RESEARCH ARTICLE

Solubility Enhancement of BCS Class II Antibiotic (Azithromycin) by Solid Dispersion Technique by Using Skimmed Milk

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ABSTRACT

Azithromycin has a low water solubility; Hence, dissolution represents a rate-limiting process. The goal of the present investigation is to improve azithromycin dissolution and solubility rate. The purpose of this study was to create, characterize, and test the dissolving characteristics of an Azithromycin solid dispersion with skimmed milk. Formulated tablet of optimized batch compared with marketed formulation and study its drug release and make a formulation that gives the highest rate of solubility. This experiment was conducted utilizing the solid dispersion method. The rationale for solid dispersion is that it produces better results than other methods while costing less. Skimmed milk is used as a carrier to increase the solubility of azithromycin. Azithromycin purity is certified using assessment tests such as HPLC assay, UV spectroscopy, FTIR, and DSC. Azithromycin solid dispersion (Azithromycin in skimmed milk) SD2 consistently performs well in all physiochemical tests as compared to all batches. The designed tablet F2 batch releases the drug more effectively than the marketed one. Azithromycin's solubility was successfully enhanced by utilizing the solid dispersion method with skimmed milk. Batch SD 2 gives the highest results in all parameters like solubility. Preformulation study, mainly in tablet formulation, also it gives the highest solubility.

Keywords: Solid dispersion, Phase solubility, Solubility enhancement, Azithromycin, Skimmed Milk.

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INTRODUCTION

Drugs with low solubility in water are particularly challenging to dissolve in the digestive tract, which is required for optimal bioavailability.[1] Researchers face a problem in generating novel drugs that are both pharmacologically proactive and sufficiently well soluble to dissolve rapidly at the site of administration, which is frequently the gastrointestinal system.[2,3] Pharmaceutical researchers face major hurdles in creating stable and more soluble medications due to their low solubility (BCS class II).[4,5] Water insolubility creates formulation and development difficulties in over 40% of orally administered dose formulations.[6,7] An active medicinal ingredient's solubility determines its dissolution, absorption, and distribution, along with excretion.[8,9]

Solid dispersions are more efficient than other particulate size-reduction approaches for increasing solubility since other size-reduction methods limit particle size to roughly 2 to 5 microns.[10,11] This does not result in significant improvement in medication solubility along with drug dissolution in the small intestine to enhance bioavailability.[12,13]

This method has various advantages, including the elimination of hazardous components, a straightforward process, formulation adaptability, decreased pre-systemic metabolic processes, and increased drug solubility and dissolving rates.[14,15] It is especially effective for BCS class II medicines.[16]

Azithromycin is effective for a wide range of disorders, including pulmonary sickness, pneumonia, respiratory tract infections, bronchiectasis, and nontuberculous mycobacterial lung diseases.[17,18] Based on BCS categorization, azithromycin (AZM) is a class II medication, which means that it is inadequate water-soluble.[19]

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In this study, we developed a solid dispersion containing azithromycin using skimmed milk. Skimmed milk is commonly available, affordable, and simple to use. Hence, it has been utilized as a solid dispersion vehicle for enhancing the dissolution and bioavailability of poor water-soluble medications.[20] The recipe contains suitable amounts of skimmed milk powder, which covers the disagreeable taste of the therapeutic substance. Skimmed milk is a colloidal solution comprising micelles of casein, protein globules, and lipoprotein particles.[21] The essential casein fractions are α-s1, α-s2, β-casein, and κ-casein. Milk contains whey proteins, including β-lactoglobulin (BLG), which is present in cow and goat milk but not human milk. Whey contains α-lactalbumin, albumin from bovines, and immune globulin, which make up around 50% of the protein and 0.2 to 0.4% of skim milk. These compounds have been shown to be surface functioning, with enhanced solubility.[22]

Materials

Azithromycin Trihydrate was procured from Leben Laboratories Pvt. Ltd. Ethanol, DMSO, hydrochloric acid, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, and sodium chloride were purchased from S D Fine Chem Industries Mumbai, LOBA, RANKEM of AR grade.

