

Design and Development of Bi-layered Sustained Release Azithromycin Tablets

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ABSTRACT: The objective of the current study was to develop a bilayer tablet of Azithromycin containing both immediate and sustained layer and evaluate the effect of formulation variables on drug release. Thirty different formulations (F-1 to F-30) were prepared by direct compression. When the fraction of polymer was increased from 5.55% to 10%, the rate of drug release was found to be slower. Maximum release of Azithromycin was from F-11 (within 8 hours), which contained 50 mg (5.55%) of HPMC 50 cps. Slowest release was observed from F-30 containing 90 mg (10%) of Carbopol 974 P. The IR spectral analysis revealed that all rate regarding agents and excipients used in this study are compatible with the active Azithromycin.

Key words: Azithromycin, bilayer tablet, HPMC, Carbopol, sustained release.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. It remains as the most favorable and preferred route of drug administration both by patient and physicians.¹ The major challenge with the design of oral dosage forms lies with their poor bioavailability compared to injectable and implants. Pharmaceutical products intended for oral administration are cheaper and currently greater than sixty percent of drugs are marketed as oral products.² Researchers and pharmaceutical companies are increasingly aware of the need for earlier assessment of new drug entities for their potential as oral candidates.³ Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with

consequent undesirable toxicity and poor efficiency. Many factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance.⁴ Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablets in which one layer is immediate release as initial dose and second layer is maintenance dose.⁵

Here Azithromycin has been chosen as the experimental drug. It is a semisynthetic macrolide antibiotic, which is commonly used for a wide variety

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of mild-to-moderate bacterial infections. Azithromycin is used to treat or prevent certain bacterial infections, most often those causing middle ear infections, strep throat, pneumonia, typhoid, and sinusitis.⁶

The present research work was undertaken with the aim to formulate bilayer tablets of Azithromycin through its incorporation of an oral dosage form by using a simple and easy-to-scale-up formulation strategy.

MATERIALS AND METHODS

General experimental procedures. Azithromycin was kindly provided by Eskayef Bangladesh Limited as a gift sample. Different grades of HPMC were collected from Colorcon Limited, India. Microcrystalline cellulose (Avicel PH 102), Lactose, Carbopol 934P and Carbopol 974P, Providone K 30 and Magnesium stearate were kind gifts from Nipa Pharmaceuticals Limited, Dhaka. Potassium dihydrogen phosphate, HCl (37%) of Merck (Germany) and purified water from our Research laboratory were used. Among the instruments and machineries, vernier caliper of Erweka (Germany), Shimadzu UV Spectrophotometer (Japan), hardness tester and dissolution tester were from Erweka (Germany), Pharmatest disintegration tester (Germany), mini drum blender of Cadmach Machinery (India), friability tester of Logan (USA), Hanna pH meter (Portugal), stainless steel sieve (Bangladesh) and Manesty 16 station compression machine (England) were used.

Preparation of bilayer tablets of Azithromycin. For layer I of Azithromycin immediate release tablet preparation, the active drug was weighed and placed into mortar and pestle for mixing. Then all materials were properly mixed for five minutes in one way direction. A coloring agent was used in this mixer for differentiation between the immediate and sustained layer. Then lubricant was added and mixed for two minutes and then placed for compression (Table 1).

Azithromycin sustained release layer were prepared by wet granulation method.⁷⁻⁸ The active

ingredient, HPMC K4M and microcrystalline cellulose were passed through mesh # 40 and were mixed homogenously. Providone K30 was added as a binder to the above blend and was mixed to get a final coherent mass. Obtained coherent mass was passed through mesh #20 to get desired granules. The granules were primarily air dried and were finally dried at 50°C until a constant loss on drying (LOD) reaches 3-4%, analyzed by moisture analyzer. The whole blend of dried granules was lubricated and homogenously mixed by magnesium stearate and talc.

Table 1. Formulation of immediate release Azithromycin layer.

