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FORMULATION AND CHARACTERIZATION OF AZTREONAM IV INFUSION

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ABSTRACT

Intravenous fluid administration should be considered as any other pharmacological prescription. There are three main indications: resuscitation, replacement, and maintenance. Moreover, the impact of fluid administration as drug diluent or to preserve catheter patency should also be considered. As for antibiotics, intravenous fluid administration should follow the four Ds: drug, dosing, duration, de-escalation. Among crystalloids, balanced solutions limit acid–base alterations and chloride load and should be preferred, as this likely prevents renal dysfunction. Among colloids, albumin, the only available natural colloid, may have beneficial effects. The last decade has seen growing interest in the potential harms related to fluid overloading. In the fluid management that maintains adequate organ perfusion while limiting fluid administration should represent the standard of care. Protocols including a restrictive continuous fluid administration alongside bolus administration to achieve hemodynamic targets have been administered.

Keywords: Formulation, intravenous, infusion, Aztreonam.

INTRODUCTION

The first known attempt at IV therapy was in 1658 when Sir Christopher Wren designed an IV administration set with a quill and a pig's bladder to instill wine, ale, and opium into a dog's veins. About six years later, J.D. Major attempted to inject impure compounds into human veins with devastating results. By the 18th century, O'Shaughnessy and Latta were credited for treating cholera patients with intravenous fluids [1]. In order to accomplish this, Latta used a small silver tube attached to a syringe filled with a hypertonic solution of sodium, chloride and bicarbonate [2].

Drugs may be administered to patients by one of several routes, including oral, topical, or parenteral routes of administration. Examples of parenteral routes of administration include intravenous, subcutaneous, and intramuscular. Intravenous (IV) drug solutions may be given either as a bolus dose (injected all at once) or infused slowly through a vein into the plasma at a constant or zero-order rate. The main advantage for giving a drug by IV infusion is that IV infusion allows precise control of plasma drug concentrations to fit the individual needs of the patient [3].

Intravenous fluid therapy is essential when clients are unable to take sufficient food, medications and fluids orally. Intravenous therapy is an efficient and effective method of supplying fluids directly into the intravascular fluid compartment and replacing electrolyte losses. IV solutions can be classified as isotonic, hypotonic and hypertonic depending on their purpose. Table 1 illustrates different types of IV fluids, and outlines nursing implications for each category of IV solution.

The goal of all IV therapy is to maintain fluid and electrolyte balance and/or the delivery of IV medication. Monitoring a gravity-drip IV infusion, and discusses rationale. Intravenous pumps provide more accuracy and safety and should be used whenever possible [4].

AZTREONAM

- Aztreonam among others, is an antibiotic used primarily to treat infections caused by gram-negative bacteria such as *Pseudomonas aeruginosa* [5].
- This endometritis, intra-abdominal infections, pneumonia, urinary tract infections, and sepsis.
- It is given by intravenous or intramuscular injection or by inhalation [6].

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Mechanism of Action

Aztreonam is similar in action to penicillin. It inhibits synthesis of the bacterial cell wall, by blocking peptidoglycan crosslinking. It has a very high affinity for penicillin-binding protein-3 and mild affinity for penicillin-binding protein-1a. Aztreonam binds the penicillin-binding proteins of Gram-positive and anaerobic bacteria very poorly and is largely ineffective against them [7, 8]. Aztreonam is bactericidal, but less so than some of the cephalosporins.

Materials and Method

Aztreonam was purchased from Lupin Pharmaceuticals, Tween 80 was purchased from Reachem Laboratories Chem. Pvt. Ltd. Chennai, Propylene Glycol was purchased from Crystal Chemical Tirunelveli.

METHODOLOGY

Assay of the drug content:

The content of CA in the suspensions was determined by using a SPD- 10A VP UV-Visible spectrophotometer. The UV detector was operated at 278nm. Solutions of floating tablet of CA Standard were prepared at a concentration of about 0.1 mg/ml of CA was comparatively studied with test tablets [9].

