DEVELOPMENT AND EVALUATION OF NICOTINAMIDE AND SACCHARIN GLIBENCLAMIDE CO-CRYSTAL MOUTH DISSOLVING TABLET

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ABSTRACT:
The aim of present work was to prepare glibenclamide (GBC) co-crystal using co-crystallization approach with an objective to improve solubility study and dissolution rate of formulation. Co-crystallization of GBC was prepared by using solvent evaporation technique with the help of coformer i.e. nicotinamide and sodium saccharin co-crystal. The prepared co-crystal were characterized for melting point, solubility, micromeritics properties, FTIR, XRD, DSC and SEM. Various batches of tablet (F1-F4) were successfully prepared using GBC nicotinamide and saccharin co-crystal, further was evaluate for physical properties, disintegration time and drug release and compared with powder GBC co-crystal and pure GBC (F5 – F6). Ethanol solubility study of pure GBC (4.021 µg/ml) and its co-crystal result reveals that solubility of GBC co- crystal with nicotinamide (39.27µg/ml) is 8-9 fold higher than pure GBC. Microscopic analysis of crystal revealed visual difference between the co-crystal and pure GBC. DSC data of co-crystal shows difference in melting point which confirms formation of stable crystal. Disintegration and dissolution study for all the formulation indicate that F1 showed rapid disintegration (56 sec) and drug release of 100% in 8 min. Based on melting point, solubility study, micromeritics properties, FTIR, XRD, DSC, SEM, disintegration and drug release study it can be concluded that the mouth dissolving tablet of GBC nicotinamide and saccharin co-crystal can be successfully prepared with significantly enhanced solubility, rapid disintegration and drug release.
Keywords: Glibenclamide (GBC), nicotinamide, saccharin, co-crystal, Co-crystallization, Mouth Dissolving Tablet.

1. INTRODUCTION:

Oral route is the most common preferred route for drug delivery due to convenience and ease of ingestion. Drug treatment is more effective with orally administration medication as compared with other routes of drug administration i.e. parenteral and hence patient compliance is better [1, 2]. Although orally administration of drug substance are highly depend on solubility of that compound in aqueous medium. However, since 1995 more than 90 % of drug approved have poor solubility. Many pharmaceutical companies identified that 40 % of new chemical entities in combinatorial screening program are poorly water soluble[3]. Solubility of any drug depends on physical form, temperature, pressure of system and solvent medium. In recent years many techniques have been developed to enhance the solubility of the drug. Enhancement of solubility can be done by different techniques viz., particle size, and crystal habit modification, drug dispersion in carrier complexation, salt formation, co solvent, co crystallization, and solublisation by surfactant etc[4].

Co-crystal has recently been rediscovered as powerful technique to modify key solid state properties of pharmaceutical such as solubility, stability and dissolution rate [6]. The present work is an attempt to formulate the mouth dissolving tablet of poorly water soluble GBC with enhance solubility and dissolution rate.

2. MATERIAL AND METHODS:

2.1 Materials

Glibenclamide was a generous gift from USV Ltd. Ethanol, chloroform, water, nicotinamide, sodium hydroxide, Sodium saccharin, sodium starch glycolate, croscarmellose, magnesium stearate, talc was purchased from Loba Chemie Pvt. Ltd. All the chemicals used in this study were of analytical grade.

2.2 Methods

2.2.1. Preparation of GBC co-crystal:

Liquid Assisted Grinding (LAG) Technique[7, 8]:

Physical mixture of GBC and co-crystal former (nicotinamide and sodium saccharin) in 1:1 stoichiometric ratio were prepared. To this 2 drops of solvent (ethanol) were added and mixed well using spatula. Then the resultant mixture was ground for 30 min in mortar and pestle. To avoid degradation of material, milling time was kept short. To enable better mixing the solids were scrapped from side of mortar wall at mid of grinding experiment. By using LAG method composition of different batches were prepared as shown in Table 1.

Solvent evaporation technique[7]:

This technique is the common way to synthesize co-crystals. In this method co-crystal components or co-crystal formers (nicotinamide and sodium saccharin) are taken in stoichiometric ratio and solubilize in ethanol. The resultant solution is allowed to evaporate slowly. The resulting co-crystal were filtered, washed with distilled water and dried. Composition of different batches prepared by solvent evaporation technique as shown in table1. This technique works on the principle that, when different

molecules of complimentary functional groups afford hydrogen bonds that are more favorable than each of the individual molsecular components. In this case, the co-crystal is likely to be thermodynamically favored.

