PREPARATION AND EVALUATION OF DAPSONE-SACCHARINE COCRYSTAL

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ABSTRACT:
Cocrystallization is a technique to optimize solid forms that shows great potential to improve the solubility of active pharmaceutical ingredients (APIs). Dapsone belongs to a class of drugs called Ant leprosy Agents. Dapsone is classified as a class II drug according to the Biopharmaceutics Classification System, which exhibits high permeability and low solubility and hence results in low bioavailability. The present work illustrates the attempt to improve the solubility of dapsone via a crystal engineering approach. Solid form of dapsone with saccharine cocrystals was obtained through solvent evaporation method. Cocrystals are characterized by differential scanning calorimetry, Fourier transform infrared spectroscopy. It was predicted that two molecules are associated through a hydrogen bond. The cocrystals exhibited faster dissolution rate owing to co crystallization as evident from 2.8 times increase in the extent of dissolution.

Keywords: co crystallization, dapsone, saccharine, solubility, bioavailability, crystal engineering

INTRODUCTION:

Cocrystals are made up of an API and one or more coformers that are bonded together by hydrogen bonds in the same crystal lattice. A neutral guest compound or another API could be used as the conformer [1]. Dapsone (DAP) (4,4-diaminodiphenyl sulfone) is a sulfonamide that was first used in 1947, according to the literature [2]. DAP has a dual mechanism of action as an antimicrobial and an anti-inflammatory/immunomodulator, making it useful for the treatment and prevention of infectious diseases caused by pathogens like Pneumocystis and Mycobacterium, as well as the treatment of chronic inflammatory diseases like acne vulgaris and Henoch-Schönlein Purpura [3-7]. It is now one of the medications recommended by the World Health Organization (WHO) for the treatment of leprosy (infections caused by Mycobacterium leprae), and it can be used in a multiple drug therapy with rifampicin and clofazimine [8,9].

According to the Biopharmaceutics Classification System, DAP is a class II medication with high permeability and poor solubility in water (log P = 0.97) [10]. It comes in four anhydrous forms, each of which is denoted by a Roman numeral in the order of their melting points: I 179°C, II 177°C, III converts to II when heated, and IV 170°C. The most stable polymorph of the four is Form III, which is found in commercial products [11].

To be bioavailable in the body, drug compounds must have a certain solubility. According to estimates, up to 90% of new chemical entities and 40% of existing therapeutic products have low water solubility and hence cannot be given to the body via traditional methods [12].

Cocrystal formation with the right coformer has the potential to improve solubility by changing the underlying crystal structure, thereby making the molecule bioavailable. The breadth of application areas for physical property manipulation by cocrystal formation has grown as cocrystal research has developed. Solubility, stability, bioavailability, and mechanical characteristics have all improved over time [13,14]. The aim of present study was to formulate these cocrystals into tablets, optimize the formula and enhance the solubility of dapsone cocrystals.

- **MATERIALS AND METHODS:**

Material:

Dapsone was received as a gift sample from Glaxo Smithkline. All required solvents and excipients were provided by LOBA CHEMIE PVT LTD. Molecular docking was performed on Schrodinger suit version 9.0 software. Experimental design was performed using design expert version 12.0 software.

Method:

Solubility parameter:

Solubility parameter was calculated by solubility parameter calculator for a homopolymer by macromedia Inc**.**

Preparation of dapsone- saccharine cocrystal:

1. Solvent evaporation method:

A specific quantity of dapsone and coformer was weighed and ground with mortar pestle for 10 minutes. The powdered mass then transferred to a glass beaker and dissolved in methanol with

constant stirring. The stirring was continued until a clear solution is obtained. The solution then filtered through a filter paper into a petri dish and the solvent was evaporated at room temperature until a dry mass is obtained. And then screened with sieve of mesh size 60 and stored in airtight container [15,16].

2. Slurry conversion method:

1:1 molar ratio of dapsone and coformer was taken in a mortar pestle and triturated for several minutes. Then small quantity of methanol was added to form a slurry like consistency. Along with constant stirring small quantity of methanol was added at intervals to prevent complete drying of the mixture. After 30 minutes of grinding the slurry was transferred to the petri dish and let it to dry at room temperature to get dry mass. The mass then screened with sieve of mesh size 60 and stored in airtight container [17].

