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(RESEARCH ARTICLE)

Quantification of cefixime drug substances in pharmaceutical formulations by analytical GC

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Abstract

The present study was conducted to develop and validate an analytical procedure for the determination of cefixime in Pharmaceutical Formulations. The analytical test attributes and evaluated as per the guidelines of ICH Q2 (R1). The method was validated for the determination of Assay in finished products of cefixime and the method validation parameters were evaluated for the analytical test attribute cefixime meets the acceptance criteria. The results obtained were within the specified limits and the samples were analyzed for test item concentration by Gas Chromatography.

Keywords: Cefixime; Validating the Assay; Gas Chromatography; ICH Q2 (R1)

1. Introduction

The improved controlled drug delivery system of the present invention is designed to deliver effectively a drug to a patient over a specific time period (temporal control) and from particular portion of the patients gastrointestinal tract (spatial control). The improved controlled drug delivery system avoids dose dumping and results in the most therapeutic administration of a particular drug to a particular person with a particular ailment. Various pharmacokinetic advantages like, maintenance of constant therapeutic level over a prolonged period of time and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. For the present study cefixime is selected as drug candidate, it fulfills the following characteristics which indicate its suitability for fabrication into the floating drug delivery system. Cefixime is a very poorly soluble in water after its oral administration; it is slowly and incompletely absorbed from the gastrointestinal tract, which resulting into the poor bioavailability i.e., 40-50%. (Aulton, et. al., 2000, Singh, e.t al., 2000, Atyabi, et. al., 1996). So, in order to improve the therapeutic effect of the drug by increasing its bioavailability, we are planning to formulate Cefixime gas powered systems for controlled release with increased gastric retention. The present development study of Cefixime in the form of tablet or capsule which provides a combination of spatial and temporal control of drug delivery to patients for effective therapeutic results (Okeke, et. al., 1998).

- Formulation of floating tablet containing Cefixime as a drug candidate which would remain in stomach or upper part of GIT for prolonged period of time, therefore the maximum drug release is maintained at desired site.
- Cefixime having good absorption in GIT.
- Cefixime having low pKa which remain unionized in stomach for better absorption.
- For beta-lactum antibiotics the pharmacodynamic parameter that best correlates with eradication is more than above the MIC (minimum inhibitory concentration). It means that the drug should remain in the body above MIC for longer time. Talwar et. al., developed a once daily formulation for oral administration of ciprofloxacin.

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The formulation was composed of 69.9% ciprofloxacin base, 0.34%sodiumalginate, 1.03%xanthan gum, 13.7% sodium bicarbonate and 12.1% cross linked polyvinyl pyrrolidone. Theviscolyzing agents initially and the gel forming polymer later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach or upper part of the small intestine (spatial control). The hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the drug. Baumgartner developed floating tablets of ciprofloxacin Hydrochloride offer a new possibility of treating the stomach infected with Helicobacter pylori (Baumgartner et. al., 2001). The objective of this study was to select suitable materials such as polymers hydroxyl ethyl cellulose (HEC), hydroxyl-propylcellulose (HPC), HPMCK4M and obtained controlled drug release for more than 8hr from non-disintegrated matrices plays an important role in prolonging gastric residence time.

Zou developed a floating-pulsatile drug delivery system intended forchronopharmaco therapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by burst release (Zou, et. al., 2008).

