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Co-Crystal Approach for Improving Poorly Soluble Drug Agomelatine by Using Acid Coformer for Tablets

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ABSTRACT

Agomelatine is an antidepressant agent BCS class II drug of low solubility and high permeability. Pharmaceutical co-crystals of agomelatine were prepared with co-crystal formers, such as benzoic acid and glutaric acid to improve drug solubility. Solvent drop grinding method was successful to make agomelatine co-crystals. All new crystalline forms were characterized by IR spectroscopy, differential scanning calorimetry, and X-ray diffraction to confirm their purity and homogeneity. Co-crystals with benzoic acid and glutaric acid showed a faster powder dissolution rate than the reference active pharmaceutical ingredient (API). Co-crystals of agomelatine with glutaric acid showed the highest solubility 7 times as compared with API while co-crystals with agomelatine and benzoic acid showed comparably good solubility 3 times faster than the API up to 120 min. The study showed Co-Crystal Approach improving for poorly soluble drug agomelatine by using acid co-former for tablets.

INTRODUCTION

The improvement of the physicochemical properties, biopharmaceutical and *in-vivo* of active pharmaceutical ingredients (APIs) has become a major concern in the pharmaceutical industry[1]. Both branded and generic pharmaceutical companies spend considerable efforts and resources on the discovery of new crystalline forms of their API's[2]. This intense research has been driven by the need for improving undesirable properties of API's witnessed in the commercialization pipelines[3,4]. Pharmaceutical co-crystals is reliable method to improve drug physicochemical and mechanical properties such as solubility, dissolution rate, stability hygroscopicity, compressibility and *in vivo* performance without altering their pharmacological behavior and hence this is a potential new alternative in the selection of optimal solid forms in drug product development[5,6]. Pharmaceutical co-crystals can be defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non-covalent interactions, primarily hydrogen bonding[7]. The resulting multicomponent crystalline phase maintains the intrinsic activity of the parent API. The screening of co-crystal is based upon some traditional methods such as solvent evaporation, crystallization from melts and grinding[8,9]. Co-crystals can be considered for non-ionizable drugs for which salts cannot be attained also, for ionizable drugs, the number of suitable co-crystal ligands can exceed the number of suitable counterions[10].

Agomelatine antidepressant has been considered as a model drug forco-crystallization due to its low water solubility. Improvement of its dissolution is challenging job and rational problem. Commercially available agomelatine particles are crystalline rough surfaces and show poor flowability, poor compaction behavior and a tendency to stick to the tablet punches. To overcome these problems, a suitable size and shape of agomelatine crystal is desirable that could be directly compressed[11,12].

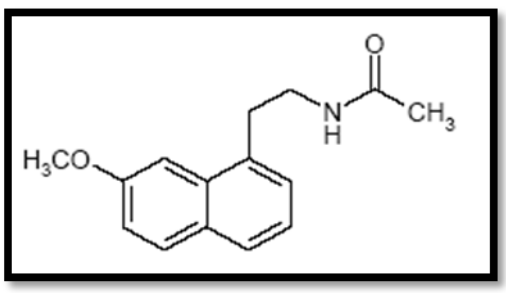

Fig No 1.Structure of Agomelatine

A range of co-crystallization techniques solvent evaporation technique, solid state grinding or mechanical milling technique, solvent reduced technique, slurrying technique, solvent drop technology, hot melt extrusion, ultrasound assisted solution co-crystallization technology etc have been explored to formulate co-crystals[13,14].

The main objective of the present research work was to formulate co-crystals of agomelatine using benzoic acid and glutaric acid as the coformer via utilization of solvent drop technology. The changes in the inherent crystal lattice of the drug were confirmed by techniques like differential scanning calorimetry, infrared spectroscopy, X-ray diffractometry studies. The effect of co-crystallization on pharmaceutical parameters like drug release and flow properties was also evaluated.

2. MATERIALS AND METHODS

2.1 Materials:

Agomelatine was received as a gift sample from the Enaltec Lab Industry, Ambernath, India. Other chemicals and solvents were obtained from different commercial suppliers.

2.2 Preparation of Co-crystals:

Pharmaceutical co-crystals of agomelatine were prepared with different co-crystal formers using solvent drop grinding method. Agomelatine- benzoic acid and glutaric acid co-crystal were prepared by grinding 1:1 molar ratio in a pestle and mortar for 180 minutes with addition of a few drops of methanol. The solid powder was then scratched from walls of mortar and stored in vial. The solid obtained in experiments were then characterized using various analytical techniques.

Trial 1:

API – Agomelatine

CCF – Benzoic acid

Solvent: Methanol

Method:

Solvent drop grinding:

0.4866 g of Agomelatine and 0.2442 g of benzoic acid were weighed. AGO-BA 1:1 co-crystal was prepared by grinding Agomelatine and benzoic acid in 1:1 molar ratio in a pestle and mortar for 180 minutes with addition of a few drops of methanol (approximately 10% of weight). The solid powder was then scratched from walls of mortar and stored in vial. The sample was sending for analysis.

Trial 2:

API – Agomelatine

CCF – Glutaric acid

Solvent: Methanol

Method:

Solvent drop grinding:

0.4866 g of Agomelatine and 0.2642 g of glutaric acid were weighed. AGO-GA 1:1 co-crystal was prepared by grinding agomelatine and glutaric acid in 1:1 molar ratio in a pestle and mortar for 180 minutes with addition of a few drops of methanol (approximately 10% of weight). The solid powder was then scratched from walls of mortar and stored in vial. The sample was sending for analysis.

