Research Article

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Formulation and Evaluation of Orodispersible Tablets of Cefuroxime axetil

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Abstract:
Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs.

Keywords:
Cefuroxime axetil, Oral Drug Delivery,

1. INTRODUCTION

1. Ideal Properties of ODTs:

The performance of ODTs depends on the technology used during their manufacture. The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water. Various technologies have been developed that enable ODT to perform this unique function[1].

An ideal ODT should meet the following criteria

- Does not require water for oral administration yet disintegrates and dissolves in oral cavity within a few seconds
- Has sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling
- Allow high drug loading
- Has a pleasant mouth feel
- Is insensitive to environmental conditions such as humidity and temperature is adaptable and amenable to existing processing and packaging machineries[2]

2. The need for development of ODT

The need for non-invasive delivery systems persists due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

A. Patient Factors

Orally disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

- Pediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms
- Patients who are unwilling to take solid preparation due to fear of choking
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of a typical antipsychotic.
- A patient with persistent nausea, who may be journey, or has little or no access to water.

B. Effectiveness Factor

Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pregastric absorption from some formulations in those cases where

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drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre- gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pre- gastric segments of GIT.

C. Manufacturing and Marketing Factors

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size. As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, product line extension, and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and under-treated patient populations. As examples, Eisai Inc. launched Aricept ODT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U.S. in 2005 in response to a generic challenge filed in the U.S. by Ranbaxy. Merck's Japanese subsidiary launched Lipola M (simvastatin ODT), a line extension of its block-buster, Zocor®, a cholesterol-lowering drug, in response to seventeen generic registrations of simvastatin applied for in Japan in 2004. Marketers build a better brand and company image when they offer a unique easier-to-take form that satisfies the need of an underserved patient population.

4. Significance

Orally disintegrating tablets offer all advantages of solid dosage forms and liquid dosage forms along with special advantages, which include:

- As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.
- No risk of obstruction of dosage form, which is beneficial for traveling patients who do not have access to water.
- Easy to administer for pediatric, geriatric, and institutionalized patients (specially for mentally retarded and psychiatric patients)
- Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.
- Medication as "bitter pill" has changed by excellent mouth feel property produced by use of flavors and sweeteners in ODTs.
- Bioavailability of drugs that are absorbed from mouth, pharynx, and oesophagus is increased[3].
- Pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.

5. Challenges In Formulating ODTs

A. Palatability

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance[4].

B. Mechanical strength

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs[5].

C. Hygroscopicity

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging[6].

D. Amount of drug

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers[7].

E. Aqueous solubility

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and

hence, impart rigidity to the amorphous composite[8].

F. Size of tablet

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve[9].

7. Various Technologies Used In The Manufacture Of Orodispersible Tablets

The performance of orodispersible tablets depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop orodispersible tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation. Following technologies have been used by various researchers to prepare orodispersible tablets:

A. Lyophilization or Freeze-Drying

Formation of porous product in freeze-drying process is exploited in formulating ODTs. Lyophilization is a process, which includes the removal of solvent from a frozen suspension or solution of drug with structure-forming additives. Freeze-drying of drug along with additives imparts glossy amorphous structure resulting in highly porous and lightweight product. The resulting tablet has rapid disintegration and dissolution when placed on the tongue and the freeze-dried unit dissolves instantly to release the drug.

Several technologies are patented involving lyophilization process, which are discussed in this article. However, the ODTs formed by lyophilization has low mechanical strength, poor stability at higher temperature, and humidity.10Along with above complications and its expensive equipment freeze-drying use is observed to be limited.

B. Tablet Molding

Molding process includes moistening, dissolving, or dispersing the drug with a solvent then molding the moist mixture into tablets (compression molding with lower pressure than conventional tablet compression), evaporating the solvent from drug solution, or suspension at ambient pressure (no vacuum lyophilization), respectively.

The molded tablets formed by compression molding are air-dried. As the compression force employed is lower than conventional tablets, the molded tablet results in highly porous structure, which increases the disintegration and dissolution rate of the product. However, to further improve dissolution rate of the product powder mixture should be sieved through very fine screen. Molding process is employed usually with soluble ingredients (saccharides) which offer improved mouth feel and disintegration of tablets. However, molded tablets have low mechanical strength, which results in erosion and breakage during handling[11].

C. Cotton Candy Process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process[12] involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized 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 ODT. This process can accommodate high doses of drug and offers improved mechanical strength.

D. Spray Drying

Highly porous, fine powders are obtained by this method. The ODT formulations are prepared by using hydrolyzed/unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulking agent and sodium starch glycolate or croscarmellose sodium as disintegrating agent.

Disintegration and dissolution were improved by adding effervescent components, i.e. citric acid[13] (an acid) and sodium bicarbonate (an alkali). The formulation was spray dried to yield a porous powder. The ODT made from this method disintegrated in <20 sec. However, high-process temperature limits the use of this process.

E. Mass Extrusion

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets[14].

F. Melt granulation

ODT is prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Superpolystate is a waxy material with an melting point of 33-37°C and a hydrophilic lipophilic balance of 9. It not only acts as a binder and increases the physical resistance of tablets, but also helps the

disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue.

Super polystate was incorporated in the formulation of ODT by melt granulation method where granules are formed by the molten form of this material. Crystallized paracetamol was used as model drug and in addition the formulation included mannitol as a water-soluble excipient and croscarmellose sodium as disintegrating agent.

G. Phase transition process

It investigate the disintegration of ODT by phase transition of sugar alcohols using erythritol (melting point 122°C), xylitol (melting point 93-95°C), trehalose (97°C) and mannitol (166°C).

Tablets were produced by compressing a powder containing two sugar alcohols with high- and low-melting points and subsequent heating at a temperature between their melting points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol[15].

H. Sublimation

The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of ODT. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tableting process, which sublimated from the formed tablet[16].

ODT utilizing camphor, a subliming material that is removed from compressed tablets prepared using a mixture of mannitol and camphor. Camphor was sublimated in vacuum at 80^0C for 30 min after preparation of tablets.

