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ENHANCEMENT OF SOLUBILITY OF ACETAZOLAMIDE BY SOLID DISPERSION TECHNIQUE

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Abstract

Acetazolamide is a Carbonic Anhydrase Inhibitors drug characterized by low solubility and high permeability which corresponds to BCS class II drug. The purpose of the study was to develop solid dispersion by different methods and investigate them for in vitro and in vivo performance for enhancing dissolution and solubility. The solid dispersion was prepared using PEG 6000, povidone, cross povidone, lactose, Mcc102 as carriers in different ratios by different methods and was characterized for FT-IR. In vitro dissolution studies were performed in 0.1 N HCl and biorelevant media showed enhanced dissolution rate as compared to marketed formulation. The dissolution of prepared formulation (F8) was relatively higher (96%) than marketed formulation. On the basis of the result obtained, it was concluded that solid dispersion is a good approach to enhance solubility of poorly water-soluble Acetazolamide.

Key words: Acetazolamide, solid dispersion, PEG 600, Solubility.

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INTRODUCTION

The oral route of drug administration is the route of choice for the formulators and continues to dominate the area of drug delivery technologies. However, though popular, this route is not free from limitations of absorption and bioavailability in the milieu of gastrointestinal tract. Whenever a dosage form is administered orally, drug in the dosage form is released and dissolves in the surrounding gastrointestinal fluid to form a solution. This process is solubility limited. Once the drug is in the solution form, it passes across the membranes of the cells lining the gastro-Intestinal tract. This process is permeability limited. Then onwards the drug is absorbed into systemic circulation. In short, the oral absorption and hence bioavailability of drug is determined by the extent of drug solubility and permeability. [1]

A drug with poor bioavailability is the one with [2]

1. Poor aqueous solubility and slow dissolution rate in the biological fluids.
2. Poor stability of the dissolved drug at the physiological pH.
3. Inadequate partition coefficient and thus poor permeation through the bio membrane.
4. Extensive pre systematic metabolism.

Three approaches in overcoming the bioavailability problems due to such causes are

1. The pharmaceutics approach which involves modification of formulation, manufacturing process, or the physiochemical properties of the drug without changing the chemical structure.
2. The pharmacokinetic approaches in which the pharmacokinetics of the drug is altered by the modifying its chemical structure.
3. The biological approach whereby the route of the drug administration may be changed such as changing from oral to parental route.

The second approach of chemical modification has a number of drawbacks of being very expensive and time consuming, require repetition of clinical study and long time for regulatory aspects. The attempts ,whether optimizing the formulation ,manufacturing process, or physiochemical properties of the drug, are mainly aimed at enhancement of dissolution rate as it is the major rate limiting step in the absorption of the most drugs. The poor solubility of drug substances in water leads to low dissolution rate and thus to insufficient bioavailability

Dissolution [3]

Dissolution is a process in which a solid substance solubilizes in a given solvent i.e. mass transfer from the solid surface to the liquid phase.

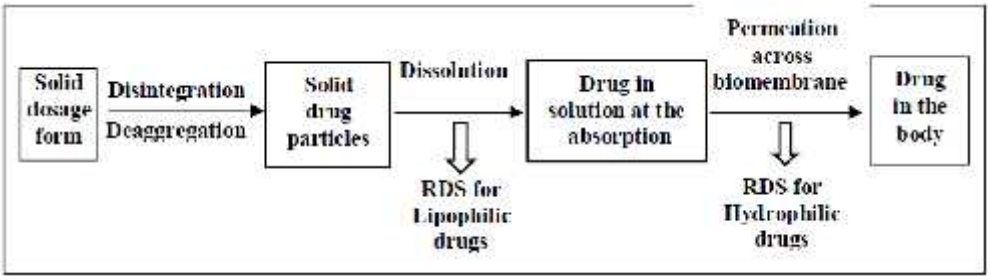


Fig. no.1: Two rate determining steps (RDS) in the absorption of drugs from orally administered formulations

Solubility is a key property in the distribution of the compound from the gastrointestinal tract to the blood [4]. Solubility is extremely difficult to calculate. Dozens of methods exist, but none is reliable enough to be used in the entire chemical diversity space populated by infinite drug candidates. Experimental solubility errors are relatively high and frequent. Moreover, solubility can change dramatically with the purity of the compounds, stability, and time [5]. It is usually not difficult to determine the solubility of solids, which are moderately soluble (greater than l mg/mL), but the direct determination of solubility much less than l mg/mL is not straightforward.

