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FUROSEMIDE-EXCIPIENT COMPATIBILITY STUDIES FOR ADVANCED DRUG DELIVERY SYSTEMS DEVELOPMENT

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ABSTRACT

Furosemide is a potent loop diuretic that acts on the kidneys to ultimately increase water loss from the body. It is an anthranilic acid derivative. Furosemide is used for edema secondary to various clinical conditions, such as congestive heart failure exacerbation, liver failure, renal failure, and high blood pressure. The main objective of the present study was to the preformulation studies were performed to know the development of formulation and evaluation of Furosemide Orodispersible Tablets to improve the bioavailability of Furosemide. 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 Furosemide present in Orodispersible Tablets Delivery System ODTs. Preformulation, formulation and evaluation of Furosemide to avoid problems associated with conventional delivery system and one of the most recent antihypertensive agents. 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 Furosemide and various excipients such as MCC as diluent, and sodium starch glycolate, crospovidone as superdisintegrants and sodium lauryl sulfate as wetting agent were evaluated for preformulation studies parameters. It was

concluded that the drug Furosemide was found to be compatible with various excipients which were selected for the formulation development of the Furosemide 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: Furosemide, 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 Furosemide -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.

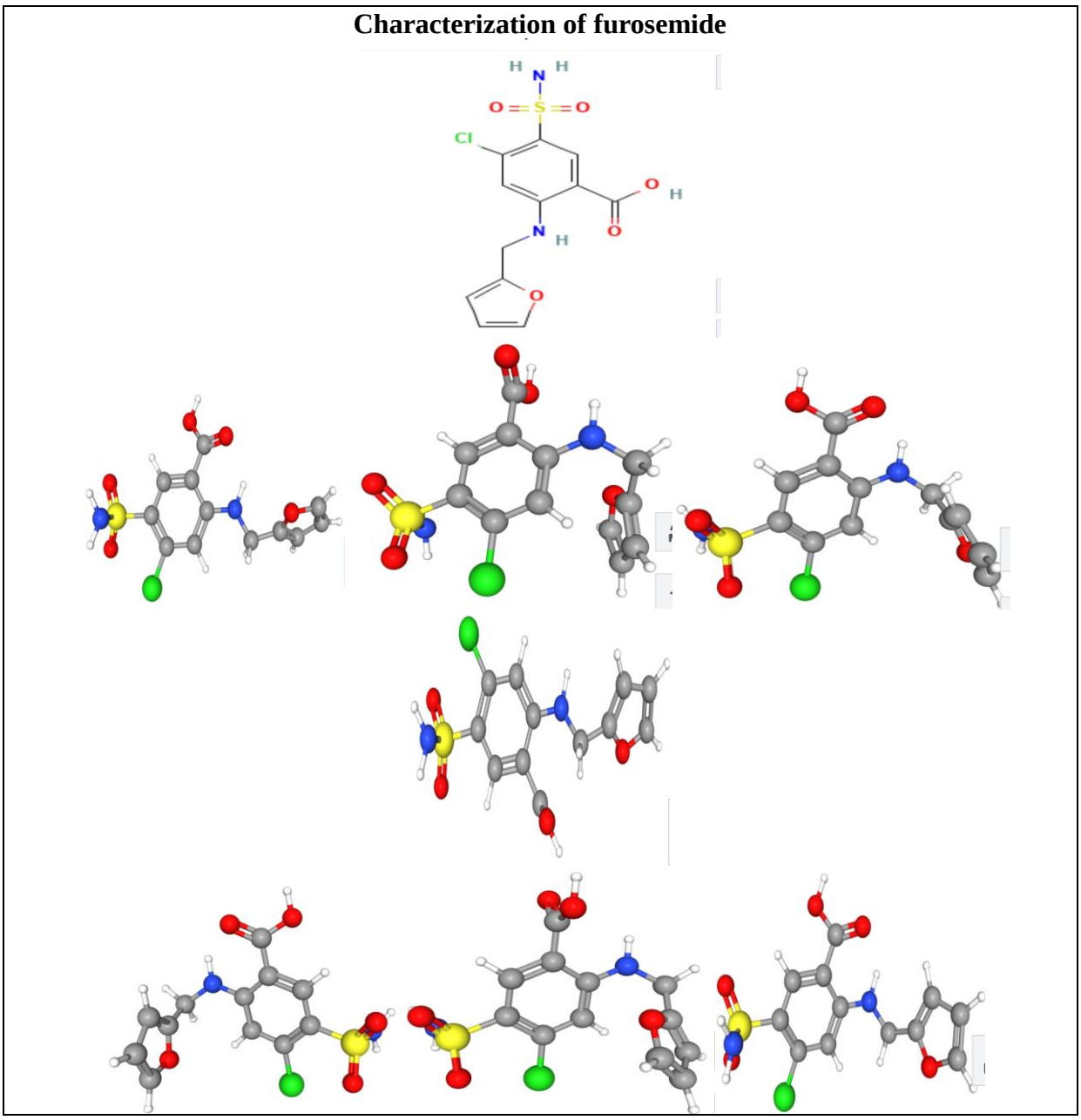
MATERIALS AND METHODS

Furosemide was obtained as a gift from (Biopharm Pharmaceutical Industry Company-Yemen). While Crospovidone**,** Microcrystalline Cellulose, Sodium Starch Glycolate**,** Magnesium Stearate**,** Sodium Lauryl Sulfate (SLS)**,** Aspartame and other materials were obtained as a gift from (Shaphaco Pharmaceutical Industry Company-Yemen).

Evaluation of Drug-Excipient Compatibility Studies Methods[45-255]

Table 1: Furosemide data.

Characterization of furosemide