3. Antisolvent addition method:

In a beaker dapsone and coformer mixture of 1:1 molar ratio was dissolved in methanol and stirred using magnetic stirrer. Then the water was added drop wise as an antisolvent at a specific rate until we get the precipitate of the cocrystals. Then filter the cocrystal and dry at room temperature to get dry mass. The mass then screened with sieve of mesh size 60 and stored in airtight container [18,19].

Characterization of cocrystal:

1. Differential scanning calorimetry:

The DSC data of pure Drug and co-crystal was collected on a Mettler Toledo 823. The samples were heated from 30° to 300°C at a heating rate of 10°C/min under nitrogen atmosphere [20].

2. Infra-red Spectroscopy

IR was used for collecting the IR samples. The spectra were collected over the range of 4000-600 cm-1 in 32 scans, with resolution of 4 cm-1 for each sample (Jasco FTIR 4100).

3. In-vitro drug release:

Dissolution test (n=3) of Co-crystal and dapsone was carried out in 0.1 N HCl (900 ml, 37±0.5°C, 50 RPM) for 60 min using the USP II paddle apparatus. At predetermined time intervals, 10 ml samples were withdrawn and spectrophotometrically assayed for drug concentration at 290 nm.

4. Solubility study:

Solubility study of dapsone and dapsone cocrystals was tested in distilled water by shake-flask method. 100 mg of dapsone and cocrystals was fed in 250ml of conical flask containing 100 ml of distilled water. Flask was shaken by orbital shaker (REMI Instruments CIS-24BL) with stirring speed 150 RPM at temperature 37±0.5°C for 12 hour. Filtered through (0.45µm filter) concentration was determined from water calibration. Test was conducted with three repetitions.

5. Ex vivo study:

Ex-vivo permeation technique is used for study of absorption mechanism. Dapsone and dapsone cocrystals was performed on Albino Wistar Rat intestine segment. The intestine was washed carefully using Krebs ringer solution. A length of 8-10 cm was rapidly removed and everted over glass rod. Then everted intestine was kept in flat dish containing Ringer solution oxygenated with O2/CO2 (95%/5%) at 370C. The in-vitro system consisting of USP dissolution apparatus type II operated at 50

rpm containing 0.1 N HCl (900 ml) as dissolution medium maintained at 37±0.50C. Modified perfusion apparatus holding isolated everted intestine segment was placed in dissolution vessel. In this system drug diffusion from formulation and permeation across everted intestine occurred simultaneously. Dapsone and dapsone cocrystals was transferred in separate dissolution vessels. The aliquots were collected at pre-determined time intervals of 0, 10, 20, 30, 40, 45min. The sample was analysed on UV spectrophotometer at 290 nm wavelength [21]

Evaluation of micromeritics property

For micromeritic properties of dapsone and dapsone-saccharine co-crystals. various powder flow properties were evaluated of drug like angle of repose, Hausner's ratio and carr's index were determined as described in literature [22,23].

Preparation of tablets

Dapsone-saccharine cocrystal, with excipients like starch glycolate as super disintegration, microcrystalline cellulose as binder, Lactose as diluent, magnesium stearate as lubricant and talc as glidant. Compressed using 8 mm punch using B tooling on Rimek MINI PRESS-II MT.

Experimental Design

Experimental Design 3^2 full factorial design was used to evaluate two variables at 3 levels viz. Lactose: MCC in ratio (90:10, 80:20, 70:30 mg) and concentration of Sodium starch glycolate (10, 15, 20 mg) in order to determine their hardness, friability and % drug release. The layout of experimental design is shown in table 1. Two factors were evaluated each at three levels & experimental trials were performed at all possible nine combinations as shown in table 2.

Evaluation of tablets: The tablets were evaluated for attributes such as hardness, friability, uniformity of weight as per methods in literature. The invitro dissolution rate study was performed.