Ingredients	Amount (mg)
Azithromycin	400
Microcrystalline cellulose	96.4
Providone K 30	15.6
Mg stearate	4.4
Purified talc	5.6
Spectrocolquinoline yellow LK	8.6
Total=	525

The bi-layered tablet compression was achieved using 8.00 mm flat punch on a 12-station rotary tablet machine. The sustained release Azithromycin granules were introduced first into the die cavity and a light pre-compression was imparted so that the layer gets uniformly distributed in the die cavity doesn't mix up with the other layer. Further, immediate release layer blend was added above the previously light pre-compressed sustained release layer and final compression was carried out with optimum compression force.⁹⁻¹⁰

To evaluate the formulation variables on the release rate of bilayer tablets of Azithromycin, formulations were prepared by using six different polymers i.e. HPMC K4M (F1 to F5) and HPMC K15M (F6 to F10) in table 2, HPMC 50cps (F11 to F15) and HPMC 100cps (F16 to F20) in table 3, Carbopol 934P (F21 to F25) and Carbopol 974P (F26 to F30) in table 4, as hydrophilic polymers. All the preparations were then stored in airtight containers at room for further study.

Measurement of physical properties of the prepared tablets.

Bulk density. Apparent bulk density (D_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (W) was determined.⁷ The bulk density (D_b) was calculated using following formula:

$$D_b = W/V_b$$

Tapped density. The measuring cylinder containing a known mass of blend (W) was tapped for a fixed time (100 tapping). The minimum volume (V_t) occupied in the cylinder and weight of the blend (W) was measured.⁸ The tapped density (D_t) was calculated using the formula, $D_t = W/ V_t$.

Carr's compressibility index and Hausner's ratio. The Carr's compressibility index (also called as Carr's Consolidation index or Carr's Index) and Hausner's ratio can be calculated from the measured values of tapped density (D_t) and bulk density (D_b), as follows^{9,10}:

$$\text{Carr's compressibility index} = (D_t - D_b)/D_t \times 100$$

$$\text{Hausner's ratio} = D_t/D_b$$

Angle of repose: Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained.¹¹ Radius of the heap (r) was measured and angle of repose (θ) was calculated using the following formula, $\theta = \tan^{-1}(h/r)$.

In vitro release studies of Azithromycin from the prepared tablets. The release rate of Azithromycin from tablets was determined using USP Type II (Rotating paddle method) dissolution testing apparatus. According to USP XXIII, the dissolution test was performed using 900 ml of phosphate buffer as dissolution medium at $37 \pm 0.5^\circ\text{C}$ and 100 rpm. A sample of 10 ml was withdrawn from the dissolution apparatus at predetermined time intervals of 0.30th hour, 1st hour, 2nd hour, 3rd hour, 4th hour, 5th hour, 6th hour, 7th hour and 8th hour. The same volume of dissolution medium is replaced to maintain sink condition. Samples withdrawn were filtered through 0.45 μm membrane filter and

suitably diluted with phosphate buffer. Absorbance of these solutions was measured at 226 nm using a UV-1800 SHIMADZU UV spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve. Dissolution rate was studied for all designed formulation.

Drug-excipient compatibility studies. The compatibility of drug with their respective excipients was studied by FT-IR spectroscopy. The IR spectra of both the drugs and the mixture of their excipients and their bilayer tablets were analyzed between wave numbers 4000 to 700 cm^{-1} (Figure 1).

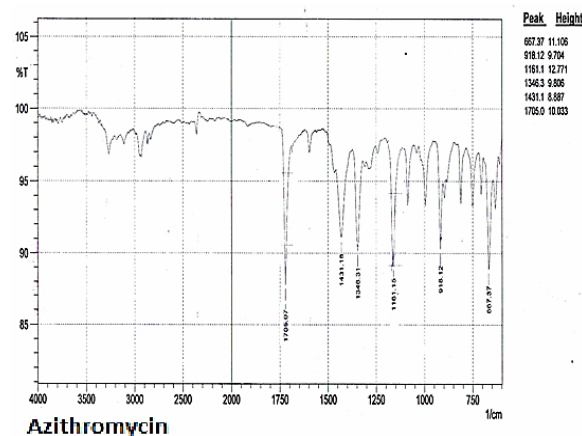


Figure 1. FT-IR spectrum of pure Azithromycin

Statistical analysis. In this study, one-way analysis of variance (ANOVA) (performed at 5% significance level using SPSS, version 16.0) was used to compare the difference of dissolution profiles of the test matrix tablets.

