FORMULATION DEVELOPMENT AND EVALUATION OF DEFERASIROX DISPERSIBLE TABLETS

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,

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In partial fulfillment of the requirements for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

By

(REG.NO:261210402)

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APRIL– 2014.

CERTIFICATE

This is to certify that the investigation described in the dissertation entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF DEFERASIROX DISPERSIBLE TABLETS"** submitted by Reg.No:261210402 was carried out in the Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnankoil-626 126, which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under my supervision and guidance for the partial fulfillment of degree of MASTER OF PHARMACY in PHARMACEUTICS.

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Examiners:

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INTRODUCTION

The most widely accepted route of administration is the oral route. Up to 50-60% of total dosage forms are administered by oral route. Of this, the most commonly used dosage form for pharmaceutical preparation is tablet. Tablets, as a dosage form offer many advantages. They are cost effective, convenient to dispose and store and easy for the patient to administer.

When a new drug is discovered, one of the first questions that arise is whether the drug can be effectively administered for its intended effect by the oral route. They are the first formulations for any new drug. If the drug cannot be administered by this route, then it is relegated to administration in a hospital setting.

Tablets may be defined as a solid pharmaceutical dosage form containing drug substances with or without suitable diluents and prepared either by compression or molding methods. Although are frequently discoid in shape, they may also be round or oblong amongst many other shapes. They may vary in size and weight depending on the amount of drug substance present and the intended method of administration. Tablets can be classified as follows depending on the function and route of administration.

TYPES OF TABLETS:

A. Oral Tablets for Ingestion:

   i. Standard Compressed Tablets

   ii. Modified Release Tablets

   iii. Delayed Action Tablets

   iv. Targeted Tablets

   v. Chewable Tablets

   vi. Dispersible Tablets

vii. Multi Compressed Tablets

a. Compression Coated Tablets

b. Layered Tablets

c. Inlay Tablets

B. Tablets Used in Oral Cavity

i. Lozenges and Troches

ii. Sublingual Tablets

iii. Buccal Tablets

iv. Dental Cones

v. Mouth Dissolved Tablets

C. Tablets Administered by Other Routes

i. Vaginal Tablets

ii. Implants

D. Tablets Used to Prepare Solutions

i. Effervescent Tablets

ii. Hypodermic Tablets

iii. Soluble Tablets

Tablets, as dosage forms, suffer their share of disadvantages, despite their wide usage. Some of them are formulation of drugs that resist compression; bioavailability problems; unpalatable taste; swallowing problems in pediatric and geriatric patients; difficulty in administration to patients suffering from severe nausea.

Pharmaceutical suspensions are uniform dispersions of solid drug particles in a vehicle in which the drug has minimum solubility. These are usually formulated to improve chemical stability of drug, mask the unpleasant taste and in instances where liquid dosages form is preferred. Suspension as a dosage form, however, is associated with issues such as microbial growth, sedimentation and non uniformity of dose, high cost of manufacturing, difficult to carry, etc.

Solid oral dosage forms are most convenient from patient as well as from manufacturing chemist's perspective. They ensure uniformity of dosage, are most robust, have less biological issues compared to liquid dosage forms. However, immediate release tablets cannot act as a substitute for suspension. Thus, there is a need for a formulation, which overcomes the problems associated with the swallowing of the solid dosage forms and act as a viable substitute for suspensions. One such dosage form is dispersible tablets. Dispersible tablets are defined in Ph. Eur. are uncoated or film coated tablets intended to be dispersed in water before administration giving a homogenous dispersion. Usually, about 10-15 ml of water is used and the resulting dispersion is administered to the patient. However, they can also be placed directly on the tongue and sucked

.

Figure1:Step by step representation of disintegration process of a dispersible tablets.

Dispersible tablets are required to disintegrate within 3 minutes in water at 15-25 ℃. Also the dispersion produced from a dispersible tablet should pass through a sieve screen with a nominal mesh aperture of 710 microns. The dispersion properties of dispersible tablets can be facilitated by the inclusion of an acid\base couple in which the base liberates carbon dioxide when the components of the couple are dissolved in water.

IDEAL CHARACTERISTICS OF DISPERSIBLE TABLETS:

- They require water or other liquid at the time of administration.
- Should easily disintegrate and dissolve.
- Mask or overcome unpalatable taste of the drug.
- They should have high drug loading.
- They should have pleasant feel in the mouth.
- They should have low sensitivity against environmental conditions like moisture, temperature, etc.
- Ease of administration for patients who are mentally ill, disabled and uncooperative.
- Should be portable without fragility concern.
- They should be manufactured using conventional tablet processing and packaging equipment at low cost.

SPECIAL FEATURES OF DISPERSIBLE TABLETS:

Dispersible tablets are not intended to be chewed or swallowed whole. They should not be dispersed in carbonated drinks or milk due to foaming or slow dispersion. The purpose of dispersible tablet is to provide a unit dosage form of medication which can be easily administered to infants and children or to the elderly, who may have difficulty swallowing an intact tablet.

ADVANTAGES OF DISPERSIBLE TABLETS:

- They are particularly suitable both for elderly and children.
- Rapid disintegration and absorption along with quick onset of action.
- Certain dispersible tablets can also be divided.
- The bitter taste is masked.
- Patient compliance.
- Convenient to carry, easy to manufacture and stable.
- Improved bioavailability, reduced side effects.

LIMITATIONS OF DISPERSIBLE TABLETS:

One common limitation of these formulations is settling of the insoluble solids at the bottom of the container of the prepared dispersion, which may lead to the loss of part of the drug during administration, resulting in suboptimal dosing.

DISADVANTAGES OF DISPERSIBLE TABLETS:

- Lack mechanical strength. Light weight and fragile. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet.
- Susceptible to degradation via temperature and moisture.

TABLE NO.1, Dispersible tablets available for common disease:

DISEASE CONDITION	DISPERSIBLE TABLETS AVAILABLE
Tuberculosis	Rifampicin/ Isoniazid
Diarrhea	Zinc sulfate
Malaria	Artemether/ Lumefanatrine (AL), Artesunate+Amodiaquine
HIV	Lamivudine/ Stavudine
Pneumonia	Amoxicillin, amoxicillin/Clavulanate, Sulfamethoxazole/ Trimethoprim
Pain and fever	Paracetamol

DEVELOPMENTAL CHALLENGES IN DISPERSIBLE DRUG DELIVERY

- **Ease of administration:**

These systems are easy to administer and handle hence, leads to better patient compliance. Usually, geriatric and pediatric patients experience difficulty in swallowing the conventional dosage forms because of tremors of extremities and

dysphasia. Fast Dissolving Delivery Systems may offer a solution for these problems.

- **Taste of the active ingredient:**

  Some drugs have relatively no taste, and simply adding a suitable flavor can hide any unpleasant sensation. However, most drugs require taste masking if they are to be incorporated into dispersible formulations. Simple wet granulation or roller compression with other excipients to minimize the presented surface area of the drug is one of the methods used to achieve this purpose. Spray coating can also be used. Coating can be done using coating material such as HPMC, EC, methacrylate and PVP. Cyclodextrins have been shown to provide some degree of taste masking by trapping the drug within the cyclic structure long enough to render initial dissolution. Electrochemical, hot-melt and supercritical fluid coating can also be used.

- **Dose:**

  High dose drugs present challenges to development of dispersible formulations which include,

  a. Taste masking of active ingredient

  b. Mouth feel or grittiness

  c. Tablet size

  The degree of bitterness along with the relative dose of the drug will affect the final tablet size. For example, coating of a tablet to mask the taste may increase the size of the tablet. The extent to which this increase will affect the mouth feel and tablet size will depend on the dose of the drug and the amount of coating material required for masking the taste.

- **Hygroscopicity:**

Several fast dissolving drugs are hygroscopic and cannot maintain integrity under normal conditions of temperature and humidity. Hence they require protection from humidity that calls for specialized product package.

- **Friability:**

In order to allow dispersible tablets to disintegrate rapidly in the mouth, they are made of either very porous or soft molded matrices or compressed into tablets with low compression force, which make the tablet friable and difficult to handle, often requiring peel off blister packing.

- **Mouth feel:**

patients should receive a product that is pleasant. Any large particles which are insoluble or slowly soluble in the mouth will lead to an unpleasant or gritty feel. This can be avoided by keeping the particle size limits below the detectable size. Effervescence and flavor can be added to improve the feel.

TABLET MANUFACTURING METHODS

There are three basic methods of manufacture:

- Direct compression
- Dry granulation
- Wet granulation

GRANULATION:

Primarily granules are prepared to improve flow and compression characteristics of the blend. But there are many other reasons, sometimes, multiple reasons for granulation, such as:

- Improving flow properties and hence uniformity of dose.

- Increasing the bulk density of the product.
- Facilitating metering or volumetric dispensing.
- Controlling the rate of drug release.
- Decreasing dust generation and employee exposure to the product.
- Improving product appearance.

Wet granulation

This is the most widely used process of granulation in the pharmaceutical industry. It involves the addition of a liquid to powders, to form a wet mass or it forms granules by adding the powder together with an additive. The wet mass is then dried and sized to obtain granules. The liquid added binds the moist powder particles by a combination of capillary and viscous forces in the wet state. More permanent bonds are formed during the subsequent drying state which leads to the formation of agglomerates.

Steps involved:

- Mixing of drugs and excipients
- Preparation of binder solution
- Mixing of binder solution with powder mixture to form a wet mass
- Coarse screening of wet mass using a suitable sieve
- Drying of moist granules
- Screening of dry granules through a suitable sieve
- Mixing of screened granules with disintegrants, glidant and lubricant
- Compression to form tablets

Dry granulation:

In dry granulation process, the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact material by compression and then to mill the compact to obtain granules. Two methods are used for dry granulation. The most widely used method is slugging, where the powder is pre compressed and the resulting tablets or slugs are milled to yield the granules. The other method is to pre compress the powder with pressure rolls using a machine such as chilosonator.

Advantages

The main advantages of dry granulation or slugging are that it uses less equipment and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step involved in wet granulation. Slugging can be used for advantages in the following situations:

- For moisture sensitive material.
- For heat sensitive material.
- For improved disintegration since powder particles are not bound together by a binder.

Disadvantages

- It requires a specialized heavy duty tablet press to form slugs.
- It does not permit uniform color distribution achieved with wet granulation where the dye can be incorporated into the binder liquid.
- The process tends to increase the production of dust which may cause contamination.

Steps involved:

- Milling of drugs and excipients
- Mixing of milled powders
- Compression into large, hard tablets to make a slug
- Screening of slugs
- Mixing with lubricants and disintegrating agents
- Tablet compression

Slugging: granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy and condition of the slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

Roller compaction: The compaction of powder by means of pressure roll can also be accomplished by a machine called chilosonator. Unlike tablet machine, the chilosonator turns out a compact mass in a steady continuous flow. The powder is fed between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules.

PRINCIPLE

The dispersible tablets are mainly based on the principle of employing super disintegrants in their formulation which at low concentrations, facilitate quick disintegration of the tablets. An ideal disintegrants should have poor solubility, poor gel formation, good hydration capacity, good compressibility, flow properties and no tendency to form complexes with the drugs.

As superdisintegrants are of prime importance, a careful selection of superdisintegrants based on the following factors is critical in the formulation.

- The disintegrants must possess quick wicking action for generating the hydrostatic pressure required for faster disintegration.

- Smaller particles are preferred over larger particles as the latter produce gritty mouth feel. The gel forming superdisintegrants are avoided for patient non-compliance.

- A more compactable superdisintegrant is preferred to avoid friability.

Method of addition of superdisintegrants:

- **INTERNAL ADDITION:**

  In wet granulation method, the superdisintegrant is added to the other excipients before wetting the powder with the granulating fluid to incorporate it within the granules. Whereas, in dry granulation method, the superdisintegrant is added to other excipients before compressing the powder between the rollers.

- **EXTERNAL ADDITION:**

  In both wet and dry granulation methods, the superdisintegrant is added to the granules during the dry mixing step prior to compression.

- **INTERNAL AND EXTERNAL ADDITION:**

  In this method, disintegrants is divided into two portions. Ne portion is added before granule formation and the remaining is added to granules with mixing prior to compression. The former is called intra granular disintegrants and the latter inter granular disintegrants. If both methods are used, the inter granular portion break the tablet into granules and the intra granular portion will help break the granules to release the drug substance into solution.

MECHANISM OF ACTION OF SUPERDISINTEGRANTS

The various mechanisms of disintegration are:

1. **Swelling:** High swelling force is observed in tablets with low porosity and vice versa. During swelling the adhesiveness of the other ingredients is considerably reduced and thereby facilitates the disintegration of the tablet.

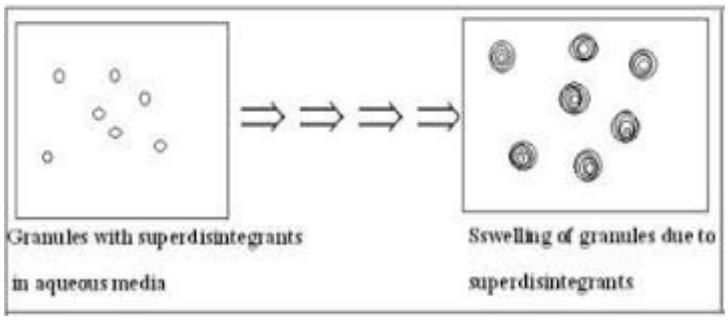


Figure2:Swelling action:Particles swell and breakup the particles

2. **Wicking:** The main principle involved here is porosity and capillary action. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the inter particulate bonds causing the tablet to break apart.

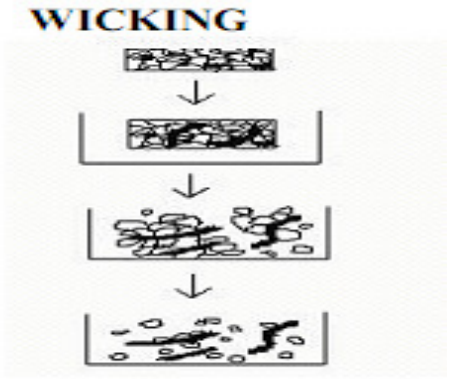


Figure3:Wicking action:Water is pulled by the disintegrant and reduces the physical bonding force between the particles..

3. **Electrostatic repulsion:** In this mechanism water is required for disintegration which is mainly due to electrostatic repulsions between the particles. Wicking may sometimes be the secondary mechanism of disintegration in such cases.

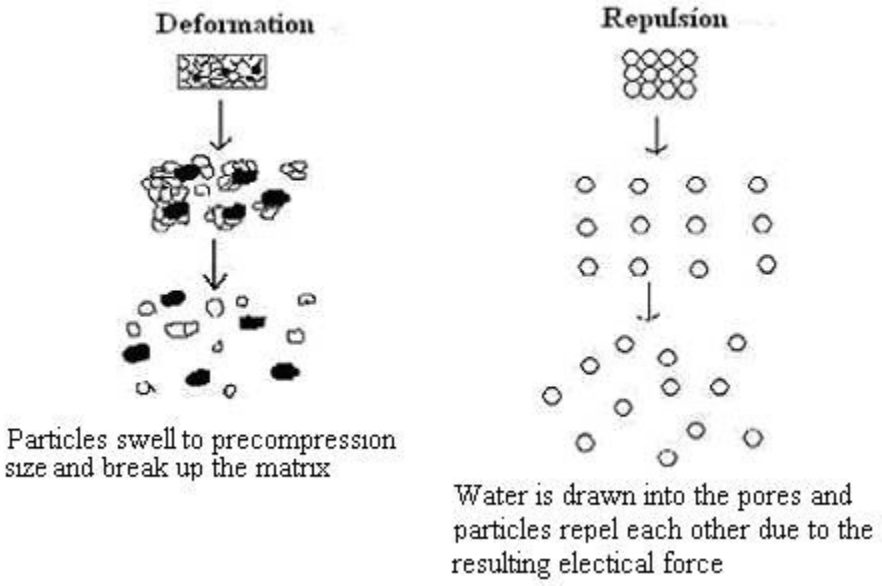


Figure4:Deformation and repulsion of particles

Table no.2,List of commonly used super disintegrants.

Superdisintegrant	**Mechanism of action**	**Properties**
Crosscarmellose sodium	Swells 4-8 folds in less than 10 seconds	Swells in two dimensions

	Swelling and wicking both	Direct compression or granulation
Crospovidone	Swells very little and returns to original size after compression but act by capillary action	Water insoluble and spongy in nature so gives porous tablets
Sodium starch glycolate	Swells 7-12 folds in less than 30 seconds	Swells in three dimensions and high level serves as sustained release matrix
Calcium silicate	Wicking action	Highly porous, light weight. Optimum concentration is 20-40%
Cross linked alginic acid	Rapid swelling action in aqueous medium or wicking action	Promotes disintegration in both wet and dry granulation.

METHOD OF PREPARATION:

1. **Spray drying:** Spray drying is one of the oldest forms of drying and one of the few technologies available for the conversion of a liquid to a dry solid. This process is carried out in three fundamental stages. The first stage is atomization of a liquid feed into fine droplets. In the second stage, spray droplets mix with the heated gas stream and the dried particles are produced by the evaporation of the liquid from the fine droplets. The final stage involves the separation of the dried powder from the gas stream and collection of these powders in a chamber. Allen and Wang produced a particulate support matrix for use in dispersible tablets by a spray drying technique. The components include supporting agents like non hydrolyzed and hydrolyzed gelatin, a bulking agent like mannitol and a volatilizing agent.

2. **Lyophilization or freeze drying:** Freeze drying or lyophilization is a process in which solvent is removed from a frozen drug solution or a suspension containing structure forming excipients. Freeze drying process normally consists of three steps:

    - Material is frozen to bring it below the eutectic point.
    - Primary drying to reduce the moisture around 4% w/w of dry product.
    - Secondary drying to reduce the bound moisture up to the required final volume.

    The resulting tablets are very light and have highly porous structures that allow rapid dissolution or disintegration. The freeze drying process may result in a glassy amorphous structure of excipients as well as the drug substance leading to an enhanced dissolution rate.

3. **Sublimation:** In this technique, highly volatile substances like camphor, urea and urethane are added to the blend before compression. When highly volatile substances are compressed, they can be easily removed by sublimation. This improves the dissolution rate as the end product is a porous structure due to the evaporation of the volatile substances. Additionally, several solvents like cyclohexane, benzene etc can also be used as pore forming agents.

