Acta Chimica & Pharmaceutica Indica

Acta Chim. Pharm. Indica: 4(1), 2014, 7-19
ISSN 2277-288X

FORMULATION AND EVALUATION OF HYDRODYNAMICALLY BALANCED FLOATING TABLETS OF ANTIDIABETIC AGENT

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(*Received : 10.12.2013; Revised : 17.12.2013; Accepted : 19.12.2013*)

ABSTRACT

The objective of the present study was to develop a hydrodynamically balanced system of metformin as a single unit floating tablet. Various grades of low-density polymers such as HPMC K4M, HPMC K 15M and Polyethylene oxide were used in different concentrations along with gas generating agent sodium bicarbonate and tablets were prepared by using direct compression technique to study the effect these polymers on floating behaviors. The physicochemical properties of different formulations, their buoyancy lag time and total floatation time and swelling index were evaluated. It is found that the high viscosity grade polymers given better controlled release drug profile. The *in vitro* release studies indicated that the floating dosage forms containing (P3) polyethylene oxide polymer showed good drug release rate up to 12hrs in comparison to other batches. The results indicated that hydrodynamically balanced tablets of Metformin containing polyethylene oxide provides a better option for sustained release action.

Key words: Hydrodynamically balanced system, Polyethylene oxide, Floating behaviors, Buoyancy lag time.

INTRODUCTION

Oral route of administration gets the highest priority for the delivery of drug as well as better patient compliance. Floating tablet is selected for achieving a prolonged and predictable drug delivery profile in the gastrointestinal tract to control the gastric residence time using a gastro retentive dosage forms that will provide as with new and important therapeutic options. The design of oral controlled drug delivery system primarily be aimed at achieving more predictable and increase availability of drug. The principle of floating preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.[1]

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism associated with absolute or relative deficiencies in insulin secretion or insulin action. Diabetes particularly non-insulin dependent diabetes mellitus (NIDDM) or Type II diabetes mellitus accounts for over 85% of the worldwide population and is the consequence of a deficiency in insulin action due to abnormalities at the cell surface or within the cell, a deficiency in insulin secretion or a combination of these processes. The deficit in insulin action results in hyperglycemia and other metabolic disturbances. (FDDS) Floating drug delivery system can be retained in the stomach due to their lower bulk density than the gastric contents and remain buoyant in the stomach for prolonged period of

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time without affecting the gastric emptying rate of other contents.[2]

Metformin hydrochloride comes under the class of biguanides. Chemically it is (N, N-dimethylimidodicarbonimidic diamide monohydrochloride), molecular formula is C_4 H_{11} N_5, HCl and its molecular weight is 165-62. It has been widely used as an anti-diabetic agent.[3]

Floating drug delivery offers a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. Metformin is an antihyperglycemic agent, which improves glucose tolerance in type II diabetes. It has been reported that the absolute bioavailability of metformin when given orally is 50–60%. Biological half-life of metformin is 1.5-1.6 h and the main site of its absorption is proximal small intestines.[4]

The main objective of the present study was aimed to develop floating tablets of metformin hydrochloride, and their *in-vitro* characterization.

EXPERIMENTAL

Materials and methods

Metformin HCl was obtained as gift sample from Balaji Drugs, Gujrat, India. HPMC K4M, HPMC K15M, PVP-K-30, Lactose was obtained as gift sample from Qualigens Fine Chemicals (Glaxo), Hyderabad. Methyl Cellulose, Poly Ethylene Oxide, Sodium Bicarbonate was obtained as gift sample from S D Fine Chem Ltd, Mumbai. All other chemicals and solvents used were of analytical grade.

Preparation of floating tablets by direct compression method

Metformin sustained release floating tablets were prepared by direct compression method. For the preparation of tablets, all the ingredients were weighed accurately and were screened through sieve (#40). Metformin and other polymers were mixed in a poly bag for 15 minutes, followed by the addition of diluent lactose and further mixed for 5-10 minutes. Finally talc and magnesium stearate were added to the previous blend and mixed it again, for uniform distribution. Then the tablets were compressed by using 6-station Rotary tablet punching machine with 14 mm oval shape punches. Each tablet contains 500 mg of Metformin and the weight of the tablet is 900 mg.

