https://doi.org/10.33472/AFJBS.6.6.2024.1761-1775

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Formulating Amorphous Azithromycin Solid Dispersion using Mannitol and Povidone K30 for Improving Aqueous Solubility and Dissolution Rate (*in vitro*)

Mrs. Pallavi Swarup[1,2], Dr. Gopal Prasad Agrawal[2]*

1. Agra Public Pharmacy College, Heera lal Ki Pyau, Village Artoni, Delhi–Agra National Highway (NH 2), Agra - 282007, INDIA
2. Institute of Pharmaceutical Research, GLA University, Mathura-281406 (U.P.) INDIA

*Corresponding Author e-mail: gopalprasad.agrawal@gla.ac.in
Ph. No- +91-9917929841

Article Info

Volume 6, Issue 6, May 2024

Received: 30 March 2024

Accepted: 24 April 2024

Published: 28 May 2024

doi: 10.33472/AFJBS.6.6.2024.1761-1775

Abstract

The primary objective of this investigation was to improve the aqueous solubility as well as dissolution rate of Azithromycin using Mannitol and Povidone K30 for formulating solid dispersions of the drug. Various by weight ratios (1:1, 1:2 & 1:3) of the drug and carrier were used in kneading and melt agglomeration methods for formulating the solid dispersions. Solubility study was performed in distilled water while the dissolution studies were carried out in phosphate buffer pH 7.4. The differential scanning calorimetry theromogram revealed that no interaction between the drug and the carriers occurred. The SD was able to improve the solubility of AZI from around 4 to 16 times. The formulation **F7** (1:1, Povidone K30, kneading) released minimum AZI (16.43 % ± 0.709 %) while **F6** (1:3, Mannitol, melt agglomeration) released the highest amount of AZI (84.23 % ± 1.677 %) after 30 min of dissolution study. Our results led to the conclusion that the aqueous solubility and dissolution rate of Azithromycin could be effectively enhanced using Mannitol and Povidone K30 as carriers for solid dispersion. Furthermore, the simplicity of the methods used for formulating the solid dispersion meets the objectives of the study.

Keywords

Azithromycin, Kneading, Melt Agglomeration, Solid Dispersion, Mannitol, PVP K30

Introduction

Azithromycin (AZI) (Figure 1) is a semisynthetic macrolide antibiotic and is one of the most commonly prescribed antibiotics for pediatric patients[1]. It has poor aqeuous solubility and low dissolution rate in the gastrointestinal tract, which limits the bioavailability after oral administration[2,3]. The drug has an oral bioavailability of around 37% and pKa of 8.74[4]. Additionally a unpleasantly bitter taste of AZI makes it non-compliant for oral administration to pediatric patients[5].

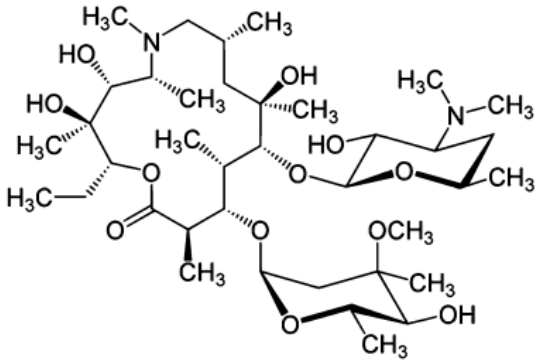


Figure 1 Chemical structure of AZI

Drug with poor aqueous solubility are expected to exhibit absorption dependent on dissolution of the drug. Therefore increasing the solubility leads to an improved absorption and eventually bioavailability of the drug[6]. Various methods like cosolvency, micronization, nanonization, self-emulsification, solubilization, solid dispersion and complexation are employed in the enhancement of solubility of poorly soluble drugs[7].

Solid dispersion (SD) is a technique wherein the active pharmaceutical ingredient (API) is dispersed in an inert matrix or polymer. Solid dispersions of many poorly water-soluble drugs by incorporating them into a water-soluble polymer matrix have been considered as an effective method for improving drug dissolution rate and their saturation solubility in the gastrointestinal fluids[8]. SD is widely accepted as an effective formulation technology to improve dissolution and bioavailability of the molecules as well as to mask unpleasant taste of API by virtue of its ability to reduce particle size, create high porosity and wettability as well as formation of amorphous API[9-11].

Kneading has been employed to prepare binary systems containing Povidone (PVP) and has displayed enhancement in solubility significantly[12]. Melt-Agglomeration (MA) is also established as an effective technique for formulation of amorphous SD[13]. Even though studies have been previously carried out for formulating SD of AZI using polymers like Poly ethylene glycol, Primogel, Kolliphor etc[4,14-23], a void is still present in obtaining a highly effective binary system of AZI and its use in oral solutions.

The objective of the present study is to achieve enhanced solubility and dissolution of AZI by formulation as SD for utilizing the SD for preparation oral solution The SD were prepared using mannitol as well PVP K30 as the carrier and utilizing melt-agglomeration and kneading methodology.

Material and Methods

Materials

AZI was obtained as a generous gift sample from Ind-Swift Laboratories Limited, Baddi. Mannitol was purchased from Fisher Scientific and PVP K30 was procured from Himedia. All additional materials utilized were of pharmacopoeial grade and obtained from a variety of commercial sources.

Methods

Solubility Study

AZI (15 mg) was added to 20 mL distilled water in conical flask, and shaken at 28°C room temperature for 24 h. Resultant samples containing undissolved solid dispersions suspended in the test medium were centrifuged at 10,000 rpm for 5 min, and the clear supernatants obtained was filtered, suitably diluted with distilled water, and analyzed by spectrophotometer. The drug content in the solution was determined using the equation obtained from the calibration curve.

Preparation of solid dispersions by Melt Agglomeration method

The SD containing AZI were prepared using two different carrier viz. mannitol and PVP K30 in 1:1, 1:2 and 1:3 ratios by mass. AZI and carrier were accurately weighed and mixed physically in a dry porcelain dish and the mixture was heated on a paraffin bath till molten[24-26]. The molten mixture was poured on a clean tile and allowed to cool and solidify. The resulting solidified mass was dried, and pulverized and finally passed through 100 mesh sieve. The powdered SD was stored in screw capped vials at room temperature for further analyses.

