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OPTIMIZATION AND EVALUATION OF CLARITHROMYCIN FLOATING TABLET USING DIFFERENT NOVEL POLYMERS

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ABSTRACT

H. pylori is a substantial contributor to peptic ulcers Getting the antibiotic into the stomach right away is one way to increase the effectiveness of the H. pylori eradication process. The creation of hydrodynamically balanced devices or floating drug delivery systems can accomplish this. This study deals with optimization and evaluation of clarithromycin floating tablet using different novel polymers. The formulation & evaluation of floating tablet was performed according to standard protocol. Results showed that, the formulation AF3 was specifically analysed to study the effect of hardness on floating lag time, revealing that increasing hardness led to an increase in floating lag time due to reduced porosity. Regarding in-vitro dissolution, batch AF3 containing HPMC K15M demonstrated a favourable drug release rate compared to the other batches. Clarithro ER indicated that the optimized formulation AF3 offered superior control over the release rate. Consequently, it was concluded that formulation AF3 containing HPMC K15M displayed a better-controlled drug release rate compared to other polymers.

Keywords: Ulcer, *H. pylori*, Gastro retentive drug delivery system, Floating tablet, Clarithromycin, HPMC K15M, Novel polymers

INTRODUCTION

In many people all over the world, H. pylori is a substantial contributor to peptic ulcers. The primary course of treatment for patients with active H. pylori-infected duodenal or gastric ulcers is antibiotic therapy. However, because of H. pylori's particular traits, complete eradication of the infection is difficult. The bacterium is found in the gastric mucous gel, which prevents antimicrobial medications from reaching the infection site through the stomach lumen or the gastric blood supply. Therapeutic drugs must penetrate the gastric mucus layer to interfere with the colonization mechanism in the stomach environment in order to effectively cure the illness (Suerbaum and Michetti, 2002; Goodwin *et al*., 1997).

Getting the antibiotic into the stomach right away is one way to increase the effectiveness of the H. pylori eradication process. The creation of hydrodynamically balanced devices or floating drug delivery systems can accomplish this.

Drugs with poor solubility and low stability in intestinal fluids can be administered using floating drug delivery systems (FDDS), which were developed to keep the medicine in the stomach. Making the dose form less dense than the gastric juices allows it to float on them, which is the principle underpinning FDDS. FDDS are hydrodynamically

controlled low-density systems that have enough buoyancy to float over the contents of the stomach and stay buoyant there without significantly slowing down the gastric emptying process. With the drug's release, the stomach's residual system is emptied. This improves stomach residence time and provides stable plasma medication concentrations as a result (Arora *et al*., 2005; Shah *et al*., 2009).

The concept of buoyant preparation offers a straightforward and useful method for extending the dosage form's stay in the stomach and ensuring prolonged medication release. Under certain conditions, it is preferable to prolong the stomach retention of a delivery system to increase the therapeutic efficacy of the pharmacological component. For instance, medications with limited solubility and those that degrade in an alkaline pH are effective in extending gastric retention. These drugs also exhibit greater absorption at the proximal section of the gastrointestinal tract. Additionally, prolonging gastric retention of the therapeutic moiety allows for sustained drug delivery to the stomach and proximal small intestine in the treatment of some ulcerative conditions. This has a number of benefits, including increased bioavailability and therapeutic efficacy with decreased dosing frequency (Chandel *et al*., 2012; Singh and Kim, 2000).

Preparing gastroretentive medication delivery devices has been approached in a variety of ways. These include sachet systems, gel-forming fluid or suspension systems, high-density systems, bioadhesive systems, altered shape systems, and floating systems. In order to accomplish more than just lengthen a drug's effective release period, floating drug delivery formulations and the polymers employed in these systems have evolved significantly. Current floating drug release systems, for instance, are capable of adapting to changes in the biological environment and delivering or ceasing to deliver medications in response to these changes. Tablets, capsules, microparticles, and other materials have been used to create floating drug delivery systems (FDDS), which should result in targeted delivery systems, in the stomach (Namdev and Jain, 2019; Patil *et al*., 2006).

