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FORMULATION AND CHARACTERIZATION OF INVASOMES GEL OF TOBRAMYCIN FOR EFFECTIVE TREATMENT OF TOPICAL DISEASE

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ABSTRACT

The present study aimed to formulate and characterize tobramycin-loaded invasomal gel for effective topical drug delivery. Invasomes were prepared using phospholipids, ethanol, and terpene components to enhance skin permeation and drug retention. The prepared formulations (F1–F6) were evaluated for vesicle size and entrapment efficiency. The vesicle size was found in the range of 198.30–248.40 nm, indicating suitability for enhanced skin penetration. Among all formulations, F2 showed the smallest vesicle size and highest entrapment efficiency (83.55%), and was selected as the optimized formulation. The optimized invasomes were incorporated into gel formulations (IG-1 to IG-3) and evaluated for physicochemical parameters such as pH, viscosity, drug content, extrudability, and spreadability. All formulations exhibited acceptable properties suitable for topical application. Among them, IG-2 showed optimal characteristics with high drug content and appropriate consistency. In-vitro drug release studies demonstrated that the invasomal gel provided sustained drug release up to 12 hours (90.25%), whereas the pure drug showed rapid release within 4 hours. Release kinetics indicated that the formulation followed Higuchi and Korsmeyer–Peppas models, suggesting a diffusion-controlled release mechanism. In conclusion, the developed invasomal gel system enhances drug entrapment, provides controlled release, and improves topical delivery of tobramycin. The optimized formulation shows potential for effective treatment of topical infections with improved therapeutic efficacy and patient compliance.

KEYWORDS: Tobramycin, Invasomes; Invasomal gel, Vesicular drug delivery, Topical drug delivery, Entrapment efficiency, Particle size, Controlled drug release, Higuchi model, Korsmeyer–Peppas model, Skin permeation, Pharmaceutical formulation.

INTRODUCTION

Topical drug delivery systems have gained considerable attention in recent years due to their ability to deliver drugs directly to the site of action, thereby enhancing therapeutic efficacy and minimizing systemic side effects (Ezike et al., 2023).

However, the major challenge associated with conventional topical formulations is their limited penetration through the stratum corneum, which acts as a strong barrier to drug permeation. To overcome this limitation, novel vesicular drug delivery systems such as invasomes have been developed to enhance skin permeation and improve drug bioavailability (Prausnitz et al., 2012).

Invasomes are advanced lipid-based vesicular systems composed of phospholipids, ethanol, and terpene components, which work synergistically to enhance drug penetration across the skin. The presence of ethanol and terpenes disrupts the lipid packing of the stratum corneum, thereby increasing membrane fluidity and facilitating deeper drug permeation. Due to these unique properties, invasomes have emerged as a promising carrier system for topical and transdermal drug delivery (Jain et al., 2021).

Tobramycin is a broad-spectrum aminoglycoside antibiotic widely used in the treatment of bacterial infections, particularly those affecting the skin and soft tissues. Despite its potent antimicrobial activity, its topical delivery is often limited by poor penetration and rapid clearance from the site of application. Therefore, incorporation of tobramycin into an invasomal system can significantly enhance its permeation, retention, and overall therapeutic effectiveness in topical infections (Jodh et al., 2022).

The incorporation of invasomes into a gel base further improves patient compliance by providing ease of application, better spreadability, and prolonged residence time at the site of application. Gel formulations also offer improved stability and controlled drug release compared to conventional formulations. The combination of invasomes with gel systems thus provides a dual advantage of enhanced permeation and sustained drug delivery.

The present study is focused on the formulation and characterization of tobramycin-loaded invasomal gel for effective treatment of topical diseases. The developed formulation is expected to enhance drug permeation, improve therapeutic efficacy, and provide controlled release of the drug. Various formulation and evaluation parameters such as vesicle size, entrapment efficiency, drug content, viscosity, spreadability, and in-vitro drug release will be studied to ensure the effectiveness and stability of the developed system.

MATERIAL AND METHODS

Material

Tobramycin was obtained as a gift sample from a pharmaceutical source. Soya phosphatidylcholine, ethanol, and terpene (such as limonene or cineole) were used for the preparation of invasomes. Carbopol 934 was used as a gelling agent, while triethanolamine was used for pH adjustment. Propylene glycol was used as a permeation enhancer and humectant. All other reagents and solvents used were of analytical grade, and distilled water was used throughout the study. Standard laboratory instruments such as a magnetic stirrer, probe sonicator, pH meter, viscometer, and centrifuge were used for formulation and evaluation.

Methods

Formulation of Invasome of Tobramycin

Tobramycin-loaded invasomes were prepared using the mechanical dispersion method as described by Dragicevic-Curic et al. (2010). The procedure was performed as follows: Accurately weighed soya phosphatidylcholine (as per formulation, Table 1) was dissolved in ethanol. The mixture was vortexed for 5 minutes to ensure complete dispersion of the lipid in the solvent. Tobramycin and the specified terpene were added to the lipid-ethanol mixture. The combined mixture was continuously vortexed and sonicated for 5 minutes to achieve uniform dispersion and reduce the particle size. A fine stream of distilled water (up to 10% v/v of the total volume) was slowly added dropwise to the mixture using a syringe while maintaining continuous vortexing. This step allowed the formation of vesicular structures through gradual hydration. After the complete addition of water, the formulation was vortexed for an additional 5 minutes to obtain the final invasomal dispersion of Tobramycin (Dragicevic-Curic *et al.*, 2010).