Preparation of SD by kneading

Accurately weighed quantity of AZI and the carrier were triturated using mortar and pestle to obtain the physical mixtures. The physical mixtures were triturated using a small volume of ethanol-water (1:1) solution to make a thick paste, which was then knead and then dried at 45°C in an oven. The dried mass that was obtained was passed through 24 mesh sieve, dried again and sieved through 100 to obtained fine powder of SD[25].

Particle size of SD

SD particles are observed under microscope using calibrated ocular micrometer (ERMA) to calculate the average particle size of the solid dispersion. SD was dispersed in water and a drop of the dispersion was placed on glass slide and viewed under microscope. The number of divisions of ocular micrometer occupied by particles was counted.

Calibration curve of AZI

The calibration curve of AZI was prepared in the range 10 to 50 µg/ml by dissolving 10 mg of AZI in 10 ml of 0.1M HCl to obtain the stock solution. The working standards were prepared by pipetting required quantity of stock solution in 10 ml volumetric flasks and making up the volume up to mark by phosphate buffer pH 6.8.The UV absorption maximum of AZI was scanned in phosphate buffer pH 6.8 and was found to be 210 nm[27].A plot of concentration versus absorbance was prepared and the regression equation was obtained using MS Excel software.

Drug content in SD

Accurately weighed amount of SD (15 mg) was dissolved in phosphate buffer pH 6.8 and the amount of drug is calculated using absorbance data at 210 nm using UV Visible spectrophotometer[27].

Phase-Solubility Study

AZI, physical mixture of AZI with PVP K30 (PMPVP) & AZI with mannitol (PMMan) and SD equivalent to 15 mg of AZI were added to 20 mL distilled water in conical flask, and shaken at 28°C room temperature for 24 h[28,29]. Resultant samples containing undissolved solid dispersions suspended in the test medium were centrifuged at 10,000 rpm for 5 min, and the clear supernatants obtained were filtered, suitably diluted with distilled water, and analyzed by spectrophotometer. The drug content in the solution was determined using the equation obtained from the calibration curve.

Thermal Analysis

Differential scanning calorimetric (DSC) method was used to study the effect of heat on the stability of AZI as well as to observe the interaction of the drug and the carriers. Briefly, 3.100 mg of sample was pressed in aluminum pan disc and placed on the heating head of DSC instrument (Jade DSC, Perkin) and temperature of the DSC furnace was gradually increased from 30°C to 300°C. The thermogram was obtained from the software (Pyris 6 DSC).

In vitro Dissolution of SD

The *in vitro* dissolution study was done using paddle type dissolution apparatus (Labtronics, LT-731), stirred at 50 rpm, maintaining the temperature of the dissolution media (phosphate buffer, pH 7.4) at 37±1°C[28]. AZI or SD equivalent to 100 mg AZI were used for the study. Sample (5 mL) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted, and assayed for AZI.

Stability study

The solid dispersion kept under accelerated conditions (4°C, RT and 40°C) for stability study in a stability oven (Labtronics, LAB-1852) for three months. At the end of the third month, the drug content in the solution under each storage condition was determined to assess the stability of the solid dispersion

Results and Discussion

Solubility of AZI

The solubility study of AZI was performed in water and the amount of drug solubilized was calculated by the calibration curve equation. It was found that only 19 µg drug was soluble in per ml of water.

Preparation of SD

The SD containing AZI were prepared in various mass ratios of drug and carrier (Table 1).Six SD formulations each were prepared using MA method (F1-F6) and kneading method (F7-F12). Previous studies involving SD preparations containing AZI has widely investigated solvent evaporation method[30]. Nevertheless in the present study MA and kneading methods were utilized as these methods have lesser chances of residual solvents in the final preparation due to non-use or very limited use of organic solvents[31].

Table 1 Design table for preparation of SD using MA and kneading techniques

Formulation	**F1/F7**	**F2/F8**	**F3/F9**	**F4/F10**	**F5/F11**	**F6/F12**
X1 (D:P)	1:1	1:2	1:3	1:1	1:2	1:3
Quantity used (g)	0.5/0.5	0.5 /1.0	0.5 /1.5	0.5/0.5	0.5 /1.0	0.5 /1.5
X2 (Polymer)	PVP K30	PVP K30	PVP K30	Mannitol	Mannitol	Mannitol

Morphology and particle size

A calibrated ocular micrometer was used to measure the size of the SD particles under a microscope equipped with image analyser. The particles were irregular to spherical in shape (Figure 2) and the average particle size ranged from 34.90 to 38.09 µm for the particles. The particularly stable size was obtained as all the particles were finally passed through sieve of 100 mesh.

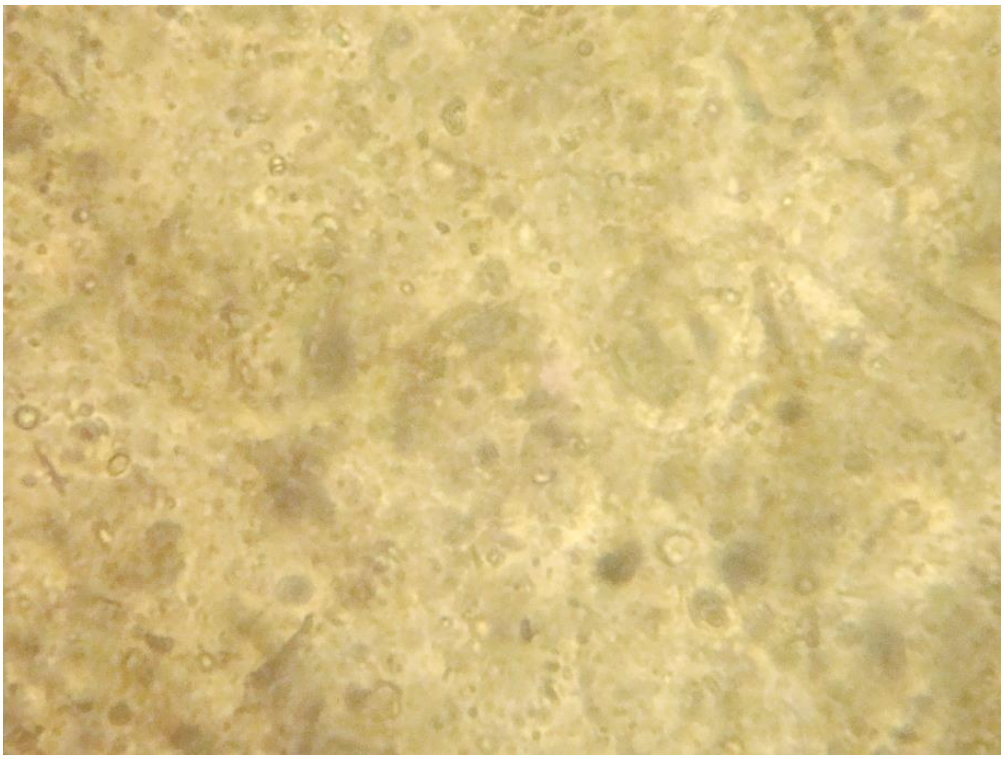


Figure 2 Microscopic image of F2 (200X magnification) showing spherical particles of solid dispersion