4. **Molding:** The molding method is a very effective technique used for taste masking of bitter drugs. The major components used in this technique are water soluble. This technique is similar to the conventional tablet compression technique except that low pressures are used here. The powder blend is moistened with the solvent and the tablet is molded. This process is called solvent molding. The low compressional pressure used results in a porous structure which leads to enhanced dissolution rates. For further improvement in the dissolution rate, the powder blend is generally passed through a very

fine screen. The major drawback of the molded tablets is that they lack mechanical strength.

The molded forms have also been prepared directly from a molten matrix in which the drug is dissolved or dispersed (known as heat molding) or by evaporating the solvent from a drug solution or suspension at ambient pressure.

5. **Cotton candy process:** The process is so named as it utilizes a unique spinning mechanism to produce floss like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallised to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to dispersible tablets. This process can accommodate high doses of drugs and offers improved mechanical strength. However, high process temperatures limit the use of this process.

6. **Direct compression:** This method can be applied to manufacturing dispersible tablets by choosing appropriate combinations of excipients which can provide fast disintegration and good physical resistance. This technique us mainly preferred because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

    a) **Superdisintegrants:** the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. Tablet disintegration time can be optimized by concentrating the disintegrants. Below critical concentration tablet disintegration time is inversely proportional to disintegrants concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases.

b) **Sugar based excipients:** these have been widely used as bulking agents because of their high aqueous solubility, sweetness, pleasing mouth feel and good taste masking. Nearly all formulations for dispersible tablets incorporate some sugar materials in their formulations. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactitol, maltitol, sorbitol, starch hydrolysate, polydextrose and xylitol which display high aqueous solubility and sweetness and hence impart taste masking property and pleasing mouth feel.

7. **Nanonization:** A recently developed nanomelt technology involves reduction in particle size of drug to nano size by wet milling technique. Surface adsorption of the nano crystals of the drug is done on selected stabilizers for stabilizing them against agglomeration, which are then incorporated in to the dispersible tablets. This technique is mainly advantageous for poorly water soluble drugs and also for wide range of doses (up to 200 mg of drug per unit).

TABLE 3: **Advantages and Disadvantages of the different technologies for preparing rapidly disintegrating pharmaceutical forms.**

Technology	**Advantages**	**Disadvantages**
Freeze drying	Immediate dissolution.	Very poor physical resistance. High cost of production. Low dose of water soluble drugs.
Molding	Very rapid dissolution. High dose.	High cost of production. Weak mechanical strength. Possible limitations in stability.

Tableting	Low cost of production Use of standard equipment/materials. High dose. Good physical resistance.	Disintegration capacity markedly limited by the size and hardness of the tablets.

TABLE 4: Some examples of marketed products

Marketed Product	Active Ingredient	Therapeutic Ingredient	Manufacturer
Methadose	Methadone	Narcotic analgesic	Gen pharma
Voltarol	Diclofenac sodium	NSAID	Alpa pharma
Clarinex Redi Tabs	Desloratidine	Anti-histamine	Yash pharma
Riamet	Artemether and Lumefanatrine	Anti malarial	Novartis Australia
Lamotrigine	Lamotrigine	Anti epilepsy and bipolar disease	Actavis
Ranmoxy distab	Amoxicillin trihydrate	Anti bacterial	Ranbaxy
Rapidol	Paracetamol	Analgesic and antipyretic	Ethypharm industries, France
Analtra-DT	Tramadol HCl	Central analgesic	May Flower, India
Azcin-DT	Azithromycin	Macrolide antibiotic	West coast pharmaceuticals
C Pod dispersible tablets	Cefpodoxime Proxetil	Antibiotic	Yash pharma laboratories
Dispersible acyclovir tablets	Acyclovir	Antiviral	Yash pharma laboratories
Lovan tablets	Fluoxetin HCl	SSRI	Alphapharm P/L
Ivamer	Ivermectin	Anti helminthetic	Gen pharma

Ivaver DT plus	Ivermectin and Albendazole	Anti helminthetic	Gen pharma
Cefocef LB	Cefixime trihydrate	Cephalosporin antibiotic	Centaur pharma
Piram D	Piroxicam	NSAID	Mylan laboratories
Montasma	Montelukast sodium	Leukotriene receptor antagonist	Icarus healthcare

TABLE 5: Marketed technologies of fast disintegrating tablets

Patented technology	**Technique employed**	**Innovator company**	**Active ingredient and brand names**	**Advantages**
Zydis	Lyophilization	R. P Scherer Corp	Loratidine (Claritin, Reditab pharmaceuticals)	Highly porous
Durasolv	Molding	CIMA Labs	HyoscymineSulphate (NuLev)	Good rigidity
Wowtab	Compression molded tablets	Yamanouchi Pharma	Famotidine (Gaster D)	Adequate dissolution rate
Flashdose	Cotton Candy Process	Fuisz Technology Ltd	Tramadol Hcl(Reliviaflash dose)	Highly porous in nature,it shows pleasant mouthfeel property
Flashtab	Effervescent Disintigrant	Prographarm Group	Ibuprofen(Nurofen Flash dose)	Conventional tabletting technology

Ziplets	Molding	EurandInternational	Ibuprofen(Cibalgina due fast)	Sufficient mechanical strength
Oraquick	Micromask taste	KV Pharma co,inc	Hyoscyamine sulfate ODT	Significant friability is present in tablets

CHELATORS:

Chelators are small molecules that bind very tightly to metal ions. Some Chelators are the molecules that can be manufactured [e.g. ethylene diamine tetra acetic; EDTA]. The other Chelators are proteins made by living organisms [e. g. transferrin]. The key property shared by all Chelators is that the metal ion bound to the Chelators is chemically inert. Consequently, one of the important roles of Chelators is to detoxify metal ions and prevent poisoning.

Chelating agents were introduced into medicine as a result of the use of poison gas in World War-1. The first widely used chelating agent, the organic dithiol compound dimercaprol [also named British Anti- Lewisite or BAL], was used as an antidote to the arsenic-based poison gas, Lewisite. The sulphur atoms in BAL's mercaptan groups strongly bond to the arsenic in Lewisite, forming a water-soluble compound that entered the bloodstream, a allowing it to be removed from the body by the kidneys and liver. BAL had severe side-effects.

After World War -11, a large number of navy personnel suffered from lead poisoning as a result of their jobs repainting the hulls of ships. The medical use of EDTA as a lead chelating agent was introduced. Unlike BAL, it is a synthetic amino acid and contains no mercaptans. EDTA side effects were not considered as severe as BAL.

In the 1960s, BAL was modified into DMSA, a related dithiol with far fewer side effects. DMSA quickly replaced both BAL and EDTA, becoming the US standard of care for the treatment of lead, arsenic, and mercury poisoning, which it remains today.

Research in the former Soviet Union led to the introduction of DMPS, another dithiol, as a mercury-chelating agent. The Soviets also introduced ALA, which is transformed by the body into dithiol dihydrolipoic acid, a mercury and arsenic-chelating agent. DMPS has experimental status in the US FDA, while ALA is a common nutritional supplement.

Since the 1970s, iron chelating therapy has been used as an alternative to regular phlebotomy to treat excess iron deposition in people with haemochromatosis.

Several chelating agents are available, having different affinities for different metals. Common chelating agents include:

- Alpha lipoic acid (ALA)
- Aminophenoxyethane-tetra acetic acid (BAPTA)
- Deferasirox
- Deferiprone
- Deferoxamine
- Diethylene triamine penta acetic acid (DTPA)
- Dimercaprol (BAL)
- Dimercapto propane sulfonate (DMPS)
- Dimercaptosuccinic acid (DMSA)
- Ethylenediamine tetra acetic acid(calcium disodium versanate) ($CaNa_2$.EDTA)
- Ethylene glycol tetra acetic acid (EGTA)
- D-penicillamine

IRON OVERLOAD

Iron overload is the result of many disorders and can lead to the development of organ damage with increased mortalities. In humans, total body iron concentrations are maintained within the range of 200-1500 mg by inadequate adjustment of intestinal absorption, since no excretory mechanisms exist. In normal individuals, feedback mechanisms inhibit iron absorption as storage iron increases. Each condition that induces an increased net entry of iron within the body inevitably leads to iron overload. It can be classified as primary or secondary depending whether it results from a primary defect in the regulation of iron balance or acquired disorders. A known example of primary iron overload is hereditary *haemochromatosis [HHC], in* which iron is absorbed in excess because of increased iron transfer from the enteral cells to the blood. The secondary includes iron overload either due to, or associated with, ineffective erythropoiesis, chronic liver diseases, parenteral administration or ingestion of excessive amounts of iron. Thalassemia major and sideroblastic anemia are the two best examples of iron overload secondary to blood transfusions and ineffective erythropoiesis. Frequent blood

transfusions lead to excessive accumulation of iron with a toxic accumulation in 3-10 years.

The toxicity of iron results from two related events:

1. Excess iron concentration in various tissues of the body, particularly in liver, heart and endocrine organs with the consequence of liver diseases, diabetes mellitus and other complications.
2. Free iron that catalyses the formation of highly reactive hydroxyl radicles which lead to membrane damage and denaturation of proteins.

Once iron exceeds a certain level, these effects lead to significant morbidity and mortality. Without specific chelation therapy to remove iron, in 3-10 years almost all regularly transfused patients will have acquired a toxicity of iron. The main cause of death is cardiac complications.

Treatment of iron overload:

The aim of treatment of iron storage disease is to remove from the body the excess iron that has accumulated. This can be done by employing iron Chelators. Iron Chelators can be classified using a number of criteria such as their origin (synthetic versus biologically produced molecules), their interaction with solvents such as water (hydrophobic versus hydrophilic) or their stoichiometric interaction (bidentate versus hexadentate). Some of these properties have an important impact on the clinical utility of the chelator. One of the key clinical features is the degree to which they are absorbed from the gastrointestinal tract.

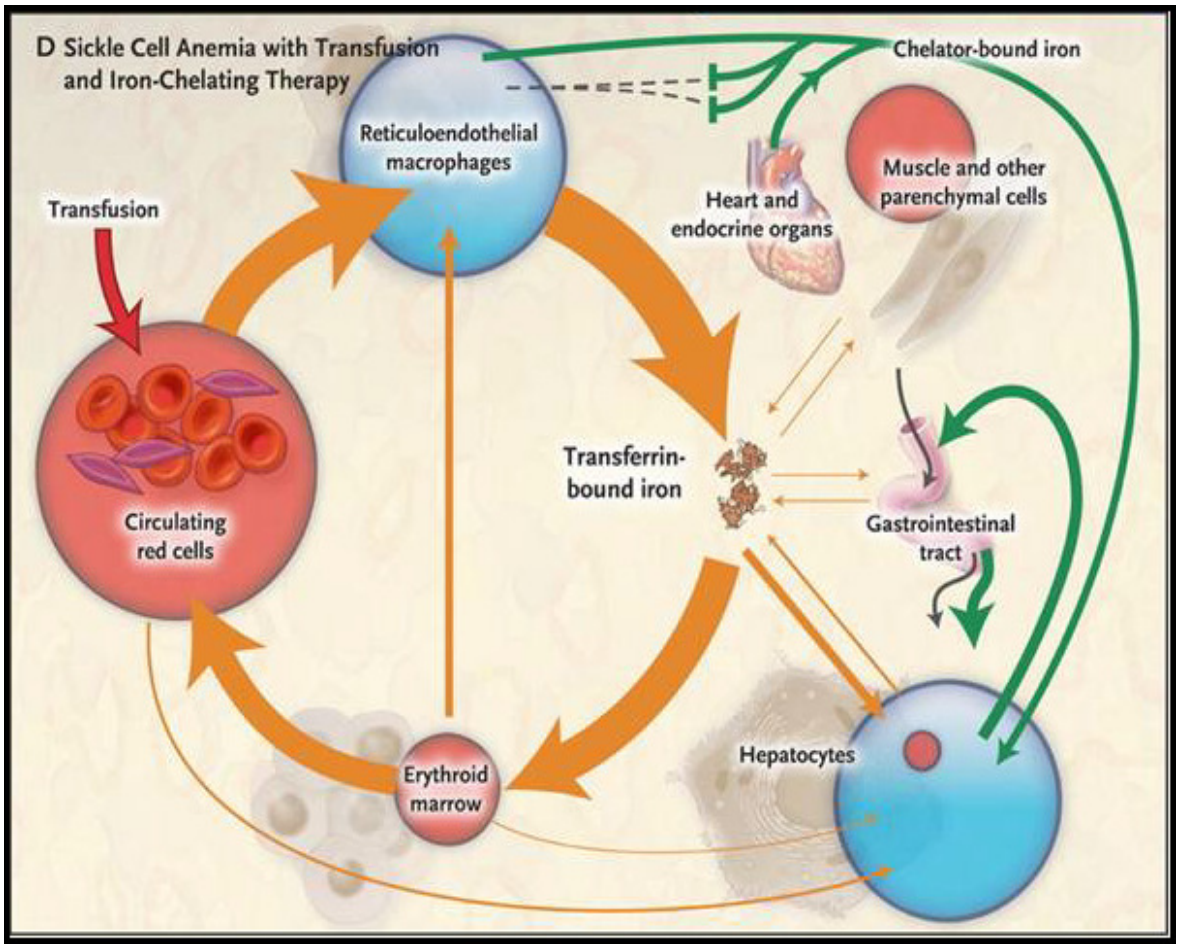


Figure5:Mechanism of action of iron chelater

By increasing the dose of Chelators in an attempt to speed up iron removal, there is a risk of increasing toxicity of iron Chelators by chelating iron, which is needed for normal tissue metabolism. Therefore, while the slow process of decreasing tissue iron to safe levels is being achieved; second goal is to make the iron as safe as possible by binding the toxic iron pools responsible for causing tissue damage. Iron chelation therapy reduces iron related morbidity, reduces and retards liver diseases, diabetes and other endocrine failures, normalizes growth and sexual development, prevents, and in some cases reverses cardiac insufficiency and improves quality of life.

TABLE 6: Available iron chelating agents used for the treatment of iron overload.

Agent	**Brand name(manufacturer)**	**Pharmacology**	**Route of administration**
Deferasirox	Exjade (Novartis)	Tridentate molecule; 2:1 stoichiometry for iron	Oral
Deferiprone	Ferriprox (Apotex)	Bidentate molecule; 3:1 stoichiometry for iron	Oral
Deferoxamine	Desferal (Novartis)	Hexadentate molecule; 1:1 stoichiometry for iron	IV

Excipients used in the formulation of dispersible tablets:

Excipients are inert substances used as diluents or vehicles for a drug. In the pharmaceutical industry it is a catch all term which includes various sub groups comprising diluents or fillers, binders or adhesives, disintegrants, glidants, flavors, colors and sweetners. All of these must meet certain criteria as follows:

- They must be physiologically inert.
- They must be acceptable to regulatory agencies.
- They must be physiologically and chemically stable.

- They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
- They must not interfere with the bioavailability of the drug.
- They must be commercially available in the form and purity commensurate to pharmaceutical standards.
- Cost must be relatively inexpensive.
- They must confirm to all regulatory requirements.

To assure that no excipient interferes with the utilization of the drug, the formulator must carefully and critically valuate combinations of the drug with each of the contemplated excipients and must as certain compliance of each ingredient with existing standards and regulations.

The screening of drug-excipient and excipient-excipient interactions should be carried out routinely in pre formulation studies. Determination of the optimum drug-excipient compatibility has been adequately presented in the literature.

TABLE 7: List of excipients used in the formulation of dispersible tablets

Excipients	**Function**	**Example**
Diluents	Fillers used to make the required bulk of the tablet. Also used as disintegrants in the dispersible and orally disintegrating tablets. Secondary function is to provide better tablet properties like improve cohesion, flow, compactibility, stability, etc.	Lactose, spray dried lactose, microcrystalline cellulose (Avicel 101 and 102), mannitol (Pearlitol SD200 and 25 C), sorbitol, dibasic calcium phosphate dehydrate
Binders	Impart cohesive strength to powdered materials	Gelatin, glucose, lactose, cellulose derivatives, EC, HPMC, PVP, CMC, acacia etc
Superdisintegrants	They facilitate tablet breaking when it comes in contact with water in oral cavity/ GIT	Ac-di-sol, Crospovidone, starch, sodium starch glycolate.
Lubricants	Prevent adhesion of tablet material to dies and punches, reduce interparticulate friction.	Insoluble-stearic acid, magnesium state, talc, calcium stearate.

	Facilitate easy ejection of tablet from dies.	Soluble- SLS, PEG-400,600,800 etc
Glidants	Reduce friction between the particles and improve flow properties	Colloidal silicon dioxide, corn starch, talc.
Ant adherents	These are added to prevent adhesion of tablet material to punches and dies.	Talc
Sweetners	To produce a palatable dosage form	Sucrose, sucralose, saccharin, aspartame etc
Flavors	Improve taste of dosage form	Peppermint, vanilla, orange, banana, cinnamon,
Colors	For better appearance	Sunset yellow

Packaging of dispersible tablets:

Some of the dispersible tablets are stable during storage, E.G., for two years or even 3 years in conventional packing and these type of dosage forms are stored in HDPE bottles, strip packs and blister packs.

AIM AND OBJECTIVE

The objective of the current study was to development optimize a oral disintegration tablets. Deferasirox is a rationally designed oral Iron chelator.

Its main use is to reduce chronic Iron overload in patients who are receiving long term blood transfusions for conditions . such as “beta-thalassemia”.

It is the first oral medication of oral disintegration tablets were prepared by direct compression method using different super disintegrating agents . such as cross povidone, sodium starch glycolate & cross carmellose sodium.

The main objective of this study was .

To perform reformulation studies. To formulate deferasirox oral dispersible tablets. To select formulation based on invitor studies of oral dispersible tablets. To perform stability studies on the most satisfactory formulation. To correlate innovator product.To formulate deferasirox oral dispersible tablets. To obtain a suitable dosage form of better “taste masking & invitro drug release”.

