FORMULATION DEVELOPMENT AND EVALUATION OF TASTE MASKED CEFUROXIME AXETIL ORAL SUSPENSION

Dissertation submitted to

The Tamilnadu Dr. M.G.R Medical University, Chennai

In partial fulfillment for the requirement of the degree of

MASTER OF PHARMACY
(Pharmaceutics)

MARCH-2012

DEPARTMENT OF PHARMACEUTICS

KMCH COLLEGE OF PHARMACY

KOVAI ESTATE, KALAPPATTI ROAD,

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Submitted by
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This is to certify that this dissertation work entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF TASTE MASKED CEFUROXIME AXETIL ORAL SUSPENSION"** was carried out by **SREEJITH.G(Reg.no:26107110).** The work mentioned in the dissertation was carried out at the Department of Pharmaceutics, Coimbatore - 641 048, under the guidance of **Mrs.J.PADMAPREETHA.M.Pharm.,** for the partial fulfillment for the Degree of Master of Pharmacy and is forward to The Tamil Nadu Dr.M.G.R. Medical University, Chennai.

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EVALUATION CERTIFICATE

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DECLARATION

I do hereby declare that this dissertation entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF TASTE MASKED CEFUROXIME AXETIL ORAL SUSPENSION"** submitted to the TamilNadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the Degree of Master of Pharmacy in Pharmaceutics was done by me under the guidance of **Mrs.J.PADMAPREETHA M.Pharm.,** Asst Professor, Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, during the year 2011 – 2012.

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Acknowledgment

ACKNOWLEDGEMENT

First and foremost it gives me great pleasure to record my deep sense of gratitude and indebtedness to my esteemed guide **Mrs.J.PADMAPREETHA. M.Pharm.,** Asst Professor, Department of Pharmaceutics, KMCH College of Pharmacy, for his constant insight, guidance, countless serenity, encouragement and painstaking efforts in my project work . I am indebted to his kindness and never failing co-operation.

I extend my gratitude to **Dr.A.RAJASEKARAN, M.Pharm., Ph.D.,** Principal, KMCH College of Pharmacy, Coimbatore, for his constant encouragement, support and facilities provided.

I extend thanks to our respected chairman **Dr.NALLA G.PALANISWAMI, MD, AB (USA)** and respected trustee madam **Dr.THAVAMANI D. PALANISWAMI, MD, AB (USA),** Kovai Medical Center Research and Education Trust, Coimbatore for the facilities provided by them to carry out this project in a nice manner.

I owe my heartfelt thanks to my esteemed and beloved staffs **Dr. K.S.G. Arulkumaran M.Pharm.,PhD., Mr.J.Dharuman, M.Pharm.,Ph.D., Dr.Arunkumar.N M.Pharm.,PhD.,Dr.C.Sankar M.Pharm.,Ph.D.,Mr.Renju prabhakar M.Pharm** for their sensible help and suggestions.

My sincere thanks to all other staffs of KMCH College of Pharmacy, Coimbatore who directly or indirectly gave a helping hand to me while carrying out the study.

This project would not be a resplendent one without the timely help and continous support by ever-loving friends of the Dept of Pharmaceutics (Lincy varghese , Lincy john, Sandra, Mazin, Christine, Ambika , Dinesh,Arun Raj) .

I also express our heartfelt thanks to Ms.Thiruveni, Lab technician (Dept of Pharmaceutics) for her valuable support and timely help during the course of the entire work.

With immense pleasure I express my deep gratitude to computer lab technicians, library staff and other lab technicians of KMCH College of Pharmacy, and one all those who helped directly and indirectly in every aspect of constructing this work.

Above all I dedicate myself before the unfailing presence of GOD and constant love and encouragement given to me by my beloved father and mother, who deserve the credit of success in whatever I did.

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Abbreviations

ABBREVIATIONS

e.g	Example
i.e.	That is
%	Percentage
kg	Kilogram
g	Gram
mg	Miliigram
ml	Milliliter
µg	Microgram
w/w	Weight by volume
v/v	Volume by volume
avg	Average
hrs	Hours
pH	Hydrogen ion concentration
°C	Degree centigrade
RPM	Revolution per minute
t	Time
MCC	Microcrystalline
Abs	Absorbance
Conc	Concentration
Fig	Figure
Tab	Table
UV- VIS	Ultra violet and visible spectroscopy
mm	millimetre
C.I	Compressibility index
CD	cyclodextrin
CA	cefuroxime axetil

Introduction

SECTION 1: INTRODUCTION

Although a variety of delivery systems are being developed for different routes of administration like the oral, parenteral, nasal, and transdermal, the oral route remains attractive for drug delivery because this mode of administration is an easy, convenient, non-invasive and familiar method of drug delivery. The common oral dosage forms include: liquid mixtures like solutions, suspensions, solid dosage forms like tablets and capsules and liquid filled capsules etc. However, patients at the extremes of age, such as children and the elderly, often experience difficulty in swallowing solid oral dosage forms. For these patients the drugs are mostly provided in liquid dosage forms such as emulsions and suspensions. These dosage forms usually lead to perceptible exposure of the active drug ingredient to taste buds and this is a very serious problem when the drug has an extremely unpleasant or bitter taste.

The bitter taste of the drugs, which are orally administered, is disadvantageous in several aspects. Taste is an important parameter governing the compliance. ***"****The worse the taste of the medication, the better the cure"* was once the prevailing attitude. A change in patient attitude and development of taste masking technique has reversed this opinion. Patients now expect and demand formulations that are pleasantly, or at least tolerably, flavoured. The disagreeable taste of drugs causes difficulties in swallowing (dysphagia) or causes patients to avoid their medication thereby resulting in low compliance of patients. Conventional taste masking techniques such as use of sweetener, amino acids, flavouring agents are often unsuccessful in masking the taste of the highly bitter drugs like quinine, barberin, antibiotics like levofloxacin, ofloxacin, sparfloxacin, ciprofloxacin, cefuroxime axetil, erythromycin, and clarithromycin. Thus taste masking technologies are considered important and developed by many researchers. [1]

The current work is concerned with pharmaceutical compositions containing the 1-acetoxyethyl ester of cefuroxime, which has the approved name Cefuroxime axetil. The presence of 1-acetoxyethyl esterifying group results in significant absorption of the compound from the gastro-intestinal tract, whereupon the esterifying group is hydrolysed by enzymes present to yield the antibiotically active acid. Cefuroxime axetil has therefore extended the valuable therapeutic potential of cefuroxime by making available a form of antibiotic which may be administered orally.

A convenient means of presenting antibiotics for oral administration is in the form of granules which may be administered as a solution or suspension. Syrups are particularly

convenient for oral administration of antibiotics to children. They are particularly aimed at patients with nausea, vomiting, motion sickness and institutionalised patients. However Cefuroxime axetil has an extremely bitter taste which is long lasting and this remains a challenge[2]

1.1 DRY SYRUP

Dry syrups are oral reconstitutable suspensions commercially available as dry mixtures that require the addition of water at the time of dispensing.

TABLE 1: Commonly used ingredients in dry syrups

Frequent	**Infrequent**
Suspending agent	Anti caking Agent
Wetting agent	Flocculating agent
Sweetener	Solid diluents
Preservative	Antifoaming agent
Flavour	Granule binder
Buffer	Granule disintegrant
Colour	Antioxidant
	Lubricant

Advantages of Dry syrup

1. Easy to formulate.
2. Convenient method of administration for paediatrics, geriatrics, convalescent patient.
3. Dissolution and bioavailability is more as it bypasses disintegration process.
4. More palatable formulation for administration of bitter antibiotics.
5. They have the advantage of both solid and liquid dosage forms, as they remain solid during storage, which aid in avoiding the physical stability problems like viscosity changes, conversion of polymorphic form, incompatibility, crystal growth, caking of dosage forms and when transform into liquid, has bioavailability.
6. Reduces the weight of final product

1.2. BACKGROUND

Sense of taste [3,4,5,6]

Taste is a survival mechanism, alerting us to potentially harmful or potentially nutritious substances. We process taste at three levels: the receptor level, the circuit level, and the perceptual level. At the receptor level are approximately 10,000 chemoreceptors or taste

buds, residing primarily on the tongue, with some delocalized receptors at the back of the throat. These receptors fall into five primary categories: bitter, sour, umani, salt, and sweet, with grouped receptors dissipated over the surface of the tongue for each stimulus. Sweet signals carbohydrates or certain amino acids. Sour characterizes vitamins. Salt detects needed minerals. Umani indicates protein and amino acids. In general, we experience these tastes as pleasant. Bitter sensation, however, is often unpleasant, suggesting alkaline water, alkaloid poisons, and spoiled foods. APIs, of course, usually fit into the bitter category. Chemoreceptors for taste and olfaction (smell) respond to chemicals in an aqueous environment. Chemicals dissolved in saliva excite the taste receptors of the mouth, and airborne chemicals dissolved in epithelial mucus excite the olfactory receptors of the nose. The senses are complementary, with smell and taste working together to respond to, and more narrowly define, the same stimuli[3].

Taste depends on physiological and psychological factors. Physiological properties such as temperature and texture, clearly affect the perception of taste (consider the limited appeal of a cold cup of coffee). Human taste also appears to change with age. Many children dislike fresh vegetables, yet grow to enjoy them in adult life. Psychological factors can also influence taste perception: a childhood memory of badly formulated cough medicine can significantly modify taste perception of a modern formulation. Such factors underscore the role of taste in manufacturing a product that achieves patient compliance. Culture influences perceived palatability.

Market research has revealed standard combinations of specific sweeteners with relevant flavours and colours, which may vary by country and target market. National favourites include “green tea” in Japan, “bubblegum” in the United States, “citrus” notes in Europe, and “licorice” in Scandinavia. A bubblegum or cherry flavour married with a red colour and high intensity sweetener may suit a US pediatric market, while a less intense sweetener may be more appropriate for Japan. Similarly, a mint flavour coupled to a white unit may be a more traditional approach for an adult market. Regardless of the flavour system used, the challenge is how to deliver unpleasant compounds (APIs) while maintaining patient acceptability, efficacy, and compliance. Several formulation approaches may mask an unpleasant tasting API.[4,5]

Threshold for taste is the minimum concentration of a substance that evokes perception of a taste.

TABLE: 2.SPECIFIC AREA OF TONGUE AND THRESHOLD CONCENTRATION FOR PRIMARY SENSATIONS[6]

TASTE	AREA OF TONGUE	THRESHOLD CONCENTRATION
Sweet(sucrose)	Tip of tongue	0.5%
Sour(Hcl)	Sides of tongue	0.007%
Salt(Nacl)	Tip and sides of tongue	0.25%
Bitter(Quinine)	Back of tongue	0.00005%

1.3. TECHNIQUES OF TASTE MASKING

Taste masking techniques

To achieve the goal of taste abatement of bitter or unpleasant taste of drug, various techniques have been reported.[3]

1. Addition of flavouring and sweetening agents.
2. Microencapsulation / Coating with inert agents
3. Ion-exchange resins
4. Inclusion complexation
5. Granulation
6. Adsorption
7. Prodrug approach
8. Bitterness inhibitor and potentiators
9. Multiple emulsion technique
10. Liposome preparation
11. Gel formation
12. Solid dispersions
13. Molecular complex
14. Mass extrusion
15. pH modifiers
16. Miscellaneous approaches

1. Addition of flavours and sweeteners [3,4]

Addition of flavours & sweeteners is the most simplest approach for taste masking especially in the case of paediatric formulation. Flavouring and perfuming agents can be obtained from either natural or synthetic sources. Natural products include fruit juices,

aromatic oils such as peppermint and lemon oils, herbs, spices and distilled fractions of these. They are available as concentrated extracts, alcoholic or aqueous solutions, syrups or spirit[4]. Clove oil has been found to be a good taste masking component for a number of medicinal, because of its spicy and anaesthetic effect. Aspartame is a prominent sweetener for bitterness reduction. A concentration of as small as 0.8% was effective in reducing the bitterness of a 25% formulation of acetaminophen. Acesulfame potassium is an artificial sweetener which is 180-200 times sweeter than sucrose and as sweet as aspartame. Lactose, Saccharin, Sucralose are some of the commonly used sweeteners. This approach is also used to improve the aesthetic appeal of the product especially to make it more attractive for paediatric patient as well as used for the liquid formulation & the chewable tablets. Cooling effect of certain flavouring agent aids in reducing perception of bitterness. A combination of flavouring agents are usually employed.

TABLE 3: RELATIVE SWEETENESS OF COMMONLY USED SWEETENERS

Sweetening Agents	**Relative sweeteness***	**Comment**
Aspartame	200	Not very stable in solution
Acesulfame potassium	137-200	Bitter after taste if used in higher concentration
Cyclamate	40	Banned
Glycerrhizin	50	Moderately expensive
Lactose	0.16	Large amount required
Manitol	0.60	Negative heat of solution
Saccharin	450	Unpleasent after taste
Sucrose	1	Most commonly used
Sucralose	600	Synergistic sweetening effect

*Sucrose is taken as a standard of 1 for comparison.

2. Microencapsulation

Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a film or polymeric material.[7] Coating is an extremely useful technique to completely mask a bitter drug, while at the same time, not adversely affecting the intended drug release profile[8]. Any nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH, would be an acceptable alternative for taste masking.[9] Only soluble portion of the drug can generate the sensation of taste. Coating the active drug with a polymeric film creates a physical barrier between the drug and the taste buds and reduces its solubility in saliva thus taste could be masked.[10]

Techniques of microencapsulation are:

- Air suspension
- Coacervation-phase separation
- Spray drying and spray congealing
- Solvent evaporation
- Multiorifice - centrifugal process
- Pan coating
- Interfacial polymerisation

The air suspension coating process is the most commonly used method. It can be described as an upward moving, expanded, fluidized bed in central portion of the coating chamber coupled with a downward-moving, more condensed fluidized bed on the periphery of the column. Three types of air suspension coater are available, namely, top spray coater, wurster bottom spray coater and tangential spray coater. The coating polymers should be such that it prevents the release of active agent in the oral cavity, following per oral intake, but allows it in stomach or small intestine where the drug is expected to be absorbed. Polymers, which are mainly insoluble at salivary pH 6.8 but readily, dissolve at gastric fluid pH 1.2 could be a good candidate for taste masking.[10]

3. Ion exchange resin

Ion exchange resins are synthetic inert insoluble cross-linked organic polymers or polyelectrolytes consisting of a hydrocarbon network to which ionisable groups are attached and they have the ability to exchange their labile ions for ions of equal charge present in the solution with which they are in contact. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. The long-term

safety of ion exchange resins, even while ingesting large doses as in the use of cholestyramine to reduce cholesterol is established.[7] They contain positively or negatively charged functional group and are thus classified as either anionic or cationic exchangers. Within each category, they are classified as strong or weak, depending on their affinity for capable counter ions[3]. These insoluble ion exchange resins may be supplied in case of cation exchangers as sodium, potassium or ammonium salts and of anion exchangers usually as the chloride. Charged drugs are normally loaded on to ion exchange resins by two methods, viz, column method and batch method.

Column method

In this method a highly concentrated drug solution is passed through a column of resin particles. Since the reaction is an equilibrium phenomenon, maximum potency and efficiency is best obtained by the column method.

Batch method

In this method the drug solution is agitated with a quantity of resin particles until equilibrium is established.

Most of the bitter drugs have amine as a functional group, which is the cause of their obnoxious taste. If the functional groups are blocked by complex formation the bitterness of the drug reduces drastically. A drug: resin complex is made from the bitter drugs & ion - exchange resins. The nature of the drug: resin complex is such that the average pH of 6.7 and cation concentration of about 40 meq/ lit in saliva are not able to break the drug: resin complex but it is weak enough to be broken down by the hydrochloric acid present in the stomach. Thus the drug: resin complex is absolutely tasteless and stable, with no after taste, but at the same time its bioavailability is not affected.[11]

Classification of Ion Exchange Resins[11]

There are four major types of ion exchange resins available today:

- Strongly acidic cation exchange resins with sulfonic acid functionality e.g. Dowex 50, Amberlite-120 and Sodium polystyrene sulfonate.
- Weakly acidic cation exchange resins with carboloxylic functionality e.g. Amberlite IPR-88, Amberlite IPR-64 & IPR-64M and Amberlite IRC-50.
- Strongly basic anion exchange resins with quaternary ammonium functionality e.g. Dowex1, Amberlite IR400.

- Weakly basic anion exchange resins with secondary and tertiary amine functionality e.g. Amberlite IR 4B, Dowex 2, polyamine methylene resin.

Equilibrium phenomenon[12]

The principal properties of these resins are their exchange capacity to exchange its insoluble ions with those in solution. Soluble ions may be removed from the solution through exchange with the counter ions absorbed on the resin as illustrated in this equation:

$$\text{Resin- Drug}^+ + \text{X}^+ \text{ Resin} \longrightarrow \text{X}^+ + \text{Drug}^+$$

$$\text{Resin- Drug}^+ + \text{Y}^+ \text{ Resin} \longrightarrow \text{Y}^+ + \text{Drug}^+$$

Where X and Y are ions in the gastrointestinal tract.

$$\text{Re-SO}_3^- \text{Na}^+ + \text{drug}^+ \longrightarrow \text{Re-SO}_3^- \text{drug}^+ + \text{Na}^+$$

$$\text{Re-N(CH}_3)_3{}^+\text{Cl}^+ + \text{drug}^+ \longrightarrow \text{Re-N(CH}_3)_3{}^+ \text{drug}^- + \text{Cl}^-$$

Strong acid cation resins (sulfonated styrenedivinyl benzene copolymer products) can be used to mask the taste of basic drugs having bitter taste, as they function throughout the entire pH range. Weak acid cation exchange resins function at the pH values above 6. Similarly, strong base anion exchange resin function throughout the entire pH range, while the weak base anion exchange resins function well below pH 7.[13]

The ion-exchange resins suitable for use in the pharmaceutical preparations consist of a pharmacologically inert organic or inorganic matrix. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene), or partially synthetic (e.g., modified cellulose and dextrans). The matrix can also be inorganic, e.g., silica gel, or aluminosilicates, natively charged or modified by the addition of ionic groups. The covalently bound salt forming groups may be strongly acidic (e.g., sulfonic or sulfate acid groups), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., quaternary ammonium), weakly basic (e.g., primary amine), or a combination of acidic and basic groups.

