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COMPARATIVE STUDY OF THREE DIFFERENT APPROACHES USED FOR MANUFACTURING OF ANTIDIABETIC ORODISPERSIBLE TABLETS

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ABSTRACT: Diabetes mellitus basically a chronic metabolic disorder that results in boosting up blood glucose level to higher concentrations. It is associated with bunch of diseases. To overcome patient's common problems i.e. throat pain, vomiting, non-compliance, inconvenience and ineffective therapy plan or to enhance patient compliance and effectiveness of therapy scientists have launched orodispersible tablets to attract patients for improving their quality of life. Methods of preparation along with superdisintegrants are the major players in the success of this dosage form. In the present work, antidiabetic orodispersible tablets (ODT's) containing drugs (Metformin HCl and Glibenclamide) and superdisintegrants (pregelatinize starch and sodium starch glyconate) were prepared by three different techniques i.e. direct compression, effervescent method and sublimation technology. Fifteen formulations (F1-F15) were prepared by using these techniques. Pre-compression studies including rheological analysis (Bulk density, Tapped density, Angle of repose, Carr's compressibility index, Hausner's ratio) and compatibility studies such as Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared spectroscopy (FTIR) were performed. Post compression studies on various parameters i.e. tablet hardness, weight variation, friability, disintegration time, dissolution studies wetting time, wetting volume, water absorption ratio, modified disintegration, uniformity of contents and stability studies were conducted according to ICH (International conference on harmonization) guidelines. Finally, results were statistically evaluated by using one way ANOVA test and mean. Formulation F8 prepared by sublimation method was found good relative to disintegration time, wetting volume, wetting time, release studies etc. having short disintegration time and rapid release of drugs.

INTRODUCTION: A large number of patients feel difficulty in swallowing solid dosage forms especially tablets and capsules which may lead to throat pain, vomiting, non-compliance, inconvenience and ineffective therapy plan [1].

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Dysphagia affects 35% of general population also associated with numerous pathological conditions like strokes, Parkinson's disease, Brain disorders, motion sickness, AIDS, unavailability of water and unconsciousness. Oral cavity have shown three different types of mucosa i.e. Masticator mucosa, Lining mucosa and Specialized mucosa having surface area of 100 cm^2 within the oral cavity [2].

From the last twenty years, the major focus of drug developers is patient compliance towards all existing and newly developing dosage forms. Newer technologies are emerging three fold yearly.

As it is very difficult to synthesize new chemical entity and formulate into a new dosage forms, efforts are being made to introduce new and new drug delivery systems with improved safety, efficacy and bioavailability with minimal dosing frequency and adverse effects [3].

Orodispersible tablets are the tablets that disintegrates within few seconds and dissolve rapidly in saliva without any need of water or chewing action as for media or for breakdown into small particles respectively. Orodispersible tablets usually dissolve within 15 seconds to 3 minutes. This dosage form basically includes incorporation of superdisintegrants and taste masking agents in its composition [4].

Oral disintegrating tablets are getting importance day by day due to many factors like fast disintegration time, pleasant mouth feel, require no water, best for incorporating acid sensitive drugs, easily swallowed with saliva, mask bitter taste of drugs etc [2].

In the present study, orodispersible tablets of Metformin HCl and Glibenclamide were prepared by three different techniques i.e. direct compression, sublimation and effervescent method using pregelatinized starch and sodium starch glyconate.

Objective of the study was to formulate antidiabetic orodispersible tablets with three different techniques that disintegrate and release drug contents in short time period even in seconds within oral cavity. To find out the best method that produces orodispersible tablets with optimum and efficient parameters over the others.

MATERIALS AND METHODS:

Materials: Metformin HCl, Glibenclamide, Pregelatinized starch, Primojel, Mg-stearate, Talc, Lactose, Camphor, Sodium bicarbonate, Tartaric acid, Orange flavor and Saccharine. Metformin HCl and Glibenclamide were obtained as gift sample from Fynk Pharmaceutical's Gujranwala road, Lahore, Punjab, Pakistan. Saccharine Sodium and orange flavor were obtained as a gift sample from Madly Pharmaceutical's and Amson Pharmaceutical's Islamabad respectively. All the chemicals used were of analytical grade.

