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Development and Optimization of Oral Fast dissolving films of Glibenclamide

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ABSTRACT

The objective of the work was to design oral fast dissolving films of a Glibenclamide meant for management of chronic disease like type-2 diabetes mellitus .Various batches of FDFs were developed by the solvent casting method using water soluble polymers like Guar gum ,Xanthum gum, Sodium alginate, HPMC K4 as film formers; Propylene glycol as plasticizers; Sodium starch glycollate as super disintegrating/channeling agent; Citric acid as salivary stimulating agent ; Sodium saccharin as a sweetener and vanillin as flavouing agent. The FTIR studies showed that there is no interaction between the drug and polymer The formulation containing drug with HPMC K4 with propylene glycol as plasticizer showed lowest disintegration time, more uniform and faster dissolution profile with in 6 minutes with drug release 98.5%, and had better taste, good in stability studies.

Keywords : Diabetes mellitus, Fast dissolving films, HPMC K4, Glibenclamide , propylene glycol

INTRODUCTION

Oral drug delivery has been known as the most widely used route of drug administration when compared to all the other routes that have been explored for delivery of different dosage forms to systemic circulation. Although several technologies are available, few have reached commercial marketed products. Several methods are employed in the preparation of oral fastdispersing tablets, such as modified tabulating systems, floss, or Shear form formation by application of centrifugal force and controlled temperature, and freeze-drying[1]. Although oral film systems, the third class, have been in existence for a few years, they have recently become the new area of interest in fastdissolve pharmaceutical drug delivery. Dissolvable oral thin films (OTFs) or oral strip (OS) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to OTF formats[2]. Today, OTFs are a proven and accepted technology for the systemic delivery of APIs for over the counter (OTC) medications and are in the early- to mid-development stages for prescription drugs. A solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form. Recent study showed that 26% of 1576 patients had trouble in swallowing tablets. The most common complaint was tablet size, followed by surface, form and taste. To overcome the difficulties experienced by geriatric and paediatric patients in swallowing conventional oral dosage forms, oral fast dissolving films were developed[3]. They undergo rapid disintegration in the salivary fluids of the oral cavity in less than a minute, where they release the drug which is swallowed orally with the saliva and the absorption of drug takes place in the gastro-intestinal tract. Glibenclamide is a BCS class II oral hypoglycaemic agent that is widely indicated for the management of type 2 diabetes mellitus and has the ability to pass through the gastrointestinal mucosa. Glibenclamide, also known as glyburide, is a medication used to treat diabetes mellitus type 2. It is recommended that it be taken together with diet and exercise. It may be used with other antidiabetic medication. It is not recommended for use by itself in diabetes mellitus type 1. The need to rapidly maintain glucose levels in the body is subject to design systems that can release drugs into the systemic circulation in a very short time[4]. A variety of polymers can be used alone or in combination to obtain the desired strip properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation[5]. The robustness of the strip depends on the type of polymer and the amount in the formulation. On the other hand, fast dissolving strip dosage form should have the property to disintegrate in seconds when placed in mouth and deliver the drug to the oral cavity instantaneously. The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations[6]. Generally, acids which are used

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in the preparation of food can be utilized as salivary stimulants.Monographs of common dosage forms are provided by the pharmacopoeias (e.g., Ph. Eur., USP). Even though dosage forms for application in the oral cavity such as Medicated chewing gums, Oro mucosal preparations, Oro dispersible tablets or oral Lyophilizates are included, monographs and specifications for oral films of diverse dissolution kinetics has not yet been established. There are inadequate pharmaceutical technical procedures for analysis in development and quality control of oral films as well[7]. For instance, disintegration and dissolution testing procedures may be provided, but the recommended conditions such as volumes of media do not reflect the natural conditions in the oral cavity.

MATERIALS AND METHODOLOGY:

Glibenclamide was obtained as a gift sample from Hetero Pharmaceuticals Pvt Ltd, Hyderabad India, Guar gum, Sodium alginate, Polyethylene glycol 400, Sodium starch glycolate, Vanillin, Sodium Saccharin these are all was procured from Research -lab fine Chem industries Mumbai.