Once the selection of resin is made the next step involves preparation of its complex with drug. Following steps are involved in the preparation of resinate:[11]

- Purification of resin by washing with ethanol and water.
- Changing of ionic form of IER might occasionally be required to convert resin from one form to another, if it doesn't have desired counter ions. Na^+ form of resin can be converted to H^+ by soaking the resin with HCl.

The drug: resin complexation process depends on several factors, which can affect the percent complexation of drug with resin, which are

- ✓ Effect of mixing time on Complexation
- ✓ Effect of Activation of ion exchange resin
- ✓ Effect of pH
- ✓ Effect of Temperature
- ✓ Effect of Mode of mixing
- ✓ Effect of swelling time
- ✓ Effect of concentration of loading solution

Drug release from drug: resin complex[14]

(Resinate) depends upon two factors:

- The ionic environment (i.e. pH and electrolyte concentration) within the gastrointestinal tract.
- The properties of resin.
- Selection of resin
- If drug is an acid, then use an anion exchange resin that has functionality such as amine and quaternary ammonium salt. If the drug is a base, then use a cation exchange resin, which has functionality such as sulfonic acid or carboxylic acid

4. By inclusion complex formation[16]

In inclusion complex formation, the drug molecules fits into the cavity of a complexing agent ie; the host molecule forming a stable complex. The complexing agent is capable of masking the bitter taste of the drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste. Van der Waals forces are mainly involved in inclusion complexes. Betacyclodextrin is most widely used complexing agent for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch. Strong bitter taste of carapentane citrate syrup was reduced to approximately 50% by preparing a 1:1 complex with cyclodextrin. The cyclodextrin itself is slightly sweet substance.

The cavity of CD is occupied by water molecules (about 13–14% w/w) both in crystalline state as well as in aqueous solution. Roughly half of this water is so-called ‘crystal water’ and the other half is ‘inclusion water’. The ‘crystal water’ is located and bound between the adjacent CD molecules, while ‘inclusion water’ is included into the hydrophobic cavity of CD. Hydrophobic drugs form complex by replacing ‘inclusion water’ while easily migrating (hydrophilic, well soluble) drugs form complex, assuming replacement of ‘crystal water’. CD is the ‘host’ molecule and an important component of the ‘driving force’ for the

inclusion complex formation is the substitution of high enthalpy water molecules by the 'guest' molecules. As the guest molecule is included into the CD molecule, which is enwrapped into a hydrate shell, the interaction of the guest molecule with cell membranes and receptors is considerably inhibited, resulting in reduced cytotoxicity or reduced taste. [17]

5. Granulation[18,19]

Mixture of bitter medicaments and sweeteners, hydrophobic polymers, lipids or waxes can be processed by dry, wet and melt granulation techniques to prepare taste masked oral solid or liquid dosage forms. Bertelsen *et al.* (2006) described the melt granulation to achieve the taste masking of calcium-containing compounds like calcium carbonate. Melt granulation of a calcium-containing compound with a sugar alcohol as a binding agent resulted in granules with an acceptable taste and mouth feel.

Granulation is a less expensive, rapid operation and an easily scalable taste masking technology. Polymers, flavours and waxes have been used as granulating agents to achieve the taste masking of bitter medicaments. Liquid and low melting point waxes such as glycerol palmitostearate, glyceryl behenate and hydrogenated castor oil are commonly used ingredients during the granulation to achieve taste masking. Sugar alcohols and flavors are also added in the blend to increase the efficiency of taste masking. Both pH dependent and independent water insoluble polymers, especially the swelling polymers such as MCC and polycarbophil have been employed. During granulation, particle coating may remain incomplete. However, a swelling matrix phenomenon can reduce the overall diffusion of the bitter active. Thus, swellable polymers can give a better taste masking in granulation compared to non swellable polymers. Taste masked granules of bitter tasting drug pirenzepine and oxybutynin have been prepared by the extrusion using aminoalkyl methacrylate copolymer.

6. Adsorption[18,19]

Adsorption involves preparing a solution of the drug and mixing it with an insoluble powder that will adsorb the drug, removing the solvent, drying the resultant powder, and then using this dried adsorbates in the preparation of the final dosage form. Many substrates like veegum, bentonite, silica gel and silicates can be used for the preparation of adsorbate of bitter drugs[3]. Adsorbates are commonly used with other taste masking technologies. The drug may be adsorbed or/and entrapped in the matrix of the porous component, which may result in a delayed release of the bitter active during the transit through the oral cavity thereby achieving taste masking. Kashid *et al.(*2007) developed a taste masked loperamide

formulation where Loperamide and phenyl propanolamine have been adsorbed on magnesium aluminum silicate also known as Veegum F, by blending , and further granulating with hydrophobic polymers to achieve taste masking.[18]

7. Prodrug

A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent drug.

Prodrug for bitter taste masking [20]

Parent molecule	**Reversible modification**
Chloramphenicol	Palmitate or phosphite ester
Clindamycin	Alkyl ester
Erythromycin	Alkyl ester
Lincomycin	Phosphate or alkyl ester
Tetracyclin	3,4,5-Trimethoxy benzoate salts

8. Bitterness inhibitors and potentiators [21]

Bitter substances are commonly hydrophobic in nature hence lipoprotein (PA-LG) composed of phophatidic acid and β-lactoglobulin can mask the target sites for bitter substances on the taste receptor membrane without affecting responses to salts, acids, sugars or sweet amino acids. Bitter taste of brucine, berberine, chloride, caffeine, denatonium benzoate, glycyl L-leucine, L-phenylalanine, naringin, propranolol hydrochloride, quinine hydrochloride, strychnine nitrate and theophylline have been suppressed by lipoprotein.

Potentiators increase the perception of the taste of sweeteners and mask the unpleasant after taste. Potentiators such as thaumatine, neohesperidine dihydrochalcone(NHDC) and glycyrrhizin can increase the perception of sodium or calcium saccharinates, saccharin, aspartyl-pheny-lalanine, acesulfame, cyclamates, and stevioside. Thaumatine was used with sugar alcohols to achieve the taste masking of bromhexine

9. Multiple emulsion technique[22,23]

The w/o/w or o/w/o type multiple emulsions are vesicular systems in which active ingredients can be entrapped in internal phase. The entrapped substances can be transferred from internal phase to external phase through the ‘membrane phase’. This phase controls the release of drug from system. These system could be used for controlled-release delivery of pharmaceuticals. If the system is stable enough for a reasonable shelf life, the formulation

could also mask the taste of drug. Both w/o/w or o/w/o multiple emulsions of chloroquine phosphate have been prepared and reported to be partially effective in masking the bitter taste of drug.

10. Gel formation[24]

Water insoluble gelation on the surface of tablet containing bitter drug can be used for taste masking. Sodium alginate has the ability to cause water insoluble gelation in presence of bivalent metal ions. Tablet of amiprolose hydrochloride have been taste masked by applying a undercoat of sodium alginate and overcoat of calcium gluconate. In presence of saliva, sodium alginate react with bivalent calcium and form water insoluble gel and thus taste masking achieved.

11) Solid dispersions[25,26,27]

Specific interactions between poorly soluble drugs and hydrophilic polymers can increase the solubility of the drug; likewise specific interactions between the drug and the hydrophobic polymers might decrease the solubility of a drug.[25] Recently solid dispersions were introduced as a taste masking technology. Tsau and Damani(1994) disclosed a drug-polymer matrix composition to achieve the taste masking of dimenhydrinate. Amine or amido group of dimenhydrinate can have a physical and chemical interaction with the carboxylic acid and esters groups of copolymers such as shellac, zein and cellulose acetate phthalate.[26]

Hydrophobic polymers and long chain fatty acids have been used to achieve the taste masking by solid dispersion. This approach usually requires a higher concentration of excipients compared to other taste masking techniques. Natural polymers such as shellac and zein, and enteric polymers like derivatives of acrylic acid polymers and phthalate are good choices to develop the taste masked solid dispersions.

Solid dispersion of cephalosporins and cellulosic or methacrylic polymer was formulated to mask the unpleasant taste of the medicament. Additional excipients such as meglumine and magnesium silicate were added to increase the efficiency of taste masking

TABLE 4: EXAMPLES OF DRUGS, EXCIPIENTS AND THE RATIO USED FOR TASTE MASKING

Excipients	Drugs	% of excipients
A methacrylic acid copolymer and a phthalate polymer	Cefuroxime axetil	Ratio of methacrylic acid copolymer to phthalate polymer is between 1:9 and 9:1 and ratio of the polymers to the drug is at least 1:4
Shellac	Crude drug	Ratio of the polymers to the drug is 4:1
Zein	Crude medicine extract	Ratio of the polymers to the drug is between 2:1 and 4:1
Higher fatty acids(stearic acid or palmitic acid)	Levofloxacin or Ofloxacin	Ratio of the drug to the fatty acids is between 1:0.3 to 1:4

1) Melting method In this method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed and pulverized.

2) Solvent method In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion.

3) Melting-solvent method In this method the drug in solution is incorporated into a molten mass of polyethylene glycol at a temperature below 700 ˚C without removing the solvent.

12. Mass extrusion method (Dispersion coating)[21]

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and 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. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

13. pH Modifiers[19,28]

pH Modifying agents are capable of generating a specific pH microenvironment in aqueous media that can facilitate *in situ* precipitation of the bitter drug substance in saliva thereby reducing the overall taste sensation for liquid dosage forms like suspension. Redondo

and Abanades (2003) developed taste masked liquid formulation of ibuprofen by using sodium saccharin and pH regulating agents.

14. Taste masking using Liposomes:[29]

Another way of masking the unpleasant taste of therapeutic agent is to entrap the drug into liposome. For example, incorporating into a liposomal formulation prepared with egg phosphatidylcholine masked the bitter taste of chloroquine phosphate in HEPES (N-2-hydroxyethylpiperzine-N'- 2- ethane sulfonic acid) buffer at pH 7.2.

15. Molecular complexes of drug with other chemicals:[20]

The solubility and adsorption of drug can be modified by formation of molecular complexes. Consequently lowering drug solubility through molecular complex formation can decrease the intensity of bitterness of drug.

16. Miscellaneous taste masking approaches:[28]

- **By effervescent agents:**

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have been employed for use as taste masking agents for dosage forms.

- **Rheological modification:**

Increasing the viscosity with rheological modifier such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds.

- **Continuous multipurpose melt Technology:**

The CMT method was developed for the continuous granulation and coating of pharmacologically active substances. This method could be successfully applied for taste masking of bitter drugs.

1.4. FACTORS AFFECTING SELECTION OF TASTE MASKING TECHNOLOGY[19]

A. Extent of Bitter Taste

With aggressively bad tasting medicaments even a little exposure is sufficient to perceive the bad taste. For example, sweeteners could not achieve taste masking of oral formulation of ibuprofen due to its dominating taste. Coating is more efficient technology for aggressively bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique [16]

B. Dose of Active Pharmaceuticals

Dose of a drug may dictate whether a particular formulation strategy would be suitable to achieve taste masking. In paediatric formulations, the dose is small enough so as to allow the usage of flavouring agents to mask the taste of the medicine. For example, low dose palatable paediatric aspirin oral formulation was developed by adding sweeteners, but the same approach failed to address the problem of drugs like acetaminophen because of its high dose. In such cases, coating is preferred to achieve taste masking along with sweeteners to attain an acceptable final dosage form size [18].

C. Drug Particle Shape and Size Distribution

Particle characteristics of the drug would affect the taste masking process efficiency. Core materials with irregular shapes and small particle size lead to poor taste masking efficiency and varying dissolution of coated particles [18]. Fines, abrasion and variable coating thickness can lead to situations wherein the taste mask coating is compromised. Multilayer coating using inner spacing layer to sequester the drug from taste masking layer helps to reduce or eliminate such coating imperfections. Taste masked granules of gatifloxacin and dextromethorphan were formulated by multilayer coating consisting of inner spacing layer followed by outer taste masking layer.

D. Dosage Forms

It is estimated that 50% of the population have problem of swallowing tablets, especially the paediatric and geriatric population. Chewable tablets and liquid oral dosage forms have been used to address these problems. For formulations which are swallowed unchewed: capsules, coated tablets and slowly disintegrating hard tablets have been used as preferred taste masking technologies. Chewable tablets and liquid oral formulations are preferable in case of large dose drugs for an ease of intake. Microencapsulation of the unpleasant tasting active agent with ethyl cellulose or a mixture of ethyl cellulose and hydroxypropyl cellulose or other cellulose derivatives has been used to provide chewable taste-masked dosage forms.

However, this approach suffers from the disadvantage that the polymer coating releases the active agent in an inconsistent fashion and may not provide an immediate release. Moreover, coating is more suitable when the formulation is stored in a dry form.

E. Drug Solubility

Physicochemical properties of the drug play an important role in the selection of taste masking technology. For example, ondansetron has a relatively lower water solubility at higher pH, based on which a rapidly disintegrating taste masked composition of ondansetron was formulated by adding an alkalizing agent(sodium bicarbonate) to reduce the water solubility and the consequent taste perception.

F. Ionic Characteristics of the Drug

Ionic characteristics of drugs govern the selection of ion exchange resin polymers and the suitability of the drug candidate for this technology. For example, anionic polymers (e.g. alginic acid) are good candidates for cationic drugs like donepezil hydrochloride, and the cationic polymers are choice of excipients for anionic drugs like sildenafil.

To conclude, there are a number of technologies available which effectively mask the objectionable taste of drugs but require skilful application which does not affect the bioavailability of drug. With application of these techniques and proper evaluation of taste masking effect, one can improve product preference to a large extent. Moreover, the development of taste masking methodology requires great technical skill, and experimentation.

Aim and Objectives

SECTION 2: AIM AND OBJECTIVE

The aim of this study is formulation development and evaluation of taste masked Cefuroxime Axetil Oral suspension. Many conventional tablets are available in adult strength and the administration of accurate dosage for children is critical. Oral suspension can be formulated in paediatric strength. Swallowing difficulty is another drawback with conventional tablet dosage form, that can be overcome by Oral suspension formulation.

Cefuroxime Axetil is a second generation cephalosporin antibiotic. It is used in the treatment of uncomplicated urinary tract infections, respiratory tract infections, otitis media, and Lyme disease.

The taste of Cefuroxime Axetil is extremely bitter. Marketed preparations of Cefuroxime Axetil currently available are not completely devoid of bitterness problem. So children cannot tolerate the bitter taste of the drug and vomit out during administration. The formulation of taste masked oral suspension was aimed to administer Cefuroxime Axetil in a more palatable form to obtain a "patient-friendly dosage form" especially for paediatric patients and hence that will increase the patient compliance. In the present work the problem is addressed and better taste masking methodologies were used for rectification.

OBJECTIVE

- To design and formulate a taste masked formulation of Cefuroxime axetil Oral Suspension
- To apply different taste masking technology
- To evaluate the oral suspension
- To optimise the formula for the suspension
- To take a scale up batch of the same.
- To charge the oral suspension for stability testing.

Plan of Work

SECTION 3: PLAN OF WORK

1 Literature survey

2 Preformulation studies

Evaluation of API for its

I. Physical parameters such as organoleptic properties, particle size, solubility, bulk density, tapped density, angle of repose, compressibility index, hausner ratio.

II. Analytical parameters such as assay and water content

III. Drug excipient compatibility

DSC

Physical Compatibility

3. Innovator product evaluation

4. Development stages

Trials based on

a. Sweeteners and flavours

b. Coating with stearic acid

c. Complexation

- Inclusion complex with beta cyclodextrin

5. Formulation evaluation

I. Physical evaluation

a) Fill weight

b) Pourability

c) Viscosity

d) Mouth feel

e) Taste

f) Flavour

g) Angle of repose

h) Bulk density

II. Analytical evaluation

a) Dissolution

b) p H

c) Assay

6. Optimisation of formula

7. Taste evaluation
8. DSC study
9. pH stability study
10. Scale up study
11. Stability studies

Review of Literature

SECTION 4: REVIEW OF LITERATURE

Mukherji *et al*[30] developed a taste masked dry syrup formulation prepared by dissolving the active ingredient, the methacrylic acid copolymer and the phthalate polymer in a solvent and recovering the composition thereof. In this study the ratio of drug to polymer was 1:1 in a solvent mixture of acetone and water was 1:1. The granules thus obtained released 100% of the drug from the matrix within 45 minutes in Ph 6.8 buffer.

Pandey Shivanand *et al* [31] formulated taste masked fast disintegrating tablets of lisinopril. The beta cyclodextrins were useful for masking the taste as well as enhanced the solubility of drug. The complexation was done by slurry method in a ratio of 1:5. The technology was found to be more effective.

Gedam Shweta S.[32], Tapar K. K, Borse M. D and Ghuge R. A. Developed taste masked microparticles of diphenhydramine using HPMC and PVP as polymer by spray drying technique and concluded that the amount of drug and polymer has its own significant complementary role in enhancement of the process rather than having an exclusive effect.

Birhade *et al* [33]reported the utilisation of cyclodextrin binary systems as an approach for taste masking of rizatriptan benzoate. The complexation was done by physical and kneading mixture methods in different ratios. The binary systems showed effective taste masking without any limiting effect on the drug release.

