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Formulation and *in-vitro* characterization of floating microspheres of Metfomin HCl

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ABSTRACT

Floating drug delivery system is one of the novel drug delivery system. Floating drug delivery system have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time.This present study involves Formulation and evaluation of floating microspheres of Metformin Hcl as model drug for prolongation of gastric residence time. The microspheres were prepared by the Non Aqueous solvent diffusion method using polymers hydroxy propylmethyl cellulose and ethyl cellulose. The melting point study was performed by differential scanning calorimetry, compatability studies between the drug and polymer was observed by using the FTIR Analysis.The melting point is determined by DSC. The shape and surface morphology of prepared microspheres was characterized by motic and scanning electron microscopy, respectively. In vitro drug release studies were performed, and drug release kinetics were evaluated using the linear regression method. The prepared microspheres exhibited prolonged drug release (12 hr) and remained buoyant for > 13 hr. The mean particle size increased and the drug release rate decreased at higher polymer concentration. In vitro studies demonstrated super case II transport diffusion from the microspheres. By the observation and of all formulations results we concluded that formulation 9 having the better drug release.

Key words: Floating Microspheres,Metformin HCl,Non Aqueous Solvent Diffusion Method,*In-Vitro* Drug Release Studies; Stability Studies.

INTRODUCTION

Oral controlled release (CR) dosage forms(DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance andflexibility in formulation.[1]. control of placement of a drug delivery system(DDS) in a specific region of the GI tract offers advantages for a variety of important drugscharacterized by a narrow absorption windowin the GIT or drugs with a stability problem [2]. control of placement of a drug delivery system (DDS) in a specific region of the GItract offers advantages for a variety of important drugs characterizedby a narrow absorption window in the GIT or drugs with a stability problem the bioavailability of drugs with an absorption window in the upper small intestine is generally limited with conventional pharmaceutical dosage forms. The residence time of such systems and thus, of their drug release into the stomach and upper intestine is often short. To overcome this restriction and to increase the bioavailability of these drugs, controlled drug delivery systems with a prolonged residence time in the stomach can be used[3]. Incorporation of the drug into a CR-delivery system, which releases its payload in the stomach over a prolonged time period, can lead to significant therapeutic advantages owing to various pharmacokinetic and Pharmacodynamic aspects. Gastro retentive dosage forms (GRDFs) are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged

retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome. The challenge to develop efficient gastro retentive dosage forms began near about 20 years ago[4] . Many attempts have been made to devise an extended release GRDDS where the dosage form is small enough to ingest and then retained in the GI area for a long enough time for the active agent to be dissolved and eventually absorbed. For example, many swelling and expanding systems have been attempted. There are dosage forms that swell and change their size thereby floating to the surface[5]. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion[6]. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. [7].

Metformin Hcl is a biguanide antihyperglycemic agent that improves glucose tolerance in patients with type II diabetes. Metformin Hcl is incompletely absorbed from gastrointestinal tract,it has absorption window confined to upper part of gastrointestinal tract .It has half life of 5-6 hours and its absolute bioavailability is reported to be about 50-60% of the administered dose, hence The aim of present study was to develop floating microspheres of Metformin Hcl by Non aqueous solvent diffusion method. Metformin Hcl whose physicochemical properties and short half life makes it suitable candidate for floating drug delivery system. It is a suitable candidate for gastroretentive floating drug delivery system.

MATERIALS AND METHODS

Metformin HCl was obtained from Harman finochem,Aurangabad as a gift sample. Ethyl Cellulose from Centaur pharmaceutical,Hingewadi pune,,HPMC K15 M and HPMC K100M were obtained from Kopran Pharmaceuticals, khopoli Raigad.All other chemicals and solvents used for analytical grade only.

Physical observation compatibility studies

Physically accurately weighed quantities (different ratio) of drug and polymers were mixed well and stored in Petri dishes. Correctly marked for each Petri dish different ratios of drug and polymer . Then the prepared Petri dishes were stored in different temperatures . and seen for colour change .

Analytical compatibility studies[8].

FTIR spectral analysis of pure drug and polymers was carried out and observation was made weather changes in the chemical constitution of drug after combining it with the polymers occurred. i.e. 25 and 40°C. Then observe any colour changes are there in the physical mixture of the drug and polymers. The Petri dishes were observed in three times such as first day, first week and second week

Preparation of Floating Microspheres[9]

The floating Microspheres were prepared by Non aqueous solvent diffusion method. Drug and polymers (Ethyl Cellulose, HPMC K 15M and HPMC K 100M) were mixed in ethanol at various ratios by using blending solvent e.g. Isopropyl alcohol. The prepared slurry was introduced into 200ml of liquid paraffin while being stirred at 1200 rpm by homogenizer for 2 hours at room temperature. To allow for solvent evaporate completely and the microspheres were collected by filtration. The collected floating microspheres washed repeatedly with petroleum ether, until free from oil. The collected microspheres were dried for 2 days at room temperature.Formulation batches of drug and polymer were shown in the table No: 03.

Determination of Percentage Yield [10]

Dried Microspheres were weighed and the percentage yield of microsphere of different formulations was calculated by using the formula.

% Yield = Pracical yield (gm)/Therotical yield ×100

Micromeritic Properties[11, 12]

Angle of repose

Angle of repose of different formulations was measured according to fixed funnel method. Completely dried Microspheres were weighed and passed through the funnel, which was kept at a height ‘h’ from the horizontal surface. The passed micropsheres formed a pile of the height ‘h’ above the horizontal surface and the diameter of the pile was measured and the angle of repose was determined for all the formulation using the formula,

tan θ = h / r
Angle of repose (θ) = $\tan^{-1}$ (h / r)
Where, h is the height of the pile and r is the radius.