Table 1: 3^2 full factorial design for optimization dapsone- saccharine co-crystal tablet

Sr no	Factors				Response
1	Lactose: MCC	-1	0	1	Percentage Drug Release, hardness, friability
2	SSG	-1	0	1	

Table 2: Composition of dapsone-saccharine co-crystal tablet (mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dapsone cocrystals	87	87	87	87	87	87	87	87	87
Lactose and MCC ratio	90:10	80:20	70:30	90:10	80:20	70:30	90:10	80:20	70:30
Sodium Starch Glycolate	4	6	8	4	6	8	4	6	8

Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200

Optimization and validation model

The response from the release data was fed to the design expert software 12.0 and the equations were generated. The numerical optimization was done using desirability function and predicted formula was prepared analyzed to test whether the result matches to the optimized release data by DOE.

- **RESULT AND DISCUSSION:**

Solubility parameter:

The solubility parameter is a numerical value that indicates the relative solvency behaviour of a specific solvent. [24]. Out of various coformers dapsone and saccharine has closest solubility parameter.

Table 3: Solubility parameter

Sr no.	Name of drug/ coformer	Solubility parameter	Difference
1	Dapsone (drug)	14.1	-
2	nicotinamide	13.6	0.5
3	Malonic acid	13.1	1
4	Oxalic acid	15.2	-1.1
5	Sodium saccharine	15.3	-1.2
6	Tartaric acid	12.7	1.4
7	PABA	12.6	1.5
8	Salicylic acid	12.5	1.6
9	Acetamide	12.4	1.7
10	Fumaric acid	12.3	1.8
11	Succinic acid	11.9	2.2
12	Glutamic acid	11.2	2.9
13	Benzoic acid	10.9	3.2
14	Cinnamic acid	10.3	3.9
15	Citric acid	9.6	4.5
16	Stearic acid	8.3	5.8

Out of these coformers saccharine and nicotinamide were selected on the basis of solubility parameter of drug and coformer.

Preparation of cocrystals In methanol, dapsone and saccharine are both slightly soluble. When two incompatibly soluble components co crystallize, the less soluble component precipitates preferentially, resulting in a solid mixture of cocrystal and cocrystal components or the failure to form cocrystals [25].

Cocrystallization is the process of forming cocrystals, which are crystals composed of two or more molecular species in a specific stoichiometric ratio within a crystal lattice. The coformers are the various molecular species involved in the formation of the cocrystal. Noncovalent interactions, such as hydrogen or halogen bonds, hold the coformer molecules together [26]. The best method and coformer were chosen based on percent drug release, namely solvent evaporation and saccharine as coformers.

Table 4: Percent drug release for different methods

Cocrystals ratios	Method of cocrystal formation	Percent drug release	Increased percent drug release in folds
Dapsone	-	25.24%	-
Dapsone: saccharine	Solvent evaporation method	72.54%	2.87
Dapsone: saccharine	Slurry conversion method	42.98 %	1.69
Dapsone: saccharine	Antisolvent addition method	47.02 %	1.86