LITERATURE REVIEW

PAST WORK CARRIED ON DEFERASIROX:

Elliott Vichinsky *et. al.,* (2007) evaluated the safety and tolerability of Deferasirox in comparision with Deferoxamine in this population. Assessment of efficacy, as measure by the change in liver iron concentration (LIC) using biosusceptometry, was a secondary objective. A total of 195 adult and pediatric patients received Deferasirox (n=132) or Deferoxamine (n=63). Adverse events most commonly associated with Deferasirox were mild, including transient nausea, vomiting. Diarrhea, abdominal pain and skin rash. Abnormal laboratory studies with Deferasirox were occasionally associated with mild non progressive increase in serum creatinine and reversible elevations in liver function tests. Discontinuation rates from Deferasirox and Deferoxamine were similar. Over 1 year, similar dose-dependant LIC reductions were observed with Deferasirox and Deferoxamine. Once daily oral Deferasirox has acceptable tolerability and appears to have similar efficacy to Deferoxamine in reducing iron burden in transfused patients with sickle cell disease.

Brad *et. al.,* (2009) described the safety profile of open-label, adjunctive Deferasirox iron chelation therapy in eight patients with biopsy-proven mucormycosis. Deferasirox was administered for an average of 14 days [range, 7 to 21] at 5 to 20 mg/kg of body weight/day. The only adverse effects attributable to Deferasirox were rashes in two patients. Deferasirox treatment was not associated with changes in renal or liver function, complete blood count, or transplant immunosuppressive levels. Thus, Deferasirox appears safe as an adjunctive therapy for mucormycosis.

Renzo Gallenello *et. al.,* (2008) investigated the effect of food and time of food intake on the pharmacokinetics of Deferasirox on healthy volunteers and patients with transfusional hemosiderosis. The bioequivalence of a single oral dose of Deferasirox (20 mg/kg) was assessed following administration either before a high fat or standard breakfast or concurrent with a standard breakfast in comparision with fasted conditions in healthy

volunteers. The bioavailability of Deferasirox was determined following a single oral dose (20 mg/kg) under fed and fasted conditions in patients. These data showed that the type of food, calorie content and fat content of the meal influence bioavailability of Deferasirox when consumed concurrently. In conclusion, it is recommended that Deferasirox be administered atleast 30 mins before meals.

Romain Sechaud *et. al.,* (2008) evaluated the absolute bioavailability of a single 375 mg oral dose of Deferasirox administered in the form of a tablet compared with a 130 mg intravenous infusion of Deferasirox. The main study phase consisted of 17 healthy male volunteers. Plasma concentrations of Deferasirox were measured following each treatment, and pharmacokinetic parameters including absolute oral bioavailability were determined. Absolute oral bioavailability of the Deferasirox tablets was 70% (90% confidence interval, 62%-80%).

Cappelilini *et. al.,* (2006) conducted a comparitive phase III trial to demonstrate the efficacy of Deferasirox in regularly transfused patients with beta-Thalassemia aged 2 years or older. Patients were randomized and received treatment with Deferasirox (n=296) or Deferoxamine (n=290), with dosing of each according to baseline liver iron concentration (LIC). The primary end point was maintenance or reduction of LIC; secondary end points included safety and tolerability, change in serum ferritin level, and net body iron balance.

Deborah Chirnomas *et. al.,* (2009) performed a prospective study of oral Deferasirox pharmacokinetics (PK), comparing 10 transfused patients with inadequate Deferasirox response (rising ferritin trend or rising liver iron on Deferasirox doses >30mg/kg per day) with control transfusion dependant patients (n=5) with adequate response. Subjects were admitted for 4 assessments: Deferoxamine infusion, urinary iron measurement, quantitative hepatobilary scintigraphy, a 24 hour Deferasirox PK study following a single 35 mg/kg dose of oral Deferasirox; and pharmacogenomic analysis. Patients with inadequate response to Deferasirox had significantly lower systemic drug exposure compared with control patients ($p< 0.00001$). C_{max}, **V** volume of distribution/ bioavailability and elimination half life were not different between the groups, suggesting

bioavailability as the likely discriminant. Effective dosing regimens for inadequately responding patients to Deferasirox must be determined**.**

Andrej Skerjanee *et. al.,* (2010) investigated the pharmacokinetic interactions of Deferasirox with Midazolam, Rifampicin and Repaglinide in healthy volunteers. In the induction assessment, single dose Deferasirox pharmacokinetics was obtained in the presence and absence of a repeated dose regimen of rifampin. In the CYP3A interaction evaluation, midazolam in the presence and absence of steady state concentrations of Deferasirox. To test for interaction at the level of CYP2C8, single dose Repaglinide pharmacokinetics/pharmacodynamics were determined with and without repeated dose administration of Deferasirox. After rifampin, a significant reduction (44%) in AUC to Deferasirox was observed. Upon co administration of midazolam, there was a modest reduction of up to 22% in midazolam exposure (AUC, C_{max}), suggesting a modest induction of CYP3A4/5 by Deferasirox. Deferasirox caused increase in Repaglinide plasma C_{max} and AUC of 1.5 fold to over 2 fold, respectively, with little change in blood glucose measures.

Schienfled *et. al., (*2007) reviewed the dermatologic uses and effects of Deferasirox, bortezomib, dastinib and cyclosporine eye drops. He reviewed that Deferasirox, an oral iron chelator could be an effective treatment against porphyria cutanea tarda, haemochromatosis and pathogens such as mucor that thrive in iron rich environments.

REVIEW OF WORK DONE ON DISPERSIBLE TABLET:

Sandeep patil B et al Formulated quick dispersible tablet of olanzapine by direct compression method. Effect of super disintegrant crospovidone on wetting time, disintegration time, drug content & *in-vitro* release has been studied. Disintegration time decreased and percent drug dissolved increased with increase in the level of crospovidone.

Kuchekar BS et al Formulation dispersible tablets of norfloxacin using natural substances as disintegrants such as isapghula husk powder, Cassia tora powder(defatted) and Cassia nodosa powder in different concentration by direct compression method. The study reveals that natural gums used as disintegrants were effective in low concentration.

Snehalatha et al Formulated dispersible tablets of piroxicam using different natural disintegrants in order to get required theoretical release profile. The influence of the disintegrant concentration and granulation technique on the release of piroxicam was studied. The study reveals that the formulation prepared by direct compression exhibits better dissolution, disintegration at low concentration of distegration of natural distintegrants.

Mohanachandran et al Formulated mouth dispersible tablets of amlodipine besylate by direct compression method using different super disintegrants. FDT's were evaluated for its physicochemical properties and *in-vitro* dissolution. Effect of different superdisintegrant on disintegration behavior of tablets was evaluated in phosphate buffer pH 7.2. All formulations were evaluated for pre-compression and post-compression parameters. Wetting time of formulations containing crosscarmellose sodium was least and tablets showed faster disintegration. FT-IR studies revealed that there physio-chemical interaction between amlodipine besylate and other excipients.

Suresh Kulkarni V et al Formulated disintegrating meloxicam tablets by wet granulation method. The influence of superdisintegrants, crosspovidone and crosscarmellose sodium on disintegration time, wetting time and water absorption ratio are studied. Tablets contained crospovidone exhibit quick disintegration time than tablets containing croscaremellose sodium. The fast disintegrating tablets of meloxicam with shorter disintegration time, acceptable taste and sufficient hardness could be prepared using crospovidone and other excipients at optimum concentration.

Avani Gosai R et al formulated oro-dispersible tablets of ondansetron hydrochloride by direct compression using super-disintegrants such as sodium starch glycolate and croscarmellose as superdisintegrants, as the combination of these two agents gives better disintegration of the tablet. Dissolution study revealed faster release rate of ondansetron hydrochloride from the tablets as compared to pure drug and marketed conventional tablet formulation of andansetron hydrochloride. It was concluded that superdisintegrants addition technique is a useful method for preparing oro dispersible tablets by direct compression method.

PLAN OF WORK

- Pre formulation studies of excipients and their compatibility with the API.
- Innovator product evaluation.
- Development of various formulations and preparation of dispersible tablets by
  - ✓ Direct compression method
  - ✓ Wet granulation technique
- Selection and optimization of the best formulation.
- Comparision of the optimized formulation with the innovator product.
- To perform stability studies on the most satisfactory formulation as per ICH guidelines.

I. Pre-compression parameters:

- Angle of repose
- Bulk density
- Tapped density
- Hausner's ratio
- Compatibility study

II. Post-compression parameters:

- Hardness uniformity
- Uniformity of thickness
- Friability test
- Weight uniformity test
- Drug content uniformity
- Wetting time
- *In vitro* dispersion time
- *In vitro* disintegration time
- *In vitro* dissolution studies
- Final comparisons between evaluated results of direct compression.

LIST OF EQUIPMENTS:

Table 8: List of equipments

Equipments	Manufacturer
Electronic balance	Mettler-Toledo, USA
Bulk density apparatus	Electrolab, Mumbai
Rapid Mixer Granulator (RMG)	Anchor Mark Pvt. Ltd.
Rotary Tablet punching machine	Rimek, Mumbai
Friability test apparatus	Electrolab, Mumbai
Tablet dissolution apparatus	Electrolab, Mumbai
Disintegration apparatus	Electrolab, Mumbai
Helium lamp (LOD)	Mettler-Toledo
Thickness (Vernier Calipers)	Mitutogo Vernier Calipers
Environmental Chambers	Thermolab
Hot air oven	Eltek motors, Mumbai
High performance liquid chromatography (HPLC)	Waters, Hyderabad
Sieves	Jayanth test sieves, Mumbai
Hardness tester	Dr.Schleuniger pharmatron USA
Fluidized bed drier	Anchor Mark Pvt. Ltd.

LIST OF CHEMICALS: Table no:9

Ingredients	Manufacturer	Supplier
Deferasirox	Natco Pharma Ltd.,Hyderabad	Natco Pharma Ltd, Hyderabad
Crospovidone XL	ISP Technologies Inc, USA	Ansul Agencies, Mumbai
Starch 1500	DMV International GmbH,	KMV Enterprises, Hyderabad

	Netherlands	
MCC pH 101	FMC Biopolymer, USA	Signet Chemical Corporation, Mumbai
MCC pH102	FMC Biopolymer, USA	Signet Chemical Corporation, Mumbai
SLS	Merck limited, Mumbai	Vasco Scientifics Pvt. Ltd., Secunderabad
Povidone K30	ISP Technologies Inc, USA	Signet Chemical Corporation, Mumbai
Aerosil	Mayur Chemicals, Mumbai	Mayur Chemicals, Mumbai
Magnesium stearate	Ferro Industries Quimica, Portugal	Signet Chemical Corporation, Mumbai
SSG	JRS Pharma, Germany	KMV Enterprises, Hyderabad
Tween 80	Merck limited, Mumbai	Vasco Scientifics Pvt. Ltd., Secunderabad
SSF	JRS Pharma, Germany	Merck chemicals, Mumbai
Talc	Luzenac Valchisone, Italy	Signet Chemical Corporation, Mumbai
L-HPC-LH11	DMV International GmbH, Netherlands	KMV Enterprises, Hyderabad
Lactose Monohydrate	DMV International GmbH, Netherlands	KMV Enterprises, Hyderabad
Sucralose	M.B.Sugars & Pharmaceuticals Limited, Maharastra	Signet Chemical Corporation, Mumbai
Orange Flavor	Firmenich Asia India Pvt. Ltd.	Manish Global Industries

DRUG PROFILE

DEFERASIROX:

Category: Iron chelator

Molecular formula: $C_{21}H_{15}N_3O_4$

Molecular weight: 373.4

Structural formula:

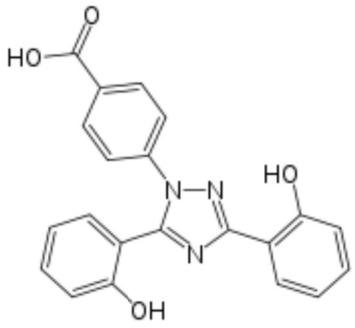


Figure no:6

Chemical name: 4-[3, 4-Bis (2-hydroxyphenyl)-1H-1, 2, 4-triazol-1yl]-benzoic acid

Description: Deferasirox is a white to slightly yellow powder that is freely soluble in dimethyl formamide and dimethyl sulfoxide, slightly soluble in methanol, practically insoluble in water.

Indication: Deferasirox is indicated in for the treatment of Chronic Iron Overload due to blood transfusions in adult and pediatric patients (aged 2 years and over).

Mechanism of action:

Deferasirox mobilize tissue iron by forming soluble, stable complexes that are then excreted in the feces. It is a tridentate iron chelator requiring two molecules of the drug to form the stable complex. Iron is chelated, both from the reticuloendothelial cells (RE

cells) as well as various parenchymal tissues. The chelated iron is cleared by the liver and excreted through bile. It also has the ability to prevent myocardial cell iron uptake, remove iron directly from myocardial cells. In fact, ICL 670 readily yields iron to DFO. In animal models, on molar basis, it has been shown to be 5 times more potent than DFO and ten times more potent than Deferiprone. Iron removal also depends on plasma concentration, host factors, degree of loading and rate of accessibility of accumulation iron to chelator.

Pharmacodynamics:

Pharmacodynamic effects tested in an iron balance metabolic study showed that Deferasirox (10, 20 and 40 mg/kg per day) was able to induce a mean net iron excretion (0.119, 0.329 and 0.445 mg Fe/kg body weight per day, respectively) within the clinically relevant range (0.1-0.5 mg/kg per day). Iron excretion was predominantly fecal.

Pharmacokinetics:

ABSORPTION:

Deferasirox is absorbed following oral administration with median times to maximum plasma concentration (T_{max}) of about 1.5-4 hours. The C_{max} and AUC of Deferasirox increase linearly with dose after both single administration and under steady state conditions. Exposure to Deferasirox increased by an accumulation factor of 1.3-2.3 after multiple doses. The absolute bioavailability of Deferasirox tablets for oral suspension is 70% compared to an intravenous dose. The bioavailability was variably increased when taken with a meal.

DISTRIBUTION:

It is highly protein bound (~99%) almost exclusively to serum albumin. The percentage of Deferasirox confined to the blood cells was 5% in humans. The volume of distribution at steady state (V_{ss}) of Deferasirox is 14.37 ±2.69 L in adults.

METABOLISM:

Glucouronidation is the main pathway with subsequent bilary excretion. Deconjugation of glucouronides in the intestine and subsequent reabsorption is likely to occur. The drug is mainly glucouronidated by UGT1A1 and to a lesser extent by UGT1A3. CYP450-catalysed metabolism of Deferasirox appears to be minor in humans (about 8%). Deconjugation of glucouronides in the intestine was confirmed in a clinical study in which the administration of cholestyramine 12g daily twice (strongly binds to Deferasirox and its conjugates) 4 and 10 hours after administration after a single dose of Deferasirox resulted in a 45% decrease exposure (AUC) by interfering with the enterohepatic cycling of the drug.mai

EXCRETION:

Deferasirox and its metabolites are primarily excreted in the feces (~84%). Renal excretion of Deferasirox and metabolites is minimal (8% of the administered dose). The mean elimination half life ranged from 8-16 hours following oral administration.

Dosage and administration:

Recommended initial daily dose is 20mg/kg body weight.

Maintenance daily dose to be adjusted if necessary every 3 to 6 months based on serum ferritin trends.

Maximum daily dose is 30mg/kg body weight.

Deferasirox must be taken once daily on an empty stomach at least 30 mins before food. Deferasirox tablets are dispersed by stirring in a glass of water or apple or orange juice [100-200ml] until affine suspension is obtained.

Contraindication:

Deferasirox is contraindicated in patients with:

Creatinine clearance <40ml/min or serum creatinine > 2 times the age appropriate upper limit of normal.

Poor performance status and high-risk myelodysplastic syndromes or advanced malignancies.

Platelet counts < 50x 1000000000/l

Hypersensitivity to Deferasirox or to any of the excipients.

Drug interactions:

The concomitant administration of Deferasirox and aluminum containing antacid preparations has not been formally studied. Although Deferasirox has a lower affinity for aluminum than iron, do not administer Deferasirox with aluminum containing antacid preparations.

Deferasirox is contraindicated in people already taking iron chelator due to an increased risk of toxicity.

Side effects:

Deferasirox has a manageable side effect profile and when patients do experience side effects, they are generally mild to moderate and transient.

Gastrointestinal disturbances (mainly nausea, vomiting, diarrhea or abdominal pain) occurred in approximately 26% of patients in clinical trials. Diarrhea was reported more often in pediatric patients aged 2-5 years than in older children and adults.

Rare cases of anaphylaxis and angiodema have been reported.

Skin rash was seen in 7% of the patients and was mostly mild to moderate and generally transient.

As with other iron chelator therapy, high frequency hearing loss and early cataracts have been uncommonly observed.

Warnings:

Must not be chewed or swallowed whole.

It should also not be dispersed in carbonated drinks or milk due to foaming and slow dispersion.

It should not be combined with other iron chelator therapies as the safety of such combinations has not been established.

Renal, hepatic failures and gastrointestinal hemorrhage.

Risks and precautions:

Some reports have been reported of kidney impairment associated with Deferasirox use.

Could cause cytopenia.

Liver failure, sometimes leads to death, has been reported during treatment of people with pre existing severe liver damage such as cirrhosis.

Thus tests which determine these functions during this treatment must be carried out.

Dizziness while using Deferasirox, so care should be taken while engaging in activities requiring alertness such as driving or using machinery.

Storage:

Store at room temperature at 77□F (25□C), away from light and moisture. Brief storage between 59-86□F (15-30□C) is permitted. Keep away from children and pets.

Uses:

The medication is used to treat ongoing high levels of iron in the body caused by multiple blood transfusions. Frequent blood transfusions are needed in certain types of blood diseases. Blood transfusions have very helpful benefits, but they can cause the body to hold onto too much iron. The extra iron can build up in various organs and cause problems such as heart failure, liver disease and diabetes. Getting rid of extra iron can decrease the risk of these diseases.

EXCIPIENT PROFILE

LACTOSE, MONOHYDRATE:

Nonproprietary name: Lactose

Synonym: Capsulac, Lactochem, Tablettose.

Chemical name: O-β-D-Galactopyranosyl-(1,4)-α-D-glucopyranose monohydrate.

Empirical name: $C_{12}H_{22}O_{11}.H_2O$

Molecular weight: 360.31

Functional category: dry powder inhaler carrier, lyophilization aid, tablet binder, tablet and capsule diluents and tablet and capsule filler.

Description: In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions. Lactose occurs as white to off white crystalline powder or particles. Lactose id odorless and slightly sweet tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

Solubility: practically insoluble in chloroform, ethanol and water (1 in 5.24, 1 in 3.05 at 40□C, 1 in 2.30 at 50□C, 1 in 1.71 at 60□C. 1 in 0.96 at 80□C)

Stability and storage conditions: mould growth may occur under humid conditions. Lactose may develop a brown color on storage, the reaction being accelerated by warm, damp conditions. It should be stored in a well closed container in a cool, dry place.

