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Original Research Article

DESIGNING AND PERFORMANCE EVALUATION OF CLARITHROMYCIN BIOADHESIVE TABLET

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Abstract: The objective of present research work was to design and evaluate bioadhesive tablets of clarithromycin. Tablets were prepared by wet granulation technique and evaluated for pre-compression as well as post compression parameters. Different formulation batches (C1-C6) were prepared and evaluated for characteristics parameters like hardness, friability, drug content, weight variation etc. Tablets were also evaluated for bioadhesive strength, and in vitro release profile. Further data obtained from in vitro release study was subjected to release kinetics. Results suggested that batch C1 showed controlled release with excellent bioadhesive strength.

Key words: Bioadhesive, Controlled release, Granulation, Compression, Release kinetic

Introduction: The oral route of administration still persists to be the most prefer route due to its assorted advantages comprise ease of ingestion, pain averting, adaptability and most importantly patient conformity. Out of them the most popular dosage forms being tablets and capsules[1-2].Tablets are the solid dosage forms usually prepared with the aid of suitable pharmaceutical excipients [2].

Bioadhesive drug delivery systems are those systems having a bulk density less than that of the gastric fluids and thus these systems remain buoyant for a prolonged period of time in the stomach without being affected by the gastric emptying rate. The drug is released slowly at the desired rate from the system and after release of the drug; the residual system is emptied from the stomach [3]. Most of the bioadhesive systems previously reported are single unit systems such as tablets and capsules. Helicobacter pylori (H. pylori) infection is the causative organism in chronic active gastritis, duodenal ulcers and gastric adenocarcinoma [4]. This bacterium is highly adapted for colonization in the human stomach; the majority of these bacteria are free living in the gastric mucus layer although about 20% is in close contact with epithelial cells [5]. Antimicrobial

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resistance, patient's poor compliance with the antibiotic regimen, and drug-related side effects are said to be the major problems with eradication of H. pylori [6]. Clarithromycin is a new semi-synthetic antimicrobial 14-membered macrolide exhibiting a broad *in vitro* antibacterial spectrum. Clarithromycin appears to have more activity against *Mycoplasma pneumoniae* and *Chlamydia trachomatis*. Furthermore, clarithromycin (in combination with its microbiologically active metabolite, 14-hydroxyclarithromycin) has shown an additive or even synergistic activity against Haemophilus injluenzae, a species that often is resistant of intermediate susceptibility to erythromycin. The 14-hydroxy-clarithromycin itself is twice as active as the parent compound [7-8].

Materials and Methods

Materials: Clarithromycin was obtained as drug sample. Carbapol, Sodium alginate, SCMC, Magnesium stearate, Talc and Lactose all ingredients were of analytical grade and purchased from Loba Chemie, Mumbai, India.

Preparation of bioadhesive tablets by wet granulation technique

Clarithromycin, SCMC, Sodium Alginate, carbopol 974P and lactose were blended homogeneously in mortar as the quantity given in Table 1. Blended mixture was passed through the 60 Sieve and magnesium stearate 1% was added and blended. The homogeneously blended mixture was compressed in rotary tablet press with the 13.7 mm flat punch [9-11].

Table 1 Formulation of Clarithromycin bioadhesive tablets

Ingredients	CB1	CB2	CB3	CB4	CB5	CB6
Clarithromycin	250	250	250	250	250	250
Carbapol	115	130	-	-	-	-
Sodium alginate	-	-	115	130	-	-
SCMC	-	-	-	-	115	130
Magnesium stearate	10	10	10	10	10	10
Talc	10	10	10	10	10	10
Lactose	65	50	65	50	65	50

Evaluation of the pre-compression parameters of powder mixtures:

Pre-compression parameters like bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio were carried out [12].

Evaluation of bioadhesive clarithromycin tablets: Evaluation was performed to assess the physiochemical properties and release characteristics of developed formulation.

Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined [13-15].

