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Development and evaluation of tablet formulation containing combination of dapsone and acetazolamide for treatment of severe burn

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***Abstract*---**The aim of this study was to develop and optimise a bilayer tablet containing Dapsone and Acetazolamide for the effective treatment of severe burns. Preformulation studies, including drug excipient compatibility, were studied for both drugs. The compatibility studies showed that there was no interaction between the drug and excipients and also drug-drug. The bilayer tablet was formulated in such a way that the immediate release layer contains Dapsone and the sustained release layer contains Acetazolamide. The formulated batches of bilayer tablets F1-F4 were evaluated. The parameters t90%, Drug release, Friability, Hardness, Drug content, and Angle of repose

are considered for the evaluation of a tablet. The kinetic study showed that the drug release follows the matrix model as the best fit model. In vitro dissolution studies of bilayer tablets in USP type II apparatus resulted in 98.04% drug release of Dapsone for 60 minutes and 94.21% drug release of Acetazolamide for a period of 12 hours. According to the findings of this study, the drug and excipients used in the formulation were at the appropriate concentrations.

***Keywords*---**bilayer tablets, angioedema, diuretic agent, antibiotic agent, immediate release, sustained release, kinetic analysis.

Introduction

Recent advancements in drug pharmacokinetics and pharmacodynamics behaviour have enabled a more rational approach to the development of optimal drug delivery systems. Nowadays, more focus has been devoted to the development of controlled and immediate release drug delivery systems. Conventional dosage forms cause a wide range of fluctuations in drug concentrations in the bloodstream and tissues, resulting in undesired toxicity and inefficiency. In the last decade, interest in developing a combination of two or more active pharmaceutical ingredients (API) in a single dosage form (bilayer tablet) has increased. [1,2] The main objectives of combination therapy are to encourage the use of lower doses of drugs to treat patients and also to minimise dose-dependent side effects and adverse reactions. [3-6] To overcome the drawbacks of single-layer combination tablets, this concept came into force. [7] Bilayer tablets can be a primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles (i.e., immediate release with extended release). [2]

In severe burn cases, an edematous condition occurs, also known as angioedema. This results in swelling of the lower layer of skin (dermis) and tissue just beneath the skin (subcutaneous tissue) or mucous membranes. Therefore, in such cases, a combination of treatment with an antibiotic, for example, Dapsone, to treat the bacterial infection at the site of action along with a diuretic agent for reduction of swelling, is used. The objective of the present study was to develop and evaluate a bilayer tablet containing Dapsone as an antibiotic agent and Acetazolamide as a diuretic agent.

Materials and Methods

Dapsone was purchased from Research-Lab Fine Chem Industries, Mumbai. Acetazolamide was purchased from Nakoda Chemicals Ltd., Telangana. Benecel™ E4M polymer was supplied as a gift sample by Ashland Co. Netherland. Croscarmellose Sodium- Ac-Di-Sol®, Microcrystalline cellulose- AVICEL PH102, Magnesium stearate, Talc, and Sodium saccharin were supplied as a kind gift from Fine Chem Ltd., Mumbai. All other chemicals and reagents used were of analytical grade and were purchased from local suppliers.

Methods

Identification of Pure drug

a) *FTIR* [8]
Identification of pure drug Dapsone and Acetazolamide was carried out by Fourier Transform Infra-red Spectrophotometry (Shimadzu 8400s) scanned in the range of 400-4000cm^{-1}.

b) DSC
A differential scanning calorimeter (Mettler Toledo) was used for thermal analysis of both drugs for identification purposes. Individual drugs were weighed directly into the DSC aluminium crucible. The samples were scanned in a dry nitrogen atmosphere at a temperature ranging from 200-400 °C. The heating rate was 10°C·min^{-1} and the thermograms obtained were observed for the identification of pure drugs.

c) *UV-spectroscopy* [9,10]
The absorption maximum for both Dapsone and Acetazolamide drugs was determined by running the spectrum of the drug solution in a double-beam ultraviolet spectrophotometer. (UV-1800, Shimadzu) A stock solution of 200 ppm was made by accurately weighing 100 mg of Dapsone drug and dissolving it in 0.1N hydrochloric acid in a 100 ml volumetric flask. 0.1ml, 0.2ml, 0.3ml, 0.4ml, and 0.5ml aliquots of drug solution were transferred into a series of 10ml volumetric flasks and brought to final volume with 0.1N hydrochloric acid. The spectrum of this stock solution was run in the 200–400 nm range in an ultra-visible spectrophotometer. (UV-1800, Shimadzu) Similarly, a stock solution of 100 ppm was made by accurately weighing 10 mg of Acetazolamide drug and dissolving it in distilled water in a 100ml volumetric flask. 0.2ml, 0.4ml, 0.6ml, 0.8ml, and 1.0ml aliquots of drug solution were transferred into a series of 10ml volumetric flasks and brought to final volume with distilled water. The spectrum of this stock solution was run in the 200–400 nm range in an ultra-visible spectrophotometer. (UV-1800, Shimadzu)

Drug-excipient compatibility study

Drug-excipient compatibility studies are necessary to ensure that drugs and excipients are compatible. DSC graph and IR spectra are used to study drug-excipient compatibility.

a) *FTIR study* [11]
FTIR (Shimadzu 8400s) spectrophotometer were used in the range of 400-4000 cm^{-1} using potassium bromide discs [Mixing ratio- 1:1 (Drug: Excipient/s)] to study drug-excipient compatibility.

b) *DSC study* [12,13]
A differential scanning calorimeter (Mettler Toledo) was used for thermal analysis of drug and excipient mixtures. Individual drug and excipient samples, as well as physical mixtures, were weighed directly into the DSC aluminium crucible [Mixing ratio- 1:1 (Drug: Excipient/s)]. The samples were scanned in a dry nitrogen atmosphere at a temperature ranging from

200-400°C. The heating rate was 10°C·min^{-1} and the thermograms obtained were observed for interactions.