In vitro dissolution

In vitro dissolution behaviors of the two kinds of CA dry suspensions and its commercial dry suspensions were investigated using a Chp2010 type 2 dissolution apparatus (paddle method), and all the test were carried out in triplicate. A volume of 900ml pH 7.0 phosphate buffer was used as the release medium and the temperature was maintained at 37±0.5ºc with a paddle speed of 50rpm/min. A certain amount of dry suspensions equivalent to 125mg CA were used in all of the dissolution testes. At pre-determined time intervals (5,10,20,30,40 min), an aliquot of 5ml of the release medium was withdrawn and passed through a 0.22μm filter immediately. An equal volume of fresh medium was replaced. The concentration of CA suspension filtrate was determined using a UV spectrophotometer (Beijing Rayleigh Analytical instrument co.) at 280nm.

The dissolution of commercial dry suspension and dry suspensions prepared by wet granulation method and solid dispersion method were performed in pH 7.0 phosphate buffer and the corresponding profiles Both formulations are higher and faster release than that of the commercial suspension. The solid dispersion suspension displayed a significant improvement in dissolution rate with more than 70% of the drug dissolved within 20 min, owing to the amorphous state of drug in the solid dispersion. In comparison with the self-made formulations, the commercial dry suspension showed a lower and slower release, and only around 50% of the drug dissolved within 20 min.

Modulated Differential Scanning Calorimetry (MDSC)

The thermal analysis was carried out on DSC, TA Q1000. The thermogram was recorded from -20^{0}C to 90^{0}C under the nitrogen flow of 50 mL/min at a heating rate of 10^{0}C per minutewith a modulation temperature of 1^{0}C per min.

Weighed about 15 mg sample into aluminum pan and distributed uniformly as a thin layer. The glass transition was recorded as the inflection point up to the step changed base line.

The heat flow was calibrated by enthalpy of indium (28.51J/g) or by the specific heat capacity of Sapphire. The specific heat method used the specific heat of sapphire over a user-defined temperature range. The baseline and sample curves were measured and the calibration was then built automatically. The calibration was checked before running samples by measuring the melting enthalpy of Indium by using the same instrumental parameters [10].

Table 1: Formula for iv infusions of aztreonam

S.no	ingredients	Quantity(mg)	
		F1	F2
1	Aztreonam	250	250
2	Lysine	25	25
3	surfactants	**Tween 80** 10	**Span 80** 10
4	Propylene glycol	15	15
5	Water for injection	Q. S	Q.S

Table 2: XRD of Aztreonam IV Infusion formulation –A

SL.NO	2 θ	PEAK INTENSITY
1.	05.68	19.76
2.	07.17	17.76
3.	08.76	15.65
4.	10.76	13.75
5.	11.99	11.54

6	13.65	09.98
7	15.76	07.99
8	17.76	05.65
9	19.43	03.99

Table 3: XRD of Aztreonam IV Infusion formulation -B

SL.NO	2 θ	PEAK INTENSITY
1.	05.69	19.65
2.	07.19	17.76
3.	08.15	15.87
4.	10.79	13.67
5.	11.24	11.56
6	13.13	09.54
7	15.28	07.45
8	17.39	05.23
9	19.16	03.09

Table 4: XRD of aztreonam iv infusion comparative study with marketed infusion

SL.NO		2 θ	PEAK INTENSITY
F1	1	10.68	13.43
	2	13.16	11.65
	3	15.15	10.99
	4	17.76	08.54
	5	19.25	06.54
F2	1	10.29	13.65
	2	12.87	11.98
	3	15.87	09.87
	4	17.38	07.87
	5	15.19	05.76
STD	1	10.09	13.41
	2	13.54	11.43
	3	11.09	09.76
	4	09.58	07.87
	5	07.27	05.89

Figure 1: DSC OF Aztreonam IV Infusion (Formulation-F1)

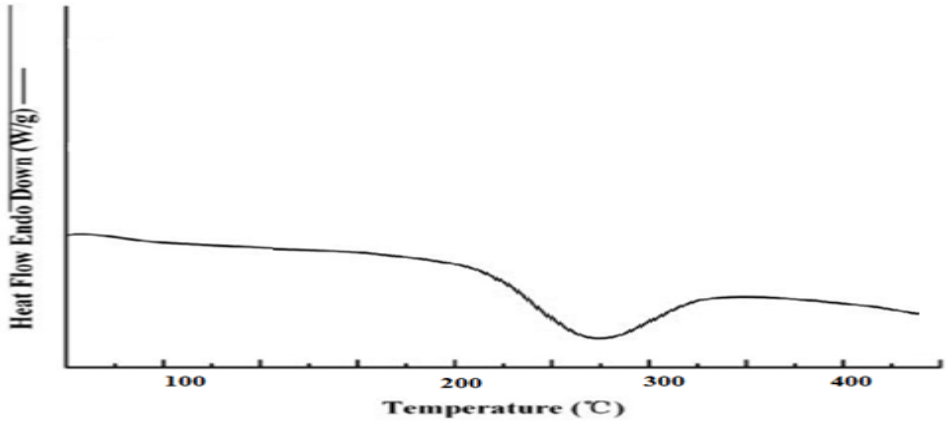


Figure 2: DSC OF Aztreonam IV Infusion (Formulation F2)

