Development and evaluation of floating microspheres loaded with anti diabetic drug-GLIMEPIRIDE

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ABSTRACT :The objective of the present study was to develop Glimepiride floating microspheres in order to achieve an extended retention in the upper GIT. Which may result in enhance the absorption and improve the bioavailability. The microspheres were prepared by emulsion solvent diffusion-evaporation method using different ratios of rate controlling polymers ethyl cellulose and hydroxy propyl methyl cellulose, Glimepiride is used in each formulation at constant ratio.The prepared microspheres were evaluated for percentage yield, particle size, entrapment efficiency, shape and surface characterization, buoyancy, in vitro dissolution studies and drug release mechanism was interpretated by kinetic model. The effect of polymer concentration on these parameters was investigated. The studies revealed that increase in concentration of hydrophillic polymer (HPMC) increased the drug release from the floating microspheres. The formulation F9 (Glimepiride:HPMC:EC is 1:3:2) was selected as best formulation, and it follows zero order drug release with 86.63% entrapment efficiency, 98.16% drug content, 90% buoyancy, 87.48% In-vitro drug release at 12th hour

INTRODUCTION Most of the pharmaceutical products designed for oral delivery are conventional drug delivery systems.Oral route is considered most popular, convenient and safe due to ease of administration, patient acceptance, and cost-effective manufacturing process.Problem encountered with conventional dosage forms are: drugs with short half life require frequent administration, which may increase chance of missing dose of drug leading to poor patient compliance. Fluctuations in drug plasma concentration this may accumulate side effects. In order to overcome the drawbacks of conventional drug delivery system, several technical advancements have led to development of CONTROLLED DRUG DELIVERY SYSTEM Controlled release systems include any drug delivery systems that achieve slow release of drug over an extended period of time. that could revolutionize method of medication and provide a number of therapeutic benefits. However, such oral drug delivery devices have a physiological limitation of gastric retention time (GRT). Variable and short gastric emptying time can result in incomplete drug release from the drug delivery system ,to overcome these limitations, several approaches being proposed to prolong the GRT include Floating drug dosage systems (FDDS). Floating drug delivery systems (FDDS) or hydrodynamically balanced systems (HBS) are among the several approaches that have been developed to increase the GRT of dosage forms Both single and multiple unit systems have been developed,Single-unit systems are unreliable in prolonging the GRT owing to their ‘all-or-nothing’ emptying process resulting high variability in bioavailability and local irritation In contrast, multiple-unit particulate dosage forms (e.g. microspheres) have the advantages that they pass uniformly through the GIT to avoid the vagaries of gastric emptying and provide an

adjustable release, thereby reducing the intersubject variability in absorption and risk of local irritation. Various multiple-unit floating systems have been developed in different forms MICROSPHERES over conventional multi dose therapy recent trends indicate that microparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. using microspheres as carriers for drug is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without unwanted effect Microspheres are matrix systems and essentially spherical in shape, whereas microcapsules may be spherical or non-spherical in shape

FLOATING MICROSPHERES Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers. Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs the increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability, and extensive first pass metabolism

Diabetes: It is a complex metabolic disorder resulting in hyperglycemia. Hyperglycemia may be attributed to defects in pancreatic β- cells, insulin secretion, hepatic glucose output, glucose uptake of peripheral tissues and immune function. It is also a disorder of carbohydrate, protein and fat metabolism results an imbalance between insulin ability and insulin need. A person with uncontrolled diabetes is unable to transport glucose in to fat and muscle cells, as a result, the body cells are starved and the breakdown of fat and protein is increased.

GLIMEPIRIDE is an anti-diabetic drug comes under the category of second-generation sulfonylurea, and is very potent. It acts as insulin sensitizer Its half life is 5 hrs, more than 99% bind to plasma proteins, and is mainly excreted through urine remaining through faeces. Glimepiride should be administered with breakfast or the first main meal. Recommended dose is minimum 2 mg to maximum 8 mg. 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. The mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells, and increasing sensitivity of peripheral tissues to insulin

MATERIALS & INSTRUMENTS: Glimepiride (Medrich Pvt. Ltd), Ethyl cellulose N10 (Loba chemie pvt.ltd,Mumbai)Hydroxy propyl methyl cellulose K100M(Loba chemie pvt.ltd, Mumbai) ,Dichloromethane(Medrich Pvt. Ltd) Ethanol (Medrich Pvt. Ltd) Tween 80 (Loba chemie pvt.ltd, Mumbai)

Digital balance (Shimadzu ELB 300)Probe sonificator(Elektro craft India Pvt.Ltd, Mumbai) Orbitek shaker (Orbitek shaker, chennai), Dissolution apparatus USP XXIII(Veego tablet dissolution apparatus, Chennai), Double beam UV spectrophotometer (Perkin Elmer Lambda-25 UV/VIS spectrometer)

METHODS:

PREFORMULATION STUDIES: Preformulation studies give the information need to define the nature of drug substance and provide a frame work for a drug combination with pharmaceutical exciepients in the fabrication of a dosage form.

