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FORMULATION AND EVALUATION OF ACETAZOLAMIDE EXTENDED RELEASE CAPSULES

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ABSTRACT The present study was to develop an extended release formulation of Acetazolamide to maintain constant therapeutic levels of the drug for over 12 hrs. An efficient extended release formulation of Acetazolamide could be designed as extended release capsules. The optimised formulation (F12) was developed by using Eudragit RS100 (6%) and Eudragit RL100 (4%). Regulated drug release in first order manner was attained by using these polymers. This extended release formulation (F12) was found similar and comparable to the innovator product based on the f2 value (69.70) obtained. The developed extended release capsule formulation was quite stable with regard to drug content, physical properties and dissolution rate in the accelerated stability studies.

KEYWORDS :

Acetazolamide [1,2,3]

Acetazolamide is a synthetic carbonic anhydrase inhibitor, effective in the control of fluid secretion.

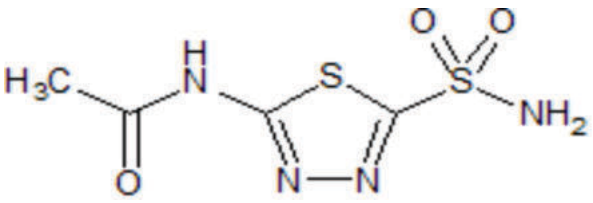

Fig. 1 Structure of Acetazolamide

Procedures:

F_1 to F_{16} different preparations are done

Evaluation[4]

Similarity Factor And Dissimilarity Factor Calculation[5]

$f1 = \{ [\ _{t=1}{}^{n}R_t - T_t\ ] / [\ _{t=1}{}^{n}R_t\ ] \} . 100$

$f2 = 50. \log \{ [1 + (1/n)\ _{t=1}{}^{n} (R_t - T_t)^2]^{-0.5} . 100\}$

Where 'R_t' and 'T_t' are the cumulative percentage dissolved at each of the selected n time point of the reference & test product respectively.

Table 1: Similarity factor f2 and its significance

S. No.	Similarity factor (f2)	Significance
1.	<50	Test and reference profiles are dissimilar.
2.	50 -100	Test and reference profiles are similar.
3.	100	Test and reference profiles are identical.
4.	>100	The equation yields a negative value.

Analytical Methods[6]

Dissolution

Medium: 0.01N hydrochloric acid; 900 mL
Apparatus: USP I (Basket)
RPM: 100 rpm
Time: 20 hrs
Time points: 1, 3, 6, 9, 12 and 20 hours

ASSAY

Mobile phase preparation-

4.1g of anhydrous sodium acetate was dissolved in 950mL of water; 20mL of methanol and 30mL of acetonitrile were added and mixed. pH was adjusted to 4.0±0.05 glacial acetic acid. The solution was filtered and degassed.

Standard acetazolamide stock solution preparation -

25mg of USP Acetazolamide RS, accurately weighed, was transferred to a 25-mL volumetric flask; 10mL of 0.5N sodium hydroxide was added and mixed to dissolve. Then it was diluted with water to volume, and mixed.

Internal standard solution preparation -

100mg of sulfadiazine was transferred to a 100-mL volumetric flask, 10mL of 0.5N sodium hydroxide was added and mixed to dissolve. Then it was diluted with water to volume, and mixed.

Standard preparation-

10.0mL of Standard acetazolamide stock solution and 10.0mL of Internal standard solution was transferred to a 100-mL volumetric flask, 10mL of 0.5N sodium hydroxide was added and diluted with water to volume, and mixed to obtain a solution having a known concentration of about 0.1mg of USP Acetazolamide RS per mL.

Assay preparation-

The contents of 20 capsules were emptied and weighed. 130 mg of the weighed portion of the powder, equivalent to 100mg of acetazolamide was transferred to a 100mL volumetric flask, and 10mL of 0.5N sodium hydroxide was added. Then it was sonicated for 5 minutes. Later it was cooled to room temperature, diluted with water to volume, and mixed. Then the solution was filtered, discarding the first 20mL of the filtrate. 10.0mL of the clear filtrate was transferred to a 100mL volumetric flask and 10.0mL of internal standard solution and 10mL of 0.5N sodium hydroxide were added and diluted with water to volume and mixed.

Chromatographic system-

The HPLC equipped with a 254-nm detector and a 4.6X250 mm column was used. The flow rate was adjusted to 2mL per minute. The peaks were recorded for the Standard preparation.

Procedure-

Separately equal volumes (about 20μL) of the Standard preparation and the assay preparation were injected into the chromatograph, the chromatograms were recorded and the responses for the major peaks were measured. The relative retention times are about 0.7 for acetazolamide and 1.0 for sulfadiazine.