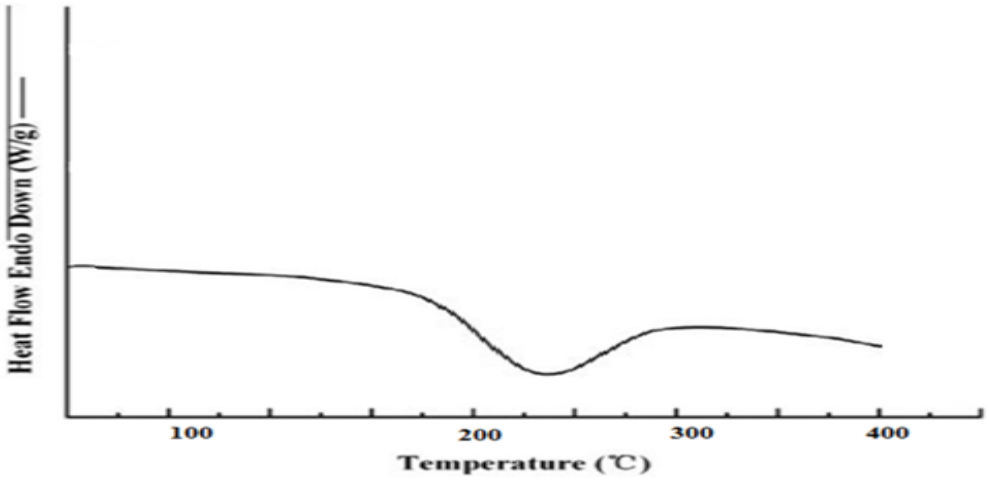


Figure 3: DSC OF Aztreonam IV Infusion (Formulation "F2" Vs Marketed Drug)

