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Research Article

FORMULATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF AMOXYCILLIN TRIHYDRATE

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ABSTRACT

The present study was designed to formulate and evaluate balanced Floating Drug Delivery Systems as controlled release modules, which prolongs the release rate of the drugs. Amoxycillin is an anti- bacterial acts by inhibiting the synthesis of bacterial cell walls. It inhibits cross-linkage between the linear peptidoglycan polymer chains that make up a major component of the cell walls of both Gram-positive and Gram-negative bacteria. Helicobacter pylori exists in the gastric mucous layer or epithelial cell surfaces. Thus, the concentration and resident time of Amoxycillin trihydrate in stomach would be effective for complete eradication of Helicobacter pylori. Formulation of Amoxycillin trihydrate as gastro retentive drug delivery systems (GRDDS) is especially advantageous over other prolonged type drug delivery systems and conventional tablets because the drug is having absorption window in upper part of gastro intestinal tract and having relatively short half life. Amoxycillin trihydrate was taken as the model drug to optimized formulations was prepared. The single unit floating matrix tablets of Amoxycillin trihydrate with different natural and synthetic polymers such has HPMC K4M, HPMC K15M, HPMC K100M by taking single polymer in the formulation.The evaluation of physicochemical characteristics of all formulations and to carryout in vitro drug release studies using USP XXIV apparatus and data were analyzed at 272nm.The drug release of Amoxycillin trihydrate from formulations containing HPMC K4M,HPMC K15M followed zero order kinetics where has formulation containing combination of xanthan gum(natural polymer) and HPMC K100M(synthetic polymer) followed Higuchi and First-order pattern respectively. Of all the formulations in which combination of polymers has retarded the drug successfully upto 12 hours.

Keywords: Amoxycillin trihydrate, xanthan gum, Helicobacter pylori, Ethocel, HPMC K4M.

INTRODUCTION

Gastro-retentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically, gastroretentive system retains in the stomach for a number of hours and continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract[21].The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance. Therefore, Sustained release DDS possessing gastric retention properties may be potentially useful. Various approaches have been proposed to increase gastric residence of drug delivery systems in upper part of the gastrointestinal tract includes floating drug dosage systems(FDDS) swelling or expanding systems, mucoadhesive systems, maodified-shape systema, high-density systems and other delayed gastric emptying devices. Among these systems, FDDS have been commonly used[8].

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.

Most floating systems reported in the literature are single unit systems, such as HBS and floating tablets. The systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered due to their all or nothing empting process[15]. On the other hand, multiple unit dosage forms, such as hollow microsphere (microballoons), granules, powder, and pellets, are more suitable since they are claimed to reduce the inter- and intra-subject variability in absorption and reduce the probability of dose dumping[10].

The present work was undertaken on Amoxycillin trihydrate, with less half life of 1.7hrs, so as to design a low density gastro retentive dosage forms that can reside for a prolonged period of time with in the body there by offering better pharmacological action[13,20].

MATERIALS AND METHODS

Amoxycillin trihydrate was a gift sample from Hetero Laboratories; HYD. MCC ph102 was a gift sample from Hetero drugs Pvt Ltd, France. HPMC and HPMC K4M (Methocel) was purchased from Colorcon Asia Pvt. Limited. Xanthan gum was purchased from ISP, Hyderabad.

PREPARATION OF SINGLE UNIT FLOATING MATRIX TABLETS

Accurately weighed quantities of polymer and MCC were taken in a mortar and mixed geometrically, to this required quantity of Amoxycillin trihydrate was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder is passed through sieve no 40 and mixed with the Amoxycillin trihydrate blend which was also passed through sieve no 40. The whole mixture was mixed for 3 minutes. To this Magnesium stearate was added and mixed for minutes, later Talc was added and mixed for 2 minutes. The mixture equivalent to 850mg was compressed into tablets with 13.5mm capsulate punches at a hardness of 6 kg/cm^2.The composition of various formulations such has F1,F2,F3,F4,F5,F6,F7,F8,F9,F10,F11,F12 and F13 was given in table 1.

EVALUATION OF FLOATING TABLET OF AMOXYCILLIN TRIHYDRATE[19,20]

Friability test: Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Loss in the weight of tablet is the measure of friability and is expressed in percentage as:

% Friability = $[(W_1 – W_2) / W_1] \times 100$

Where W_1 = Initial weight of 20 tablets

W_2 = Weight of the 20 tablets after testing

Hardness test: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Mansanto hardness tester. It is expressed in kg/cm^2. Five tablets were randomly picked from each batch and the hardness of the tablets was determined.