Conditions:

Column : μbondapak C18, 250*4.6 mm, 5μ
Wave length (λ) : 254nm
Column temp : 30° C
Flow : 2.0mL /min
Injection Volume : 20μL
Run time : 10min
Sample tray temperature : 12° C

Preformulation Studies - Results

Table 2 Particle size analysis of API

Sieve number	MICRONS	Wt. of sieve (A)	Final weight (B)	% retained (B-A)	Cumulative % weight retained
50	300	334.6	361.7	27.1	27.1
70	212	334.4	382.8	48.4	75.5
100	150	335.6	342.1	6.5	82.0
150	125	383.3	384.9	1.6	83.6
170	90	331.4	343.5	12.1	95.7
200	75	316.2	319.2	3.0	98.7
220	71	378.2	378.9	0.5	99.2
Pan	-	533.3	533.6	0.3	99.5

Table 3: Flow Properties:

BATCH	BULK DENSITY(g/mL)	TAPPED DENSITY(g/mL)	ANGLE OF REPOSE (°)
API	0.70	0.601	33.6
F1	0.535	0.714	30.9
F2	0.515	0.647	32.5
F3	0.500	0.647	34.3
F4	0.555	0.673	31.2
F5	0.597	0.740	30.6
F6	0.520	0.657	33.4
F7	0.465	0.712	34.2
F8	0.333	0.691	28.2
F9	0.897	0.660	26.7
F10	0.636	0.777	24.3
F11	0.462	0.806	41.5
F12	0.510	0.806	35.5
F13	0.462	0.833	41.9
F14	0.500	0.657	35.5
F15	0.500	0.675	35.1
F16	0.526	0.789	30.7

FORMULATIONS – RESULTS

The objective of the study was to formulate and evaluate Acetazolamide ER capsules 500 mg comparable to the innovator product.

Table 4: Charcteristics Of Innovator:

S.No	Weight (mg)	Assay (%)*†	Dissolution (in % after 20hrs.)**†
1	765.6	99.14	99.2
2	766.3	101.17	98.9
3	765.7	100.21	101.6
4	764.2	98.90	99.2
5	763.9	98.76	98.3
6	766.2	99.23	102.1

*** Values represent mean ± Standard Deviation (SD), n=6**
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† Of different units

Charcteristics Of Optimised Formulation

Table 5: Dissolution Profiles†

BATCH	TIME (hrs)	0	1	3	6	9	12	20
INNOVATOR		0	14.7±1.2	33.2±0.9	65.7±1.1	83.3±1.3	91.9±1.6	98.2±1.4
F1		0	26.5±2.6	36.1±2.9	45.8±1.8	62.2±2.2	73.5±1.9	84.4±2.4
F2		0	24.2±2.1	37.9±1.4	40.3±1.9	66.1±2.2	70.8±2.0	82.2±1.7
F3		0	33.2±1.6	40.1±2.1	56.7±2.3	68.2±1.9	78.5±2.1	97.2±2.2
F4		0	80.7±2.1	97.9±2.3	98.8±1.6	97.9±2.4	97.6±1.9	97.5±1.8
F5		0	41.26±1.8	62.1±2.1	77.9±1.6	82.3±1.4	83.8±1.7	85.2±1.7
F6		0	13.5±2.1	19.9±1.8	26.9±2.2	31.8±2.3	35.7±1.9	41.8±1.6
F7		0	16.0±2.4	25.6±2.1	31.9±1.8	36.6±1.6	55.3±1.7	65.8±1.9
F8		0	5.8±1.8	15.0±2.1	22.7±1.9	28.1±2.4	32.5±2.1	42.9±1.8
F9		0	7.0±1.9	16.0±2.3	22.6±1.6	28.3±1.8	32.7±2.0	36.6±2.3
F10		0	25.7±2.2	41.7±1.8	55.8±2.7	67.0±2.3	76.1±1.6	85.4±1.9
F11		0	15.4±2.3	29.0±1.8	42.1±2.6	53.1±2.5	76.5±2.3	81.9±1.7
F12		0	18.2±2.4	30.4±1.6	61.9±1.7	79.8±2.0	86.4±1.7	96.1±1.4
F13		0	29.1±2.0	47.9±1.6	84.2±2.4	97.2±1.9	97.8±1.5	101.2±2.1
F14		0	44.6±1.5	90.4±1.8	97.0±1.6	97.3±2.1	96.4±2.0	95.0±1.6
F15		0	12.0±2.3	36.2±2.6	54.8±1.8	76.7±2.4	76.2±2.2	84.7±1.7
F16		0	6.7±1.9	12.9±2.2	17.7±1.7	22.4±2.3	26.2±2.0	33.7±1.6