Conventional methods

Conventional methods in formulating tablets such as

A. Dry granulation

B. Wet granulation[17] and

C. Direct compression

These methods are adapted to produce ODTs. In formulating ODTs, one of the important components is the super disintegrants.

Several excipients are investigated for rapid disintegration of ODTs.

A. Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of orodispersible tablets because of the availability of improved18 excipients especially superdisintegrants and sugar based excipients. The steps involved are:

Raw → Weighing→Screening→Mixing→Compression material

Superdisintegrants and ODT

Super disintegrants plays the major role in oral disintegrating tablet. The disintegration efficiency is based on the force-equivalent concept the combined measurement of swelling force development and amount of water absorption. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1 – 10 % by weight relative to the total weight of the dosage unit.

Common disintegrants used are Croscarmellose sodium (Vivasol, Ac-Di-Sol), Crospovidone (Polyplasdone), Carmellose (NS-300), Carmellose calcium (ECG-505), Sodium starch glycolate (SSG) etc. Recently few ion exchange resins (e.g., Indion 414) are found to have superdisintegrant property and are widely used in pharmaceutical industry.

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

Method of Addition of Disintegrants

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment.19 There are three methods of incorporating disintegrating agents into the tablet:

1. Internal Addition (Intragranular)
2. External Addition (Extragranular)
3. Partly Internal and External

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In Internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules. When these methods are used, part of disintegrant can be added internally and part externally. This provides immediate disruption of the tablet into previously compressed granules while the disintegrating agent within the granules produces further erosion of the granules to the original powder particles.

Mechanism of Tablet Disintegrants

The tablets are broken into small pieces and the produced a homogeneous suspension which is based on the following mechanisms.

Capillary action/ water wicking

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. The ability of a disintegrant to draw water into the porous network of a tablet is essential for effective disintegration. Wicking is not necessarily accompanied by a volume increase.

By swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate into the tablet and disintegration again slows down.

Air expansion /Heat of wetting

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. Due to disintegrating particle/particle repulsive forces.

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Non-swelling particles cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

Due to deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

Due to release of gases

Carbon dioxide is released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

By enzymatic reaction

Here, enzymes presents in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration.

Sugar Based Excipients

This is another approach to manufacture orodispersible tablets by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel.

Sugar - based excipients can be classified into two types on the basis of molding and dissolution rate.

Type 1: Saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type 2: Saccharides (maltose and maltilol) exhibit high mouldability but low dissolution rate.

Mouldability is defined as the capacity of the compound to be compressed or molded. The mouldability of type 1 saccharide can be improved by granulating it with type 2 saccharides.

4. Patented Technologies

Zydis technology

Zydis is patented by R.P. Scherer. This technology includes physical trapping of the drug in a matrix composed of a saccharide and a polymer.Polymers generally employed are partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginates, polyvinyl alcohol, polyvinyl pyrrolidine, acacia, and these mixtures. The methodology involves solution or dispersion of components is prepared and filled in to blister cavities, which are frozen in a liquid nitrogen environment. The frozen solvent is removed or sublimed to produce porous wafers. Peelable backing foil is used to pack Zydis units. Zydis formulation is sensitive to moisture and may degrade at humidity greater than 65%[20].

Desired characteristics of Zydis technology

- Drug should be chemically stable
- Water insoluble
- Particle size should be smaller than 50 μm.
- Dose for water-soluble drugs is limited (60 mg)

Lyoc

Lyoc technology is patented by pharmalyoc. Oil in water emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Non homogeneity during freeze-drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered.21

Quick Solv

This technology is patented by Janssen Pharmaceuticals. It utilizes two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling[21].

Nano Crystal Technology

This is patented by Elan, King of Prussia. Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled in to blister pockets. This method avoids manufacturing process such as granulation, blending, and tableting, which is more advantageous for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug[22].

Flashtab Technology

This is patented by Ethypharm France. This technology includes granulation of excipients by wet or dry granulation method and followed by compressing into tablets. Excipients used in this technology are of two types.

Disintegrating agents include reticulated polyvinyl pyrrolidine or carboxy methylcellulose. Swelling agents include carboxy methyl cellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. These tablets have satisfactory physical resistance. Disintegration time is within 1 min[23].

Orasolv Technology

This technology is patented by CIMA Labs. This includes use of effervescent disintegrating agents compressed with low pressure to produce the ODT. The evolution of carbon dioxide from the tablet produces fizzing sensation, which is a positive organoleptic property. Concentration of effervescent mixture usually employed is 20-25% of tablet weight[24].

As tablets are prepared at low compression force, they are soft and fragile in nature. This initiated to develop Paksolv, a special packaging to protect tablets from breaking during storage and transport. Paksolv is a dome-shaped blister package, which prevents vertical movement of tablet within the depression. Paksolv offers moisture, light, and child resistance packing.

Durasolv Technology

This technology is patented by CIMA Labs. The tablets produced by this technology utilize the conventional tableting equipment. Tablets in this are formulated by using drug, non direct compression fillers, and lubricants.

Non direct compressible fillers are dextrose, mannitol, sorbitol, lactose, and sucrose, which have advantage of quick dissolution and avoid gritty texture, which is generally present in direct compressible sugar. The tablets obtained are strong and can be packed in conventional packing in bottles and blisters. Nondirect compressible fillers generally used in the range of 60-95%, lubricant in 1-2.5%[25].

WOW Tab Technology

Yamanouchi patented this technology. WOW means with out water. This technology utilizes conventional granulation and tableting methods to produce ODT employing low- and high-moldability saccharides. Low moldability saccharides are lactose mannitol, glucose, sucrose, and xylitol. High-moldability saccharides are maltose, maltitol, sorbitol, and oligosaccharides. When these low- and high-moldable saccharides used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combinations are used. This technology involves granulation of low-moldable saccharides with high-moldable saccharides as a binder and compressing into tablets followed by moisture treatment. Thus tablets obtained showed adequate hardness and rapid disintegration[26].

Dispersible tablet technology

Lek, Yugoslavia patents this technology. It offers development of ODT with improved dissolution rate by incorporating 8-10% of organic acids and disintegrating agents. Disintegrating agent facilitates rapid swelling and good wetting capabilities to the tablets that results in quick disintegration.