RESULTS AND DISCUSSION

In the present study, thirty different formulations of bilayer tablets of Azithromycin were prepared by using six different polymers of HPMC K4M, HPMC K15M, Carbopol 934P, Carbopol 974P, HPMC 50cps and HPMC 100cps at the concentration of 5.55%, 6.66%, 7.77%, 8.88% and 10% as rate retarding agent.

Analysis of physical properties. To evaluate the physical properties of the prepared tablets, we have

determined the average weight, thickness, diameter, hardness and percent of friability of the HPMCK4M, HPMC K15M, Carbopol 934P, Carbopol 974P, HPMC 50cps and HPMC 100cps containing matrix tablets of Azithromycin (Table 5). We observed that the prepared Azithromycin tablets followed and met all the criteria specified in the monograph (Table 5).

Analysis of flow properties. In the present experiment, the flow properties of the excipients have

been evaluated. Bulk density, tapped density, Carr's compressibility index and Hausner's ratio have been calculated and presented in table 6. It was found that all the individual excipients and the mixture had the flow parameters within the range allowing desirable flow property.

Table 5. Physical properties of Azithromycin bilayer tablets.

Formulation	Average weight (mg)*	Average thickness (mm)*	Average diameter (mm)*	Average hardness (kgf)*	Friability (%)
F-1	901.33 ± 4.23	7.11 ± 0.04	18.23 ± 0.02	15.17 ± 1.25	0.39
F-2	902.03 ± 5.33	7.12 ± 0.03	18.23 ± 0.01	15.58 ± 1.86	0.11
F-3	901.5 ± 3.94	7.14 ± 0.04	18.22 ± 0.02	15.88 ± 1.96	0.12
F-4	901.83 ± 4.07	7.11 ± 0.02	18.23 ± 0.02	15.83 ± 1.63	0.42
F-5	898.33 ± 5.72	7.13 ± 0.03	18.23 ± 0.02	15.93 ± 1.1	0.13
F-6	901.83 ± 3.82	7.12 ± 0.04	18.24 ± 0.01	15.33 ± 1.78	0.05
F-7	901.33 ± 4.08	7.14 ± 0.04	18.23 ± 0.02	15.87 ± 1.74	0.33
F-8	901.24 ± 4.42	7.13 ± 0.04	18.23 ± 0.02	15.62 ± 0.94	0.38
F-9	902.68 ± 3.79	7.13 ± 0.03	18.22 ± 0.01	15.95 ± 1.17	0.11
F-10	900.33 ± 3.93	7.13 ± 0.02	18.23 ± 0.01	15.75 ± 1.26	0.18
F-11	901.67 ± 4.08	7.13 ± 0.04	18.23 ± 0.02	15.95 ± 1.54	0.23
F-12	898.33 ± 1.75	7.12 ± 0.03	18.23 ± 0.02	15.83 ± 1.31	0.25
F-13	900.89 ± 3.69	7.13 ± 0.03	18.23 ± 0.02	16.05 ± 1.17	0.22
F-14	899.21 ± 5.4	7.12 ± 0.05	18.23 ± 0.01	15.97 ± 1.55	0.22
F-15	898.5 ± 4.51	7.14 ± 0.03	18.24 ± 0.01	16.25 ± 1.75	0.19
F-16	900.67 ± 3.69	7.13 ± 0.04	18.23 ± 0.02	16 ± 1.23	0.33
F-17	899.78 ± 4.73	7.11 ± 0.04	18.24 ± 0.02	16.25 ± 1.69	0.36
F-18	898.67 ± 1.63	7.14 ± 0.03	18.23 ± 0.02	15.13 ± 0.74	0.22
F-19	901.39 ± 4.24	7.12 ± 0.04	18.23 ± 0.01	16.77 ± 1.21	0.19
F-20	900.33 ± 2.94	7.12 ± 0.02	18.23 ± 0.02	15.7 ± 0.99	0.22
F-21	898.24 ± 5.44	7.13 ± 0.05	18.23 ± 0.02	16.63 ± 1.33	0.37
F-22	901.50 ± 4.64	7.14 ± 0.05	18.23 ± 0.02	16.07 ± 1.22	0.35
F-23	900.69 ± 4.43	7.12 ± 0.05	18.23 ± 0.02	15.85 ± 1.38	0.21
F-24	901.87 ± 4.38	7.12 ± 0.02	18.24 ± 0.02	16.2 ± 1.66	0.25
F-25	901.17 ± 4.12	7.11 ± 0.01	18.24 ± 0.02	15.92 ± 1.55	0.16
F-26	900.33 ± 4.51	7.12 ± 0.02	18.24 ± 0.02	16.23 ± 1.02	0.13
F-27	900.67 ± 4.08	7.13 ± 0.02	18.23 ± 0.02	15.97 ± 1.69	0.17
F-28	898.83 ± 4.79	7.12 ± 0.03	18.23 ± 0.02	16.43 ± 1.18	0.32
F-29	900.17 ± 3.43	7.14 ± 0.03	18.24 ± 0.02	15.97 ± 1.69	0.25
F-30	902.97 ± 3.69	7.11 ± 0.02	18.23 ± 0.01	16.58 ± 1.32	0.29