3. PRELIMINARY CHARACTERIZATION:

3.1 Melting point:

Melting point of the sample Agomelatine- benzoic acid and glutaric acid co-crystal were determined by open capillary method by using melting point apparatus. The melting point was done in triplicate. (Omega Scientific Industries, India).

3.2 IR Spectroscopy:

Infrared spectroscopy analysis of agomelatine- benzoic acid and glutaric acid co-crystal 1:1 was performed by attenuated total reflectance (ATR Bruker Alpha)

3.3 Differential scanning calorimetry:

The DSC thermogram of agomelatine- benzoic acid and glutaric acid co-crystal1:1 was recorded by differential scanning calorimeter equipped with a computerized data station. The DSC measurements were performed on a DSC 60, Shimadzu, Japan instrument. Accurately weighed sample were placed in a sealed aluminum pans before heating under nitrogen flow (20ml/min) at a scanning rate of 10^0c/min. An empty aluminum pan was used as a reference. Melting point was determined for identification of API and co-crystal former.

3.4 X-ray Diffraction:

For characterization of crystalline state, the powder x-ray diffraction (XRD) pattern of agomelatine- benzoic acid and glutaric acid co-crystal 1:1 was determined. Powder X-ray diffraction (XRD) was carried out using a Bruker AXS Advance D-8 scanner with filter Ni, Cu- Kά radiation, voltage 40kV and a current 20mA. The scanning rate employed was 10/min over the 50 to 500 diffraction angle (2Θ) range.

3.5 Scanning Electron Microscopy:

Scanning electron microscopy of agomelatine- benzoic acid and glutaric acidco-crystal1:1 was carried to determine the external morphology. The sample was mounted directly onto the SEM sample holder using double-sided sticking tape and images were recorded at the required magnification at acceleration voltage of 20 kV using scanning electron microscope.

3.6 Phase Solubility:

The phase solubility of AGO-BA 1:1 and AGO-GA 1:1 was determined in phosphate buffer 6.8. The solubility of drug and co-crystals were determined by taking an excess amount of drug (10 mg), co-crystals(equivalent to 10 mg of drug) and added them in 10 ml of above solvent, in vials. The samples were kept at equilibrium for a period of 48 hrs in incubator at 37± 0.5^0C with occasional shaking. The supernatant collected from vials was filtered through Whatman filter paper and analyzed by UV-Visible spectrophotometer (V630, Jasco) at respective wavelength.

3.7 Flow properties:

Flow properties and compressibility were determined by determining bulk density, tapped density angle of repose, compressibility index and hausner's ratio.

4. RESULT AND DISCUSSION

4.1 Melting point determination:

Melting point of the drug sample and co-crystals were determined by open capillary method by using melting point apparatus and found to be shown in Table 1.

Table No. 1: Melting point of Agomelatine, Co-crystal former and co-crystals

Sr. No	Nature	Sample	Observed Melting point (^{0}C)
1	API	Agomelatine	110-112
2	Co-crystal former	Benzoic acid	122-125
		Glutaric acid	96-99
3	Co-crystal	Agomelatine-benzoic acid	64-68
		Agomelatine- glutaric acid	60-64

It was found that melting point of co-crystals get decreased as compared to API and co-crystal former.

4.2 IR Spectroscopy:

A)

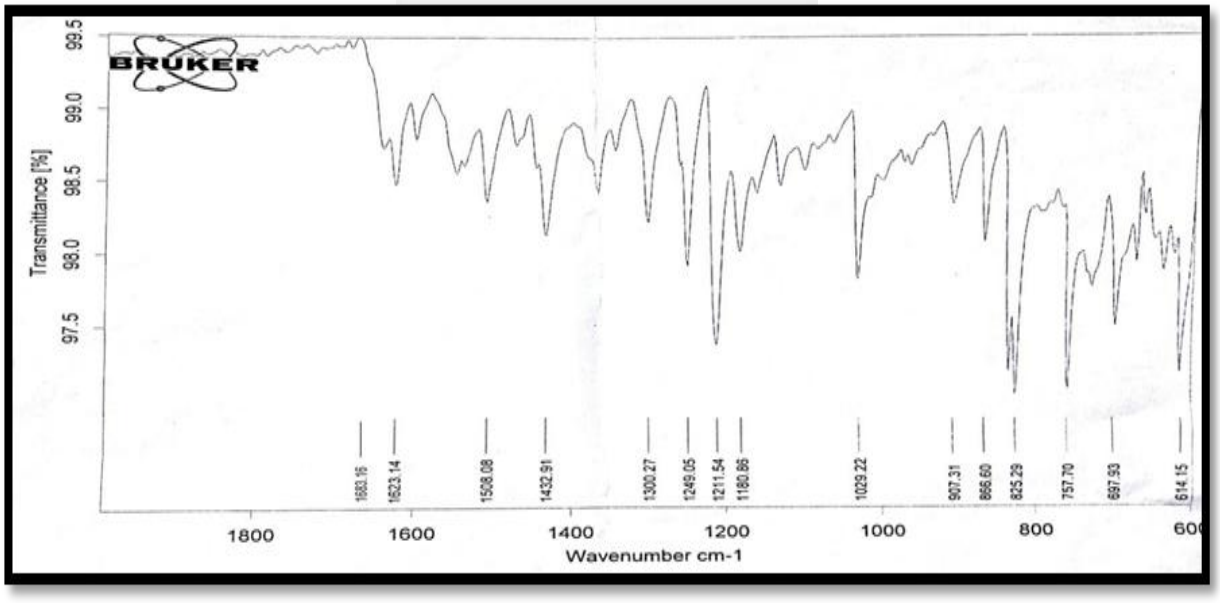

Fig No.2: IR spectra of Agomelatine (AGO)

