Pharmaceutical Products. Remington: The Science and Practice of Pharmacy, 2005; 01: 1029-30.
76. Kumar BP, Sahu RK, Ramamurthy KV, Rao S, Ramu B. A Review on Mechanism, Importance and Methods of Compatibility Testing in the Formulation of Dosage Forms. Journal of Chemical and Pharmaceutical Sciences, 2011; 4(4): 141-151.
77. Nishath F, Tirunagari M, Husna KQ, Nandagopa A, Rao JV. Drug-Excipient Interaction and its Importance in Dosage Form Development. J Applied Pharma Sci, 2011; 1(06): 66-71.
78. Crowely P, Martini LG. Drug Excipient Interactions. Pharmaceutical Technology, 2001; 3: 0582.
79. Chadha R, Arora P, Bhandari S, Bala M. Thermomicroscopy and its Pharmaceuticals Applications. Current Microscopy Contributions to Advances in Science and Technology, 2012; 1017-23.
80. Harding L, Qi S, Hill G, Reading M, Craig DQM. The Development of Microthermal Analysis and Photo Thermal micro-Spectroscopy as Novel Approaches to Drug–Excipient Compatibility Studies. Int J Pharm, 2008; 354: 149-57.

81. Stephenson GA, Forbes RA, Reutzel-Edens SM. Characterization of the Solid State: Quantitative Issue. Advanced Drug Delivery Reviews, 2001; 48: 67-90.
82. Tishmack PA, Bugay DE, Byrn SR. Solid-State Nuclear Magnetic Resonance Spectroscopy-Pharmaceutical Applications. J Pharm Sci, 2003; 92: 441-474.
83. Karin LA, Trine GL, Birgitte W, Holma R. Solid State Compatibility Studies with Tablet Excipients Using Non Thermal Methods. J Pharm and Biomedical Analysis, 2011; 55: 424-28.
84. Deokate U, Gorde AM. Forced Degradation and Stability Testing: Strategies and Analytical Perspectives. Int J Pharm Sci Rev and Res, 2014; 42: 242-250.
85. Lena Ohannesian, Antony J. Streeter. Handbook of Pharmaceutical Analysis, Marcel Dekker, Inc, 2002.
86. Banker G, Rhodes CT. Modern Pharmaceutics, Marcel Dekker, Inc, 2000.
87. Harry G Britain. Spectroscopic Methods for the Characterization of Drug Substances, Marcel Dekker, Inc, 2008.
88. Lewis IR, Edwards HGM. Handbook of Raman Spectroscopy, New York: Marcel Dekker, 2001.
89. Blachere JR, Harry G. Brittain. X-Ray Diffraction Methods for the Characterization of Solid Pharmaceutical Materials, Marcel Dekker, Inc, 2008.
90. US Pharmacopoeia 30, National Formulary 25, USP Convention, Rockville, 2007.
91. Pires SA, Mussel WN, Yoshida MI. Solid-State Characterization and Pharmaceutical Compatibility between Citalopram and Excipients Using Thermal and Non-thermal Techniques. J Therm Anal Cal, 2017; 127: 535- 542.
92. Dave, VS, et al. Investigation of the Physical-Mechanical Properties of Eudragit(R) RS PO/RL PO and their Mixtures with Common Pharmaceutical Excipients. Drug Dev Ind. Pharm, 2013; 39(7): 1113-1125.
93. Cantor SL, et al. Development and Optimization of Taste-Masked Orally Disintegrating Tablets (ODTs) of Clindamycin Hydrochloride. Drug Dev Ind Pharm, 2014; 7: 1-9.
94. Tita B, et al., Compatibility Study between Ketoprofen and Pharmaceutical Excipients Used in Solid Dosage Forms. J Pharm Biomed Anal, 2011; 56(2): 221-227.
95. Tita D, et al., Compatibility Study of the Acetylsalicylic Acid with Different Solid Dosage Forms Excipients. J Therm Anal Calorim, 2013; 112(1): 407-419.
96. USFDA, Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach., 2004.
97. USFDA, Guidance for Industry - ICH Q8 (R2) Pharmaceutical Development, C. CDER, Editor. USFDA: Silver Spring, MD, 2009; 1-20.