SEM was used to elucidate the exterior and form characteristics of the samples. The physical mixture displayed heterogeneous crystals of variable sizes (Figure 3(A)). The SD prepared with mannitol on the other hand displayed smoother surface leaving behind the morphology of the original components of the mixture and a few acicular crystals were present on the surface (Figure 3(B)). The SD prepared using PVP were having smooth surface not showing much crystals on the surface (Figure 3(C)). These results suggest that AZI might have been dispersed homogenously in the matrix of the SD and could possibly be existing in amorphous state.

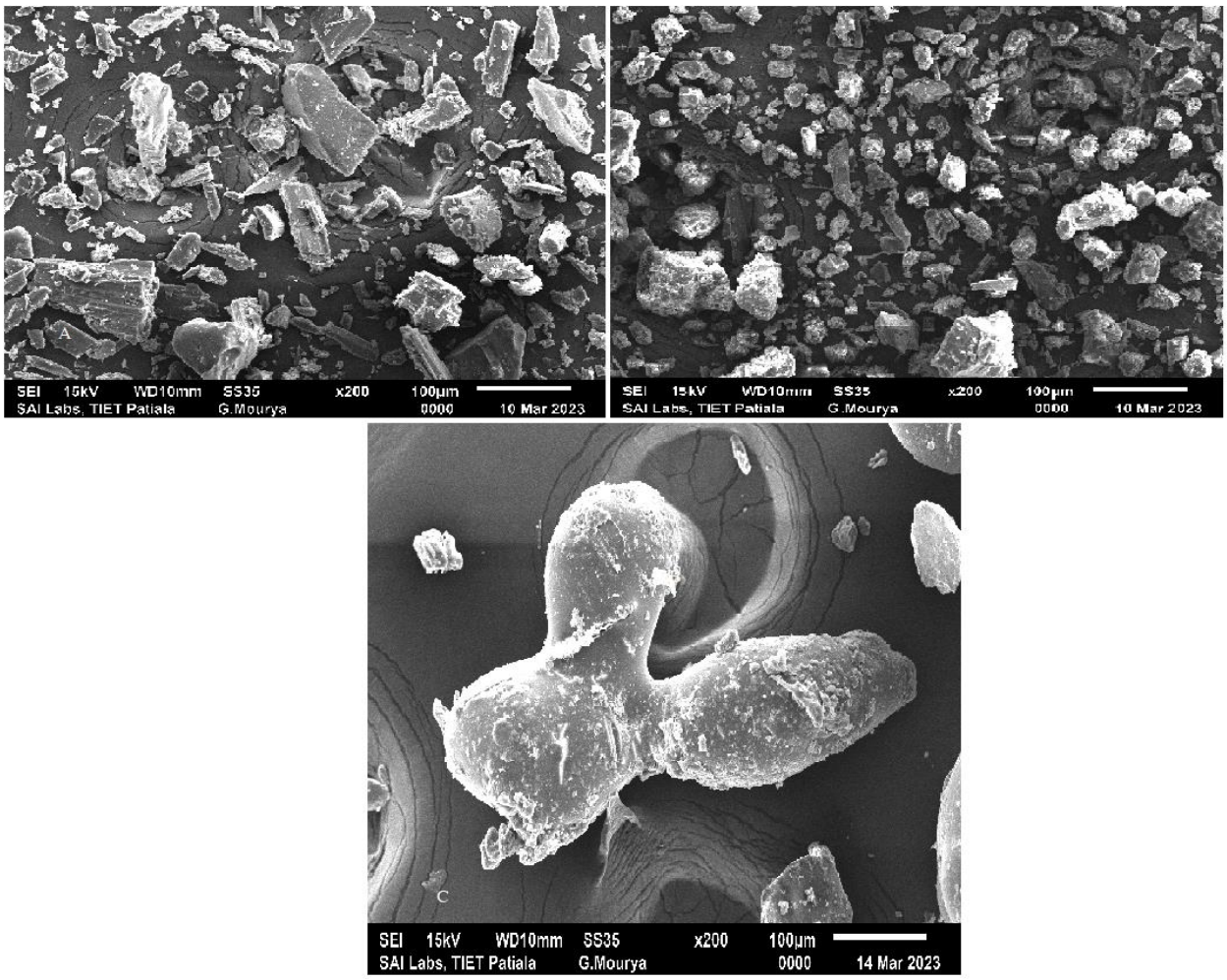


Figure 3 SEM images (A) Physical mixture (B) SD with mannitol (C) SD with PVP

The XRD pattern of the AZI, physical mixture and SD is shown in Figure 4. The XRD of AZI displayed low intensity peaks at 30°, 33°, 35°, 40°, 42.5° and 46.2° (2θ). The low intensity diffraction values exhibit a low crystallinity in the structure of AZI. The crystalline peaks were even lower in intensity in the physical mixture suggesting dilution. In the diffraction pattern of the SD, the peaks of AZI were completely missing suggesting formation of an amorphous form of the product wherein the crystalline structure was completely absent.