Friability: Roche friabilator was used for testing the friability. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined [6].

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Weight variation: Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated [16].

Drug content: Ten tablets were weighed and powdered and 500 mg equivalent weight of clarithromycin was accurately weighed and transferred into a 100 ml volumetric flask. It was dissolved and made up the volume with 0.1N HCL pH 1.2. Subsequently the solution in volumetric flask was filtered and suitable dilutions were made and analyzed at 275 nm using UV-Visible spectrophotometer (Shimadzu UV-1601). The drug content of each sample was estimated from standard curve of clarithromycin using 0.1N HCL pH 1.2 [17-19].

Results and discussion

Pre-compression parameters of powder mixtures: The angle of repose of the powder mixture for all formulations (CB1–CB6) ranged from 23.50 to 25.32 indicating excellent flow properties [20-25]. Bulk and tapped density of the powder mixture for all formulations varied from 0. 4252 to 0.4717gm/cm3 and from 0.5156 to 0. 5633 gm/cm^3, respectively. Compressibility indices ranged from 14.15 to 16.29. The results of flow properties are acceptable for granules [26].The values of compressibility indices further confirmed the good compressibility of the prepared granules [13].

Table 2 Micrometric study of Clarithromycin bioadhesive tablets

Formula code	Angle of repose (θ)	Bulk density gm/ml	Tapped density gm/ml	Carr's index %
CB1	23.50±1.41	0.4717±0.014	0.5124±0.052	15.15±0.87
CB2	23.62±1.42	0.4218±0.033	0.5633±0.027	14.15±0.79
CB3	25.32±1.51	0.4314±0.031	0.5491±0.047	16.29±1.32
CB4	25.03±1.25	0.4653±0.026	0.5547±0.053	15.81±0.43
CB5	24.07±1.51	0.4252±0.052	0.5156±0.045	15.43±0.41
CB6	25.30±1.08	0.4537±0.042	0.5502±0.010	17.53±1.37

All values are mean of 3 readings ± standard deviation

Post-compression parameters for tablets: Concerning appearance, the bioadhesive tablets were whitish-buff or white in color, all were round concave, with smooth surface in both sides and no visible cracks were observed.

The mean diameter of bioadhesive tablets was 13.06± 0.0 mm while mean thickness ranged from 6.5 to 7.5 mm. Mean hardness was in the range of 7.02 Kg/cm^2 indicating that the tablets are of sufficient strength to withstand physical abrasion [27]. The percentage friability for all formulations was less than 1% which is an indication of satisfactory mechanical resistance of the tablets [13]. The formulated tablets showed no evidence of capping, cracking, cleavage or breaking after being removed from the friabilator. The percentage of mean drug content ranged from 98.7–99.3% which met the standard pharmacopeial requirements (90–110%) [28]. Since the mixtures of powders used were free flowing, the obtained tablets were of uniform weight due to uniform die fill. The mean weight of formulated tablets was 450± 0.0 mg, (n= 20). The USP specification is generally ±5% [22]. This means that no difference was observed in the weight of individual bioadhesive tablets from the labeled weight indicating uniformity of weight.