Table: 1. Physical observation test for drug polymer compatibility studies

Sr no	Polymer	Physical Observation					
		First Day		After one Week		After Two Week	
		25°c	40°c	25°c	40°c	25°c	40°c
1	Ethyl Cellulose	NC	NC	NC	NC	NC	NC
2	HPMC K 15 M	NC	NC	NC	NC	NC	NC
3	HPMC K 100 M	NC	NC	NC	NC	NC	NC
4	HPMC K 15M: HPMC K 100M	NC	NC	NC	NC	NC	NC

Table :2. FTIR interpretation results of drug and polymers

Sr.no	Name of compound	Wave number (cm^{-1})
1	Metformin Hcl	1473, 1732, 3565 , 3837.
2	Ethyl Cellulose	881,918,1053,1375,1442,2870,2974.
3	HPMC K 15 M	945,1053,1193,1313,1373,1452,2839, 2904,2920,3226,3377,3414.
4	HPMC K 100 M	1362, 1748, 2064, 2837, 3836
5	Drug and polymer combination	634,651,1060,1417,1446,1473, 1508,1533,1544,1620,3149.

Table :3. Formulation table for for floating microsphere of Metformin Hcl.

Formulation code	Liquid paraffin (ml)	Drug (mg)	Ethyl cellulose (mg)	HPMC K15 M (mg)	HPMC K100 M (mg)
MTFM -1	200 ml	500	100	100	100
MTFM -2	200 ml	500	100	100	50
MTFM -3	200 ml	500	100	100	150
MTFM -4	200 ml	500	100	50	100
MTFM -5	200 ml	500	100	50	50
MTFM -6	200 ml	500	100	50	150
MTFM -7	200 ml	500	100	150	100
MTFM -8	200 ml	500	100	150	50
MTFM -9	200 ml	500	100	150	150

Bulk density and Tapped Density

The loose bulk density (LBD) and tapped bulk density (TBD) of microspheres were determined. The prepared microspheres was poured into a calibrated measuring cylinder (10 ml) then noted initial volume. Then the cylinder was allowed to fall under its own weight onto the hard surface from the height of 2.5 cm at 2 seconds intervals. The tapping was the continued no further change in volume was noted. LBD and TBD were calculated using following equation,

$$LBD = \frac{\text{weight of the powder}}{\text{volume of the packing}}$$

$$TBD = \frac{\text{weight of the powder}}{\text{tapped volume of the packing.}}$$

Compressibility Index

The compressibility index (Carr's Index) of the all formulations were determined by using the below mentioned equation,

$$\text{Carr's Index (\%)} = \frac{(TBD - LBD)}{TBD} \times 100$$

Hausner's Ratio

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

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25)

Determination of Drug Content [13]

An accurately weighed quantity of the floating microspheres equivalent to 50mg of the drug was taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1 N HCl repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance was measured after suitable dilution at 232 nm by using UV-visible spectrophotometer. The drug content was estimated in triplicate using a calibration curve constructed in the same solvent.

Determination of Drug Entrapment Efficiency[14, 15]

Amount of drug entrapped in to the microspheres is determined by using the formula.

$$\%\text{Entrapment efficiency} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

Determination of Mean Particle Size of Microspheres

Particle size determination of microspheres was carried out by sieve analysis method. A mixture quantity of dried microspheres was placed on the top slide of the sieve. Then switch ON the instrument for specified time with specified RPM. After the completion of sieving separate the individual sieve and weigh the microspheres. Then calculate the size of the microspheres.

Table .4 Percentage yield, Drug content (mg), Drug loading in microsphere (mg), Entrapment Efficiency (%).

Formulation code	Percentage yield (%)	Drug content (mg)	Drug loading in microsphere (%)	Entrapment Efficiency (%)
MTFM -1	94.5%	39.1±0.03	36.9	78.2±0.01
MTFM -2	95.7%	40.5±0.21	38.7	81.0±0.031
MTFM -3	90.5%	43.4±0.02	39.3	86.8±0.014
MTFM -4	96.0%	44.6±0.11	42.8	89.2±0.07
MTFM -5	98.0%	45.2±0.03	44.2	90.4±0.012
MTFM -6	91.1%	47.1±0.2	42.9	94 ±0.032
MTFM -7	93.6%	46.9±0.16	43.9	93.8±0.039
MTFM -8	85.7%	48.0±0.14	41.1	96.0±0.022
MTFM -9	99.6%	49.6±0.25	49.4	99.2±0.28

Scanning Electron Microscopy[16]

The surface morphology and particle size of microspheres were determined by Scanning Electron Microscopy using a JEOL JSM-6360A scanning microscope performed at University of Pune. Dry microspheres were placed on an scanning electron microscope brass stub and coated with Platinium in an ion sputter. Picture of microspheres were taken by random scanning of the stub.

***In Vitro* Buoyancy Studies**[, 17, 18,19]

300 mg of Microspheres were spread over the surface of the dissolution medium (simulated gastric fluid, SGF, pH 1.2 containing 0.02%w/v of Tween 20) that was agitated by a paddle rotation speed at 100 rpm. After agitation for a predetermined time interval, the microspheres that floated over the surface of the medium and those settled at the bottom of the flask were recovered separately. After drying, each fraction of the microparticles was weighed and their buoyancy was calculated by the following equation.

$$\underset{(\%)}{\text{Buoyancy}} = \frac{Q_f}{Q_f + Q_s} \times 100$$

Where Qf and Qs are the weight of the floating and the settled microspheres, respectively.

