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Research Article

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Formulation and evaluation of certain hypoglycemic agents

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ABSTRACT

The aim of this investigation was to prepare fast dissolving tablets of (glibenclamide and glimepiride each alone) using solid dispersion and various concentrations of superdisintegrant agents like Ac-Di-Sol , crospovidone and sodium starch glycolate by direct compression method. Nine formulations having superdisintegrants at different concentration levels were prepared. These tablets were evaluated for drug content , weight variation, friability, hardness, and invitro disintegration time . Among the formulations tablets choose F6 and F7 from glibenclamide formulations and F3, F6 from glimepiride formulations with excellent in-vitro disintegration time as compere to other formulations. For stability study tests for 12 weeks at humidity 75 % and temperature (40 , 50 , and 60 °C). All formulations are stable at 40 °CIt was concluded that solid dispersion technique is a useful method for preparing fast dissolving tablets by direct compression method. Direct compression is the easiest method to manufacture fast dissolving tablets (FDTs). The great advantage of direct compression is its low manufacturing cost. It uses conventional equipment, commonly available excipients and a limited number of processing steps .

Keywords: glibenclamide, glimepiride, fast dissolving tablets, Ac-Di-Sol, crospovidone, sodium starch glycolate.

INTRODUCTION

Many patient find it difficult to swallow tablets and hard gelatin capsules and thus not comply with prescription that results in high incidence of non-compliance and ineffective therapy fast dissolving tablets are gaining prominence as new drug delivery systems . These dosage forms dissolves or disintegrate in oral cavity within a 15 s or in a minute without the need of water or chewing . In this study , an effort has been made to formulate fast dissolving tablets of (glibenclamide and glimepiride each alone) using different disintegrants [1,2,3,4,5]. Glibenclamide and Glimepiride are a white crystalline powder , relatively insoluble in water[6-7] . Solubility and dissolution was improved by formulating solid dispersion . Keeping in view the advantage of this delivery system , in the present study [8], attempts were made to formulate mouth dissolving tablet glibenclamide and glimepiride , which is useful to reduce sudden increased glucose level in the treatment of non-insulin dependent diabetes mellitus (NIDDM) [9]. Glibenclamide and Glimepiride are a hypoglycaemic agent of the sulphonylurea group .

It stimulates insulin secretion from functional pancreatic beta-cells and increases the sensitivity of the beta-cells to a glucose stimulus.Orodispersible tablets are those when put on tongue disintegrate instantaneously , releasing the drug which dissolve or disperses in the saliva . Six faster the drug in the solution , quicker the absorption and onset of clinical effect [10] . Some drugs are absorbed from the mouth , pharynx and oesophagus as the saliva passes down in to the stomach . in such cases ,bioavailability of a drug is significantly greater than those observed from conventional tablet dosage form . The advantages of mouth dissolving dosage form are increasingly being recognized in both , industry and academia . their growing importance was underline recently when European

pharmacopoeia adopted the term " fast dissolving " as tablet that is to be place in the mouth where it dissolves rapidly before swallowing .[11,12]

EXPERIMENTAL SECTION

2.1. Materials and Instruments:

2.1.1. Apparatus

Disintegration apparatus (ERWEKA ZT 32 Germany), Friabilityapparatus (Scientific model TF-2D , Germany), Tablet press (Rimek model mini press –II, Germany), Ovens(osworldindia), HPLC (Waters model 2487 , USA) ,Column-C18(ODS) 5µm (150x4.6mm) Teknokroma (spain), Ultrasonik cleaner(Wisd model wuc – A 10 H, Cyprus), UV/Vis Spectrophotometer (Shimadzu uv-160 IPC, Japan), Infrared spectrophotometer (Infrared spectrophotometer), pH meters (Sartorius model PB – 11, Germany), Balance (Sartorius model TF-2D, Germany) .