Preparation of immediate release layer and sustained release layer

The compressed tablets of the immediate release layer according to batches (D1-D4) were formulated by using Croscarmellose Sodium- Ac-Di-Sol® as a superdisintegrant. All ingredients were weighed accurately. The composition of the immediate release layer is listed in Table 1. The above mixture was triturated for 5minutes and lubricated with magnesium stearate and talc. Similarly, the compressed tablets of the sustained release layer according to batches (A1-A4) were formulated by using Benecel™ E4M polymer. All ingredients were weighed accurately. The composition of the sustained release layer is listed in Table 2. The above mixture was triturated for five minutes and lubricated with magnesium stearate and talc.

Table 1- Composition of Dapsone as Immediate release tablet of batches D1-D4

Ingredients / Batch	Dapsone (mg)	Ac-Di-Sol (mg)	Avicel PH102 (mg)	Talc (mg)	Magnesium stearate (mg)	Sodium saccharin (mg)
D1	50	50	88	8	2	2
D2	50	40	98	8	2	2
D3	50	30	108	8	2	2
D4	50	20	118	8	2	2

Table 2- Composition of Acetazolamide as Sustained release tablet of batches A1-A4.

Ingredients / Batch	Acetazolamide (mg)	E4M polymer (mg)	Avicel PH102 (mg)	Talc (mg)	Magnesium stearate (mg)	Sodium saccharin (mg)
A1	250	50	38	8	2	2
A2	250	40	48	8	2	2
A3	250	30	58	8	2	2
A4	250	20	68	8	2	2

Preparation of bilayer tablets

The direct compression method was used for the preparation of bilayer tablets. The sustained release layer was poured first into the die cavity, followed by the immediate release layer, which was poured and compressed into the tablets using a 12 station tablet compression machine (Rimek, Mini Press-II MT, Karnavati Engineering Ltd., 12 station) with an average hardness of 4.0-6.0 kg/cm^2. (Monsanto hardness tester)

Evaluation of powder blends (Pre compression study) [14,15]

- Angle of Repose θ

The angle of repose of the powder blend was determined by the fixed funnel method. The accurately weighed powder blend was allowed to flow through the funnel, which was adjusted to a height of 2 cm. The angle of repose was calculated using the following equation:

$$\theta = \tan^{-1}\frac{h}{r} \quad \text{---------- Equation 1}$$

Where, θ, h, r are the angle of repose, pile height, and pile base radius, respectively.

- Bulk density (BD)

Bulk density is the ratio of the mass of powder to the bulk volume. It is usually expressed as g/ml. Bulk density was calculated using the following equation:

$$\rho_b = \frac{M}{Vb} \quad \text{---------- Equation 2}$$

Where, ρ_b = Bulk density, M = mass in grams, and V_b = bulk volume in milliliters.

- *Tapped density (TD)*

The tapped density of a powder is the ratio of the powder's mass to the volume occupied by the powder after it has been tapped for a specified time. The tapped density of a powder is measured in g/ml and represents its random dense packing. Tapped density was calculated using the following equation:

$$\rho_t = \frac{M}{Vt} \quad \text{---------- Equation 3}$$

Where, ρ_t = Tapped density, M = mass in grams, and V_t = Tapped volume in milliliters.

- *Carr's Index*

This property is also known as percent compressibility and is indirectly related to the flow rate, cohesiveness, and particle size. Carr's index was calculated using following equation:

$$\text{Carr's Index} = \frac{\rho t - \rho b}{\rho t} \times 100 \quad \text{---------- Equation 4}$$

Where, ρt = Tapped Density; ρb = Bulk Density

- *Hausner's Ratio*

It is the ratio of the tapped density to the bulk density. A good flow has been indicated by a Hausner's ratio greater than 1.25, and a poor flow may have a value of 1.5. It is calculated using following equation:

$$\text{Hausner's ratio} = \frac{Tapped\ density\ (\rho t)}{Bulk\ density\ (\rho b)} \quad \text{---------- Equation 5}$$

Evaluation of tablets (Post compression study) **[14,15,16,18]**

- *Weight Variation*

About 20 tablets from each batch F1-F4 were selected and weighed collectively and individually. From the collective weight, an average weight was calculated. Each tablet's weight was then compared with the average weight to determine whether it was within permissible limits or not. To pass the test, not more than two of the individual weights deviated from the average weight by more than 5.0%. *ess* Randomly selected tablets from all batches were tested for thickness using a vernier caliper. (Mitutoyo Corporation, Japan) Standard deviation values were determined and were found within the range.

- *Hardness*
- The hardness of tablets from batches F1-F4 was determined by using the Monsanto hardness tester (n=3) and expressed in Kg/cm^2. The lower plunger of the hardness tester was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force.
- *Friability test*
- The friability test was performed by weighing the initial weight of 20 tablets of batches F1-F4 individually and placing them in the Roche Friabilator (Electrolab, Mumbai, India). The drum of the friabilator was rotating at 25 rpm for 4 minutes. Pre-weighed samples of tablets were placed in the friabilator and subjected to 100 revaluation, dedusted and reweighed. The percent friability for each formulation was determined using the following equation:

$$\% \text{ Friability} = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100 \qquad \text{---------- Equation 6}$$

Drug content **[19]**

All tablets of formulated batches D1-D4 were subjected for %drug content. For all batches, about 20 tablets were weighed and finely powdered. Transferred an accurately weighed quantity of the powder equivalent to about 50mg of Dapsone in a 200ml volumetric flask. Add 150 ml of methanol and sonicate the solution for 15 minutes at 35°C. Then the solution was cooled to room temperature and made up to the mark by using methanol. Filter the solution through the whatmann filter paper to get the clear solution. Filled a 50ml volumetric flask with 5ml of clear solution, diluted with methanol, and mixed. Withdraw 0.8ml, 1.0ml, and 1.2ml of the stock solution to prepare 8ppm, 10ppm, and 12ppm solutions, respectively. The absorbance was measured spectrophotometrically (UV-1800, Shimadzu) by scanning wavelengths in the range of 400 nm to 200 nm, using methanol as a blank.

