

COMPATIBILITY STUDIES OF FUSIDIC ACID WITH PHARMACEUTICAL EXCIPIENTS TO DEVELOPMENT CREAM NOVEL DRUG DELIVERY SYSTEMS FOR ENHANCED DIABETIC WOUND HEALING

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ABSTRACT

Chronic diabetic wounds are challenging to treat due to combined issues of impaired tissue repair and high infection risk. Fusidic Acid (an antibiotic effective against skin pathogens including MRSA) each address different facets of diabetic wound pathology. The main objective of the present study was to the preformulation studies were performed to know the development of formulation and evaluation of Fusidic Acid Cream NDDS for topical application. In the present study that the compatibility was assessed by, FTIR spectroscopy, and melting point apparatus, preformulation parameters. Results showed that physical mixtures of Atorvastatin and various excipients such as cetostearyl alcohol, stearic acid, Vaseline (petroleum jelly), liquid paraffin, antioxidant: butylated hydroxyanisole (BHA), preservative: chlorocresol, aqueous phase components: propylene glycol, and emulsifier: Tween 80 were evaluated for preformulation studies parameters were investigated by FTIR it was detected that there was no variation or minor deviation in the characteristic peaks in FTIR

spectroscopy. It was concluded that the drug Fusidic Acid was found to be compatible with various excipients which were selected for the formulation development of the Fusidic Acid Cream NDDS. These formulations favorable properties and efficacy indicate it as a promising strategy for improving outcomes in infected diabetic wounds. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the NDDS (Novel Drug Delivery Systems) product development process.

KEYWORDS: Fusidic Acid, NDDS, Compatibility, Excipients, Development, Preformulation, Cream, Infected Diabetic Wounds.

INTRODUCTION

Background^[1-38]

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia due to insulin deficiency or resistance. Affecting 589 million adults globally, with projections reaching 853 million by 2050, with an estimated 44.7% of cases remaining undiagnosed. Chronic hyperglycemia is a primary driver of systemic complications, including neuropathy, retinopathy, and cardiovascular disease. Among these, impaired wound healing is a devastating consequence, affecting an estimated 19% to 34% of diabetic patients and contributing to prolonged recovery, and mortality. This compromised healing capacity is further exacerbated by a markedly increased risk of infection; diabetic patients are 1.5 to 4 times more likely to develop infections compared to their non-diabetic counterparts, with the extremities being particularly vulnerable.

Mechanistically, hyperglycemia induces oxidative stress and advanced glycation end-products (AGEs), which impair collagen synthesis, angiogenesis, and macrophage function. These systemic defects create a microenvironment resistant to repair, prolonging inflammation and elevating infection risks, with *Staphylococcus aureus* being the most commonly isolated pathogen in chronic diabetic wounds. Delayed healing culminates in severe complications: over 60% of non-traumatic lower-limb amputations are diabetes-related, with a 5-year mortality rate exceeding 50% and 70% post-amputation.

Current clinical treatments for diabetic wounds inadequately address the multifactorial pathology of delayed healing. Topical antibiotics, such as silver sulfadiazine, reduce bacterial load but impair epithelialization and exacerbate oxidative stress, prolonging recovery.

Growth factor-based therapies, including recombinant platelet-derived growth factor (PDGF-BB), enhance angiogenesis but lack antimicrobial activity, leaving wounds vulnerable to infection. Hydrogel dressings, though widely used for moisture retention, fail to resolve hyperglycemia-driven collagen degradation or chronic inflammation, even advanced modalities like negative pressure wound therapy (NPWT) struggle with biofilm persistence and high recurrence rates. These therapies target isolated aspects of healing, neglecting the dual challenges of infection and impaired tissue repair. Consequently, 50% of chronic diabetic wounds fail to heal within 12 weeks, often progressing to amputations.

Fusidic Acid is a steroidal antibiotic characterized by a unique mechanism of action involving the inhibition of bacterial protein synthesis by binding to elongation factor G (EF-G), thereby preventing peptide translocation and ribosome disassembly. It is primarily bacteriostatic and exhibits a spectrum of activity predominantly against Gram-positive bacteria of particular relevance to diabetic wounds is its potent efficacy against *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA) strains, which are among the most common and problematic pathogens colonizing and infecting these wounds. Fusidic acid has a long history of successful use in topical formulations, such as creams and ointments, for the treatment of various primary and secondary skin infections. Its established antimicrobial profile against key pathogens implicated in the infection of diabetic wounds makes it a logical and rational candidate for the antibiotic component in a combination therapy aimed at improving healing outcomes.

Pharmaceutical Research Paths^[39-107]

Pharmaceutical research is characterized by having both a natural source and synthetic source for primary active raw materials and excipients, each source is mainly prepared to the effectiveness and safety of the drug.

The Pharmaceutical Research Paths include: Pharmacognosy deals with natural sources of drug, Pharmaceutical Chemistry specializes in synthetic sources of drug, Pharmaceutics specializes in designing of pharmaceutical dosage forms and drug delivery systems from natural and synthetic sources of active pharmaceutical ingredients and excipients that help in developing dosage forms and drug delivery systems.