Disintegrants include starch, modified starches, micro crystalline cellulose, alginic acid, cross-linked sodium carboxy methyl cellulose and cyclodextrins. Combination of disintegrants improved disintegration of tablets usually less than 1 min[27].

Pharma burst technology

SPI Pharma, New Castle, patents this technol-

ogy. It utilizes the coprocessed excipients to develop ODT, which dissolves within 30-40s. This technology involves dry blending of drug, flavor, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles[28].

Frosta technology

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. Plastic granules composed of:

- Porous and plastic material
- Water penetration enhancer
- Binder

The process involves usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30s depending on size of tablet[30].

Oraquick

This technology is patented by K.V Pharmaceuticals. It utilizes taste masking microsphere technology called as micro30 mask, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product. This process involves preparation of micro particles in the form of matrix that protects drug, which can be compressed with sufficient mechanical strength. Low heat of production in this process makes it appropriate for heat-sensitive drugs. Oraquick product dissolves within few seconds.

Ziplets/advatab

This technology is patented by Pessano con Bornago, Italy. It utilizes water-insoluble ingredient combined with one or more effective disintegrants to produce ODT with improved mechanical strength and optimal disintegration time at low compression force. This technology handles high drug loading and coated drug particles and does not require special packaging, so they can be packed in push through blisters or bottles[31].

Flashdose

Fuisz has patented Flashdose technology. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flashdose technology is the first commercial product launched by Bioavail Corporation. Flashdose tablets consist of self-binding shear form matrix termed as "floss." Shear form matrices are prepared by flash heat processing[32].

2. Materials and Methodology

2.1 Materials

Table 1: List of materials used

S. No	Name of ingredients	Suppliers
1	Cefuroxime axetil	Aurobindo Pharma, Hyderabad
2	mannitol	Rankem Limited, Mumbai, India
3	Microcrystalline cellulose	Rankem Limited, Mumbai, India
4	Alginic acid NF	Rohm Gmbh, Thane, India
5	Magnesium stearate	Rankem Limited, Mumbai, India
6	Xanthan gum	Rankem Limited, Mumbai, India

Table 2: List of equipments used

S. No.	Name of Instrument	Manufacturer
1	Tablet Dissolution Tester	Electrolab, Mumbai.
2	Millipore Water System	Millipore Pvt.,Pune.
3	Sonicator (Ultrasonic Cleaner)	Prama Instruments Pvt., Ltd., Mumbai.
4	Digital pH meter	ELICO Ltd., Mumbai.
5	Rotary Shaker	Rajendra Electrical Industries Ltd., Mumbai.
6	Mettler Electronic Analytical Balance	Mettler Toledo India Pvt Ltd., USA.
7	UV-Vis Spectrophotometer	Shimadzu (Asia Pacific) PTE Ltd.
8	Tablet Hardness Tester	Electrolab, Mumbai.
9	Tablet Friability Tester	Electrolab, Mumbai.
10	Tablet Disintigrator	Electrolab, Mumbai.
11	Tap Density Apparatus	Electrolab, Mumbai.
12	Electronic Weighing Balance	Essae, Mumbai.
13	Tablet Machine Mini press II	Cadmach, Mumbai.
14	Differential Scanning Calorimeter	Mettler Toledo India Pvt Ltd. USA.
15	FTIR Spectrophotometer	Bruker FT- IR Spectrophotometr, Thane.

16	Digital vernier Callipers	Mitutoyo-Digimatic, Mumbai.

2.2. Methodology:

2.2.1. Evaluation of API

Bulk characterization

Evaluation of API

A. Organoleptic evaluation

Organoleptic characters of drug was observed and recorded by using descriptive terminology.

B. Analytical Evaluation

2.2.2. Preformulation Studies

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of a drug with the goal of designing an optimum drug delivery system. Preformulation testing is defined as investigation of physical and chemical properties of drug substances alone and when combined with excipients prior formulation.

The tablet blend was tested for angle of repose, bulk density, tapped density, carr's index, hausner's ratio.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure of the flow ability of powder/granules. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform.

About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

Angle of repose was calculated from the average radius using the following formula.

$$\theta = \mathrm{Tan}^{-1}\,(h/r)$$

Where,
θ = Angle of repose
h = Height of the pile
r = Average radius of the powder cone

Flow properties corresponding to Angle of repose

Table 3: Angle of repose range

Angle of repose	Type of flow
<25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

Higher the angle of repose the rougher and more irregular is the surface of the particles.

Bulk and Tapped Density

An accurately weighed quantity of the granules (w) that was previously passed through # 40 was carefully poured into the graduated cylinder and the volume (vo) was measured. The graduated measuring cylinder was tapped for 100 times and after that, the volume (vf) was measured and continued the operation till the two consecutive readings were equal. Bulk density and tapped density determines the floating capacity of the formulation. The bulk density and tapped density were calculated using the formulas below

Bulk density = w/vo

Tapped density=w/vf

Where w - Weight of powder
vo - Initial volume
vf - Final volume

Percentage compressibility

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. A useful empirical guide is given by the Carr's compressibility or compressibility index.

Compressibility measures gives idea about flow property of the granules as per Carr's index which is as follows.

Table 4: Compressibility Index range

% Compressibility	Flow description
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair
23 – 35	Poor
35 – 38	Very poor
< 40	Extremely poor

Hausner's ratio

It provides an indication of the degree of densification which could result from vibration of the feed hopper.

Table 5: Hausner's ratio range

Hausner's ratio	Type of flow
<1.25	Good flow
1.25 – 1.5	Moderate
>1.5	Poor flow

Characterization

FTIR

FTIR spectroscopy was found to be the most reliable technique for predicting the possible interaction between the drug and the polymer and excipients used for formulation. The IR spectra of physical mixtures were studied using KBr disc method.