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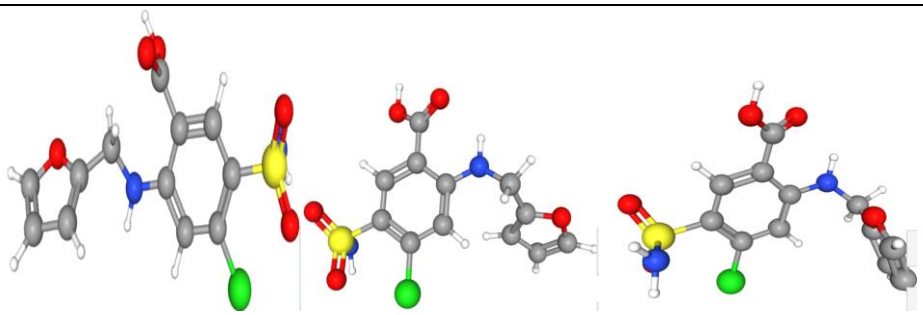
<tr><td colspan="4"> 
Furosemide Structure and 3D Conformer</td></tr>
<tr><td>Chemical Structure</td><td>5-(Aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)-amino]-benzoic acid</td><td>Appearance</td><td>Is White or slightly yellow Solid-crystals Solid-powder</td></tr>
<tr><td>Chemical Formula</td><td>$C_{12}H_{11}ClN_2O_5S$</td><td>Drug Solubility</td><td>Furosemide: Practically insoluble in water; very slightly soluble in chloroform; soluble in alcohol; slightly soluble in ether; freely soluble in acetone; dimethyl formamide; methyl alcohol and solutions of alkali hydroxides.</td></tr>
<tr><td>Molecular Weight</td><td>330.77 g/mol</td><td>BCS</td><td>Class- IV Drug</td></tr>
<tr><td>Drug Action and Use</td><td colspan="3">Furosemide inhibits the luminal Na+ /K+ /2Cltransporter (NKCC2) in the TAL of Henle‟s loop. This agent reduces the reabsorption of NaCl and diminish the lumen-positive potential that comes from K+ recycling. Also, it causes an increase in Mg+2 and ca+2 excretion and the prolonged use can cause significant hypomagnesemia.
Furosemide is a diuretic. This medicine is used to rid the body of excess fluid (salt and water). Patients who frequently have this problem are ones with weakened hearts (congestive heart failure), poor kidney function, or poor liver function. It can be used to reduce blood pressure in these patients.
Furosemide is indicated for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome, in adults and pediatric patients.
Oral furosemide is indicated alone for the management of mild to moderate hypertension or severe hypertension in combination with other antihypertensive medications.
Intravenous furosemide is indicated as adjunctive therapy in acute pulmonary edema when a rapid onset of diuresis is desired.
Subcutaneous furosemide is indicated for the treatment of congestion due to fluid overload in adults with NYHA Class II/III chronic heart failure. This drug formulation is not indicated for emergency situations or in patients with acute pulmonary edema.</td></tr>
<tr><td colspan="4">Furosemide Pharmacokinetics</td></tr>
<tr><td>Drug</td><td>Following oral</td><td>Drug</td><td>Volume of distribution: he</td></tr>
</table>