Preparation of Skim Milk Powder

Skimmed milk powder was produced using the spray drying process. Double-toned milk was subjected to spray drying at 120°C inlet temperature and 50°C outlet temperature. The aspiration was kept at 28. The spray-dried skimmed milk powder was obtained as a dried fine powder, which was utilized to prepare a solid dispersion of azithromycin trihydrate.[23,24]

Solid Dispersion of Azithromycin

In the present study, we take 20 g of azithromycin trihydrate heat at 60°C to melt after melting and 20 g of skimmed milk powder. Allow mixture to cool and evaporate liquid substance. After removal of moisture, solidify the mixture, then triturate into a motor pestle and pass through sieve #44[25,26]. Four batches we taken in the current investigation with various concentration ratios like (1:0.5,1:1,1:1.5,1:2), which are entitled in batches (SD1, SD2, SD3, SD4) see (Table 1). Prepared solid dispersion is ready for the study of all parameters in the present investigation. The amount of azithromycin trihydrate and prepared skimmed milk powder varies as previous mention concentration batches SD1 to SD4.

Phase Solubility

To investigate phase solubility, the above-all solid dispersion mixture from SD1 to SD4 was used. A solid dispersion of azithromycin with skimmed milk was dissolved in phosphate buffer 6.8 and produced in screw-capped vials at rising molecular concentrations (0, 3, 6, 9, 12, and 15 mM) at 25°C.

Table 1: Solid dispersion batches

Ingredients	*SD 1*	*SD 2*	*SD 3*	*SD4*
Azithromycin: Skimmed milk	1:0.5	1:1	1:1.5	1:2

Following that, in consistent quantities, azithromycin was added to the previously mentioned solutions and mixed using a rotary shaker (Remi, India) for 48 hours.[26,27] The stirring time was established during the preliminary procedure to achieve equilibrium. Following that, the mixed solution was passed through filters and diluted accordingly, and the azithromycin contents were determined at 215 nm. (UV/visible spectrophotometer, the Shimadzu company)[27] (Figure 1).

Solubility study of Azithromycin in Organic solvents and phosphate buffers

To evaluate azithromycin solubility, take a pure drug and dissolve it in one solvent at a time. For example, take 100 mg of azithromycin and sonicate in water for 5 minutes. Dilute to appropriate concentrations: 1, 2, 3, 4, and 5 µg/mL. The absorbance of these samples was measured with a Shimadzu -1700 UV-visible spectrometer. The present investigation's organic solvent is ethanol (DMSO) (Figure 2).

The same approach was used for all phosphate buffers. Phosphate buffers 1.2, 4, 5, 6.8, and 7.2 were made using the same procedure as the Indian Pharmacopoeia (IP). The