Solid Dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Chiou and Riegelman defined solid dispersions as “the dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states” [6]. Sekiguchi and Obi in 1961 first developed the concept of solid dispersion to enhance absorption of poorly water-soluble drugs. It involved the formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures, and once the carriers dissolved, the drug precipitated in a finely divided state in water. Later, Goldberg et al. demonstrated that a certain fraction of the drug might also be molecularly [7].

Classification of Solid dispersions [19]

Solid dispersions have been classified as follows depending on the type of carrier used for their preparation (Figure. 2)

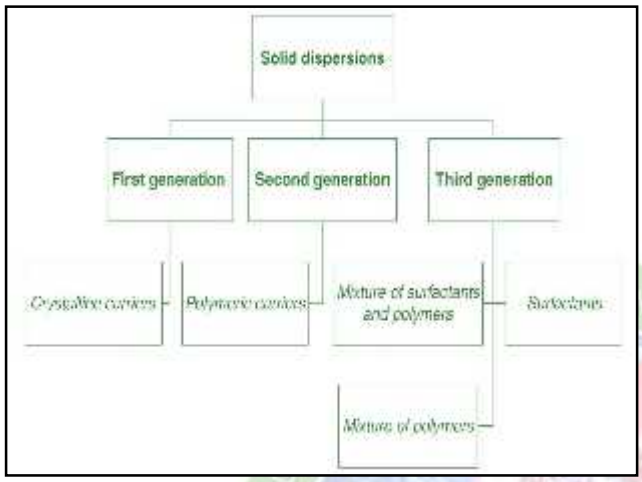


Fig. 2: The Classification of Solid Dispersions

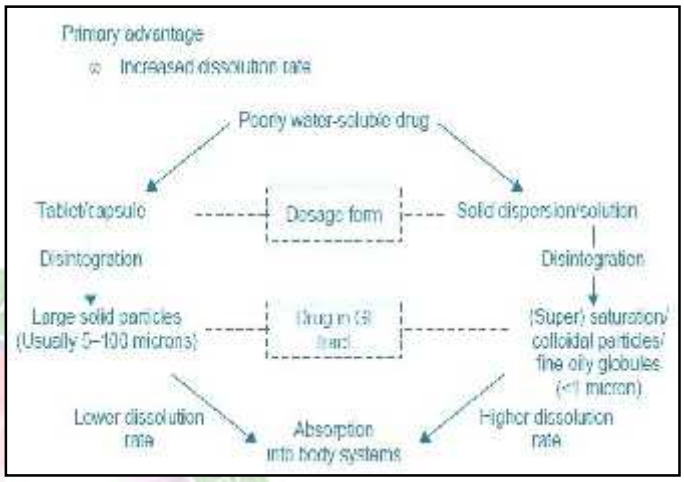


Fig. no.3: Advantages of a solid dispersion formulation, as compared to conventional capsule or tablet formulations

Solubility Enhancement Strategies in Solid Dispersions

Melting and solvent evaporation methods have been the two major processes of preparing solid dispersions melting on lab scale[20]. Industrially relevant and applicable methods for solid dispersion manufacturing are explained in Figure 4.

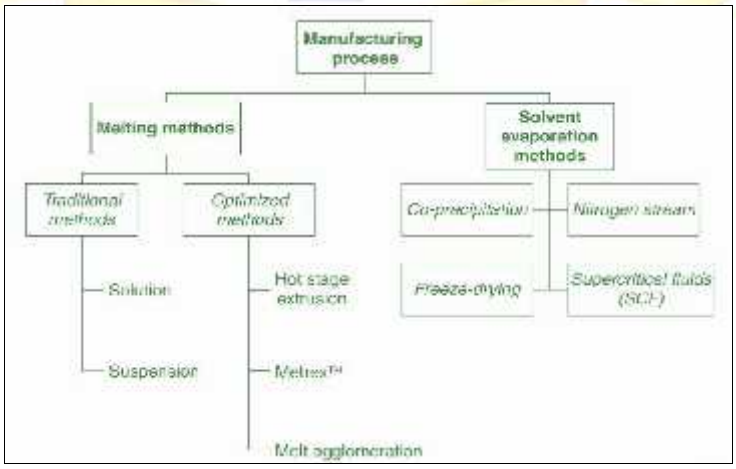


Fig. no. 4: Manufacturing processes used to produce solid dispersions

MATERIALS AND METHODS

Acetazolamide, PEG6000, Povidone, Lactose, Cross povidone, Micro crystalline, cellulose102, Aerosil, Magnesium Stearate, Methanol obtained from Pharma Train Research Lab, Hyderabad.