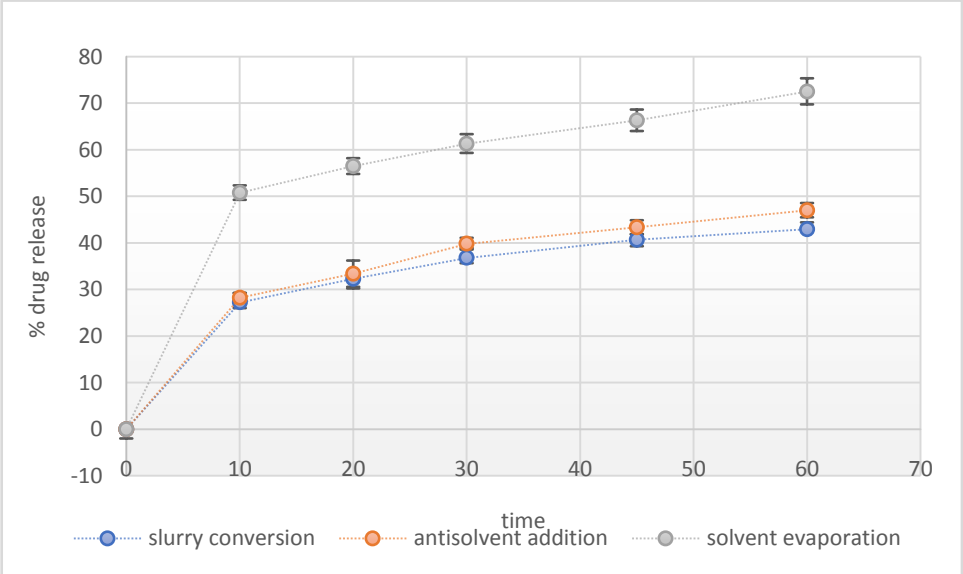

Fig. 1: Percent drug release for different methods

Differential Scanning Calorimetry (DSC)

DSC was conducted to investigate the molecular state of dapsone into cocrystal. Overlay of DSC thermograms obtained for dapsone cocrystals shown in (Figure 1) Melting point of pure dapsone was observed 177.5°C while coformer shows melting point at 132.49°C. The formulated cocrystal

endothermic peak was observed at 85.73°C which is less than the pure drug and coformer which is due to amorphization and possibility of crystal lattice arrangement between dapsone and saccharine cocrystal.

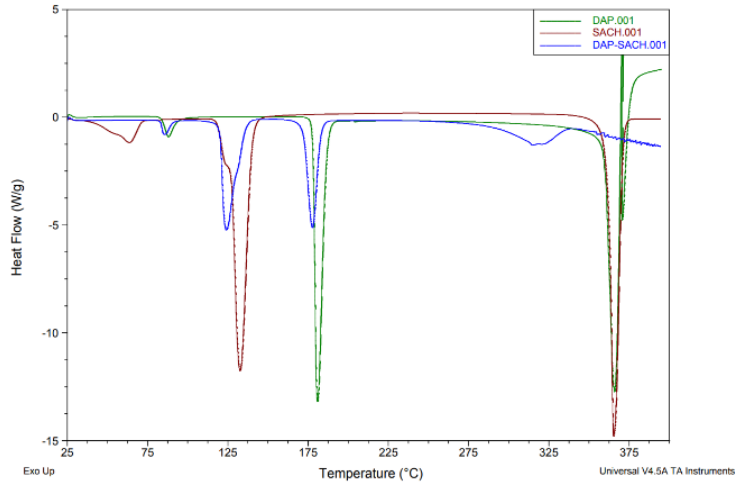

Fig 1- DSC thermogram of dapsone, saccharine, dapsone- saccharine cocrystals

Infrared spectroscopy:

The IR spectrum for pure drug, coformer and cocrystal was recorded and shown in Figure 2. The principle bands were identified and associated changes were recorded. The IR spectrum of pure dapsone shows the presence of the characteristic peaks which were recorded at 3334.92, 3454.5 cm^{-1} for NH stretching, 3050 cm^{-1} for aromatic CH stretch, 1141.86 cm^{-1} for S=O stretch.

The IR spectrum of pure saccharin shows the presence of the characteristic peaks which were recorded at 3072.6 cm^{-1} for aromatic -CH stretch, 3535.52 cm^{-1} for NH stretch, 1647.2cm^{-1} for C=O and 1338.6, 1151.5 cm^{-1} for S=O.

For confirmation of cocrystal,

Peaks of aromatic CH stretch, NH stretch, C=O stretch, S=O stretch were confirmed at 3364.89 cm^{-1}, 3334.92 cm^{-1} , 1639.49 cm^{-1} , 1147.65 cm^{-1} .

The functional groups obtained of the dapsone- saccharin cocrystal showed the similar intact functional groups that were individually found in the IR spectrum of efavirenz and cinnamic acid. This could confirm that the prepared formulation had no degradation of the API as well as excipient.