The Pharmaceutical Research Paths link steps are manufacturing and development of drug according to the standard parameters evaluation such as physiochemical properties,

preformulation, formulation, evaluation, drug stability, Pharmaceutical analysis, pre-clinical, post-clinical stages, pre-marketing, post-marketing, Pharmacovigilance, Pharmacoeconomics, Pharmacy Management, Pharmacology, Toxicology, Therapeutics, Pharmaceutical Care, Health Care, Advanced Industrial Pharmacy, Biopharmaceutics and Pharmacokinetics, Advanced Clinical Pharmacokinetics, Pharmaceuticals Cosmetics, Pharmaceutical Biotechnology, Drug Design, Pharmacy Law and Ethics, Pharmacogenomics, Good Manufacturing Practice, and Good Pharmacy Practice etc.

All of these Pharmaceutical Research Paths are interconnected, and whenever the link between them is made in a scientific relationship and the goal of pharmaceutical care is achieved gradually according to plan of a scientific pharmaceutical research path.

Pharmaceutical Research Paths are the scientific methods through which the scientific relationship between the pharmaceutical team, research, supervisor or specialist researcher, the scientific research materials, equipment's, scientific institution, pharmaceutical companies, reference standards, and the goals of pharmaceutical research improve and development of community services of pharmaceutical care and health care.

Pharmaceutical Scientists are considering natural sources and medicinal herbs in the pharmaceutical industry an important part of drug development because natural sources of drugs have properties that are greater than industrial sources of drugs in NDDS. And the pharmaceutical industry strategies depend on the development of different pharmaceutical dosage forms and recent novel drug delivery systems. Using medicinal herbs and natural sources as important goals of drug development. It is part of the art of innovation in drug development with different of novel drug delivery systems and pharmaceutical care for patients and society, it's the basic of development of the new pharmaceutical industry by developing different novel drug delivery systems from different sources.

Compatibility Studies^[108-154]

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 Fusidic Acid -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 Atorvastatin Cream NDDS for topical application. These formulations favorable properties and efficacy indicate it as a promising strategy for improving outcomes in infected diabetic wounds.

MATERIALS AND METHODS

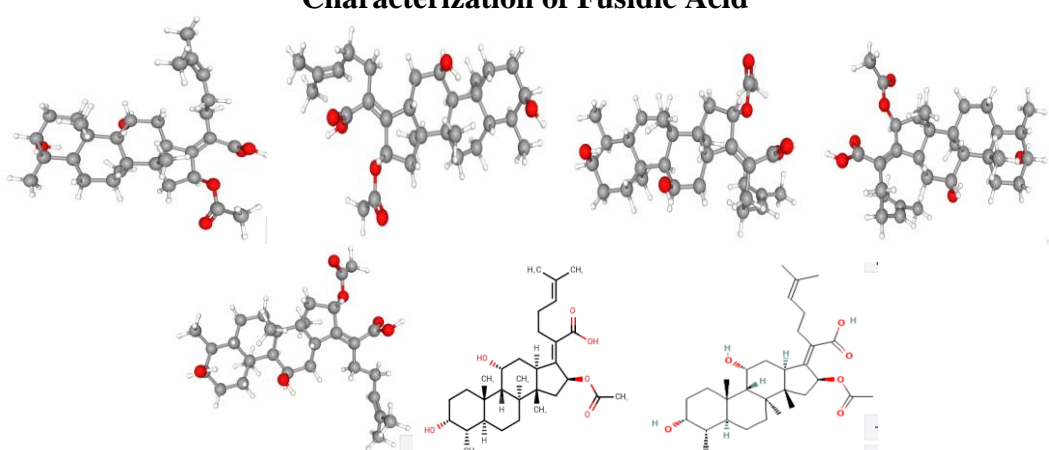
All raw materials, including active pharmaceutical ingredient (API), excipients, and analytical reagents, were kindly provided by Modern Pharma Industry (Sana'a, Yemen). Fusidic acid (FA) were used as API. Excipients employed in the formulations include oil phase components: cetostearyl alcohol, stearic acid, Vaseline (petroleum jelly), liquid paraffin, antioxidant: butylated hydroxyanisole (BHA), preservative: chlorocresol, aqueous phase components: propylene glycol, and emulsifier: Tween 80. Reagents for analytical procedures and buffer preparation, including methanol (HPLC grade), hydrochloric acid (HCl), sodium hydroxide (NaOH), potassium dihydrogen phosphate (KH_2PO_4), and glacial acetic acid, were of analytical grade.

Equipment and Instruments

Major analytical instruments included a Varian 50 Conc. UV-Visible Spectrophotometer (Varian, USA) and a Varian 2000 scimitar series FTIR Spectrophotometer (Varian, USA). A Stuart SMP1 melting point apparatus (Stuart Scientifics, UK) was used for MP assessment.

Evaluation of Drug-Excipient Compatibility Studies Methods^[138-201]

Table 1: Fusidic Acid Data.

Characterization of Fusidic Acid			
			
Fusidic Acid Structure and 3D Conformer			
Chemical Structure	(2Z)-2-[(3R,4S,5S,8S,9S,10S,11R,13R,14S,16S)-16-acetyloxy-3,11-dihydroxy-4,8,10,14-tetramethyl-2,3,4,5,6,7,9,11,12,13,15,16-dodecahydro-1H-cyclopenta[a]phenanthren-17-ylidene]-6-methylhept-5-enoic acid	Appearance	Is a white to off white crystalline powder or slightly yellow.
Chemical Formula	C₃₁H₄₈O₆	Drug Solubility	Solubility: it behaves as a weak carboxylic acid (pKa ≈ 5.3) with pronounced lipophilicity and very low water solubility. Melting Point: 190-193°C.
Molecular Weight	516.7g/mol	BCS	Class-II Drug
Drug Action and Use	<p>Fusidic Acid: An antibiotic isolated from the fermentation broth of <i>Fusidium coccineum</i>. (From Merck Index, 11th ed) It acts by inhibiting translocation during protein synthesis. It is often used topically in creams and eyedrops but is available in systemic formulations including tablets and injections</p> <p>Fusidic Acid, a steroidal antibiotic first isolated from the fungus <i>Fusidium coccineum</i> in 1960s. It has been widely used topically against Gram positive skin infections. In particular, it is routinely used to treat <i>Staphylococcus</i> and <i>Streptococcus</i> skin/soft-tissue infections (e.g. impetigo, infected eczema, folliculitis).</p>		

