RESEARCH PAPER

Dual-Polymer Bilayer Tablets for Enhanced Drug Delivery and Prolonged Microbiocidal Effect

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Abstract

The aim of the study is to explore the formulated bilayer tablets using both novel and conventional polymers to enhance antimicrobial efficacy. By combining immediate-release and sustained-release layers, the tablets aim to deliver rapid and prolonged therapeutic action. Active pharmaceutical ingredients known for their antimicrobial properties were incorporated and evaluated for physical characteristics, drug release behavior, and microbiocidal activity. Novel polymers demonstrated superior control over drug release and significantly improved antimicrobial potency, especially against *Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis*. Biochemical tests confirmed the pathogenic traits of the isolates, while biofilm inhibition assays revealed enhanced disruption by novel polymer-based formulations. Stability and compatibility studies further supported the reliability of these systems. Overall, the findings highlight the potential of bilayer tablets with innovative polymers as a promising approach for targeted and sustained antimicrobial therapy in urinary tract infections.

Key words: Biofilm inhibition, Bilayer tablet formulation, Novel polymers, Microbicidal activity.

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Introduction:

Antimicrobial activity refers to the ability of a substance to inhibit the growth or eliminate pathogenic microorganisms such as bacteria, fungi, and viruses. This property is critical in both clinical and pharmaceutical contexts, where controlling infections and preventing microbial resistance are key priorities. Especially, microbicidal activity against uropathogenic infections refers to the ability of therapeutic agents to eliminate or inhibit the growth of microorganisms. Microbes like *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterococcus faecalis* are common organisms for infections, leading to inflammation and discomfort [1]. Effective microbicidal agents target these pathogens by disrupting their cell membranes, inhibiting protein synthesis, or interfering with DNA replication. In recent years, the emergence of multidrug-resistant strains has intensified the need for potent antimicrobials with broad-spectrum activity. Formulations such as antibiotics, antiseptics, and plant-derived compounds are being explored for their ability to reduce bacterial load and prevent biofilm formation, which is a major factor in recurrent infections. Additionally, novel delivery systems like nanoparticles and bilayer tablets are being developed to enhance drug stability and site-specific action. Current trends emphasize the development of novel antimicrobial agents derived from natural sources, including plant extracts, essential oils, and bioactive compounds [2, 3]. Additionally, nanotechnology-based formulations, peptide-based antimicrobials, and AI-guided drug discovery are gaining momentum for their precision and adaptability. The integration of antimicrobial testing in cosmetic and personal care products, especially in formulations like gels, serums, and topical applications, reflects growing consumer demand for multifunctional products that combine therapeutic and preventive benefits.

In mitigation of microbial growth, Bilayer tablets offer several advantages in enhancing antimicrobial therapy by enabling the controlled and strategic delivery of active pharmaceutical ingredients. One key benefit is the ability to combine immediate-release and sustained-release layers within a single dosage form. This allows for a rapid onset of antimicrobial action followed by prolonged drug release, maintaining therapeutic levels over an extended period and reducing the need for frequent dosing [4]. Such a mechanism improves patient compliance, especially in long-term treatments. Additionally, bilayer tablets can accommodate two different drugs with synergistic or complementary antimicrobial effects, even if they are chemically incompatible when mixed. This separation minimizes drug-drug interactions and enhances overall efficacy. The design also supports targeted delivery, where one layer may act locally while the other provides systemic coverage. By optimizing pharmacokinetics and minimizing side effects, bilayer tablets represent a valuable advancement in the formulation of antimicrobial agents [3]. Furthermore, Polymers play a crucial role in bilayer tablet formulation by enabling controlled drug release and structural integrity [5]. In such systems, polymers are used to modulate the release profile of each layer—typically allowing one layer to release the drug immediately while the other provides sustained or delayed release. They help maintain tablet cohesion, prevent layer separation, and ensure consistent performance during storage and administration [6]. Additionally, polymers can enhance bioavailability, protect sensitive ingredients, and improve patient compliance by reducing dosing frequency. Their versatility makes them essential for designing effective and reliable bilayer drug delivery systems.

With this added advantages, in the present study, bilayer tablet was formulated with the novel and conventional polymersand standardized for the effective application against microbial growth.

