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Research Article

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Pulsatile drug delivery of chitosan coated beads of miglitol with fast dissolving glimepiride tablet

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ABSTRACT:

Pulsatile drug delivery system was developed which have three parts fast dissolving tablet of glimepiride, sustained release chitosan coated microbeads of miglitol and plug of HPMC E5 and spray dried lactose. After pre-formulation studies fast dissolving tablets were prepared by direct compression method; which shows instant drug release and % CDR of glimepiride fast dissolving tablet was found to be 70.81%. polymer plug have lag time 2.30 hr, chitosan coated miglitol beads shows sustained release upto 81.66% .this system is evaluated using different physicochemical parameters and in-vitro studies. Result suggests that the system can be applicable for diabetes treatment.

Key words: Pulsatile, microbeads, sustained release, miglitol, glimepiride.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery system which release the drug with constant or variable release rates.[1] Dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release.[1,2,3]

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired character gastric residence time restricts. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. [4, 5]

Fast dissolving tablet (FDT) as “a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue.” Fast dissolving tablets dissolve or disintegrate in the oral cavity without the need of water. [6-8]

Diabetes mellitus is a condition in which a person has a high blood sugar level, either because the body doesn’t produce enough insulin, or because body cells don’t properly respond to the insulin that is produced. Insulin is a hormone produced in the pancreas which enables body cells to absorb glucose, to turn into energy. If the body cells do not absorb the glucose, the glucose accumulates in the blood, leading to vascular, nerve, and other complications.

Diabetes mellitus is mainly classified as four types. They are, Type -I, Type –II, Gestational diabetes, and other types of diabetes. [9]

Glimepiride is the first III generation sulphonyl urea it is a very potent sulphonyl urea with long duration of action. It is practically insoluble in water. Soluble in dimethyl formamide, slightly soluble in methanol, sparingly soluble in methylene chloride. It also dissolves in dilute alkali and in dilute acids. Half life is Approximately 5 hours following single dose. Completely (100%) absorbed following oral administration. Glimepiride is used with diet to lower blood glucose by increasing the secretion of insulin from pancreas and increasing the sensitivity of peripheral tissues to insulin.[10]

Miglitol is a alpha-glucosidase enzyme inhibitor that delays the digestion of ingested carbohydrates, there by resulting in a smaller rise in blood glucose concentration following meals. As a consequence of plasma glucose reduction, miglitol reduces levels of glycosylated hemoglobin in patients with Type 2 diabetes mellitus. Miglitol regulates the postprandial glucose levels directly by inhibiting the enzyme reversibly and also indirectly by including the secretion of glucagon like peptide-The aims of this study were to design sustained release formulation of miglitol which would inhibit the alpha-glucosidase enzyme for a longer duration of time thus reducing the dosing frequency. Sustained release beads are prepared to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The frequency of drug administration is reduced, patient compliance can be improved and drug administration can be made more convenient. The total amount of drug administered can be reduced, thus maximizing availability with a minimum dose. Overall, administration of sustained release forms enables increased reliability of therapy. [11,12]

EXPERIMENTAL SECTION

I. Methods of preparation-

1. Fast dissolving tablets of Glimepiride were prepared by direct compression method.

Table No.1

Ingredients	F_1	F_2	F_3	F_4	F_5
Glimepiride	4 mg	4 mg	4 mg	4 mg	4 mg
Sodiumstarch glycolate	4 mg	5 mg	6 mg	7 mg	8 mg
Avicel pH 102	42 mg	42 mg	42 mg	42 mg	42 mg
Lactose	46 mg	45 mg	44 mg	43 mg	42 mg
Magnesium stearate	2 mg	2 mg	2 mg	2 mg	2 mg
Talc	2 mg	2 mg	2 mg	2 mg	2 mg

2. Formation of plug- plug is prepared by direct compression method.

Table No.2

Ingredients	P1	P2	P3	P4
HPMC E5	85	85	85	85
Spray Dried Lactose	15	15	15	15
Pressure Applied	1	2	3	4

3. Formation of chitosan coated Microbeads of miglitol-Prepared by ionotropic gelation method.[13-16]
Chitosan coated Microbeads containing miglitol was prepared by ionotropic gelation method. In brief beads were prepared employing chitosan in different ration with sodium alginate. Homogenous dispersion of sodium alginate and miglitol was prepared in distilled water by continues stirring on magnetic stirrer. Chitosan was dissolved in 2% acetic acid solution by stirring on magnetic stirrer, dispersion of sodium alginate and drug was extruded in previously prepared CaCl2 solution with 21gauge needle with stirring on magnetic stirrer at 100 rpm for half hour. Beads were separated and washed with distilled water and kept for 24 hours at room temperature and dipped in chitosan solution for 2 hours. Beads were removed from this solution and dried for 24 hours.