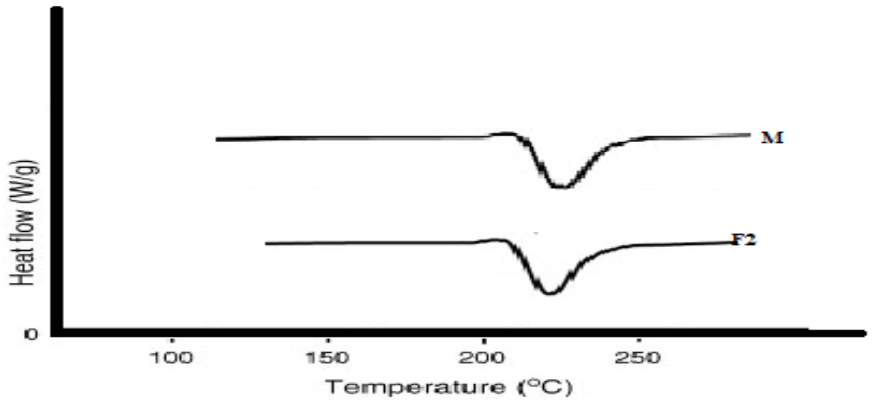


Figure 4: XRD of Aztreonam IV Infusion formulation –A

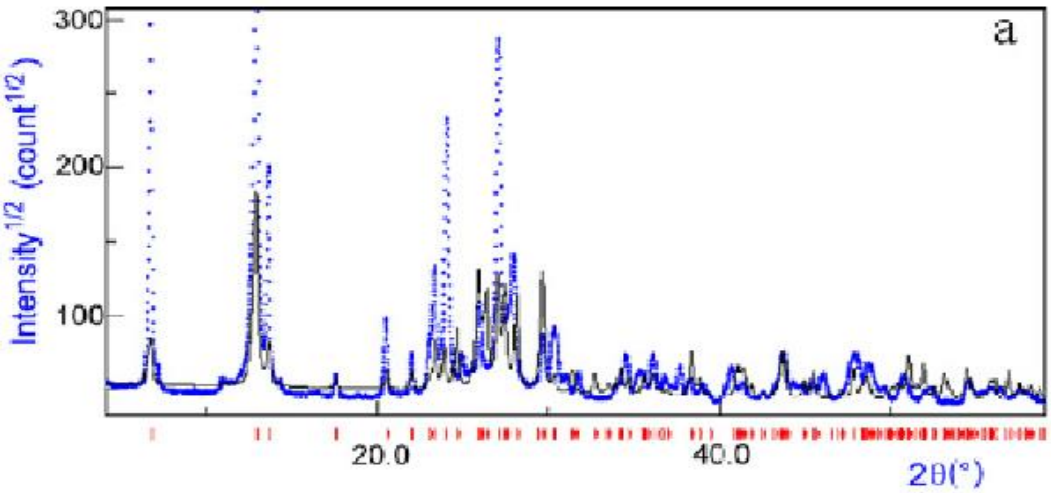


Figure 5: XRD of Aztreonam IV Infusion formulation –B

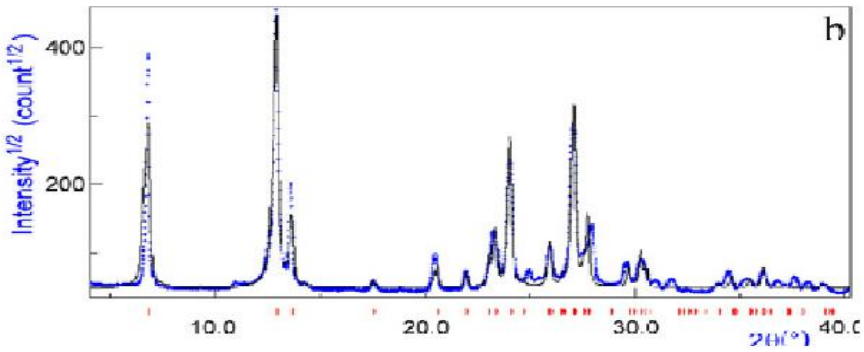


Figure 6: XRD of aztreonam iv infusion comparative study with marketed infusion

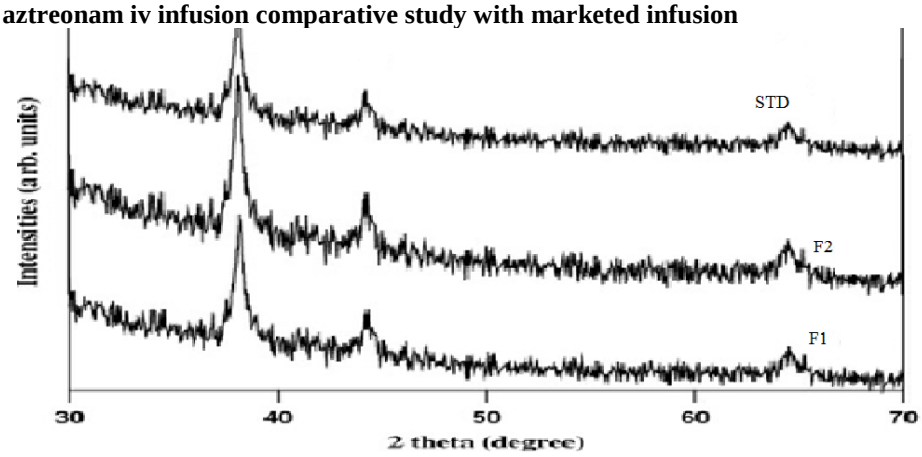


Figure 7: SEM of aztreonam iv infusion comparative study with marketed formulations

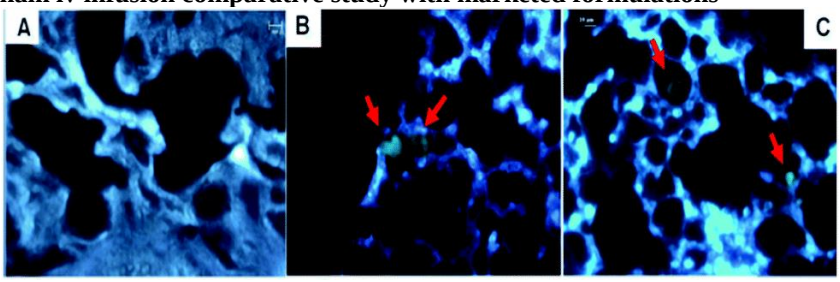


Figure 8: FT-IR Stability study of aztreonam i.v infusion of test and standard (3 months)