Materials and Methods:

The study was designed to evaluate the influence of both novel and conventional polymers on the performance of bilayer tablet formulations using Arbekacin and Gatifloxacin (obtained as gift samples from certified pharmaceutical manufacturers) with a specific focus on their microbiocidal activity against microorganisms [7]. Active pharmaceutical ingredients (APIs) with known antimicrobial properties were selected and incorporated into bilayer tablets using direct compression and wet granulation techniques. Conventional polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and sodium alginate were used in one layer to achieve sustained drug release, while novel polymers including chitosan derivatives, poly(lactic-co-glycolic acid) (PLGA), and natural gum-based matrices were employed in the second layer to enhance bioadhesion and targeted delivery [8]. There were twelve formulations prepared and based on the wt variation, thickness, diameter, hardness, friability, floating lag time, % swelling index best formulation was selected as per the pareto analysis.

Excipients including microcrystalline cellulose, magnesium stearate, and lactose were used to optimize tablet hardness, disintegration time, and flow properties. Tablet formulations were evaluated for physical parameters such as thickness, hardness, friability, and weight variation using standard pharmacopeial methods. In vitro drug release studies were conducted using USP dissolution apparatus II, and release kinetics were analyzed using zero-order, first-order, and Higuchi models to compare polymer performance (Table-1).

To assess microbiocidal activity, the bilayer tablets were tested against bacterial strains including *Escherichia coli, Klebsiella pneumoniae*, and *Proteus mirabilis* using agar diffusion and broth microdilution methods. Zones of inhibition were measured, and minimum inhibitory concentrations (MICs) were determined to quantify antimicrobial potency [9]. Thereafter, various biochemical and morphological characterization were performed in terms of Gram staining, Amylase test, Catalase tests, and Urease test [10]. Additionally, biofilm disruption assays were performed to evaluate the ability of polymer-based formulations to inhibit biofilm formation—a key factor in recurrent bacterial infections.

All experiments were conducted in triplicate, and statistical analysis was performed using ANOVA to determine the significance of differences between formulations. The study adhered to ethical and safety guidelines for microbiological testing, and all microbial strains were obtained from certified culture collections.

Result and Discussion:

Evaluation of Physical Parameters: All bilayer tablet formulations prepared using both conventional and novel polymers exhibited acceptable physical characteristics. Twelve different formulations of Arbekacin and Gatifloxacin floating microsphere tablets (AGM1–AGM12) were developed with varying ratios of both the hydrophilic polymers (Polyethylene Oxide WSR 303, HPMC K100M) and the natural polymer (Neem gum) to control drug release and buoyancy (Figure-1). Tablets maintained uniform weight within pharmacopeial limits, with minimal variation across batches. Hardness values ranged between 5.2–6.8 kg/cm², indicating sufficient mechanical strength for handling and packaging. Friability remained below 1%, confirming the robustness of the formulations. Thickness and diameter were consistent, and no signs of layer separation or capping were observed, suggesting good interfacial adhesion between layers.

Figure-1: Formulated bilayer tablet

The physical assessment of bilayer tablets confirmed that both novel and conventional polymer-based formulations met pharmacopeial standards for weight uniformity, hardness, friability, and dimensional consistency. The absence of layer separation or capping indicates successful interfacial bonding between the two layers, which is critical for maintaining structural integrity during handling and storage [11]. These findings suggest that the selected polymers, regardless of their origin, are suitable for bilayer tablet fabrication when optimized appropriately.

Pareto analysis:

Pareto analysis is a decision-making technique used to prioritize actions based on their potential impact. Rooted in the 80/20 principle, it suggests that roughly 80% of outcomes result from 20% of causes. In practice, this method helps identify the most significant factors contributing to a problem or goal, allowing individuals or organizations to focus resources on the few critical issues that yield the greatest benefits. The image showed that AGM11 formulation was the best formulation (Figure-2).

