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FORMULATION AND EVALUATION OF GASTRORETENTIVE TABLETS OF AMOXICILLIN TRIHYDRATE

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ABSTRACT: The gastroretentive tablets of amoxicillin will provide site-specific drug delivery and thereby extend its duration of action. Gastro retentive drug delivery systems of Amoxycillin trihydrate were prepared with the objective to obtain site-specific drug delivery for the stomach and to extend its duration of action. The sustained release of amoxicillin is desired because of its short biological half-life. Particularly to treat Helicobacter pylori infections, the sustained release is desired to be confined to the stomach. The gastroretentive tablets of amoxicillin will provide site-specific drug delivery and thereby extend its duration of action. The dosage form was designed by Drug, Polymer mixture and effervescent mixture in the ratio of 1:2:0.4 polymers as matrix forming agents, sodium bicarbonate as gas-generating agent and other excipients. Direct compression technique was used for formulation of tablets. The pharmaceutical properties of formulations, their buoyancy lag time and total floatation time and in vitro drug release were evaluated. It is found that the hardness of the tablet will affect the buoyancy characteristics of the dosage form. The in vitro release data was treated with mathematical equations, and it was concluded that Amoxicillin released from the tablet followed Peppas model with non-Fickian diffusion. Hence gastro retentive drug delivery system of Amoxycillin trihydrate is a promising approach as it can lead to decrease in the frequency of administration and ultimately lead to better patient compliance.

Introduction:

Gastric colonization with H. pylori can lead to variety of upper gastrointestinal disorders, such as chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer1. The absorption of an antibiotic into the mucus through the mucus layer (from the gastric lumen) is believed to be more effective for H. pylori eradication than absorption through the basolateral membrane (from blood)2. Local delivery of antibiotic could be improved by reformulating antibiotics to enhance gastric retention by variety of approaches like

Floating systems3. Amoxicillin is a semisynthetic, orally well absorbed, broad spectrum antibiotic. Conventional oral or parental preparation of amoxicillin, when given with omeprazole and clarithromycin can eradicate H. pylori4.Although H. pylori are sensitive to a wide range of antibiotics in vitro, they all fail as mono therapy in vivo. The reason for the incomplete eradication of H. pylori is probably due to short residence time of antimicrobial agents in the stomach so that effective antimicrobial concentration cannot be achieved in the gastric mucous layer or epithelial cell surfaces were H. pylori exists5.

Material and Methods: -

Amoxycillin trihydrate was obtained as gift sample from Bharat Parenterals Pvt. Ltd. Hydroxy Propyl Methyl Cellulose E50LV (LR) Hydroxy Propyl Methyl Cellulose K15M (LR) were as gift sample received from Astron Chemicals, Ahmedabad India. Carbopol 934 P (LR) and Carbopol 940 P (LR) were obtained from Loba Chem Pvt. Ltd., Mumbai. Guar gum (LR), Sodium Bicarbonate (LR), CaCO3 (LR), and Citric Acid (LR) were obtained from SD Fine Chemicals, Ahmedabad. All other chemicals were of analytical reagent grade.

Method of preparation of floating tablets

- Weighed amount of dry powder of Amoxicillin trihydrate, polymer mixture (HPMC K15M, Carbopol 940P and/or guar gum) and mixture of gas forming agents (containing NaHCO3 and CaCO3; used in combination of 1:1 ratio) along with Magnesium stearate (lubricant) and talc (glident) were passed from sieve # 44. After sieving, all the ingredients were mixed together using blender.
- The powder mixture was compressed at low pressure by using 12 mm flat punch in Rotary Tablet Punching Machine. (So, formulated matrix tablets have less hardness as well as possibly more air entrapment, both of the factors may improve the buoyant property of the prepared formulations.)

Table 1: Composition of Gastro-retentive Tablets of Amoxicillin Trihydrate (in mg)

Formulation Code	Amoxicillin trihydrate	HPMC E50LV	Carbopol 934P	Guar gum	$NaHCO_3$	Citric Acid	Mg Stearate	Talc	Total
F7	114.9	160	20	20	32	8	11.3	11.3	377.6
F6	114.9	140	30	30	32	8	11.3	11.3	377.6
F5	114.9	170	0	30	32	8	11.3	11.3	377.6
F4	114.9	170	30	0	32	8	11.3	11.3	377.6
F3	114.9	140	0	60	32	8	11.3	11.3	377.6
F2	114.9	140	60	0	32	8	11.3	11.3	377.6
F1	114.9	200	0	0	32	8	11.3	11.3	377.6

Evaluation of Flow properties

Bulk Density

The loose bulk density (LBD) and tapped bulk density (TBD) were determined by 10 g of the blend were accurately weighed and transferred into the 100 mL graduated cylinder. The volume occupied by blend was measured "as it is" and loose bulk density is determined by equation (a). Tapped bulk density was determined by tapping the same graduated cylinder for 100 times onto a hard wooden surface and calculated by using equation (b).