Table No.3

Ingredient	A_1	A_2	A_3	A_4	A_5
Sodium alginate	5%	5%	5%	5 %	5%
Chitosan	0.1 %	0.2 %	0.3 %	0.4 %	0.5 %
$CaCl_2$	3 %	3 %	3 %	3 %	2 %

II. Evaluation and Characterization:-

1. Evaluation of formulated tablet of Glimepiride. [17, 18]

Evaluation of Pre-compression Parameters: It is very important parameter to be measured, since it affects the mass of uniformity of the dose. It is usually predicted in terms of angle of repose, bulk density and tapped density.

Evaluation of Post compression Parameters: The formulated tablets were evaluated for the following parameters such as weight variation, hardness, friability, disintegration and In-vitro dissolution studies are carried out.

2. Evaluation of plug: Prepared plug is evaluated for hardness, thickness and dissolution time.[19]

3. Evaluation of chitosan coated Microbeads: Determination of Production Yield, Encapsulation Efficiency, Swelling study, Scanning Electron Microscopy, Infrared Spectroscopy, Differential Scanning Calorimetry. [20]

RESULTS AND DISCUSSION

1. Glimepiride tablet-

1.1 Pre-formulation study-

Table No.4

Sr. no.	Batch No.	Angle of repose	Bulk density	Tapped density	Compressibility Index	Hausner's ratio
1.	A1	22.13	0.4	0.47	15	1.176
2.	A2	23.57	0.39	0.43	10	1.11
3.	A3	22.90	0.40	0.43	7.5	1.08
4.	A4	22.61	0.39	0.43	10	1.11
5.	A5	22.13	0.39	0.45	12.5	1.14

