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FORMULATION AND EVALUTION OF GASTRO RETENTIVE FLOATING TABLETS OF GLIPIZIDE

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ABSTRACT

A gastro retentive floating drug delivery system containing glipizide was prepared in the form of tablet and evaluated for its processing parameters and *in vitro* release behaviour. Glipizide is a selective second-generation sulphonyl urea used in treatment of hyperglycemia and it absorbs rapidly and completely. However its absorption is erratic in diabetic patient due to its impaired gastric motility or gastric emptying. To overcome these drawbacks, the present investigation was to develop a gastro retentive floating tablets of glipizide. Ten formulations containing retardant materials such as hydroxypropylmethylcellulose K4M and K15M, sodium bicarbonate was used as a gas generating agent to reduce floating lag time and other release promoters. Tablets remained buoyant over 12 hours in the release medium, and the amount of sodium bicarbonate found to be significant for not only to remaining buoyant without causing disintegration of the tablet, but also to release of the drug in the acidic medium. Final F6 optimized formulation released approximately 99% drug in 12 hours *in vitro*, while the floating lag time was 39 sec and tablet remained floatable throughout all studies. *In vitro* gastro retentive study of tablets gave successful results by floating in gastric content over a period of 24 hours. The results of the current study clearly indicate, a promising potential of the glipizide floating system as an alternative to the conventional dosage form.

KEYWORDS: Glipizide, Gastro retentive floating tablets, Hydroxypropylmethylcellulose,

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INTRODUTION

During the last decade, many studies have been performed concerning the sustain release dosage forms of drug, which have aimed at the prolongation of gastric emptying time (GET). The GET has been reported to be from 2 to 6 hours, in humans in fed state.[1] Retention of drug delivery system in the stomach prolongs overall gastro intestinal transit time, thereby resulting in bioavailability. Drugs that required to be formulated into gastro retentive dosage forms include, drugs acting locally and primarily absorbed in stomach, drugs that are poorly soluble at an alkaline pH, those with a narrow window of absorption, drugs absorbed rapidly from GI tract and drugs that degrade in colon.[1] Scientigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms were subjected to basically two complication; that of short gastric residence time and unpredictable gastric emptying rate. Various approaches have been worked out to improve the retention of oral dosage forms: swelling and expanding system, [2] alter dosage forms,[3] low density or floating drug delivery system,[2] bioadhesive system,[4] high density non-floating drug delivery system,[5] modified shaped system.[5] Depending on the mechanism of buoyancy, two distinctly different methods viz., effervescent and non-effervescent system have been used in the development of floating drug delivery system (FDDS).[6] Effervescent drug delivery system utilize matrices prepared with swellable polymers such as methocel[5] or polysaccharides and effervescent components e.g., sodium bicarbonate and citric acid or tartaric acid.[7]

Glipizide is a selective second generation sulphonylurea used in the treatment of hyperglycemia. It is poorly soluble in the acidic environment. When it is given orally in healthy people, it absorbs rapidly and completely. However, its absorption is erratic in diabetic patients due to the impaired gastric motility or gastric emptying. This erratic absorption of glipizide is clinically relevant, since the efficacy of short acting sulphonylurea is dependent upon the absorption rate of the drug.[8] To overcome these drawbacks, in the present study gastric retentive controlled release dosage form of the drug in the form tablet was formulated with hydroxypropylmethylcellulose K4M and K15M as both retardant and low density materials. The aim of the present study was not only preparing a floating system but also to release the drug in controlled fashion. Polymers were added in different concentrations with varying amount of retardant material and investigated the release profile following USP type II *in vitro* dissolution model.

MATERIALS AND METHODS

Materials

Glipizide was obtained as gift sample from Apex laboratories, Chennai. Polyvinyl pyrrolidone and Sodium lauryl sulfate was obtained from Loba Chemie, Pvt, Ltd, Mumbai. Hydroxypropylmethylcellulose K15M and K4M were purchased from Madras pharmaceuticals, Chennai. Other reagents and solvents were of analytical grade.

METHODS

Preparation of gastro Retentive floating tablets of glipizide

Gastro retentive floating tablets of glipizide were prepared by direct compression method. The powder mixture containing drug, polymers (HPMC K4M and HPMC K15M) and other excipients including talc 1% as lubricant was blended thoroughly in mortar and pestle and passed through sieve no. 100. Then the mixture was compressed using 8mm flat faced punch on Cemach 12 station rotator tablet compression machine. Ten formulations were prepared and coded them F1 to F10. The detail of composition of each formulation is given in Table 1.