Table 6. Characteristics of powder formulations.

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility Index (%)	Hausner's ratio	Angle of repose
F-1	0.523	0.561	6.77	1.07	22.5
F-2	0.542	0.582	6.87	1.07	23.1
F-3	0.533	0.571	6.65	1.07	22.1
F-4	0.556	0.597	6.87	1.07	22.8
F-5	0.543	0.586	7.34	1.08	20.5
F-6	0.576	0.617	6.65	1.07	19.6
F-7	0.612	0.662	7.55	1.08	22.7
F-8	0.589	0.624	5.61	1.06	22.5
F-9	0.485	0.523	7.27	1.08	20.6
F-10	0.477	0.511	6.65	1.07	21.3
F-11	0.525	0.556	5.58	1.06	22.3
F-12	0.540	0.575	6.09	1.06	22.9
F-13	0.531	0.563	5.68	1.06	21.7
F-14	0.555	0.591	6.09	1.06	23.1
F-15	0.539	0.573	5.93	1.06	21.3
F-16	0.570	0.613	7.01	1.08	20.1
F-17	0.605	0.639	5.32	1.06	22.3
F-18	0.581	0.619	6.14	1.07	21.9
F-19	0.576	0.615	6.34	1.07	21.5
F-20	0.556	0.597	6.87	1.07	20.7
F-21	0.495	0.531	6.78	1.07	21.5
F-22	0.510	0.556	8.27	1.09	21.9
F-23	0.512	0.549	6.74	1.07	19.9
F-24	0.499	0.552	9.60	1.11	23.2
F-25	0.522	0.568	8.10	1.09	21.2
F-26	0.521	0.569	8.44	1.09	22.5
F-27	0.513	0.545	5.87	1.06	20.9
F-28	0.500	0.533	6.19	1.07	21.3
F-29	0.568	0.601	5.49	1.06	19.6
F-30	0.569	0.611	6.87	1.07	20.5

Table 7. *In vitro* dissolution data from formulations F1 to F30 of Azithromycin tablets.

Polymer name	Formulation	Drug release with drug polymer ratio 1:0.07(50mg)	Formulation	Drug release with drug polymer ratio 1: 0.09 (60 mg)	Formulation	Drug release with drug polymer ratio 1: 0.11 (70 mg)	Formulation	Drug release with drug polymer ratio 1: 0.12 (80 mg)	Formulation	Drug release with drug polymer ratio 1: 0.14 (90 mg)
HPMC K4M	F1	88.34%,	F2	71.78%	F3	66.48%	F4	63.18%	F5	62.31%
HPMC K15M	F6	86.35%,	F7	72.71%	F8	64.28%	F9	62.04%	F10	66.67%
HPMC 50 cps	F11	97.33%,	F12	93.83%	F13	90.49%	F14	72.86%	F15	71.87%
HPMC 100 cps	F16	96.34%	F17	94.84%	F18	87.49%	F19	70.86%	F20	73.83%
Carbopol 934P	F21	93.91%,	F22	71.09%	F23	70.32%	F24	63.71%	F25	61.09%
Carbopol 974P	F26	84.78%,	F27	75.27%	F28	62.05%	F29	59.46%	F30	58.87%

