Original Research Article

Formulation Development & Evaluation of Floating tablets containing anti-diabetic drugs using different polymers

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Abstract

The objective of the present study was to develop a pharmaceutically equivalent, stable, robust, cost effective and quality improved formulation of Glimepiride Non-effervescent floating tablets by using different grades of controlled release polymer. The design of dosage form was performed by choosing HPMC K 100M, HPMC K15M, HPMC K4M, Accural, MCC Magnesium stearate, and Talc in different ratios. The drug-polymer compatibility studies were performed. Blend Uniformity was studied and accordingly the flowability was optimized for the powder blend. Tablets were prepared by direct compression with free flowing powder. The network formed by HPMC, MCC and DCP had been coupled satisfactorily with the controlled resistance, in vitro release and FT-IR. Mean dissolution time was also reported to compare various dissolution profiles. The formula was finalized by comparing the in vitro dissolution with that of the innovator SR and IR tab.

Keywords: Glimepiride, Non-effervescent, HPMC.

Introduction

Diabetes appears to be one of the most challenging diseases in terms of its devastating impact on global population. According to a recent report from world health statistics in 2012, every single person out of 10 suffers from this disease worldwide. The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery has recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation[1]. Glimepiride stimulates the secretion of insulin granules from the pancreatic beta cells and improves the sensitivity of peripheral tissues to insulin to increase peripheral glucose uptake, thus reducing plasma blood glucose levels. The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells[2-4]

Material and Methods

Drug was obtained as a gift sample from Natco labs. Chemicals Ltd, Ahmedabad. Microcrystalline cellulose, Talc and Magnesium Stearate was procured from SD Fine Chemicals Ltd., India. All the other chemicals used were of analytical grades.

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Analytical method development for Glimepiride

Preparation calibration curve

100 mg of Glimepiride pure drug was dissolved in 100ml of 0.1N HCl (stock solution)10ml of solution was taken and make up with100ml of 0.1N HCl (100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 1,2,3,4 and 5µg/ml of Glimepiride per ml of solution. The absorbance of the above dilutions was measured at 266 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight-line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis[5-8].

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters

The Quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia[9-10].

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The

radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ θ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticle interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density

Tap = Tapped Density

Formulation development of Tablets

Glimepiride

All the formulations were prepared by direct compression. The compression of different formulations is given in Table 1 below. The tablets were prepared as per the procedure given below and aim is to prolong the release of Glimepiride. Total weight of the tablet was considered as 500mg. Glimepiride and all other ingredients were individually passed through sieve no ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method[5-10].

Table 1: Formulation composition for floating tablets

Formulation No.	Glimepiride	HPMC K4M	HPMC K15M	HPMC K100M	Accural	Mag. Stearate	Talc	MCC pH 102
F1	80	10	-----	-----	120	6	6	QS
F2	80	20	-----	-----	120	6	6	QS
F3	80	30	-----	-----	120	6	6	QS
F4	80	-----	10	-----	120	6	6	QS
F5	80	-----	20	-----	120	6	6	QS
F6	80	-----	30	-----	120	6	6	QS
F7	80	-----	-----	10	120	6	6	QS
F8	80	-----	-----	20	120	6	6	QS
F9	80	-----	-----	30	120	6	6	QS

Table 2: Formulation composition for floating tablets (F10-F15)

Formulation No.	Glimepiride	HPMC E5	HPMC E50	HPMC K4M	HPMC K15M	HPMC K100M	Accural	Mag. Stearate	Talc	MCC pH 102
F10	80	20	----	-----	----	-----	120	6	6	QS
F11	80	----	20	-----	----	-----	120	6	6	QS
F12	80	10	10	----	----	-----	120	6	6	QS
F13	80	----	----	20	---	-----	120	6	6	QS
F14	80	-----	----	----	20	-----	120	6	6	QS
F15	80	-----	----	----	-----	20	120	6	6	QS

Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche Friabilitor was used to determine the friability by following procedure. Preweighed tablets were placed in the Friabilitor. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W1] × 100

Where, W1 = Initial weight of three tablets, W2 = Weight of the three tablets after testing

Determination of drug content for Glimepiride floating tablets

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Glimepiride were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* Buoyancy studies**

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

***In vitro* drug release studies**

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was continued from 0 to 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptor's fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analysed by spectrophotometrically at 244 nm using UV-spectrophotometer.