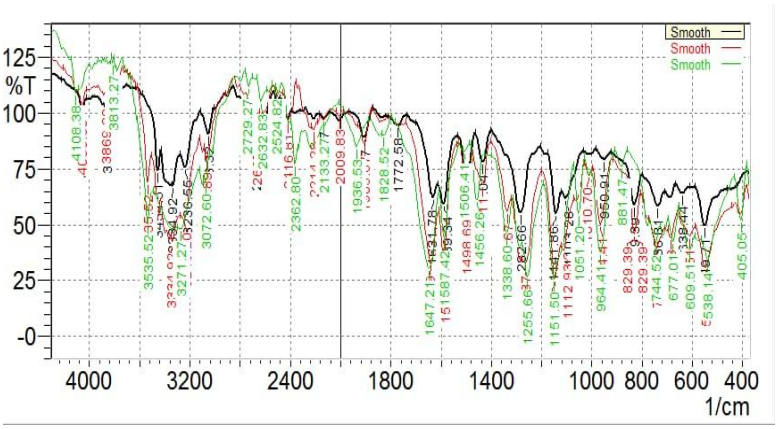

Fig 2: IR spectra of dapsone

In vitro drug release:

The In-Vitro dissolution profiles of the cocrystal using two different coformers and three different method of preparation Solvent evaporation, slurry conversion and antisolvent addition method were compared with that of dapsone. The In-Vitro dissolution rate of cocrystal was increased compared to the drug. Dapsone shows 25.24% drug release after 60 min, whereas cocrystals with 1:1 ratio of dapsone saccharine and preparation method is solvent evaporation show 72.54%. The high dissolution rate of prepared cocrystal can be attributed to change in crystallinity of dapsone due to possible hydrogen bond interaction with conformer (n=3).

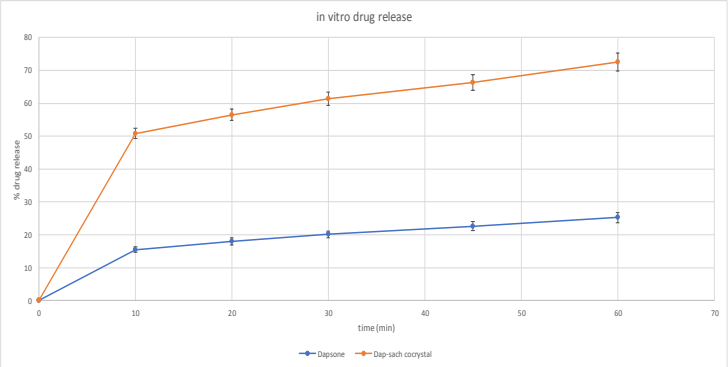

Fig. 3: Percentage drug release of dapsone and Cocrystals

Ex-vivo permeation study:

Dapsone showed 17.95 % absorption in fig 4. while dapsone-saccharine cocrystal showed 50.62 % absorption. Increase in the absorption might be due to the increase in solubility and dissolution rate. (n=3).

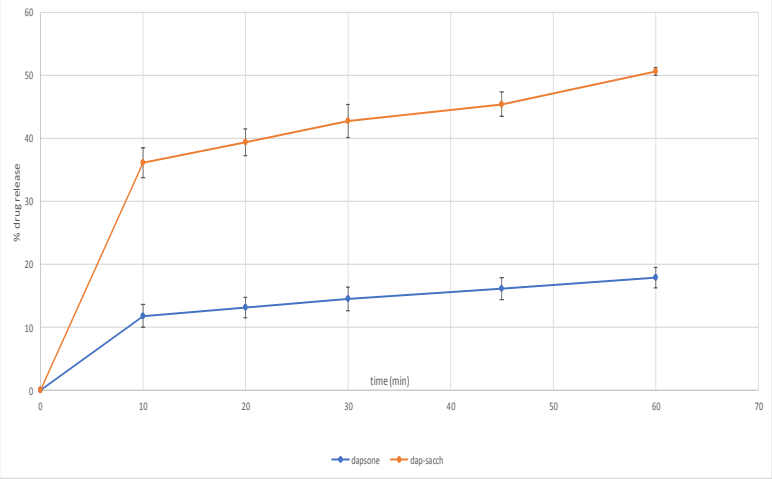

Fig. 4: percentage drug absorption of dapsone and Cocrystals

Solubility Study:

Solubility study was performed in distilled water by shake flask method. An excess sample (100 mg) was fed into 250 ml conical flask with 100 ml distilled water. At 150 rpm at 37±0.5°C temperature. Dapsone showed (n=3) 34.88µg/ml solubility while cocrystals showed 44.63µg/ml solubility. Solubility of dapsone cocrystals was increased by 1.95-folds.