Drug-Excipient compatibility studies:

Drug-excipients compatibility studies were carried out using FT-IR. The study was carried out on individual pure drug and its physical mixture with the excipients used in the study.

FTIR Study:

The pure drug and the excipients were mixed separately with IR grade KBr in the ratio of 100:1, and corresponding discs were prepared by applying 5.5 metric tons of pressure in a hydraulic press. The discs were scanned over a wave number range of 4,000–400 cm^{-1}.

Preparation of Standard Calibration Curve for Acetazolamide:

UV scanning was done for pure drug 200-300nm in methanol. The lambda max was found at 266nm.

Reagents : Methanol 0.1N HCL Buffer Solution

Standard solution of Acetazolamide:

100mg of drug is dissolved in 100ml of methanol. This is first stock solution.10ml of 1^{st} stock solution is diluted with 100ml of buffer.. This is 2^{nd} stock solution. Now from 2^{nd} stock, various concentrations of 10ug/ml, 15ug/ml, 20ug/ml, 25ug/ml, and 30ug/ml were prepared by using buffer. Blank was also prepared with same buffer composition except the drug. All the samples were analyzed at 266 lambda max with respect to the blank.

Preparation of Tablets:

Method 1:

- Lactose was melted in crucible china dish at 100-120.
- For batches with PEG add it along with lactose and heat around 50-70 as the tg of lactose is lowered because of PEG.
- Shift all the extragranular excipients through mesh no 40 and add these to granules obtained in step 2 and blend.
- Compress using suitable.

Method 2:

- Dissolve the drug in ethanol and transfer this solution to carry to make slurry. And with batches containing copovidone/PEG add these to drug solution.
- Dry the slurry at 50-60 to evaporate ethanol completely.
- Pass the dried granules through mesh no 40
- Sift all the extragranular excipients through mesh no 40 and add these to granules obtained in step 2 and blend.
- Compress using suitable punch.

Table 1: Different formulations of Acetazolamide

Formulation code/Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)
Acetazolamide	125	125	125	125	125	125	125	125	125	125
PEG6000						10			20	
Povidone			10	10	20		20	20		
Mcc102	150		145				67.5	65	66	
Lactose		150		145	135	145	67.5	65	65	
Cross povidone								5	5	
Methanol	qs	Qs	qs	qs	qs	qs	qs	qs	qs	qs
Extragranular excipients										
MCC102	40	40	35	35	35	35	35	35	35	
Cross povidone	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Aerosil	1	1	1	1	1	1	1	1	1	
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	325	325	325	325	325	325	325	325	325	134

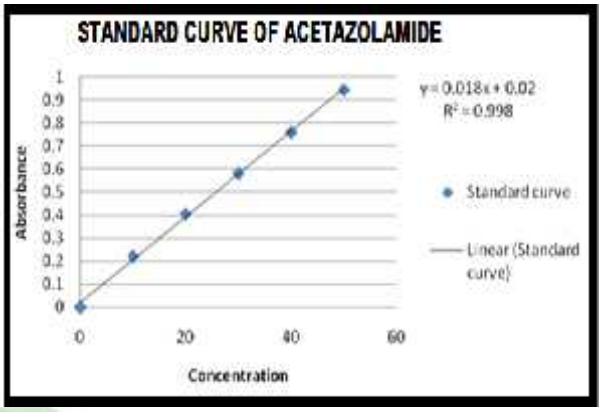
RESULTS & DISCUSSION:

Standard Curve of Acetazolamide: Standard curve of Acetazolamide was determined by plotting absorbance V/s concentration at 266 nm and it follows the Beer's law. The results were shown in table no (12). The r^2 value was found to be 0.998.

Table 2: Standard curve of Acetazolamide

S.no	Concentration (mcg/ml)	Absorbance at 266nm
1	10	0.221
2	20	0.405
3	30	0.581
4	40	0.76
5	50	0.944

Fig 5: Standard curve ofAcetazolamide



Solubility

It is very slightly soluble in water and only slightly soluble in ethanol and methanol; it is practically insoluble in ether and chloroform.