***In- Vitro* Drug Release Studies**[, 20, 21,22]

The *In-Vitro* drug release studies were carried out using USP type II (Electro Lab.) paddle type dissolution apparatus. Drug loaded microspheres were weighed equivalent to 100 mg of drug was introduced into the 900 ml of dissolution medium (1.2 pH HCl buffer) maintained at 37±0.5ºC with paddle rotating at 100 RPM. The samples were withdrawn with 1 h intervals up to 12 hours. Aliquots were withdrawn and the same volume of fresh medium was refilled for the maintenance of sink condition. The prepared test solutions were measured at 232 nm by U.V Spectrophotometer. The dissolution studies were carried out in triplicate and then mean values were plotted as percentage cumulative drug release against time.

Table .5 . Derived properties and flow properties

Formulation code	Angle of repose	Bulk density	Tapped density	Carrs index	Hausners Ratio
MTFM -1	26.5±0.19	0.51±0.09	0.54±0.024	7.407±0.9	1.018±0.04
MTFM -2	25.5±0.011	0.53±0.02	0.60±0.011	11.666±0.04	1.132±0.02
MTFM -3	28.3±0.06	0.54±0.06	0.59±0.023	8.474±0.08	1.092±0.01
MTFM -4	25.7±0.02	0.48±0.012	0.54±0.011	11.111±0.05	1.125±0.06
MTFM -5	26.1±0.011	0.44±0.031	0.49±0.018	10.204±0.03	1.113±0.09
MTFM -6	27.1±0.03	0.50±0.022	0.56±0.002	10.714±0.06	1.120±0.11
MTFM -7	28.3±0.07	0.46±0.01	0.51±0.016	9.803±0.013	1.108±0.13
MTFM -8	23.5±0.024	0.48±0.016	0.56±0.09	14.285±0.08	1.116±0.22
MTFM -9	25.3±0.04	0.52±0.014	0.57±0.006	10.280±0.02	1.140±0.03

Kinetics of Drug Release

To study the drug release kinetics, data obtained from *In-Vitro* release were plotted in various kinetic models such as Zero order equation, Higuchi kinetics and Korsmeyer– Peppas equation. If n value is 0.45 or less, the release mechanism follows “Fickian diffusion” and higher values of 0.45 to 0.89 for mass transfer follow a non-fickian model (anomalous transport). The drug release follows Higuchi model of drug release and case II transport if the n value is 0.89. For the values of n higher than 0.89, the mechanism of drug release is regarded as super case II transport. The model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slop of the plot of log cumulative % of drug released Vs log time.

Stability Studies for MTFM –9[23, 24, 25]

From the prepared floating microspheres which showed appropriate balance between the buoyancy and the percentage release was selected for stability studies. The prepared formulation MTFM –9were placed in borosilicate screw capped glass containers and stored at two different temperature (25±2°C, 60% RH), Oven temperature (40±2°C, 75% RH) in in stability chamber for a period of 90 days. The samples were evaluated for cumulative percentage drug release at regular intervals of two week.

Infrared spectrum:

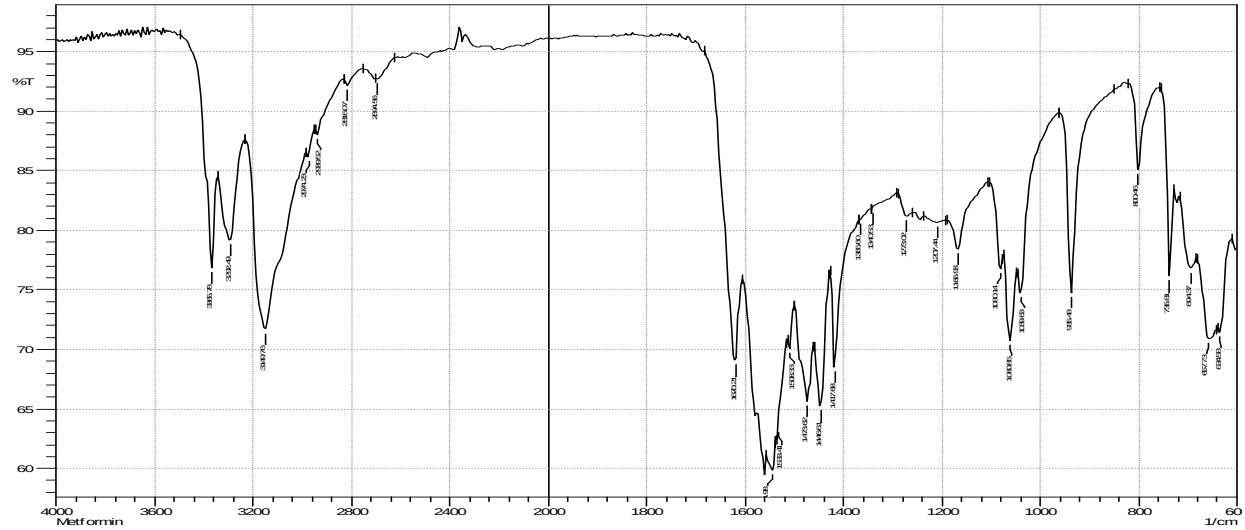

Fig.1. FTIR Spectral studies for Metformin Hcl.

