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Formulation and Evaluation of Taste Masked Suspension of Azithromycin Dihydrate

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ABSTRACT

The article describes strategy for masking the intensely bitter taste of Azithromycin Dihydrate(AZT) by using complexation with Kyron T-134. The resinates prepared with drug-Kyron T-134 ratio (1:3) at pH 8, gave maximum drug loading. Suspension containing, resinate showed more than 90% *in-vitro* drug release within 45min. Prepared formulation showed good stability and retention of palatable taste. Thus, the "patient-friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and non cooperative patients, can be successfully formulated using this technology.

Keywords: Azithromycin Dihydrate, taste masking, Kyron T-134.

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INTRODUCTION

The problem of providing pediatric and geriatric patient with drug dosage forms that are palatable has been around for long time. Children and infants in particular, are most sensitive to bitter and sweet tastes than adults. Different taste masking technologies have been used to address the problem of patient compliance. Conventional taste masking techniques such as the use of sweeteners, amino acids and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs[1]. Complexation with Ion exchange resin (IER) provides alternative method for taste masking. In this method, weak acid anion exchange resin, Kyron T-134, was used for taste masking.[2] The drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected. AZT is a orally absorbed drug used in the treatment or prevent certain bacterial infections, most often those causing middle ear infections, throat, pneumonia, typhoid, bronchitis and sinusitis[3]. Being highly bitter drug AZT posses a challenge particularly in the formulation of a pediatric dosage form.

MATERIALS AND METHOD

Materials

AZT was gift sample from CIPLA Ltd .Pharma R & D (India). Kyron T-134was obtained as gift sample from Corel Pharma Chem, (Ahmedabad, India). Sucrose, sorbitol, glycerine, xanthane gum, aerosil 200, sucralose , sodium methyl paraben, sodium propyl paraben, Butylated Hydroxy Toulene, menthol, Tween 80, and strawberry flavour was obtained from different manufacturers as gift sample. All other chemicals/solvents were of analytical grade.

Preparation of AZT- Kyron T complex[4]

A quantity 15 ml of distilled water was kept for stirring with the help of a magnetic stirrer. A weighed quantity of Kyron T -134 (3 times more than that of the drug) was added to the above water and stirred continuously for around 10mins. AZT was added to the above solution under continuous stirring. After 20 minutes the pH was checked. The pH should be in between the range of 8.5 to 11 as the drug is stable in alkaline pH. If not in this range the pH had to be adjusted with 20% KOH solution and stirred for 1-2 hours. This wet complex was used for preparing the final suspension.

EVALUATION OF AZT- KYRON T COMPLEX

- **Molecular complex of drug resin complex**

The IR spectra of AZT- Kyron T complex were recorded using Fourier transform infra-red spectrophotometer (IR Affinity -1 Fourier Transform Infrared Spectrophotometer Shimadzu). Sample preparation involved, drying of Potassium Bromide (KBr) in the oven to get rid of any

moisture content then mixing the sample with KBr by triturating in glass mortar. Finally preparing of pellet and placing in the sample holder. The spectrum was scanned over a frequency range 4000– 400 cm^{-1}.

- **DSC**

The thermal analysis of the complex was carried out on Exstars II DSC 6220. The pan used was made up of aluminium and the temperature range was from 30^0C to 300^0C under a continuous stream of inert gas nitrogen at a rate of 10^0C/min. The sample taken was approximately accurate weight of 10 mg.

- **Drug entrapment efficiency by HPLC**

10mg of the complex was dissolved in methanol and volume made upto 10ml by Mobile phase (Phosphate Buffer pH 7.6(20 mM : ACN) = 20:80 v/v) to obtain stock solution of 1000 µg/ml. 1ml of this solution was diluted to 10 ml with mobile phase to obtain a concentration of 100 µg/ml .A standard Chromatogram was obtained at wavelength of 215 nm.