Kinetics study of *In-vitro* dissolution study

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model[4-10].

Results and Discussion

Graphs of Glimepiride was taken in 0.1N HCl at 244 nm.

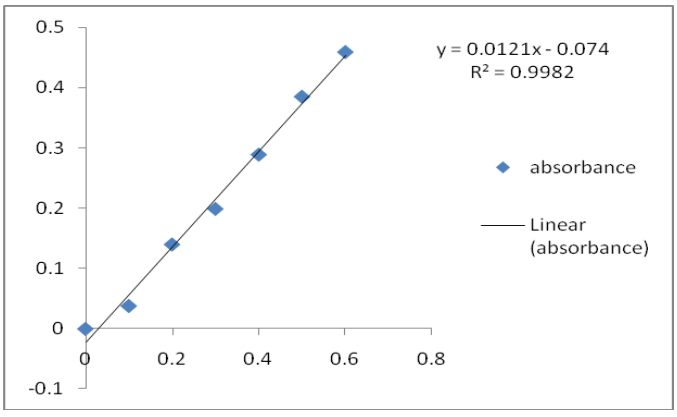

Figure 1: Standard graph of Glimepiride in 0.1N HCl

Table 3: Preformulation parameters of powder blend for Glimepiride

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02
F10	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F11	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F12	26.13	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F13	26.09	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F14	24.02	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F15	27.23	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

Table 4: Quality Control Parameters For tablets

Formulation code	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
F1	302.5	4.5	0.52	4.8	99.76	4.0
F2	305.4	4.2	0.54	4.9	99.45	4.2
F3	298.6	4.4	0.51	4.9	99.34	4.5
F4	300.6	4.5	0.55	4.9	99.87	4.1
F5	299.4	4.4	0.56	4.7	99.14	4.0
F6	300.7	4.2	0.45	4.5	98.56	4.4

F7	302.3	4.1	0.51	4.4	98.42	4.5
F8	301.2	4.3	0.49	4.7	99.65	4.6
F9	308.3	4.5	0.55	4.6	99.12	4.7
F10	302.5	4.5	0.51	4.7	99.76	4.0
F11	305.4	4.2	0.45	4.5	99.45	4.2
F12	298.6	4.4	0.51	4.4	99.34	4.5
F13	300.6	4.5	0.49	4.7	99.87	4.1
F14	299.4	4.4	0.55	4.7	99.14	4.0
F15	300.7	4.2	0.45	4.9	98.56	4.4

