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MIXED HYDROTROPY TECHNIQUE USED FOR SOLUBILITY ENHANCEMENT OF ALBENDAZOLE

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Keywords:

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ABSTRACT: Purpose: Albendazole (ABZ) is a drug that shows anthelmintic activities, also used for treating neurocysticercosis, also known as pork tapeworm infection caused by contact with infected human stool, infected food, and water. But the serious challenge is the hydrophobicity of albendazole, which slow down the dissolution rate and bioavailability, so it can be given in high concentration, which can cause residual toxicity, so the purpose of this research article is to enhance the solubility of albendazole by mixed hydrotropic technique. Hydrophobic drug shows the difficulty in absorption when reaching the aqueous area, leading to failure in formulation development. **Method:** Solid dispersion was prepared by using a blend of citric acid and piperazine by mixing them with ABZ with the help of ethanol as solvent, carried out the content in a china dish on a magnetic stirrer until solvent evaporated completely, use of FTIR for functional group determination, determination of melting point by capillary method, determination of thermal behaviour by DSC, XRD studies were done, Further evaluation of solid dispersion were done for determination of drug content, Percentage yield, solubility studies, and In-vitro evaluation. **Results:** In the present observation, an attempt was made to enhance the solubility of hydrophobic drug albendazole by using a blend of hydrotropes such as Citric acid and piperazine as hydrotropes and ethanol as a solvent which enhanced the solubility of ABZ up to 5 times. **Conclusion:** Based on research work, it was concluded that mixed hydrotropy enhanced the solubility of ABZ by using piperazine and citric acid as hydrotropes which also reduces the chances of residual toxicity.

INTRODUCTION: Solubility has the maximum amount of solute dissolved in a specific amount of solvent at a specific temperature, pH, and pressure. Drug solubility is directly proportional to bioavailability.

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According to their aqueous solubility and intestinal permeability, all drugs are categorized into four biopharmaceutical classification systems (BCS) [1].

Most of the drug is given through the oral route, and their solubility plays a crucial role in their absorption, so various techniques have been used to improve the solubility of hydrophobic drug [2]. Highly soluble drugs show greater solubility in 250 ml of aqueous phase at pH of 1.0- 7.5 and highly permeable drugs show 90% permeability in intestinal membrane [3]. Albendazole (ABZ) is a hydrophobic drug that comes under II class of

biopharmaceutical classification system. It shows anthelmintic activities [4], used to inhibit or kill helminths species such as Ascaris Lumbricoides, *A. suum*, and Necator americanus [5]. Enhancing the effectiveness of ABZ can be possible by improving its dissolution [6]. To enhance the solubility of ABZ, the most desirable technique for solubility enhancement is mixed hydrotropy [7]. The mixed hydrotropy technique has been used to enhance the hydrophobic drug's solubility by using hydrotropic blends of desirable hydrotropes, or we can say that a large concentration of secondary hydrophilic solute is added with a drug that enhances the aqueous solubility of the hydrophobic drug. Hydrotropes are those compounds that have been used to enhance in solubility of hydrophobic drugs [8].

Advantages of Hydrotropes: Hydrotropy is the most important tool for the other solubilization methods, such as micellar solubilization, spray drying, salting, and miscibility, because of the independent character of the solvent. Chemical modification is not required in the hydrotropic method. It is efficient and simple for various pharmaceutical industries as organic transformations. They are easily available, having low cost. It reduces the chances of residual toxicity. Hydrotropes do not need any specific temperature when dissolved in water [9].

MATERIALS AND METHODS:

Materials: Lasa super generics ltd provided the drug ABZ to conduct this study. Ideal suppliers gave the remaining materials such as ethanol, citric acid and piperazine.

Pre-Formulation Study:

Fourier Transform Infrared Spectroscopy: FTIR was used to determine the functional group. The sample containing the group was combined with Potassium bromide, which was compressed to the discs, and hydraulic pressure was implemented to 5 tons [10].

Melting Point: The drug was filled in a sealed capillary, put inside the melting point apparatus, and observed the value at which the drug melted [11].

