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Solubility Enhancement of Spironolactone by Fluid Bed Hot Melt Granulation Technique

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1. Abstract

Spironolactone (SPL) is a potassium-sparing diuretic. SPL is a Biopharmaceutics Classification System (BCS) Class II drug. Its poor aqueous solubility presents a significant challenge as it can lead to slow dissolution and reduced bioavailability. In present investigation the solubility of Spironolactone is enhanced by Fluid Bed Hot Melt Granulation (FBHMG) using wax co-solvents like PEG 6000, Beeswax. The FBHMG based formulation was optimized by Central Composite design to study the effect of independent variables i.e. amount of Microcrystalline Cellulose and Crosspovidone on dependent variables like disintegration time and % drug release. From the results obtained, optimized formulation batch was selected which showed suitable disintegration time and % drug release.

Keywords: Spironolactone, Fluid Bed Hot Melt Granulation, Solubility, Dissolution, Tablet.

2. Introduction

Granulation is an important process in the production of solid dosage forms tablets and capsules. Granules for tableting are either prepared by wet granulation, which utilize liquid in the process, or by dry granulation, where no liquid is utilized. High shear mixer granulation and fluidized-bed granulation are most commonly used in wet granulation methods.

Fluid Bed Hot-melt granulation (FBHMG) is a pharmaceutical processing technique used to improve the physicochemical properties of drug powders, particularly those with poor solubility, by agglomerating them with a molten co-solvent used as binder. Recent advancement has helped to combine FBHMG with Fluid Bed Technology called FBHMG. It is a solvent-free process, which offers several advantages over traditional wet granulation methods [1]

Fluid Bed Hot Melt Granulation is based on agglomeration carried out by means of spray congealing of lipidic excipient, which is solid at room temperature and softens and melts at higher temperature (i.e., 50–70°C). In melt state, the action of the co-solvent is similar to that of binder in a wet-granulation process. Water-soluble binders used for Fluid Bed Hot Melt Granulation are Polyethylene Glycol (PEG). The binder may also be added either in a powder form to the starting material at ambient temperature, followed by heating the binder above its melting point. [2,3]

In this study, FBHMG has been applied for processing granules and tablets of Spironolactone. PEG 6000 was used to improve solubility of SPL. [6,7]

3. Formulation of Spironolactone Tablet by using Hot Melt Granulation

3.1 Materials

The following substances were used for the preparation of Granules and Tablet:

Spironolactone (ZESLA Chemicals & Pharmaceuticals), Polyethylene glycol 6000 (Pallav Chemicals & solvent Pvt. Ltd. Mumbai), Microcrystalline Cellulose (ANALAB Fine Chemicals Mumbai).

Crosspovidone (RESEARCH Lab Fine Chem. Industries Mumbai), Magnesium Stearate (ANALAB Fine Chemicals Mumbai), Talc (ANALAB Fine Chemicals Mumbai), Aerosil (RESEARCH Lab Fine Chem. Industries Mumbai).

Methods

Experimentation Setup: The Fluidized Bed Granulator GPCG 1.1 make ACG Engineering Pvt Ltd, India., was used for the preparation of granules as shown in Figure 7. The stainless-steel container was equipped with 1.2 mm top spraying specialized insulated nozzle attached with hot atomization air and 200 mesh dutch sieve at bottom. The air was passing through a Dutch-mesh into attached container to accomplish fluidization of the charged substrate on bed. The hot melt solution tank (Make: ACG Engineering Pvt Ltd, India) with overhead stirrer (Make: Remi, India) was used for melting of selected excipient. A peristaltic pump (Make: Flow tech Model: FP01) fitted with insulated tubing was used to transfer the melted polymer solution to the insulated nozzle, and hot compressed air was used to atomize the melted solution into droplets.

Fluid Bed Hot Melt Solution Preparation: PEG 6000, having a melting range of 58–60 °C (Ref), was charged into the hot melt tank and allowed to melt for 15 minutes until a clear liquid was obtained.