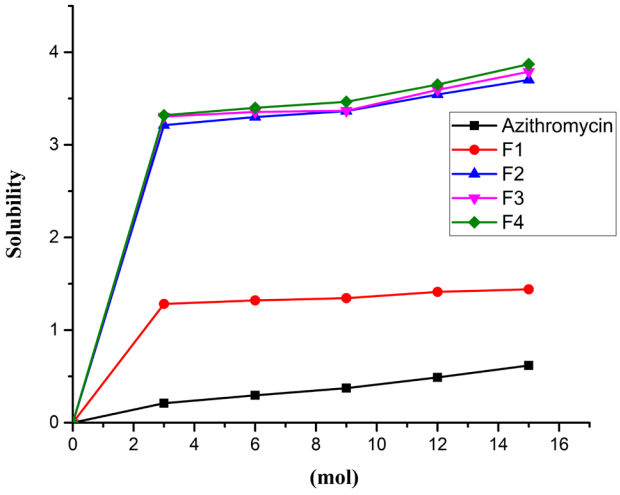

Figure 1: Phase solubility of azithromycin with solid dispersion in all batches

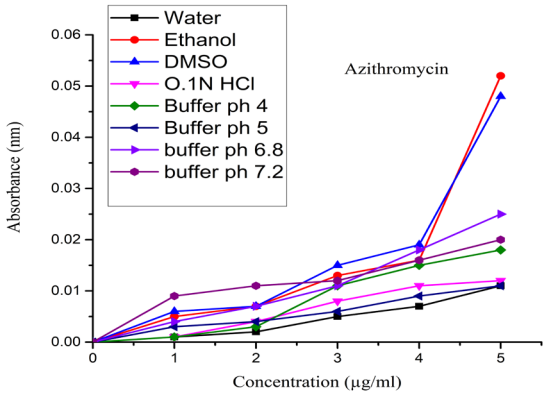

Figure 2: Solubility study of azithromycin in water, organic solvents, phosphate buffers

rationale for utilizing 1.2, 6.8, and 7.2 phosphate buffers is that they are the most essential solvents for oral drug administration. Any preparation we ingest orally is passed through these three main atmospheric solvents[28]. Thus, we investigate the effect of azithromycin in all phosphate buffers.

Solubility study of all batches SD1 to SD4 (Azithromycin: Skimmed milk) in organic solvents and phosphate buffers

Solubility study of Solid Dispersion all ratio SD1 to SD4 of (Azithromycin: Skimmed milk) is done by taking pure Solid dispersion and dissolving in one solvent at a time. For example, in SD2, Water is taken as a solvent. SD2(Azithromycin: Skimmed milk) dissolved in water and sonicated for 5 minutes. Suitably diluted and make dilutions in concentrations like 1, 2, 3, 4, 5 µg/mL. The absorbance of each sample was determined using a Shimadzu -1700 UV/Visible spectrometer. Present investigation organic solvent used as (Ethanol, DMSO) (Figures 3–6).

The above same procedure is applied to all phosphate buffers. Phosphate buffers 1.2, 4, 5, 6.8, 7.2 were prepared by using the same procedure as per Indian Pharmacopoeia (IP). The rationale behind using 1.2, 6.8, 7.2 phosphate buffer is that this is most important solvents for oral drug delivery. Any preparation we take orally get passed to these three important atmosphere solvents. Hence we examine the solubility effect of SD1 to SD4 (Azithromycin: Skimmed milk) all phosphate buffers.

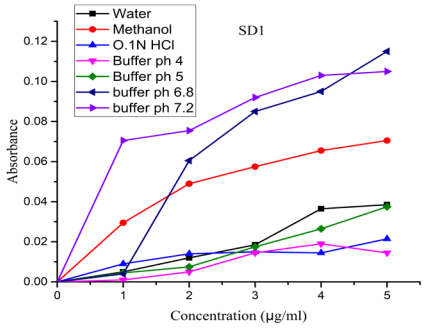

Figure 3: Solubility study of batch SD1(1:0.5 Azithromycin: Skimmed milk) in water, organic solvents, phosphate buffers

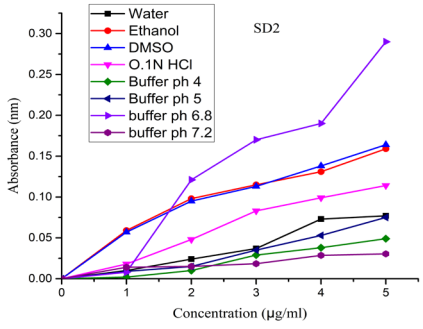

Figure 4: Solubility study of batch SD2 (1:1 Azithromycin: Skimmed milk) in water, organic solvents, phosphate buffers

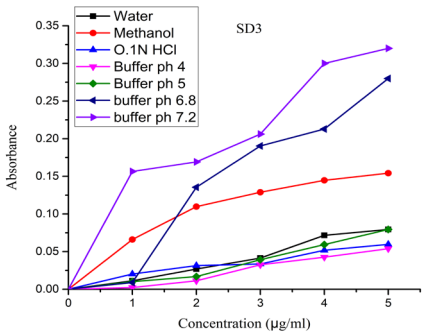

Figure 5: Solubility study of batch SD3(1:1.5 Azithromycin: Skimmed milk) in water, organic solvents, phosphate buffers