† Values represent mean ± Standard Deviation (SD), n=6

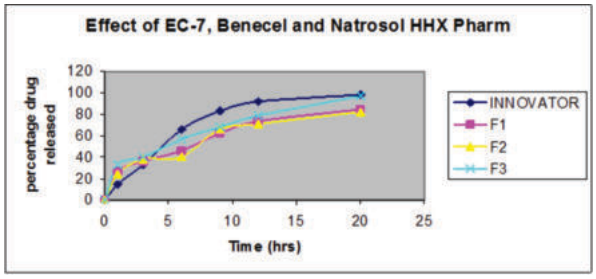

Fig 1 - Dissolution profile of Innovator, F1, F2 and F3 batches

The effect of these polymers on the release of acetazolamide from the capsules is shown in the following graph.

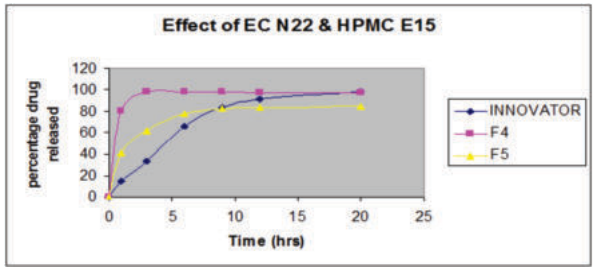

Fig2 - Dissolution profile of Innovator, F4 and F5 batches

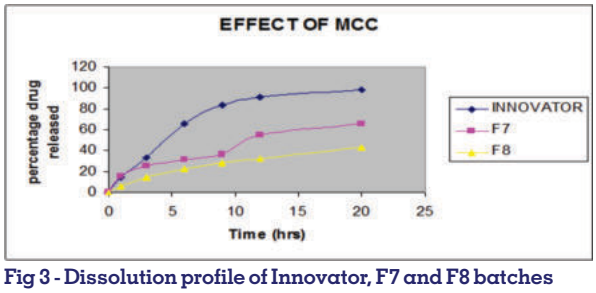

Fig 3 - Dissolution profile of Innovator, F7 and F8 batches

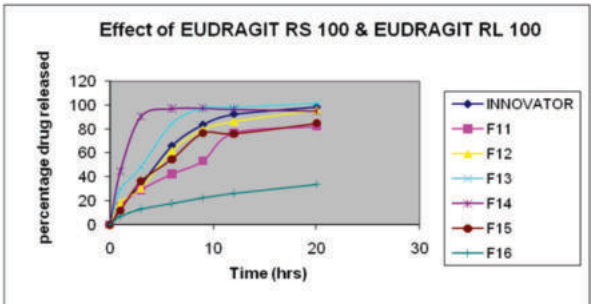

Fig 4 - Dissolution profile of Innovator, F11, F12, F13, F14, F15 and F16 batches

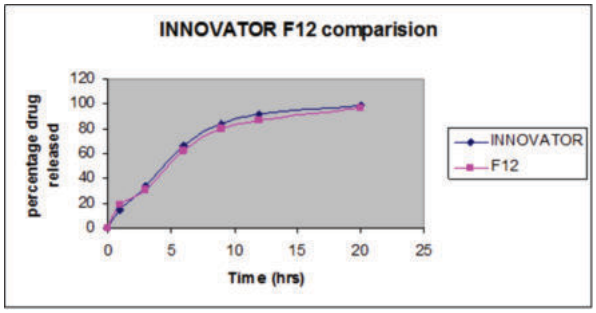

Fig 5 - Dissolution profile of Innovator and F12 batches

Zero order plot for optimised formulation (F12)

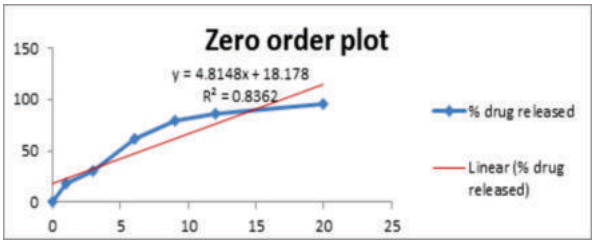

Fig 6 - Zero order plot for optimised formulation

Higuchi plot for optimised formulation (F12)

