DESIGN AND EVALUTION OF GASTRORETENTIVE FLOATING TABLETS OF CEPHALEXIN

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Summary

A gastroretentive floating drug delivery system containing cephalexin was prepared in the form of tablet by wet granulation method using the hydrophilic polymer hydroxypropylmethylcellulose K4M, gas generating agent sodium bicarbonate and citric acid. A 3^2 full factorial design was employed to study the effect of independent variables, amount of citric acid (X1) and amount of hydroxypropylmethylcellulose K4M (X2). The percentage drug release at 12 hours (Q_{12}) and percentage drug release at 6 hours (Q_6) were selected as dependent variables. The tablets were evaluated with different parameters like diameter, thickness, average weight, hardness, friability, drug content, *in vitro* buoyancy study and swelling characteristics. 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. The optimized formulation released 99.46 % of drug at the end of 12 hours by *in vitro* release study. The drug release followed the Korsmeyer and Peppas model controlled mechanism of cephalexin tablets.

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Introduction

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 gastroretentive 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]

Cephalexin is the first generation antibiotic and have good absorption in GIT, low pKa, which remain unionized in stomach for better absorption. Cephalexin is a semisynthetic cephalosporin β lactum antibiotic intended for oral administration used to treat urinary tract infections, respiratory tract infections, skin and soft tissue infections. Pharmacokinetic parameters of cephalexin such as absorption from the gastrointestinal tract, protein binding 14%, and metabolism 90% excreted unchanged in the urine, half life is 1 hour. It degraded in alkaline pH, so as to prevent degradation, which degrades in small intestine. Low viscosity hydrophilic polymers were found to be good floating properties.

The aim of the present study was not only preparing a cephalexin floating system but also to release the drug in controlled fashion, therefore the maximum drug release is maintained at desired site. The effect of amount of polymer and amount of retardant material effect was investigated on

the formulation to monitor the sustained release effect respectively. For the present study HPMC K4M was used as polymer to fulfills the above characteristics, which indicate its suitability for fabrication into the floating drug delivery system.

Materials and Methods

Materials

Cephalexin was obtained as gift sample from Apex laboratories, Chennai. Hydroxypropylmethylcellulose K4M was purchased from Madras pharmaceuticals, Chennai. Sodium bicarbonate, citric acid, magnesium stearate, talc were purchased from poona chemicals Laboratories, Pune. Other reagents were of analytical grade.

Methods

Preparation of gastro retentive floating tablets of glipizide

Gastroretentive floating tablets of cephalexin were prepared by wet granulation method. The powder mixture containing drug, polymers (HPMC K4M) and gas generating agent (Sodium bicarbonate and citric acid). All the ingredients were mixed thoroughly except magnesium stearate and talc. Granules were prepared manually with a solution of polyvinyl pyrrolidone in sufficient isopropyl alcohol as binder. The wet mass was passed through a 16 mesh sieve no. And the wet granules produced were dried in hot air oven for 30 min at 50^0C. The dried granules were mixed with lubricant and glidant and compressed using 13 mm flat faced punch on Cemach 12 station rotator tablet compression machine (Table 1).

Full Factorial design

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and bi is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2)

show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. On the basis of the preliminary trials a 3^2 full factorial design was employed to study the effect of independent variables i.e. amount of citric acid (X_1) and amount of HPMC K4M (X_2) on dependent variables the percentage drug release at 12 hours (Q_{12}) and percentage drug release at 6 hours (Q_6).

Table 1 Composition of floating tablets of cephalexin

Ingredients (mg)	**F 1**	**F2**	**F 3**	**F 4**	**F 5**	**F 6**	**F 7**	**F 8**	**F 9**
Cephalexin	500	500	500	500	500	500	500	500	500
HPMC K4M	75	100	125	75	100	125	75	100	125
Citric acid	20	20	20	25	25	25	30	30	30
Sodium bicarbonate	120	120	120	120	120	120	120	120	120
MCC	70	70	70	70	70	70	70	70	70
PVK-K30	40	40	40	40	40	40	40	40	40
Magnesium stearate	15	15	15	15	15	15	15	15	15
Talc	10	10	10	10	10	10	10	10	10
Total Weight (mg)	850	875	900	855	880	905	860	885	910

Characterization of cephalexin

Description

The pure drug cephalexin was analyzed for colour, odour and taste.

Melting point

The melting point of drug was determined by open capillary method.

Standard curve

Standard curve of cephalexin was estimated by UV spectrophotometric method.

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}.

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.