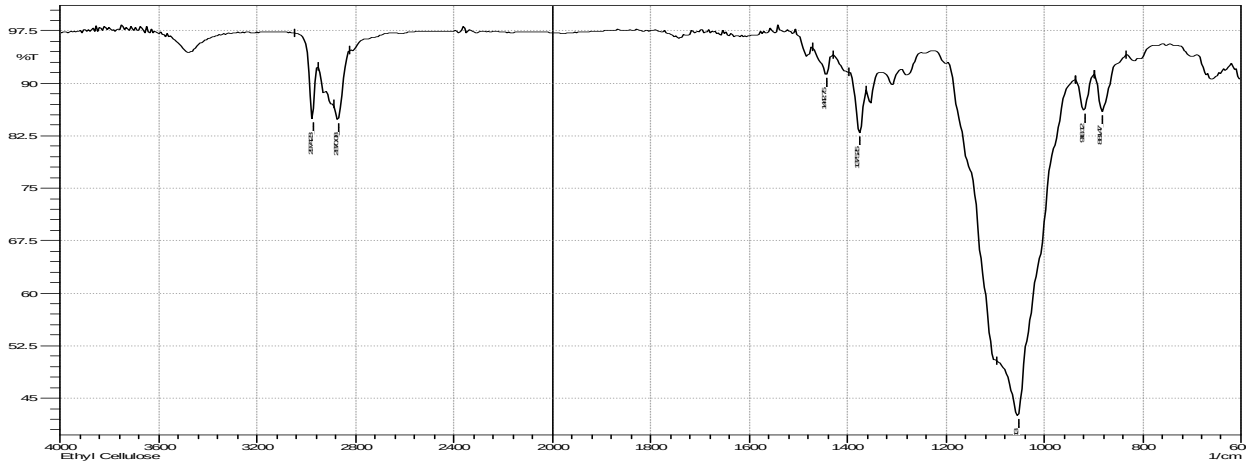

Fig.2. FTIR Spectral studies for ethyl cellulose

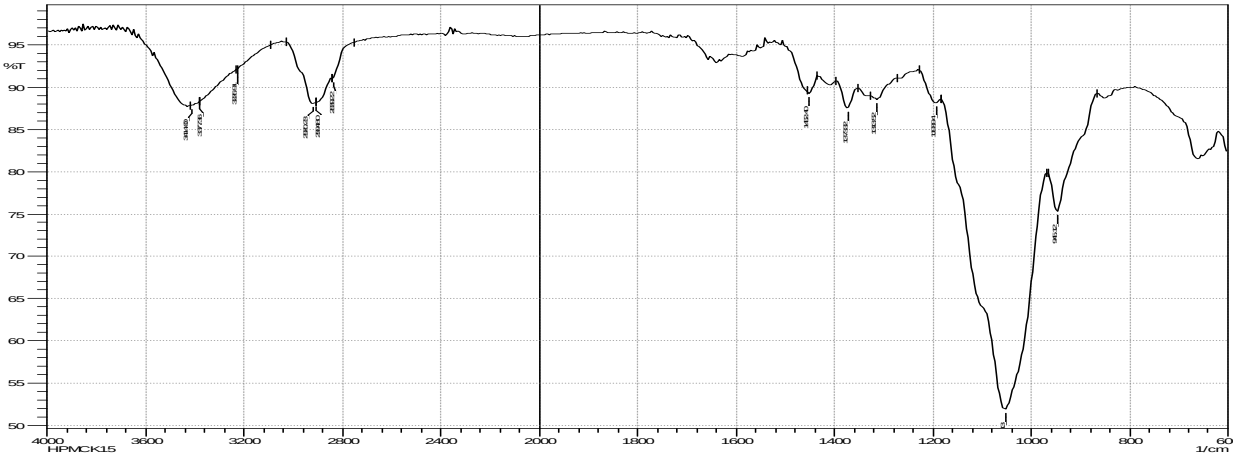

Fig .3. FTIR Spectral studies for HPMC K15 M.

