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FORMULATION AND EVALUATION OF FLOATING TABLETS OF METFORMIN HYDROCHLORIDE

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Abstract

Sustained release gastroretentive dosage forms enable prolonged and continuous input of the drug to the upper parts of gastrointestinal tract and improve the bioavailability of medication that is characterized by narrow absorption window. Gastroretentive floating drug delivery systems (GFDDS) of metformin hydrochloride, an antidiabetic drug with an oral bioavailability of only 50% (because of its poor absorption from lower gastrointestinal tract) have been designed and evaluated. Hydroxy propyl methyl cellulose HPMC K4M and HPMC K15M were used as polymers and sodium bicarbonate as gas generating agent to reduce floating lag time. Tablets were prepared by wet granulation method. Floating tablets were evaluated for hardness, friability, weight variation, drug content, floating properties and *in vitro* release pattern. The *in vitro* drug release followed first order kinetics and drug release was found to be diffusion controlled.

Key Words: Metformin HCl, Floating drug delivery system, HPMC K4M, HPMC K15M.

Introduction:

During the last decade, many studies have been performed concerning the sustained release dosage forms of drugs, which have been aimed at the prologation of gastric emptying time (GET). The GET has been reported to range from 2 to 6 h, in humans in the fed state [1]. Retention of drug delivery systems in the stomach prolongs the overall gastrointestinal transit time, thereby resulting in improved bioavailability. Scintigraphic studies determining gastric

emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications, that of short gastric residence time and unpredictable gastric emptying rate (2). Depending on the mechanism of buoyancy, two distinctly different methods viz., effervescent and non effervescent systems have been used in the development of floating drug delivery systems (FDDS) (3). Effervescent drug delivery systems utilize matrices prepared with swellable polymers such as methocel [4] or polysaccharides and effervescent components e.g., sodium bicarbonate and citric or tartaric acid. Floating drug delivery systems offer important advantages: as they are less prone to gastric emptying resulting in reduced intra and inter subject variability in plasma drug levels, effective for delivery of drugs with narrow absorption windows, reduced dosing and increased patient compliance, reduced C_{max} and prolonged drug levels above the minimum effective concentration and improved safety profile for drugs with side effects associated with high C_{max}. 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 1.7 hours and its absolute bioavailability is reported to be about 45-50% of the administered dose, hence it is a suitable candidate for gastroretentive floating drug delivery system.

Materials and Methods:

Metformin HCl was received as gift samples from Sohan Health Care Pvt. Ltd. HPMC K4M and HPMC K15M were received as gift samples from Colorcon Asia Pvt. Ltd. PVP K 29/32 were procured commercially from National Scientific Products, Mumbai. Sodium bicarbonate, Citric acids were procured from Finar Chemicals Ltd. Talc from Luzenac and magnesium stearates were procured from Ferro Corporation. All other chemicals used were of analytical reagent grade.

Preparation of Floating tablets:

Tablets were prepared by wet granulation method. Metformin HCl (500 mg) was mixed with required amount of polymers and other excipients. All the excipients were passed through sieve no. 60, mixed and granulated with 5% solution of PVP K-30 in isopropyl alcohol. The wet mass was passed through sieve no.12 and dried at 45ºC for 2h. Dried granules were passed through sieve no. 24 and mixed with magnesium stearate and talc. Granules were compressed into tablets using single station tablet compression machine (Cadmach) [6].

Table-1: Composition of floating tablets of Metformin HCl. Ingredients (mg/tablet).