(a) Bulk density = Mass of Powder mixture / unsettled apparent volume of Powder mixture obtained (V0)

(b) Tapped density = Mass of Powder mixture / Volume of Powder mixture after tapping (V)

Compressibility index and Hausner Ratio

It is obtained from under mentioned equation.

% Compressibility index = (1 – V/V0)*100

= [1-(Tapped volume/bulk volume)]*100

= [1-(bulk density/Tapped density)]*100

Here, V and V0: Volumes of the sample after and before the standard tapping, respectively.

Hausner Ratio = Bulk volume/tapped volume

Angle of repose

Angle of repose (θ) was determined by a fixed funnel method and calculated as, $\tan\theta = 2H/D$

Here, H: The standing height of the cone formed by powder mixture

D: Diameter formed on a graph paper after the flow of powder mixture from the glass funnel.

Compression parameter evaluation

Tablet thickness and tablet diameter

A vernier caliper was used to determine thickness and tablet diameter of 10 randomly selected tablets. Results were expressed as mean values ± SD.

Tablet hardness

The hardness of tablet of each formulation was measured by randomly taking 10 tablets by using Monsanto hardness tester.

Friability

Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 minutes, the tablets were weighed and the percentage loss in tablet weight was determined.

Percentage loss = (Initial wt. of tablets–Final wt. of tablets) x 100/Initial wt. of tablets

Friability of the developed tablet formulations should be less than 1%. This test was run once (USPNF, 2007).

Uniformity of Weight of formulated dosage form

20 tablets/capsules were weighed individually and the average weight was determined. The % deviation was calculated and checked for uniformity of weight as per IP, 2007.

Floating lag time and Total floating time:

The lag time was carried out in beaker containing 100 ml of simulated gastric fluid (pH: 2) as a testing medium maintained at 37 °C.

The time required for the tablet to rise to the surface and float was considered as floating lag time.

Total floating time is the time, during which the tablet floats in simulated gastric fluid (dissolution medium) (including floating lag time).

Dissolution studies of Gastroretentive Matrix Tablets

Dissolution studies of amoxicillin from floating tablets/capsules were performed using the USP Dissolution Testing Apparatus II (Paddle type) at 37 ºC ± 0.5 ºC and 50 rpm using 900 ml simulated gastric fluid (pH: 2), as the dissolution media. A 5 ml aliquot of sample was withdrawn at regular time intervals, filtered and assayed spectrophotometrically at 272 nm. The cumulative % drug release was calculated for the formulations.

The in-vitro release data were treated to different equations and kinetic models to explain the release kinetics of Amoxicillin from the floating tablets.

Curve fitting analysis: The mechanism of Amoxicillin released from the matrix system was studied by fitting the dissolution data obtained to following equations.

(a) Korsmeyer – Peppas equation.
(b) Zero order equation.
(c) First order equation.
(d) Higuchi square root equation

Result and Conclusion

Flow properties evaluation results : The values obtained for angle of repose for all formulations are tabulated in Table no. 2. The values of Hausner ratio, compressibility index and Angle of repose were found between 220.67' to 24.29', 1.293 to 1.321 and 27.82 to 31.73 respectively. This indicates good flow property of the powder blend. Compressibility index value indicating that the powder blend has the suitable flow property for direct compression.

Table-2: Flow properties of various Formulations F1 to F7

Formulation Code	*Bulk density (g/cm^3)*	*Tapped density (g/cm^3)*	*Hausner Ratio*	*Compressibility index*	*Angle of repose (θ)**
F1	0.882	1.165	1.321	24.290	28.23 ± 2.62
F2	0.931	1.204	1.293	22.670	27.82 ± 1.38
F3	0.985	1.275	1.294	22.745	33.62 ± 2.81
F4	0.907	1.195	1.318	24.100	28.12 ± 1.48
F5	0.934	1.230	1.317	24.065	31.73 ± 2.15
F6	0.958	1.239	1.293	22.680	30.86 ± 1.67
F7	0.933	1.221	1.309	23.587	30.15 ± 2.31

Friability of all the formulations was less than less than 1% as per official requirement of IP (n=20 Tablets). Weight Variation test complied the official requirement as per IP-2007 and USPNF-2007 (n=20 Tablets).

