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# Development and Evaluation of Clarithromycin Bilayer Tablet Using Synthetic and Natural Polymer

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**Vaishali Pardhe[1*], A.K Singhai[2], Rama Shukla[3], Nipuna Kumar Bhoi[1]**

*[1*] Research Scholar, Lakshmi Narain College of Pharmacy, Bhopal, M.P, India.*

*[2] Principal and Professor, Dept. of Pharmaceutics, Lakshmi Narain College of Pharmacy, Bhopal, M.P, India.*

*[3] Assistant Professor, Dept. of Pharmaceutics, Lakshmi Narain College of Pharmacy, Bhopal, M.P, India.*

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**ABSTRACT**

Bi-layer tablets have been amplified to reach controlled delivery of different drugs with pre-defined release profiles. Bilayer tablet is a new age with the successful production of controlled release formulation, along with various technologies to provide an effective drug delivery system. Bilayer tablets offer distinct points of interest over regular discharge detailing of similar medication. A few pharmaceutical organizations are now creating bi-layer tablets. For an assortment of reasons: patent augmentation, helpful, advertising to give some examples. To diminish capital speculation, frequently existing however altered tablet presses are utilized to create and deliver such tablets. The present research work was envisaged to develop bilayer tablets to improve therapeutic efficacy in the gastrointestinal tract. Natural polysaccharides and dried mucilage have been reported as an emulsifying, suspending agent, binding agent, disintegrating agent, and as a sustained-release matrix. They have been utilized in a variety of formulations like mucoadhesive, gastro retentive, colon-specific drug delivery systems.

## INTRODUCTION

Oral ingestion has for some time been the most helpful and usually utilized course of medication conveyance because of its simplicity of organization. Notably, changed discharge measurement structures may offer one or more advantages over immediate-release formulations of the same drug. Bilayer tablets can be a primary alternative to prevent chemical incompatibilities by the physical separation between Active Pharmaceutical Ingredients (APIs) and to allow the creation of specific product release profiles. [1]

The manufacture of bilayer tablets, produced by sequential compaction of loose powder layers has become of increased interest within the pharmaceutical industry due to the tailored release profiles of active ingredients that may be obtained. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as a loading dose and the second layer is the maintenance dose. In the case of bilayer tablets, drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity. [2,3]

**Advantages of the Bilayer Tablet:[4]**

1) It offers the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.

2) The cost is lower compared to all other oral dosage forms.

3) Lighter and compact also easy to swallow with the least tendency for hang-up.

4) Easiest and cheapest to pack and strip.

5) Suitable for large scale production.

6) Greatest chemical and microbial stability overall oral dosage forms.

7) Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

**Disadvantages of Bilayer Tablet:[5]**

1) Difficult to swallow in case of children and unconscious patients.

2) Some drugs resist compression into dense compacts, owing to amorphous nature, low-density character.

3) Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

4) Bitter testing drugs, drugs with an objectionable odor, or drugs that are sensitive to oxygen may require encapsulation or coating.

## MATERIALS AND METHODS

### Materials

Clarithromycin was a Gift sample from Bio plus Life Science, Bangalore. Polyvinylpyrrolidone was purchased from S. D. Fine Chem. Ltd., Mumbai. Talc, Lactose, Sodium Starch glycolate, Croscarmellose sodium, Crospovidone, Microcrystalline cellulose were obtained from Loba Chemie Pvt. Ltd Mumbai. Sodium bicarbonate was bought from Chem pure Pvt. Ltd. Magnesium stearate was bought from Jiangsu Huaxi International. HPMC was purchased from Ozone International, Mumbai. Citric acid was purchased from Qualigens fine chemicals, Mumbai.

### Methods

### Preparation of Instant Layer of Clarithromycin (Phase-1)

Clarithromycin Bilayer tablets were prepared by the direct compression method after incorporating different super disintegrates such as croscarmellose sodium (Ac-Di-Sol), crospovidone, and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in dry and clean mortar. Then the ingredients were passed through mesh #60. Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed. The composition of tablets is mentioned in Table No. 1.