❖ COMPATIBILITY STUDIES Present work a study was carried out by using FTIR spectrophotometer and Differential scanning calorimeter (DSC) to find out if there is any possible chemical interaction of Glimepiride with hydroxyl propyl methylcellulose (HPMC), ethyl cellulose (EC).

❖ CONSTRUCTION OF STANDARD CURVE FOR GLIMEPIRIDE Glimepiride can be estimated spectrophotometrically at 224 nm as it obeys Beer's-Lambert's law limit is the range of 5-25 µg/ml

❖ PREPARATION OF FLOATING MICROSPHERES BY EMULSION SOLVENT DIFFUSION EVAPORATION TECHNIQUE Accurately weighed amount of Glimepiride, ethyl cellulose and hydroxy propyl methyl cellulose K100M were dissolved in a mixture of Dichloromethane (DCM): Ethanol (ETN) (1:1) at room temperature. This solution was poured into 100ml distilled water containing 0.1% Tween 80 maintained at a temperature of 300-400C.The resultant emulsion was stirred with a propeller type agitator at 1200 rpm for 45 mins to allow volatile solvent to evaporate. The resultant microspheres were filtered and dried

The formulations of different batches of Glimepiride floating microspheres are given in table 4.

Formulation code	Drug:Polymer: Polymer	Glimepiride in (mg)	Hydroxyl propyl methyl cellulose K100M in (mg)	Ethyl cellulose in (mg)
F1	1:1:0	10	10	0
F2	1:2:0	10	20	0
F3	1:3:0	10	30	0
F4	1:1:1	10	10	10
F5	1:2:1	10	20	10
F6	1:3:1	10	30	10
F7	1:1:2	10	10	20
F8	1:2:2	10	20	20

F9	1:3:2	10	30	20
F10	1:1:3	10	10	30
F11	1:2:3	10	20	30
F12	1:3:3	10	30	30

EVALUATION OF THE PREPARED FLOATING MICROSPHERES

Particle size analysis

The particle size of the microsphere is determined by using the optical microscopy method. Microspheres are counted for particle size using a calibrated optical microscope.

Shape and surface characterization The shape and surface characterization of microspheres are observed under scanning electron microscope(SEM).The microspheres are mounted directly on the SEM sample stub, using double-sided sticking tape, and coated with gold film(thickness 200mm) under reduced pressure (0.001 tort) and photographed

Determination of drug content

Accurately weighed 10 mg of crushed microspheres were dissolved in 0.1N HCl, and then transferred to 100 ml volumetric flask. The volume was made up to 100mL with 0.1N HCl. The solution was filtered using Whatman filter paper no. 41. The samples were assayed for drug content using UV spectrophotometer at 224 nm.

Determination of percentage yield of microspheres

Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formula given below.

$$\text{percentage yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer}} \text{X100}$$