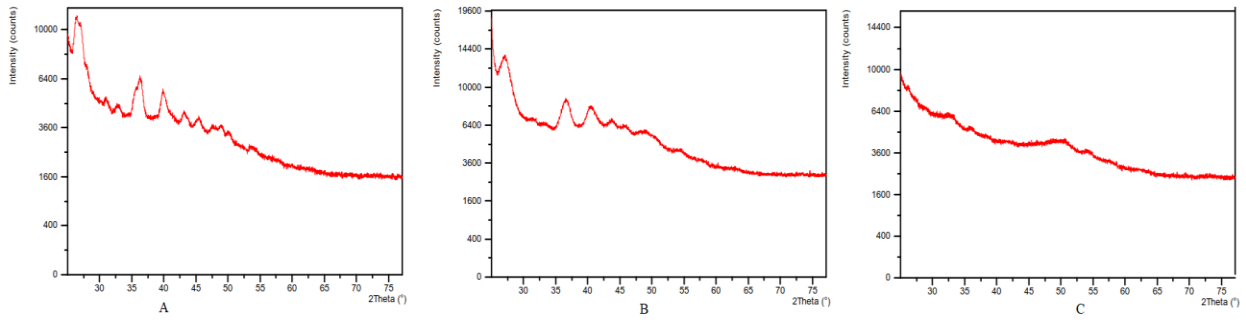


Figure 4 XRD pattern of (A) AZI (B) Physical mixture (C) SD

Calibration curve of AZI

The calibration curve was found to be linear in the concentration range of 10 to 100µg/ml with regression coefficient (R^2) value of 0.993 (Table 2, Figure 5). The linearity equation of the calibration curve was used to calculate the amount of AZI in the samples of drug content, solubility and dissolution.

Table 2. Absorbance data of azithromycin in phosphate buffer pH 6.8

Concentration (µg/mL)	Absorbance
10	0.089 ± 0.0020
20	0.179 ± 0.0026
30	0.241 ± 0.0026
40	0.311 ± 0.0005
50	0.368 ± 0.0026
60	0.426 ± 0.001
70	0.511 ± 0.0021
80	0.575 ± 0.0015
90	0.650 ± 0.0025
100	0.769 ± 0.0021

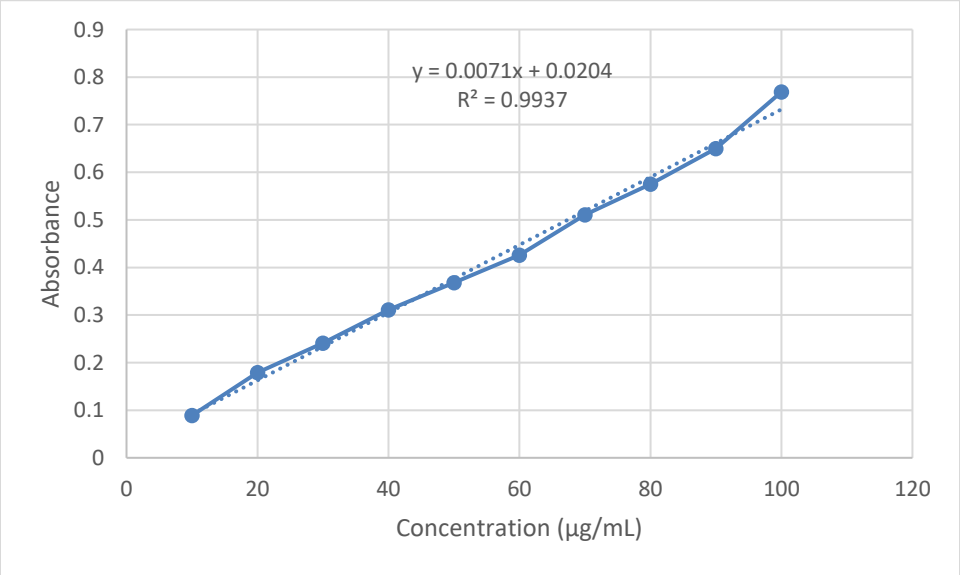


Figure 5 Calibration curve of AZI in phosphate buffer pH 6.8

Yield of SD and Drug content

The yield of the SD was highest for F12 (98.3%) and least for F1 (77.6%). For all the formulations the yield was nevertheless higher than 75% suggesting a proper binary mixture

formation. The highest drug content was found to be 98.3% in F10 whereas it was least in F1 (95.3%). The drug content ranged from 95.3% to 98.3% for all the SD formulation depicting higher content in the SD prepared by kneading method (Figure 6). The high amounts of drug content in the SD reflect amorphous nature of the SD[4].

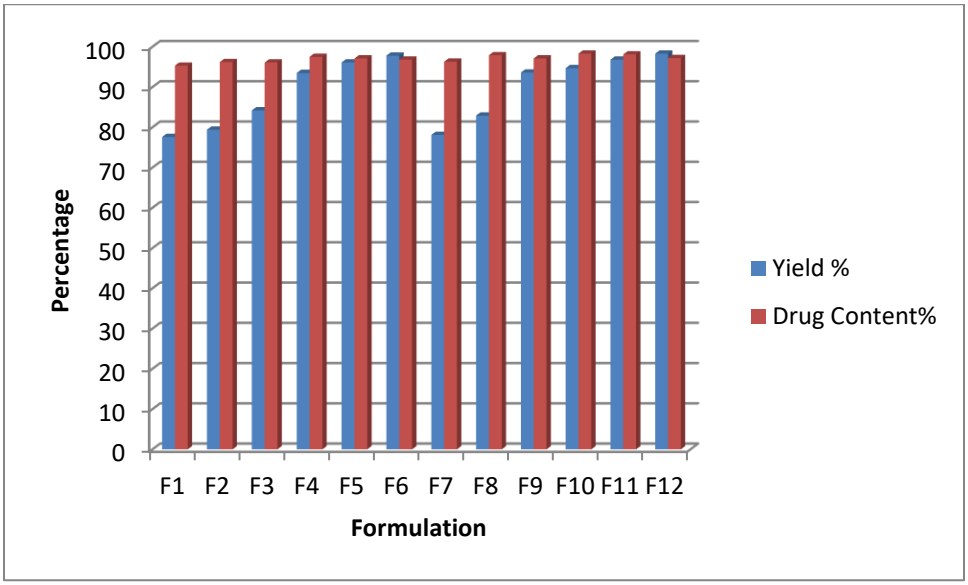


Figure 6 Drug content and yield of SD

Solubility determination

The solubility of AZI in aqueous solutions was evaluated using flask shaking method and it was found the pure AZI was poorly water soluble exhibiting a solubility of 19µg/mL. The physical mixture improved the solubility of AZI from 2 to 4 times whereas the SD were able to improve the solubility of AZI from around 4 to 16 times. The solubility enhancement of AZI exhibited by SD is presented in Table 3.