2.1.2. Materials and Reagents

Glibenclamide (Tianjin gencom, China) kindly supplied by Modern pharma Yemen , Glimepiride (Gkm new pharmaindia) kindly supplied by Modern pharma Yemen ,Talc (Merk , Germany)Microcrystalline cellulose 102 (Viva pure (JRS PHARMA) ,Germany) , Aspartame (Natura sweet powder, China) , Ac-di-sol (croscarmellose) (Viva pure (JRS PHARMA) ,Germany) Sodium starch glycolate (Viva pure (JRS PHARMA) ,Germany) , Acetonitrile (Scharlab S.L., Spain) ,Orange flavor (Aromas co., England) , Ammonium di hydrogen phosphate (Scharlab S.L., Spain) , Phosphoric acid (Scharlab S.L., Spain) , tris (hydroxymethyl) methylamine (Sigma – Aldrich , Germany) , Sodium hydroxide (Scharlab S.L., Spain) , hydrochloric acid (Scharlab S.L., Spain) Modern pharma Yemen , Sodium stearylfumarate (Beckmann-kenko GMBH, Germany) gift from shibapharma company Yemen ,Crosspovidone (Gulf exports, India) gift from pharmacare company Yemen Poly ethylene glycol 6000(Sigma –Aldrich , Germany) gift from global pharma company Yemen.

2.2. Methods:

2.2.1. Preparation of mouth dissolving tablet

Different (Glibenclamide and Glimepiride)mouth dissolve tablets were prepared according to the proportions given in table 1&2 .The raw materials were passed through a screen (40 mesh)prior to mixing . powdered1:5 solid dispersion , containing amount equivalent to 5 mg glibenclamide and 3 mg glimepiride , were mixed with the other excipients and compressed on a rotatary tablet punching machine (remake rotatary tablet punching machine)equipped with flat-faced 4 mm punches . the tablet weight was adjusted to 150 mg [13].

2.2.2. Solid dispersions prepared by melting the carrier

Solid dispersions (SDs) preparations containing different weight ratios of (Glibenclamide and Glimepiride) in PEG 6000 (1:1 , 1:2 ,1:5) were prepared by the melting method. (Glibenclamide and Glimepiride) was added to the melted PEG 6000 at 75 c and the resulting homogenous preparation was rapidly cooled in a freezing mixture of ice and sodium chloride , and stored in desiccators for 24h . Subsequently , the dispersion was ground in a mortar and sieved through 50# .[13]

2.2.3. Weight Variation Test:

Twenty tablets were separately weighed and their average weighed and standard deviation were calculated.

2.2.4. Uniformity of Tablets Thickness and Diameter:

The diameter and thickness of ten tablets were measured and the average of the ten tablets was calculated.

2.2.5. Friability:

Friability test was carried out as following: Ten tablets from each formula were accurately weighed and then placed in the drum of the friabilator. The drum rotated at 25 rotation per minute for 4 minutes. The tablets were weighed again and the present loss in weight was calculated.

2.2.6. Hardness:

The hardness (breaking strength in KP) of ten tablets from each formula was measured using hardness tester, and then the average of the ten tablets was calculated.

2.2.7. Hardness/Friability Ratio (H.F.R):
The H.F.R. was calculated for each formula by dividing the average hardness by its friability. H.F.R. is a good criterion for the mechanical strength.

2.2.8. Disintegration Test:
One tablet was placed in each of the six cells of the disintegration apparatus. Water was used as immersed solution maintained at 37+ 0.5°C then the apparatus was operated until no residue of the tablets aggregates remaining on the basket mesh, at this point the time of disintegrating was recorded.[14,15,16,17]

2.2.9. Drug content for Glibenclamide tablets :
By use HPLC method were done assay for glibenclamide tablets as BP 2013 monograph [6]

Mobile phase :
2.6 g (NH4)H2PO4 : 450 ml water : 550 ml acetonitrile
PH = 5.25 with H3PO4 OR 1N NaOH

Preparation of standard solution :
Weight 20 mg glibenclamide standard into 50 ml volumetric flask add 10 ml distilled water and complete the volume with acetonitrile give 0.4 mg/ml glibenclamide.

Preparation of sample solution :
4 tablets were crushed which equivalence 20 mg glibenclamide transfer into 50 ml volumetric flask add 10 ml distilled water and complete the volume with acetonitrile give 0.4 mg/ml glibenclamide then filtrate.