Alija Uzunovic [34]and Edina Vranic conducted a study on the stability of cefuroxime axetil oral suspension at different temperature storage conditions. Determination of cefuroxime was performed by dissolution testing. It concluded that oral suspension preserves its stability for 10 days after reconstitution under room and refrigerated conditions.

Donn KH *et al* [35]conducted a study to determine if the cefuroxime axetil formulations are bioequivalent. They concluded that bioequivalence between the suspension and tablet was not observed and further the addition of surfactant in the suspension did not alter the bioavailability of the formulation

M Krishnakumar [36]*et al* developed a stable taste masked coated, non disintegrating pellets comprising the steps of reducing the particle size of one or more cephalosporins, said pellets being further coated with one or more layers of film coating to achieve taste masking

Fernandez G, *et al* [37]developed a formulation in particulate form, the particles being provided with integral coatings of lipid or mixture of lipids which are insoluble in water and which disperse or dissolve on contact with gastrointestinal fluid. Applicants have discovered that the sweetner system and texture modifier act synergistically to overcome both the bitter

taste and also improve mouth feel thereby aiding patient compliance. The simultaneous use of the texture modifier helps to provide a creamier texture improving mouth "feel" and, in addition, reducing the number of lipid coated particles left in the mouth when the preparation is swallowed further reducing the bitter taste effect.

Abdul Rehman Khan *et al* [38]developed an oral composition of cefuroxime axetil in tablet form where the drug is contained in the core, coated with double layered film coat. The first film coat serves to mask the bitter taste of drug and the second film coat serves to delay the rupture time beyond 40 seconds.

Nighute A.B., *et al*[39] prepared the microcrystal of cefuroxime axetil and concluded that reduced size of drug particles in presence of the surfactant on the surface of drug microcrystals are responsible for enhanced solubility, dissolution velocity along with stability. HPMC E-15LV was found to be the best surfactant in their study.

Sihshu *et al* (2001)[40] reported the formulation of bitter taste masked liquid oral suspension of nalidixic acid. In this work drug was taste masked by microencapsulation technique. In this a pH sensitive polymer E-100 and then taste masked microsphere were formulated into liquid oral suspension. .

D.P Venkesh *et al*.[41] developed a formulation of bitter taste masked oral dispersible tablet of antiemetic drug Odansetron by complexation with ion exchange resin. They described that taste masked drug polymer complex eliminate the extreme bitterness of the drug to make orodispersible dosage form palatable using cationic exchange resin like Indion 204,Indion 234 and Thulsion 334

Thoshihiko Izhizaka *et al* [41]studied the suppression of enhanced bitterness intensity of clarithromycin dry syrup mixed with an acidic powder. Accordingly a best way to achieve taste masking was to first administer clarithromycin dry syrup mixed with chocolate jelly which has a neutral pH followed by L-carbocystein suppression.

Sohi H. *et al.* [42]reviewed that any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability. This article reviews the earlier applications and methodologies of taste masking and discuss the most recent developments and approaches of bitterness reduction and inhibition for oral pharmaceuticals

P. Dellamonica[43] has compiled informations regarding the chemistry, microbiology, pharmacology, pharmacokinetics, antimicrobial activity, clinical studies, drug interactions, therapeutic uses in detail. Science direct

S.B. Sateesha *et al* [44]prepared stable and palatable norfloxacin suspension formulation for oral administration. The granules were prepared by coating with different levels of acrycoat E100-40. The interaction between norfloxacin and eudragit E100 was analysed by FTIR. Rheological studies reveal a plastic thixotropy of the reconstituted dry syrup. *In vitro* dissolution studies performed at Ph 1.2 showed satisfactory dissolution rate for all the formulations. Drug content of reconstituted liquid suspension on day 1 and at day 5 were within the limits. Stability studies of dry suspension formulation conducted at 40 ± 2˚C for three months were found to be stable and percentages of drug remaining were higher than 98% of initial concentration.

Santosh Shelke *et al* [45]developed a simple accurate cost effective and reproducible spectrophotometric method for the estimation of cefuroxime axetil in bulk and pharmaceutical dosage form. UV spectrophotometric method, which is based on measurement of absorption at maximum wavelength 281nm.The percentage recovery of cefuroxime axetil ranged from (99.97 ± 0.3969) in pharmaceutical dosage form. The developed method was validated with respect to linearity, accuracy (recovery), precision and specificity. Beers law was obeyed in the concentration range of 4-28µg/ml having line equation y = 0.0346x + 0.0566 with correlation coefficient of 0.9999. Results of the analysis were validated statistically and by recovery study.

Diego A. Chiappetta *et al* [46]developed indinavir pediatric anti- HIV/AIDS formulations enabling convenient dose adjustment, ease of oral administration , and improved organoleptic properties by means of the generation of drug loaded microparticle made of a polymer that is insoluble under intake conditions and dissolves fast in the stomach in order to completely release the active agent. Indinavir loaded microparticles made of a Ph- dependent polymeric excipient soluble at Ph<5, Eudragit E 100, were prepared using double emulsion solvent diffusion technique and characterized.

Alonso *et al*[47] reported the encapsulation of cefuroxime axetil, a highly bitter drug, in Ph sensitive acrylic microspheres in order to formulate a suspension dosage form. The acrylic polymers used were eudragit E, eudragit RL100, eudragit L100-55. The cationic polymer eudragit E showed a negative interaction with cefuroxime axetil. The cationic polymer

eudragit L100-55 showed a favourable release in alkaline Ph. The release of cefuroxime axetil was studied in basic media.

Dantzig *et al*[48]showed that cefuroxime axetil is hydrolyzed to cefuroxime in the intestinal lumen by the esterases reducing the cefuroxime axetil concentration in the lumen and resulting in reduced absorption, leading to low bioavailability of Cefuroxime axetil in humans. Cefuroxime axetil already has a low bioavailability of 32-50% and hence further reduction in the bioavailability due to the formulation aspects should be minimized. The taste masking formulations should be so designed that the bioavailability of the drugs is not compromised and the use of certain polymers like the enteric coatings should not affect the time to peak. Further the drug should be sufficiently absorbed to ensure effective therapeutic concentration in the plasma.

Meyer *et al.*[49] used prolamine, applied as single coating in weight ratio 5% to 100% relative to active substance being coated result in the production of a liquid suspension which effectively masked the taste of orally administered drugs which are extremely bitter. Prolamine coating does not restrict the immediate bioavailbility of the active substance Prolamine coating is effective in masking the taste of antibiotics, vitamins, dietary fibers, analgesic, enzymes, and hormones.

Yajima *et al.*[50] in their patent have described a composition comprising of a drug with unpleasant taste of polymer solution and D-crystals of monoglycerides. Eudragit E (100 g) was dissolved in melted stearic acid monoglyceride (600 g) and then Erythromycin (300 g) were added to the mixture to obtain a powder, which was again mixed with sorbitol, magnesium oxide and starch to give taste masked granules of Erythromycin.

Danielson *et al*[51]. invented a dosage form comprising granules containing the histamine receptor antagonist which are provided with taste masking coating comprising a water insoluble, water permeable methacylate ester copolymer in which the coating is applied to the granules in an amount which provides a taste masking effect for a relatively short period during which the composition is being chewed by a patient but which allows substantially immediate release of the histamine receptor antagonist after the composition has been chewed and ingested.

J. Park[52] investigated an effect of excipients in Cefuroxime axetil (CFX) formulas. The tablets were manufactured including polymethacrylate, L-HPC, Lactose, Cellactose and croscarmellose sodium, sodium starch glycolate, corspovidon, magnesium trisillicate, magnesium stearate as diluents and concluded that, polymethacrylate, L-HPC and croscarmellose sodium inhibited the tendency of CFX to form a gel and provided good dissolution profiles than lactose, Cellactose, crospovidone and sodium starch glycolate. And it was found that L-HPC, polymethacrylate and croscarmellose sodium resulted in better dispersibility and dissolution rate than another diluents. The effect of excipients was evaluated by statistical coefficient with a dissolution test and its behaviour.

Pateli A.R.,Vavia P.R[53] prepared and evaluated taste masked famotidine formulation using beta cyclodextrin and reports that the complex with higher stability constant will usually require greater dilution to affect the release of drug; complex with lower stability constant will release the drug even at lower dilution (ie; oral cavity). Stability constant increasing effect of complexation with beta cyclodextrin results in effective taste masking.

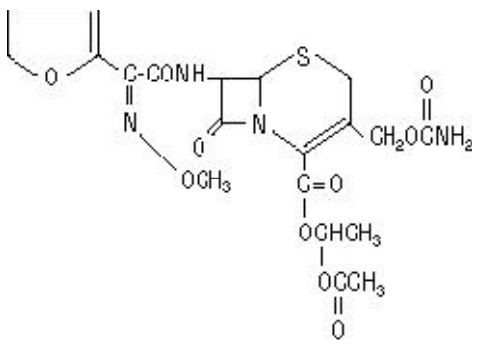
Drug & Excipient Profile

SECTION 5: DRUG AND EXCIPIENT PROFILE

DRUG PROFILE[54]

DRUG : Cefuroxime Axetil.

STRUCTURAL FORMULA :



MOLECULAR FORMULA :

$C_{20}H_{22}N_4O_{10}S$.

MOLECULAR WEIGHT : 510.48.

CHEMICAL NAME : Cefuroxime Axetil is a mixture of the 2 diastereoisomers of (1RS)-1-(acetyloxy) ethyl(6R,7R)-3-[(carbamoyloxy)methyl]-7-[[(Z)-2-(furan-2-yl)-2-(methoxyimino) acetyl]amino]-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylate.

CATEGORY : Second Generation Cephalosporin; Antimicrobial.

DOSE : 250-500 mg every 12 hours.

DESCRIPTION : A white or almost white powder.

SOLUBILITY : Slightly soluble in water and ethanol. Soluble in acetone, ethyl acetate and methanol.

MELTING POINT : 135°C.

PHARMACOKINETICS:

Cefuroxime Axetil is absorbed from the Gastro intestinal tract and is rapidly hydrolysed in the intestinal mucosa and blood to Cefuroxime. Peak plasma concentrations are reported about 2 to 3 hours after an oral dose. Cefuroxime is widely distributed into most body tissues and fluids, including pleural fluid, sputum, bone, synovial fluids, gall bladder, liver, kidney and bile. It crosses the placenta and is 33% to 50% protein-bound. The plasma half life is 1.3 hours. Cefuroxime is primarily excreted in urine by renal tubular secretion and glomerular filtration. Small amounts of Cefuroxime are excreted in bile and breast milk.

MECHANISM OF ACTION:

The cell walls of bacteria are essential for their normal growth and development. Peptidoglycan is a heteropolymeric component of the cell wall that provides rigid mechanical stability by virtue of its highly cross-linked latticework structure. Cefuroxime Axetil interfere with the synthesis of bacterial cell wall peptidoglycan by binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall and causes Cell lysis.

ANTI-MICROBIAL SPECTRUM:

Cefuroxime is active against a wide range of Gram-positive and Gram-negative bacteria including Haemophilus influenzae, Enterobacter, Staphylococcus aureus, Streptococcus pneumoniae, Neisseria species and inactive against Pseudomonas aeruginosa.

ADVERSE REACTIONS:

Anaphylaxis, pseudomembranous colitis, nausea, vomiting, headache, dizziness, diarrhea, transient elevation of liver enzymes, over dose may cause cerebral irritation and convulsions.

INDICATIONS:

- Cefuroxime axetil is used in treating Upper and Lower respiratory tract infections, skin and soft tissue, urinary tract, bone and joint infections.
- It is used to treat Gonorrhoea, otitis media, impetigo and meningitis.
- It is also indicated in treating and preventing Lyme disease.

CONTRAINDICATIONS:

Contraindicated in patients with hypersensitivity to cefuroxime or other cephalosporins, severe renal impairment, pregnancy and lactation.

DOSAGES:

Oral suspension must be administered with food.

A dose for children more than 3 months of age is 125 mg twice daily or 30 mg/kg twice daily given in 2 divided doses for 10 days. In case of pharyngitis and tonsillitis children over 3 months to 12 years of age 20mg/kg daily in 2 divided doses for 10 days to a maximum of 500 mg daily. For respiratory tract infections and impetigo in Children 3 Months to 12 Years of Age 30mg/kg daily should be given in 2 divided doses for 10 days. Lyme disease: Adults and Children above 12 years: 500 mg b.i.d. for 20 days.

STORAGE:

Preserve in air tight containers, protect from light and kept in cool dark place.

MARKETED PRODUCTS:

ZINNAT 125,250 mg/5ml

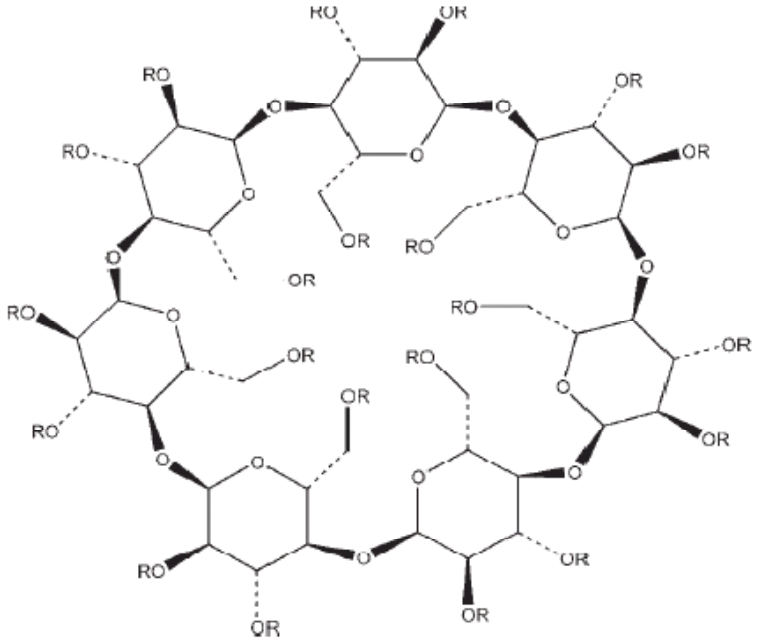
OTHER FORMULATIONS:

Cefuroxime Axetil is available in the market in various dosage forms including dispersible tablet, Tablets, Film coated tablets, Capsules.

EXCIPIENT PROFILE

BETA CYCLODEXTRIN[55]

STRUCTURAL FORMULA :



SYNONYMS	**:**	Beta-cycloamylose; beta-dextrin, betadexum
CHEMICAL NAME	**:**	β – cyclodextrin.
EMPIRICAL FORMULA	**:**	$C_{42}H_{70}O_{35}$.
MOLECULAR WEIGHT	**:**	1135.
PHYSICAL STATE	**:**	Cyclodextrins occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.
SOLUBILITY	**:**	Soluble 1 in 200 parts of propylene glycol, 1 in 50 parts of water at 20°C, 1 in 20 at 50°C, practically insoluble in acetone, ethanol (95%) and methylene chloride.
MELTING POINT	**:**	255-265°C.
BULK DENSITY	**:**	0.523 g/ cm^3.
TAPPED DENSITY	**:**	0.754 g/ cm^3.
pH	**:**	5.0 – 8.0.
STABILITY AND STORAGE	**:**	It is stable material in solid state if protected from high humidity. Cycodextrins should be stored in

		tightly sealed container, in a cool and dry place.
APPLICATIONS	**:**	β-cyclodextrin is considered to be nontoxic when administered orally and has thus primary used in tablet and capsule formulation. It is used in the formulations to form inclusion complexes for a wide range of drugs which ultimately results in improved bioavailability, solubility, masking unpleasant taste and sometimes conversion of a liquid to a solid material.
INCOMPATIBILITIES	**:**	The activity of some antimicrobial preservatives in a aqueous solution can be reduced in the presence of cyclodextrins.

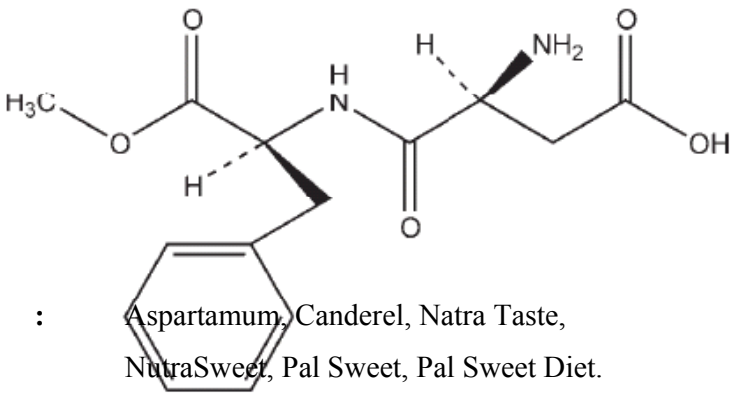
XANTHAM GUM[56]

SYNONYMS	**:**	Corn sugar gum, ,Rhodogel,
CHEMICAL NAME	**:**	Xanthan gum
MOLECULAR WEIGHT	**:**	2,000,000
PHYSICAL STATE	**:**	Xantham gum occurs as a cream or white colored, odorless, free flowing, fine powder.
SOLUBILITY	**:**	Partially insoluble in ethanol and ether. Soluble in cold or warm water.
MELTING POINT	**:**	$260^{o}C$
p^{H}	**:**	6.8 (1%w/v aqueous solution)
STABILITY AND STORAGE CONDITIONS	**:**	Xantham gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3-12). The bulk material should be stored in a well closed container in a cool, dry place.
APPLICATIONS	**:**	Stabilizing agent, suspending agent, viscosity increasing agent Xantham gum is widely used in

		oral and topical pharmaceutical formulations. It is used as a thickening and emulsifying agent.
SAFETY	**:**	Xantham gum is widely used in oral & topical pharmaceutical formulations. It is generally regarded as an essentially nontoxic and nonirritant.