The drug content of the developed formulations was within the acceptance value provided by USPNF-2007 (n=10 Tablets).

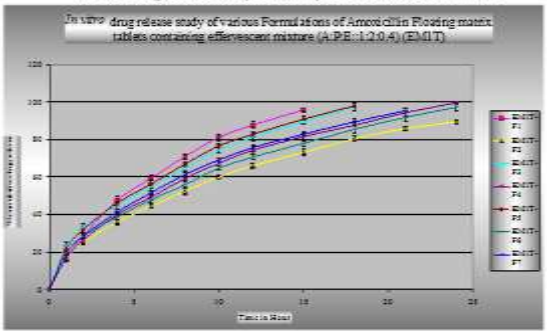
Evaluation of Dimensional and Buoyant properties:

Table-3: Dimensional and Buoyant properties of various Formulations

Formulation Code	Diameter** (in mm) Mean ± S.D.	Thickness** (in mm) Mean ± S.D.	Floating Time* (in Hours) Mean ± S.D.	Floating Lag Time* (in Seconds) Mean ± S.D.
F1	11	5.02 ± 0.07	T.D.T.	2 ± 2
F2	11.05 ± 0.02	5.16 ± 0.08	6.27 ± 0.63	18 ± 6
F3	11	4.89 ± 0.05	T.D.T.	2 ± 2
F4	11.03 ± 0.01	5.09 ± 0.04	8.78 ± 0.82	11 ± 4
F5	11	4.95 ± 0.06	T.D.T.	2 ± 2
F6	11.03 ± 0.01	5.04 ± 0.05	9.37 ± 0.68	9 ± 2
F7	11.02 ± 0.01	5.01 ± 0.04	>24	4 ± 1

* n=3 Tablets; ** n=10 Tablets; T.D.T. = till the disappearance of tablets

***In vitro* drug release study and analysis of release mechanism:**



Analysis of 'K' of Zero order Equation

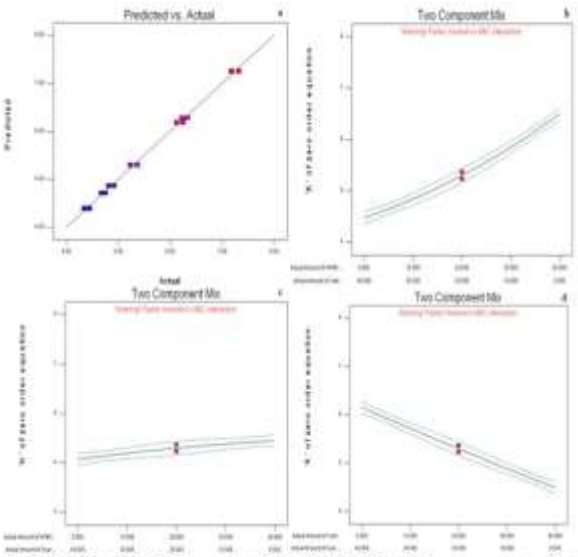


Fig 2 : (a) Plot of Predicted vs. Actual (b), (c), (d) Effect of Two component mixture

- It was concluded from the figure-2 (b), if the amount of guar gum (C) is kept constant and amount of HPMC E50LV (A) increases and amount of carbopol 934P (B) decreases, 'k' of zero order equation is increased proportionally.

- It was observed from the figure-2 (c), if the amount of carbopol 934P (B) is kept constant and amount of guar gum (C) decreases and amount of HPMC E50LV (A) increases 'k' of zero order equation is increased slightly.

- It was detected from the figure-2 (d), if the amount of HPMC E50LV (A) is kept constant and amount of carbopol 934P (B) increases and amount of guar gum (C) decreases 'k' of zero order equation is decreased simultaneously.

Analysis of 'n' of peppas equation.

