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DISSOLUTION ENHANCEMENT OF POORLY SOLUBLE AZITHROMYCIN USING SOLID DISPERSION METHOD

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ABSTRACT

Solid dispersion technique is used to improve solubility and dissolution. So the main purpose of this investigation was to increase the solubility and dissolution rate of Azithromycin is incorporated with water soluble carriers with PEG 6000, Poloxamer 407, PVP K30 using solvent evaporation method. Physical mixtures and solid dispersions of Azithromycin were prepared by using as water-soluble carrier in various proportions (1:1, 1:2, 1:4, 1:6, by weight), by employing solvent evaporation method. Dissolution studies showed satisfied drug release. The prepared formulations were evaluated for percentage yield, drug content studies The drug and the carrier compatibility study were determined with the help of IR spectroscopy.

KEYWORD: Solid dispersion, PEG 6000, Poloxamer 407,PVP K30, Azithromycin.

INTRODUCTION

An enhanced demand for more patient-friendly and compliant dosage forms since past few years has been observed. Most preferred method of drug delivery is by oral route due to its convenience and ease of ingestion. Despite phenomenal advances in the inhalable, injectable, transdermal, nasal and other routes of administration, the unavoidable truth is that oral drug delivery remains well ahead as the preferred delivery route. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication.

Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption.

Oral bioavailability of drugs depends on its solubility and dissolution rate, so the major problems associated with these drugs was its very low solubility in body fluids, which results into poor bioavailability after oral administration. A drug with poor aqueous solubility will typically exhibit low dissolution rate so low absorption, and drug with poor membrane permeability will typically exhibit low permeation rate so low absorption Therefore, pharmaceutical researchers' focuses on two areas for improving the oral bioavailability of drugs include:

(i) Enhancing solubility and dissolution rate of poorly water-soluble drugs.

(ii) Enhancing permeability of poorly permeable drugs. (figure)

The demand for developing new technologies has been increasing annually. As the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost effective dosage forms**.** Example of such system is to develop the solid dispersions.

So solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs. [5]

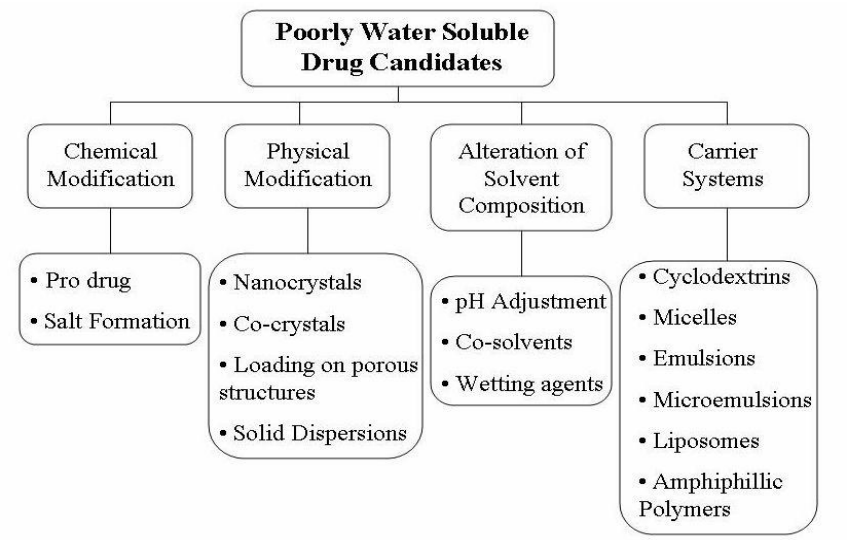


Figure: Approaches to Increase solubility /dissolution[2]

Definition of Solid dispersion

Chiou and Riegelman 1971, solid dispersion refers as group of solid product consist of at least two difference components, a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. Solid dispersion can also be referred as a dispersion of one or more active ingradients in a inert matrix at solid state prepared by the melting, solvent and melting solvent method. (figure) [8]

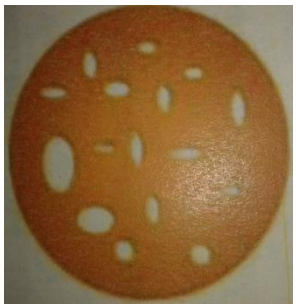


Figure: Solid dispersion of API in polymer matrix

MATERIAL

All the materials used were of pharmaceutical grade purity. Azithromycin obtained as a gift sample from Cipla Limited, Kurkumb, Daund. PEG 6000,Poloxamer 407,PVP K30 were of pharmaceutical grade. All other solvents and reagents were of analytical grades.

METHOD

Characterization and identification of drug

Physical characterization of drug

The drug was evaluated for physical characters and nature, odor, color and taste. The drug was putting on a clear surface and observing it by naked eye and noted down.