Selection of Pro-eminent Hydrotropes: Four hydrotropes were used for solubility enhancement, such as Piperazine, Citric acid, Tannic acid and Caffeine. The hydrotropes that showed high solubility were selected using the solubility determination technique.

The drug ABZ showed different solubility with each hydrotropes, and the procedure for solubility determination is as follows first, take 4 beakers in which an appropriate quantity of distilled water was taken, added each hydrotropes individually; after that, an excessive amount of ABZ was also added.

Kept the solution on a magnetic stirrer for 24 hrs. When the equilibrium state was reached, then filtration of the solution takes place; the filtrate was collected, diluted, and observed through UV spectrophotometry at 308 nm[12].

Solubility Studies: Solubility was performed in triplicate according to Higuchi and Connors's method to evaluate the increment in the solubility of ABZ (solid dispersion). An Excess amount of ABZ (approximately 50mg) was added to the container containing hydrotropes. The container was then placed in a magnetic stirrer for 24 hrs.

After that, the solution was filtered, diluted and analyzed using UV spectroscopy at λmax in the range of 308nm. The observed solubility was compared with pure drug solubility, and the obtained data from solubility studies were used to determine the solubility enhancement ratio formula given below [13].

Solubility Enhancement = Solubility of a drug in hydrotropic solution / Solubility of a drug in distilled water × 100

Preparation of Solid Dispersion by Solvent Evaporation Method: For the preparation of solid dispersion, first mix ABZ with the blend of citric acid and piperazine in an appropriate ratio such as (1:2, 1:4, 1:6, 2:1,2:4) with the help of ethanol to form homogenous mixtures which were stirred by stirring rod until it dissolved completely and put it inside the China dish placed on a magnetic stirrer.

When solvent evaporated completely, scratched out the sample through a spatula, put in butter paper, and placed inside the oven, temperature should be maintained at 55±2°C and passed through sieve no. 40 and then the prepared solid dispersion (SD1-SD5) were stored in the desiccators for further evaluation [13,14].

Characterization of Formulated Batches (SD1-SD5):

FTIR Studies: Fourier transform infrared spectroscopy is used to detect the impurity of the drug. The sample was prepared as KBr pellet method. The range of wavelength was selected from 400 -2000. Selected IR peak was obtained for solid dispersion of ABZ, and the best optimized solid dispersion was selected according to drug release and the solubility of the solid dispersion of drug [10, 17].

DSC Studies: DSC studies help understand the hydrotropic blend's thermal behavior [15].

XRD Studies: The XRD of solid dispersion were determined using the X-ray, and diffract meter, respectively to investigate change in the crystalline of ABZ and the scanning speed of the instrument was 4°C per minute over a range of 5°C [13].

Drug Content: Solid dispersion, equivalent to 50 mg of ABZ was dissolved in a suitable solvent such as ethanol; after that, the solution was filtered using whatman filter paper. The final sample was analyzed by UV spectrophotometry at 308nm, and the concentration of ABZ was determined by using the formula below [13, 15].

Drug content (%) =Practical amount of solid dispersion / Theoretical amount of solid dispersion × 100

Percentage Yield: The percentage yield was used to determine the amount of loss ingredient during the preparation of solid dispersion. It was calculated by using the formula given below [14].

Percentage Yield (%) = Practical amount of solid dispersion / Theoretical amount of solid dispersion × 100

***In-vitro* Dissolution Studies:** Dissolution studies are the study of drug release when it reaches inside the human body. It solubilizes at a definite time interval. The apparatus used to determine drug release was "USP Basket Type 1 apparatus" and maintained the biological condition such as pH temperature similar to the human body. Rotation was set to 100 rpm, and drug release was observed for up to 60 minutes and compared the dissolution rate of pure drug with the formulation having a maximum dissolution rate [13].