Ingredients(mg)	F1	F2	F3	F4	F5	F 6	F7	F8	F9	F10	F11
Metformin HCl	500	500	500	500	500	500	500	500	500	500	500
NaHCO3	75	75	75	75	75	75	75	75	75	75	75
HPMC K4M	100	150	170	-	-	-	75	75	62.5	50	75
HPMC K15 M	-	-	-	100	150	170	62.5	50	75	75	75
Citric acid	20	20	20	20	20	20	20	20	20	20	20
Microcrystalline cellulose	570	520	500	570	520	-	532.5	545	532.5	545	520
PVP K 29/32	40	40	40	40	40	40	40	40	40	40	40
Magnesium stearate	15	15	15	15	15	15	15	15	15	15	15
Talc	10	10	10	10	10	10	10	10	10	10	10
Total	830	830	830	830	830	830	830	830	830	830	830

Table-2: Physicochemical Characteristics of Tablets.

Formulation code	Angle of repose	Bulk density	Tapped density	Carr`s index	Hausner`s ratio
F1	26.72± 0.182	0.489± 0.007	0.614± 0.016	20.35± 0.010	1.275± 0.057
F2	25.55± 0.075	0.590± 0.062	0.702± 0.058	15.69± 0.055	1.189± 0.046
F3	38.24± 0.023	0.356± 0.028	0.497± 0.026	28.37± 0.046	1.396± 0.013
F4	23.32± 0.011	0.416± 0.013	0.528± 0.063	21.21± 0.056	1.26± 0.025
F5	26.42± 0.007	0.416± 1.052	0.514± 0.084	14.12± 0.048	1.16± 0.013
F6	36.17± 0.182	0.334± 0.010	0.423± 0.011	20.80± 0.086	1.366± 0.021
F7	26.18± 0.012	0.432± 0.058	0.526± 0.098	17.82± 0.012	1.217± 0.049

F8	30.14± 0.075	0.482± 0.011	0.580± 0.042	16.97± 0.022	1.203± 0.053
F9	29.27± 0.010	0.383± 0.069	0.456± 0.016	15.96± 0.010	1.190± 0.012
F10	23.12± 0.282	0.372± 0.015	0.430± 0.010	13.54± 0.053	1.155± 0.019
F11	30.10± 0.010	0.425± 0.010	0.505± 0.012	15.86± 0.055	1.188± 0.043

***Weights of formulations F3 and F6 are out of limits. And friability ranges of formulations F1, F3, F4, F6 are out of limits so these four formulations are rejected.**

Evaluation of Tablets

Weight Variation

Twenty tablets were selected randomly and the average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight.

Hardness and Friability

Hardness of tablets (n=3) was determined using Monsanto hardness tester. Friability of the tablets was checked using Roche Friabilator. Preweighed sample of tablets was placed in the Friabilator, operated for 100 revolutions. Tablets were then dusted and reweighed. The experiment was repeated three times. [7]

***In vitro* drug release profile of floating formulations**

Table-3: *In vitro* drug release profile of F2 Formulation.

TIME (Hrs)	%drug release	%drug release retained	Log% drug release	log% drug release retained	Log time	√T
0	0	100	-	2	-	-
1	38.16	61.84	1.581	1.791	0	1
2	59.08	40.92	1.771	1.611	0.301	1.414
3	67.73	32.27	1.830	1.508	0.477	1.732
4	75.48	24.52	1.877	1.389	0.602	2
5	83.23	16.77	1.920	1.224	0.698	2.236
6	87.18	12.82	1.940	1.107	0.778	2.449

7	88.36	11.64	1.946	1.065	0.845	2.645
8	91.56	8.44	1.961	0.926	0.903	2.828
9	92.28	7.72	1.965	0.887	0.954	3
10	97.03	2.97	1.986	0.472	1	3.162
11	98.16	1.84	1.991	0.26481782	1.041	3.316
12	99.24	0.76	1.996	-0.11918641	1.079	3.464

Table-4: *In vitro* drug release profile of F5 Formulation.