ASPARTAME[56]

STRUCTURAL FORMULA :

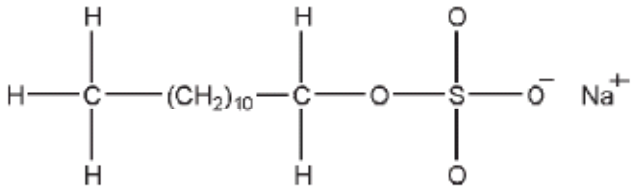


SYNONYMS	:	Aspartamum, Canderel, Natra Taste, NutraSweet, Pal Sweet, Pal Sweet Diet.
CHEMICAL NAME	:	N-α-L-Aspartyl-L-phenylalanine 1-methyl ester.
EMPIRICAL FORMULA	:	$C_{14}H_{18}N_2O_5$.
MOLECULAR WEIGHT	:	294.31.
PHYSICAL STATE	:	Aspartame occurs as an off white, almost odourless crystalline powder with an intensely sweet taste.
SOLUBILITY	:	Slightly soluble in ethanol (95%); sparingly soluble in water. Solubility increases at higher temperature and at more acidic pH.
MELTING POINT	:	246-247°C.
BULK DENSITY	:	0.5-0.7g/cm^3 for granular grade; 0.2-0.4g/cm^3 for powder grade.
TRUE DENSITY	:	1.347g/cm^3.
pH	:	4.5-6.0 (0.8% w/v aqueous solution).
STABILITY AND STORAGE	:	Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L-phenylalanine and 3-benzyl -6-carboxy methyl-2, 5-diketopiperazine.The bulk material should be stored in a well closed container in a cool, dry place.

APPLICATIONS	**:**	Aspartame is used as a intense sweetening agent in beverage products, food products, table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes and vitamin preparations. It enhances flavour systems and can be used to mask some unpleasant taste characteristics.
INCOMPATIBILITIES	**:**	Aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate. Reactions between aspartame and sugar alcohols are also observed.

SODIUM LAURYL SULFATE[56]

STRUCTURAL FORMULA :



SYNONYMS	**:**	Dodecyl sodium sulfate, sodium mono lauryl sulfate, Empicol.
CHEMICAL NAME	**:**	Sulfuric acid monododecyl ester sodium salt.
EMPIRICAL FORMULA	**:**	$C_{12}H_{25}NaO_4S$.
MOLECULAR WEIGHT	**:**	288.38.
PHYSICAL STATE	**:**	Sodium lauryl sulphate consists of white or cream to pale yellow coloured crystals, flakes or powder having a smooth feel, a soapy, bitter taste and a faint odour of fatty substances.
SOLUBILITY	**:**	Freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and ether.
MELTING POINT	**:**	204-207°C.
pH	**:**	7.0 – 9.5 (1% w/v aqueous solution).
STABILITY AND STORAGE	**:**	Sodium lauryl sulphate 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 bisulphate. It should be stored in a well closed container in a cool, dry place.
APPLICATIONS	**:**	Sodium lauryl sulphate is employed in a wide range of non-parenteral pharmaceutical formulations and cosmetics.

It is a detergent and wetting agent effective in both alkaline and acidic conditions.

INCOMPATIBILITIES **:** Sodium lauryl sulphate reacts with cationic surfactants causing loss of activity even in concentrations too low to cause precipitation.

It is incompatible with dilute acids, calcium and magnesium ions.

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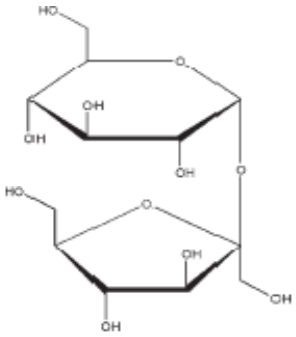
SUCROSE[56]

STRUCTURAL FORMULA :



SYNONYMS	:	Beet sugar; cane sugar; a-D-glucopyranosyl-b-D-fructofuranoside; refined sugar; saccharose; saccharum; sugar.
CHEMICAL NAME	:	b-D-fructofuranosyl-a-D-glucopyranoside
EMPIRICAL FORMULA	:	$C_{12}H_{22}O_{11}$
MOLECULAR WEIGHT	:	342.30
PHYSICAL STATE	:	Sucrose occurs as colorless crystals, as Crystalline masses or blocks, or as a white crystalline powder; it is odorless and has a sweet taste.
SOLUBILITY	:	soluble in water and practically insoluble in chloroform.
MELTING POINT	:	160–186^{0}C (with decomposition)
BULK DENSITY	:	0.93 g/cm^3.
TAPPED DENSITY	:	1.03 g/cm^3
STABILITY AND STORAGE	:	Sucrose has good stability at room temperature and at moderate relative humidity. It absorbs up to 1% moisture, which is released upon heating at 90^{0}C. Sucrose caramelizes when heated to temperatures above 160^{0}C. Dilute sucrose solutions are liable to fermentation by microorganisms but resist decomposition at higher concentrations, e.g. above 60% w/w

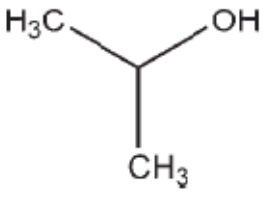
concentration. Aqueous solutions may be sterilized by autoclaving or filtration

APPLICATIONS : Confectionery base; coating agent; granulation aid; suspending agent; sweetening agent; tablet binder; tablet and capsule diluent; tablet filler; therapeutic agent; viscosity-increasing agent.

INCOMPATIBILITIES : Powdered sucrose may be contaminated with traces of heavy metals, which can lead to incompatibility with active ingredients, e.g. ascorbic acid. Sucrose may also be contaminated with sulphite from the refining process. With high sulfite content, color changes can occur in sugar-coated tablets; for certain colors used in sugarcoating the maximum limit for sulfite content, calculated as sulfur, is 1 ppm. In the presence of dilute or concentrated acids, sucrose is hydrolyzed or inverted to dextrose and fructose (invert sugar). Sucrose may attack aluminum closures.

ISOPROPYL ALCOHOL[56]

STRUCTURAL FORMULA :



SYNONYMS : Alcohol isopropylicus; dimethyl carbinol; IPA; isopropanol.

CHEMICAL NAME : Propan-2-ol.

EMPIRICAL FORMULA : C_3H_8O.

MOLECULAR WEIGHT : 60.1.

PHYSICAL STATE	**:**	Isopropyl alcohol is a clear, colourless, volatile, flammable liquid with a characteristic, spirituous odour resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.
SOLUBILITY	**:**	Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions.
BOILING POINT	**:**	88.5°C.
STABILITY AND STORAGE	**:**	Stable under ordinary conditions. Isopropyl alcohol should be stored in an air tight container in a cool, dry place.
APPLICATIONS	**:**	Isopropyl alcohol is used in cosmetics and pharmaceutical formulations, primarily as a solvent in topical formulations. Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation.
INCOMPATIBILITIES	**:**	Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition.

STEARIC ACID[56]

STUCTURAL FORMULA :

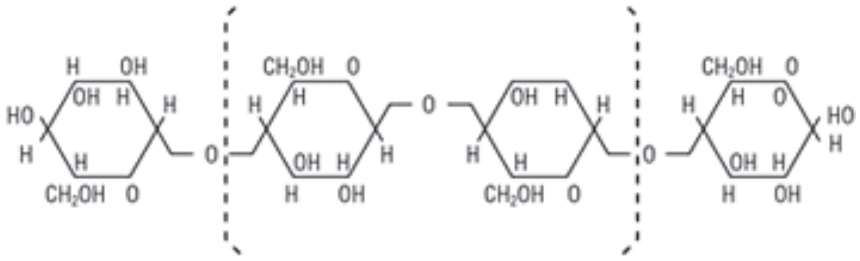
SYNONYMS	**:**	Acidum stearicum; Crodacid; Cristal G, Emersol,hystrene,Industrene,Kortacid1895 Pristerene.
CHEMICAL NAME	**:**	Octadecanoic acid.
EMPIRICAL FORMULA	**:**	$C_{18}H_{36}O_2$
MOLECULAR WEIGHT	**:**	284.47
PHYSICAL STATE	**:**	Stearic acid is a hard ,white or faintly yellow colored, Somewhat glossy,crystalline solid or a white or yellowish white powder.it has a slight odor and taste.
SOLUBILITY	**:**	Freely soluble in benzene,carbon tetrachloride, chloroform,and ether, soluble in ethanol(95%) hexane and propylene glycol,practically insoluble in water.
MELTING POINT	**:**	69-70^{0}c
BULK DENSITY	**:**	0.537 g/cm^3
TAPPED DENSITY	**:**	0.571 g/cm^3
STABILITY AND STORAGE	**:**	Stearic acid is a stable material. An antioxidant may also added to it. The bulk material should be stored in a well closed container in a cool, dry, place.
APPLICATIONS	**:**	Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant although it may also be used as a binder or in combination with shellac as a tablet coating

agent. In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. It is used as hardening agent in glycerin suppositories. It is also used in cosmetics and food products.

INCOMPATIBILITIES **:** Stearic acid is incompatible with most metal hydroxides and may be incompatible with reducing agents and oxidizing agents. Ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when compounded with zinc or calcium salts. Stearic acid has been reported to cause pitting in the film coating of tablets when coated using an aqueous film coating technique.

MICROCRYSTALLINE CELLULOSE[56]

1.STRUCTURAL FORMULA :



2. NONPROPRIETARY NAME :

- BP : Microcrystalline cellulose
- JP : Microcrystalline cellulose
- PhEur : Cellulosum microcrystallinum
- USPNF : Microcrystalline cellulose

3. SYNONYM : Avicel ; Cellulose gel ; tabulose
Crystalline cellulose; E460;
Emcocel Fibrocel;vivacel

4. CHEMICAL NAME : Cellulose

5. EMPIRICAL FORMULA : $(c_6H_{10}O_5)n$

6. MOLECULAR WEIGHT : ≈36000 where n≈220.

7. FUNCTIONAL CATEGORY : Adsorbent;suspending agent;
capsule and tablet diluents ; tablet disintegrant**.**

8. PHYSICAL STATE : It is a purified, partially depolymerised Cellulose that occurs white odourless, Tasteless, crystalline powder composed of porous particles. It is commercially available in different particle size and moisture grades which have different properties and applications.

9. TYPICAL PROPERTIES:

Density (bulk) : 0.337 g/cm^3

Density (tapped) : 0.478 g/cm^3

Density (true) : 1.512-1.668 g/cm^3

Melting point : Chars at 260-270^{o}C

Moisture content : Less than 5% w/w

10. SOLUBILITY : Slightly soluble in 5%w/v sodium Hydroxide solution,Practically insoluble in water ,dilute acids,and most Organic solvents.

11.STABILITY AND STORAGE CONDITION : Microcrystalline cellulose is a stable, though hygroscopic material. The bulk material should be stored in in a well closed container in a cool,dry,place.

12. INCOMPATIBILITIES : Incompatible with strong Oxidizing agents.

13. APPLICATIONS : It is widely used in pharmaceuticals, primarily as a binder/ diluents in oral tablet and capsule formulations. Where it is used in both wet granulation and direct compression processes. Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. It is also used in cosmetics and food products.

LACTOSE ANHYDROUS[56]

1. NONPROPRIETARY NAME :

- BP : Anhydrous lactose
- JP : Anhydrous lactose
- PhEur : Lactosum anhydricum
- USPNF : Anhydrous lactose

2. SYNONYM : Milk sugar, pharmatose, tablettose

3. CHEMICAL NAME : O-β-D-Galactopyranosyl-(1→4)-β-D-glucopyranose

4. EMPIRICAL FORMULA : $C_{12}H_{22}O_{11}$

5. MOLECULAR WEIGHT : 342.30

6. FUNCTIONAL CATEGORY : Binding agent; directly compressible tableting excipients, lyophilization aid, tablet and capsule filler.

7. PHYSICAL STATE : White to off-white crystalline particles or powder.

8. TYPICAL PROPERTIES:

Angle of repose : 39^{o}

Density (bulk) : $0.68 g/cm^3$

Density (true) : $1.589 g/cm^3$

Melting point : 223.08◦C for anhydrous a-lactose;
252.28◦C for anhydrous b-lactose;
232.08◦C (typical) for commercial anhydrous lactose

Moisture content : contains upto 1% w/w

9. SOLUBILITY : soluble in water; sparingly soluble in ethanol(95%) and ether.

10. STABILITY AND STORAGE CONDITION : Under humid conditions (80% relative humidity and above), mold growth may occur. On storage , lactose may develop a brown colouration, the reaction being accelerated by warm, damp conditions.

11. INCOMPATIBILITIES : Lactose anhydrous is Incompatible with strong Oxidizers.

12. APPLICATIONS : Anhydrous lactose can widely used in direct compression tabletting applications and as a tablet and capsule filler and binder. Anhydrous lactose due to its low moisture content can be used with moisture- sensitive drugs.

Materials & Methods

SECTION 6: MATERIALS AND EQUIPMENTS USED

MATERIALS

TABLE 5: LIST OF MATERIALS USED AND THE SUPPLIERS AND MANUFACTURERS

S.NO	MATERIALS	SUPPLIERS	MANUFACTURERS
1.	Cefuroxime axetil	Dhanuka laboratories ltd, Haryana	Dhanuka laboratories Ltd, Haryana
2.	Sucrose	Indras agencies	Eid Parry India Pvt Ltd
3.	Sucralose	Kawarlal and Company , Chennai	Unitech , China
4.	Aspartame	Kawarlal and Company , Chennai	The Nutrasweet Company, USA
5.	Acesulfame k	The Sunett	The Nutrasweet Company, USA
6.	Xanthum gum	Signet chemicals	CP Kelco US Inc. USA
7.	MCC	MItutiyo,India	MItutiyo,India
8.	Lactose anhydrous	Signet chemicals	CP Kelco US Inc. USA
9.	Tuttifrutti flavour	K. P. Manish Global Ingredients	Firmenich Aromatics . India
10.	Peppermint flavour	K. P. Manish Global Ingredients	Firmenich Aromatics . India
11.	Beta cyclodextrin	Signet chemicals	Roquette , France
12.	Sodium lauryl sulphate	Kawarlal excipients , Chennai	Cognis Pharma
14.	Triethyl citrate	Chemport India Pvt Ltd, Mumbai	Chemport India Pvt Ltd, Mumbai
15.	Methylene chloride	Ponpure Chemicals Pvt Ltd	Solvay Chemical International
16.	Iso propyl alcohol	Nice chemicals, Cochin	Nice chemicals, Cochin
17.	Citric acid	Amjal India Pvt Ltd ,	Ruskin Chemipharma

EQUIPMENTS

TABLE 6: LIST OF THE EQUIPMENTS USED AND THE MANUFACTURERS

S.No	Name of the Equipment	Model of equipment	Manufacturer
1.	Weighing balance	HJ - 3	Hercules Electronic Scales
2.	Mechanical homogeniser	RQT - 124 A	Remi Elektrotechchnik Ltd., Mumbai
3.	Tray dryer	I- 0550	Gem pharma Machineries, Navi Mumbai
4.	Hot air oven	STR - 392	Servewell Instruments Pvt Ltd, Banglore
5.	Bulk density apparatus	I- 0576	Veego
6.	Digital pH meter	I -0372	Digisun Electronics Hyderabad
7.	Dissolution test apparatus	TDL - 08 L	Electrolabs, Banglore
8.	HPLC	I- 0750	Shimadzu Corporation, Japan
9.	Kf titrator	I- 0378	Lasco laboratory services
10.	Ultrasonicator	I - 0412	PCI Mumbai
11.	UV visible spectrophotometer	I - 0319	Shimadzu Corporation, Japan
12.	Differential Scanning Calorimeter	S- 0810	Mettler Laboratories
13.	Stability chamber	I - 0396	Servewell Instruments Pvt Ltd, Banglore

CONSTRUCTION OF STANDARD GRAPH FOR CEFUROXIME AXETIL

PREPARATION OF 0.07 N HYDROCHLORIC ACID :

Measure 5.95ml of hydrochloric acid in 1 litre standard volumetric flask and make up the volume using demineralized water.

CALIBRATION OF STANDARD CURVE:

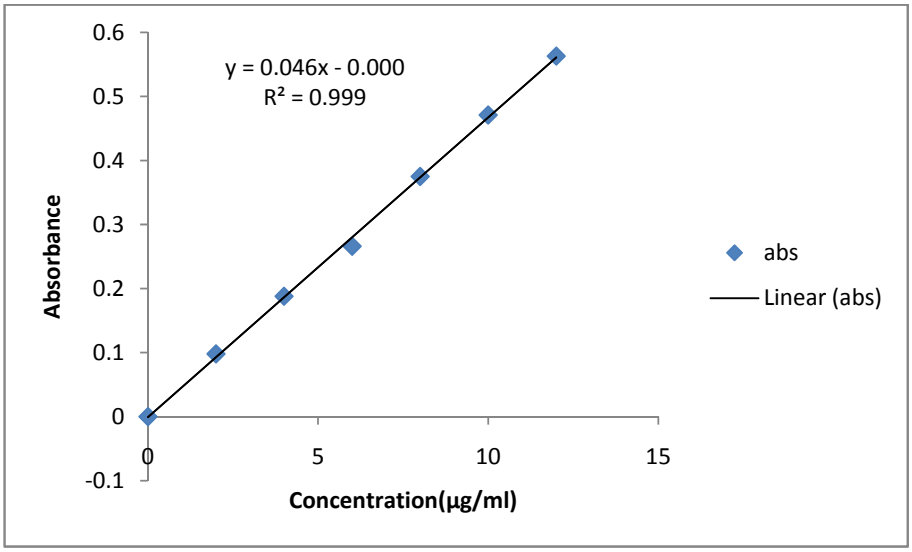
Accurately weighed Cefuroxime axetil which is equivalent to 100 mg of cefuroxime in a 100ml standard volumetric flask and dissolved in methanol. The volume was made upto 100ml using 0.07N Hydrochloric acid to obtain a stock solution-1(1000µg/ml).From this stock solution -1,10ml was pippetted out into a 100ml standard volumetric flask and made upto the mark using 0.07N Hydrochloric acid (stock solution-2).From this stock solution -2,aliquots of 2ml,4ml,6ml,8ml,10ml,and 12ml,were pipetted out into a series of 100ml standard volumetric flasks and the volume was made upto the mark with 0.07N Hydrochloric acid to get drug concentration in the range of 2 to 12µg/ml.The absorbance of the resulting solution was then measured at 278nm using UV double beam spectrophotometer against 0.07N Hydrochloric acid as blank.The standard curve was obtained by plotting concentration(µg/ml)values in X-axis and the absorbance values in Y-axis.