To overcome limitations of various approaches for imparting buoyancy, they generate the system which consist of three different parts a core tablet containing the active ingredients, an erodible outer shell and a top cover buoyant layer. The buoyant layer, prepared with methocel K4M,Carbopol, 934P, and sodium bicarbonate, provides buoyancy to increase the tension of the oral dosage form in the stomach. Developed formulations were evaluated for their buoyancy, mass degree of swelling, weight variation, hardness, thickness, friability, dissolution, pharmacokinetic parameters. Krogel developed floating-pulsatile drug delivery systems based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating (Krogel, et. al., 1999). Preliminary studies identified important core and coating properties for the two systems. For the floating system, a polymer coating with a high elongation value and high water-and low CO2 permeability's was selected (Eudragit® RL: acetyl tributyl citrate 20%, w:w), while for the pulsatile DDS, a weak, semi permeable film, which ruptured after a certain lag time was best (ethyl cellulose : dibutyl sebacate 20%, w:w). A polymer (cellulose acetate or hydroxyl propyl methyl cellulose) was added to the core to control the drug release. The time to flotation could be controlled by the composition and hardness of the tablet core and the composition and thickness of the coating. For the pulsatile system, a quick releasing core was formulated in order to obtain a rapid drug release after the rupture of the polymer coating. The lagtime prior to the rapid drug release phase increased with increasing core hardness and coating level. Badve developed a hollow calcium pectinate bead by simple process of acid-base reaction during ionotropic cross linking (Badve, e.t al., 2006).Invivo studies by gamma scintiography determined on rabbits showed gastro retention of beads up to5h.The floating beads provided expected two-phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer. This approach suggested the use of hollow calcium pectinate microparticles as promising floating-pulsatile drug delivery system forsite and time specific release of drugs acting as per chronotherapy of diseases. Dave optimized a gastro retentive drug delivery system of ranitidine hydrochloride. Guar gum, xanthan gum and hydroxyl propyl methyl cellulose were evaluated for gel-forming properties (Dave, et. al., 2004) Sodium bicarbonate was in corporated as a gas generating agent. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated. Full factorial design was applied to systemically optimize the drug release profile. The results of the full factorial design indicated that allow amount of citric acid and a high amount of stearic acid favours sustained release of ranitidine hydrochloride from a gastro retentive formulation. A theoretical dissolution profile was generated using pharmacokinetic parameters of ranitidine hydrochloride. The similarity factor was applied between the factorial design batches and the theoretical dissolution profile. No significant difference was observed between the desired release profiles. These studies indicate that the proper balance between a release rate enhancer and a release rate retardant can produce a drug dissolution profile similar to a theoretical dissolution profile. Xiaoqiang studied three floating matrix formulations of phenoporlamine hydrochloride based on gas forming agent. Hydroxy propyl methylcellulose K4MandCarbopol971P NF was used in formulating the hydro gel drug delivery system (Xiaoqiang, et. al., 2006). Incorporation sodium bicarbonate into matrix resulted in the tablet floating over simulated gastric fluid for more than 6 hr. The dissolution profiles of all tablets showed non-Fickian diffusion in simulated gastric fluid. Invivo evaluations of these formulations of phenoporlamine hydrochloride were conducted in six healthy male human volunteers to compare the sustained release tablets with immediate release tablets. Yang developed as well able asymmetric triple-layer tablet with Floating ability using hydroxyl propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the ratecontrolling polymeric membrane excipients (Yang, et. al., 1999). Tetracycline and metronidazole were in corporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The flotation was accomplished by incorporating gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2ratios) along with the polymers. Nur developed floating tablets of captoprilusing HPMC (4000and 15000cps) and carbopol934P. Invitro studies revealed that buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles and tablet porosity (Nur, et. al., 2000). A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24hrs controlled release from the dosage form of captopril was achieved. Ozdemir developed floating bilayer tablets with controlled release for furosemide (Ozdemir,

et. al., 2000). One layer contained the polymers HPMC 4000, HPMC 100 and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The in vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours. Nur developed floating tablets of captopril using HPMC (4000 and 15000cps) and carbopol 934P. Invitro studies revealed that buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles and tablet porosity. A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24hrs controlled release from the dosage form of captopril was achieved. Pentewar developed a floating drug delivery system of cefixime trihydrate matrix tablet using polymer blends of different viscosity grades of HPMC (Pentewar, et. al., 2010). Gas producing agent used was sodium bicarbonate. The effect of citric acid on the drug release was also investigated by dissolution studies.

- Name of the Product: Cefixime (Cephalosporin product)
- Therapeutic Category: Antibacterial
- Storage condition: Store in an air tight container below 25°C

Table 1 Gas Chromatogram (Method)

Formula	**Molecular Formula : ************ **Formula Weight : **********
Sampling procedure	Sampling to be performed as per current version of SOP No.KQC509
Testing procedure	Testing to be performed as per STP as per current version of TFPCCM13
Storage Conditions	Store in an air tight container below 25°C Store in an air tight container at 2-8°C for Micronized material
Handling Precautions (If Any)	--
Retest Period	3 years (Expiry date)
Packing Instructions	Pack the material in to double lined LLDPE bag. Close the inner LLDPE bag with Plastic Strip Seals. Close the outer LLDPE bag with Plastic Strip Seals, after removing the trapped air from the bag as far as possible. For Micronized material after twist tying the outer LLDPE bag with plastic strip seal then seal in the triple laminated bag sealer. Affix product label duly filled on to the outer bag. Close the HDPE container and tighten the lid with the Stainless steel seals. Secure the drum with Stainless steel seals with company logo and serial number inscribed.

