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Formulation and Evaluation of Mouth Dissolving Tablets of Gliclazide Containing Fenugreek Seed Powder

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ABSTRACT

Tablet is the most popular dosage form of all existing dosage forms , but in some cases due to the large size of dosage forms, in case of uncooperative, pediatric and dysphasia patients, it may create problems, to overcome this , a new form of dosage form is developed, which is known as fast dissolving tablets or mouth dissolving tablets. These dosage forms are also used to attain instant higher concentration of drug in body for immediate actions. Gliclazide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Fenugreek seed powder was added to this formuation because of its various pharmacological benefits as well as its self disintegrating property. Mouth dissolving tablets were prepared using direct compression method .Formulations were optimized to develop tablets having minimum possible disintegration time. Tablets were evaluated for hardness, weight variation, friability, wetting time, disintegration time and stability. The main objective of the present research is formulation and evaluation of mouth dissolving tablets of gliclazide which is an antidiabetic drug ,containing fenugreek seed powder as disintegrating agent.

Keywords : mouth dissolving tablets, gliclazide, fenugreek seed powder, solid dispersion, evaluation .

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INTRODUCTION

Oral routes of drug administration have wide acceptance among 50-60% of total dosage forms. Solid dosage forms are popular because of their ease of administration, accurate dosage ,self medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is difficulty in swallowing. Sometimes people experience inconvenience in swallowing conventional dosage forms as tablet when water is not available, in the case of the motion sickness and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reasons tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.[1]

Mouth dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. Bioavailability of drug in such cases is significantly greater than those observed from conventional tablet . The disintegration time for good FDT's varies from several seconds to about a minute.[2,3]

Need for MDT [4]

1. Patients: MDT aims to develop non invasive delivery systems that can be used for patients having swallowing problems like in case of geriatrics and pediatrics patients .
2. Industry: The current need of industry to provide improved solubility, stability, bioavailability enhancement, along with safety and compliance.
3. Market: By 2010 200 drugs lost patent, so it becomes necessary to formulate into a new and improved form and to extend market exclusion.

Superdisintegrants :

Disintegrants play a major role in the disintegration and dissolution of MDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rate. The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, whereas if concentration of superdisintegrant is above critical concentration, the disintegration time remains almost constant or even increases. Sodium starch glycolate, Ac-di-sol(crosscarmellose sodium), Crospovidone, Microcrystalline cellulose, Pregelatinised

starch are some of examples of disintegrants.[5,6,7]

Mechanism of action of disintegrants: [8,9,10]

a. By capillary action

b. By swelling

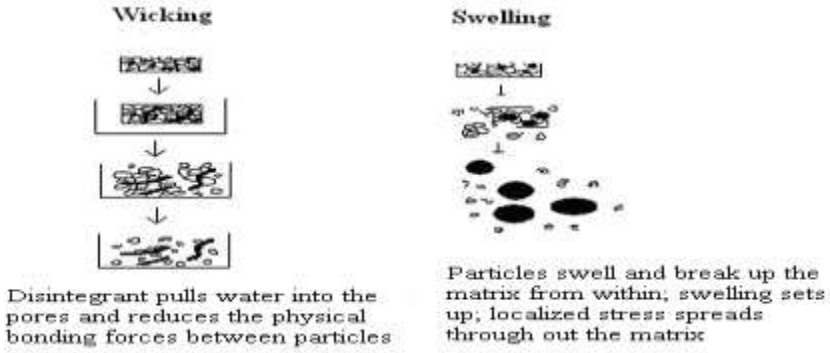

Figure1 : Disintegration of Tablet by Wicking and Swelling

c. Because of heat of wetting (air expansion) : When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet.

d. Due to release of gases : Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet.

e. By enzymatic reaction : Here, enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration.