EVALUATION OF GRANULES

Angle of repose

Angle of repose were determined using funnel method.[9] The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (Q) was calculated using the formula.

$Q = \tan^{-1} (h/r)$

Bulk density

Apparent bulk density (p_b) were determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula.[9]

$p_b = M/ V_b$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend were measured. The tapped density (ρ_t)[9] was calculated using formula.

$\rho_t = M/ V_t$

Compressibility index

The simplest way for measuring of free flow of powder was compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (I)[9] was calculated as follows.

$I = V_0 - V_t/V_O \times 100$

Where, Vo is the bulk volume and Vt is tapped volume.

Hausner's ratio

Hausner's ratio[10] was an indirect index of ease of powder flow. It was calculated by the following method

Hausner ratio = ρ_t/ρ_d

Where, ρ_t tapped density and ρ_d bulk density lower hausner ratio.

Weight variation

Twenty tablets were selected randomly from each formulation and weighed individually using an electronic balance to check the weight variations as per pharmacopoeia.[9]

Friability

Friability of the tablets was determined using Roche friabilator.

Hardness

Hardness of the tablets was measured using Monsanto tablet hardness tester for each formulation.[9]

Thickness

10 tablets were taken from each formulation and their thickness was measured using digital vernier calipers.

DRUG CONTENT ESTIMATION

Five tablets were taken and amount of drug present in each tablet was determined as follows: Tablet was crushed in mortar and transferred to 100 mL flask. The powder was dissolved in 3 mL of methanol and volume was made up with 0.1 N HCl. The sample was mixed by using Remi mixer for 5 minutes, after which it was filtered through Whatman filter paper. The filtered solutions after appropriate dilution (1 to 10 mL) with 0.1

N HCl were analyzed by validated UV spectrophotometric method at 276 nm.

***In Vitro* Dissolution Studies**

The dissolution study was carried out in 0.1 N HCl using USP XXIII dissolution test apparatus employing paddle stirrer. In this study, one tablet containing 20 mg of glipizide was placed inside the 500 mL dissolution medium and speed of paddle was set at 75 rpm. Samples were (5 mL) withdrawn at a time interval of 1 hour and same volume of fresh medium was replaced. The samples were analyzed for drug content against 0.1 N HCl as a blank at 276 nm. The percentage drug release was plotted against time to determine the release profile.

***In Vitro* Buoyancy Studies**

The *in vitro* buoyancy was determined by floating lag time, as per the method described by (Rosa M, Zia H, Rhodes T 1994). The tablets were placed in a 100 mL beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies were performed on drug, excipient and the optimized formulation using FTIR. The sample were analysed between wave numbers 4000 and 400 cm^{-1}.

RESULTS

The shape of the tablets of all formulations remained circular with no visible cracks. The content uniformity test (Table 3) revealed that the tablets from different formulations remained within the pharmacopoeial limit. Also the tablets remained buoyant for a period of > 24 hrs. The formulations exhibited good flow property and compressibility index (Table 2). Angle of repose and compressibility index (%) ranged from 26.73 to 29.30 and 11.26 to 15.90, respectively. Drug content was ranged from 97.2% to 101.12%. The thickness of the tablets ranged from 4.38 mm to 4.62 mm. The average percentage deviation of 20 tablets from each formulation was remained within ± 5%. The average hardness is 5.5 kg/cm^2 and percentage friability of the tablets of all the batches remained in the range of 0.47 to 0.91 respectively. *In vitro* dissolution studies of the formulations F1, F2, F3, F4 and F5 the drug released 97%, released were 99.7%, 96.4%, 89.9%, 86.6% and 79.9% of drug in 12 hours. These formulations are similar to the 92%, 86%, 85% and 75% drug respectively at the end of 6 hours were shown in Table 4. These formulations vary in amount and type of polymers used. Formulations F6, F7, F8, F9 and F10 the drug formulations mentioned before except the grade of polymer used. These formulations thus can be compared with the earlier formulations to study the effect of polymers on drug release rate. Among the all formulations F6 was found to be better with respect to the release.