The experimental work was conducted at Hi-tech and Industrial Labs, Faculty of Pharmacy, University of Sargodha; Sargodha, 40100, Punjab, Pakistan in 2012.

Methods:

Preparation of powder blend: All the materials were weighed on electric weighing balance of analytical grade and mixed properly in polythene bags and sieved through sieve no.60 after subsequent grinding in pestle and mortar where required in order to bring uniformity in the powder blend.

Direct Compression Method: All ingredients were weighed accurately on electric weighing balance (Shimadzu A x 200, Japan) of analytical scale. They were subjected to the manual grinding in pestle and mortar in order to bring uniformity in contents and to reduce particle size of saccharine crystals. Powder mixture was than sieved through sieve no.60. At the end after mixing powder was subjected to manually operated ten station rotary tablet compression machine using 7mm round flat punch with compression force 3N [5].

By this method, five formulations i.e. F1 – F5 were prepared by using pregelatinized starch, Primojel alone and in combination of different concentrations as shown in **table 1**.

Effervescent Method: All the ingredients were weighed accurately using electric balance (Shimadzu A x 200, Japan). Sodium bicarbonate and tartaric acid were pre-heated at 80°C for 30minutes in order to remove any moisture content. Then all ingredients were grinded manually in pestle and mortar. After that the powder blend was sieved through sieve no.60. Powder was subjected to compression on ten station rotary machine using 7mm round flat punch [6].

By this method, five formulations i.e. F6 – F10 were prepared by using Pregelatinized starch, Primojel alone and in combination of different concentrations as shown in table 1.

TABLE 1: COMPOSITION OF ORODISPERSIBLE TABLETS F1 –F15

Ingredients (mg)	Direct Compression tablets (F1-F5)					Sublimation tablets (F6-F10)					Effervescent tablets (F11-F15)				
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Metformin HCl	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Glibenclamide	02	02	02	02	02	02	02	02	02	02	02	02	02	02	02
Pregelatinize Starch	12	-	9	6	3	12	-	9	6	3	12	-	9	9	3
Primojel	-	12	3	6	9	-	12	3	6	9	-	12	3	9	9
Mg-Stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Lactose	77	77	77	77	77	67	67	67	67	67	47	47	47	47	47
Orange Flavour	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Saccharine Sodium	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Camphor	-	-	-	-	-	10	10	10	10	10	-	-	-	-	-
$NaHCO_3$	-	-	-	-	-	-	-	-	-	-	15	15	15	15	15
Tartaric Acid	-	-	-	-	-	-	-	-	-	-	15	15	15	15	15
Total Weight	150mg					150mg					150mg				

Sublimation Method: In this method, camphor was used as subliming agent along with other ingredients of the formulation. All the ingredients of the formulation were weighed accurately on weighing balance (Shimadzu A x 200, Japan) and mixed manually in polythene bags for 20minutes. Than powder was sieved through sieve no 60. Powder blend was subjected to the compression on ten station rotary machine using 7mm round flat punch. Tablets were kept in hot air oven for 6 hours at 60+1˚C for sublimation of camphor [7]. By this method, five formulations i.e. F11 – F15 were prepared by using pregelatinized starch, primojel alone and in combination of different concentrations. Camphor was used as subliming agent in these formulations as shown in table 1.

RESULTS AND DISCUSSION: The results of pre-compression (bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index) and post compression parameters(weight variation, hardness, thickness, friability, disintegration and wetting time, wetting volume, dispersion time, ph of tablet and water absorption ratio) are presented in **tables 2, 3 and 4**.