Drug polymer interaction study:

Compatibility studies were performed using FT-IR spectrophotometer. The FT-IR spectrum of pure drug and physical mixture of drug and polymers were studied. The interpretation results were summarized in table no (11)

Table 11: FT-IR Interpretation

S No	Wave number(cm^{-1})	Type of stretch
1	3355	N-H
2	1714	C=O
3	2964	C-H
4	1618	1^0&2^0 Amines

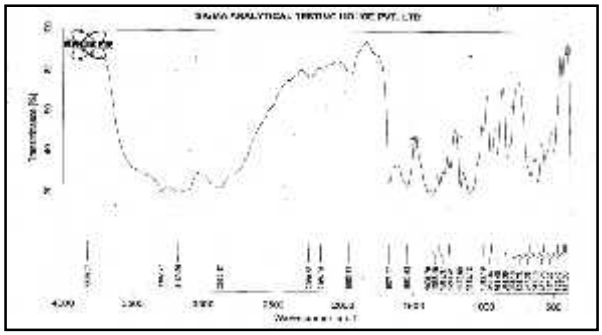


Fig 2: IR spectra of Acetazolamide

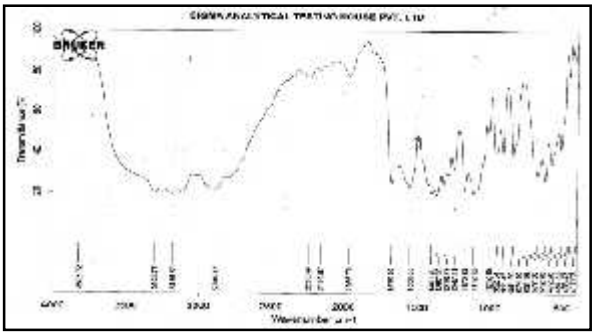


Fig 3: IR spectra of API+PEG6000

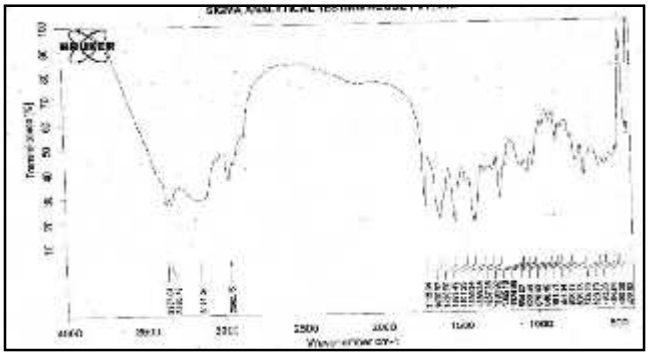


Fig 4: IR spectra of API + Crospovidone

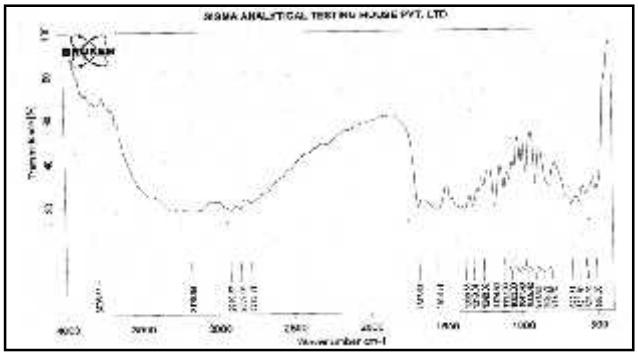


Fig 5: IR spectra of API + Lactose

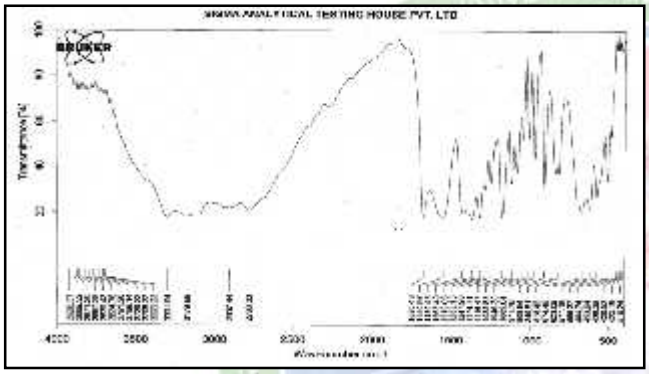


Fig 6: IR spectra of API + Povidone

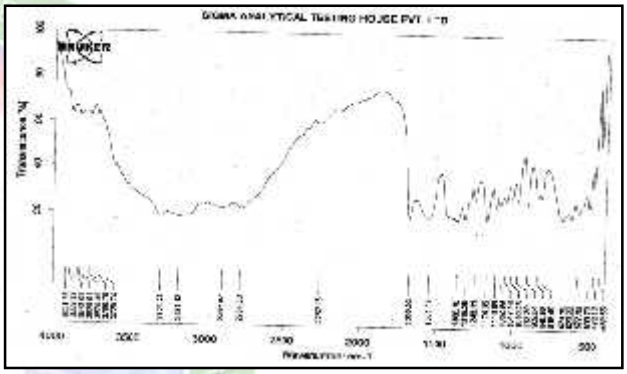


Fig 7: IR spectra of API + MCC

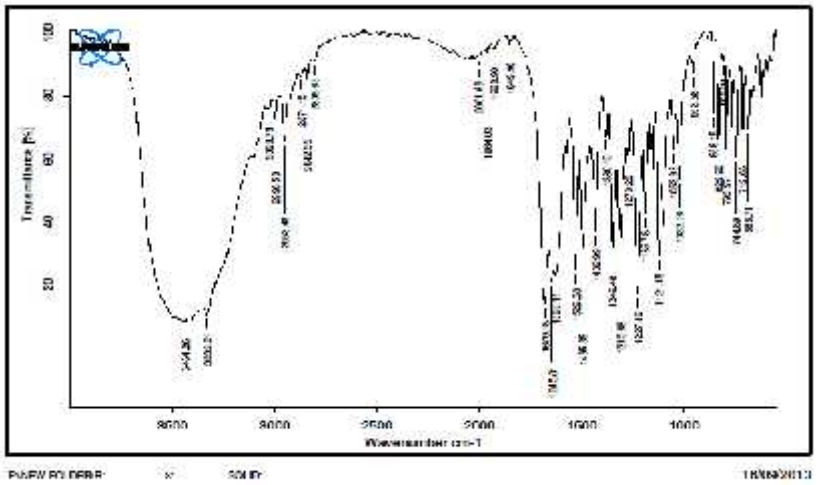


Fig 11: IR spectra of Optimized Formulation

Pre-Formulation Parameters

Precompression parameters such as bulk density, tapped density, angle of repose, Carr's index and Hausner ratio which are evaluated for prepared tablets are given in following table

Table 5: Precompression characteristics of blend of all formulation

Formulation code	Bulk Density (g/cc)	Tapped density (g/cc)	Angle of repose	Carr's index (%)	Hausner ratio
F1	0.49	0.57	27.40	14.04	1.16
F2	0.48	0.55	26.06	12.72	1.14
F3	0.46	0.53	24.38	13.20	1.15
F4	0.43	0.49	23.72	12.24	1.14