1.2 Standard calibration curve of Glimepiride in Phosphate buffer pH6.8

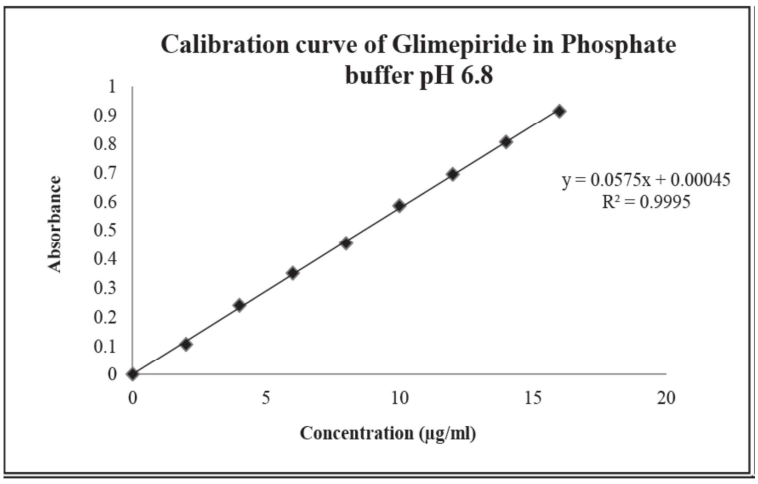


Figure.No.1

1.3 Differential Scanning Calorimetry (DSC)

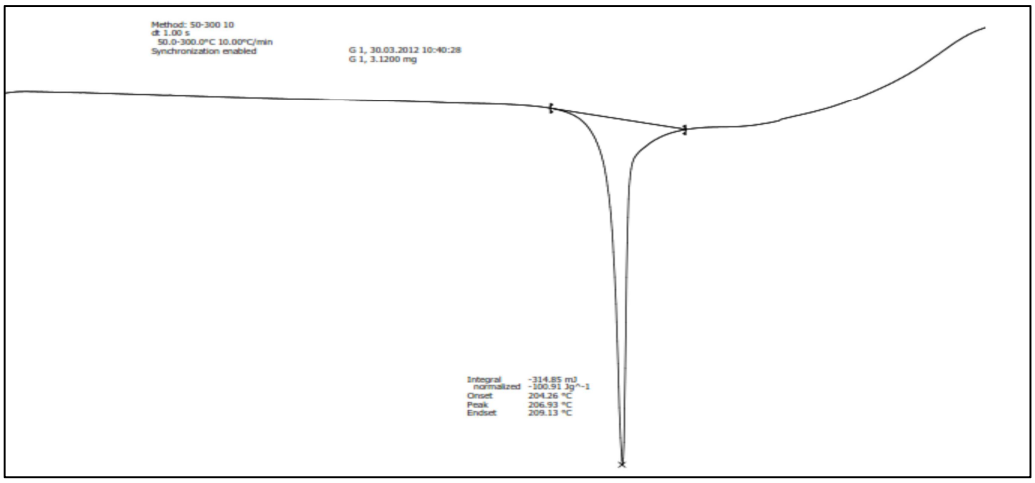


Figure.No.2

1.4 FTIR Spectroscopy

Figure.No.3

1.5 Post- compression parameters-

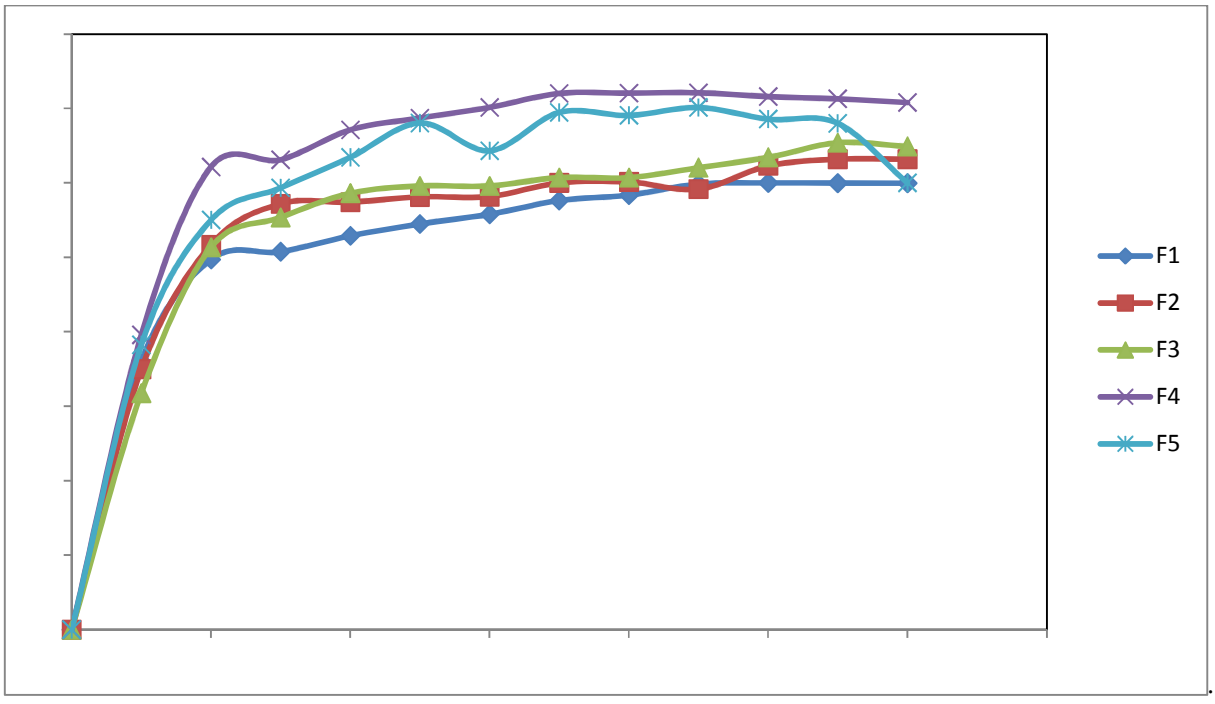
Table No.5

Batch No.	Thickness n= 10 (mm)	Diameter n= 10 (mm)	Hardness n= 5 (kg/cm^3)	In vitro disintegration time n= 5 (Sec.)	Friability (%)	Wetting time (Sec.)	Water absorption ratio	Drug content %
A1	3.01±0.01	7.01±0.02	3±0.01	31.6±0.54	0.012	74±7.07	2.66±1.006	4.002
A2	3.01±0.02	7.01±0.01	3±0.02	30.6±0.54	0.012	79±6.7	3.486±0.438	3.97
A3	3.01±0.01	7.01±0.05	3±0.03	29.4±0.54	0.037	71±6.7	4.25±1.0009	4.01
A4	3.01±0.04	7.01±0.03	3±0.02	36.4±0.54	0.05	58±8.36	3.498±0.55	3.79
A5	3.01±0.01	7.01±0.01	3±0.01	34.6±0.54	0.025	55±5	3.44±0.27	3.87

Batch no. Time	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	36.03±0.0476	34.97±0.00015	31.76±0.0002	39.59±0.002	38.24±0.0002
10	49.72±0.0047	51.68±0.0003	51.53±0.0004	62.15±0.0001	55.01±0.0003