- **Taste Evaluation**

The taste of complex was checked by panel method. The study protocol was explained and written consent was obtained from volunteers. For this purpose 8 human volunteers were selected. Once placing the complex in the mouth for 60 seconds, bitterness recorded using a numerical scale. The numerical scale bears values as 0 = Good, 1 = Tasteless, 2 = slightly bitter, 3 = bitter, 4 = very bitter, which was determined by formulator.

Preparation of AZT suspension [5, 6]

1. A sufficient quantity of distilled water was boiled. To this 25 gm sugar was added to prepare a sugar syrup, which was filtered. To this 5 gm of 70% sorbitol solution was added.
2. A quantity of Xanthan gum as mentioned in the Table 1 was added to hot purified water with continuous stirring to form a paste. This paste was cooled at room temperature and added to the above solution with continuous stirring. In case of Batch 1 no Xanthan gum was used.
3. A specified quantity of Aerosil, Sucralose, Sodium Methyl Paraben, Sodium Propyl Paraben and Glycerine were added in above solution with continuous stirring.
4. Drug –Resin Complex was added to above solution under continuous stirring.
5. BHT was dissolved in warm Tween 80 with continuous stirring and added to above solution.

6. Menthol was dissolved in flavoring and added to the above step under continuous stirring.
7. Finally colour solution was added and volume was made up with water and pH was observed to be in the range 8.5 to 11.

Table 1: Formula for preparation of AZT suspension

Batch No	BM1	BM2	BM3
Azithromycin Dihydrate (mg)	627	627	627
Kyron T- 134(gm)	1.881	1.881	1.881
Sugar (gm)	25	25	25
Sorbitol (70%) (gm)	5	5	5
Xanthan gum (mg)	-	0.0625	0.125
Aerosil(mg)	0.25	0.25	0.25
Sucralose(mg)	0.075	0.075	0.075
Na Methyl Paraben (mg)	0.065	0.065	0.065
Na Propyl Paraben(mg)	0.0065	0.0065	0.0065
Glycerin(gm)	2.5	2.5	2.5
BHT(mg)	0.005	0.005	0.005
Tween 80(gm)	0.05	0.05	0.05
Menthol(mg)	0.02	0.02	0.02
Strawberry Flavour (ml)	0.1	0.1	0.1
Colour	qs.	qs.	qs.
Distilled water	q.s	q.s	q.s

Evaluation of Taste Masked Suspension:[7]

Sedimentation volume (F) is a ratio of the final or ultimate volume of sediment (Vu) to the original volume of sediment (VO) before settling. It can be calculated by following equation.

$$F = V u / VO$$

Where, Vu = final or ultimate volume of sediment

VO = original volume of suspension before settling.

Viscosity of Suspension

The viscosity of suspension was determined at ambient condition, using Brookfield's viscometer with spindle no 3.with adequate amount of the sample.

Viscosity =Dial reading * Factor

Particle size measurement:

Optical microscopy was carried out to study the size of suspended particles. The mean particle size was calculated by measuring the size of 200 particles with the help of calibrated ocular micrometer

***In Vitro* Drug Release Studies** [9]

The release rate of Azithromycin Dihydrate Suspension was determined using USP dissolution

testing apparatus II (paddle method). The dissolution test was performed using 900 ml of pH 6.8 Phosphate Buffer, at 37 ±0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 0, 10, 15, 20, 30 and 45min, filtered. The samples were replaced with fresh dissolution medium of same quantity. Peak Area of these solutions was measured at 215 nm using a HPLC[8] system. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Scanning Electron Microscopy

The morphology of Azithromycin Dihydrate Suspension (Globules) prepared under the optimum condition was observed under scanning electron microscope.

Zeta Potential

Zeta potential is determined by using Zetasizer

Accelerated Stability Studies

Formulation batch BM2 of Azithromycin dihydrate Suspension, were packed individually in glass container in such a manner that any mechanical damage was minimal.

These were then stored at following conditions:

1)Long term storage (25°C ± 2°C/60% RH ± 5% RH or30°C ± 2°C/65% RH ± 5% RH) for 3 months in glass dessicator containing Sodium nitrite at or30°C ± 2°C

2) Accelerated 40°C ± 2°C/75% RH ± 5% RH for 3 months (in humidity controlled oven)

Suspension was examined for taste, Particle size, Viscosity, Sedimentation volume, In-vitro dissolution.