Micromeritic properties:

Table 5: Micrometric flow properties of dapsone and dapsone saccharine cocrystal

Parameters	Dapsone	Dapsone: saccharine cocrystal (solvent evaporation)
Weight	5 gm	5 gm
Angle of repose	57.050^0 (very poor)	26.960^0 (Excellent)
Bulk density	0.3728 gm/ml	0.5132 gm/ml
Tapped density	0.4226 gm/ml	6.2 gm/ml
Carr's index	35.40% (very poor)	9.5% (Excellent)
Hausner's ratio	1.50 (very poor)	1.61 (Excellent)

Experimental Design

For formulation of tablets as per 3^2 full factorial design the concentrations of lactose: MCC ratio and SSG were considered as the two independent factors. Design comprised of 9 experimental runs to evaluate the significance of individual and combined effects of the lactose: MCC and SSG on hardness, friability and percent drug release. Quantitative effect of independent variable in the obtained equation are mean results obtained by changing one factor from its low to high value keeping another factor constant. Response surface methodology is a most practiced approach in the development and optimization of formulation variables. The results were visualized with the help of 3D response Surface Graphs.

Table 6. Experimental run & responses for optimization of co-crystal tablet using 3^2 full factorial design.

	Factor 1	Factor 2	Response 1	Response 2	Response 3
Runs	Lactose: MCC	SSG	Hardness Kg/cm^2	Friability %	% Drug release
1	70:30	6	2.5	0.44	62.78
2	90:10	6	4.5	0.6	48.73
3	80:20	6	3.1	0.53	53.3

4	80:20	4	3.2	0.55	50.11
5	70:30	8	2.3	0.45	65.42
6	90:10	4	4	0.46	43.27
7	70:30	4	2.4	0.43	57.05
8	90:10	8	4.2	0.6	51.10
9	80:20	8	3	0.51	60.91

Analysis of optimized data:

The formulations prepared as per the experimental design was evaluated and the analysis of experimental results was done by using Stat-Ease Design Expert. The ANOVA, P-value and Model F-value for % drug release were obtained (Table 7).

The drug release between experimental batches varied between 43.27-65.42%. The hardness varied between 2.3-2.6 Kg/cm 2, and friability between 0.43-0.6 %. The response surface graph shows a direct dependence of hardness on lactose: MCC and SSG concentration whereas the lactose MCC ratio increased friability to small extent due to reduction of MCC and SSG showed as small contribution to improve friability. (Figure 5,6,7) Thus, the formulation batch giving % drug release was chosen as the optimized batch based on desirability function. Thus, the optimized batch consisted concentration ratio of diluent & binder that is lactose & MCC and super disintegrant sodium starch glycolate. Thus the SSG contributed slightly to hardness and had slight negative effect on friability [27]. The optimized formula was subjected to verification and no significant difference was found between the theoretical and the actual values of hardness, friability and % drug release are given in Table 8

Hardness= +3.24 +0.92 *A -0.017*B +0.075 *A*B

Friability= +0.52 +0.080 *A -3.333E-003 *B -5.000E-003 *A*B

Drug release= +54.74 -7.03*A +4.50 *B -0.14 *A*B

The interaction terms has very little lowering effect on all the three responses studies.

With p values, the two-factor interaction model was found to be significant. If the p-value is less than or equal to the significance level, you can conclude that the response variable and the term have a statistically significant relationship. A higher R2 value indicates a better fit of the model to the data. The signal-to-noise ratio is referred to as adequate precision. It compares the predicted value range at each design point to the average prediction error. Model discrimination is adequate when the ratio is greater than 4.