Cooling Crystallization (CC) [7]:

The physical mixture of drug and co-crystal former (nicotinamide and sodium saccharin) in ratio 1:1 was added to 15 ml of dimethyl formamide 0 (DMF) and was heated till all solutes totally dissolved in a solvent. Then temperature was fall down by placing solution in refrigerator. Then co-crystal precipitate was filtered, washed and dried. Composition of various batches prepared by cooling crystallization method as shown in Table 1.

Table 1: Composition of batches by different methods

Method	Batch	CCF	Solvent
Liquid Assisted Grinding method (LAG)	C1	Nicotinamide	Ethanol
	C2	Saccharin Sodium	
Solvent Evaporation Technique	C3	Nicotinamide	Ethanol
	C4	Saccharin Sodium	
Cooling Crystallization (CC)	C5	Nicotinamide	Ethanol
	C6	Saccharin Sodium	

2.2.2. Preparation of mouth dissolving tablet

Tablets were prepared by direct compression method using single punch tablet machine (Lab press). All the ingredients shown in table were passed through sieve no. 60 and co- grounded in a glass pestle motor. The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. The mixed blend of excipients was compressed using a single punch tablet machine to produce flat faced tablets weighing 100 mg each with 3 mm thickness and 5 mm in diameter.

Table 2. Formulation of mouth dissolving tablet of optimized co-crystal tablet

Sr. no	Ingredients	Quantity (mg)					
	Formulation code	F1	F2	F3	F4	F5	F6
1	GBC co-crystal	6.4	6.4	6.4	-	6.4	-
2	Pure GBC	-	-	-	6.4	-	6.4
3	Crosscarmellose sodium	4.6	-	-	4.6	-	-
4	Crosspovidone	-	4.6	-	-	-	-
5	Sodium starch glycolate	-	-	5	-	-	-
5	Sodium saccharin	47.50	47.50	47.50	47.50	-	-
6.	Avicel	35.2	35.2	35.2	37	-	-
6	Magnesium Stearate	2.7	2.7	2.3	2.3	-	-
7	Talc	3.6	3.6	3.6	3.6	-	-
	Total	100	100	100	100	-	-

2.3 Evaluation Parameters:

Evaluation of tablet formulation done by using different parameters in two ways -

2.3.1 Preformulation Study: The mixture of drug and excipient were evaluated for organoleptic properties, melting point, solubility analysis, bulk density, tapped density, angle of repose.

2.3.2 Post compression study: It is done for evaluation of co-crystal tablet.

Friability [9, 10]:

The friability of tablets was determined by using Roche Friabilator (HKM-1601). Twenty tablets were initially weighed and transferred into friabilator and then it was operated at 25 rpm for 4 minutes. Friability was determined. It is expressed in percentage (%).

Formula-

Friability = Initial wt. – final wt. / Initial wt. ×100

Disintegration time [sec]:
The time required under a given set of conditions for a group of tablets to disintegrate into particles and will pass through a 10 # mesh screen. Disintegration time is useful in quality assurance tool for conventional dosage forms.

Wetting time [sec] [9]:
Five 10 cm diameter circular tissue paper was placed in petri dish. Then 1ml of methylene blue dye was added to petri dish and to this tablet was carefully placed on tissue paper. Wetting time was noted as time required for water to reach upper surface of tablet.

***Invitro* drug release [10]:**
Dissolution test carried out using USP Type II Paddle apparatus (Electro Lab). Tablet placed in 900 ml of Phosphate buffer pH 6.8 at 50 rpm, temperature 37 ± 0.5 ^{0}C. Sampling 0.5 ml withdrawn until 60 min at the fixed interval (2, 4, 6, 8, 10, 12, 15, 20….60 min). The solutions was filtered through whatmann filter paper and were analyzed by UV spectrophotometrically and the absorbance were recorded at 300 nm using UV spectrophotometer against a dissolution medium as a blank and calculate the drug release.