98. Wu Y, et al. Reactive Impurities in Excipients: Profiling, Identification and Mitigation of Drug-Excipient Incompatibility. AAPS PharmSciTech, 2011; 12(4): 1248-1263.
99. Narang A, et al. Impact of Excipient Interactions on Solid Dosage Form Stability. Pharm Res, 2012; 29(10): 2660-2683.
100. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. Sixth Edition. London. APhA/Pharmaceutical Press, 2009.
101. Sims J, et al. A New Approach to Accelerated Drug-Excipient Compatibility Testing. Pharm Dev Technol, 2003; 8(2): 119.
102. Skotnicki M, et al. Bisoprolol and Bisoprolol-Valsartan Compatibility Studied by Differential Scanning Calorimetry, Nuclear Magnetic Resonance and X-Ray Powder Diffractometry. Pharm Res, 2014.
103. Liltorp K, et al. Solid-State Compatibility Studies with Tablet Excipients Using Non-Thermal Methods. J Pharm Biomed Anal, 2011; 55(3): 424-428.
104. Épshtein NA. Compatibility of Medicinal and Excipient Substances in the Development of Medicinal Formulations. Pharm Chem J, 2018; 52(7): 648–57.
105. ICH Topic Q8 (R2). Pharmaceutical development, 2009; 8.
106. Thomas VH, Naath M. Design and Utilization of the Drug-Excipient Chemical Compatibility Automated System. Int J Pharm, 2008; 359(1– 2): 150–7.
107. Michael E Aulton, Pharmaceutics- The Sciences of Dosage Form Design, 4rth International Edition, Churchill Livingstone, USA, 2013; 367-389.
108. Leon Lachman, Lieberman's. The Theory and Practice of Industrial Pharmacy. Indian 4rth Edition, CBS Publisher, Reprint, 2020; 217-251.
109. Mark Gibson. Pharmaceutical Preformulation and Formulation. HIS Health Group, CRC, United state of America, 2004; 20- 45.
110. WHO. Annex. Pharmaceutical Development of Multisource (Generic) Finished Pharmaceutical Products, 3.
111. Rewar S, Singh CJ, Bansal BK, Pareek R, Sharma AK. Oral Dispersible Tablet: an Overview, Development, Technologies and Evaluation. Int J Res Dev Pharma Life Sci, 2014; 3(4, 6): 1223-35.
112. Sunil Kumar BG, Felix JV, Vishwanath BA. Formulation and Evaluation of Dispersible Tablet of Cefixime Trihydrate. Int J Pharma Drug Analysis, 2014; 2(1): 858-68.
113. Walke PS, Pawar AY, Sonawane DD, Bhamber RS. Liquisolid. A Novel Technique to Enhance Solubility and Dissolution Rate of BSC Class II Pharmaceutical. J Pharm Res, 2011; 4(11): 4011-4.

114. Brough C, Williams RO. Amorphous Solid Dispersions and Nanocrystal Technologies for Poorly Water-Soluble Drug Delivery. Int J Pharm, 2013; 453: 157–66.
115. Samal HB, Debata. Solubility and Dissolution Improvement of Aceclofenac Using β-Cyclodextrin. Int J Drug Dev Res, 2012; 4: 326-33.
116. Zingone G, Rubessa F. Preformulation Study of the Inclusion Complex Warfarin-β-Cyclodextrin. Int J Pharm, 2005; 291: 3-10.
117. Hrishav DP, Nath B. Formulation and Evaluation of Oral Fast Disintegrating Tablet of Ibuprofen Using Two Super Disintegrants. Int J Curr Pharm Res, 2017; 9: 92-5.
118. Guo Y, Luo J, Tan S, Otieno BO, Zhang Z. The Applications of Vitamin E TPGS in Drug Delivery. Eur J Pharm Sci, 2013; 49(2): 175-86.
119. Lipinski CA, Lombardo. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. Adv Drug Deliv Rev, 2011; 46: 3-26.
120. Alburyhi MM. Doctor Thesis, Faculty of Pharmacy, Cairo University, 2009.
121. Bary AA, El-Gazayerly ON, Alburyhi MM. Formulation of Immediate Release Lamotrigine Tablets and Bioequivalence Study. Journal of Chemical Pharm Research, 2013; 5(10): 266–271.
122. Alburyhi MM, Hamidaddin MA, Noman MA, Saif AA, Yahya TA, Al-Ghorafi MA. Rivaroxaban -Excipient Compatibility Studies for Advanced Drug delivery Systems Development. European Journal of Pharmaceutical and Medical Research, 2024; 11(9): 370-404.
123. Saif AA, Alburyhi MM, Noman MA, Yahya TA, Al-Ghorafi MA. Famotidine-Excipient Compatibility Studies for Advanced Drug delivery Systems Development. World Journal of Pharmaceutical Research, 2024; 13(18): 1346-1408.
124. Al-Ghorafi MA, Alburyhi MM, Saif AA, Noman MA, Yahya TA. Drotaverine-Excipient Compatibility Studies for Advanced Drug delivery Systems Development. World Journal of Pharmaceutical Research, 2024; 13(18): 1285-1340.
125. Saif AA, Alburyhi MM, Noman MA. Formulation and Evaluation of Ketoprofen Fast Dissolving Tablets. International Journal of Sciences, 2018; 7(09): 27- 39.
126. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Pandanus Odoratissimus Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Breast Cancer. World Journal of Pharmaceutical Research, 2024; 13(8): 1092-1112.