3.2 Pre-Formulation Studies

3.2.1 Physical Parameters of Spironolactone:

Appearance, Solubility of Spironolactone was checked in different solvents like Water, Methanol, Ethanol and acetone. Melting Point were obtained using Capillary Tube Method. Results for physical parameters are given below in table 1.

Table 1: Physical Parameters of API

Parameters	Observation
Appearance	White crystalline powder with slight odor & slight bitter taste
Solubility	Practically Insoluble in water and Soluble in Methanol, Ethanol Acetone
Melting Point	134 °C

3.2.2 Calibration Curve

Calibration curve was plotted in Ethanol: Water and Methanol separately at 242 & 238nm seen in table 2&3. The calibration curve was plotted as seen in figure 1&2 respectively.

a) Calibration Curve of Ethanol: Water (30:70)

Table 2: UV Absorbance

Sr. No.	Concentration	Absorbance
1	0	0
2	2	0.1432
3	4	0.2374
4	6	0.3792
5	8	0.4939
6	10	0.6096
7	12	0.7321
8	14	0.9172

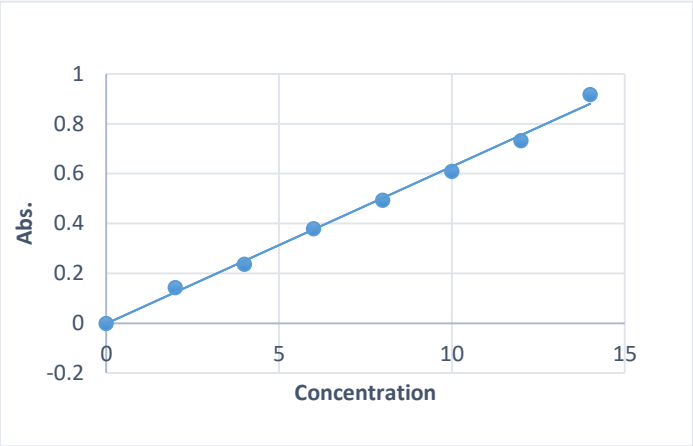

Fig.1: Calibration Curve of Spironolactone at 242 in Ethanol/Water

b) Calibration curve in Methanol:

Table 3: UV Absorbance

Sr. No.	Concentration	Absorbance
1	0	0
2	2	0.1012
3	4	0.2904
4	6	0.4234
5	8	0.5810
6	10	0.7822
7	12	0.8903
8	14	0.9101

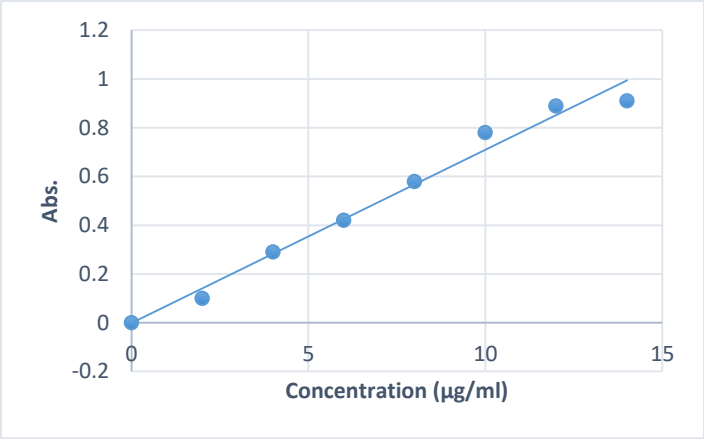

Fig.2: Calibration Curve of Spironolactone at 238 in Methanol

3.3 Compatibility Study:

3.3.1 Fourier-Transform Infrared Spectroscopy (FTIR)

The FTIR study was used to carried out compatibility of SPL with Excipients used. FTIR spectra were recorded for SPL, SPL: PEG 6000 and SPL tablet using Shimadzu FTIR. Data were collected over a spectral region from 4000 to 500 $cm^{-1.}$ The FTIR spectra of SPL, SPL: PEG 6000 and SPL tablet are shown in figure 3,4 & 5 respectively. The Observations of functional groups are shown in table 4,5 & 6 respectively.