The IR absorption spectra of the pure drug and with different excipients were taken in the range of 4000-400 cm^{-1} using KBr disc method. Triturate 1-2 mg of the substance to be examined with 300-400 mg, specified quantity; of finely powered and dried potassium bromide .These quantities are usually sufficient to give a disc of 10-15mm diameter and spectrum of suitable intensity by a hydraulic press. The Infrared spectrum of cefuroxime axetil was recorded by using FTIR spectroscopy and observed for characteristic peaks of drug.

Post formulation Studies

Thickness

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale (Mitutoyo- Digimatic) and the average thickness was determined in mm. The tablet thickness should be controlled within a ± 5% variation of a standard.

Weight Variation

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the IP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

Table 6: Limits for Weight variation

Dosage form	Average weight of tablet (mg)	% deviation
Uncoated and film coated tablets	80 mg or less	10
	More than 80 mg but not less than 250 mg	7.5
	250 mg or more	5

Hardness Test

The crushing load which is the force required to break the tablet in the radial direction was measured using Electrolab hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm^2.

Friability

If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650 mg the number of tablets equivalent to a weight of 6.5 g were taken. The tablets were rotated in the Roche Friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed. The percentage friability should be not more than 1% w/w according to IP and 0.5% w/w according to USP of the tablets being tested.

The percentage friability is expressed as the loss of weight and is calculated by the formula:

$$\% \text{ Friability} = [(W0 — Wf) / W0] \times 100$$

W0 = Initial weight of tablets
W f = Final weight of tablets

Disintegration Time

The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml which is maintained at 37±20C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (#10) was considered as the disintegration time of the tablet. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30 sec.

Dissolution Studies

The dissolution test was carried out in USP Apparatus Type II (paddle). The samples were drawn at 5, 10, 15, 20, 25 and 30. Fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

Preparation of Dissolution Medium:

A. Preparation of 0.1N HCl / pH 1.2 buffers:

Place 85 ml of 0.2M HCl dissolved in 1000ml of water.

B. Preparation of pH 6.8 buffer:

Place 22.4 ml of 0.2M NaOH in 1000ml of distilled water.

Preparation of standard curve:

Standard calibration curve of cefuroxime axetil in 0.1 N HCl were prepared. First dissolve 100mg of pure drug in 100ml 0.1 N HCl buffer this is prima-

ry stock solution. From the above primary stock solution pipette out 10ml of solution and again make up to 100ml this is secondary stock solution. From this secondary stock solution different concentrations of cefuroxime axetil (2, 6, 10, 14, 18, 22, 26, 30µg/mL) in 0.1 N HCl buffer were prepared & absorbance of these solutions measured at 281 nm by spectrophotometrically (Shimazdu-1700, UV/Visible spectrophotometer, Shimadzu Corp, Kyoto, Japan) using 0.1 N HCl as reference solution.

Wetting Time

A piece of tissue paper folded double was placed in clean and dry petri plates containing 6 mL of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds.

Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity etc.

Accelerated study:

The product is subjected to accelerated stability studies at $40^0C\pm2^0C$ / 75%±5% RH for 6 months.

Table 7: Storage conditions for stability studies

S. No.	Storage Condition	Test Period
1	$40^0C\pm2^0C$/75% ± 5% RH	1st month
		2nd month
		3rdmonth
2	$25^0C\pm2^0C$/60% ± 5% RH	1st month
		2nd month
		3rdmonth

Formulation of Cefuroxime axetil orally disintegrating tablets

By varying the proportion of alginic acid and xanthan gum of formulation different ratios design into 6 batches which is summarized in table

Table 8: Formulation of Cefuroxime axetil tablets

S. No	Excipient (mg)	Formulations					
		F1	F2	F3	F4	F5	F6
1	Drug	150	150	150	150	150	150
2	Mannitol	10	10	10	10	10	10
3	MCC	60	59	60	59	58	58
4	Mg stearate	9	9	9	9	9	9
5	Xanthan gum	1	2	-	-	1	2
6	Alginic acid	-	-	1	2	2	1

