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FABRICATION AND CHARACTERIZATION OF AMOXICILLIN TRIHYDRATE IP LOADED MICROBEADS FOR GRDDS

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ABSTRACT

The main aim of present research work is to develop gastro retentive drug delivery systems of Amoxicillin trihydrate. The impact of Carbopol 940 in HPMC different grades in matrix formation demonstrated in this work. The swelling property and controlled drug release profile also analysed comprehensively. The floating tablets of Amoxicillin trihydrate was developed to achieve a site specific drug delivery. The reason for developing Amoxicillin trihydrate as floating drug delivery systems is to treat Helicobacter pylori infections in stomach. It is desirable to treat the infection in thestomach. The dosage form releases more amount of drug in the stomach which offers better therapy than conventional tablets. The purpose of this investigation was to design and develop floating microspheres of Amoxicillin Trihydrate by ionotropic gelation method with combination of two polymers and to get the best possible formulation out of that with the various aspects. Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. The formulations were designedby using various grades of hydroxyl propyl methylcellulose polymers (HPMC K4M and E15LV) and Carbopol 940. The excipients such as sodium Bicarbonate, citric acid also incorporated in theformulation as gas forming agent. The *in vitro* studies were analysed by various pharmacokinetic models. The swelling index, buoyancy lag time and total floating time were also reported in this work.

KEYWORDS: Amoxicillin Trihydrate, HPMC E15 LV, HPMC K4M, Carbopol 940, Microspheres, Ionotropic Gelation Method, Ethyl cellulose, Hydroxy propylmethyl cellulose.

INTRODUCTION

Oral delivery of the drug is by far the most preferable route of drug delivery due to the easeof administration, patient compliance and flexibility in the formulations. From immediaterelease to site-specific delivery, oral dosage form has really progressed. It is evident fromthe recent scientific and patented literature that an increased interest in novel dosage forms thatare retained in the stomach forprolong and predictable period of time exist today in academic and industrial research groups. Various attempts have been made to develop Gastro retentive delivery systems. Over the pastthree decades, the pursuit and exploration of devices designed to be retained in the upperpart of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. This technology benefits drugs that have a narrow window of absorption in the stomach and upper GI tract. Gastro retentive systems can remain in the gastric region forseveral hours and hence significantly prolongthe gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, andimproves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Floating Drug Delivery Systems (FDDS)

Floating systems, first described by Davis in1968, have bulk density lower than that of the gastric fluid, and thus remain buoyant instomach for prolong period. Floating drug delivery systems are classified depending onthe use of 2 formulation variables:

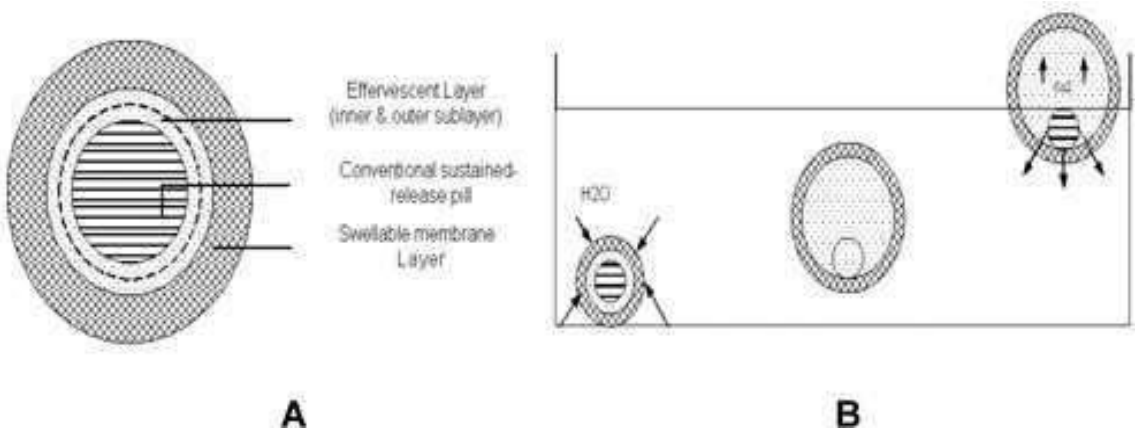
EFFERVESCENT AND NON-EFFERVESCENT SYSTEMS

A. Effervescent Floating Dosage Forms

1) Volatile liquid containing systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device mayalso consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit thespontaneous ejection of the inflatablesystems from the stomach. (Figure A and B)[8] developed floating capsules

