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DICLOFENAC-EXCIPIENT COMPATIBILITY STUDIES FOR ADVANCED DRUG DELIVERY SYSTEMS DEVELOPMENT

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ABSTRACT

Diclofenac is a non-steroidal anti-inflammatory drug used to treat mild to moderate pain and inflammation. It is commonly prescribed to treat various types of arthritis and pain or inflammation post-surgery. Diclofenac is poorly water soluble and the mean drug half-life in plasma is approximately 2 hours after oral doses. 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 aim of the present study was to the preformulation studies were performed to know the physicochemical and mechanical properties of Diclofenac for Orodispersible tablets ODTs. The drug-excipient compatibility studies were conducted to characterize the drug Diclofenac present in Orodispersible tablets Drug Delivery System

ODDs. Preformulation, formulation and evaluate of Diclofenac to avoid problems associated with conventional delivery system such as limited permeation, low dissolution and also to improve bioavailability and to treat various types of pain or inflammation. In the present study that the compatibility was assessed by, FTIR spectroscopy, and melting point apparatus. Results showed that physical mixtures of Diclofenac and various excipients such as mannitol, microcrystalline cellulose, lactose anhydrous, pregelatinized starch, as diluents, and sodium starch glycolate, croscarmellose sodium, and crospovidone as superdisintegrants and citric acid anhydrous, HPMC were investigated by FTIR it was detected that there was no variation or minor deviation in the characteristic peaks in FTIR spectroscopy. The Diclofenac formulations precompression were evaluated which were found to be within limits. It was concluded that the drug Diclofenac was found to be compatible with various excipients which were selected for the formulation development of the Diclofenac ODTs. Formulation scientist from his experience and knowledge have to significantly in the preformulation study and is an important factor in the ADDS product development process.

KEYWORDS: Diclofenac, Compatibility, Excipients, Development, Preformulation, Formulation.

INTRODUCTION

Compatibility studies[1-110]

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.

Preformulation study includes

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 are 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 such as colour, odour, taste of the new drug must be recorded as shown in Table 1, changes in dissolution performance, decrease in potency, and increase in degradation rate etc.

Table 1: Organoleptic Properties.

Colour	Odour	Taste
Acidic	Pungent	Off-White
Bitter	Sulphurous	Cream Yellow
Bland	Fruity	Tan
Intense	Aromatic	Shiny
Sweet	Odourless	-----
Tasteless	-----	-----

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

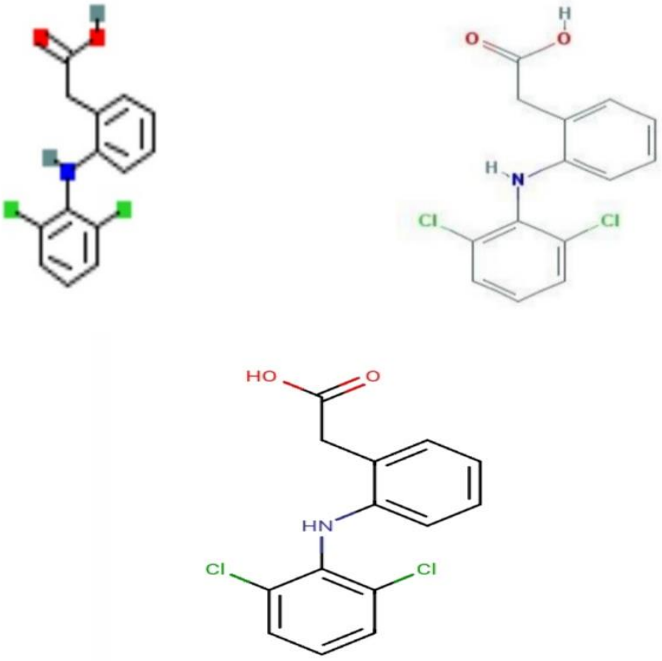
In the present study, it was proposed to drug-excipient compatibility studies of Diclofenac, with commonly different excipients using for development of formulation ODTs.

MATERIALS AND METHODS

Diclofenac Acid was obtained as a gift from (Shaphaco Pharmaceutical Industry Company-Yemen). While Mannitol, Microcrystalline Cellulose (Avicel), Croscarmellose Sodium , Crospovidone, Sucralose, Peppermint Flavor Powder, Lactose Anhydrous , Citric Acid Anhydrous, Colloidal Silicon Dioxide (Areosil), Magnesium Stearate , Sodium Starch Glycolate, Hydroxy Propyl Methyl Cellulose , Xylitol , Pregelatinized Starch, Methanol, Ethanol, HCl, Buffer Solutions, and other materials, were obtained as a gift from (Modern Pharmaceutical Company -Yemen).