B)

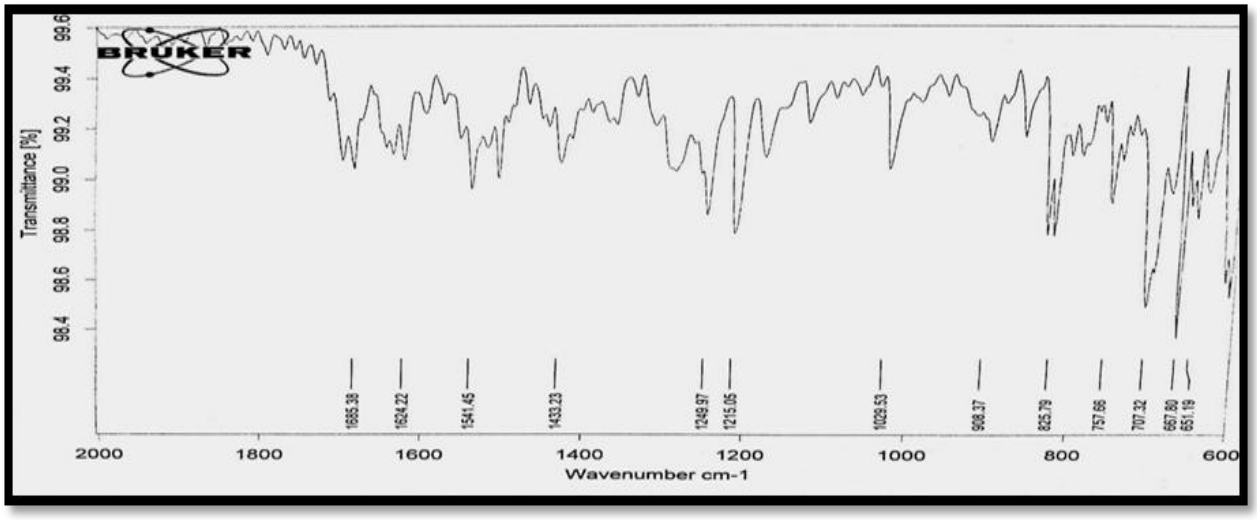

Fig No.3: IR spectra of Agomelatine-Benzoic Acid (AGO-BA)

C)

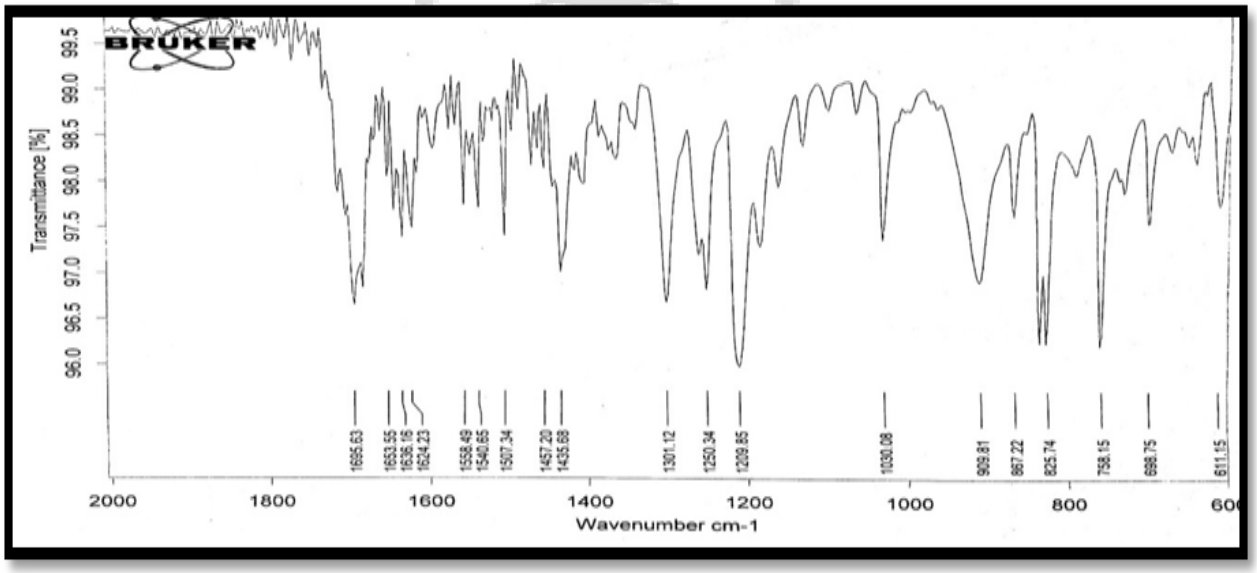

Fig No.4: IR spectra of Agomelatine-Glutaric acid. (AGO-GA)

Infrared spectroscopy helps in preliminary identification of new crystalline form. From comparison, indicated shifts at peaks of functional group represent the new crystalline form. It is confirmed from shift at –C=O stretch and also C-O stretch strongly indicate formation of hydrogen bond in between Agomelatine and Benzoic acid and Glutaric acid.