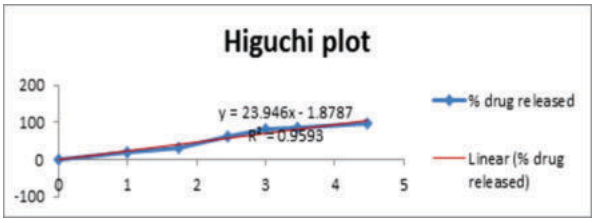

Fig 7 - Higuchi order plot for optimised formulation

Peppas curve for optimised formulation (F12)

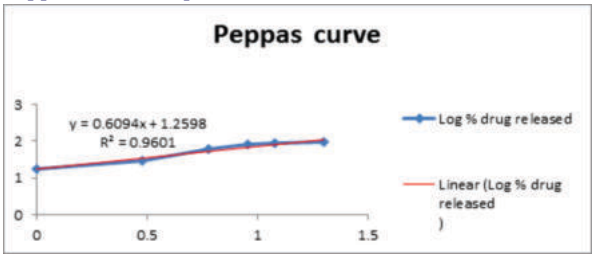

Fig 8 - Peppas curve for optimised formulation

Table 6: Drug Release Kinetics

Batch	Zero order		First order		Higuchi	
	r2	K0 (mg/L/hr)	r2	K1 (h-1)	r2	KHg (h-1)
INNOVATOR	0.8167	5.0277	0.9962	0.206809	0.9849	25.163
F1	0.8632	3.8274	0.9796	0.089817	0.9838	18.972
F2	0.8435	3.76	0.9566	0.084059	0.9658	18.682
F3	0.8659	4.2393	0.9473	0.163282	0.9868	21.014
F4	0.2771	2.7199	0.3231	0.128737	0.5849	17.776
F5	0.5521	3.3103	0.7207	0.087514	0.8281	18.824
F6	0.8299	1.8353	0.8812	0.024642	0.9829	9.3138
F7	0.9132	3.0349	0.9603	0.051356	0.9706	14.528
F8	0.9256	2.0603	0.964	0.027175	0.9935	9.9112
F9	0.8433	1.758	0.8833	0.022339	0.9811	8.7991
F10	0.8118	3.832	0.9687	0.093041	0.9789	19.538
F11	0.8934	4.0669	0.9454	0.088895	0.9692	19.669
F12	0.8362	4.8148	0.9956	0.164894	0.9593	23.946
F13	0.6996	4.7354	0.9006	0.251717	0.9091	25.064
F14	0.4162	3.462	0.4495	0.139331	0.7049	20.92
F15	0.7939	4.23	0.9099	0.098107	0.9446	21.424
F16	0.9173	1.5704	0.9849	0.019345	0.999	7.6098

* **r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.**

Table 7: Drug Release Kinetics (contd.)

Batch	Korsmeyer-Peppas		f2 value	T50%	T75%	T90%
	r2	n		in hours (approximately)		
INNOVATOR	0.9566	0.6803	-	5	8	12
F1	0.9704	0.4069	37.94339	7	8	12
F2	0.9429	0.4226	36.37011	7	8	13
F3	0.9641	0.3726	43.86922	5	10	18
F4	0.6135	0.0581	17.61706	<1	<1	<1
F5	0.9112	0.2516	35.33344	2	6	-
F6	0.9978	0.3869	16.76463	-	-	-
F7	0.9586	0.4694	23.4409	10	-	-
F8	0.9848	0.6603	15.59202	-	-	-
F9	0.9743	0.5629	15.01946	-	-	-
F10	0.9936	0.4132	42.80014	5	12	-
F11	0.9836	0.5836	35.00303	8	12	-
F12	0.9601	0.6094	69.70331	5	8	18
F13	0.9272	0.4573	42.44476	4	5	8
F14	0.6891	0.2399	24.22079	2	3	3
F15	0.9352	0.67	47.88738	5	9	-
F16	0.9983	0.50	13.09687	-	-	

Release Mechanism

Based on the "n" value of 0.6094 obtained for F12 formulation, the drug release was found to follow Anomalous (non-Fickian) diffusion. This value indicates a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and indicates that the drug release was controlled by more than one process. Based on the value of "n" (n=0.6803) for innovators product, it was also found to follow the same release mechanism.

The "r" value for Higuchi plot was found to be 0.9593 indicating that drug release included diffusion as one of the release mechanisms.

The dissolution profiles of formulation F12 and innovator product were compared by calculating differential factor (f1) and similarity factor (f2). The f1 and f2 were found to be 2.97 and 69.70 respectively for the comparison of dissolution profiles of formulation F12 and innovator product. Hence these two products were considered to be similar.