Determination of melting point

Capillary melting point or melting point apparatus are the most often used for the determination of the melting point of a solid. A few crystals of drug was placed in a thin walled capillary tube, closed to one end. The capillary which contains the sample and a thermometer were then suspended in melting point apparatus, so they can be heated slowly and evenly. The temperature range over the sample was observed to melt was taken as the melting point.

UV Spectroscopy of drug

Determination of ƛ max

A standard stock solution of drug was by dissolving accurately weighed 100 mg of pure drug and transferred into 100ml volumetric flask. The volume is made up using 0.1 N HCl to get a concentration of 1 mg/ml. from this solution. From this solution 10ml is withdrawn into 100 ml volumetric flask and it was diluted to 100 ml with 0.1N HCl to get a concentration of 100µg/ml. Again from this solution 1 mi is withdrawn into 10 ml volumetric flask diluted up to 10 ml with 0.1N HCl to get 10µg/ml. then UV spectrum was recorded in the wavelength range 200-400 nm.

Preparation of calibration curve for Azithromycin

Preparation of Azithromycin Stock Solution

100mg of Azithromycin was weighed and dissolved in few ml of ethanol. The drug solution obtained was filtered into 100ml volumetric flask and was further diluted to 100 ml with ethanol to get 1 mg/ml stock solution.

Preparation of Azithromycin Standard Dilutions

A standard solution was formed by dissolving 100 mg of Azithromycin in 100 ml of 0.1 N HCl. It was further diluted with 0.1N HCl to get concentration 100µg/ml. from this 2, 4, 6, and 8ml are pipette out into 10 ml volumetric flask and diluted with 0.1N HC to get concentration range of 20, 40, 60, and 80µg/ml respectively. Absorbance of this solution was measured at 215 nm using UV spectrophotometer. Using concentration and absorbance data, a beer and Lambert's plot was obtained.

Determination of solubility of Azithromycin

Saturated solution of drug was prepared using 10 ml 0.1N HCl in 25 ml volumetric flask in triplicate. Precaution was taken so that the drug remains in medium in excess. Then by using vortex shaker, the flask were shaken for 48 hrs at the under temperature of 25°C. The sample withdrawn (1 ml after filtration) was diluted with appropriate medium and analysed by using UV spectrophotometer at 215 nm for 0.1N HCl respectively. The average value of tree trials was taken.

Stability studies

Solid state stability studies:- The drug and polymer must be compatible with one another to produce a product that is stable efficacious, attractive, and easy to administer and safe. Drug and polymers in 1:1 ratios were mixed and store in a glass vials at different temperature and relative humidity. The samples were analyzed for any color change, cracking, liquefaction and discoloration.

Solution state stability: it is determined by placing the drug in 0.1N HCl and then by taking the scan of samples at various time intervals 12, 24, 48 hours for determination of ƛ max.

- **Formulation Of Solid Dispersion**

Preparation of solid dispersion

Solid dispersion containing different ratios of Azithromycin and three different carriers i.e. the first carrier PEG 6000, second carrier Poloxamer 407 and third carrier Polyvinylpyrrolidone (PVP K30) were prepared by melting solvent method (Melt Evaporation). The ratio of drug and carrier were 1:1, 1:2, 1:4, 1:6.

Method of preparation of solid dispersion

- The solid dispersions of Azithromycin and PEG 6000 (carrier) in various drug-to-carrier weight ratios were 1:1, 1:2, 1:4 and 1:6, prepared by melting solvent method (Melt Evaporation). The 100 mg of Azithromycin was dissolved in 20 ml of ethanol in a beaker and carrier was melted in another beaker then incorporating the drug solution directly into the melt of PEG 6000 (carrier), which is then evaporated on a hot plate until a clear, solvent free film is left. The film is further dried to constant weight. Solid Dispersions prepared were crushed, pulverized and sifted through mesh number 80 and prepared solid dispersion stored in well closed container in the desicator.

The solid dispersions of Azithromycin and Poloxamer 407 (carrier) in various drug-to-carrier weight ratios were 1:1, 1:2, 1:4 and 1:6, prepared by melting solvent method (Melt Evaporation). The 100 mg of Azithromycin was dissolved in 20 ml of ethanol in a beaker and carrier was melted in another beaker then incorporating the drug solution directly into the melt of PEG 6000 (carrier), which is then evaporated on a hot plate until a clear, solvent free film is left. The film is further dried to constant weight. Solid Dispersions prepared were crushed, pulverized and sifted through mesh number 80 and prepared solid dispersion stored in well closed container in the desicator.