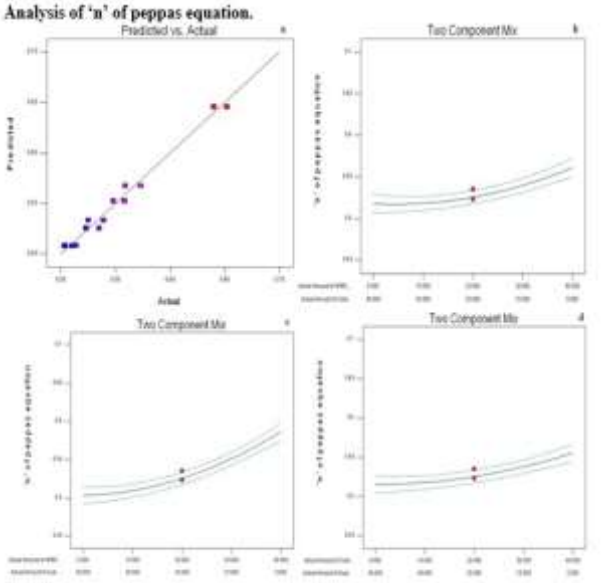


Fig 3 : (a) Plot of Predicted vs. Actual (b), (c), (d) Effect of Two component mixture

- It was concluded from the figure-3 (b), if the amount of guar gum (C) is kept constant and amount of HPMC E50LV (A) increases or amount of carbopol 934P (B) decreases, 'n' of peppas is increased slightly.

- It was observed from the figure-3 (c), if the amount of carbopol 934P (B) is kept constant and amount of guar gum (C) decreases or amount of HPMC E50LV (A) increases 'n' of peppas equation is increased.

- It was detected from the figure-3 (d), if the amount of HPMC E50LV (A) is kept constant and amount of carbopol 934P (B) increases or amount of guar gum (C) decreases 'n' of peppas equation is increased slightly.

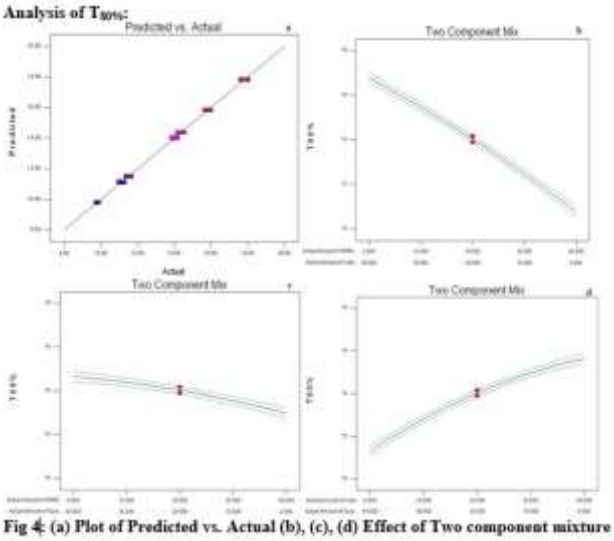
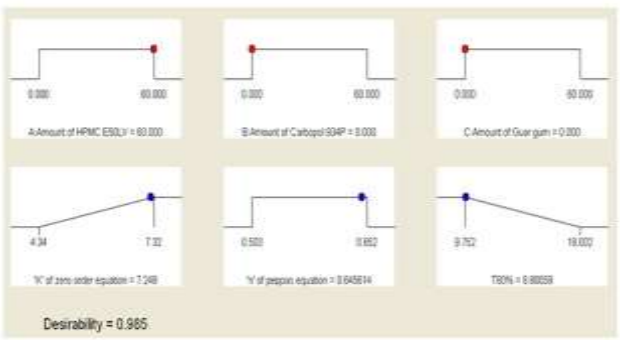


Fig 4: (a) Plot of Predicted vs. Actual (b), (c), (d) Effect of Two component mixture

- It was concluded from the figure-4 (b), if the amount of guar gum (C) is kept constant and amount of HPMC E50LV (A) increases or amount of carbopol 934P (B) decreases, T80% is decreased proportionally.
- It was observed from the figure-4 (c), if the amount of carbopol 934P (B) is kept constant and amount of guar gum (C) decreases or amount of HPMC E50LV (A)increases T80% is decreased slightly.
- It was detected from the figure-4 (d), if the amount of HPMC E50LV (A) is kept constant and amount of carbopol 934P (B) increases or amount of guar gum (C) decreases T80% is increased simultaneously.

Obtained solution for optimized formulation having release profile with zero order for 12 h from various predicted formulations of F1 to F7.

Formulation Code	Amount of HPMC E50LV	Amount of Carbopol 934P	Amount of Guar gum	'K' of zero order equation	'n' of peppas equation	$T_{80\%}$	Desirability
T-12h	60	0	0	7.249	0.645614	9.80058	0.9851



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