	Fusidic Acid acts by binding bacterial elongation factor G (EF-G) on the ribosome, locking EF-G onto the ribosome after GTP hydrolysis and thereby blocking the translocation step of protein synthesis. Its antimicrobial spectrum is narrow but powerful against Gram-positive cocci: potent activity is seen against <i>Staphylococcus aureus</i> (including many MRSA strains) and <i>Streptococcus spp.</i> , which are key pathogens in diabetic wound infections.		
Fusidic Acid Pharmacokinetics			
Drug Absorption	Fusidic Acid is high lipophilicity yields very favorable topical behavior: it penetrates intact or broken skin and achieves deep dermal concentrations well above the MIC for <i>S. aureus</i> . Systemic uptake from topical application is negligible, so effective antibacterial levels are maintained in epidermis/ dermis with minimal serum exposure.	Drug Distribution	Protein binding: Fusidic Acid is highly bound to plasma proteins and over 97 to 99%
Drug Metabolism	Fusidic Acid is metabolized Dicarboxylic ester/ acid 3 -keto Fusidic acid, hydroxy Fusidic acid, glucuronide fusidic acid, glycoly metaboliate.	Drug Excretion	Route of Elimination: Clearance:
The Elimination Half-Life (T_{1/2})	Plasma elimination half-life: The half-life of Fusidic acid is 5-6 hours.	Availability	Tablets, Ointments, Creams.

Table 2: Pharmaceutical Excipients Data.

Nonproprietary Name	Synonyms	Functional Category	Incompatibilities
Cetostearyl alcohol	Alcohol cetylicus et stearylicus; cetearyl alcohol; cetyl stearyl alcohol; Crodacol CS90; LanetteO; Speziol C16-18 Pharma; TegoAlkanol1618; TegoAlkanol6855.	Emollient; emulsifying agent; viscosity-increasing agent.	Incompatible with strong oxidizing agent and metal salts.
Stearic acid	Acidumstearicum; cetylacetic acid; Crodadid; CristalG; CristalS; Dervacid; E570; Edenor; Emersol; ExtraAS; ExtraP; ExtraS; Extra ST; 1-heptadecanecarboxylic acid; Hystrene; Industrene; Kortacid1895; Pearl Steric; Pristerene; stereophanic acid; Tego stearic.	Emulsifying agent; solubilizing agent; tablet and capsule lubricant.	Stearic acid is incompatible with most metal hydroxides and may be incompatible with bases, reducing agents, and oxidizing agents. In ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when compounded with zinc or calcium salts.
Petrolatum	Merkur; mineral jelly; petroleum jelly; Silkolene; Snow White; Soft White; vaselinum flavum; yellow petrolatum; yellow petroleum jelly.	Emollient; ointment base.	Petrolatum is an inert material with few incompatibilities.
Butylated hydroxyanisole	BHA; tert-butyl-4-methoxyphenol; butylhydroxyanisolum; 1,1	Antioxidant.	Butylated hydroxyanisole is phenolic and undergoes reactions

(BHA)	dimethylethyl-4-methoxyphenol; E320; NipanoxBHA; Nipantiox 1-F; TenoxBHA.		characteristic of phenols. It is incompatible with oxidizing agents and ferric salts. Trace quantities of metals and exposure to light cause discoloration and loss of activity.
Chlorocresol	Aptal; Baktol; chlorocresolum; 4-chloro-m-cresol; p-chloro-m-cresol; 1-chloro-4-hydroxy-2-methylbenzene; 2-chloro-5-hydroxy toluene; 6-chloro-3-hydroxytoluene; 4-chloro-3-methylphenol; 3 methyl-4-chlorophenol; Nipacide PC; parachlorometacresol; PCMC.	Antimicrobial preservative; disinfectant.	Chlorocresol can decompose on contact with strong alkalis, evolving heat and fumes that ignite explosively. It is also incompatible with oxidizing agents, copper, and with solutions of calcium chloride, codeine phosphate, diamorphine hydrochloride, papaveretum, and quinine hydrochloride. Chlorocresol may be lost from solutions to rubber closures, and in contact with polyethylene may initially be rapidly removed by sorption and then by permeation, the uptake being temperature dependent. Chlorocresol may also be taken up by polymethylmethacrylate and by cellulose acetate. Losses to polypropylene or rigid polyvinyl chloride are usually small.
Propylene glycol	1,2-dihydroxypropane, E1520, 2-hydroxypropanol; methylethyleneglycol, methyl glycol, propane-1,2diol, propylglycol.	Antimicrobial, preservative, disinfectant, humectant, plasticizer, solvent, stabilizing agent, water miscible cosolvent.	Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate
Tween 80	Monolaurates, polyoxyethylene sorbitan, polysorbate	Emulsifying agent for the preparation of stable oil-in-water emulsions.	Incompatible with alkalis, heavy metal salts, phenols, tannic acid.
Purified water	Filtered water, Distilled water, Deionized water, Purified H ₂ O, Clear water, Pure water, clean water, Pristine water, Crystal-clear water, Treated water	solvent	In pharmaceutical formulations, water can react with drugs and other excipients that are susceptible to hydrolysis (decomposition in the presence of water or moisture) at ambient and elevated temperatures. Water can react violently with alkali metals and rapidly with alkaline metals and their oxides, such as calcium oxide and magnesium oxide. Water also reacts with anhydrous salts to form hydrates of

			various compositions, and with certain organic materials and calcium carbide.
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According to Fusidic Acid and excipients data as shown in Tables 1 and 2, it was selected that the different excipients to preformulation study with Fusidic Acid in the present study.