FTIR Studies

As a part of the pre formulation studies, drug-polymer interaction study was performed by using Fourier Transform Infrared Spectroscopy [FTIR]. The FTIR spectra of Zolmitriptan, HPMC E5, and their physical mixture were recorded individually. The samples were scanned in the range of 400-4000cm-1[8].

Preparation of Glibenclamide fast dissolving oral films:

It was prepared by using specified polymer by solvent casting method. The specified amount of polymer was weighed and dissolved in specified amount of water for overnight to get a uniform dispersion of different % (w/v) solutions. Drug, sodium starch glycolate, vanillin was dissolved in specific amount of water in a beaker. The drug solution was added to the polymer solution and mixed using magnetic stirrer for 1 hour. The resulting solution was degassed so as to remove any bubbles formed.

The bubble free solution was casted on to a Petri dish of surface area 30 cm^2. It was dried for 24 hours at room temperature. The film was removed from the Petri dish very carefully and observed for any imperfections. Film that was clear and bubble free was selected for further studies[9]. Film of area 2.25 cm^2 (1.25 X 1.25) was cut and stored in a butter paper covered with aluminium foil and stored in desiccators. The formulation of the preparation is shown in the table no :1

Table 1:Composition of various fast dissolving oral films formulations:

S.NO	Ingredients [mg/film]	F1	F2	F3	F4	F5	F6	F7	F8
1	Glibenclamide	5	5	5	5	5	5	5	5
2	Guar gum	5	7.5	-	-	-	-	-	-
3	Xanthan gum	-	-	5	7.5	-	-	1	1.5
4	HPMC K4	-	-	-	-	5	7.5	-	-
5	Sodium alginate	-	-	-	-	-	-	5	7.5
6	Citric acid	2	2	2	2	2	2	2	2
7	Sodium Starch Glycolate	2	2	2	2	2	2	2	2
8	Propylene glycol	25	25	25	25	25	25	25	25
9	Vanillin	1	1	1	1	1	1	1	1
10	Sodium Saccharine	1	1	1	1	1	1	1	1
11	Water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Evaluation Of Mouth Dissolving Films [10,11]:

Appearance - All prepared films were checked for their appearance either they are transparent or opaque or presence of air bubble.

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Thickness uniformity:
The thickness of the film was measured using digital Vernier Calliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different Spots of the film and average was taken and Standard Deviation was calculated.

Weight variation of the film:
2×2cm of the film was cut at three different places in the caste film**.** The weight of each filmstrip was taken and the weight variation was calculated

Folding endurance:
Folding endurance of the film was determined repeatedly by folding a small strip of film (2 cm x 2 cm) at the same place until it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.

Surface pH:
The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 1 h. pH was noted with the electrode of the pH meter.

Drug content[12]:
This parameter was determined by dissolving film of 2 × 2 cm diameter (an area of 4 cm2) containing 5 mg of glibenclamide in 50 ml simulated salivary fluid with occasional shaking. Filtration was carried out to remove insoluble residue, 1 ml of the filtrate was diluted to 10 ml with simulated salivary fluid (pH 6.8). The absorbance was measured at 293 nm using an UV spectrophotometer.

Disintegration Time[13]:
In vitro disintegration time was determined visually in a Petri dish containing 25 ml of pH 6.8 simulated salivary fluids with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

Stability studies [14]:
The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized formulation was sealed in aluminium packaging laminated with polyethylene. Sample were kept at 40 ^{0}C and 75% RH for 3 months. At the end of the study period, the formulation was observed for change in physical appearance, colour, drug content and drug release characteristics. The optimized formula was subjected for the stability studies. And the results are shown in the Table no :4 and 5

Invitro dissolution rate:

Invitro dissolution studies were carried out in USP type I apparatus (basket), 900 ml of phosphate buffer pH 6.8 was used as dissolution media at 37+0.5 ^{0}c. 2×2cm^2 OFDF's was placed in dissolution basket. Dissolution was carried out by withdrawing aliquot of 5ml samples at regular time intervals 1, 2, 3, 4 and 5min time intervals and the fresh medium was replaced. Samples were filtered and diluted suitably and analysed by using a UV spectrophotometer at 293nm[4].