*column: C8 15 cm * Flow rate: 2 ml/min * wavelength: 254 nm

*sensitivity: 1 * pressure : 21.5 Mpa * End time : 5 min

2.2.10. Drug content for glimepiride tablets:
By use HPLC method were done assay for glimepiride tablets as USP 32 monograph[7]

Mobile phase :
Dissolve 0.5 gm of NaH2PO4 in500 ml of water . adjust pH to 2.4 with H3PO4 and add 500 ml of acetonitrile .
Preparation of standard solution :
Weigh accurately equivalent to 21 mg of glimepiride into 100 ml volumetric flask and dissolve and dilute to volume with acetonitrile solution 80% and mix well (0.21 mg/ml) of glimepiride).

Preparation of sample solution :
Weight 7 tablets of glimepiride into 100 ml volumetric flask and dissolve and dilute to volume with solution of (water to acetonitrile 20:80) and mix well (0.21 mg/ml) of glimepiride).

HPLC condition
*column : C815 cm * Flow rate : 2 ml/min * wavelength: 228 nm
*sensitivity: 1 * pressure : 21.5 Mpa * End time : 5 min

RESULTS AND DISCUSSION

1- The present study fast dissolving drug delivery system of (glibenclamide and glimepiride)were successfully developed in the form of mouth dissolving tablets with improved dissolution characteristics by forming solid dispersion with PEG 6000 , which offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increase bioavailability . (tables 1,5)
2- Total numbers of nine formulations were prepared by direct compression technique .
3- The value of pre-compression parameters evaluated were within prescribed limit and indicated good free flowing property (tables 2,6).
4- I.R. spectroscopy was used as means of studying drug-excipient compatibility and confirmed undisturbed structure of (glibenclamide and glimepiride) , which indicate no drug-excipient interaction .(figures 7,8)

5- The data obtained of post-compression parameters such as hardness , friability , weight variation , amount of drug content and in-vitro disintegration time are shown in(tables 3,7)
6- The hardness was found to be in the range of 2.4 to 3.2 kg / cm2 for all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling .
7- In all the formulations the friability values are less than 1% and meet the IP limits .
8- All the tablets passed weight variation test as the percentage weight variation was within the pharmacopeia limit . the weight of all the tablets was found to be uniform with low standard deviation value indicating efficient mixing of drug , disintegrants , and excipients .
9- The percentage drug contents of all the tablets were found to be between 99.6% to 106.3% of (glibenclamide and glimepiride) , which was within the acceptable limits .
10- The in vitro disintegration time was found in the range of 27.2 to 47.3 seconds.
11- I.R. spectra of drug with other excipients has not shown any interaction and also selected formulation was stable after stability study (see chromatograms in result and discussion).

Discussion IR spectra :
The IR spectra of SDs and PMs were compared with the standard spectrum of glibenclamide . IR spectrum of glibeclamide is characterized by the absorption of carbonyl (c=o) sulphonyl urea group at 1706 cm-1. In spectra of SDs and PMs , this band was shifted towards higher frequencies at 1725 and 1711 cm-1 respectively . also the NH group which is located at 3265 cm-1 from the IR spectrum of glibenclamide shifted to 3365 cm-1 in SDs . the sulphonyl group bands are located at 1349 and 1162 cm-1 in pure glibenclamide . in SDs , the asymmetric vibration peak of s=o band was shifted from 1349 to 1341 cm-1 with decreased frequencies.

Table 1 : Formulation of Glibenclamide Fast Dissolving tablets

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Solid dispersion 1:5	30	30	30	30	30	30	30	30	30
Microcrystalline cellulose 102	114.65	113.15	111.65	114.65	113.15	111.65	114.65	113.15	111.65
Ac-di-sol	1.5	3	4.5						
Crosspovidone				1.5	3	4.5			
Sodium starch glycolate							1.5	3	4.5
Sodium stearylfumarate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1	1	1	1	1	1	1	1	1
Orange flavor	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Total	150	150	150	150	150	150	150	150	150