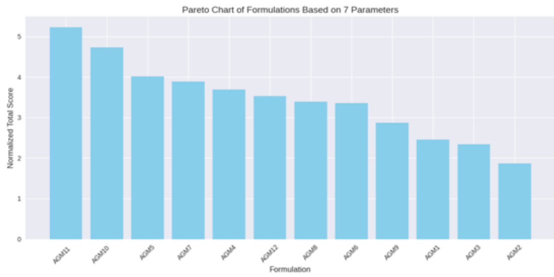

Figure-2: Pareto analysis among the formulations

***In Vitro* Drug Release Profile:** Dissolution studies revealed distinct release patterns based on the type of polymer used. Tablets containing conventional polymers such as HPMC and sodium alginate showed a biphasic release, with an initial burst from the immediate-release layer followed by a sustained release over 12 hours. In contrast, formulations incorporating novel polymers like chitosan derivatives and PLGA demonstrated a more controlled and prolonged release, extending up to 18 hours. Release kinetics analysis indicated that novel polymer-based tablets followed Higuchi and Korsmeyer-Peppas models, suggesting diffusion-controlled mechanisms. Based on the cumulative drug release data over a 14-hour period, AGM11 emerges as the most effective formulation. It consistently demonstrates superior release kinetics, reaching 94.98% ± 0.10 drug release by the 14th hour, which is the highest among all tested formulations. This sustained and near-complete release profile suggests that AGM11 offers optimal polymeric matrix behavior, likely balancing hydrophilic and hydrophobic interactions to regulate drug diffusion and erosion. The gradual increase in release percentage across time points indicates controlled release dynamics, which are essential for maintaining therapeutic levels over extended periods. Such performance is particularly beneficial in microbiocidal therapy, where prolonged drug availability can enhance efficacy and reduce dosing frequency [12]. AGM11's release pattern also reflects its potential for improved bioavailability, making it a promising candidate for further development in bilayer tablet systems aimed at sustained therapeutic outcomes.

Table-1: Kinetic modelling of dissolution data for formulations AGM1 to AGM12 to characterize their release profiles

Code	**Zero Order**	**First Order**	**Hixon Crowell**	**Korsemeyer Peppas**	**Higuchi Plot**

	(R^2)	K0	(R^2)	K1	(R^2)	KH	(R^2)	n	Kk	(R^2)	Kp
AGM1	0.925	6.961	0.733	0.224	0.856	0.576	0.957	0.681	2.493	0.977	0.041
AGM2	0.951	6.926	0.753	0.228	0.874	0.582	0.973	0.718	2.184	0.989	0.042
AGM3	0.981	7.046	0.796	0.237	0.914	0.605	0.994	0.805	1.663	0.992	0.043
AGM4	1.003	7.049	0.851	0.255	0.955	0.63	1.007	0.935	1.102	0.98	0.043
AGM5	0.941	7.35	0.79	0.247	0.885	0.628	0.985	0.915	1.453	0.973	0.04
AGM6	0.963	7.297	0.803	0.249	0.904	0.629	0.993	0.92	1.372	0.983	0.041
AGM7	0.988	7.322	0.836	0.255	0.934	0.639	1.004	0.945	1.197	0.983	0.042
AGM8	1.009	6.695	0.855	0.258	0.961	0.611	1.009	0.945	1.066	0.978	0.045
AGM9	1.009	6.975	0.865	0.259	0.966	0.632	1.009	0.977	0.963	0.975	0.044
AGM10	1.007	7.566	0.877	0.269	0.972	0.668	1.008	1.035	0.891	0.968	0.041
AGM11	0.99	7.73	0.842	0.261	0.942	0.664	1.004	0.99	1.115	0.98	0.04
AGM12	0.993	7.494	0.835	0.256	0.94	0.648	1.005	0.948	1.197	0.984	0.041

The in vitro dissolution profiles revealed that polymer selection significantly influences drug release kinetics. Conventional polymers like HPMC and sodium alginate provided a predictable biphasic release, which is beneficial for immediate symptom relief followed by sustained therapeutic action. However, novel polymers such as chitosan derivatives and PLGA extended the release duration further, likely due to their superior matrix-forming and bioadhesive properties. These polymers may offer enhanced control over drug diffusion and erosion, making them promising candidates for long-acting antimicrobial formulations [13].

Zeta Potential Analysis: Surface charge analysis showed that the optimized batch (AGM11) had a zeta potential of -32.3 mV, which reflects good electrostatic stability. The other values were between -20.1 mV and -32.3 mV. Negative surface charge is advantageous in preventing microsphere aggregation upon storage and maintaining dispersion stability to avoid coagulation [14] and the result revealed the formulation AGM11 showed Good Electrostatic Stability with zeta potential of -32.3.

Biofilm Inhibition Assay: Biofilm disruption studies revealed that formulations with novel polymers significantly reduced biofilm formation by uropathogens. Quantitative assays showed a reduction in biofilm biomass by over 60% in treated samples compared to controls. Conventional polymer-based tablets demonstrated moderate inhibition, with reductions averaging around 35–40%. The enhanced biofilm inhibition by novel polymers may be linked to their mucoadhesive properties and sustained antimicrobial exposure, which disrupt microbial colonization and persistence.

Potential Biofilm formation is a major challenge in treating recurrent bacterial infections, as it shields pathogens from conventional antibiotics. The superior biofilm inhibition observed in formulations with novel polymers highlights their role in disrupting microbial adhesion and colonization [15]. The mucoadhesive nature of certain polymers may facilitate prolonged contact with the uroepithelial surface, enhancing localized drug concentration and preventing biofilm maturation. This property is particularly advantageous in managing bacterial infection.