To concentrate drug delivery at the stomach area of the GI tract, polymers are utilized in floating systems. The floating drug delivery system makes use of both synthetic and natural polymers. Natural polymers including guar gum, chitosan, xanthan gum, gellan gum, sodium alginate, etc. are employed in floating systems. HPMC, Eudragit, ethyl cellulose, and other artificial polymers are utilized for the floating medication delivery (Prajapati *et al*., 2011).

A macrolide antibiotic called clarithromycin is used to treat many different bacterial infections, including acute otitis, tonsillitis, pharyngitis, respiratory tract infections, simple skin infections, and helicobacter pylori infections. By attaching to the bacterial 50S ribosomal subunit, clarithromycin, a semi-synthetic macrolide antibiotic developed from erythromycin, prevents bacteria from synthesizing proteins. During translation and protein synthesis, binding prevents peptidyl transferase activity and obstructs amino acid translocation. Depending on the organism and drug concentration, clarithromycin may have bacteriostatic or bactericidal effects (Peters

and Clissold, 1992). This study deals with optimization and evaluation of clarithromycin floating tablet using different novel polymers.

MATERIALS & METHODS

Chemicals & reagents

HPMC K4M, HPMC K15M, Chitosan, Sodium bicarbonate, Lactose (Monohydrate), agnesium Stearate, Hydrochloric Acid were also obtained from Kopran Ltd. Mumbai.

Formulation of Clarithromycin Tablet

Floating matrix tablets containing Clarithromycin were prepared by direct compression technique using varying concentrations of different grades of polymers with sodium bicarbonate. All the ingredients except magnesium stearate were blended in glass mortar uniformly. After sufficient mixing of drug as well as other components, magnesium stearate was added and further mixed for additional 2-3 minutes. The tablets were compressed with 13mm punch using hydraulic press. The weight of the tablets was kept constant for formulations F1 to F10.

Evaluation of Hydrodynamically Balanced Tablets

Shape of Tablets

Directly compressed tablets were examined under the magnifying lens for the shape of the tablet.

Tablet Dimensions

Thickness and diameter were measured using a calibrated dial caliper. Three tablets of each formulations were picked randomly and thickness was measured individually.

Thickness

The dimensions of the tablet like thickness, length were measured using vernier- calipers. Ten tablets were selected randomly for this test and the average value was reported.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets were determined using Monsanto hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the same tablets from each tablets was determined.

Friability test

The friability of tablets were determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The % friability was then calculated by dividing initial weight minus final weight divided by initial phase multiplied by 100 (Park *et al*., 2000).

Weight variation test

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation is allowed in the weight of a tablet by U.S. Pharmacopoeia. The following percentage deviation in weight variation is allowed. In all formulations, the tablet weight is more than 324mg, hence 5% maximum difference allowed.

Test for Content Uniformity

Tablet containing 500mg of drug is dissolved in 100ml of 0.1N HCl taken in volumetric flask. The drug is allowed to dissolve in the solvent. The solution was filtered, 1ml of filtrate was taken in 50ml of volumetric flask and diluted up to mark with 0.1N HCl and analysed spectrophotometrically at 203nm. The concentration of Clarithromycin in mg/ml was obtained by using standard calibration curve of the drug. Claimed drug content was 500mg per tablet. Drug content studies were carried out in triplicate for each formulation batch (Joseph et al., 2002).

Tablet Density

Tablet density is an important parameter for floating tablets. The tablet will only float when its density is less than that of gastric fluid (1.004).

Buoyancy / Floating Test

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Swelling Study

The swelling behaviour of a dosage form is measured by studying its weight gain or water uptake. The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time.

Effect of hardness on Buoyancy Lag Time (BLT) or Floating Lag Time (FLT)

Formulation F2 was selected to study the effect of hardness on buoyancy lag time. The tablets of batch F2 were compressed at three different compression pressures to get the hardness of 5kg/cm2, 7kg/cm2 and 9kg/cm2. The tablets were evaluated for Buoyancy Lag Time. The method followed is same as that of Buoyancy test.