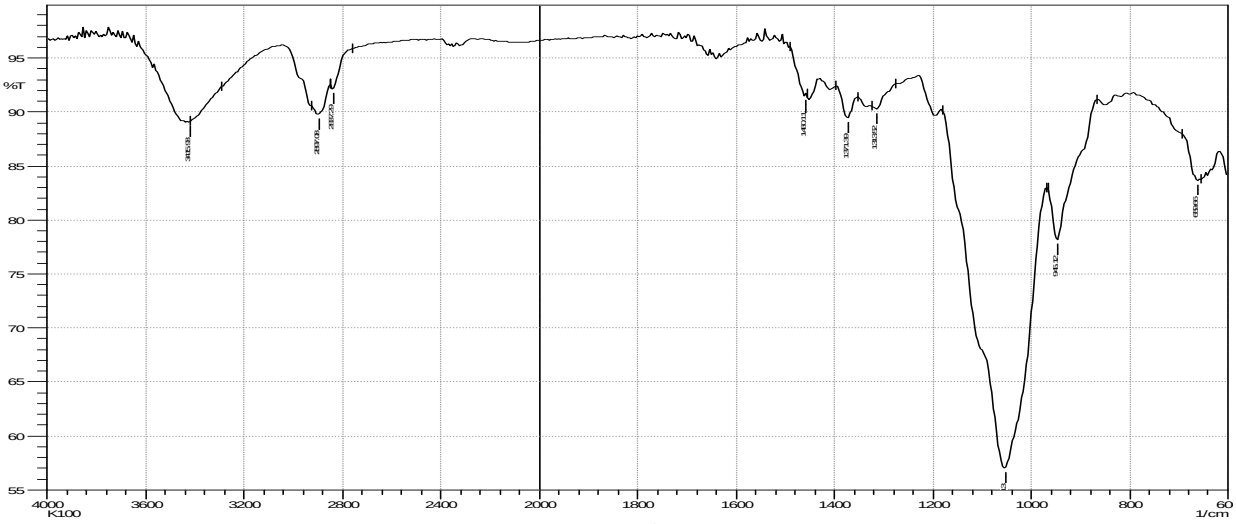

Fig .4. FTIR Spectral studies for HPMC K100 M

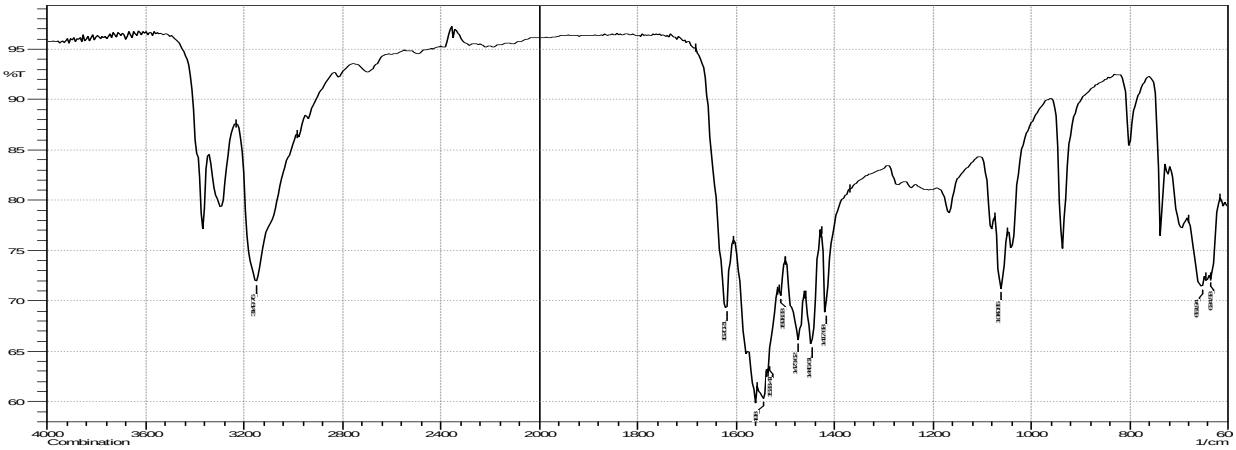

Fig.5. FTIR Spectral studies for Formulation.

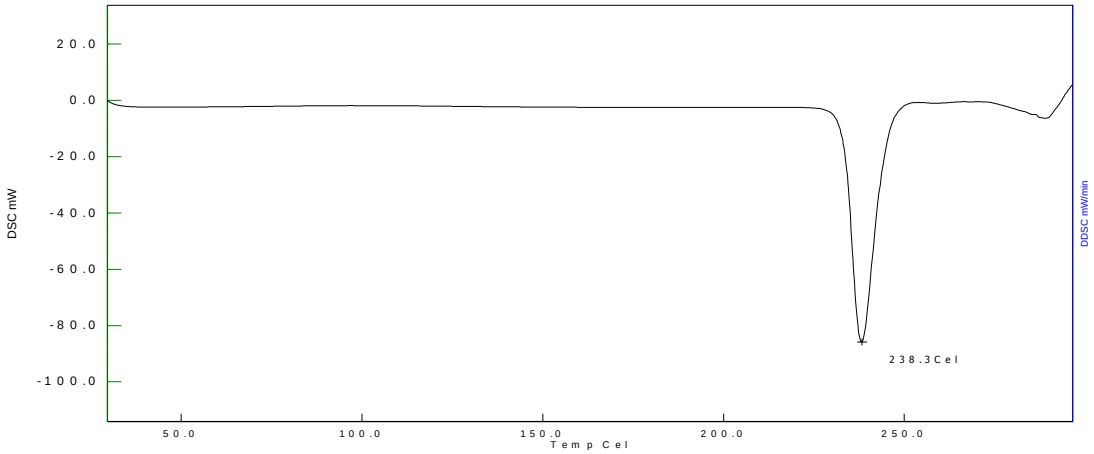

Fig.6.DSC of Pure Drug.

