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Research Article

Development of targeted drug delivery systems of combination therapy for treatment of *H. Pylori* infection

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ABSTRACT

Helicobacter pylori infection causes chronic gastritis, which can progress to severe gastroduodenal pathologies, including peptic ulcer, gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma. H. pylori is usually transmitted in childhood and persists for life if untreated. The infection affects around half of the population in the world but prevalence varies according to location and sanitation standards. H. pylori have unique properties to colonize gastric epithelium in an acidic environment. The pathophysiology of H. pylori infection is dependent on complex bacterial virulence mechanisms and their interaction with the host immune system and environmental factors, resulting in distinct gastritis phenotypes that determine possible progression to different gastroduodenal pathologies.

Keynote: H. Pylori infection, Combination therapy, Omeprazole, Amoxicilline, Targeted therapy

Introduction:

H. pylori (Helicobacter pylori) is a type of bacteria that infects your stomach. It's the most common chronic bacterial infection in humans. It affects more than half of the world's population [1]. But it doesn't cause illness in most people. Helicobacter pylori (pronounced "hel-i-ko-bak-ter pai-law-rai") infections mostly occur during childhood. It's more common in developing countries. In the U.S., about 5% of children under the age of 10 have H. pylori bacteria [2]. Infection is most likely to occur in children who live in crowded conditions and areas with poor sanitation. H. pylori bacteria are spiral-shaped and can live in the harsh acidic environment of your stomach by producing enzymes that neutralize the acid [3]. This allows H. pylori to burrow into your stomach lining, where they can cause chronic inflammation and irritation. Most children with H. pylori infection don't have symptoms. Only about 5% to 10% do. If they do, symptoms and signs arise from peptic ulcers or gastritis. One symptom they may experience is a dull or burning pain in their stomachs [4]. More often, this happens a few hours after eating and at night. Their pain may last minutes to hours and may come and go over several days to weeks. In most people with H. pylori infection, their poop will appear normal. This is because many people experience no symptoms or only mild ones. But there's a warning sign to look for in your poop that can be a point to a more serious complication: blood. If your poop appears dark, black or tarry, this could mean you have bleeding in your upper digestive tract, possibly due to an ulcer from H. pylori [5]. Blood in your poop that appears red can be a sign of bleeding lower in your digestive system. If you notice any signs of blood in your poop, it's important to see a healthcare provider right away. They can determine the cause of the bleeding and recommend the appropriate treatmen [6]t. If you have an H. pylori infection, you have an increased risk of stomach cancer later in life. If you have a strong biological family history of stomach cancer and other cancer risk factors, your healthcare provider may recommend being tested for H. pylori antibodies. They may suggest this even if you don't have symptoms of a stomach ulcer [7]. Current state of art is witnessing a revolution in new techniques for drug delivery. Nevertheless, convenience of manufacturing and patient compliance has maintained their significant importance in the design of drug delivery systems. One such drug delivery system is the conventional oral drug delivery system. The objective of the project is to develop a stable and robust formulation of coating technology of the selected antibiotics over core tablet of proton pump inhibitor (PPI). Regimens for eradication of Helicobacter pylori infection are typically chosen empirically, on the basis of regional bacterial resistance patterns, local recommendations,

and drug availability. The proposed study deals with characterization and evaluation of solventless coating technology in over core tablet formulation in which a single drug is incorporated in core tablet i.e the outer shell over the internal core tablet. Here sustained release formulation avoids the side effects associated with the immediate release formulation & also provides effects for longer period of time.

MATERIAL AND METHODS

Formulation of immediate release tablets: Weighed quantity of drug omeprazole 20mg, croscarmellose sodium (50 mg) was passed through # 40 mesh and mixed cage blender for 10 minutes at 20 rpm. Accurately weighed PVP K-30 (10mg) was dissolved in purified water to prepare a binder solution. Granules were prepared from the blend, dried and size reduced. Accurately weighed croscarmellose sodium (50 mg), avicel PH 102 (50 mg) was passed through a sieve. Finally prepared granules were lubricated by tal and sodium stearate at blender. The finaaly prepared granules were compressed into 90 mg tablets using flat-faced, round punches 4 mm in diameter [8].