TIME(Hrs)	**%drug release**	**%drug release retained**	**Log% drug release**	**log% drug release retained**	**Log time**	**√T**
0	0	100	-	2	-	-
1	38.23	61.77	1.582	1.790	0	1
2	57.349	42.65	1.758	1.629	0.301	1.414
3	66.712	33.288	1.824	1.522	0.477	1.732
4	78.026	21.974	1.892	1.341	0.602	2
5	80.366	19.634	1.905	1.293	0.698	2.236
6	86.99	13.01	1.939	1.114	0.778	2.449
7	91.68	8.32	1.962	0.920	0.845	2.645
8	97.381	2.619	1.988	0.418	0.903	2.828
9	99.82	0.18	1.999	-0.744	0.954	3
10	100.021	-0.021	2.000	-	1	3.162
11	94.052	5.9479	1.973	0.774	1.041	3.316
12	91.261	8.738	1.960	0.941	1.079	3.464

Table-5: *In vitro* drug release profile of F7 Formulation

TIME(Hrs)	%drug release	%drug release retained	Log% drug release	log% drug release retained	Log time	√T
0	0	100	-	2	-	-
1	35.40	64.6	1.549	1.810	0	1
2	42.85	57.15	1.631	1.757	0.301	1.414
3	49.46	50.54	1.694	1.703	0.477	1.732
4	53.21	46.79	1.725	1.670	0.602	2
5	62.89	37.11	1.798	1.569	0.698	2.236
6	65.75	34.25	1.817	1.534	0.778	2.449
7	77.12	22.88	1.887	1.359	0.845	2.645
8	80.59	19.41	1.906	1.288	0.903	2.828
9	86.72	13.28	1.938	1.123	0.954	3
10	95.86	4.14	1.981	0.617	1	3.162
11	97.21	2.79	1.987	0.445	1.041	3.316
12	100.112	-0.18	1.00	-0.744	1.079	3.464

Table-6: *In vitro* drug release profile of F8 Formulation.

TIME(Hrs)	%drug release	%drug release retained	Log% drug release	log% drug release retained	Log time	√T
0	0	100	-	2	-	-
1	16.86	83.14	1.226	1.919	0	1
2	29.36	70.64	1.467	1.849	0.301	1.414
3	36.03	63.97	1.556	1.805	0.477	1.732
4	43.38	56.62	1.637	1.752	0.602	2
5	50.19	49.81	1.700	1.697	0.698	2.236

6	57.51	42.49	1.759	1.628	0.778	2.449
7	64.23	35.77	1.807	1.553	0.845	2.645
8	71.11	28.89	1.851	1.460	0.903	2.828
9	78.18	21.82	1.893	1.338	0.954	3
10	84.31	15.69	1.925	1.195	1	3.162
11	86.32	13.68	1.936	1.136	1.041	3.316
12	89.05	10.95	1.949	1.039	1.079	3.464

Table-7: *In vitro* drug release profile of F9 Formulation.

TIME(Hrs)	**%drug release**	**%drug release retained**	**Log% drug release**	**log% drug release retained**	**Log time**	**√T**
0	0	100	-	2	-	-
1	20.65	79.35	1.314	1.899	0	1
2	31.16	68.84	1.493	1.837	0.301	1.414
3	41.08	58.92	1.613	1.770	0.477	1.732
4	49.98	50.02	1.698	1.699	0.602	2
5	60.08	39.92	1.778	1.601	0.698	2.236
6	69.21	30.79	1.840	1.488	0.778	2.449
7	77.73	22.27	1.890	1.347	0.845	2.645
8	83.83	16.17	1.923	1.208	0.903	2.828
9	85.51	14.49	1.932	1.161	0.954	3
10	88.98	11.02	1.949	1.042	1	3.162
11	89.48	10.52	1.951	1.022	1.041	3.316
12	95.54	4.46	1.980	0.649	1.079	3.464

Table-8: *In vitro* drug release profile of F10 Formulation.