RESULT:

Pre-formulation Studies:

Fourier Transform Infrared Spectroscopy: The presence of different bands was observed, which showed the presence of the functional group in **Fig. 1** and the various functional groups with different peaks shown in **Table 1,** and the spectrum of ABZ is shown in **Fig. 1.**

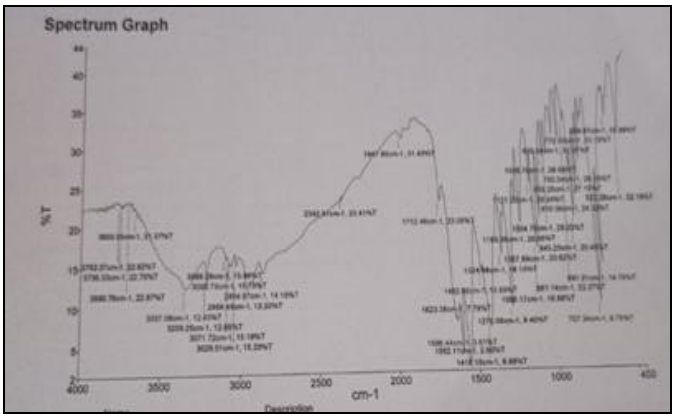

FIG. 1: SPECTRUM OF ABZ

TABLE 1: FTIR PEAK NAME WITH FUNCTIONAL GROUP

Peak name	Functional group
3752.07 cm^{-1}, 3026.51cm^{-1}cm	OH stretching
3337.26cm^{-1}, 1947.90cm^{-1},1712.46cm^{-1}, 1416.16cm^{-1}	S-H stretching
3071.72cm^{-1}	N-H stretching

Melting Point: The melting point of albendazole was found to be 208.1℃

Solid dispersion of ABZ: By solvent evaporation method, solid dispersion was prepared with the help of a hydrotropic blend of piperazine and citric acid and ethanol as solvent. And the ratio of drug with hydrotropic blend is shown in **Table 2,** and photos of different solid dispersion are shown in **Fig. 2.**

TABLE 2: RATIO OF SOLID DISPERSION (DRUG: HYDROTROPIC BLEND)

Formulation no.	Ratio of solid dispersion (Drug: Hydrotropic blend)	Hydrotropic blend
SD1	1:1:2	1:2
SD2	1:1:4	1:4
SD3	1:1:6	1:6
SD4	1:2:1	2:1
SD5	1:4:1	4:1

FIG. 2: DIFFERENT FORMULATION IMAGES OF PREPARED SOLID DISPERSION

Evaluation Parameters:

FTIR: The range of wavelength was selected from 400 -2000. Selected IR peak was obtained for solid dispersion of ABZ and the best optimized solid dispersion was selected according to drug release and the solubility of the solid dispersion of the drug. And the FTIR peak with a functional group is shown in **Table 4.**

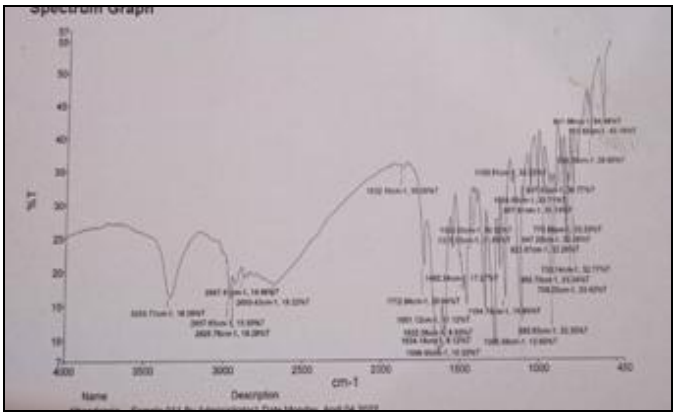

FIG. 3 FTIR OF SOLID DISPERSION

TABLE 3: FTIR PEAK NAME WITH FUNCTIONAL GROUP IN SOLID DISPERSION

Peak name	Functional group
3333.71 cm^{-1}, 2669.51cm^{-1}cm	OH stretching
1832cm^{-1}, 2957cm^{--1}	S-H stretching
2925.76 cm^{-1}	N-H stretching