The solid dispersions of Azithromycin and Polyvinylpyrrolidone (PVP K30) carrier in various drug-to-carrier weight ratios were 1:1, 1:2, 1:4 and 1:6, prepared by melting solvent method (Melt Evaporation). The 100 mg of Azithromycin was dissolved in 20 ml of ethanol in a beaker and carrier was melted in another beaker then incorporating the drug solution directly into the melt of PEG 6000 (carrier), which is then evaporated on a hot plate until a clear, solvent free film is left. The film is further dried to constant weight. Solid Dispersions prepared were crushed, pulverized and sifted through mesh number 80 and prepared solid dispersion stored in well closed container in the desicator.

Table: Details of Formulation composition

Formulation code	Carrier	Drug:Carrier ratio	Method
SD1	PEG 6000	1:1	Melting solvent Method (Melt Evaporation)
SD2		1:2	
SD3		1:4	
SD4		1:6	
SD5	Poloxamer 407	1:1	Melting solvent Method (Melt Evaporation)
SD6		1:2	
SD7		1:4	
SD8		1:6	
SD9	PVP K30	1:1	Melting solvent Method (Melt Evaporation)
SD10		1:2	
SD11		1:4	
SD12		1:6	

*One part is equal to 100 mg

RESULT AND DISCUSSION

Characterization and Identification of Drug

A) Physical characterization of the drug

The drug was evaluated for physical characters, color, and taste was noted down.

Table: Characterization of drug

State	Crystalline powder
Physical state	Crystalline powder
Color	White
Taste	Bitter

B) Determination of melting point

The melting point was found in triplicate 112°C, 114°C, 111°C.

The average melting point was found to be 112.33°C.

The reported melting point is 113°C.

C) UV Spectroscopy study

1) Determination of ƛ max

The UV visible spectrum of Azithromycin in 0.1N HCl phosphate buffer is ƛmax shown at maximum corresponding to 215 nm.

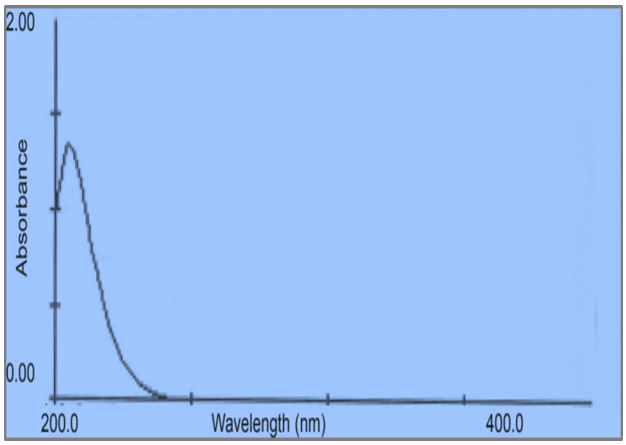


Figure: UV spectra of azithromycin

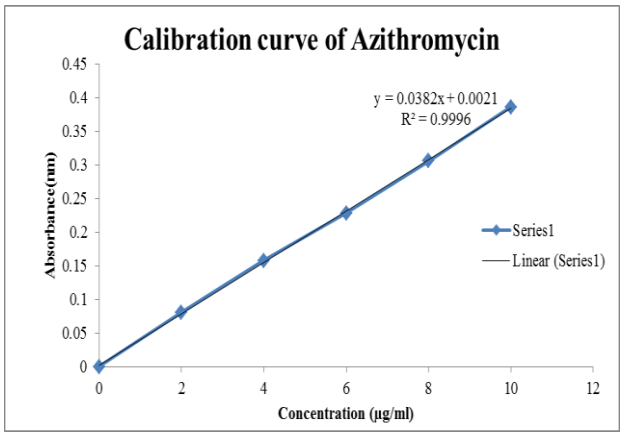


Figure: Calibration curve for the Estimation of Azithromycin in 0.1N HCl buffer.

Table: Result of calibration curve

Parameters	Result
Regression equation	Y=0.038X-0.002
Correlation coefficient (R^2)	0.999
Calibration range	2-10

Solubility measurement

The solubility of Azithromycin was determined and found very as µg/ml in 0.1N HCl. The solubility in 0.1N HCl was found to be 0.58 mg/ml, i.e. Azithromycin slightly soluble in 0.1N HCl.

2) Calibration curve of Azithromycin in 0.1N HCl

The table shows the absorbance value of different concentration of Azithromycin in 0.1N HCl at 215 nm. The calibration curve was plotted as shown in figure in concentration range of 2-10µg/ml after regression of data as shown in table the value of R^2 was found to be 0.999 which indicate accuracy of result.