Table 1: Formulation of metformin floating tablets

Composition (mg)	H1	H2	H3	H4	H5	H6	M1	M2	M3	P1	P2	P3
Metformin	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K4M	135	180	225	-	-	-	-	-	-	-	-	-
HPMC K 15M	-	-	-	135	180	225		-	-	-	-	-
Methyl cellulose	-	-	-	-	-	-	135	180	225	-	-	-
Polyethylene oxide	-	-	-	-	-	-	-	-	-	135	180	225
Sodium bi carbonate	90	90	90	90	90	90	90	90	90	90	90	90
PVP-k-30	18	18	18	18	18	18	18	18	18	18	18	18
Lactose	139	94	49	139	94	49	139	94	49	139	94	49
Talc	9	9	9	9	9	9	9	9	9	9	9	9
Magnesium stearate	9	9	9	9	9	9	9	9	9	9	9	9

Drug-Excipients compatibility study

FTIR studies

The successful formulation of a suitable and effective solid dosage form depends upon the careful selection of the excipients. Excipients are added to facilitate administration, promote the consistent release and bioavailability of drug. It's necessary to study the compatibility of excipients with drug. Here IR spectroscopy was used to investigate and predict any physicochemical interaction between components in a formulation and to the selection of suitable compatible Excipients. FTIR studies were conducted and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of, dispersing a sample (drug alone, and mixture of drug and polymers in KBr and compressing into discs by applying a pressure of 7 tons for 5 min in a KBr press. The pellet was placed in the light path and the spectrum was obtained.

Pre compresion parameters[5-8]

The evaluations of Pre-compression studies of formulated floating tablets of Metformin Hydrochloride were done as per standard procedures. The following parameters were evaluated.

Bulk density (D_b)[9,10]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. The initial volume is called the bulk volume. From this, bulk density is calculated by using the following ormula. It is expressed in g/cc and is given by

(D_b) Bulk density = (M) mass of powder/(V_b) bulk volume of powder

Tapped density (D_t)

The tapped density was obtained by dividing the mass of powder by tapped volume of the powder. Tapped volume was measured by tapping the sample contained in the graduated measuring cylinder. It is calculated by using the following formula. It is expressed in g/cc and is given by –

Bulk density D_t = M mass of the powder /V_t Tapped volume of the powder

Carr's index

It is the simple test to evaluate the bulk density and tapped density of a powder and the rate at which it packed down. It is expressed by the given formula,

Carr's Index (%) = [(Tapped density – Bulk density) × 100] / tapped density

Hausner's Ratio: It is the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density / Bulk density

Angle of repose (θ)

This is the maximum angle possible between the surface of the pile of the powder or granules and the horizontal plane. The powder mixture was allowed to pass through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of the powder formed.

$\tan \theta = h/r$

θ = angle of repose, h = height of the heap, r = radius of the heap

Post compression parameters

Tablet thickness and diameter

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier calipers.

Hardness

The hardness of the tablet is also known as crushing strength. The hardness of the tablet is defined as the compressional force required to break or fracture the tablet. The tablet is required to possess sufficient hardness to prevent its chipping, its breakage encountered during the transport or storage. The hardness was measured with Monsanto hardness tester. The hardness is usually measured in terms of Kg/cm^2. Three tablets randomly selected from each formulation and the average hardness was noted.

Weight variation test[5,11]

Twenty tablets were selected at random and weighed individually. The average weight (W_A) of 20 tablets was calculated. Individual weights of the tablets were compared with average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage show in the following table.

$$\% \text{ Weight variation} = 100 \text{ X } (W_A\text{-}W) / W_A$$

Friability test

This test is performed to know the effects of friction and shocks. The friability of the tablets was measured in a Roche friabilator. Pre-weighed sample of 10 tablets were placed in the friabilator (Electrolab, India) and rotated at 25 rpm for 4 minutes. The dusted tablets were de-dusted and reweighed. The percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

$$\text{Friability} = [(\text{Initial weight} - \text{Final weight}) / (\text{Initial weight})] \text{ x } 100$$

Drug content uniformity[12]

Drug content of the tablets were determined by using UV visible spectrophotometer. Five tablets were taken and powdered in a mortar. Accurately weighed quantity of powder containing 500 mg of Metformin was transferred into a 100 mL volumetric flask and the volume was made up to 100 mL with distilled water. 1 mL of the aliquot was further diluted to 100 mL with distilled water and the solution was filtered by using filterpaper. The absorbance was measured by using UV spectrophotometer at 232 nm.