4.3 Differential Scanning Calorimetry (DSC):

A)

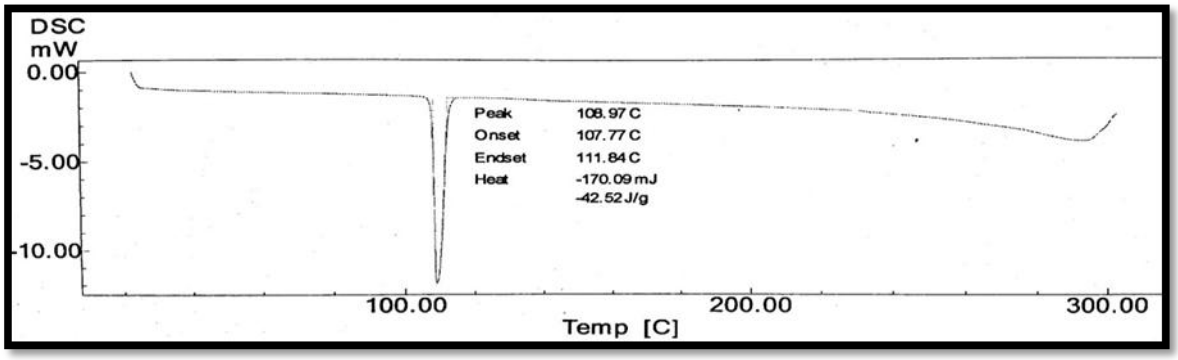

Fig No.5: DSC thermogram of Agomelatine (AGO)

B)

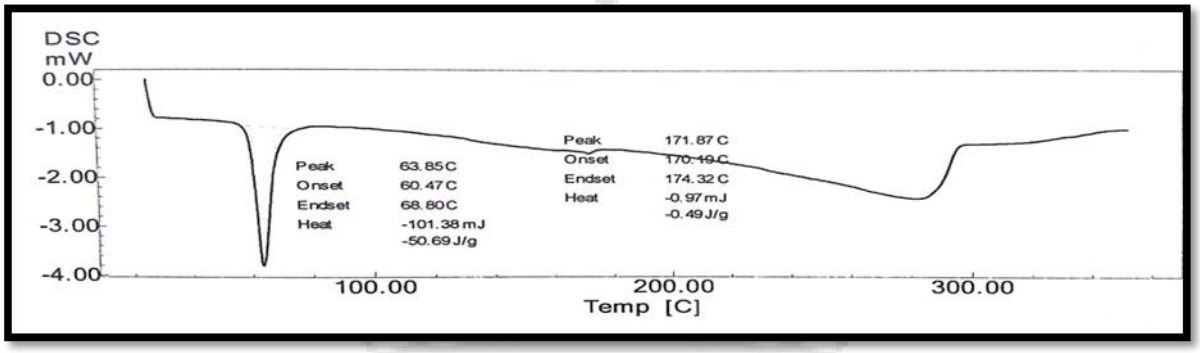

Fig No.6: DSC thermogram of Agomelatine-Benzoic acid (AGO-BA)

C)

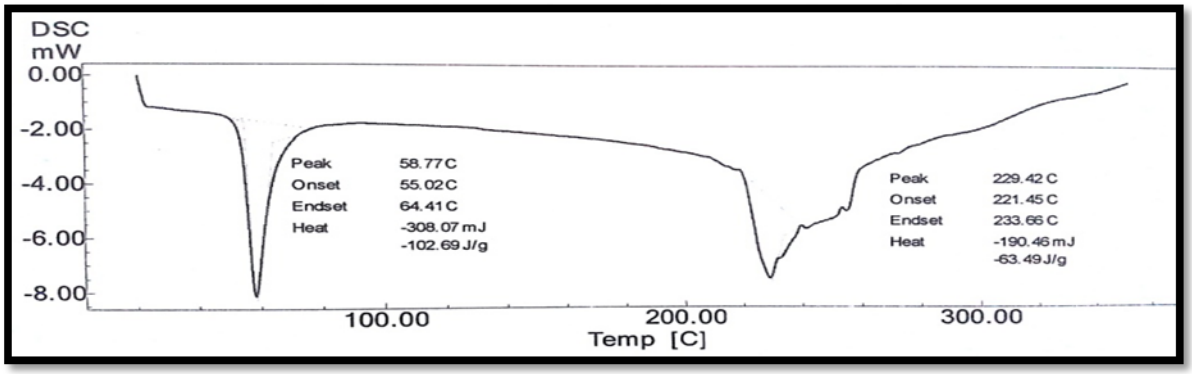

Fig No.7: DSC thermogram of Agomelatine-Glutaric acid (AGO-GA)

The DSC thermogram of Agomelatine- benzoic acid and glutaric acid co-crystals was recorded by using a differential scanning calorimeter with a computerized data station.DSC experiment was carried out to study the thermal behavior of the Agomelatine-Benzoic acid, Glutaric acid co-crystals had shown single endothermic peak maxima at 63.85^0C and 58.77^0C

due to melting of co-crystals. The thermal behavior was distinct, with a different melting transition from that seen with either of the individual components; this suggests formation of new phase co-crystals. The melting point of co-crystals was found to be below the melting point of both the drug and co-crystal former.

