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Solubility And Dissolution Enhancement Of Azitromycin Dihydrate Solid Dispersion By Using Spray Drying

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Azitromycin Dihydrate (Poorly water soluble drug), when prepared as solid dispersion showed improved solubility and dissolution using spray drying .main objective of this work to improve solubility of azitromycin Dihydrate by using physical mixture and solid dispersion. We have prepared batches having (1:1, 1:2, 1:3) concentration using PVPK-30 and β- Cyclodextrin. In vitro drug release was studied and it was found that the dissolution rate and the dissolution parameters of the drug from the physical mixture as well as solid dispersion were studied and its higher than those of the intact drug. FT- IR spectra revealed no chemical incompatibility between drug and urea. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC) and Powder X-Ray Diffraction (PXRD).

Keywords: Azithromycin Dihydrate, Solid dispersion, PVPK-30, β- Cyclodextrin

Introduction:

Azithromycin is a semi-synthetic antibiotic obtained from erythromycin. It is a Macrolide antibiotic. This drug is a nitrogen-containing macrolide (Azalide), with indications and usage similar to Erythromycin. All macrolides, such as azithromycin inhibit RNA dependent protein synthesis by binding reversibly to the 50S ribosomal subunits of susceptible microorganisms. Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solvent is generallya liquid, which can be a pure substance or a mixture of two liquids. One may also speak of solid solution, but rarely of solution in a gas. The extent of solubility ranges widely, from infinitely soluble (fully miscible) such as ethanol in water, to poorly soluble, such as silver chloride in water. The term insoluble is often applied to poorly or very poorly soluble compounds.

Spray drying is presently one of the most exciting technologies for the pharmaceutical industry, being an ideal process where the end-product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density and morphology. Spray drying starts with the atomization of a liquid feedstock into a spray of

droplets. Next, the droplets are put in contact with hot air in a drying chamber. The sprays are produced by either rotary (wheel) or nozzle atomizers of different types. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. Powder is continuously discharged from the drying chamber and recovered from the exhaust gases using a cyclone or a bag filter. The whole process generally takes no more than a few seconds. This process of drying is a one step rapid process and eliminates additional processing. The liquid feed is pumped through an atomizer device that produces fine droplets into the main drying chamber. Atomizers vary with rotary, single fluid, two-fluid, and ultra-sonic designs. These different styles have different advantages and disadvantages depending on the application of the spray drying required.

MATERIAL AND METHODS:

MATERIAL: Azithromycin dehydrate, PVPK-30, β- Cyclodextrin were gifted from METHA laboratory. Ethanol, Methanol Were purchased from laboratory chem.

METHODS:

a) Preparation of physical mixture:

Accurately weighed amount of Azithromycin Dihydrate and PVP – 30 AND β –Cyclodextrin (carrier) in various drug-to-carrier weight ratios were thoroughly blended in glass mortar for 5 min.The composition of various batches is shown in Table The products were kept in for further study.

Table no: 1Composition batches containing Azitromycin Dihydrate and PVP – 30 AND β –Cyclodextrin (weights in Mg)

Sr. no	Batches	Drug carrier ratio	Azithromycin Dihydrate	PVP–30	β –Cyclodextrin
1	PM1	1:1	100	100	-
2	PM2	1:2	100	200	-
3	PM3	1:3	100	300	-
4	PM4	1:1	100	-	100
5	PM5	1:2	100	-	200
6	PM6	1:3	100	-	300

b. Preparation of solid dispersion using solvent evaporation through spray drying:

Accurately weighed amount of Azithromycin Dihydrate and PVP – 30 AND β –Cyclodextrin (carrier) in various drug-to-carrier weight ratios Weighed quantity shown in table was dissolved in dichloromethane to obtain clear solution. Spray drying was carried out by using laboratory scale spray dryer (Labultima Instruments and system Pvt. Ltd, Mumbai, India), under the following conditions: flow rate of the solution 10ml/min; inlet temperature 120^0C; out let temperature 50^0C; aspirator -40mmWC.