Pre-Formulation Studies

Pre-formulation studies were conducted to establish the fundamental physicochemical properties of the APIs and to ensure their compatibility with the selected excipients, a critical prerequisite for rational dosage form design.

Qualitative Characterization of API

The identity and purity of the incoming AT and FA raw materials were verified using standard pharmacopeial methods prior to their use in formulations.

UV-Vis Spectrophotometer Analysis of Fusidic Acid

UV spectrophotometry was conducted in accordance with United States Pharmacopeia (USP) General Chapter <857> Ultraviolet-Visible Spectroscopy to confirm the identity of the API (USP). A stock solution of Fusidic Acid (1 mg/100 mL) was prepared in methanol; 1 mL aliquot of this stock was further diluted to 25 mL with methanol from which a working solution of 0.4 µg/mL was made. The absorbance spectra of these solutions were recorded from 200 to 400 nm using a Shimadzu UV-1800 spectrophotometer with 1-cm quartz cuvettes against a methanol blank. The observed maximum absorption wavelengths (λ -max) were compared to reference values, of 210-240 nm for Fusidic Acid.

Melting Point Melting point of the Fusidic Acid 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. Melting point analysis was performed using the capillary method as described in USP General Chapter <741> Melting Range or Temperature to assess API melting point. using an Electrothermal 9100 apparatus (USP-NF). Samples were heated at 1°C per minute. The temperature range from the onset of melting to complete liquefaction was recorded and compared to the established standards for each API. Standard values are 190-193°C for Fusidic Acid.

Pre-Formulation Study A stage of development during which the physicochemical properties of the drug substance are characterized and established. A complete knowledge of the relevant therapeutic and physicochemical properties of the drug enables determination of its proper formulation and delivery method. Preformulation study is to develop the elegant (stable, effective, and safe) dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish physico-chemical parameter of new drug substance.

Solubility Study A qualitative assessment of the solubility of Fusidic Acid was conducted at ambient laboratory temperature (22–25 °C) in a range of aqueous and non-aqueous media. This step is fundamental to preformulation, as it informs the selection of appropriate solvents and excipients to achieve a stable and effective formulation.

For aqueous solubility assessment, 100 mg of each API was individually dispersed in 1mL of three different media: purified water, 0.1 N HCl, acetate buffer (pH 4.5), and phosphate buffer (pH 6.8) prepared according to (USP). Each mixture was manually stirred for 5 minutes and sonicated for 10 minutes to facilitate dissolution. If the API did not fully dissolve, portions of the corresponding medium were added incrementally to achieve total volumes of 10 mL, 30 mL, 50 mL, 100 mL, and up to 600 mL. Solubility was qualitatively classified based on the volume of solvent required for complete visual dissolution (USP). Non-aqueous solubility was assessed by dispersing 100 mg of each API into 1 mL of glycerin, 1% & 2% (w/v) Tween 80, binary mixtures comprising 1mL of propylene glycol (PG) with 1mL of 1% or 2% Tween 80. Each sample was manually stirred, sonicated for 5 minutes, and visually examined for homogeneity, phase separation, creaming, foaming, or floating aggregates. No quantitative solubility measurements were performed; observations were recorded qualitatively to determine apparent solubility and dispersion behavior. This comprehensive solubility assessment establishes fundamental data for subsequent formulation optimization work as shown in Table 3.

Table 3: Solubility Specification of Drugs.

Descriptive Term	Parts of Solvent Required for 1 Part of Solute:
Very Soluble	Less than 1
Freely Soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very Slightly Soluble	From 1000 to 10000
Practically Insoluble, or Insoluble	Greater than or equal to 10,000.

Drug and Excipients Compatibility Study

Drug and drug-excipients compatibility study is a critical step in preformulation; to de-risk the development process by identifying potential detrimental interactions early, and to ensure the Physicochemical stability of the APIs in the presence of selected excipients. compatibility studies were conducted visually, and by Fourier-Transform Infrared (FTIR) spectroscopy. Drug physical mixtures of Fusidic Acid were prepared with the selected excipients in a 1:1 ratio. Each mixture was sealed in borosilicate glass ampoules and stored under accelerated conditions at $40 \pm 2^\circ\text{C}$ and 75% relative humidity (RH) for 14 days. Control samples containing the pure APIs were also prepared. This stress-testing protocol is designed to accelerate degradation reactions and predict long-term stability issues.