15	50.75±0.002	57.19±0.0006	55.37±0.00037	63.11±0.0004	59.34±0.0001
20	52.89±0.00023	57.41±0.0005	58.60±0.00015	67.12±0.0002	63.44±0.0002
25	54.48±0.002	58.13±0.00047	59.59±0.00015	68.72±0.00015	68.05±0.0001
30	55.79±0.0001	58.17±0.00015	59.59±0.0002	70.14±0.00015	69.32±0.0001
35	57.63±0.0002	60.00±0.00015	60.72±0.00015	72.02±0.00015	69.47±0.0001
40	58.36±0.0001	59.15±0.0002	60.71±0.00015	72.06±0.00015	69.06±0.0002
45	59.84±0.0001	59.31±0.00015	62.04±0.0002	72.11±0.00015	70.12±0.0002
50	60.00±0.0002	62.28±0.0002	63.42±0.0002	71.59±0.00015	68.56±0.0002
55	59.97±0.0002	63.19±0.00015	65.40±0.0002	71.29±0.00015	68.01±0.0002
60	59.96±0.0001	63.18±0.0004	64.89±0.00032	70.79±0.0002	68.00±0.0004

1.6 In vitro dissolution of Glimepiride fast dissolving tablet-

Table No.6



Comparative drug release profile of fast dissolving tablet F1-F5

Figure.No.4

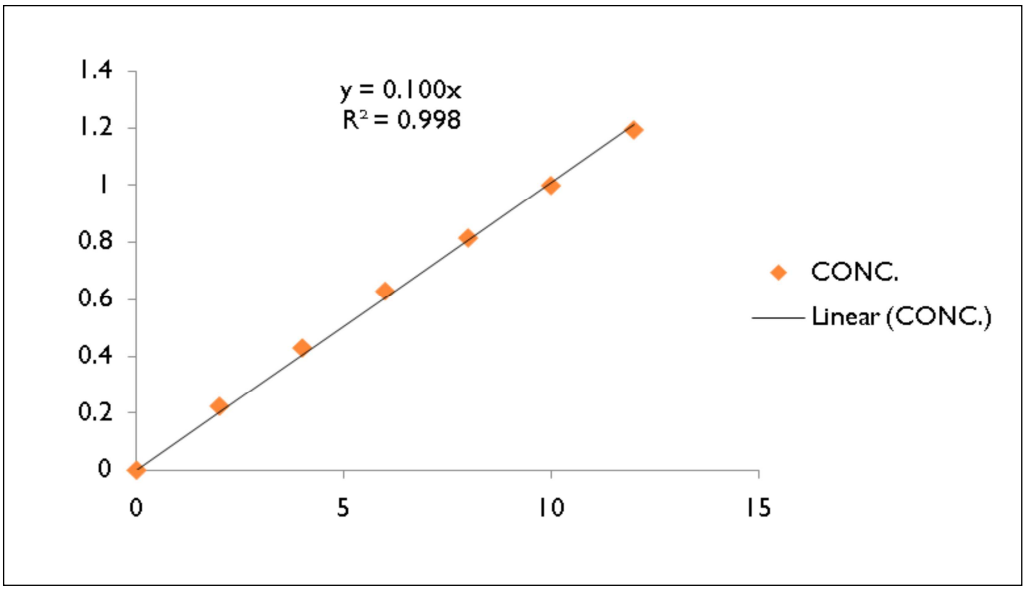
2. Evaluation of plug

Table No.7

Batch No.	Thickness (mm)	Hardness (Kg/cm3)	Diameter (mm)	Lag time (hr)
P1	3.01	5	6	2
P2	3.01	5	6	2.30
P3	3.01	5	6	2.45
P4	3.01	5	6	3