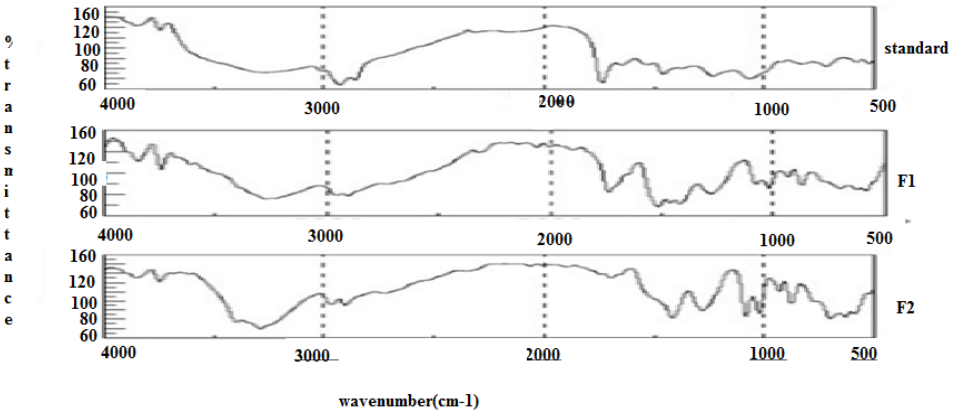


Figure 9: FT-IR Stability study of aztreonam i.v infusion of test and standard (6 months)

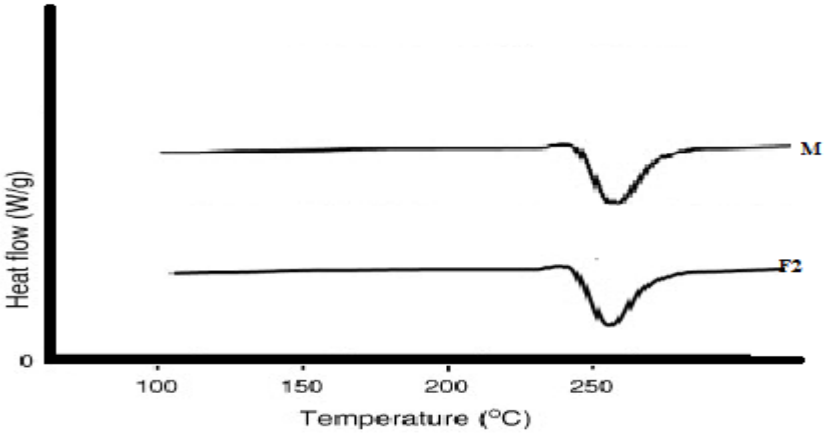


Figure 10: DSC Stability study of Aztreonam IV Infusion (Formulation B Vs Marketed Drug) (3 months)

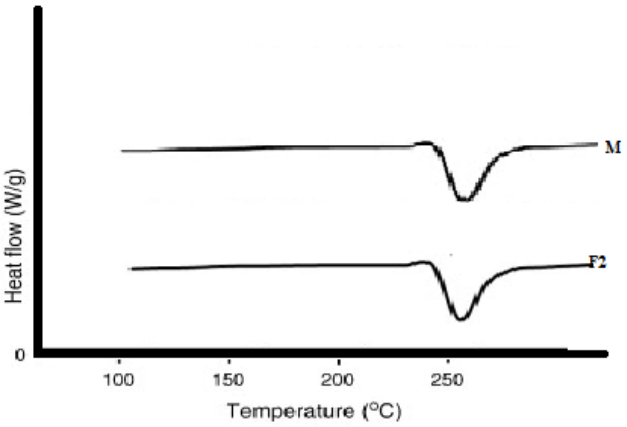


Figure 11: DSC Stability study of Aztreonam IV Infusion (Formulation B Vs Marketed Drug) (6 months)