F5	0.41	0.47	21.94	12.76	1.14
F6	0.49	0.57	27.40	14.04	1.16
F7	0.46	0.53	24.38	13.20	1.15
F8	0.41	0.47	21.94	12.76	1.14
F9	0.43	0.49	23.72	12.24	1.14

Physico-Chemical Properties of tablet:

Weight variation:

Twenty tablets were randomly selected from each batch individually weigh, the average weight and standard deviation of 20 tablet calculated (Krishanaiah et al., 2003). Table no-6

Thickness:

The thickness of the tablet was measured by using digital venire caliper, twenty tablets from each batch were randomly selected and thickness was measured (The British Pharmacopoeia, 2005).

Hardness:

Hardness was measured using Pfizer hardness tester, for each batch three tablets were tested (The United State of Pharmacopoeia, 1995). (Table no-6)

Friability:

Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted and weighed. (Chaudhari PD, 2005).

The results of hardness, thickness, diameter friability, and weight variation of the tablets are given in the below Table (6). All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 297 and 301 mg. The hardness of the tablets ranged from 3.0-4.0kg/cm^2 and the friability values were less than 1% indicating that the matrix tablets were compact and hard. All the formulations satisfied the content of the drug as they contained 98-102 of Acetazolamide and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control. The results were summarized in the table no (14).