FTIR Spectroscopy Study

IR study was aimed to study the compatibility of excipients with Fusidic Acid in room condition. Each excipient was mixed with Fusidic Acid in equal amounts, then from each sample a small amount was taken (approx. 1:1 %) and mixed with about 100 mg of potassium bromide. The KBr- sample mixtures were grinded separately for each sample using agate mortar and pestle. The grinded powders were compressed into discs under pressure of about 10000 pounds per square inch. The tablets were mounted in IR compartment and analyzed. The infrared spectra of the drug - excipient mixtures were recorded over a wave number of 4000 cm^{-1} to 500 cm^{-1} . On analysis of the IR spectra of the reference spectra given in British Pharmacopoeia and pure drug, no major differences were observed in the characteristic absorption peak pattern as shown in Table 4.

Table 4: The Drug and Excipients Compatibility Studies.

Sample Code	Drug with Excipients	Ratio (Drug: Excipient)
1	Fusidic Acid	1
2	Atorvastatin Calcium +Fusidic Acid	1:1
3	Mixture with BHA	1:1
4	Mixture with Vaseline	1:1
5	Mixture with Chlorocresol	1:1
6	Mixture with Cetostearyl Alcohol	1:1
7	Mixture with Propylene Glycol	1:1
8	Mixture With Stearic Acid	1:1
9	Mixture with Liquid Paraffin	1:1
10	Mixture with Tween 80	1:1

RESULTS AND DISCUSSION

Pre-Formulation Studies

For qualitative Characterization of API, Solubility measure and compatibility study:

Qualitative Characterization of API

UV Spectrophotometry

UV spectrophotometric analysis of Fusidic Acid in methanol demonstrated two characteristic absorption maxima, at 203.8 nm and 216.0 nm. The primary peak at 203.8 nm corresponds to the reported reference range of 204–205 nm, while the secondary peak at 216.0 nm falls within the known absorption region for Fusidic Acid. The spectral profile for compound showed no evidence of extraneous peaks within the scanned range (200–400 nm). as shown in Figure 1.

Characterization of Fusidic Acid by UV Spectroscopy

UV Scanning of Fusidic Acid in Methanol

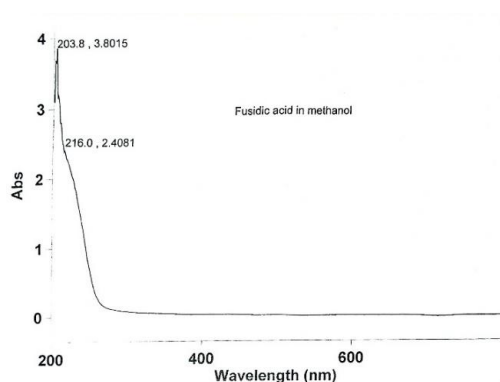


Fig. 1: Wavelength of Fusidic Acid in UV Spectrophotometer.

Solubility Study

The dissolution characteristics of Fusidic Acid were systematically investigated in multiple solvent systems at ambient temperature ($25\pm 1^\circ\text{C}$). The study employed a dropwise addition method with continuous agitation to determine saturation points, with solubility categorization according to USP standards, as shown in **Error! Reference source not found.** The solubility of Fusidic Acid was evaluated in various aqueous and non-aqueous media at 25°C . Solvent (aqueous or non-aqueous) was added dropwise under constant stirring until no further API dissolution was observed; total volume was then adjusted to 600 mL. Solubility classifications follow USP guidelines: Practically insoluble: $< 0.1\text{ mg/mL}$, sparingly soluble: $0.1\text{--}1\text{ mg/mL}$ and slightly soluble: $1\text{--}10\text{ mg/mL}$. Aqueous media (0.1 N HCl, phosphate buffer pH 4.5, purified water, phosphate buffer pH 6.8): Drug API was

classified as practically insoluble (< 0.1 mg/mL) in all media (Table 5). A relative ranking, based on the minimum detectable solubility.

Table 5: Qualitative Solubility Ranking of Fusidic Acid in Aqueous Media.

Medium	Fusidic Acid
0.1 N HCl	Practically Insoluble
pH 4.5 buffer	Practically Insoluble
Purified water	Practically Insoluble
pH 6.8 buffer	Practically Insoluble
Relative ranking	pH 6.8 > H ₂ O > pH 4.5 > HCl

Fusidic Acid was marginally more “soluble” at near-neutral pH (6.8). Non-aqueous media (glycerin; propylene glycol; propylene glycol + Tween 80; liquid paraffin, liquid paraffin + Tween 80 + propylene glycol (PG), Neither API dissolved in glycerin alone. Addition of surfactant (Tween 80) with or without co-solvent (PG) yielded stable milky/creamy dispersions with visible foam or floating phases (Table), indicative of emulsification rather than true solubilization.

Table 6: Visual Appearance of Fusidic Acid in Non-Aqueous Dispersions.

Medium	Fusidic Acid
Glycerin	Insoluble
1% Tween 80	Cream-Like Dispersion
2% Tween 80	Cream-like Dispersion; Foam
1% Tween 80 + PG	Cream-Like Dispersion
2% Tween 80 + PG	Cream-Like Dispersion; Foam

Melting Point Determination of Fusidic Acid

Melting point of pure Fusidic Acid was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Fusidic Acid 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 Fusidic Acid was identical to reference melting point stated in MP (190–192°C). The sample started to melt at 190°C, and turned into liquid at 192°C, indicating that the sample used is pure. That reading has stated in melting point tester.as shown in Table 7.

Table 7: Results of Melting Point of Fusidic Acid.