Twenty tablets from formulated batches A1-A4 were taken to calculate the percent drug release. The tablets were weighed and crushed into fine powder, and from this, 10 mg of powder was weighed and transferred into a 100ml volumetric flask. To this, 70 ml of methanol was added and sonicated for 30 minutes to dissolve completely. After attaining room temperature, the volume was made up with the same solvent and shaken well to obtain a homogeneous solution. After discarding

the first 20 ml of solution, the tablet solution was filtered through whatmann filter paper. The resultant clear solution was a 100 µg/ml sample stock solution, which was further diluted with methanol to obtain working stock solutions of 8 ppm, 10 ppm, and 12 ppm, respectively. These working stock solutions were prepared in triplicate and scanned at 263.00nm using an UV-spectrophotometer. (UV-1800, Shimadzu)

In vitro Dissolution studies

A dissolution study for formulated batches was performed separately for the immediate and sustained release layers as per USP by using USP-II apparatus (paddle type) dissolution test apparatus (Electrolab TDT08L, Mumbai, India). The dissolution medium for the immediate release tablet layer and for the sustained release layer were 900ml of 0.1N hydrochloric acid and 900ml of 0.01N hydrochloric acid, respectively. The medium was allowed to equilibrate to a temperature of 37±0.5°C. A tablet from each batch was placed in the vessel and covered; the apparatus was operated for up to 1 hour at 100 rpm for the immediate release layer and 12 hours for the sustained release layer. The sample was withdrawn at specified time intervals and replaced with a fresh 1ml of medium. The aliquots were filtered through Whatmann filter paper No. 42. The absorbance of the sample solution was measured using UV spectroscopy against the corresponding media as a blank for the immediate release layer and the sustained release layer at 290 nm and 265 nm, respectively.

Kinetic analysis of In vitro drug release study [14,16]

The data from the in vitro dissolution study were plotted to investigate release kinetics in various kinetic models, including zero order, first order, matrix, korsmeyer-peppas, and Hixon–Crowell.

- *Zero order*
  In-vitro dissolution data was evaluated as cumulative percent drug release *vs.* time. It was expressed in concentration/ time. Where, K is the zero order release constant and t is time in hours.

$$C = K_o t \qquad \text{---------- Equation 7}$$

- First order model

Drug release data in this model depends on concentration. Where, C is concentration, C_o is the initial concentration, and K is the first order constant.

$$Log\ C = Log\ C_o - kt / 2.303 \qquad \text{----------Equation 8}$$

- *Korsmeyer-peppas model*

In this model, drug release data is constructed as log cumulative % drug release *vs.* log time.

$$Mt/ M\infty = Ktn \qquad \text{---------- Equation 9}$$

Where, $Mt/ M\infty$ is a fraction of drug release at time t, K is release rate constant, n is release exponent.

- Hixson and Crowell model [17]

In this type, particle regular area is proportional to the cubic root of its volume and is described by the following equation:

$$M_o^{1/3} - M^{1/3} = K_{HC}\, t \qquad \text{---------- Equation 10}$$

Where, M_o is the initial amount of drug, M amount of remaining drug on time t, K_{HC} is constant of incorporation.

Results and Discussion

Identification of Pure drugs

FTIR study

Identification and confirmation of pure drugs were carried out by observing the obtained spectra. Dapsone showed characteristic peak values at 3063.06 (=C-H stretching); 3333.10 (N-H stretching); 1589.40 (C=C stretching); 1280.78 (C-N stretching) and 1134.18 (S=O stretching). These peak values were in accordance with previously reported spectra of Dapsone. (Fig. 1) Acetazolamide showed characteristic peak values at 3302.24 (C=O stretching); 1365.65 (S=O stretching); 2353.23 (C=N stretching) and 1674.27 (R-C(=O)NH_2 stretching). These peak values were in accordance with previously reported spectra of Acetazolamide. (Fig. 2)

Fig. 1: FTIR spectra of pure Dapsone.

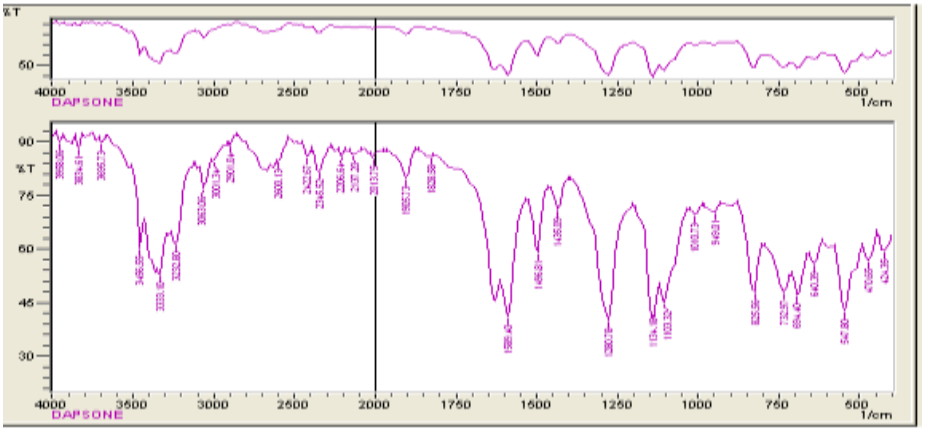
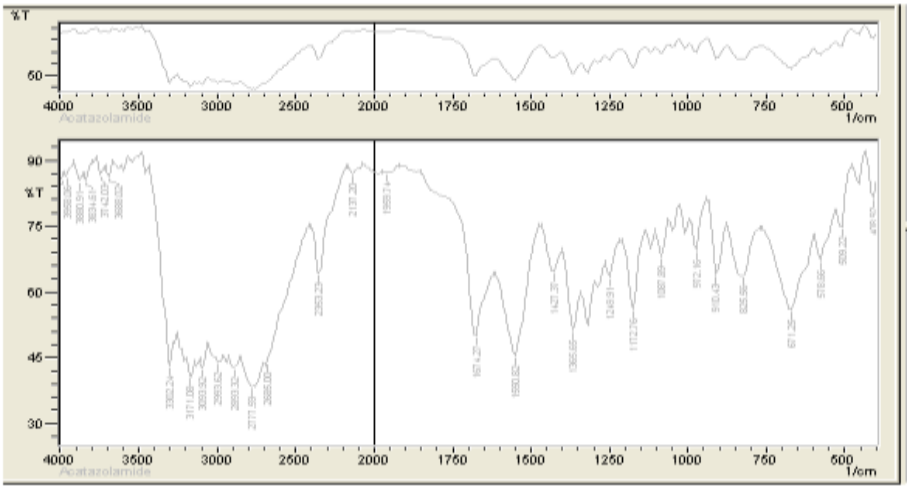


Fig. 2: FTIR spectra of pure Acetazolamide



DSC study

The DSC thermograms of the Dapsone alone show the peak onset temperature (Tonset) is [178.13°C] and peak transition temperature (Tpeak) is [178.73°C].(Fig.3) Similarly for Acetazolamide alone, the peak onset temperature (Tonset) is [271.16°C] and the peak transition temperature (Tpeak) is [272.11°C]. (Fig.4). These results indicate the purity of the drug.