RESULTS AND DISCUSSION:

Evaluation of AZT- Kyron T complex

IR Spectroscopy

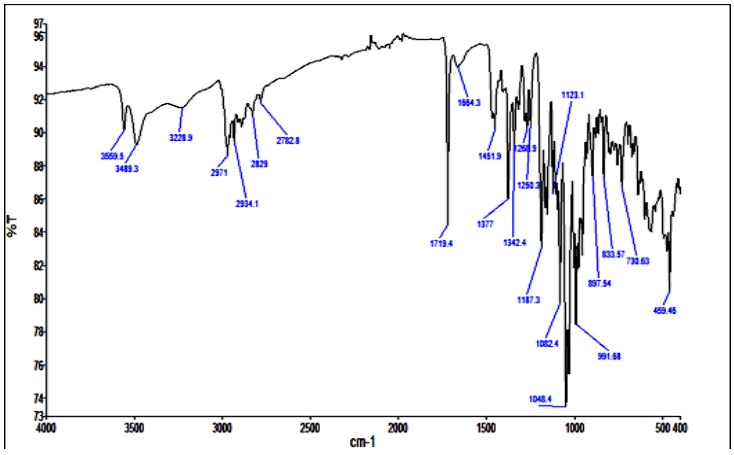


Figure 1: FTIR spectrum of AZT

In the FTIR spectrum of Kyron T -134- AZT complex new peaks appear at 2850 cm^{-1}, 992 cm^{-1}, 955 cm^{-1} which is not present in any of the components, thus a complex between AZT and Kyron T 134 is formed, which can be further confirmed by DSC analysis.

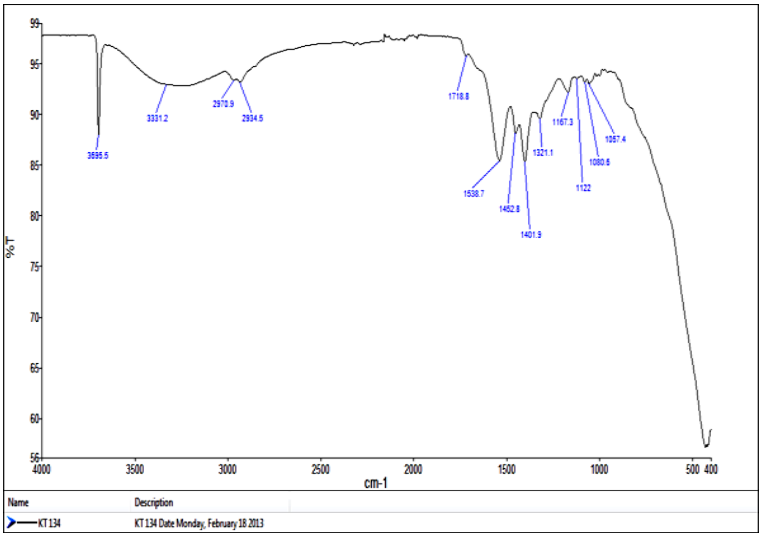


Figure 2: FTIR spectrum of Kyron T-134

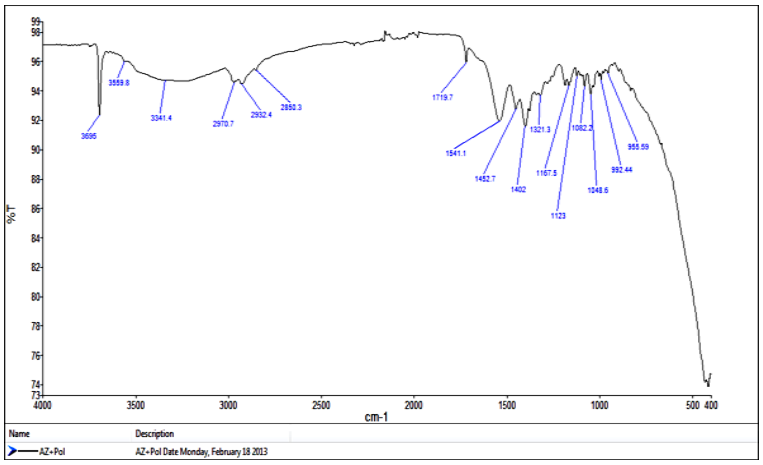


Figure 3: FTIR spectrum of Kyron T -134- AZT complex

DSC (Differential Scanning Calorimeter)