***In-vitro* dissolution Study**

In-vitro release studies were carried out using USP XXIII dissolution test apparatus. 900ml of 0.1N HCl (pH 1.2) was filled in dissolution vessel and the temperature of the medium was set at 37^0C□0.10^0C. For the study ring/mesh assembly was used. The tablet was put inside the ring assembly and placed inside the dissolution vessel. The speed was set at 50 rpm. 1ml of sample was withdrawn at predetermined time intervals for 8 hours and same volume of fresh medium was replaced. The samples were analyzed for drug content against 0.1N HCl as a blank at□□max 203nm using U.V. spectrophotometer.

Curve fitting analysis:

The mechanism of Clarithromycin released from the matrix system was studied by fitting the dissolution data obtained to following equation.

1. Korsmeyer – Peppas equation
2. Zero order equation
3. Higuchi square root equation

Comparison with commercial marketed product

The promising formulation was compared with marketed product formulation by

checking various physicochemical parameters.

Stability study

The optimum formulation was tested for a period of 12 weeks at 40c with 75% rh for drug content and other parameters.

RESULTS AND DISCUSSION

The tablets from each formulation batch showed circular shape with no cracks. The average thickness of the tablets (n=3) was found to be consistent across all five formulations, ranging from 5.13mm to 5.18mm. Similarly, the tablet diameter ranged between 12.98 mm to 12.99 mm. Hradness of tablet was found between 4.1 to 4.7 kg/cm^2. The % friability was found less than 1% in all the formulations which ensure good mechanical strength of tablet. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. Drug content was found between 97.20% to 99.60% of Clarithromycin, which was within acceptable limits. Further all batches of formulated tablets exhibited a density lower than that of the gastric fluid (1.004g/cm^3). Formulation F3, which contained HPMC K15M, exhibited a BLT of 49 seconds. In contrast, the formulations containing chitosan alone or in combination with HPMC K15M displayed the highest BLT and TFT, both of which were less than 12 hours. In conclusion, the tablets formulated with only HPMC polymers demonstrated superior floating behavior with extended BLT and TFT, while the presence of chitosan, either alone or in combination with HPMC K15M, resulted in decreased BLT and TFT due to challenges in entrapping the generated gas within the tablet's gel layer. This information highlights the importance of the polymer selection and gas-generating agent in achieving optimal buoyancy characteristics for such dosage forms.

Notably, among all the batches, tablets from batch F3 containing HPMC K15M with a nominal viscosity of 15,000 cps exhibited the highest swelling index. This indicates that the viscosity of the polymer played a significant role in the swelling process, matrix integrity, and floating capability of the tablets.

Further, tablets with hardness levels of 5kg/cm^2, 7kg/cm^2, and 9kg/cm^2 exhibited floating lag times of 104, 490, and 660 seconds, respectively. Batch F3, with a hardness of 4kg/cm^2, displayed a buoyancy lag time of 49 seconds.

Tablets from batches F1, F2, and F3, containing the same polymer amount but different grades (HPMC K4M, HPMC K15M, and a combination of both), showed drug release rates of 91.65%, 92.11%, and 90.43%, respectively. Overall, batch AF3 demonstrated the best control over drug release, suggesting that increased polymer viscosity resulted in reduced drug release rates.

Also, in the *in-vitro* dissolution study, Clarithro ER (500mg) released 92.31% of the drug within 10 hours. Formulation AF3, demonstrated better control over drug release with 90.43% released in the same 10-hour study. Overall, AF3 exhibited excellent drug content uniformity and improved drug release control over the marketed product. Additionally, Fioating tablets of clarithromycin (AF3) were stable under these conditions at least for three months.