Table 2 Test procedure

Test no.	**Test**	**Specification**
1	Residual solvents (byGC)ppm* Methanol Ethanol Ethyl acetate	Not more than 3000 ppm Not more than 5000 ppmNotmorethan5000ppm

2. Residual Solvents

2.1. (By GC) Equipment

Gas chromatograph system with Flame Ionization Detector (Shimadzu 2010 or equivalent) Head space auto sampler (AOC 5000 or equivalent) Data handling system (GC solution) Reagents:

- Methanol: AR grade
- Ethanol: AR grade
- Ethyl acetate: AR grade
- N,N-Dimethylformamide (DMF):
- AR grade Sodium Chloride:
- AR grade:
- Water: Mill-Q grade

Note: purity of N, N-Dimethylformamide (DMF) and water used in the analysis should be checked for any impurities eluting at the same relative retention times as that of different residual solvents analyzed by this method.

2.2. Gas Chromatographic Conditions

Column : DB-1701 [14% Cynopropyl phenyl and 86% dimethyl polysiloxane] capillary column of 30m length, 0.32 mm I.D. And film thickness 1.0□m

- Detector : FID
- Attention : 0
- Carrier gas : Nitrogen
- Purge gas : Nitrogen
- Flow : Hydrogen - 60 kpa equivalent to 50ml.min Zero air- 50 KPA equivalent to 500ml/min Nitrogen - 100 kpa equivalent to 40ml/min
- Column Flow (pressure) : 20 kPa equivalent to 0.53 ml/min.
- Split : 1:10
- Stop time : 32 minutes
- Temperature : 40°c
- Capillary Injector : 220°C
- Detector : 260°C
- 15°C/min.
- Column oven temp: 40°C (15 min.) 220°C (5 min.)

Table 3 Head Space Condition

Cycle	HS-inj
Syringe	2.5ml-HS.
Sample volume	1ml
Incubationtemperature:80°C	
Incubation time	20min.
Agitation speed	500rpm
Syringe temperature	110°C.

- Fill speed : 1 ml/sec.
- Pull-up delay : 500 msec.
- Inject to : GC-inj.
- Inject speed : 1 ml/sec.

2.3. Preparation of solutions

2.3.1. Blank solution

Add 0.5 ml of dimethyl formamide (DMF) and 0.5 ml of water to the headspace vial containing about 0.5 g of sodium chloride and seal the vial immediately.

2.3.2. Preparation of Standard solution

Solution A

Weigh accurately and transfer about 0.3 g of Ethyl acetate, into a 10 ml volumetric flask containing 5 ml of DMF and make up to volume with the same DMF. Solution B: Weigh accurately transfers about 0.3 g of Methanol, 0.5 g of Ethanol, into a 50 ml volumetric flask containing about 25 ml of DMF and make up to volume with the same DMF.

Solution C

Take 0.5 ml of solution A and 0.25 ml solution B into a 25ml clean dry Volumetric flask contain about 15 ml DMF, mix and make up to volume with the same DMF.

Transfer 0.5 ml of the solution C to the headspace vial containing about 0.5 g of sodium chloride. Add 0.5 ml of water and seal the vial immediately.

Sample solution

Transfer about 0.1 gm of Cefixime weighed accurately, to the headspace vial containing about 0.5 gm of sodium chloride. Add 0.5 ml of DMF and 0.5 ml of water and seal the vial immediately.

2.4. Evaluation Blank

Place the sealed vial of blank solution in the sample tray and run the headspace analyzer, record the chromatogram. No interfering peak should be observed at the retention time of analyte peaks.

2.5. Evaluation of System Suitability

Place sealed vial of standard solution in the sample tray and run the headspace analyzer, record the chromatogram. No interfering peak should be observed at the retention time of analyte peaks.