127. Alburyhi MM, Noman MA, Saif AA, Salim YA, Hamidaddin MA, Yahya TA, Al-Ghorafi MA, Abdullah JH. Lisinopril-Excipient Compatibility Studies for Advanced Drug delivery Systems Development. World Journal of Pharmaceutical Research, 2024; 13(16): 59-111.
128. Alburyhi MM, Noman MA, Saif AA, Hamidaddin MA, Yahya TA, Al-Ghorafi MA. Rosuvastatin-Excipient Compatibility Studies for Advanced Drug delivery Systems Development. World Journal of Pharmaceutical Research, 2024; 13(13): 1549-1582.
129. Alburyhi MM, Noman MA, Saif AA, Al-Ghorafi MA, Yahya TA, Yassin SH, Al Khawlani MA. Diclofenac-Excipient Compatibility Studies for Advanced Drug delivery Systems Development. World Journal of Pharmaceutical Research, 2024; 13(14): 1297-1333.
130. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Aloe Vera Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Controlling Diabetes. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(4): 1408-1423.
131. Hamidaddin MA, Alburyhi MM, Noman MA, Saif AA. Formulation and Evaluation of Rosuvastatin Fast Dissolving Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2023; 12(9): 2293-2303.
132. Saif AA, Alburyhi MM, Noman MA, Almaktari AM. Formulation and Evaluation of Trimetazidine Hydrochloride and Clopidogrel Bisulphate Multi-Unit Solid Dosage Forms. Journal of Chemical Pharm Research, 2014; 6(2): 421-426.
133. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Curcuma Longa Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Cancer. European Journal of Biomedical and Pharmaceutical Sciences, 2024; 11(6): 37-43.
134. Alburyhi MM, Saif AA, Noman MA, Al Ghoury AA. Formulation and Evaluation of Antimalarial Drugs Suppositories. World Journal of Pharmaceutical Research, 2023; 12(20): 89-108.
135. Alburyhi MM, Saif AA, Noman MA, Salim YA, Hamidaddin MA. Formulation and Evaluation of Lisinopril Orally Disintegrating Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2023; 12(9): 357-369.
136. Alburyhi MM, Saif AA, Noman MA. Stability Study of Six Brands of Amoxicillin Trihydrate and Clavulanic Acid Oral Suspension Present in Yemen Markets. Journal of Chemical Pharm Research, 2013; 5(5): 293-296.

137. Alburyhi MM, Saif AA, Saif RM. Preformulation Study of Ceftriaxone and Ciprofloxacin for Lipid Based Drug Delivery Systems. EJUA-BA, 2022; 3(4): 339-350.
138. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Tribulus Terrestris Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Controlling Diabetes. World Journal of Pharmaceutical Research, 2024; 13(7): 1264-1282.
139. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Antitumor Activity of Artemisia Arborescence Extract Capsules as Dietary Supplement Herbal Product Against Breast Cancer. World Journal of Pharmaceutical Research, 2024; 13(3): 95-114.
140. Alburyhi MM, Hamidaddin MA, Saif AA, Noman MA. Formulation and Evaluation of Rivaroxaban Orodispersible Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(2): 2066-2092.
141. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Aloe Vera Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Cancer. World Journal of Pharmaceutical Research, 2024; 13(8): 1052-1072.
142. Alburyhi MM, Noman MA, Saif AA, Al-Ghorafi MA, Al Khawlani MA, Yahya TA. Formulation and Evaluation of Anti-acne Spironolactone Emulgel Novel Trend in Topical Drug Delivery System. World Journal of Pharmaceutical Research, 2023; 12(22): 96-119.
143. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Aloe Rubroviolaceae Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Hepatoprotective. European Journal of Biomedical and Pharmaceutical Sciences, 2024; 11(4): 53-61.
144. Alburyhi MM, Saif AA, Noman MA, Hamidaddin MA. Formulation and Evaluation of Clopidogrel Orodispersible Tablets. World Journal of Pharmaceutical Research, 2024; 13(6): 42-64.
145. Alburyhi MM, Saif AA, Noman MA, Yahya TA. Formulation, Development and Evaluation of Famotidine Orodispersible Tablets. European Journal of Pharmaceutical and Medical Research, 2023; 10(10): 56-62.
146. Noman MA, Alburyhi MM, El-Shaibany A, Alwesabi NA. Preformulation and Characterization Studies of Pandanus Odoratissimus L Extract Active Ingredient in Treatment of Nocturnal Enuresis. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(2): 1603-1620.

147. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Antibacterial Orodispersible Tablets of Artemisia Arborescence Extract Herbal Product. European Journal of Pharmaceutical and Medical Research, 2024; 11(2): 409-417.
148. Alburyhi MM, Saif AA, Noman MA, Yassin SH. Formulation and Evaluation of Simvastatin Orodispersible Tablets. World Journal of Pharmaceutical Research, 2023; 12(16): 1033-1047.
149. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Oral Pharmaceutical Solution of Pandanus Odoratissimus L Extract Herbal Product in Treatment of Nocturnal Enuresis. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(1): 1840-1851.
150. Al-Ghorafi MA, Alburyhi MM. Evaluation and Formulation of Antifungal Activity of Dragon Blood Extract and Inorganic Salts on Dermatophytosis and Candidiasis. European Journal of Pharmaceutical and Medical Research, 2024; 11(1): 09-17.
151. Alburyhi MM, Saif AA, Noman MA, Saif RM. Recent Innovations of Delivery Systems for Antimicrobial Susceptibility Study of Ciprofloxacin Biodegradable Formulations for Post-Operative Infection Prophylaxis. European Journal of Pharmaceutical and Medical Research, 2023; 10(9): 32-36.
152. Alburyhi MM, Saif AA, Noman MA, Al khawlani MA. Formulation and Evaluation of Bisoprolol Fast Dissolving Tablets. World Journal of Pharmaceutical Research, 2023; 12(16): 01-10.
153. Alburyhi MM, Saif AA, Noman MA, Al-Ghorafi MA. Comparative Study of Certain Commercially Available Brands of Paracetamol Tablets in Sana'a City, Yemen. European Journal of Pharmaceutical and Medical Research, 2018; 5(12): 36-42.
154. Saif AA, Alburyhi MM, Noman MA. Evaluation of Vitamin and Mineral Tablets and Capsules in Yemen Market. Journal of Chemical Pharm Research, 2013; 5(9): 15-26.
155. Patel PA, Ahir K, Patel VB et al. Drug-Excipient Compatibility Studies: First Step for Dosage form Development. Pharm Innov, 2015; 4: 14-20.
156. Panakanti R, Narang AS. Impact of Excipient Interactions on Drug Bioavailability from Solid Dosage Forms. Pharm Res Dordr, 2012; 29: 2639-2659.
157. Da Silveiraa LM, Fiorota AB, Xaviera TP, et al. Drug-Excipient Compatibility Assessment of Solid Formulations Containing Meloxicam. Eur J Pharm Sci, 2018; 112: 146-151.
158. Cortese F, Gesualdo M, Cortese A, et al. Rosuvastatin: Beyond the Cholesterol-Lowering Effect. Pharm Res-Dordr, 2016; 107: 1-18.

159. McTaggart F. Comparative Pharmacology of Rosuvastatin. Atherosclerosis Supp, 2003; 4: 9-14.
160. Mishra A, Sinha VR, Sharma S, et al. Molecular and Qualitative Characterization of Compatibility Between Valacyclovir Hydrochloride and Excipients as Raw Materials for Development of Solid Oral Dosage Formulation. Am J Biopharmacy Pharm Sci, 2023.
161. Berthomieu C, Hienerwadel R. Fourier Transform Infrared (FTIR) Spectroscopy. Photosynth Res, 2009; 101: 157-170.
162. Krishna BJ, Satyanarayana J, Rao NR. Rivaroxaban: Compatibility with Pharmaceutical Excipients using DSC and FTIR Spectrophotometry. J Pharm Res Int, 2022; 43-50.
163. Bele AA, Khale A. An Overview on Thin Layer Chromatography. Int J Pharm Pharm Sci, 2011; 6: 256-267.
164. Iqubal MK, Singh PK, Shuaib M, et al. Recent Advances in Direct Compression Technique for Pharmaceutical Tablet Formulation. Int J Pharm Res Develop, 2014; 6: 49-57.
165. Chavan H, Chhabra G, Gujarathi N, et al. Comparative Study of in-Process and Finished Products Quality Control Test for Tablet and Capsules According to Pharmacopoeias. Asian J Pharm Res Develop, 2018; 6: 60-68.
166. Bozal-Palabiyik B, Uslu B, Ozkan Y, et al. In-Vitro Drug Dissolution Studies in Medicinal Compounds. Curr Med Chem, 2018; 25: 4020-4036.
167. Jain P, Goel A, Sharma S, Parmar M. Solubility Enhancement Techniques with Special Emphasis on Hydrotrophy. International Journal of Pharmaceutical Research, 2009; 1(1): 34-45.
168. Patil S K, Wagh K S, Parik V B, Akarte A M, Baviskar D T. Strategies for Solubility Enhancement of Poorly Soluble Drugs, Int J Pharm Sci Rev Res, 2011; 8(2): 74-80.
169. Tyagi S, Patel C, Dadrwal P, MangukiaD, Sojitra I, NimbiwalBk, Sigh V, Subrahmanyamkv. Anovel Concept for Solubilization and Bioavailability of Poorly Soluble Drugs: Hydrotropy. Int J Pharmes and Bio Sci, 2013; 2(1): 372-381.
170. Aulton's Pharmaceutics: Pharmaceutics-the Science of Dosage Forms Design. Churchill Livingstone Elsevier. 3rd Edition, 2007; 322-538.
171. Jagtap S, Magdum C, Jadge D, Rajesh Jagtap R. Solubility Enhancement Technique: A Review Published by Journal of Pharmaceutical Sciences & Research, 2018; 10(9): 2205-2211.