Table: Calibration curve of Azithromycin in 0.1N HCl

Sr. no.	Concentration (µg/ml)	Absorbance (nm)
0	0	0
1	2	0.081
2	4	0.158
3	6	0.228
4	8	0.306
5	10	0.386

Stability studies

A) Solid state stability study: Solid state compatible study was done for 30 days at different temperature. Initially at 0 day drug and polymers were mix and check its compatibility like color, odor and moisture content. There is no change at different temperature. After that it was stored for 30 days at different temperature. After 7 days , sample of Azithromycin and carrier were observed there is no change. In 15 days, check the sample at different temperature there was no change in color, odor and moisture content. After 30 days, sample of Azithromycin with carrier was again checked and there is no change in any physical appearance. There is no changes in color or any other type of incompatibility as tabulated in table 6.4. So we can say that both drug and carrier are compatible with each other.

Table: Drug and carrier stability study

Sample	Ratio	30 Days 25°C/60%RH				30 Days 30°C/65%RH				30 Days 40°C/75%RH			
		0 Day	7 Day	15 Day	30 Day	O Day	7 Day	15 Day	30 Day	0 Day	7 Day	15 Day	30 Day
Drug	1	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Drug+ PEG6000	1:1	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Drug+ poloxamer 407	1:1	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Drug+ PVP K30	1:1	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC

NC: No change

B) Solution state stability study

The ƛmax obtained for drug by taking scan at time interval of 12, 24 and 48 hrs of sample is constant i.e. 215 and it is not changing with the various time interval as mention below in table 6.6. So drug is stable in the solution at various intervals of time.

Table: Solution state solubility of Azithromycin

Serial No.	Time (hrs.)	ƛ max
1	12	215
2	24	215
3	48	215

Evaluation Of Formulation

Estimation of practical yield

Percentage practical yield was calculated to know about percent yield or efficacy of any method, thus its help in selection of appropriate method in production. The practical yield increases as polymer concentration increases. The highest practical yield is 93.1 and minimum practical yield is 69.8.

Table: Estimation of practical yield of Axithromycin solid dispersion

S. No.	FORMULATION	% PRACTICAL YIELD OF SOLID DISPERSION
1	SD1	71.2
2	SD2	69.8
3	SD3	85.9
4	SD4	87.3
5	SD5	86.7
6	SD6	82.3
7	SD7	90.5
8	SD8	93.1
9	SD9	75.4
10	SD10	79.2
11	SD11	74.8
12	SD12	91.7

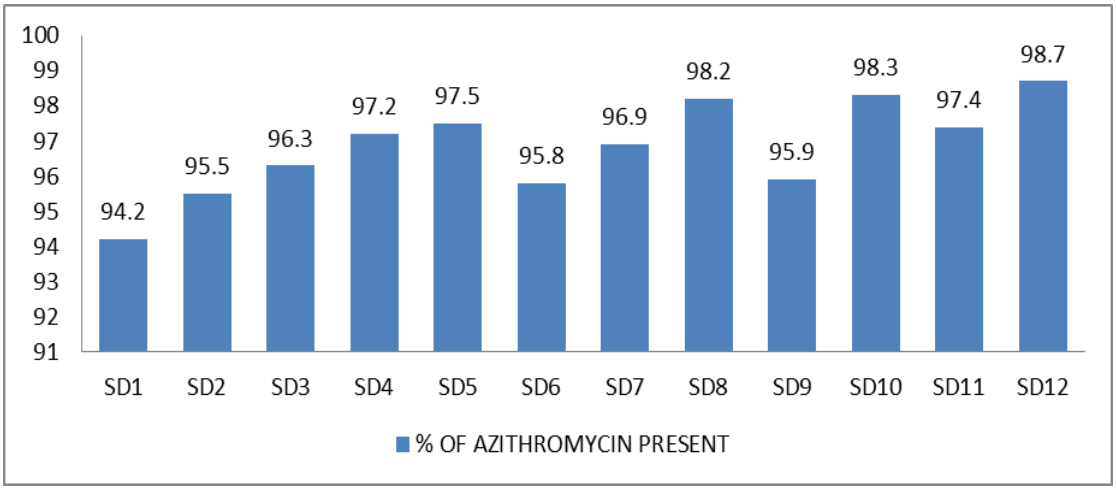


Figure: % practical yield of solid dispersion

Drug content uniformity

The drug content uniformity was in the range of 94.2 to 98.3. All solid dispersion showed presence of high drug content and low standard deviation results. It is indicated that drug is uniformly dispersed in the powder formulation.

Table: Estimation of drug content uniformity

S.NO	FORMULATION	% OF AZITHROMYCIN PRESENT
1	SD1	94.2
2	SD2	95.5
3	SD3	96.3
4	SD4	97.2
5	SD5	97.5
6	SD6	95.8
7	SD7	96.9
8	SD8	98.2
9	SD9	95.9
10	SD10	98.3
11	SD11	97.4
12	SD12	98.7

The result indicating that the

- The formulation SD4 prepared using PEG 6000 showed 97.2% of drug content.
- The formulation SD8 prepared using poloxamer 407 showed 98.2% of drug content.
- The formulation SD12 prepared using PVP K30 showed 98.7% of drug content.