Incompatibilities: a maillard type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown or yellow brown coloured products. It is also incompatible with amino acids, amphetamines and lisinopril.

Applications: lactose is widely used as filler and diluents in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluents in dry powder inhalations.

Related substances: lactose, anhydrous; lactose, inhalation; monohydrate and corn starch.

CROSPOVIDONE:

Nonproprietary name: Crospovidone.

Synonyms: crospovidonum; polyplasdone XL; polyvinyl polypyrrolidone.

Chemical name: 1-Ethenyl-2-pyrrolidone homopolymer

Empirical formula: $(C_6H_9NO)_n$

Molecular weight: >1, 000, 000

Functional category: tablet disintegrants

Description: Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Solubility: practically insoluble in water and most common organic solvents.

Stability and storage conditions: since Crospovidone is hygroscopic, it should be stored in airtight container in a cool and dry place.

Incompatibilities: Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, Crospovidone may form molecular adducts with some materials.

Applications: Crospovidone is a water insoluble tablet disintegrants and dissolution agent used at 2-5% concentration in tablets prepared by direct compression or wet and dry granulation methods. It can also be used as a solubility enhancer.

Related substances: Crospovidone, Povidone.

STARCH:

Nonproprietary name: pregelatinised starch.

Synonyms: compressible starch, Lycatab C, starch 1500 G, Tablitz.

Chemical name: pregelatinised starch.

Empirical formula: $(C_6H_{10}O_5)_n$ where n=300-1000

Functional category: tablet and capsule diluents, tablet and capsule disintegrants, tablet binder.

Description: pregelatinised starch occurs as a moderately coarse to fine, white to off white color powder. It is odorless and has a slight characteristic taste. Examination of fully pregelatinised starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinised granules, i.e., no 'maltese crosses' characteristic of the starch birefringence pattern.

Solubility: practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending on the degree of pregelatinisation. Pastes can be prepared by sifting the pregelatinised starch into stirred, cold water. Cold water soluble matter for partially pregelatinised starch is 10-20%.

Stability and storage conditions: pregelatinised starch is a stable but hygroscopic material, which should be stored in a well closed container in a cool dry place.

Related substances: corn starch and pregelatinised starch; starch, sterilizable maize.

Applications: partially pregelatinised starch is a modified starch used in oral capsule and tablet formulations as a binder, diluents and disintegrants. Both partially and fully pregelatinised starch may also be used in wet granulation processes. Fully pregelatinised starchs can be used to make soft capsule shells and coatings as well as binders in tablets.

MICROCRYSTALLINE CELLULOSE:

Nonproprietary name: microcrystalline cellulose.

Synonyms: Avicel PH; Celex; crystalline cellulose; emcocel; tabulose.

Chemical name: cellulose.

Empirical formula: $C_6H_{10}O_5)_n$ where n~220

Molecular weight: ~36000

Functional category: adsorbent; suspending agent; tablet and capsule diluents; tablet disintegrant.

Description: microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particle. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Solubility: slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids and most organic solvents.

Stability and storage conditions: microcrystalline cellulose is a stable through hygroscopic material. The bulk material should be stored in a well closed container in a cool, dry place.

Incompatibilities: microcrystalline cellulose is incompatible with strong oxidizing agents.

Applications: it is widely used in pharmaceuticals primarily as a diluents/binder in oral tablet and capsule formulations where it is used in both wet granulations and direct

compression processes. It also has some lubricant and disintegrants properties that make it useful in tabletting. It is also used in cosmetics and food products.

Related substances: microcrystalline cellulose and carrageenan; microcrystalline cellulose and carboxy methyl cellulose sodium; microcrystalline cellulose and guar gum; powdered cellulose.

SODIUM LAURYL SULFATE:

Nonproprietary name: sodium lauryl sulfate

Synonyms: dodecyl alcohol hydrogen sulfate, sodium salt; dodecyl sodium sulfate; sodium monolauryl sulfate.

Chemical name: sulfuric acid monododecyl ester sodium salt (1:1)

Empirical formula: $C_{12}H_{25}NaO_4S$

Molecular weight: 288.38

Functional category: anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.

Description: SLS consists of a white or cream to pale yellow colored crystals, flakes or powder having a smooth feel, a soapy, bitter taste and a faint odor of fatty substances.

Solubility: freely soluble in water giving an opalescent solution; practically insoluble in chloroform and ether.

Stability and storage conditions: sodium lauryl sulfate is stable under normal storage conditions. However, in solution, under extreme conditions, i.e., pH 2.5 or below, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate. The bulk material should be stored in a well closed container away from strong oxidizing agents in a cool and dry place.

Incompatibilities: SLS reacts with cationic surfactants causing loss of activity even in concentrations too low to cause precipitation. Unlike soaps, it is compatible with dilute acids and calcium and magnesium ions. It is incompatible with salts of polyvalent metal ions, such as aluminum, lead, tin or zinc, and precipitates with potassium salts.

Applications: SLS is an anionic surfactant employed in a wide range of nonparenteral pharmaceutical formulations and cosmetics. It is a detergent and wetting agent effective in both alkaline and acidic conditions. It acts as a tablet lubricant in the concentration of 1.0-2.0%

Related substances: cetosteryl alcohol; Cetyl alcohol; magnesium lauryl sulfate; wax.

POVIDONE:

Nonproprietary name: Povidone

Synonyms*:* kollidon; plasdone; polyvinylpyrrolidone

Chemical name*:* 1-Ethenyl-2-pyrrolidone homopolymer

Empirical formula*:* $(C_6H_9NO)_n$

Molecular weight*:* 2500-3,000,000

Functional category*:* disintegrants; dissolution enhancer; suspending agent; tablet binder.

Description*:* Povidone occurs as a fine, white to creamy white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K90 and higher K value Povidones are manufactured by drum drying and occurs as plates.

Solubility: freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water; practically insoluble in ether, hydrocarbons, and mineral oil.

Stability and storage conditions*:* Povidone darkens to some extent on heating at 150□C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110-130 □C. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. As the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities: Povidone is compatible in solution with a wide range of inorganic salts. Natural and synthetic resins and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital, Tannins and other compounds.

Applications*:* it is primarily used in solid dosage forms as a tablet binder, tablet diluents or a coating agent in the concentration of 0.5-5%. Povidone is used as a suspending agent and dispersing agent in the concentration of 5%.

Related substances*:* Crospovidone.

COLLOIDAL SILICON DIOXIDE:

Nonproprietary name: colloidal anhydrous silica

Synonyms: aerosol, Cab-O-Sil, colloidal silica

Chemical name: silica

Empirical formula: SiO_2

Molecular weight: 60.08

Functional category: adsorbent, anti caking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrants; thermal stabilizer; viscosity-increasing agent.

Description: colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15nm. It is light, loose, bluish-white colored, odorless, tasteless amorphous powder.

Solubility: practically insoluble in organic solvents, water, antacids, except t hydrofluoric acid. Soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water. For aerosil, solubility in water is 150 mg/L at 25□C (pH 7)

Stability and storage conditions: colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. Colloidal silicon dioxide powder should be stored in a well closed container.

Incompatibilities: incompatible with diethylstilbestrol preparations.

Applications: colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tabletting and capsule filling. It acts as a glidant in the concentration of 0.1-1%.

Related substances: hydrophobic silicon dioxide.

MAGNESIUM STEARATE:

Nonproprietary name: magnesium stearate

Synonyms: magnesium octadecanoate; octadecanoic acid; magnesium salt.

Chemical name: octadecanoic acid magnesium salt

Empirical formula: $C_{36}H_{70}MgO_4$

Molecular weight: 591.24

Functional category: tablet and capsule lubricant.

Description: magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Solubility: practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in warm benzene and warm ethanol (95%).

Stability and storage conditions: it is stable and should be stored in a well closed container in a cool and dry place.

Incompatibilitie: incompatible with strong acids, alkalis and iron salts. Avoid mixing with oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins and most alkaloidal salts.

Applications: magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations of 0.25% and 0.5% w/w.

Related substances: calcium stearate; magnesium aluminum silicate; stearic acid; zinc stearate.

SUCRALOSE:

Nonproprietary name: sucralose

Synonyms: sucralose; sucralosum; sucraplus

Chemical name: 1, 6-Dichloro-1, 6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside.

Empirical formula: $C_{12}H_{19}C_{13}O_8$

Molecular weight: 397.64

Functional category: sweetening agent

Description: sucralose is a white to off white colored free flowing crystalline powder.

Solubility: freely soluble in ethanol (95%), methanol and water; slightly soluble in ethyl acetate.

Stability and storage conditions: sucralose is a relatively stable material. In aqueous solution at highly acidic conditions (pH<3), and at high temperatures (<35 □C), it is hydrolyzed to a limited extent, producing 4-chloro-4-deoxygalactose and 1, 6-dichloro-1, 6-deoxyfructose. It should be stored in a well closed container in a cool, dry place at a temperature exceeding 21 □C.

Applications: sucralose is used as a sweetening agent in beverages, foods and pharmaceutical applications. It has a sweetening power of approximately 300-1000 times that of sucrose and has no aftertaste.

Related substances: sucrose.

SUNSET YELLOW:

Synonyms: FD&C yellow #6, yellow orange S

Empirical formula: $C_{16}H_{10}N_2Na_2O_7S_2$

Molecular weight: 452.37

Functional category: colorant; opacifier

Description: reddish yellow powder. Aqueous solutions are bright orange colored.

Solubility: solubility at 20 □C-Acetone (1 in 38.5), ethanol (1 in 333), glycerin (1 in 5), propylene glycol (1 in 5).

Incompatibilities: poorly compatible with citric acid, saccharose solutions, and a saturated bicarbonate solutions.

SODIUM STARCH GLYCOLATE:

Nonproprietary name: sodium starch glycolate

Synonyms: carboxy methyl starch, sodium salt; primojel; tablo.

Chemical name: sodium carboxymethyl starch

Functional category: tablet and capsule disintegrant.

Description: sodium starch glycolate is a white or almost free flowing very hygroscopic powder.

Solubility: practically insoluble in methylene chloride. It gives a translucent suspension in water.

Incompatibilities: sodium starch glycolate is incompatible with ascorbic acid.

Applications: it is widely used in oral pharmaceuticals as a disintegrants in tablet formulations. It is commonly used in tablets prepared by either direct compression or wet granulation process. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient.

SODIUM STEARYL FUMARATE:

Nonproprietary name: sodium stearyl fumarate

Synonyms: fumaric acid, octadecyl ester, sodium salt; Pruv; sodium monostearyl fumarate.

Chemical name: 2-Butenedioic acid, monooctadecyl ester, sodium salt.

Empirical formula: $C_{22}H_{39}NaO_4$

Molecular weight: 390.5

Functional category: tablet and capsule lubricant.

Description: it is a fine white powder with agglomerates of flat, circular-shaped particles.

Solubility: practically insoluble in acetone, chloroform and ethanol, slightly soluble in methanol, water (1 in 20, 000 at 25 □C, 1 in 10 at 80 □C, 1 in 5 at 90 □**Stability and**

storage conditions: at ambient temperature, sodium stearyl fumarate is stable for up to 3 years 2when store in amber bottles with polyethylene screw caps. The bulk material should be stored in a well closed container in a cool and dry place.

Incompatibilities: it is reported to be incompatible with chlorhexidine acetate.

Applications: it is used as a lubricant in capsule and tablet formulations at 0.5-2.0% w/w concentrations. It is also used in food preparations.

TALC:

Nonproprietary name: talc

Synonyms: hydrous magnesium calcium silicate; powdered talc

Chemical name: talc

Empirical formula: $Mg_6 (Si_2O_5)_4(OH)_4$

Functional category: anti caking agent; glidant; tablet and capsule diluents; tablet and capsule lubricant.

Description: talc is a very fine, white to grayish white, odorless, impalpable, unctuous, crystalline powder. It adheres to the skin and is soft to touch and free from grittiness.

Solubility: practically insoluble in dilute acids and alkalis, organic solvent and water.

Stability and storage conditions: it is a stable material and can be sterilizes by heating at 160□C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma radiation. It should be stored in a well closed container in a cool and dry place.

Incompatibilities: incompatible with quaternary ammonium compounds.

Applications: used as a diluents and lubricant.

Widely used as a dissolution retardant in the development of controlled release product.

Topically used as dusting powder.

Related Substance: Bentonite, magnesium aluminium stearate, magnesium silicate, magnesium trisilicate.

HYDROXYPROPYL CELLULOSE

Nonproprietary Names: Low-substituted Hydroxypropyl cellulose.

Synonyms: cellulose, 2-hydroxypropyl ether, 2_hydroxypropyl ether, low-substituted cellulose, hyperlose , low substituted L-HPC.

Chemical Name: cellulose, 2-hydroxypropyl ether(low-substituted)

Functional Category: Tablet and capsule disintegrant, tablet binder.

Description: Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odourless or has a slight, characteristic odour and it is tasteless.

Solubility: Practically insoluble in ethanol (95%) and in ether. Dissolves in a solution of sodium hydroxide (1 in 10) and produces a viscous solution. Insoluble but swells in water.

Stability and Storage conditions: low-substituted hydroxypropyl cellulose is a stable, though hygroscopic material. The powder should be stored in a well closed container.

Incompatibilities: Alkaline substance may interact. If a tablet formation contains such a material, the disintegration time may be extended after storage.

Applications:

Low-substituted hydroxypropyl cellulose is widely used in oral solid-dosage forms.

It is primarily used as a disintegrant and as a binder for tablets and granules in wet or dry granulation.

It has been used in the preparation of rapidly disintegrating tablets produced by direct compression methods.

METHODOLOGY

Pre-formulation studies :

Drug-Excipient compatibility studies:

The proper design and the formulation of a dosage form require consideration of the physical, chemical and biological characteristics of the drug and excipients used in fabricating the product. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, easy to administer and safe.

The compatibility studies provide the frame work for the drugs combination with excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets.

Compatibility studies were carried out by mixing definite proportions of drug and excipient and kept in glass vials, which are stored at 55^0C(2 weeks) and 40 ± 2^0c/75±5% RH(4 weeks).

Preparation of standard calibration curve of Deferasirox:

10mg of drug was accurately weighed and transferred to a 100ml volumetric flask, volume was made up with phosphate buffer of pH 6.8 containing 0.5% tween 0.2,0.4,0.6,0.8 and 1ml of the above stock solution were transferred into a series of 10ml volumetric flasks and made up the volume with phosphate buffer of pH 6.8 containing 0.5% tween 20 solvent system. The absorbance values were measured at λ_{max} 245nm against phosphate buffer of pH, linearity of the standard curve was assessed from square of correlation coefficient (r^2) which is determined by least square linear regression analysis

Pre-compression parameters[60, 61]

Angle of Repose:

The internal angle between the surface of the pile of blend and the horizontal surface is known as the angle of repose.

Method:

The blend was passed through a funnel fixed to a burette stand at a height of 4cm. A graph paper was placed below the funnel on the table. The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula:

$$\text{Angle of repose } (\theta) = \tan^{-1}(h/r)$$

Where, h = height of the pile

r = radius of the pile.

Bulk density:

The bulk density is used as a measure to describe packing materials or granules.

Method

Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by transferring an accurately an accurately weighed amount (25gm) of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was anted. Ratio of weight of the sample to the volume it occupied was calculated.

$$\text{Bulk density} = W/V_0 \text{ g/ml}$$

Where, W = mass of the blend,

V_0 = Untrapped volume.

Tapped density Method:

It was measured by transferring a known quantity (25gm) of blend into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus was set for 500, 750 and 1250 taps. The tapped density was determined as the ratio of mass of the blend to the tapped volume.

$$\text{Tapped density} = W/V_f \text{ g/ml}$$

Where, W = Mass of the blend

V_f = tapped volume

Compressibility index

It is the propensity of a powder to be compressed.

Method

It is measured by tapped density apparatus for 500, 750 and 1250 taps for which the difference be not more than 2%. Based on the apparent bulk density and tapped density the compressibility of the blend was determined using the following formula.

$$\% \text{ Compressibility index} = [(V_0-V_f)/V_0] \text{ ¿ } 100$$

$$\% \text{ compressibility} = [(\text{Tapped density} - \text{Bulk density})/ \text{Tapped density}] \text{ ¿ } 100$$

Hausner ratio

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powder is called Hausner ratio.

$$\text{Hausner ratio} = \text{Tapped density}/ \text{Bulk density}$$

Table 10: Flow properties and corresponding Angle of repose, Compressibility index and Hausner ratio

S.no	Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner ratio
1	Excellent	25-30	<10	1.00-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Passable	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Very very poor	>66	>38	>1.6

Loss on drying:

The loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. The loss on drying of the blend (1g) was determined by using electronic LOD (helium lamp) apparatus at 105^0C.

Evaluation parameters of Dispersible tablets

Physical appearance

The tablets were inspected for smoothness, absence of cracks, chips and other undesirable characteristics. If they are colored, it includes examination for mottling and other evidence of uniform color distribution except where they are used intentionally.

Weight variation test

20 tablets were randomly selected from each formulation and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight

Table: 11 Weight variation requirements

Average weight of tablet (mg)	% Difference
130 or less	10%
From 130 to 324	7.5%
>324	5%

Hardness

The hardness test is performed to measure the tablet strength. Tablet should be hard enough to withstand packing and shipping. Schluenzier hardness tester was used for the determination of hardness of tablets. The hardness of 10 tablets was noted and the average hardness was calculated. It is expressed in kp or kg/cm^2.

Thickness:

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm. the thickness of the tablet is mostly related to the tablet hardness and can be used as an initial control parameter.

Percentage Friability:

The friability test gives an indication of tablets ability to resist chipping and abrasion on handling during packaging and shipping. Usually for conventional tablets friability value of 1.0% or less is desirable. If the weight is ≥650mg 10 tablets were taken and initial weight was noted. The tablets were rotated in the Roche friabilator for 100 revolutions at 25rpm. The tablets were dedusted and reweighed. The tablets that loose less than 1% were considered to be compliant. The percentage friability is expressed as the loss of weight and is calculated by the formula:

% Friability = (A-B/B) ¿ 100

Where,

A = Initial weight of tablets

B = Final weight of tablets after 100 revolutions

Uniformity of dispersion:

This test is applicable only to dispersible tablets. In this method, two tablets were placed in 100ml of water and stirred gently until completely dispersed. A smooth dispersion must be obtained which passes through a sieve screen with a nominal mesh aperture of 710µm (sieve no.22).