DISCUSSION

The present study was aimed at not only to improve the release of drug, glipizide, in the acidic pH, but also to release the drug in controlled fashion. Also, to make the formulation remain in the stomach for longer period of time, gastro retentive dosage form was designed, to make the therapy more effective as the drug is known for incomplete absorption in diabetic patients as explained before. The polymers used in the formulation are well established polymers for the said dosage form. The roles of polymers are to control the release as well as to make the formulation buoyant. The tablets were prepared by direct compression method after mixing the ingredients with the help of mortar and pestle. The granules of different formulations were evaluated for angle of repose, compressibility index, and drug content. The results of angle of repose (26 to 29) indicate reasonably good flow property of granules. The compressibility index values in the range of 11.2 to 15.9 (< 25), further support flow property of granules. The drug content of all the formulations was found to be more or less uniform (Table 2). Tablets of all the formulations were subjected to many in-process parameters evaluation such as physical appearance, thickness, content uniformity, weight variation, hardness, and friability tests. All the formulations showed thickness in the range of 4.38 mm to 4.62 mm. Also the tablets were circular in shape with no visible cracks with smooth appearance. Weight variation test revealed that the tablets were within the range of pharmacopoeial limit. Good uniformity in drug content was found among different formulations of the tablets, and the percentage drug content was more than 96%. All the formulations show edreasonably good hardness value of 5.5 kg/cm^2 approximately. Further, to strengthen these values, friability test values are also considered. The weight loss of less than 1% in friability test is considered as acceptable value for conventional tablet. This indicates that the tablets can withstand the mechanical shocks reasonably well during handling.

Formulations were prepared by different concentrations HPMC K4M and K15M with carbopol 974P polymers. All the polymers were chosen as they are well established in the similar studies and have good swelling properties. The rate of swelling of polymer depends upon the amount of water taken up by polymer. Sodium bicarbonate is added in the formulation which upon

contact with HCl liberates carbon dioxide and expels from the dosage form creating pores through which water can penetrate in to dosage form and increase wetting. As the concentration of HPMC K4M and HPMC K15M increased from 30 mg to 70 mg the release rate was decreased. Theoretically speaking this behaviour is expected since more amount of polymer always delays the release (Figure 1 and 2). The amount of sodium bicarbonate in formulation is also believed to play a very important role as far as the drug release is concerned. Besides its buoyancy effect due to the liberation of CO_2 and subsequent entry of water through pores increase the wetting rate of polymers as well as the alkalizing effect of sodium bicarbonate contributes to the solubility of the drug better in all the formulation. All the formulations were designed as dosage form for 12 hours. In order to check the 100% dissolution release profile, optimized formulations were subjected to dissolution studies for 12 hours. Among the ten formulations F6 formulation was best and shows 99% drug release in the end of 12 hours, respectively. Figure 2 shows the drug release profiles of these optimized formulations. FTIR spectra revealed that there was no such interaction between the drug and the polymers used for microsphere formulations (Figure 3, 4 and 5).

CONCLUSION

The present study was carried out to develop the floating drug delivery with controlled release of glipizide tablets using two different polymers HPMC K4M and HPMC K15M at different concentrations. As the concentration of polymer increased floating lag time decreased. Use of high viscosity polymer can also decrease the floating lag time and viscosity of polymer should directly proportional relationship with swelling characteristics of tablets. This may overcome solubility problems and clinical problems associated with glipizide showed sufficient release for extended period of time. As a result the frequent dosing and possible incomplete absorption of drug can be avoided. The prepared tablets were evaluated and all the formulations gave satisfactory results. Hence it was concluded that the formulations with HPMC K15M was optimized for better release.