TABLE 7:

STANDARD CURVE DATA OF CEFUROXIME AXETIL

Sl.No	CONCENTRATION (µg/ml)	ABSORBANCE at 278nm
1	2	0.098
2	4	0.188
3	6	0.266
4	8	0.375
5	10	0.471
6	12	0.563

FIGURE-1



Caliberation curve of cefuroxime axetil

SECTION 7 : METHODS AND PROCEDURE

7.1 PREFORMULATION STUDIES

It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

EVALUATION OF API

7.1.1 Organoleptic Properties

Organoleptic properties like colour, odour and taste of Cefuroxime Axetil were studied

7.1.2 . Particle Size Analysis

Particle size distribution of the drug was estimated by sieving method. The sieves are stacked on top of one another in ascending degrees of coarseness. The test powder, for example 50g, was placed on the top sieve. The nest of sieves was subjected to a standard period of agitation. The weight of material retained on each sieve was accurately determined. Percentage of powder retained on each sieve was calculated.

7.1.3 Solubility

Solubility is defined as the number of gram of substance which will dissolve in 100 grams of solvent at a stated temperature. The solubility of drug was studied in different solvents such as water, acetone, ethanol, sodium hydroxide, hydrochloric acid by measuring how many parts of solvent is required for one part of solid.

Very soluble: 1 part of the substance is soluble in less than 1 part of the solvent.

Freely soluble: 1 part of substance is soluble in 1 to 10 parts of solvent.

Soluble: 1 part of substance is soluble in 10 to 30 parts of solvent.

Sparingly soluble: 1 part of substance is soluble in 30-100 parts of solvent.

Slightly soluble: 1 part of substance is soluble in 100 to 1,000 parts of solvent.

Very slightly soluble: 1 part of substance is soluble in 1,000 to 10,000 parts of solvent.

Practically insoluble or insoluble: More than 10,000 parts of solvent is required to dissolve 1 part of substance.

7.1.4 Flow property

Flow property of powder determines its flow from hopper while manufacturing. This is measured in terms of angle of repose, bulk density, tapped density, compressibility index, hausner ratio.

Angle of repose[57] : It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane. The value gives the quantitative measure of the cohesive and frictional effects under low levels of external loading.

$$\theta = \tan^{-1}(h/r)$$

Where,

h is the height of the pile from the surface of the pile

r is the radius of the base of the pile formed.

Bulk density[58] : Bulk density is defined as powder mass divided by its bulk volume without any tapping. It is the density of the powder when loosely packed in a measuring cylinder. Powder bulk density depends primarily on particle size distribution, particle shape, and the tendency of particles to adhere to each other. Some particles may pack loosely, leading to fluffy and light powder, while others may contain smaller particles that sift between larger particles to fill the void, leading to dense and heavy powder. Bulk density is often used to calculate the batch size for blender.

Weighed quantity of powder blend from each formulation was taken in a measuring cylinder and the initial volume of the powder blend in the measuring cylinder was noted. Bulk density of the powder blend was calculated by using the following formula:

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Bulk Volume occupied}}$$

Tapped density[59] : Tapped density of a powder is the ratio of the mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time.

Tapped density was measured by introducing the known quantity of powder into a graduated cylinder and carefully levelling off the powder without compacting it. The cylinder was mechanically tapped by placing on the bulk density apparatus. The volume was measured by tapping the powder blend for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. The tapped density was calculated by using the following formula:

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped volume}}$$

The compressibility index is a measure of the propensity of a powder to consolidate. As such, it is a measure of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions; bridging between particles often results in lower bulk density and a greater

difference between the bulk and tapped densities. These differences in particle interactions are reflected in the compressibility index.

The **compressibility index (CI) and hausner ratio** (HR) are also helpful in determining the flow characteristics. Compressibility index has been proposed as an indirect measure of bulk density, size, surface area, moisture content and cohesiveness of material. Both of these are determined from bulk volume and tapped volume of a powder.

$$\text{Carr's compressibility index} = \frac{(\text{bulk volume} - \text{tapped volume}) * 100}{\text{Bulk volume}}$$

$$\text{Hausner ratio} = \frac{\text{Initial volume}}{\text{Final volume}}$$

TABLE 8: FLOW PROPERTY

S.NO	FLOW CHARACTER	ANGLE OF REPOSE	CARR'S INDEX	HAUSNER'S RATIO
1	Excellent	25– 30	1 – 10	1.0 – 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	□1.60

7.1.5 HPLC Assay for cefuroxime axetil

Mobile phase is degassed mixture of 0.2M Monobasic ammonium phosphate and methanol (620:380).

Internal standard solution is a solution of acetanilide in methanol containing 5.4 mg per ml.

Standard preparation : Transfer about 30 mg of the drug to a 25 ml volumetric flask, dissolve in methanol, dilute with methanol to volume and mix. Promptly transfer 10 ml of this solution to a 50 ml volumetric flask add 5 ml of internal standard solution and 3.8 ml of methanol, dilute with 0.2M Monobasic ammonium phosphate to volume and mix.

Procedure: Separately inject equal volumes of the standard preparation and the assay preparation into the chromatograph, record the chromatograms, and measure the responses. The chromatogram is recorded at 278 nm.

7.1.6 Water content

The water content is determined titrimetrically by Karl Fischer titration.

$$\text{Water content} = \frac{\text{Titre volume} \times \text{mean KF factor}}{10 \times \text{weight of the sample}}$$

7.1.7 DRUG- EXCIPIENT COMPATIBILITY

Compatibility studies were performed by preparing blend of different excipients with drug and stored at 40°C/75%RH for one month. The blend was evaluated for every 15 days for changes like caking, liquefaction, discoloration and odour formation.

TABLE 9: DRUG EXCIPIENT COMPATIBILITY

SL.NO	COMPOSITION	QUANTITY	RATIO (Drug:Excipient)
1	Cefuroxime axetil	1gm	-
2	Cefuroxime axetil + Beta cyclodextrin	2gm	1:1
3	Cefuroxime axetil+ Eudragit L 100	2gm	1:1
4	Cefuroxime axetil + Xanthum gum	2gm	1:1
5	Cefuroxime axetil + Colloidal Silicon Dioxide	2gm	1:1
6	Cefuroxime axetil + Purified Talc	2gm	1:1
7	Cefuroxime axetil + Sodium lauryl sulphate	1.25gm	1:0.25
8	Cefuroxime axetil +Aspartame	2gm	1:1
9	Cefuroxime axetil +Sucralose	2gm	1:1
10	Cefuroxime axetil + Acesulfame K	2gm	1:1
11	Cefuroxime axetil + Sucrose	2gm	1:0.25
12	Cefuroxime axetil + Peppermint flavor	1.25gm	1:0.25
13	Cefuroxime axetil + Tutti frutti flavour	1.25gm	1:0.25
14	Cefuroxime axetil + Citric acid	2gm	1:1
15	Cefuroxime axetil + PVP K30	2gm	1:1
16	Cefuroxime axetil +stearic acid	2gm	1:1
17	Cefuroxime axetil + lactose anhydrous	2gm	1:1
18	Cefuroxime axetil + MCC	2gm	1:1
19	Cefuroxime axetil +HPMC	2gm	1:1
20	Cefuroxime axetil +Neotame	1.25gm	1:0.25
21	Cefuroxime axetil +HPC	2gm	1:1
22	Cefuroxime axetil +sodium methyl paraben	1.25gm	1:0.25

23	Cefuroxime axetil +sodium propyl paraben	1.25gm	1:0.25
24	Cefuroxime axetil +sodium CMC	2gm	1:1

7.2 INNOVATOR PRODUCT EVALUATION

Cefuroxime axetil Oral suspension 250mg/5ml is available in market under the trade name Zinnat manufactured by Glaxo Smith Kline, UK Limited. The product was evaluated with respect to its taste, viscosity, fill weight and grittiness. The analytical parameters were also evaluated.

SPECIFICATIONS OF CEFUROXIME AXETIL ORAL SUSPENSION AS PER USP

Assay	90-110 %
Water content	not more than 6 %
pH	3.5 – 7.0
Dissolution medium	0.07M Phosphate buffer
Volume of medium	900 ml
Apparatus	Type II paddle
Rpm	50
Duration	30 minutes
Sample withdrawal	5 ml
Limit	not less than 60 % in 30 minutes
pH of media	7.0±0.1

7.3 Development stages

Different technologies have been used to address the problem of taste masking

FORMULATION OF ORAL SUSPENSION

In the present work three methods were adopted for taste masking of the bitter API to formulate the oral suspension.

1. Addition of sweeteners and flavours
2. Coating with stearic acid
3. Complexation

a) Beta cyclodextrin

7.3.1 DETERMINATION OF THE AMOUNT OF DRUG REQUIRED TO BE USED TO FORMUALTE THE SUSPENSION

Molecular weight of Cefuroxime is 424.4 g.

Molecular weight of Cefuroxime Axetil is 510.48 g

The amount of API required for each 5 ml of the suspension is based on the conversion factor calculated from HPLC assay and water content determined by Karl Fischer titration.

$$\text{Conversion factor} = \frac{100}{\text{Assay (anhydrous basis)}} \times \frac{100}{(100 - \%\ \text{water content})}$$

Required quantity of drug = Conversion factor × Label claim

7.3.2 ADDITION OF SWEETENERS AND FLAVOURS

The trial F1, F2, F3 employed sweetener and flavour technology of taste masking. The formulation is expressed below.

TABLE 10: TRIAL F1, F2, F3

S.no	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)
1.	Cefuroxime axetil	298.500	298.500	298.500
2.	Sucrose	2634.500	2593.500	2595.500
3.	Aspartame	15.000	35.000	35.000
4.	Acesulfame K	25.000	25.000	25.000
6.	Xanthum gum	8.000	8.000	8.000
7.	Tutti frutti flavour	15.000	35.000	35.000
8.	Peppermint flavour	4.000	5.000	3.000
	Weight per 5 ml	**3000.000**	**3000.000**	**3000.000**

Manufacturing procedure

1. API was sifted through sieve # 30.
2. Sucrose was sifted through sieve # 30.
3. All the other ingredients were passed through sieve # 40.
4. The sugar was dried at 60˚C for one hour.
5. Divided the sugar into two equal portions.
6. The first portion of the sugar was milled and passed through sieve # 60.

7. Geometrically mixed the milled sugar with the API.

8. Geometrically mixed the excipients in step 3 with the above blend.

9. The above portion was mixed with unmilled portion of sugar.

10. The powder was blended thoroughly.

11. Weighed and dispensed in bottles.

7.3.3 COATING WITH STEARIC ACID

Trial T1-T6 employed coating with stearic acid

Coating specifications:

Coating technique : Pan coating

Inlet temperature : 50°C-70°C

Pan speed : 3 rpm

Spray rate : 3ml/minute

Atomization pressure : 1.2 kg/cm^2

COATING COMPOSITION -1

TABLE 11

S.NO	INGREDIENTS	QUANTITY (g)
1.	API	89.550
2.	Stearic acid	18.990
3.	PVP K30	2.151
4.	Isopropyl alcohol	25ml

COATING COMPOSITION -2

TABLE 12

S.NO	INGREDIENTS	QUANTITY (g)
1.	API	98.325
2.	Lactose anhydrous	98.250
3.	Stearic acid	19.658
4.	PVP K30	0.393
5.	Isopropyl alcohol	35ml

COATING COMPOSITION -3

TABLE 13

S.NO	INGREDIENTS	QUANTITY (g)
1.	API	98.325
2.	MCC pH 102	98.250
3.	Stearic acid	19.658
4.	PVP K30	0.393
5.	Isopropyl alcohol	35ml

FORMULA FOR BLENDING:

TABLE 14

S.NO	INGREDIENTS	QNTY /5 ml (mg)	QNTY /5 ml (mg)
		T1	**T2**
1.	API:stearic acid granules	366.000	366.000
2.	Sucrose	2497.000	2531.000
3.	Xanthum gum	8.000	8.000
4.	Sodium lauryl sulphate	30.000	-
5.	Aspartame	35.000	35.000
6.	Acesulfame K	25.000	25.000
7.	Tutti frutti flavour	35.000	35.000
8.	Peppermint flavour	4.000	
	Weight / 5ml	**3000.000**	**3000.000**

TABLE-15

S.NO	INGREDIENTS	QNTY /5 ml (mg)	QNTY /5 ml (mg)	QNTY /5 ml (mg)	QNTY /5 ml (mg)
		T3	**T4**	**T5**	**T6**
1.	API:stearic acid granules	366.000	366.000	366.000	366.000
2.	Sucrose	2497.000	2531.000	2497.000	2531.000
3.	Xanthum gum	8.000	8.000	8.000	8.000
4.	Sodium lauryl sulphate	30.000	-	30.000	-
5.	Aspartame	35.000	35.000	35.000	35.000
6.	Acesulfame K	25.000	25.000	25.000	25.000
7.	Tutti frutti flavour	35.000	35.000	35.000	35.000
8.	Peppermint flavour	4.000		4.000	
	Weight / 5ml	**3000.000**	**3000.000**	**3000.000**	**3000.000**

Manufacturing procedure

1. The coating solution was prepared with the calculated composition.
2. The solvent was stirred under the mechanical stirrer for 5 minutes.
3. Stearic acid was added to the vortex of the solvent under stirring. Continued stirring for 10 minutes
4. PVP K30 was added to the above solution and stirred for 10 minutes.
5. The drug and the channeling agent was sifted through sieve # 60.
6. The drug was preheated in the conventional coating pan.
7. The spray solution was passed at a spray rate of 3ml/minute and an atomisation pressure of 1.2kg/cm^2. Pan rpm was 3.
8. After a time the spray was halted and allowed the granules to dry in a stream of hot air.
9. The coated granules were sifted through sieve # 60.
10. The granules were subjected to another coat of spray, dried the granules again.
11. Sifted the granules through sieve # 40.
12. The coated granules after cooling were used for formulation.
13. The sugar was dried at 60˚C for one hour.
14. Divided the sugar into two equal portions.

15. The first portion of the sugar was milled and sifted through sieve # 60.
16. Geometrically blended the milled sugar with the coated granule.
17. Geometrically blended the excipients with the above blend.
18. The above portion was mixed with unmilled portion of sugar.
19. The powder was blend thoroughly.
20. Weighed and dispensed in bottles.

7.3.5. COMPLEXATION USING BETACYCLODEXTRIN

CALCULATIONS FOR THE AMOUNT OF CEFUROXIME AXETIL REQUIRED PER 5 ml

Molecular weight of cefuroxime axetil (CA) is 510.48 g

Molecular weight of beta cyclodextrin (CD) is 1135 g

Therefore, to prepare 1:1 ratio of drug: beta CD

1g (1000mg) of drug CA ≡ 2.223 g (2223mg) of beta CD.

The formulation development progressed with different trials each differing in one or the other parameter. Initially preliminary trials P1 to P9 were taken to optimize each parameter and then the final formulations P8 was developed. The formulations are listed below.

TABLE 16 : PRELIMINARY TRIALS P1 – P6

S.NO.	INGREDIENTS	P1(mg)	P2(mg)	P3(mg)	P4(mg)	P5(mg)	P6(mg)
1.	CA:BetaCD complex	962.066	962.066	962.066	962.066	962.066	962.066
2.	Sucrose	1934.934	1904.934	1934.934	1904.934	1934.934	1904.934
3.	Ratio	1:1	1:1	1:1	1:1	1:1	1:1
4.	Water	100%	100%			50%	50%
5.	Isopropyl alcohol	-	-	100%	100%	50%	50%
6.	Xanthum gum	8.00	8.00			8.00	8.00
7.	Sodiumlauryl sulphate		30.00		30.00	-	30.00
8.	Aspartame	35	35	35	35	35.00	35.00
9.	Acesulfame K	25	25	25	25	25.00	25.00
10.	Tutti fruti flavour	35	35	35	35	35	35
11.	Avg weight in mg/5ml	3000	3000	3000	3000	3000	3000

The quantity of sucrose compensates the final average weight per 5ml.