***In vitro* Disintegration studies:**

Disintegration time is the time required for a tablet to breakup into granules of specified size (or smaller), under carefully specified test conditions. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75cm length and 2.15mm in diameter the bottom of which of which consists of a 10 mesh sieve. The basket is raised and lowered 28-32 times per minute in the medium of 900ml which is maintained at37 ± 2^0C.Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the sieve (# 10) was considered as the disintegration time of the tablet. This test is performed to ensure disintegration of tablets in water, if it is to be used as a dispersible tablet. Dispersible tablets must disintegrate within 3 mins when examined by the disintegration test for tablets as per the compliance in the pharmacopoeia.

***In vitro* Dissolution studies (by UV method):**

The dissolution test measures the rate of release of the drug from the dosage form *in vitro*, it is usually expressed as extent of dissolution (%drug content) occurring after a given time under specified conditions. For effective absorption of oral solid dosage form, simple disintegration of the dosage form is not adequate and the dissolution of the drug into the surrounding medium plays a vital role. Though dissolution is not a predictor of therapeutic efficacy it can be looked upon a tool which can provide valuable information

about biological availability of drug and batch to batch consistency. Dissolution is considered as one of the most important quality control tests performed for pharmaceutical dosage form.

Instrument:

UV-Visible absorption spectrophotometer

Apparatus:

- Analytical balance
- Volumetric flasks
- Pipettes
- 0.45µm membrane filters
- Syringes
- Dissolution apparatus
- Deferasirox working standard
- Potassium dihydrogen phosphate
- Methanol-HPLC grade
- Sodium hydroxide
- Tween-20(poly oxy ethylene sorbitan monolaurate)
- Water

Dissolution conditions:

Medium : pH 6.8 phosphate buffer containing 0.5% tween-20

Volume : 900ml

Temperature : $37^0C \pm 0.5^0C$

Apparatus : USP Type-II (paddle)

RPM : 50

Time intervals : 10, 20, 30 & 45min.

Procedure:

The *in vitro* dissolution study was carried out in the USP dissolution test apparatus, type II (paddle). One tablet was placed in each of the six dissolution flasks containing 900ml

of dissolution medium, previously maintained $37^0C \pm 0.5^0C$. After completion of each specified time interval, a portion of the solution was withdrawn from zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1cm from vessel wall and filtered through 0.45µm membrane filter. The samples were collected at specified time intervals and diluted to required volume with dissolution medium. The absorbance of the standard and sample preparations was measured in 1cm cells, with a suitable spectrophotometer using dissolution medium as blank preparation. Finally the percentage drug dissolved of Deferasirox tablets was calculated.

Assay (By HPLC method)

Instrument: High performance liquid chromatography equipped with UV detector and data handling system

Apparatus

- Analytical balance
- Volumetric flasks
- Pipettes
- pH meter
- Filtration unit
- 0.45µm membrane filters

Chemicals and reagents

- Ammonium dihydrogen orthophosphate
- Ortho-phosphoric acid
- Purified water
- Acetonitrile-HPLC grade
- Methanol-HPLC grade
- Deferasirox working standard

Chromatographic conditions

Column :Develosil ODS HG-5(150 ¿ 4.6mm)5µm

Flow rate : 1.5ml/min

Injection volume : 10µl

Column temperature: 40^0C

Runtime : 15min

Preparations:

Mobile phase preparation:

1.58g of ammonium dihydrogen ortho phosphate was accurately weighed and transferred int a 100ml volumetric flask. Then 60ml of diluent was added and was dissolved by sonication. The solution was cooled to the room temperature and diluted to the volume with diluent. 2ml of the above solution was transferred into a 100ml volumetric flask and diluted to the required volume with diluent.

Diluent preparation:

Acetonitrile and methanol were mixed in the ratio of 50:50v/v respectively.

Standard preparation:

40mg of deferasirox working standard was accurately weighed and transferred into a 100ml volumetric flask. Then 60ml of diluent was added and was dissolved by sonication. The solution was cooled to the room temperature and diluted to the required volume with diluent .2ml of the above solution was transferred into a 100ml volumetric flask and diluted to the required volume with diluent.

Sample preparation;

20 tablets were accurately weighed and finally powdered. From this powdered tablet equivalent to 400mg of deferasirox was weighed and transferred into a 250ml volumetric flask, to this 180ml of the diluent was added and sonicated for 30 mins with occasional stirring. Then the solution was cooled to room temperature and diluted to the required volume with diluent. The solution was filtered through 0.45µm membrane filter. 1ml of

the above filtered solution was transferred into a 200ml volumetric flask and diluted to the required volume with diluent.

Procedure:

Equal volumes (10µl) of the diluent as blank, standard preparation and sample preparations were injected separately into the chromatograph, the chromatograms were recorded and the peak area responses for the major peaks were measured. Finally the percentage content of deferasirox in the portion of the deferasirox tablets was calculated.

$$\% \text{ Content of deferasirox} = \frac{TA \times SW \times 2 \times 250 \times 200 \times P \times Avg.wt \times 100}{SA \times 100 \times 100 \times TW \times 1 \times 100 \times LA}$$

Where,

TA = Peak area response due to deferasirox from sample preparation.

SA = Peak area response due to deferasirox from standard preparation.

SW = Weight of deferasirox working standard taken in mg.

TW = Weight of sample taken in mg.

P = Purity of deferasirox working standard.

Avg. wt.= Average weight of deferasirox tablet taken in mg.

LA = Label amount of deferasirox.

Water content (By KF method)

Instrument: Karl Fischer titrator

35ml of a mixture of methanol was transferred to the titration vessel and titrated with Karl Fischer reagent to the electrometric end point, to consume any moisture that may be present (disregard the volume consumed, since it does not enter into calculation). Powder from 5 tablets was used, ground to a fine powder in an atmosphere of temperature and relative humidity known not to influence the results. 300-500mg of the

powder was accurately weighed and transferred into the titration vessel, mixed and titrated with Karl Fischer reagent to the electrometric end point. Finally the water content of the specimen in mg was calculated.

Stability studies:

The purpose of stability testing is to provide evidence of the quality of the drug substance or drug product and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air etc.). The formulation was packed in suitable packing like blister and strips packs and then they will be kept at different temperature, humidity conditions and the samples will be analyzed for their physical and chemical properties.

The formulation is subjected to

- Long-term testing at 25±2^{0}C and 60±5% RH for 12 months
- Accelerated testing at 40±2^{0}C and 75±5% RH for 6 months

Innovator product details:

Innovator product details including their manufacturer name, description, physical parameters and dissolution profile were given in the following table

Table 12: Innovator product details

Name of the product	ASUNRA 400mg
Manufacturer name	Novartis Pharma Stein AG, Switzerland
Color	Off white
Description	Off white square shaped tablet, debossed with NRS on one side and J400 on other side
Package	Alu-Alu blister pack. Each carton contains 5 blister packs and each blister contains 6 tablets (5×6=30 tablets)

Table: 13 Physical parameters of innovator product

Parameters	400mg
Weight of the tablet (mg)	1392
Thickness(mm)	5.31
Hardness (kp)	7.2
Length (mm)	17.9
Diagnol (mm)	20.95
Disintegration time (sec)	33
Dispersion time (sec)	60

Table no: 14 Dissolution Profile of Innovator Product (ASUNRA)

Time (min)	Cumulative Percentage Drug Release
10	79.7
20	86.4
30	92.1
45	98.6

Characterization of Active pharmaceutical ingredient (API)

Table 15: Active pharmaceutical ingredients characterization

Tests	Results
Description	Off white crystalline powder
Solubility	Freely soluble in dimethyl formamide and dimethyl sulfoxide, slightly soluble in methanol, practically insoluble in water.
Angle of repose	39.41

Bulk density (gm/ml)	0.460
Tap density (gm/ml)	0.795
Compressibility index (%)	42.105
Hausner ratio	1.727
Loss on drying	0.10% w/w

FORMULATION DEVELOPMENT OF DEFERASIROX DISPERSIBLE TABLETS

Direct compression method:

Table 16: Formula for F-1

S.No.	Ingredient	mg/tab(F-1)
1	Deferasirox	400
2	Lactose monohydrate	144
3	Crospovidone	50
4	MCC pH102	300
5	Starch 1500	30
6	SLS	6
7	Aerosil	10
8	Magnesium stearate	10

Procedure for Formulation 1:

- All the ingredients were weighed except Aerosil and Magnesium stearate and were passed through #40 mesh, then mixed for 2 mins in a blender.
- The above mixture was pre lubricated using Aerosil for 5mins and then lubricated with magnesium stearate in blender for 2mins.
- Then the lubricated was compressed using 15mm round flat punches.

Wet granulation method 1

Table 17: Formula for F-2, F-3, F-4, F-6, F-7,F-8.F-9

S.No.	Ingredient	F-2	F-3	F-4	F-6	F-7	F-8	F-9
1.	Deferasirox	400	400	400	400	400	400	400
2.	Lactose monohydrate	97	97	97	97	-	-	-
3.	Crospovidone XL	25	30	35	50	100	100	100
4.	MCC pH 101	333.5	308.5	303.5	258.5	305.5	292	292
5.	Starch 1500	-	-	-	30	30	30	30
6.	Povidone K30	25	45	45	45	45	45	45
7.	SLS	6	6	6	6	6	6	6
8.	Sucralose	-	-	-	-	-	8	8
9.	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
10.	Color	-	-	-	-	-	0.5	0.5
11.	Aerosil	9	9	9	9	9	9	9
12.	Flavour	-	-	-	-	-	5	5
13.	Magnesium stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5

Procedure for Formulation 2:

- API, Lactose monohydrate, SLS, Crospovidone XL, MCC pH 101 were weighed and mixed for 2mins.
- The above mixture was passed through #40mesh.
- Povidone K30 was dispersed in sufficient quantity of purified water by stirring.
- Then the above mixture was granulated using binder solution (Povidone K30 and water)
- The wet mass was passed through #12 mesh.
- The sieved mixture was dried using Fluid Bed Drier and the temperature was maintained at 60^0C until the moisture content in the blend comes to 1.0 to 2.0%
- The dried blend was passed through #18mesh and then pre lubricated using Aerosil for 5min and then lubricated with magnesium stearate in blender for 2mins.
- Then finally the lubricated blend was compressed using 15mm round flat punches.

Procedure for Formulation 3:

- API, lactose monohydrate, SLS, Crospovidone XL, MCC pH101 were weighed and mixed for 2mins.
- The above mixture was passed through #40mesh.
- Povidone K30 was dispersed in sufficient quantity of purified water by stirring.
- Then the above mixture was granulated using binder solution(Povidone K30 and water).
- The wet mass was passed through #12 mesh.
- The sieved mixture was dried using Fluid Bed Drier and the temperature was maintained at 600C until the moisture content in the blend comes to 1.0 to 2.0%
- The dried blend was passed through #18mesh and then pre lubricated using Aerosil for 5min and then lubricated with magnesium stearate in blender for 2mins.
- Then finally the lubricated blend was compressed using 15mm round flat punches.

Procedure for Formulation 4:

- API, lactose monohydrate, SLS, Crospovidone XL, MCC pH101 were weighed and mixed for 2mins.

- The above mixture was passed through #40mesh.
- Povidone K30 was dispersed in sufficient quantity of purified water by stirring.
- Then the above mixture was granulated using binder solution (Povidone K30 and water).
- The wet mass was passed through #12 mesh.
- The sieved mixture was dried using Fluid Bed Drier and the temperature was maintained at 60^0C until the moisture content in the blend comes to 1.0 to 2.0%.
- The dried blend was passed through #18mesh and then pre lubricated using Aerosil for 5min and then lubricated with magnesium stearate in blender for 2mins.
- Then finally the lubricated blend was compressed using 15mm round flat punches.

Wet granulation method 2

Table 18: Formula for F-5

S.No.	Ingredient	mg/tabs(F-5)
1.	Deferasirox	400
2.	SSG	80
3.	MCC pH 101	302
4.	L-HPC-LH11	44
5.	Tween 80	4
6.	Povidone K30	45
7.	Water	q.s
8.	Aerosil	10

9.	SSF	6
10.	Talc	9
Total		900

Procedure for Formulation 5:

- API, SSG, MCC pH101, Hydroxy propyl cellulose (L-HPC-LH11) were weighed and mixed for 2mins.
- The above mixture was passed through #40mesh.
- The binder was prepared by dispersing povidone K30 and tween 80 in sufficient quantity of water.
- The binder solution was added to the dry mixture until a wet mass is formed.
- Then the above mixture was granulated using binder solution (Povidone K30 and water).
- The wet mass was passed through #12 mesh.
- The sieved mixture was dried using Fluid Bed Drier and the temperature was maintained at 600C until the moisture content in the blend comes to 1.0 to 2.0%
- The dried mass mixture was passed through #18mesh.
- The sieved mixture was lubricated with SSG, Aerosil and Talc first for 2mins and then mixed with SSF for 1-2mins.
- Then the lubricated blend was passed through #40mesh.
- Then finally the lubricated blend was compressed using 15mm round flat punches.

Procedure for Formulation 6:

- API, lactose monohydrate, Starch 1500, Crospovidone XL, MCC pH101 were weighed and mixed for 2mins.
- The above mixture was passed through #40mesh.
- Povidone K30 was dispersed in sufficient quantity of purified water by stirring.
- Then SLS was added to the binder solution and was allowed to dissolve.
- The binder solution was added to the dry mixture.
- The wet mass was passed through #12mesh.
- The sieved mixture was dried using Fluid Bed Drier and the temperature was maintained at 600C until the moisture content in the blend comes to 1.0 to 2.0%.
- The dried mass mixture was passed through #18mesh.
- The sieved mixture was lubricated with Aerosil, crospovidone XL and SLS for 2min.
- Magnesium stearate was passed through #40 mesh and added to the above mixture and then mixed for 2mins.
- Then finally the lubricated blend was compressed using 15mm round flat punches.

Procedure for Formulation 7:

- API, Starch 1500, Crospovidone XL, MCC pH101 were weighed and mixed for 2mins.
- The above mixture was passed through #40mesh.
- The binder was prepared by dispersing povidone K30 in sufficient quantity of water.
- Then SLS was added to the binder solution and was dissolved by stirring.
- The binder solution was added to the dry mixture.
- The wet mass was passed through #12mesh.
- The sieved mixture was dried using Fluid Bed Drier and the temperature was maintained at 600C until the moisture content in the blend comes to 1.0 to 2.0%.
- The dried mass mixture was passed through #18mesh.
- The sieved mixture was lubricated with Aerosil, crospovidone XL and SLS for 2min.
- Magnesium stearate was passed through #40 mesh and added to the above mixture and then mixed for 2mins.
- Then finally the lubricated blend was compressed using 15mm round flat punches.

Procedure for Formulation 8:

- API, Sucralase, Starch 1500, Crospovidone XL, MCC pH101 were weighed and mixed for 5mins.
- The above mixture was passed through #40mesh.
- The binder was prepared by dispersing povidone K30, SLS and Colour slowly in sufficient quantity of water by stirring.
- The binder solution was added to the dry mixture.
- The wet mass was passed through #12mesh.
- The sieved mixture was dried using Fluid Bed Drier and the temperature was maintained at 600C until the moisture content in the blend comes to 1.0 to 2.0%.
- The dried mass mixture was passed through #18mesh.
- The sieved mixture was lubricated with Aerosil, Crospovidone XL, SLS and Flavour for about 3 minutes and was passed through #40 mesh.
- Magnesium stearate was passed through #40 mesh and added to the above mixture and then mixed for 2mins.
- Then finally the lubricated blend was compressed using 15mm round flat punches.

Procedure for Formulation 9:

- API, Sucralase, Starch 1500, Crospovidone XL, MCC pH101 were weighed and mixed in RMG for 5mins.
- The impeller was adjusted to slow.
- The binder was prepared by dispersing povidone K30, SLS and Colour slowly in sufficient quantity of water by stirring.
- The binder solution was added to the dry mixture within 2mins with impeller fast.
- The wet mass was mixed for 1min with impeller and chopper fast.
- The wet mass was dried using Fluid Bed Drier and the temperature was maintained at 60^0C until the moisture content in the blend comes to 1.0 to 2.0%.
- The dried mass mixture was passed through #18mesh.
- The sieved mixture was lubricated with SLS, Aerosil, Crospovidone XL, Flavour and Magnesium stearate in a blender.
- Then finally the lubricated blend was compressed using 15mm round flat punches.

RESULTS AND DISCUSSION

The present investigation was undertaken to formulate deferasirox into dispersible tablet for the treatment of chronic iron overload. For the development and formulation of dispersible tablets, wet granulation and direct compression techniques were carried out with combination of various approved excipients. All the experimental formulation batches have been subjected to various evaluation parameters viz, average weight, thickness, hardness, friability, disintegration, uniformity of dispersion, dissolution studies, water content and assay.

Formulation F-1 was carried out by direct compression method using ingredients such as lactose mono hydrate, Crospovidone XL, MCC pH 102, Starch 1500, SLS, Aerosil and Magnesium stearate. Here poor flow property was observed, hardness and friability values were also not satisfactory. The disintegration time and dispersion time were found to be 36 and 71 sec respectively. The percentage of drug release was 88.8% (in 45 mins) and it does not comply with the innovator product. So, we planned to forward the next batch using wet granulation method.

Formulation F-2 was carried out by wet granulation technique. Here Povidone K30 was used as a binder which was dispersed in water to make a solution. The other excipients are same as the previous formula except MCC pH 102 which is replaced by MCC pH101 and starch (excluding from the formulation). In this formula both the binder and superdisintegrant concentrations were taken as 25mg/tab each. Here hardness was found to be less and the friability value does not comply with the specifications. The disintegration time and dispersion time were found to be 40 and 63sec respectively. The percentage of drug release was 87.9% (in 45mins) and it was found to be less when to compared with the innovator product. So, we planned to forward the next batch by increasing both the binder and superdisintegrant concentrations.

Formulation F-3 was carried out by using the same excipients as that of the previous formula. Here binder and super disintegrant concentrations were raised to 45mg/tab and 30mg/tab respectively. Improvement in the hardness was observed. The disintegration time (62 sec) and dispersion time (118 sec) does not comply with the innovator product.

The percentage of drug release was found to be 86.4 %(in 45 mins). So, for better disintegration the next batch was planned by increasing super disintegration concentration.