Weight Variation test: 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 weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula.

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

Drug content: Twenty tablets were taken, powdered and the powder equivalent to one dose each was transferred to a 100 mL volumetric flask and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and diluted suitably and Amoxycillin trihydrate content in the samples was estimated using UV- Visible spectrophotometer at λ_{max} of 272 nm.

Thickness and diameter: The thickness of the tablets was measured using vernier caliper. It is expressed in mm.5 tablets of each batch were picked randomly and its thickness were measured individually. The thickness of the tablet is mostly related to the tablet hardness.

In vitro buoyancy studies: The in vitro buoyancy was determined by floating lag time, as per the method.The tablets were placed in a beaker containing 100 mL of 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time for which the dosage form constantly remained on the surface of medium was determined as the total floating time[17].

Swelling Study: The swelling behavior of a dosage form is measured by studying its weight gain or water uptake (WU). The study was done by immersing the dosage form in 0.1 N Hcl at 37^{o}C and determining these factors at regular intervals up to a period of 8 hours. Water uptake was measured in terms of percent weight gain, as given by the equation.

$WU = (W_t – W_o) \times 100 / W_o$

W_t = Weight of the dosage form at time t.

W_o = Initial weight of the dosage form.

In vitro Drug Dissolution Studies: USP Type II dissolution apparatus was used. The dissolution fluid was 900ml of 0.1N hydrochloric acid, a speed of 50 rpm and a temperature 37±0.50C were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filter of 0.45µm at different time intervals, suitably diluted and assayed for Amoxycillin trihydrate by measuring absorbance at 272 nm using UV Spectrophotometer.

Drug release kinetics: Various models were tested for explaining the linear and non-linear kinetic models to describe release mechanisms and to the obtained data were fitted into zero-order, first order, Higuchi and Korsmeyer-Peppas release model[16.]

RESULTS AND DISCUSSION

Floating tablets of Amoxycillin trihydrate were formulated using direct compression technique, using polymers like HPMC (K4M,K15M & K100M), xanthan gum polymer in tablet with the formulation codes F1, F2, F3, F4,F5, F6, F7, F8,F9,F10,F11,F12 and F13 were prepared. All the formulations were evaluated for their various physical parameters. The thickness and hardness of the tablets were in the range of 6.50mm to 6.86mm and 5.09 to 6.80 kg/cm^2 respectively. The values of average weight were within the limit. Drug content was in the range of 98.12% to 99.72% indicating good content uniformity in the prepared formulation shown in table 2. The in-vitro Buoyancy study was conducted. As the density of the tablet falls below 1, the tablet became buoyant. All the formulations were tested for floating properties like floating lag time and total floating time The floating lag time results were in the range of 79 Sec to 101 Sec. All the batches showed good in vitro buoyancy.

From the dissolution study of batch F1 to F13, it was concluded that release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. In this single polymer was used for a batch and combination of natural polymer and artificial polymer in one batch. The drug release was carried out up to 12 hrs. The percentage drug release from batch F1 to RF13 vary from 96.7 to 101.45%, which is shown in figure 1. For the formulation batch from F1 to F3 showed that the polymer HPMC K4M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F1, F2 and F3 was 96.71% in 6hrs, 99.71% in 10hrs, and 98.3% in 12hrs respectively. Formulation F1 was unable to sustain the drug release to desired period of time (total drug was released within 6 hr). Formulations F2 was failed to release the drug within the desired time. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. For the formulation batch from F4 to RF7, drug release was more retarded as HPMC K15M were used in these formulations the percent of drug release from formulations F4, F5, F6, and F7 was 97.24% in 6hrs, 97.60% in 8hrs, 86.49% and 98.8% in 12hrs respectively. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. The formulation batch from F8 to F10 the polymer HPMC K100M has sustaining effect on the release of drug from the floating matrix tablet. The formulation batch from F10 to F13 the polymers having xanthan gum and HPMC K100M sustaining effect on the release of drug from the floating matrix tablet difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymers. But the optimized formulation F13 (combination of HPMC K100M + Xanthan gum) showed satisfactory drug release (99.8%) during the final period of study.

DRUG RELEASE KINETICS

Regression co-efficient value (R^2) and n values for all formulation were shown in table 6. The release profile of the optimized formula F13 fitted best to Korsmeyer-Peppas model with R^2 value of 0.981. As the n value for the Korsmeyer-Peppas model was found to be less than 0.89, it follows case-2 transport.