DSC: The differential scanning calorimetry shows a sharp endothermic peak near 200, corresponding to the melting point of ABZ. And DSC of SD5 is shown in **Fig. 4.**

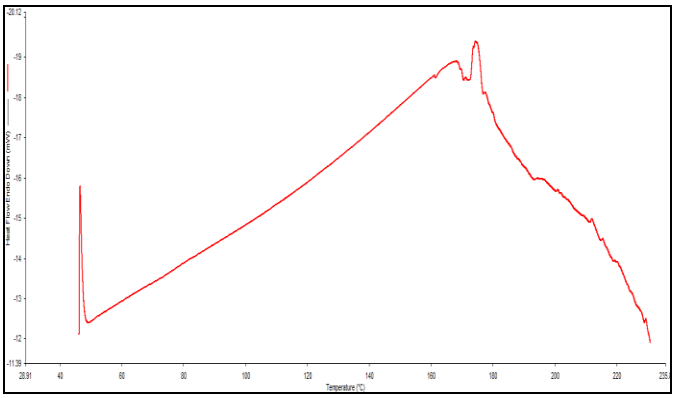

FIG. 4: DSC OF SOLID DISPERSION (SD5)

XRD: Solid albendazole dispersion was prepared using the solvent evaporation method .and diffractograms of five formulations (SD1-SD5) were observed in an X-ray diffractometer. The conditions for measuring were followed as voltage should be 40 Kv, 300 mA. The SD5 formulation showed a peak in **Fig. 5.**

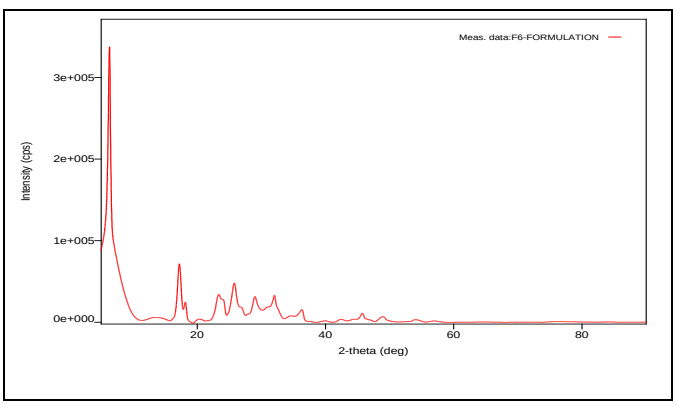

FIG. 5: XRD OF SOLID DISPERSION (SD5)

Percentage Yield and Drug Content: The percentage yields and drug content were determined by the formula mentioned in the previous procedure and the result is given below in **Table 4.**

TABLE 4: PERCENTAGE YIELD AND DRUG CONTENT OF VARIOUS FORMULATIONS

Formulation	Percentage yield	Drug content
SD1	89.85 ±0.02	81.05± 0.05
SD2	96.4± 0.12	90.82 ±0.02
SD3	92.8 ±0.04	90.78± 0.08
SD4	89.28 ±0.08	86.92± 0.01
SD5	92.72 ±0.01	89.20± 0.02

Saturation Solubility: Saturation solubility of various solid dispersions was measured. And saturation solubility of the different formulations is mentioned in **Table 5**. Based on the solubility of hydrotropes, two hydrotropes, piperazine, and citric acid, show high solubility, which was mentioned in **Table 6** with their solubility enhancement ratio.