3. EXPERIMENTAL RESULTS

3.1. Analytical Method Development

3.1.1. Standard plot of cefuroxime axetil in 0.1N Hcl

Table 9: Standard plot of cefuroxime axetil

Concentration	Absorbance at 281 nm
2	0.073
4	0.177
6	0.288
8	0.395
10	0.504

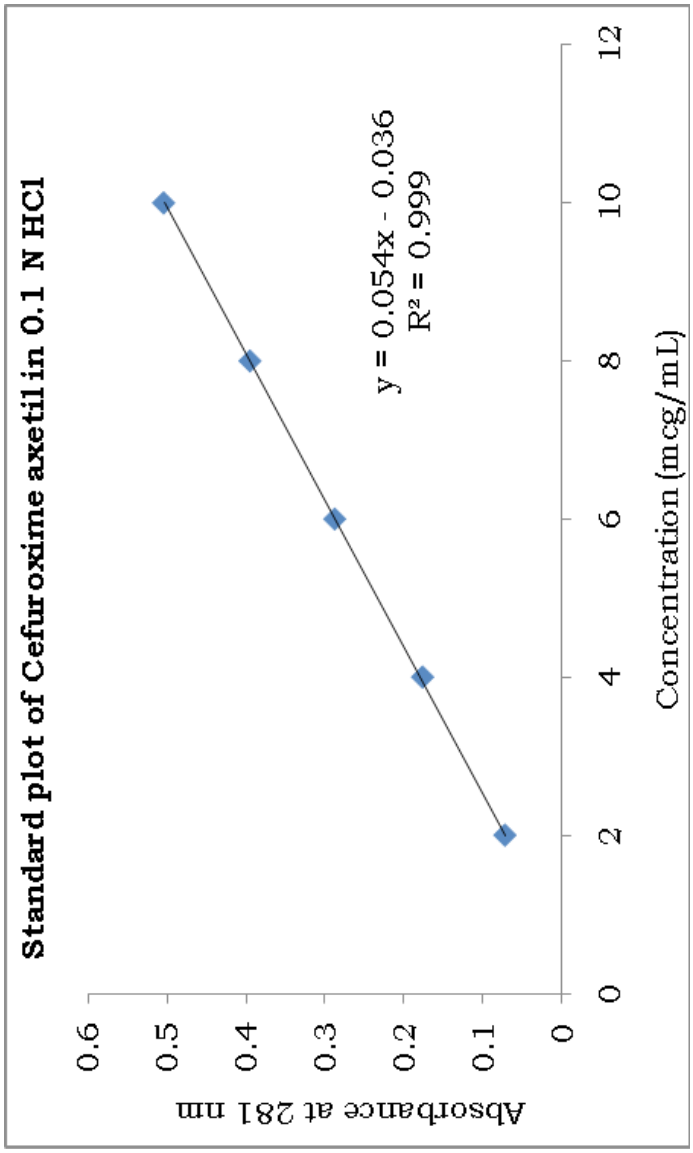

Fig. No. 1: Standard plot in Cefuroxime axetil 0.1N Hcl

3.2 Preformulation Studies of Cefuroxime Axetil Orally Disintegrating Tablets

Table 10: Preformulation studies of Tablet blend

Formulation	Angle of repose (°)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Hausner's ratio	Compressibily index (%)
F1	24.55±1.052	0.633±0.007	0.721±0.009	1.136±0.22	12.23±1.033
F2	24.58±0.921	0.626±0.010	0.731±0.006	1.30±0.014	14.44±1.031
F3	23.92±1.435	0.635±0.007	0.727±0.011	1.14±0.021	14.29±1.123
F4	24.38±0.722	0.633±0.002	0.733±0.005	1.15±0.021	13.58±1.632
F5	22.96±1.495	0.633±0.006	0.728±0.012	1.14±0.014	12.98±1.102
F6	24.55±0.868	0.629±0.002	0.724±0.008	1.14±0.025	13.18±1.851

All values were expressed as mean ± S.D; Number of trials (n) = 3

4.3. Characterization of Cefuroxime Axetil

4.3.1 Fourier Transform Infrared spectroscopy

The IR absorption spectra of the pure drug was taken in the range of 4000-400 cm-1 using KBr disc method .The major peaks were reported for evaluation of purity.