Composition batches containing Azitromycin Dihydrate and PVP – 30 & β – Cyclodextrin (weights in Mg)

Sr. no	Batches	Drug carrier ratio	Azithromycin Dihydrate	PVP–30	β –Cyclodextrin
1	SD1	1:1	100	100	-
2	SD2	1:2	100	200	-
3	SD3	1:3	100	300	-
4	SD4	1:1	100	-	100
5	SD5	1:2	100	-	200
6	SD6	1:3	100	-	300

COMPATIBILITY STUDIES

1.) Fourier-Transform Infra Red spectroscopic studies

An excellent opportunity for chemical recognition of a compound is provided by IR spectroscopy. Using the potassium bromide pellet method, the FTIR spectra of pure azithromycin Dihydrate were obtained separately in the presence of polymers to examine the drug-polymer interface. A small amount of potassium bromide (1:100 parts of drug: KBr) and an insignificant amount of active ingredient were physically mixed and triturated in a mortar. The set assortment was exposed to an infrared beam while enclosed in a pellet, and Spectra were noted. Within the 400–4000 cm–1 range (Perkin Elmer).

2.) Differential scanning calorimetric analysis:

DSC study was completed to rule out any physicochemical exchanges between excipients used. Small quantity of drug, little amounts of model was placed in a 50 micro liter capacity perforated aluminum pan and closed. Heat rounds from 50 ^{0}C to 300 ^{0}C using nitrogen as purging gas for each sample were set and analysis was performed.

Identification of drug

a) Melting points:

A tiny a capillary tube with one was filled with a quantity of the drug. Closed end. To ascertain the drug's melting point. The capillary tube was positioned using the thermoelectric equipment for melting points, as well as the temperature where the medication melted was recorded. Three readings were averaged.

b) UV-spectroscopy:

Finding the λ Max the wavelength at which a medicine absorbs the most light is known as its λ max. The λ max of a substance is a unique property that is hard to change. A stock solution of 1 mg/ml was prepared by dissolving 100 mg of azithromycin in a tiny amount of methanol

and then diluting it further with 100 ml of phosphate buffer (pH 6.8). This was done in order to determine the drug's λ max. The stock solution was significantly diluted to produce solutions in the 2–12 µg/ml range. Scanning in the 200–400 nm region allowed us to determine the solution's λ max.

c) FTIR:
To verify the pure drug used in the formulation, the FTIR spectra of the pharmaceuticals was recorded using an FTIR emission spectrometer (Perkin Elmer**)** between 400 and 4000 cm−1. the pure drug's FTIR spectra, were obtained independently. The sample was placed on a suitable-sized disk for measurement after being grounded with KBr Pure azithromycin dehydrates infrared spectra revealed two distinct peaks at 3083.38 and 3335.62, respectively, attributed to the CH aromatic stretch and the NH secondary stretch.

d) Differential Scanning Calorimetry (DSC)
The product to be evaluated should be put in 50 µl sealed perforated aluminum pans with an amount between 3 and 5 mg. Using nitrogen as a purging gas, heat runs were set for each sample, ranging from 5000C to 3000C. The samples were then examined.

e) Powder X-ray diffraction:
Azitromycin X-ray diffraction grams were captured using a Bruker AXS D8 Advance, GmbH, Germany X-ray diffractometer. After being exposed to mono chromatized Cu Kα radiation (1.542 A°), the samples were examined at 2θ between 50 and 500. The applied voltage was 30 kV, while the applied current was 30 mA. The chart speed was 10 mm/2θ, and the range was 5×103 CPS.

In vitro Dissolution Studies:
The US Pharmacopeia XXIV type II dissolution test apparatus was used for the dissolution studies. Samples equal to 100 mg of azithromycin Dihydrate and batches from PM1 to PM6 & SD1 to SD6 were put in a dissolution vessel with 900 mL of distilled water kept at 37.0 ±0.5°C and stirred at 100 rpm. Samples were taken out and replaced with new dissolution medium on a regular basis. After filtering, the concentration of azithromycin Dihydrate was measured spectrophotometrically at 211 nm.