A single endothermic transition for the co-crystals indicates the absence of any unbound or absorbed solvent or water and also demonstrates the stability of the phase until the melting point.

4.4 X-Ray Diffraction:

A)

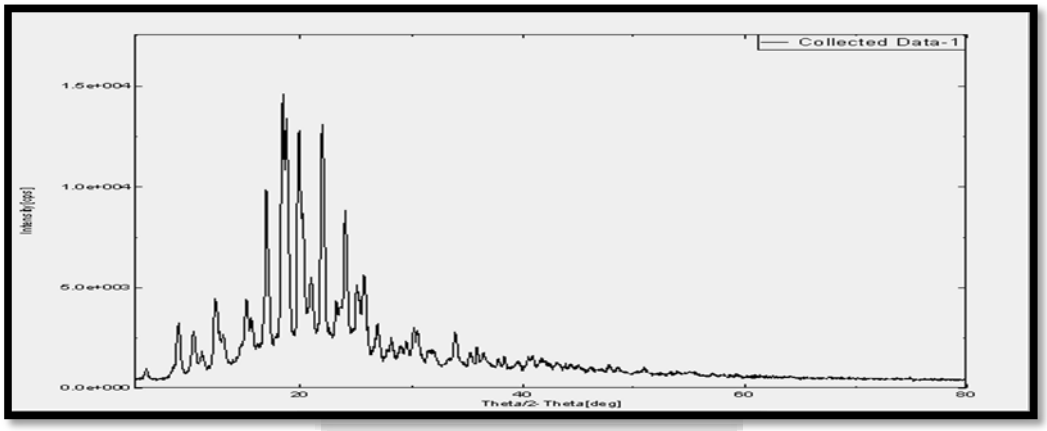

Fig No.8: XRD pattern of Agomelatine (AGO)

B)

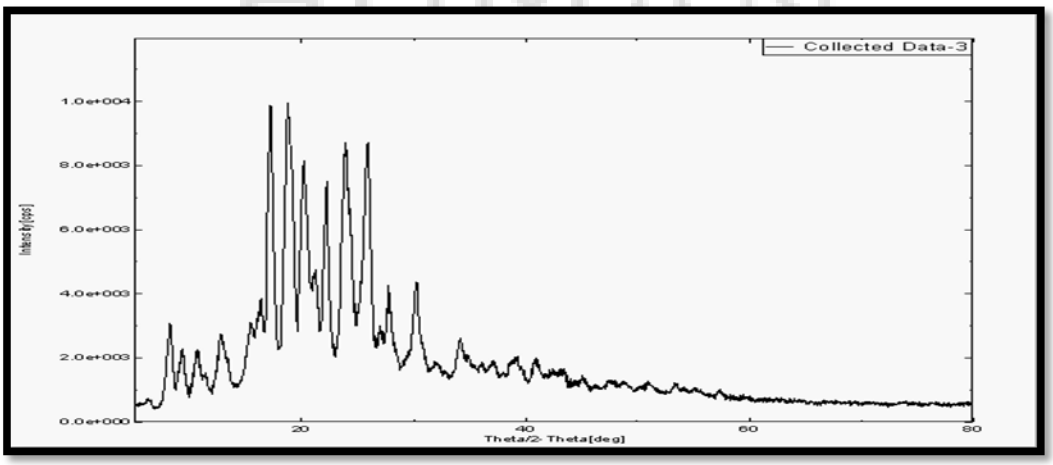

Fig No.9: XRD pattern of Agomelatine-Benzoic acid (AGO-BA)

C)

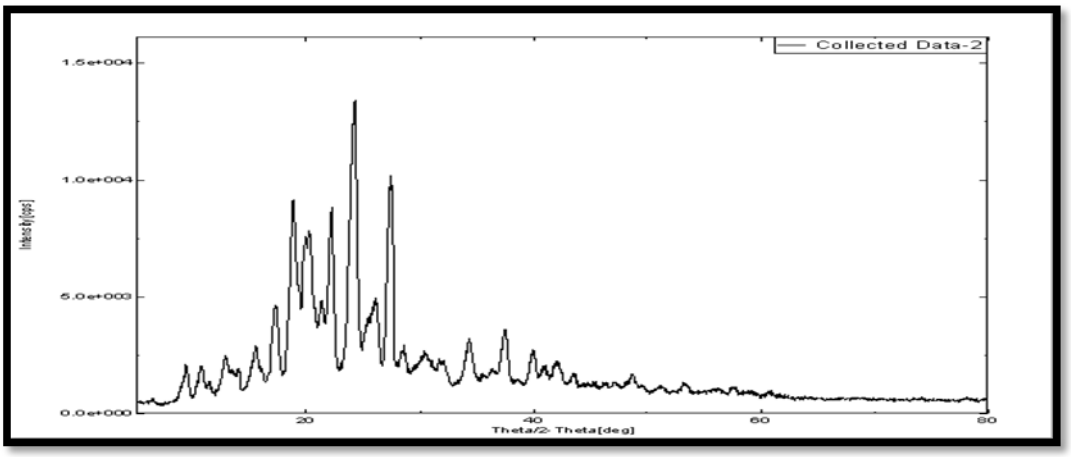

Fig No.10: XRD pattern of Agomelatine- Glutaric acid (AGO-GA)

Agomelatine exhibited intense crystalline peak between 5^0 to 50^0.Characteristic diffraction peaks at 12.35^0, 15.11^0, 16.93^0, 18.36^0, 18.73^0, 19.84^0, 21.89^0 and 23.98^0 were observed with intense peak at 18.36^0 indicating crystalline nature of agomelatine.