Scanning Electron Microscopy (SEM) HITACHI (S-3700N):
By using SEM surface characteristics of crystal was studied. By using aluminium stab with double sided adhesive tape and sputter coated with a thin layer of gold at 10 torr vacuum before examination the powder sample was mounted. The specimen was scanned with an electron beam of acceleration potential of 20 kV and the images were collected as secondary electron mode. SEM analysis has been performed for the pure drug and co-crystals.

Drug content:
Co-crystals of GBC with nicotinamide10mg was accurately weighed and transferred to volumetric flask (100 ml). It was dissolved properly in ethanol and diluted up to the mark with ethanol to obtain final concentration of 100 µg/ml and used as a stock solution (Stock solution I). One ml of stock solution I was withdrawn and further diluted by ethanol to give 10 µg/ml. This solution was scanned in the UV region of 230-360 nm. The spectrum was obtained to determine the maximum absorbance (λmax). They were analyzed by UV Visible spectrophotometer by measuring the absorbance at 300 nm.
Y= mx + c
Where,
Y= Absorbance,
M= slope,
C=intercept

3. RESULT AND DISCUSSION

3.1 PREFORMULATION STUDY

Physical characteristic of GBC

Table 3: Physical characteristic of GBC

Sr.no	Test	Observation	Inference
1	Color	White	Complies
2	Odour	Odorless	Complies
3	Surface Nature	Crystalline Powder	Complies

Melting point of GBC

Table 4: Melting point of GBC

Sr. no	Std. M.P of GBC	Practically found M.P of GBC	Inference
1	164-170 ^{0}C	164 ^{0}C	Complies

Melting point was found in the range of 164-170 ^{0}C. While as per standard literature, it is concluded it was in a pure state.

CHARACTERIZATION AND OPTIMIZATION OF DRUG AND CO-CRYSTAL:

Solubility study

1. Solubility of GBC in water: 0.0016 µg/ml
2. Solubility of GBC in ethanol: 4.021µg/ml
3. Solubility of GBC co-crystals with Nicotinamide (1:1): 39.81µg/ml

Table 5: Solubility study of GBC and co-crystal

Formulation	Solubility Conc. µg/ml			
	Water	6.8 Phosphate buffer	7.4 phosphate buffer	Ethanol
GBC (API)	0.0016	3.3912	0.7053	4.021
Co-crystal C_1	2.002	24.8	15.21	27.21
C_2	2.061	19.62	14.03	26.42
C_3	**2.012**	**29.46**	**17.02**	**39.17**
C_4	1.87	24.62	14.57	37.24
C_5	0.987	23.021	15.47	32.42
C_6	1.112	19.51	9.22	30.056

Out of them C_3 shows significant enhancement solubility, so batch no C_3 was used for extensive study.

Drug content:

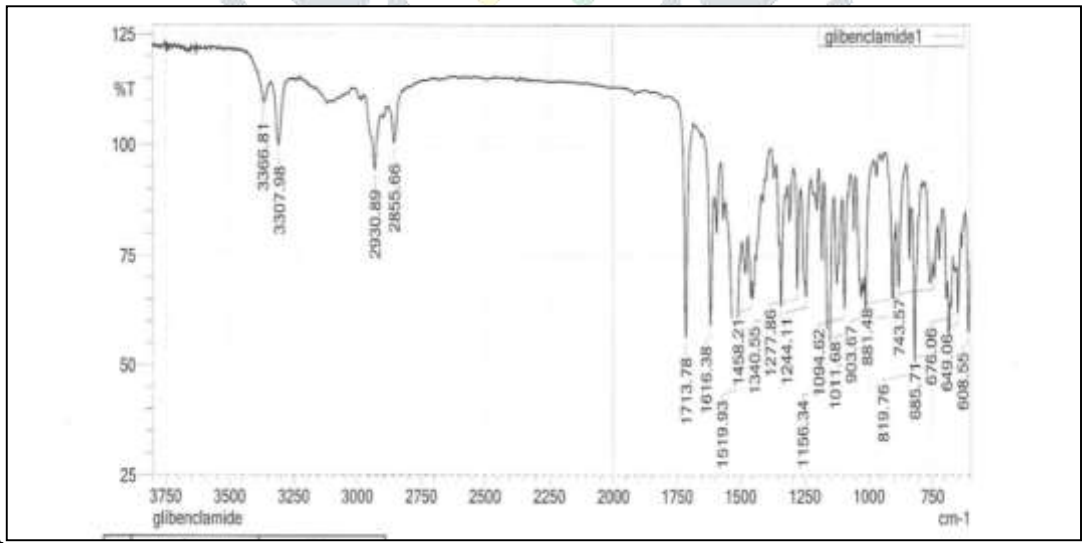
The drug content in each co-crystal was determined by UV- spectroscopy method. The maximum percent drug content for the all formulation was found to be 99.37 % and minimum percent drug content from the all formulation was found to be 96.45%. Formulation C3 and C4 show 99.37 % and 98.54 % drug content respectively as shown in table 6