Stability and Compatibility Assessment: Stability studies conducted over a 3-month accelerated period indicated that all formulations retained their physical integrity and antimicrobial efficacy. However, tablets with novel polymers showed better retention of drug content and minimal changes in dissolution behavior, suggesting superior stability. FTIR and DSC analyses confirmed no significant chemical interactions between the drug and excipients (Figure-3), supporting the compatibility of both conventional and novel polymers with the active pharmaceutical ingredients.

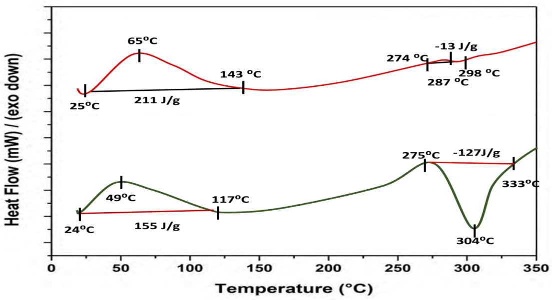

Figure-3: DSC thermogram of Pure drugs and AGM11

Stability studies confirmed that all formulations retained their physical and functional properties over the test period, with novel polymer-based tablets showing slightly better retention of drug content and release characteristics. This may be attributed to the protective matrix formed by these polymers, which can shield the active ingredients from environmental degradation. Compatibility studies using FTIR and DSC further validated the absence of chemical interactions, ensuring formulation safety and efficacy. These findings support the long-term viability of bilayer tablets incorporating novel polymers for antimicrobial applications.

Microbicidal activity: Antimicrobial testing against *Escherichia coli, Klebsiella pneumoniae*, and *Proteus mirabilis* demonstrated that bilayer tablets containing novel polymers exhibited superior microbicidal activity especially formulation AGM11. The zone of inhibition for these formulations ranged from 14.2 to 18.6 mm (formulation: AGM11), significantly higher than those with conventional polymers, which showed zones between 9.5 and 12.3 mm. Minimum inhibitory concentration (MIC) values were also lower for novel polymer-based tablets, indicating enhanced potency. This improved activity is attributed to better drug release kinetics and potential synergistic effects of the polymers with the active agents. Further, the microbial activity was assessed with biochemical and staining tests to characterize the bacterial strains. Gram staining revealed that the predominant isolates were Gram-negative bacilli, consistent with common bacteria such as *Escherichia coli* and *Klebsiella pneumoniae*. The catalase test showed positive results, indicating the presence of catalase enzyme capable of breaking down hydrogen peroxide into water and oxygen—a trait typical of aerobic bacteria. The amylase test confirmed starch hydrolysis in several isolates, suggesting enzymatic activity linked to nutrient acquisition. Urease test results were positive in select strains, particularly *Proteus mirabilis*, indicating their ability to hydrolyze urea into ammonia and carbon dioxide, which contributes to urinary alkalinization and stone formation. These findings support the pathogenic potential and metabolic versatility of the tested microbes.

The microbiocidal evaluation demonstrated that bilayer tablets containing novel polymers exhibited stronger antimicrobial activity. The larger zones of inhibition and lower MIC values suggest improved drug availability and possibly synergistic interactions between the polymers and active agents [16]. Chitosan, for instance, is known for its intrinsic antimicrobial properties, which may have contributed to the enhanced efficacy. These results underscore the potential of novel polymers not only as release modulators but also as active participants in microbial suppression. Thereafter, the biochemical profiling provided essential insights into their metabolic traits and pathogenic potential [17]. The Gram-negative nature of the isolates aligns with the typical profile of bacteria, particularly *E. coli* and *K. pneumoniae*. Positive catalase and amylase tests indicate robust oxidative and enzymatic activity, which may contribute to tissue invasion and nutrient acquisition. The urease-positive results, especially in Proteus species, suggest a role in urinary alkalinization and stone formation, reinforcing the need for effective antimicrobial strategies that target both planktonic and biofilm-associated bacteria.

Conclusion:

The study successfully demonstrated that bilayer tablet formulations incorporating novel polymers offer significant advantages in enhancing antimicrobial efficacy especially the formulation AGM11 among twelve formulations. By combining immediate and sustained drug release profiles, these formulations achieved improved therapeutic outcomes, better biofilm inhibition, and greater microbial suppression compared to conventional polymer systems. The inclusion of innovative polymers not only optimized drug delivery but also contributed to stability, compatibility, and targeted action. These findings highlight the potential of bilayer tablets as a promising platform for advanced antimicrobial therapy, paving the way for safer, more effective treatments in managing bacterial infections.

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