Scanning Electron Microscopy (SEM):
The surface morphology of samples was determined using an analytical scanning electron microscope the samples were placed on a sample disc carrier carbon stub (10 mm diameter, 3 mm height) and coated with gold under vacuum (0.25 Torr). The images were generated using a 30 kV electron beam.

RESULTS:

1. **Melting point determination:**
Using the capillary method, the melting point of azithromycin Dihydrate was ascertained. It was discovered that azithromycin Dihydrate had a melting point of 120ºC.It meets

requirements, demonstrating the drug sample's purity.

2. UV-spectroscopy

Azithromycin Dihydrate λmax in pH 6.8 phosphate buffer measured at 211 nm. Using distilled water to create adequate dilutions, the stock solution of 1 mg/ml azithromycin Dihydrate in pH 6.8 phosphate buffers was diluted to a concentration of 2-10µg/ml.

A UV-visible spectrophotometer was used to scan the range from200 to 400 nm for maximum absorbance. After 211nm was discovered to be the absorption maximum, λmax was utilized to estimate azithromycin Dihydrate

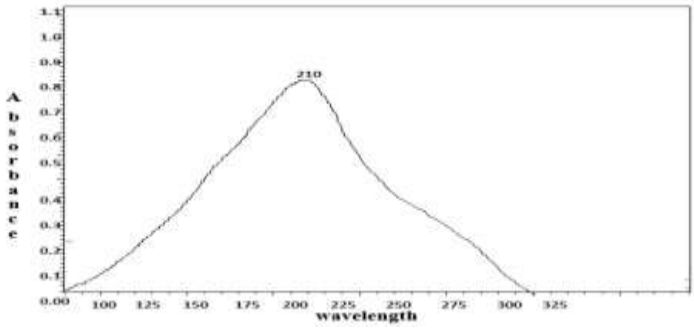


Figure: λmax of Azitromycin Dihydrate at 211 nm in pH6.8phosphate buffer

3. FTIR Studies:

For the pure medication, FTIR was used. The pure azithromycin dihydrate's IR spectra (figure 4) showed two distinct peaks: 3031.62 from the NH secondary stretch and 2909.7 from the CH aromatic stretch.C=O stretch causes 1729.30 cm-1, while C-N stretch causes 1441.18 cm-1. Because of the C=O stretch, 1159.24 cm-1.