Agomelatine-benzoic acid shows characteristic at 12.76^0, 16.20^0, 17.19^0, 18.78^0, 20.16^0, 22.16^0, 23.87^0 and 25.92^0 and intense peak was observed at 18.78^0 indicating crystalline nature of AGO-BA. The shift in intense peak indicates formation of new crystalline form.

Agomelatine-glutaric acid shows characteristic at 12.85^0, 15.50^0, 17.28^0, 18.80^0, 20.12^0, 22.21^0, $24.12^0$and 26.16^0 and intense peak was observed at 24.12^0 indicating crystalline nature of AGO-GA. The shift in intense peak indicates formation of new crystalline form.

4.5 Scanning Electron Microscopy:

A)

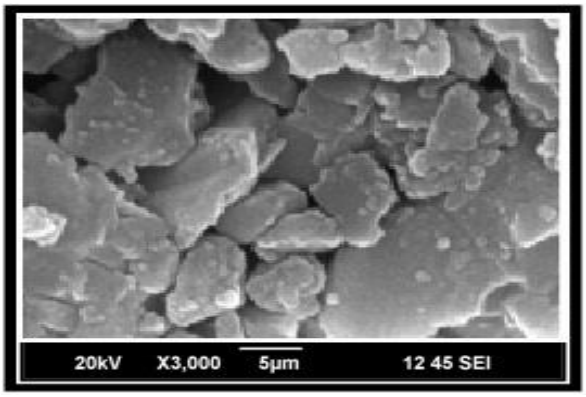

Fig No11: Scanning Electron Microscopy of Agomelatine. (AGO)

B)

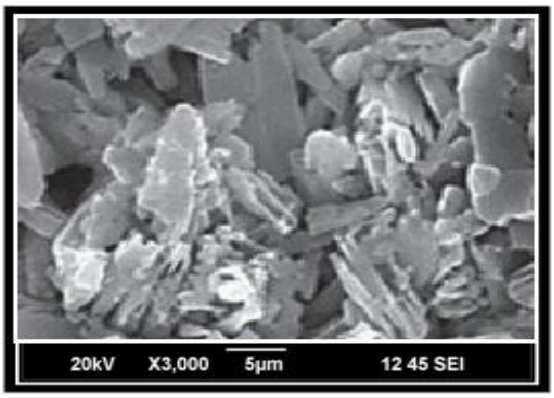

Fig No.12: Scanning Electron Microscopy of Agomelatine- Benzoic acid (AGO-BA)

C)

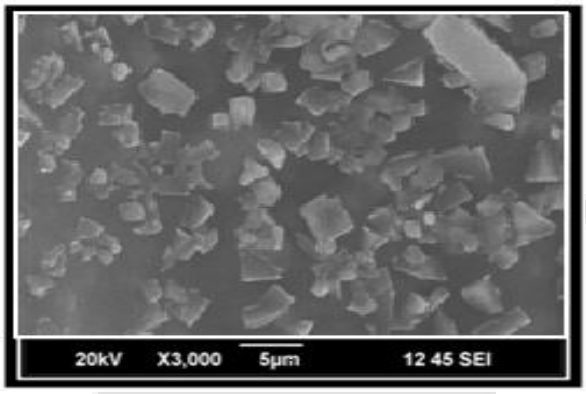

Fig No.13: Scanning Electron Microscopy of Agomelatine- Glutaric acid (AGO-GA)

SEM of agomelatine indicated needle shaped fracture surface. Agomelatine- benzoic acid and Agomelatine- glutaric acid co-crystals indicated change in surface morphology, development of irregular shaped crystal were seen.

4.6 Phase solubility:

Solubility studies were performed in order to analyze solubility enhancing properties of co-crystals. Solubility studies gave the basis for selection of best ratio that is to be forwarded for formulation. The results of the same are shown in Table 2.

Table No.2: Phase solubility of Agomelatine-benzoic acid and

Agomelatine-glutaric acid co-crystals

Sr. No.	Sample	Solubility (mg/ml)	Increase in Solubility (folds)
1	Agomelatine	0.49	-
2	Agomelatine-Benzoic acid	1.43	2.918
3	Agomelatine-Glutaric acid	3.46	7.061

4.7 Flow properties

The flow properties of agomelatine with benzoic acid and glutaric acid co-crystals have been determined and compared in Table 3 shows the flowability represented in terms of the angle of repose, carr's index and hausner's ratio of co-crystals were much improved compared to those of the original drug crystals.