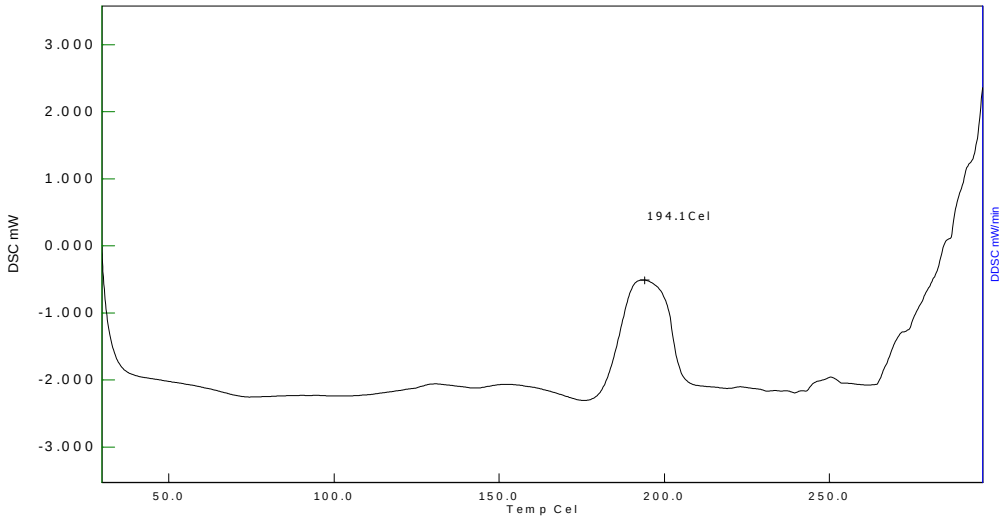

Fig.7.DSC of Ethyl Cellulose

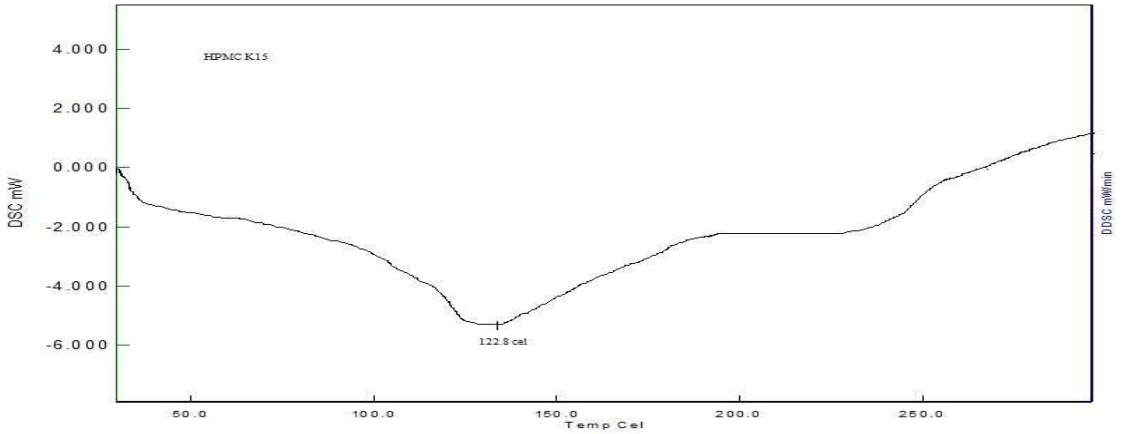

Fig.8..DSC of HPMC K15

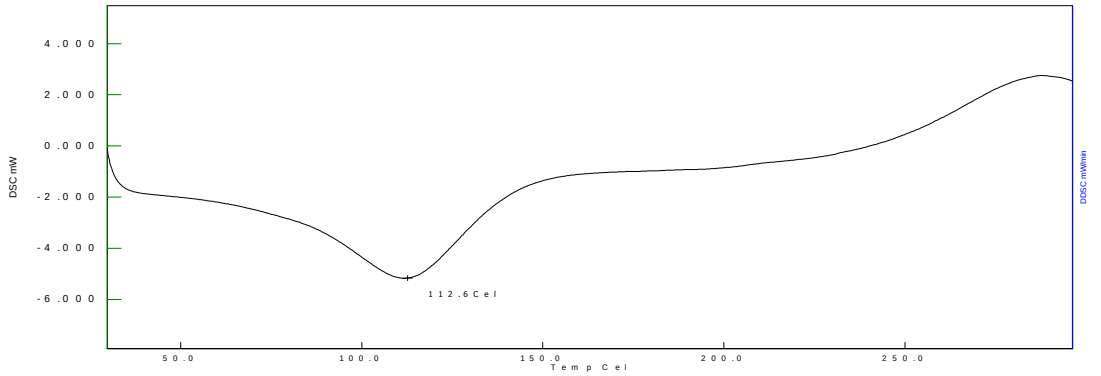

Fig.9.DSC of HPMC K100

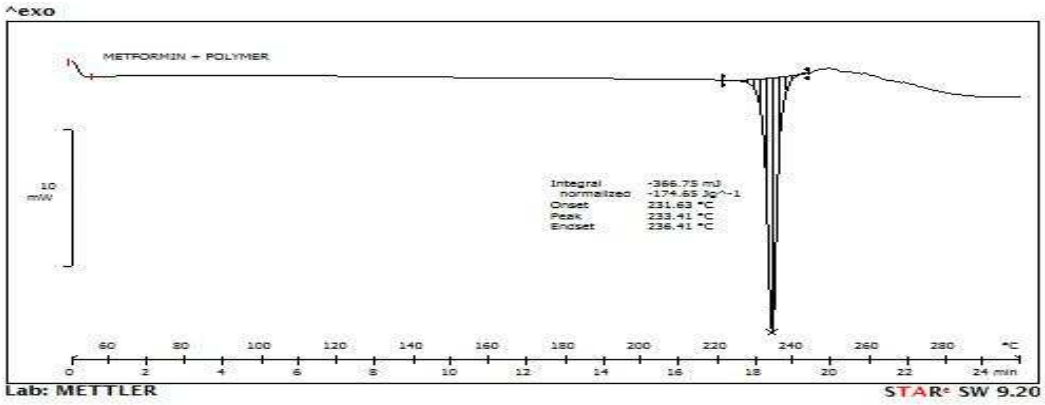

Fig.10.DSC of formulation

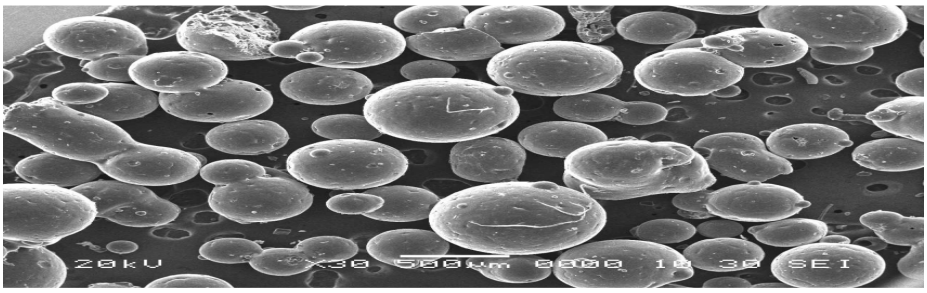

Fig .11. SEM Pictures of prepared best formulation microsphere (MTFM –9

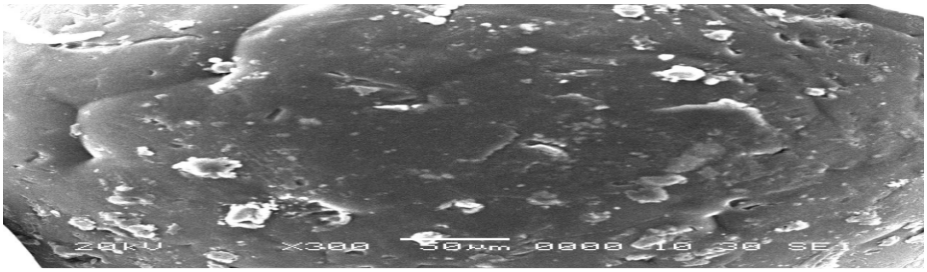

Fig .12. SEM(internal) Pictures of prepared best formulation microsphere (MTFM –9) internal

RESULTS AND DISCUSSION

In this study, an attempt was made to develop Metformin Hcl floating microspheres using Ethyl cellulose, HPMC K15 M and HPMC K100 M polymers by using Non aqueous emulsion solvent diffusion technique. metformin Hcl an antidiabetic was selected for design of FDDS in the form floating microspheres. Metformin Hcl is well known drug widely used for the treatment of diabetic. However, due to its short half-life,and low bioavalability.

Table 6. Size of prepared floating microsphere, Shape floating microsphere, In –Vitro buoyancy

Formulation code	Size of prepared floating microsphere in (µm)	Shape of Microsphere	In –vitro buoyancy (%)
MTFM -1	476.7±0.43	Irregular	83.6±0.19
MTFM -2	477.2±0.19	Slightly irregular	84.7±0.08
MTFM -3	481.7±0.98	Spherical	90±0.7
MTFM -4	488.4±0.11	Slightly irregular	88±0.36
MTFM -5	494.9±0.28	Spherical	86.8±0.06
MTFM -6	497.8±0.64	Spherical	85.6±0.27
MTFM -7	502±0.85	Spherical	86.6±0.11