REFERENCES

1. Tayade P. Gastro retentive drugs. A review, Express Pharma Pulse 2003; 14: 1- 4.
2. Vyas SP and Khar RK. Gastro retentive systems in controlled drug delivery: Concept and advances. First edn, CBS Publication, New Delhi 2002: 196 - 217
3. Deshpande AA, Shah NH, Rhodes CT, and Malick AW. Controlled release drug delivery System for prolonged gastric residence: An overview. Pharma Res 1996; 22: 531-539
4. Chickering DE, Jacob JS and Mathowitz E. Bioadhesive microspheres: Characterization and evaluation of bioadhesion involving hard, erodible polymers and soft tissues, reactive polymers 1995; 25: 189-206.
5. Garg S and Sharma S. Review: Gastro retentive drug delivery system. Pharma Tech 2003; 13: 160-166.
6. Hilton AK, Deasy PB. In vitro and in vivo evaluation of oral sustained release floating dosage form of amoxicillin trihydrate. Int J Pharm 1992; 86: 79-88.
7. Rubinatein A and Friend DR. Specific delivery to the gastro intestional tract, in polymeric site specific pharmacotherapy. Wiley Chichester 1992; 282-283.
8. Singh BN and Kim KH. Floating drug delivery system: approach to oral controlled drug delivery via gastric retention. J Control Release 2000; 63: 235-59.
9. Marshall K, Lachaman L, Leon Liberman HA and Kanig JL, The theory and practice of industrial pharmacy edition 3, Varghese publishing house 1987; 66-99.
10. Lindberg N, Palsson M, pihl A, Freeman R, Freeman J, Zetezener H and Enstand G. Flowability measurement of pharmaceutical powder mixture with poor flow using five different techniques. Drug Dev Ind Pharm 2004; 30: 785-791.
11. Levis SR and Deasy PB. Pharmaceutical application of reduced grades of surfactants co- processed Micro crystalline cellulose. Int J pharm 2001; 230: 25-33.
12. Chien YW. Novel drug delivery systems. 2nd Edn. New York. Marcel Dekker Inc; 1992.
13. Robinson JR and Lee VHL. Controlled drug delivery. 2nd Edn, New York. Marcel Dekker Inc; 1987.
14. Menon A, Wolfgang A, Ritschel A, Sakr A. Development and evaluation of monolithic floating dosage form for furosemide. J Pharm Sci 1994; 83: 239-245.
15. Klausner EA, Lavy E, Friedmon M and Hoffman A. Expandable gastro retentive dosage forms. J Control Release 2003; 90: 143-62 .

Table 1. Composition of glipizide floating tablet formulations

Ingredients	F 1	F2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10
Glipizide	10	10	10	10	10	10	10	10	10	10
HPMC K4M	70	60	50	40	30					
HPMC K15M						70	60	50	40	30
Carbopol 974P	30	40	50	60	70	30	40	50	60	70
Sodium bicarbonate	35	35	35	35	35	35	35	35	35	35
MCC	52	52	52	52	52	52	52	52	52	52
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1	1
Total Weight (mg)	200	200	200	200	200	200	200	200	200	200

Table 2. Evaluation of granules

Formulations	Angle of Repose (Q)	Compressibility Index (%)	Hausner Ratio
F1	28^0. 70’	12.3	1.15
F2	29^0. 32’	15.9	1.19
F3	27^0. 64’	12.8	1.13
F4	28^0. 10’	15.7	1.17
F5	28^0. 46’	12.4	1.14
F6	27^0. 90’	11.2	1.13
F7	26^0. 74’	12.3	1.18
F8	28^0. 76’	12.3	1.15
F9	29^0. 36’	15.9	1.19
F10	27^0. 60’	12.8	1.13

Table 3. Evaluation of glipizide floating tablets

Formulations	Weight (mg)	Hardness (kgs)	Friability	Thickness (mm)	Drug Content (%)	Floating Lag Time (sec)	Floating Time (hours)
F1	200.8 ± 0.74	6.1 ± 0.3	0.65 ± 0.11 %	4.55 ± 0.09	99.01 ± 1.2 %	19	18
F2	194.6 ± 0.33	5.8 ± 0.3	0.71 ± 0.15 %	4.38 ± 0.06	101.02 ± 3.2 %	18	16
F3	201.7 ± 0.14	5.6 ± 0.2	0.81 ± 0.21 %	4.49 ± 0.03	98.2 ± 2.5 %	16	16
F4	205.9 ± 0.28	5.4 ± 0.2	0.89 ± 0.45 %	4.58 ± 0.03	97.28 ± 3.1 %	14	15
F5	197.3 ± 1.14	5.1 ± 0.6	0.91 ± 0.10 %	3.48 ± 0.05	99.12 ± 0.5 %	13	15
F6	207.6 ± 0.85	6.1 ± 0.7	0.47 ± 0.05 %	4.60 ± 0.03	102.06 ± 0.9 %	39	> 24
F7	201.4 ± 1.01	5.9 ± 0.1	0.54 ± 0.12 %	4.46 ± 0.01	100.07 ± 3.5 %	30	> 24
F8	195.1 ± 0.52	5.8 ± 0.4	0.63 ± 0.11 %	4.62 ± 0.06	100.01 ± 3.4 %	24	> 24
F9	198.2 ± 0.34	5.5 ± 0.2	0.69 ± 0.14 %	4.48 ± 0.03	99.01 ± 0.8 %	20	> 24
F10	202.1 ± 0.48	5.4 ± 0.4	0.71 ± 0.21 %	4.45 ± 0.05	101.2 ± 2.4 %	19	> 24