Table 6: Drug content of different batches of co-crystal

Batch No.	Drug content (µg/ml)	% Drug content (%)
C1	15.762	98.02
C2	15.101	96.45
C3	16.007	99.37
C4	15.820	98.54

***FT*-IR:**

FT-IR spectra of GBC:

A 

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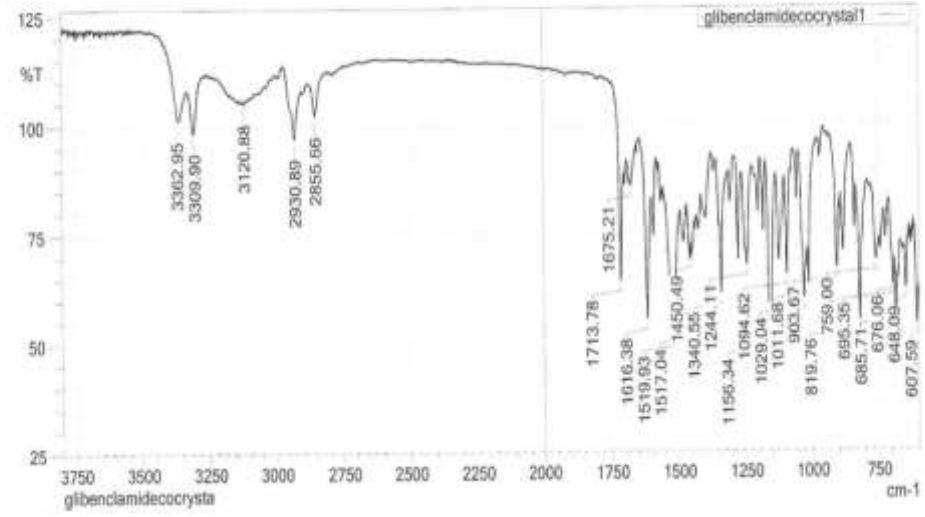

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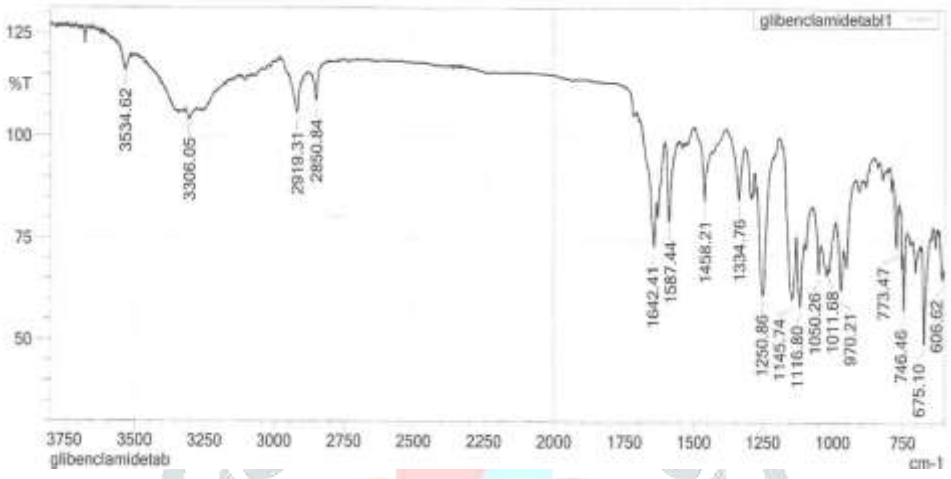