Evaluation of Drug–Excipient Compatibility Study Methods[50-179]

Table 2: Diclofenac data.

Characterization of diclofenac acid			
 **Diclofenac acid structure**			
Category	Non-Steroidal Anti-inflammatory Drug	**Appearance**	Crystals from ether-petroleum ether
Chemical Structure	2-[2-(2,6-dichloroanilino)phenyl]acetic acid	**UVmax**	283nm (methanol) 276nm (phosphate buffer, pH7.2)
Chemical Formula	C14H11Cl2NO2	**Solubility**	In water 2.37 mg/L (at 25 °C) a poorly water-soluble drug
Molecular Weight	296.15 g/mol	**pH**	2.7
BCS	Class-II Drug	**pKa**	4.15
Action and use	The primary mechanism of Diclofenac (NSAID) is responsible for its anti-inflammatory, antipyretic, and analgesic action is thought to be inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX). Therapeutic uses: Osteoarthritis, Rheumatoid arthritis, Low back pain, Dental pain, Gynaecological pain, Inflammation and pain in conditions of ear, nose and throat infection.	**Melting point**	156-158 °C (DrugBank) 283- 285°C (HSDB)

Pharmacokinetics of Diclofenac			
Absorption	Rapidly absorbed after oral administration and the bioavailability is about 100% and Peak plasma concentrations (6.8-8.9 mg/L) are reached approximately 1 to 2h. due to first-pass metabolism, one reason for preparation of fast dissolving diclofenac is that only about 50% of the absorbed dose is systemically available. When diclofenac free acid Extended-release Tablets are taken with food, there is a delay of 1 to 2 hours in the Tmax and a two-fold increase in Cmax values. The extent of absorption of diclofenac, however, is not significantly affected by food intake.	**Distribution**	The apparent volume of distribution (V/F) of diclofenac is 0.04 L/kg. diclofenac is more than 99.7% bound to human serum proteins, primarily to albumin. Highly protein-bound (>99.7%). The volume of distribution is about 25 Liter.
Metabolism	Metabolized by CYP2C9 pathway to the main metabolite 4-hydroxyDiclofenac. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy- and 3'-hydroxy-Diclofenac. In patients with renal dysfunction, peak concentrations of metabolites 4'-hydroxyand 5-hydroxy-Diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects.	**Excretion**	The mean plasma elimination half-life is 2h, approximately 60-70% of drug excreted by renal route (urine) as glucuronide of diclofenac and 30% in feces. Clearance has a plasma clearance 16L/h.
The Elimination Half-Life (t1/2)	Half-Life: 2 hr.	**Availability**	Tablets: 50 mg, 75 mg, 100mg. Parenterals, Suppositores, Gel, Powder.

Table 3: Pharmaceutical excipients data.

Nonproprietary Name	Chemical Name	Functional Category	Concentration%	Solubility	Incompatibilities	Notes
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
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%	It gives a translucent suspension in water	incompatible with ascorbic acid.	Very hygroscopic
Microcrystalline Cellulose (Avicel PH)	Cellulose	Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.	5–20% 20–90%	Practically insoluble in water	incompatible with strong oxidizing agents.	Crystalline powder
Mannitol (Emprove)	Mannitol	Diluent, plasticizer, sweetening agent, tablet	10–90%	Freely soluble in water	incompatible with may be salted out by potassium	Crystalline powder

		and capsule diluent, therapeutic agent, tonicity agent.			chloride or sodium chloride. Sodium cephapirin. xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.	
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
Sucralose (SucraPlus)	,6-Dichloro-1,6-dideoxy-b-D-fructofuranosyl-4-chloro-4-deoxya-D-galactopyranoside	Sweetening agent.	0.03–0.24%	Freely soluble in water	---	Crystalline powder
Lactose Anhydrous (Anhydrous Lactose)	O-b-D-Galactopyranosyl-(1!4)-b-D-glucopyranose]	Directly compressible tablet excipient, dry powder inhaler carrier, lyophilization aid, tablet and capsule diluent, tablet and capsule filler.	widely used in pharmaceutical formulations	Soluble in water	incompatible with strong oxidizers. When mixtures containing a hydrophobic leukotriene antagonist. -hydrolysis of the ester and amidine groups.	white to off-white crystalline particles or powder.