Formulation F-4 was carried out by using the same excipients as that of the previous batch. Here the binder was same as the previous batch but the superdisintegrant concentration was raised to 35mg/tab. Then also the disintegration and dispersion of the compressed tablets was slightly poor i.e. a small amount of substance was retained on the sieve while passing through sieve no.22. It indicates that this batch also fails the specific test for dispersible tablets. The disintegration time and dispersion time were found to be 58 and 109sec respectively. The percentage of drug release was 89.3 %(in 45mins) and it does not comply with the innovator product. So, the next batch was carried out by changing the formula.

Formulation F-5 was made by using a new formula i.e. hydroxyl propyl cellulose (L-HPC_LH11), SSG, Magnesium stearate, Talc and SSF. The binder solution was prepared by dispersing Povidone K30 and Tween *0. The disintegration time and dispersion time were 67 sec and 125 sec respectively. Even though SSG was used as a superdisintegrant, poor dispersion was occurred and the residue was retained on the sieve when it was passed through sieve no.22. The percentage of drug release was found to 73.6 %(in 45 mins) and it does not comply with the innovator product. So, in order to get a better dispersion the next batch was planned by incorporating starch 1500 and increasing the concentration of superdisintegrant.

Formulation F-6 was made by using the same formula as that of F-4 and additionally starch 1500 was added. Here the superdisintegrant concentration was raised to 50mg/tab. The disintegration time and dispersion time were found to be 49 and 92 sec respectively. Even though starch 1500 was added to the formula for better dispersion still amount of residue remained on the sieve while passing. The percentage of drug release was 91.4% (in 45 mins) and it does not comply with the innovator product. So, next batch was planned by excluded lactose monohydrate and increasing the concentration of superdisintegrant.

Formulation F-7 was made by using the same formula of the previous batch by excluding lactose monohydrate and the concentration of superdisintegrant was increased to 100mg/tab. The disintegration time (32sec) and the dispersion time (65 sec) were found to be satisfactory and the percentage of drug release (97.2%) also improved by comparing with the previous batches and it was found to match with the innovator product. Here the dispersed mixture passed freely from sieve without any residue. So, the next batch was performed by adding colour, flavor and sweetener for better taste and appearance of the tablet.

Formulation F-8 was performed by using the same formula of the previous batch by including colour, flavor and sweetener. This batch was taken to improve the appearance as well as for better acceptability. The disintegration time (35sec), dispersion time (67 sec) and the percentage of drug release(98.3% in 45mins) were found to be satisfactory and it matches with innovator product(ASUNRA). So, the next batch performed by increasing the batch size to check the reproducibility.

Formulation F-9 was performed by using the same formula of the previous batch by increasing the batch size for reproducibility. The disintegration time (34sec), dispersion time (62sec) and percentage of drug release (97.4% in 45 mins) matches with that of the innovator (ASUNRA). Then the formulated tablets were loaded for stability as per ICH guidelines.

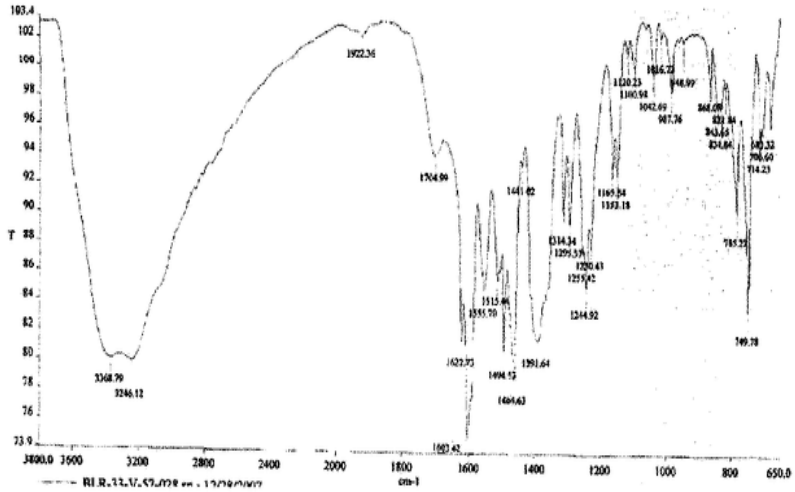


Figure7:FTIR specta of deferasirox

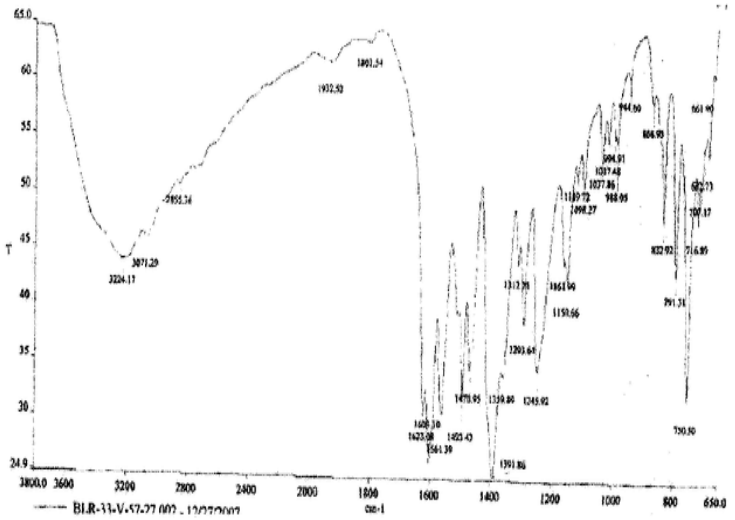


Figure8: FTIR sprctra of deferasirox and polymers

HPLC method:

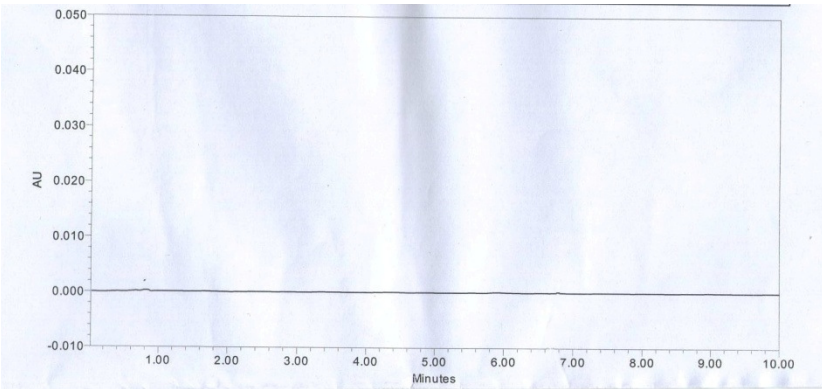


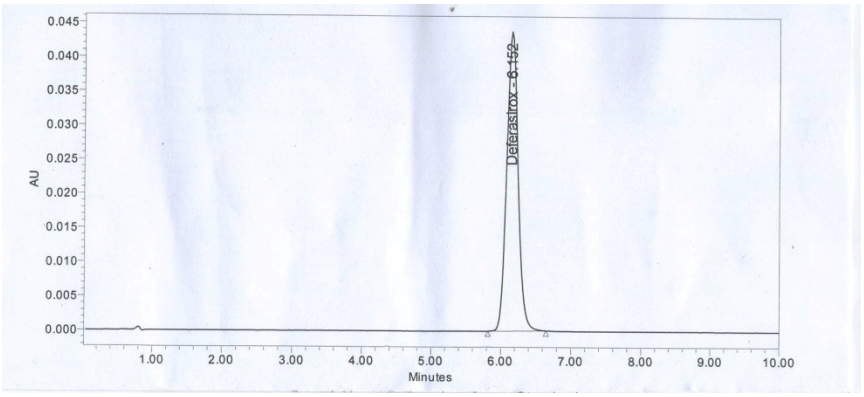
Figure9:Sample name deferasirox assay in Blank

Table no19.:Deferasirox assay blank:

S.no	Peak Name	Vial	RT	RT	Area	%Area	Height(µV

				Ratio			)
1	Deferasiro x						

Deferasirox assay standard:



Figur10.:Standard graph

Table no20.Assay standard:

Peak name	Vial	RT	RT Ratio	Area	%area	Height (µv)	USP Tailing	USP Plate count	USP Resolution
Deferasirox	3	6.152		496349	100.00	43872	1.14	6879	

Assay of deferasirox sample:

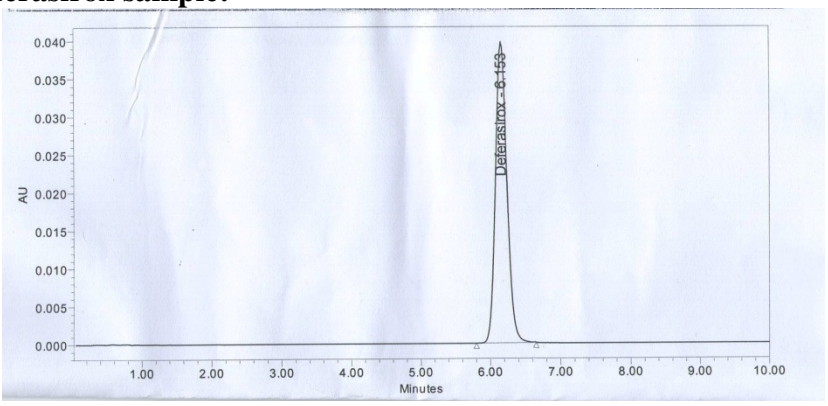


Figure11:Sample of deferasirox

Table no21:Assay of deferasirox in sample:

Peak name	Vial	RT	RT Ratio	Area	%area	Height(µv)	USP Tailing	USP Plate count	USP Resolution
Deferasirox	4	6.153		498686	100.00	39784	1.13	6899	

Pre-formulation studies

Table 22: Drug-excipient compatibility studies

S.No	Ingredients	Ratio	Description		
			Initial	55^0C(2 weeks)	40 ± 2^{0C}C/75±5%
1.	API	1	Off white	No change	No change
2.	Lactose monohydrate	1	Off white	No change	No change
3.	Crospovidone XL	1	White	No change	No change
4.	Starch 1500	1	White	No change	No change
5.	MCC pH 101	1	Off White	No change	No change
6.	SLS	1	White	No change	No change
7.	Povidone K30	1	Off white	No change	No change
8.	Aerosil	1	White	No change	No change
9.	Magnesium stearate	1	White	No change	No change
10.	L-HPC-LH11	1	White	No change	No change
11.	SSG	1	White	No change	No change
12.	Tween 80	1	Pale yellow	No change	No change

13.	SSF	1	White	No change	No change
14.	Talc	1	White	No change	No change
15.	Sucralose	1	White	No change	No change
16.	Orange flavor	1	Off white	No change	No change
17.	Sunset yellow (SUPRA)	1	Reddish yellow	No change	No change
18.	API+Crospovidone XL	5:1	Off white	No change	No change
19.	API+Starch 1500	5:1	Off white	No change	No change
20.	API+MCC pH101	1:5	Off white	No change	No change
21.	API+SLS	5:1	Off white	No change	No change
22.	API+Povidone K30	5:1	Off white	No change	No change
23.	API+Aerosil	5:1	Off white	No change	No change
24.	API+Magnesium stearate	5:1	Off white	No change	No change
25.	API+L-HPC-LH11	5:1	Off white	No change	No change
26.	API+SSG	5:1	Off white	No change	No change
27.	API+Tween 80	5:1	Pale yellow	No change	No change
28.	API+SSF	5:1	Off white	No change	No change
29.	API+Talc	5:1	Off white	No change	No change
30.	API+Sucralose	5:1	Off white	No change	No change
31.	API+Orange flavor	5:1	Off white	No change	No change
32.	API+Sunset yellow(SUPRA)	5:1	Pale pink	No change	No change

Table 23: Post compression parameters for formulations F-1 to F-9

Formula	Avg.weight	Thickness	Hardness (kp)	Friability (%)

	(mg)	(mm)		
F-1	952.6	4.97	4.02	1.92
F-2	904.1	4.52	4.13	1.99
F-3	897.2	4.31	5.48	0.62
F-4	901.0	4.27	5.52	0.39
F-5	905.7	4.60	5.44	0.50
F-6	903.0	4.38	5.79	0.31
F-7	902.0	4.36	5.85	0.29
F-8	903.4	4.43	5.80	0.23
F-9	903.0	4.41	5.89	0.20

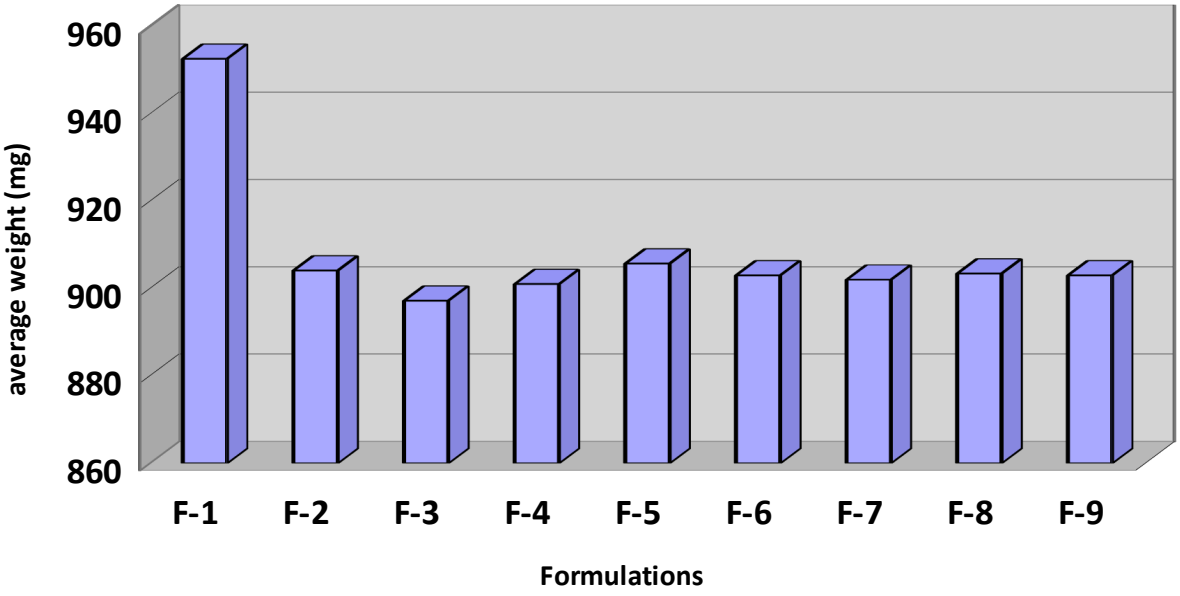


Figure 12: Comparison of average weight of different formulations.