Differential scanning calorimetry (DSC):
Pure Glibenclamideand the prepared film subjected to DSC studies using TA instruments Q20 model. Empty Aluminium sample pan was used as reference material. Samples are scanned at the rate of 100 C/ min from room temperature to 300° C where in nitrogen gas is used as purge gas at a flow rate of 50mL/min. the results are shown in the Fig no 3 and 4.

Powder X-ray diffraction (XRD) studies:
Pure Glibenclamide, and the prepared film were subjected to XRD studies. The scanning rate employed was 2° per min, and samples were analysed between 2θ angles 10-80° a voltage of 40kB and a current of 30aM.the results are shown in the Fig no 5 and 6.

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RESULTS & DISCUSSION

FTIR studies:

The comparison of the IR spectrum exposed that there is no appreciable change in the positions of characteristic absorption bands of groups and bonds. The spectra of these, even though slightly differ in appearance but no change is observed in the positions of the bands in the spectra. This clearly suggests that the drug remains in the same form even in its formulations representing that there is no interaction between the drug and polymer used for the study. The results are shown in the Fig :1 and 2

Appearance: The appearance of all the films was uniform having transparent in appearance and having smooth surface.

Thickness uniformity: Thickness of the films was found to be between 0.12±0.02 to 0.28±0.01 mm. A very low standard deviation values indicates that the method used for the formulation of film is reproducible and give film of uniform thickness and hence dosage accuracy Weight in each film can be ensured. The results are shown in Table no :2

Variation of the film: All batches do not have uniform amount of ingredient in it, so their weight was varied. Weight uniformity of the films was found to be between 42.6 ±0.47 to 57.16 ±0.87mg. The results are shown in the Table no :2

Folding endurance: Folding endurance measurement gives an indication of brittleness of the film. The value depends on hydrophilic polymer as well as plasticizer concentrations used. Folding endurance test result indicated that the film would not break and would maintain their integrity. Folding endurance for all the formulation was found to be more than 150 which was satisfactory to reveal good film property. Folding endurance of the films was found to be between 110±6.02 to160±2.15and the results are shown in the Table no 2 .

Surface pH: The surface pH of the films was ranging from 6.71±0.2 to 6.85±0.2. Since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity.

Drug content: All the formulations of Glibenclamide containing HPMC K4M and Polyethylene glycol polymers show uniform drug. The results are shown in the Table no :2

Disintegration Time: The disintegration time of films was found to be decreased with increase in the concentration of the polymer. When placed over the tongue, the film dissolved instantly. The disintegration time of formulation F5 film was lowest, so they release drug faster than other formulation. And the results are shown in the Table no :2

In-vitro dissolution studies: In vitro drug release study was carried out using USP dissolution apparatus, type-I. Being the fast-disintegrating formulations the release rates of all the formulations were very rapid. Formulation F5 released glibenclamide completely faster. This may be due to HPMC K4M and propylene glycol that result in increased wettability and penetration of water into the film matrices and hence increased diffusion of the drug. Whereas release rates of other formulation were comparatively slowest. The results are shown in the Table no :3

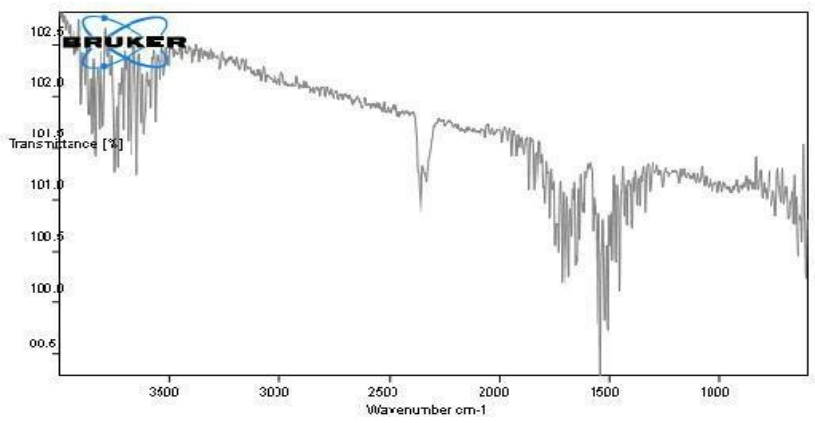

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Fig 1: FTIR Studies of Glibenclamide (pure drug)