Hydroxy Propyl Methyl Cellulose	Hydroxy Propyl Methyl Cellulose C3H7O*	As a stabilizer, as an emulsifier, as a protective colloid, and as a thickener.	widely used in oral and topical pharmaceutical products.	Soluble in water(50mg/ml) clear to very faintly turbid.	Incompatible with some oxidizing agents. Will not complex with metallic salts or ionic organics to form insoluble precipitates.	Powder-white to cream
Colloidal Silicon Dioxide (Aerosil)	Silica. SiO2	Adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent.	0.1–1.0% 2.0–10.0% widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient.	Practically insoluble in organic solvents, water. -hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system.	Incompatible with diethylstilbestrol preparations	a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.
Citric Acid Anhydrous (Acidum citricum)	2-Hydroxy-1,2,3-propanetricarboxylic acid	Acidifying agent, antioxidant, buffering	0.1–2.0 0.3–2.0	Soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part	Citric acid is incompatible with potassium tartrate, alkali	Translucent crystals, or as a white crystalline,

		agent, chelating agent, flavor enhancer, preservative.		of water; sparingly soluble in ether.	and alkaline earth carbonates and bicarbonates, acetates, and sulfides. Incompatibilities also include oxidizing agents, bases, reducing agents, and nitrates. It is potentially explosive in combination with metal nitrates.	efflorescent powder
Copovidone (Povidone K30) (Polyvinylpyrrolidone)	Acetic acid ethenyl ester, polymer with 1-ethenyl-2-pyrrolidinone	Film-forming agent, granulation aid, tablet binder.	2.0–5.0	Greater than 10% solubility in water, methanol, PG….	Copovidone is compatible with most organic and inorganic pharmaceutical ingredients.	white to yellowish-white amorphous powder.
Menthol (Peppermint Flavor)	1RS,2RS, 5RS)-()-5-Methyl-2-(1-methylethyl) cyclohexanol	Flavoring agent, therapeutic agent.	0.005–0.015 0.05–10.0	very slightly soluble in glycerin, practically insoluble in water.	Incompatible with: butylchloral hydrate, camphor; chloral hydrate, chromium trioxide, b-naphthol, phenol, potassium permanganate, pyrogallol,	a free-flowing or agglomerated crystalline powder,

					resorcinol, and thymol.	
Pregelatinized Starch		Binding agent; compression aid; disintegrant; tablet and capsule diluent; tablet and capsule filler.		Insoluble in water		white free-flowing powder.
Xylitol (Klinit)	xylo-Pentane-1, 2,3,4,5-pento	Coating agent; diluent; emollient; humectant; sweetening agent; tablet and capsule diluent; tablet filler	Xylitol solutions are employed in tablet-coating applications at concentrations in excess of 65% w/w.	Water 1 in 1.6	incompatible with oxidizing agents.	white, granular solid comprising crystalline

According to Diclofenac acid and excipients data as shown in Tables 2and 3, it was selected that the different excipients to preformulation study with Diclofenac in present study.

Table 4: The Equipment's Used.

Sr. No.	Equipment's
1	Fourier Transform Infrared Spectrophotometer
2	UV/VIS Spectrophotometer
3	Melting Point Tester
4	Moisture Tester
5	Density Tester
6	Digital pH Meter
7	Electronic Balance

Determination of the organoleptic properties of drug

The organoleptic properties of the drug substance were assessed: physical appearance, for Diclofenac sample was inspected and studied by visual inspection.

pH Determination

This was done by shaking a 1% w/v dispersion of the API sample in water for 5min and the pH determination using a digital pH meter.

Determination of solubility

Quantitative solubility

Quantitative solubility analysis of drugs was done by 5 ml each solvent and drug in gm(s) into the solvent till saturation of solvent. Different solvents were used for the solubility determination like methanol, distilled water, phosphate buffer (pH 7.4), Phosphate buffer (pH 6.8), HCl (0.1N). This is done to determine the capacity of the solvent for dissolving the drug in it. The concentration of drug is measured by UV spectrophotometer**.**

UV-Visible Spectrophotometric Method

UV-Visible Spectrophotometrically Study

Weighed 10 mg of Diclofenac and dissolved in 10 ml of pH 6.8 phosphate buffer solution (1000µg/ml). From this solution 1ml was taken and diluted to 10ml with phosphate buffer solution to get a solution containing 100µg/ml. From this 1ml was diluted to 10ml to get working standard solutions of 10µg/ml. This solution was scanned between 200-400 nm and an absorption maximum was determined.

