International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE
V-1, I-3, 2012

Gas Powered Bioadhesive Tablets of Metformin Hydrochloride: In Vitro Evaluation

Abrar Z*, Aamer Q, Maksud P, Almas S

Department of Pharmaceutics, K.T.Patil College of Pharmacy, Osmanabad-413501, India

Manuscript No: IJPRS/V1/I3/00158, Received On: 30/08/2012, Accepted On: 07/09/2012

ABSTRACT

The low bioavailability and short half life of Metformin HCl make the development of gas powered mucoadhesive dosage forms desirable. However, drug absorption is limited to upper gastrointestinal tract thus requiring suitable drug delivery system providing complete release during stomach to jejunum transit. This study was undertaken to develop a Metformin HCl gas powered bioadhesive formulation in compliance with these requirements. The strategy proposed is based on direct compressed tablets consisting of a combination of Metformin HCl with different viscosity grades of HPMC (K4M, K15M, and K100M), Carbopol 934P, Xanthan gum and gas generating agent sodium bicarbonate with citric acid. Compatibility among the formulation components was assessed by FTIR. All the tablets were examined for post compressional analysis, drug release and bioadhesive strength. The result of the kinetics study obtained permits us to conclude that the fabricated tablets in this case, deliver the drug through diffusional dominated mechanism.

KEYWORDS

Bioadhesive, Gaspowered, Gastrointestinal, Jejunum.

INTRODUCTION

Oral sustained drug delivery system is complicated by limited gastric residence times (G R T s) Rapid G I transit can prevent complete drug release in the absorption zone & reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the majority of small intestine. To overcome these limitations, several controlled oral drug delivery systems with prolonged gastric residence times have been reported recently such as floating drug dosage system (FDDS), swelling or expanding systems, mucoadhesive system, modified shape systems, high density system and other delayed gastric emptying devices. Among these system FDDS have been most commonly used[1].

Floating drug delivery system is also defined as gaspowered system (GPS), which can float in the contents of stomach and release the drug in controlled manner for prolonged periods of time. The release rate will be controlled depending upon the type and concentration of the polymer that swells, leads to diffusion and erosion of the drug[2].

The otherwise excellent concept of floating system suffers from a disadvantage that it is effective only when the fluid level in the stomach is sufficiently high. However, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage forms may be impeded. This serious limitation can be overcome by using bioadhesive polymers to enable it to adhere to the mucous lining of the stomach wall. Floating and bioadhesive drug delivery system offers the advantage of increased contact time with stomach mucosa, more effective absorption and bioavailability of drugs with absorption windows near proximal intestine and stomach and low dosing frequencies.

***Address for Correspondence:**
Zikriya Abrar
Department of Pharmaceutics,
K.T.Patil College of Pharmacy, Osmanabad, India.
E-Mail Id: zikriyaabii@rediffmail.com

Based on the mechanism of buoyancy two distinctly different technologies i.e. non effervescent and effervescent systems have been utilizes in the development of floating system;

1. Non-effervescent system that use commonly gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers.
2. Effervescent system that utilize the matrices prepared with swellable polymers such as HPMC and effervescent compound such as sodium bicarbonate, citric acid or tartaric acid or matrices containing chambers of liquid that gasify at body temperature[3].

Different mass transport process may occur during the drug release from the polymer based matrix tablets including water imbibitions into the system, polymer swelling, and drug dissolution, drug diffusion out of tablet and polymer dissolution.

Metformin hydrochloride is an orally administered biguanide, which is widely used in the management of type II diabetes a common disease that combines defects of both insulin secretion and insulin actions[4]. Unlike other antidiabetic drug metformin hydrochloride does not induce hypoglycemia at any reasonable dose, and hence it is called as an antihyperglycemia rather than hypoglycemic drug[5]. It is hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract and the absolute bioavailability is reported to be of 50-60%[6]. An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea and diarrhea that especially occurs during the initial period of treatment. The compound has relatively short plasma half life of 1.5-4.5 hr and the low absolute bioavailability of 50-60%. Side effects, short half lives, low bioavailability and the need for the administration two to three times a day when larger doses are required can decrease patient compliance, effectiveness, low influence of the physiological variables on its release behavior and broad regulatory acceptance[7]. Many researchers investigated various natural, semi synthetic and synthetic polymeric materials. Cellulose ethers such as hydroxyl propyl methyl cellulose and some natural gums like guar gum and xanthan gum are widely used hydrophilic polymers as release retardants[8].