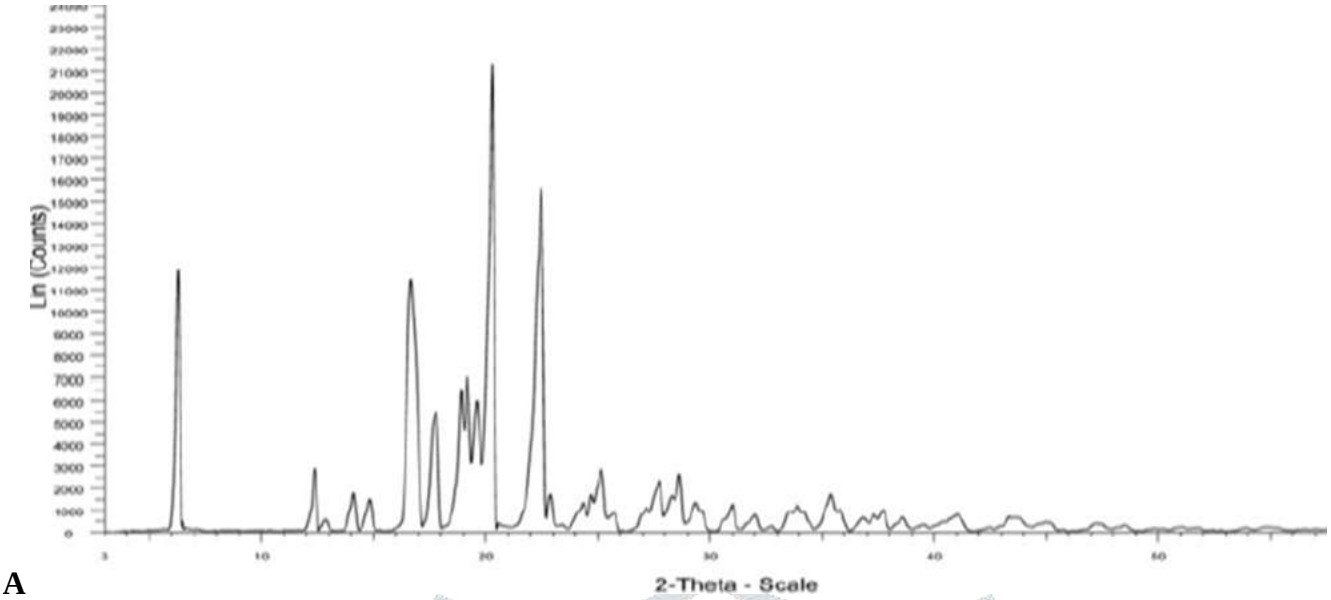
Figure 1: FTIR spectra of A) GBC B) GBC co-crystal (batch C3) C) Optimized GBC co-crystal tablet

Table 7: FTIR interpretation data of GBC

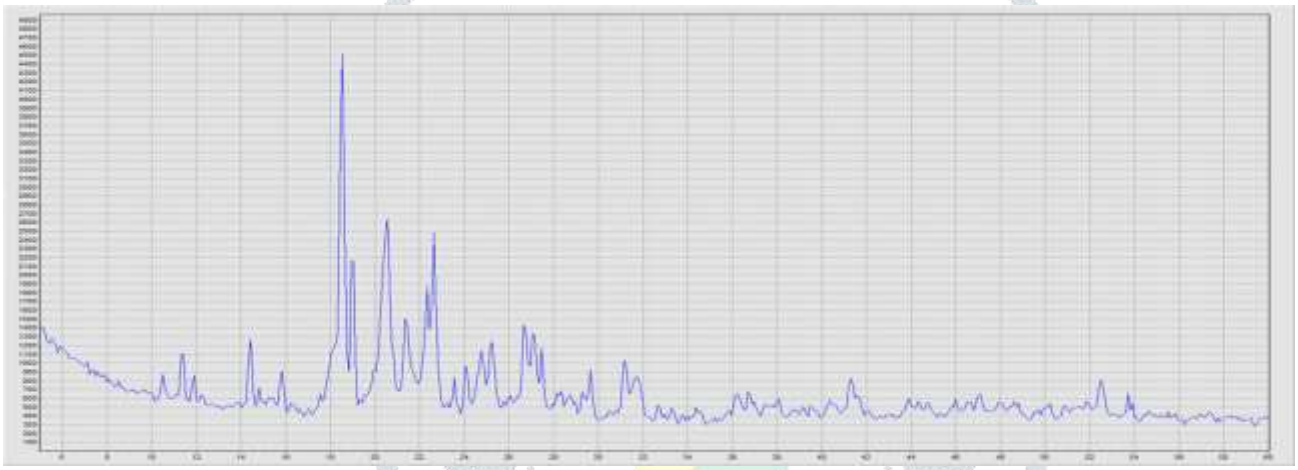
Assignment	Observed Frequencies cm^{-1}			Std. Frequencies in cm^{-1}
	A	B	C	
CH asymmetric stretching	-	-	-	5007
CH_2 stretching	-	-	-	4511
NH(amide)	3307	3309	3306	3314
CH=CH	3366.81	3362.95	3534.62	3529
C=C(ring)	2855.66	2855.66	2850.84	2830
C=C,S=O	-	-	-	2474
C=O	1713.78	1713.78	1642.41	1720,1715
$S=O_2$	1340.55	1340.55	1334.76	1316
C-C, C-N, C-O	1340.55, 1156.34, 1094.62	1340.55,1156 , 1094.62, 608.55	1334.76, 1116.80, 1050.26, 607	1332,1124,1028 ,569