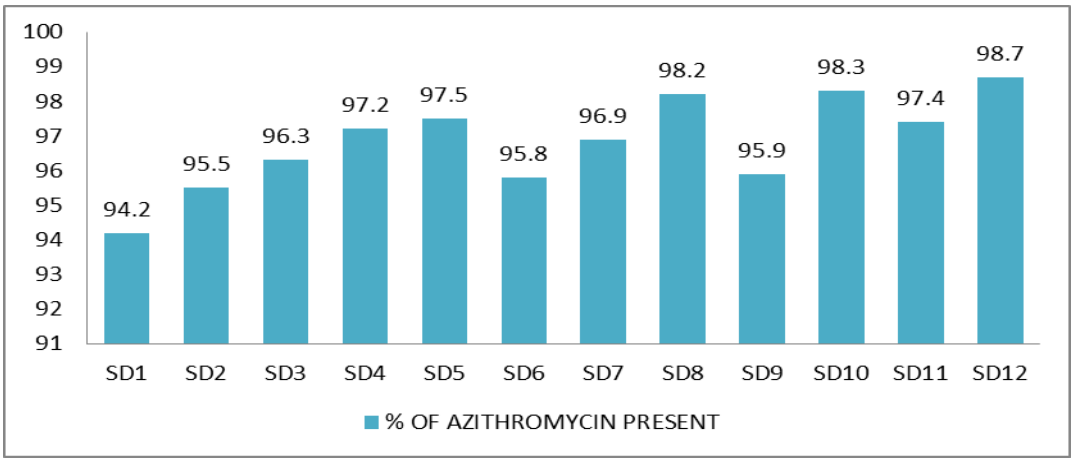
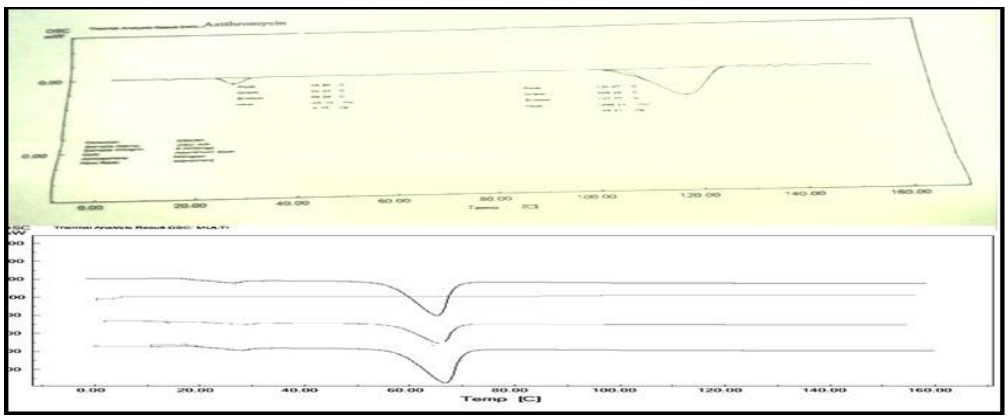


Figure: Drug content uniformity of Azithromycin in solid dispersion

DSC study

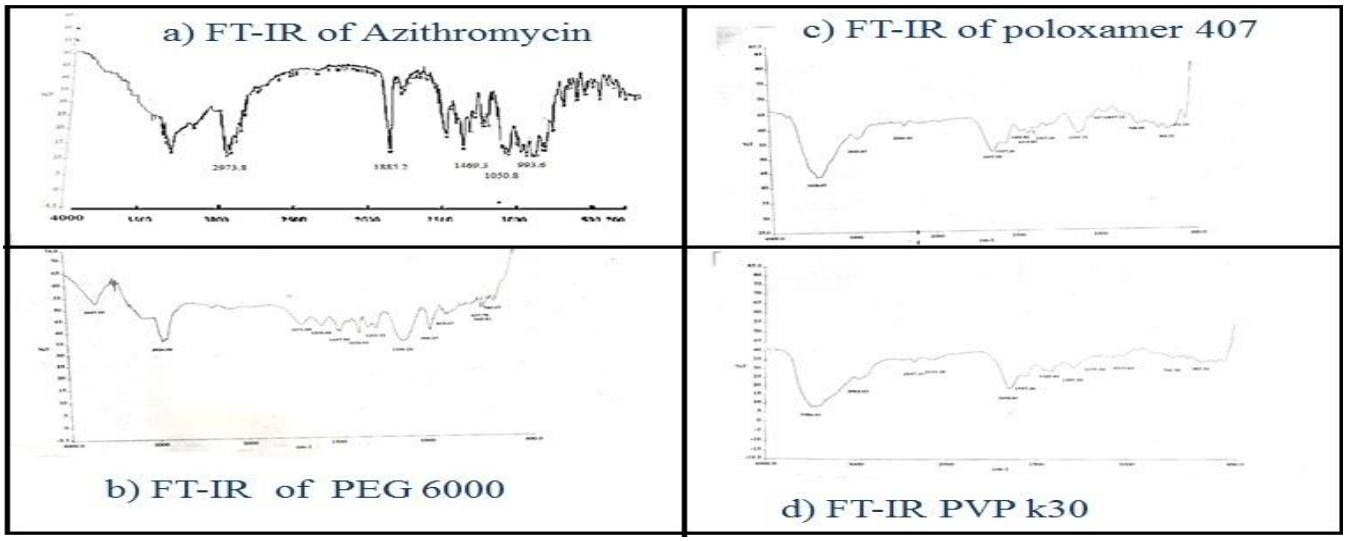
The DSE curve of pure drug and drug with carrier was carried out by DSC Pyrix 1 Perkin Elmer. DSC spectra of pure Azithromycin and solid dispersion of Azithromycin with PEG 6000, Poloxamer 407 and PVP K30 was obtained.