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

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, a 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

$$\text{Hausner ratio} = \rho_t / \rho_d$$

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

Evaluation of tablets

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.[9]

Thickness

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

Drug content estimation

Twenty tablets were taken and amount of drug present in each tablet was determined as follows: The powder equivalent to 10 mg was taken and dissolved in 10 mL 0.1 N HCl. This stock solution was shaken for 20 min on a sonicator. This resulting solution was further diluted with 0.1 N HCl upto 10 g/mL and the absorbance measured by UV spectrophotometric method at 257 nm.

***In vitro* buoyancy study**

The *in vitro* buoyancy was determined by floating lag time and total floating time, as per the method described by (Rosa M, Zia H, Rhodes T 1994). This test was performed using a USP type II paddle apparatus using 900 mL of 0.1 N HCl at paddle rotation of 50 rpm at 37 ± 0.5^0C. The time required for the tablet to rise to the surface and float was determined as floating lag time and total floating time respectively.[10]

***In vitro* drug release study**

The dissolution study was carried out in 0.1 N HCl using USP type II dissolution test apparatus employing paddle stirrer of 50 rpm at 37 ± 0.5^0C. A Sample (5 mL) of the solution was 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 257 nm. The percentage drug release was plotted against time to determine the release profile.[11]

Water uptake study

The swelling properties were determined by placing the tablet in the dissolution test apparatus, in 900 mL of 0.1 N HCl at 37 ± 0.5^0C. The tablets were removed periodically from dissolution medium. After draining free from water, these were measured for weight gain.[13-15]

Results

The shape of the tablets of all formulations remained circular with no visible cracks. The sample of cephalexin was off white or almost, white, crystalline powder, odor characteristic. The melting point values were observed in the range of 326^0C. The absorption maximum was scanned between 200 to 400 nm and the absorption maximum was found to be 257 nm. FTIR spectra revealed that there was no interaction between the drug and the polymers.

Drug content was in range of 99% to 116% indicating good content uniformity in prepared formulation. Also the tablets remained buoyant for a period of > 24 hrs. The formulations exhibited good flow property and compressibility index. Angle of repose and compressibility index (%) ranged from 26^0.73" to 29^0.30" and 11 to 16%, respectively (Table 2).

Table 2 Evaluation of granules

Formulations	Angle of repose(Q)	Compressibility index (%)	Hausner ratio
F1	28^0. 70'	12.34	1.15
F2	29^0. 32'	15.92	1.19
F3	27^0. 64'	12.83	1.13
F4	28^0. 10'	15.72	1.17
F5	28^0. 46'	12.42	1.14
F6	27^0. 90'	11.20	1.13
F7	26^0. 74'	12.30	1.18
F8	28^0. 76'	12.38	1.15
F9	29^0. 36'	15.90	1.19
F10	27^0. 60'	12.86	1.13

*All readings were average ± (SD)

Drug content was ranged from 99 % to 115 %. The thickness and diameter of the tablets ranged from 4.38 mm to 4.62 mm and 13.06 mm. The average hardness is 6.1 kg/cm^2 and percentage friability of the tablets of all the batches remained in the range of 0. 0010 to 0.0025 respectively were shown in Table 3.

Table 3 Tablet properties of cephalexin floating tablets

Formulations	Hardness (kgs)	Friability (%)	Thickness (mm)	Diameter (mm)	Drug Content (%)	Floating Lag Time (sec)	Floating Time (hours)
F1	6.1 ± 0.3	0.0025 ± 0.01	4.55 ± 0.09	13.07 ± 0.05	99.01 ± 0.12	35	18
F2	5.8 ± 0.3	0.0011 ± 0.06	4.38 ± 0.06	13.06 ± 0.04	101.02 ± 0.13	35	16
F3	5.6 ± 0.2	0.0021 ± 0.02	4.49 ± 0.03	13.04 ± 0.06	98.2 ± 0.12	30	16
F4	5.4 ± 0.2	0.0010 ± 0.04	4.58 ± 0.03	13.02 ± 0.02	104.28 ± 0.22	30	15
F5	5.1 ± 0.6	0.0019 ± 0.01	4.38 ± 0.05	13.06 ± 0.06	102.12 ± 0.15	30	15
F6	6.1 ± 0.7	0.0018 ± 0.05	4.60 ± 0.03	13.06 ± 0.04	102.06 ± 0.19	40	> 24
F7	5.9 ± 0.1	0.0021 ± 0.02	4.46 ± 0.01	13.06 ± 0.06	100.07 ± 0.15	30	> 24
F8	5.8 ± 0.4	0.0018 ± 0.01	4.62 ± 0.06	13.04 ± 0.08	115.73 ± 0.14	35	> 24
F9	5.5 ± 0.2	0.0015 ± 0.01	4.48 ± 0.03	13.05 ± 0.05	99.01 ± 0.18	30	> 24