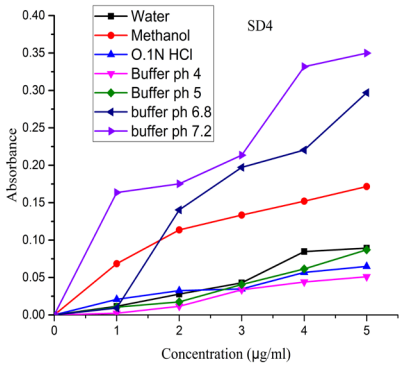

Figure 6: Solubility study of batch SD4(1:2 Azithromycin: Skimmed milk) in water, organic solvents, phosphate buffers

Calibration Curve of Azithromycin

Azithromycin calibration curve prepared by using both 0.1N HCl along with phosphate buffer solution 6.8.[29] As both show linearity as like r^2 is 0.9952 and 0.9967 method was simple: dissolve azithromycin in a suitable solvent and kept as a standard solution. Pippete out a suitable amount of solution and make concentrations like 10 to 50 µg/mL. All concentration was measured using a Shimadzu -1700 UV/ Visible spectrometer, λmax was found to be 215 nm (Figure 7).

Assay of Azithromycin by HPLC

Chromatographic conditions

Two individual organic solvents such as (acetonitrile and methanol), different volume fractions of filter and decontaminated methanol along with acetonitrile (50, 60, 70, 80, and 90 v/v), and a phosphate buffer solution with changing pH (6.0, 8.0) at concentrations of 0.2 M and 0.02 M were tested as appropriate mobile phases.[30] The wavelength was maintained at 215 nm. This wavelength was chosen because it provides a UV maximum with the sensitivity required for measuring small amounts of drugs in pharmaceutical dosage forms. The column's temperatures were varied (25–50°C). The mobile phase of the experiment was pumped at several rates of flow (1.0, 1.5 mL/min) using a 500 µL injection volume (Figure 8).

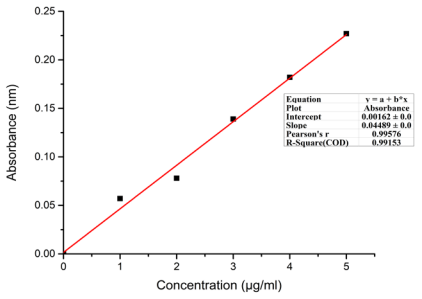

Figure 7: Calibration curve of azithromycin

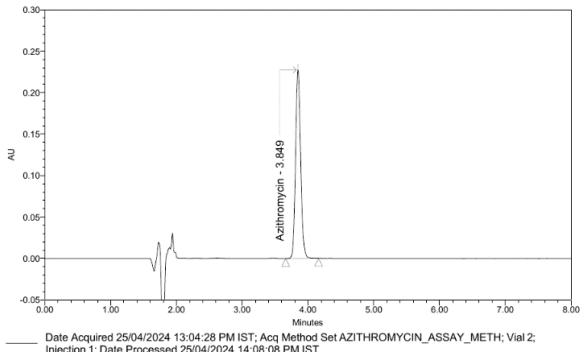

Figure 8: Assay of azithromycin by HPLC method

Preparation of standard solutions

Azithromycin (10 mg) was precisely measured and passed on to a 10 mL volumetric flask, followed by being addition and dissolving of about 5 mL of the mobile phase. The mobile phase increased the solution's volume and fully mixed it, yielding the last concentration of 1.0 mg/mL. The freshly made stock solution was kept in a glass vial at 4°C. Prior to analysis, standard solutions were created fresh from this stock solution.[31,32]

Physical Evaluation of Powder of Solid Dispersion

Formulation of tablet

Table 2 illustrates the composition of a tablet.