The DSC of pure Azithromycin exhibit a sharp endothermic fusion peak corresponding to the melting point of drug. Onset of melting point was observed at 124.9°C and indicate the crystalline nature of the drug. However, the characteristic sharp endothermic peak corresponding to the drug melting was broadened and shifted towards a lower temperature with reduced intensity in solid dispersion.

FT-IR study

FT-IR studies were done to detect the possible interactions between the Azithromycin and carrier. The characteristic peaks of Azithromycin, PEG 6000, poloxamer 407 and PVP K30 are presented in Annexure. It was revealed that there were no differences in the positions of the absorption bands, hence providing evidence for the absence of interactions in the solid state between Azithromycin and carrier.



- Pure Azithromycin spectra showed sharp characterstic peaks at 2973.80, 1985.20, 1469.30, 1050.80 and 993.60cm^{-1}. Its show (aromatic C-H stretching), (C=O steching vibration), (asymmetric aromatic O-H stretching).
- The band of solid dispersion with Azithromycin and PEG 6000 was 3667.09, 2924, 1661.69, 1106.22 and 859.07.
- The band found with poloxamer 407 and Azithromycin solid dispersion were 3438.67, 2360.07, 1637.39 and 563.21.
- The peak with PVP K30 solid dispersion were 3486.01, 2347.25, 1650.61 and 741.91.

All characterstic peaks appear in the spectra of all solid dispersion at same wave number indicating no modification or interaction between the drug and polymers.

***In vitro* dissolution study**

The dissolution rate of pure Azithromyein Dihydrate was very poor and during 90 min a maximum about 32.8% of the drug was released. The reason for the poor dissolution of pure drug could be poor wettability and/ or agglomeration or particles size.The formulation of solid dispersion of Azithromycin with different carriers like PEG 6000, poloxamer 407 and PVP K30 were screened for selection of suitable carriers. These carrier were found to be encouraging since they did not undergo any chemical change during the preparation of solid dispersion. The solid dispersion of Azithromycin with carriers PEG 6000, poloxamer 407 and PVP K30 showed a marked increase in the dissolution rate in 0.1N HCl. Dissolution of the Azithromycin increased with increasing proportion of carriers and form all the formulation, the formulation, the carrier (Poloxamer 407) in the ratio of **Azithromycin:PVP K30 (SD12)(1:6)** shows the higher dissolution rate. These observations indicate the enhanced dissolution of solid dispersions with increase in the concentration of carriers possible due to wet-ability of the drug by the carrier, drug particle size reduction in the course of solid dispersion preparation, polymeric transformation of drug crystals.

Table In vitro release of Azithromycin with PEG 6000

Time (min)	% Cumulative drug released				
	Azithromycin	SD1	SD2	SD3	SD4
5	3.43	5.65	29.25	34.18	19.78
10	5.28	8.25	35.43	37.35	24.13
20	9.69	14.59	40.76	45.23	27.98
30	13.95	20.73	43.69	53.46	35.62
45	18.75	28.85	46.19	61.32	42.47
60	27.58	41.57	49.98	78.75	55.62
90	32.80	48.95	55.12	89.67	62.38