TIME(Hrs)	%drug release	%drug release retained	Log% drug release	log% drug release retained	Log time	√T
0	0	100	-	2	-	-
1	17.72	82.28	1.248	1.915	0	1
2	28.78	71.22	1.459	1.852	0.301	1.414
3	34.82	65.18	1.541	1.814	0.477	1.732
4	40.90	59.1	1.611	1.771	0.602	2
5	47.85	52.15	1.679	1.717	0.698	2.236
6	58.82	41.18	1.769	1.614	0.778	2.449
7	63.04	36.96	1.799	1.567	0.845	2.645
8	68.82	31.18	1.837	1.493	0.903	2.828
9	79.68	20.32	1.901	1.307	0.954	3
10	89.08	10.92	1.949	1.038	1	3.162
11	90.68	9.32	1.957	0.969	1.041	3.316
12	92.44	7.56	1.965	0.878	1.079	3.464

Table 9: *In vitro* drug release profile of F11 Formulation

TIME(Hrs)	%drug release	%drug release retained	Log% drug release	log% drug release retained	Log time	√T
0	0	100	-	2	-	-
1	15.91	84.09	1.201	1.924	0	1
2	24.53	75.47	1.389	1.877	0.301	1.414
3	31.08	68.92	1.492	1.838	0.477	1.732
4	39.38	60.62	1.595	1.782	0.602	2
5	46.23	53.77	1.664	1.730	0.698	2.236

6	53.16	46.84	1.725	1.670	0.778	2.449
7	59.70	40.3	1.775	1.605	0.845	2.645
8	66.83	33.17	1.824	1.520	0.903	2.828
9	74.11	25.89	1.869	1.413	0.954	3
10	78.39	21.61	1.894	1.334	1	3.162
11	84.86	15.14	1.928	1.180	1.041	3.316
12	89.63	10.37	1.952	1.015	1.079	3.464

Table-10: Dissolution kinetics of Metformin HCl floating tablets.

Formulation	first order plot	Higuchi plot	Best fit model
	R^2	R^2	
F7	0.760	0.988	Higuchi, first order plot

Table-11: Evaluation of floating lag time and total floating time

Formulation batch code	floating lag time (sec)	total floating time (hrs)
F2	5 sec	18.30
F5	6 sec	20
F7	8 sec	23.30
F8	6 sec	19.20
F9	5 sec	23
F10	5 sec	23.20
F11	8 sec	24

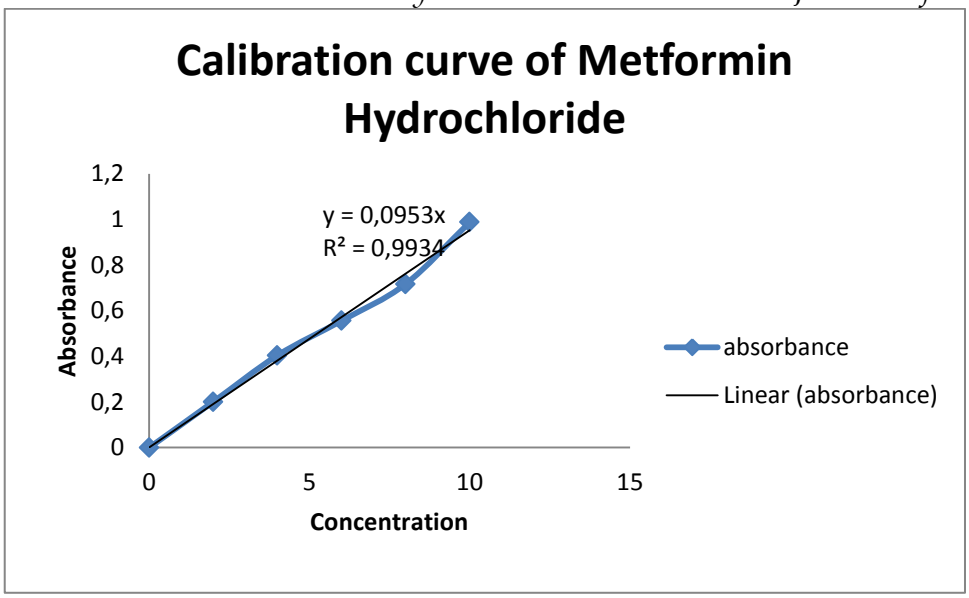

Fig: 1 Calibration plot of Metformin Hydrochloride.

