Research Article

Formulation and Evaluation of Floating Tablets of Pioglitazone Hydrochloride

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ABSTRACT

Pioglitazone Hydrochloride is an oral anti-diabetic agent, which acts primarily by increasing insulin-dependent glucose disposal. There is a need for sustained release Pioglitazone formulations, which overcome the various problems associated with the use of this drug in the prevention and treatment of diabetes. In the present work efforts have been made to develop floating drug delivery system for Pioglitazone Hydrochloride containing HPMC of different viscosity grades and poly vinyl pyrollidine to achieve a sustained release for 24 hrs. The tablets of all formulation were subjected to various physico – chemical evaluation parameters such as thickness, diameter, weight variation, hardness, friability, drug content, in-vitro buoyancy lag time, total floating time, tablets density, swelling index and in-vitro dissolution study. The results of all these tests were found to be satisfactory within the prescribed limits. The formulations showed higher R^2 values for zero order plots indicating that drug release followed zero order kinetics and drug release from these floating tablets were by both diffusion and erosion.

Keywords: Pioglitazone Hydrochloride, HPMC, floating drug delivery system.

INTRODUCTION

Tremendous advances have been seen in oral controlled drug delivery systems in the last two decades. In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time. Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence times usually range between 5 minutes and 2 hours.

Drugs having a short half-life are eliminated quickly from the blood circulation. Various oral controlled delivery systems like gastro retention dosage forms have been designed to overcome this problem and release the drug to maintain its plasma concentration for a longer period of time.[1]

Advantages[2]

1. The principle of HBS can be used for any particular medicament or class of medicament.
2. The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach.
3. The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
4. The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.
5. Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid

Pioglitazone Hydrochloride is an oral anti-diabetic agent, which acts primarily by increasing insulin-dependent glucose disposal. There is a need for sustained release Pioglitazone formulations, which overcome the various problems associated with the use of this drug in the prevention and treatment of Diabetes. The present

study focus on the development of floating tablets of Pioglitazone hydrochloride using different polymer grades to achieve a sustained release for 24 hrs.

Materials used

Pioglitazone hydrochloride was obtained as a gift sample from Lee Pharma, Hyderabad. HPMC 5LV, 15LV, 50LV and Polyvinyl Pyrrolidone were obtained from Colorcon Asia Pvt.Ltd. All other excipients were of laboratory grade and received from Loba Chemie, Ltd.

Methods

Determination of melting point

Melting point of Pioglitazone was determined by capillary method.

Solubility

Solubility of Pioglitazone was determined in distilled water, 0.1N HCl.

The drug was practically slightly soluble in water and freely soluble in acetone, soluble in alcohol and completely soluble in 0.1N Hcl.

Compatibility Studies[3]

Fourier transform infrared spectrometry (FTIR)

Compatibility study of drug with the excipients was determined by I.R. Spectroscopy (FTIR) using Perkin Elmer spectrum RX1 FT-IR spectrometer model. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100.The pellets thus prepared were examined and the spectra of the drug and other ingredients in the formulations were compared with that of the pure drug.

Preparation of Standard Curve of Pioglitazone[4]

Method

Pioglitazone can be estimated spectrophotometrically at 270 nm using 0.1N Hcl.

Formulation of floating tablets of pioglitazone hydrochloride[5]

The floating tablets were prepared by Wet-granulation method. All the ingredients were mixed well and dry blend was granulated with PVP, dissolved in iso propyl alcohol and passed through sieve: 22. The dried granules were then passed through sieve: 18 and lubricated with magnesium stearate and talc. The granules were compressed in cadmach single punch machine using standard concave punches.

Pre-Compression Parameters[6]

Angle of repose

In order to determine the flow property, the angle of repose was determined using the standard procedure. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plane.

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

Determination of bulk density and tapped density

A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

The bulk density, and tapped density were calculated using the following formulae -

$$\text{Bulk density} = W / V_O$$

$$\text{Tapped density} = W / V_f$$

Where, W = weight of the powder, V_O= initial volume, V_f = final volume

Compressibility index (Carr's index)

It was identified using the formula,

$$CI = 100 (V_O - V_f) / V$$

Hauser's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hauser's Ratio = $(W / V_f) / (W / V_0)$

Where, W / V_f = Tapped density, W / V_0 = Bulk density

Post-Compression Parameters[7]

Shape of Tablets

The compressed tablets were examined under the magnifying lens for the shape of the tablet.