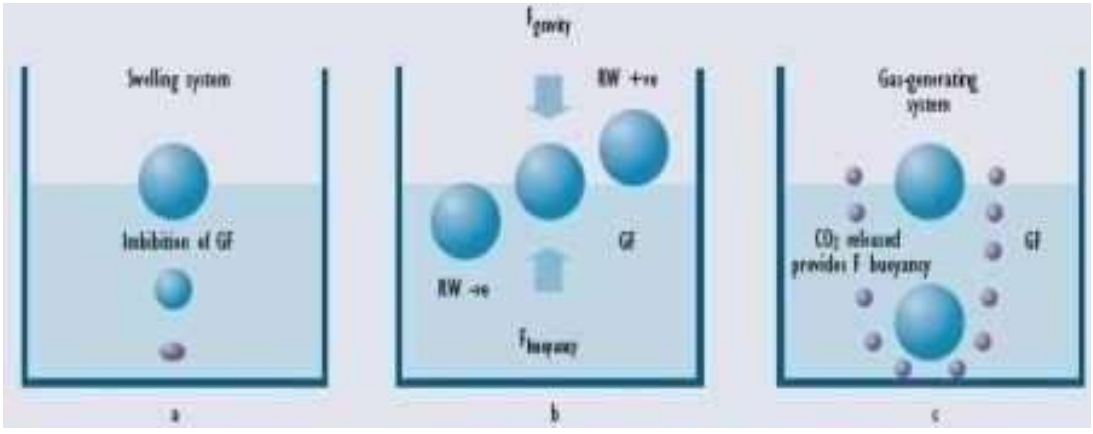
composed of a plurality of granules that have different residence times in the stomach and consist of aninner foamable layer of gas-generating agents.



Multiple-unit oral floating drug delivery system

(B) Working principle of effervescentfloating drug delivery system

2) This layer was further divided into 2 sublayers, the outer containing sodium bicarbonate and the inner containing tartaric acid. This layer was surrounded by an expansive polymeric film(composed of poly vinyl acetate [PVA] and shellac), which allowed gastric juice to pass through, and was found to swell by foam produced by the action between the gastric juices and the gas-generating agents. It was shown that the swellable membrane layer played an important role in *maintaining the buoyancy of the pills for an extended period of time.*



The Mechanism of Floating System

1. MATERIALS AND METHODS

❖ **Materials**

Amoxicillin Tri hydrate was obtained as gift sample from P.V.S Laboratories Ltd Andhra

Pradesh, India. HPMC K4M, HPMC E15 LV, Carbopol 940 obtained from Loba Chemie Pvt. Ltd, Mumbai, India. sodium bicarbonate, citric acid and lactose were procured from Finar Chemicals Limited, Ahmedabad, India. Microcrystalline cellulose was purchased from Merck Specialties Private limited, Worli, Mumbai. Talc and Magnesium sterate obtained from SD Fine Chem Ltd. Mumbai. The other reagents and chemicals used were ofanalytical grade.