Table 4. *In vitro* drug release studies of floating tablets with HPMC K4M polymer

TIME (hours)	F1	F2	F3	F4	F5
0.5	22.1 ± 0.6	20.3 ± 1.2	19.4 ± 2.1	16.8 ± 2.5	10.7 ± 1.3
1	36.8 ± 2.1	29.4 ± 3.1	29.7 ± 1.3	25.8 ± 2.8	22.1 ± 1.2
2	54.8 ± 1.3	50.4 ± 2.6	48.7 ± 2.6	36.5 ± 3.6	28.2 ± 2.6
3	75.4 ± 2.3	59.6 ± 1.8	55.6 ± 3.2	49.8 ± 2.1	56.1 ± 3.2
4	81.3 ± 1.3	74.8 ± 1.6	72.5 ± 2.4	67.7 ± 2.4	64.1 ± 1.5
6	97.1 ± 2.5	92.0 ± 3.1	86.1 ± 3.5	85.1 ± 1.2	75.1 ± 1.9

Table 5. *In vitro* drug release studies of floating tablets with HPMC K15M polymer

TIME (hours)	F 6	F 7	F 8	F 9	F10
0.5	14.8 ± 2.5	12.9 ± 3.6	15.4 ± 2.1	10.3 ± 1.5	8.1 ± 1.5
1	22.7 ± 2.3	20.8 ± 2.5	23.3 ± 1.6	18.8 ± 2.4	16.2 ± 0.8
2	29.6 ± 2.6	33.7 ± 1.6	28.7 ± 1.5	26.7 ± 1.6	22.5 ± 3.4
3	45.9 ± 1.4	41.6 ± 2.5	38.6 ± 0.6	42.6 ± 3.4	36.8 ± 2.5
4	59.5 ± 2.6	63.2 ± 3.6	52.5 ± 2.6	51.0 ± 4.5	48.1 ± 2.6
6	74.7 ± 3.6	68.0 ± 1.8	66.3 ± 2.6	63.9 ± 2.6	60.8 ± 2.4
8	83.4 ± 4.5	79.7 ± 3.7	75.1 ± 2.7	72.1 ± 3.6	68.4 ± 3.5
10	92.1 ± 2.3	85.8 ± 4.5	81.6 ± 3.4	79.2 ± 4.5	75.8 ± 2.1
12	99.7 ± 2.6	96.4 ± 3.8	89.9 ± 1.4	86.6 ± 2.8	79.9 ± 1.4

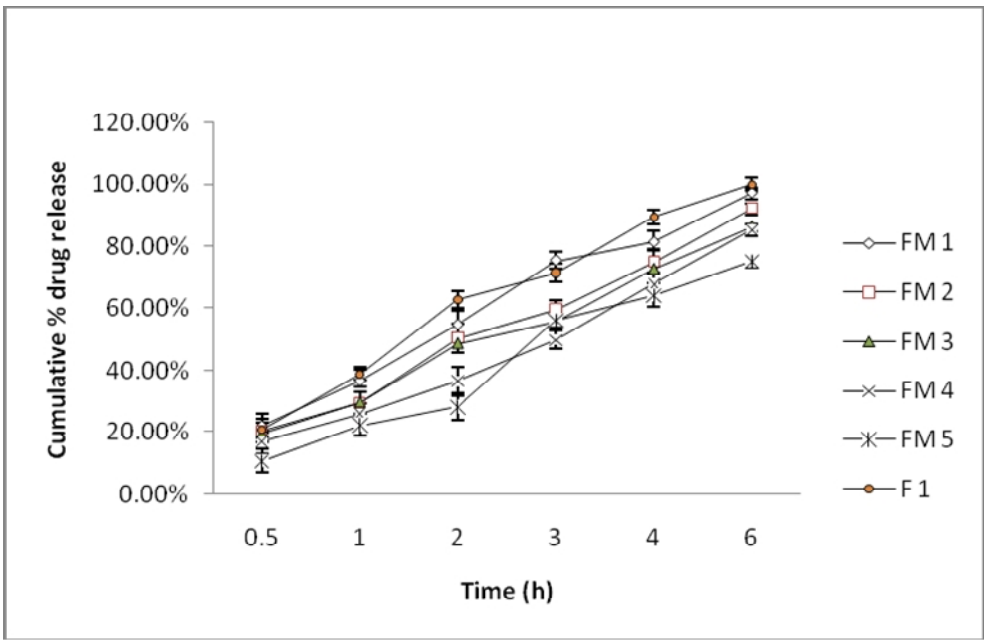

FIGURE 1. COMPARATIVE DRUG RELEASE PROFILE OF HPMC K4M FORMULATIONS (F1 TO F5)