Floating lag time and total floating time

It was the time taken by the dosage to float on to the surface and remain buoyant when it was immersed in a beaker containing 100 mL of 0.1 N HCl solution (pH 1.2) without disintegration and the total floating time was also noted.

Swelling index

The swelling behaviour of the dosage form was measured by studying the weight in grams. The dosage form was placed in basket of dissolution apparatus which is filled with dissolution media (stimulated gastric fluid or 0.1 N HCl at 37 ± 0.5□C) and rotated at 50 rpm. At specified time intervals tablets were

removed from the baskets and lightly blotted with tissue paper to remove excess water and weighed. this process was continued till 6 hrs.

Swelling index calculated by using the following formula

$$\text{Swelling index (S.I.)} = 100 \times (W_t - W_o)/W_o$$

S.I. = Swelling index

W_t = Weight of tablet at time t

W_o = Weight of the dry tablet before placing in the basket

In vitro drug release

In vitro drug release studies were carried out by using the USP dissolution apparatus type II at 50 rpm. 900 mL of 0.1 N hydrochloric acid (pH 1.2) was used as dissolution medium which was maintained at 37 ± 0.5°C. Samples of 5 mL were collected at regular time intervals and analyzed for drug release at absorbance 228 nm. The volume withdrawn at each time interval was replaced with fresh volume of dissolution medium. Cumulative percent drug release was calculated and plotted against time.

Kinetic analysis of dissolution data

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Peppas and Hixson-Crowell cube root law. Based on the r-value, the best-fitted model was selected.

Zero order kinetics[13-16]

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$Q_t = Q_o + K_o t$

Q_t = amount of drug dissolved in time t.

Q_o = initial amount of the drug in the solution and

K_o = zero order release constant.

First order kinetics[17-19]

To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$\text{Log } Q_t = \log Q_o + K_1 t/2.303$$

where, Q_t = The amount of drug released in time t

Q_o = The initial amount of drug in the solution

K_1 is the first order release constant.

Higuchi model[20-22]

Higuchi developed several theoretical models to study the release of water soluble and low soluble

drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

$$Q_t = K_H \cdot t_{1/2}$$

where, Q_t = Amount of drug released in time t,

K_H = Higuchi dissolution constant

Peppas release model[23-25]

To study this model the release rate data are fitted to the following equation,

$$M_t / M_\infty = K \cdot t_n$$

where, M_t / M_∞ = The fraction of drug release

K = The release constant

t = The release time

n = The diffusion coefficient for the drug release that is dependent on the shape of the matrix dosage form.

RESULTS AND DISCUSSION

The FTIR study was carried out to determine the physical or chemical interaction between drug and polymers. IR spectra were recorded for Metformin and the formulation. Pure Metformin spectra showed sharp characteristic peaks at 3367.91, 3291.05, 3147.75, 1621.01, 1166.08, 1059.36, 935.63 cm^{-1}. FTIR characteristic peaks of drug appear in the spectra of formulation at the same wave number indicating no interaction between the drug and the polymers used. This proves the fact that there is no potential incompatibility of the drug with the polymers used in the formulations. Comparative study of FTIR graph is shown in Figs. 1 and 2.

Evaluation of floating tablets of Metformin hydrochloride

Pre-compression parameters and Carr's index of the formulations were found to be within the range that the formulations had good flow property.