2.6. System Suitability

The resolution between any two analytes in the standard solution is not less than 2.0 places the sealed vials of standard solution, in six replicate in the sample tray and run the headspace analyzer. Record the chromatograms and measure the peak areas of analytes. RSD for the peak area of six replicate injections of the standard solution is not more than 10.0 %.

3. Results

3.1. Procedure

Place the sealed vials of sample solution in duplicate in the sample tray and run the headspace analyzer. Record the chromatograms and measure the peak areas of analytes.

The retention time of N, N-Dimethyl formide is about 27 min.

Table 4 Elution Order

Sr. No.	Name	RRT
1	Methanol	~0.28
2	Ethanol	~0.36
3	Ethyl Acetate	~0.62
4	N,N-Dimethylformamide	=1.00

Calculation: For residual solvent content (ppm) $\frac{ATDS_PP_X}{AS\ DT} \times \frac{10^6}{100}$

Whereas

- AT: Average area of test sample
- AS: Average area of standard solvent
- DS : Dilution of standard solution
- DT : Dilution of test sample P: Purity of standard

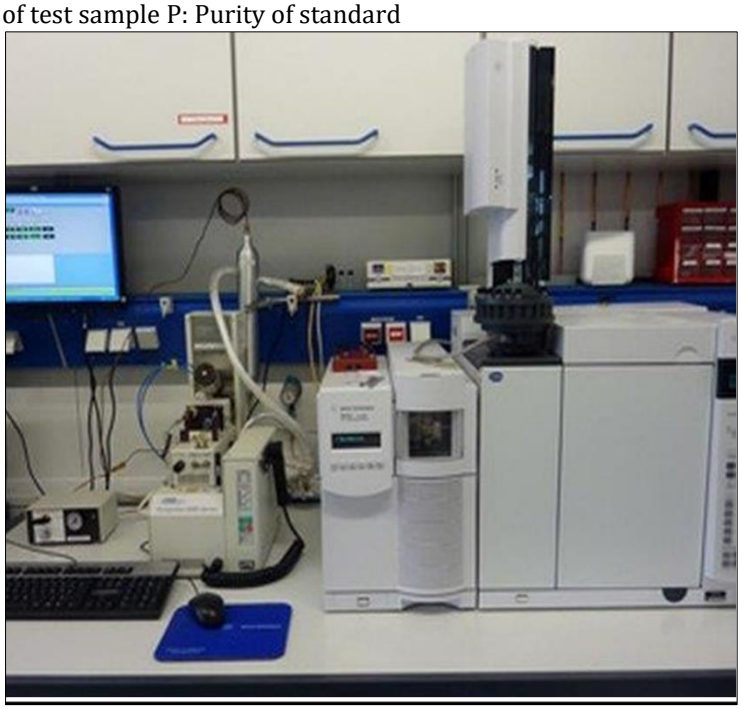

Figure 1 Gas chromatogram (Photograph)