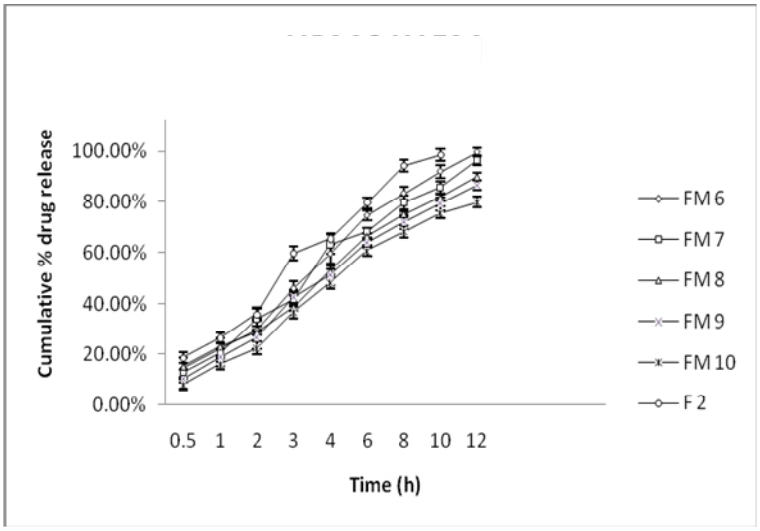

FIGURE 2. COMPARATIVE DRUG RELEASE PROFILE OF HPMC K15M FORMULATIONS (F6 TO F10)

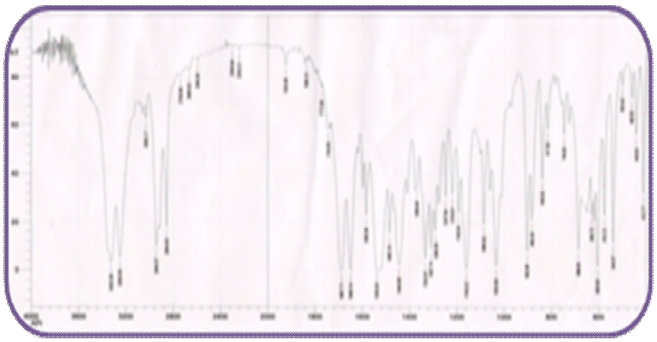

FIGURE 3. FTIR STUDIES OF PURE DRUG

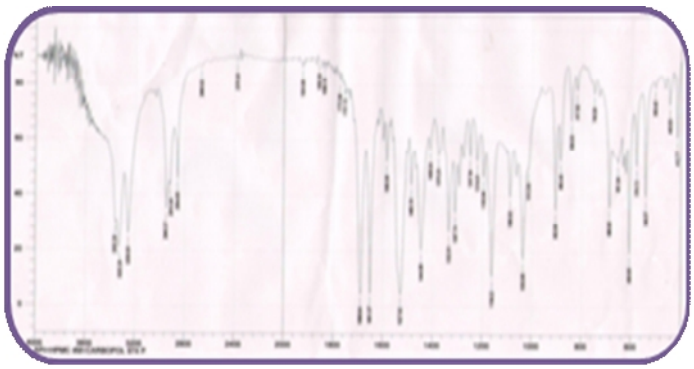

FIGURE 4. FTIR STUDIES OF HPMC K4M FORMULATION

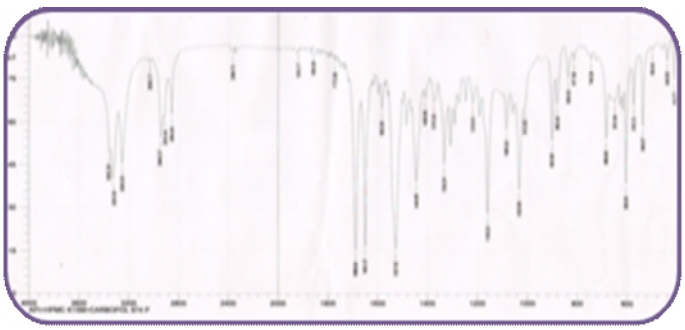

FIGURE 5. FTIR STUDIES OF HPMC K15M FORMULATION

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