Preparation of various compressed gastroretentive tablet by direct compression tablet:

The prepared immediate release tablets of omeprazole was further compression coated by direct compression technology with other drug (amoxicillin) containing blend of different weight ratios as shown in Table 1. The antibiotic formulation of amoxicillin coating blend (700 mg) in different ratio was prepared by direct compression technique. A mixture of magnesium stearate and talc (1:2) was used for lubricating on coated blend. First, the die cavity (12 mm) was filled with 30% of coating polymer blend containing amoxicillin. Now the core tablet carefully placed in the center of the die cavity over the coating material and then the core tablet covered with the remaining 70% of the coating material blend in upper portion of the die. The placed coating material was compressed around the core tablet (OIR4; 20 mg) with a maximum compression force using 12mm round and concave punches. Finally, the whole content was compressed using 12 mm concave punches [9].

Table 1: Composition of amoxicillin tablet coating with core omeprazole 120 mg prepared by direct compression coating

Composition	Ingredients	Amount (mg / tablet)								
		AOT 1	AOT 2	AOT 3	AOT 4	AOT 5	AOT 6	AOT 7	AOT 8	AOT 9
Core Tablet	Omeprazole IR tablet (OIR4)	90	90	90	90	90	90	90	90	90
Coating material	Amoxicillin	500	500	500	500	500	500	500	500	500
	Guar gum (mg)	35	30	20	35	30	20	35	30	20
	Xanthan gum (mg)	20	25	35	20	25	35	20	25	35
	Carrageenan (mg)	10	10	10	7.5	7.5	7.5	5	5	5
	HPMC (mg)	5	5	5	7.5	7.5	7.5	10	10	10
	Microcrystalline cellulose (Avicel pH 102)	10	10	10	10	10	10	10	10	10
	Di basic calcium Phosphate dihydrate (DBP)	30	40	50	60	70	45	40	35	30
	Potato Starch	-	-	-	-	-	30	25	20	15
	Purified Talc	5	5	5	5	5	5	5	5	5

Evaluation of various compressed gastroretentive tablet:

Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed here.

Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation.

Thickness:

The thickness of the core tablets was determined using a screw gaze, and the results are expressed as mean values of ten determinations

Hardness:

The limit of hardness of usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness testers (Monsanto tablet hardness tester). It is expressed in kg or pound [10].

Friability:

To achieve % friability within limits (0.1-0.9 %) for tab in tablet is a challenge for a formulator since all methods of manufacturing of various compressed gastroretentive tablet are responsible for increasing the % friability values. Friability of each batch was measure in "Electro lab friabilator". Ten pre-weighed tablets were rotated at 25 rpm for 4 min or total 100 revolutions, the tablets were then reweighed and the percentage of weight loss was calculated by the following equation.

$$F = \frac{(W\text{initial} - W\text{final})}{W\text{initial}} \times 100$$

Disintegration test:

To test for disintegration time, one tablet was placed in each tube, and the basket rack was positioned in a 1-liter beaker of the medium at 37±2 °C. The standard motor driven device was used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. Perforated plastic discs were placed on top of the tablets.

Determination of drug content:

Ten tablets were finely powdered, and a quantity of powder equivalent to 100 mg of amoxicillin (AOT) was accurately weighed. The weighed sample transferred to 100 ml volumetric flasks containing approximately 50 ml of pH 1.2 phosphate buffer. The flasks were shaken for solubilizing the drug and sonicated for 10 min. The volume was diluted made up to 100 ml by pH 1.2 phosphate buffer and mixed thoroughly. The drug samples were diluted with same solvent up to 10 µg / ml. The solutions were filtered through a 0.45 µm membrane filter and analyzed for the content of plumbagin at 232 nm using above UV method [11].