Table-12: Standard graph of Metformin HCl at 232 nm.

S.No	Concentration (µgm/ml)	absorbance
1.	0	0.000 ± 0.0000
2.	2	0.201± 0.0012
3.	4	0.404± 0.0016
4.	6	0.556± 0.0017
5.	8	0.717± 0.0016
6.	10	0.988± 0.0015

*Each reading is a mean of three determinations.

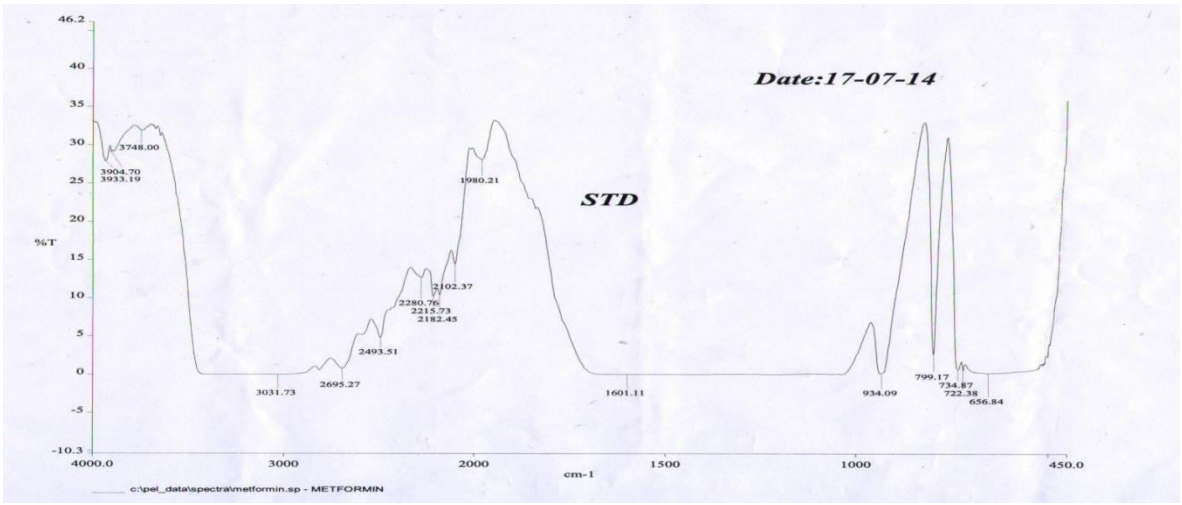

Fig: 2. FTIR Spectra of Metformin Hydrochloride pure drug.