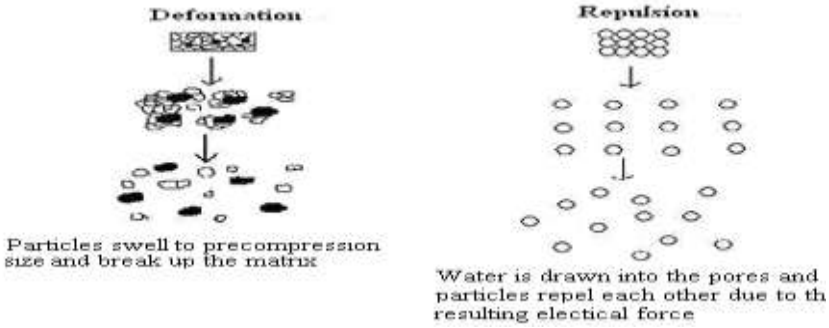

Figure 2 : Deformation And Repulsion

f. Due to disintegrating particle/particle repulsive forces

g. Due to deformation

Fenugreek Seed Powder: [10,11,12,13]

Fenugreek has been used since ancient times both as a food and medicine by the people living on the shores of Mediterranean and across Asia. Fenugreek seeds are used for removing dandruff.

Fenugreek is rich in Vitamin A and D. It also contains oil that resembles cod liver oil. Fenugreek is rich in minerals and is high in protein. It has Vitamin B1, B2, B3 and contains chlorine, lecithin and iron. Fenugreek can minimize the menopause symptoms, as it contains chemicals like diosgenin and estrogenic isoflavone, which closely resembles the female hormone estrogen. Fenugreek is considered as a great aid to digestion. Fenugreek can loosen up cough and mucus, thereby helping to expel them from the body. By lowering the level of cholesterol, it can reduce the risk for developing heart and cardiovascular diseases. Diabetes, both type 1 and type 2 diabetes can be treated by using fenugreek seeds. Fenugreek is an effective home remedy for heartburn and acid reflux disease. Fenugreek can also help to control acne by purifying the blood. Fenugreek is known to stimulate perspiration that helps to bring down body temperature or reduce fever. However, like other herbal medicine, fenugreek should also be used in moderation. Excessive intake of fenugreek can cause nausea, stomach upset and other side effects.

Gliclazide : [15,16,17]

Gliclazide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It belongs to the sulfonylurea class of insulin secretagogues, which act by stimulating β cells of the pancreas to release insulin. Sulfonylureas increase both basal insulin secretion and meal-stimulated insulin release. Medications in this class differ in their dose, rate of absorption, duration of action, route of elimination and binding site on their target pancreatic β cell receptor. Sulfonylureas also increase peripheral glucose utilization, decrease hepatic gluconeogenesis and may increase the number and sensitivity of insulin receptors. Gliclazide has been shown to decrease fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin (HbA1c) levels (reflective of the last 8-10 weeks of glucose control). Gliclazide is extensively metabolized by the liver; its metabolites are excreted in both urine (60-70%) and feces (10-20%)

MATERIALS AND METHOD :

Material used :-

1. Gliclazide (obtained as a gift sample from akum laboratory , haridwar)
2. Crosspovidone
3. Crosscarmelose sodium
4. Sodium starch glycolate
5. Fenugreek seed powder

6. Pregelatinized starch
7. PEG-6000
8. Camphor
9. Menthol
10. Magnesium stearate
11. Purified talc
12. Ethanol
13. Chloroform
14. Calcium chloride
15. Saccharin

METHOD :[18]

Method of Preparation

Tablets are prepared by solid dispersion technique or direct compression technique. It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially Tablet disintegrants and sugar-based excipients. Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. In many fast dissolving tablet technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution. The introduction of superdisintegrants and a better understanding of their properties have increased the popularity of this technology. Tablet disintegration time can be optimized by concentrating the disintegrants. Below critical concentration, tablet disintegration time is inversely proportional to disintegrants concentration. Suitable formulations are prepared by varying the compositions by keeping the API (active pharmaceutical ingredient) constant and varying the percentages of excipients that goes into the formulation at different stages of tablet preparation.

Preparation of solid dispersionof gliclazide :

Calculated quantity of drug was dissolved in chloroform and mixed with the solution of PEG-6000 prepared in ethanol. The mixture was stirred with a glass rod for 15 minutes and evaporated to dryness for 48 hours in a desiccator (fused calcium chloride was used) at room temperature to remove the solvent. The lump so obtained was powdered in a mortar. The powder was passed through sieve no#60. The powder was stored in a screw capped amber colour vial until used.