Table 2 : Micromeritic properties of Glibenclamide Fast Dissolving powder blend

Formula no.	Angle of repose (**ɵ**)	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner ratio	Compressibility index	Carr's index
F1	23.68	0.4	0.56	1.394	28.6	0.286
F2	22.69	0.4	0.57	1.428	30	0.298
F3	24.06	0.39	0.58	1.487	32.8	0.328
F4	24.23	0.39	0.57	1.462	31.6	0.316
F5	23.2	0.38	0.56	1.474	32.1	0.321
F6	22.17	0.38	0.57	1.513	33.3	0.333
F7	23.68	0.36	0.56	1.555	35.7	0.357
F8	24.59	0.38	0.58	1.526	34.5	0.345
F9	25.77	0.38	0.57	1.468	33.3	0.333

Table 3: Evaluation of Glibenclamide Fast Dissolving table

Formula no.	General appearance	Uniformity of weight (mg)	Hardness (kg/cm²)	Friability (%)	Thickness tablets (mm)	In vitro disintegration time (sec)	Drug content (%)
F1	Passes	145.4	3.1±0.2	0.209	4.5 ± 0.1	12±2	103.2
F2	Passes	145.6	3.1±0.1	0.296	4.42±0.02	14±1	103.5
F3	Passes	149.8	3.2±0.2	0.333	4.3±0.2	15±2	104.9
F4	Passes	148.4	2.9±0.2	0.235	4.3±0.1	20±2	104.7
F5	Passes	150.1	3.3±0.1	0.075	4.15±0.02	18±1	105.4
F6	Passes	151.4	3.1±0.4	0. 234	4.3±0.2	25±2	103.8
F7	Passes	150.2	3.3±0.2	0.033	3.9±0.1	17±2	103
F8	Passes	149.5	3.1±0.3	0.342	4.55±0.03	19±2	106.2
F9	Passes	149.9	3.2±0.3	0.615	4.5±0.02	21±1	104.1

Table 4 :Assay of Glibenclamide Fast Dissolving tablet by HPLC

No.of formula	Conc. (mg/ml)	Area mean (μ v*sec)	Percentage of drug content
STD	0.4	2500455	xxxx
F1	0.4	2571035	103.2
F2	0.4	2577758	103.5
F3	0.4	2612799	104.9
F4	0.4	2607387	104.7
F5	0.4	2624416	105.4
F6	0.4	2585219	103.8
F7	0.4	2564081	103
F8	0.4	2643053	106.2
F9	0.4	2592587	104.1

Table 5 : Formulation of Glimepiride Fast Dissolving tablets

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Solid dispersion 1:5	18	18	18	18	18	18	18	18	18
Microcrystalline cellulose 102	126.65	125.15	123.65	126.65	125.15	123.65	126.65	125.15	123.65
Ac-di-sol	1.5	3	4.5						
Crosspovidone				1.5	3	4.5			
Sodium starch glycolate							1.5	3	4.5
Sodium stearylfumarate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1	1	1	1	1	1	1	1	1
Orange flavor	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Total	150	150	150	150	150	150	150	150	150

Table 6 : Micromeritic properties of Glimepiride Fast Dissolving powder blend

Formula no.	Angle of repose (**ɵ**)	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner ratio	Compressibility index	Carr's index
F1	24.9	0.377	0.54	1.432	30.188	0.3
F2	23.2	0.365	0.555	1.444	30.769	0.34
F3	23.68	0.377	0.571	1.515	33.975	0.34
F4	24.59	0.37	0.526	1.421	29.629	0.3
F5	22.54	0.357	0.547	1.532	34.734	0.35
F6	21.62	0.363	0.54	1.486	32.727	0.33
F7	22.69	0.372	0.535	1.438	30.467	0.3
F8	23.09	0.35	0.54	1.54	35.087	0.35
F9	24.59	0.358	0.54	1.459	31.481	0.31

Table 7 : Evaluation of Glimepiride Fast Dissolving tablet

Formula no.	General appearance	Uniformity of weight (mg)	Hardness (kg/cm²)	Friability (%)	Thickness tablets (mm)	In vitro disintegration time (sec)	Drug content (%)
F1	passes	147.51	3.2±0.3	0.551	4.5±0.2	12±2	106.7
F2	passes	145.82	3.3±0.2	0.416	4.43±0.03	11±3	102.2
F3	passes	145.99	3.3±0.1	0.387	4.4±0.05	10±2	102.1
F4	passes	147.4	3±0.1	0.263	4.4±0.02	17±2	108.6
F5	passes	145.63	3.1±0.1	0.144	4.42±0.04	12±3	106.7
F6	passes	146.58	3.2±0.3	0.282	4.45±0.05	10±3	101.2
F7	passes	148.15	2.9±0.1	0.209	4.38±0.05	12±2	105.3
F8	passes	146.16	3.3±0.2	0.513	4.49±0.05	10±2	106.7
F9	Passes	146.27	3.3±0.1	0.27	4.35±0.08	11±3	102.6