Swelling index (%):

Swelling ratio was determined using following equation: Swelling Ratio (%) = $(A_t - A_o) / A_{tablet} * 100$

A_t, weight of the tablet and basket at time t (g);

A_o, weight of the tablet and basket at the beginning (g);

A_{tablet}, weight of the dry tablet (g).

The prepared tablets were placed in the wire basket of six basket dissolution apparatus. The basket was immersed in a beaker containing 0.1 N HCl (900 ml) for 2 h and allowed to swell at 37 ºC. The tablets were removed and changes in weight were measured before and after swelling.

in-vitro ex-vivo mucoadhesive strength:

The mucoadhesive strength of the prepared tablet was determined by modified physical balance. The assembly consist of a modified double beam physical balance in which left sided pan is removed and attached with glass slide with an additional weight is added with slide to balance the weight of both the pan. Fresh intestine mucosa of goat was used as membrane obtained from local slaughter house and kept in kerb solution during transportation and 0.1 N HCl (pH 1.2 phosphate buffer) was use for moistening the mucosa. The underlying mucous membrane was separated by the help of surgical blade and tied with the glass slide with the help of thread. Now the tablet was made to stick with the wooden block and made contact with the mucous membrane and the tablet. The additional weight was increased on the right pan until the tablet detaches from the membrane and the weight used was noted as mucoadhesive strength in grams and force of adhesion was calculated [12].

in-vitro drug release dissolution test:

The dissolution methods for various compressed gastroretentive tablet are practically identical to conventional tablet. Commonly the drugs may have dissolution conditions as in USP monograph. 0.1N HCl pH 1.2 buffers should be used for evaluation of TT in the same way as their ordinary tablet counterparts. USP 2 paddle apparatus is most suitable and common choice for dissolution test of TT tablets as compared to USP1 (basket) apparatus due to specific physical properties of tablets. In paddle apparatus the paddle speed of 50 rpm is commonly used. Since the dissolution of various compressed gastroretentive tablet is very fast when using USP monograph conditions hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets (≥1gram) may produce a mound in the dissolution vessel which can be prevented by using higher paddle speeds. The amount of drug released was analysed using UV-Visible Spectrophotometer at 273 nm [13].

in-vitro drug release kinetic study:

The drug release and mechanism release can be determined by matching the data with various release models like Higuchi, Korsmeyer-Peppas, zero order and first order plots. The kinetics of drug release was studied in various kinetic models by plotting the data obtained from in vitro drug release study. The zero-order kinetics was studied by plotting cumulative amount of drug released versus time. Whereas first order kinetics was studied by plotting log cumulative percentage of drug remain versus time. Higuchi's model of kinetics was studied by plotting cumulative percentage of drug released versus square root of time. The

mechanism of drug release from the formulation was confirmed by fitting the in vitro drug release data with the Korsmeyer–Peppas model by plotting log cumulative percentages of drug release versus log time. The release exponent 'n' and 'k' values were calculated from the Y intercept and slope of a straight line respectively [14-15].

1. Zero-order: Cumulative % of drug released versus time;
2. First order: Log cumulative % of drug remaining versus time;
3. Higuchi: Cumulative % of drug released versus square root of time; and
4. Korsmeyer–Peppas: Log cumulative % of drug released versus log time.

The linearity of the plots was obtained from the values of regression coefficient (r2). The model with the highest linearity (r2 value approaching unity) was chosen as the best fit kinetic model.

