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Analytical Validation and Development of Cefixime Drug Substances in Pharmaceutical Formulations by Gas Chromatography

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KEYWORDS
Cefixime, Validating the Assay, Chromatography, ICH Q2 (R1)

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 Chromatography.

INTRODUCTION

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).

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. The viscolyzing 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-propyl cellulose (HPC), HPMCK4M and obtained controlled drug release for more than 8hr from non disintegrated matrices plays an important role in prolonging gastric residence time.

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

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with a high elongation value and high water-and low CO2 permeability's was selected (Eudragit® RL: acetyltributyl 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 : dibutylsebacate 20%, w:w).

Badve developed a hollow calcium pectinate bead by simple process of acid-base reaction during ionotropic cross linking (Badve, e.t al.,2006). 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. Xiaoqiang studied three floating matrix formulations of phenoporlamine hydrochloride based on gas forming agent. Hydroxy propyl methylcellulose K4M and Carbopol 971P NF was used in formulating the hydro gel drug delivery system (Xiaoqiang, et. al., 2006). 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 rate controlling polymeric membrane excipients (Yang, et. al., 1999). Nur developed floating tablets of captopril using 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). 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. 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.

METHODOLOGY

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

RESIDUAL SOLVENTS (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.

Gas Chromatographic Conditions:
Col DB-1701 [14% Cynopropylphenyl 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
	: 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.)

EXPERIMENTAL

Head Space Condition:

Cycle	: HS-inj
Syringe	: 2.5 ml -HS.
Sample volume	: 1ml
Incubation temperature: 80°C	
Incubation time	: 20 min.
Agitation speed	: 500 rpm
Syringe temperature	: 110°C.
Fill speed	: 1 ml/sec.
Pull-up delay	: 500 msec.
Inject to	: GC-inj.
Inject speed	: 1 ml/sec.

Preparation of solutions:
Blank solution:
Add 0.5 ml of dimethyl formamide (DMF) and 0.5 ml of water to the headspace vialcontaining about 0.5 g of sodium chloride and seal the vial immediately.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4s), 336-342 | ISSN:2251-6727

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 sameDMF.

Solution C**:** Take 0.5 ml of solution A and 0.25 ml solution B into a 25ml clean dry Volumetricflask 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 sodiumchloride. 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 vialimmediately.

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.

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.

Procedure:

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

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

Elution Order:

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

Chromatograms

Journal of Chemical Health Risks

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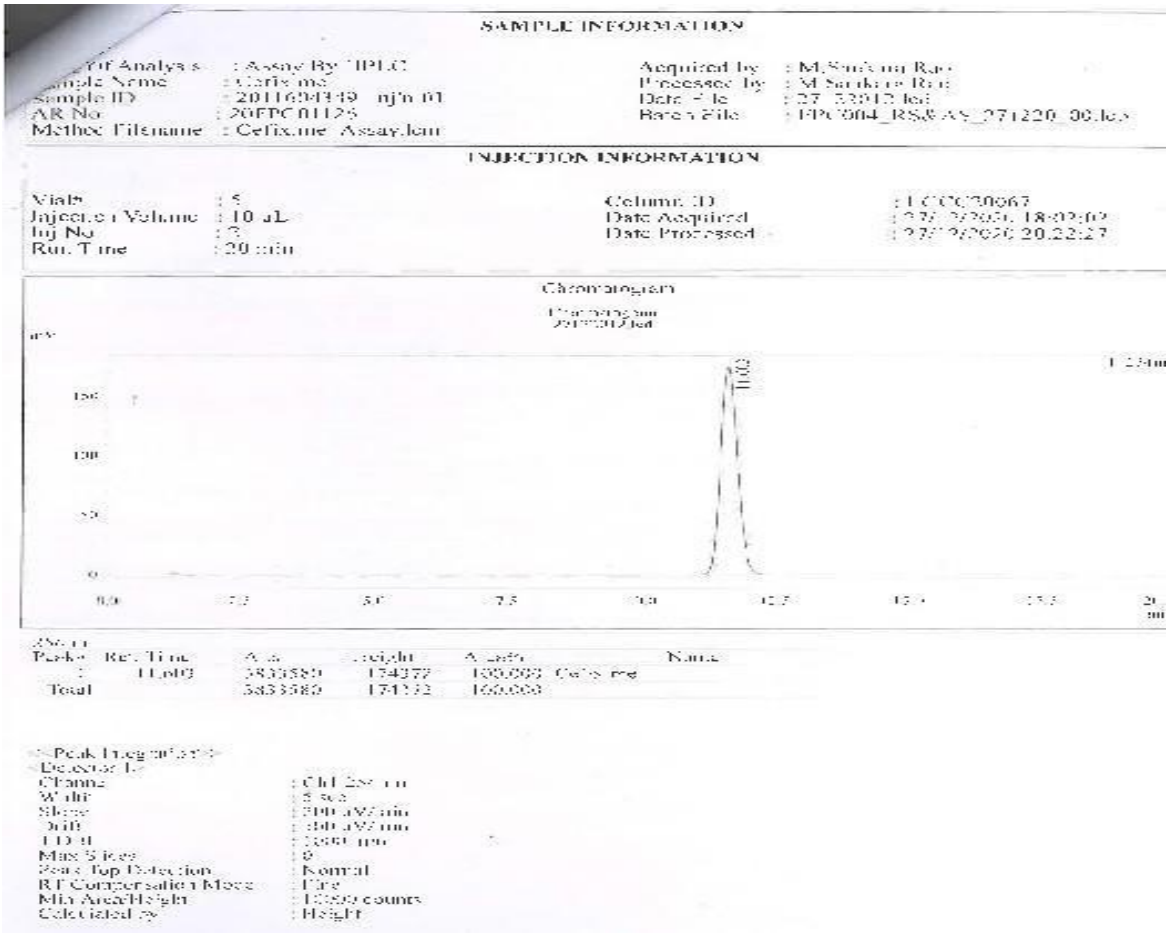
JCHR (2023) 13(4s), 336-342 | ISSN:2251-6727



SAMPLE INFORMATION

Type of Analysis	: Assay By HPLC	Acquired by	: M.Sasikumar Rao
Sample Name	: Cefixime	Processed by	: M.Sasikumar Rao
Sample ID	: 20116041949 mj'n 01	Data File	: 27_53012.lcd
AR No.	: 20FPC 01125	Batch File	: HPC004_RS&AS_271220_06.lcs
Method Filename	: Cefixime Assay.lcm		

INJECTION INFORMATION

Vials	: 5	Column ID	: LCCC20067
Injection Volume	: 10 uL	Date Acquired	: 27/12/2020 18:03:02
Inj No	: 3	Date Processed	: 27/12/2020 20:22:27
Run Time	: 20 min		

Chromatogram

mV

Peak#	Ret. Time	Area	Height	Area%	Name
1	11.603	5833580	134377	100.000	Cefixime
Total		5833580	134377	100.000	

Peak Integration

Detector 1

Channel	: Ch1 288 nm
Width	: 5 sec
Slope	: 200 uV/min
Drift	: 300 uV/min
T.D.F	: 2000 mV
Min Size	: 0
Peak Top Detection	: Normal
RF Compensation Mode	: Fire
Min Area/Height	: 10000 counts
Calculated by	: Height