Absorption	administration, furosemide is absorbed from the gastrointestinal tract. It displays variable bioavailability from oral dosage forms, ranging from 10 to 90%. The oral bioavailability of furosemide from oral tablets or oral solution is about 64% and 60%, respectively, of that from an intravenous injection of the drug	**Distribution**	volume of distribution following intravenous administration of 40 mg furosemide were 0.181 L/kg in healthy subjects and 0.140 L/kg in patients with heart failure. Protein binding: Plasma concentrations ranging from 1 to 400 mcg/mL are about 91-99% bound in healthy individuals. The unbound fraction is about 2.3-4.1% at therapeutic concentrations. Furosemide mainly binds to serum albumin
Drug Metabolism	The metabolism of furosemide occurs mainly in the kidneys and the liver, to a smaller extent. The kidneys are responsible for about 85% of total furosemide total clearance, where about 40% involves biotransformation.[5] Two major metabolites of furosemide are furosemide glucuronide, which is pharmacologically active, and saluamine (CSA) or 4-chloro-5-sulfamoylanthranilic acid.	**Drug Excretion**	The kidneys are responsible for 85% of total furosemide total clearance, where about 43% of the drug undergoes renal excretion.5 Significantly more furosemide is excreted in urine following the I.V. injection than after the tablet or oral solution. Approximately 50% of the furosemide load is excreted unchanged in urine, and the rest is metabolized into glucuronide in the kidney **Drug Clearance** Following intravenous administration of 400 mg furosemide, the plasma clearance was 1.23 mL/kg/min in patients with heart failure and 2.34 mL/kg/min in healthy subjects, respectively
The Elimination Half-Life (T1/2)	The half-life from the dose of 40 mg furosemide was 4 hours following oral administration and 4.5 hours following intravenous administration. The terminal half-life of furosemide is approximately 2 hours following parenteral	**Availability**	Available in oral solution (8 or 10 mg/ml), 12.5 mg tablets,20 mg tablets, 40 mg tablet, 50 mg tablets, 80 mg tablets (and injectable).

	administration. The terminal half-life may be increased up to 24 hours in patients with severe renal failure.		

Table 2: Pharmaceutical excipients data.

Nonproprietary Name	Chemical Name	Functional Category	Concentration%	Solubility	Incompatibilities	Notes
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
Aspartame	N-a-L-Aspartyl-L-phenylalanine 1-methyl ester	Sweetening agent. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.	The WHO has set an acceptable daily intake for aspartame at up to 40 mg/kg body-weight.	slightly soluble in ethanol (95%); sparingly soluble in water. At 20°C the solubility is 1% w/v at the isoelectric point (pH 5.2).	incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate.	Occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.
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
Sodium Lauryl Sulfate	Dodecyl alcohol hydrogen	Anionic surfactant; detergent;	10% 0.5–2.5% 1.0–2.0%	Freely soluble in water,	Incompatible with salts of polyvalent metal ions, such	White or cream to pale yellow

	sulfate, sodium salt, dodecyl sodium sulfate, dodecyl sulfate sodium salt, Elfan 240. C12H25NaO4S	emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.		giving an opalescent solution; practically insoluble in chloroform and ether.	as aluminum, lead, tin or zinc	colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances

According to Furosemide and excipients data as shown in Tables 1 and 2, it was selected that the different excipients to preformulation study with Furosemide 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

Organoleptic properties like color, odour and taste of Furosemide were studied. Color: a small amount of Furosemide was taken in paper and investigated by the eye in well-illuminated place. Taste and odour: Very small amount of Furosemide was used to assess the taste with the help of tongue as well as smelled to get odor.

Solubility analysis

Solubility of Furosemide in water, 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

Determination of λ Max for Furosemide

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

Preparation of working solutions

Furosemide solubility test is performed in buffer phosphate pH6.8.

Preparation of Phosphate Buffer pH 6.8

Dissolving 0.896 g of NaOH and 6.804 g of KH2 PO4 dissolved in sufficient quantity of water, complete volume to 1000 ml with distilled water and mixed well by sonication. Filtration of solution that contains the active ingredient, then measure the solubility under UV spectrophotometer.

UV Visible Spectrophotometer

UV Scanning of Furosemide in Phosphate Buffer pH 6.8

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

Preformulation studies

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

Melting point determination of furosemide

The most common and most basic method of determination is the capillary method. Melting point of the Furosemide 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 Furosemide 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 Furosemide 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 Furosemide in room condition as shown in Table 5.

Infrared spectral study of samples after stored two weeks

Compatibility studies were performed by preparing blend of different excipients with drug and stored at 40°C ±2°C /75±5%RH for two weeks. The blend was evaluated after two weeks 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 Furosemide and Different excipients for compatibility studies.