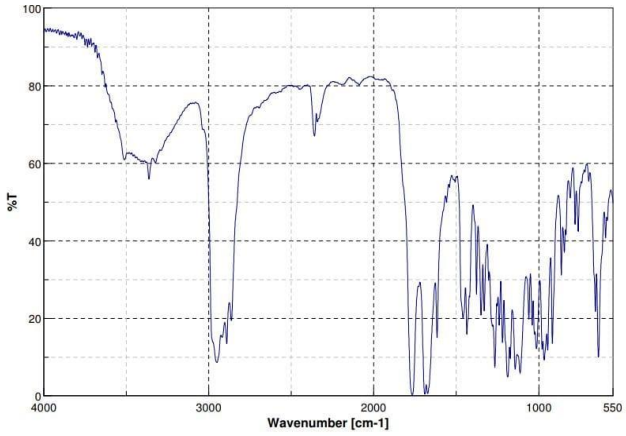

Fig.3: FTIR Spectra of Spironolactone

Table 4: FTIR spectra readings

Sr. no.	**Stretching**	**Functional Group**	
		Reported	**Observed SPL**
1	C=O	1700-1780	1775
2	C=C	1600-1680	1640
3	O-H	3200-3600	3450
4	C-H	2850-3000	2930

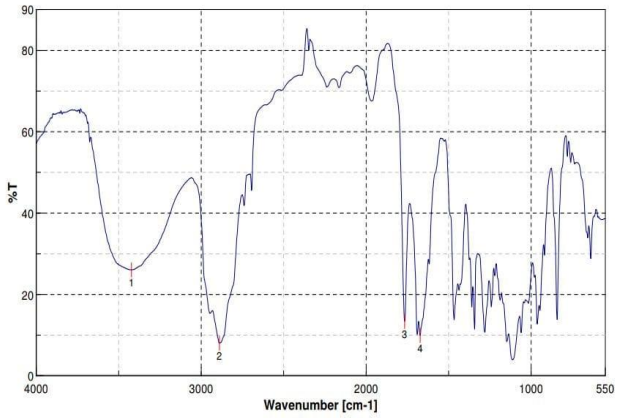

Fig.4: FTIR spectra of Spironolactone: PEG 6000 (1:2) ratio

Table 5: FTIR Spectra Readings

Sr. no.	Stretching	Functional Group	
		Reported	Observed SPL +PEG 6000 (1:2)
1	C=O	1700-1780	1766
2	C=C	1600-1680	1653
3	O-H	3200-3600	3450
4	C-H	2850-3000	2930

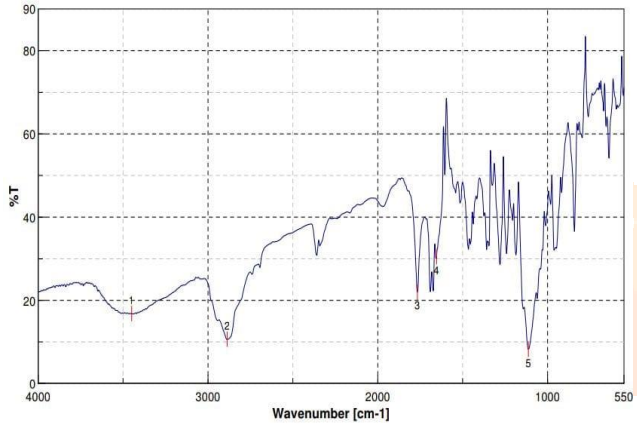

Fig. 5: FTIR spectra of Spironolactone Table

Table 6: FTIR Spectra Readings

Sr. no.	Stretching	Functional Group	
		Reported	Observed SPL Tablet
1	C=O	1700-1780	1762
2	C=C	1600-1680	1660
3	O-H	3200-3600	3450
4	C-H	2850-3000	2886

In the above table 4, 5 & 6 the observed FTIR peak values between pure Spironolactone, Spironolactone: PEG 6000 (1:2) mixture & Spironolactone Tablet indicate no significant difference and hence can be said to be compatible.