Table 1: Composition of different invasomal formulation of Tobramycin.

Formulation	Drug (% w/v)	Terpene (%v/v)	Ethanol (ml)	Phosphatidylcholine (%w/v)
F1	50	0.25	10	0.25
F2	50	0.50	10	0.25
F3	50	0.75	10	0.50
F4	50	0.25	10	0.50
F5	50	0.50	10	0.75
F6	50	0.75	10	0.75

Characterization of Tobramycin-loaded invasomes

Entrapment Efficiency

Ultracentrifugation method was used for determining the percentage drug entrapment of the invasomal formulation. 1 ml of invasomal formulation was centrifuged for 40 minutes in an ultra-centrifuge (at 15000 rpm). The supernatant was further diluted with ethanol. UV-visible spectrophotometry was used for analysing the Tobramycin content at a wavelength of 221 nm (Aggarwal and Kaur, 2005). Percentage drug entrapment was calculated using the equation:

$$\% \text{ Entrapment efficiency} = \frac{\text{Total amount of drug} - \text{Amount of Free Drug}}{\text{total amount of drug}} \times 100$$

Vesicle Size

Microscopic analysis was performed to determine the average size of prepared invasomes. Formulation was diluted with distilled water and one drop was taken on a glass slide and covered with cover slip. (Ayman *et al.*, 2001; Amnuaikit *et al.*, 2018; Manchanda and Sahoo, 2018).

Preparation of Tobramycin loaded Invasomal Gel

Invasomal formulation having good entrapment efficiency, small particle sizewas incorporated in Carbopol 934 gel base. 1%, 2% and 3% i.e IG-1 (1%), IG-2 (2%) and IG-3 (3%) Carbopol gel base was prepared by mixing carbopol 934 with distilled water and leaving it in the dark to allow the gelling agent to completely swell. Triethanolamine was added to the dispersion drop by drop to create a transparent viscous gel. Finally, the optimised invasomal formulation was gently mixed with Carbopol gel base which was moderately stirred with a mechanical stirrer (Singh *et al.*, 2020).

Evaluation of Tobramycin loaded invasomal gel

Determination of physiochemical properties

Physical appearance, clarity, washability, occlusiveness and organoleptic characteristics of the gel were studied by visual observation. A pH metre was used to evaluate the pH of Tobramycin invasomal gel. The measurements were taken in triplicate, and the average value was determined (Kumar *et al.*, 2021).

Homogeneity and Grittiness

Grittiness of the invasomal gel was determined by pressing a small amount of gel between the index finger and the thumb. The gel was closely observed for the presence of any coarse particles on the fingers for determining its consistency. The homogeneity of the gel under evaluation was detected by rubbing a small proportion of gel on the skin at the backside of the hand (Chandra *et al.*, 2019).

Spreadability

The spreadability of the invasomal gel was studied by measuring the change in diameter when 500 mg of gel was placed between two horizontal plates of 20×20 cm2 with a standardized weight of 125 g placed over it (Bachhav and Patravale, 2009).

Extrudability Study

The prepared invasomal gel was filled in collapsible tubes and its extrudability was estimated in terms of weight in grams required to produce a 0.5 cm ribbon of gel in 10 seconds (Sareen *et al.*, 2011).

Viscosity

For determining the viscosity of the invasomal gel Brookfield viscometer (DV-E Brookfield Engineering Laboratories, MA, USA) at 37 °C with spindle No.7 was used. An appropriate amount of gel was placed onto the centre of the viscometer plate directly below the spindle using the spatula and viscosities were measured.

Content uniformity analysis of gel

To validate that the Tobramycin in the developed invasomal gel was homogeneous, 0.5 g samples were drawn from three separate sections of the gel. Samples were extracted using methanol (10 ml) followed by centrifugation (3000 rpm) for 15 minutes. The supernatant was filtered, and Tobramycin content was determined using a UV-visible spectrophotometer with a λ_{max} at 221nm.

***In vitro* drug release**

In vitro drug release study was conducted using Franz's diffusion cell with receiver cell volume and effective permeation area of 10 ml and 0.196 cm^2 respectively. The donor cell containing the invasomal gel was placed over the receptor cell in which phosphate buffer saline (pH 7.4) was filled. A pre-treated dialysis membrane of molecular weight cut off 12-14 kD was placed between the donor and receptor compartments using a clamp. The experiment was conducted for 24 hours at a temperature of 37 ± 1°C with constant magnetic stirring at 600 rpm. Samples were estimated for Tobramycin content using UV spectrophotometer at 221 nm which were withdrawn from the receptor cell at premediated time gaps i.e., 1, 2, 3, 4, 5, 6, 8 and 12 hours with simultaneously addition of fresh release medium in the receiver compartment to balance the sink conditions. To know the release kinetics of invasomal gel, the data was treated according to different release kinetics models (Kumar *et al.*, 2021).