No	Component(s)	Amount(5mg:5mg)
1	Furosemide	1
2	Furosemide and MCC	(1:1)
3	Furosemide and SSG	(1:1)
4	Furosemide and SLS	(1:1)
5	Furosemide and Crospovidone	(1:1)
6	Furosemide and Aspartame	(1:1)
7	Furosemide and Mg. Stearate	(1:1)

Preparation of furosemide formulations

Mixing was done by using geometric mixing, in where all excipients accurately weighed then all of them except magnesium striate were blended with specified quantity of Amlodipine for 15minutes, whereas the other excipients were blended for 5 minutes and added to the former excipients. Then all formulae were passed through sieve # 18 for particle size uniformity. This method of ordering mixing of excipients with Furosemide in first sex formulae. Then each mixture has compressed directly into tablets using rotary tablet compression machine of punch size 6.25mm (7mm) to prepare tablets each weighing 150 mg after testing powder properties that will be shown in Preformulation tests as shwon in Table 6.

Table 6: Composition of Furosemide Formulations ODTs.

Ingredients	Quantity Per Tablet					
	Formulation Code					
	F1	F2	F3	F4	F5	F6
Furosemide	20	20	20	20	20	20
Microcrystalline Cellulose	115.4	115	116	116	115	115.4
Sodium Starch Glycolate	---	---	---	9	8	8.6
Crospovidone (XL)	8.6	9	8	---	---	---
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Sodium Lauryl Sulfate SLS	1.5	1.5	1.5	1.5	1.5	1.5
Aspartame	3	3	3	3	3	3

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 raztio

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 and 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 furosemide

The organoleptic properties of Furosemide were shown in Table 9.

Table 9: Organoleptic Properties of Furosemide (API).

Tests	Specification	Observation
Color	White	White
Odor	Odorless	Odorless
Taste	Tasteless	Tasteless

Physical identification of furosemide

Furosemide is white crystalline powder.

The organoleptic properties like color, odor and taste of the API were evaluated. The color of Furosemide was found to be white powder, no characteristic odor and no taste were observed in the study. Furosemide showed similar color, taste and odor.

Solubility analysis

The solubility profile of Furosemide was present in Table 10.

Table 10: Solubility Analysis of Furosemide (API).

Raw Material (API)	Solubility
Furosemide	Freely soluble in pH 6.8
	Freely soluble methanol
	Freely soluble ethanol and acetone

The solubility studies of drug (API) revealed that Furosemide was freely soluble in pH 6.8, methanol, ethanol and acetone.

Characterization of Furosemide by UV Spectroscopy

Wave length of Furosemide in phosphate buffer (pH 6.8) by UV Scanning show in Figure 1, at 276nm.

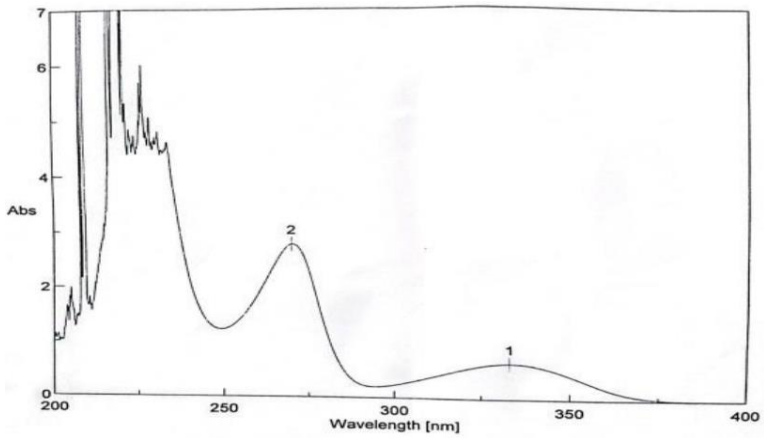


Fig. 1: UV Scanning of Furosemide in Phosphate Buffer (pH 6.8).

Melting point determination of furosemide

Melting point of pure Furosemide was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Furosemide by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath. The rise in temperature was viewed through screen. The temperature at which the drug started d melting was recorded. The melting point range of Furosemide was identical to reference melting point stated in MP (218-220°C). The sample started to melt at 219.4°C, and turned into liquid at 220°C, indicating that the sample used is pure. That reading has stated in melting point tester.as shown in Table 11.

Table 11: Results of melting point of furosemide.

Test	Temp Rang Analyzed (Melting)	Results
Test I Furosemide	(218-220°C)	220 °C
Test II Furosemide	(219.4-220°C)	220 °C

Characterization of Furosemide by FTIR

FTIR spectrum studies indicated that major functional groups present in Furosemide show characteristic peaks in IR spectrum. Figures (2) to (8) 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 Furosemide. Hence, it was confirmed that there was compatibility between drug and various excipients, thus

conforming that no interaction of drug occurred with the components of the formulation excipients.