Table 1: Formulation of Hydrodynamically Balanced Tablets of Clarithromycin (in mgs)

Ingredients(in mgs)	AF1	AF2	AF3	AF4	AF5	AF6	AF7	AF8	AF9	AF10
Clrithromycin	500	500	500	500	500	500	500	500	500	500
HPMC K 15M	-	-	200	-	-	100	-	100		100
HPMC K 10M	-	200	-	-	100	-	-	100	100	
HPMC K 4 M	200	-	-	-	100	100	100	-	-	-
Chitosan	-	-	-	200	-	-	100	-	100	100
Sodium bicarbonate	75	75	75	75	75	75	75	75	75	75
Lactose	10	10	10	10	10	10	10	10	10	10
Mag.stearate	15	15	15	15	15	15	15	15	15	15

Table 2: Physical properties of tablets of batch AF1 to AF10

Batch	Diameter	Thickness	Hardness	Friability	Weight variation	Drug content
AF1	12.99 ±0.04	5.16 ±0.01	4.7 ±0.47	0.40	800.63 ±1.28	97.20
AF2	12.98 ±0.01	5.15 ±0.03	4.4 ±0.2	0.41	800.42 ±1.13	98.35
AF3	12.98 ±0.006	5.15 ±0.02	4.4 ±0.33	0.35	800.51 ±1.73	99.60
AF4	12.98 ±0.07	5.16 ±0.02	4.3±0.41	0.37	800.04 ±1.36	97.38
AF5	12.98 ±0.04	5.14 ±0.02	4.2±0.42	0.36	801.11 ±1.12	99.38
AF6	12.99 ±0.067	5.13 ±0.06	4.1±0.54	0.39	799.52 ±1.20	98.02
AF7	12.98 ±0.05	5.16 ±0.06	4.1±0.32	0.41	799.86 ±1.64	99.23
AF8	12.99 ±0.06	5.14 ±0.02	4.3±0.62	0.36	800.05 ±1.14	98.67
AF9	12.98 ±0.02	5.16 ±0.03	4.4±0.41	0.39	800.62 ±1.39	98.99
AF10	12.98 ±0.056	5.18 ±0.01	4.5±0.35	0.38	801.63 ±1.50	98.38

Table 3: Tablet Density, Buoyancy Lag Time, Total Floating Time

Batch	Tablet density	Buoyancy lagtime (sec)	Total floating time(Hrs)
AF1	0.94	61	>12
AF2	0.87	55	>12
AF3	0.81	50	>12
AF4	0.98	132	>6
AF5	0.86	59	>12
AF6	0.88	56	>12
AF7	0.96	124	>7
AF8	0.85	117	>12
AF9	0.94	108	>9
AF10	0.91	101	>10

Table 4: Swelling Index of Tablets of Batch AF1 to AF10

Time in Hrs	AF1	AF2	AF3	AF4	AF5	AF6	AF7	AF8	AF9	AF10
1	29	30	32	30	29	30	28	31	31	32
2	45	46	47	42	44	42	45	47	48	46
3	60	62	63	61	61	62	61	61	62	62
4	80	80	82	74	78	80	78	82	82	81
5	91	92	94	87	90	91	87	91	92	93

Table 5: Effect of Hardness on Buoyancy Lag Time of Batch AF3

Hardness in kg/cm^2	Buoyancy Lag Time (sec)
$4kg/cm^2$	52
$5kg/cm^2$	104
$7kg/cm^2$	490
$9kg/cm^2$	660

Table 6: Cumulative % Drug Released from Tablet Formulations F1 to F10

Time in Hrs	AF1	AF2	AF3	AF4	AF5	AF6	AF7	AF8	AF9	AF10
1	23.51	22.64	21.70	26.24	22.96	22.64	25.94	22.45	24.73	24.41
2	31.43	32.97	32.54	49.67	33.65	34.34	50.57	32.52	40.47	39.72
3	46.56	46.35	47.87	58.43	48.24	48.72	64.27	48.28	58.84	58.62
4	59.53	57.59	54.12	68.56	57.57	57.78	70.81	55.58	64.71	62.28
5	71.20	66.41	63.14	82.98	66.12	65.84	84.53	65.39	74.59	72.17
6	74.67	72.28	69.45	98.24	71.24	70.38	92.75	68.47	80.28	78.47
7	81.12	76.67	74.85		78.98	77.51	98.42	76.52	89.69	86.53
8	82.76	81.12	79.34		81.79	78.20		80.47	94.35	89.26
9	90.89	89.43	85.35		88.97	87.36		84.91	99.43	93.74
10	91.65	92.11	90.43		92.64	91.95		91.93		97.31