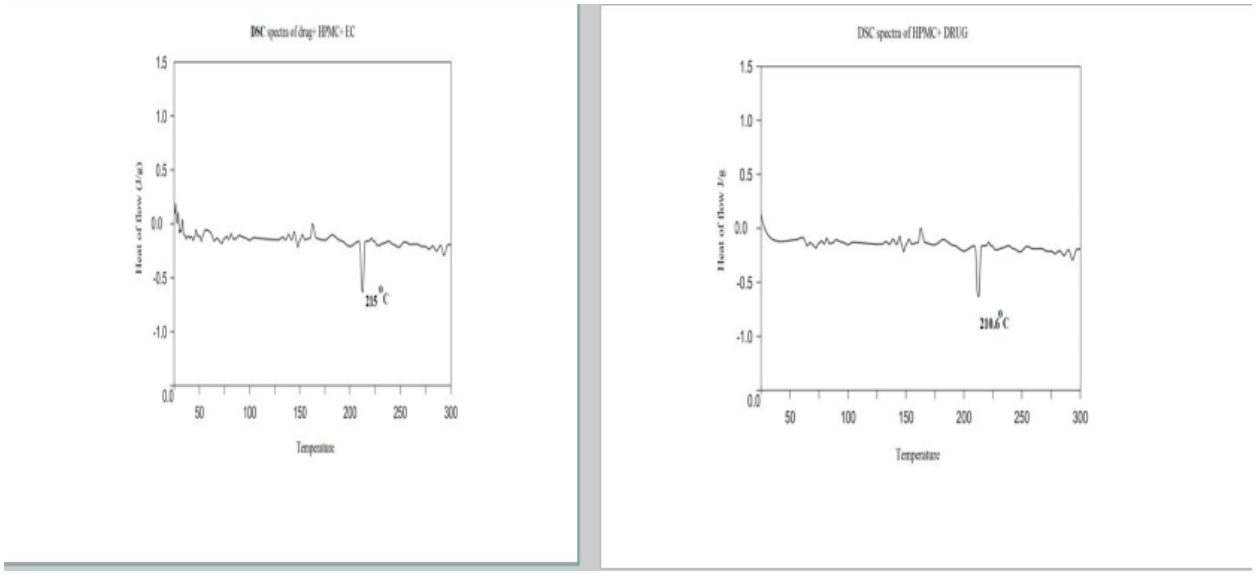
Kinetics of drug release

In order to understand the mechanism and kinetic of drug release, the drug release data of the in-vitro dissolution study are analysed with various kinetic model like zero order, first order,higuchi's, peppa's and coefficient of correlation (r) values are calculated for the linear curves by regression analysis of the above plots.

RESULTS AND DISCUSSION:

Fourier Transform Infrared Spectrophotometer (FTIR) Infrared spectra for pure drug Glimepiride, HPMC, EC, and physical mixture of drug and polymer were determined to check the interaction of drug in the polymer mixture, their spectrums are shown

Differential scanning calorimeter (DSC) DSC provides information about physical properties of sample as crystalline or amorphous nature and demonstrates the possible interaction between drug and other polymers