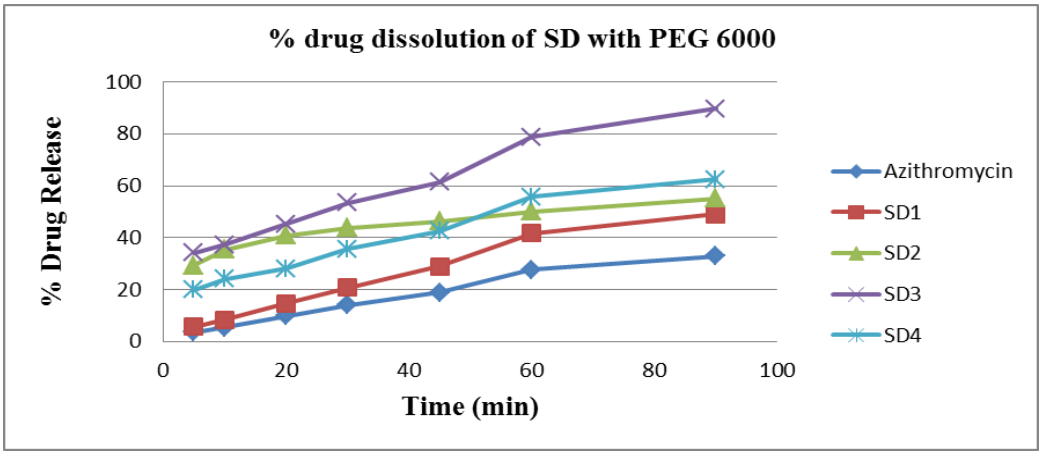


Figure: dissolution profile of PEG 6000 Solid Dispersion

The result showed that

- The dissolution of pure Azithromycin was found drug release minimum 3.43 and maximum 32.80.
- The in vitro dissolution study of all formulation having PEG 6000, shows the cumulative % of drug release minimum 48.95 and maximum 89.67 at the end of 90 minutes.
- The result indicated that SD3 having higher cumulative release of drug with PEG 6000. Possible mechanisms of increased dissolution rates of drug in solid dispersions due to wettability and disposability of drug from the dispersion, solubilization effect of carrier, absence of aggregation of drug, reduction in drug crystallinity and conversion of drug to the amorphous state.

Table: In vitro release of Azithromycin with Poloxamer 407

Time (min)	% Cumulative drug released				
	Azithromycin	SD5	SD6	SD7	SD8
5	3.43	5.26	7.64	17.69	25.15
10	5.28	9.46	11.00	27.54	32.86
20	9.69	16.82	19.26	38.15	40.53
30	13.95	26.35	31.85	46.56	48.25
45	18.75	36.69	39.73	54.25	57.35
60	27.58	40.25	44.68	62.58	69.95
90	32.80	46.89	49.78	69.35	81.65

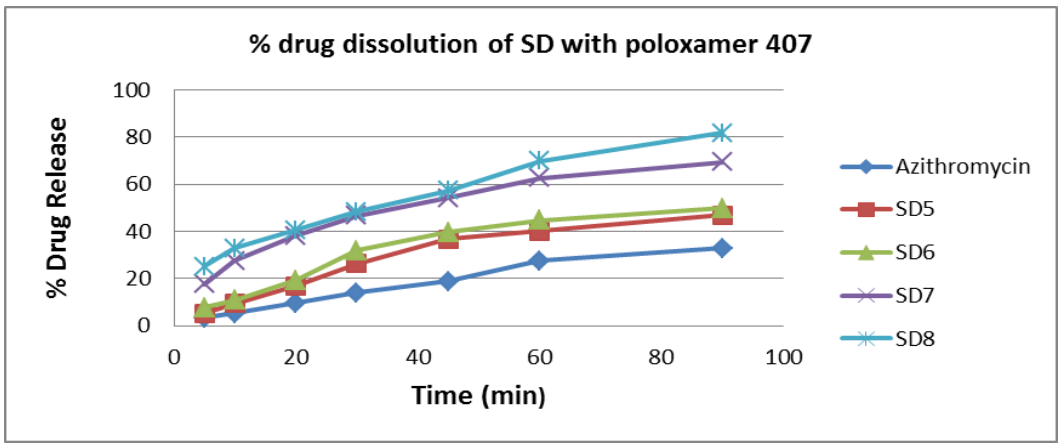


Figure: Dissolution profile of poloxamer 407 solid dispersion

The result showed that

- The dissolution of pure Aithromycin was found drug release minimum 3.43 and maximum 32.80
- The in vitro dissolution study of all formulation having poloxamer 407, shows the cumulative % of drug release minimum 46.89 and maximum 81.65 at the end of 90 minutes.
- The result indicated that SD8 having higher cumulative release of drug with poloxamer 407. The increase in dissolution rate due to wetting, solubilization and change of drug into amorphous phase.