Table 6: Physico- chemical properties of all formulations

S.No.	Formulation	Weight variation	Hardness (kg/cm2)	Diameter (mm)	Thickness (mm)	Friability (%)
1	F1	complies	3.24	9.0	4.01	0.60
2	F2	complies	3.50	9.2	4.05	0.51
3	F3	complies	3.04	9.5	4.03	0.37
4	F4	complies	3.62	9.4	4.01	0.49
5	F5	complies	3.75	9.1	4.02	0.85
6	F6	complies	3.34	9.4	4.04	0.51
7	F7	complies	3.24	9.5	4.02	0.49
8	F8	complies	3.90	9.2	4.00	0.41
9	F9	complies	3.74	9.0	4.04	0.69

Table 7: In-vitro release data of Acetazolamide compacts

	Percentage Cumulative Drug Release									
Time(hrs)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**Marketed formulation**
10	30	37	36	41	43	43	45	48	45	15
15	49	53	53	59	65	65	64	65	65	32
30	68	75	76	80	82	78	85	86	85	48
45	80	86	88	92	94	90	95	96	94	69

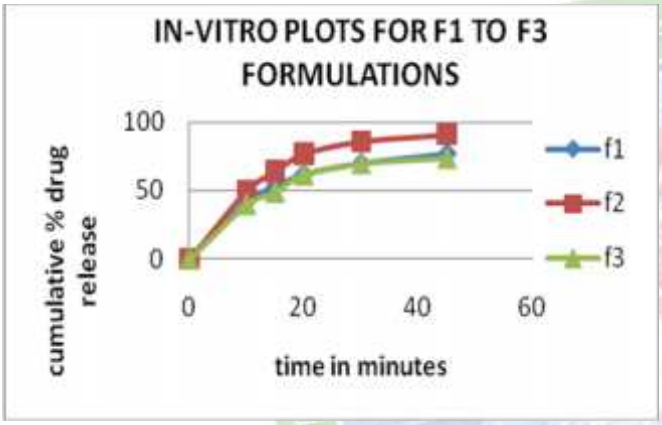


Fig 12: In-vitro plots for F1, F2, and F3

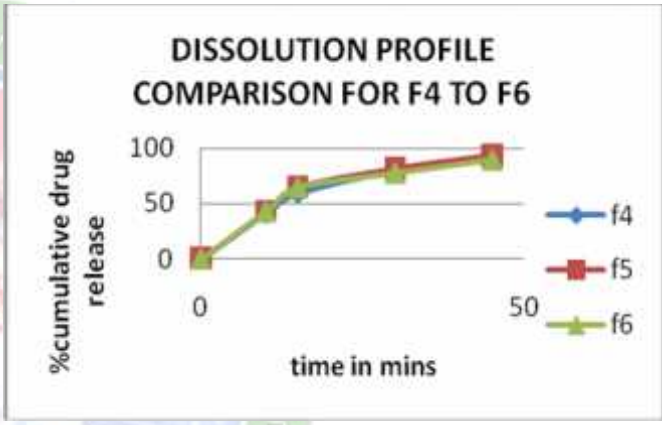


Fig 13: In-vitro plots for F4, F5, and F6

The *In vitro* dissolution study of F1, F2 and F3 were performed for 1hr time period. The results indicated that F1 and F2 and F3 formulations were unable to control the release of drug over 1hr time period. The results of dissolution studies of formulations F1, F2 and F3 were shown in figure (12).

The dissolution study for F4, F5 and F6 were performed for 1hr time period. The F4 formulation containing Povidone and lactose releases 92% of drug in 45 minutes time period. F5 formulation consisting of Povidone and lactose controls the drug release for 1hr and 94% of drug is released in 45 minutes time period.

F6 formulation containing lactose was unable to control the drug release over 1 hr time period. The drug release at 45 minutes was 90%. The results of dissolution studies of formulations F4, F5 and F6 were shown in figure (13).