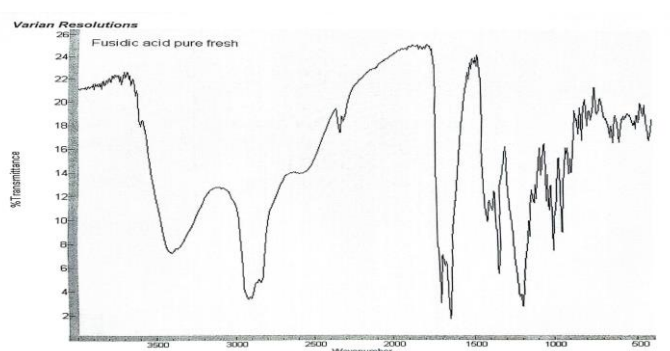
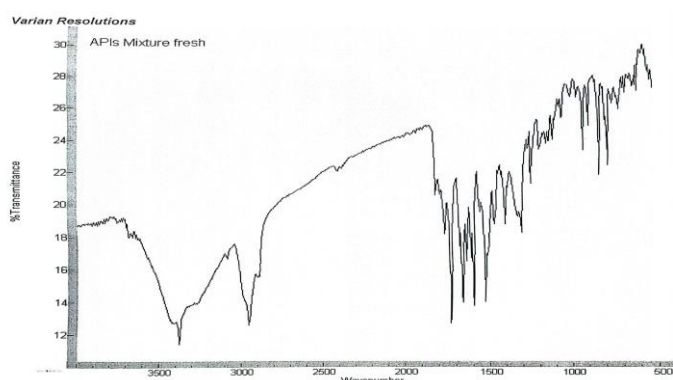
Test	Temp Rang Analyzed (Melting)	Results
Test I Fusidic Acid	(190–192°C)	192°C
Test II Fusidic Acid	(190–192°C)	192°C

Excipient and Drug Compatibility Study

Physical mixtures of Fusidic Acid (1:1 ratio) with all excipients and pure API controls maintained their initial physical state following 14-day storage under accelerated conditions ($40 \pm 2^\circ\text{C}$, 75% RH). No color changes, liquefaction, caking, or gas evolution were observed in any sample.

Characterization of Fusidic Acid by FTIR

FTIR spectrum studies indicated that major functional groups present in Fusidic Acid show characteristic peaks in IR spectrum. Figures (2) to (13) 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 Fusidic Acid. 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 Spectra of Pure Fresh Fusidic Acid.****Fig. 3: FTIR Spectra of APIs Mixture.**

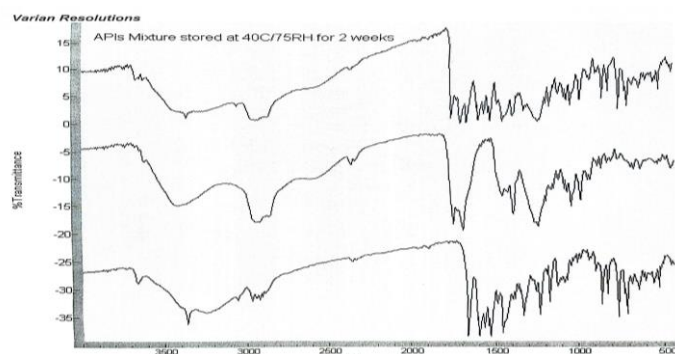


Fig. 4: FTIR Spectra of Atorvastatin, Fusidic.

Acid and Their Stored Mixture

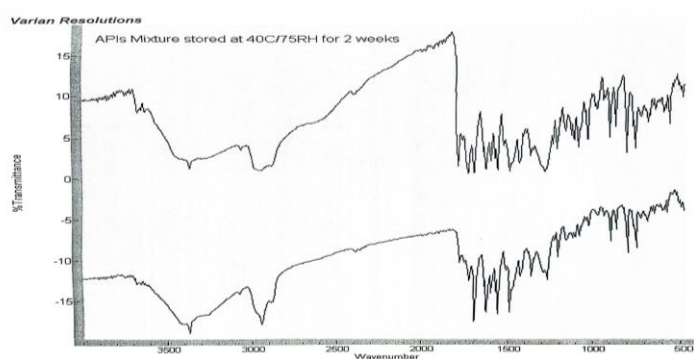


Fig. 5: FTIR Spectra of Fresh APIs Mixture, and Their Stored Mixture.

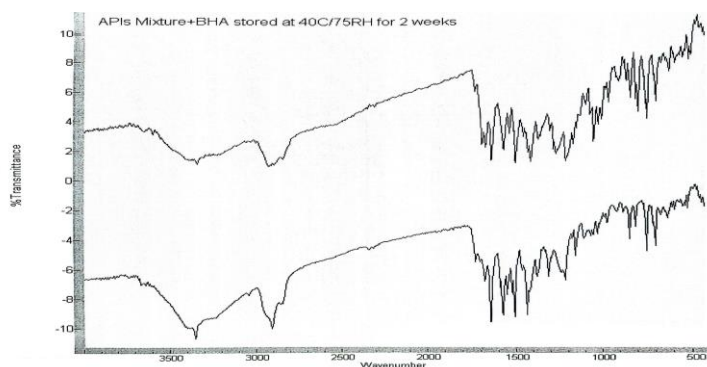


Fig. 6: FTIR Spectra of the API Mixture to the Stored Drug-Excipient Mixture with BHA.