TABLE 2: BULK DENSITY, TAPPED DENSITY, ANGLE OF REPOSE, HAUSNER'S RATIO AND CARR'S INDEX

Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Angle of Repose (Ɵ)	Hausner's Ratio	Carr's Index
F1	0.623	0.731	23.5	1.17	14.77
F2	0.619	0.739	22.4	1.19	16.23
F3	0.621	0.734	22.9	1.18	15.39
F4	0.609	0.719	24.2	1.18	15.29
F5	0.617	0.731	23.9	1.18	15.59
F6	0.611	0.727	24.1	1.18	15.95
F7	0.614	0.735	23.7	1.19	16.46
F8	0.625	0.731	24.6	1.16	14.50
F9	0.633	0.742	25.3	1.17	14.69
F10	0.636	0.749	23.6	1.17	15.08
F11	0.627	0.739	24.8	1.17	15.15
F12	0.631	0.737	22.2	1.16	14.38
F13	0.629	0.735	24.8	1.16	14.42
F14	0.637	0.744	23.7	1.16	14.38
F15	0.619	0.730	25.8	1.17	15.20

TABLE 3: WEIGHT VARIATION, HARDNESS, THICKNESS, FRIABILITY, DISINTEGRATION AND WETTING TIME

Formulations	Wt. variation (mg)	Hardness Kg/cm^2	Thickness (mm)	Friability* (%)	Disintegration* (Sec)	Wetting* Time (Sec)
F1	150.34	3.4	2.66	0.720 ± .01	51 ± 2.30	57 ± 2.08
F2	149.90	3.2	3.00	0.676 ± .00	59 ± 1	79 ± 1.52
F3	151.89	3.5	2.87	0.645 ± .01	34 ± 4	48 ± 2
F4	143.70	3.0	2.59	0.564 ± .01	55 ± 1.5	70 ± 2.51
F5	142.56	3.1	2.50	0.654 ± .02	57 ± 1.5	74 ± 1

F6	148.34	3.2	2.79	0.698 ± .01	46 ± 2.0	46 ± 1.52
F7	149.67	3.6	2.67	0.443 ± .00	56 ± 1.5	64 ± 1.52
F8	148.77	3.4	2.49	0.598 ± .00	30 ± 1	41 ± 1.52
F9	140.72	3.6	2.86	0.604 ± .00	49 ± 1.3	48 ± 1.52
F10	148.78	3.3	2.96	0.687 ± .02	53 ± 1	50 ± 3.05
F11	147.83	3.2	3.00	0.725 ± .00	49 ± 1	50 ± 1
F12	149.23	3.4	2.78	0.467 ± .00	58 ± .57	67 ± 1
F13	151.35	3.6	2.73	0.565 ± .00	31 ± 1.5	44 ± 1
F14	145.31	3.5	3.90	0.527 ± .00	52 ± 1.52	55 ± 1
F15	148.56	3.2	2.74	0.679 ± .00	56 ± 2.5	58 ± 0.5

*Average of three determinations; Standard Deviation (S.D).

TABLE 4: WETTING VOLUME, DISPERSION TIME, pH OF TABLET AND WATER ABSORPTION RATIO

Formulation	Wetting* volume (ml)	Dispersion* time (Sec)	pH of Tablet Sol	Water* Absorption Ratio
F1	21 ± 1.73	47 ± 1.15	7.0	1.10± .1
F2	27 ± 2	59 ± 1.52	7.1	0.85± .02
F3	16 ± 1.52	40 ± 2.08	7.0	1.20± .25
F4	23 ± 1.15	51 ± 1.15	7.2	1.05± .04
F5	22 ± 2.08	55 ± 2.08	6.9	0.90± .1
F6	19 ± 1.52	42 ± 1.73	7.0	1.00± .06
F7	21 ± 1.52	53 ± 1.15	6.8	0.95± .02
F8	14 ± 1.52	30 ± 1.73	7.1	1.40± .17
F9	21 ± 1.52	46 ± 1.15	7.2	1.10± .11
F10	23 ± 3.05	52 ± 1.73	7.0	1.05± .01
F11	20 ± 1	43 ± 1.15	7.1	1.10± .17
F12	24 ± 1	56 ± 1.52	6.8	1.05± .01
F13	17 ± 1	35 ± 1.15	6.9	1.25± .03
F14	24 ± 1	47 ± 1.15	7.2	1.00± .06
F15	21 ± 0.5	54 ± 1.15	7.3	0.95± .04

*Average of three determinations; Standard Deviation (S.D).