3.3.2 Solubility Improvement study:

Since, Spironolactone belongs to BCS class II, trials for improving solubility were conducted by adding various ratio of PEG 6000 by FBHMG.

Mixture of SPL with PEG 6000 in different ratios were prepared and its solubility & dissolution were checked and compared with plain drug.

The results are shown in table no. 7

Table 7: Spironolactone Solubility Study ratios

Sr. No.	SPL + Solubilizer	Ratio	Observations (mg/ml)
1	SPL + PEG 6000	1:1	0.946
2	SPL + PEG 6000	1:2	1.010
3	SPL + PEG 6000	1:3	0.887
4	SPL + PEG 6000	1:4	0.691
5	SPL + PEG 6000	1:5	0.602

In vitro dissolution studies were performed of the results are shown in table no. 8

Table 8: Drug release through Mixture (SPL: PEG 6000)

Time (min.)	Pure SPL	Spironolactone: PEG 6000				
		(1:1)	(1:2)	(1:3)	(1:4)	(1:5)
15	29.75	31.43	34.20	32.32	31.47	33.94
30	31.75	46.98	51.79	48.01	41.68	42.06
45	38.42	59.19	64.12	56.03	50.92	54.57
60	41.43	70.89	78.40	62.41	55.50	56.96

Graph of % Drug release verses Time of SPL: PEG 6000 Mixture are shown in figure 6.

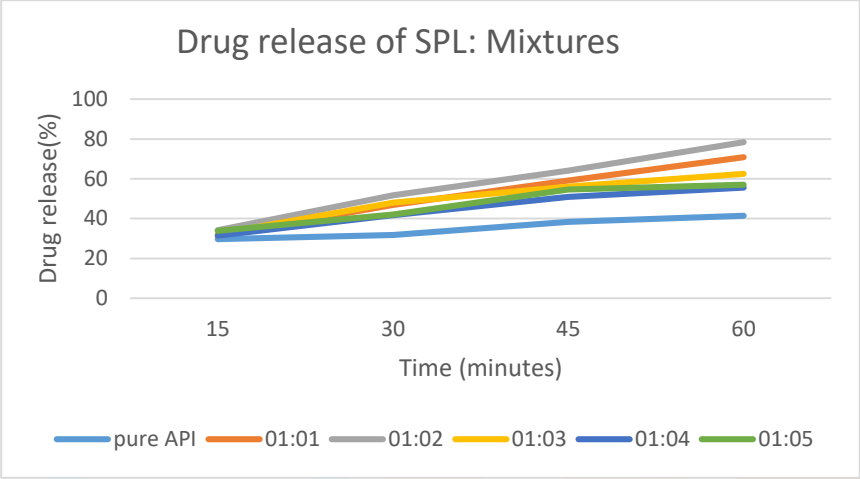

Fig. 6: Drug release of SPL: PEG 6000

In the above Figure 6, 1:2 ratio of Spironolactone: PEG 6000 shows maximum drug release amongst all the ratios. The decrease in dissolution could be due to increase in wax like material of PEG 6000.

3.3 Formulation of Fluidised Bed Hot Melt Granules

Formulation trial batches with 1:2 ratio of SPL & PEG was prepared as seen in table 9.

Table 9: Trial batches formulation table

Ingredients (Mg)	F01	F02	F03	F04	F05	F06
Spironolactone	50	50	50	50	50	50
PEG 6000	100	100	-	100	100	100
MCC	-	20	70	20	20	20
Lactose	-	-	73	23	23	-
Magnesium Stearate	2	2	2	2	2	2
Talc	3	3	3	3	3	3
Aerosil	2	2	2	2	2	2
Crosspovidone	-	20	20	20	20	43
Total	177	200	220	220	220	220

Trials F01–F06 were prepared using the Top Spray Fluid Bed Hot Melt Granulation technique in a GPCG 1.1 fluid bed processor. The formulation ingredients, as listed in Table 9, were accurately weighed and passed through Sieve No. 40. The active pharmaceutical ingredient Spironolactone, along with Microcrystalline Cellulose (MCC) and Crosspovidone, was blended thoroughly to ensure uniform mixing.