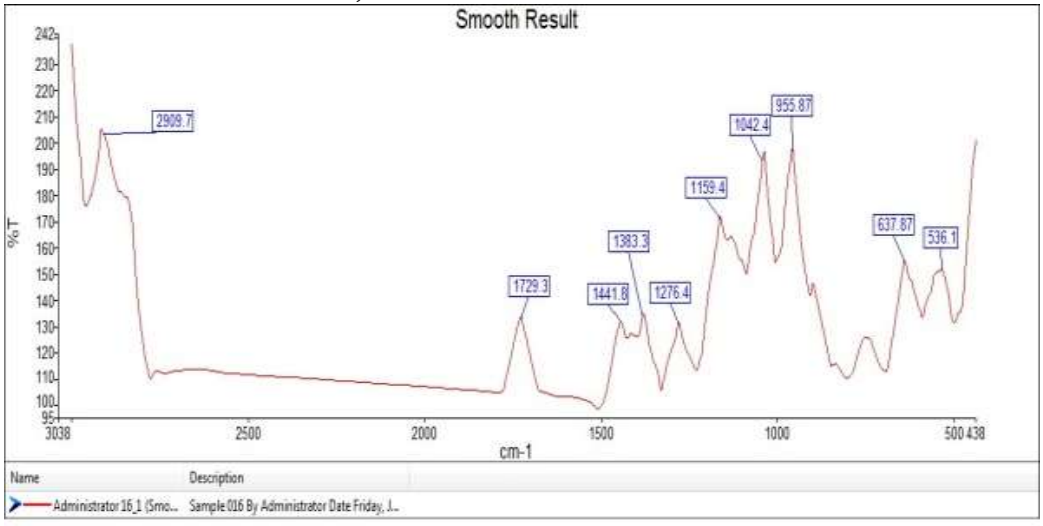


Figure: FTIR Spectra of Azitromycin Dihydrate

Sr. No.	Wave number (cm^{-1})	Comments
1.	3031.62	-CH stretching
2.	2909.70	-NH stretching
3.	1729.30	-C=O stretching
4.	1441.18	-C=O stretching
5.	1159.24	-C=O stretching

4. Differential Scanning Calorimetry (DSC)

The DSC thermo gram of azithromycin dihydrate clearly shows peaks, including a distinct endothermic peak at 120 0C, which falls inside the compound's melting temperature range (Tm). This endothermic peak indicates that the azithromycin dihydrate was used in an unadulterated crystalline state.

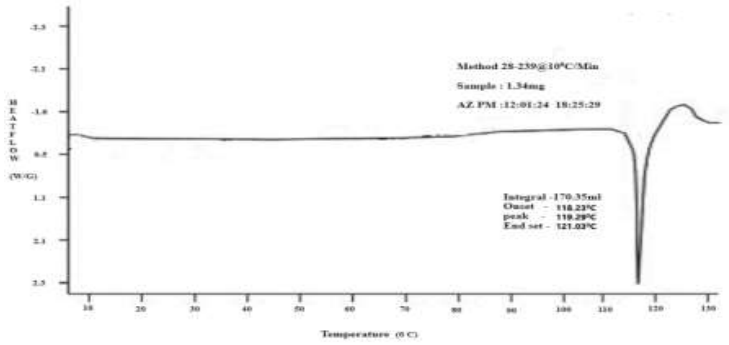


Figure: DSC of Azitromycin dihydrate

5. Powder X-ray diffraction:

Figure shows grams of pure azitromycin dihydrate powder X-ray diffractometer. The PXRD study reveals that the sample Azitromycin dihydrate is crystalline in nature, as evidenced by distinct peaks in the X-ray diffraction spectrum. These peaks appear at a diffraction angle of 2θ at 7.6, 9.04, 10.69, 12.81, 14.53, 15.75, 16.00, 16.07, 17.11, 17.82, 19.57, 21.32, 22.57, 25.79, 26.97, 30.39, 39.00, 40.65, 45.87, etc.

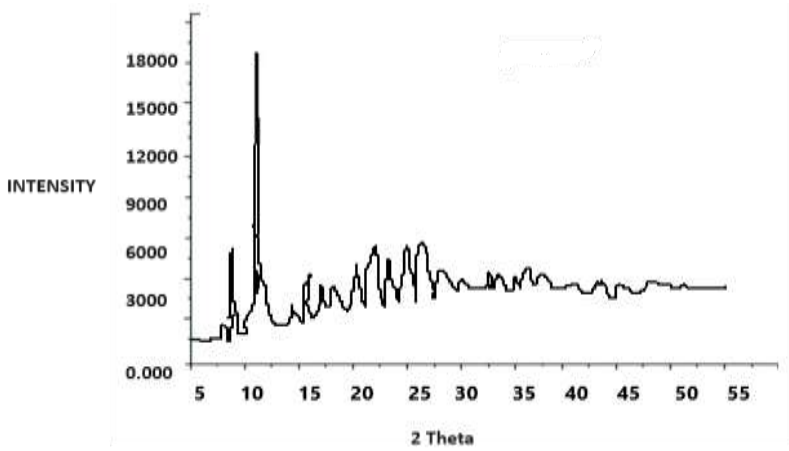
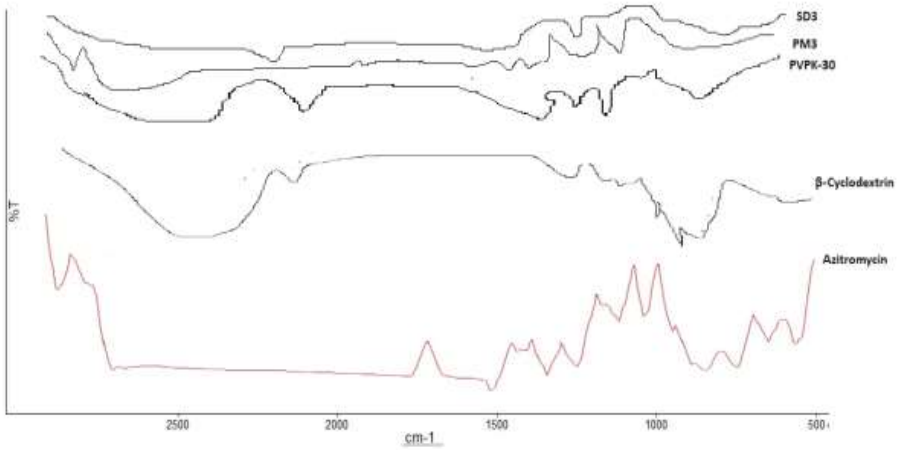