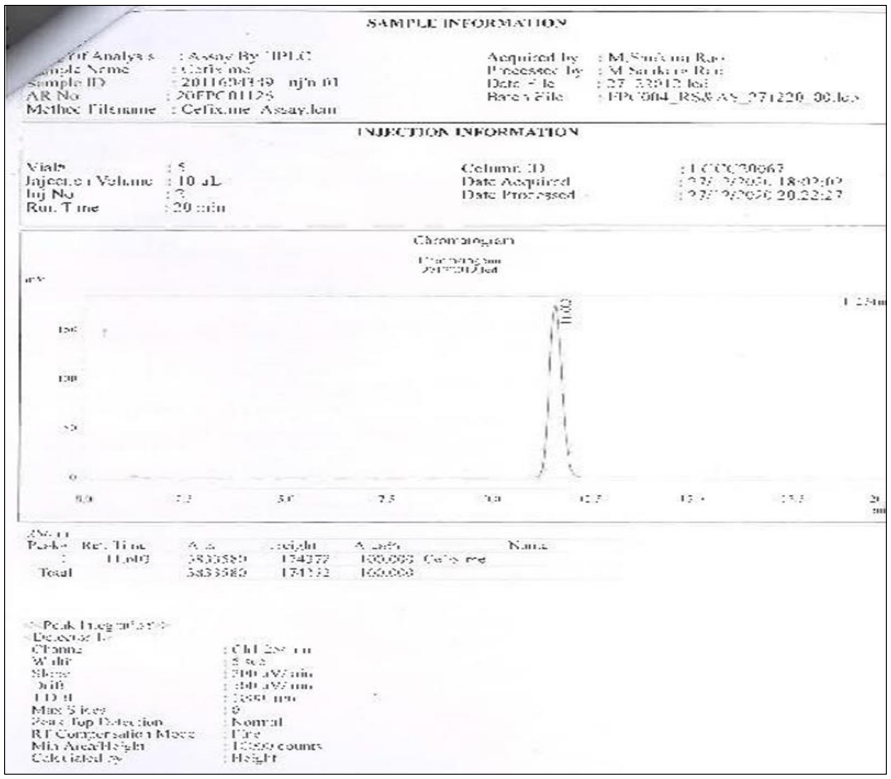

Figure 2 Chromatograms

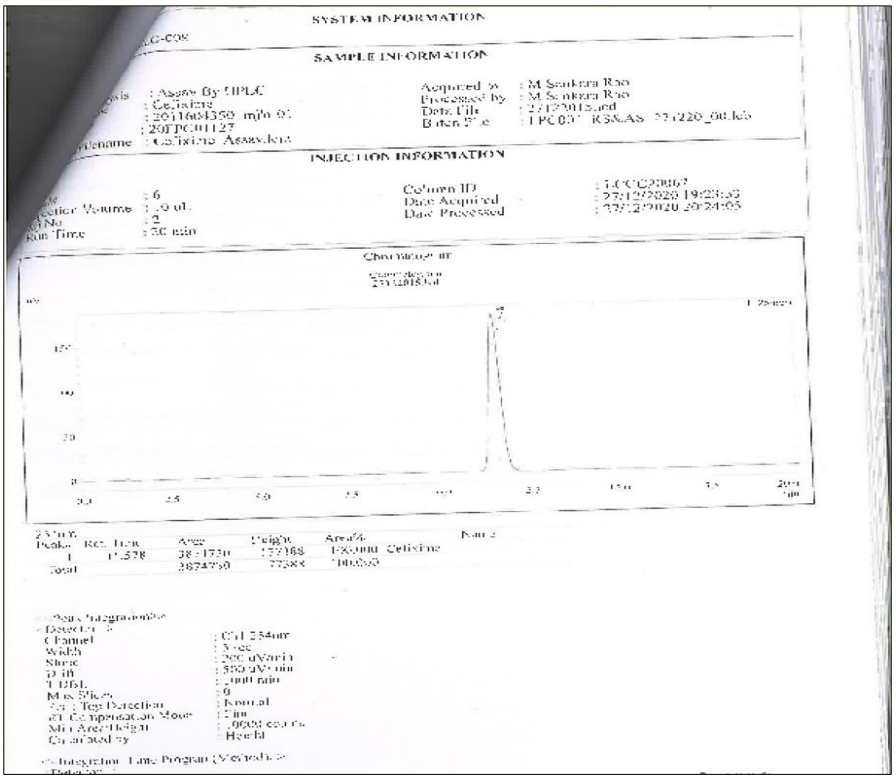

Table 5 Analytical results

Experimental Results			Results		
Test No	**Test**	**Specification**	**Ist Batch**	**IInd Batch**	**IIIrd Batch**
1.	Description	A white to light yellow, crystalline powder.	Light yellow crystalline powder	Light yellow crystalline powder	Light yellow crystalline powder
2.	Solubility	Soluble in methanol and in propylene glycol; slightly soluble in alcohol, in acetone, and in glycerin; very slightly soluble in 70%sorbitol and in octanol; practically insoluble in ether, in ethyl acetate, in hexane, and in water.	Complies	Complies	Complies
3.	Identification (ByIR)	IR spectrum must exhibit maxima at the same wave numbers as the Cefixime working standard spectrum.	Complies	Complies	Complies
4.	Specific rotation (°)(Testsolution10mg/ml, in sodium bicarbonate solution (2 in100ml) (on anhydrous basis)	Between-75and-88	-82°	-83°	-83.0°
5.	Crystallinity	The particles should show bi refringence and extinction positions	Complies	Complies	Complies