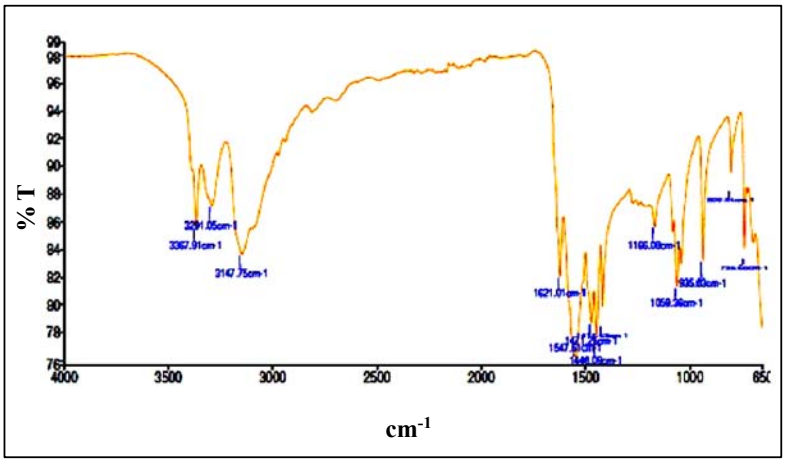

Fig. 1: FT-IR spectra of Metformin

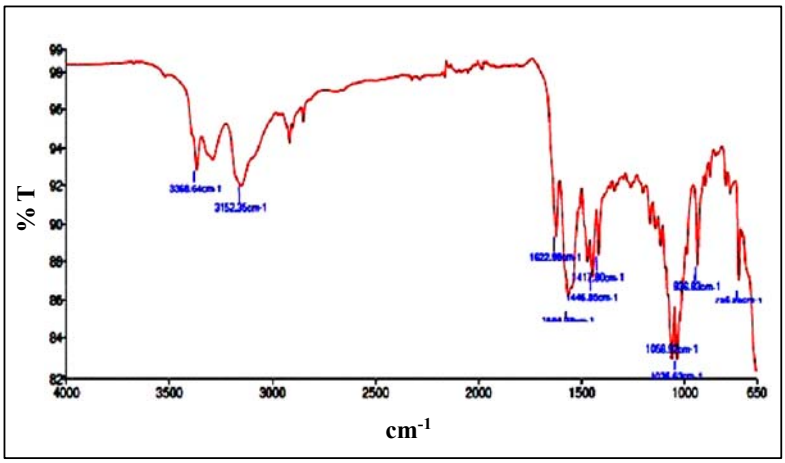

Fig. 2: FT-IR Spectra of mixture of polymers + Metformin

Table 2: Pre-compression studies for formulations H1 to P3

Powder blend	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio
H1	28.3	0.429	0.493	13.10	1.151
H2	27.5	0.439	0.496	11.46	1.129
H3	28.0	0.450	0.500	10.00	1.111
H4	28.5	0.462	0.526	12.31	1.140
H5	29.3	0.439	0.504	12.93	1.148
H6	30.2	0.450	0.507	11.25	1.127
M1	26.4	0.462	0.522	11.54	1.130
M2	27.2	0.450	0.501	10.25	1.114
M3	27.8	0.429	0.488	12.14	1.138
P1	25.2	0.409	0.480	14.77	1.173
P2	24.5	0.409	0.485	15.68	1.186
P3	24.2	0.419	0.486	13.95	1.162

Hardness and friability

The hardness of all the formulations ranged from 4.7 to 5.4 Kg/cm^2. The percentage friability values of the all batches were in between 0.33% to 0.88%, which indicates that the formulations have sufficient mechanical strength and are with in the acceptable limits i.e less than 1%.

Thickness: Thickness of the tablets was found to be in the range of 5.75 mm to 6.30 mm.

Weight variation: The average weights of the tablets of various batches were in between 896 mg to 903 mg. The Weight variation was found within the pharmacopoeial limits.

Drug content uniformity

All the formulations passed the drug content uniformity test, which indicates that there is a uniform dose distribution among all formulations.