MTFM -8	505.3±0.36	Spherical	92±0.1 5
MTFM -9	511.7±0.54	Spherical	98±0.91

Table 7. Dissolution studies profile for first 5 formulations

Sr. NO	TIME IN Hr	Cumulative % drug release				
		MTFM -1	MTFM -2	MTFM -3	MTFM -4	MTFM-5
1	1	21.6±0.2	20.3±0.033	21.6±0.04	16.0±0.001	21.6±0.3
2	2	28.2± 0. 15	28.2±0.4	29.7±0.1	18.4±0.7	24.6±0.15
3	3	40.4± 0. 5	31.6±0.07	41.1±0.6	24.0±0.3	33.2±0.04
4	4	56.3±0.02	39.2±0.12	47.1±0.003	34.1±0.5	41.5±0.02
5	5	64.6±0.06	46.4±0.02	62.6±0.31	43.5±0.01	56.3±0.07
6	6	77.5±0.7	54.7±0.06	69.2±0.001	47.1±0.4	60.6±0.34
7	7	83.5±0.2	90.0±0.023	88.4±0.01	62.3±0.14	80.1±0.09
8	8	96.7±0.9	95.3 ±0.01	94.4±0.08	87.4±0.7	88.4±0.17
9	9	-	-	-	93.1±0.05	94.5±0.014

Table 8. Dissolution studies profile for second 4 formulations

Sr. NO	TIME IN Hr	Cumulative % drug release				Marketed formulation
		MTFM -6	MTFM -7	MTFM -8	MTFM -9	
1	1	14.7±0.014	21.3±0.05	18.7±0.51	16.4±0.01	19.3±0.07
2	2	23.3±0.019	27.9±0.29	24.3±0.07	27.9±0.04	26.6±0.6
3	3	32.2±0.07	33.5±0.08	38.5±0.05	37.5±0.03	32.2±0.1
4	4	38.8±0.05	37.2±0.27	46.7±0.32	45.1±0.05	33.6±0.13
5	5	49.7±0.003	44.1±0.2	54.0±0.06	56.6±0.03	46.7±0.02
6	6	53.4±0.06	53.1±0.7	60.3±0.07	66.2±0.01	53.7±0.05
7	7	60.7±0.5	62.0±0.08	67.0±0.09	73.6±0.07	69.6±0.6
8	8	80.2±0.8	79.5±0.04	84.5±0.24	76.3±0.04	77.2±0.13
9	9	90.8±0.24	90.5±0.09	90.5±0.31	81.3±0.06	86.5±0.04
10	10	95.5±0.4	95.7±0.05	93.6±0.37	88.3±0.05	90.2±0.1
11	11	-	-	98.6±0.06	95.6±0.04	97.6±0.16
12	12	-	-	-	99.7±0.01	99.9±0.6