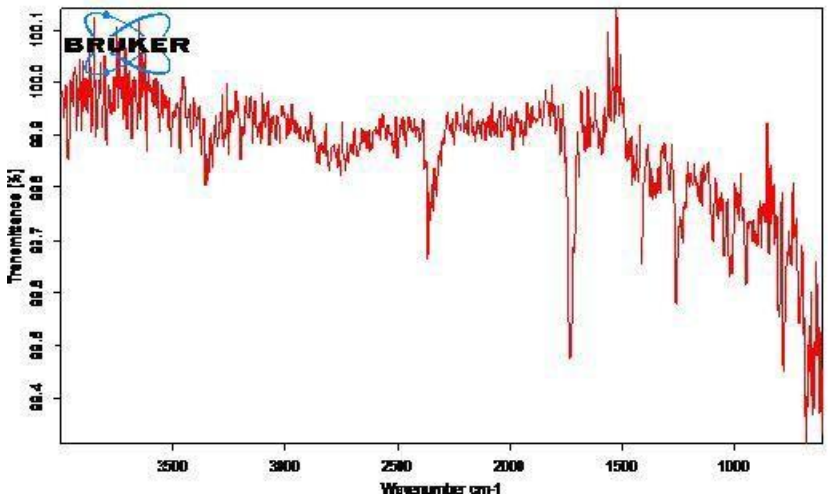

Fig2: FTIR Studies of Glibenclamide + HPMC K4

Table 2: Evaluation of fast dissolving oral films

Formulation code	Weight variation (mg)	Thickness (mm)	Tensile strength (mpa)	Folding endurance (no of folds)	Disintegration time (sec)	Drug content (%)
F_1	43.06 ±0.51	0.23±0.025	3.83±0.02	160±2.15	45±2	99.4%
F_2	55.75 ±0.56	0.28±0.01	4.22±0.02	151±3.60	53±2	97.2%
F_3	44.8 ±0.6	0.19±0.01	3.76±0.06	134±8.14	46±1	97.6%
F_4	57.16 ±0.87	0.24±0.01	3.59 ±0.01	152±11.01	48.33±1.15	94.8%
F_5	42.4 ±0.43	0.12±0.02	1.80±0.01	175±6.25	35.33±3.05	95.2%
F_6	53.2 ±0.65	0.15±0.01	2.12±0.02	110±6.02	48.33±1.52	92.8%
F7	42.6 ±0.47	0.22±0.02	2.53±0.02	142±2.08	49±1	96.4%
F8	53.98 ±0.41	0.28± 0.01	2.99 ± 0.01	157 ± 4.16	58.33 ± 0.57	95%

Table3: Comparative evaluations of *In-vitro* dissolution profiles of fast dissolving oral films

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Time in min			Cumulative % of drug release					
	F1	F2	F3	F4	F5	F6	F7	F8
1	11 %	9.2%	10.3%	12.6%	27%	23%	9.4%	9%
2	25 %	24.6%	24%	24%	46%	42%	18%	14.6%
3	42 %	35.3%	40.8%	32%	61.3%	54.5%	34%	29%
4	54.5%	46.9%	50.3%	40.8%	79.3%	69.3%	45%	40%
5	68.5%	62%	62%	48%	92.8	82%	54%	45%
6	76.3%	72%	70%	59%	98.5%	92.9%	61%	57%
7	85.3%	80.3%	75.3%	72%	-	95.8%	69%	64%
8	95.3%	86.3%	82%	82%	-	96.8%	78%	72%
9	96.5%	90.3%	92.9%	89%	-	-	85%	79%
10	96.4%	93%	93.4%	92.5%	-	-	92%	90%
11	96.8%	94.1%	94%	95%	-	-	94.8%	93%
12	97.3%	94.9%	95.5%	96.5%	-	-	94.9%	94.8%
13	97.5%	95.6%	96.6%	97.6%	-	-	96.3%	95.5%
14	97.8%	95.9%	97%	97.8%	-	-	-	96.4%
15	98.6%	96.4%	-	98%	-	-	-	97.5%
16	-	97.1%	-	-	-	-	-	97.6%
17	-	97.5%	-	-	-	-	-	98%
18	-	97.6%	-	-	-	-	-	-
19	-	97.8	-	-	-	-	-	-
20	-	98	-	-	-	-	-	-