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies**

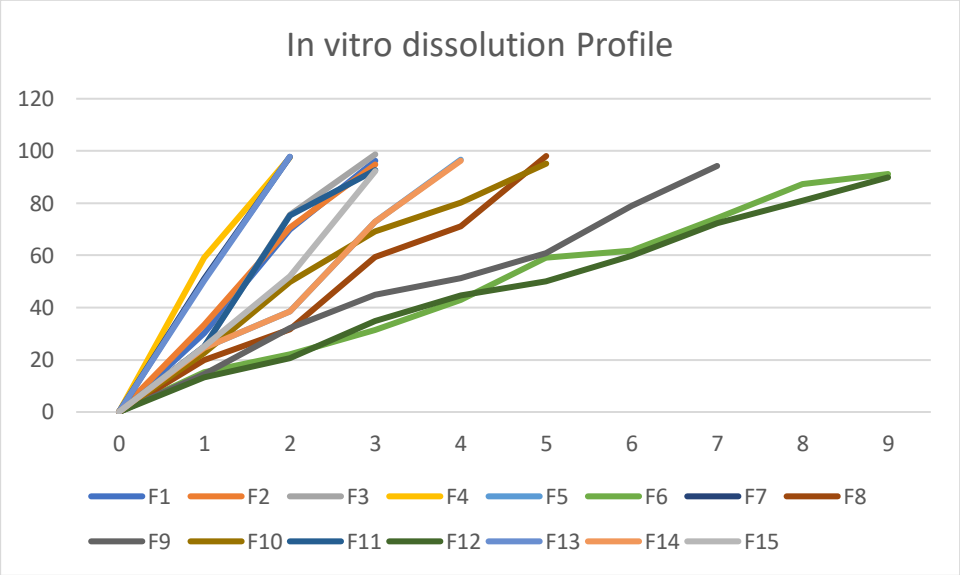

Figure 2: In vitro dissolution Profile(F1-F15)

From the dissolution data it was evident that the formulations prepared with HPMC k15m as polymer were unable to retard the drug release up to desired time period i.e., 9 hours. Whereas the formulations prepared with hpmck100m retarded the drug release in the concentration of 30 mg showed required release pattern i.e., retarded the drug release up to 9 hours and showed maximum of 91.17 % in 9 hours (Formulation F6) with good floating lag time and floating buoyancy time. Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 5: *In- Vitro* Release kinetics data for optimised formulation (F6)

Cumulative (%) Release Q	Time (T)	Log (%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release / T)	1/Cum % Release	Peppas Log Q/100	% Drug Remaining
0	0			2.000				100
19.62	0.5	1.293	-0.301	1.905	39.240	0.0510	-0.707	80.38
27.86	1	1.445	0.000	1.858	27.860	0.0359	-0.555	72.14
36.35	2	1.561	0.301	1.804	18.175	0.0275	-0.439	63.65
41.45	3	1.618	0.477	1.768	13.817	0.0241	-0.382	58.55
47.8	4	1.679	0.602	1.718	11.950	0.0209	-0.321	52.2
55.25	5	1.742	0.699	1.651	11.050	0.0181	-0.258	44.75

60.24	6	1.780	0.778	1.599	10.040	0.0166	-0.220	39.76
66.73	7	1.824	0.845	1.522	9.533	0.0150	-0.176	33.27
71.34	8	1.853	0.903	1.457	8.918	0.0140	-0.147	28.66
78.52	9	1.895	0.954	1.332	8.724	0.0127	-0.105	21.48
80.17	10	1.904	1.000	1.297	8.017	0.0125	-0.096	19.83
88.75	11	1.948	1.041	1.051	8.068	0.0113	-0.052	11.25
96.33	12	1.984	1.079	0.565	8.028	0.0104	-0.016	3.67