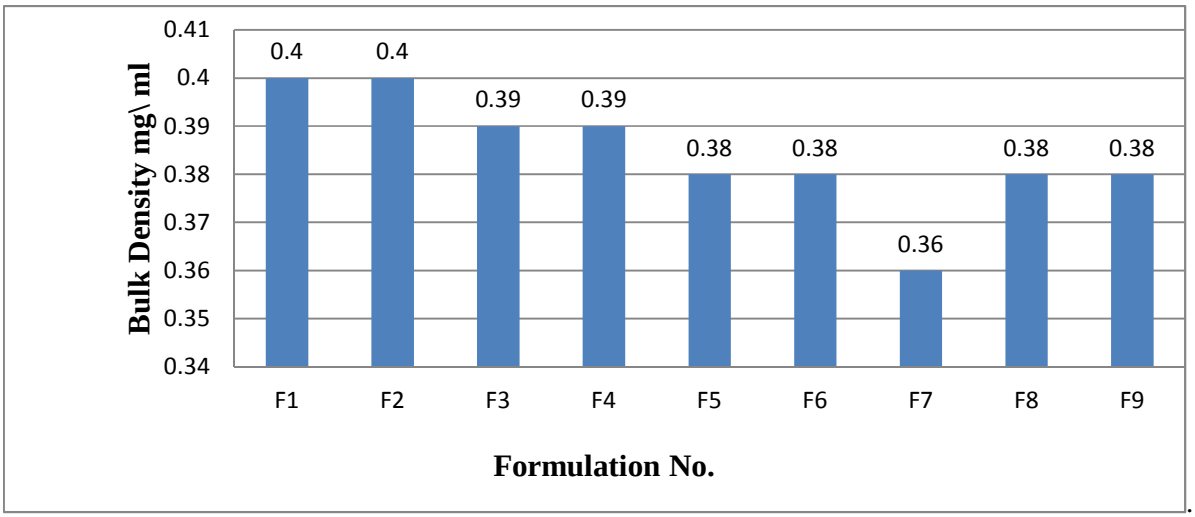

Figure 1: Bulk Density for Glibenclamide Fast Dissolving powder blend

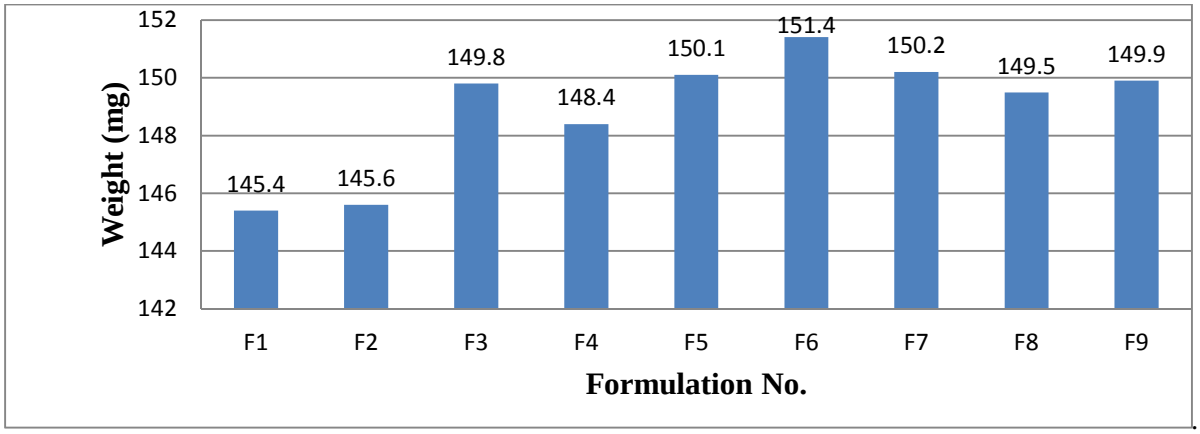

Figure 2 : Uniformity weight of Glibenclamide Fast Dissolving tablets

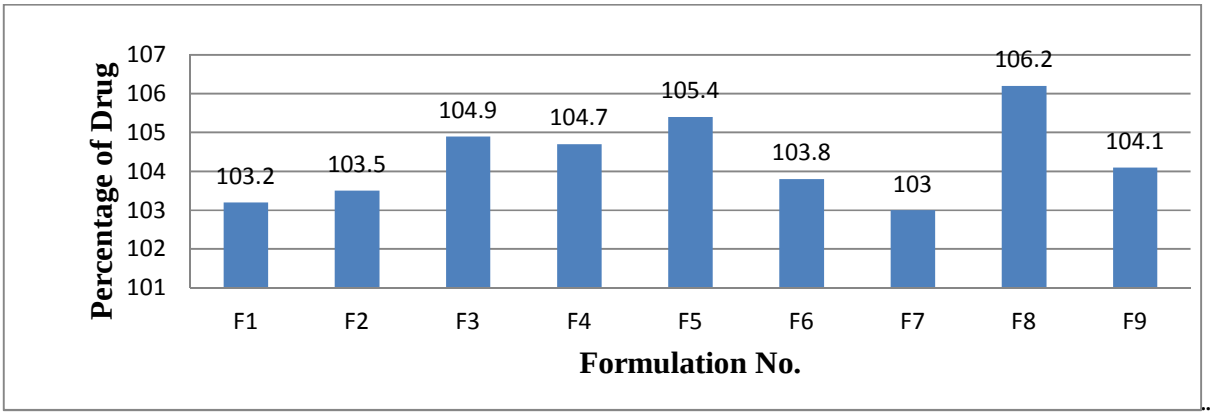

Figure 3:Assay for Glibenclamide Fast Dissolving tablets by HPLC

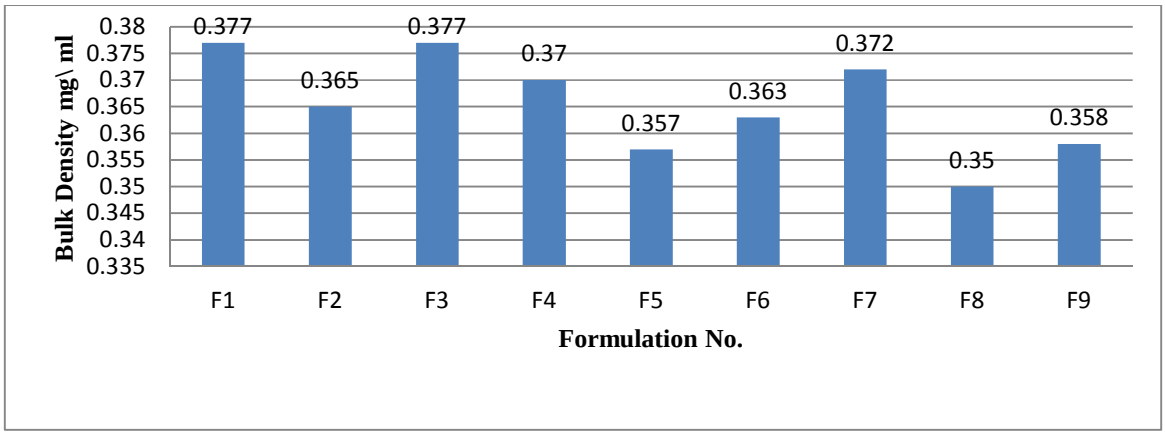

Figure 4: Bulk Density for Glimepiride Fast Dissolving powder blend