Preparation of fast dissolving tablets:

Required quantity of optimized solid dispersion (drug: polymer,1:2 ratio) was triturated with different proportions of superdisintegrants viz Crosscarmellose,Sodium starch glycolate , Crosspovidone, fenugreek seed powder. Mixed with other ingredients such as pregelatinized starch (filler) saccharin (sweetener) and camphor (sublimating agent) in geometric ratio of their weight and powdered in a mortar. The blend was transferred to a poly bag; purified talc and magnesium stearate were added and mixed for 10 minutes. The blend was directly compressed to obtained flat rounded tablets weighing ~200mg. Sublimation of camphor from the tablets was performed under vacuum at 700C for 8 hours

Evaluation :

Bulk characterization :[19,20]

Angle of Repose:

The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the3 following formula,

$$\mathbf{Tan\ q = h / r}$$

Therefore q = tan -1 h / r

Where, q =- angle of repose

h =height of the cone

r = radius of the cone base

Loose Bulk Density: Loose bulk density is defined as the ratio of weight of blend in Gms to the loose bulk volume (Untapped volume) in cm. loose bulk density is given by

$$\mathbf{Loose\ bulk\ density\ p\ u = Weight\ in\ gms / Vb}$$

Where, Vb = Bulk volume (untapped volume)

Tapped bulk density is defined as the ratio of weight of blend in gms to the tapped bulk density in cm. tapped density is given by

$$\mathbf{Tapped\ density = weight\ in\ gms / Vt}$$

Carr's Index And Hausner's Factor :

It indicates powder flow properties. It is expressed in percentage and is given by

$$\mathbf{I = (Dt - Db)/ Dt * 100}$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Hausner's ratio:

Hausner's ratio is an indirect index of ease of powder flow. It was calculated by the following formula.

Hausner's ratio = Dt / Db

Where, Dt is the tapped density; Db is the bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Evaluation of tablets: [21,22,23,24]

General Appearance:

The general appearances of a tablet include size , shape, colour, taste, odour, surface texture.

Size, Shape, Thickness And Diameter:

The size and shape of tablet can be dimensionally described, monitored and controlled. thickness of tablets is an important characteristic for appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. ten tablets were taken and their thickness measured by vernier caliper.

Uniformity of Weight:

In Indian pharmacopeia procedure for uniformity of weight was followed, ten or twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. the average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

Hardness of Tablets:

Hardness of tablets is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion, or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto hardness tester.

Friability of Tablets:

Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. the tablets were rotated in the friabilator for atleast 4 minutes. at the end of test tablets were dusted and reweighed, the loss in the tablet is the measure of friability and is expressed in percentage as,

%friability = initial weight – final weight / initial weight * 100

Wetting Time :

In this method measure wetting time , simple tissue paper (12 cm × 10.75 cm) folded twice was placed in a small petridish (ID =6.5 cm) containing Sorenson's buffer ph 6.8 . a tablet was put on the paper, and the time for complete wetting was measured. three trials for each batch and the standard deviation were also determined.

In Vitro Disintegration Test:

In vitro disintegration time was measured by dropping a tablet and a beaker containing 50 ml of Sorenson's buffer pH 6.8. three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

In Vivo Disintegration Test:

The test was carried out on 2-3 tablets using in the mouth and the time in second taken for complete disintegration of the tablet was measured in few seconds.

In Vitro Dissolution Test:

In vitro dissolution study was performed by using USP TYPE II apparatus (paddle type) at 50 rpm. phosphate buffer pH 6.8, 900 ml was used as dissolution medium which maintained at 37 ± 0.5^0 c. an aliquot of dissolution medium (10 ml) was withdrawn at specific time intervals (2 min.) and was filtered. the amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 248.0 nm. three trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded.