FT-IR studies revealed presence of characteristic peaks (figure 4.1) of pure GBC & co-crystal of GBC with nicotinamide and GBC co-crystal shows peak at 3307 cm^{-1}, 3366.81 cm^{-1}, 3534.62cm^{-1}, 2850.84 cm^{-1}, 1340 cm^{-1}, 1334.76 cm^{-1}, 1156.34 cm^{-1}, 1094.62 cm^{-1},1050.26 cm^{-1}. There is also decrease in intensity of some characteristic peaks (3314 cm^{-1} and 1720cm^{-1}, 1124 cm^{-1}). The presence of additional peaks indicates that no chemical interactions occurred between drug and carrier

X-Ray Diffraction of Powder (XRPD)



A



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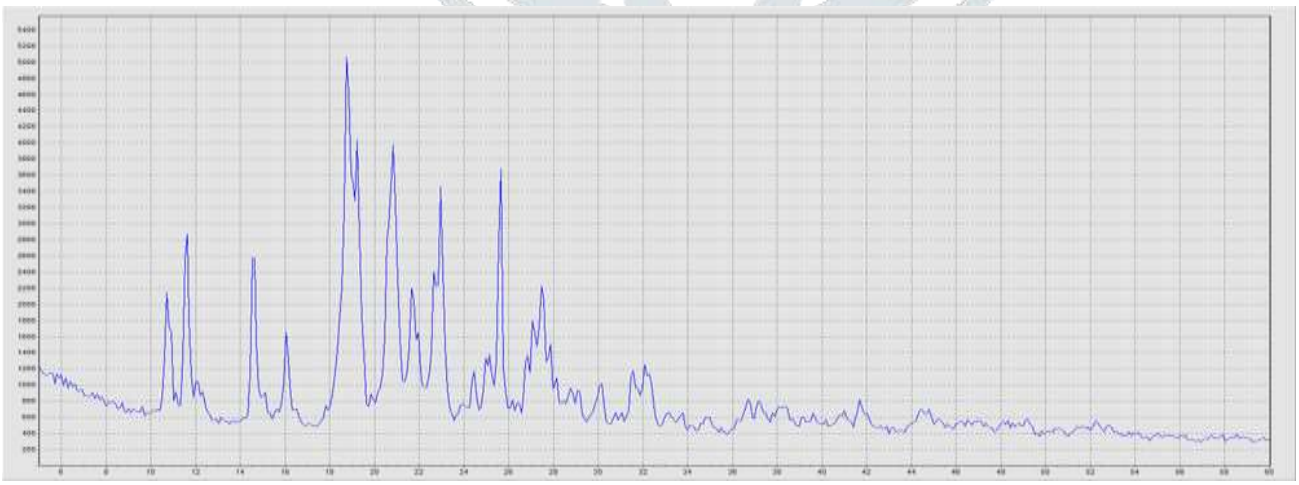

C

Figure 2: XRD spectra of (A) GBC; (B) GBC: nicotinamide co-crystals ;(C) GBC: saccharin sodium co-crystal