STABILITY STUDY

According to ICH guidelines, 60 days stability study at 40^0C $\pm2^0$C for 60 days at RH 75±5% of optimized formulation (F13) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference in the drug content between initial and formulations stored at 40^0C $\pm2^0$C for 60 days at RH 75±5% for 60days.

CONCLUSION

From the above study it can be concluded that promising controlled release by gastro retentive floating tablets of Amoxycillin trihydrate with HPMC K4M, HPMC K15M, HPMC K100M, and Xanthan gum by taking single polymer in the formulations in which F13 gave better controlled drug release and floating properties in comparison to the other formulations. The floating tablet of Amoxycillin trihydratewas capable of maintaining plasma drug concentration through 12 hrs. The release rate of the drug from the floating tablets was significantly influenced by the proportion as well as viscosity of the polymer used. The formulation F13 was selected as an optimized formulation because it gave the best result in terms of the required in-vitro buoyancy study, good floating integrity and drug release in sustained release manner. The release profile of the optimized formula, fitted best to Korsmeyer-Peppas model with R^2 value of 0.981. As the n value for the Korsmeyer-Peppas model was found to be less than 0.89, it follows case-2 transport. Stability studies indicated no appreciable changes in the drug content and In-vitro drug release rates of formulation F13.

Table 1. Formulation composition of Floating tablets of Amoxycillin trihydrate

Batch Code	Drug (mg)	HPMC K4 M (mg)	HPMC K15 M (mg)	HPMC K100 M (mg)	Xanthan gum (mg)	Pvp K90 (mg)	Sodium bicarbonate (mg)	Micro crystalline cellulose (mg)
F1	575	100	-	-	-	-	72	87
F2	575	125	-	-	-	-	72	62
F3	575	150	-	-	-	-	72	37
F4	575	-	75	-	-	-	72	107
F5	575	-	100	-	-	-	72	87
F6	575	-	150	-	-	-	72	37
F7	575	-	135	-	-	-	72	52
F8	575	-	-	50	-	-	72	137
F9	575	-	-	75	-	-	72	112
F10	575	-	-	100	-	-	72	87
F11	575	-	-	50	50	48	40	71
F12	575	-	-	70	30	48	40	71
F13	575	-	-	80	30	48	40	61

HPMC- Hydroxy propyl methyl cellulose.Pvp-polyvinylpyrrolidone. All the formulations contained 1% of Magnesium stereate and 1% Talc.

Table 2. Post Compression studies of Amoxycillin trihydarte floating tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	850.38±3.84	6.8±0.5	6.84±0.05	0.22	99.65
F2	849.52±2.87	5.9±0.2	6.76±0.06	0.37	98.65
F3	852.23±2.73	6.8±0.5	6.86±0.03	0.23	98.45
F4	848.6±2.13	6.8±0.4	6.76±0.04	0.29	99.64
F5	850.19±3.48	6.8±0.5	6.63±0.06	0.23	98.45
F6	849.71±2.3	5.9±0.2	6.65 ±0.06	0.29	99.64
F7	847.2±1.19	6.8±0.5	6.68±0.05	0.37	98.12
F8	849.46±2.27	6.5±0.3	6.55±0.25	0.23	99.72
F9	850.67±3.84	6.8±0.5	6.506±0.04	0.29	98.45
F10	848.38±3.84	6.7±0.2	6.62±0.07	0.37	99.64
F11	848.6±2.13	6.8±0.4	6.76±0.04	0.29	99.64
F12	850.19±3.48	6.8±0.5	6.63±0.06	0.23	98.45
F13	849.71±2.3	5.9±0.2	6.65 ±0.06	0.29	99.64

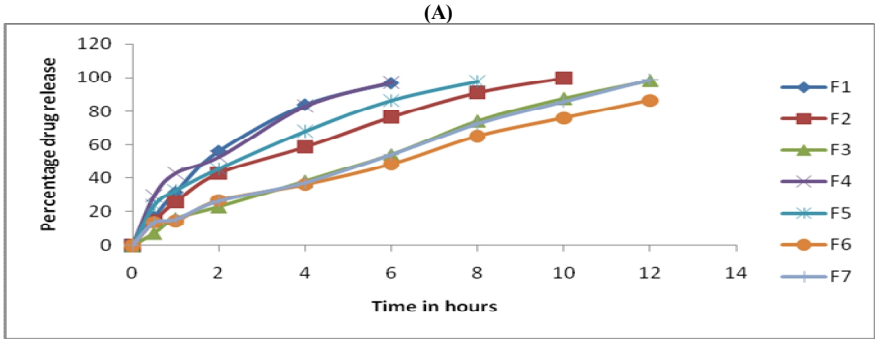
Table 3. In-vitro Buoyancy study of Amoxycillin trihydrate Floating Tablets