MATERIAL AND METHOD

Material

Metformin hydrochloride was purchased from Rajesh Chemicals, Mumbai. The polymers like HPMC (K4M, K15M, K100M) and Carbopol 934P was purchased from Vishal Chemicals, Sholapur. Sodium bicarbonate, citric acid, talc and magnesium sterate were purchased from P.H.Gandhi Pune. All other chemicals were of analytical grade.

Preparation of Gas powered Bioadhesive Tablets

All the gas powered bioadhesive tablets were fabricated by using direct compression technique. In this case all the bioadhesive polymers and the active ingredients were passed through sieve no. 40 individually. Accurately weighed quantity of metformin hydrochloride powder, polymer, effervescent agent and excipients were thoroughly mixed in a glass mortar-pestle and with help of automatic punching machine by using 12mm flat punch and 4-6 kg/cm^2 pressure, tablet were prepared of desired shape, size and hardness. In the present work, 9 formulations (F1 to F9) gas powered bioadhesive tablets of metformin hydrochloride were prepared using variable concentrations of HPMC (K4M, K15M, K100M) and Carbopol 934P as shown in the Table No.01.

In-vitro Characterization

a. Weight Uniformity Test[9]

If the drug forms greater part of the tablet, any variation in the tablet weight obviously indicates a variation in the active ingredient this test resembles weight uniformity test. 20 tablets were selected at random and average weights were determined. Then individual tablets

weighed and the individual weight was compared with the average.

Table 1: Formulation compositions of different batches

Sr. No	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Metformin HCl	500	500	500	500	500	500	500	500	500
2	HPMC K 4M	120	110	100	-	-	-	-	-	-
3	HPMC K 15	-	-	-	120	110	100	-	-	-
4	HPMC K 100	-	-	-	-	-	-	120	110	100
5	Carbopol 934 P	50	60	70	50	60	70	50	60	70
6	Xanthan gum	55	55	55	55	55	55	55	55	55
7	Sodium bicarbonate	80	80	80	80	80	80	80	80	80
8	Citric acid	15	15	15	15	15	15	15	15	15
9	PVP K-30	20	20	20	20	20	20	20	20	20
10	Magnesium Stearate	5	5	5	5	5	5	5	5	5
11	Talc	5	5	5	5	5	5	5	5	5

* Weight taken in to mg.

b. Hardness Uniformity Test[9]

The hardness of prepared formulation was measured by using Pfizer hardness tester. Five gas powered bioadhesive tablets were used for hardness uniformity studies. The hardness data used to calculate mean and standard deviation.

c. Thickness Uniformity Test[9]

The thickness uniformity studies were carried out by using Vernier Calliper. Three tablets were used for thickness uniformity studies and denoted in millimeter. The data obtained was used to calculate mean and standard deviation.

d. Friability (F)[10]

The friability of tablet was determined using Roche Friabilator. It is expressed in percentage (%).20 tablets were initially weighed (W initial) and transferred into the friabilator. The friabilator was operated at 25 rpm per min for 4 min (100 revolutions). The tablets were weighed again (W final).