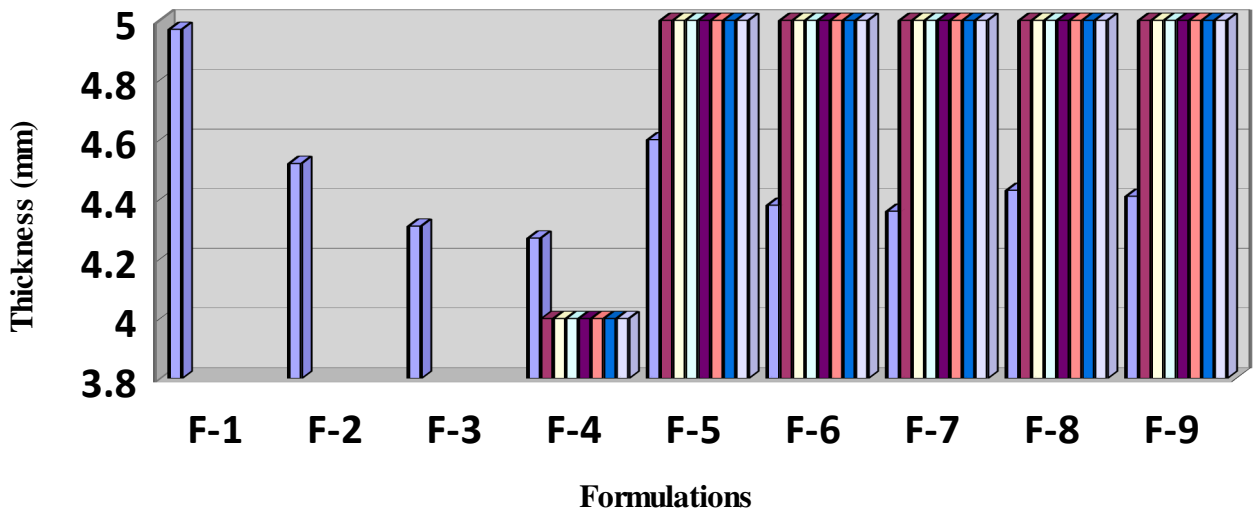


Figure 13: Comparison of thickness of different formulations

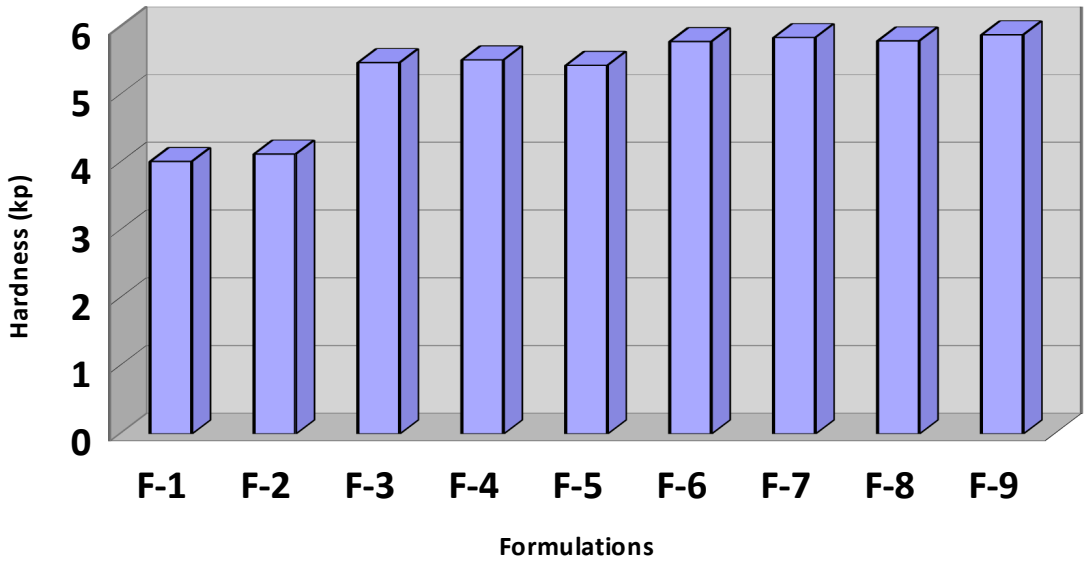


Figure 14: Comparison of Hardness of different formulations

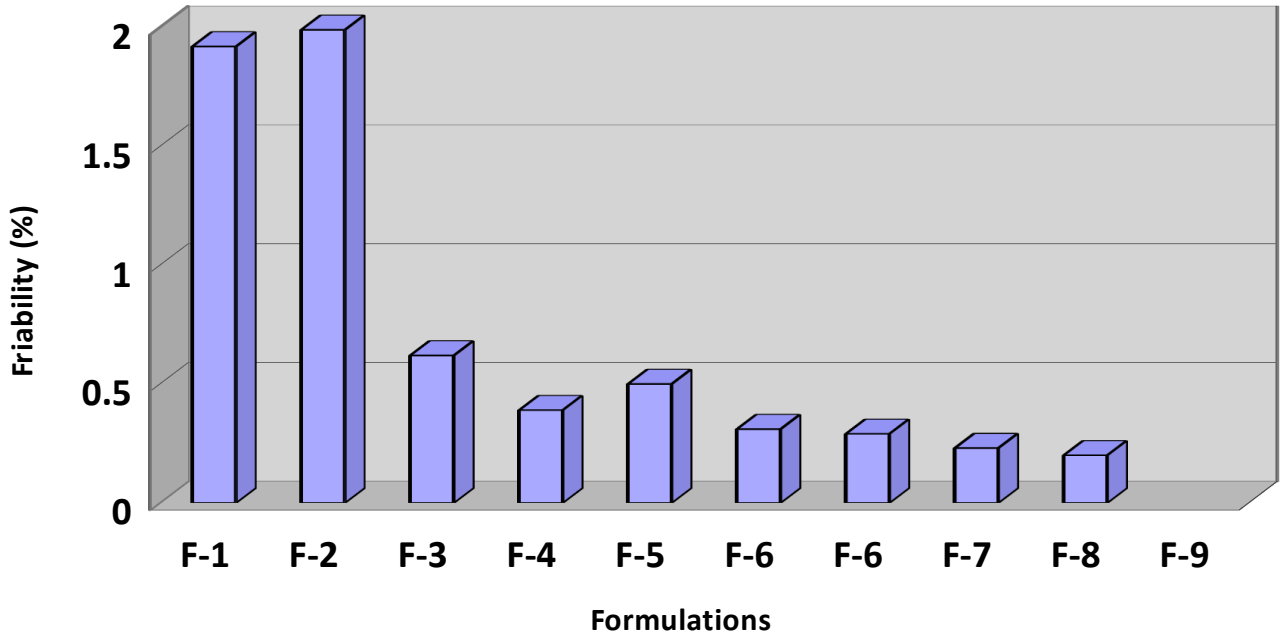


Figure 15: Comparison of percentage Friability of different formulations

Table 24: Disintegration time, Dispersion time, Water content and Assay values for Formulations F-1 to F-9.

Formula	Disintegration time(sec)	Dispersion time (sec)	Water content (w/w)	Assay (%)
F-1	36	71	3.5	99.8
F-2	40	63	3.1	98.3
F-3	62	118	4.2	101.0
F-4	58	109	3.6	99.5
F-5	67	125	4.3	100.7
F-6	49	92	4.0	98.1
F-7	32	65	3.7	99.7
F-8	35	67	3.4	100.2
F-9	34	62	3.5	99.98

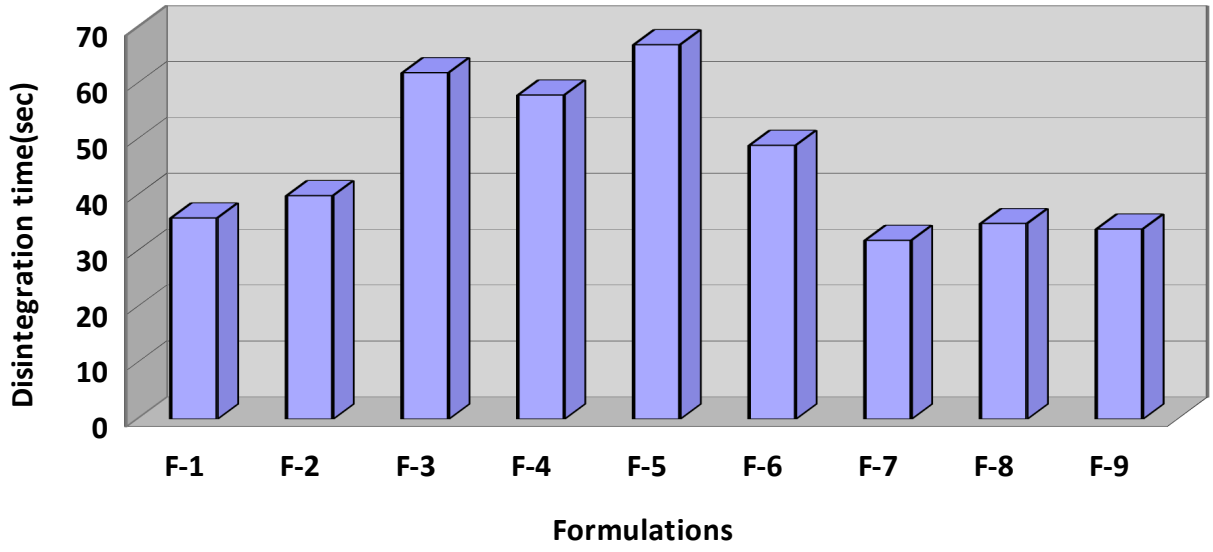


Figure 16: Comparsion of Disintegration time of different formulations

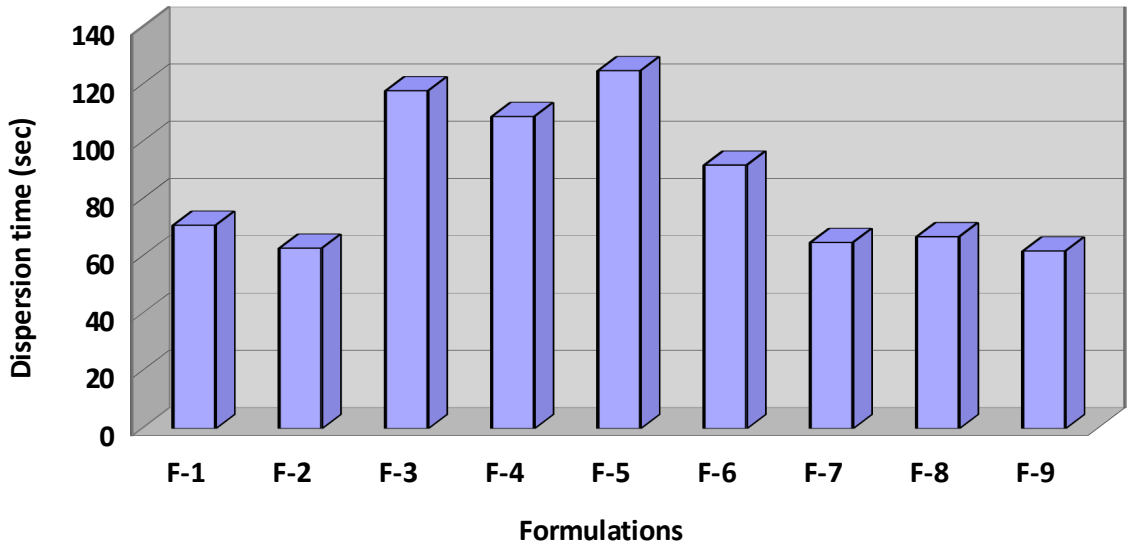


Figure17:Comparision of Dispersion time of different formulation

Table no;25 Dissolution profiles of different formulations (F-1 to F-9)

Sampling time(min)	Cumulative Percentage Drug Release								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
10	72.5	50.7	49.6	54.9	56.8	69.6	78.4	77.2	78.0
20	78.0	66.4	63.3	70.0	60.2	80.5	84.3	84.8	85.1
30	83.6	78.5	74.1	79.5	65.3	87.7	90.1	91.4	90.6
40	88.8	87.9	86.4	89.3	73.6	91.4	97.2	98.3	97.4

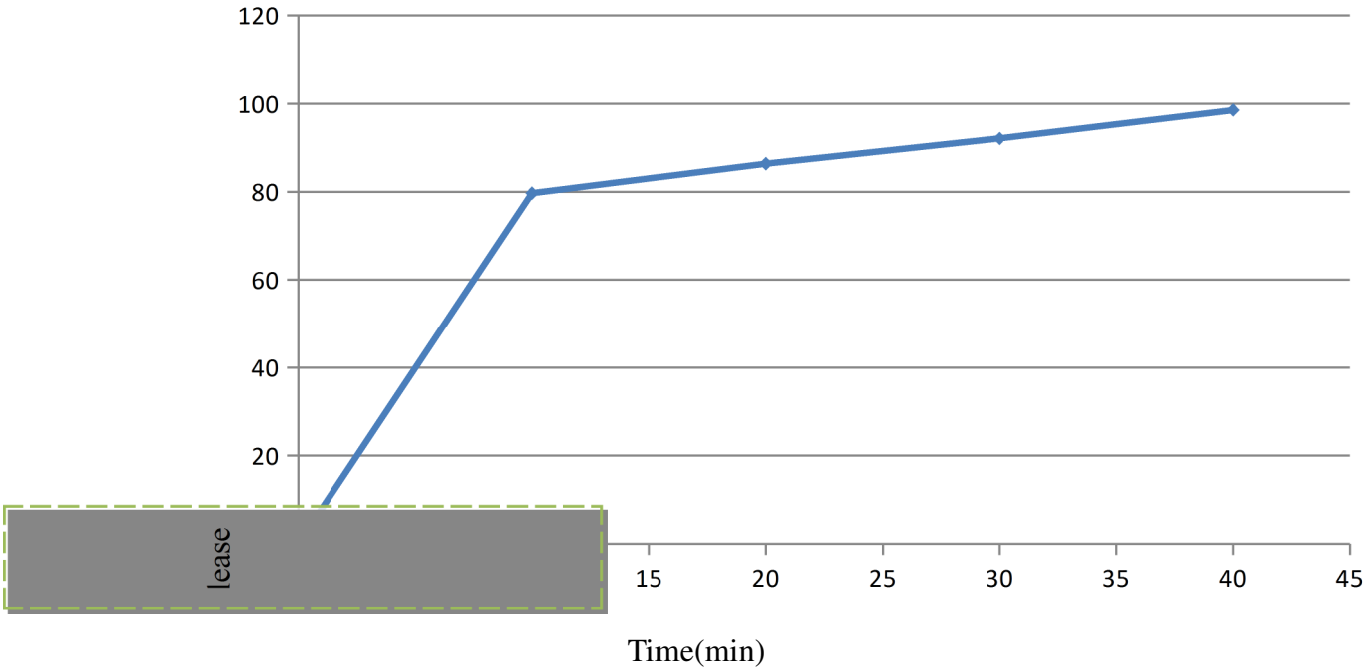


Figure 18: Dissolution Profile of Deferasirox Innovator (ASUNRA)

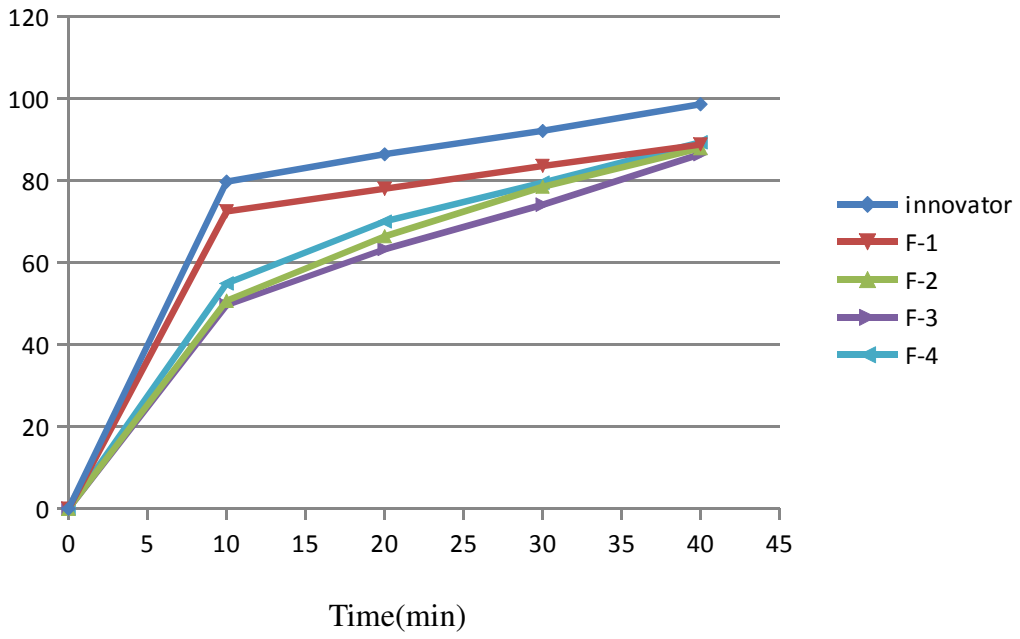


Figure19: Dissolution Profile of formulation 1-4 compared with innovator

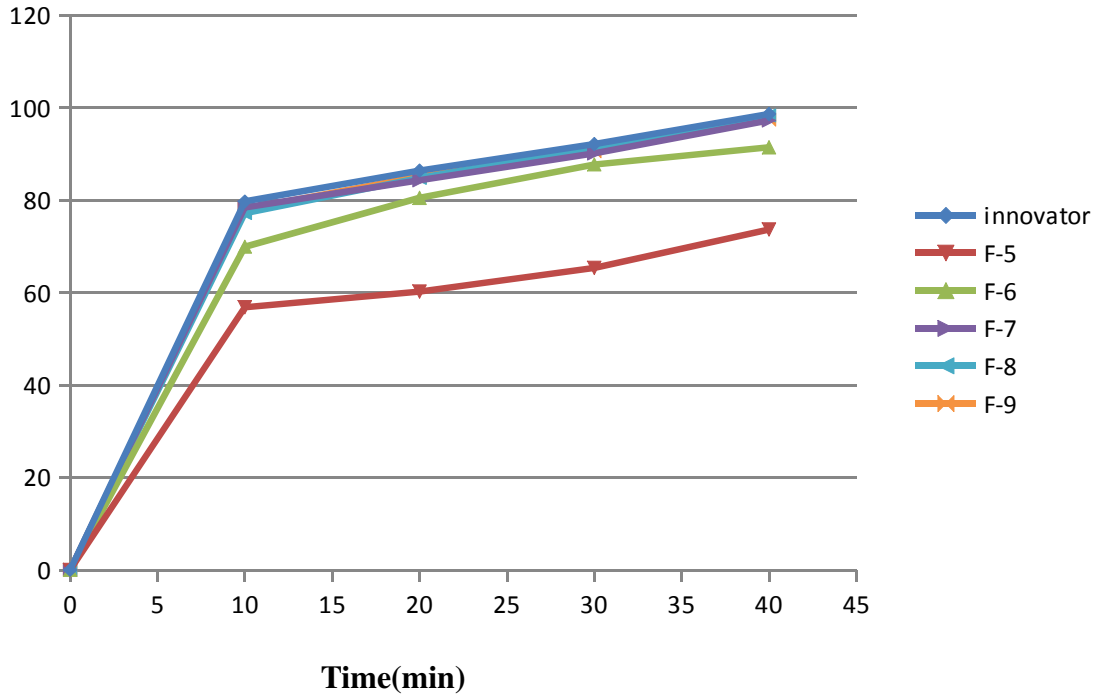


Figure 20: Dissolution profile of formulation 5-9 compared with innovator

Selection of Final formula:

- Based on, f_2 values (similarity factor) comparative with reference product final formula was selected.