Results and Discussion

The oral sustained release dosage form with prolonged residence time in the stomach helps in absorption of the drugs which are less soluble or unstable in the alkaline pH and those which are absorbed from the upper gastrointestinal tract. In the present study an attempt was made to develop a sustained release action properties tablet of gliplazide with variation of natural polysaccharide polymeric combination with adhesion properties at gastric mucosa. Such type of proposed formulations increases the gastric residence time, thus increase the bioavailability. The results of immediate release tablets formulation was optimized best for the preparation and evaluation of antidiabetic formulation by tab in tablet technology. Pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were evaluated for powder blend. The compressed gastroretentive tablet technology (AOT1-AOT9) tablets were prepared by the direct compression method, using MCC, DBT, Lactose etc. as excipient blend [16]. The compressed gastroretentive tablet technology dosage form helps in absorption of the drugs from the upper gastrointestinal tract. The other characterization includes weight variation, thickness, hardness, friability, mechanical strength, measurement of tablet porosity, wetting time and water absorption ratio, moisture uptake studies, in-vitro dispersion time, disintegration test, determination of drug content, *in-vitro* drug release dissolution test, *in-vitro* drug release kinetic study and stability study. The flow properties of powder blend were evaluated in terms of carr's index, hausner's ratio and angle of repose. All the blend powders exhibited good flow properties. The physical properties (i.e., weight, thickness, hardness, friability, water uptake capacity, swelling ratio, disintegration time and drug content) of compressed gastroretentive tablet were studied. The tablet was varies from 0.210 to 0.213 cm in diameter and 0.191 to 0.192 cm in thickness, average weight was varies from 812.9 to 817.6 mg, hardness was varies from 5.22 to 5.32 kg / cm^2, friability was varies from 0.42 to 0.49 %, disintegration time was varies from 1.04 to 1.18 hr and drug content was varies from 98.0 to 98.8 % for for AOT1 to AOT2. The release of drug from the antidiabetic tablets was influenced significantly by the variation of excipents of tablet in dissolution media. This was evidenced by the whole amount of drug released from tablets through direct compression tablets. The preliminary and screening studies were performed using different polymers and the polymers citric acid, sodium bicarbonate, HPMC, promised excellent properties for controlled release and muco-adhesion. Using selected polymers, the final batches were prepared by direct compression method and were evaluated for buoyancy lag time and total buoyant time, swelling index, drug content, ex-vivo mucoadhesive strength, in-vitro dissolution study [17]. The formulation AOT3 was found to be the best formulations in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer-Peppas and Higuchi's equation. The regression coefficient (r^2) value of various models was found to be non-fickinon drug release diffusion mechanism and followed supercase II transport mechanism respectively.

Table 2: The various parameters of compressed targeted tablet

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner Ratio	Angle of Repose
AOT1	0.149	0.133	15.63	1.12±0.021	24.1±0.187
AOT2	0.176	0.167	16.45	1.23±0.015	24.5±0.102
AOT3	0.165	0.158	13.45	1.16±0.012	24.1±0.103
AOT4	0.162	0.153	15.35	1.19±0.011	26.3±0.112
AOT5	0.169	0.158	14.63	1.16±0.011	22.1±0.102
AOT6	0.171	0.161	14.21	1.13±0.011	23.4±0.111
AOT7	0.168	0.161	15.12	1.19±0.012	22.9±0.121
AOT8	0.173	0.164	16.02	1.15±0.014	23.8±0.131
AOT9	0.168	0.162	14.25	1.21±0.021	25.2±0.114

Table 3: The various parameters of compressed targeted tablet

Formulation code	Weight variation (mg)	Thickness (cm)		Hardness (kg/cm²)	Friability (%)	Disintegration Time (h)	Swelling Index (%)	Percent Drug content (%)
		Diameter	Thickness					
AOT1	822.9±6.00	0.211±0.003	0.192±0.002	5.27	0.44	1.04	150.23	98.2±0.89
AOT2	827.6±6.22	0.213±0.002	0.191±0.002	5.29	0.45	1.11	159.55	98.8±1.01
AOT3	823.6±6.80	0.210±0.001	0.193±0.001	5.28	0.43	1.18	156.17	98.1±1.22
AOT4	827.6±5.75	0.212±0.001	0.192±0.001	5.29	0.49	1.11	158.18	98.7±0.92
AOT5	823.5±6.26	0.213±0.001	0.191±0.001	5.32	0.47	1.12	157.62	98±0.58
AOT6	819.2±6.17	0.211±0.002	0.192±0.002	5.27	0.42	1.08	156.71	98.7±0.09
AOT7	821.1±6.01	0.212±0.003	0.193±0.002	5.38	0.46	1.16	157.58	98.4±0.11
AOT8	824.3±6.02	0.210±0.002	0.192±0.003	5.34	0.43	1.15	156.59	98.6±0.13
AOT9	826.2±6.21	0.212±0.002	0.193±0.002	5.29	0.47	1.11	156.25	98.3±0.12

