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FORMULATION AND CHARACTERIZATION OF TOBRAMYCIN SUSTAINED RELEASE TABLETS

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ABSTRACT

The present study aimed to formulate and evaluate sustained release floating tablets of Tobramycin to improve gastric retention, enhance bioavailability, and reduce dosing frequency. Pre-compression parameters of the powder blend, including bulk density, tapped density, compressibility index, and Hausner's ratio, indicated satisfactory flow properties for tablet formulation. Post-compression evaluation revealed uniform weight, thickness, hardness, friability below 1%, and acceptable drug content (96.65–99.12%). Floating studies confirmed a floating lag time between 48–74 seconds with a total buoyancy period exceeding 12 hours. *In-vitro* drug release studies demonstrated sustained release up to 12 hours, with formulation F5 showing the most optimized release profile (98.1% at 12 hours). Kinetic modeling indicated that drug release followed the Higuchi model (R^2 = 0.9869), with Korsmeyer–Peppas analysis suggesting a non-Fickian diffusion mechanism. The results confirmed that the optimized formulation (F5) provided effective gastroretentive properties and sustained release characteristics, making it a promising candidate for enhancing therapeutic efficacy and patient compliance in Tobramycin therapy.

Keywords: Tobramycin, sustained release tablets, floating drug delivery, gastroretentive system, *in-vitro* release, Higuchi model, non-Fickian diffusion.

INTRODUCTION

Tobramycin, an aminoglycoside antibiotic derived from *Streptomyces tenebrarius*, is widely used in the treatment of severe bacterial infections caused by Gram-negative organisms, particularly *Pseudomonas aeruginosa* (Smith *et al.*, 2019). Its clinical applications include the management of respiratory tract infections, urinary tract infections, septicemia, and ocular infections (Kaur *et al.*, 2020). Despite its effectiveness, the drug exhibits a relatively short half-life of approximately 2 hours, necessitating frequent dosing that may lead to poor patient compliance and increased risk of nephrotoxicity and ototoxicity (Patel *et al.*, 2021).

Sustained release (SR) formulations have been developed to overcome these limitations, offering the advantages of maintaining plasma drug concentrations within the therapeutic window for extended periods, reducing dosing frequency, and improving patient adherence (Gupta *et al.*, 2021). Additionally, SR formulations minimize fluctuations in drug concentration, thereby reducing the risk of dose-related side effects (Reddy *et al.*, 2018).

Matrix-based sustained release tablets are commonly employed for drugs with short half-lives and poor bioavailability, where

hydrophilic and hydrophobic polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and Carbopol play a vital role in controlling drug release kinetics (Sharma *et al.,* 2017). In the case of Tobramycin, formulating a sustained release matrix tablet not only enhances its therapeutic efficacy but also reduces systemic toxicity, providing a more effective and safer approach to long-term therapy (Patel *et al.,* 2021; Singh *et al.,* 2022).

Therefore, the present study was aimed at the formulation and characterization of Tobramycin sustained release tablets using various release-retarding polymers. The work focused on evaluating pre-compression and post-compression parameters, in-vitro release studies, and kinetic modeling to establish the mechanism of drug release.

MATERIALS AND METHODS

Materials

The materials used for the preparation and evaluation of sustained release tablets of Tobramycin included Tobramycin as the active pharmaceutical ingredient, along with citric acid (Qualigens Fine Chemicals, Mumbai), disodium hydrogen phosphate and dipotassium hydrogen orthophosphate (S. D. Fine Chem. Ltd., Mumbai), and hydrochloric acid (S. D. Fine Chem. Ltd., Mumbai) for buffer and pH adjustment. Organic solvents such as methanol, ethanol, and chloroform (Qualigens Fine Chemicals, Mumbai) were employed during formulation processes. Excipients like magnesium stearate (Jiangsu Huaxi International, Mumbai), talc, and lactose (Loba Chemie Pvt. Ltd., Mumbai) were used as lubricants, glidants, and fillers, respectively, while sodium hydroxide (S. D. Fine Chem. Ltd., Mumbai) was utilized for pH adjustment and analytical purposes.