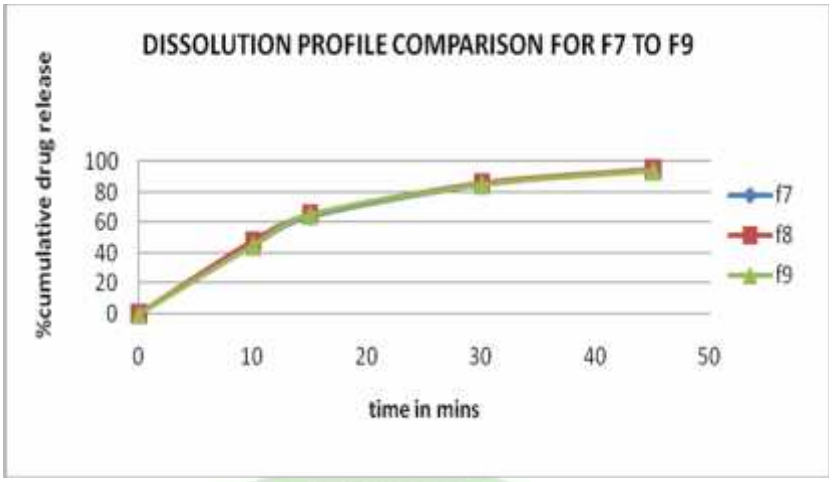


Fig 14: In-vitro plots for F7, F8, and F9

The dissolution study for F7 F8 and F9 were performed for 1hr time period. F7 formulation containing povidone, MCC102 and lactose controls the drug release for 1hr time period. The drug release at 45 minutes was 95%.F8 formulation containing povidone, MCC102 and lactose higher in concentration than in F7 formulation release 96% of drug in 45 minutes time period. F9 formulation consisting of crosspovidone and MCC102l was able to control the drug release and releases 94% of the drug in 45 minutes time period. The results of dissolution studies of formulations F7and F8 and F9 were shown in figure (14).

F8 formulation consisting of povidone, MCC102, lactose and cross povidone was able to control the drug release and it releases 96% of drug at 45th minute. So it is considered as the optimized formulation as it shows better drug release than other formulations.

Table 8: Dissolution profile of prepared and optimized formulation

Time (min)	% cumulative drug release of prepared conventional formulation	% cumulative drug release of optimized formulation F8
0	0	0
10	15	48
15	32	65
30	48	86
45	69	96

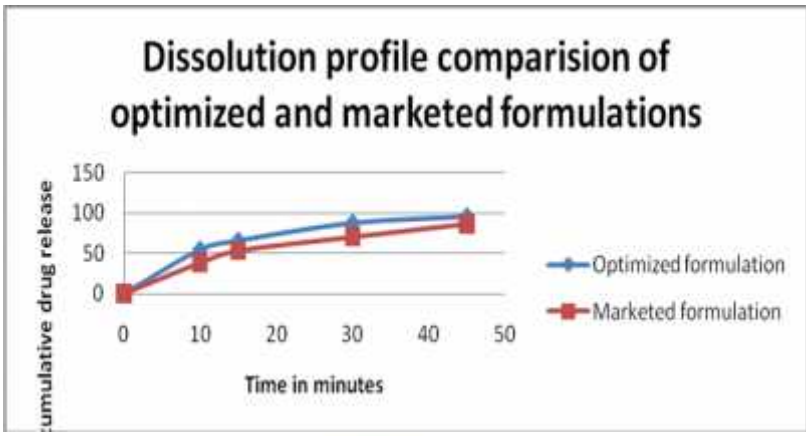


Fig 15: Dissolution profile of comparison of prepared conventional and optimized formulation

The dissolution profiles of optimized and marketed formulations were compared. From the results it was confirmed that the optimized formulation (F8) showed better drug release i.e. 96% than marketed formulation which showed 69% drug release at the end of 45th minute. The results were shown in the figure (15).

CONCLUSION

The present work on enhancement of solubility of Acetazolamide tablets by solid dispersion technique utilize PEG 6000, povidone, lactose and Mcc102 to increase the solubility of the formulation in 1hr time period. F8 formulation showed better drug release of 95% drug release at the end of 45th minute compared to other formulations and marketed formulation. So F8 is the optimized formulation. Among the polymers used the role of PEG6000, cross povidone, MCC 102 and lactose is noteworthy in enhancing the solubility. Drug-excipients interaction was carried out for pure drug and optimized formulations by using FTIR study. In this analysis drug – excipients compatibility interactions were not observed. From the results obtained it was concluded that the optimized formulation follows zero order release kinetics.

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