1.1. Fabrication of Floating Tablets

The Amoxicillin trihydrate floating tablets were prepared by direct compression technique. Accurate amounts of hydrophilic polymers such as HPMC K4M, HPMC E15LV, Carbopol 940, Micro crystalline cellulose, sodium bicarbonate, citric acid and lactose were weighed according to the formulation design given in the Table **1**. All the ingredients of the formulation were forced through sieve No #80 mesh before blending. The ingredients already passed through sieve No #80 was blended thoroughly for 15 min. Then the accurately weighed quantity of talc and magnesium stearate was incorporated in the blend and mixed for about 10 minutes. The final resultant blend was then compressed by 16 station tablet compression machine (Cadmach machinery Co. Private limited Ahmadabad, Gujarat, India) using 12.66mm round shaped plain punches.[10,11]

Composition of Gastro-Retentive Tablets of Amoxicillin Trihydrate

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Amoxicillin trihydrate	250	250	250	250	250	250	250	250	250	250	250	250
HPMC K4M	50	100	50	75	100	----	----	----	----	----	----	----
HPMC E15LV	----	----	----	----	----	50	100	50	75	100	----	----
Carbopol 940	----	----	100	75	50	----	----	100	75	50	50	100
Micro Crystaline Cellulose	80	80	----	----	----	80	80	----	----	----	----	----
Sodium Bi Carbonate	100	100	100	100	100	100	100	100	100	100	100	100
Citric Acid	25	25	25	25	25	25	25	25	25	25	25	25
Lactose	50	50	50	50	50	50	50	50	50	50	50	50
Magnesium Sterate	15	15	15	15	15	15	15	15	15	15	15	15
Talc	10	10	10	10	10	10	10	10	10	10	10	10
Total weight	580	630	600	600	600	580	630	600	600	600	500	550

1.1. Pre-Compression Evaluation

Prior to compression the prepared powders of each formulation were evaluated for their characteristic parameters such as Bulk density, Tapped density, and Angle of repose.[1] Carr's compressibility index was calculated from the bulk density and tapped densities usingtapped density apparatus Table **2** (Sisco, Maharashtra).

1.2. Post-Compression Evaluation

The tablets were evaluated for their thickness, hardness, weight variation and friability by using appropriate recommended procedure. The results were shown in Table **3**.

1.3. *In Vitro* Buoyancy Studies

The buoyancy tablet was studied at 37±0.5ºC. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface of the liquid tofloat was determined as the Buoyancy lag time (BLT) or Floating lag time (FLT) and the duration of time of the tablet constantly floating on the dissolution medium was noted as total floating time http://www.youtube.com/watch?v=C07-_SLResE (TFT).

1.4. Swelling Study

One tablet from each formulation was weighed and placed in a beaker containing 200 ml of distilled water. At predetermined time intervals the tablets were removed from the medium. The excess fluid was blotted with tissue paper and immediately weighed. The percentage weight gained by the tablet was calculated by using the appropriate formula.

1.5. Mechanism of Drug Release

The drug release data was evaluated by the model- dependent (curve fitting) method. In the present study zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson Crowell methods were applied to describe the release pattern of the drug. The Peppas model describing drug releasing from polymeric system was used as a confirmatory method to analyse mechanism of drug release from polymeric system. The model was taken into consideration when drugrelease mechanism deviates from flicks law.

Where M_t is the drug release at time t, $M\infty$ the quantity of drug released at infinite time, k the kinetic constant and ‘n’ is the release exponent. The ‘n’ value indicates the release mechanism of the dosage form related to its geometrical shape. The release data was furthertreated to Higuchi equation $Q = k.t^{1/2.}$ Where, Q is the percent of drug released at time t and k is the kinetic constant. When ‘n’ is approximately about 0.5, a Fickian /diffusion controlled release is demonstrated, where $0.5<n<1.0$ is non-Fickian transport and if n=1 zero order (case –II transport) is implied. When the ‘n’ value was closure to 1 it concludes that releaseprofile approaching Zero order.

1.6. Stability Studies and Data Interpretation

The formulation which met all the desirable tablet quality control parameters and showed better colon targeting drug release profile was selected and subjected to stability studies for three months at 40˚C/75% RH. These samples were again subjected to drug release study.