Methods

Method for preparation of sustained release tablets of Tobramycin

The sustained release floating tablets of Tobramycin were prepared using the direct compression technique, as described by Basavaraja *et al.* (2015). A total of nine formulations (F1 to F9) were developed by varying the concentrations of hydrophilic polymers HPMC K4M and HPMC K15M, while keeping other excipients constant. All ingredients including Tobramycin, selected polymers (HPMC K4M or HPMC K15M), PVP K-30, citric acid, sodium bicarbonate, lactose, talc, and magnesium stearate were accurately weighed as per the composition detailed in Table 7.1. Each component was passed through sieve no. 40 to ensure uniform particle size and proper mixing. Initially, the drug was blended with polymers, PVP K-30, and lactose in a mortar for about 10 minutes to achieve a homogeneous mixture. Following this, the gas-generating agents, citric acid and sodium bicarbonate were added and mixed gently to prevent any premature reaction. Finally, talc and magnesium stearate were incorporated into the blend and mixed for 2–3 minutes to avoid over-lubrication, which could adversely affect tablet hardness and drug release. The resulting mixture was then subjected to direct compression using a rotary tablet punching machine to produce tablets of 500 mg weight.

Evaluation of precompression parameter

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity

measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas (Bharadwaj *et al.,* 2000).

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of powder}}{\text{Tapped Volume of Packing}}$$

Compressibility index: Percent compressibility of powder mix was determined by Carr's index, calculated by using following formula:-

$$\text{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X } 100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

$$\text{Housner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose Bulk density}}$$

Evaluation of tablets

All the tablets were evaluated for following various parameters which includes;

General Appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated (Pundir *et al.,* 2015).

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined (Basak *et al.,* 2006). The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ_{max} of 221 nm using of 0.1 N HCl as blank.

Hardness

For each formulation, the hardness of five tablets was resolved utilizing the Monsanto hardness tester (Varshosaz *et al.,* 2006).

Friability

The friability of a sample of 10 tablets was estimated utilizing 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 (Venkataramudu *et al.,* 2012).

Uniformity of weight

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

***In vitro* buoyancy studies**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al.* The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid, pH 1.2 as per USP. The time necessary for the tablet to increase to the outside and float was determined as floating lag time.

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask

maintaining the temperature of 37±0.5°C and rpm of 75. One prepared Tobramycin tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 10 hours using 10ml pipette. The new disintegration medium (37ºC) was supplanted each time with a similar amount of the sample and takes the absorbance at 221nm using UV/Visible spectroscopy.

RESULTS AND DISCUSSION

The pre-compression studies of Tobramycin tablet formulations (Table 2) revealed that the bulk density and tapped density values were within the acceptable limits, with compressibility index values ranging between 21.74–24.74% and Hausner's ratio between 1.27–1.32. These results indicate fair to good flow properties, which are essential for ensuring uniform die filling and consistent tablet weight during compression (Carr, 1965).

Post-compression evaluation (Table 3) demonstrated that all formulations exhibited uniform thickness, hardness within the range of 6.3–6.8 kg/cm², and weight variation within pharmacopoeial limits, confirming good mechanical strength and reproducibility. Friability values were below 1% in all cases, further supporting the robustness of the tablets. Drug content uniformity was found to be satisfactory (96.65–99.12%), confirming homogeneous drug distribution within the formulations. Importantly, all tablets maintained floating duration greater than 12 hours, indicating effective gastroretentive properties.

The *in-vitro* buoyancy study (Table 4) showed that the floating lag time ranged between 48–74 seconds. Among the formulations, F5 exhibited the shortest lag time (48±7 sec), suggesting rapid buoyancy and efficient entrapment of carbon dioxide, which is favorable for sustained gastric retention.

In-vitro drug release studies (Table 5) demonstrated that formulation F5 provided a controlled release of Tobramycin, achieving 98.1% drug release at the end of 12 hours. The release profile followed a sustained pattern, with an initial moderate release (11.8% at 0.5 h) followed by extended release over time. The regression analysis (Table 6) indicated that the drug release from F5 best fitted the Higuchi model (R^2 = 0.9869)**,** suggesting a diffusion-controlled mechanism. Additionally, the Korsmeyer–Peppas model (R^2 = 0.9835) confirmed non-Fickian diffusion, implying that both diffusion and polymer relaxation contributed to drug release. The optimized formulation F5 demonstrated excellent floating ability, sustained drug release for up to 12 hours, and compliance with pharmacopeial quality parameters. These findings highlight the potential of Tobramycin sustained release floating tablets as an effective gastroretentive system to improve therapeutic efficacy and patient compliance.