Fig. 3: DSC graph of pure Dapsone.

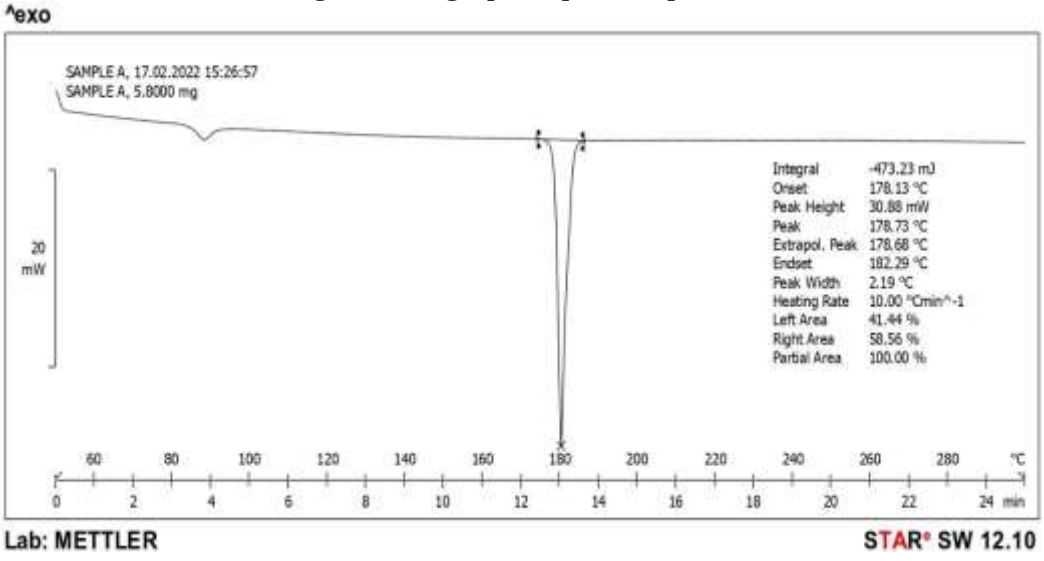
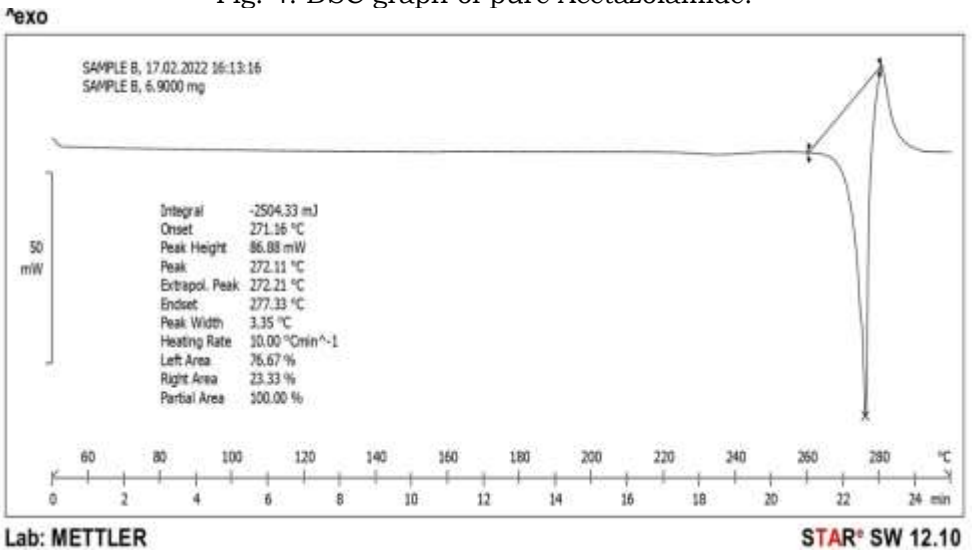


Fig. 4: DSC graph of pure Acetazolamide.



UV spectroscopy

The linearity of the responses of both drugs was verified at 2–10 µg/ml concentrations. The calibration curve was obtained by plotting the absorbance versus the concentration data and was treated by linear regression analysis. The equation of the linearity curve for Dapsone obtained was y = 0.1238x + 0.0066. The linearity curve was found to be linear in the aforementioned concentrations (the correlation coefficient (r^2) of determination was 0.9996) (Fig.5). Similarly, the equation of the linearity curve for Acetazolamide obtained was y = 0.0823x + 0.0074. The linearity curve was found to be linear in the aforementioned concentrations. (The correlation coefficient (r^2) of determination was 0.9992) (Fig.6)