The % friability was then calculated by

$$F = \frac{W\ initial - W\ final}{W\ initial} \times 100$$

e. Content Uniformity[11]

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in a suitable solvent and make up the final volume with the suitable buffer solution. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer, using buffer solution as a blank.

f. In vitro Buoyancy / Floating Study

In vitro buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

g. Swelling Index[12]

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium pH 6.8 buffers at 37 ± 0.50C. After 0.5, one, two, three, four, five, six, seven and eight hours, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, AX 120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.

$$WU\ \% = \frac{\text{Weight of swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

h. In vitro Dissolution Studies[13]

The release rate of metformin hydrochloride from gaspowered bioadhesive tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of pH 1.2 HCl buffer for more than 8 hrs. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with of pH 1.2 HCl. Absorbance of these solutions was measured at 233 nm using a UV/Visible spectrophotometer.

i. FT-IR Spectra[14]

Infrared spectroscopy is one of the most powerful analytical techniques, which offers the possible chemical interaction between drug and excipients used. Fourier transform infra red analysis (FT-IR) measurements of pure drug, polymers and drug loaded gas powered bioadhesive tablets formulations were obtained using a model name Jasco FT-IR Spectrophotometer, the spectra were scanned over the wave number range of 4000-600 cm-1 at an ambient temperature.

j. Drug Release Kinetics[15]

The success of HPMC (K4M, K15M and K100M) in controlling the release of the drug was studied under the following heads to understand the order and probable underlying mechanism involved in the release pattern. To analyze the mechanism of drug release from the prepared formulations, the data obtained from in vitro release studies were subjected to Higuchi's model, Zero order model and Korsmeyer's model.

k. Bioadhesion Test[16]

Bioadhesive strength of the tablet was measured on the modified physical balance. The design used for measuring the bioadhesive strength was shown in Fig. No.1.The apparatus consist of a modified double beam physical balance.

Goat stomach was obtained from slaughter house and isotonic phosphate buffer (IPB) pH 6.8 was used as the moistening fluid. The stomach membrane was excised by removing

the underlying tissues. It was washed thoroughly with isotonic phosphate buffer (IPB) pH6.8 and then tied over Teflon block using a thread. The block was lowered into the glass container filled with IPB pH 6.8 at 37±2°C such that the buffer just touched the sides of the stomach membrane. The two sides of the balance were made equal, before the study, by keeping sufficient weight on the right pan. The glass container was kept below the left hand side of the balance. The tablet was stuck onto the lower side of the hanging Teflon cylinder using either a little moisture or a double sided tape. The preload weight from the right pan was removed. This was kept undisturbed for 2.0 min. Then the water is added drop wise by using burette till the tablet just separated from the stomach membrane surface. The excess weight on the right pan, that is, total weight minus preload weight was taken as a measure of the bioadhesive strength.

Force of adhesion (N) = $\frac{\text{Bioadhesive strength}}{1000} \times 9.81$

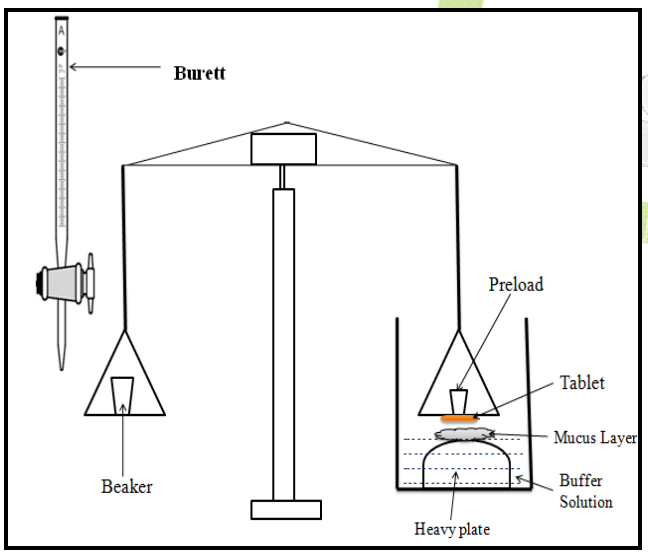

Figure 1: Mucoadhesion Test Assembly

RESULT AND DISCUSSION

EVALUATION OF TABLETS

Weight Variation, Thickness, Hardness and Friability

The results showed that weight variation, thickness were lying within limits. Because of variation in the compressional forces there is a slight variation in hardness of tablets. The friability loss was found to be within the limits in all the formulations. The results of Physical properties of metformin hydrochloride gas powered bioadhesive tablets are given in Table No. 2 and the results revealed that the tablets are mechanically strong.