Table4: Stability studies for F5

Parameters	Stability data	
	Initial	3 months (40^0C±75%RH)

Time (Days)	Appearance	*In-vitro* Disintegration Time (Sec)	% CDR
Initial (0Days)	Transparent and Acceptable	34.33 ± 3.09	99.5%
1 month (30 Days)	Transparent and Acceptable	33.05 ± 2.96	97%
3 months (90 Days)	Transparent and Acceptable	31 ± 2.69	98.6%

Thickness(mm)	0.56±0.07	0.56±0.008
Folding endurance	22±0.01	21±0.01
Tensile strength(gm/cm^2)	60.3	59
Invitro disintegration(sec)	20	21

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In vitro dissolution (%)	98.4	98.1

Table no 5: Stability studies of F5

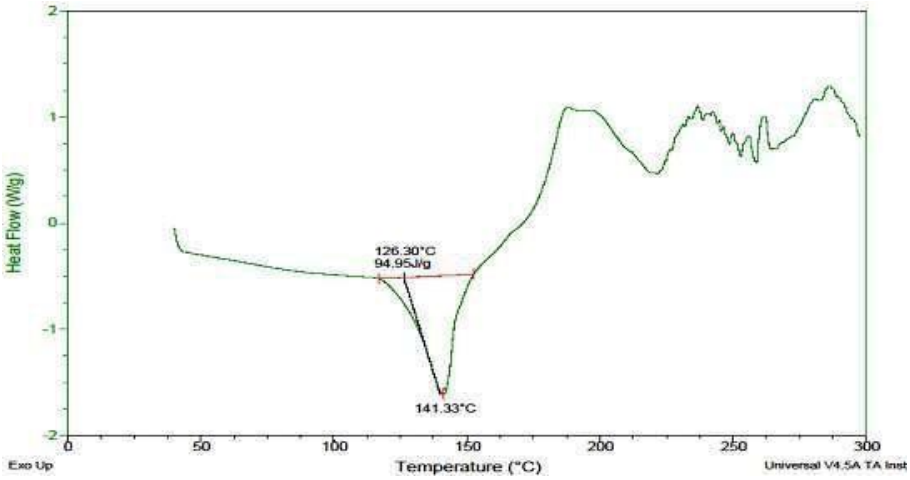

Fig 3: DSC spectra of Glibenclamide oral film

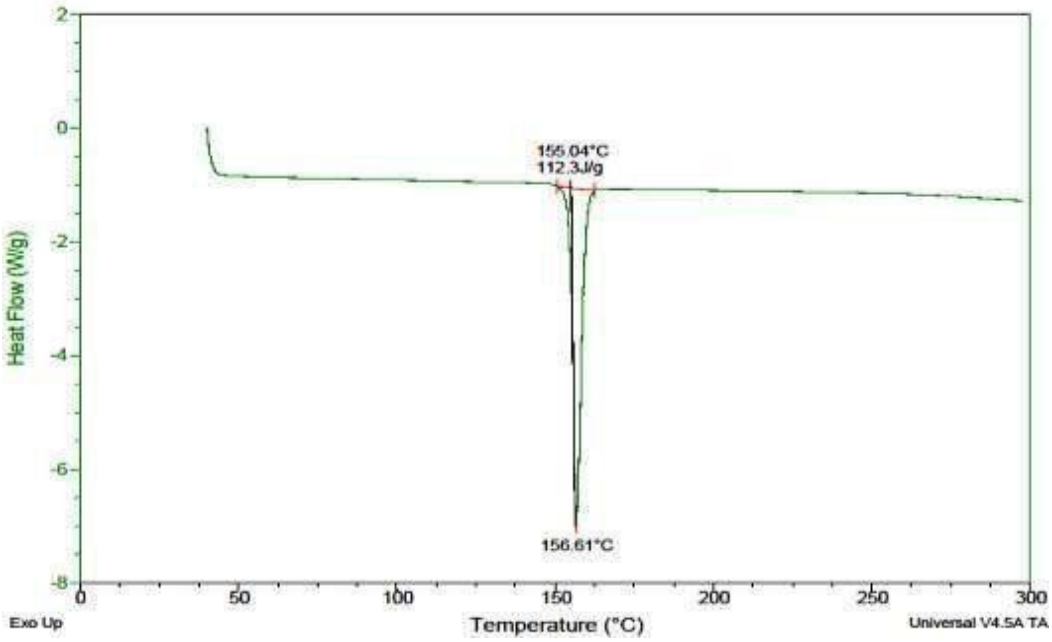

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Fig 4 : DSC spectra of Glibenclamide pure drug

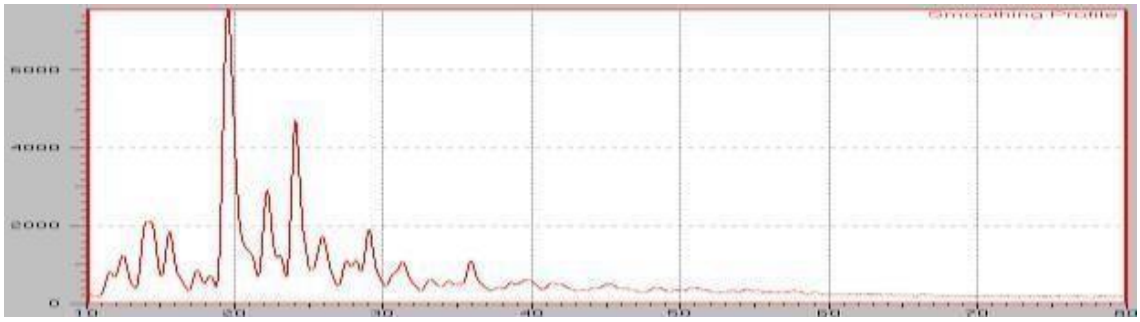

Fig 5 : XRD: Oral fast dissolving film

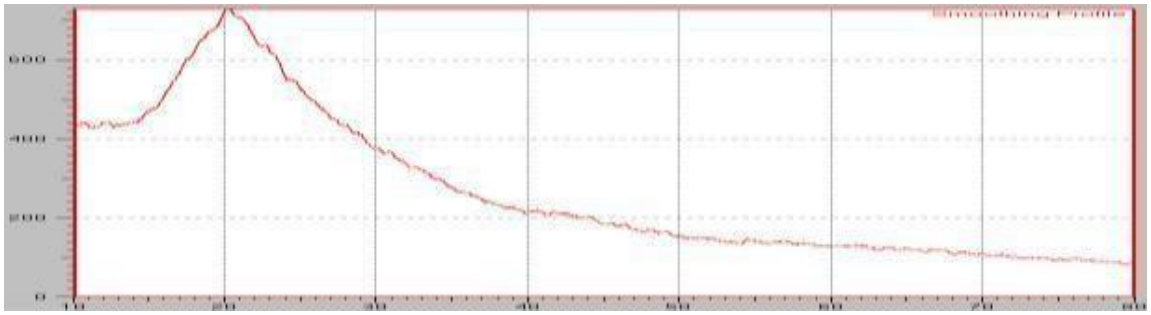

Fig 6 : XRD: Glibenclamide pure drug

CONCLUSION

Pre formulation study involving FTIR study showed no interaction between drug and polymer. Fast dissolving films prepared in the study exhibited good film characteristic features as indicated by thickness measured, folding endurance, and mouth dissolving time, percentage moisture loss,tensile strength and drug content.

The prepared films were found to be uniform, flexible and 98.5% of drug was released from F5 film within 6 minutes which was desirable for fast absorption. Later stability studies of this formulation were indicating that there was no degradation of the formulation at high temperature and humidity conditions. It was indicating that this formulation was stable.

From the present investigation it can be concluded that oral thin film formulation can be a potential novel drug dosage form for geriatric and also for general population. Hence fast dissolving films of Glibenclamide were found to be suitable for eliciting better therapeutic effect in the treatment of Diabetics.

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