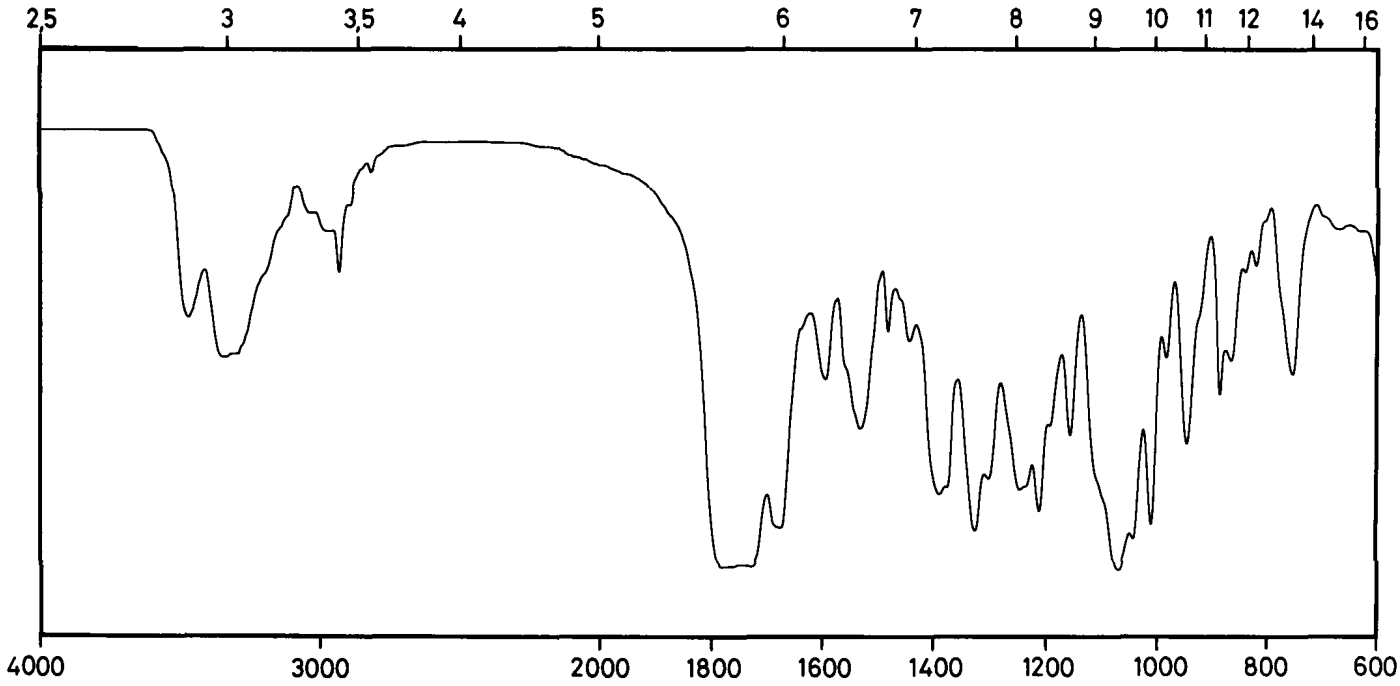

Fig. No. 2: FTIR spectral analysis of cefuroxime axetil

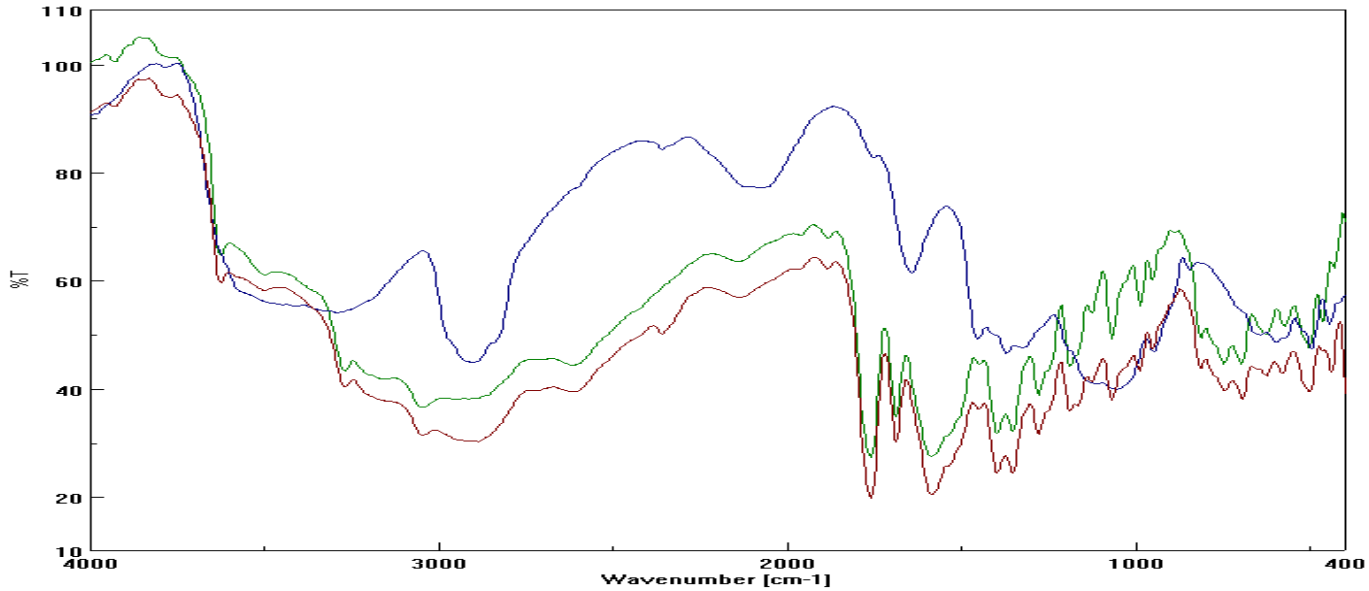

Fig. No. 3: Overlay spectra of a) cefuroxime axetil (green), b) xanthan gum (brown) and c) alginic acid (blue)

4.4. POST COMPRESSION PARAMETERS

Table 11: Evaluation of cefuroxime axetil tablets

Formulation Code	Weight Variation (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)
MRKT	240 ± 0.51	4.8±0.32	3.4 ±0.32	0.5 ± 0.11
F1	228.3±0.15	4.0±0.05	3.1± 0.85	0.25±0.21
F2	226.6±0.15	4.9±0.10	3.3±1.04	0.30±0.25
F3	232±0.23	4.1±0.10	3.1±0.86	0.27±0.02
F4	230±0.32	4.1±0.10	3.0±0.85	0.28±0.01
F5	228.3±0.52	4.2±0.05	3.2±0.74	0.29±0.16
F6	226.3±0.20	5.1±0.05	3.4±0.90	0.29±0.13

All values were expressed as mean ± S.D; Number of trials (n) = 3

Table 12: Evaluation of cefuroxime axetil tablets

Formulation code	Wetting Time(sec)	Disintegration Time(sec)	Content uniformity (%)
MRKT	35 ±0.5	38±0.5	101.10±0.1
F1	37±0.4	39±0.4	100.08±0.01
F2	31±0.5	32±0.5	99.38±0.23
F3	39±0.5	41±0.3	99.32±0.15
F4	34±0.3	36±0.2	100.82±0.4
F5	30±0.6	30±0.4	99.48±0.2
F6	28±0.5	29±0.4	99.58±0.6

All values were expressed as mean ± S.D; Number of trials (n) = 3

4.5. In vitro dissolution studies

Table 13: In vitro drug release for all formulation

Time (min)	% Drug released						
	MRKT	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
5	48±0.2	49±0.43	44±0.23	44±0.22	50±0.31	56±0.61	62±0.12
10	62±0.3	68±0.34	58±0.16	69±0.41	69±0.43	74±0.59	80±0.23
15	74±0.3	79±0.36	71±0.21	79±0.35	76±0.55	89±0.26	89±0.24
20	86±0.2	85±0.27	88±0.43	86±0.47	89±0.29	95±0.29	99.6±0.41
25	92±0.4	96±0.50	94±0.63	97±0.28	98±0.27	100.4±0.31	100.6±0.25
30	100±0.5	101±0.19	100.8±0.23	100.1±0.29	101.2±0.41	101.3±0.29	101.2±0.48