Buoyancy and Total Flotation test

From the results, it was observed that as the buoyancy lag time and the total floating time was studied for all the formulations. Total floating time was determined and for F1, F2, and F3 were found to be 8 hrs, for F4, F5 and F6 were found to be 9 hrs and for F7, F8 and F9 were found to be more than 12 hrs. The buoyancy lag time was found in the range of 20 – 115 sec for the formulation as shown in Table no. 3.

Table 3: Floating Properties

Batch Code	Buoyancy Lag Time (sec)	Total Floating Time (hrs)
F1	95	9
F2	104	9
F3	115	9
F4	64	10
F5	49	10
F6	20	10
F7	50	12
F8	40	12
F9	25	12

Table 2: Pre-compressional Evaluation Parameters

Batch code	Thickness (mm) ± S.D	Hardness (Kg/cm^2) ± S.D	Friability (%)	Weight Variation (mg) ± S.D
F1	5.28 ± 0.01	5.82 ± 0.16	0.62	849.36 ± 0.12
F2	5.16 ± 0.03	5.38 ± 0.07	0.54	849.00 ± 0.15
F3	5.30 ± 0.02	5.65 ± 0.07	0.80	849.15 ± 0.05
F4	5.75 ± 0.04	5.76 ± 0.12	0.44	848.66 ± 0.25
F5	5.78 ± 0.08	5.49 ± 0.15	0.82	848.91 ± 0.52
F6	5.40 ± 0.01	5.24 ± 0.06	0.64	849.41 ± 0.02
F7	5..57 ±0.08	5.31 ±0 .13	0.68	849.20 ± 0.37
F8	5.35 ±0.04	5.55± 0.08	0.58	848.85 ± 0.13
F9	5.35 ±0.01	5.45 ± .11	0.52	848.63 ± 0.37

Table 4: Data showing swelling index for all the formulation

Time (Hrs)	Swelling Index (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	30.40	35.03	38.79	33.84	36.62	33.72	38.88	39.54	35.66
2	34.20	37.58	45.78	44.45	45.54	41.42	47.92	50.23	40.87
3	45.48	46.57	54.32	56.60	55.64	50.41	56.68	62.70	48.69
4	54.51	56.61	62.63	63.56	64.80	58.69	65.56	69.35	54.73
5	62.11	64.65	69.63	70.28	71.93	66.74	73.84	75.53	62.32
6	70.19	72.57	75.44	78.65	77.64	74.55	80.47	81.59	69.54
7	78.62	80.61	80.42	83.72	82.52	81.65	86.74	86.57	75.35
8	85.27	86.76	86.47	88.56	87.75	86.86	91.83	90.61	81.87
9	91.44	92.55	94.42	91.50	92.50	91.47	95.73	94.65	86.61
10	-	-	-	96.69	95.60	93.60	98.57	98.33	91.35
11	-	-	-	-	-	-	100.74	102.01	95.49
12	-	-	-	-	-	-	103.55	105.46	98.81

Drug content of all the formulations are within the acceptable range which shows the proper mixing of the drug with excipients as shown in Table no. 05.

Table 5: Drug Content

Batch code	Drug Content (%)
F1	99.06
F2	88.26
F3	94.99
F4	93.54
F5	96.82
F6	97.06
F7	96.42
F8	98.98
F9	99.59

In-vitro Drug Release

In-vitro drug release study for all the formulations was conducted and tabulated in Table no. 06. As the concentration of polymer HPMC (K4M, K15M, and K100M) decreases the drug release rate increases.

Drug Release Kinetics

From the data of drug release, it was found that, all the tablet formulations follow diffusion mechanism for the drug release. The Higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion. Results revealed that all the prepared formulations follow Higuchi kinetics while the drug release follows diffusion mechanism is **Anomalous** (non-Fickian) diffusion (n= 0.6359) as shown in Table no.07.