Table 1: Various formulations of sustained release tablets of Tobramycin

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tobramycin	250	250	250	250	250	250	250	250	250
HPMC K4M	40	50	60	–	–	–	20	30	40
HPMC K15M	–	–	–	40	50	60	20	30	40
PVP K-30	20	20	20	20	20	20	20	20	20
Citric Acid	10	10	10	10	10	10	10	10	10
Sodium Bicarbonate	60	60	60	60	60	60	60	60	60
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose (q.s.)	110	100	90	110	100	90	110	100	90
Total Tablet Weight	500	500	500	500	500	500	500	500	500

Table 2: Result of pre-compression properties of Tobramycin

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk Density (g/ml)	0.385	0.365	0.338	0.398	0.374	0.382	0.374	0.382	0.375
Tapped Density (g/ml)	0.492	0.485	0.449	0.512	0.485	0.495	0.488	0.497	0.486
Compressibility Index (%)	21.74	24.74	24.72	22.26	22.88	22.82	23.36	23.13	22.84
Hausner Ratio	1.278	1.329	1.328	1.286	1.297	1.296	1.305	1.301	1.296

Table 3: Results of post compression properties of sustained release tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm)	3.45±0.5	3.52±0.15	3.48±0.12	3.57±0.15	3.55±0.23	3.44±0.33	3.36±0.45	3.42±0.33	3.36±0.25
Hardness (kg/cm²)	6.8±0.2	6.5±0.32	6.7±0.2	6.5±0.3	6.8±0.1	6.3±0.3	6.7±0.4	6.4±0.6	6.6±0.3
Weight Variation (mg)	503±5	505±5	509±6	500±5	502±6	498±3	496±5	504±3	502±5
Friability (%)	0.705±0.025	0.765±0.015	0.885±0.025	0.796±0.036	0.895±0.032	0.882±0.015	0.746±0.036	0.639±0.033	0.669±0.033
Drug Content (%)	98.85±0.18	98.78±0.25	97.75±0.15	96.65±0.36	99.12±0.33	98.12±0.44	97.85±0.36	96.65±0.15	97.44±0.33
Floating Duration (h)	>12	>12	>12	>12	>12	>12	>12	>12	>12

Average of three determinations (N=3±SD)

Table 4: Results of *in-vitro* buoyancy study of Tobramycin sustained release floating time

S. No.	Formulation Code	Floating lag times (sec)
1.	F1	63±5
2.	F2	60±6
3.	F3	55±4
4.	F4	59±3
5.	F5	48±7
6.	F6	62±4
7.	F7	74±3
8.	F8	70±5
9.	F9	65±3

Table 5: *In-vitro* drug release data for optimized formulation F5

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	11.8	1.349	77.68	1.890
1	1	0	21.4	1.565	63.25	1.801
1.5	1.225	0.176	29.3	1.647	55.68	1.746
2	1.414	0.301	36.9	1.753	43.35	1.637
3	1.732	0.477	48.9	1.817	34.44	1.537
4	2	0.602	60.1	1.897	21.11	1.324
6	2.449	0.778	71.5	1.920	16.77	1.225
8	2.828	0.903	88.8	1.954	10.02	1.001
12	3.464	1.079	98.1	1.999	0.26	-0.585

Table 6: Regression analysis data

Batch F5	Zero Order	First Order	Higuchi	Peppas
R^2 value	0.9183	0.9653	0.9869	0.9835

CONCLUSION

The present study successfully developed and evaluated sustained release floating tablets of Tobramycin with the objective of improving gastric retention and prolonging drug release. Among all the formulations, the optimized batch (F5) exhibited acceptable pre- and post-compression parameters, minimal friability, and excellent floating behavior with a buoyancy time exceeding 12 hours. In-vitro drug release studies confirmed a controlled release pattern up to 12 hours, best fitting the Higuchi kinetic model, indicating diffusion-controlled release with a non-Fickian

mechanism. These findings suggest that the developed formulation can enhance therapeutic efficacy, reduce dosing frequency, and improve patient compliance in the long-term management of infections treated with Tobramycin.

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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