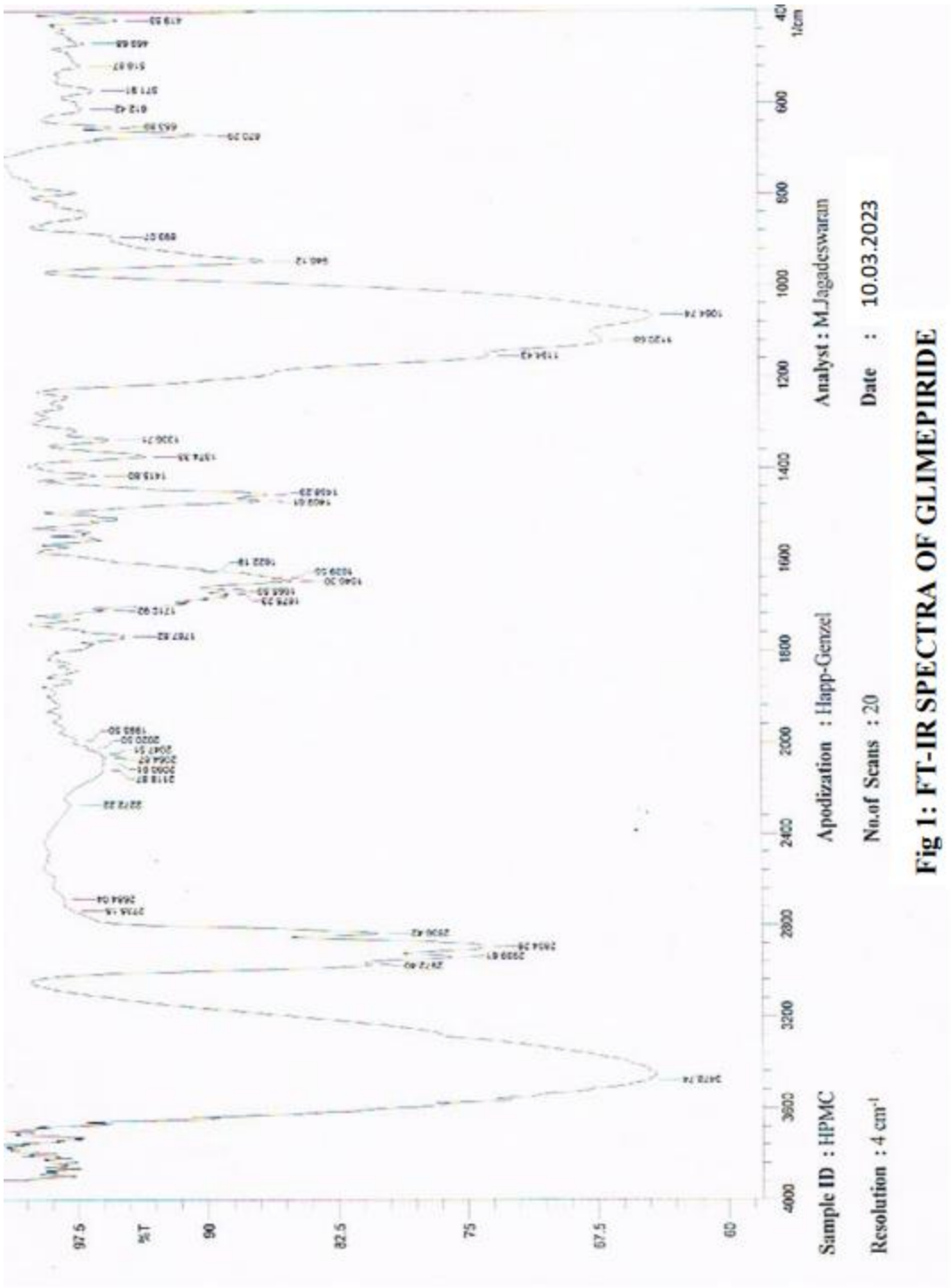
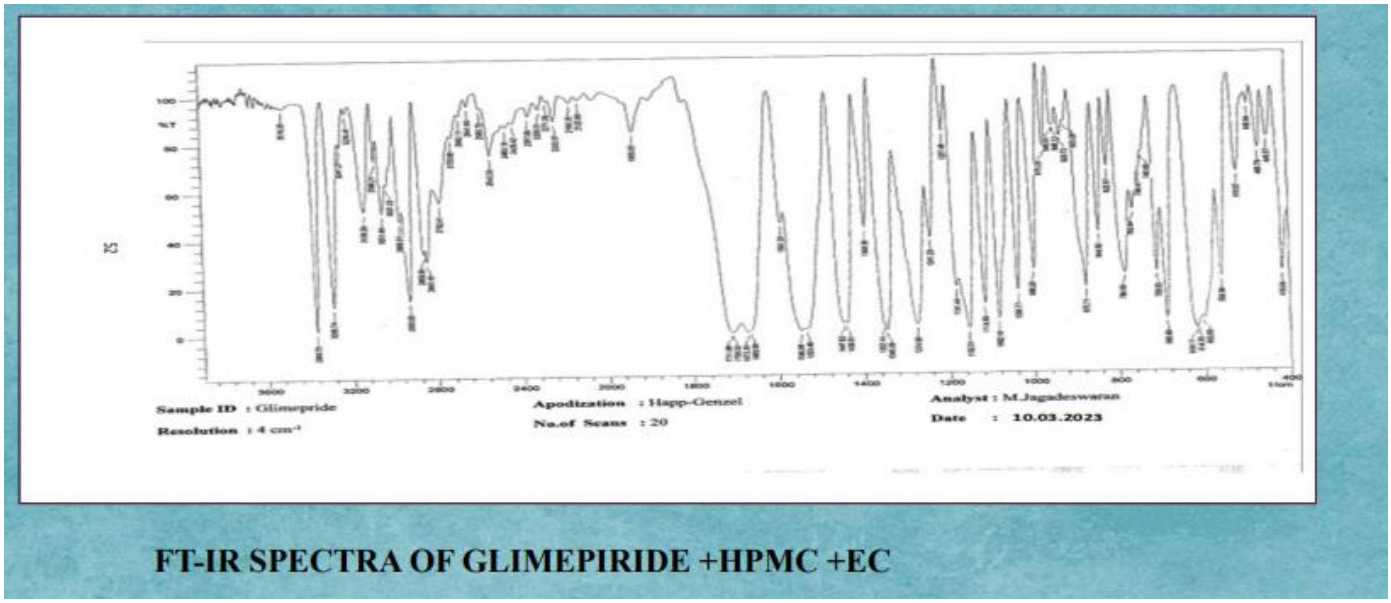