**Method for Preparation of Clarithromycin SR Floating tablet**

**Table 1: Composition of Fast Dissolving Tablets**

| Ingredients(mg) | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | IF1 | IF 2 | IF 3 | IF 4 | IF 5 | IF 6 | IF 7 | IF 8 | IF 9 |
| Clarithromycin | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Sodium Starch glycolate | 10 | 20 | 30 | - | - | - | - | - | - |
| Croscarmellose sodium | | - | - | 10 | 20 | 30 | - | - | - |
| Crospovidone | | - | - | - | - | - | 10 | 20 | 30 |
| Microcrystalline cellulose | 75 | 65 | 55 | 75 | 65 | 55 | 75 | 65 | 55 |
| Talc | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Total weight | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |

Direct compression was followed to manufacture the gas generating floating tablets of Clarithromycin. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, & F9) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using it into the formulation. The amount and ratio of drug and polymers were weighed as per given in table No. 2 and all the formulation was used for further evaluation parameters.

**Table No. 2: Formulation of Fast Dissolving Tablets**

| Excipient (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Clarithromycin | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| HPMC K 4 | 40 | 60 | 80 | - | - | - | 20 | 30 | 40 |
| HPMC K 15 | - | - | - | 40 | 60 | 80 | 20 | 30 | 40 |
| PVP K30 | 15 | 15 | 15 | 15 | 15 | 15 | - | - | - |
| Xanthan gum | - | - | - | - | - | - | 10 | 15 | 20 |
| Gaur Gum | - | - | - | - | - | - | 5 | 10 | 15 |
| Citric acid | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| $NaHCO_3$ | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| $Mg(C18H35O2)2$ | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Lactose | 60 | 40 | 20 | 60 | 40 | 20 | 60 | 40 | 20 |
| Total Weight | 350 | 350 | 350 | 350 | 350 | 350 | 350 | 350 | 350 |

Sodium bicarbonate and citric acid were used as gas generating agent. Citric acid was also used as an antioxidant. Steps involved in the manufacture of tablets, first the drug; polymer, and other excipients selected were passed through 40- mesh sieve. The required quantity of drug, polymer, and excipients was weighed properly and transferred into polyethylene bag and the blend was mixed for at least 15 min. The blend obtained was then lubricated by adding magnesium stearate and again mixed for another 5min.

**Formulation development of bilayer tablet**

Optimized formulation IF-4 of Instant release layer and optimized formulation of F-7 for control release used for the formulation of a Bilayer tablet.

**EVALUATION OF BILAYER TABLETS:**

**1. General Appearance**

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. The appearance was judged visually.

**2. Thickness and diameter**

The thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

**3. Hardness [6]**

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

**4. Friability [7]**

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

**5. Uniformity of weight**

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

**6. Drug content [8]**

Twenty tablets were taken and the amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 25 mg of Clarithromycin was transferred to 100ml standard flask. The powder was dissolved in 25 ml of 0.1 N HCl and made up to volume with 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.1 ml to 10 ml suitably (10ppm of Clarithromycin) the Conc. of drug determined using UV Vis. spectroscopy at 416nm.

**7. Dissolution rate studies [9,10]**

In-vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12 hrs period for Clarithromycin SR and 1 hr for Clarithromycin IR, using an automated paddle dissolution system (Labindia 3000+). A minimum of 6 tablets per batch was tested.

**RESULTS AND DISCUSSION:**

**Instant layer of Clarithromycin:**

Fast disintegrating tablets were prepared firstly using different excipients (binders and super disintegrants) and then evaluated for various parameters like friability, hardness, and disintegration time to select the best combination for the formulation of fast disintegrating tablets.