Stability Study

(Temperature Dependent): The fast dissolving tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. (1) 40 ± 1^0 c (2) 50 ± 1^0 c (3) 37 ± 1^0c and RH 75% ±5%

Table 1: Formulation of Gliclazide FDTS By Direct Compression Method

	Gliclazide (solid dispersion)	Fenugreek seed powder	Crosspovidone	Sodium starch glycolate	Camphor	Saccharin	Pregelatinised starch	Purified talc	Magnesium stearate	**Total**
I	12 gm	-	5 gm	-	1 gm	300 mg	1.2 gm	200 mg	300 mg	200 mg
II	12 gm	-	-	5 gm	1 gm	300 mg	1.2 gm	200 mg	300 mg	200 mg
III	12 gm	5 gm	-	-	1 gm	300 mg	1.2 gm	200 mg	300 mg	200 mg
IV	12 gm	10 gm	-	-	1 gm	300 mg	1.2 gm	200 mg	300 mg	250 mg
V	12 gm	15 gm	-	-	1 gm	300 mg	1.2 gm	200 mg	300 mg	300 mg

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (visual defects, hardness, friability, disintegrations and dissolution etc.) and drug content. the data obtained is fitted into first order equations to determine the kinetics of degradation. accelerated stability data are plotting according Arrhenius equation the shelf life at 25^0 C.

RESULTS AND DISCUSSION :

In the present investigation the solubility of poorly water soluble Gliclazide was enhanced by preparing solid dispersion with PEG-6000 (solid dispersion method). Appropriate quantity of solid dispersion was blended with superdisintegrants. After adding filler, sublimating agent, sweetener, glidant and lubricating agent; FDTs were prepared by direct compression method.

All five formulations were physically evaluated for angle of repose , loose bulk and tapped densities, carr's index , hausner's ratio ,weight uniformity , hardness , friability , wetting time , drug content , disintegration time , dissolution profile .

Pre-compressive parameters :

1. The values for angle of repose were found in the range of 26.35 to 37.9°.
2. Loose bulk and tapped densities of the blend was found as 0.421 to 0.519 and 0.431 to 0.573 respectively.
3. Carr's index of the prepared blends falls in the range of 10 to 15.4% and this is also supported by Hausner's factor values which were in the range of 1.1 to 1.8. Hence the prepared blends possessed good flow properties and can be used for manufacturing of tablets.
4. Hence the prepared blends possessed good flow properties and can be used for manufacturing of tablets (see table 3).

Post-compressive parameters :

All the tablets were prepared under similar experimental conditions. The Formulations I AND II exhibited white color while Formulations iii , iv and v exhibited yellow colour , All formulations were odorless, flat shaped with almost smooth surfaces .

- The average weight of the FDTs prepared by direct compression method was 197.50 to 201.40 mg for formulation I II & III and 248.26 to 295.50 for formulation IV & V .
- Hardness of prepared FDTs was between 3.065 to 3.7 kg/cm^2.
- The percent friability of formulations was found to be 0.47 to 0.65 (less than 1.0%) and thus hardness and friability of all formulations were within acceptable limits.
- The disintegration time is very important and it is desired to be less than 1 minute. The quick disintegration may assist quick swallowing and drug absorption in buccal cavity, thus greater
- bioavailability of the drug. Disintegration time of prepared FDTs was found in the range of 22 to 32 seconds . The above finding suggested that, formulation containing sodium starch glycol ate and formulation containing high amount of fenugreek seed powder showed least time for disintegration .

- Wetting time is the indicator for the ease of disintegration of the tablet in buccal cavity. It was observed that wetting time of tablets was in the range of 25 to 39.5 seconds. It was found that the nature and combination of the superdisintegrants(s) present affected the wetting of the tablets. The formulation containing sodium starch glycol ate and fenugreek seed powder in high concentration took less time for wetting than compared to other formulations .
- Assay for the prepared formulations was performed to determine drug content uniformity and it was found between 96.32 to 97.88% (see table 4).