Preparation of Calibration Curve in Phosphate Buffer (pH 6.8)

Weighed 10 mg of Diclofenac and dissolved in 10 ml of pH 6.8 phosphate buffer solution (1000µg/ml). From this solution 0.5 ml, 1ml, 2ml, 3ml, 4 ml, 5ml was taken and diluted up to 100ml using pH 6.8 phosphate buffer solution to obtain a working standard solution of 5- 50 µg/ml. The prepared concentrations were analyzed in UV-Visible spectroscopy at 276nm.

Linearity and Calibration

The linearity of the calibration curve was estimated by plotting the graph in between absorbance (nm) (y) versus concentration (µg/ml) (x) of Diclofenac in the concentration range 5-50 µg/ml. A calibration curve was prepared by measure the absorbance at 276nm. The Statistical evaluation parameter like as the slope, intercept, regression coefficient, standard deviation (R^2), and relative standard deviation were determined.

UV Spectrophotometric Studies

The absorbance maximum was found to be 276nm in phosphate buffer pH 6.8. Spectrophotometric method of USP was used for estimation of Diclofenac. The method is based on the measurement of absorbance at 276nm in phosphate buffer of pH 6.8.

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

Melting point of API sample was determined by using melting point apparatus. A few quantities of API sample were taken and placed in a thin-walled capillary tube; the tube was approximately 10-12 cm in length with 1mm in diameter and closed at one end. The capillary which contains API sample was placed in melting point apparatus and heated and when API sample was melted the melting point of API sample powder was recorded.

Drug-Excipient compatibility studies

A physical mixture including API and excipient was created in a 1:1 ratio, and it was subjected to analytical techniques such as FTIR spectroscopy. FTIR, of both pure API 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 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 Diclofenac 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.

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

Sr. No	Component(s)	Amount(5mg:5mg)
1	Diclofenac	1
2	Diclofenac and Crospovidone	(1:1)
3	Diclofenac and SSG	(1:1)
4	Diclofenac and HPMC	(1:1)
5	Diclofenac and MCC	(1:1)
6	Diclofenac and Citric Acid Anhydrous	(1:1)
7	Diclofenac and Peppermint Flavor	(1:1)
8	Diclofenac and Sucralose	(1:1)
9	Diclofenac and Colloidal Silicon Dioxide	(1:1)
10	Diclofenac and CCS	(1:1)
11	Diclofenac and Mannitol	(1:1)
12	Diclofenac and Pregelatinized Starch	(1:1)
13	Diclofenac and Mg. Stearate	(1:1)

14	Diclofenac and Povidone K30	(1:1)
15	Diclofenac and Lactose Anhydrous	(1:1)
16	Diclofenac and Xylitol	(1:1)

Preparation of diclofenac formulations

Formula (F1) consist of croscarmellose and crospovidone as superdisintegrants, mannitol as sweeting and cooling agent, sucralose as sweeting agent, colloidal silicon dioxide (Aerosil) as glidant, magnesium stearate as lubricant and anti-adherence, microcrystalline cellulose as diluent, Peppermint as flavoring agent were used. Formula (F2) consist of xylitol was used as sweeting, cooling agent and Pregelatinized starch as diluent and disintegrant as shown in Tables 6,7and 8**.**

Table 6: Ingredients Used in The Preparation of F1 and F2 Diclofenac Acid Formulations.

No	Ingredients	F1	F2
		Percentage %	Percentage %
1	Diclofenac Free Acid	23.57%	23.57%
2	Croscarmellose Sodium	10%	6 %
3	Crospovidone	6%	10 %
4	Microcrystalline Cellulose	20.73%	---
5	Mannitol	30%	---
6	Pregelatinized Starch	---	17.93 %
7	Sucralose	5%	7.50 %
8	Xylitol	---	30%
9	Colloidal Silicon Dioxide	1.70 %	1.50%
10	Magnesium Stearate	1 %	0.75 %
11	Citric Acid Anhydrous	---	0.75%
12	Peppermint Flavor	2%	2%
	Total	100 %	100 %

Formula (F3) consist of microcrystalline cellulose and hydroxy propyl methyl cellulose as diluent agent and citric acid anhydrous. Formula (F4) consist of lactose anhydrous were used as diluent and citric acid anhydrous.

Table 7: Ingredients Used in The Preparation of F3 and F4 Diclofenac Acid Formulations.