The DSC melting curve of AZT showed a melting peak at 124.61^{0}C which corresponds to the melting point AZT. The DSC thermogram of Kyron T 134 shows a melting peak at 125.3^{0}C. The DSC thermogram of AZT-Kyron T 134 complex showed a single melting peak at 121.1^{0}C which does not correspond to the melting of any of the components, suggesting there is a formation of a complex between AZT and Kyron T 134.

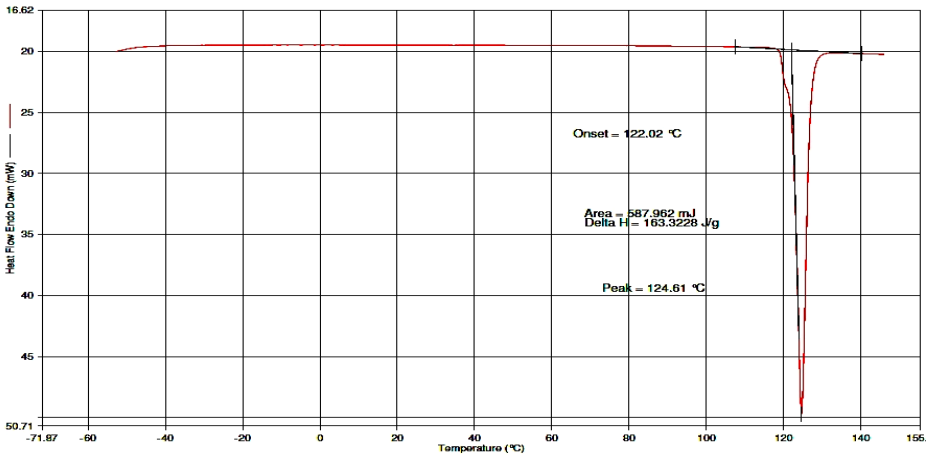


Figure 4: DSC melting curve of AZT

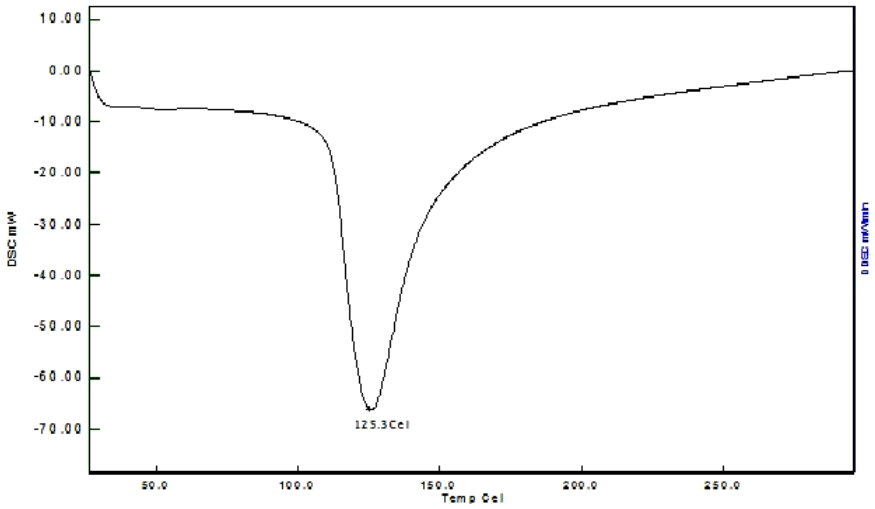


Figure 5: DSC melting curve of Kyron T 134

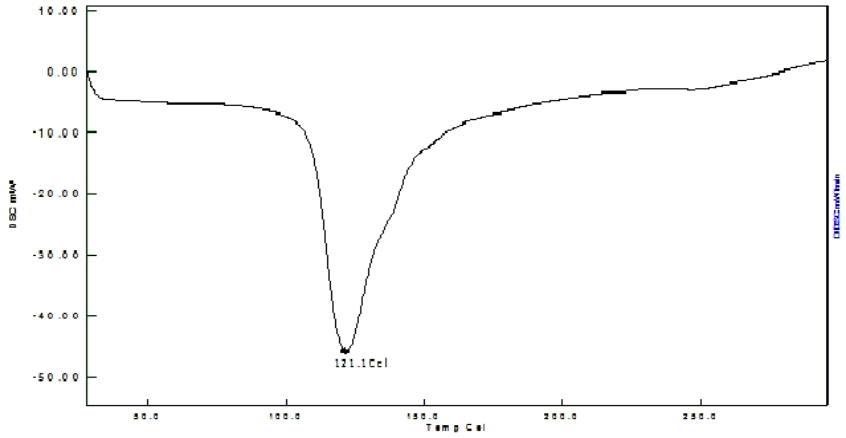


Figure 6: DSC melting curve of AZT- Kyron T 134 complex

Drug entrapment efficiency

The percent drug entrapment efficiency was found to be 90%.

Taste Evaluation

The objective of this study is to conduct and evaluate the palatability of complex of AZT- Kyron T 134.

When the batch of AZT- Kyron T 134 complex were evaluated by human volunteers, the volunteers did not feel any bitter taste after keeping the complex in the mouth for 60 seconds, which confirmed that the bitter taste of AZT was masked successfully. This is confirmed by the scale marking of the volunteers.

Table 2: Evaluation of Taste

Batch No.	Volunteers							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	0	1	0	0	0	0	0	0

Scale: 0 = Good, 1 = Tasteless, 2 = slightly bitter, 3 = bitter, 4 = very bitter

Evaluation of Taste Masked suspension

Sedimentation volume

The sedimentation volume can have values ranging from less than 1. The ultimate height of the solid phase after settling depends on the concentration of solid and the particle size. To obtain an acceptable suspension the value of F should be atleast 0.9. In the present formulation there is little sedimentation after 14 days and it could be easily redispersed to give a uniform dispersion after shaking for all the three batches.