Table: In vitro release of Azithromycin with PVP K30

Time (min)	% Cumulative drug released				
	Azithromycin	SD9	SD10	SD11	SD12
5	3.43	23.85	25.23	27.95	33.64
10	5.28	31.75	32.63	35.30	41.24
20	9.69	38.89	40.56	42.76	52.85
30	13.95	49.56	52.36	54.35	65.25
45	18.75	58.25	63.85	65.15	78.75
60	27.58	66.45	68.25	72.56	85.32
90	32.80	69.68	74.45	80.68	92.69

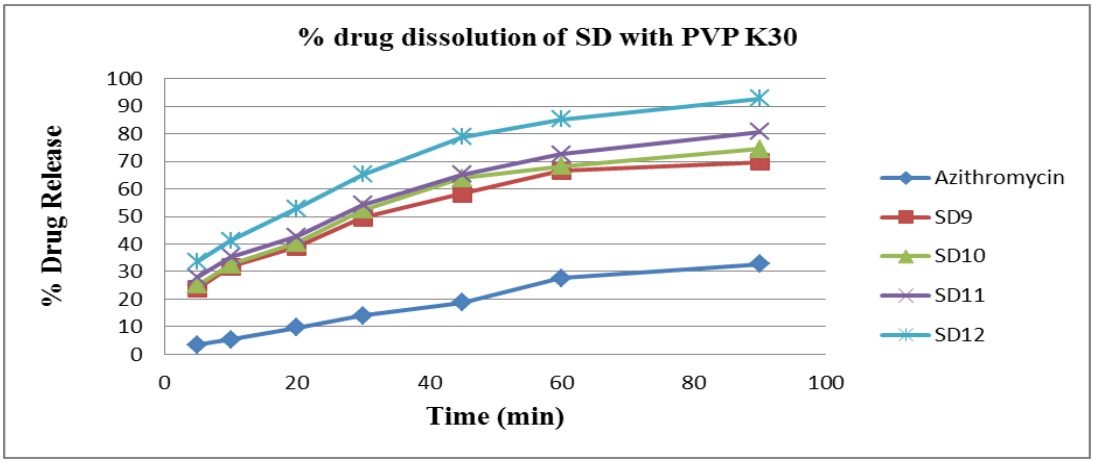


Figure: Dissolution profile of PVP K30 solid dispersion

The result showed that

- The dissolution of pure Azithromycin was found drug release minimum 3.43 and maximum 32.80.
- The in vitro dissolution study of all formulation having PVP K30, shows the cumulative % of drug release minimum 69.68 and maximum 92.69 at the end of 90 minutes.
- The result indicated that SD12 having higher cumulative release of drug with PVP K30 because of wettability, change in amorphous state and surface active properties and solubilization effect of polymer.

The increase in dissolution rate in order of
PVP K30>PEG 6000>poloxamer 407
From above it mean that PVP show higher dissolution rate.

In the present research work dissolution of azithromycin solid dispersion enhanced by using different carrier, hence solubility and bioavailability of azithromycin also enhanced by using solid dispersion method.

Summary
In this work an attempt was mad to formulate and evaluate solid dispersion for the drug of Azithromycin by melting solvent method (Melt Evaporation). Low water solubility, low molecular weight, good permeability and shorter half life of Azithromycin made it suitable drug candidate for the development of solid dispersion.

The main objective of formulating solid dispersion was enhance the dissolution, solubility and bioavailability of Azithromycin drug and increase the frequency of administration and improve the patient compliance.

The Three different carriers used i.e. PEG 6000, Poloxamer 407 and PVP K30 Twelve formulation were prepared using these carriers in different ratios. Solid dispersion were evaluated for % practical yield, % drug content, stability and dissolution study.

FT-IR used for identification of drug and drug-carrier compatibility. DSC gradually decreases in crystallinity of drug with increase proportions of carriers. The in vitro dissolution study was carried out in 0.1N HCl for 90 minutes. The release data obtained for formulations SD1-SD12 are table 6.9, 6.10, 6.11. Figure 6.4, 6.5, 6.6, 6.7, shows the plot of cumulative % drug released after 90 minutes was PEG 6000: 89.67%, poloxamer 407: 81.65% and PVP K30: 92.69% respectively and was 32.8% in 90 min of pure Azithromycin.

The formulation with PVP K30 in the ratio of 1:6 showed the best dissolution study.
There is scope for the further study and development of solid dispersion.

CONCLUSION

- Azithromycin, a macrolide antibiotic drug has been selected which has low water solubility and low half time. Hence in the present work an attempt has been

made to provide solid dispersion using water soluble carriers with Azithromycin as a drug model.

- IR study shows that there is no incompatibility between drug and carriers.
- The solid dispersion were prepared using fusion method using different carriers PEG 6000. Poloxamer 407 and PVP K30 in different ratios.
- The in vitro dissolution study shows there is increased in the dissolution rate of Azithromycin of all solid dispersion when compared with pure Azithromycin. The increase in dissolution rate and solubility in the order of PVP K30>PEG 6000>poloxamer 407.
  The maximum % cumulative release was 92.69% over a period of 90 minutes using PVP K30 (1:6).

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