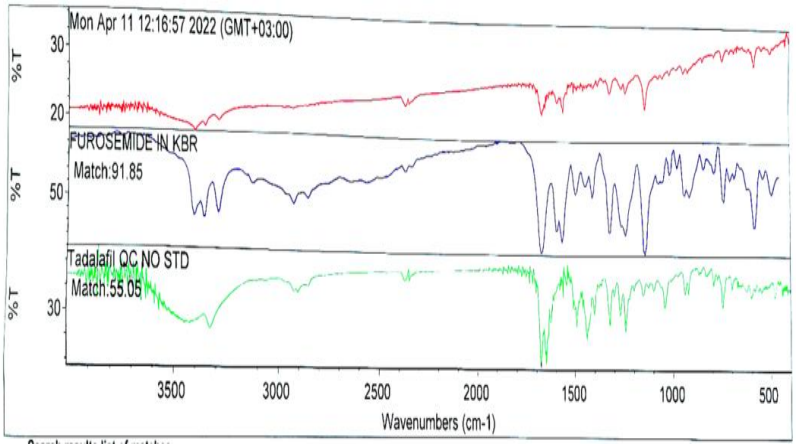


Fig. 2: FTIR Spectrum of Pure Furosemide.

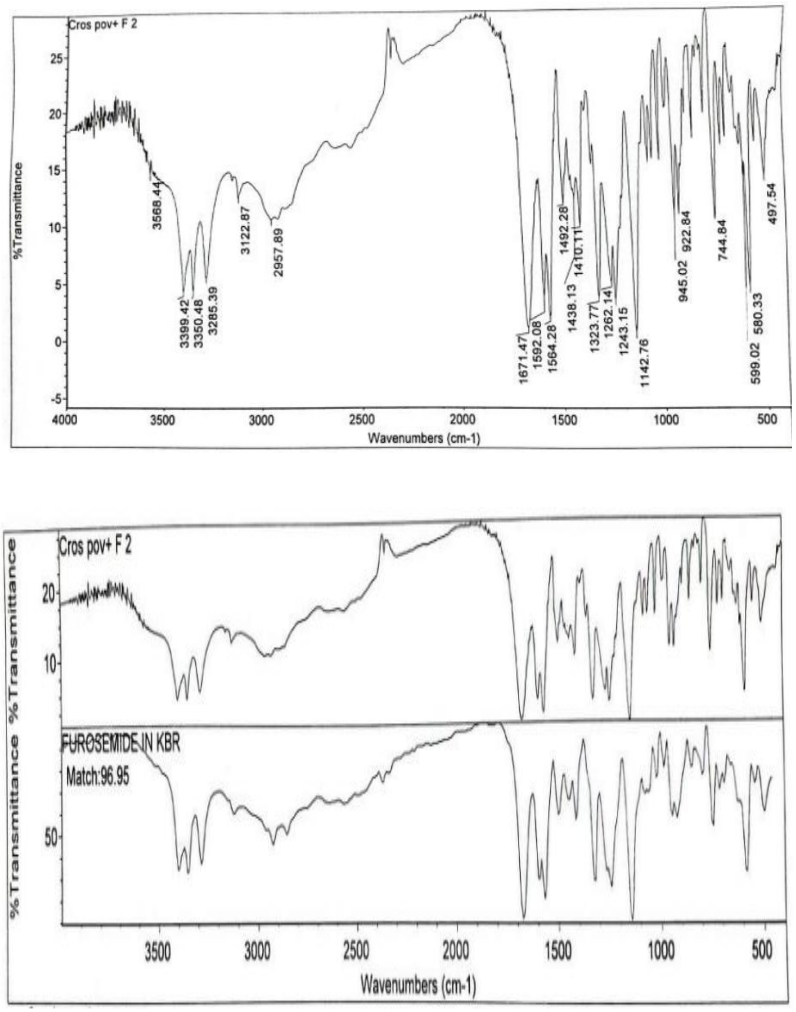


Fig. 3: FTIR Spectrum of Physical Mixture Furosemide and Crospovidone.