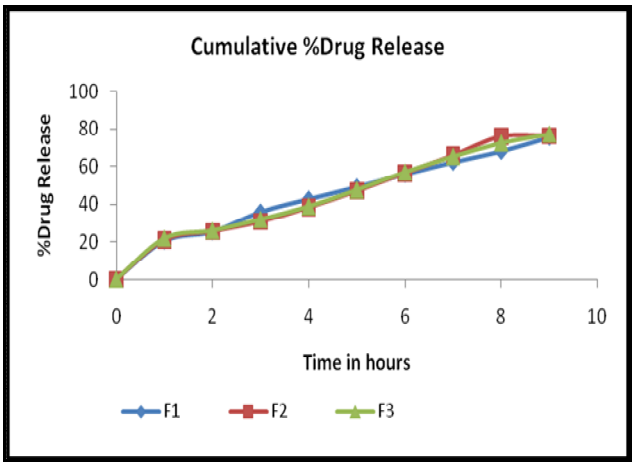

Figure 2: Cumulative % drug release for F1, F2 and F3

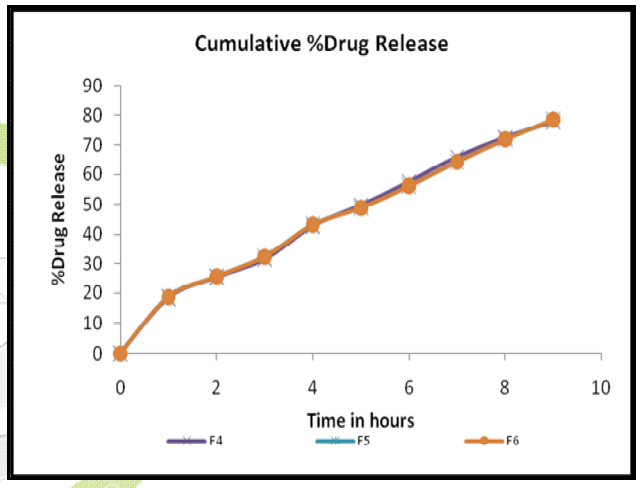

Figure 3: Cumulative % drug release for F4, F5 and F6

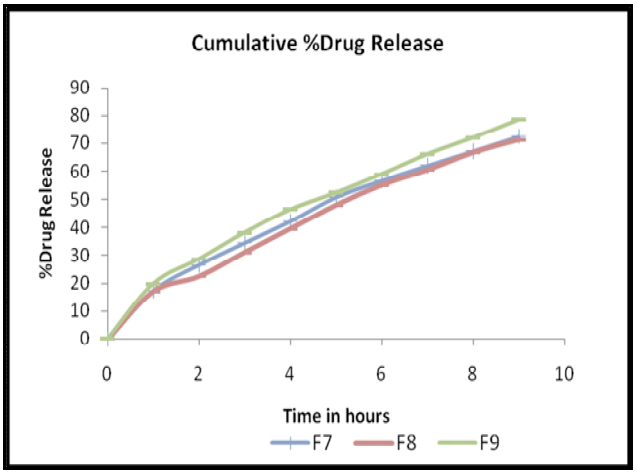

Figure 4: Cumulative % drug release for F7, F8 and F9

Table 6: Data showing comparative *In-Vitro* % drug release profiles for all the prepared formulations

Time (Hr)	% Drug Release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	20.46	21.10	21.87	18.34	18.74	18.74	17.21	17.11	19.77
2	25.36	25.64	26.01	25.36	25.66	25.66	26.54	22.50	28.67
3	35.84	30.89	31.97	31.45	32.44	32.44	34.51	31.20	38.19
4	42.58	38.32	38.79	42.68	43.17	43.17	42.28	39.69	46.41
5	48.87	46.89	47.38	49.55	48.84	48.84	50.81	48.01	52.28
6	55.62	56.30	56.75	57.37	56.11	56.11	56.66	55.09	58.87
7	62.04	65.68	65.05	65.81	64.31	64.31	62.02	60.43	66.03
8	67.83	75.84	72.27	72.44	71.92	71.92	67.24	66.65	71.99
9	75.27	76.21	77.00	77.74	78.68	78.68	72.51	71.26	78.46
10	-	-	-	79.28	82.19	82.19	77.35	76.59	83.84
11	-	-	-	-	-	-	81.67	81.11	88.05
12	-	-	-	-	-	-	86.10	86.62	92.78