Tablet Dimensions

Thickness and diameter were measured using a calibrated dial caliper. Three tablets of each formulation were taken randomly and thickness was measured individually.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability Test

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (w_0 initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (w). The % friability was then calculated by

Percentage of Friability = $100 (1-w/w_0)$

Weight Variation Test

Twenty tablets were selected at random and the average weight was determined.

% Maximum positive deviation = $(W_H - A/ A) \times 100$
% Minimum negative deviation = $(A-W_L/ A) \times 100$

Where, W_H = Highest weight in mg, W_L= Lowest weight in mg, A= Average weight of tablet.

Tablet Density

The density was determined using following formula.

$$v = \pi r^2 h$$
$$d = m/v$$

Buoyancy / Floating Test

The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT). The in-vitro buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCL. The time required for the table to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of the medium was determined as the total floating time.

Swelling Study

The individual tablets were weighed accurately and kept in 50ml of water. Tablets were taken out carefully after 60min, blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling was calculated by using formula,

Swelling Index = wet weight – dry weight/ dry weight × 100

Test for Content uniformity

The amount of Pioglitazone present in tablets can be calculated by standard procedures using the standard formula

In-Vitro Drug Release Study[7]

In-vitro release studies were carried out using USP XXIII, paddle dissolution test apparatus. 900ml of simulated gastric fluid (pH 1.2) was taken in dissolution vessel and the temperature of the medium was maintained at $37^0C \pm 0.5^0C$. The speed was 100 rpm. 1ml of sample was withdrawn at predetermined time intervals and same volume of fresh medium was replaced. The samples were analyzed for drug content against 0.1N HCl as a blank at λmax 270nm using U.V. Spectrophotometer.

Fitting of Results into Different Kinetic Equations[8, 9]

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:

1. Zero - order kinetic model - Cumulative % drug released versus time.
2. First – order kinetic model - Log cumulative percent drug remaining versus time.
3. Higuchi's model - Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model - Log cumulative percent drug released versus log time.

RESULTS

Preformulation Studies

Melting point determination

Melting point of Pioglitazone Hydrochloride was found to be in the range 188 - 192 ^{o}C, which complied with I. P. standards, indicating purity of the drug sample.

Solubility

Pioglitazone Hydrochloride is highly soluble in 0.1 N HCl. Practically insoluble in water, but freely soluble in DMSO.

Compatibility Study

FTIR study

The FT- IR Spectrum of pure Pioglitazone drug was compared with the FT- IR spectrum of physical mixture of Pioglitazone with all the polymers of different grades. There was no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug and the polymers used in the tablets. The presence of peaks at the expected range confirms that the materials taken for the study are genuine.

Standard curve of Pioglitazone

Standard Curve of Pioglitazone was determined by plotting absorbance (nm) versus concentration (mcg/ml) at 270 nm and it was found to follow the Beer's law in the range 10 – 60 mcg/ml.

Pre-compression parameters

The granules of different formulation were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index, and Hauser's ratio. The results of these evaluations are given in Table-02.

In-vitro drug release Studies

All the formulations of prepared floating tablets of Pioglitazone were subjected to *in - vitro* release studies were carried out using dissolution apparatus, 0.1N HCl (pH 1.2). The values are tabulated in the Table - 05.

DISCUSSION

The presently preferred route of administration for Pioglitazone hydrochloride is oral route. In the present work efforts have been made to develop floating drug delivery system for Pioglitazone hydrochloride containing HPMC of different viscosity grades and Poly vinyl pyrollidine.

The FTIR spectral analysis showed that there was no appearance or disappearance of any characteristic peaks of pure drug in the physical mixture of drug and polymer, which confirms the absence of chemical interaction between drug and polymers. The granules were prepared by wet granulation method and the granules of all formulation were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and drug content. The result indicates the granules were having a good free flowing property suitable for tablet formulation.