Table 3: Sedimentation volume of the suspension batches

Days	Azithromycin Dihydrate Masked Suspension				Taste		Sedimentation Volume (F) (Vu/Vo)		
	Vu	Vo	Vu	Vo	Vu	Vo	BM1	BM2	BM3
0	46.5	50	48	50	45.5	50	0.93	0.96	0.91
14	44.5	50	45	50	42.5	50	0.89	0.90	0.85

Viscosity of Suspension

Sedimentation rate depends on the viscosity of the medium. From the sedimentation volume data, it can be seen that suspension is stable and redispersible after 14 days. Thus, viscosity of the suspension is sufficient for the stability of the suspension.

Table 4: Viscosity of the suspension batches

Batch Code	Viscosity (Cps) 0 day	Viscosity (Cps) 14 days
BM1	330	300
BM2	350	340
BM3	320	310

Particle size measurement

The particle size remains reasonably constant after 14 days. The resin produces a swollen porous network structure that is capable of allowing the drug molecules to permeate/ diffuse inside and also get complexed with the resin.

Table 5: Particle size of the suspension batches

Batch Code	Mean Particle Size Diameter (µ) [0 day]	Mean Particle Size Diameter (µ) [14 days]
BM1	13.69	13.50
BM2	14.23	14.02
BM3	14.56	14.31

***In Vitro* Drug Release Studies**

AZT release from the suspension was observed in the average salivary pH of 6.8. The invitro drug release in the average salivary pH of 6.8 was about 90% within 45 minutes. The presence of exchangeable ions of ionizable electrolytes in the salivary fluid, followed by drug diffusion through the polymer matrix of the resonates may be responsible for this release. The drug- resin complex is stable in salivary pH for a period of administration. It also shows that the resin does not retard the release of drug from suspension.