Fig. 5: Calibration Curve for Dapsone

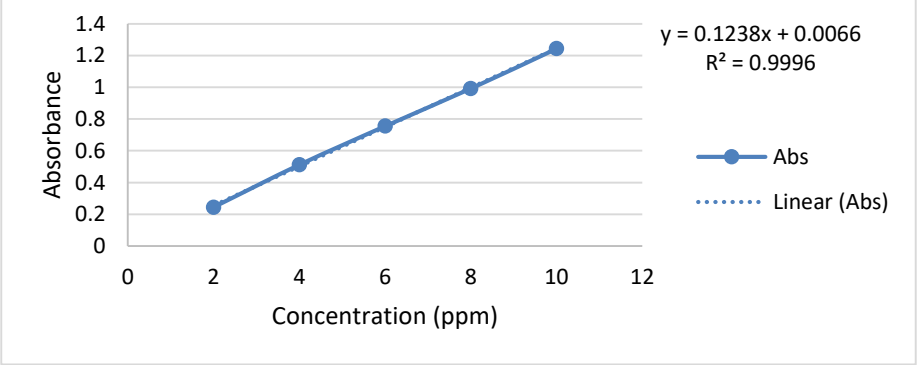
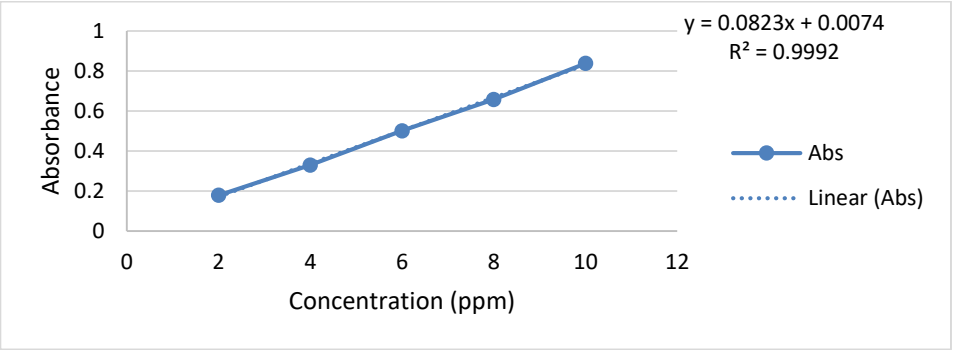


Fig. 6: Calibration Curve for Acetazolamide



Drug-excipient compatibility study

FTIR spectroscopy-

The FTIR spectrums of pure Dapsone as well as Acetazolamide and physical mixtures of drugs and polymers were studied separately as per the excipients used in the formulation. It was observed that there were no major shifts in the main peaks of either drug. This indicates that there were no compatibility problems with the drug with the polymers and excipients used in the formulation. Dapsone had peaks at 3063.06 (=C-H stretching), 3333.10 (N-H stretching), 1589.40 (C=C stretching), 1280.78 (C-N stretching), and 1134.18 (S=O stretching), (Fig.7,8) while Acetazolamide had peaks at 3302.24 (C=O stretching), 1365.65 (S=O stretching), 2353.23 (C=N stretching), and 1674.27 (R-C(=O)NH_2 stretching). These peak values were in accordance with previously reported spectra of Dapsone and Acetazolamide. (Fig. 9, 10)

Fig.7 : FTIR spectra of Dapsone + Ac-Di-Sol

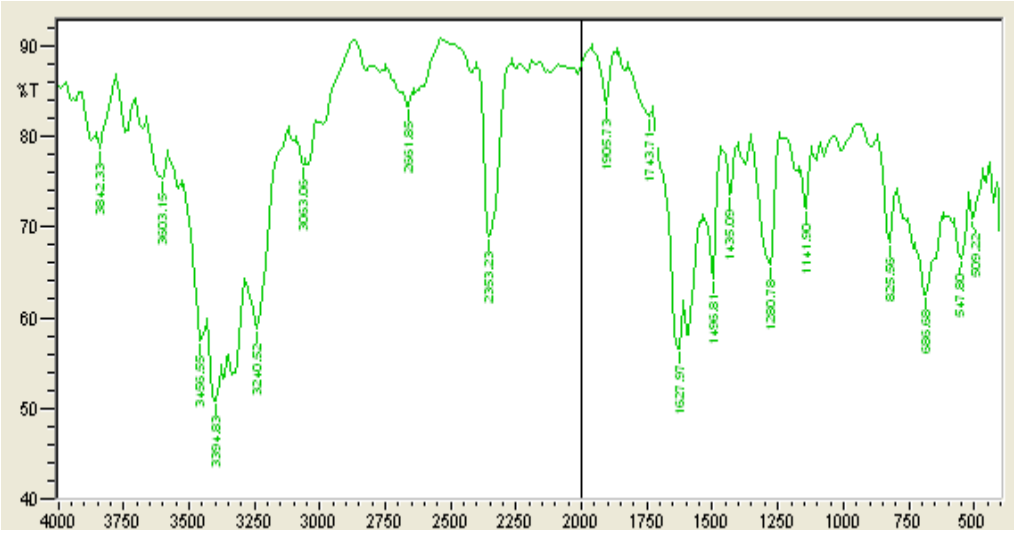


Fig.8 : FTIR spectra of Dapsone + MCC + Talc + Magnesium stearate + Sodium saccharin