TABLE 5: SATURATION SOLUBILITY OF VARIOUS FORMULATIONS

Formulation	Saturation solubility(mg/ml)
SD1	0.098
SD2	0.123
SD3	0.156
SD4	0.184
SD5	O.230

TABLE 6: SOLUBILITY OF ABZ IN DIFFERENT HYDROTROPES AND THEIR SOLUBILITY ENHANCEMENT RATIO

S. no.	Hydrotropes 40% (w/v)	Solubility in (mg/ml)	Solubility enhancement ratio
1.	Piperazine	2.8	14
2.	Citric acd	3.76	18.8
3.	Tannic acid	0.89	4.45
4.	Caffeine	1..97	9.85

Dissolution Studies: Table 7 shows the dissolution of ABZ in different solid dispersion along with per, which increases with increment in hydrotropic blend ratio. All Solid dispersion samples showed an improved dissolution rate of ABZ as compared to pure ABZ. The *in-vitro* drug dissolution profile of pure drug and SD5 are mentioned in **Fig. 6.**

TABLE 7: DISSOLUTION STUDY OF PURE DRUG WITH VARIOUS FORMULATIONS

Time(min)	Pure drug	SD1	SD2	SD3	SD4	SD5
10	1.23±0.765	15.05±0.871	18.90±0.009	22.99±0.8	25.73±0.87	32.87±0.76
20	2.67±0.620	18.07±0.654	23.87±0.001	27.90±0.87	39.87±0.54	47.98±0.875
30	3.82±0.987	19.09±0.89	28.98±0.98	34.89±0.56	43.98±0.61	54.43±0.123
40	8.40±0.832	21.39±0.876	35.59±0.87	42.41±0.65	49.77±0.098	59.08±0.543
50	11.92±0.721	28.00±0.009	39.76±0.43	47.03±0.876	55.95±0.765	67.09±0.554
60	19.20±0.532	34.00±0.856	42.97±0.543	54.98±0.654	60.40±0.87	72.98±0.631

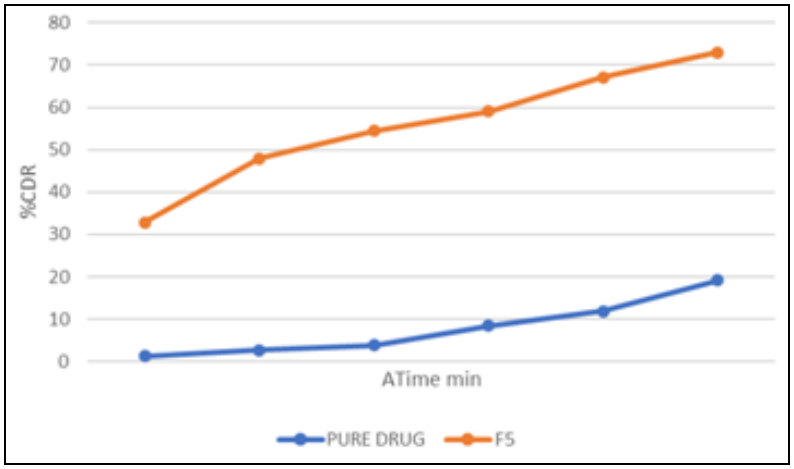

FIG. 6: DISSOLUTION PROFILE OF PURE DRUG WITH SD5 FORMULATION

DISCUSSION: ABZ is a drug that comes under the BCS II class, with low solubility and high permeability and is categorized as anthelmintic. SO solubility studies were conducted, and the mixed hydrotropy method was used to enhance the solubility of ABZ by adding a blend of piperazine and citric acid because they both showed high solubility of ABZ, so they were chosen for further work. Solid dispersion was prepared using different ratios of the drug, solvent and hydrotropic blend. Five formulations were prepared from which SD5 was selected, which improved the solubility of ABZ drastically and was then used for further evaluation, such as FTIR, XRD and DSC.

CONCLUSION: In this present research work, the aim was to enhance the solubility of albendazole by using the mixed hydrotropy technique by preparing a hydrotropic blend of piperazine and citric acid. Piperazine and citric acid show high improvement in solubility of hydrophobic drug albendazole. Mixed hydrotropic can be a safe and simple process for increasing the dissolution rate of albendazole as they reduce the residual toxicity by combining two hydrotropes. The drug release of pure drug of albendazole was observed at 19.20 in 60 minutes, and after using hydrotropic blend, the dissolution rate was observed as 72.98 in 60 minutes. The solubility was increased up to 5 times.

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CONFLICTS OF INTEREST: The authors declare there is no conflict of interest.