172. Chavda HV, Patel CN, Anand IS. A Review Article on Biopharmaceutics Classification System: Published by Systematic Reviews in Pharmacy, January-June, 2010; 1(1).
173. Shukla AK, et al. Review Article on Biopharmaceutical Classification System: Tool Based Prediction for Drug Dosage Formulation, Advance Pharmaceutical Journal, 2017; 2(6): 204-209.
174. Verma S, Rawat A, Kaul M, Saini S. Solid Dispersion: A Strategy for Solubility Enhancement. Int J Pharm Technol, 2011; 3: 1062-99.
175. Vidya N. Remington the Science & Practice of Pharmacy 21st Edition Volume 1st Lippincott Williams & Wilkins. International Journal of Pharmaceutical Sciences and Research, 2016; 7(12): 4882-4892.
176. Lindenberg M, Kopp S, Dressman J. Classification of orally administered drugs on the WHO model list of essential medicines according to biopharmaceutical classification system. European Journal of Pharmaceutics & Biopharmaceutics, 2004; 58(2): 265-278.
177. Jatwani S, Rana AC, Singh G, Aggarwal G. An Overview on Solubility Enhancement Techniques for Poorly Soluble Drugs and Solid Dispersion as an Eminent Strategic Approach. International Journal of Pharmaceutical Sciences and Research, 2012; 3(4): 942-956.
178. Thorat YS, Gonjari ID, Hosmani AH. Solubility Enhancement Techniques: A Review on Conventional and Novel Approaches. International Journal of Pharmaceutical Sciences and Research, 2011; 2(10): 2501-2513.
179. Pokharkar V, Khanna A, Venkatpurwar V, Dhar S, Mandpe L. Ternary Complexation of Carvedilol, β-Cyclodextrin and Citric acid for Mouth-Dissolving Tablet Formulation. Acta pharmaceutica, 2009; 59(2): 121-132.
180. Wells J. Pharmaceutical Preformulation, the Physiochemical Properties of Drug Substances in: M. E. Aulton (Ed), Pharmaceutics-the Science of Dosage Forms Design. 2nd Ed. Churchill LivingStone, CN, London, 2002; 113-138.
181. www.drugbank.com.
182. Patel VP, Soniwala MM. Pulsatile Drug Delivery System for Treatment of Various Inflammatory Disorders: A Review. International Journal of Drug Development and Research, 2012; 4(3).
183. Sandeep P, Venkateswara Reddy B, Navaneetha K. Formulation and Evaluation of Rosuvastatin Pulsatile Drug Delivery System by Using Press Coating Technique. Int J Res Pharm Sci, 2014; 5(1): 46-52.

184. Garg BK, Gnanarajan G, Kothiyal P. Formulation and Evaluation of Pulsatile Drug Delivery System of Rosuvastatin Calcium Using Different Swelling Polymers. The Pharma Innovation, 2012; 1(7).
185. Rane AB, Gattani SG, Kadam VD, Tekade AR. Formulation and Evaluation of Press Coated Tablets for Pulsatile Drug Delivery Using Hydrophilic and Hydrophobic Polymers. Chemical and Pharmaceutical Bulletin, 2009; 57(11): 1213-1217.
186. Jayasree B, Sridhar Babu G, Srikanth L. Formulation and Evaluation of Press Coated Pulsatile Delivery of Flurbiprofen Tablets. International Journal of Innovative Research in Technology, 2021; 8(3).
187. Giri S, Mohapatra S. Formulation and InVitro Characterization of Time Release Tablets of Propranolol Hydrochloride. Indian Journal of Pharmaceutical Sciences, 2020; 82(2): 216-221.
188. Kumar PJ, Muzib YI, Misra G. Formulation and Evaluation of Pulsatile Drug Delivery of Lovastatin. Research Journal of Pharmacy and Technology, 2018; 11(7): 2797-2803.
189. Reddy NV, Kishore K, Kumar GV. Formulation and Evaluation of Enalapril Floating Pulsatile Tablets. EPRA International Journal of Research & Development (IJRD), 2021; 6(11): 1-11.
190. Golla C. Design and Evaluation of Press Coated Pulsatile Delivery of Doxofylline Tablets. Acta Scientific Pharmaceutical Sciences, 2018; 2(11): 58- 62.
191. Borgaonkar PA, Bushetti SS, Najmuddin M. Formulation and Evaluation of Pulsatile Drug Delivery System of Metoprolol Tartrate Using Core in Cup Tablet. American Journal of Medicine and Medical Sciences, 2012; 2(6): 114-122.
192. Adhikari C, Kulkarni GS, Swamy S. Formulation and Evaluation of Pulsatile Drug Delivery System of Salbutamol Sulfate for the Chronotherapy of Asthma. Asian J Pharm Clin Res, 2018; 11(9): 305-311.
193. Gupta MK, Saraf S. Formulation and Evaluation of Pulsatile Drug Delivery System of Ramipril for Controlling Morning Spate of BP. Journal of Pharmaceutical Research, 2018; 17(1): 2-12.
194. Rambabu S, Vallabhbhai P. Formulation and Optimization of Press-Coated Pulsatile Tablet of Felodipine by Chronopharmaceutical Approach in Treatment of Hypertension. International Journal of Pharmacy and Pharmaceutical Research, 2015; 4(2): 2349-7203.