Table 3 Solubility of AZI in SD

Formulation	Solubility (mg/mL)	% increase in solubility	Times Increase in solubility
Pure AZI	0.0186 ± 0.0005	-	-
PMPVP	0.0366 ± 0.0005	96.58 ± 8.199	1.96 ± 0.0819
PMMan	0.0486 ± 0.0005	160.91 ± 10.138	2.60 ± 0.1013
F1	0.074 ± 0.001	296.58 ± 8.199	3.96 ± 0.0819
F2	0.112 ± 0.0025	502.43 ± 32.004	6.02 ± 0.3200
F3	0.129 ± 0.0026	591.81 ± 36.053	6.91 ± 0.3605
F4	0.106 ± 0.002	468.42 ± 27.850	5.68 ± 0.2785
F5	0.239 ± 0.002	1180.99 ± 31.338	12.80 ± 0.3133
F6	0.293 ± 0.0015	1472.61 ± 57.457	15.72 ± 0.5745
F7	0.072 ± 0.001	278.94 ± 5.2631	3.78 ± 0.0526
F8	0.105 ± 0.0005	456.14 ± 3.0386	5.56 ± 0.0303

F9	0.117 ± 0.0011	517.54 ± 6.0773	6.17 ± 0.0607
F10	0.099 ± 0.0015	422.80 ± 8.0396	5.22 ± 0.0803
F11	0.152 ± 0.001	700.00 ± 5.2631	8.00 ± 0.0526
F12	0.237 ± 0.0015	1150.87 ± 8.039	12.50 ± 0.0803

It was evident that increasing the concentration of carrier was involved in higher solubility of the drug. The highest solubility was obtained in F6, exhibiting 1472.61 ± 57.45% increase in solubility equivalent to 15.72 ± 0.57 times more soluble than the pure AZI as such. In earlier studies the solubility of AZI was improved from 3 to 11 times using various carriers. The best increase was found using Kolliphor P 237 in mass ratio 1:2 whereas decreasing the concentration of the carriers was found to decrease the solubility[15,16]. In our study it could be correlated that the use of mannitol as the carrier could improve the solubility better that by using PVP K30. This was also visible in the physical mixture where mannitol increased the solubility of AZI by 160.91 % as whereas PVP K30 increased by 96.58%. The local solubilizing potential of the carriers, a decreased particles size of the drug as well as improved wettability and reduced particle aggregation could be the possible factors that lead to the enhancement of solubility of the drug in the SD.

Thermal analysis of SD and AZI

The thermal analysis (DSC) was used to study interaction of the drug and carriers as well as the effect of temperature on the stability of the drug. The DSC thermogram shows that no chemical interaction occurs between the carriers and AZI. The thermogram of AZI revealed sharp endothermataround 140°C depicting the melting point of AZI. On the other hand the endotherm of AZI was completely absent in SD suggesting the absence of the crystalline form of AZI which might be due to the conversion of the crystalline AZI to amorphous form (Figure 7-8).