All values were expressed as mean ± S.D; Number of trials (n) = 3

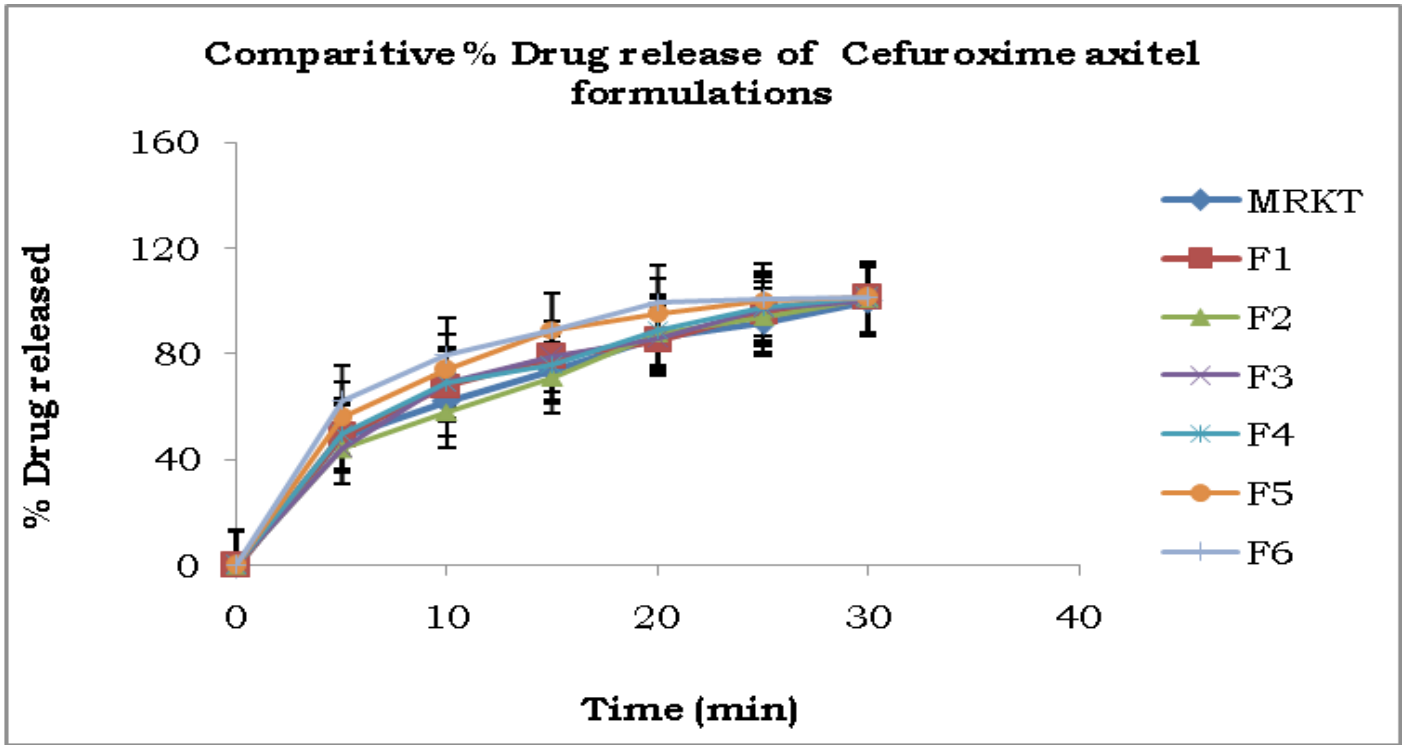

Fig. No. 4: Plot for in vitro drug release for all formulation

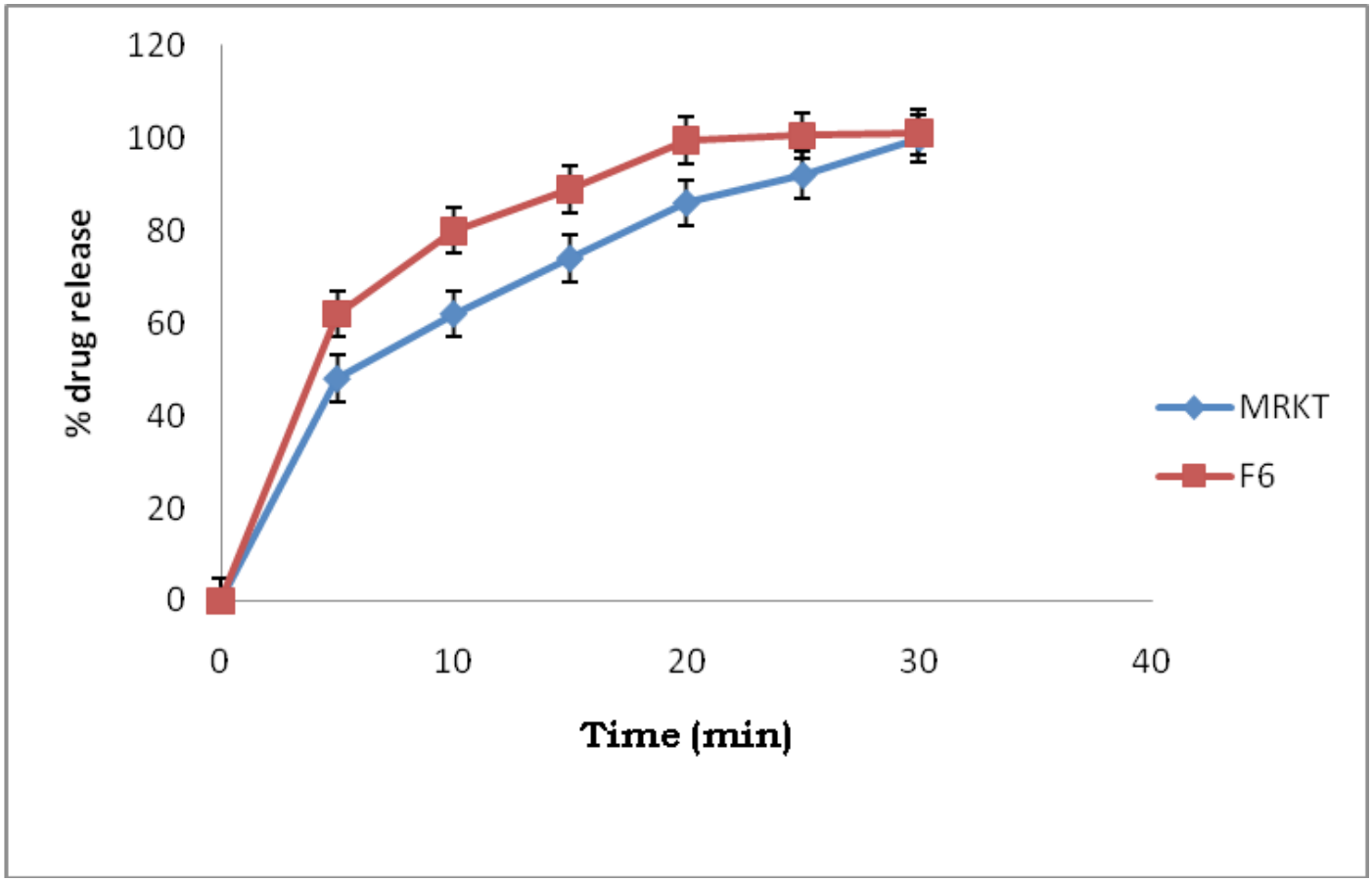

Fig. No. 5: Plot for in vitro drug release for marketed and F6

Statistical treatment of Dissolution data

Table 14: Statistical treatment of dissolution data of F6 formulation

Dissolution medium	f1	f2
Phosphate buffer pH 6.8	26.85	29.06

5. DISCUSSION OF RESULTS:

5.1. Evaluation of API

Organoleptic Evaluation

Cefuroxime axetil is White to off-white powder.

5.2. Characterization

FTIR spectroscopic Analysis

The IR absorption spectra of the pure drug was taken in the range of 4000-400 cm-1 using KBr disc method .The major peaks were reported for evaluation of purity.