The tablets of all formulation were subjected to various evaluation parameters such as thickness, diameter, weight variation, hardness, friability, drug content, in-vitro buoyancy lag time, total floating time, tablet density, swelling index and in-vitro dissolution study. The results of all these tests were found to be satisfactory. The results of *in vitro* drug release studies show that F6 had better-sustained release than the other formulations.

The release profiles appear to be biphasic with initial burst effect followed by a polymer

controlled slower release in the second phase. The difference in burst effect of the initial time is a result of difference in the viscosity of polymers.

The polymeric system with low viscosity polymer (HPMC K100LV) yielded a faster initial burst effect. Incorporation of PVP decreased the release of Pioglitazone hydrochloride from the GFDDS. The formulations with high viscosity polymer (HPMC K50LV) showed good sustaining activity for 24 Hrs.

The formulations showed higher R^2 values for zero order plots indicating that drug release followed zero order kinetics and drug release from these floating tablets were by both diffusion and erosion.

Table 1: Composition of floating tablets of Pioglitazone hydrochloride

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Drug (mg)	30	30	30	30	30	30	30	30
HPMC 5 Lv (mg)	120	-	-	60	-	60	-	-
HPMC 15 Lv (mg)	-	120	-	60	60	-	-	-
HPMC 50 Lv (mg)	-	-	120	-	60	60	-	60
Ethyl cellulose (mg)	-	-	-	-	-	-	120	60
PVP (mg)	4	4	4	4	4	4	4	4
Sodium bicarbonate (mg)	20	20	20	20	20	20	20	20
Talc (mg)	2	2	2	2	2	2	2	2
Magnesium stearate (mg)	2	2	2	2	2	2	2	2
Lactose (mg)	21	21	21	21	21	21	21	21
Iso – propyl alcohol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S	Q.S

Table 2: Flow Properties of Granules

Formulation	*Angle of repose(θ)	*Bulk Density (gm / cc)	*Compressibility Index	*Hauser's Ratio
F1	21^0 68”	1.24	7.274 ± 1.024	0.931 ±0.022
F2	22^0 02”	1.08	7.148 ± 1.525	0.906 ±0.010
F3	24^0 77”	0.78	8.187 ± 1.286	0.927 ±0.017
F4	26^0 32”	0.72	8.584 ± 1.412	0.826 ±0.012
F5	22^0 41”	0.63	8.826 ± 2.101	0.923 ±0.101
F6	23^0 94”	0.58	9.169 ± 1.224	0.910 ±0.222
F7	21^0 28”	0.82	9.212 ± 0.278	0.921 ±0.005
F8	22^0 62”	1.14	9.289 ± 1.496	0.917 ±0.074

*Average of Three trials ± Standard Deviation

Table 3: Post-Compression Parameters

Formulation	*Diameter (mm)	*Thickness (mm)	*Hardness (Kg/Cm^2)	*Friability (%)	*Weight Variation (mg)	*Drug Content uniformity (mg)
F1	11.425±0.182	5.12±0.220	5.40± 0.25	0.74	204.43±4.14	98.78± 0.56
F2	13.081 ±0.106	6.13 ±0.420	6.23±0 .72	0.38	198.81±4.01	99.78± 0.44
F3	12.292±0.142	5.25 ± 0.13	4.44±0.24	0.44	200.14±3.76	99.56± 0.47
F4	13.308 ±0.670	6.10±0.505	5.65±0.12	0.49	202.53±3.79	99.94± 0.18
F5	13.018 ±0.024	5.33±0.062	5.31±0.11	0.67	199.08±3.24	99.45± 0.38
F6	13.626 ±0.505	6.22±0.105	6.32±0.13	0.61	203.53±2.16	98.91± 0.35
F7	12.114±0.565	5.92±0.111	5.36±0.15	0.71	201.01±3.33	99.67± 0.44
F8	13.263±0.406	6.23±0.076	5.47±0.30	0.78	199.12±3.16	99.75± 0.35

*Average of Three trials ± Standard Deviation

Table 4: Floating properties of tablets

Formulation	*Tablet Density (g/cc)	*Buoyancy Lag Time (Sec)	*Total Floating Time (Hrs)
F1	0.82	68	22
F2	0.79	70	24
F3	0.83	78	22
F4	0.96	82	23
F5	0.94	83	21
F6	0.95	85	21
F7	0.84	73	18
F8	0.96	80	20