No	Ingredients	F3	F4
		Percentage %	Percentage %
1	Diclofenac Free Acid	23.57 %	23.57%
2	Croscarmellose Sodium	10%	12.50 %
3	Crospovidone	7%	6 %
4	Mannitol	20%	18%

5	Lactose Anhydrous	---	27.43 %
6	Hydroxy Propyl Methyl Cellulose	26.93 %	---
7	Sucralose	7.50 %	5.70 %
8	Colloidal Silicon Dioxide	1.50 %	1.50 %
9	Magnesium Stearate	0.75%	0.75 %
10	Citric Acid Anhydrous	0.75 %	0.75 %
11	Peppermint Flavor	2%	2%
	Total	100 %	100%

Formula (F5) consist of sodium starch glycolate was added as superdisintegrant, and citric acid. Formula (F6) consist of lactose anhydrous and povidone k30.

Table 8: Ingredients Used in The Preparation of F5 and F6 Diclofenac Acid Formulations.

No	Ingredients	F5	F6
		Percentage %	Percentage %
1	Diclofenac Free Acid	23.57%	23.57%
2	Croscarmellose Sodium	11%	10%
3	Crospovidone	---	8.50 %
4	Sodium Starch Glycolate	6%	---
5	Microcrystalline Cellulose	34.43 %	---
6	Mannitol	12.50 %	10%
7	Lactose Anhydrous	---	15%
8	Hydroxy Propyl Methyl Cellulose	---	19.68 %
9	Sucralose	7.50 %	7.50 %
10	Colloidal Silicon Dioxide	1.50 %	1.50 %
11	Magnesium Stearate	0.75 %	0.75 %
12	Citric Acid Anhydrous	0.75 %	---
13	Povidone K30	---	1.50 %
14	Peppermint Flavor	2%	2%
	Total	100%	100 %

Evaluation of Pre-Compression Formulations

By used the FTIR spectra for formulations.

RESULTS AND DISCUSSION

Characterization of Diclofenac

The important objective for characterization of Diclofenac is to know identity, purity, and characteristic of the drug. Diclofenac was identified and its purity assessed using a variety of analytical methods, including FTIR, UV-Visible spectroscopy and melting point apparatus.

Physical identification of diclofenac

Organoleptic properties of the drug sample were found to be white powder, crystalline in nature, slightly bitter in taste and odourless.

pH Determination

The data presented here is for triplicate determinations was found to be pH 2.6.

Determination of solubility

Results of solubility of the drug in different solvents was found to be 10.50 mg/mL, at 37 °C in Phosphate buffer (pH 6.8), while 50.80 µg/mL, at 37 °C in distilled water.

UV Spectrophotometric Studies

The absorbance maximum was found to be 276nm in phosphate buffer pH 6.8.

Preparation of Calibration Curve in Phosphate Buffer (pH 6.8)

The linearity of the calibration curve was estimated by plotting the graph in between absorbance (nm) (y) versus concentration (µg/ml) (x) of Diclofenac in the concentration range 5-50 µg/ml. A calibration curve was prepared by measure the absorbance at 276 nm.

Melting point determination

Melting point of drug was found to be 157 °C, which is well within the range of literature specification, 156-158 °C indicating the identity and purity of drug sample as Diclofenac as shown in Table 9.

Table 9: Melting point results of diclofenac.

Test	Temp Rang Analyzed (Melting)	Results
Test I Diclofenac	(156-158°C)	157 °C
Test II Diclofenac	(156-158°C)	157 °C

Characterization of Diclofenac by FTIR

Spectrophotometry FTIR spectra of pure Diclofenac was recorded on an IR Spectrophotometer. The FTIR spectrum of pure Diclofenac showed an absorption band at reveals certain characteristic peaks at 3220 cm^{-1}, 2962.30 cm^{-1}, 1780.41 cm^{-1}, 1464.70 cm^{-1}, and 770.15 cm^{-1}, as shown in Figures 1,2.

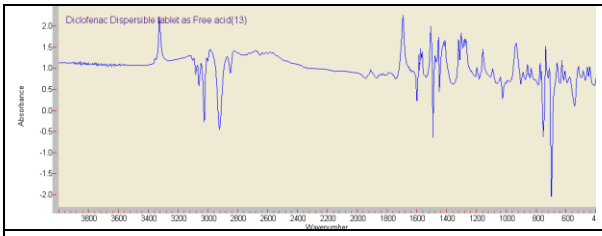


Fig. 1: FT-IR Spectrum of Diclofenac Free Acid.

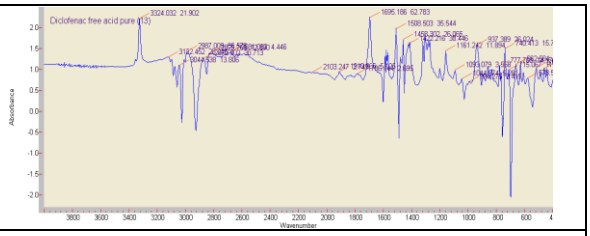


Fig. 2: FT-IR Spectrum of Pure Diclofenac Acid.