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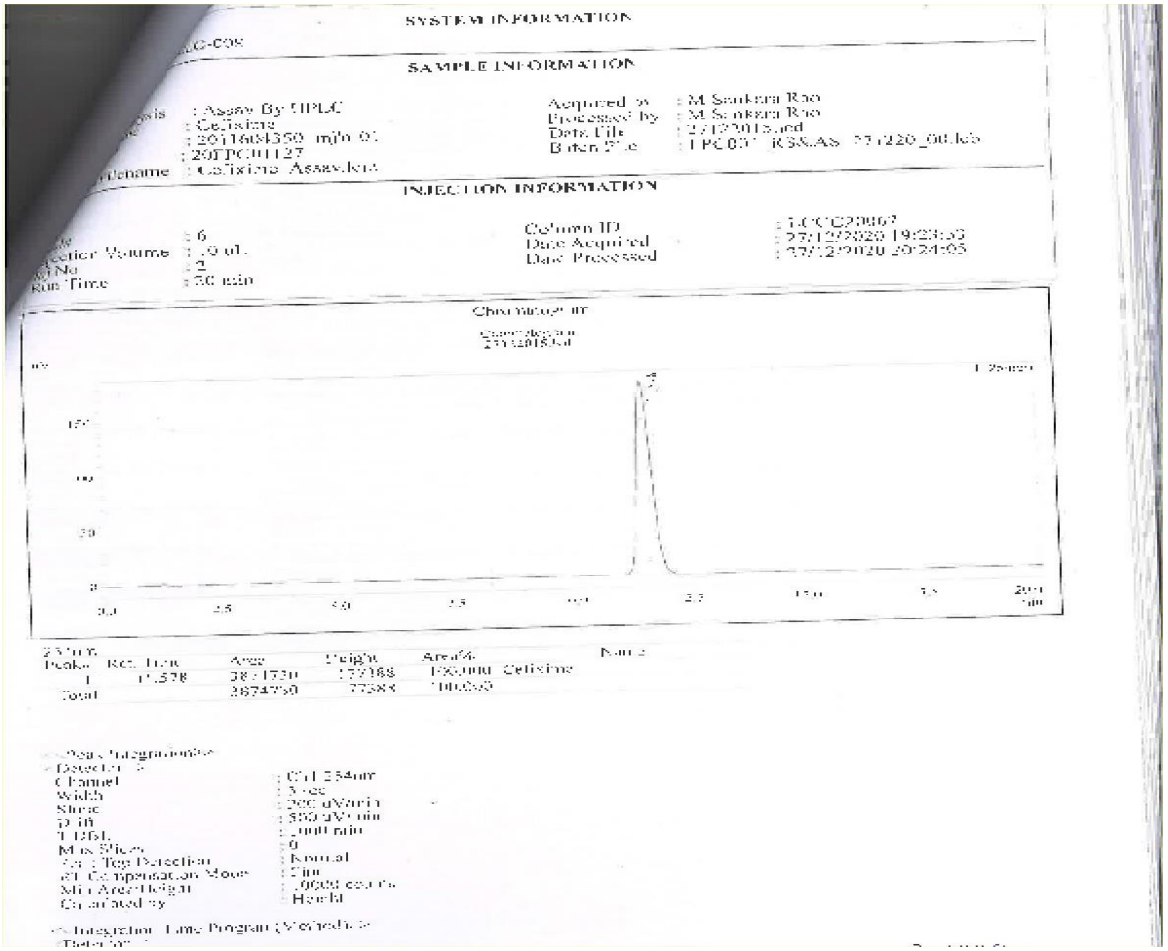
JCHR (2023) 13(4s), 336-342 | ISSN:2251-6727



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 (By IR)	IR spectrum must exhibit maxima at the same wave numbers asthe Cefixime working standard spectrum.	Complies	Complies	Complies
4.	Specific rotation (°) (Testsolution 10 mg/ml, in sodium bicarbonate solution (2 in100ml) (on anhydrous basis)	Between -75 and -88	-82°	-83°	-83.0°
5.	Crystallinity	The particles should show birefringence and extinction positions	Complies	Complies	Complies
6.	pH (0.7 mg of cefixime per ml solution in water)	Between 2.6 and 4.1	3.192	3.186	3.095
7.	Water (% w/w)	Between 9.0 to 12.0	11.4	11.3	11.4

Journal of Chemical Health Risks

www.jchr.org

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	(Determined on 0.3g)				

Experimental Results			Results		
Test No	Test	Specification	Ist Batch	IInd Batch	IIIrd Batch
8.	Chromatographic purity(**By HPLC**, % w/w) Any Individual impurityTotal impurities	Not more than 1.0Not more than 2.0	0.17 0.88	0.18 0.88	0.17 0.79
9.	Assay as Cefixime (ByHPLC, µg/mg) (Anhydrous basis)	Not less than 950 andNot more than 1030	996	987	992
10.	Bulk Density* Untapped densityTapped density	Report resultsReport 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%

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

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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Journal of Chemical Health Risks

www.jchr.org

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