195. Kumar B, Shah M, Kumar R. Comparison of Atorvastatin and Rosuvastatin in Reduction of Inflammatory Biomarkers in Patients with Acute Coronary Syndrome. Cureus, 2019; 11: e4898.
196. Shekhawat P, Pokharker V. Understanding Peroral Absorption: Regulatory Aspects and Contemporary Approaches to Tackling Solubility and Permeability Hurdles. Acta Pharma Sin B, 2017; 7: 260-280.
197. Rohini P, Pavani A, Raja Reddy R. Formulation and Evaluation of Orally Disintegrating Tablets of Rosuvastatin. Int J Pharm Sci Rev Res, 2014; 24: 209-214.
198. Karaźniewicz-Łada M, Bąba K, Dolatowski F. The Polymorphism of Statins and its Effect on Their Physicochemical Properties. Polim Med, 2018; 48: 77–82.
199. Tannebaum EJ. Oral Solid Dosage Facilities. in: Good Design Practices for GMP Pharmaceutical Facilities, 2nd Ed.; New York, NY, USA, 2005.
200. Lee B.J. Pharmaceutical Preformulation: Physicochemical Properties of Excipients and Powders and Tablet Characterization. in: Pharmaceutical Manufacturing Handbook: Production and Processes, John Wiley & Sons Inc: New Jersey, USA, 2008.
201. Narang AS, Mantri RV, Ragahavan KS. Excipient Compatibility and Functionality. in: Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice, 2nd Ed.; Elsevier Inc: London, 2017.
202. Sachin TV, Deodhar MN, Prakya V. Advances in Analytical Techniques Used in Predicting Drug-Excipient Interactions. Int J Pharm Tech, 2014; 6: 6388-6417.
203. Rameshbai M, Manikkath J, Sivkumar K. Long Circulating PEGylated-Chitosan Nanoparticles of Rosuvastatin Calcium: Development and InVitro and In Vivo Evaluations. Int J Biol Macromol, 2018; 107: 2190-2200.
204. Davies P. Oral Solid Dosage Form. in: Pharmacetuical Preformulation and Formulation, 2nd Ed., Gibson M, Ed. Informa HealthCare: New York, NY, USA, 2009.
205. Creekmore JR, Wiggins NA. Pharmaceutical Composition Comprising an HMG COA Reductase Inhibitor. European Patent Office. Patent No. EP1223918, 2002.
206. Singh J, Walia M, Harikumar S. Formulation and Evaluation of Fast Dissolving Tablets of Rosuvastatin: Research Article. Journal of Drug Delivery & Therapeutics. JDDT, 2014; 4: 173-81.
207. Kiss D, Zelko R, Novak C. Application of DSC and NIRS to Study the Compatibility of Metronidazole with Different Pharmaceutical Excipients. J Therm Anal Calorim, 2006; 84: 447-451.

208. Chamarthi, RP, Kishore GV, Krishna Mohan. Structural Identification, and Estimation of Rosuvastatin Calcium Related Impurities in Rosuvastatin Calcium Tablet Dosage Form. Anal Chem Research, 2017; 12: 17-27.
209. Schwartz JB. Scale Up of the Compaction and Tableting process. in Pharmaceutical Process Scale Up; Marcel Dekker Inc.: New York, NY, USA, 2002.
210. Zhou C, Gao W, Lu G. Preparation, Characterization, and InVitro Release of Microparticles Based on Dextran-Rosuvastatin Conjugate. Carbohydrate Polymers, 2013; 96: 156–162.
211. Chaves L, Rolim L, Gonc¸alves M, Couto A. Study of Stability and Drug-Excipient Compatibility of DiethylCarbamazine Citrate. Journal of Thermal Analysis and Calorimetry, 2013; 111: 2179–2186.
212. Hariharan M, Gupta VK. A Novel Compression Coated Tablet Dosage Form. Pharm Tech, 2001; 14–19.
213. Akbari BV, Valaki BP, Maradiya VH Akbari AK, Vidyasagar G. Development and Evaluation of Oral Dispersible Tablets of Rosuvastatin Calcium-HP-β- CD Inclusion Complex by Using Different Superdisintegrants. Int J Pharm Technol, 2011; 3(1): 1842-1859.
214. Leon La Sreenivas SA, Dangagi PM, Gadad AP, Godbole AM, Hiremath SP, Bhagawati ST. Orodispersible tablets: Newfangled Drug Delivery System-A Review. Indian J Pharm Educ, 2005; 39(4): 177-181.
215. ICH Guidelines Q1A (R2), Guidelines for Industry, Stability Testing of New Drug Substance and Product. Availale online: http://www.ICH.org.
216. Cao QR, Kim TB, Lee JB. Photoimages and the Release Characteristics of Lipophilic Matrix Tablets Containing Highly Water-Soluble Potassium Citrate with High Drug Loadings. Int J Pharm, 2007; 339: 19–24.
217. Corti G, Cirri M, Maestrelli F, Mennini N. Sustained-Release Matrix Tablets of Metformin Hydrochloride in Combination with Triacetyl-B-Cyclodextrin. European Journal of Pharmaceutics and Biopharmaceutics, 2008; 68: 303–309.
218. Furlanetto S, Cirri, M, Maestrelli F, Corti G, Mura P. Study of Formulation Variables Influencing the Drug Release Rate from Matrix Tablets by Experimental Design Pharm Tech, 2006; 62: 77–84.
219. Masaki A, Sayaka K, Yuichi O, Yukiharu N. Development and Evaluation of a Novel Dry-Coated Tablet Technology for Pellets as a Substitute for the Conventional

Encapsulation Technology. International Journal of Pharmaceutics, 2004; 336,1: 99–107.