COMPLEXATION USING BETA CYCLODEXTRIN WITH THE INCORPORATION OF SODIUM LAURYL SULPHATE:-

TABLE-17

SL NO	INGREDIENTS	QTY(mg)	QTY(mg)	QTY(mg)
	FOR COMPLEXATION	**P7**	**P8**	**P9**
1	Cefuroxime axetil	327.750	317.750	317.750
2	Beta cyclodextrin	728.588	706.358	706.358
3	SLS	6.000	15.000	30.000
4	Water	100%	100%	100%
	FOR BLENDING			
5	CA:B CD Complex	1086.772	1058.851	1072.028
6	Sucrose	1812.228	1840.149	1826.972
7	Acesulfame K	25.000	25.000	25.000
8	Aspartame	35.000	35.000	35.000
9	Xatham gum	6.000	6.000	6.000
10	Tutti frutti flavour	35.000	35.000	35.000
		3000.000	3000.000	3000.000

Manufacturing procedure:

1. The solvent was prepared .
2. The solvent was stirred under the mechanical stirrer .
3. The API and beta cyclodextrin were sifted through seive# 30,then transferred to solvent solution.
4. Stirred for 6 hours.
5. The formation of smooth slurry was obtained .
6. The slurry was dried in the oven at 45^0c.
7. Sifted the granules through sieve # 60.
8. The granules after cooling were used for formulation.
9. The sugar was dried at 60˚C for one hour.
10. Divided the sugar into two equal portions.
11. The first portion of the sugar was milled and sifted through sieve # 60.
12. Sifted the excipients through seive# 40.
13. Geometrically blended the milled sugar with the granule.
14. Geometrically blended the excipients with the above blend.
15. The above portion was mixed with unmilled portion of sugar.
16. The powder was blend thoroughly.
17. Weighed and dispensed in bottles.

7.3.6 FORMULA OPTIMISATION

Based on the preliminary formulations inferences are drawn and the trials are focused to optimise the formulation.

TABLE 18: OPTIMIZED FORMULA

S.NO	INGREDIENTS	P8
1.	API	317.750
2.	Beta CD	706.358
3.	SLS	15.000
4.	Water	100%
5	CA: B Cd complex	1058.581
6.	Sucrose	1840.149
7.	Aspartame	35
8.	Acesulfame K	25
9.	Xatham gum	6
10.	Tutti frutti flavour	35
11.	Avg weight in mg/5ml	3000

7.4. EVALUATION OF ORAL SUSPENSION

7.4.1 Taste Evaluation (Sensory Evaluation)

Sensory evaluation is defined as a scientific discipline used to measure, analyze and interpret reactions to those characteristic of materials as they are perceived by the senses of sight, smell, taste, touch and hearing.

Taste evaluation was done by taste panels. The method chosen was ranking test. For this purpose 10 human volunteers were selected. The suspension of the pure drug and formulations were coded and given to the volunteers. The intensity of bitterness was asked from volunteers. By using ranking test best taste masking technique was screened from all the adopted taste masking methods. Excellent ; good; fair ; bitter ; extremely bitter ;

7.4.2 Mouth feel

The mouth feel of the suspension is an important parameter with respect to its acceptance by the patient and thereby compliance. Gritty suspensions are usually not preferred. The data can be collected from the volunteers when given to taste.

7.4.3 Flow property

This is measured in terms of angle of repose, bulk density, tapped density, compressibility index, hausner ratio which has been described earlier in section 7.1.4

7.4.4. In vitro drug release studies

Dissolution parameters of oral suspension

Media	:	0.07M Phosphate buffer
Volume of media	:	900ml
Apparatus	:	Type II paddle
Rpm	:	50
Time	:	30 minutes
Temperature	:	37.2± 0.5˚C

Preparation of 0.07M phosphate buffer

Dissolve 3.7g of monobasic sodium phosphate and 5.7g of anhydrous dibasic sodium phosphate in 1000ml water.

Estimation of drug release using single external standard method:

The in house specifications of the industry validates single external standard to be more accurate than the widely used calibration curve method for the estimation of drug content. The method even eliminates the possible errors like slightest variation in standard absorbance arising due to the differences in analytical working conditions on any particular analytical phase during the course of study. The method requires the preparation of a working standard of cefuroxime axetil in the corresponding mediums in which the in vitro drug release studies are conducted during each particular trial of the study

Preparation of standard

Accurately weigh about 20 mg of the reference standard sample to a standard flask. Dissolve using small quantity of methanol. 10 ml of this solution is transferred to another standard flask. Make up with media to 100 ml. Observe for absorbance at 280 nm.

Procedure of dissolution study

The in vitro dissolution studies of cefuroxime axetil oral suspension is performed using USP type II dissolution apparatus (paddle type). Test 5 ml of reconstituted cefuroxime

axetil for oral suspension equivalent to 250 mg of cefuroxime. The dissolution medium consisted of 900ml of 0.07M phosphate buffer (pH=7.0) maintained at 37 ± 0.2°C. The speed of paddle was set at 50 rpm. Aliquot of samples (5ml) were withdrawn at specific time of 30 minutes.

Preparation of sample solutions:

5ml of sample withdrawn was diluted with corresponding medium and made up to volume in a 100ml standard flask. The above solution was sonicated for 5mins and the absorbance was measured at 280nm.

Measurement of absorbance in UV spectrometer:

The amount of cefuroxime axetil released is determined by using an ultraviolet visible spectrophotometer at the wavelength of maximum absorbance at about 280 nm using the formulae below

$$\text{\% Drug release} = \frac{\text{wt. of std.} * \text{sample abs.} * 900 * \text{sample dilution} * \text{potency of std.}}{\text{std. dilution} * \text{std. absorbance} * \text{label claim}}$$

7.4.5. Assay procedure for oral suspension

The assay is carried out as per USP-NF.

Standard preparation: Transfer about 30 mg of Cefuroxime Axetil to a 25 ml volumetric flask, dissolve in and dilute with methanol to volume and mix. Promptly transfer 10 ml of this solution to a 50 ml volumetric flask, add 8.8 ml of methanol, dilute with 0.2M monobasic ammonium phosphate to volume and mix.

Assay preparation: Transfer to a 100 ml volumetric flask an accurately measured portion of Cefuroxime axetil for oral suspension, freshly mixed and free from air bubbles, and equivalent to about 250 mg of cefuroxime. Add about 50 ml of methanol, and shake by mechanical means for about 10 minutes. Dilute with methanol to volume, and mix. Filter a portion of this stock solution, and transfer 5ml of the filterate to a 50 ml volumetric flask. Add 13.8ml of methanol, dilute with 0.2M monobasic ammonium phosphate to volume and mix.

Procedure: Separately inject equal volumes of the standard preparation and the assay preparation into the chromatograph, record the chromatograms, and measure the responses. The chromatogram is recorded at 278 nm.

Calculations of HPLC assay

$$\% \text{ Drug Content} = \frac{\text{wt. of standard} * \text{mean sample area} * \text{specific gravity} * \text{dilution} * \text{potency} * 100}{\text{wt. of sample} * \text{mean std area}}$$

7.4.6. DETERMINATION OF pH

The determination of pH is an important tool as the formulation is reconstituted and used. By checking this we ensure any noticeable change during its use and storage.

7.5 TASTE EVALUATION

Taste evaluation is done by taste panels. The method chosen is ranking test. The suspension of the pure drug and formulations prepared by various techniques were coded and given to the volunteers. The intensity of bitterness was asked from volunteers. By using ranking test best taste masking technique was screened.

7.6. DIFFERENTIAL SCANNING COLORIMETRY

DSC studies were conducted to know the extent of complexation. DSC thermograms of pure drug, the complexing agent beta cyclodextrin, and the formulation were recorded and observed for peaks, for presence of additional peaks or absence of peaks indicating possible interactions or phase transformations. The thermal peaks give the melting points of the samples which can be used as a test for purity analysis and also for sample characterization.

7.7. pH STABILITY STUDY

The formulation was studied for stability of pH. After reconstitution the suspension was stored at 2-8˚C and pH of the suspension was checked for 10 days

7.8. SCALE UP

Once the optimised formula was finalised a higher batch of the final formulation is taken by extrapolating the same formula for 100 bottles.

7.9 STABILITY STUDIES

Short term accelerated stability studies are performed on the optimized formulations packed in HDPE bottles of 30ml capacity. The oral suspension is subjected to stability studies at 40^0C/75%RH in a stability chamber for a period of 1 month**.** Evaluation of the oral suspensions is done initially at the time of charging and at the end of first month. The suspensions are again analyzed for its physical appearance, water content and in vitro drug release profile and HPLC assay.

MICROBIOLOGICAL ASSAY OF CEFUROXIME AXETIL

The microbiological assay of an antibiotic is based upon a comparison of the inhibition of growth of microorganism by measured concentrations of the antibiotics under examination with the product by known concentrations of a standard preparation of the antibiotic having a known activity.

The antimicrobial susceptibility of cefuroxime axetil oral suspension were tested by **Kirby-Bauer antibiotic sensitivity test.**

In this method filter paper disc of uniform size were impregnated with different concentrations of cefuroxime axetil and then placed on the surface of an agar plate that has been seeded with the organism to be tested .The efficacy of drug was determined by measuring the diameter of the zone of inhibition that results from diffusion of the drug into the medium surrounding the disc .The susceptibility of the organism to a drug was determined by the size of the zone.

Media:

Mueller Hinton Agar No-2:

The media consists of Caseine acid hydrolysate ,Beef heart infusion,Starch soluble and Agar.

Preparation of media:

Suspend 38gms of Mueller Hinton Agar media in 1000ml distilled water, mixed well and heated to boiling to dissolve the medium completely. Then it was sterilized by autoclaving at 15lbs per square inch pressure at 121^0c for 15 minutes.

Organisms:

The test organisms selected were,Escherichia coli,Bacillus subtilis,salmonella typhi.

Procedure:

1. The covers of each of the agar plates were labeled with the name of the test organism to be inoculated.
2. Using sterile techniques, all agar plates were inoculated with their respective test organisms as follows:
    a) A sterile cotton swab was dipped into a well mixed saline test culture and excess inoculum was removed by pressing the saturated swab against the inner wall of the culture tube.

b) Using the swab ,the entire agar surface were streaked horizontally,vertically and around the outer edge of the plate to ensure a heavy growth over the entire surface and all culture plates were allowed to dry for about 5 minutes.

3. The individual discs were distributed on the respective points with sterile forceps.
4. Each disc were gently pressed down with the sterile forceps to ensure that the discs adhere to the surface of the agar.
5. All the plates were incubated in an inverted position for 24 to 48 hours at 37^0c.
6. Then the plates were examined for the presence of growth inhibition and the susceptibility of the organism to the drug was determined by the size of the zone.

Results and Discussion

SECTION 8. RESULTS AND DISCUSSION

8.1 EVALUATION OF API

8.1.1Organoleptic properties of API

Colour: Yellowish

Odour: Nauseating

Taste : Very bitter

8.1.2 Particle size

Initial weight of powder = 50 gms

Final weight of powder = 41.39 gms

Percentage of drug passed = $\frac{\text{amount passed}}{\text{Initial weight}} \times 100$

= 82.78%

TABLE 19: PARTICLE SIZE DISTRIBUTION

Sieve No.	Aperture size (µm)	Amount retained(g)	Percentage retained(g)	Cumulative Percentage retained
20	850	0.00	0.00	0.00
30	650	0.14	0.28	0.28
40	425	1.48	2.96	3.24
60	250	2.09	4.18	7.42
80	180	2.89	5.78	13.20
100	150	3.01	6.02	19.22
Pan	-	40.39	80.78	100.00

From the particle size analysis it is concluded that no particle was retained on sieve # 20. Almost 81% of drug passes through all sieves. Hence not less than 80%of the particles have size less than 150µm.

8.1.3 Solubility

Solubility was studied in different solvents. Slightly soluble in water and ethanol and soluble in acetone, ethyl acetate and methanol.

8.1.4 Flow property

The flow property is a measure of cohesiveness and flow of powder through a hopper during manufacturing.

Angle of repose = 28˚

Bulk density = 0.165g/ml

Tapped density = 0.238g/ml

Hausner ratio = 1.444

Compressibility index = 30.769

8.2 PHYSICAL COMPATIBILITY STUDIES

TABLE 20: DRUG EXCIPIENTS COMPATIBILITY REPORT

SL. NO.	COMPOSITION	DESCRIPTION		
		INITIAL	2 WEEKS	4 WEEKS
1	Cefuroxime axetil	White to off white powder	No colour change	No colour change
2	Cefuroxime axetil + Beta cyclodextrin	White to off white powder	No colour change	No colour change
3	Cefuroxime axetil + Eudragit L 100	White to off white powder	No colour change	No colour change
4	Cefuroxime axetil + Xanthum gum	White to off white powder	No colour change	No colour change
5	Cefuroxime axetil + Colloidal Silicon Dioxide	White to off white powder	No colour change	No colour change
6	Cefuroxime axetil + Purified Talc	White to off white powder	No colour change	No colour change
7	Cefuroxime axetil + Sodium lauryl sulfate	White to off white powder	No colour change	No colour change
8	Cefuroxime axetil +Aspartame	White to off white powder	No colour change	No colour change
09	Cefuroxime axetil +Sucralose	White to off white powder	No colour change	No colour change
10	Cefuroxime axetil + Acesulfame K	White to off white powder	No colour change	No colour change
12	Cefuroxime axetil + Sucrose	White to off white powder	No colour change	No colour change
13	Cefuroxime axetil + Peppermint flavor	White to off white powder	No colour change	No colour change
14	Cefuroxime axetil + Tutti frutti flavour	White to off white powder	No colour change	No colour change
15	Cefuroxime axetil + Citric acid	White to off white powder	No colour change	No colour change
16	Cefuroxime axetil +stearic	White to off	No colour	No colour

	acid	white powder	change	change
17	Cefuroxime axetil +PVP K30	White to off white powder	No colour change	No colour change
18	Cefuroxime axetil +Lactose anhydrous	White to off white powder	No colour change	No colour change
19	Cefuroxime axetil +MCC	White to off white powder	No colour change	No colour change
20	Cefuroxime axetil +HPMC	White to off white powder	No colour change	No colour change
21	Cefuroxime axetil +Neotame	White to off white powder	No colour change	No colour change
22	Cefuroxime axetil + HPC	White to off white powder	No colour change	No colour change
23	Cefuroxime axetil +sodium methyl paraben	White to off white powder	Slight brown colour change	Slight brown colour change
24	Cefuroxime axetil +sodium propyl paraben	White to off white powder	Slight brown colour change	Slight brown colour change

From the above results,after 30 days of accelerated stability testing the drug excipient mixture remains unchanged except drug with Sodium methyl paraben and Sodium propyl paraben (shows slight brown colour change).Thus it was concluded that the excipients selected for the formulation were compatible with drug except sodium methyl paraben and sodium propyl paraben.

8.3 INNOVATOR PRODUCT EVALUATION

Label specification

Product name	Cefuroxime axetil granules for 100 ml
Manufacturer	Glaxo Smithkline Operations, UK ltd
Brand name	Zinnat suspension
Labeled claim	250mg/5ml
Lot no:	C 451660
Batch no.	9003354
Mfg. Date	12/2009
Exp. Date	12/2011
Direction for reconstitution :	1. Shake bottle well to loosen granules. 2. Fill the measuring cup to the line with 37 ml

water.

3. Add water to bottle in one go and replace cap.
4. Invert and rock bottle vigorously (for at least 15 seconds) to mix medicine properly.
5. To be used as directed by physician. Dose may be added to children's cold fruit juices or milk immediately before taking.

Storage instructions : Before reconstitution store below 30 ˚C. Kee medicines out of reach of children. Once recons store in a refridgerator between 2 to 8 ˚C and use wit days. Do no freeze. Contains aspartame.

Evaluation report

1. Taste : pleasant initially, has slight bitter after taste
2. Viscosity : adequate
3. Grittiness : gritty feeling
4. Dissolution value : 71.89% drug released
5. Assay : 98 %

8.3.1 AMOUNT OF CEFUROXIME AXETIL REQUIRED

The quantity of Cefuroxime axetil to be used in the formulation of a suspension containing 250 mg/ 5 ml was calculated from the assay value and the water content determined by Karl-Fischer method.

Assay on anhydrous basis = 84.65 %
Water content by KF titration = 1.04 %
Conversion factor = 1.194 %

The required amount of Cefuroxime axetil was calculated using the formula and was found to be 298.500mg.

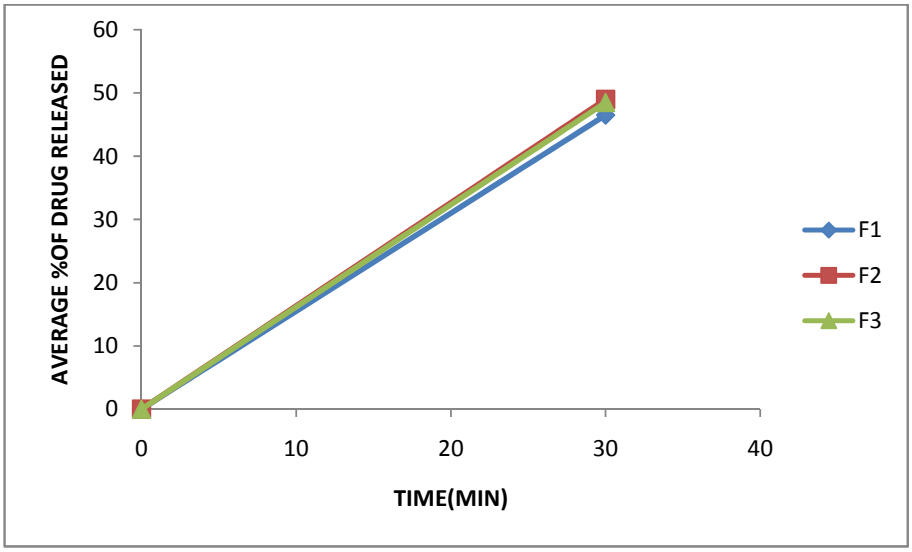
8.3.2 TASTE MASKING USING SWEETENERS AND FLAVOURS

Trials F1 F2 F3 were carried out by applying the sweetener and flavour technology.