Table 3: Weight variations, hardness, thickness and friability for formulations

Formulation code	Thickness (mm)	Avg. wt. (mg)	Hardness (Kg/cm^2)	Friability (%)	Assay (%)
H1	6.20	897 ± 1.50	5.20 ± 0.20	0.33	99.98
H2	6.25	899 ± 1.25	5.00 ± 0.20	0.39	98.15
H3	5.75	902 ± 1.55	4.87 ± 0.15	0.44	99.00
H4	6.15	900 ± 0.85	5.37 ± 0.15	0.66	101.5
H5	6.30	897 ± 1.05	4.97 ± 0.15	0.39	100.2
H6	5.95	898 ± 0.95	4.73 ± 0.25	0.45	98.85
M1	6.00	903 ± 0.89	5.03 ± 0.15	0.55	99.85
M2	5.85	896 ± 1.20	5.10 ± 0.10	0.61	99.95
M3	5.95	897 ± 1.55	5.38 ± 0.13	0.78	101.0
P1	6.25	901 ± 0.75	5.27 ± 0.12	0.69	100.5
P2	6.30	902 ± 0.85	5.20 ± 0.20	0.83	99.75
P3	6.20	902 ± 1.05	5.00 ± 0.20	0.88	101.2

Table 4: Floating characteristics of formulations

Formulation code	Floating lag time (Sec)	Total floating duration (hrs)	Swelling index
H1	32 ± 0.42	> 10	74.8
H2	24 ± 0.65	> 10	86.2
H3	16 ± 0.23	> 10	94.5
H4	40 ± 0.34	> 12	65.5
H5	22 ± 0.5 1	> 12	72.2
H6	18 ± 0.23	> 12	84.3
M1	Not float	Not float	_
M2	Not float	Not float	_
M3	Not float	Not float	_
P1	60 ± 0.34	> 16	58.8
P2	72 ± 0.65	> 16	64.6
P3	85 ± 0.56	> 16	72.7

Floating behaviour

Floating lag time was determined by using 0.1 N HCl. The formulations containing methyl cellulose M1, M2, and M3 doesn't float. The formulations containing HPMC K4M have less floating lag time and the total floating duration is upto 10 hrs only. Formulations containing HPMC K15 M have total floating duration of 12 hrs. Formulations containing poly ethylene oxide shown more floating lag time but they have

total floating duration upto 16 hrs. Formulations containing methyl cellulose doesn't float. Total floating time is higher for the formulations containing PEO when compared to formulations containing HPMC K4 M and HPMC K15M. This was due to high viscosity of poly ethylene oxide, which requires more time to hydrate and to float on the surface, hence it has more floating lag time and longer floating duration. The floating tablets composed of polymeric matrices will build up a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release from the matrix tablet. The formulations containing PEO and HPMC K15 M have exhibited good swelling and tablet integrity. As, the amount of polymer concentration is increased the water uptake ratio is also found to be increasing.

In vitro dissolution study

The *In vitro* drug release study of Metformin tablets was carried out in 1.2 pH hydrochloric acid buffer for 12 hrs. The plot of time (mins) vs percentage cumulative drug release were plotted. Formulations containing methylcellulose (M1-M3) does not float, hence they were not used further for this *in vitro* release study.

From the *in vitro* release data it was found that the drug release from the formulations containing hydroxyl propyl methyl cellulose (HPMC K4M), H1 to H3 was 97.45%, 97.37% and 98.01%, respectively after 10 hrs. Formulations containing HPMC K 15M (H4-H6) showed 98.56%, 98.69% and 96.12% drug release, respectively. Formulations containing poly ethylene oxide (PEO) (P1-P3) showed 94.24%, 91.39% and 88.94%, respectively.

It was observed from the results, that the formulations containing HPMCK4 M shown maxium drug release rate after 10 hrs where as the formulations containing HPMC K15M and PEO were shown maximum drug release after 12 hrs.