Formulation code	Floating time(sec)	Total floating time (hrs)
F1	89	>12
F2	99	>12
F3	101	>12
F4	98	>12
F5	94	>12
F6	79	>12
F7	84	>12
F8	89	>12
F9	94	>12
F10	79	>12
F11	84	>12
F12	89	>12
F13	84	>12

Table 4. Study of swelling characteristics of Floating tablets of Amoxycillin trihydrate

Batch Code	Time in hrs. (% Swelling)			
	2	4	6	8
F1	61.77	89.92	63.11	17.18
F2	47.33	65.44	55.42	27.93
F3	32.51	46.41	48.23	39.87
F4	60.51	88.56	63.43	17.26
F5	44.18	64.29	57.55	29.46
F6	91.24	97.82	84.75	73.19
F7	82.15	113.75	70.17	65.73
F8	58.19	89.73	51.79	42.65
F9	62.34	75.65	64.76	48.86
F10	54.97	82.43	47.19	40.64
F11	66.65	93.41	55.48	47.84
F12	49.92	77.11	76.44	30.29
F13	51.33	81.29	79.13	29.35

(A)



(B)

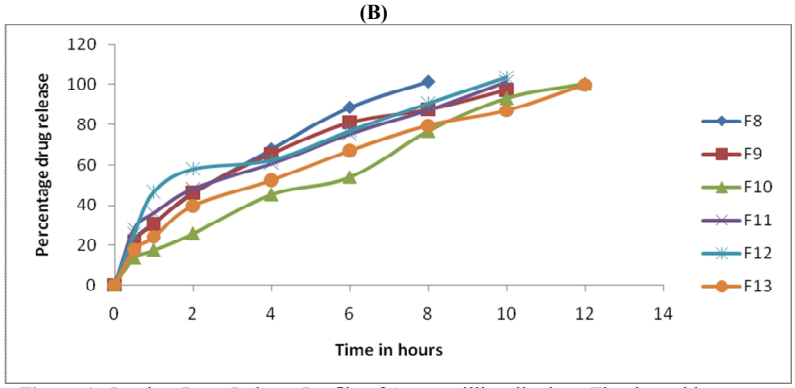


Figure 1. In-vitro Drug Release Profile of Amoxycillin trihydrate Floating tablets.
(A) HPMC K4M(F1,F2,F3) and HPMC K15M(F4,F5,F6,F7)
(B) HPMC K100M(F8,F9,F10) and HPMCK100M+Xanthan gum+ polyvinylpyrrolidone(F11,F12,F13) .

Table 5. Regression co-efficient (R^2) values of drug release data obtained from various kinetic models and n values from Krosmeyer-peppas

Formulation	R^2 value				n value
	Zero-order	First order	Higuchi	Korsmeyer- Peppas	
F1	0.9300	0.9800	0.9803	0.9776	0.620
F2	0.9400	0.8100	0.9939	0.9937	0.580
F3	0.9920	0.8750	0.9590	0.9890	0.763
F4	0.9060	0.9588	0.9947	0.9760	0.480
F5	0.9370	0.9370	0.9981	0.9980	0.540
F6	0.9840	0.9730	0.9690	0.9890	0.700
F7	0.9918	0.9470	0.9570	0.9911	0.746
F8	0.9500	0.9740	0.9950	0.9990	0.578
F9	0.9080	0.9490	0.9960	0.9930	0.502
F10	0.9850	0.8853	0.9630	0.9890	0.721
F11	0.9114	0.9876	0.9963	0.9926	0.508
F12	0.9251	0.9782	0.9936	0.9775	0.572
F13	0.9599	0.9146	0.9766	0.9815	0.726