Major peaks were observed at 1714.7cm-1, 1609.53 cm-1, 1540.73cm1,1428.33 cm-1 and 838.33cm-1 etc.

FT-IR spectrum for Cefuroxime axetil

Major peaks were observed at 1719.78 cm-1, 1610.24 cm-1, 1542.56 cm-1,1484.13 cm-1 and 866.88 cm-1 etc.

FT-IR spectrum for final blend:

Major peaks were observed at 1716.19cm-1, 1634.91 cm-1, 1569.86 cm-1,1481.2 cm-1 and 866.53 cm-1 etc. From the above peaks of FTIR graphs it was observed that no peak changes in drug, inclusion complex and final blend.

5.3. Preformulation studies

5.3.1. Bulk characteristics of cefuroxime granules

- Angle of repose of granules are in the range of 22.96 ± 1.49 to 24.58 ± 0.92
- Bulk density was in the range of 0.626±0.01 to 0.633±0.007gm/cm3.
- Tapped density was in the range of 0.721±0.009 to 0.733±0.005gm/cm3.
- Percentage compressibility was in the range of 12.23±1.633 to 14.44±1.031%.
- Hausner's ratio was in the range of 1.136±0.021 to 1.30±0.014.

From the above results it was observed that F5 formulation having better bulk characteristics than compared to remaining formulations.

5.4. Evaluation of Oral Orodispersible Tablets of Cefuroxime Axetil

Cefuroxime axetil orodispersible tablets were compressed with 3.5 mm round shaped standard punch. Weight variation was found to be in the range of 220– 240 mg. Thickness was found to be 3.0 – 3.6, hardness was found to be in the range 3 – 4 kg/cm2 indicating good mechanical strength, friability was within the USP limits, drug content was found to be within 95- 105% which is acceptable limits, in vitro disintegration time of the tablet were evaluated and found to be between 29- 41 sec. Weight variation was in the range 220- 250 mg.

Dissolution test

The dissolution results show that there was an hike in the dissolution velocity of the tablets. The maximum drug release was observed at 20 min which is acceptable and more than the marketed sample. Formulation F6 having higher concentration of xanthan gum showed more drug release.

Statistical treatment of data

f1 is the difference factor and f2 is the similarity factor. The limits for f1 are 0- 10 and for f2 50- 100. The f1 value was found to be more than the limits indicating that the drug release of F6 formulation was different from that of the marketed formulation.

The f2 value was found to be less than the limits indicating that the drug release of F6 formulation was not similar to the marketed formulation and the drug release is more than the marketed formulation.

Discussion of Results

- Weight variation was in range of 226.3±1.6 to 228.3±1.5 mg.
- Hardness was in range of 3.0±0.05 to 4.1±0.1
- Weight variation and hardness of cefuroxime axetil Tablets were within range.
- Length and breadth of tablet was as per the punch dimension.
- Percentage friability of tablet was evaluated in 100rpm and tablet passed the friability test.
- Tablets from each batch showed uniformity of weight as per IP limits. Each sample was analyzed in triplicate (n = 3).
- Content uniformity was done as per IP and the values were satisfactory.
- Wetting time was in the range of 30 to 39.3 as wetting time increases disintegration time of tablet decreases. Wetting time of combination of superdisintegrants shows lower values hence higher disintegration time. Formulations containing of xanthan gum showed somewhat lower wetting time than combination batches hence showed satisfactory disintegration time. Formulations containing of alginic acid showed very low wetting time compared to other formulations hence showed very less disintegration time than other formulations.
- Disintegration Time of tablets was evaluated and was found to be in the range of 29±1 to 41±1.52.

Higher disintegration time was for f5 and f6 formulations respectively because of combination of superdisintegrants. Formulations containing of xanthan gum in higher quantity showed good disintegration time. Formulations containing of alginic acid showed lesser disintegration time compared with other formulations.

5.4.1 In vitro dissolution studies:

Superdisintegrants has a dominant role in disintegration as well as drug release form orodispersible tablets. Both of superdisintegrants are chosen in the present work were natural superdisintegrants hence all the formulations showed better and satisfactory drug release profile. Due to the swelling and wicking action of both the superdisintegrants the tablets showed better disintegration time which in turn showed good drug release from tablet formulations.

The Dissolution study of various batches from F1- F6 shows that cefaruxmine axetil release from tablets containing combination of both alginic acid and xanthan gum at higher concentrations showed higher drug release. As concentration of xanthan gum decreased it showed lower drug release in combination batch. The formulation F2 which contain only 2 mg of xanthan gum showed 96% of drug release. The formulation F4 containing 2mg of alginic acid showed 94% of drug release. Drug release was very much less for formulations F1 and F3 which contain 1mg of xanthan gum and 1mg of alginic acid have 93% and 92% drug release respectively.

Further we can say that as concentration of superdisintegrants increases it causes higher % of drug release.

6. Summary and Conclusion

6.1. Summary

The Study was undertaken with an aim to formulate orodispersible tablets of cefuroxime axetil by using natural superdisintegrants like Xanthan gum and alginic acid.

Different formulations were prepared varying the superdisintegrant concentration. Preformulation study of the tablet blend was carried out, the tablet blends showed good flowing properties directing for the further course of formulation.

The tablets were prepared by direct compression method by 3.5 mm, round shaped, B tooling punch.

Tablet blend was evaluated for postformulation studies like hardness, weight variation, friability, wetting time, in vitro disintegration time and in vitro dissolution, stability studies.

The hardness was found to be in the range of 3.0 -4.0 kg/cm2.Weight variation was found to be in the range of 226 – 250 mg. Friability was NMT 0.5% meeting the USP limits. Wetting time was found to be within 30 sec.

The formulations were stable at both the temperatures maintained for stability studies and were found to be maintaining the same dissolution velocity.

6.2. Conclusion

It was concluded that the formulations containing xanthan gum and alginic acid as superdisintegrants can be proved to be ideal formulation considering all the evaluation parameters mainly wetting time, in vitro disintegration time and in vitro dissolution studies.

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