Separately, PEG 6000 was weighed and melted in a hot melt tank above 60 °C until fully liquefied. The molten binder was then atomized and sprayed into the fluidized dry mix within the Fluid Bed Hot Melt Granulator to initiate spray congealing, thereby forming Fluidized Bed Hot Melt Granules.

The hot melt tank oil temperature was maintained between 90–95 °C, well below the melting point of Spironolactone (134 °C), to prevent thermal degradation. The granulation process was conducted at ambient

room temperature, and the product temperature during processing was maintained between 30–35 °C to ensure proper congealing. The atomization air temperature was set at 95 °C, and the atomization air pressure was maintained at 1.6 bar. The spray pump operated at 10 RPM, delivering the molten binder at a flow rate of approximately 12 g/min. Throughout the process, the dry mix was fluidized using 35–45 CFM of ambient air, which promoted efficient cooling and faster solidification of the granules.

After granulation, the cooled mass was passed through a Sieve no. 20 to achieve uniform particle size. Lubrication was performed in a subsequent step.

Crosspovidone, Aerosil were passed through sieve no. 40 and mixed with above prepared granules. Talc and Magnesium Stearate were added to granules & mixed again. The mass ready for compression was compressed using ACG-manufactured PROTAB™ 300, a single rotary 21-station tablet press equipped with D-type tooling 8.5 mm standard biconcave punches.

Fig. 7: Fluid Bed Granulator - GPCG 1.1

Fig. 8: GPCG 1.1 with hot melt granulation setup.

Evaluation of Post-Compression parameters of Trial batches

All prepared tablets were evaluated for post compression parameters such as appearance, thickness, weight variation, friability, drug content, disintegration time, in vitro dissolution study, assay. Results are shown in table 10.

Table 10: Post-Compression evaluation parameters of trial batches

Batch	Appearance	Hardness (Kg/cm2)	Friability (%)	Avg. weight (mg)	Thickness (mm)	Disintegration Time (min.)	Drug release(%)	Drug Content (%)
F01	Smooth round white biconvex tablets	4.8	0.29	208	3.70	11.00	82.27	97.69
F02		5.0	0.22	222	3.86	6.50	88.30	98.70
F03		5.9	0.09	220	3.90	0.33	77.00	97.10
F04		2.7	0.50	180	3.80	12.00	72.67	97.20
F05		6.0	0.23	200	3.84	7.04	85.87	98.30
F06		**2.5**	**0.33**	**220.5**	**4.26**	**6.33**	**93.69**	**98.32**

The above parameter indicate that batch F06 shows acceptable results.

4. Optimization of tablets using Central Composite design

Central Composite design was selected for optimization of tablets of Spironolactone. Two factors were selected varying at two different levels (as shown in Table 11). The effect of independent variables, i.e. amount of Microcrystalline Cellulose and amount of Crosspovidone on dependent variables like

Disintegration time, % drug released were studied. Experiments were conducted using all 9 possible combinations.

Table 11: Central composite design batches variables selected

Factors	Level used	
	Low	High
Independent variables		
1) Microcrystalline Cellulose	18 (-2)	22 (+2)
2) Crosspovidone	41 (-2)	45 (+2)
Dependent Variables 1) Disintegration time 2) Drug release		

Optimized formulation batches B1 to B9 were prepared as shown in table 12.

Table 12: Optimized batch formulation table

Ingredients (Mg)	B1	B2	B3	B4	B5	B6	B7	B8	B9
SPL	50	50	50	50	50	50	50	50	50
PEG 6000	100	100	100	100	100	100	100	100	100
MCC	18	18	18	20	20	20	22	21	22
Crosspovidone	23	22	25	21	25	23	22	24	23
Aerosil	2	2	2	2	2	2	2	2	2
Crosspovidone	20	20	20	20	20	20	20	20	20
Mg- Stearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Total	218	217	220	218	222	220	221	222	222

4.1 Evaluation of Post-Compression parameters

All prepared tablets were evaluated for post compression parameters such as thickness, weight variation, friability, drug content, disintegration time and in vitro dissolution study. Results are shown in table 13.