Table 2. Composition of formulated tablet

Ingredients	*F1 (1:0.5)*	*F2 (1:1)*	*F3 (1:1.5)*	*F4 1:2*
Azithromycin (mg)	250	250	250	250
Skimmed milk (mg)	125	250	375	500
MCC (mg)	19	32	40	50
SSG (mg)	20	40	60	80
Croscarmellose (mg)	20	40	60	80
Mg stearate (mg)	4	12	14	18
Talc (mg)	2	6	7	9
Total (mg)	440	630	805	987

Bulk density

Using a glass funnel, pour approximately 20 g of granules into a 100 mL graduated cylinder. The volume of granules that occupied the measurement cylinder without compact was measured and recorded (Vo) [33] (Table 3).

Bulk density was computed using the formula: Bulk density (g/mL) = M/Vo

Where M = mass of powder

V o = apparent unstirred volume

Tapped density

The tapped density was determined by pouring 20 g of solid dispersion grains through a glass funnel in a graduated cylinder with a volume of 100 mL. The cylindrical container containing granules was tapped until a consistent volume was reached.[34] The total amount of particles filled after tapping was recorded, and the tapped density was determined (Table 3).

Tapped density (g/mL) = M/Vf

Where,

M = weight of sample powder

Vf = tapped volume

Carr's index

The compressibility index was determined by comparing the bulk and tapped densities.[35] Carr's index provides valuable empirical guidance (Table 3).

$$\text{Carr's Index} = \text{Tapped density} - \text{Bulk density}/\text{Tapped density} \times 100$$

Hausner's ratio

It displays the amount of density that could occur as a result of feed hopper vibration. Another statistic for assessing granule flow capabilities. A significant value indicates that the lower the Hauser ratio, greater the flowability.[36] (Table 3)

$$\text{Hausner ratio} = \text{Tapped density}/\text{Bulk density}.$$

Angle of repose

Each powder mixture was tested utilizing the glass funnel methodology. I weighed the powder sample correctly and ran it through the funnel, resulting in a heap. The funnel's height was adjusted so that the tip could only reach the top of the heap.[37,38] The diameter of the powdered cone was determined by measuring it & the angle of repose determined using the equation shown below (Table 3).

$$\tan\theta = h/r$$

Where h = height of cone, r = radius of powder cone

Post compression evaluation of tablet

All post-compression evaluation test for tablets was performed. Test like weight variation test was performed by using digital weighing balance, Hardness test done by using Monsanto hardness tester. Thickness test was performed by Micro Screw gauze. Friability was performed by using Roches friability apparatus. The disintegration test was done by using Lab India Disintegration test apparatus.[39] (Table 4).

Table 3: Physical evalution result of precompression study

Parameters	*F1 (1:0.5)*	*F2 (1:1)*	*F3 (1:1.5)*	*F4 1:2*
Bulk density (g/mL)	0.404 ± 0.04	0.483 ± 0.02	0.71 ± 0.3	0.79 ± 0.4
Tapped density (g/mL)	0.553 ± 0.6	0.528 ± 0.11	0.90 ± 0.4	0.82 ± 0.2
Car's index (%)	13.8 ± 0.4	12.3± 0.02	14.7 ± 0.8	15.1 ± 0.08
Hausner's ratio	1.15 ± 0.3	1.13 ± 0.11	1.15 ± 0.4	1.16 ± 0.3
Angle of Repose (Θ)	27.9	27.2	28.5	30.3

All values are shown as mean ± SD (n = 3).

Table 4: Post-compression evaluation of azithromycin tablet

Parameters	*F1 (1:0.5)*	*F2 (1:1)*	*F3 (1:1.5)*	*F4 1:2*
Weight variation	434 ± 0.23	625 ± 0.42	798 ± 0.89	984 ± 0.77
Hardness (kg/cm^2)	5.5 ± 0.1	5.8 ± 0.01	5.6 ± 0.05	6.4 ± 0.53
thickness (mm)	4.7 ± 0.04	6.4 ± 0.031	7.3 ± 0.07	8.6 ± 0.87
Friability (%)	0.708 ± 0.5	0.601 ± 0.04	0.76 ± 0.87	0.55 ± 0.66
Disintegration (Minutes)	7.9 ± 0.26	5.07 ± 0.34	9.5 ± 0.99	11.38 ± 0.55
Drug content (%)	97.8 ± 0.33	99.3 ± 0.22	98.2 ± 0.1	98.5 ± 0.04