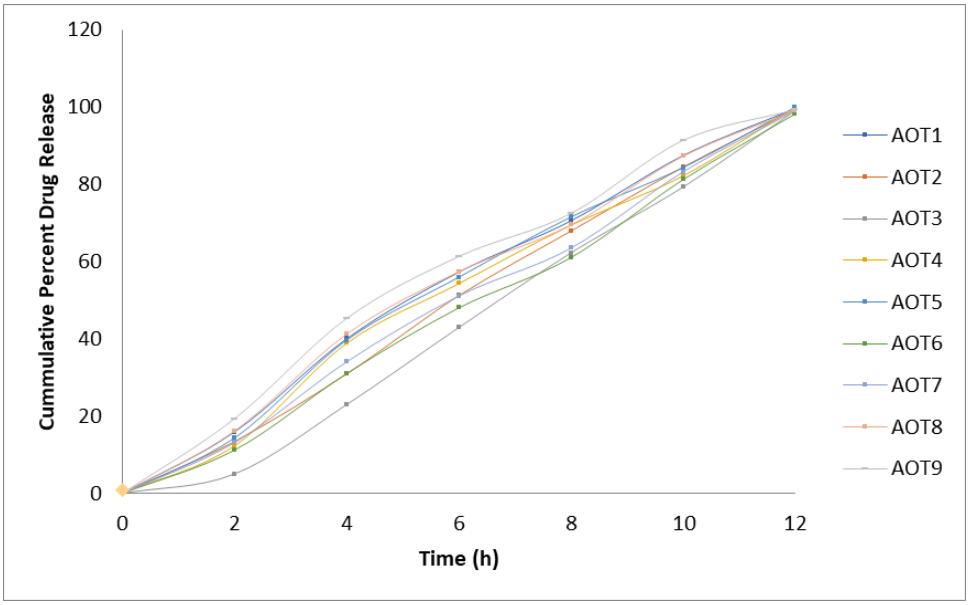

Figure 1: Zero-order kinetic plot of the prepared various compressed gastroretentive tablet (AOT1-AOT9)

Summary and Conclusion

The antidiabetic tablets were influenced significantly by the variation of excipents of tablet in dissolution media. This was evidenced by the whole amount of drug released from tablets through direct compression tablets. The preliminary and screening studies were performed using different polymers and the polymers citric acid, sodium bicarbonate, HPMC, promised excellent properties for controlled release and muco-adhesion. Using selected polymers, the final batches were prepared by direct compression method and were evaluated for buoyancy lag time and total buoyant time, swelling index, drug content, ex-vivo mucoadhesive strength, in-vitro dissolution study. The formulation AOT3 was found to be the best formulations in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation. The regression coefficient (r^2) value of various models was found to be non-fickinon drug release diffusion mechanism and followed supercase II transport mechanism respectively.