RESULT AND DISCUSSION

The floating microspheres of Amoxicillin Trihydrate were prepared by Ionotropic Gelation Method. The results of the physico-chemical characterization are shown in Table 2. The prepared floating microspheres were found to be discrete, spherical and free flowing. All batches show percent entrapment more than 50% and it is found that entrapment of drug increases with an optimum amount of the polymer. Higher amount of the HPMC and Carbopol leads to decrease entrapment of the drug. Formulation F4 shows maximum entrapment whereas formulation F1 shows minimum entrapment of the drug in the polymer as shown in table 2.All batches showed a percentage yield of greater than 88%, whereas our batches showed a yield of more than 90%. Percentage yield is found to be higher with formulation F4. Angle of repose, Hausner ratio, and Carr's index were determined to predict flow ability. A higher Hausner ratio indicates greater cohesion between particles while a high Carr index is indicative of the tendency to form bridges. The prepared microspheres exhibited good flow properties. From the sieve analysis study it was found that the formulations have the size range of 700µm-900µm. The particle size distributions of the formulations F1 to F9 are shown in table 2. Surface morphology characteristics were studied using SEM (Figure 1-4). SEM indicated that the prepared microspheres are spherical with smooth surface; distinct

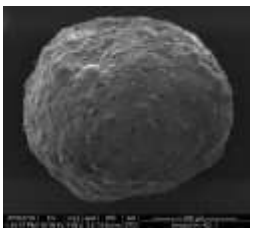


Fig: 1

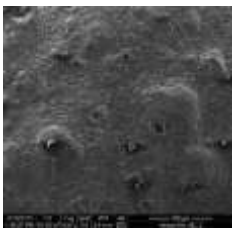


Fig: 2

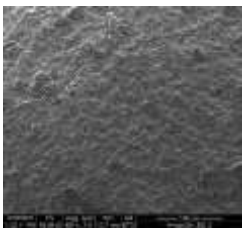


Fig: 3

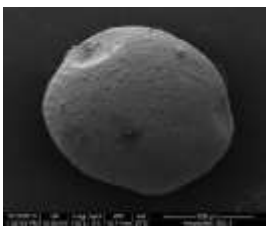


Fig: 4

Fig 1: Scanning Electron Microscopy of Amoxicillin Microsphere of batch F4 before dissolution, Fig 2: Scanning Electron Microscopy of Amoxicillin Microsphere's Surface of batch F4 before Dissolution, Fig 3: Scanning Electron Microscopy of Amoxicillin Microsphere of batch F4 after Dissolution, Fig 4: Scanning Electron Microscopy of Amoxicillin Microsphere's Surface of batch F4 after Dissolution.

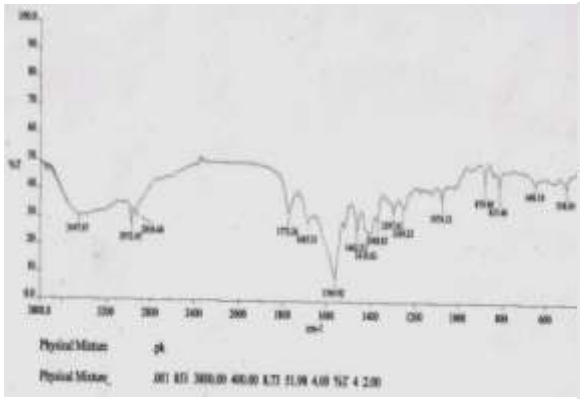


Fig 5: IR Spectra of Drug (Amoxicillin),

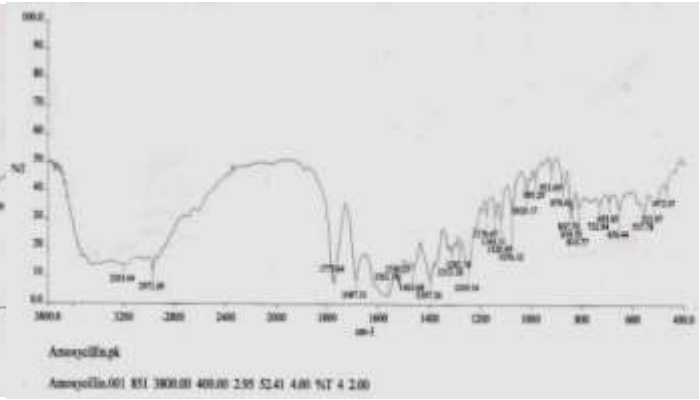


Fig 6: IR Spectra of Drug+ Polymers (Amoxicillin +HPMC+ Carbopol+ Sodium Alginate)