Figure: Powder X-ray diffraction

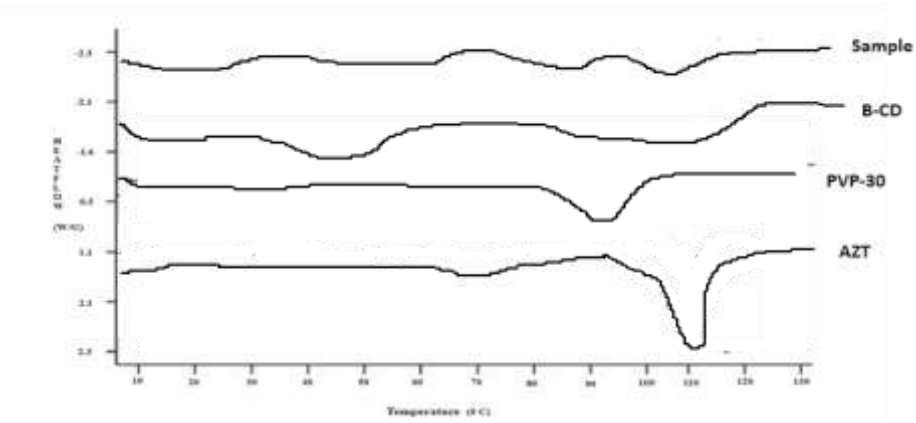
COMPATIBILITY STUDIES:

1. FTIR –overlay:

On the azithromycin vibrational bands at 2960, 1744, 1622, 1469, 1379, and 1355 cm −1, there was shaking at wavelengths of 1622, 1695, 1742, 2025, and 2219 cm -1. The vibrational bands at 2021 and 1844 cm −1 were assigned to the stretching frequency of N=C and C=O groups, respectively, while the absorption bands at 3648, 2830, and 2323 cm −1 agreed to -OH, -CH3, and O=C=O bond stretching in azithromycin. There was no discernible interaction between azithromycin and PVPK-30 or B-CYCLO DETRIN.



2. Differential scanning calorimetric analysis:



According to the above figure, there won't be any interactions with other polymers. Calorimetry using Differential Scanning (DSC) While the PVP-K-30 and B-CD complex with azitromycin did not have a melting peak of AZI, suggesting the absence of crystalline AZI in the solid dispersion, the DSC thermo gram of the AZI and PM revealed a melting peak at 119 °C (Figure), comparable to the melting peak of the pure drug. This could be the result of AZI changing from its crystalline to its amorphous state.