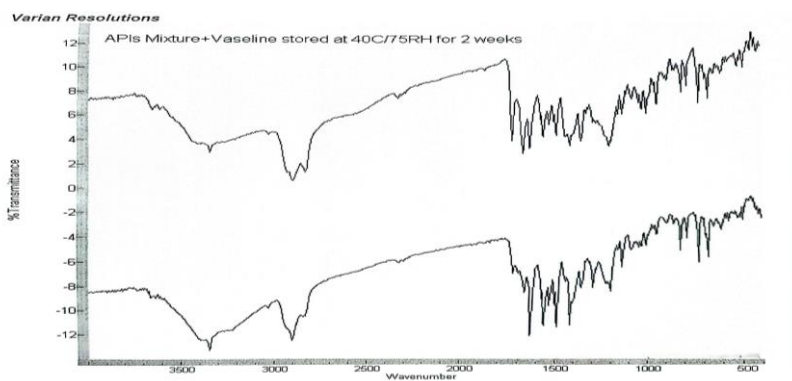


Fig. 7: FTIR Spectra of the API Mixture to the Stored Drug-Excipient Mixture with Vaseline.

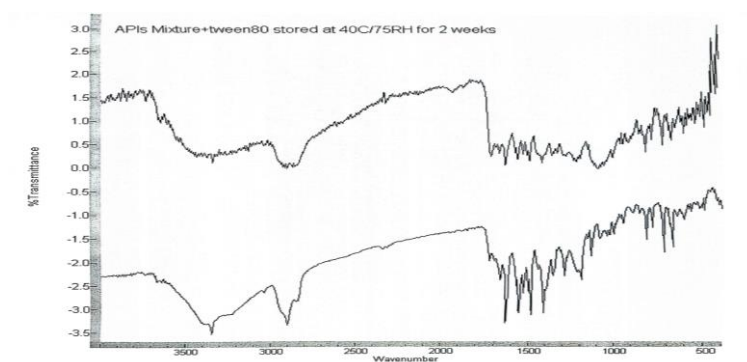


Fig. 8: FTIR Spectra of the API Mixture to the Stored Drugs-Excipient Mixture with Tween 80.

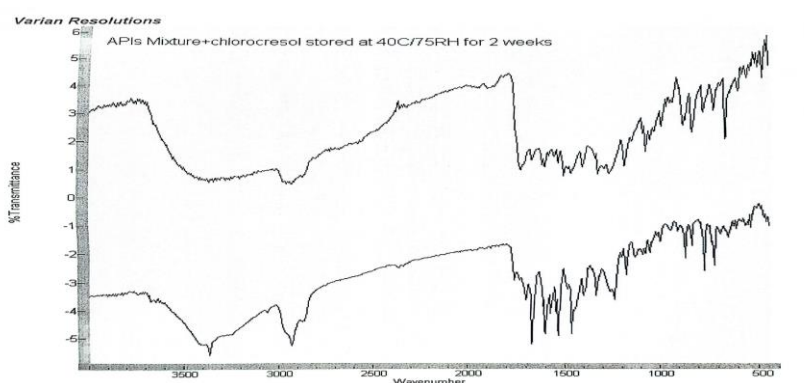


Fig. 9: FTIR Spectra of the API Mixture to the Stored Drug-Excipient Mixture with Chlorocresol.

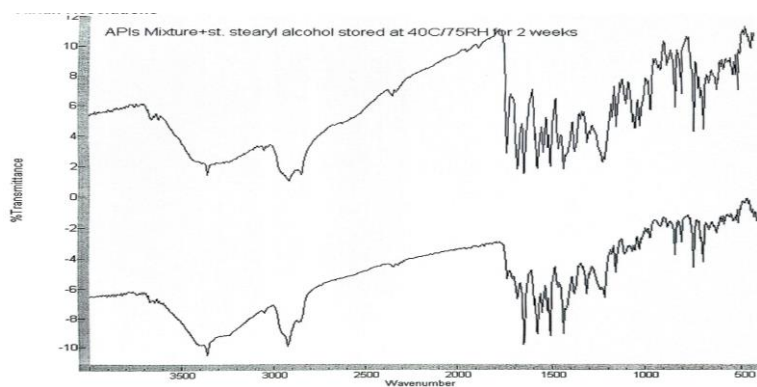


Fig. 10: FTIR Spectra of the API Mixture to the Stored Drug-Excipient Mixture with Cetostearyl Alcohol.

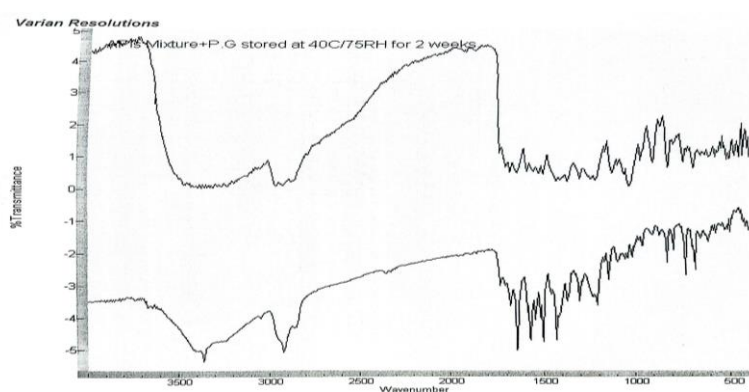


Fig. 11: FTIR Spectra of the API Mixture to the Stored Drug-Excipient Mixture with Propylene Glycol.