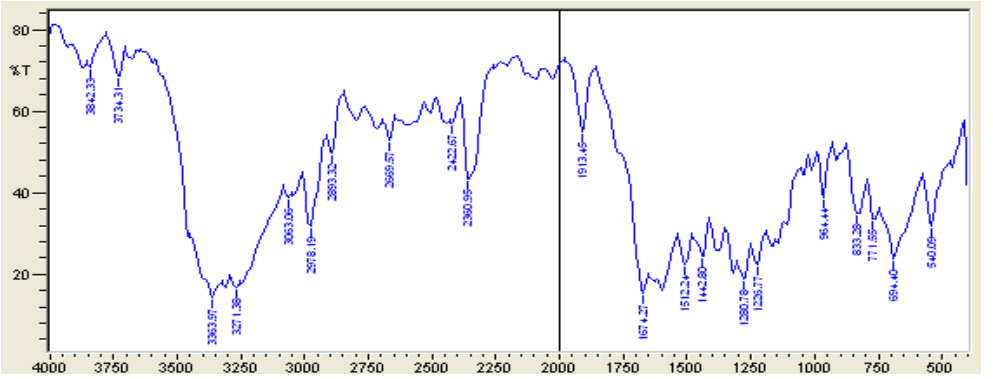


Fig.9 : FTIR spectra of Acetazolamide + E4M polymer

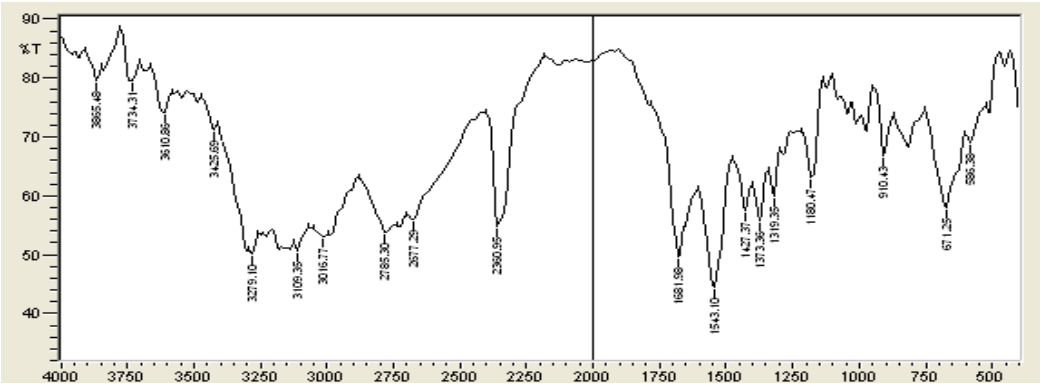
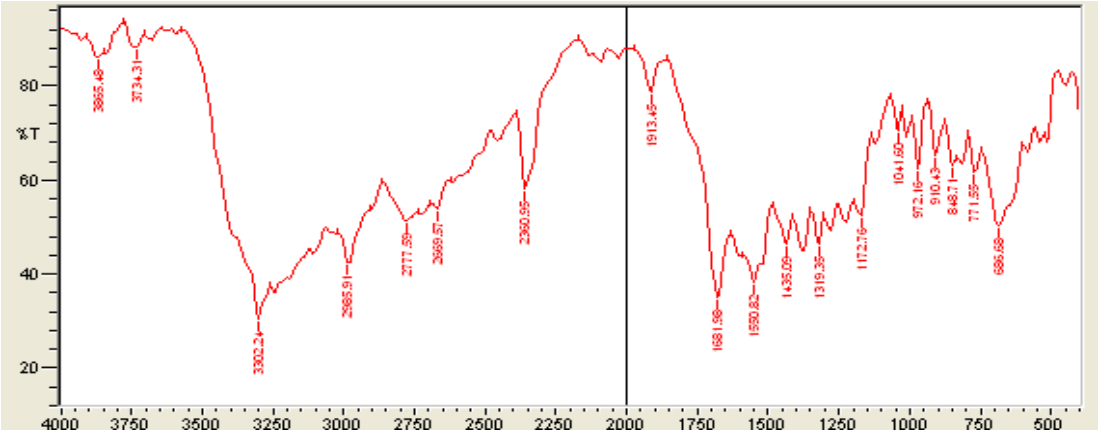


Fig.10 : FTIR spectra of Acetazolamide + MCC + Talc + Magnesium stearate + Sodium saccharin



DSC study

The DSC thermogram for Dapsone in combination with various excipients shows the peak onset temperature (Tonset) [176.86°C] and peak transition temperature (Tpeak) [179.10°C]. The thermogram of Dapsone showed a sharp endothermic peak at ~180°C and a peak onset ~176°C. In this thermogram, the melting endotherm of Dapsone (T onset and T peak) was well preserved, with light broadening shifting towards the lower temperature range. (Fig. 11) Similarly, Acetazolamide in combination with various excipients shows an onset temperature (Tonset) [258.66°C] and a peak transition temperature (Tpeak) [264.99°C]. The thermogram of Acetazolamide showed a sharp endothermic peak at ~269°C and a peak onset ~258°C. In this thermogram, the melting endotherm of Acetazolamide (T onset and T peak) was well preserved, with light broadening shifting towards the lower temperature range. (Fig. 12) These shifts in peak in both graphs to a lower temperature range might be due to the drug being mixed with excipients and do not necessarily indicate probable incompatibility.

Fig. 11: DSC graph for Dapsone with excipients

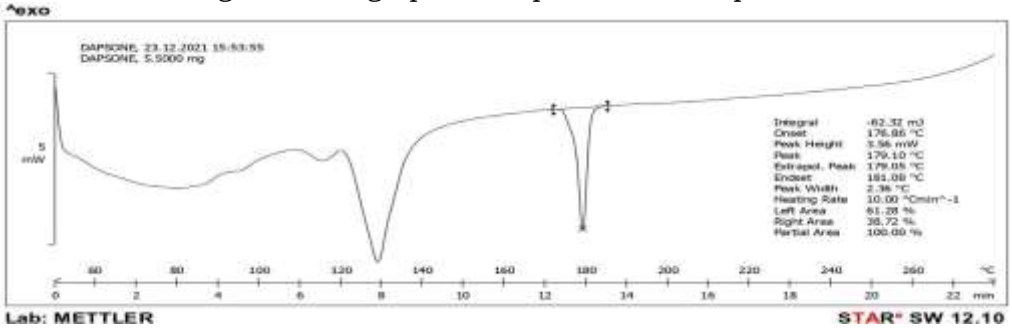
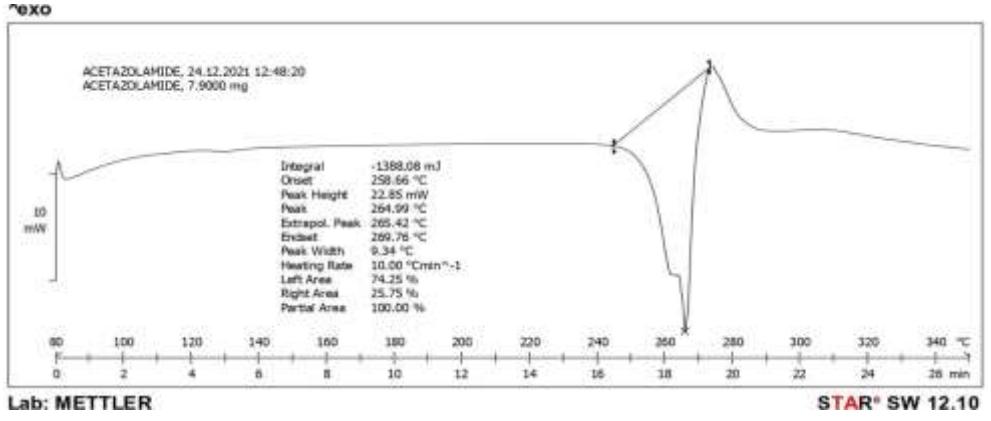