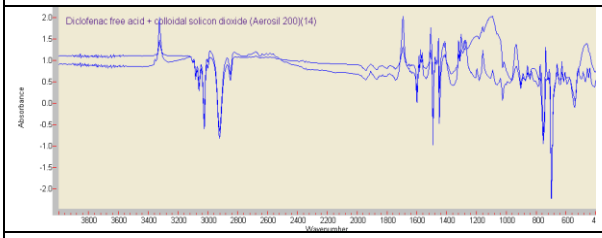


Fig. 3: FT-IR Spectrum of Diclofenac and Aerosil.

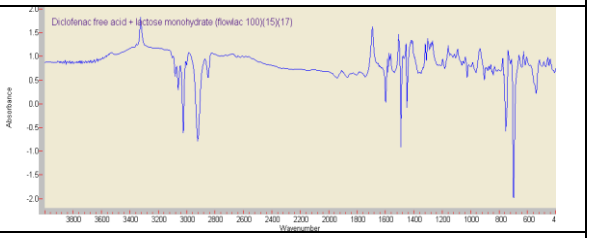


Fig. 4: FT-IR Spectrum of Diclofenac and Lactose Anhydrous.

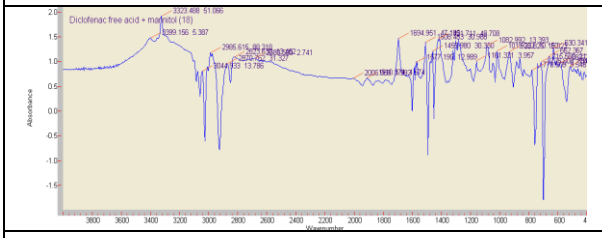


Fig. 5: FT-IR Spectrum of Diclofenac and Mannitol.

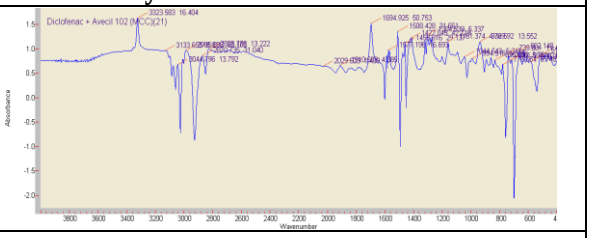


Fig. 6: FT-IR Spectrum of Diclofenac and MCC.

Fig. 7: FT-IR Spectrum of Diclofenac and CCS.

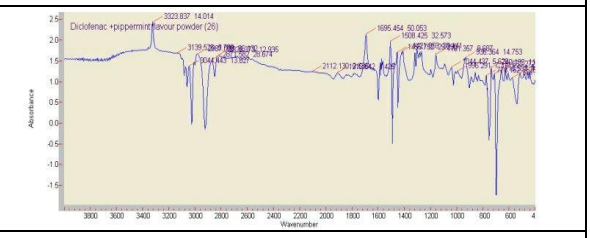


Fig. 8: FT-IR Spectrum of Diclofenac and Peppermint Flavor.

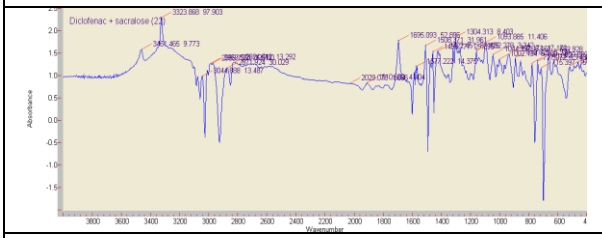


Fig. 9: FT-IR Spectrum of Diclofenac and Sucralose.

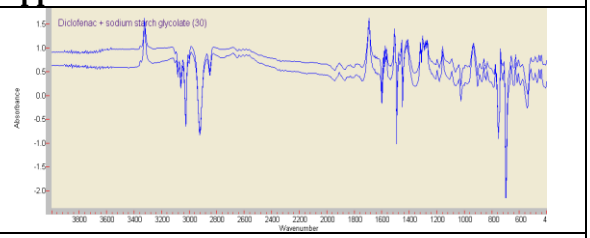


Fig. 10: FT-IR Spectrum of Diclofenac and SSG.