RESULTS AND DISCUSSION

The present study focused on the formulation and characterization of tobramycin-loaded invasomal gel for enhanced topical drug delivery. The results obtained from various evaluation parameters clearly demonstrate the effectiveness of the developed system in improving drug entrapment, stability, and controlled release.

The vesicle size of invasomal formulations (Table 2) ranged from 198.30 nm to 248.40 nm, indicating nanosized vesicles suitable for enhanced skin penetration. Among all formulations, F2 exhibited the smallest vesicle size (198.30 nm), which is advantageous for better permeation through the stratum corneum. Smaller vesicle size generally contributes to increased surface area and improved drug delivery efficiency.

Entrapment efficiency results (Table 3) showed that formulation F2 possessed the highest entrapment efficiency (83.55 ± 0.23%), indicating its superior ability to incorporate and retain the drug within the vesicular system. The higher entrapment efficiency may be attributed to the optimal composition of phospholipids, ethanol, and terpene in the formulation, which enhances drug encapsulation.

Based on vesicle size and entrapment efficiency, F2 was selected as the optimized formulation (Table 4), with a particle size of 185.65 nm and entrapment efficiency of 83.55 ± 0.28%. These results confirm that F2 is the most suitable formulation for further incorporation into gel.

The invasomal gel formulations (Table 5) exhibited acceptable physicochemical properties. The pH of all formulations ranged from 5.7 to 6.3, which is compatible with skin pH and ensures minimal irritation upon

application. Viscosity values indicated good consistency and ease of application, while extrudability and spreadability results confirmed that the gels can be easily applied and spread uniformly on the skin. Among the formulations, IG-2 showed optimal characteristics with balanced viscosity, high drug content (99.25 ± 0.30%), and satisfactory spreadability.

In-vitro drug release studies (Table 6) revealed a sustained release pattern from the invasomal gel (IG-2) compared to the pure drug. The pure drug exhibited rapid release, reaching 90.25% within 4 hours, whereas the invasomal gel showed a controlled and prolonged release, achieving 90.25% over 12 hours. This sustained release behavior is beneficial for maintaining therapeutic drug levels for an extended period and reducing the frequency of application.

The regression analysis (Table 7) indicated that the drug release from the optimized formulation IG-2 follows Higuchi (R^2 = 0.9714) and Korsmeyer-Peppas (R^2 = 0.972) models, suggesting that the release mechanism is predominantly diffusion-controlled. This confirms that the invasomal gel system effectively regulates drug release through a controlled diffusion process.

The study demonstrates that invasomal gel is a promising delivery system for tobramycin, offering enhanced drug entrapment, suitable physicochemical properties, and sustained drug release. The optimized formulation (IG-2) shows potential for effective topical treatment, improving therapeutic efficacy and patient compliance compared to conventional formulations.

Table 2: Characterization of average vesicle size of Invasome.

Invasomal Formulation	Vesicle Size (nm)
F1	228.12
F2	198.30
F3	212.75
F4	248.40
F5	239.10
F6	243.55

Table 3: Characterization of Entrapment Efficiency of Invasome.

Invasomal Formulation	Entrapment Efficiency (%)
F1	74.78±0.45
F2	83.55±0.23
F3	72.45±0.65
F4	75.68±0.85
F5	74.12±0.74
F6	73.60±0.36

Table 4: Characterization of optimized formulation of invasome

Formulation	Particle Size (nm)	Entrapment Efficiency
F2	185.65	83.55 ± 0.28

Table 5: Characterization of Invasomes gel based formulation.

Formulation	Viscosity (cps)	pH	Drug Content (%)	Extrudability (g)	Spreadability (g.cm/sec)
IG-1	3580±18	5.7±0.2	98.60±0.40	170±7	11.50±0.30
IG-2	3690±25	5.9±0.3	99.25±0.30	178±9	9.90±0.20
IG-3	3760±40	6.3±0.4	97.80±0.35	187±12	8.80±0.15

Table 6: Cumulative drug release from invasomal gel (IG-2) and pure drug of Tobramycin

Time (hrs.)	Tobramycin Invasomal Gel (%)	Pure Drug (%)
1	8.75	26.10
2	13.80	46.00
3	27.10	69.20
4	49.50	90.25
5	53.80	-
6	66.10	-
7	72.50	-
8	82.60	-
12	90.25	-

Table 7: Regression analysis of data for invasomal gel formulation IG2.

F. Code	Zero order	First order	Higuchi	Pappas
IG2 (R^2)	0.8758	0.9678	0.9714	0.972

CONCLUSION

The study successfully developed a tobramycin-loaded invasomal gel with enhanced drug entrapment and nanosized vesicles suitable for improved skin penetration. The optimized formulation exhibited desirable physicochemical properties and provided sustained drug release. The invasomal gel system proves to be an effective and promising approach for topical

drug delivery with improved therapeutic efficacy and patient compliance.

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