Fig. 12: DSC graph for Acetazolamide with excipients



Evaluation of powder blends (Pre compression study)

The directly compressible blends of the immediate release layer of Dapsone reveal that the angle of repose was found between 26.31±0.5 to 28.80±0.8, Hausner's Ratio between 1.02 to 1.05 and Carr's index between 2.38 to 4.76 %. The directly

compressible blends of the sustained release layer of Acetazolamide reveal that the angle of repose was found between 26.76±0.7 to 29.51± 0.5, Hausner's Ratio for all batches is 1.03, and Carr's index for all batches is 3.63%. These pre-compression studies indicate good flow and compression characteristics of all the immediate release and sustained release blends as per USP limits. In these immediate release and sustained release directly compressible powder blends, magnesium stearate and talc are used as lubricant and diluent, respectively, which imparts good flow and compressibility to the blends as given in table no. 3 and 4.

Table 3- Pre-compression parameters of Immediate release layer of Dapsone (D1-D4)

Formulation Code	Angle of Repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hausner's Ratio
D1	28.22±0.5	0.41±0.005	0.42±0.005	2.38	1.02
D2	27.29±0.1	0.40±0.005	0.42±0.005	4.76	1.05
D3	26.31±0.5	0.41±0.005	0.42±0.005	2.38	1.02
D4	28.80±0.8	0.41±0.005	0.42±0.005	2.38	1.02

±S.D. n=3

Table 4- Pre-compression parameters of Sustained release layer of Acetazolamide (A1-A4).

Formulation Code	Angle of Repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hausner's Ratio
A1	26.76±0.7	0.53±0.006	0.55±0.005	3.63	1.03
A2	28.71±0.4	0.53±0.006	0.55±0.005	3.63	1.03
A3	28.61±0.4	0.53±0.006	0.55±0.005	3.63	1.03
A4	29.51±0.5	0.53±0.006	0.55±0.005	3.63	1.03

±S.D. n=3

1. *Evaluation of tablet (Post compression study)*
   The general appearance of the batch (F1-F4) formulated tablets was evaluated. These tablets were round in shape, white in colour, and had a smooth texture.
2. *Weight Variation*
   The tablets from batches F1-F4 were evaluated for % weight variation, which showed a % weight variation of between 0.18-4% from the average weight of the tablet complying as per standard (for >324mg±5.0% deviation).
3. *Thickness*
   Randomly selected tablets from all batches were tested for thickness and were found to be 0.50±0.005cm. Standard deviation values were determined and were found to be within the range.

Hardness

The compressed tablets from all batches F1-F4 were found to be within the limit as per standard record, which lies in between 5.3 ±0.057 to 5.5 ±0.115 kg/cm^2 (n=3).

Friability Test

For all batches F1-F4, friability values were found to be within the range of 0.48-0.87, which conforms to the standard limit (1%, n=3).

Drug content

The formulated tablets, batches D1-D4, were tested for assay by UV spectroscopy. Dapsone absorbance in methanol is measured at 296nm (λmax). The assay was found to be in the range of 98.0% to 99.70%, which is within the standard record limit (92.5%-107.5%). The formulated tablets, batches A1-A4, were tested for assay by UV spectroscopy. Acetazolamide absorbance in methanol is measured at 263nm (λmax).The assay was found to be in the range of 99.30% to 102.07%, which is within the standard record limit (95%-105%).

Table 5- Post-compression evaluation parameters

Formulation Code	Average weight (gm)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Assay (%)	
					Dapsone	Acetazolamide
F1	0.448	0.55±0.005	5.5	0.87	99.70	100.60
F2	0.527	0.55±0.005	5.5	0.56	98.00	99.30
F3	0.533	0.55±0.005	5.5	0.56	99.65	102.07
F4	0.531	0.55±0.005	5.5	0.48	99.33	101.69

±S.D. n=3

In vitro Dissolution studies

The release profile of Dapsone from different batches of formulated matrix tablets was plotted in Figure 13. Based on the results of in-vitro dissolution testing, it was known that the formulations were compressed with different concentrations of superdisintegrant and showed different rates of drug release. The t90% increases with an increase in the quantity of superdisintegrant. These values are for a 60-minute period. But the formulation D1 showed the maximum amount of drug release, i.e., 98.04% for a period of 60 minutes. Similarly, the release profile of Acetazolamide from different batches of formulated matrix tablets was plotted in Figure 14. Based on the results of in-vitro dissolution testing, it was known that the formulations were compressed with different concentrations of E4M polymer and showed different rates of drug release. An increase in polymer

concentration results in a decrease in t90%. These values are for a 12-hour period. But the formulation A4 showed the maximum amount of drug release, i.e., 94.21% for a period of 12 hours.

Fig. 13: In-vitro drug release profile of immediate release matrix tablet of Dapsone