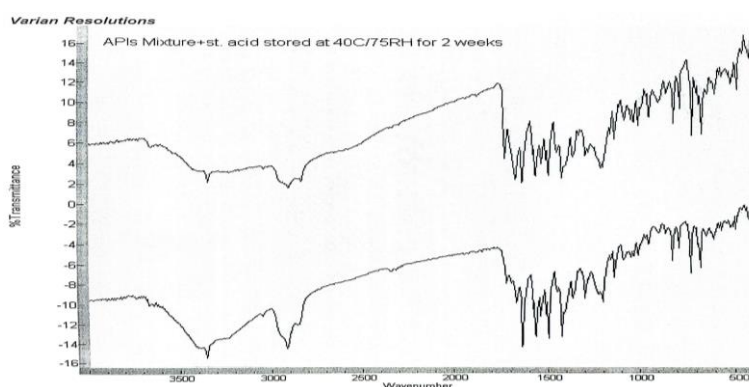


Fig. 12: FTIR Spectra of the API Mixture to The Stored Drug-Excipient Mixture with Stearic Acid.

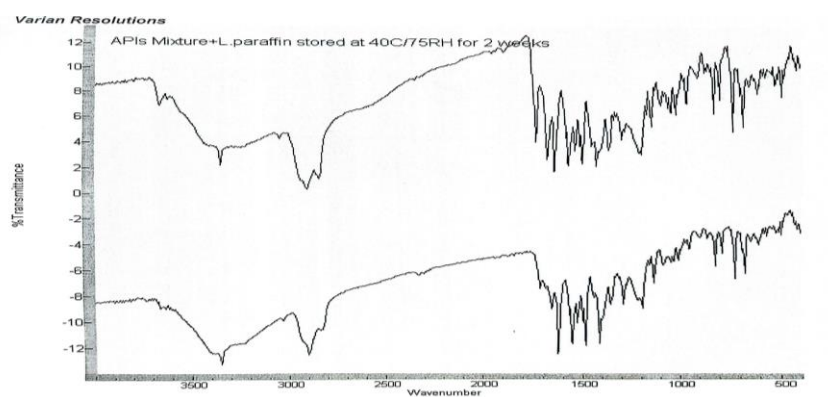


Fig. 13: FTIR Spectra of the API Mixture to the Stored Drug-Excipient Mixture with Liquid Paraffin.

DISCUSSION

The FTIR spectrum of Fresh Fusidic acid exhibited characteristic peaks at 3360 cm^{-1} (O-H stretching), 1708 cm^{-1} (carboxylic acid C=O), and 1050 cm^{-1} (C-O stretching (**Error! Reference source not found.**)). The spectrum of the fresh API physical mixture demonstrated strict superposition of these signature peaks without any noticeable positional deviations. Post-storage spectra of the API mixture revealed no shifts $>2\text{ cm}^{-1}$ in diagnostic peaks, no alterations in relative intensities, no peak broadening, and no emergence of new absorption bands within $4000\text{--}500\text{ cm}^{-1}$ (**Error! Reference source not found.2 -13**).

Comparative analysis of stored API-excipient mixtures showed no evidence of incompatibilities. For butylated hydroxyanisole (BHA), Vaseline, chlorocresol, Tween 80, stearyl alcohol, propylene glycol, stearic acid, and liquid paraffin mixtures: all spectra retained the fundamental absorption patterns of the APIs (Table), and **Error! Reference source not found.** to **Error! Reference source not found.** shows their IR spectrums. Observed spectral variations were attributable solely to excipient-specific absorptions, with no detectable covalent interaction signatures. Minor intensity fluctuations in hydroxyl and carbonyl regions were consistent with expected hydrogen bonding effects and remained within pharmacopeial acceptance thresholds for compatibility. Overall, no physical or spectroscopic evidence indicated incompatibilities between the APIs or with any tested excipient under accelerated storage conditions.

Table 8: FTIR Spectra Observations of Drug-Excipient Compatibility after 14-Day Storage at 40°C/75% RH.

Excipient	Key Spectral Observations	Compatibility Assessment
BHA	API peaks retained; no new bands beyond characteristic BHA aromatic/O-H signals	Compatible
Vaseline	API signatures persistent despite hydrocarbon masking; no reaction-specific peaks	Compatible
Chlorocresol	API spectral profile maintained; C-Cl absorptions distinct from API peaks	Compatible
Tween 80	API absorption regions identifiable; no covalent interaction evidence despite surfactant spectral interference	Compatible
Cetostearyl alcohol	API peaks preserved alongside strong alcohol-derived O-H/C-H vibrations	Compatible
Propylene glycol	API patterns retained; O-H region variations consistent with H-bonding	Compatible
Stearic acid	Carbonyl region superposition observed; no acid-base reaction indicators	Compatible
Liquid paraffin	API peaks identifiable without positional shifts; hydrocarbon dominance caused partial masking without peak alterations	Compatible

CONCLUSION

The compatibility studies of physical mixtures of Fusidic Acid with different used excipients such as cetostearyl alcohol, stearic acid, Vaseline (petroleum jelly), liquid paraffin, antioxidant: butylated hydroxyanisole (BHA), preservative: chlorocresol, aqueous phase components: propylene glycol, and emulsifier: Tween 80 were evaluated for preformulation studies parameters were investigated by FTIR it was detected that there was no variation or minor deviation in the characteristic peaks in FTIR spectroscopy. It was concluded that the drug Fusidic Acid was found to be compatible with various excipients which were selected for the formulation development of the Fusidic Acid Cream NDDS. These formulations favorable properties and efficacy indicate it as a promising strategy for improving outcomes in infected diabetic wounds. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the NDDS (Novel Drug Delivery Systems) product development process.

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