***In vitro* release rate of Azithromycin from the prepared bilayer tablets.** It was observed that use of different polymers influences the drug release

patterns. Formulations were prepared with batches F1-F5 containing HPMC K4M, F6-F10 with HPMC K15M, F11-F15 containing Carbopol 934P, F16-F20

containing Carbopol 947P, F21-F25 containing HPMC 50cps and F26-F30 containing HPMC 100cps. The release pattern of Azithromycin was monitored up to eight hours. Maximum release of Azithromycin was observed from F-11 (within 8 hours) as it contained 50 mg of HPMC 50cps with drug polymer ratio 1:0.07 and methyl cellulose 60 mg. Slowest release was found from F-30 which contained 90 mg of Carbopol 974P with drug polymer ratio 1:0.14 with methyl cellulose 20 mg. It can be seen that with the increase of the polymer and decrease of the methyl cellulose the release of the drug also decrease, it means drug release retardation is directly proportional to the concentration of the polymer and inversely proportional with methyl cellulose. Drug release with drug polymer ratio is shown in the table 6. In this study, optimum rate retarding action was obtained by incorporating 90mg of Carbopol 974P>HPMC K15M>Carbopol 934P>HPMC K4M>HPMC 50cps>HPMC 100cps.

On the other hand, maximum drug release was obtained by incorporating 50mg of HPMC 50 cps> HPMC 100 cps>Carbopol 934P> HPMC K4M> HPMC K15M>Carbopol 974P. It was found that, some polymers which allows fast release of drug at a lowest concentration, may produce significant drug retardation capability with the increase of the concentration e.g. HPMC 50 cps shows fast release at 50 mg concentration, but shows good retardation properties at 90 mg concentration. If the polymer level is too low, a complete gel layer may not form.¹²In most studies, increased polymer level in the formulation results in decreased drug-release rates. Higher polymer content in the matrix decreases the rate an extent of the drug release because of increased matrix strength and gel formation around the matrix.¹¹⁻¹² In the present study carbopol polymer shows greater and reliable drug retardation ability compared to HPMC polymer.

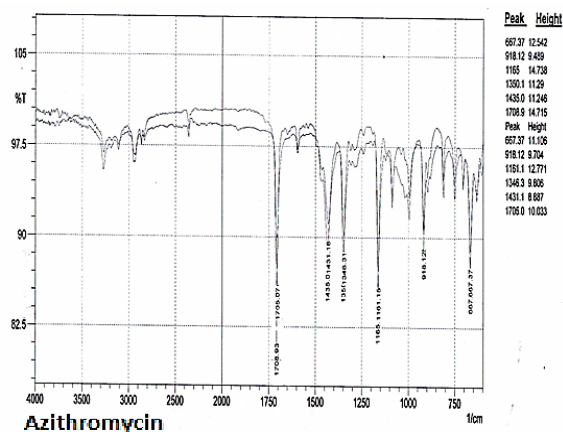


Figure 2. FT-IR spectrum of Azithromycin with HPMC.

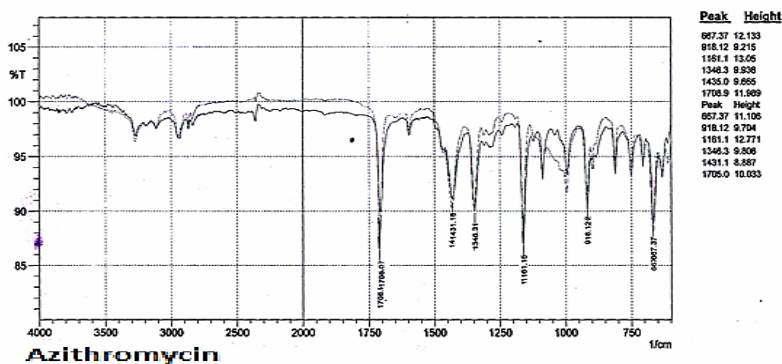


Figure 3. FT-IR spectrum of Azithromycin with Carbopol.

Drug-excipient compatibility studies by FT-IR. As part of compatibility studies, FT-IR studies were performed as shown in figures 1-3 for the drug along with the excipients to detect any major interference between the drug and excipients. No incompatibilities were observed as evident from the IR spectra.

CONCLUSION

The study allowed us to develop new sustained formulation of Azithromycin by using different types of HPMC (HPMC K4M, HPMC K15M, HPMC 50cps and HPMC 100cps) and Carbopol (934P and 974P) to evaluate the effect of HPMC and Carbopol as rate controlling polymer. Further studies may be conducted by formulating new formulations with the combination of polymers of HPMC and carbopol to evaluate the combination efficacy of both polymers.

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