**Table 3: Post-Compression parameters**

| F. Code | Hardness test (kg/cm$^2$) | Friability (%) | Weight variation (%) | Thickness (mm) | Drug content (%) | Disintegration Time (Sec.) Mean ± SD |
|---|---|---|---|---|---|---|
| IF1 | 2.8±0.1 | 0.745±0.042 | 150±3 | 2.1±0.1 | 98.56±0.45 | 98±1 |
| IF2 | 2.9±0.2 | 0.658±0.041 | 155±4 | 2.1±0.2 | 98.65±0.32 | 95±3 |
| IF3 | 2.7±0.1 | 0.712±0.023 | 147±2 | 2.2±0.1 | 98.74±0.25 | 92±2 |
| IF4 | 2.8±0.2 | 0.742±0.047 | 149±5 | 2.2±0.2 | 99.45±0.26 | 69±4 |
| IF5 | 2.8±0.1 | 0.723±0.052 | 148±4 | 2.3±0.2 | 99.12±0.54 | 72±5 |
| IF6 | 2.7±0.2 | 0.745±0.056 | 150±2 | 2.2±0.1 | 98.74±0.65 | 56±4 |
| IF7 | 2.8±0.1 | 0.854±0.056 | 154±3 | 2.1±0.2 | 98.65±0.41 | 78±2 |
| IF8 | 2.9±0.2 | 0.812±0.036 | 152±4 | 2.2±0.1 | 98.78±0.58 | 71±3 |
| IF9 | 2.7±0.1 | 0.825±0.047 | 145±1 | 2.1±0.1 | 98.98±0.65 | 69±4 |

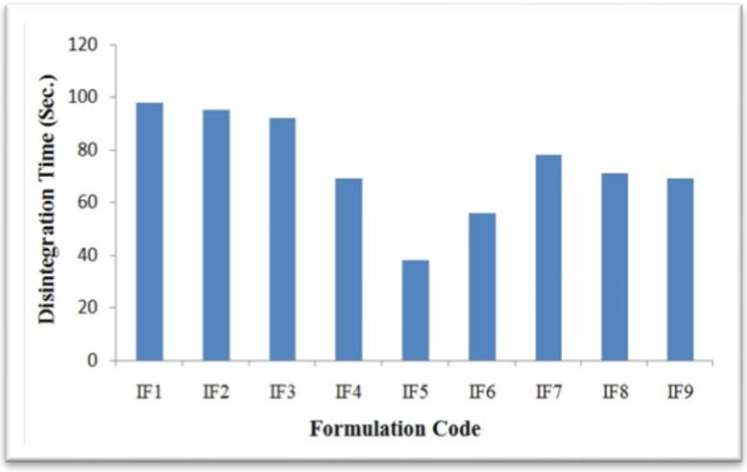


**Figure 1: Post compressional Parameters**

**Control layer of Clarithromycin:**

**Table 4: Cumulative %drug release**

| Time | %Cumulative drug release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| hr | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 0.5 | 44.56 | 40.23 | 38.89 | 36.65 | 32.23 | 30.14 | 26.65 | 22.12 | 20.23 |
| 1 | 65.89 | 69.98 | 59.98 | 49.98 | 41.36 | 39.98 | 33.36 | 26.65 | 24.45 |
| 1.5 | 83.32 | 76.65 | 66.65 | 69.98 | 63.32 | 60.45 | 45.56 | 35.85 | 30.65 |
| 2 | 99.12 | 90.32 | 74.12 | 73.32 | 73.35 | 69.98 | 54.78 | 44.48 | 38.89 |
| 3 | - | 98.45 | 86.65 | 80.23 | 82.32 | 80.45 | 65.58 | 55.65 | 42.56 |
| 4 | - | - | 98.65 | 98.85 | 94.45 | 91.36 | 75.68 | 65.54 | 48.87 |
| 6 | - | - | - | - | 98.98 | 96.65 | 84.71 | 72.23 | 56.65 |
| 8 | - | - | - | - | - | 98.87 | 90.65 | 76.65 | 65.58 |
| 12 | - | - | - | - | - | - | 98.89 | 80.32 | 72.32 |

**Table 5: Post compression Results**

| Code | Thickness (mm) | Hardness ($kg/cm^2$) | Weight variation(mg) | Friability % | Drug content % | Total floating (hr) | Floating lag time (sec) |
|---|---|---|---|---|---|---|---|
| **F1** | 3.48 | 5.2 | 345 | 0.856 | 98.12 | >12 | 65 |
| **F2** | 3.52 | 5.5 | 350 | 0.874 | 98.45 | >12 | 69 |
| **F3** | 3.47 | 5.4 | 348 | 0.965 | 98.65 | >12 | 72 |
| **F4** | 3.69 | 5.5 | 352 | 0.846 | 98.74 | >12 | 75 |
| **F5** | 3.53 | 5.3 | 354 | 0.846 | 98.65 | >12 | 69 |
| **F6** | 3.47 | 5.2 | 356 | 0.874 | 98.74 | >12 | 79 |
| **F7** | 3.52 | 5.1 | 348 | 0.865 | 99.12 | >12 | 63 |
| **F8** | 3.42 | 5.4 | 347 | 0.845 | 98.78 | >12 | 85 |
| **F9** | 3.51 | 5.3 | 342 | 0.865 | 99.14 | >12 | 90 |