Table 2 : Pre-compression Parameters

Formulation	Angle of Repose (±SD)	Bulk density (±SD)	Tapped density (±SD)	Carr's index (±SD)	Hausner's ratio (±SD)
I	26.35±0.04	0.421±0.02	0.549±0.003	10.04±0.88	1.15±0.04
II	22.75±0.01	0.466±0.008	0.518±0.008	10.03±1.20	1.11±0.20
III	37.9±0.06	0.519±0.02	0.573±0.004	10.0057±0.80	1.1±0.24
IV	36.5±0.08	0.445±0.004	0.52±0.002	14.3±1.14	1.16±0.12
V	29.47±0.04	0.431±0.005	0.431±0.002	15.4±1.02	1.18±0.18

Table 3: Post Compression Parameters

Formula	Weight uniformity (±SD)	Hardness (kg/cm^2) (±SD)	Friability (%) (±SD)	%drug content	Wetting time (sec)	Disintegration time(sec)
I	201.42±1.2	3.065±0.24	0.64±0.16	96.32±1.50	26±0.36	27±2.14
II	198.28±0.8	3.076±0.08	0.65±0.24	97.84±0.64	25±0.50	23±0.04
III	197.56±1.4	3.7±0.18	0.65±0.15	97.88±1.20	39±0.63	32±2.64
IV	248.26±0.6	3.5±0.26	0.47±0.23	96.55±1.43	36±0.27	29±0.04
V	295.5±0.8	3.4±0.11	0.52±0.34	97.88±1.34	34±0.25	25±0.82

Table 4 : Dissolution profile of prepared fast dissolving tablets

Sampling time in Minutes	Cumulative percent drug release data for prepared MDTs ± sd Formulation Codes				
	I	II	III	IV	V
0	0.00	0.00	0.00	0.00	0.00
1	11.77±1.3	13.71±0.7	10.17±0.9	11.22±0.2	13.82±0.6
2	33.56±1.0	30.86±1.5	23.31±2.1	30.4±2.5	29.7±1.1
3	52.55±1.2	54.57±2.2	44.02±1.2	48.52±1.6	53.6±2.6
4	72.23±2.1	72.45±0.3	63.08±2.7	65.26±0.4	74.23±1.9
5	94.26±3.4	92.86±1.1	84.22±2.3	88.54±0.6	93.5±0.8