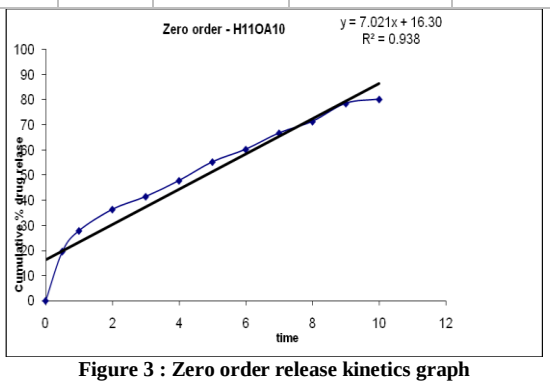

Figure 3 : Zero order release kinetics graph

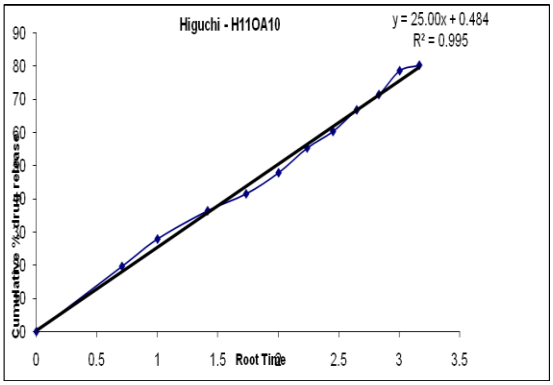

Figure 4 : Higuchi release kinetics graph

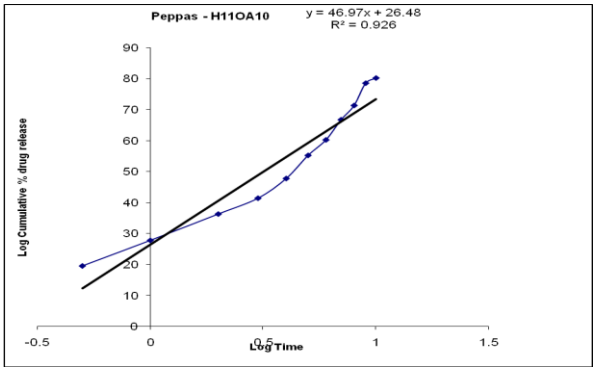

Figure 5 : Karr's Mayers peppas graph

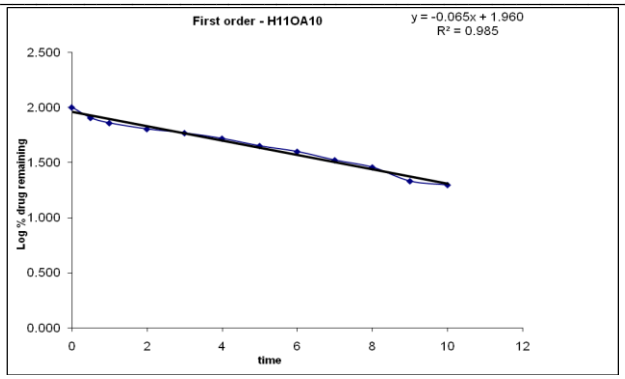

Figure 6: First Order Kinetic Graph

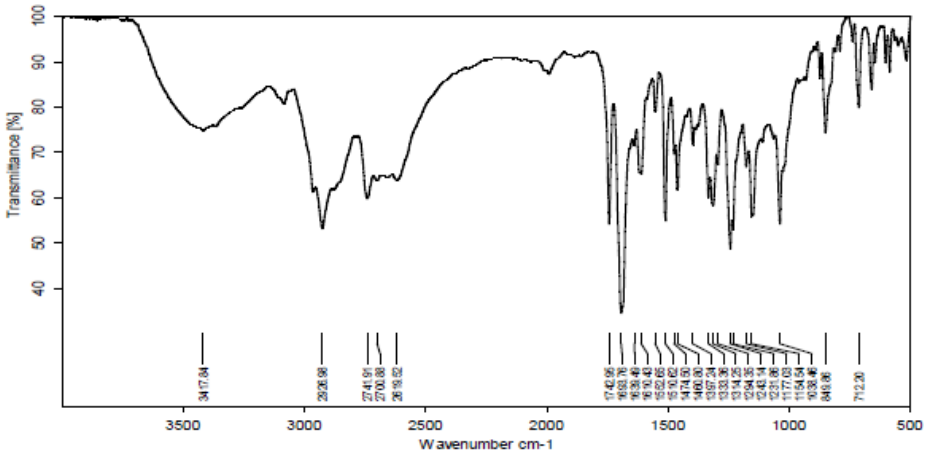

Figure 7: FTIR Spectra of Pure Glimepiride

Conclusion

In the present research work gastro retentive non effervescent floating matrix formulation of Glimepiride were formulated by using various hydrophilic polymers. the formulation was developed by using different concentrations of polymers of various grades of HPMC. Among all the formulations the formulations prepared by using HPMC K100M were unable to produce desired drug release, they were unable to retard drug release up to 9 hours. The formulations F6 prepared with HPMC K15M retarded the drug release up to 9 hours in the concentration of 30 mg. Hence, they were considered. The optimized formulations dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

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