TABLE 21: RESULTS OF TRIALS F1, F2, F3

Parameters	F 1	F 2	F 3
Taste	Bitter	Initially sweet; Bitterness persist	Bitter after taste
Flavour	Flavour is less	Peppermint flavour predominates	Flavour is ok
Mouth feel	Gritty	Slightly gritty	Slightly gritty
Pourability and viscosity	Sufficient	Sufficient	Sufficient
Bulk density	0.769	0.744	0.76
Tapped density	0.930	0.680	0.808
Angle of repose	32.18	31.92	30.42
Compressibility index	17.307	8.571	6
Hausner ratio	1.209	1.09	1.06
Dissolution (%)	46.5	49	48.5
pH	5.8	5.72	5.91

FIGURE-2 DISSOLUTION PROFILE OF TRIALS F1,F2 &F3



Discussion

Sucrose and aspartame are the two sweeteners used. Sucrose is used as a sweetening agent in beverages, foods, and pharmaceutical applications. Flavours include Peppermint and Tutti frutti. In the formulation xanthum gum acts as the viscosity building agent.

In trial F1 15mg/5ml of aspartame were used. The bitter taste of drug persisted. Hence in trial F2 the amount of sweeteners was doubled. Flavour was less in both the trials. So the amount of both the flavour was increased in the third trial F3. A combination of all these was supposed to mask the bitter taste. The formulation was gritty in nature. Besides, caking or undissolved gel sediments were observed at the bottom of the dissolution bowl. This may be due to increase in percentage of xatham gum. So the percentage of xatham gum may be reduced in next trial .

Conclusion

The bitter taste still persist even after increasing the amount of sweetener and flavour; the average dissolution value falls far less than the expected limit of 60 %. Hence it was concluded that taste masking of Cefuroxime axetil oral suspension with sweetener and flavour technology was unsatisfactory. Therefore, alternate method was adopted in the next trial.

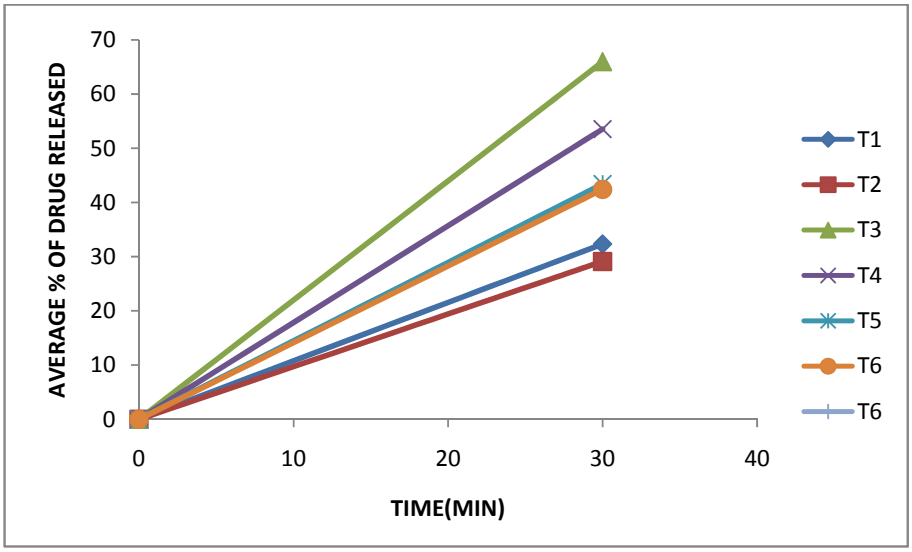
8.3.3 TASTE MASKING BY COATING

Trial T1-T6 employed coating of the drug particle with stearic acid, which is chemically octadecanoic acid. The results are tabulated below.

TABLE-22

Parameters	**T1**	**T2**	**T 3**	**T 4**	**T5**	**T6**
Taste	Bitter	Bitter	Slightly Bitter	Slightly Bitter	Bitter	Bitter
Flavour	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
Mouth feel	Gritty	Gritty	Gritty	Gritty	Gritty	Gritty
Pourability and viscosity	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
Bulk density	0.698	0.658	0.674	0.694	0.568	0.574
Tapped density	0.796	0.768	0.758	0.790	0.698	0.658
Angle of repose	31.28	32.41	32.82	32	30.98	31.10
Compressibility index	10.14	9.09	13.00	10.56	13.33	13.62
Hausner ratio	1.074	1.142	1.136	1.13	1.12	1.20
Dissolution	32.32	29.12	65.97	53.55	43.40	42.41
pH	5.36	6.28	6.47	6.25	6.24	6.18
Assay	82	82.58	98.12	98.54	88	87.20

FIGURE-3 DISSOLUTION PROFILE OF TRIALS T1-T6



Discussion

Large amount of drug and coating solution is required for coating. The formulation is gritty in nature. Hard granules were formed during coating process.

Conclusion

The polymer is used in taste masking as it provides a barrier between the drug and the taste buds and reduces the drug solubility in saliva. In the present trial the feasibility of coating cefuroxime axetil with stearic acid is less in conventional coating pan. Large amount of drug and coating solution is required. Hence alternate method was adopted for the next trial.

8.3.5 TASTE MASKING BY INCLUSION COMPLEX FORMATION

TABLE 23: RESULTS OF PRELIMINARY TRIALS P1-P6

Parameters	P 1	P 2	P 3	P 4	P5	P6
Taste	Bitter	Bitter	Slightly Bitter	Slightly Bitter	Slightly Bitter	Slightly Bitter
Flavour	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
Mouth feel	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
Pourability and viscosity	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
Bulk density	0.689	0.75	0.689	0.776	0.749	0.769
Tapped density	0.740	0.857	0.783	0.878	0.832	0.853
Angle of repose	31.28	32.41	32.82	32	31.98	31.56
Compressibility index	6.89	12.5	12	11.5	6.82	4.852
Hausner ratio	1.074	1.142	1.136	1.13	1.09	1.12
Dissolution	39.72	41.02	50	49.58	35.69	34.46
pH	5.36	6.28	6.47	6.25	6.12	6.34

FIGURE-4 DISSOLUTION PROFILE OF TRAILS P1-P6

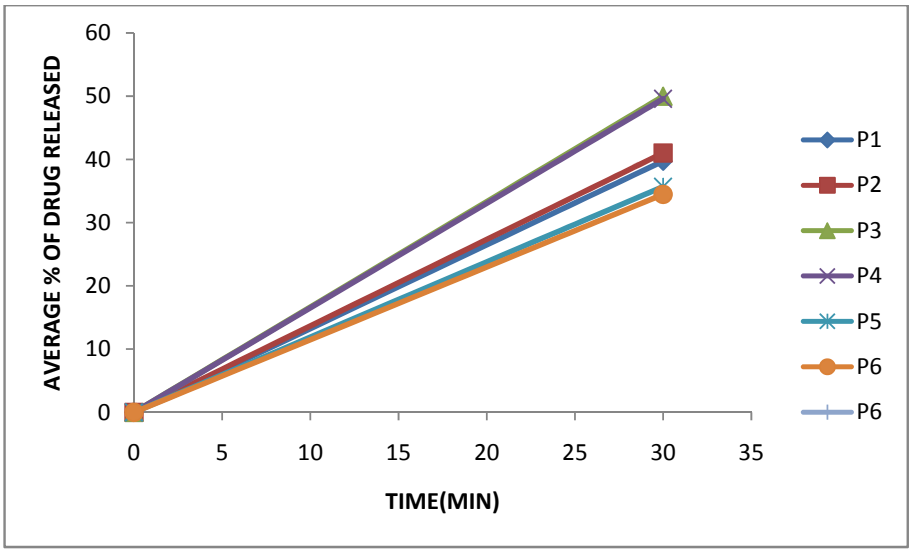
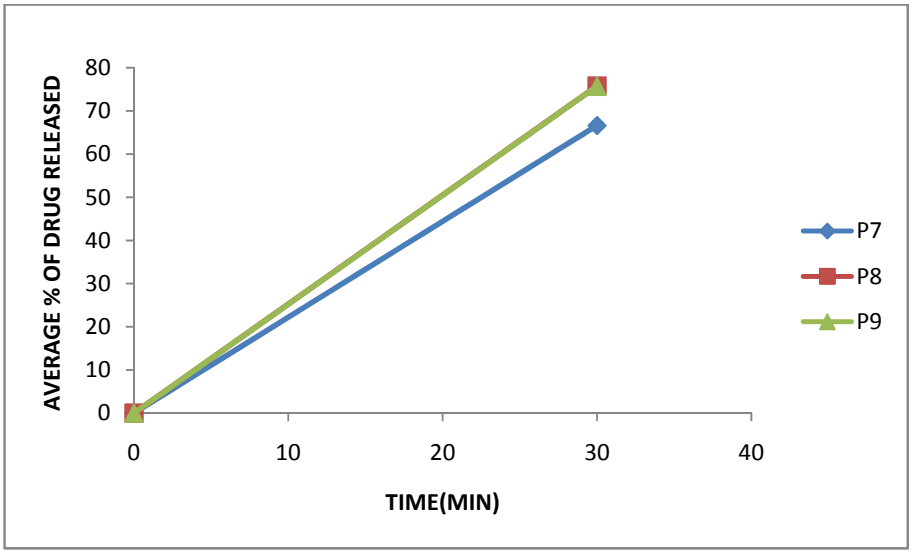


TABLE 24: RESULTS OF PRELIMINARY TRIALS P7-P9

Parameters	**P 7**	**P 8**	**P 9**
Taste	Slightly bitter	Slightly bitter	Slightly bitter
Flavour	Sufficient	Sufficient	Sufficient
Mouth feel	Smooth	Smooth	Smooth
Pourability and viscosity	Sufficient	Sufficient	Sufficient
Bulk density	0.769	0.777	0.709
Tapped density	0.836	0.84	0.758
Angle of repose	31.48	28	29.62
Compressibility index	8	7.4	6.45
Hausner ratio	1.086	1.08	1.068
Dissolution	66.61	75.77	75.70
pH	6.45	6.38	6.15
Assay	98.12	98.42	98

FIGURE-5 DISSOLUTION PROFILE OF TRIALS P7-P9



Discussion

Initial six trials were taken by without adding SLS to the complexation part.So the dissolution was not improving .But in the trials P7-P9 SLS was incorporated into the complexation part .Here SLS improved the solubility of the Cefuroxime axetil:Betacyclodextrin complex.

Conclusion

For initial 2 trials taste was not good,bitter taste and the dissolution was not in the limit .For trials P3-P6 taste was good,slightly bitter taste and the dissolution was not in the limit.For trails P7-P9 the taste was good,slight bitter after taste and the dissolution were increasing with increasing the concentration of SLS. In the case of P9 slight irritation on the throat occurs when increasing the SLS concentration.so P8 was choosen as best formulation.

Inferences from preliminary trials:

From the 9 preliminary trials certain inferences were drawn. They are as follows.

1. The ideal ratio of drug : beta cyclodextrin was found to be 1: 1taken on weight basis.
2. The fill weight was optimised at 3.0 grams per 5ml.
3. The taste of the bitter drug is improved when iso propyl alcohol is used in the solvent. But dissolution of drug beta CD complex is bit hindered.
4. Water is a good solvent with respect to dissolution. Hence a 100% water was taken as solvent.
5. Ideal volume of complexing medium is 500 ml.
6. Ideal stirring time is 5-7 hrs.
7. The sweeteners along with sucrose contributes to taste abatement.
8. Sodium lauryl sulphate enhances dissolution.
9. A 30-35mg/5ml tutti frutti flavour works good at masking the bitter taste.
10. As the pH of the formulation remains below 6.5 there was no need to add any buffer.

8.3.6 FORMULA OPTIMIZATION

TABLE 25 : RESULT OF OPTIMIZED FORMULA

Parameters	**P8**
Taste	Slightly bitter
Flavour	Sufficient
Mouth feel	Smooth
Pourability and viscosity	Sufficient
Bulk density	0.777
Tapped density	0.84
Angle of repose	28
Compressibility index	7.4
Hausner ratio	1.08
Dissolution (%)	75.77
pH	6.38
Assay	98.42

Trial P8 was chosen as the optimised formula. The bitter taste of the drug was masked to a larger extent by the complexation method . The flavour together with sweeteners have further improved the taste of the formulation. The average dissolution values lies at 75.77. The pH of the formulation was maintained below 6.38which omits the use of any buffer.

FIG 6: DISSOLUTION PROFILE OF OPTIMIZED FORMULATION.

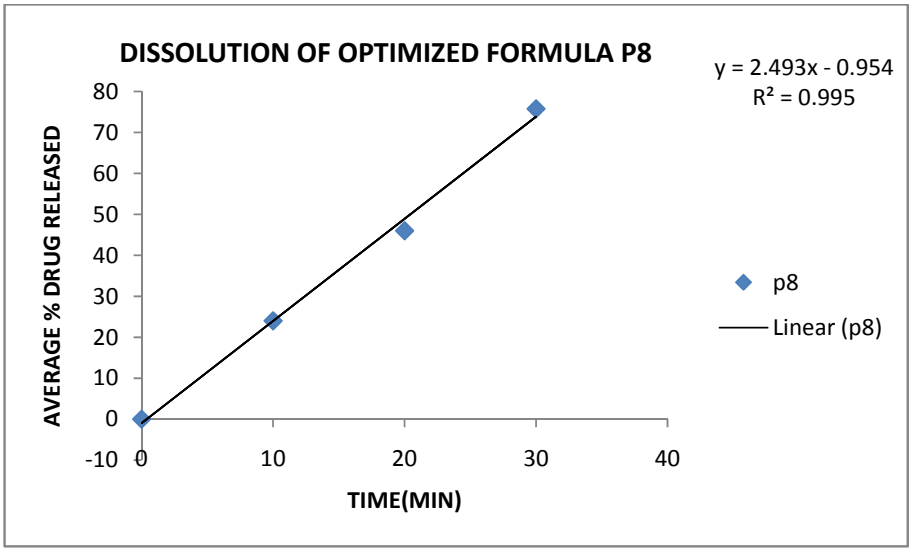
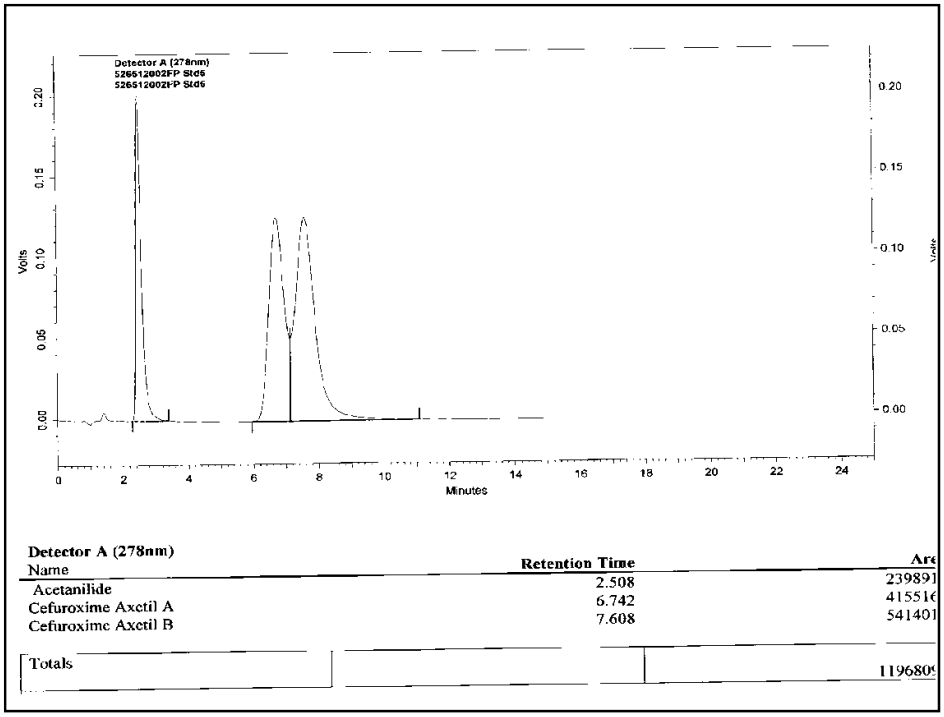
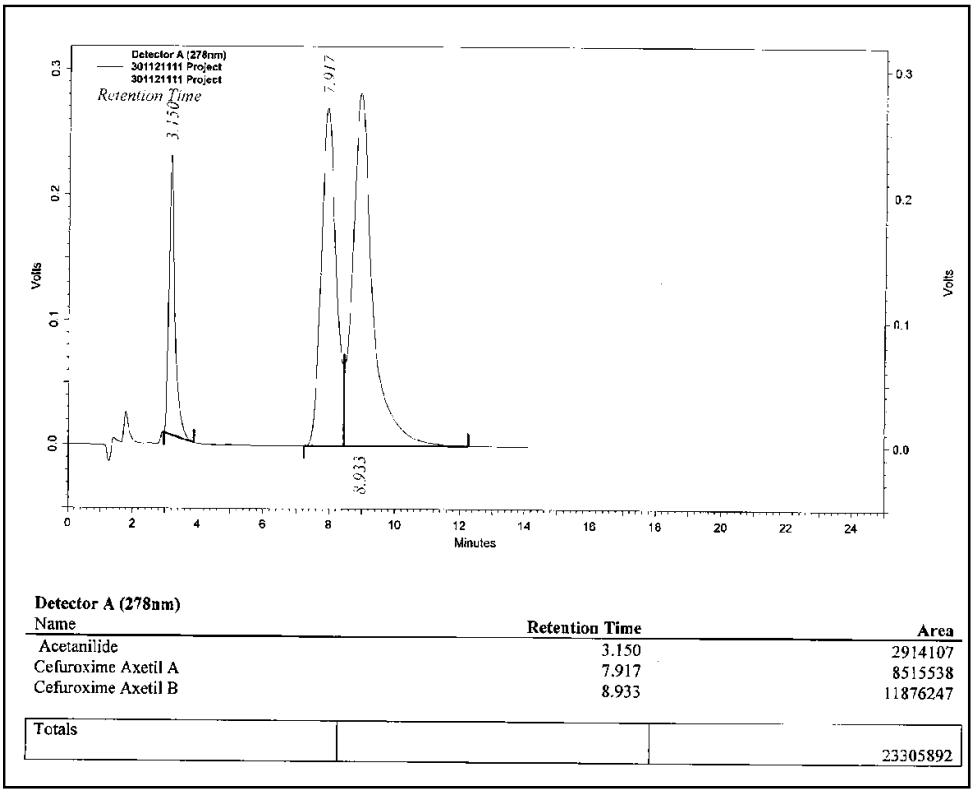


FIG 7: ASSAY OF OPTIMIZED FORMULA P8



Detector A (278nm)

Name	Retention Time	Are
Acetanilide	2.508	239891
Cefuroxime Axetil A	6.742	415516
Cefuroxime Axetil B	7.608	541401
Totals		1196809



Detector A (278nm)

Name	Retention Time	Area
Acetanilide	3.150	2914107
Cefuroxime Axetil A	7.917	8515538
Cefuroxime Axetil B	8.933	11876247
Totals		23305892

PACKING INSTRUCTION

The dry powder for suspension is packed in HDPE bottles of 30 ml capacity. The bottles are sealed through induction sealing and labelled properly.