Table 7: Data showing drug release kinetics for all the prepared formulations

Batch Code	r^2 value				
	Zero order	**First order**	**Higuchi model**	**Korsmeyer & Peppas**	**Hisxon-Crowell**
F1	0.984	0.996	0.991	0.988	0.986
F2	0.946	0.984	0.993	0.986	0.964
F3	0.963	0.992	0.989	0.985	0.977
F4	0.985	0.986	0.991	0.986	0.911
F5	0.971	0.995	0.995	0.987	0.989
F6	0.967	0.982	0.996	0.987	0.987
F7	0.985	0.983	0.998	0.999	0.998
F8	0.975	0.988	0.992	0.991	0.990
F9	0.952	0.989	0.997	0.996	0.988

Bioadhesion Test

The bioadhesion test was performed using goat mucosa and the bioadhesion strength was found in the range of **15.36-22.32g** and bioadhesion force **0.15-0.21N.**

Table 8: Comparative Data for Bioadhesion Strength

Batch	Bioadhesion Strength(gm ±SD)	Bioadhesion Force (N)
F1	15.36 ± 0.03	0.15
F2	16.56 ± 0.05	0.16
F3	17.78 ± 0.04	0.17
F4	16.21 ± 0.02	0.15
F5	17.44 ± 0.02	0.17
F6	18.59 ± 0.04	0.18
F7	20.16 ± 0.02	0.19
F8	21.39 ± 0.03	0.20
F9	22.32 ± 0.03	0.21

FT-IR Data

FT – IR of pure metformin hydrochloride, various polymers, other excipients and F9 formulation were recorded as shown in Figure no.05- 09. The metformin hydrochloride present in the formulation F9 was confirmed by FT- IR. No predominant drug interaction was detected between drug and polymers along with excipients. The region 3359 – 3371cm^{-1} was a stretching region of the functional group N-H, C-H deformation (1478- 1481 cm^{-1}), C=N stretching (2217-2218cm $^{-1}$) and C- H stretching aliphatic (2813-2817cm^{-1}). All the peaks have appeared in pure metformin hydrochloride and formulation F9 indicating no chemical interaction between metformin hydrochloride and excipients.

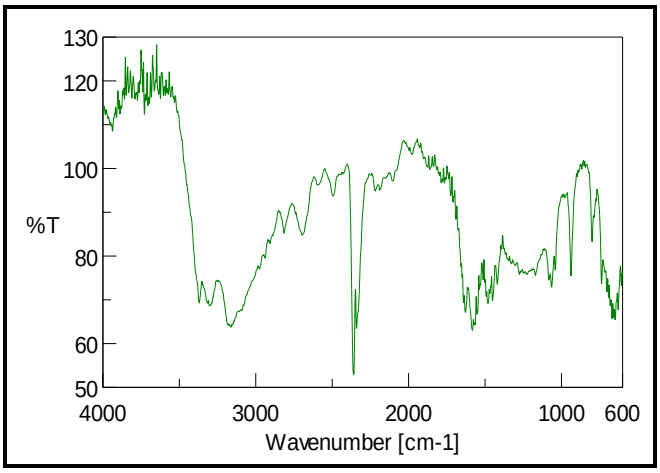

Figure 5: FTIR for Metformin Hydrochloride (Pure Drug)