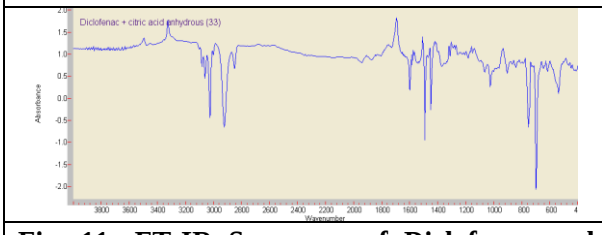


Fig. 11: FT-IR Spectrum of Diclofenac and Citric Acid Anhydrous.

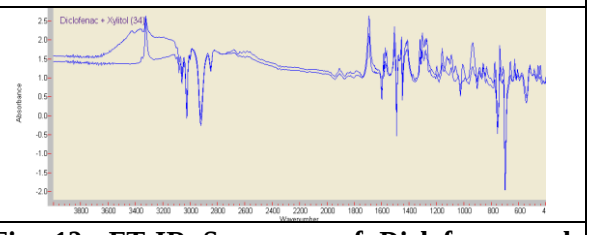


Fig. 12: FT-IR Spectrum of Diclofenac and Xylitol.

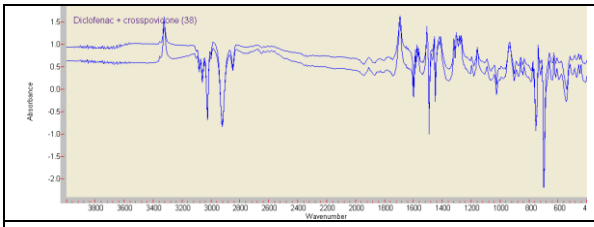


Fig. 13: FT-IR Spectrum of Diclofenac and Crospovidone.

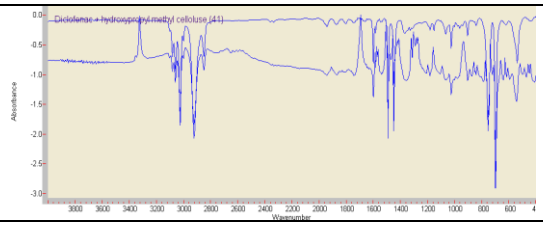


Fig. 14: FT-IR Spectrum of Diclofenac and HPMC.

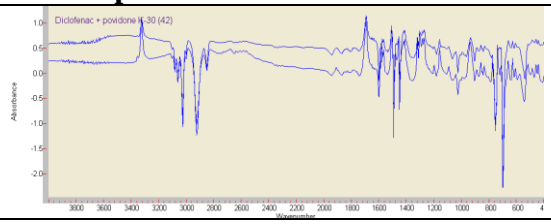


Fig. 15: FT-IR Spectrum of Diclofenac and PVP K30.

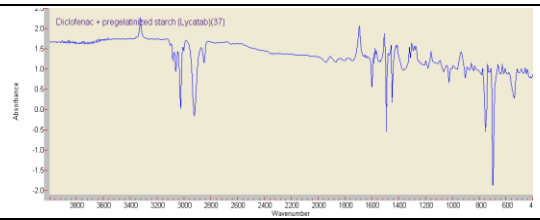


Fig. 16: FT-IR Spectrum of Diclofenac and Pregelatinized Starch.

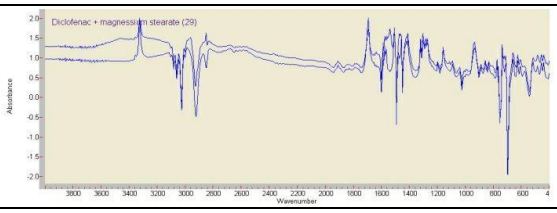


Fig. 17: FT-IR Spectrum of Diclofenac and Mg. Stearate.

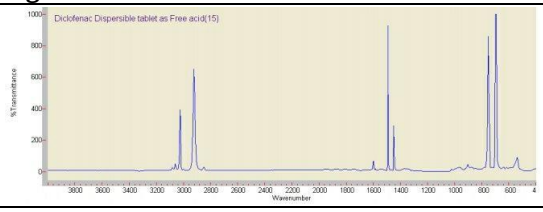


Fig. 18: FT-IR Spectrum of Diclofenac Acid.

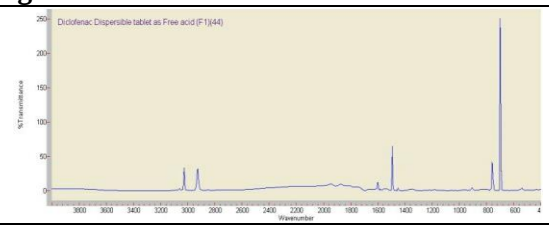


Fig. 19: FT-IR Spectrum of Diclofenac Acid F1.