Table 26: Similarity (f_1) and difference (f_2) factors for various formulations are

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Difference factor (f_1)	9.5	20.5	23.37	17.68	28.27	7.73	1.90	1.42	1.59
Similarity factor (f_2)	53.31	35.33	32.98	38.69	29.85	56.8	84.9	86.8	50

STABILITY DATA:

Table 27: Physical and chemical parameters of Deferasirox dispersible tablets (F-9) after 1st and 2nd month 40±2^{0}C/75±5%RH (Packing: HDPE Bottle)

Parameter	Initial	1 month	2 month
Description	Light orange coloured round shaped uncoated tablets	No change	No change
Avg.wt (mg)	903.0	903.2	903.4
Hardness (kp)	5.89	5.83	5.77
Thickness (mm)	4.41	4.48	4.53
Friabilty (%)	0.20	0.23	0.26
Water content (w/w)	3.7	3.8	3.5
Assay(%)	99.98	100.5	99.47

Table 28: Dissolution profiles of Deferasirox dispersible tablets (F-9) after 1st and 2nd month at 40±2^{0}C/75±5%RH(Packing: Blister pack)

Time interval(min)	Cumulative percentage drug release		
	Initial	1 month	2 month
10	78.0	78.12	78.4
20	85.1	84.3	84.7
30	90.6	91.4	91.9
40	97.4	97.1	96.6

Table 29: Physical and chemical parameters of Deferasirox dispersible tablets (F-9) after 1st and 2nd month 40±2^{0}C/75±5%RH (Packing: Blister pack)

Parameters	Initial	1 month	2 month
Description	Light orange coloured round shaped uncoated tablets	No change	No change
Avg.wt (mg)	903.0	903.2	903.1
Hardness (kp)	5.89	5.86	5.82
Thickness (mm)	4.41	4.50	4.54
Friability (%)	0.20	0.24	0.23
Water content (w/w)	3.7	3.6	3.8
Assay (%)	99.98	100.2	99.41

Table 30: Dissolution profiles of Deferasirox dispersible tablets (F-9) after 1st and 2nd month at 40±2^{0}C/75±5% RH (Packing: Blister pack)

Time interval (min)	Cumulative percentage drug release		
	Initial	1month	2month
10	78.0	78.4	78.7
20	85.1	85.6	84.9
30	90.6	90.0	89.5
40	97.4	96.9	96.3

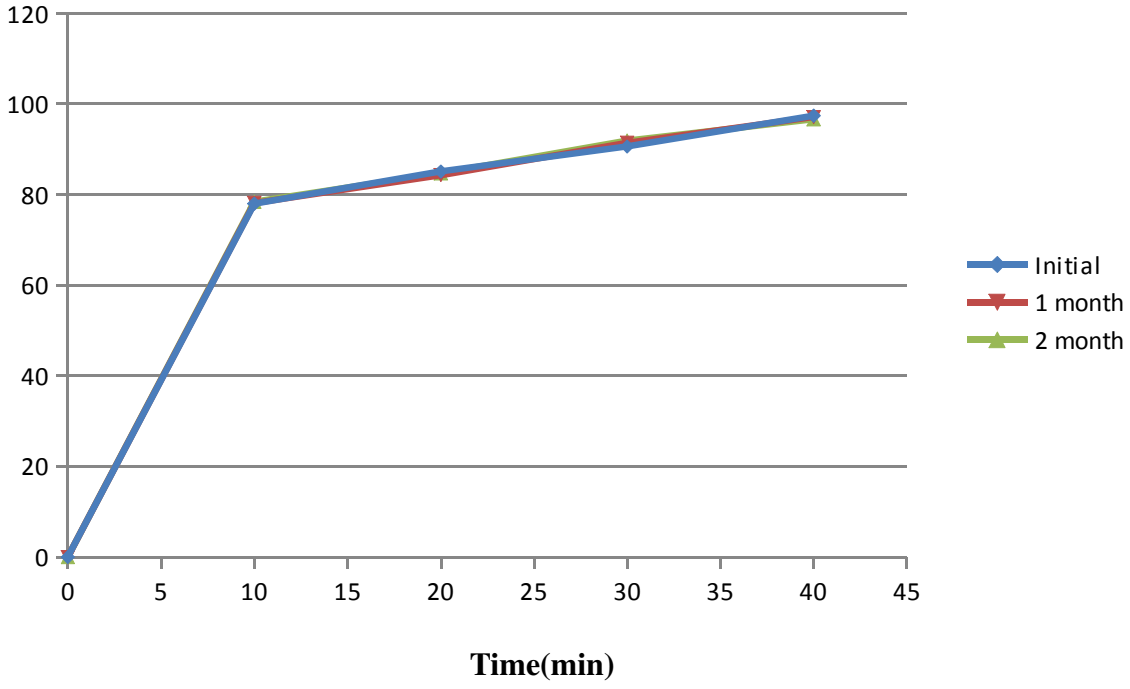


Figure21:Graphical representation of Dissolution profiles of stability studies conducted at 40±50C /75±5% RH for formulation 9(Packing: HPDE Bottle)

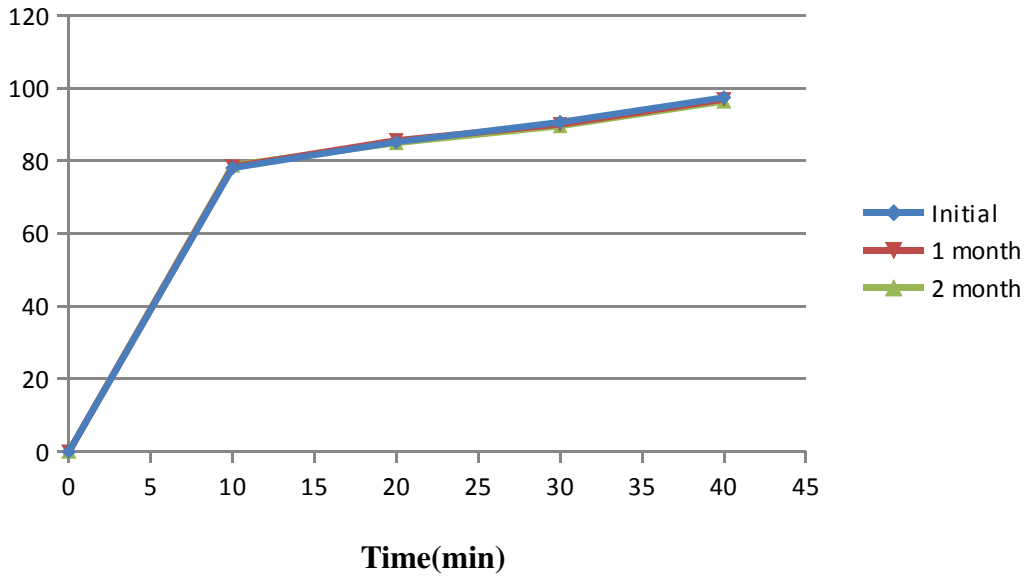


Figure no.22:Graphical representation of Dissolution profiles of stability studies conducted at 40±5^{0}C /75±5% RH for formulation 9(Packing: Blister pack)

SUMMARY AND CONCLUSION

The topic for the present study ***is "Formulation Development and Evaluation of Deferasirox dispersible tablets".***

Introduction is presented in ***chapter 1*** which gives details about chronic iron overload and its mode and ***choice of drugs for the treatment of chronic iron overload. This chapter also gives the overall view about*** dispersible tablets and their methods of development.

Aim and Objective is presented which gives the information regarding the present study.

Literature of review is presented in which provides an extensive detail of the related research work pertaining to the present study.

Drug profile is presented which gives details about the mechanism of action, pharmacodynamics, dosage and administration, precautions and side effects of the drug selected.

Excipient profile which gives details about the different excipients used in the formulation development.

Materials and methods which gives details about the list of chemicals, equipments used for the study. This chapter also gives information about the methods involved in the development of formulation.

Experimental investigation which gives information about different formulas developed in the formulation of dispersible tablets and the comparative evaluation of the developed formulation with that of the innovator product.

Results and discussion which deals with the completed information regarding physical and chemical analysis of the present study with suitable tables, graphs and figures.

Summary and conclusion which provides detailed information about each chapter.

Deferasirox is indicated in for the treatment of chronic Iron overload due to blood transfusions in adult and pediatric patients (aged 2 years and over).

Pre-formulation studies were performed for the drug and excipients as per the standard procedures.

The innovator product characterization was performed.

Formulation 1 was made by direct compression method. In this poor flow property was observed and also hardness and friability values were not satisfactory.

Formulations 2,3,4,6,7,8,9 were made by using wet granulation method. In formulaton2 hardness was found to be less and the friability value does not comply with the specifications. In formulations 3, 4, 6 in order to get a better dispersion the concentration

of superdisintegrant was increased. Here the disintegration time, dispersion time and percentage of drug release does not comply with the innovator product. In formulations 7,8,9 the disintegration time, dispersion time and percentage of drug release were found to match with the innovator product. All the physicochemical characteristics of the finished product were found to be satisfactory.

Formulation 5 was also made by wet granulation method with a different formula. Here the disintegration time, dispersion time and percentage drug release does not match with the innovator.

All the formulations were subjected to physicochemical analysis and out of them ***Formulation 8*** was found to be satisfactory when compared to other formulations. The disintegration time (35 sec), dispersion time (67 sec) and percentage of drug release (98.3%) were found to be satisfactory and it matches with the innovator. So, the batch size was increased in further trial to check the reproducibility ***(Formulation 9).*** Finally loaded for stability as per the ICH guidelines.

BIBLIOGRAPHY

1. Ansel H., Allen L. and Jr. Popovich N, 2005. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Eighth Edition: 227-259.
2. Liberman H, Lachman L. The Theory and Practice of Industrial Pharmacy. III[rd] editionBombay : Verghese Publication House; 1991.pg.no.293.
   Lachman L and Lieberman H. and Kanig J., 2000. 'The Theory and Practice of Industrial Pharmacy': Third ed., 377-390, 293-346-373,392-393
3. Yeola B, Pisal S, Paradkar A, Mahadik K. New drug delivery system for Elderly. Indian drugs, 2000; 37(7):312-8.
4. Chang R, Guo X, Burnside B. A review of fast dissolving tablets. Pharm. Tech.2000; 52-4.
5. Kuchekar BS, Badhan AC, Mahajan HS. Mouth Dissolving Tablets: A novel drug delivery system. Pharma times; 35:10-7.
6. http://www.faqs.org/patents/app/20080312168.
7. Reddy LH, Ghosh B, Rajneesh, Fast-dissolving drug delivery systems: A Brief Overview. Indian J Pharm Sci. Jul 2002; 64(4):331-336.
8. Brahmeshwar Mishra, Mouth Dissolving Tablets I: An overview of Formulation Technology. Sci Pharm. 2009; 77: 309-326.
9. Jaccard T.T Leyder Ji, Emerging Trends In The Development Of Orally Disintegrating Tablet Technology. Ann. Pharm. Fr.1985; 43(2): 123-131.
10. Sreenivas SA, Dandagi PM, Gadad AP, Godbloe Am, Hiremath SP, Mastiholimath VS, Orodispersible tablets: New-fangled drug delivery systems-A review. Indian J Pharm Educ Res. Oct 2005; 39(4): 177-81.
11. Brown D, Orally disintegrating tablets-taste over speed. Drug Delivery technol.2001:3(6):58-61.
12. Habib W, Khankari R, Hontz J, Fast-dissolving Drug Delivery Systems. Critical Reviews TM Therapeutic Drug Carrier Systems. 2000; 17(1):61-72.
13. H. Seager, Drug Delivery Products and the Zydis Fast-dissolving Dosage form.Journal.Pharm.Pharmcol.1998; 50:375-385.
14. Dispersible Tablets: A novel dosage form for children. Practical pharmacy for developing countries.
15. Dispersible tablets [internet].2010[updated 2010 may 7; cited 2012 september 24]. Available from: http://www.unicef.org/supply/index_53571.html.
16. Kaur t, Gill B, kumar S, Gupta GD. Mouth dissolving tablets: A novel approach to drug delivery. Int J Curr Pharm Res. 2011;3(1):1-7.

17. Banker G., and Rhodes C., 1996. 'Drug and Pharmaceutical Sciences': Modern Pharmaceutics; Third Edition; 333-394.
18. Bentley's., E A Rawlins 2003. Text book of Pharmaceutics. Eighth edition. All India Traveller book sellers, Delhi 270-281.
19. Biljana Govedarica. Etal (2011) Formulation and evaluation of immediate release tablets with different types of paracetamol powders prepared by direct compression. African journal of Pharmacy and Pharmacology.
20. C.Rowe. et al (2007) Comparison of neurofuzzy logic and decision trees in discovering knowledge from experimental data of an immediate release tablet formulation.
21. Kumar GP, Rangu N. Fundamental aspects of superdisintegrants: A concise review. J Glob Pharm Tech. 2012; 4(2): 1-12.
22. Formulation and Excipients Used in Fast Dissolving Tablet [Internet]. 2011[cited 2012 October 20]. Available from: http://formulation.vinensia.com/2011/10/formulation-and-excipients-used-in-fast.html.
23. Parakh SR, Gothosakar AV. A review of Mouth Dissolving Tablet technologies. Pharm Technol. 2003; 27(11):92-100.
24. Mohanachandran PS, Sindhumol PG, Kiran TS. Superdisintegrants: An Overview. Int J Pharm Sci Rev Res.2011 ;(6):2-22.
25. Ram DK, Patel Vid et al. A review on mouth dissolving tablet tecniques. Ijrap. 2001; 2(1):66-74.
26. Prajapati VD, Jani Gk, Goswami JM, Formulation and Evaluation of New Super Disintegrants for the development of Dispersible Tablets. AAPS 2007.
27. Rajesh YV, Balasubraniam J, Bindu K, Sri devi R, Swetha M, Rao Vu. Impact of superdisintegrantson Efavirenz release from tablet formulations. Acta Pharm. 2010; 60(2):185-95.
28. Guyot-Hermann Am, Ringard J. Disintegration mechanisms of tablets containing starches. Hypothesis about the particle-particle repulsive force. Drug Dev Ind Pharm. 1981; 7(2):155-77.
29. Qbaidat AA, Rana M. Development and evaluation of fast- dissolving tablets of meloxicam-β-cyclodextrin complex prepared by direct compression. Acta Pharmaceutica. 2011; 61(1):83-91.
30. A review on New Innovations and Technologies in the formulations of orally disintegrating tablet [Internet]. 2012 [updated on 2012 October 23; cited on 2012

October 25]. Available from: http://www.pharmatutor.org/articles/review-on-new-innovations-technologies-informulation-of-orally-disintegrating-tablets/page=0, 1.

31. Fu Y, Yang S, Jeong SH< Kimura S, Park K. Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Marking and Clinical Studies. Critical Rev Ther Drug Car System. 2004;21(6):433-75.
32. Swarbrick J. Handbook of Pharmaceutical Granulation Technology. New York: Taylor & Francis Group. 2005. P.129-55.
33. Bhowmik D, Chiranjib B, Krsihnakanth, Pankaj, Chandra RM. Rapid Dissolving Tablet: An Overview. J Chem Pharm Res. 2009;1(1):163-77.
34. Shoukri RA, Ahmed IS, Shamma RN. In Vitro and IN vivo Evaluation of Nimesulide Lyophilized Orally Disintegrating Tablets. Eur J Pharm Biopharm. 2009; 73:162-71.
35. Madan J, Sharma AK, Singh R. Rapid Dissolving Tablets of Aloe Vera Gel. Topical J Pharm Res.2009; 8(1):63-70.
36. Rai RR, Chirra P, Thanda V. Fast Dissolving Tablets: A Novel Approach to Drug Delivery: A Review. Int J Preclinical Pharm Res. 2012; 3(1):23-32.
37. Bhattacharya s, Pal TK. A Review on Fast Dissolving Tablet Technology. PHARMATUTOR-ART-1075.
38. Sharma S and Gupta GD. Pharma buzz 2009; 4(1): 30-41.
39. Setty CM, Prasad DVK, Gupta VRM. Development of Fast Dispersible Aceclofenac Tablets: Effect of Functionality of Superdisintegrants. Ind J Pharm Sci. 2008; 70(2):180-5.
40. Kumar A, Kaushik V, Malodia K, Kumar S, Rakha P. A Recent Approach on fast Dissolving Tablets. Res J Pharm Biol Chem Sci. 2012;3(3):1209-19.
41. Khan T, Nazim S, Shaikh S, Shaikh A, Khairnar A, Ahmed A. An Approach for rapid Disintegrating Tablet: A review. Int J Pharm Res Dev. 2011; 3(3):170-83.
42. Ozeki T, Yasuszawa Y, Katsuyama H, Takshima Y, Kasai T, Eguchi T, et al. Design of rapidly disintegrating oral tablets using acid treated yeast cell wall: A technical note. APPS PharmaSciTech.2003,4(4):561-4.
43. Shihora H, Panda S. Superdisintegrants, Utility in Dosage Forms: A quick Review. J Pharm Sci Biosci Res. 2011; 1(3):148-53.
44. Keberle H. The biochemistry of deferoxamine and its relation to iron metabolism. Ann NY Acad Sci.1964; 758-75.
45. Kash RA. Metals in medicine. Alternative Therapies in Health and Medicine. 2005; 11(4):18-25.

46. Mendes Al, Ferro a, Martin R. Non-classical hereditary haemochromatosis in Portugal: novel mutations identified in iron metabolism-related genes. Ann Haematol.2009; 88(3):229-34.
47. Choudhry VP, Naithani R. Current Status of Iron Overload and Chelation with Deferasirox. Indian J Pediatr.2007; 74(8):759-64.
48. Herbert A. Lieberman, Leon Lachman, Joseph B. Schwartz, Pharmaceutical dosage forms: Tables. Vol1.Pg.no.133-136.
49. Alfonso R Gennaro, Remington: The Science and Practice of Pharmacy, 20th ed. Vol 1. Pg. no.889-894
50. http://www.rxlist.com/exjade-drug.html.
51. Elliott Vichinsky, Onyinye Onyekwere, John Porter, Paul Swerdlow, james Eekman, Peter Lane, et al. A randomized comparision of Deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. Bri J Haematol.2007; 136(3):501-3.
52. Spellberg B, Andes D, perez M, Anglim A, Bonilla H, Glenn E. Mathisen. Safety and Outcomes of Open-Label Deferasirox Iron Chelation Therapy for Mucormycosis. Anti mi Ag & Chemother.2009;53(7):3122-5.
53. Galanello R, Piga A, Cappellini MD, Forni GL, Zappu A, Origa R, et al. Effect of Food, Type of Food, and Time of FoodIntake on Deferasiox Bioavailability: Recommendation for an Optimal Deferasirox administration Regimen. J Clin Pharmacol.2008, 48:428.
54. Sechaud R, Robeva A, Belleli R, Balez S. Absolute Oral Bioavailability and Disposition of Deferasirox in Healthy Human Subjects. J Clin Pharmacol.2008; 48(8):919-25.
55. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. A phase # study of Deferasirox (ICL670), a once-daily oral iron chelator, in patients with β-thalassemia. J Am Soc Hematol.2006; 107(9):3455-62.
56. Deborah Chirnomas, Amber Lynn Smith, Jennifer Braunstein, Yaron Finkelstein, Luis Pereira, Anke K. Bergmann, et al. Deferasirox pharmacokinetics in parients with adequate versus inadequate response. J Am Son Hematol.2009; 114(19):4009-13.
57. Andrej Skerjanec, Jixian Wang, Kelly Maren, Lisa Rojkjaer, Investigation of the Pharmacokinetic Interactions of Deferasirox, a Once-Daily Oral Chelator, with Midazolam, Rifampin, and Repaglinide in Healthy Volunteers. J Clin Phormacol.2010; 50(2):205-13.

58. Pennell DJ, Porter JB, Cappellini MD, El-Beshlawy A, Chan LL, Aydinok Y, et al. Efficacy of Deferasirox in reducing and preventing cardiac iron iron overload in β-thalassemia. J Am Soc Hematol.2010; 115(12):2364-71.
59. Raymond C Rowe, Paul J Sheskey, Marian E Quinn, Handbook of Pharmaceutical Excipients, 6th ed. Pg.no. 128-133,185-188,189-193,208-210,322-324,364-367,404-407,581-585,663-666,667-669,691-694,701-703,728-730.
60. United States Pharmacopoeia XX, 2002; Vol 1 and 2, Pg. no. 242, 643,731.
61. Milind P Wagh, Chetan P Yewale, Santosh U Zate, Paresh I Kothawade, Ganesh H Mahaale, Formulation and Evaluation of fast dispersible tablets of aceclofenac using different superdisintegrant. Int J Pharm Pharm Sci. 2010;4(2):154-7.