6.	pH (0.7 mg of cefixime per ml solution in water)	Between2.6and4.1	3.192	3.186	3.095
7.	Water(%w/w) (Determinedon0.3g)	Between9.0to12.0	11.4	11.3	11.4
8.	Chromatographic purity(By HPLC, %w/w)Any Individual impurity Total impurities	Not more than 1.0Notmorethan2.0	0.17 0.88	0.18 0.88	0.17 0.79
9.	Assay as Cefixime (By HPLC, µg/mg)(Anhydrous basis)	Notlessthan950andNot more than1030	996	987	992
10.	Bulk Density*Untapped density Tapped density	Report results Report results	0.81 0.91	0.81 0.91	0.77 0.86
11.	Particle size* By Sieve (% w/w) /By Malvern(µ)	Report results	#40(P)-100%	#40(P)-100%	#40(P)-100%

Table 6 Experimental Results

Experiment Results				**Results**		
Sr. No	**Parameters**		**Limit**	**Ist Batch**	**IInd Batch**	**IIIrd Batch**
1.	Residual solvents (by GC) ppm					
	a.	Methanol	Not more than 3000	29	28	24
	b.	Ethanol	Not more than 5000	81	86	84
	c.	Ethyl Acetate	Not more than 5000	691	698	823

4. Discussion

- After concluding this product manufacturing process if it is deviate in the standard parameters like temperature, raw material charging quantity, vacuum, pressure, maintenance, pH it is directly impact on the product quality and yield range.
- In analysis suitable column should be use (like IR, GC, HPLC and pH) otherwise it was failed in the final analysis.
- It may also use for the formulation of cefixime tablets and other dosages.
- It is prescribed in mg daily dosage as per regulatory authorities.

4.1. Cefixime uses

- Cefixime is used to treat certain infections caused by bacteria such as bronchitis (infections of the airway tubes leading to the lungs), gonorrhoea (sexually transmitted disease) and infections of the ears, throat, tonsils and urinary treat, cefixime is in a class of medications called cephalosporin antibiotics.
- Antibiotics such as cefixime will not work for cold, flu, or other viral infections. Using antibiotics when they are not needed increases yours risk of getting an infection later that resists antibiotics treatment.

4.2. How this medicine should be used

- Cefixime comes as a tablet, chewable tablet, capsule, and suspension (liquid) to take by mouth. It is usually taken with t without food every 12 or 24 hours. When used for the treatment of gonorrhoea it may be given in a single dose. Take cefixime at around the same times every day follow the direction on you prescription label carefully, and ask your doctor or pharmacist to explain any part you do not understand. Take cefixime exactly as directed. Do not take more or less of it or take it more often than prescribed by your doctor.
- Shake the suspension well before each use to miss the medication evenly.
- If you are taking the chewable, tablet, chew these tablets completely before swallowing, do not swallow the chewable tablets whole. If you have trouble chewing you may crush them before swallowing.
- Cefixime tablet come with a line down the middle of the tablet. If your doctor tells you to take half a tablet break

it carefully on the line. Take half the tablet as directed, and save the other half for your next dose.

- Different cefixime products are absorbed by the body in different ways and cannot be substituted for one another. If you needed to switch from one cefixime product to another, you doctor may need to adjust your dose.
- You should begin to feel batter during the first few days of the treatment with cefixime. If you symptoms do not improve or get wore, call your doctor.
- Continue to take cefixime even if you feel batter. If you stop taking cefixime too soon or skip doses, your infection may not be completely treated and the bacteria may become resistant to antibiotics.

4.3. How to take Cefixime medicine

- Before you start taking Cefixime, read the manufacture's printed information leaflet from inside your pack. The manufacture's leaflet will give you more information about the antibiotic and a full list of side-effects which you may experience from taking it.
- You should take Cefixime exactly as your doctor tells you to. The usual dose for adults and for children over 10 years of age is 1 or 2 tablets daily, you will be told whether to take this as a single dose each day, or as two doses, morning and evening. The dose for younger children is calculated from this age or weight. Your doctor will tell you what dose is right for you, and this information will printed on the labels of the pack to remind you.
- You can take Cefixime before or after food, swallow the tablets whole with a drink of water. Of you are taking more than on dose a day, space your doses out, evenly though out the day.
- Keep taking the antibiotic until the course is finished unless you are told to stop by your doctor, taking the full course is important (even if you feel your infection has cleared up) in order to prevent the infection from coming back. If you forget to take a dose, take one as soon as you remember, try to take the correct number of doses each day.