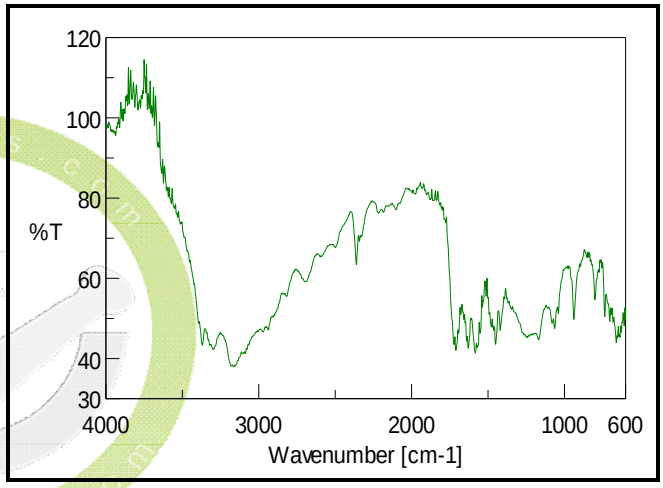

Figure 6: FTIR for Metformin Hydrochloride +HPMC K4M + Carbopol 934P

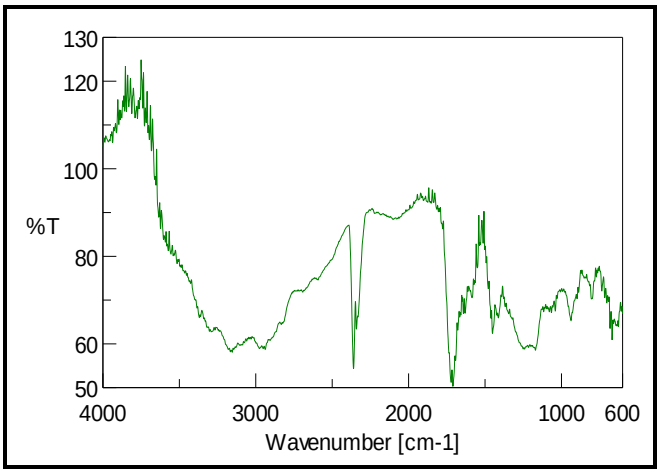

Figure 7: FTIR for Metformin Hydrochloride +HPMC K15M + Carbopol 934P

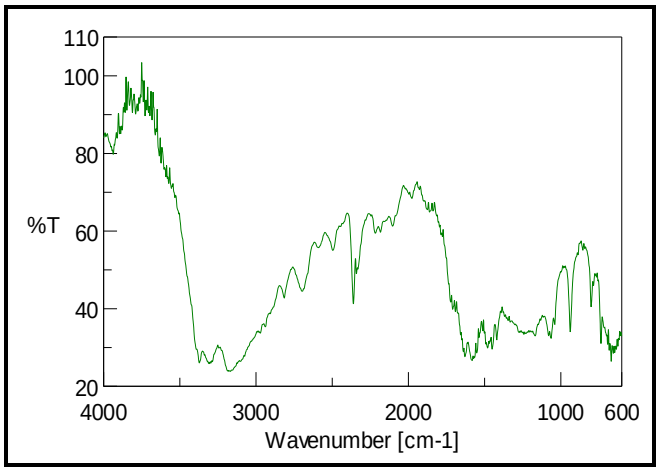

Figure 8: FTIR for Metformin Hydrochloride +HPMC K100M + Carbopol 934P

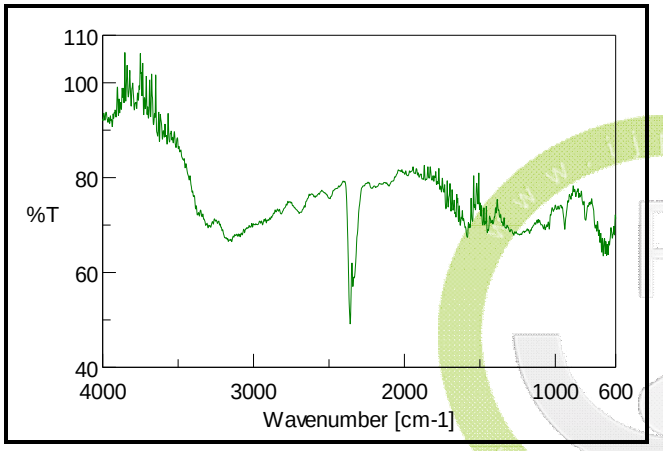

Figure 9: FTIR of Batch F9

CONCLUSION

The present study aimed at formulating Metformin HCl into gastroretentive gaspowered bioadhesive tablets, preferred due to its ability to retaining drug delivery system in GIT and improving bioavailability especially for drugs exhibiting specific absorption window in GI tract. Tablets were subjected to various evaluation parameters such as weight variation, hardness, friability, drug content, swelling index, in vitro buoyancy study and bioadhesive studies. It was revealed that tablets of all batches have acceptable physical parameters. FTIR studies revealed that there was no interaction between Metformin HCl and other excipients used in the formulation. The drug release kinetics follows Higuchi model and mechanism was found to be non- Fickian/ anomalous.

ACKNOWLEDGEMENT

The authors are thankful to K.T.Patil College of Pharmacy for allowing this research work to perform in the laboratory of the College, Mr. Siraj and Mr. Sudhir Pange for their valuable suggestion to fulfill this research work in research work in a successful manner.

REFERENCES

1. Choi BY et al, “Preparation of Alginate Beads for Floating Drug Delivery System: Effects of CO2 Gas-forming Agents”, International Journal of Pharmaceutics, 2002, 239, 81–91.
2. Patil P et al, “Formulation and *In Vitro* Evaluation of Floating Matrix Tablets of Ofloxacin”, Asian J. Res. Pharm. Sci., 2011, 1(1), 17-22.
3. Sungthongjeen S et al, “Design and Evaluation of Floating Multi-layer Coated Tablets Based on Gas Formation”, European Journal of Pharmaceutics and Biopharmaceutics 2008, 69, 255–263.