Table 6: In-vitro drug release study of AZT suspension

Time (min)	Formulation(Batches)		
	BM1	BM2	BM3
0	0	0	0
10	42.73	45.45	35.56
15	54.89	61.86	51.76
20	65.32	72.55	60.98
30	79.51	86.78	78.45
45	92.53	99.10	95.98

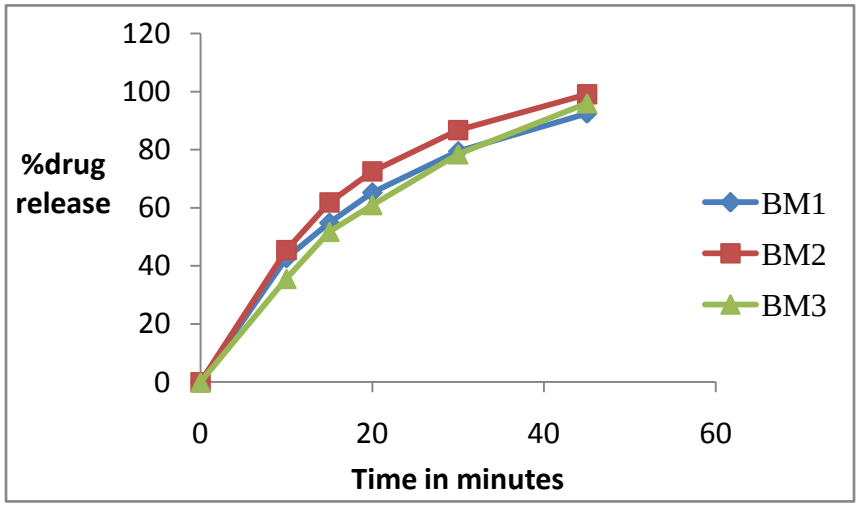


Figure 7: Release profile of AZT in suspension in pH buffer 6.8

Scanning Electron Microscopy

Scanning Electron Microscopy is used to study the microscopic aspects of the formulation.

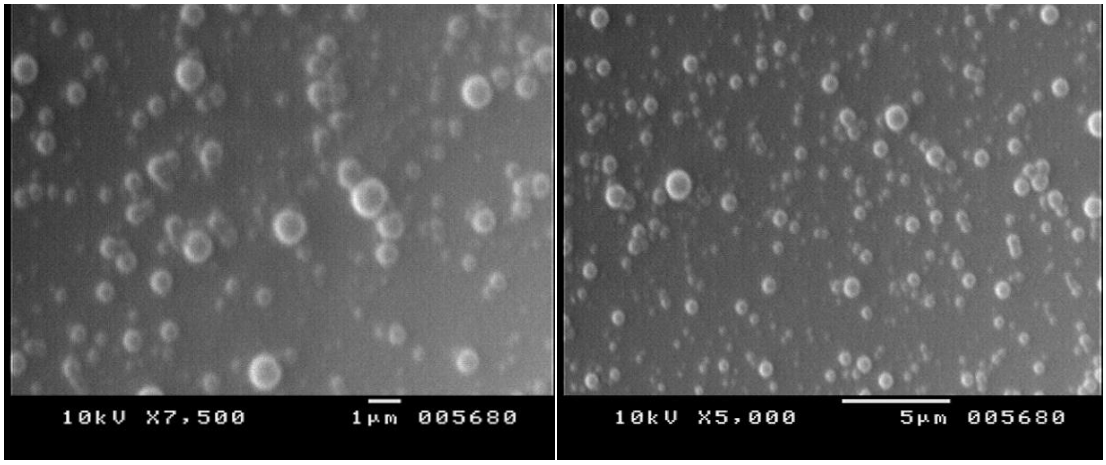
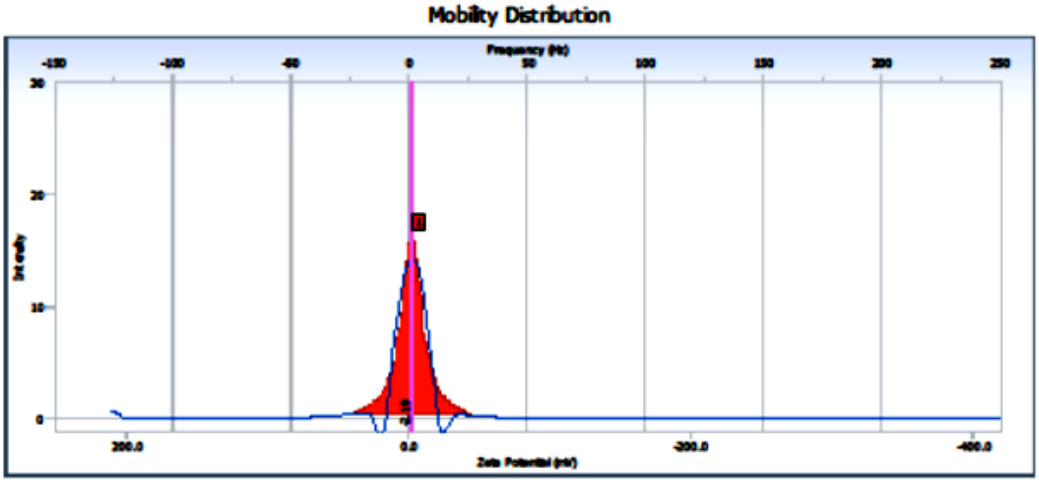