Table 3 Postcompression study of formulated bioadhesive tablets

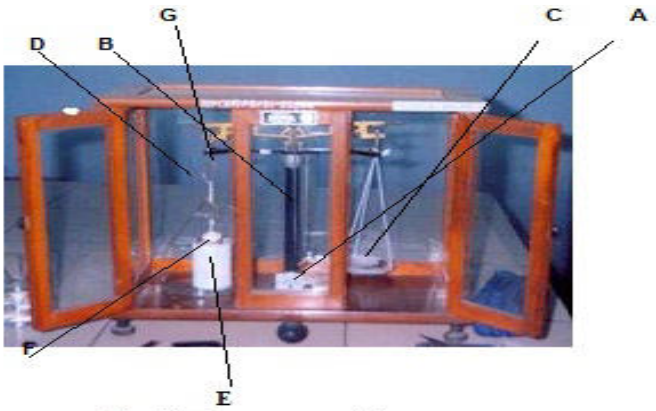
Formula code	Hardness Kg/cm^2	Friability % Loss	Weight variation mgs	Diameter mm	Drug content %	Thickness mm
CB1	6.5± 0.14	0.52± 0.42	450.25± 0.57	13.08± 0.02	99.24±0.63	5.23±0.062
CB2	6.8± 0.30	0.68± 0.45	450.76± 0.12	13.04± 0.03	98.97± 0.32	5.12±0.056
CB3	6.9± 0.45	0.64± 0.58	450.78± 0.34	13.09± 0.07	99.98± 0.43	5.42± 0.031
CB4	7.3± 0.35	0.85± 0.34	450.39± 0.19	13.07± 0.05	98.68± 0.09	5.64± 0.075
CB5	7.2± 0.84	0.76± 0.83	450.38± 0.99	13.09± 0.04	99.85± 0.21	5.73± 0.024
CB6	7.5± 0.42	0.60± 0.58	450.34± 0.41	13.07± 0.06	98.69± 0.13	5.84± 0.023

All values are mean of 3 readings ± standard deviation

***In-vitro* Bioadhesion Study:** Bioadhesive-strength of the tablet was measure on a modified physical-balance Fig. 1. This apparatus posses of a modified two pa ns physical-balance in which a lighter pan has replace the right-pan and left-pan has been replace by a Teflon-cylinder (height and diameter) hanged by copper-wire and Teflon-ring [28-30]. The left-side of the apparatus was precisely weighty than the right-side by 5 gms. Other Teflon-block of 3.8cms diameter and 2 cms height was designed, on one-side with a n upward protrusion of 2cms height and 1.5 cm diameters. This was kept in petridish, which was the n kept below the left-hand set o f the balances [29-30].

Bioadhesive strength

$$\text{Force of adhesion (N)} = \frac{\text{Bioadhesive strength}}{100} \times 9.81$$



Bioadhesion test assembly

FOOTNOTES

A – Scale,
B –Pointer,
C– Pan,
D – Teflon ring for balancing,
E – Teflon cylinder for sticking the tablet,
F – Teflon block with protrusion
G – Copper wire,

Fig.1 Bioadhesion test assembly

Table: 4 Bioadhesive strength of formulated tablets

Batch Code	Bioadhesive strength (g m) (Mean + S. D.)	Force of adhesion (N)
CB1	8.730 + 0 .239	0.856
CB2	8.270 + 0 .147	0.811
CB3	9.220 +0.152	0.904
CB4	9.750 + 0 .249	0.956
CB5	7.790 + 0 .339	0.764
CB6	14.250 + 0.296	1.398