DIRECTIONS FOR RECONSTITUTION

1. Shake bottle well to loosen granules.
2. Fill the measuring cup to the line with 18 ml water.
3. Add water to bottle in one go and replace cap.
4. Invert and rock bottle vigorously (for at least 15 seconds) to mix medicine properly.
5. To be used as directed by physician. Dose may be added to children's cold fruit juices or milk immediately before taking.

STORAGE INSTRUCTION

Suspension granules should be stored below 30°C.

Multidose bottles : Store in cold condition after reconstitution at 2-8°C. Do not use not more than 10 days after reconstitution.

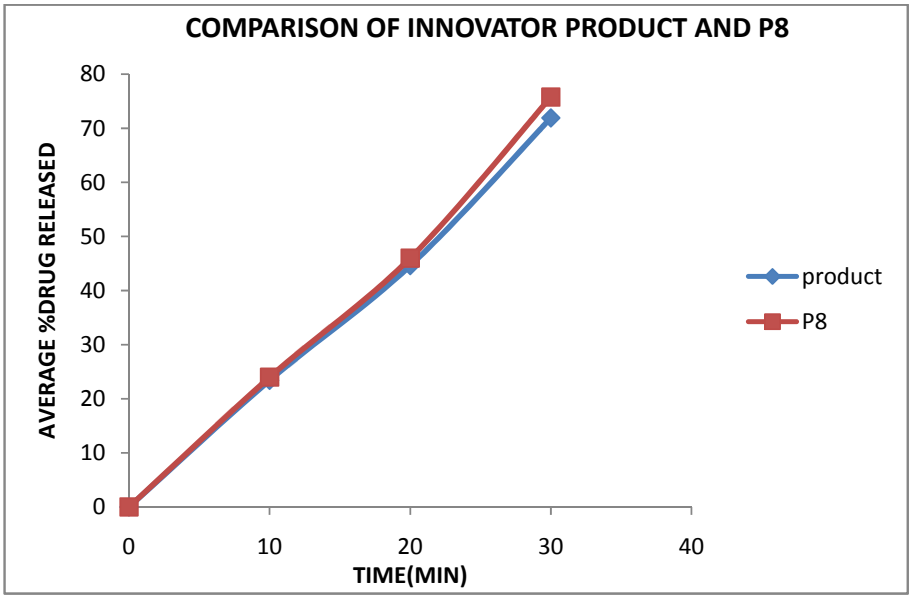
8.4 COMPARISON OF INNOVATOR PRODUCT WITH THE OPTIMZED FORMULATION

The dissolution profile of the innovator product and the optimised formulation was compared and the results are shown below.

TABLE 26: COMPARISON OF INNOVATOR PRODUCT WITH THE OPTIMZED FORMULATION

Time (min)	Average % drug released	
	Innovator product	P8
10	23.4	24
20	44.6	46
30	71.89	75.77

FIG 8: COMPARISON OF DISSOLUTION PROFILE



8.5. TASTE EVALUATION:

The efficacy of four methods in masking the bitter taste of Cefuroxime axetil was evaluated by taste panels using ranking test.

TABLE 27: TASTE EVALUATION REPORT

		RANK				
		0	1	2	3	4
Pure Drug		-	-	-	-	✓
TASTE MASKING METHODS						
Addition of Flavors and Sweeteners	F1	-	-	-	✓	-
	F2	-	-	-	✓	-
	F3	-	-	✓	-	-
Coating with stearic acid	T1	-	-	✓	-	-
	T2	-	-	✓	-	-
	T3	-	✓	-	-	-
	T4		✓			
	T5	-	-	✓	-	-
	T6	-	-	✓	-	-
Complexation with β-cyclodextrin	P1	-	-	✓	-	-
	P2	-	-	✓	-	-
	P3	-	✓	-	-	-
	P4	-	✓	-	-	-
	P5	-	✓	-	-	-
	P6	-	✓	-	-	-
Complexation with β-cyclodextrin with the incorporation of SLS	P7	✓	-	-	-	-
	P8	✓	-	-	-	-
	P9	✓	-	-	-	-
Innovator product		✓	-	-	-	-

0 = Acceptable; 1 = Slightly Bitter; 2= Bitter; 3 = Very Bitter, 4 = Extremely Bitter.

8.6 DSC STUDY

DSC study was carried out at the Sophisticated Analytical instruments Facility, STIC, Cochin University of Science and Technology, Cochin-22 using Mettler Toledo Star System model. DSC studies were conducted to know the extent of complexation. DSC thermograms of pure drug, the complexing agent beta cyclodextrin, and the formulation were recorded and observed for peaks, for presence of additional peaks or absence of peaks indicating possible interactions or phase transformations.

FIG 9 : DSC DATA OF PURE API

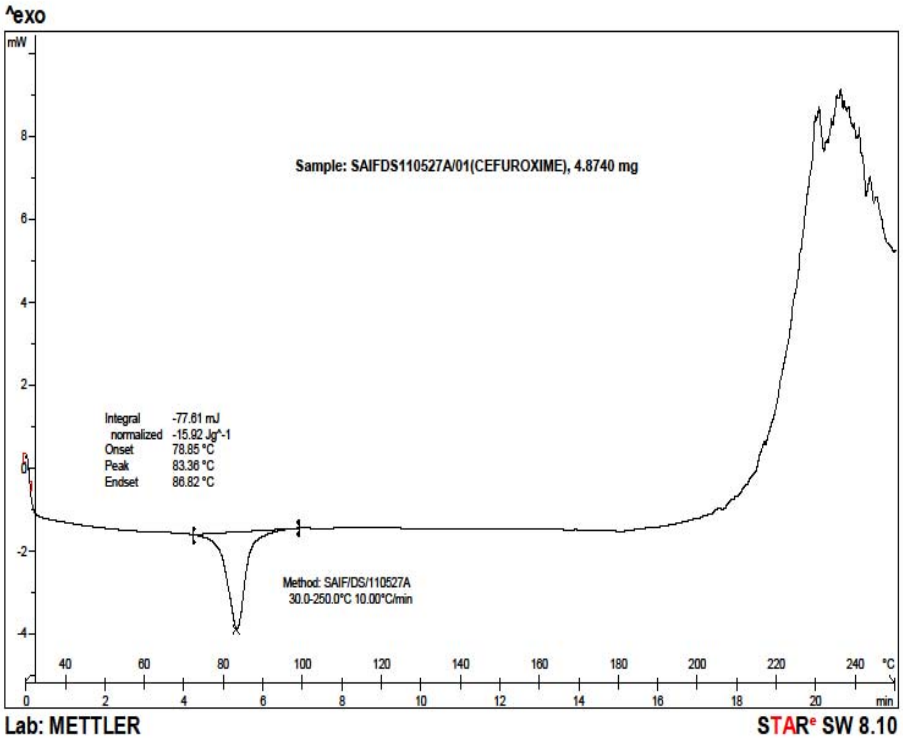


FIG 10: DSC DATA OF BETA CYCLODEXTRIN

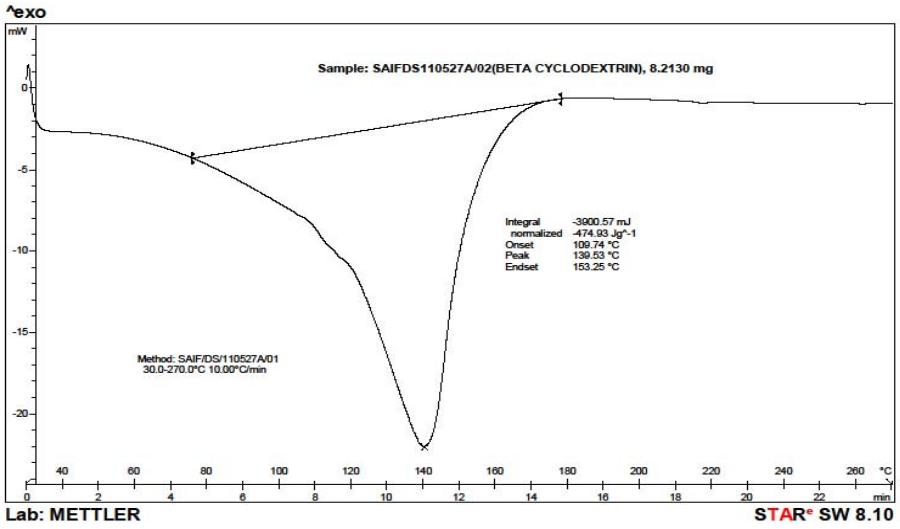
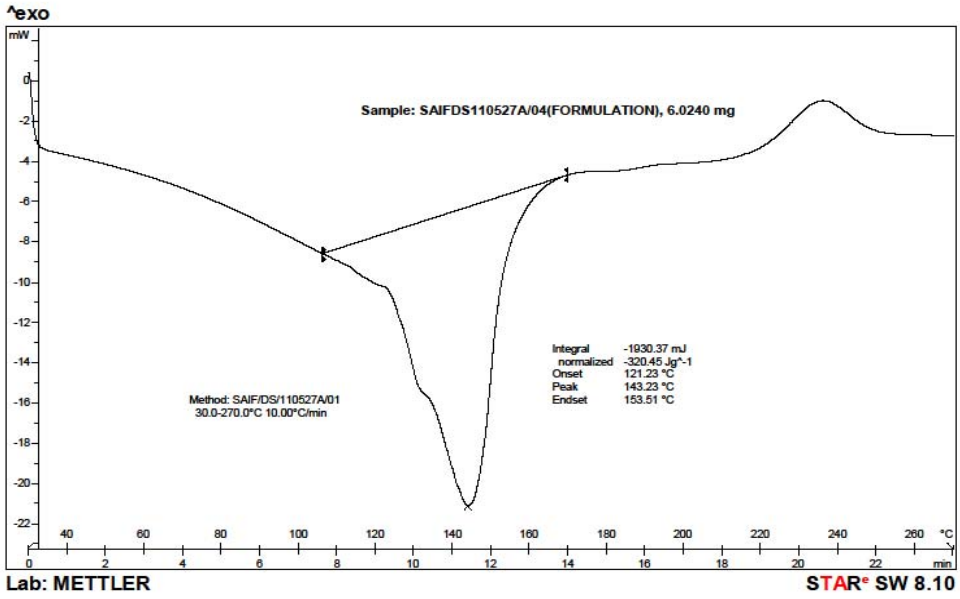


FIG 11: DSC DATA OF OPTIMISED FORMULATION



OBSERVATION & CONCLUSION

The thermogram of pure API shows a single sharp endothermic peak having a peak maximum of 83.36˚C with an onset temperature of 78.85˚C. DSC thermogram of complexing agent shows one endotherm of fusion, having a peak maximum of 139.53˚C. It showed a single, sharp, melting endotherm with an onset temperature of 109.74˚C. DSC curve of the optimised formulation shows a single endothermic peak of fusion, having a peak maximum of 143.23˚C.

From the above thermograms it was concluded that the disappearance of API peak as well as the beta cyclodextrin peak in the thermogram of optimised formulation confirms complexation between Cefuroxime axetil and Beta cyclodextrin.

8.7. pH STABILITY STUDY

The dry powder after reconstitution were packed in HDPE bottles of 30 ml capacity and stored at 2-8˚C. The pH of the formulation was checked for 10 days.

TABLE 28: pH STABILITY STUDY

DAYS	pH
Day 1	6.38
Day 2	6.09
Day 3	6.42
Day 4	6.55
Day 5	6.48
Day 6	6.32
Day 7	6.55
Day 8	6.46
Day 9	6.50
Day 10	6.50

8.8. SCALE UP STUDY

The trial P8 was selected as the lead for the scale up. The composition of scale up batch is listed below.

TABLE 29: COMPOSITION FOR SCALE UP

SL NO	INGREDIENTS	Qty/5ml(mg)	Qty/30ml(g)	Qty/Batch in g
	FOR COMPLEXATION			
1	Cefuroxime axetil	317.750	1.907	63.531
2	Beta cyclodextrin	706.358	4.238	110.409
3	Sodium lauryl sulphate	15.000	0.090	1.500
4	Water	100%	100%	100%
	FOR BLENDING			
5	CA:B CD Complex	1058.851	6.353	63.531
6	Sucrose	1840.149	11.041	110.41
7	Acesulfame K	25.000	0.150	1.500
8	Aspartame	35.000	0.210	2.100
9	Xatham gum	6.000	0.036	0.360
10	Tutti frutti flavour	35.000	0.210	2.100
		3000.000	18.00	180.000

The scale up batch was an extention of the trial. The dry powders were filled into HDPE bottles of 30 ml capacity using dry syrup filling machine. The cap was sealed by induction sealing.

8.9. STABILITY STUDIES

Short term accelerated stability studies were performed on the optimized oral suspension formulations packed in HDPE bottles of 30 ml capacity. Fifty oral suspensions were subjected to stability studies at 40^0C/75% RH in a stability chamber for a period of 2 months. Initial evaluation of the suspension was done and at the end of first and second

month the suspensions were again analyzed for its physical appearance, assay, water content and in vitro drug release profile.

Study conditions: 40^0C/75%RH

Packing: HDPE bottles of 30 ml

Equipment : Humidity chamber I- 0396

TABLE NO. 30: ACCELERATED STABILITY STUDY REPORT

PERIOD	Dissolution (%)	pH	Assay (%)	Appearance
INITIAL	75.77	6.38	98.42	White Colour
1st MONTH	76.2	6.40	98.27	White Colour
2nd MONTH	78.1	6.52	97.2	White Colour

Conclusion : The accelerated stability studies reveal that the formulation has not undergone any physical or chemical degradation during the period. There are no significant differences in the in vitro drug release, pH and the drug content of the optimized formulation.

ANTI MICROBIAL ASSAY OF CEFUROXIME AXETIL

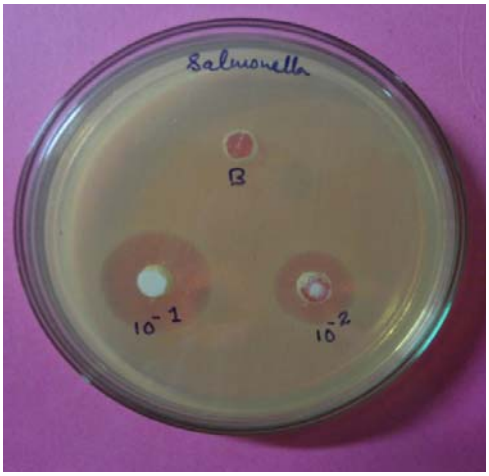
Three different wells were made in each petriplates for blank (B) and two dilutions($10^{-1}$and 10^{-2}).Test sample was serially diluted in saline upto 10^{-2} dilutions.

TABLE-31

Sl.No	Name of organism	Diameter of inhibition zones in different dilutions of sample	
		10^{-1}	10^{-2}
1	E.coli	28mm	18mm
2	Bacillus subtilis	23mm	9mm
3	Salmonella typhi	22mm	15mm


B. Subtilis
B
10^{-1}
10^{-2}


E. Coli
B
10^{-1}
10^{-2}


Salmonella
B
10^{-1}
10^{-2}

Conclusion

CONCLUSION

The bitter taste of drugs remains a big challenge to the pharma sector especially when it deals with oral pharmaceutical to paediatric population. Cefuroxime axetil is a betalactum antibiotic used for infections in the urinary tract, sinusitis, otitis media and so on. The highly bitter taste of drug reduces its patient compliance. In the present work the taste masking of the drug employed various techniques like masking with sweetener and flavour, drug particle coating with stearic acid and finally complexation with betacyclodextrin.

Of this, inclusion complex formation with betacyclodextrin proved to be highly efficacious, cost effective and simple method. The drug is entrapped within the hydrophobic core of cyclodextrin thus reducing the solubility of drug in saliva. The complex is thought to separate inside the gastric environment thus releasing the drug. The drug is better absorbed from the upper part of intestine.

The complexation method is the most simplest method. All the formulation parameters were crucially scrutinised and optimised the final formula. DSC data of drug, complexing agent and optimised formulation confirms complexation. The suspension was taken on a scale up quantity and charged for stability studies. The report of the same has been furnished. The suspensions were evaluated as per USP standards. The in vitro studies of the suspension concludes here. Thus an attempt to mask the bitter taste of second generation cephalosporin antibiotic has been made.

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