Table 7: Comparison of Optimization formulation AF3 with marketet product

Time in Hrs	F3	Marketed product
1	21.70	25.31
2	32.54	35.25
3	47.87	49.63
4	56.12	60.47
5	63.14	67.65
6	69.45	75.74
7	74.85	79.96
8	79.34	82.94
9	85.35	91.70
10	90.43	93.31

Table 8: *In-vitro* drug release study

Time in hours	√ T	Log T	Cumulative % drug release	Cumulative % drug remain	Log cumulative % drug release	Log cumulative % drug remain
0	0	0	0	100	0	2
1	1.0	0	22.70	77.3	1.356	1.888
2	1.414	0.301	33.54	66.46	1.525	1.809
3	1.732	0.477	46.87	53.13	1.670	1.725
4	2.0	0.602	55.12	44.88	1.741	1.652
5	2.236	0.698	64.14	35.86	1.807	1.554
6	2.449	0.778	70.45	29.55	1.847	1.470
7	2.645	0.845	75.85	24.15	1.879	1.382
8	2.828	0.903	80.34	19.66	1.904	1.293
9	3.0	0.954	86.35	13.65	1.936	1.135
10	3.162	1.0	91.43	8.57	1.961	0.932

Table 9: Kinetic studies of optimum formulation AF3

Time in hours	√ T	Log T	Cumulative % drug release	Cumulative % drug remain	Log cumulative % drug release	Log cumulative % drug remain
0	0	0	0	100	0	2
1	1.0	0	22.70	77.3	1.356	1.888
2	1.414	0.301	33.54	66.46	1.525	1.809
3	1.732	0.477	46.87	53.13	1.670	1.725
4	2.0	0.602	55.12	44.88	1.741	1.652
5	2.236	0.698	64.14	35.86	1.807	1.554

6	2.449	0.778	70.45	29.55	1.847	1.470
7	2.645	0.845	75.85	24.15	1.879	1.382
8	2.828	0.903	80.34	19.66	1.904	1.293
9	3.0	0.954	86.35	13.65	1.936	1.135
10	3.162	1.0	91.43	8.57	1.961	0.932

Table 10: Characteristics of optimized tablet

	Drug Content (%) ±SD	**Hardness (Kg/cm^2) ±SD**	**Floating behaviour**	
			Floating lag time (sec)	**Floating duration (hrs)**
After one month	88.24 ±0.12	4.3 ±0.32	51	12
After two months	88.04 .±0.23	4.±0.43	54	12
After three months	87.87 ±0.26	4.46 ±0.36	60	11

CONCLUSION

In the current study, Gastroretentive delivery systems of Clarithromycin were successfully developed as Hydrodynamically Balanced Tablets to enhance local action and ultimately improve bioavailability. The tablets were formulated using various grades of polymers (HPMC K4M, HPMC K15M, and Chitosan) along with an effervescing agent (NaHCO3). The formulation AF3 was specifically analyzed to study the effect of hardness on floating lag time, revealing that increasing hardness led to an increase in floating lag time due to reduced porosity. Regarding in-vitro dissolution, batch AF3 containing HPMC K15M demonstrated a favorable drug release rate compared to the other batches containing chitosan, HPMC K4M, and HPMC K10M, which were unable to sustain their release for up to 10 hours. Furthermore, a comparison study with the marketed product Clarithro ER indicated that the optimized formulation AF3 offered superior control over the release rate. Consequently, it was concluded that formulation AF3 containing HPMC K15M displayed a better-controlled drug release rate compared to other polymers, and the release rate decreased as the viscosity of the polymer increased.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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