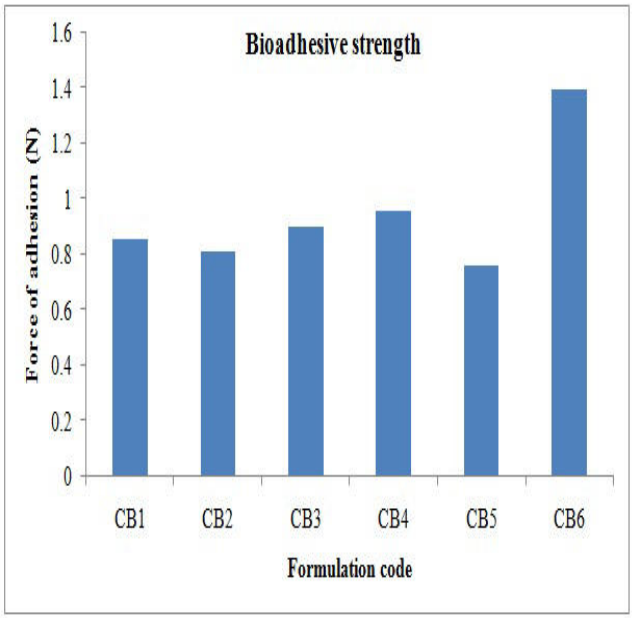


Fig. 2 Bioadhesive strength of formulated bioadhesive tablets

***In-vitro* release profile:** Drug release stud y *In-vitro* of Clarithromycin bioadhesive buccal tablets was done with the use of apparatus basket Type USP I a t 50 rpm. Medium of 500 ml phosphate buffer solution 6.8 pH and for maintaining sink condition 20% methanol was used for release rate study. Whole assembly was maintained at 37^0C throughout the study period. At the interval of 0.5, 1, 2 , 3 … up to 10 hrs, 5 ml of sample was withdrawn and maintained the sink condition with fresh medium. Then spectroscopically at 275 nm determined the amount of clarithromycin released [31-33].

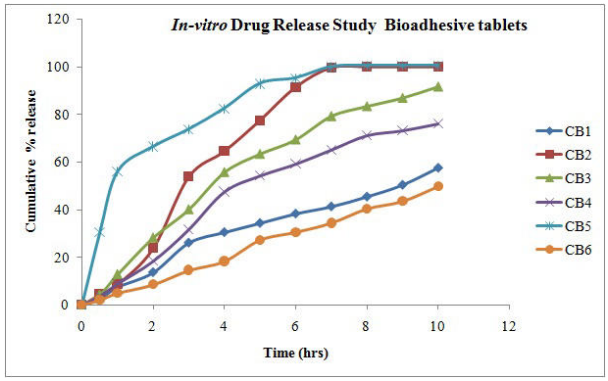


Fig.3 *In-vitro* drug release profile for bioadhesive tablets.

The release profiles of Clarithromycin from bioadhesive tablets are shown in Figure 3. Concerning effervescent formulations CB1, CB3 and CB5: Formula CB1 exhibited burst release since about 13.62% drug released in 2h. Whereas, formulae CB3 and CB5 released 28.15% and 66.44% Clarithromycin, respectively, in 2h.. Concerning effervescent formulations CB2, CB4 and CB6. Formula CB2 exhibited burst release since about 23.77% drug released in 2h. Whereas, formulae CB4 and CB6 released 18.41% and 8.47% Clarithromycin, respectively, in 2h.

Release Kinetics: The release kinetics of clarithromycin from bioadhesive tablets can be obtained from *in-vitro* release data were treated according to the model-dependent methods, zero order, first order, Higuchi model, Korsmeyer–Peppas model, Hixson–Crowell model and Weibull equation. Criteria for selecting the most appropriate model was based on best fit indicated by the value of coefficient of determination (R^2) nearer to 1 [11, 34-35].

Concerning CB1, CB2 and CB4 the highest values of R^2 were obtained after fitting the data into Peppas equation. The value of (n) allows the release to be characterized as either Fickian diffusion n 60.5, anomalous diffusion (non-Fickian) (0.5< n< 1) or zero-order release (n =1) [11-12]. The n values for CB2 and CB4 were 0.57 and 0.56 (Table 5) respectively, that indicated anomalous diffusion (non-Fickian) which refers to a combination of both diffusion and erosion controlled-drug release [22, 36]. Whereas, the value of (n) in case of CB1 (n = 0.37) revealed a Fickian diffusion mechanism of formulated bioadhesive tablets.