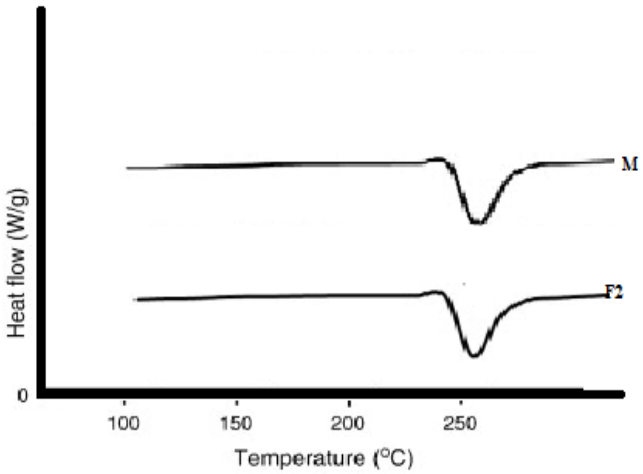


Figure 12: XRD Stability study of aztreonam iv infusion comparative study with marketed infusion (3 months)

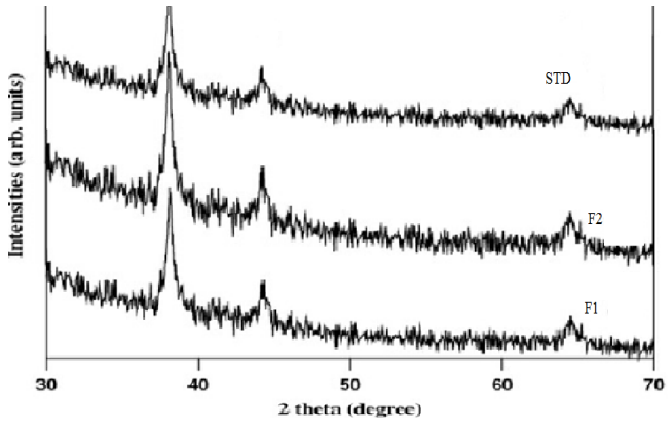
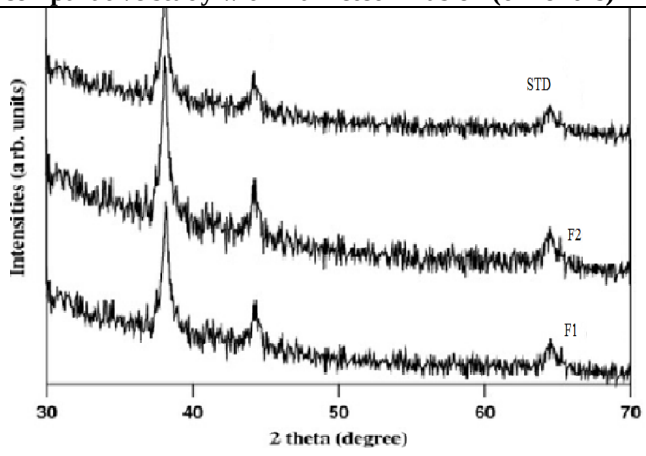
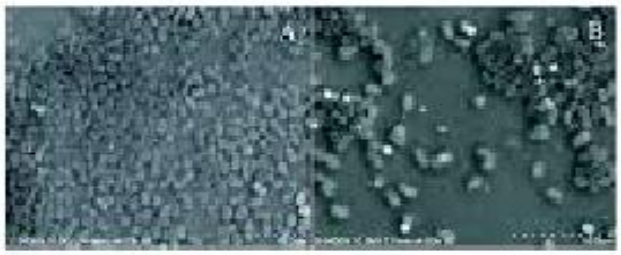
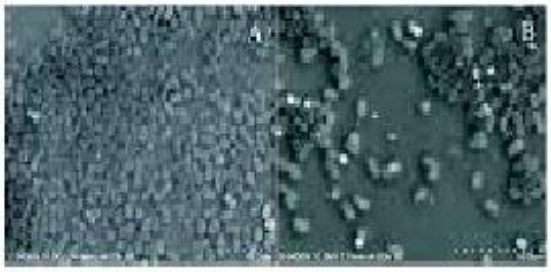


Figure 13: XRD Stability study of aztreonam iv infusion comparative study with marketed infusion (6 months)



Sem Stability Study Of Aztreonam Iv Infusion Comparative Study With Marketed Infusion (3 months) **Figure 14: XRD Stability study of aztreonam iv infusion comparative study with marketed infusion (3 months)**	**Sem Stability Study Of Aztreonam Iv Infusion Comparative Study With Marketed Infusion (6 months)** **Figure 15: SEM stability study of aztreonam iv infusion comparative study with marketed infusion (6 months)**
	

FTIR

The IR spectrum of drugs in KBr/MeOH is presented in IR spectra (KBr pellets) of the different polymorphic forms of the formulations [11].