*Average of Three trials ± Standard Deviation

Table 5: In vitro dissolution profile of various formulations

Time (hrs)	*Cumulative % of Drug Release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	16.37	13.70	11.30	10.91	6.810	6.084	9.826	6.055
2	20.63	16.78	13.01	13.67	9.225	12.03	11.99	8.301
3	23.02	19.49	16.19	15.84	12.66	15.65	14.75	11.59
4	26.34	22.43	18.44	18.25	15.43	18.54	17.34	14.04
5	30.51	25.48	20.66	20.44	18.60	21.44	19.96	17.05
6	34.19	27.79	22.57	23.38	20.02	22.14	23.11	19.98
7	38.21	30.42	25.44	26.38	23.43	25.22	26.48	24.07
8	42.04	34.22	26.22	28.48	26.38	27.31	29.31	27.35
9	47.10	36.31	27.42	30.99	29.60	30.39	32.90	29.45
10	50.75	41.53	32.37	33.11	33.58	32.36	35.47	34.32
12	56.24	46.88	43.50	40.32	41.46	37.85	41.12	39.79
16	67.21	60.80	52.81	55.48	54.14	42.73	52.92	51.25
20	78.52	74.10	66.08	69.38	67.03	57.10	63.98	64.90
24	89.47	86.52	79.52	82.21	78.18	72.85	74.29	77.38

*Average of Three trials ± Standard Deviation

Table 6: Kinetic Profile of In-vitro drug release from various formulations

Formulation Code	Zero-order			First-order		Higuchi		Korse Meyer Peppa's		Possible mechanism of drug release
	n	R^2	Release rate constant	n	R^2	n	R^2	n	R^2	
F1	3.4789	0.9526	3.4789	0.0351	0.9505	18.168	0.9918	0.5277	0.9923	zero-order, Non-fickian
F2	3.3586	0.9897	3.3586	0.0304	0.9362	17.128	0.9473	0.6022	0.9516	zero-order, Non-fickian
F3	3.0687	0.9871	3.0687	0.0243	0.9358	15.551	0.9173	0.635	0.9266	zero-order, Non-fickian
F4	3.1859	0.9913	3.1859	0.0264	0.9259	16.132	0.9183	0.652	0.9405	zero-order, Non-fickian
F5	3.2134	0.9977	3.2134	0.0249	0.9559	16.46	0.9318	0.7954	0.9776	zero-order, Non-fickian
F6	2.7647	0.9821	2.7647	0.0196	0.9503	14.313	0.9547	0.7121	0.9866	zero-order, Non-fickian
F7	2.7557	0.9951	2.7557	0.0189	0.9637	14.217	0.9465	0.8063	0.9938	zero-order, Non-fickian
F8	2.8091	0.9987	2.8091	0.0189	0.9708	14.528	0.9416	0.9443	0.9969	zero-order, Non-fickian

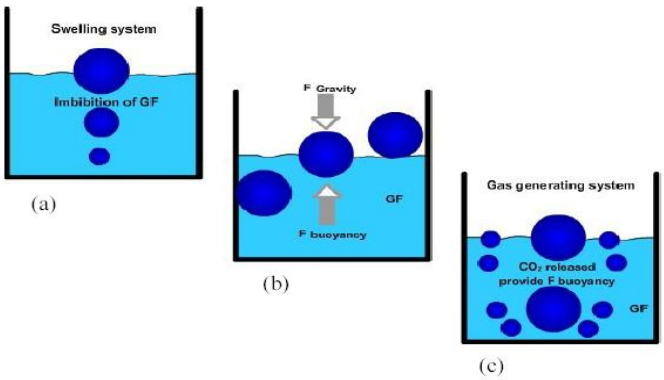

Fig. 1: Mechanism of floating systems

CONCLUSION

The present study reports for the development of gastric floating tablet for sustained release of Pioglitazone hydrochloride following oral administration. The results demonstrated that the release of the drug is dependent on viscosity of the polymer used. It can be conclusively stated that the gastric floating tablet appears to be a promising system for the delivery of sustained release Pioglitazone hydrochloride for the treatment of diabetes.

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