220. Holte K, Onsøyen E, Myrvold R, Karlsen J. Sustained Release of Water-Soluble Drug from Directly Compressed Alginate Tablets, E. J of Pharmaceutical Sciences, 2003; 20: 403–407.
221. Jeong HS, Park K. Development of Sustained Release Fast-Disintegrating Tablets Using Various Polymer Coated Ion-Exchange Resin Complexes. Int J Phar, 2008; 353: 195–204.
222. Indian Pharmacopoeia, The Indian Pharmacopoeia Commission, Ghaziabad, 6th Ed, 2010; 2: 806, 1337, 2071.
223. Martindale. The Extra Pharmacopoeia, The Complete Drug Reference, edited by Sean C Sweetman, Pharmaceutical press, 2005; 34, 862, 915, 966, 968: 996-997.
224. Herbert A Lieberman, Leon Lachman, Joseph B, Schwartz. Pharmaceutical dosage forms tablets. Marcel Dekker, New York, USA, 2009; 2.
225. Leon Lachman, Lieberman H A. The Theory and Practice of Industrial Pharmacy, Lea and Febiger, Philadelphia, USA, 2003; 3.
226. Markl D, Zeitler JA. A Review of Disintegration Mechanisms and Measurement Techniques, Pharmaceutical research, 2017; 34(5): 890.
227. Seo KS, Bajracharya R, Lee SH, Han HK. Pharmaceutical Application of Tablet Film Coating, Pharmaceutics, 2020; 12(9): 853-862.
228. Aboghanem A, Alburyhi MM, Noman MA. Effect of Different Excipients on Formulation of Immediate Release Artemether/Lumefantrine Tablets. Journal of Chemical Pharm Research, 2013; 5(11): 617-625.
229. Alburyhi MM, Saif AA, Noman MA, Saeed SA, Al-Ghorafi MA. Formulation and Evaluation of Diclofenac Orodispersible Tablets. European Journal of Pharmaceutical and Medical Research, 2023; 10(9): 01-06.
230. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Dictyota Dichotoma Extract Medicinal Seaweed Capsules Delivery System as an Advanced Phytotherapy Approach for Cancer. European Journal of Biomedical and Pharmaceutical Sciences, 2024; 11(4): 63-70.
231. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Celery Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Gout. World Journal of Pharmaceutical Research, 2024; 13(11): 2383-2404.

232. Raweh SM, Noman MA, Alburyhi MM, Saif AA. Formulation and Evaluation of Anti-acne Gel of Azadirachta Indica Extract Herbal Product. European Journal of Pharmaceutical and Medical Research, 2024; 11(2): 427-433.
233. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Acalypha Fruticosa Extract Tablets Delivery System as an Advanced Phytotherapy Approach for Controlling Diabetes. World Journal of Pharmaceutical Research, 2024; 13(8): 1073-1091.
234. Al-Ghorafi MA, Alburyhi MM. Formulation and Evaluation of Novel Antiaging Cream Containing Dragon's Blood Extract. European Journal of Pharmaceutical and Medical Research, 2024; 11(1): 239-244.
235. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Pandanus Odoratissimus Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Hepatoprotective. European Journal of Pharmaceutical and Medical Research, 2024; 11(4): 06-13.
236. Noman MA, Alburyhi MM, Alqubati MA. Preformulation and Characterization Studies of Clopidogrel Active Ingredient for Orodispersible Tablets Development. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(3): 996-1015.
237. Noman MA, Alburyhi MM, El-Shaibany A, Alwesabi NA. Formulation and Evaluation of Pandanus Odoratissimus L Extract for Treatment of Nocturnal Enuresis as Orodispersible Tablets Delivery System. World Journal of Pharmaceutical Research, 2024; 13(5): 56-71.
238. Alburyhi MM, Saif AA, Noman MA. Formulation and Evaluation of Ticagrelor Orodispersible Tablets. World Journal of Pharmaceutical Research, 2024; 13(5): 26-55.
239. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Tribulus Terrestris Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Kidney Stones. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(5): 1425-1443.
240. Alburyhi MM, Noman MA, Saif AA, Salim YA, Abdullah JH. Formulation and Evaluation of Domperidone Orodispersible Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(3): 49-68.
241. Alburyhi MM, Saif AA, Noman MA, Yahya TA, Al-Ghorafi MA. Formulation and Evaluation of Drotaverine Orally Disintegrating Tablets. World Journal of Pharmaceutical Research, 2023; 12(18): 66-79.

242. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Effervescent Granules of Artemisia Arborescence Herbal Product for Foodborne Illness. World Journal of Pharmacy and Pharmaceutical Sciences, 2023; 12(12): 1429-1444.
243. Alburyhi MM, Saif AA, Noman MA, Saif RM. Recent Innovations of Delivery Systems for Antimicrobial Susceptibility Study of Ceftriaxone Biodegradable Formulations for Post-Operative Infection Prophylaxis. European Journal of Pharmaceutical and Medical Research, 2023; 10(8): 95-99.
244. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Anti-peptic Ulcer Capsules of Curcuma Longa Herbal Product. World Journal of Pharmaceutical Research, 2023; 12(22): 76-96.
245. Patel D, Patel U, Shukla M, Bhimani B, Patel G. Formulation and Evaluation of Immediate Release Tablet of Simvastatin. Research Journal of Pharmacy and Technology, 2020; 13(1): 421-224.
246. Patel MA, Pingale PL. High Functionality Coprocessed Excipients: A Review. World J Pharm Sci, 2014; 3(3): 795-806.
247. World Health Organization. Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials, Good Manufacturing Practices and Inspection, 2007.
248. Sreenivas S A, Gadad AP, Patil MB. Formulation and Evaluation of Ondansetron Hydrochloride Directly Compressed Mouth Disintegrating Tablets. Indian Drug, 2006; 43: 35-37.
249. Mishra B, Panigrahi D. Mouth Dissolving Tablets an Overview of Preparation Techniques, Evaluation and Patented Technologies', Indian Journal of Pharmaceutical Sciences, 2005.
250. Martindale: The Complete Drug Reference, 37Th Edn. The Pharmaceutical Press, London, 2011.
251. Patel KN, Patel HR, Patel VA. Formulation and Characterization of Drug in Adhesive Transdermal Patches of Diclofenac Acid. Int J Pharm Sci, 2012; 4(1): 296-299.
252. Wagh MP. Formulation and Evaluation of Fast Dispersible Tablets of Aceclofenac Using Different Superdisintegrant. Int J Pharm Pharm Sci, 2010; 2(1): 154–7.
253. Debjit B, et al. Fast Dissolving Tablet: An Overview. Journal of Chemical and Pharmaceutical Research, 2009; 1(1): 163-177.
254. Mizumoto T, et al. Formulation Design of a Novel Fast Disintegrating Tablet. Int J Pharm, 2008; 306: 3- 9.

255. Nikku D Y, Prashanth P, Sagar R T. Comparative Study on Effect of Natural and Artificial Superdisintegrants in The Fast-Dissolving Aspirin Tablets. Journal of Pharmacy Research, 2010; 3(7): 1594-1597.
256. Sudarshan K Singh, Agham A Sameer. Development and Characterization of Sublingual Tablet of Lisinopril. Asian Pacific Journal of Tropical Biomedicine, 2012; S1711-S1719.
257. Panigrahi R, Chowdary KA, Mishra G, Bhowmik M. Effect of Combination of Natural Superdisintegrants on Fast Dissolving Tablets of Lisinopril. Int J Pharma Res Allied Sci, 2012; 1(3): 73-8.
258. Rajeshree P, et.al. Formulation of Fast Dissolving Tablets of Lisinopril Using Combination of Synthetic Superdisintegrants. Asian J Pharm Tech, 2012; 2(3): 94-98.
259. Malpani A, Panda B, Bhojani R. Formulation of Lisinopril Dehydrate Tablet and Study Effect of Granulation on Response Variables. Int J Pharm sci, 2009; 12: 132-39.
260. Pandey S, Goyani M. Formulation and Evaluation of Taste Masked Fast Disintegrating Tablets of Lisinopril. Int J Pharm Tech Res, 2010; 148: 1639- 43.
261. Dandagi PM, Gayakwad VM. Taste Masked Ofloxacin Mouth Disintegrating Tablets. Indian drugs, 2005; 17: 52-54.
262. Vijay S, Himanshu C. Role of Taste and Taste Masking of Bitter Drugs in Pharmaceutical Industries an Over view. Int J Pharm Sci, 2010; 74: 14-18.
263. Gohel MC. A Review of Co-processed Directly Compressible Excipients. J Pharm Sci, 2005; 102: 76- 93.
264. Suresh S, Pandit V. Preparation and Evaluation of Mouth Dissolving Tablets of Salbutamol Sulphate. Int J Pharm sci, 2007; 12: 54-57.
265. Arora V, Gupta B, Advances in direct compression technology. Pharma times, 2007; 74: 26-27.
266. Bhupendra G P, Nayan R. A Review on Recent Patents on Fast Dissolving Drug Delivery System. Pharm Tech, 2009; 1(3): 790- 798.
267. Bhavanam, Pamula R. Formulation and Evaluation of Levofloxacin Using Different Types and Concentrations of Superdisintegrants. J Pharm Sci and Res, 2010; 1: 1-5.
268. Setty CM, Prasad DV, Gupta V. Development of Fast Dispersible Tablets: Effect of Functionality of Superdisintegrants. Ind J Pharma Sci, 2008; 180- 185.
269. Chakraborty S, Khandai M, Singh PS. Comparative Study of Effect of Natural and Synthetic Superdisintegrants in Formulation of Fast Dissolving Tablets. Int J Green Pharmacy, 2008; 2(1): 22-28.

270. Nitin M, Adhikrao Y, Vaishali K. Novel Approaches in Development of Metronidazole Orodispersible Tablets. Res J Pharm Tech, 2009; 44: 283-86.