Figure 8: SEM of AZT suspension (Batch BM2)

The images show that the uniform distribution of the drug in the formulation.

Zeta Potential

A dividing line between stable and unstable aqueous dispersions is generally taken at either +30 or -30 mV. Particles with zeta potentials more positive than +30 mV are normally considered stable. Particles with zeta potentials more negative than -30 mV are normally considered stable.



Measurement Results

Zeta Potential	: -2.19	(mV)	Doppler shift	: 1.31	(Hz)
Mobility	: -1.710e-005	(cm²/Vs)	Base Frequency	: 125.8	(Hz)
Conductivity	: 1.5467	(mS/cm)			

Zeta Potential of Cell			Diluent Properties		
Upper Surface	: -0.20	(mV)	Diluent Name	: WATER	
Lower Surface	: 0.26	(mV)	Temperature	: 25.0	(°C)
Cell Condition			Refractive Index	: 1.3328	
Cell Type	: Flow Cell		Viscosity	: 0.8878	(cP)
Avg. Electric Field	: -15.86	(V/cm)	Dielectric Constant	: 78.3	
Avg. Current	: -1.22	(mA)			

Figure 9: Zeta Potential graph of AZT suspension (Batch BM2)

Stability studies

Table 7: Stability study for batch BM2 of Azithromycin Dihydrate suspension at 30°C ± 2°C/65% RH ± 5% RH

Characteristics	1 month	2 month	3 month
Taste	Palatable	Palatable	Palatable
Particle Size (µ)	14.18	14.09	14.04
Viscosity (cps)	350	349	348
Sedimentation Rate	0.98	0.98	0.97
Dissolution Study	98.9%	98.7%	98.5%

Table 8: Stability study for batch BM2 of Azithromycin Dihydrate suspension at 40°C ± 2°C/75% RH ± 5% RH

Characteristics	1 month	2 month	3 month
Taste	Palatable	Palatable	Palatable
Particle Size(µ)	14.15	14.10	14.01
Viscosity (cps)	349	348	348
Sedimentation Rate	0.99	0.98	0.97
Dissolution Study	98.4%	98.4%	98.2%

CONCLUSION:

Use of weak cation exchange resin offers superior method for preparing taste-masked substrates of AZT. A result obtained in this work shows that drug-resin complexes effectively masked bitter taste of AZT. While liquid formulation provides easier way to administer and getting the child to swallow. Also to overcome problem with noncompliance with child especially around 8 years old for whom swallowing other dosage form can be challenging.

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