DISCUSSION:

Pre-Compression Parameters: Powder blend was first evaluated to determine the flow properties. The values of angle of repose were present between 22.2° to 25.8° which show that powder had good flow properties. Generally the values of angle of repose below 30° indicate that powder has good flow properties. The values of other rheological properties such as bulk density, tapped density, Hausner's ratio and Carr's index were also determined.

The results of these properties indicate that powder blend had best flow properties and meet the required criteria which are essential for excellent flow. Both bulk density and tapped density were calculated that were further used to measure Carr's index and Hauser's ratio. The values of Carr's index were between14.38% to 16.46% justifying that powder blend had good flow. The Hausner's ratio was below 1.25 indicates that powder has better flow. The Hausner's ratio was found to be between1.16 to 1.19 which was within the acceptable range.

Overall results of all parameters of rheological properties were well within the desired limits.

Post Compression Studies:

1. **Weight Variation:** The results of weight variation of all the formulations were lie within the Pharmacopoeial limits. It means that tablets are of proper weight and size. It also shown that there was consistency among the prepared tablets and there was minimum batch to batch variation.

2. **Hardness and Thickness:** Hardness generally indicates that tablets are able to bear stress during handling and remain stable during storage. Hardness results had shown that tablets prepared by direct compression method had more hardness as compared to both other methods. In sublimation method camphor was used as subliming agent which causes more porosity after evaporation and tablets were little bit less hard.

Overall results of hardness indicate that they were present within prescribed limits of ODTs. Thickness had also shown that results were present within given limits. All the tablets had proper thickness. The results of thickness were more accurate and precise.

3. **Friability:** The friability of all the formulations was less than 0.8% which indicates that tablets had good mechanical strength as shown in table 3. The tablets did not show any unnecessary breakdown of the particles. Statistically results of friability were tested by using one way ANOVA. Results of ANOVA between all groups had shown that P value was less than was 0.082 which was greater than 0.05 which prove that results were insignificant between the groups.

4. **Wetting Time:** Wetting time is the indication of hydrophobicity of the ingredients. The lower the wetting time faster will be the disintegration [8]. The results had shown that all the formulations had Wetting time less than 80 seconds as shown in table 3. It was observed that F8 formulation prepared by sublimation method was having wetting time 41 seconds that was less than all other fourteen formulations. Statistically results of wetting time were tested by using one way ANOVA. Results of ANOVA between all groups had shown that P value was 0.035 which was less than 0.05 it prove that results were significant between the groups and method of preparation significantly affect the wetting time of tablet prepared by other methods.

5. **Disintegration Time:** The disintegration time for ODTs is generally below 1 minute and time that patient can experience is 5 to 30 seconds. Disintegration time for all the formulations was less than 1 minute as shown in table 3. It was also observed tablets that prepared by sublimation method had low disintegration time due to porous nature of tablets as compared to tablets prepared by two other methods[9]. Statistically results of disintegration time were tested by using one way ANOVA. Results of ANOVA between all groups had shown that P value was less than was 0.096 which was greater than 0.05 which prove that results were insignificant between the groups.

6. **Wetting Volume:** The results of wetting volume were affected by method of preparation. The results of wetting volume were also according to specification. F8 formulation containing prepared by sublimation method also had less wetting volume of 14ml as shown in table 4. Statistically results of friability were tested by using one way ANOVA. Results of ANOVA between all groups had shown that P value was less than was 0.059 which was greater than 0.05 which prove that results were insignificant between the groups.