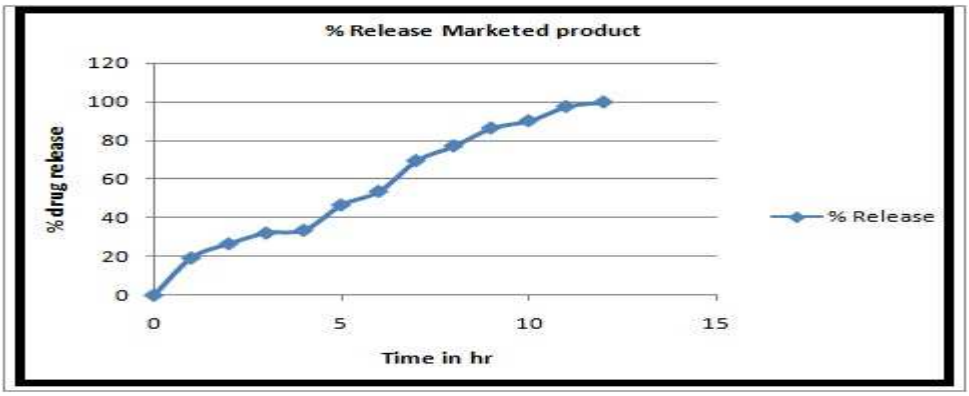

Fig.13. Dissolution studies profile for all formulations

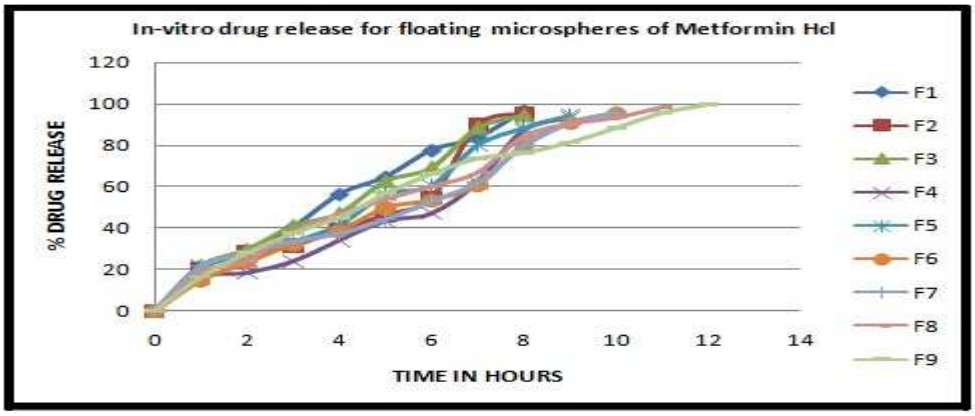

Fig.14. Dissolution studies profile for Marketed formulations

photographs and its spectral ranges of functional groups were shown in the figure No: 01 – 06. The prepared floating microspheres were characterized for their % yield, drug loading, % entrapment, mean particle size, % buoyancy and *In Vitro* drug release. The microspheres were prepared by varying the polymeric ratio the microspheres show more loading efficiency and more % drug entrapment. The SEM photographs of the microspheres revealed that the microspheres were spherical with smooth surface and slightly aggregated and size range was 470 –511 µm. The buoyancy result indicates that all formulations floated for more than 12 hours over the surface of the dissolution medium without any apparent gelation. The microsphere showing lower densities influence buoyancy, and they were to be retained for longer than 12 hours, which helped in improving the bioavailability of Metformin Hcl Percentage buoyancy of prepared microspheres are high and showing Combination of E.C and HPMC are good carrier for FDDS.

Table 9. Drug release kinetics values of different formulation with regression coefficient values

Formulation code	Drug release kinetics			
	Zero order	Higuchi	peppas release	
	(r)	(r)	(r)	(n)
MTFM -1	0.9067	0.9970	0.9879	0.9392
MTFM -2	0.9009	0.9961	0.9882	0.9527
MTFM -3	0.9207	0.9975	0.9928	0.9081
MTFM -4	0.9135	0.9969	0.9856	0.8869
MTFM -5	0.9137	0.9971	0.9907	0.9031
MTFM -6	0.9327	0.9929	0.9952	0.8987
MTFM -7	0.9339	0.9933	0.9952	0.8887
MTFM -8	0.9274	0.9934	0.9953	0.9192
MTFM -9	0.9520	0.9979	0.9945	0.8136

The *In-Vitro* drug release revealed that batch MTFM-9 was having 99.7 cumulative releases at the end of 12 th hour when compared with all batches due to increase in polymer concentration as seen in formulations. The release kinetics of floating Metformin HCl followed Super case II transport diffusion

Table 10.Stability studies of best formulation with cumulative percentage drug release

Time interval in weeks	Cumulative % drug release	
	25^{c},60%RH	40^{c},75%RH
2	99.7	99.7
4	99.6	99.6
6	99.6	99.6
8	99.2	99.1
10	98.6	98.2
12	97.3	97.8

CONCLUSION

The prepared all formulations of metformin HCl revealed the fact that developed formulation (MTFM-9) showed comparable release characteristics, thus it may have fair clinical efficacy. Hence, the formulation MTFM-9 has proved the purpose of the present study.

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