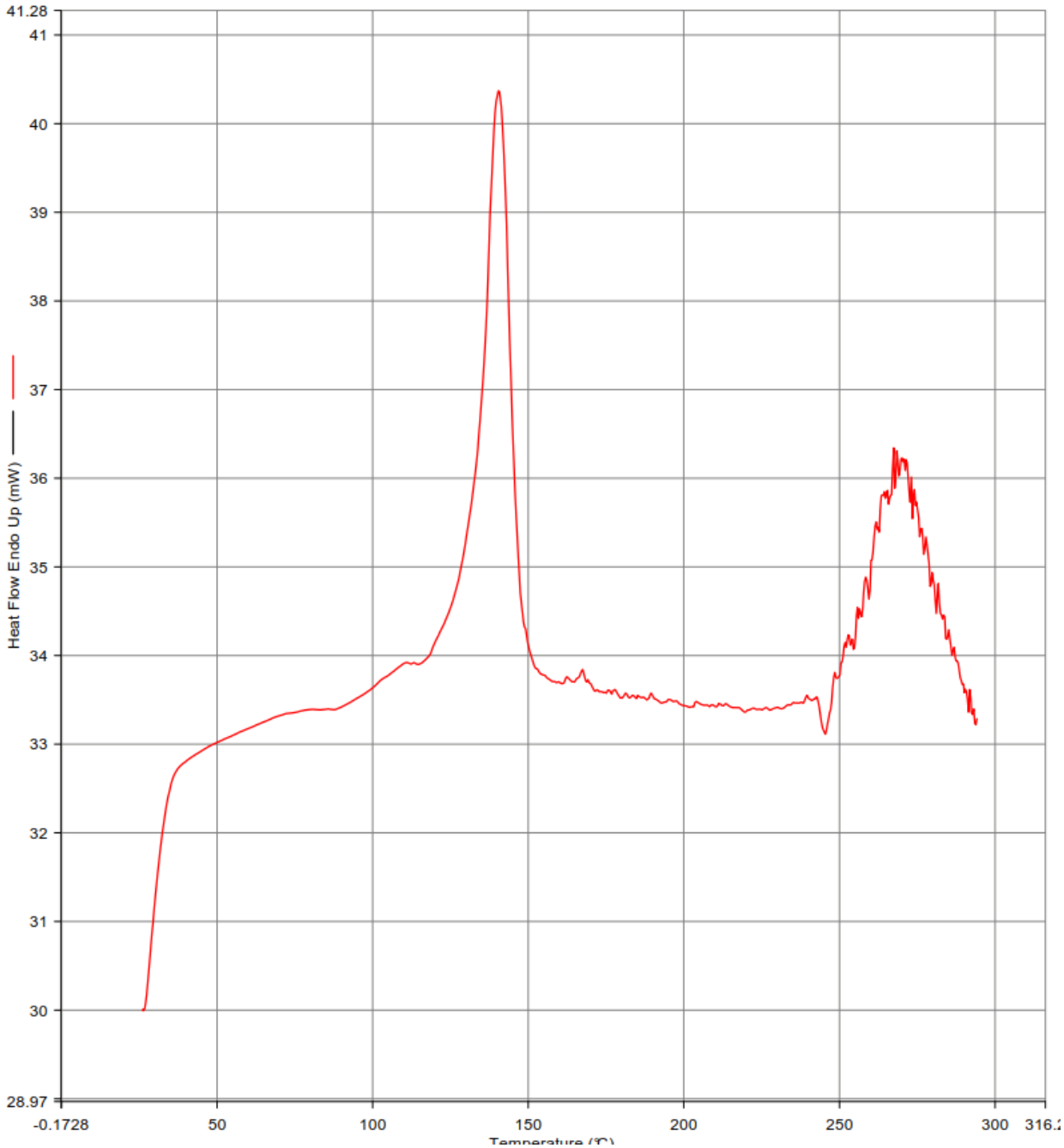


Figure 7 DSC thermogram of AZI

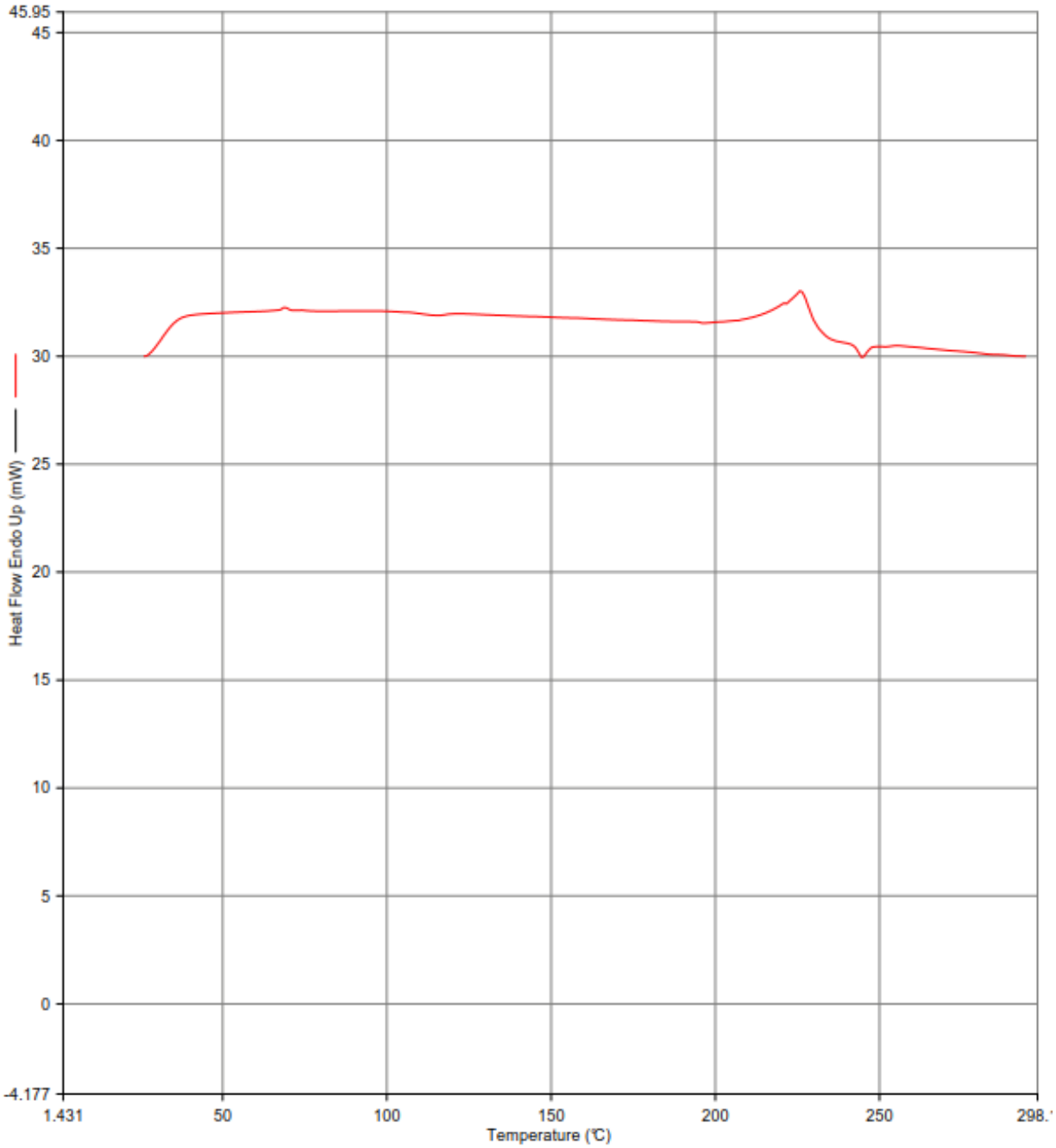


Figure 8 DSC thermogram of SD

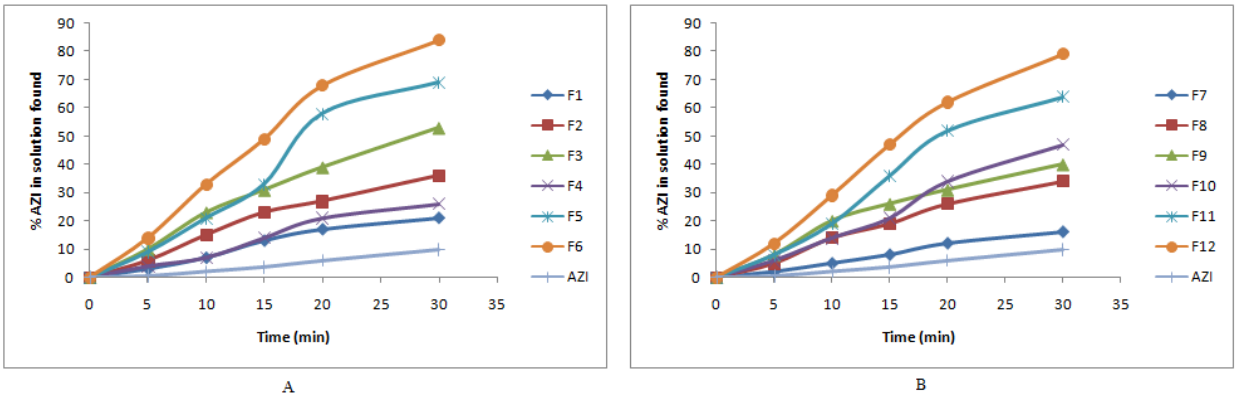
In vitro dissolution study

The *in vitro* dissolution study was performed for 30 min in anticipation of a complete release of AZI from the SD formulations. 16.43 – 84.23 % drug was found to be released from the SD in 30 min. Formulation **F7** released minimum AZI (16.43 ± 0.709 %) while **F6** released the highest amount of AZI (84.23 ± 1.677 %) at the end of the study. It was seen that the release of AZI from SD increased on increasing the ratio of the carrier. In previous study Kumar and Maxumdar[21]also found the increasing the concentration of the carrier PEG 6000 led to increased

dissolution of AZI. The release of AZI from SD is depicted in Table 4 and Figure 9. These observations confirm an increased solubility and dissolution of AZI from the SD.