The Powder X-ray diffractometry (PXRD) patterns of pure GBC and its co-crystals are shown in figure 2. (A), (B) and (C). Generally PXRD techniques is used for determining polymorphism, change in crystal habit modification in drug crystals and generation of new crystal form. The HKL value of intense peak of std. GBC was found to be 031 and for GBC co-crystal was found to be 111 for intense peak. There is shifting of intense peak from21.50 to 18.73 and 18.70. The formation of different form was stated on the basis of changes in intensity of peaks in diffractogram. It can be explained on the basis of change in internal crystal structure having different crystalline habit than that of drug crystal habit. Moreover the different co-crystal habits might also be

predicted based upon change in the relative intensities of their PXRD peaks. The XRD pattern of prepared co-crystals exhibited change in both number and intensity of peaks compared to GBC at the specific angles indicating the crystalline or 'partial amorphization of the drug in the co-crystals. However, there are some intense peaks observed at angles other than drug specific angles, which were because of the crystalline nature of the co-crystal formers.

EVALUATION OF MOUTH DISSOLVING TABLET OF OPTIMIZED CO-CRYSTAL

Micromeritic Properties. [9]

Table 8: Micromeritic properties of GBC co-crystal

Parameter	Formulation			
	F1	F2	F3	F4
Mass	5.080 gm	5.061gm	5.072 gm	4.94 gm
Bulk volume	10 ml	9.8 ml	10.15ml	9.7 ml
Bulk Density	0.5080 gm/ml	0.5164 gm/ml	0.49 gm/ml	0.50gm/ml
Tapped volume	8.5 ml	9.1 ml	9.8 ml	9.2 ml
Tapped density	0.59 gm/ml	0.5561 gm/ml	0.51 gm/ml	0.5369 gm/ml
Angle of repose	29^0	34^0	34^0	42^0

Post compression tablet evaluation data

Table 9: Post compression tablet evaluation data.

Sr. No.	Formulation / Evaluation		F1	F2	F3	F4
1)	Weight Variation(mg)	T1	104±2.70	103.21±2.21	100.01±1.59	99.23±1.34
		T2	102.62±2.31	100.07±1.07	102.32±1.69	100.44±1.86
		T3	100.2±1.87	97.3±2.7	99.72±1.89	101.50±1.93
		T4	97.2±2.14	99.2±1.8	100.85±1.23	100.05±0.47
		T5	96.20±2.8	99.20±1.8	103.10±2.47	99.20±1.13
		T6	99.6±2.4	102.10±2.1	100.60±1.19	98.1±1.48
		T7	96.32±2.6	100.50±0.5	100.50±1.10	98.35±1.23
		T8	98.10±1.9	101.25±1.25	98.70±1.89	100.10±1.52
		T9	100.83±1.9	98.35±1.65	99±1.6	99.60±1.23
		T10	98.2±1.8	98.50±1.5	101.30±0.68	99.20±1.15
2)	Thickness(mm)	T1	3±0.014	3±0.012	3±0.013	0.3±0.013
		T2	3±0.012	3±0.013	3±0.011	0.3±0.014
		T3	3±0.014	3±0.014	3±0.012	0.3±0.013
3)	Diameter(mm)	T1	5±0.0011	5±0.0019	5±0.0022	5±0.0022
		T2	5±0.0017	5±0.0017	5±0.0017	5±0.0019
		T3	5±0.0022	5±0.0019	5±0.0019	5±0.0017
4)	Hardness(Kg/cm^2)	T1	2.2±0.1	2.3±0.2	2.6±0.4	2.9±0.5
		T2	2.1±0.5	2.3±0.2	2.6±0.4	2.9±0.5
		T3	2.2±0.1	2.2±0.1	2.6±0.4	2.9±0.5
5)	Friability (%)		0.9	0.82	0.7	0.7
6)	Disintegration(Time)	T1	56	64	64	67
		T2	58	60	63	68
		T3	56	63	63	65
7)	Wetting Time(Sec)	T1	32	42	48	52
		T2	33	45	44	56
		T3	36	47	45	57
8)	Drug Content (%)		99.0	99.0	99.0	99.0

Dissolution study:

Table 10: Dissolution studies of GBC co-crystal and tablet

Time (min)	% Drug release					
	GBC co-crystal tablet			GBC tablet	GBC co-crystal	API
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	17.36	17.22	14.01	15.72	3.12	1.02
4	47.7	34.12	36.12	20.01	7.24	3.21
6	92.2	69.11	54.21	37.23	19.24	6.42
8	100	93.52	88.7	56.23	34.16	9.26
10	-	100	100	82.2	67.03	10.24
15	-	-	-	100	86.44	12.20
20	-	-	-	-	95.8	15.15
25	-	-	-	-	99.06	19.21
30	-	-	-	-	100	23.4
35	-	-	-	-	-	27.23
40	-	-	-	-	-	32.32
45	-	-	-	-	-	39.2
50	-	-	-	-	-	47
55	-	-	-	-	-	53.2
60	-	-	-	-	-	67.21

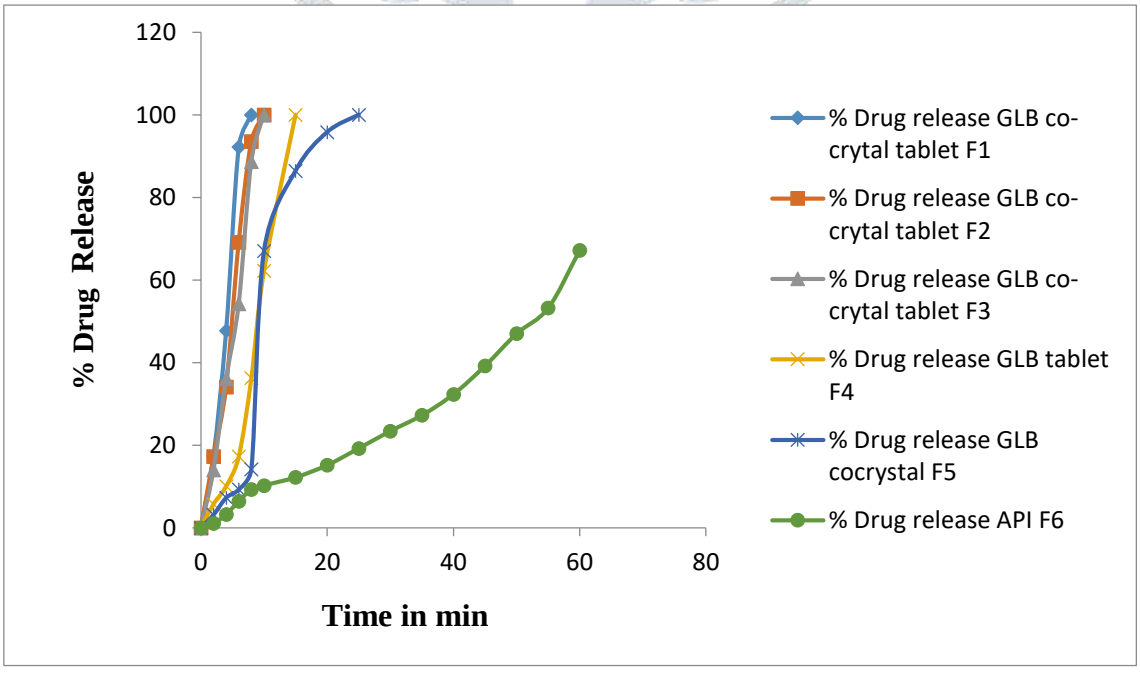

Figure 3: Graphical presentation of % drug release of GBC in formulation

The release of GBC from 6 formulations was plotted as cumulative percent drug release vs. Time in minutes as shown in figure 3. As shown in the figures, more than 100 % of the drug was dissolved out of co-crystal tablet formulation in 8-12 min while it was just 15 % in case of pure form (f6). F1, F2 and F3 showed better dissolution properties as compared to rest of the formulations which may be due to solubilize.

Discussion:

In the present investigation GBC was employed in the co crystal system for extending drug dissolution rate and absorption by enhanced solubility. In ethanol solubility study of GBC & its co crystal result reveal that GBC 4.021 µg/ml, GBC co crystal with nicotinamide 39.17 µg/ml & which suggest improvement in solubility of co crystal than pure drug as shown in table 5.

Conclusion:

Fast dissolving GBC co-crystal formulation could be prepared by using any of superdisintegrant. In vitro drug dissolution studies of formulation F1-F6 were carried out in 6.8 pH buffer solution. It is concluded that among this F1 formulation was found to be most promising and optimized formulation which contain crosscarmellose sodium and it shows 56 sec disintegration time and about 100 % drug release at the end of 8 min. So it satisfies all the criteria as Fast Dissolving Tablet.

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