REFERENCE:

1. Jagdap, Magdum C, Jadge D and Jagdap R: Solubility enhancement technique: a review. J of Pharmaceutical Sciences & Research 2018; 10(9): 2205-2211
2. Singhal P, Singhal RV, Kumar VJ, Verma A and Kaushik RD: The biopharmaceutics classification system (BCS): review. WJPPS 2017; 7(1): 269-283.
3. Shukla T, Pandey SP, Upmanyu N, Sudheesh MS, Chandel HS, Pawan K and Porwal: The biopharmaceutical classification system (BCS): past and present scenario of scientific framework for bio-waiver extension and need of its validation. J of Pharma and NDDS 2017; 1(1): 7-12.
4. Ghanbarzadeh S, Khalili A, Jouyban A, Emami S, Javadzadeh Y, Solhi M and Hamishehkar H: Dramatic improvement in dissolution rate of albendazole by a simple one-step industrially scalable technique. Research in Pharmaceutical Sciences 2016; 11(6): 435-444.
5. Mohdfaizal M, Anaanthan BP, Nurezdiani M, Azmawati MN, Norfazilah A, Hasanain FG, Mohammad SJ, Rahim SSSR and Hassan MR: Efficacy of albendazole against soil- transmitted helminthiasis among children in Asia: systematic review. Maced J of Med Sci 2020; 8(6): 70-77.
6. Koradia KD and Parikh RH: Dissolution enhancement of albendazole through nanocrystal formulation. Journal of Pharmacy Bioallied Science 2012; 4: 62-3.
7. Cherogony R, Maru SM and Ndwigah SN: Preformulation study on enhancing the solubility of albendazole. East Cent. Afr J Pharm Sci 2018; 21: 10-15
8. Kadam PS, Pande VV, Vibhute SK and Giri MA: Exploration of mixed hydrotropy strategy in formulation and development of etodolac injection. Journal of Nanomedicine Research 2016; 7(1): 11-12.
9. Ahammad Unais VP and Sahoo PK: Application of hydrotropy in HPLC; hydrotropic solution most effective and eco friendly mobile phase to solubilisation of poorly
10. Water soluble drugs. International J of Trend in Scientific Research and Development 2020; 5(1): 1365-1368
11. Fahelelbom KM, Saleh A, Moawia MA, AL-Tabakha and Akram AA: Recent application of quantitative analytical FTIR spectroscopy in pharmaceutical, biomedical and clinical fields: a brief review. Reviews on Analytical Chemistry 2022; 41(1): 21-33.
12. Easam S, Bhandaru JS, Naliganti C, Bobbala RK and Akkinepally RR: Solubility enhancement of cardevilol using drug- drug co crystallization with hydrochlorthiazide. Future Journal of Pharmaceutical Science 2020; 54(1): 55-67.
13. Saharawat A, Deepali and Nainwal N: Natural plus synthetic hydrotropic solubilisation using response surface methodology to optimize the solid dispersion of hydrochlorthiazide. Bentham Science 2022; 25: 307-323
14. Yadav VK, Jain P, Thomson SA, Mirza MA and Iqbal Z: Solubility enhancement of diclofenac using solid dispersions. IJPP 2021; 5(1): 1-6.
15. Azad AK, Jahan K, Sathi TS, Sultana R, Abbas SA and Uddin AH: Improvement of dissolution properties of albendazole from different methods of solid dispersion. JDDT 2018; 8(5): 475-480.
16. Cisse A, Peters J, Lazzara G and Chiappisi L: Pydsc; a simple tool to treat differential scanning calorimetry data. Journal of Thermal Analysis and Calorimetry 2020; 1-7.
17. Saharawat A, Deepali and Nainwal N: Natural plus synthetic hydrotropic solubilisation using response surface methodology to optimize the solid dispersion of hydrochlorthiazide. Bentham Science 2022; 25: 307-323.
18. Soni GC, Chaudhary PD and Sharma PK: Solubility enhancement of poorly water-soluble drug Aceclofenac. IJPP 2016; 3(3): 139-145.

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