Table No.3: Comparison flow properties of Agomelatine, AGO-BA and AGO-GA

Sr. No.	Evaluation Parameters	Agomelatine	`AGO-BA	AGO-GA
1	**Angle of Repose**	42.27 ± 0.76	22.20 ± 0.65	23.49 ± 0.47
	Inference	Very poor	Good	Good
2	**Bulk Density**	0.571 ±0.009	0.444 ±0.005	0.476 ± 0.011
3	**Tap Density**	0.740 ±0.016	0.512 ±0.015	0.555 ± 0.009
4	**Carr's index**	22.85 ± 0.39	13.41 ±0.026	14.21 ± 0.030
	Inference	Poor	Good	Good
5	**Hausner's Ratio**	1.29 ± 0.055	1.15 ± 0.003	1.16 ± 0.002
	Inference	Poor	Good	Good

4.8 Comparison of *in vitro* drug release of AGO-GA tablet formulation:

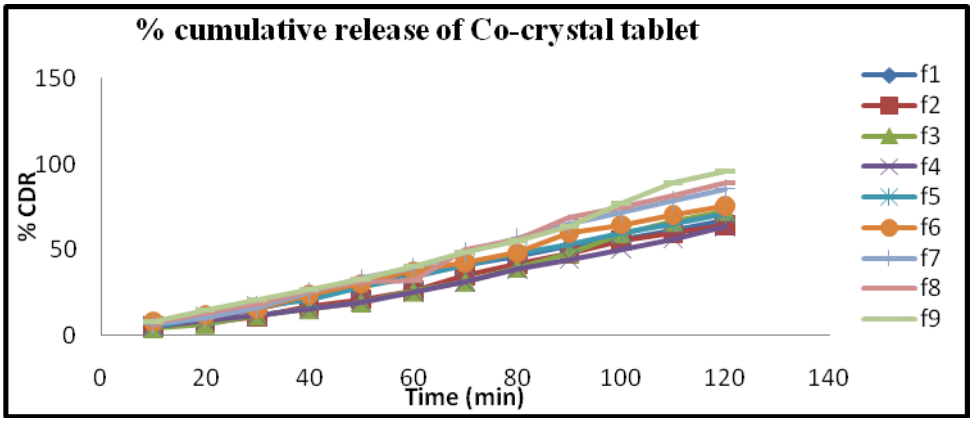

Fig No.14: *In-vitro* study of different formulations of AGO-GA

4.9 Comparative dissolution rate of Plane drug, Matrix Tablet, AGO-BA and AGO-GA.

Table No.4: Comparative dissolution rate of Plane drug, Matrix Tablet, AGO-BA and AGO-GA.

Time (min)	% Drug release (± S.D.)			
	Plain Drug	Matrix tablet	AGO-BA(F9)	AGO-GA(F9)
10	1.94± 0.06	2.34 ± 0.21	5.29± 0.010	8.01± 0.02
20	2.31 ±0.021	4.56 ± 0.20	10.6 ± 0.24	14.9 ± 0.43
30	3.55 ±0.034	6.70 ± 0.31	16.3 ± 0.32	20.7 ± 0.32
40	5.84 ± 0.06	9.22 ± 0.28	22.7 ± 0.04	27.1 ± 0.04
50	7.17 ± 0.27	12.08 ± 1.01	27.0 ± 0.02	33.0 ± 0.02
60	11.8 ±0.056	17.1 ± 1.12	33.4 ± 0.02	40.2 ± 0.023
70	15.5 ±0.013	21.7 ± 1.20	38.3 ± 0.05	48.6 ± 0.053
80	18.3 ±0.019	25.8 ± 2.01	43.1 ± 0.08	55.2 ± 0.05
90	22.4 ± 0.09	29.2 ± 2.20	58.1 ± 0.38	63.5 ± 0.39
100	26.3 ± 0.45	33.5 ± 3.12	66.3 ± 0.08	77.3 ± 0.06
110	29.2 ± 0.05	37.7 ± 1.60	75.4 ± 0.5	89.2 ± 0.6
120	33.3 ± 0.03	40.2 ± 2.00	84.7 ± 0.40	95.9 ± 0.30

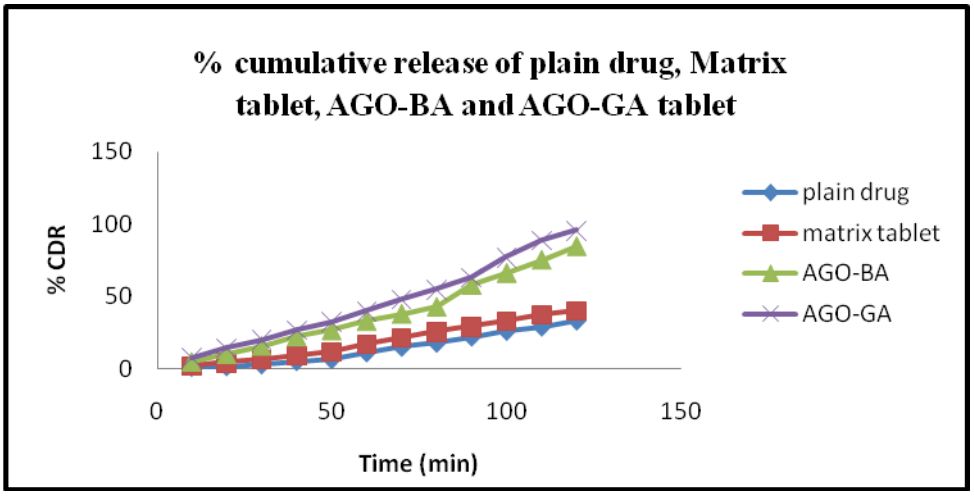

Fig No.15: *In-vitro* study of Plain drug, Matrix tablet, AGO-BA (F9) and AGO-GA (F9) Formulation.