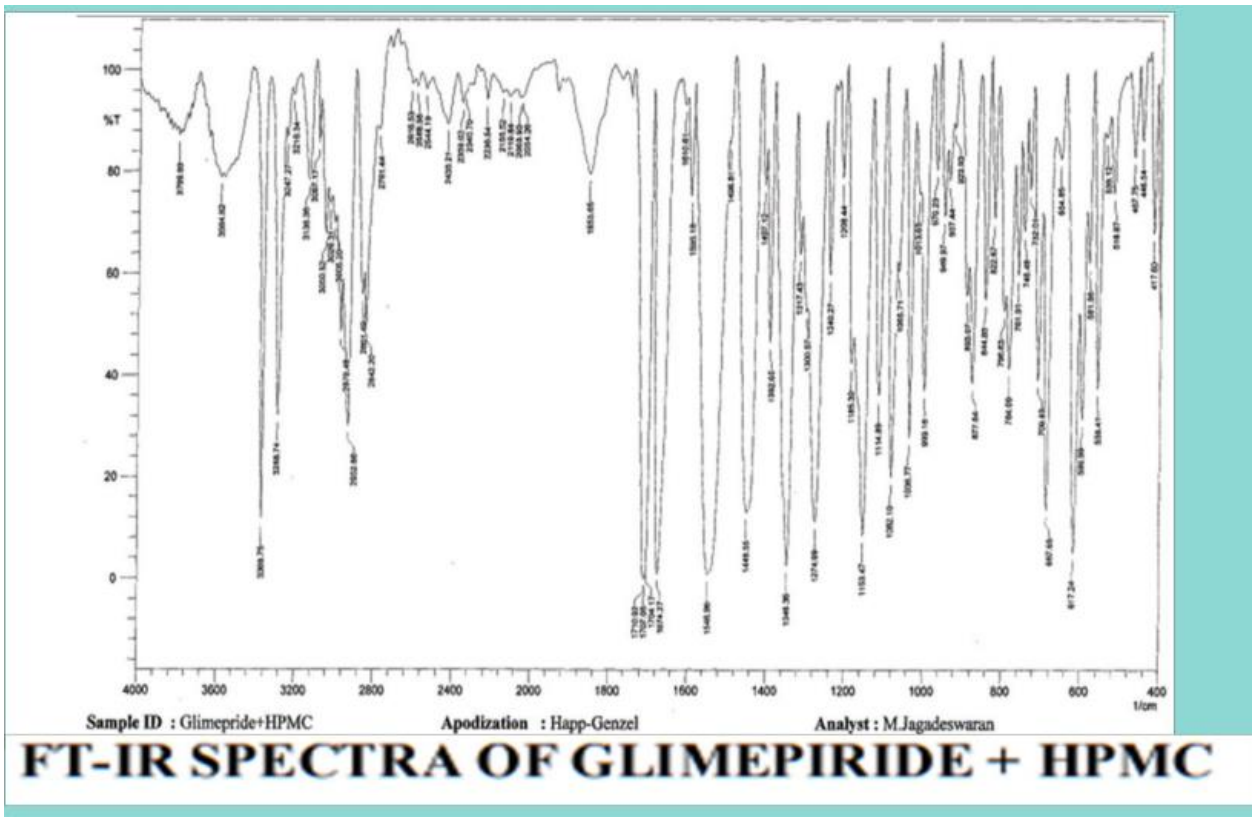