Table 4 In vitro release data of AZI from SD

	Cumulative Release (%)					
Time (min)	0	5	10	15	20	30
F1	0	2.07±0.208	5.43±0.611	8.13±0.208	12.13±0.153	15.93±0.152
F2	0	5.13±0.208	14.06±0.153	19.00±0.264	26.03±0.231	34.27±0.208
F3	0	7.97±0.208	20.37±0.305	26.53±0.513	30.83±0.251	40.1 ± 0.173
F4	0	6.27±0.058	14.33±0.115	20.87±0.058	34.07±0.058	47.23±0.115
F5	0	8.03±0.058	19.13±0.115	36.27±0.058	52.63±0.503	64.27±0.158
F6	0	12.03±0.305	28.7 ± 0.529	47.03±0.404	62.57±0.503	78.73±0.473
F7	0	3.07±0.058	7.30 ± 0.1	12.93±0.153	16.80±0.208	21.10 ± 0.2
F8	0	5.96 ± 0.153	15.07±0.231	23.20 ± 0.1	26.90±0.173	36.13±0.289
F9	0	10.07±0.058	23.10 ± 0.265	31.10 ± 0.1	38.93±0.153	53.17±0.058
F10	0	4.03 ± 0.115	7.13 ± 0.208	13.96±0.208	21.17±0.231	26.17±0.115
F11	0	9.00 ± 0.265	21.232±0.289	33.07±0.289	58.57 ± 2.25	68.90 ± 0.5
F12	0	13.93±0.231	33.26 ± 0.208	49.17±0.058	68.10 ± 0.2	83.87±0.289
pure AZI	0	0.53 ± 0.058	2.03 ± 0.028	3.67 ± 0.058	5.73 ± 0.153	9.76 ± 0.115



A B

Figure 9 Dissolution profile of AZI from SD. (A) MA method (B) Kneading method

Stability of SD

The physical stability of the SD was assessed by evaluating the drug content in the SD on storage at various conditions for accelerated stability testing as per International conference on Harmonization (ICH) guidelines. The results did not reveal any significant change in the drug content of the SD (Table 5). Hence it could be concluded that the SD were stable in all the storage conditions.

Table 5 Drug content in SD at storage conditions

Storage Condition	Drug content (%)											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Initial content	95.31	96.26	96.18	97.57	97.13	96.82	96.35	97.91	97.13	98.34	98.17	97.22
4°C	93.73 ± 0.058	95 ± 0.153	95.37 ± 0.173	96.03 ± 0.115	96.17 ± 0.153	95.13 ± 0.058	95.36 ± 0.058	96.23 ± 0.058	96.47 ± 0.153	97.77 ± 0.153	97.76 ± 0.058	96.87 ± 0.058
RT	92.63 ± 0.058	94.4 ± 0.1	94.67 ± 0.115	95.27 ± 0.058	95.77 ± 0.153	94.57 ± 0.115	94.47 ± 0.058	95.57 ± 0.058	95.37 ± 0.058	96.53 ± 0.208	96.63 ± 0.231	96.07 ± 0.115
40°C	91.33 ± 0.058	92.4 ± 0.265	92.33 ± 0.115	93.67 ± 0.115	93.2 ± 0.173	92.23 ± 0.115	93.17 ± 0.115	93.53 ± 0.153	93.17 ± 0.115	93.77 ± 0.115	94.27 ± 0.208	94.17 ± 0.153

Conclusion

In the present study, it was clearly observed that mannitol and PVP K 30 could be effectively utilized as the carrier for azithromycin to improve its aqueous solubility as well as dissolution rate by formulating as solid dispersion. Melt agglomeration and kneading methods were effective in producing solid dispersion in high yield. The ratio of the drug to carrier was found to affect the yield, drug content as well as solubility of the drug. It could be concluded that reduced crystallinity of azithromycin could have improve the wetting ability and hence improve its solubility.

Finally the utilization of kneading method was found to be more yielding but the melting method improved the dissolution. Mannitol was found to be better carrier in comparison to PVP K30 in improving the solubility of azithromycin. The best formulation depicting the highest dissolution in 30 minutes was found to be **F6** containing 3 parts of mannitol per part of azithromycin.

References

1. Smith C Egunsola O, Choonara I, Kotecha S, Jacqz-Aigrain E, Sammons H. Use and safety of azithromycin in neonates: A systematic review. *BMJ Open*, 2015; 5: e008194.
2. Firth A, Prathapan P. Azithromycin: The First Broad-spectrum Therapeutic. *Eur J Med Chem*, 2020; 207: 112739.
3. Abou Assi R, Abdulbaqi IM, Seok Ming T, Siok Yee C, Wahab HA, Asif SM, et al.Liquid and Solid Self-Emulsifying Drug Delivery Systems (SEDDs) as Carriers for the Oral Delivery of Azithromycin: Optimization, In Vitro Characterization and Stability Assessment. *Pharmaceutics*, 2020; 12: 1052.