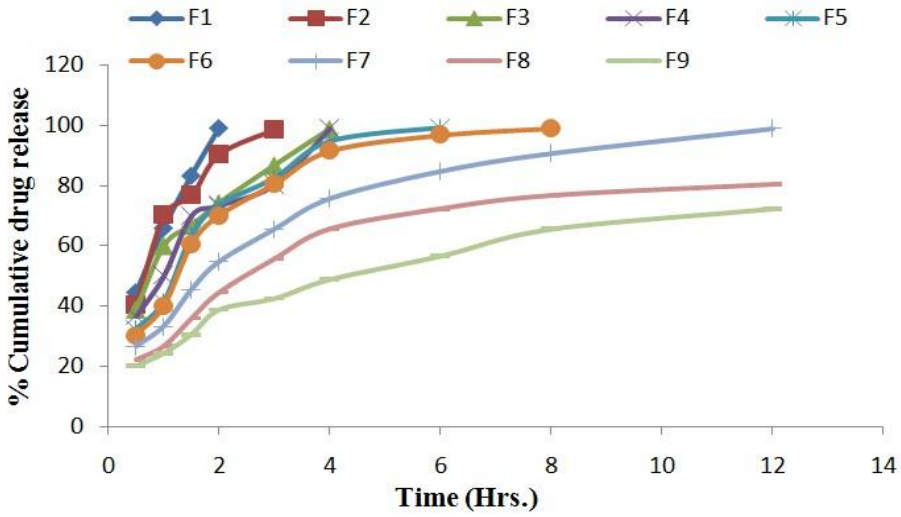


**Figure 2: *In-vitro* Drug Release Study**

**Evaluation of bilayer floating tablets:**

Optimized formulation IF-4 of Instant release layer and optimized formulation of F-7 for control release used for the formulation of a bilayer tablet.

**Table 6: Post-Compressional Parameters**

| Formulation code | Hardness test (kg/cm$^2$) | Friability (%) | Weight variation | Thickness (mm) | %Drug content |
|---|---|---|---|---|---|
| **BTF1** | 5.35 | 0.865 | 505±6 | 4.23 | 99.45 |

**Table 7: % Cumulative Drug Release**

| Time (Hour) | % Cumulative Drug Release |
|---|---|
| **0.25** | 44.23 ± 0.45 |
| **0.5** | 22.32 ± 0.32 |
| **1** | 35.65 ± 0.74 |
| **1.5** | 45.65 ± 0.65 |
| **2** | 52.23 ± 0.41 |
| **4** | 64.87 ± 0.32 |
| **6** | 76.65 ± 0.25 |
| **8** | 85.65 ± 0.65 |
| **10** | 92.23 ± 0.48 |
| **12** | 98.89 ± 0.65 |

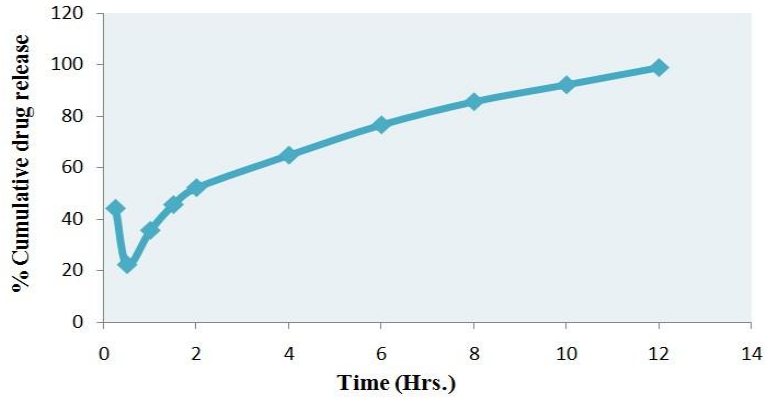


**Figure 3: Dissolution rate studies**

**DISCUSSION:**

The optimized immediate layer (IF-4) and the sustained release layer (F7) were compressed to get a bilayer tablet. The resultant bilayer tablet (BTF1) was subjected to *in vitro* dissolution studies. Figure 5.8 Indicates the initial burst effect due to the immediate-release layer of Clarithromycin and then the slow release of the drug is maintained drug release until 12 h. It releases up to 98.89±0.65% drug after 12 h.