*All readings were average ± (SD)

In vitro buoyancy studies floating lag time was in range of 30 sec to 40 sec. The swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration. *In vitro* dissolution studies of the formulations F1 to F9 the drug released vary from 72% to 99% were shown in Table 4. Among the all formulations F7 was found to be best result in terms of the required *in vitro* buoyancy study and drug release in sustained release manner. The release kinetics for Korsmeyer - Peppas model for the optimized formulation F6 shows n = 0.2511, k = 17.808, r = 0.9630 and best fit model was Peppas.

Table 4 Formulations and Dissolution Characteristics of Cephalexin by 3^2 Full Factorial Design Layouts

Batch Code	Variable levels in coded from		% release at 6 hours (Q_6)	% release at 12 hours (Q_{12})
	X1	X2		
F1	-1	-1	61.82	87.80
F2	-1	0	48.30	71.74
F3	-1	1	41.45	72.54
F4	0	-1	78.68	94.53
F5	0	0	57.56	73.96
F6	0	1	43.54	73.43
F7	1	-1	78.43	99.50
F8	1	0	62.54	88.96
F9	1	1	55.20	79.10

Variables level	-1	0	+1
Amount of citric acid (X1)	20	25	30
Amount of HPMC K4M (X2)	75	100	125

Discussion

The present study was aimed at not only to improve the release of drug, cephalexin, 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, gastroretentive dosage form was designed, to make the therapy more effective. The roles of polymers are to control the release as well as to make the formulation buoyant. The tablets were prepared by wet granulation method. The sample of cephalexin was off white or almost, white, crystalline powder, odour characteristic. The melting point values were observed in the range of 326^0C. The absorption maximum was scanned between 200 to 400 nm and the absorption maximum was found to be 257 nm. FTIR spectra revealed that there was no interaction between the drug, polymer and physical mixture (polymer and drug). The

spectrum shows all prominent peaks of cephalexin and polymer HPMC K4M. There were no significant changes and behavior in physical mixture cephalexin and HPMC K4M. The granules of different formulations were evaluated for angle of repose, compressibility index, and drug content. The results of angle of repose ($26^0.73$" to $29^0.30$") indicate reasonably good flow property of granules. The compressibility index values in the range of 11% to 16% (< 25), further support flow property of granules were shown in Table 2.

A 3^2 factorial design was constructed to study the effect of the amount of citric acid (X_1) and amount of HPMC K4M (X_2) on the drug release. The dependent variables chosen were the percentage drug release at 12 hours (Q_{12}) and percentage drug release at 6 hours (Q_6) and the responses of formulation prepared by 3^2 factorial designs are indicated in Table 4. The data clearly indicate that the Q_{12} and Q_6 were strongly dependent on the selected independent variables. The correlation coefficient of Q_{12} and Q_6 were $R^2 = 0.8470$ and $R^2 = 0.9336$ indicate good fit. It was concluded that low level of X_1 and higher level of X_2 favour the preparation of floating sustained release. An increase in the concentration of citric acid (X_1) and amount of HPMC K4M (X_2), decrease rate of release of drug. All the factorial design batches showed good *in vitro* buoyancy, having floating lag time was in range of 40 sec to 60 sec and remaining buoyant for 12 hours. The swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration. The polymer was 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 increased the release rate was decreased. Theoretically speaking this behaviour is expected since more amount of polymer always delays the release. 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 vitro* dissolution studies of the formulations F1 to F9 the drug released vary from 72% to

99%. Among the all formulations F7 was found to be best result in terms of the required *in vitro* buoyancy study and drug release in sustained release manner.

Conclusion

The results of a 3^2 full factorial design revealed that the amount of citric acid (X_1) and amount of HPMC K4M (X_2) on the drug release. The dependent variables chosen were the percentage drug release at 12 hours (Q_{12}) and percentage drug release at 6 hours (Q_6) and had significantly effect on Q_{12} and Q_6. Among the nine formulations F7 was found to be best result in terms of the required *in vitro* buoyancy study and drug release in sustained release manner and also followed best fit model for all batches were the Peppas and Matrix kinetic model. Thus, it was concluded that the drug was released from matrix diffusion mechanism. The data clearly indicate that the Q_{12} and Q_6 were strongly dependent on the selected independent variables.

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