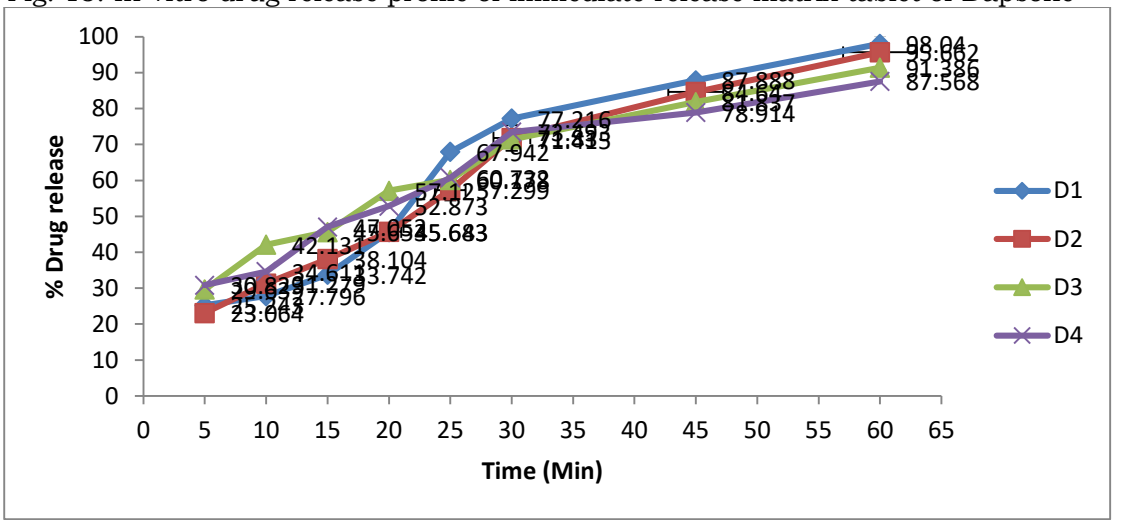
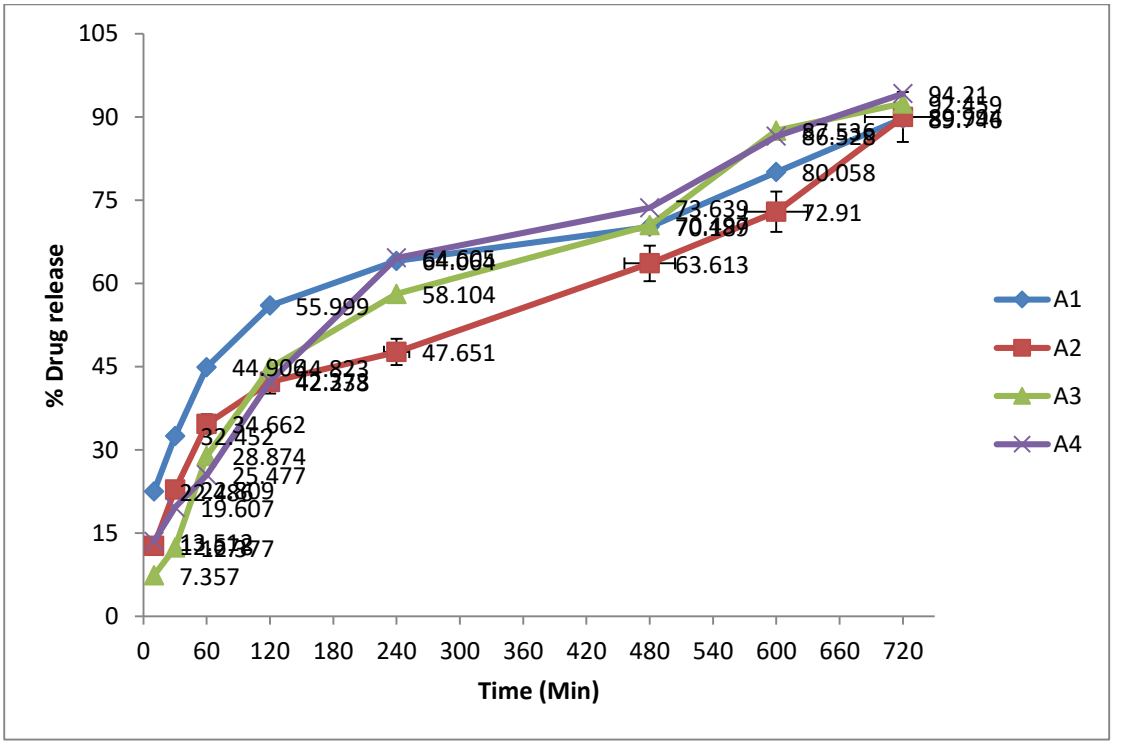


Fig. 14: In-vitro drug release profile of Sustained release matrix tablet of Acetazolamide



Kinetic analysis of In vitro drug release study [18]

In-vitro drug release profiles for prepared batches of Dapsone and Acetazolamide were applied to different kinetic models such as the zero order model, first order model, matrix model, and Haxson-Crowell model, etc. The kinetic data for all the batches is illustrated separately in tables 6 and 7. The highest correlation coefficient resulted from the matrix model, which indicates that the drug is released by dissolution with the changes in surface area and diameter of particles or tablets. The rate of dissolution is determined by the surface area of the solvent; the larger the area, the faster the dissolution.

Table 6 – Kinetics of drug release profile for Dapsone

Results		Zero order model	First order model	Matrix model	Hix. Crow. model
Sr. No.	Time (min)	29	41	229	36
1.	0	0.000	0.000	0.000	0.000
2.	5	6.186	7.869	0.780	7.254
3.	10	7.725	11.134	0.848	9.877
4.	15	6.378	10.535	0.980	8.987
5.	20	2.861	6.252	0.812	4.951
6.	25	0.013	0.885	0.749	0.439
7.	30	5.596	2.542	0.819	3.430
8.	45	0.701	0.396	0.974	0.492
9.	60	0.011	1.047	0.920	0.565

Table 7 – Kinetics of drug release profile for Acetazolamide

Results		Zero order model	First order model	Matrix model	Hix. Crow. model
Sr. No.	Time (min)	1	1	7	1
1.	10	0.000	0.000	0.000	0.000
2.	15	0.011	0.011	0.830	0.011
3.	30	0.001	0.000	0.848	0.001
4.	60	0.063	0.054	0.835	0.057
5.	120	0.199	0.171	0.704	0.180
6.	240	0.113	0.082	0.595	0.091
7.	480	0.509	0.563	0.860	0.544
8.	600	0.069	0.072	0.978	0.071
9.	720	0.237	0.276	2.980	0.263

Conclusion

The study of formulating bilayer tablets containing Dapsone and Acetazolamide was successfully achieved by using direct compression technology. Bilayer tablets contained Dapsone as an immediate release layer and Acetazolamide as a sustained release layer. This formulation was prepared using Ac-Di-Sol as the

superdisintegrant in the immediate release layer and E4M polymer in the sustained release layer. DSC and IR studies revealed that there were no compatibility issues between the API and the excipients used in the formulation. The dissolution study was performed separately for each layer for 60 min for the immediate release layer and 12 hours for the sustained release layer, which was taken as the ideal formulation to fulfil all requirements of the bilayer tablet. Analyzing regression coefficients in drug release kinetic studies, it was found to fit the matrix model. All other evaluation studies performed were found to be within the official limit range.

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Conflict Of Interest

The authors declare no conflict of interest.

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