Plane drug gave the 33.3% drug release in phosphate buffer pH 6.8 after 2 hours. Marketed tablet gave 40.2% drug release in phosphate buffer pH 6.8 after 2 hours. While AGO-GA gave 95.9% release in phosphate buffer pH 6.8 after 2 hours and AGO-BA gave 84.7% release in phosphate buffer pH 6.8 after 2 hours. This shows that co-crystal formulation shows better result than marketed tablet.

4.10: Surface response plot:

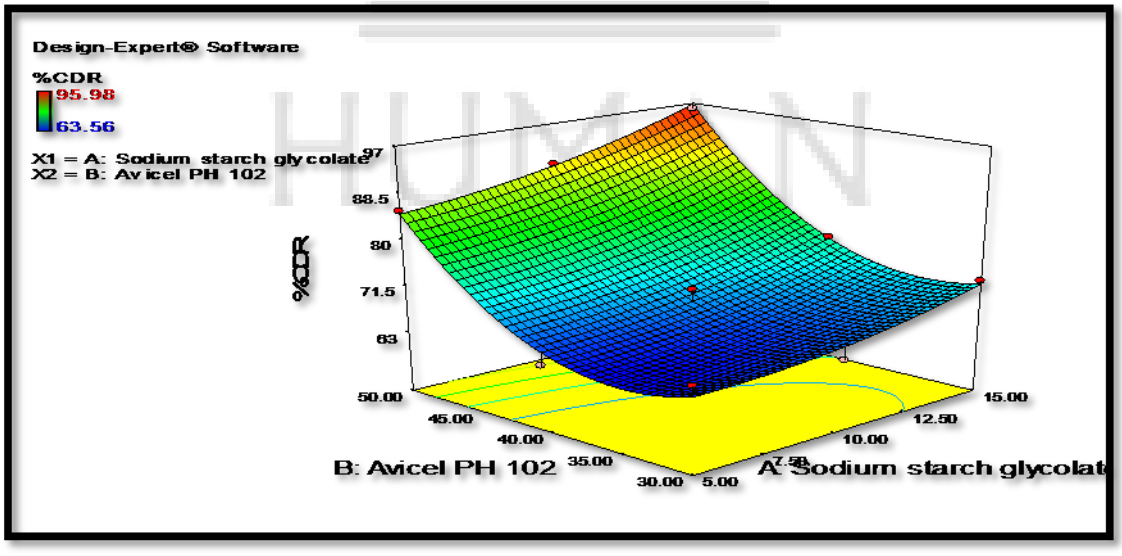

Fig No.16: Surface response plot showing effect of Sodium starch glycolate and Avicel PH 102 on % CDR.

4.11.Contour Plot:

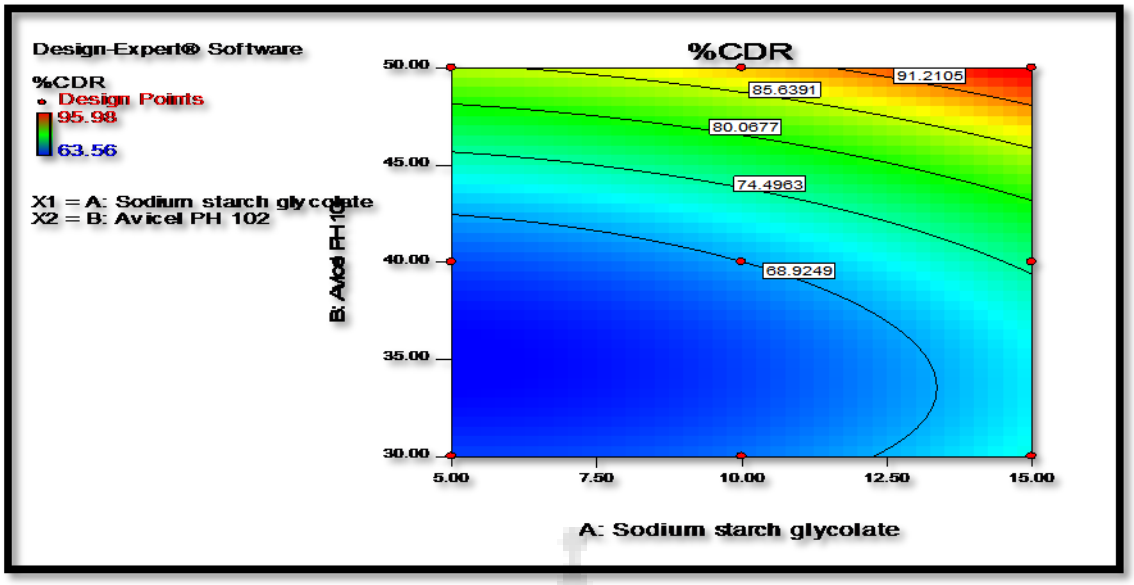

Fig No.17: Contour plot showing effect of sodium starch glycolate and Avicel pH102 on release

5. CONCLUSION

The technique of solvent drop grinding was found to be successful in formulating co-crystals of agomelatine with benzoic acid and glutaric acid. The co-crystals were found to possess morphological and physicochemical attributes different from plain drug. A comparison of drug release profile and other crystal-related data (Infrared spectroscopy, differential scanning calorimetry and x-ray diffractometry) of co-crystal with that of physical mixture of drug and coformer confirmed the changes in hydrophobicity and crystal structure of the drug by co-crystallization.

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