Table 13: Post Compression Evaluation of Central Composite Design Batches

Batch	Hardness (Kg/cm2)	Friability (%)	Avg. wt. (mg)	Thickness (mm)	Disintegration T-min.)	Drug release%	Drug Content (%)
B1	5.25	0.32	223.5	4.09	8.30	86.11	98.50
B2	5.37	0.38	222.0	3.49	9.48	84.04	98.00
B3	3.87	0.31	222.5	4.44	6.31	92.70	97.90
B4	4.37	0.37	219.5	4.27	9.11	84.97	98.10
B5	**3.93**	**0.41**	**219.2**	**4.50**	**4.10**	**94.10**	**98.86**
B6	3.83	0.39	218.0	4.39	8.09	87.20	97.10
B7	3.37	0.53	224.0	3.77	9.04	86.16	97.40
B8	2.87	0.50	222.2	4.44	7.43	89.68	98.60
B9	2.62	0.46	218.0	4.26	7.47	88.64	97.10

Above results indicates that batch B5 shows acceptable results, hence selected as Optimized formulation.

4.2 Central Composite Design:

Response 1: Disintegration time:

The visualization of interactive effects of MCC & Crosspovidone on tablet disintegration time are shown in figure 9& 10.

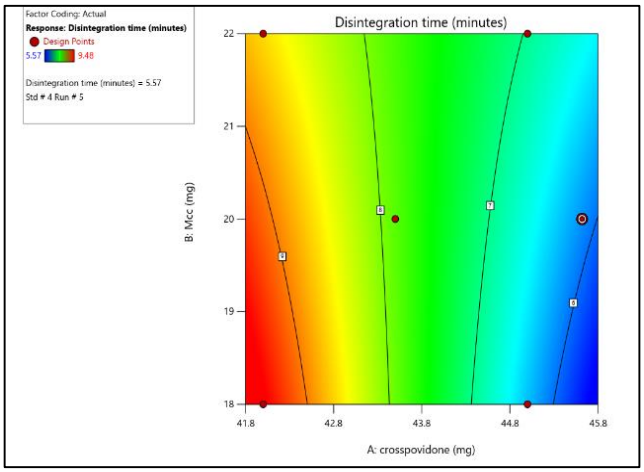

Fig. 9: Factorial design for response 1 disintegration time

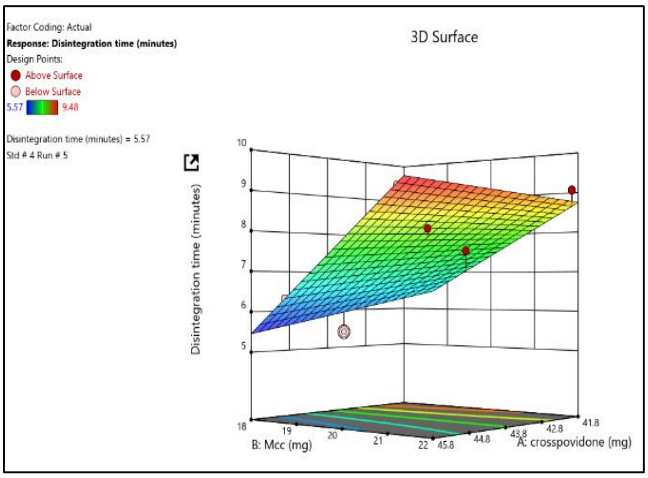

Fig. 10: 3-D plot for response 1 disintegration time

The concentration of Crosspovidone increases (moving right side along the x-axis) & the concentration of MCC increases (moving up along the Y-axis), the disintegration time appears to decreases.

Response 2: Drug release

The comprehensive visualization of interactive effects of Crosspovidone and MCC on % Drug release are shown in figure 11 & 12.