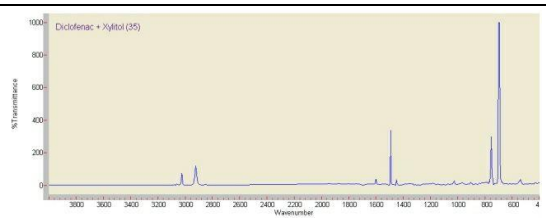


Fig. 20: FT-IR Spectrum of Diclofenac Acid F2.

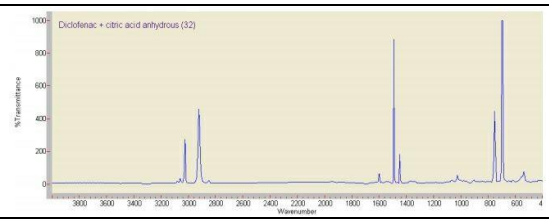


Fig. 21: FT-IR Spectrum of Diclofenac Acid F3.

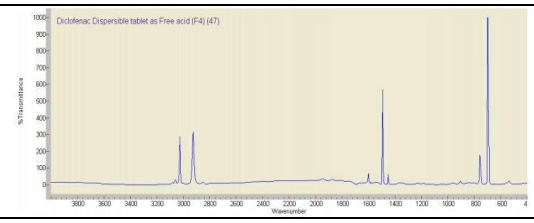


Fig. 22: FT-IR Spectrum of Diclofenac Acid F4.

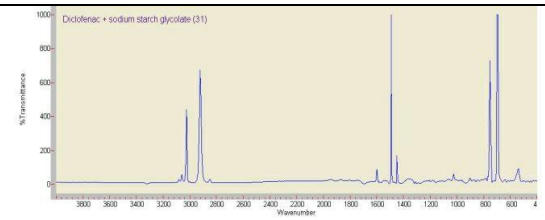


Fig. 23: FT-IR Spectrum of Diclofenac Acid F5.

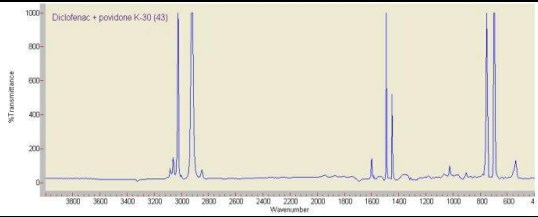


Fig. 24: FT-IR Spectrum of Diclofenac Acid F6.

Preformulation studies

Drug-Excipient compatibility studies

Visual Observation: It was noted that, under room temperature and humidity conditions, there was no color change or lump formation in any of the drug-excipient mixtures. Based on the observations made, it was determined that there was compatibility between the drug and the excipients used in the experimental study.

Drug-excipient compatibility study is essential part of preformulation step for the development of new drug. Physical mixture of drug and excipient (1:1) were prepared and compatibility studies were carried out using FTIR Spectroscopy.

Compatibility Study of Diclofenac Utilizing FTIR Spectroscopy

Diclofenac and excipients absorption bands were identified and interpreted in the spectra. The FTIR spectra of physical mixtures of Diclofenac and excipients reveal no interaction between drug and excipients. The FTIR studies from the spectra confirmed the absence of any chemical interaction between the Diclofenac and the excipients as shown in Figures 1-17.

Evaluation of Pre-Compression Formulations

Diclofenac and excipients absorption bands were identified and interpreted in the spectra. The FTIR spectra of physical mixtures of Diclofenac and excipients in formulation pre-compression reveal no interaction between drug and excipients. The FTIR studies from the spectra confirmed the no chemical interaction between the Diclofenac and the excipients in formulations as shown in Figures 18-24.

CONCLUSION

The compatibility studies of physical mixtures of Diclofenac with different used excipients such as mannitol, microcrystalline cellulose, lactose anhydrous, pregelatinized starch, as diluents, and sodium starch glycolate, croscarmellose sodium, and crospovidone as superdisintegrants and citric acid anhydrous, HPMC were investigated by FTIR it was detected that there was no variation or minor deviation in the characteristic peaks in FTIR spectroscopy. The Diclofenac formulations precompression were evaluated which were found to be within limits. It was concluded that the drug Diclofenac was found to be compatible with various excipients which were selected for the formulation development of the Diclofenac ODTs. Formulation scientist from his experience and knowledge have to

significantly in the preformulation study and is an important factor in the ADDS product development process.

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