Table 7: ANOVA output for optimization of dapsone- saccharine cocrystal tablet

Sr no.	Outcomes	% Drug release	hardness	Friability
1	Models	2FI	2FI	2FI

2	R2 Value	0.9847	0.9351	0.9554
3	F – Value	107.36	24.02	35.72
4	P – Value	0.2877	0.8327	0.5210
5	Adequate Precision	25.95	13.68	17.73

Table 8: Validation of Optimized batch

Formulation Code	Composition of optimized formulation		Predicted value	Actual value
	Lactose and MCC ratio	Sodium Starch Glycolate		
Optimized batch	80:20	8	57.27% (drug release)	52.94% (drug release)
			3.49 Kg/cm^2 (hardness)	3.07 Kg/cm^2 (hardness)
			0.54 % (friability)	0.49 % (friability)

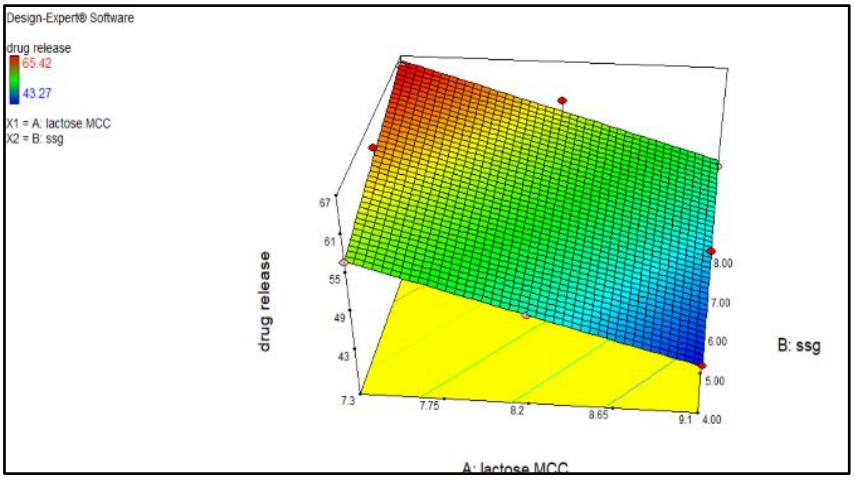

Figure 5: Response surface plot (3D) showing the effect of lactose: MCC and SSG on % drug release

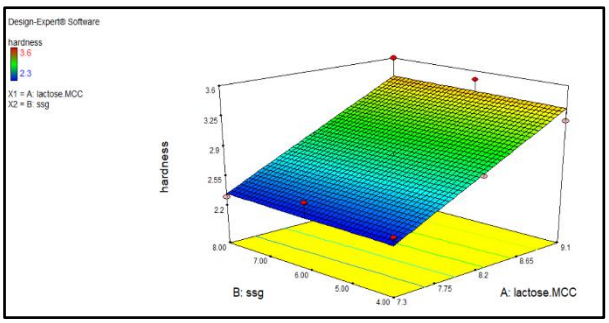

Figure 6: Response surface plot (3D) showing the effect of lactose: MCC and SSG on hardness

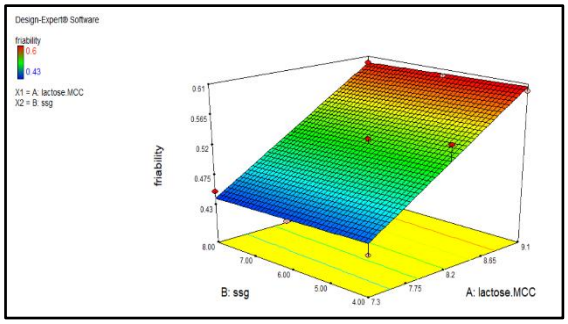

Figure 7: Response surface plot (3D) showing the effect of lactose: MCC and SSG on friability

- **CONCLUSION**

Dapsone- saccharine cocrystal was prepared by solvent evaporation method by selecting coformer by solubility parameter, aqueous solubility of cocrystals was increased by 1.95 times. Dapsone saccharine cocrystal tablet was formulated to form suitable oral dosage form. The formula for dosage form was optimized using Design Expert Software. The optimized tablet batch showed 60.73% drug release in 60 min.

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