In vitro-Dissolution Studies:

Pure azithromyein Dihydrate had an extremely low rate of dissolution; at most, 34.22% of the medication was released in 120 minutes. Poor wet ability, agglomeration, or particle size could be the cause of the pure drug's poor dissolving. It was discovered that as the amount of hydrophilic carrier in physical combination batches grew, so did the drug's rate of dissolution. This resulted from the drug's increased solubility caused by the hydrophilic carrier that surrounded the drug particles. The figure displays the relative release profiles of different azithromycin dihydrate solid dispersions using a physical mixture that has a drug: carrier ratio of 1:3 (pvpk-30).

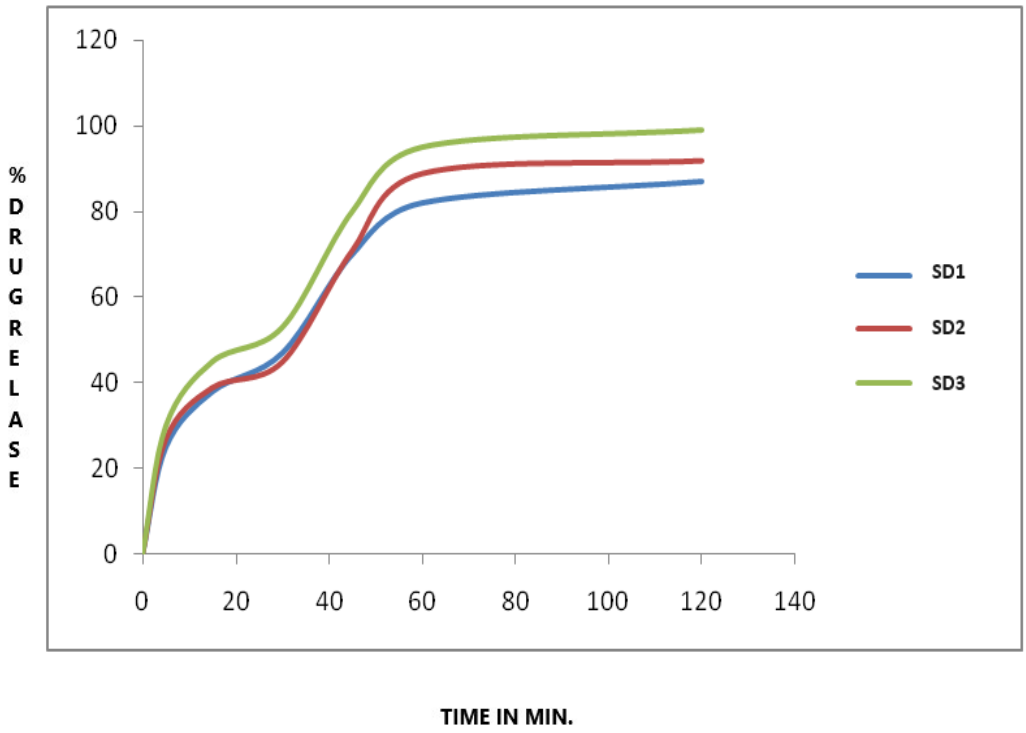


Fig: In vitro dissolution study of solid dispersion (DRUG: PVPK-30) in distilled water