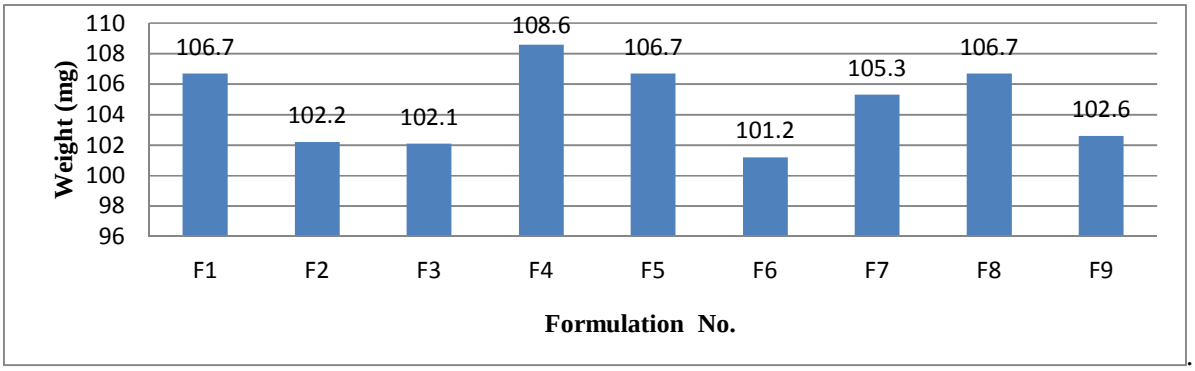

Figure 5 : Uniformity weight of Glimepiride Fast Dissolving tablets

Table 8 : Assay of Glimepiride Fast Dissolving tablet by HPLC

No.of formula	Conc. (mg⁄ml)	Area mean (μ v*sec)	Percentage of drug content
STD	0.21	6769859	xxx
F1	0.21	7115083	106.7
F2	0.21	6819779	102.2
F3	0.21	6809253	102.1
F4	0.21	7240115	108.6
F5	0.21	7118383	106.7
F6	0.21	6749317	101.2
F7	0.21	7026022	105.3
F8	0.21	7115748	106.7
F9	0.21	6842512	102.6