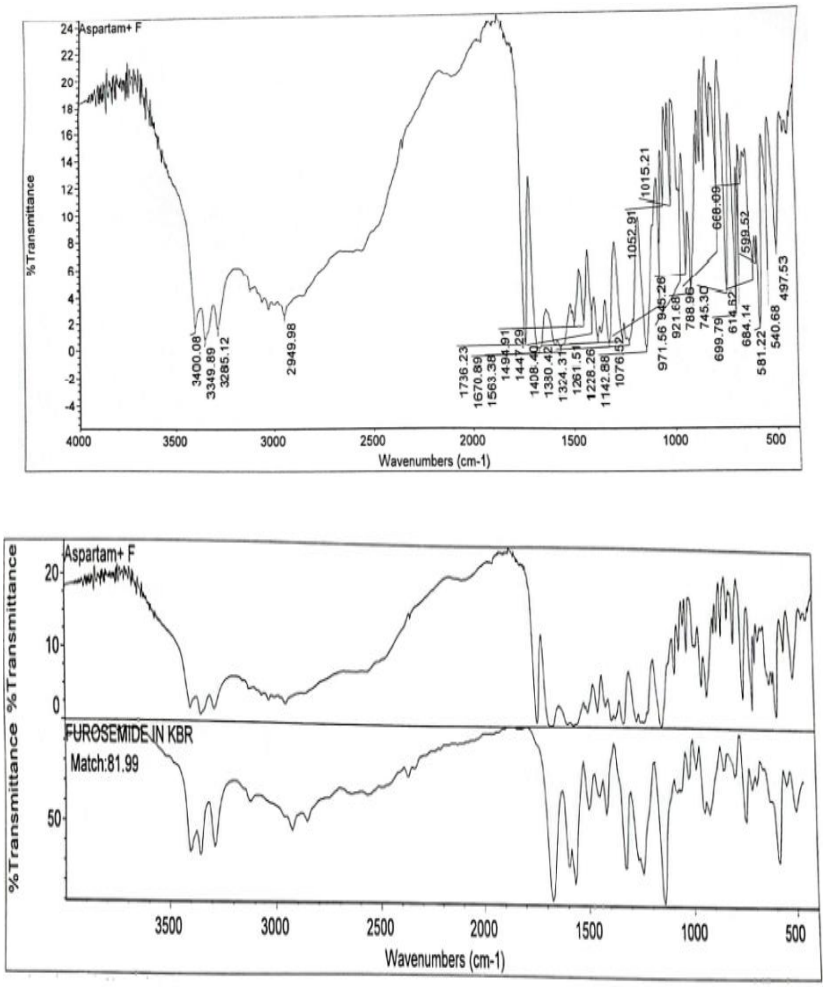
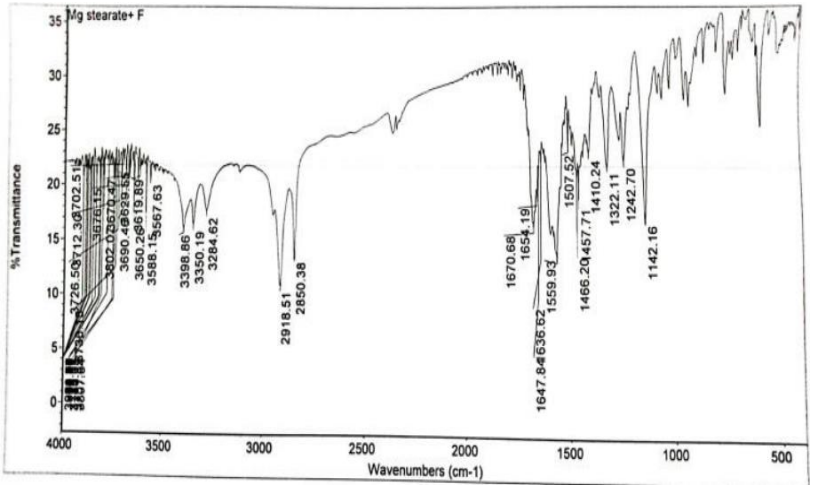


Fig. 4: FTIR Spectrum of Physical Mixture Furosemide and Aspartame.



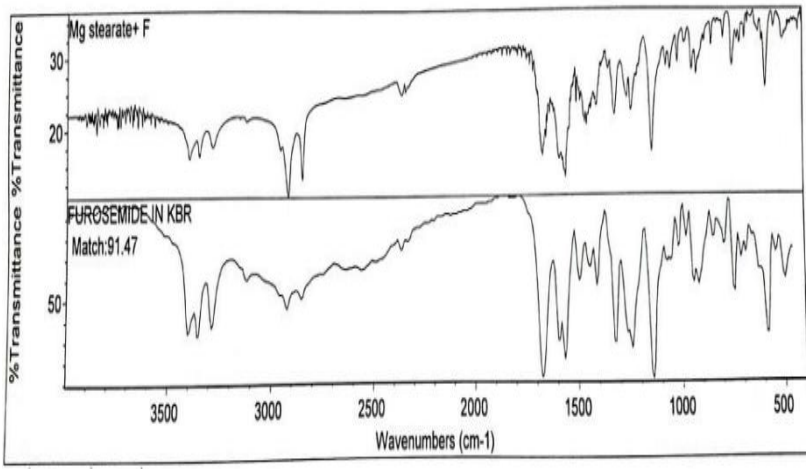


Fig. 5: FTIR Spectrum of Physical Mixture Furosemide and Mg Stearate.