7. ***In vitro* dispersion time:** *In vitro* dispersion test was performed for all of the formulations. This test was used to find dispersion time for tablets by using Petri dish method. Dispersion of tablets was affected by swelling which is due to superdisintegrant. Formulation F8 containing pregelatinized starch and primojel had shown less dispersion time 30 seconds when compared with other formulations as shown in table 4.

8. **Water Absorption ratio:** This test was used to check that how much water was absorbed by the tablet. As value of water absorption ratio increases it indicates that rapid breaking of tablets and therefore faster disintegration. Formulations prepared by direct compression and effervescent method had less water absorption ratio as compared with F8 as shown in table 4. When pregelatinized starch and primojel were used together they have showed more absorption ratio [10].

9. **Drug release studies:** The cumulative %age of drug release increased as the time increases up to 12 minutes and with increase in the concentration of superdisintegrants maximum up to 8%. Results of tablets containing pregelatinized starch and primojel had shown that formulation F8 had maximum release of drug 99.5% in 12 minutes.

   This formulation containing pregelatinized starch 6% and 2% primojel which releases drug more rapidly as compared to formulation containing same quantity of superdisintegrants. Method of preparation also affected the release of drug from tablets.

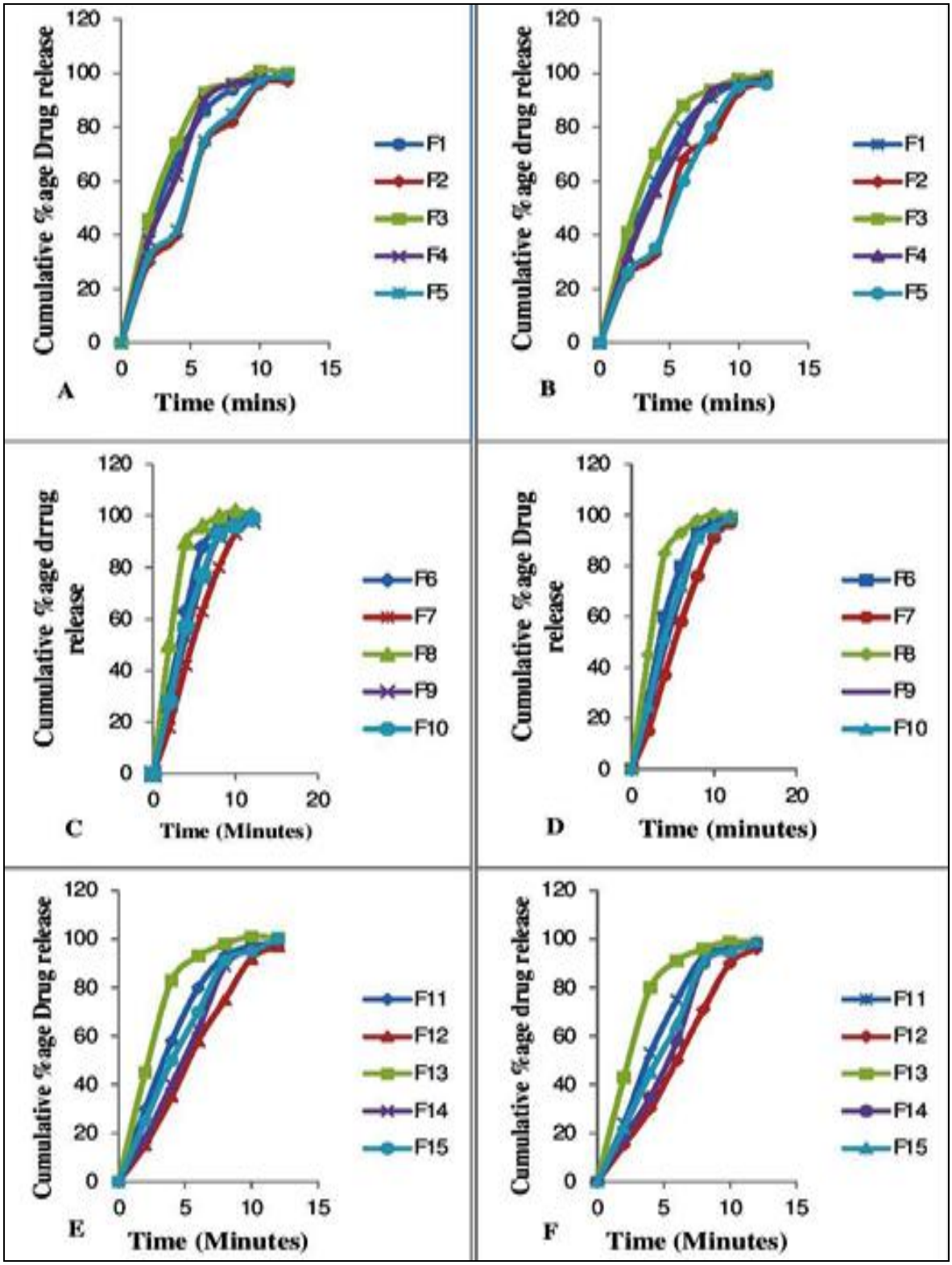

FIGURE 1: A, C, E = CUMULATIVE %AGE RELEASE PROFILE OFMETFORMIN HCl FOR F11 – F15 B, D, F = CUMULATIVE %AGE RELEASE PROFILE OF GLIBENCLAMIDE FOR F11 – F15

FTIR Studies: FTIR spectrum of optimized formulation was also determined to check any interaction between drug molecules as well as with excipients. The IR spectra of physical mixture of Superdisintegrants with Metformin Hydrochloride and Metformin HCl and Glibenclamide have showed similar characteristic peaks that confirmed the chemical stability of superdisintegrants, glibenclamide and metformin HCl as well as nonexistence of interaction between super-disintegrants and the drugs as show in **fig. 2** [11].