The sustaining action of the polymers was in the order such as PEO > HPMC K 15M > HPMC K4M. From the above results, it was concluded that the formulation containing 25% w/w of poly ethylene oxide has shown maximum sustaining action with 88.94% drug release after 12 hrs; hence it is an optimized formula among all the formulations

Table 5: Regression analysis of formulations

Formulation	r^2 values				
	Zero order	First order	Higuchi matrix	Kosmeyers peppas	
				r^2	n
H1	0.955	0.900	0.974	0.976	0.483
H2	0.959	0.913	0.977	0.973	0.455
H3	0.959	0.903	0.976	0.970	0.501
H4	0.977	0.802	0.977	0.969	0.531
H5	0.982	0.796	0.968	0.981	0.566
H6	0.979	0.857	0.970	0.975	0.547
P1	0.988	0.868	0.980	0.904	0.834
P2	0.991	0.908	0.968	0.988	0.714
P3	0.994	0.992	0.967	0.994	0.811

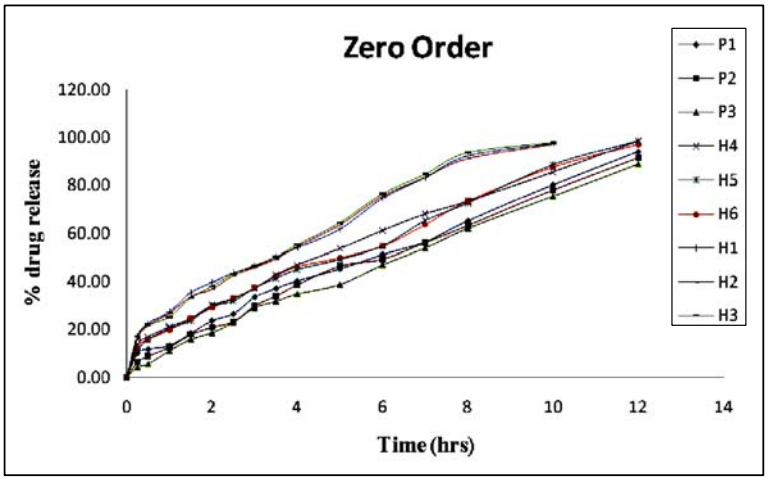

Fig. 3: Zero Order (Time vs % dug release)

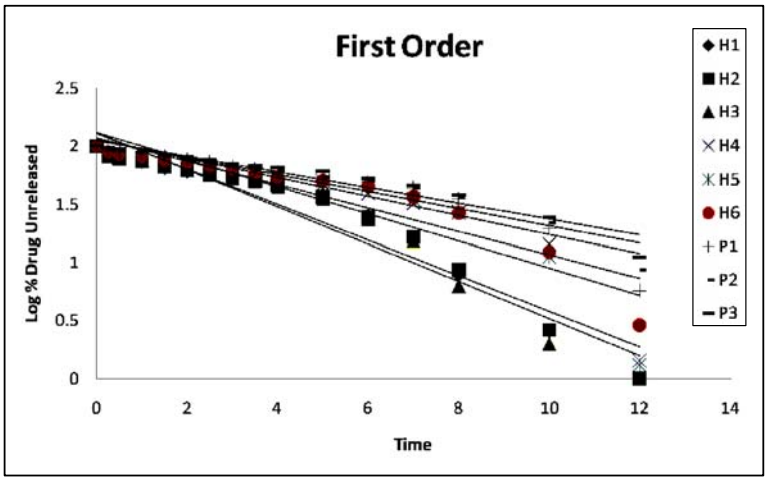

Fig. 4: First order Graphs (Time vs log % Drug Unreleased)

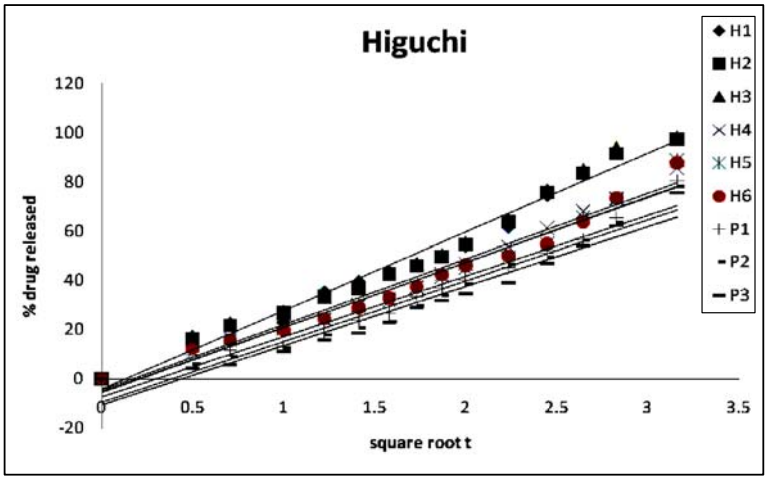

Fig. 5: Higuchi graph (square root of time vs % drug release)