All values are shown as mean ± SD (n=3)

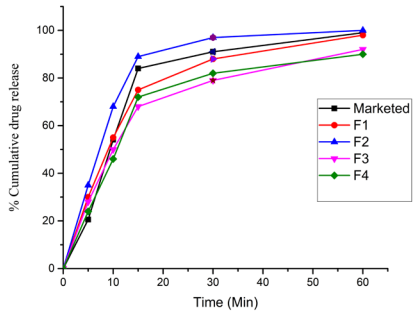

Figure 9: % Cumulative drug release of Formulated tablet vs Marketed Formulation

In-vitro study (Dissolution study)

In vitro examination of the prepared tablet and market formulation was performed employing Dissolution Apparatus (Labindia) USP II (Rotating Paddle) containing 900ml 0.1 N HCl as media at 37°C. at 50 rpm. Specific amount of solvent removal filter through #22 Whatman filter paper after filter suitably diluted and analysed on UV Spectrophotometer (SHIMANDZU-1700). After removal of solvent, it replaced by fresh solvent of equal amount immediately[40,41] (Figure 9).

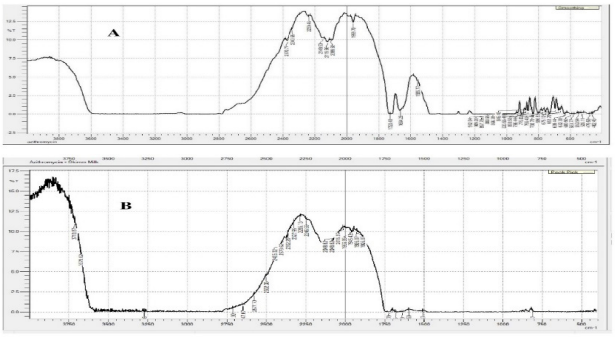

Figure 10: FTIR Result of (A) Azithromycin (B) Azithromycin: Skimmed milk Solid dispersion

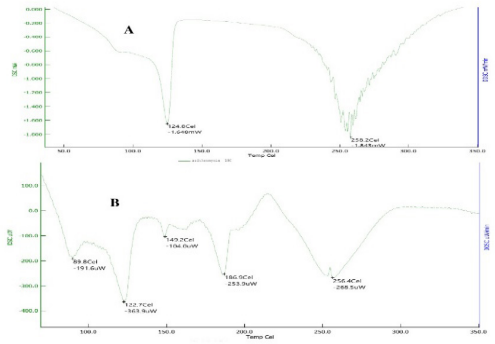

Figure 11: DSC Result of (A) Azithromycin (B) Azithromycin: Skimmed milk Solid dispersion.

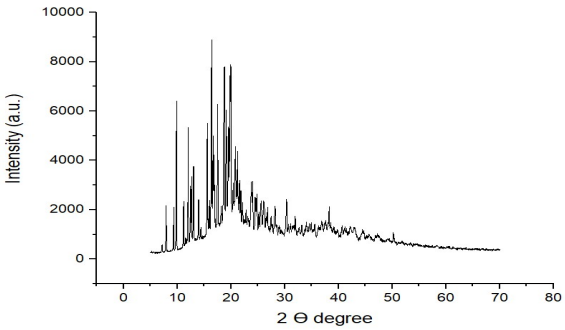

Figure 12: XRD of optimized batch SD2

Drug content test

Azithromycin and solid dispersion (Azithromycin: skimmed milk) both take equal amount and make its solution in suitable range in beers lamberts law.[42] In this case prepared 20µg/ml solution make of both azithromycin and solid dispersion (Azithromycin: skimmed milk) then it analysed on UV Spectrophotometer (SHIMANDZU-1700).