4.4. Special Precautions (Before Taking Cefixime)

- Tell your doctor and pharmacist if you are allergic to Cefixime: other cephalosporin antibiotic such as cefaclor, Cefadroxil, cefazolin, cefdinir, cefepime, cefuroxime, cephalexin Pencillin antibiotic, or any other medication.
- Tell your doctor if you are pregnant, plan to become pregnant, or are breast feeding. If you become pregnant while taking Cefixime call your doctor.
- If you have phenylketonuria (PKU, an inherited condition in which a special diet must be followed to prevent mental, retardation), you should know that Cefixime chewable tablets are sweetened with that forms phenylalanine.

4.5. Storage condition

Keep this medication in the container it come in, tightly closed, and out of reach of children. Store the tablets, chewable tablets, and capsules at room temperature and away from excess heat and moisture. Keep liquid medicine at room temperature or in the refrigerator, closed tightly, and dispose of any unused medication after14 days.

4.6. Side effects

- Stomach upset/ pain, diarrhoea, nausea, gas, headache, or dizziness may cause. If any of the effects persist or worse, notify your doctor (or) pharmacist promptly.
- It should not be take long time medicine and without doctor prescription.

4.7. Diarrhoea

Drink plenty of water to replace any lost fluids. If the diarrhoea contains for longer than 24 hours or becomes severe or contains blood, let your doctor know. Feeling sick:

Stick to simple foods. If you are not already doing so, try taking your does after meals to see if it helps.

4.8. Headache

Drink plenty of water and ask your pharmacist to recommend a suitable painkiller. If the headache continue, let you doctor know.

4.9. Feeling dizzy

Do not drive and do not use tools or machines until you feel well.

4.10. Important information about all medications

- Never take more than the prescribed dose. If you suspect that you or someone else might have taken an over dose of this medicine, go to the accident and emergency department of your local hospital. Take the container with you, even it is empty.
- This medicine is for you. Never give it to other people even if their condition appears to be the same as yours.
- If you buy any medicine check with a pharmacist that they are safe to take with your other medicines.
- If you are having an operation or any dental treatment tell the person carrying out the treatment which medicine you are taking.
- Do not keep out-of-date or unwanted medicine. Take them to your pharmacy which will dispose of them for you.
- If you have any question about this medicine ask your doctor.

4.11. Other information of this medicine

- Cefixime is also sometimes used to treat serious infections is Pencillin allergic patients, pneumonia, shigella (an infection that cause severe diarrhoea) salmonella (an infection that cause severe diarrhoea) and typhoid fever (a serious infection that is common in developing countries). Talk to your doctor about the risk of using this medication for your condition.
- This medication may be prescribed for other uses ask your doctor orpharmacist for more information.
- Cefixime may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away, diarrhoea, stomach pain, gas, heart burn, nausea, vomiting.
- Some side effects can be serious. If you experience any of the following symptoms, call your doctor immediately or get emergency medical treatment.
- Water or bloody stools, stomach cramp or fever during treatment or for up to two or more months after stopping treatment

  - rash
  - Itching
  - Hives
  - Difficulty breathing or swallowing
  - Wheezing
  - Swelling of the face
  - Throat
  - Tongue
  - Lips and eyes
  - A return of sore throat
  - Fever
  - Chills or other signs of infections

4.12. If it forgets a Dose

Take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule, do not take double dose to make up for missed one

5. Conclusion

From the comprehensive reviewed data and its subsequent evaluation during the Cefixime (Cephalosporins) project work. It is an antibiotic drug, it is demonstrated that the process is robust as all the quality attributes are found within the acceptance criteria and statistical controls as shown in the experimental results. Then we can distribute the product to the formulators. This is considering that the process is adequate and capable of producing the product Cefixime (Cephalosporin antibiotic) to meet the predefined specification.

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