4. Wadher KJ et al, “Formulation and Evaluation of a Sustained-Release Tablets of Metformin Hydrochloride Using Hydrophilic Synthetic and Hydrophobic Natural Polymers”, Indian Journal of Pharmaceutical Sciences, 2011, 73(2), 208-215.
5. Martindale SC, London: The Pharmaceutical Press, 2002. The Complete Drug Reference.
6. Wiley A, Insulin and oral hypoglycemic drugs. In: Williams DA, Lemke TL, editors. *Foyes Principle of medicinal chemistry*. New York: Lippincott Williams and Wilkins, 2002, 641–648.
7. Chien YW, New York: Marcel Dekker, 1992, Novel drug delivery systems, 1–43.
8. Ambati Brahma Reddy et al, “Aceclofenac Floating Tablets - A Promising Sustained Release Dosage Form;” International Journal of Drug Development & Research, 2011, 3(2), 290-300.
9. Leon Lachman, Herbert A. Lieberman, Joseph L. Kanig, “The Theory and Practice of Industrial Pharmacy,” Varghese Publication House, 3rd Edition.

10. Indian Pharmacopoeia, The Controller of Publications: Delhi, 1996, Vol. *II*, 734-36.
11. Sharma MS et al, "Design and Characterization of Floating Tablet of Cefpodoxime proxetil", International Journal of Biopharmaceutical and Toxicological Research, 2011, 1(1), 9-16.
12. Sasa Baumgartner A et al, "Optimization of Floating Matrix Tablets and Evaluation of Their Gastric Residence Time", International Journal of Pharmaceutics, 2000, 195, 125-135.
13. Naga Pranitha Chodavarapu et al, "Formulation and Evaluation of Abelmoschus Esculentus Mucilage Based Metformin Hydrochloride Floating Matrix Tablets", International Journal of Pharmacy & Technology, June, 2011, 3(2), 2725-2745
14. Chander Shekar B., Shireesh Kiran R., Nagendra Babu B, "Preparation and Evaluation of Gastro Retentive Floating Tablets of Ketoconazole", International Journal of Pharma Research and Development Nov, 2010, 2(9), 174-184.
15. Zawar Laxmikant R et al, "Formulation and Evaluation of Floating-Mucoadhesive Tablet of Clarithromycin", International Journal of Pharma and Bio Sciences 2010, 1(2), 1-10.