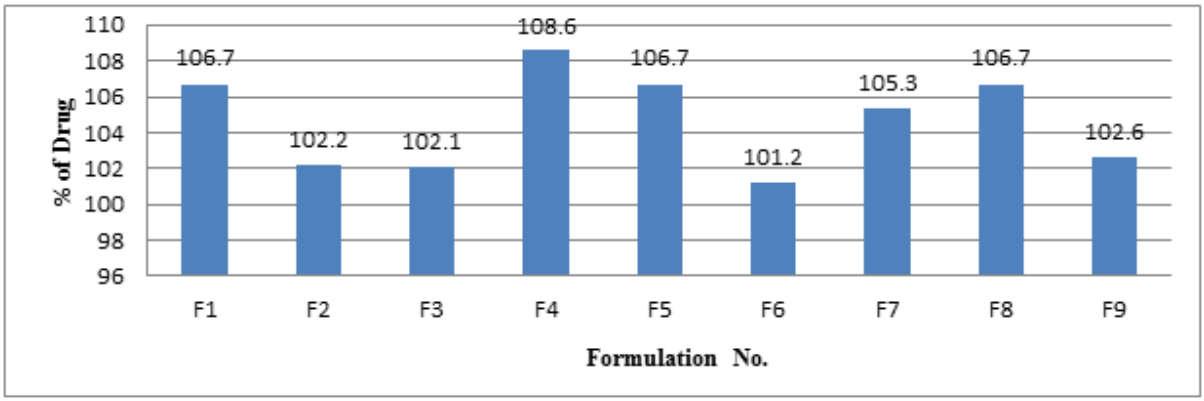

Figure 6: Assay for Glimepiride Fast Dissolving tablets by HPLC

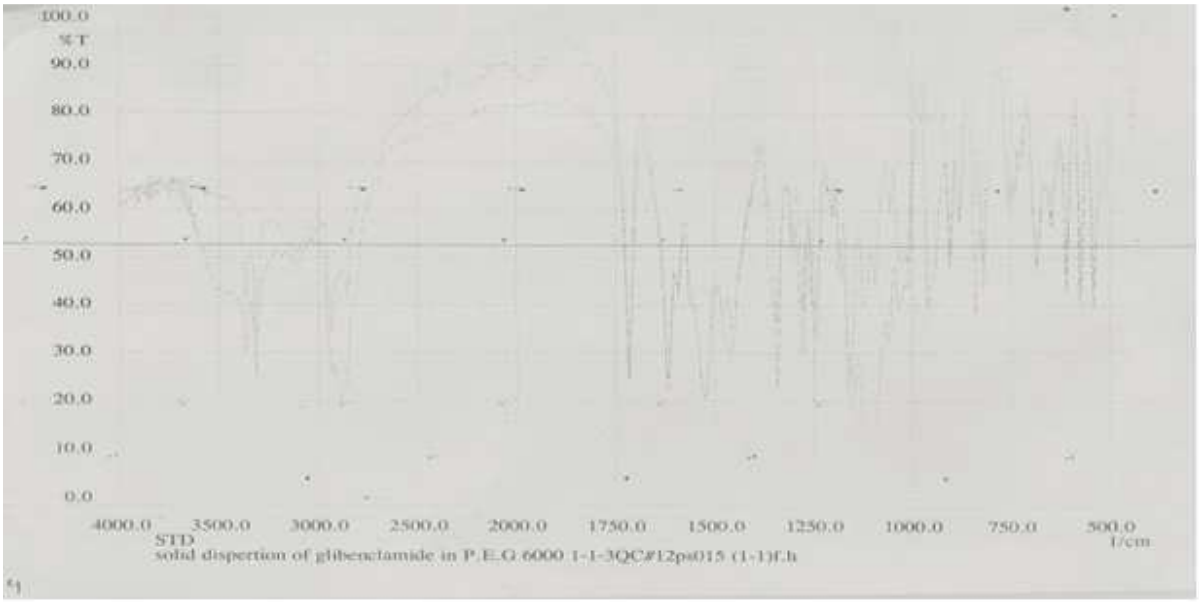

Figure 7 : I R . Scanning for Solid Dispersion of Glibenclamide in P.E.G 6000

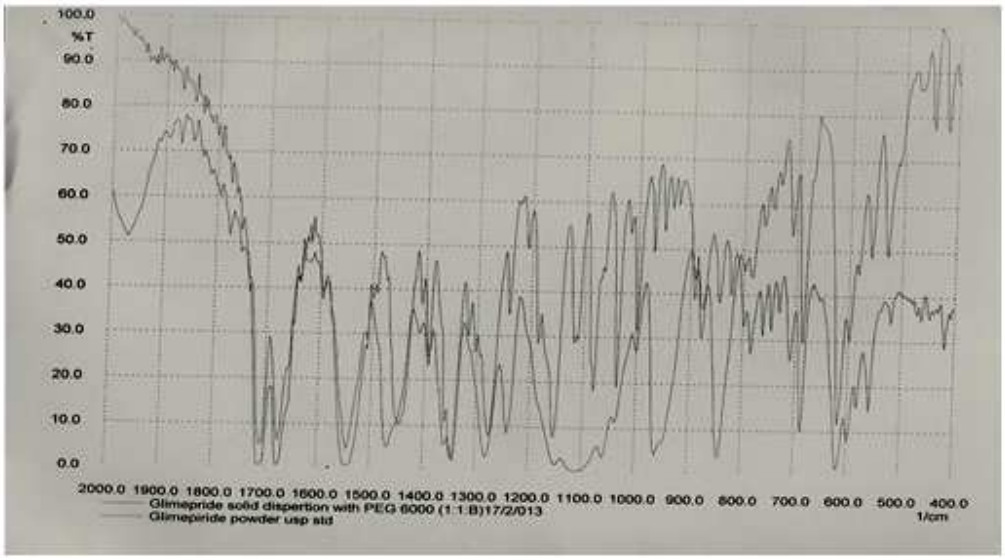

Figure 8 : I R . Scanning for Solid Dispersion of Glimepiride in P.E.G 6000

CONCLUSION

Prepared fast dissolving tablets (FDTs) by direct compression is suitable method. The great advantage of direct compression is its low manufacturing cost. It uses conventional equipment, commonly available excipients and a limited number of processing steps. In addition to this, using (sodiumstearyl Fumarate, 0.75%) as lubricants was the good choice to the sticking problem. Also it was concluded that Crospovidone , sodium starch glycolate and croscarmellose sodium are acceptable to be used as superdisintegrants inglibenclamide and glimepiride fast dissolving tablet formulations each alone. Based on the quality controltests all formulae which choices for tests are stable at 40C° for three months.

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