**CONCLUSION:**

Clarithromycin drug was formulated into a bilayer tablet comprising an immediate-release layer and sustained release layer to achieve loading dose and maintenance dose, respectively, and to give a large duration of action. A total of nine batches was prepared for a sustained release layer and nine batches for the immediate release layer. All the formulations were subjected to pharmaceutical evaluation. The drug content of all formulations of the sustained-release layer varied between 98.12 to 99.14% w/w.

The research was undertaken to formulate and evaluate the bilayer floating tablets of Clarithromycin using synthetic and natural polymers. From results obtained, it was concluded that the formulation of bilayer floating tablet of Clarithromycin containing Guar gum and Xanthan gum as natural polymer and HPMC K-4 and K15 as synthetic polymer was taken as an ideal or optimized formulation for 12 hrs release as it fulfills all the requirement of the sustained-release dosage form.

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**Declaration of Interest:**

The authors report no conflicts of financial interest. The authors alone are responsible for the content and writing of the paper.

**Ethical approval:**

This research article does not include any animal or human studies done by the authors.

**REFERENCES:**

1) Talukder R, Fassihi R. Gastroretentive Delivery Systems: A Mini-Review. Drug Dev Ind Pharm. 2004; 30(10): 1019-28.
2) Garg R, Gupta GD. Progression Controlled Gastroretentive Delivery Systems. Trop J Pharm Res. 2008; 7(3): 1055-66.
3) Patil JM, Hirlekar RS, Gide PS, Kadam VJ. Trends in floating drug delivery systems. J Sci Ind Res. 2006 Jan; 65:11-21.
4) Shaha SH, Patel JK, Pundarikakshudu K, Patel NV. An overview of gastro- retentive floating drug delivery system. Asian Journal of Pharmaceutical Sciences. 2009 Jan; 4(1): 65-80.
5) http://www.pharmainfo.net/pharma-
6) Lachman L, Liberman H, Kanig J. The theory and practice of industrial pharmacy, 3rd edn. Varghese Publishing House, Mumbai, 1987, pp. 297.
7) Indian Pharmacopoeia 1996. The Controller of Publication. Delhi, Vol-2, p-735.
8) Indian Pharmacopoeia; Controller of Publication: New Delhi, India, 1996.
9) Merchant, H. A.; Shoaib, H. M.; Tazeen, J.; You-suf, R. I. Once-daily tablet formulation and in-vitro release evaluation of cefpodoxime using hydroxypropyl methylcellulose: a technical note. AAPS Pharm Sci Tech 2006, 7, E1–E6.
10) Rao, K. V.; Devi, K. P.; Buri, P. Influence of molecular size and water solubility of the solution its release from swelling and erosion con-trolled polymeric matrices. J. Controlled Release1996, 12, 133–141.

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|---|---|
|  | ***Author Name - Vaishali Pardhe*[1]***<br>*Author Affiliation: Research Scholar, Dept. of Pharmaceutics,*<br>*Institute Address: Lakshmi Narain College of Pharmacy, Bhopal, M.P, India.* |
|  | ***Author Name - A.K Singhai[2]***<br>*Author Affiliation: Principal, Dept. of Pharmaceutics, Lakshmi Narain College of Pharmacy, Bhopal, M.P, India.* |
|  | ***Author Name - Rama Shukla[3]***<br>*Author Affiliation: Assistant Professor, Dept. of Institute Address: Pharmaceutics, Lakshmi Narain College of Pharmacy, Bhopal, M.P, India.* |
|  | ***Author Name - Nipuna Kumar Bhoi[4]***<br>*Author Affiliation: Research Scholar, Dept. of Pharmaceutics,*<br>*Institute Address: Lakshmi Narain College of Pharmacy, Bhopal, M.P, India.* |