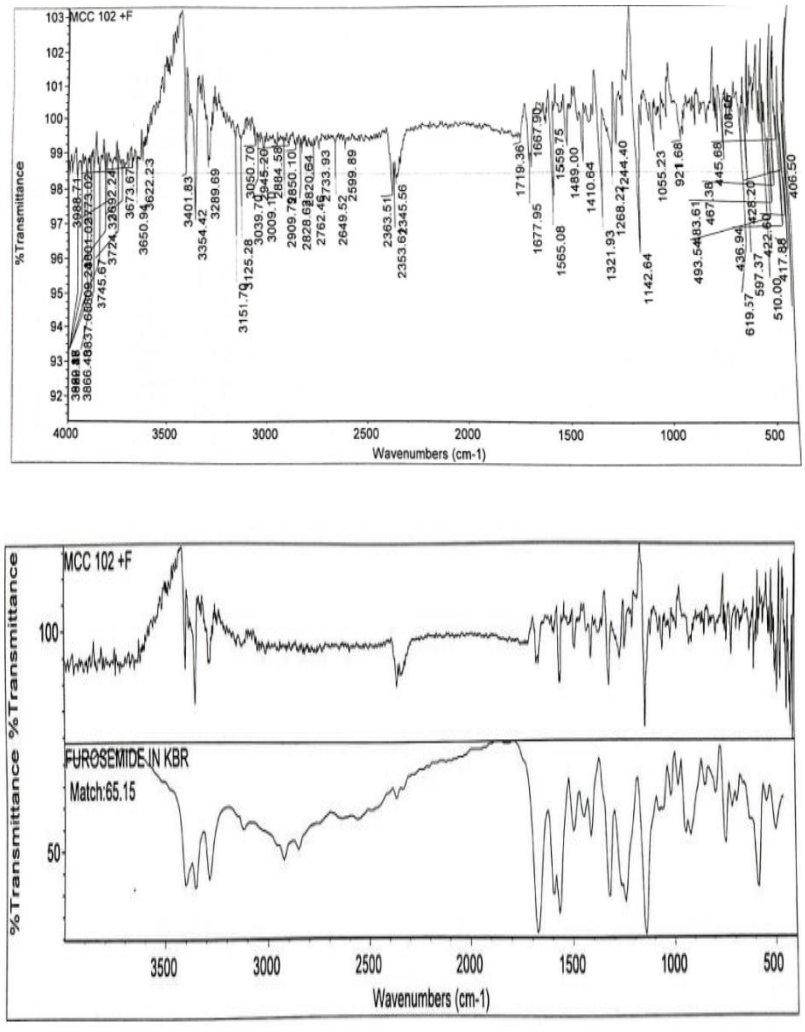


Fig. 6: FTIR Spectrum of Physical Mixture Furosemide and MCC.

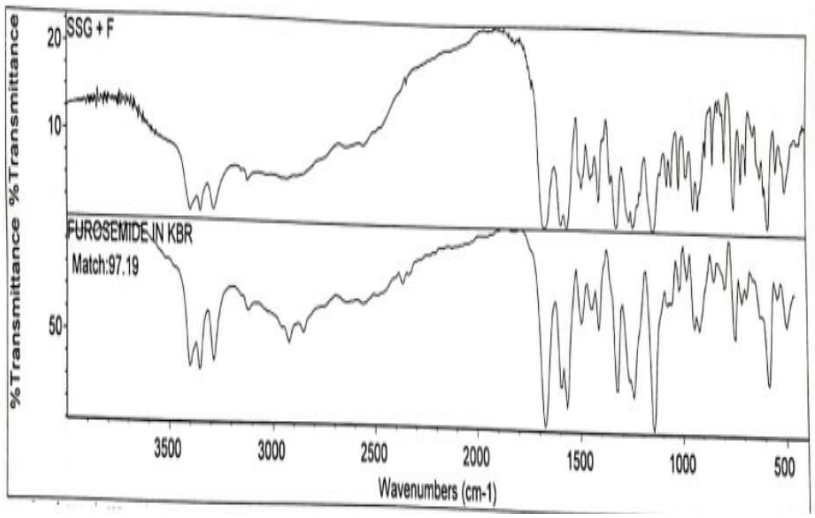
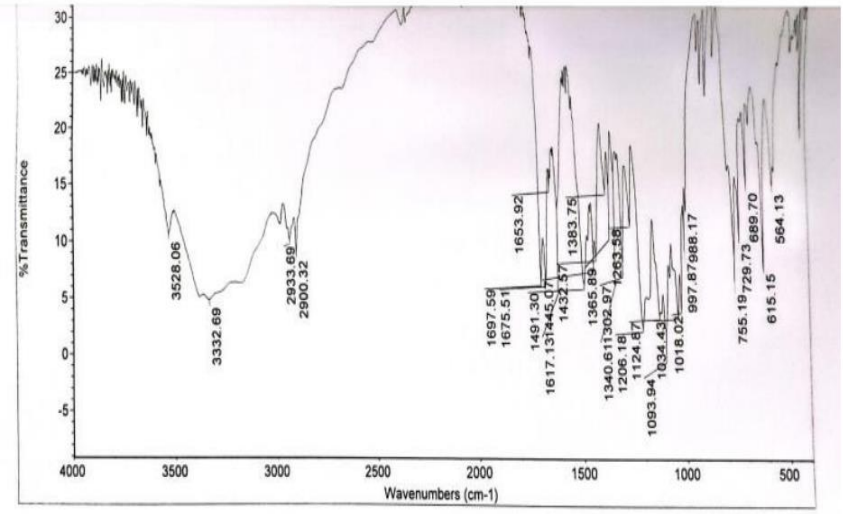