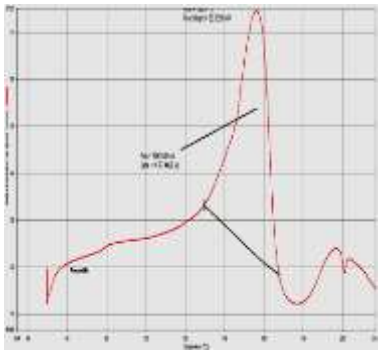


Fig: 7

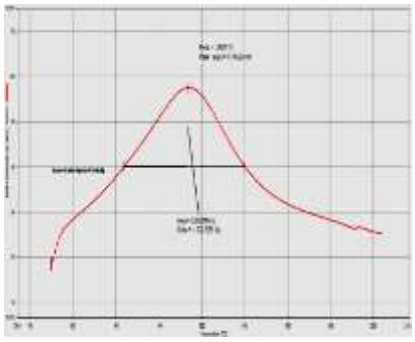


Fig: 8

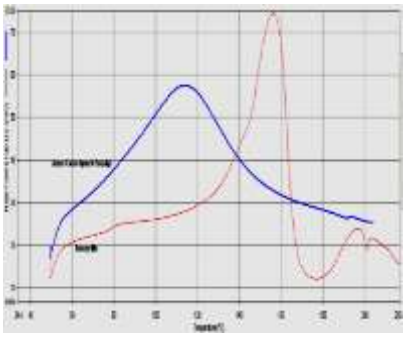


Fig: 9

Fig 7: DSC Thermogram of Drug (Amoxicillin), Fig 8: DSC Thermogram of physical mixture (Amoxicillin + Carbopol + HPMC + Sodium Alginate), Fig 9: Combined DSC Thermogram ofDrug and Physical Mixture.

From the floating efficiency study it can be conclude that microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. Buoyancy percentage of the microspheres was in the range of 60 to 90% at the end of 12 h. Formulation F4, F5 and F6 has shown the highest percentage of floating. The nature of the polymer influenced the floating behaviour of the microspheres.

The drug release from floating microspheres for the formulation 91%, 90% and 93% at the end of 10 h for F2, F3 and F6 respectively was found to be satisfactory. The data obtained from in vitro dissolution studies were fitted to zero-order, first-order, Higuchi and Korsemeyer-Peppas equations. The zero-order plots were found to be fairly linear as indicated by their high regression values of the above formulations. To confirm the exact

mechanism of drug release, the data were fitted according to Korsemeyer-Peppas equation. Slope values (0.5<n<1.0) suggest that the release of Amoxicillin trihydrate from floating microspheres followed non- Fickian diffusion mechanism.

Table 3: Release Data to Various Release Kinetics Models.

Formulation code	Zero Order Model		First-Order Model		H-M Model		Korsmeyer-Peppas Model	
	r^2	k^0	r^2	k^1	r^2	k_h	r^2	K_{kp}
F1	0.970	8.706	0.921	-0.088	0.918	36.35	0.935	0.844
F2	0.981	9.624	0.950	-0.120	0.971	41.08	0.989	0.928
F3	0.984	8.430	0.830	-0.089	0.960	35.73	0.973	0.929
F4	0.995	8.817	0.860	-0.114	0.963	37.22	0.987	0.799
F5	0.995	8.308	0.948	-0.087	0.982	35.41	0.997	0.848
F6	0.982	8.008	0.919	-0.077	0.937	33.57	0.969	0.808
F7	0.978	7.989	0.968	-0.086	0.984	34.38	0.983	0.766
F8	0.981	7.510	0.960	-0.087	0.993	32.42	0.993	0.667
F9	0.982	7.812	0.979	-0.073	0.969	33.30	0.967	0.790