Table 6. Stability studies of Amoxicillin trihydrate floating tablets

Parameters	After 15 days	After 30 days	After 45 days	After 60days
Physical appearance	No change	No change	No change	No change
Weight variation (mg)	849.71±2.3	849.61±1.9	849.59±1.30	849.56±1.13
Thickness (mm)	6.65±1.87	6.64±2.86	6.63±3.98	6.60±2.78
Hardness (kg/cm2)	5.9±0.23	5.9±0.64	5.8±0.99	5.6±0.72
Friability (%)	0.29±0.05	0.29±0.08	0.29±0.06	0.29±0.03
Drug content (mg/Tab)	99.64±0.34	99.41±0.29	99.01±0.87	98.93±0.49
Buoyancy lag time (Sec)	84±1.60	84±2.8	85±3.10	85±2.10
Duration of Buoyancy(hours)	>12	>12	>12	>12

REFERENCES

1. Chien YW. Novel drug delivery systems. 2nd ed. (NY): Marcel Decker, INC; 1992.
2. Robinson JR, Lee VHL. Controlled drug delivery: fundamentals and applications, 2nd ed. (NY): Marcel Decker, INC; 1987.
3. Rubinstein, A., 1990. Microbially controlled drug delivery to the colon. Biopharmaceutics & Drug Disposition 11, 465-475.
4. Marvola M, Kannikoski A, Aito H, Nykanen S. The effect of food on gastrointestinal transit and drug absorption of a multiparticular sustained-release Verapamil formulation. Int J Pharm 1989; 53: 145-55.
5. Burton, S., Washington, N., Steele, R.J., Musson, R., Feely, L., 1995. Intragastric distribution of ion-exchange resins: a drug delivery system for the topical treatment of the gastric mucosa. J. Pharm. Pharmacol. 47, 901-906.
6. Chen, G.-L., Hao, W.-H., 1998. In Vitro Performance of Floating Sustained-Release Capsule of Verapamil. Drug Dev. Ind. Pharm. 24, 1067-1072.
7. Remington: The science and practice of pharmacy, edition 19, vol II
8. Reddy, L.H., Murthy, R.S., 2002. Floating dosage systems in drug delivery. Crit. Rev. Ther. Drug Carrier Syst. 19, 553-585.
9. Robinson JR, Lee VHL. Controlled drug delivery: fundamentals and applications, 2nd ed. (NY): Marcel Decker, INC; 1987.
10. Rouge, N., Allémann, E., Gex-Fabry, M., Balant, L., Cole, E.T., Buri, P., Doelker, E., 1998. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high-density multiple-unit capsule and an immediate-release tablet containing 25 mg atenolol. Pharm. Acta Helv. 73, 81-87.
11. Umamaheshwari, R.B., Jain, S., Jain, N.K., 2003. A new approach in gastroretentive drug delivery system using cholestyramine. Drug Deliv. 10, 151-160.
12. Waterman, K.C., 2007. A critical review of gastric retentive controlled drug delivery. Pharm. Dev. Technol. 12, 1-10.
13. Whitehead, L., Collett, J.H., Fell, J.T., 2000. Amoxycillin release from a floating dosage form based on alginates. Int. J. Pharm. 210, 45-49.
14. Yang, L., Eshraghi, J., Fassihi, R., 1999. A new intragastric delivery system for the treatment of Helicobacter pylori associated gastric ulcer: in vitro evaluation. J. Control. Rel. 57, 215-222.
15. Kawashima, Y., Niwa, T., Takeuchi, H., Hino, T., Itoh, Y., 1992. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J. Pharm. Sci. 81, 135-140.
16. Yang, L., Fassihi, R., 1996. Zero-order release kinetics from a self-correcting floatable asymmetric configuration drug delivery system. J. Pharm. Sci. 85, 170-173.
17. Timmermans, J., Moes, A.J., 1994. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy. J. Pharm. Sci. 83, 18-24.
18. Srivastava, A.K., Wadhwa, S., Ridhurkar, D., Mishra, B., 2005. Oral Sustained Delivery of Atenolol from Floating Matrix Tablets-Formulation and In Vitro Evaluation. Drug Dev. Ind. Pharm. 31, 367-374
19. Stockwell, A.F., Davis, S.S., Walker, S.E., 1986. In vitro evaluation of alginate gel systems as sustained release drug delivery systems. J. Control. Rel. 3, 167-175.
20. Hilton, A.K., Deasy, P.B., 1992. In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate. Int. J. Pharm. 86, 79-88.
21. Chien YW. Novel drug delivery systems. 2nd ed. (NY): Marcel Decker, INC; 1992.
22. Desai, S., Bolton, S., 1993. A Floating Controlled-Release Drug Delivery System: In Vitro-in Vivo Evaluation. Pharm. Res. 10, 1321-1325.

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