References

1. Robin Warren, J.; Marshall, B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983, 321, 1273–1275.

2. Wroblewski, L.E.; Peek, R.M.; Wilson, K.T. Helicobacter pylori and Gastric Cancer: Factors That Modulate Disease Risk. Clin. Microbiol. Rev. 2010, 23, 713–739. [Google Scholar] [CrossRef] [PubMed]
3. Suzuki, H.; Moayyedi, P. Helicobacter pylori Infection in Functional Dyspepsia. Nat. Rev. Gastroenterol. Hepatol. 2013, 10, 168–174.
4. Fong, I.W. Helicobacter pylori Infection: When Should It Be Treated? In Current Trends and Concerns in Infectious Diseases; Springer International Publishing: Cham, Switzerland, 2020; pp. 81–102. ISBN 978-3-030-36966-8.
5. Gravina, A.G.; Zagari, R.M.; De Musis, C.; Romano, L.; Loguercio, C.; Romano, M. Helicobacter pylori and Extragastric Diseases: A Review. World J. Gastroenterol. 2018, 24, 3204–3221.
6. Malfertheiner, P.; Megraud, F.; O'Morain, C.A.; Gisbert, J.P.; Kuipers, E.J.; Axon, A.T.; Bazzoli, F.; Gasbarrini, A.; Atherton, J.; Graham, D.Y.; et al. Management of Helicobacter pylori Infection—The Maastricht IV/ Florence Consensus Report. Gut 2012, 61, 646–664.
7. International Agency for Research on Cancer; World Health Organization. Schistosomes, Liver Flukes and Helicobacter Pylori; IARC: Lyon, France, 1994; ISBN 9283212614.
8. Al Mutawa, O.A.; Izhari, M.A.; Alharbi, R.A.; Sindi, A.A.A.; Alqarni, A.M.; Alotaibi, F.E.; Gosady, A.R.A.; Dardari, D.M.M.; Almutairi, A.M.; Alshehri, M.; et al. Helicobacter pylori (H. pylori) Infection-Associated Anemia in the Asir Region, Saudi Arabia. Diagnostics 2023, 13, 2404.
9. Lu, C.; Yu, Y.; Li, L.; Yu, C.; Xu, P. Systematic Review of the Relationship of Helicobacter pylori Infection with Geographical Latitude, Average Annual Temperature and Average Daily Sunshine. BMC Gastroenterol. 2018, 18, 50.
10. Usarov, K.; Ahmedov, A.; Abasiyanik, M.F.; Ku Khalif, K.M.N. Forecasting of Infection Prevalence of Helicobacter pylori (H. pylori) Using Regression Analysis. IIUM Eng. J. 2022, 23, 183–192.
11. Lehours, P. Actual Diagnosis of Helicobacter pylori Infection. Minerva Gastroenterol. Dietol. 2018, 64, 267–279.
12. Li, Y.; Choi, H.; Leung, K.; Jiang, F.; Graham, D.Y.; Leung, W.K. Global Prevalence of Helicobacter pylori Infection between 1980 and 2022: A Systematic Review and Meta-Analysis. Lancet Gastroenterol. Hepatol. 2023, 8, 553–564.
13. Hooi, J.K.Y.; Lai, W.Y.; Ng, W.K.; Suen, M.M.Y.; Underwood, F.E.; Tanyingoh, D.; Malfertheiner, P.; Graham, D.Y.; Wong, V.W.S.; Wu, J.C.Y.; et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology 2017, 153, 420–429.
14. Chen, Y.-C.; Malfertheiner, P.; Yu, H.-T.; Kuo, C.-L.; Chang, Y.-Y.; Meng, F.-T.; Wu, Y.-X.; Hsiao, J.-L.; Chen, M.-J.; Lin, K.-P.; et al. Global Prevalence of Helicobacter pylori Infection and Incidence of Gastric Cancer between 1980 and 2022. Gastroenterology 2024, in press.
15. Butt, J.; Epplein, M. How Do Global Trends in Helicobacter pylori Prevalence Inform Prevention Planning? Lancet Gastroenterol. Hepatol. 2023, 8, 498–499.
16. Öztekin, M.; Yılmaz, B.; Ağagündüz, D.; Capasso, R. Overview of Helicobacter pylori Infection: Clinical Features, Treatment, and Nutritional Aspects. Diseases 2021, 9, 66.
17. Farinha, P.; Gascoyne, R.D. Helicobacter pylori and MALT Lymphoma. Gastroenterology 2005, 128, 1579–1605.