3. Evaluation of chitosan coated miglitol beads beads-

1. Characterisation of Miglitol



2. Differential scanning calorimetry (DSC) miglitol

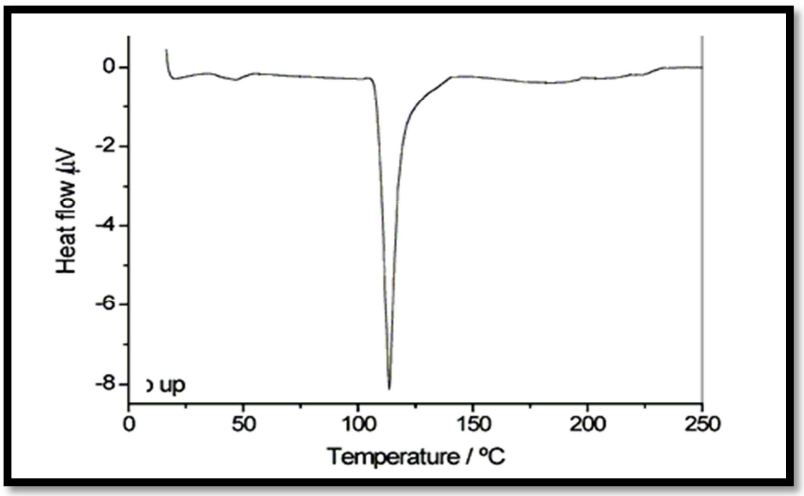


Figure.No.6

3. IR spectra of Miglitol

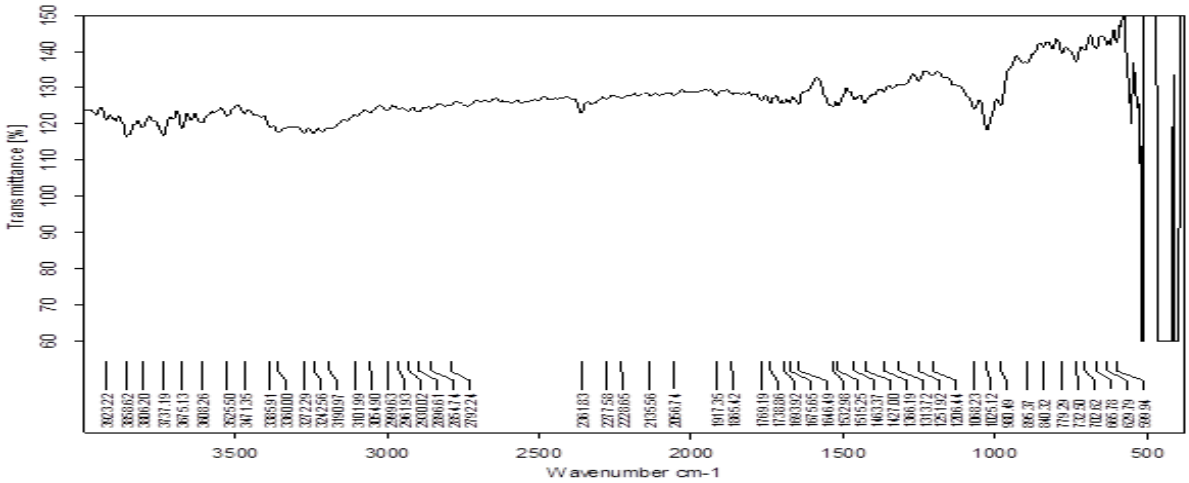


Figure.No.7

4. IR spectra of beads

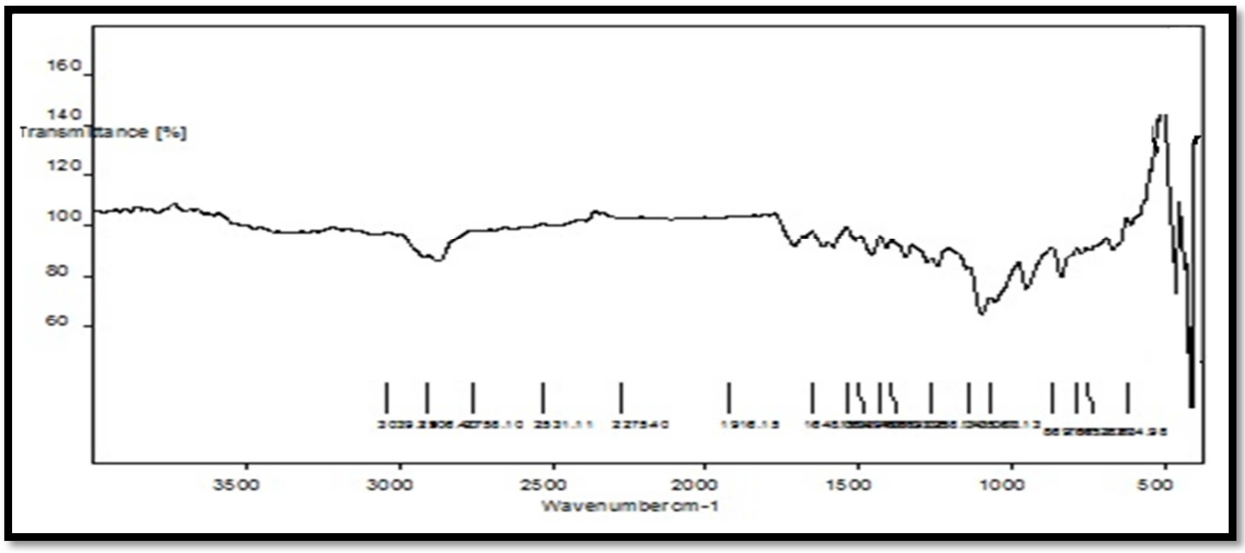


Figure.No.8

4. Evaluation of beads

Table No.8

Batches	Conc. Of sodium alginate	Concentration of chitosan	Therotical yield	Practical yield	Encapsulation efficiency
A1	5	0.1	52.42	50	43.54
A2	5	0.2	71.4	60.23	53.46
A3	5	0.3	99.85	80.21	74.23
A4	5	0.4	85.54	65.23	62.36
A5	5	0.5	85.23	65.55	62.30

6. Dissolution of beads

Table No.9

Batch no. Time Hour.	A1	A2	A3	A4	A5
0	0	0	0	0	0
1	5.21±0.01	5.24±0.3	5.34±0.43	2.13±0.036	5.28±0.3
2	9.25±0.58	9.69±0.43	9.55±0.098	9.56±0.43	9.27±0.61
3	24.06±0.97	28.86±0.82	23.55±0.53	23.55±0.22	23.47±0.41
4	25.93±1.03	49.32±0.93	46.67±0.39	46.67±0.039	50.97±0.71
5	26.32±0.54	54.51±0.76	59.32±0.1	59.32±0.01	59.37±0.43
6	27.82±0.49	57.63±0.02	64.80±0.14	61.82±0.63	59.95±0.82
7	31.80±0.62	60.53±0.55	67.27±0.34	63.95±0.31	62.18±0.33
8	43.31±0.67	67.79±0.54	64.29±0.69	65.70±0.34	61.66±0.72