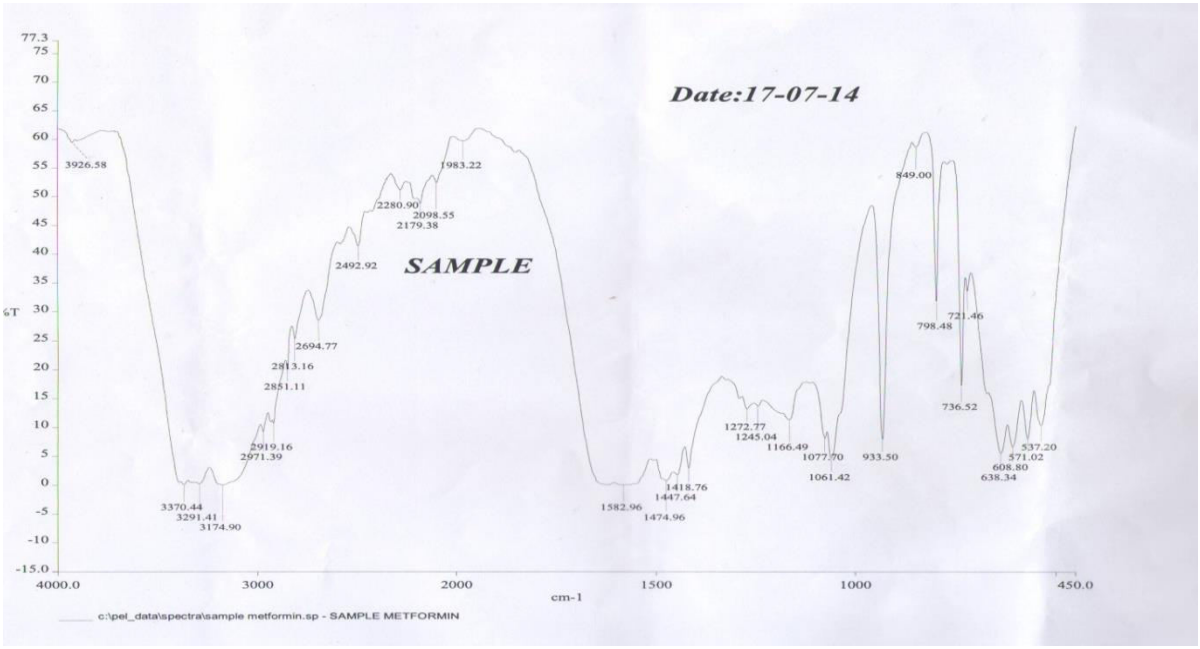

Fig: 3. FTIR Spectra of F7 formulation.

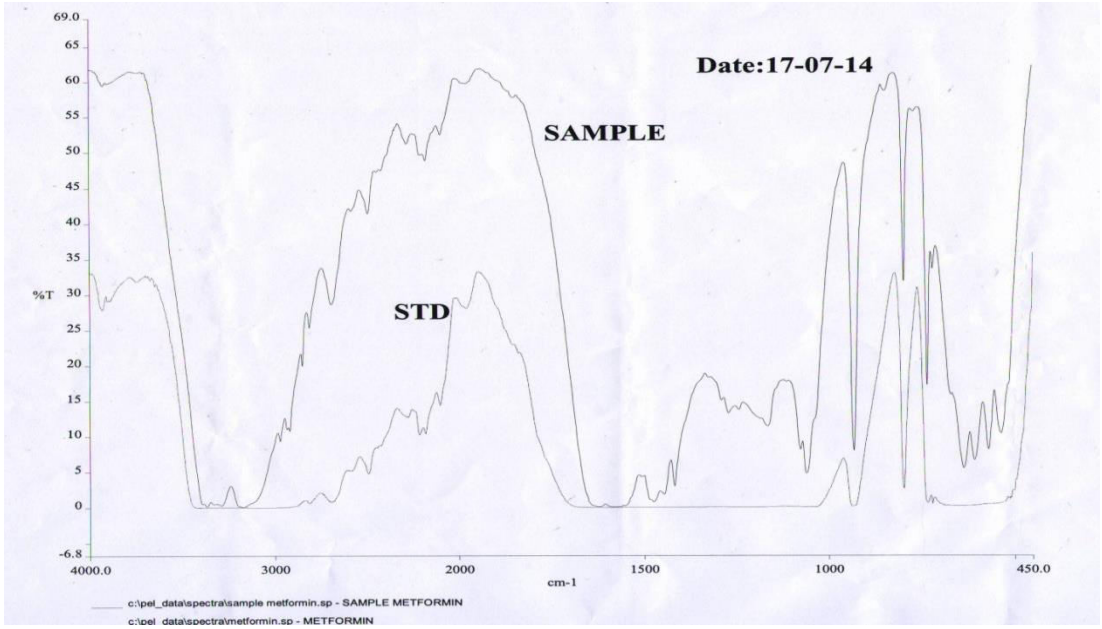

Fig: 4. FTIR Spectra of Metformin pure drug + F7 formulation.