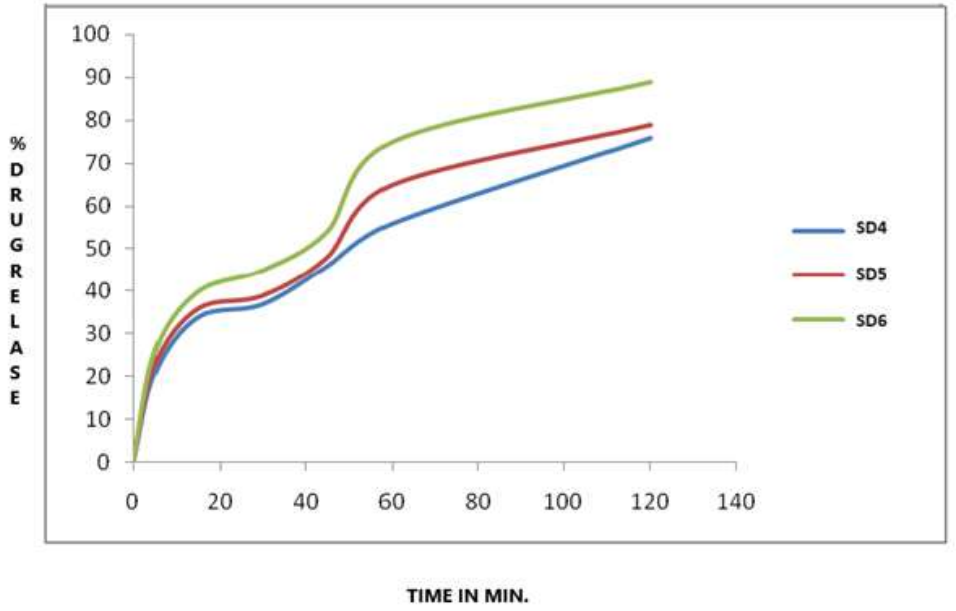


Fig: In vitro dissolution study of solid dispersion (DRUG: B-CCLODXTRIN) in distilled water

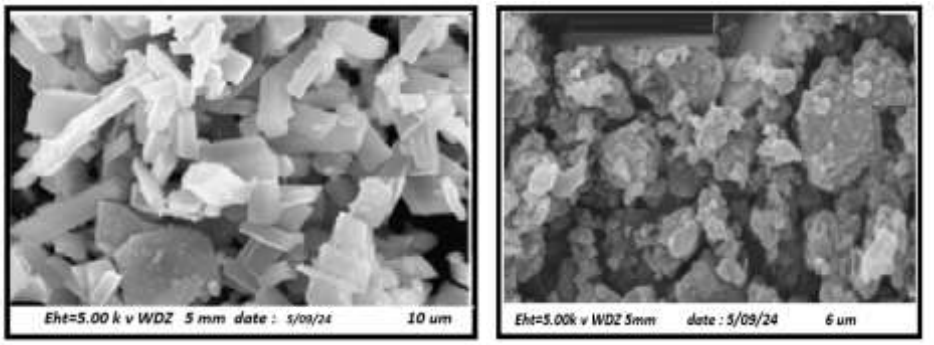


Fig: SEM OF azithromycin

SEM of batch sd3

From scanning electronic microscopy its revels that Azitromycin pure drug having flat, cubic structure indicates low solubility and solid dispersion batch SD 3 shows smaller particles which will be greater soluble than pure drug.

SUMMARY:

1. Solid dispersions significantly improved dissolution rates compared to pure Azithromycin Dihydrate.
2. FTIR and DSC studies confirmed no chemical interactions between the drug and carriers.

3. Powder X-ray diffraction revealed the crystalline nature of Azithromycin Dihydrate.
4. SEM images showed smaller particle sizes in solid dispersions, indicating increased solubility.

CONCLUSION:

The study was done to increase the dissolution and solubility of Azithromycin by using solid dispersion method. Different parameters were studied for dissolution and solubility like melting point, UV spectroscopy, FTIR, scanning, powder X-ray diffraction, and in vitro dissolution study. Melting point was determined found to be 120c .Further brief study should be carried out determined and enhanced the dissolution and solubility rate of Azithromycin.
In conclusion, this study successfully demonstrated the potential of solid dispersion technique using PVP K30 and β-Cyclodextrin as carriers to enhance the solubility and dissolution rate of Azithromycin Dihydrate by using solvent evaporation through spray drying. The optimized 1:3 drug-carrier ratio showed significant improvement in dissolution profile, making it a promising formulation strategy for improving the bioavailability of Azithromycin Dihydrate. From solid dispersion Batch SD3 shows higher solubility as well as dissolution rate as by using PVPK-30 Carrier.

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