SEM

In SEM study for different polymorphic forms of the formulations carried out index (Jeol, Japan) after sputter coating with gold in fine coat ION IFC – 1100 sputter (Jeol Japan) [12].

Formulation of AZT iv Infusion

A sample of 50 gm of the α (Alpha) Aztreonam is recrystalized from 670 ml of methanol: Water (7: 1) The hot mixture is cooled to 25ºC stirred for 1 hour and Filtered. The crystals Dried to give about 4 gm of the α form of Aztreonam verified by X – ray / DSC/FTIR/SEM/DISSOLUTION STUDY with the excipents of lysine (amini acid), surfactants (tween 80, span 80), co-surfactant (propylene glycol) [9].

RESULTS

In vitro dissolution test

The dissolution of commercial infusion of aztreonam prepared and were performed in pH 7.0 phosphate buffer and the corresponding profiles are present. Both formulations showed a higher and faster release than that of the commercial infusion of aztreonam.

DSC OF AZTREONAM IV INFUSION (FORMULATION F2)

It shows an exothermic peak at 229^0C indicating the melting of the aztreonam iv infusion F2
(fig no:2)

The above figure shows the DSC curve of aztreonam-lysinedry I.V- infusion kneaded system in 1:25 M the pure aztreonam showed exo thermic peak as 227^0 c. the curve of iv infusion displayed wide and strong exothermic effect in 229^0c. which, may be ascribed to dehydration and vaporization of ammonia, from the above DSC thermogravimetric microcomputer data expressed to as formulation F2is best iv infusion, that was compared with marketed iv infusion of aztreonam that expressed in below DSC graph.

DSC OF AZTREONAM IV INFUSION (FORMULATION "F2" VS MARKETED DRUG)

It shows an exothermic peak at 229^0C(F2) was compared with marketed iv infusion exothermic peak at 227^0C indicating the melting of the aztreonam iv infusions (fig no:3).

XRD OF AZTREONAM IV INFUSION FORMULATION -A

XRD pattern of Aztreonam IV Infusion formulation –A2theta peak were detected at scattering angles were shown in (table no:2) and the interpretations are given in (figure no:4).

XRD OF AZTREONAM IV INFUSION FORMULATION -B

XRD pattern of Aztreonam IV Infusion formulation –B 2 theta peak were detected at scattering angles were shown in (table no:3) and the interpretations are given in (figure no:5).

XRD OF AZTREONAM IV INFUSION COMPARATIVE STUDY WITH MARKETED INFUSION

XRD pattern of Aztreonam IV Infusion comparative study with marketed infusion 2theta peak were detected at scattering angles were shown in (table no:4) and the interpretations are given in (figure no:6).

The X-ray diffraction of IV infusion formulation of aztreonam A-B comparatively studied with the standard marketed formulation of IV infusion. The peak intensity, 2 theta angle formulation –B,coinsied with the marketed formulation.

XRD OF AZTREONAM IV INFUSION COMPARATIVE STUDY WITH MARKETED INFUSION

The above SEM study of aztreonam-IV infusion (a, b, c) among all of that prepared from ammonia crystals of aztreonam. The SEM of aztreonam -IV infusion dissolution, adsorption behavior briefly described in formulation "b". That shows size of aztreonam droplet very clearly dispersed in formulation "b" (size of droplet 10μm).

"a" - IV infusion of –aztreonam formulation 1

"b" - IV infusion of –aztreonam formulation 1(lysine 15%)

"c" - IV infusion of aztreonam marketed formulation

DISCUSSION

The pharmaceutics scientist must formulate this material into a dosage form that is homogeneous, callable, stable, and bio available. The excipients in the formulation can exert a strong influence on polymorphic conversion and may create new pathways that did not exist for the pure drug substance. One should expect polymorphs with similar thermodynamic energies to be prone to substantial conversion during a milling operation. The fluid of therapy is one of the most common medical acts in hospitalized patients but many of the aspects of this practice are surprisingly complex.

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