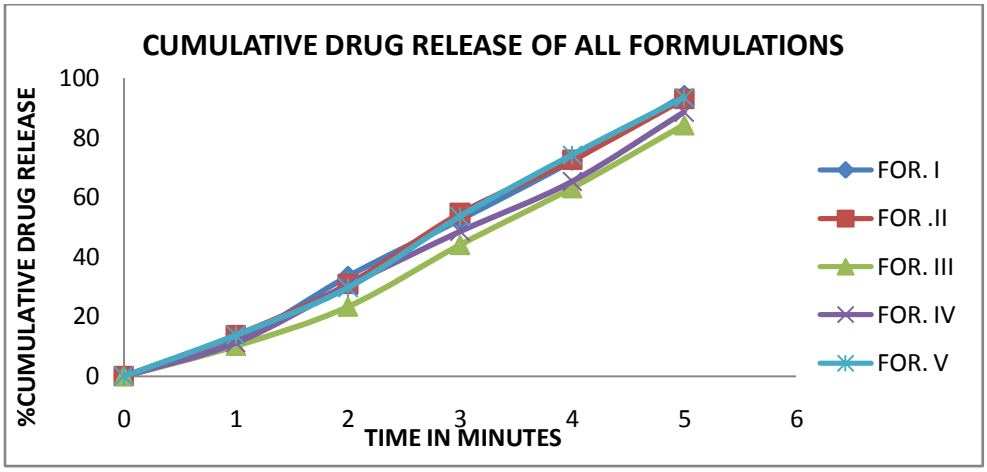

Figure 3 : Cumulative Drug Release Profile

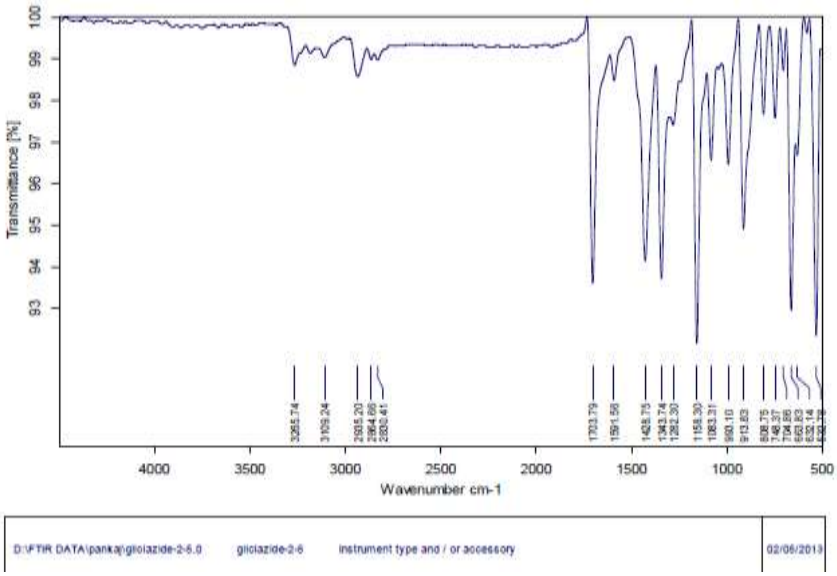

Figure 4 : I.R. Spectra of Pure Gliclazide

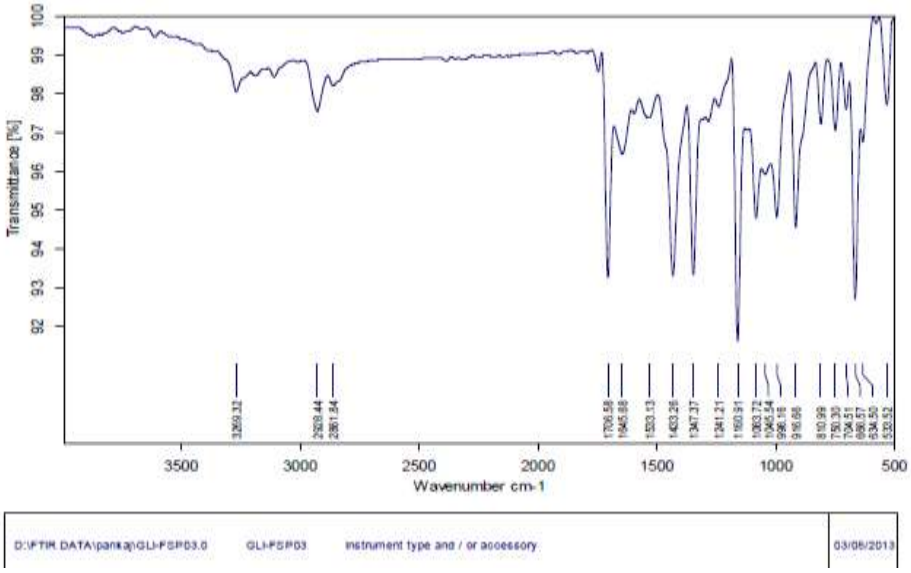

Figure 5 : I.R. Spectra of Mixture of Gliclazide and Fenugreek Seed Powder

CONCLUSION

Fast dissolving tablets dosage form proves its significance for enhancing the bioavailability of water insoluble drug by increasing its dissolution and solubility. The present investigations showed that, fast dissolving tablets of Gliclazide can be successfully prepared by using solid dispersions of the drug with PEG 6000 and then blending with suitable proportions of superdisintegrants such as; Crosspovidone, sodium starch glycolate (SSG)and fenugreek seed powder . After direct compression, sublimation of camphor provides highly porous tablets which can disintegrate quickly to provide effective dissolution within shorter period of time. Values for angle of repose , loose bulk and tapped density , carr's index and hausner's ratio were found within limits for all formulations . Hence the prepared blends possessed good flow properties and can be used for manufacturing of tablets. The tablets prepared were of good physical nature such as hardness and friability were under limits . Formulation I and II containing crosspovidone and sodium starch glycolate as disintegrating agent shows good drug release but when fenugreek seed powder was used (formulation III , IV , V) at low concentration it does not exhibit satisfactory results but when concentration is increased it starts to show better results. At the concentration of 150 mg per tablet it gives good release profile which can be as effective as the mouth dissolving tablets containing synthetic super disintegrants imparting extra pharmaceutical benefits of fenugreek seed powder to the formulations .Hence it could be concluded that the superdisintegrant (specially fenugreek seed powder) based fast dissolving tablets of Gliclazide would provide quick onset of action without need of water for swallowing or administration. Further investigations are needed to confirm the in vivo efficiency.

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