4. Wadhwa S, Singhal S, Rawat S. In vitro Dissolution Enhancement of Azithromycin in Solid Dispersion with PEG 6000 and β-CD. *J Pharm Biomed Sci*, 2016; 6(10): 551-556
5. Amin F, Khan S, Shah SMH, Rahim H, Hussain Z, Sohail M, et al. A new strategy for taste masking of azithromycin antibiotic: Development, characterization, and evaluation of azithromycin titanium nanohybrid for masking of bitter taste using physisorption and panel testing studies. *Drug Des Dev Ther*, 2018; 12: 3855–3866.
6. Sapkal SB, Adhao VS, Thenge RR, Darakhe RA, Shinde SA, Shrikhande VN. Formulation and Characterization of Solid Dispersions of Etoricoxib Using Natural Polymers. *Turk JPharm Sci*, 2020; 17(1): 7-19
7. Bhattacharya S, Pasha I, Verma A, Kothapalli R, Jafar F, Kavya HR. Formulation and evaluation of liquisolid compact of azithromycin dihydrate. *J Res Pharm*, 2019; 23(6): 1022-1032
8. Vijaya Kumar SG, Mishra DN. Preparation, characterization and in vitro dissolution of solid dispersion of meloxicam with PEG6000. *Yakugaku Zasshi*, 2006;126(8):657–64.
9. Mishra DK, Dhote V, Bhargava A, Jain DK, Mishra PK. Amorphous solid dispersion technique for improved drug delivery: Basics to clinical applications. *Drug Deliv Transl Res*, 2015; 5: 552–565.
10. Cid AG, Simonazzi A, Palma SD, Bermúdez JM. Solid dispersion technology as a strategy to improve the bioavailability of poorly soluble drugs. *Ther Deliv* 2019; 10: 363–382.
11. Budhwar V, Kaushik D. An Overview on Recent Patents and Technologies on Solid Dispersion. *Recent Pat Drug Deliv Formul*, 2020; 14: 63–74.
12. Modi A, Tayade P. Enhancement of dissolution profile by solid dispersion (kneading) technique. *AAPS PharmSciTech*. 2006; 7(3):68.
13. Swarup P, Agrawal GP. Solid dispersion: A mechanistic and realistic approach on antihypertensive drug as a drug carrier system. *Assay Drug DevTechnol*, 2021; 19(5): 282-289.
14. Arora SC, Sharma PK, Irchhaiya R, Khatkar A, Singh N, Gagoria J. Development, characterization and solubility study of solid dispersions of azithromycin dihydrate by solvent evaporation method. *J Adv Pharm Technol Res*, 2010; 1(2): 221-228
15. Ehsan A. Preparation and evaluation of azithromycin binary solid dispersions using various polyethylene glycols for the improvement of the drug solubility and dissolution rate. *Braz J Pharm Sci*, 2016; 52(1). http://dx.doi.org/10.1590/S1984-82502016000100002
16. Ehsan A, Mortazavi SA. Design, formulation and evaluation of Azithromycin binary solid dispersions using Kolliphor series for the solubility and in vitro dissolution rate enhancement. *J Pharm Investig*, 2013; DOI 10.1007/s40005-013-0108-x
17. Ehsan A. A comparative evaluation between utilizing SAS supercritical fluid technique and solvent evaporation method in preparation of Azithromycin solid dispersions for dissolution rate enhancement. *J Supercrit Fluids*, 2014; 87: 9-21

18. Zaini E, Novitasari N, Octavia MD. Preparation of amorphous solid dispersion of azithromycin dihydrate with hydroxypropyl methylcellulose (HPMC). *J Sains Farmasi Klinis*, 2017; 3(2): 165-171
19. Sathe S, Surwase D, Kore KJ, Bagade MY, Shete RV. Dissolution enhancement of poorly soluble azithromycin using solid dispersion method. *Eur J Pharm Med Res*, 2015; 2(7): 314-323
20. Maddukuri S, Radha GV. Study of enhancement of bioavailability of azithromycin dihydrate by solid dispersion with poloxamers. *Int J Curr Adv Res*, 2019; 8(4): 18476-18481
21. Kumar P, Mazumder R. Preparation and In vitro Evaluation of Azithromycin Solid Dispersion tablet using PEG-6000. *Asian J Biochem Pharm Res,* 2017; 3(7). DOI: 10.24214/AJBPR/7/3/0110
22. Wadhwa S, Singhal S, Rawat S. Physicochemical Characterization and Dissolution Study of Solid Dispersion Tablet of Azithromycin. *Asian J Pharmaceut*, 2017; 11(1): 48-52
23. Zinjad SS, Udmale DA, Suryawanshi AD, Jadhav SL, Gaikwad DD. Solubility Enhancement of Azithromycin by Solid Dispersion Method by using Polymer PVP K 90. *J Drug Del Ther*, 2019; 9(3): 121-124
24. Goswami RG, Mishra B, Mishra R. Dissolution Enhancement of Cefprozil by Solid Dispersion Technique. *J Phamacol Biomed*, 2017; 1(4): 129-133.
25. Shukla S, Upadhyay S, Gupta RK. Formulation and evaluation of griseofulvin solid dispersion incorporated gel for topical application. *Res J Pharm Tech*, 2022; 15(10): 4389-4394
26. Enose AA, Dasan PK, Sivaramakrishnan H, Shah SM. Formulation and Characterization of Solid Dispersion Prepared by Hot Melt Mixing: A Fast Screening Approach for Polymer Selection. *J Pharmaceutics*, 2014; 105382
27. Bhimani S, Sanghvi G, Pethani T, Dave G, Airao V, Sharma T, et al. Development of the UV Spectrophotometric Method of Azithromycin in API and Stress Degradation Studies. *IntLett Chem Phys Astron*, 2016; 68: 48-53
28. Li J, Li C, Zhang H, Gao H, Wang T, Wang Z, et al. Preparation of Azithromycin Amorphous Solid Dispersion by Hot-Melt Extrusion: An Advantageous Technology with Taste Masking and Solubilization Effects. *Polymers*, 2022; 14: 495
29. Higuchi T, Connors KA. Phase solubility techniques. *Adv Anal Chem Instrum*, 165; 4: 117-212
30. Swarup P, Agrawal GP. A review on delivery and bioavailability enhancement strategies of Azithromycin. *Assay Drug Dev Technol*, 2022; 20(6): 251-257.
31. Alshehri S, Imam SS, Altamimi MA, Hussain A, Shakeel F, Elzayat E, et al. Enhanced Dissolution of Luteolin by Solid Dispersion Prepared by Different Methods: Physicochemical Characterization and Antioxidant Activity. *ACS Omega*, 2020; 5: 6461-6471.