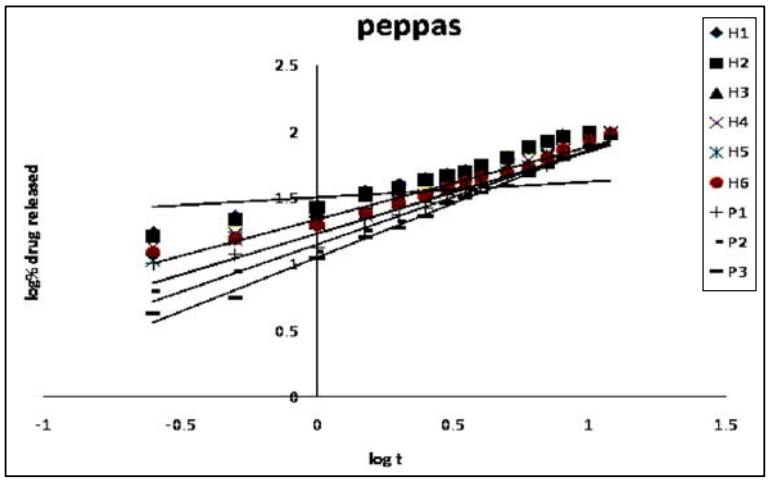

Fig. 6: Peppas plot (log t vs log % drug released)

Drug release kinetic studies

The *in vitro* drug release data of all metformin formulations Release kinetics of formulations H1 follows Peppas model with Non fickian transport, H2 and H3 formulations follows Higuchi model. Remaining all formulations H4, H5, H6, P1, P2, P3 follows Zero order release with Non Fickian Transport. Drug release mechanism understood from the diffusion release exponent values obtained from Korsmeyer-Peppas model were between 0.483, 0.455, 0.501, 0.566, 0.547, 0.834, 0.714 and 0.811 showed anomalous type drug release.

CONCLUSION

In the present study, hydrodynamically balanced system of Metformin as a single unit floating tablets were developed. Various grades of low-density polymers such as HPMC K4M, HPMC K 15M and Polyethylene oxide were used in different concentrations along with gas generating agent sodium bicarbonate and tablets were prepared by using direct compression technique to study the effect these polymers on floating behaviors. The physicochemical properties of different formulations, their buoyancy lag time and total floatation time and swelling index were evaluated. It is found that the high viscosity grade polymers given better controlled release drug profile. The *in vitro* release studies indicated that the floating dosage forms containing (P3) polyethylene oxide polymer showed good drug release rate up to 12 hrs in comparison to other batches. Effect of hydro colloids at different concentrations on drug release was observed. The results indicated that as the concentration of hydrocolloid increases, the total floating duration was increased. Formulations P1, P2, P3, selected as the optimized formulations with 94.24, 91.39, 88.94% drug release at the end of 12 hrs. It was also observed that the viscosity of the hydrocolloid plays a crucial role in floating duration of the dosage form as retardant in controlling the drug release from the dosage form.

The *in vitro* drug release data of all metformin formulations Release kinetics of formulations H1 follows Peppas model with Non fickian transport, H2 and H3 formulations follows Higuchi model. Remaining all formulations H4, H5, H6, P1, P2, P3 follows Zero order release with Non Fickian Transport. Drug release mechanism understood from the diffusion release exponent values obtained from Korsmeyer-Peppas model were between 0.483, 0.455, 0.501, 0.566, 0.547, 0.834, 0.714 and 0.811 showed anomalous type drug release. The results indicate that hydrodynamically balanced tablets of Metformin containing polyethylene oxide provides a better option for sustained release action.

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