Estimation of Drug Content

Twenty tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of drug was transferred into 100 ml volumetric flask, it was shaken with 70 ml of distilled water and volume was adjusted to 100ml with water. The solution was filtered, suitable dilutions were made and absorbance was recorded by using Elico UV spectrophotometer at 233nm.The experiment was repeated three times. [8-10]

Floating or Buoyancy Test

The time taken for tablet to emerge on the surface of the medium is called the floating lag time (FLT) or buoyancy lag time (BLT) and duration of time the dosage form constantly remains on the surface of the medium is called the total floating time (TFT).The buoyancy of the tablets was studied in USP type II dissolution apparatus at 37±0.5^{o}C in 900ml of simulated gastric fluid at pH 1.2.The time of duration of floatation was observed visually. [11-13]

***In Vitro* Drug Release Study**

In vitro release studies were carried out by using USP paddle dissolution test apparatus. 900ml of 0.1 N HCl (pH1.2) was taken in the dissolution vessel and the temperature of the medium was maintained at 37±0.5^{o}C. 100rpm was maintained, 0.5 ml of sample was withdrawn at predetermined time intervals for 12 hours and the same volume of the fresh medium was replaced. The samples were analyzed at 233nm by using a UV spectrophotometer (Elico).The dissolution data obtained were plotted as cumulative percentage drug release versus time as zero order, log cumulative percentage drug retained versus time as first order release kinetics, cumulative percentage drug release versus square root of time as higuchi equation and log of fraction of drug released versus log time as Korsemeyer-peppas equation. [14-16]

Results and Discussion

Hydrodynamically balanced tablets of Metformin HCl (intra gastric buoyant tablets) were prepared and evaluated to increase its local action and bioavailability. In the present study seven formulations with variable concentration of polymer were prepared and evaluated for physicochemical properties and *in vitro* drug release.

On immersion in 0.1 N HCl solutions at pH 1.2 at 37±0.5^{o}C tablets floats immediately after few seconds and remain buoyant upto 18-20 hrs without disintegration. Floating property of the tablet is governed by both the swelling (hydration) of the polymer when it contacts with the gastric fluid, which in turn results in increase in the bulk volume, and the presence of internal voids in the dry centre of the tablet (porosity). These two factors are essential for the tablet to acquire bulk density < 1 and so remain buoyant on the gastric fluid (5). Hardness of the tablets was in the range of 8.0 to 8.8 kg/cm^2. This ensures good handling characteristics of all the batches. Weight loss in the friability test was less than 1% in all the cases, ensuring that the tablets were mechanically stable. All the floating tablets prepared contained the drug within 100±5% of the label claim. All the formulated tablets except F3 and F6 passed the weight variation test

as the % weight variation was within the pharmacopoeial limits of ± 5% of the average weight. Table11 shows the results of buoyancy study. From the results, it is evident, that all formulations showed least floating lag time and good total floating time.

The formulation F7 was screened from the above formulations for comparing it's *in vitro* release with the marketed formulation. This is because F7 exhibited good sustained release.

From the *in vitro* dissolution data it was found that formulation F2 containing 150mg of HPMC K 4M released 91.56% of drug with in 8 hr of study, indicating that the polymer amount is not sufficient to control the drug release. F7 containing HPMC K 4M 75mg and HPMC K 15M 62.5mg released 100.11% of drug at the end of 12 hr. Hence, F7 showed better sustained release than the other formulations (F5, F8, F9, F10 and F11).

When the release data was analyzed as per zero and first order kinetic models the best fit with higher correlation was observed with first order model indicating that the drug release from all the batches followed first order kinetics. As the polymer concentration was increased, release rate was decreased. Plots of percent released versus square root of time were found to be linear (r> 0.994) with all the tablets, indicating that the drug release from the tablets was diffusion controlled.

Metformin HCl release from floating tablet F7 formulated employing HPMC K 4M 75mg and HPMC K 15M 62.5mg was similar to that from Gluformin XL-500 mg, a commercial sustained release formulation of Metformin HCl.

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