7. Comparative drug release profile of beads

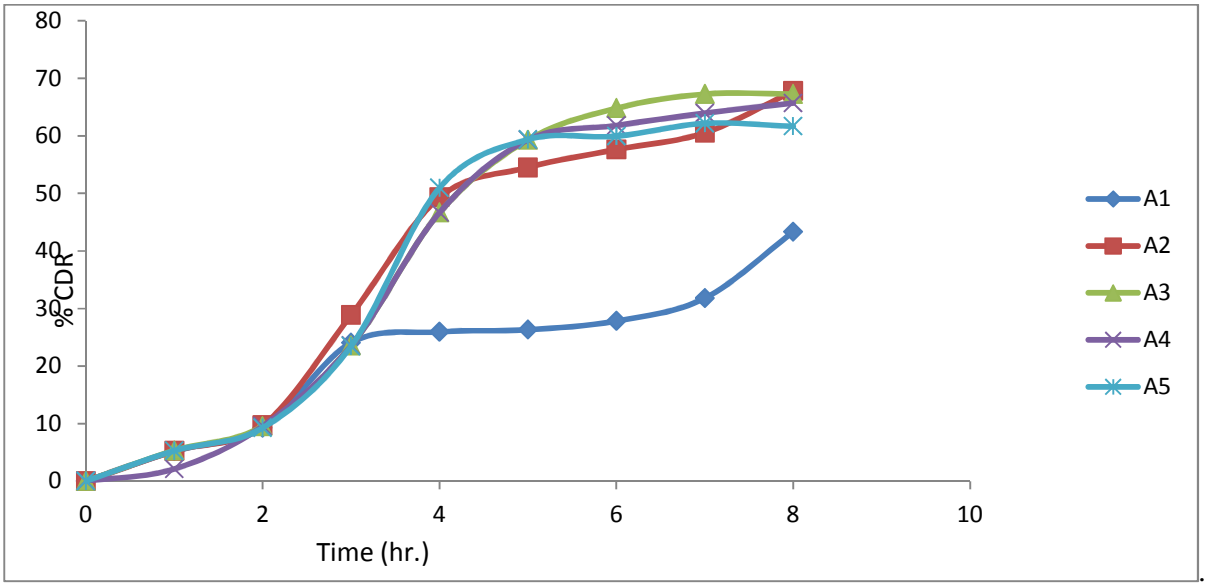


Figure.No.9

4. Coating of capsule body

- Cellulose acetate phthalate
- Acetone
- Ethanol

5. Dissolution study of final formulation-

Table No.10

Time in Min.	Absorbance			Mean	% CDR
	C1	C2	C3		
Fast dissolving tablet of Glimepiride					
5	1..012	1.0122	1.0124	1.012	39.59
10	1.5231	1.5236	0.5234	1.5233	59.59
15	1.6255	1.6259	1.6251	1.6250	63.58
20	1.7159	1.7162	1.7157	1.7159	67.12
25	1.7559	1.7590	1.7523	1.7567	68.75
30	1.7931	1.7935	1.7938	1.7934	70.16
35	1.8412	1.8407	1.8416	1.8413	72.03
40	1.821	1.8425	1.8429	1.8354	71.80
45	1.8435	1.8439	1.8441	1.8438	72.13
50	1.8301	1.8305	1.8304	1.8303	71.60
55	1.8211	1.8215	1.8219	1.8215	71.25
60	1.8102	1.8101	1.8205	1.8102	70.81
Lag time 2.30hr. Chitosan coated beads of miglitol					
1hr	0.0701	0.0706	0.0705	0.0705	5.28
2hr	0.0123	0.1237	0.1233	0.1236	9.25
3hr	0.127	0.1273	0.1271	0.1271	23.47
4hr	0.276	0.2761	0.2763	0.2761	50.97
5hr	0.3219	0.3225	0.3221	0.3221	59.47
6hr	0.3245	0.3248	0.3225	0.3476	59.95
7hr	0.3365	0.3369	0.3371	0.3368	62.18
8hr	0.4421	0.4423	0.4426	0.4423	81.66

CONCLUSION

A pulsatile drug delivery system for oral use was developed and evaluated. From the Preformulation studies it was found that powder of all formulations showed its all essential characteristics as per official specifications. Angle of repose of powder material was less than 30; Hausners ratio was less than 1.25; Carr's index was less than 15%. These all results indicated an excellent flow property of powder to formulate the tablets using Direct Compression technique.

Prepared system mainly consists of 3 parts. A FDT of Glimeperide were prepared by direct compression by using Sodium Starch Glycollate. Among the fast dissolving tablet of Glimeperide, the F4 batch formulation prepared by using sodium starch glycollate emerged as an overall best formulation based on disintegration time characteristics. Amongst the beads of Miglitol A3 batch were selected as an optimized batch.

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