Fig. 7: FTIR Spectrum of Physical Mixture Furosemide and SSG.



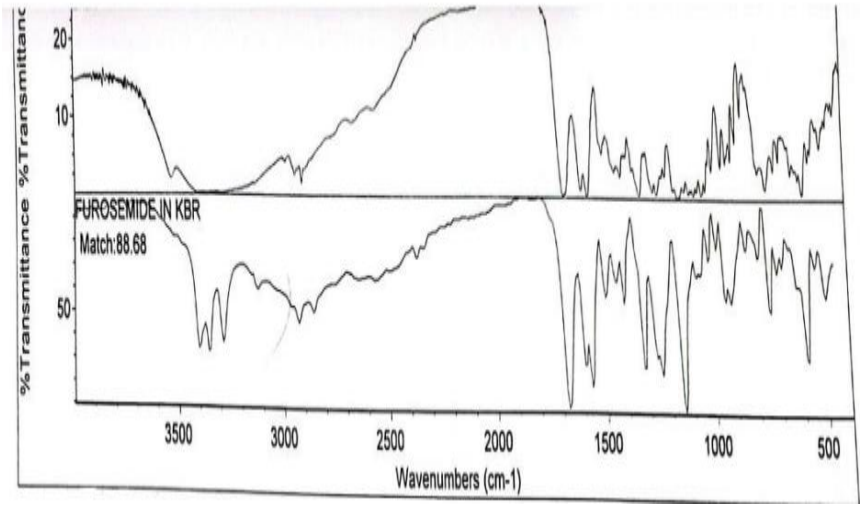


Fig. 8: FTIR Spectrum of Physical Mixture Furosemide and SLS.

Evaluation of Pre-Compression Parameters of Formulations

The powder blends were evaluated for the following parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The results were as shown in Table 12.

Table 12: Micrometric properties of formulations.

Formulation Code	Angle of Repose(θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility index (%)	Hausner's Ratio	Evaluation of Angle of Repose
F1	30.1±0.03	0.45±0.07	0.55±0.03	18.18±0.03	1.22±0.92	Good
F2	29.68±0.06	0.51±0.06	0.58±0.05	13.79±0.07	1.16±0.9	Excellent
F3	29.68±0.05	0.52±0.03	0.62±0.05	16.12±0.09	1.19±0.89	Excellent
F4	31.39±0.01	0.43±0.05	0.51±0.04	14.0±0.05	1.16±0.94	Good
F5	29.68±0.09	0.40±0.09	0.45±0.09	11.11±0.05	1.12±0.84	Excellent
F6	33.42±0.07	0.43±0.08	0.52±0.04	17.3±0.06	1.12±0.95	Good

The angle of repose of formulation F1, F4 and F6 was found to be 30.1 to 33.42 which indicates good flow property. Angle of repose of all the other formulations were found to be 29.68 which indicates excellent flow property. The bulk density was found to be between 0.40 to 0.52 g/cm^3, the tapped density was found to be between 0.45 to 0.62 g/cm^3, the compressibility index for F2, F4 and F5 was found in the range of 11.11 to 14% which indicates good flow property while other formulations were fair. And the Hauser's ratio of formulation F2, F4, F5 and F6 lies between 1.12 to 1.16 which indicates good flow property while other formulations were fair. The above results in terms of micromeritics properties revealed that the flow property of formulation F2 and F5 was Excellent and F4 was good while other formulations were fair.

CONCLUSION

The compatibility studies of physical mixtures of Furosemide with different used excipients such as MCC as diluent, and sodium starch glycolate, 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 Furosemide formulations prepared were evaluated for precompression parameters and powder flow properties which were found to be within limits. It was concluded that the drug Furosemide was found to be compatible with various excipients which were selected for the formulation development of the Furosemide 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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