Fig 1: FT-IR SPECTRA OF GLIMEPIRIDE

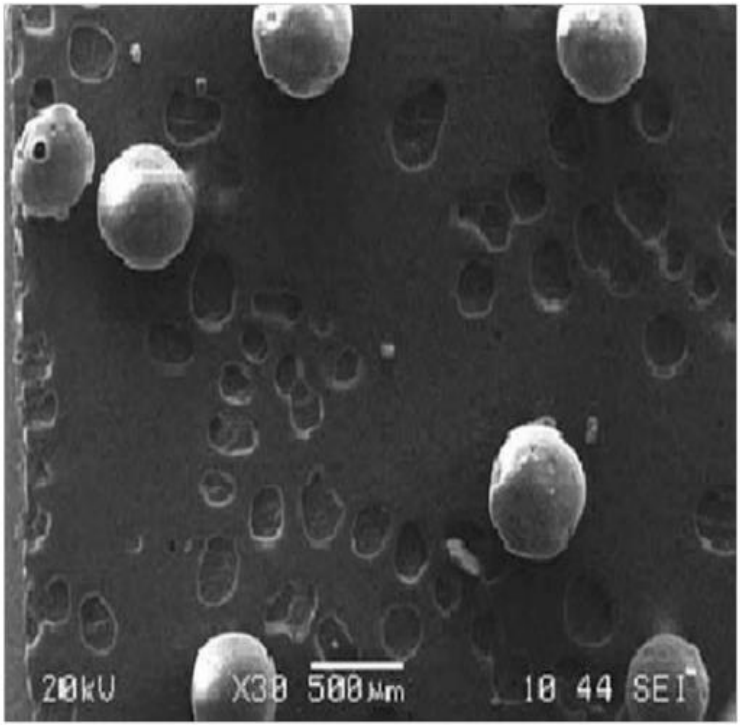


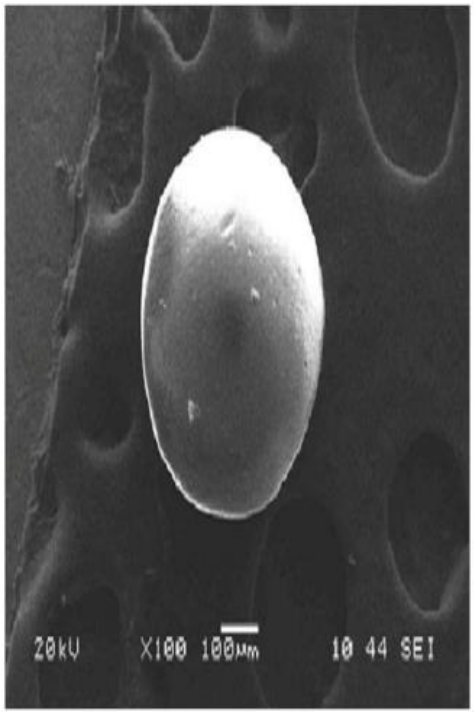
FT-IR SPECTRA OF GLIMEPIRIDE +HPMC +EC



FT-IR SPECTRA OF GLIMEPIRIDE + HPMC

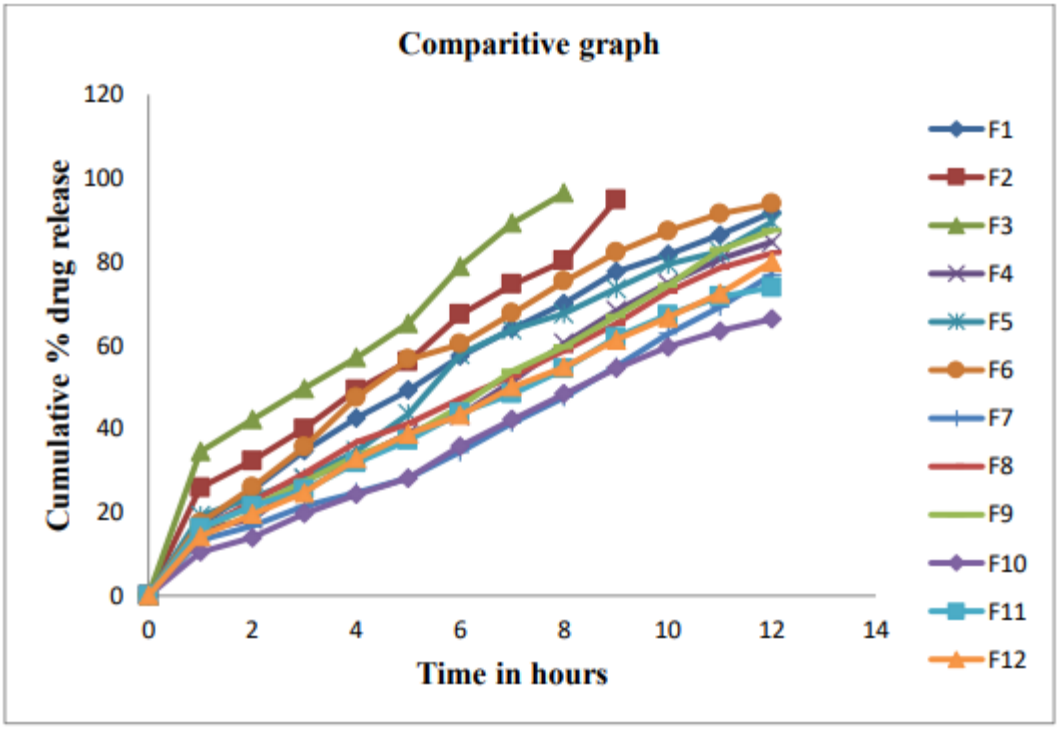
Scanning electron micrograph (SEM) of the prepared floating microspheres of glimepiride formulation