CONCLUSION

In present work controlled release floating tablets were prepared by simple direct compression technique by using the drug Amoxicillin Trihydrate and hydrophilic polymers such as HPMC K4M, HPMC E15LV and Carbopol 940. The gas generating technique was used for buoyancy of the tablets at pH 1.2. The tablets were made floating for more than 15 hours. The optimised formulations showed the lag time less than a minute. A Non-Fickian and Case-II transport was found to be the predominant release mechanism in many of the dosage forms. This meant that diffusion of drug occurred by changes in the polymers such as swelling, erosion, polymer entanglement. The tablets containing 8.33% of HPMC E15LV, 16.66% of Carbopol, 4.16% of Citric acid and 16.66% of Sodium bicarbonate was demonstrated to be the better formulation design. The duration of buoyancy and drug release profile was satisfactory. The study also proved that the amount of Carbopol 940 plays a vital role in improving various characteristics of dosage forms. The formulation F8 was found be stable in short term stability studies for 3 months but the long term stability studies was recommended for the same to study the changes occurring in various storage conditions. This method is easy and simple without complicated formulation methods. This procedure can be considered as the better alternative to marketed formulations.

REFERENCES

1. Waldwell LJ, Gardner CR, Cargill RC. US Patent, 1988; 4: 735-804.
2. Nallasamy VM, Sambathkumar P. Formulation and Evaluation of Stomach Specific Amoxicillin Loaded Mucoadhesive Microspheres. Iranian Journal of Pharmaceutical Sciences 2010; 6: 227-233. Songsurang K, Pakdeebumrung J, Praphairaksit N. Sustained Release of Amoxicillin from Ethyl Cellulose- Coated Amoxicillin/Chitosan–Cyclodextrin- based Tablets. AAPS PharmScitech, 2011; 12: 35-45.
3. Shekar BC, Kiran SR, Babu N. Preparation and evaluation of gastro retentive floating tablets of ketoconazole. International Journal of Pharma Research and Development, 2010; 2: 174-184.
4. Pandit V, Suresh S and Joshi H. Gastroretentive drug delivery system of amoxicillin: Formulation and *in vitro* evaluation. International journal of Pharma and Bio Sciences, 2010; 1: 1-10.
5. Yellanki SK, Syed JA, Goranti S. A novel approach to prolong the local action by gastric Retention. Int Res J Pharm Sci., 2010; 1: 38-41.
6. Chien YW. Novel drug delivery system, Eds. 2nd; Marcel Dekker Inc publications: NewYork, 1992; 50): 161-72.
7. Khar RK, Vyas SP. Targeted and controlled drug delivery novel carrier system, Eds. 1st CBSPublishers and Distributors. New Delhi, 2002; 417-41.
8. Timmermans J, Moes AJ. How well floating dosage form float. Int J Pharm., 1990; 62: 207-16.
9. Tanwar YS, Floating Microspheres: Development, Characterization and Applications. Pharmainfo.net, 2006, 4(3).
10. Martin A, Bustamante P, Chun AHC, Physical Pharmacy: Physical chemical principles in the pharmaceutical sciences. 2005, 4th Edition, B.I. Publications Pvt. Ltd., 423-448.
11. Kumar RP, Shankar NB. Formulation design, preparation of losartan potassium microspheres by solvent evaporation method and its in vitro characterization. Arch Pharm Sci and Res., 2009; 1(1): 166-170.
12. Sengel CT, Hascicek C, Gonul N, Development and in-vitro evaluation of modified releasetablets including ethylcellulose microspheres loaded with diltiazem hydrochloride. J.Microencapsulation, 2006; 23(2): 135-152.
13. Lachman L, Lieberman HA, Kanig JL, The theory and practice of industrial pharmacy, 1991; 4th.
14. Nayak BS, Ghosh SK, Patro KTB, Preparation and characterization of famotidine

microcapsule employing Mucoadhesive polymers in combination to enhance gastroretention for oral delivery. IJPPS, 2009; 1(2): 112-120.