Table 5: Drug release Kinetics for bioadhesive tablets

Batch	Korsmeyer – Peppas			Matrix		Mechanism of drug Release	Release kinetics
	n	R^2	K	R^2	K		
CB1	0.3771	0.9981	31.1077	0.9811	24.7943	Fickian	Peppas
CB2	0.5737	0.9981	15.1110	0.9950	17.3367	Non-Fickian	Peppas
CB3	0.5714	0.9975	17.8613	0.9966	20.3088	Non-Fickian	Peppas
CB4	0.5675	0.9981	12.6702	0.9956	14.3660	Non-Fickian	Peppas
CB5	0.5380	0.9948	20.8757	0.9967	22.3909	Non-Fickian	Matrix
CB6	0.6997	0.9868	16.2306	0.9775	23.3020	Non-Fickian	Peppas

Conclusion: Clarithromycin bioadhesive-tablet formulation (CB1) offered controlled release and bioadhesive strength ranging from 7.79-14.25 gm. The optimized formula (CB1) showed the absence of interaction between drug and the used polymer/additives which confirmed the compatibility among its ingredients. *In vivo* studies can provide a definite proof that prolonged gastric residence could be obtained. Thus, the studied can be studied for the in-*vivo* correlation to study retention of tablet in the stomach of the volunteer over the tested period providing localized drug release.

References

1. Al Remawia M, Al-akayleh F, Salem M, Al Shami M, Badwan A. Application of excipient made from Chitosan-Xanthan as a single component for the controlled release of ambroxol tablet. *J Excipients Food Chem*. 2013, 4: 48–57.
2. Bano R, Gauhar S, Naqvi SBS, Mahmood S. Pharmaceutical evaluation of different brands of levofloxacin tablets (250 mg) available in local market of Karachi (Pakistan). *Int J Curr Pharm Res*. 2011, 3: 15–22.
3. Sharma S, Prashar M, Sahu RK. Floating drug delivery system: Incredible revolution. *Pharmacology online*. 2011, 3: 1039–1054.
4. Khalifa MM, Sharaf RR, Aziz RK. Helicobacter pylori: a poor man's gut pathogen. *Gut Pathog*. 2010, 2: 1–12.
5. Hessey S, Spencer J, Wyatt J, Sobala G, Rathbone B, Axon A, Dixon M. Bacterial adhesion and disease activity in Helicobacter associated chronic gastritis. *Gut* 1990, 31: 134–138.
6. Bardonnet P, Faivre V, Pugh W, Piffaretti J, Falson F. Gastroretentive dosage forms: overview and special case of Helicobacter pylori. *J Control Release*. 2006, 111: 1–18.
7. Basak S, Jayakumar Reddy B. Formulation and release behaviour of sustained release ambroxol hydrochloride HPMC matrix tablet. *Ind J Pharm Sci*. 2006, 68: 594–598.
8. Chinthala CSK, Kota KSR, Hadassah M, Metilda EH, Sridevi S. Formulation and evaluation of gastroretentive floating tablets of gabapentin using effervescent technology. *Int J Pharm Biomed Res*. 2012, 3; 202–208.
9. Christian V, Ghedia T, Gajjar V. A review on floating drug delivery system as a part of GRDDS. *Int J Pharm Res Dev*. 2011, 3: 233–241.
10. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. *Eur J Pharm Sci*. 2001, 13: 123–133.
11. Couto RO, Martins FS, Chaul LT, Conceicao EC, Freitas LAP, Bara MTF,