DATA FOR *IN-VITRO* CUMULATIVE PERCENTAGE DRUG RELEASE OF F1 TO F12 FORMULATIONS

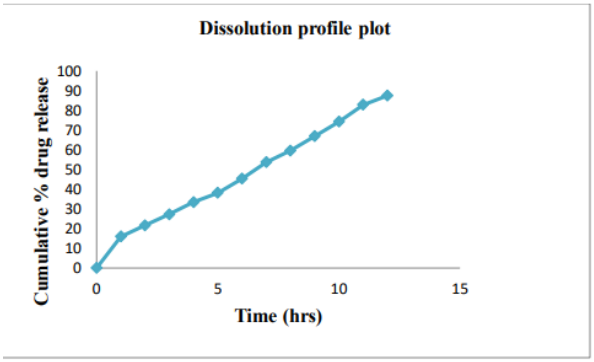
TIME in Hrs	FORMULATION CODE AND CUMULATIVE PERCENTAGE OF DRUG RELEASE											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
1	16.86	25.84	34.54	15.87	19.2	17.42	13.25	15.73	16	10.47	16.21	14.21
2	25.32	32.26	42.13	18.27	23.42	25.93	16.67	22.45	21.25	13.92	21.42	19.50
3	34.65	39.92	49.62	27.90	28.13	35.59	21.36	29.21	27.21	19.63	25.32	24.63
4	42.52	49.28	57.02	32.62	34.65	47.46	24.68	36.78	33.47	24.20	31.82	32.8
5	49.23	56.05	65.25	38.85	43.56	56.58	28.18	41.23	38.16	28.14	37.21	38.73
6	57.37	67.27	78.85	43.17	57.69	60.22	34.41	47.11	45.33	35.81	43.81	43.21
7	63.96	74.53	89.22	51.39	63.72	67.64	41.37	52.54	53.72	42.16	48.27	49.98
8	70.02	80.19	96.41	60.42	67.54	75.27	47.54	58.67	59.6	48.33	54.31	54.72
9	77.54	94.73	_	68.25	73.49	82.19	54.83	65.12	66.89	54.42	61.88	61.24
10	81.73	_	_	74.76	79.37	87.33	62.74	72.82	74.24	59.56	67.21	66.65
11	86.37	_	_	80.56	82.41	91.43	69.14	78.48	82.81	63.39	71.58	72.37
12	92.07	_	_	84.73	89.49	93.85	76.87	82.02	87.48	66.25	73.82	79.96


Comparitive graph
Cumulative % drug release
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Time in hours
F1
F2
F3
F4
F5
F6
F7
F8
F9
F10
F11
F12

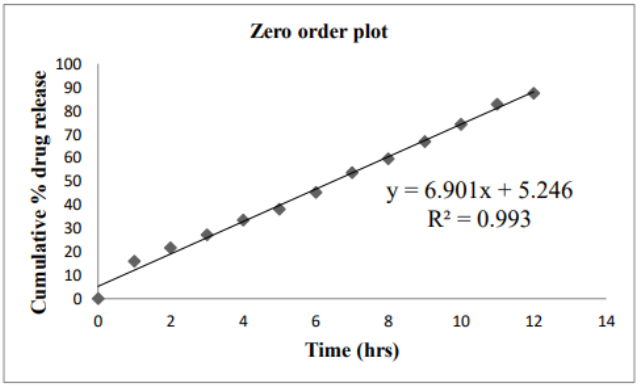
In -Vitro Drug release of Formulation F9

Time (hrs)	Absorbance (nm)	Concentration µg/ml	Amount of drug release	Cum % of drug release
0	0	0	0	0
1	0.012	0.31	2.8	16±1.527
2	0.019	0.481	4.33	21.25±1.362
3	0.024	0.604	5.44	27.21±1.185
4	0.029	0.743	6.69	33.47±1.925
5	0.033	0.848	7.63	38.16±1.643
6	0.04	1.007	9.06	45.33±1.152
7	0.047	1.193	10.74	53.72±2.059
8	0.052	1.324	11.92	59.6±1.295
9	0.059	1.486	13.37	66.89±1.592
10	0.065	1.649	14.84	74.24±1.342
11	0.073	1.84	16.56	82.81±1.346
12	0.077	1.944	17.49	87.48±1.264