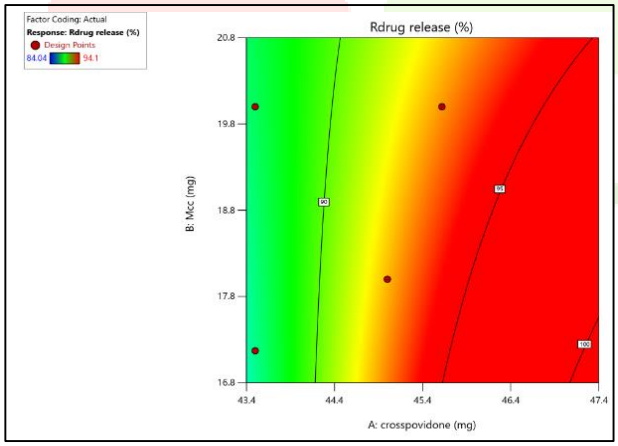

Fig. 11: Factorial design for response 2 drug release

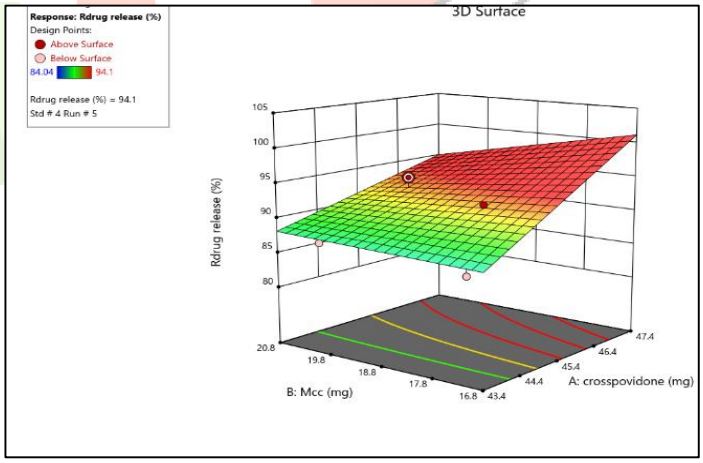

Fig. 12: 3-D plot for response 2 drug release

The concentration of Crosspovidone increases (moving right side along the x-axis) and the concentration of MCC increases (moving up along the Y-axis), the drug release appears to increase.

The optimum formulation was selected based on the criteria of attaining the constraints of variables response. Based on this data the batch B5 was selected as the final optimized batch. Upon trading of various response variables and comprehensive evaluation of feasibility search the formulation ingredients Crosspovidone and MCC (45mg & 20mg) were found to fulfil the maximum requisite of an optimum formulation (fig. 9,10,11 & 12). Based on the Central composite design data B5 was selected as the final optimized batch. A Pilot batch was prepared, by using Fluidized Bed Hot Melt Granulator (CPCG-1.1, at ACG Shirwal Pune) as per formulation batch B10, shown in table 14.

Table 14: Reproducible batch formulation table

Ingredients (gm)	B10
Spironolactone	290
Microcrystalline Cellulose	116
Crosspovidone	151
PEG 6000	580
Crosspovidone	116
Aerosil	11.6
Talc	17.4
Magnesium Stearate	11.6
Total	**1293.6**

Post-compression parameters of batch B10 shown in table 15.

Table 15: Post compression parameters of optimized batch

Parameters	Batch 10
Appearance	Smooth round white biconvex tablets
Hardness (kg/cm2)	3.5
Friability (%)	0.27
Avg. weight (mg)	223
Thickness (mm)	4.30
Disintegration Time (min.)	5.53
Drug release(%)	94.76
Drug Content (%)	98.86

5 Conclusion

This research successfully investigated the potential of Fluid Bed Hot Melt Granulation as technique to enhance solubility of Spironolactone. This enhancement in solubility is crucial as it directly addresses a major bioavailability challenge associated with Spironolactone, potentially leading to improved therapeutic efficiency. So the present study reveals that Fluid Bed Hot Melt Granulation is an ideal means for poorly water soluble drug.

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