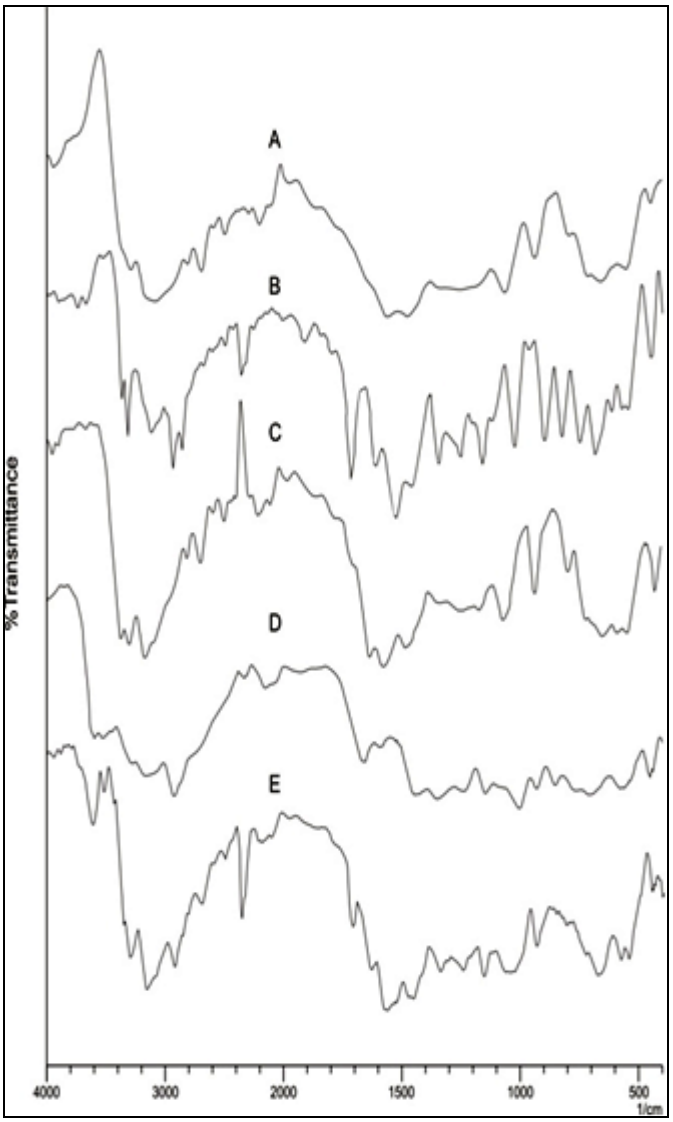

FIGURE 2: FTIR SPECTRUM OF METFORMIN HCl (A), GLIBENCLAMIDE (B), METFORMIN HCl + GLIBENCLAMIDE (C), PRIMOJEL + PRE-GELATINIZE STARCH (D), METFORMIN HCl+ GLIBENCLAMIDE+ PRIMOJEL + PREGELATINIZE STARCH (E)

DSC Studies: DSC studies were conducted to check any incompatibility among drug and excipients. DSC thermograms of these drugs (Metformin HCl and Glibenclamide) were taken with two superdisintegrants (Primojel and Pregelatinized starch). The particular DSC thermogram data was scanned.

All thermograms have not exhibited any change when drugs were tested alone or in combination with superdisintegrants. Even there was no shift of peaks while drugs were in combination as shown in **figure 3**. This study confirmed that there was present no interaction among Metformin HCl, Glibenclamide, Primojel and Pregelatinized starch when alone or formulated in combination [8].

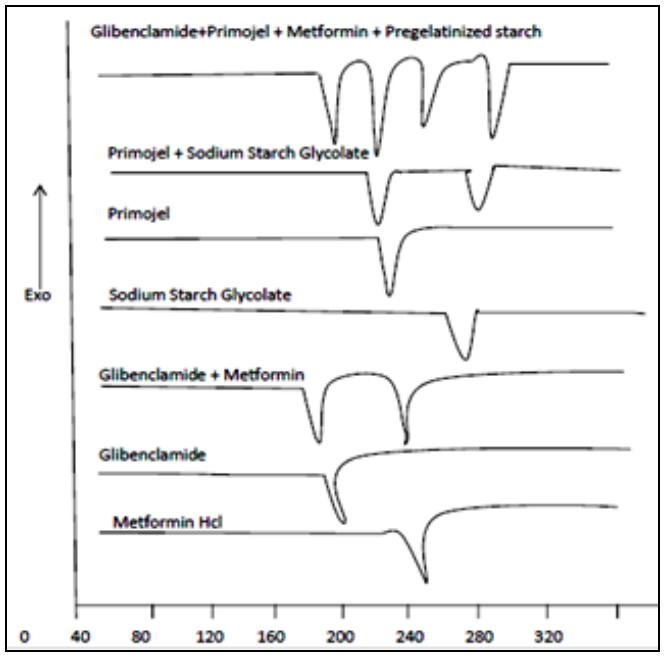

FIGURE 3: DSC SPECTRUM

Stability Studies: Stability studies of three best formulations were conducted for six month period. The tablets were kept under accelerated conditions of temperature and humidity 35±5^{o}C and 75%±5% respectively. The sample were taken after 1, 2,3,4,5 and at the end of 6 month. The tablets were evaluated for different parameters. The results had indicated that there are no significant variations occurred in drug content and in vitro dispersion time at the end of 6 months. It means that our formulations were stable under different accelerated conditions of temperature and humidity.

CONCLUSION: Formulation F8 containing Pregelatinized starch and Primojel (3:1) and camphor as Sublimating agent, prepared by sublimation method was found good relative to disintegration time, wetting time, release studies etc having short disintegration time and rapid release of drugs.

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