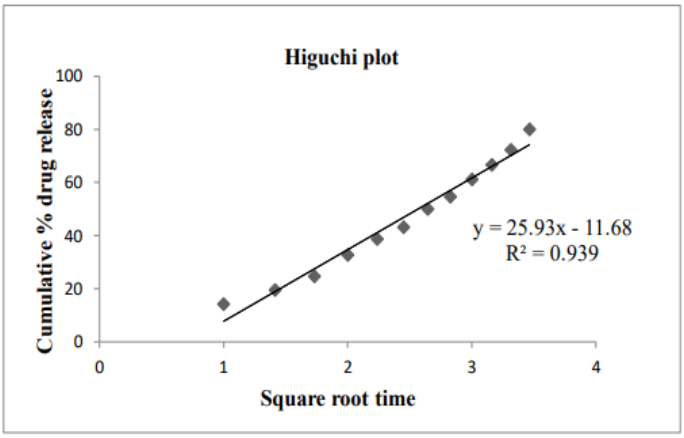
***IN-VITRO* DRUG RELEASE PLOT FOR F9**



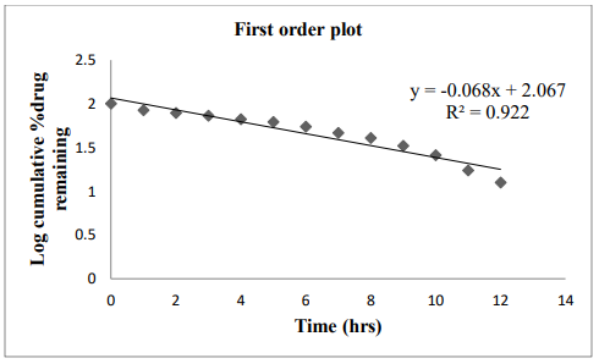
KINETIC PLOT OF ZERO ORDER DRUG RELEASE FOR F9



KINETIC PLOT OF HIGUCHI DRUG RELEASE FOR F9



KINETIC PLOT OF FIRST ORDER DRUG RELEASE FOR F9



DISCUSSION

In the present work efforts have been made to develop floating microspheres for controlled drug delivery of Glimepiride, by emulsion solvent diffusion evaporation technique using various proportions of Hydroxy propyl methyl cellulose, Ethyl cellulose as floating and rate controlling polymers. Polymer concentration is the major factor for controlling drug release and also for buoyancy. The FTIR and DSC spectral analysis showed that there was no appearance or disappearance of any characteristic peak of pure drug Glimepiride, and in the physical mixture of drug and polymer, which confirms the absence of chemical interaction between the drug and polymer **The release profile of formulations F1, F4, F5, F6, F8, F9 were best fitting with USFDA guidelines for extended drug release for 12hrs, and release the drug** not more than 20% in 1st hr and not less than 80% in 12th hr.Based on the parameters like drug content 98.16%, entrapment efficiency-86.63%, buoyancy-90% and in-vitro drug release 87.48% at 12th hr

CONCLUSION

The study showed that Glimepiride floating microspheres can be developed by Emulsion solvent diffusion-e vaporation method and the results revealed that the **formulation F9** shows desired release charecterestics in the polymer ratio of (3:2) the hydroxy propyl methyl cellulose and ethyl cellulose in order to achieve the controlled release of drug up to 12 hours. Further in-vivo studies to be carried out to confirm the formulation . In the present work efforts have been made to develop floating microspheres for controlled drug delivery of Glimepiride, by emulsion solvent diffusion evaporation technique using various proportion s of Hydroxy propyl methyl cellulose, Ethyl cellulose as floating and rate controlling polymers. Polymer concentrati on is the major factor for controlling drug release and also for buoyancy. The study showed that Glimepiride floating microspheres can be developed by Emulsion solvent diffusion-evaporation method and the results revealed that the formulation F9 shows desired release charecterestics in the polymer ratio of (3:2) the hydroxy propyl methyl cellulose and ethyl cellulose in order to achieve the controlled release of drug up to 12 hours. Further in-vivo studies to be carried out to confirm the formulation.

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