Paula JR. Spray drying of Eugenia dysenterica extract: effects of in-process parameters on product quality. *Revista Brasileira de Farmacognosia*. 2013, 23: 115–123.
12. Hadi MA, Babu VL, Pal N. Formulation and evaluation of sustained release matrix tablets of glimepiride based on combination of hydrophilic and hydrophobic polymers. *J Appl Pharm Sci*. 2012; 2: 101–107.
13. Rao NGR, Hadi MA, Panchal H, Reddy BM. Formulation and evaluation of biphasic drug delivery system of Montelukast sodium for chronotherapy. *World J Pharm Res*. 2012, 1: 757–775.
14. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol Pharm*. 2010, 67: 217–223.
15. Doodipala N, Palem C, Reddy S, Rao Y. Pharmaceutical development and clinical pharmacokinetic evaluation of gastroretentive floating matrix tablets of levofloxacin. *Int J Pharm Sci Nanotech*. 2011, 4: 1463–1469.
16. Garg A, Gupta M. Taste masking and formulation development & evaluation of mouth dissolving tablets of levocetrizine dihydrochloride. *J Drug Deliv Ther*. 2013, 3: 123–130.
17. Gisbert JP, Pajares JM. Treatment of Helicobacter pylori infection: the past and the future. *Eur J Intern Med*. 2010, 21: 357–359.
18. Gutie´rrez-Sa´nchez PE, Herna´ndez-Leo´n A, Villafuerte-Robles L. Effect of sodium bicarbonate on the properties of metronidazole floating matrix tablets. *Drug Dev Ind Pharm*. 2008, 34: 171–180.
19. Lara-Herna´ ndez B, Herna´ ndez-Leo´ n A, Villafuerte-Robles L. Effect of stearic acid on the properties of metronidazole/ methocel K4M floating matrices. *Braz J Pharm Sci*. 2009, 45: 497–505.
20. Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. *Int J Pharm*. 2003, 253: 13–22.
21. Hadi MA, Babu VL, Pal N. Formulation and evaluation of sustained release matrix tablets of glimepiride based on combination of hydrophilic and hydrophobic polymers. *J Appl Pharm Sci*. 2012, 2: 101–107.
22. Manivannan R, Chakole V. Formulation and development of extended release floating tablet of atenolol. *Int J Recent Adv Pharm Res*. 2011, 3: 25–30.
23. Mouzam MI, Dehghan M, Asif S, Sahuji T, Chudiwal P. Preparation of a novel floating ring capsule-type dosage form for stomach specific delivery. *Saudi Pharm J*. 2011, 19: 85–93.
24. Ishak RAH, Awad GAS, Mortada ND, Nour SAK. Preparation, in vitro and in vivo evaluation of stomach-specific metronidazole-loaded alginate beads as local anti-Helicobacter pylori therapy. *J Control Release*. 2007, 119: 207–214.
25. Jagdale SC, Agavekar AJ, Pandya SV, Kuchekar, BS, Chabukswar AR. Formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. *AAPS Pharm SciTech*. 2009, 10: 1071–1079.
26. Kassab NM, Amaral MS, Singh AK, Santoro MIRM. Development and validation of UV spectrophotometric method for determination of levofloxacin in pharmaceutical dosage forms. *Quı´m Nova* 2010, 33: 968–971.
27. Kitaoka H, Wada C, Moroi R, Hakusui H. Effect of dehydration on the formation of levofloxacin pseudopolymorphs. *Chem Pharm Bull*. 1995, 43: 649–653.
28. Lopes CM, Lobo JMS, Pinto JF, Costa P. Compressed mini-tablets as a biphasic delivery system. *Int J Pharm*. 2006, 323: 93–100.
29. Hajeri R, Amiji M. Stomach-specific anti-H. pylori therapy I: Preparation and

characterization of tetracycline a floating multiple-unit capsule, a density loaded chitosan microspheres. *Int J Pharm*. 2002, 235: 87-94.
30. Sawicki W. Pharmacokinetics of verapamil and norverapamil from controlled release floating pellets in humans. *Eur J Pharm Biopharm*. 2002, 53: 29-35.
31. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. *J Control Release*. 2003, 90: 143-62.
32. Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. *AAPS Pharm SciTech*. 2004, 5: 1-10.
33. Ponchel G, Irache J. Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. *Adv Drug Deliv Rev*. 1998, 34: 191-219.
34. Urquhart J, Theeuwes F. Drug delivery system comprising a reservoir containing a plurality of tiny pills. US Patent 4,434,153.1984 February 28.
35. Mamajek RC, Moyer ES. Drug-dispensing device and method. US Patent 4,207,890.1980 June 17.
36. Rednick AB, Tucker SJ. Sustained release bolus for animal husbandry. US Patent 3,507,952.1970 April 21.