FTIR study

The compatibility of the medications and additives was investigated using an FTIR spectroscopy method.[43] The improved ASDs were examined using FTIR spectroscopy

to evaluate the likely interactions between molecules of azithromycin and carrier Figure 9 depicts the FTIR spectra. The FTIR spectrum of AZ showed peaks at 1718 (C-H group), 1721 (C=C group), 3437 (C-N group). 3293 (O-H group). FTIR measurements showed that there was none intermolecular interaction (Figure 10).

DSC study

DSC was used to assess physiochemical compatibility and the interaction between the drug and the excipient. The thermograms from the DSC of Azithromycin and Sold dispersion revealed that the melting point of the drug in its pure form was identical, showing that there was little variation in the drug's melting point (Figure 11). Each sample were precisely measured to 3-5 mg in an aluminium pan and packed in standard aluminium pans with lids. A blank aluminium pan was used as a reference. The samples were heated at a rate of 100 degrees Celsius per minute from -10 to 3000 degrees. A nitrogen flow rate of 40 mL/min was used.[44-46]

XRD

X-ray diffraction (XRD) is an efficient method for analysing crystalline structure of materials, especially solid dispersions. XRD helps identify if the material is amorphous or crystalline. Composition identifies the existence of distinct chemicals. Crystal Structure reveals the arrangement of atoms within the crystal lattice. In solid dispersion tests, XRD validates the presence of the medication and the excipients, crystallinity. XRD provides useful insights into materials' solid-state properties, which aid in formulation development and optimization[47-50] (Figure 12).

DISCUSSION

HPLC analysis, calibration curves, FTIR studies, and DSC demonstrate the purity of azithromycin. The FTIR data showed that there was no intermolecular interaction between azithromycin and skimmed milk or their solid dispersion. Phase solubility was tested using a cyclomixer, and the results demonstrate that the solid dispersion of azithromycin with skimmed milk has a significant increase in solubility (Figure 1). The figure of phase solubility depicts the solubility using a graph. Similarly, the Solubility Characteristic of Azithromycin (Figure 2) and Solid Dispersion SD1 to SD4 (Azithromycin: Skimmed Milk) displayed in (Figure 3,4,5,6) demonstrates that solid dispersion (SD2) has a considerable improvement in solubility as compared to other batches and azithromycin medicine. Physical investigation of solid dispersion results in positive results, including acceptable angles of repose, Carr's index, and Hauser ratio. When we compare the solubility of the manufactured tablet with the marketed formulation, we clearly observe that azithromycin is more readily soluble in skimmed milk. Based on the findings of the preceding studies, the Solid Dispersion (1:1) Azithromycin: Skimmed Milk consistently improves solubility compared to other batches and azithromycin alone. As a result, the solubility improvement of azithromycin with a solid dispersion approach based on skimmed milk was successful.

CONCLUSION

In the present investigation Azithromycin: Skimmed milk solid dispersion was successful formulated. Batch SD2 gives highest results in all parameters like solubility, Preformulation study mainly in tablet formulation also it gives highest solubility. The FTIR data showed that there was no the intermolecular interaction between azithromycin and skimmed milk or their solid dispersion. Solubility testing and in in vitro dissolution investigations show that the prepared tablet of solid dispersion is more soluble than the marketed formulation. Azithromycin has strong permeability but low solubility in gastrointestinal fluid. Azithromycin's solubility was increased by making it a solid dispersion, which increased the drug's dissolving rate. The prepared tablet using solid dispersion has a higher percentage of drug release than the marketed formulations. As a result, we conclude that this particular solid dispersion might become extensively used on a commercial platform in the near future to achieve high bioavailability and patient compliance. The present investigation was successful in enhancing the solubility of BCS Class II drugs, including antibiotics such as azithromycin, which is consistently prescribed to children to elderly individuals alike. Enhancement of Solubility of Azithromycin or such water insoluble antibiotics might be gain great interest for researchers.

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AUTHORS CONTRIBUTIONS

Dr. Mohan Kale& Dr. Bharat W. Tekade, Dr. Nilesh Gorde give guidance to Pavankumar Dhoble to write the manuscript. Vishal Bodke, Bharat Tekade ensure that the data and analysis of the manuscript are completed. The entire team have read the work and ready for consideration for publication.

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