Drug Excipient Compatability Studies

Drug-Excipient compatibility studies form an important part of Preformulation studies. The interaction between the drug and excipients are determined after a specific time period by using suitable analytical techniques like HPLC, FTIR, DTA or DSC.

Table 8: Compatability Studies

S.	Drug + Excipient	Category	Drug: Excipient	Parameter	Initial Value of Parameter	Condition	
						40°C+7 5%RH	60°C
						4 weeks	4 weeks
01.	Acetazolamide	Active	-	Moisture content	0.12	0.17	0.11
				Total Impurity	NIL	0.01	0.01
				Assay	100	99.8	99.7
02.	Acetazolamide+Avicel PH 101	Diluent	1:1	Moisture content	0.14	0.13	0.37
				Total Impurity	0.06	0.02	0.01
				Assay	99.6	99.6	99.5
03.	Acetazolamide+ Eudragit RS100	ER Polymer	1:1	Moisture content	1.45	4.19	1.46
				Total Impurity	0.004	0.03	0.03
				Assay	99.4	99.3	99.3
04	Acetazolamide+Eudragit RL100	ER Polymer	1:1	Moisture content	1.67	2.85	1.96
				Total Impurity	0.01	0.05	0.017
				Assay	99.6	99.6	99.5
05	Acetazolamide+ SLS	Wetting agent	1:1	Moisture content	4.08	4.25	4.85
				Total Impurity	0.003	0.00	0.025
				Assay	99.7	99.6	99.6
06.	Acetazolamide+ Talc	Lubricant	1:1	Moisture content	4.95	3.26	2.55
				Total Impurity	0.01	0.09	0.043
				Assay	99.5	99.4	99.4

Infrared Spectroscopy (IR) studies

The stability studies on Acetazolamide ER capsules 500 mg in HDPE container at 40°C / 75 % RH for 2 months were conducted as per ICH protocol.

DISSOLUTION:

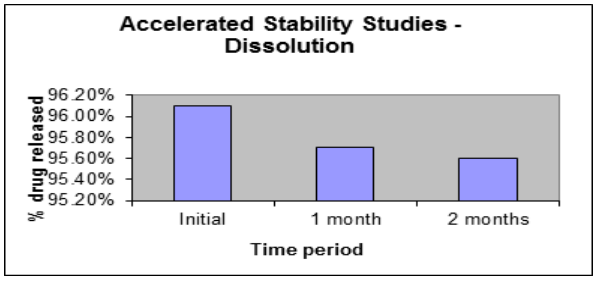

Fig - Accelerated stability studies – Dissolution

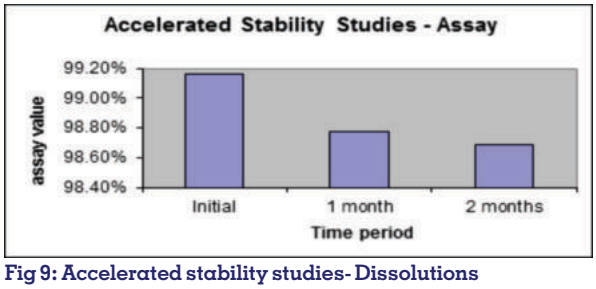

Fig 9: Accelerated stability studies- Dissolutions

Assay:

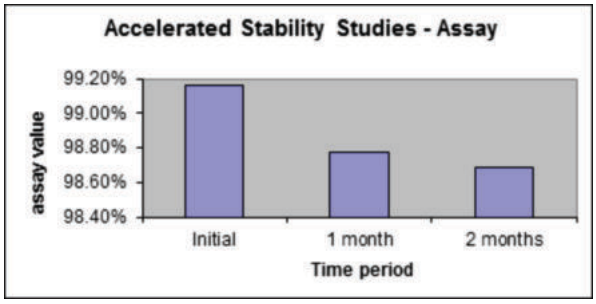

Fig 10 - Accelerated stability studies – Assay

CONCLUSION:

The aim of the present study was to develop an extended release formulation of Acetazolamide to maintain constant therapeutic levels of the drug for over 12 hrs.

An efficient extended release formulation of Acetazolamide could be designed as extended release capsules. The optimised formulation (F12) was developed by using Eudragit RS100 (6%) and Eudragit RL100 (4%). Regulated drug release in first order manner was attained by using these polymers.

This extended release formulation (F12) was found similar and comparable to the innovator product based on the f2 value (69.70) obtained. The developed extended release capsule formulation was quite stable with regard to drug content, physical properties and dissolution rate in the accelerated stability studies.

Acknowledgement:

We are thankful to the **SIMS College of Pharmacy** for the helping hand without which it is not possible.

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