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Transfersomes: A Review for Transdermal Drug Delivery

Nayana D N, Shreya K, J Baseer UL Sumeer, Lingesh Kumar M S, Oyitabu Ifunanya Mercy, V. Kusum Devi, Vijaya G Joshi, Prachi Kabra, Nidhi Malviya, Rama Bukka, Rama Nargund, Shravan L. Nargund, Shachindra L. Nargund

***Abstract*— Transfersomes are advanced carriers for targeted transdermal drug delivery, composed of phosphatidylcholine and an edge activator. They penetrate the stratum corneum through intracellular and transcellular routes using an osmotic gradient. Their benefits include broad solubility, improved skin penetration, biocompatibility, and biodegradability, though they may face oxidative degradation and higher costs. Formulated through rotary evaporation and sonication, they include phospholipids, surfactants, and drugs. Key evaluation parameters include vesicle size, zeta potential, entrapment efficiency, drug content, and in vitro release. Transfersomes are ideal for controlled release, large molecule delivery, targeted subcutaneous distribution, and transdermal immunization, enhancing drug delivery effectively.**

***Index Terms*—*Transfersomes*, phosphatidylcholine, surfactants, Transdermal, gels**

I. INTRODUCTION

Transfersomes (TF) are a targeted transdermal drug delivery system that is composed of phosphatidylcholine and an edge activator[1]. They are also known as ultra-deformable vesicles.

Nayana D N1, Shreya K1, J Baseer UL Sumeer1, Lingesh Kumar M S1, Oyitabu Ifunanya Mercy1, V. Kusum Devi2, Vijaya G Joshi3, Prachi Kabra4, Nidhi Malviya1*, Rama Bukka1, Rama Nargund5, Shravan L. Nargund1, Shachindra L. Nargund6

[1]Department of Pharmaceutics, Nargund College of Pharmacy, Bangalore -85, Karnataka

[2]Department of Pharmaceutics, NITTE College of Pharmaceutical Sciences, Bangalore-64, Karnataka.

[3]Department of Pharmaceutics, Government College of Pharmacy, Bangalore-27, Karnataka, Bharat.

[4]Department of Quality Assurance, Nargund College of Pharmacy, Bangalore -85, Karnataka

[5]Department of Pharmacology, Nargund College of Pharmacy, Bangalore -85, Karnataka

[6]Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bangalore -85, Karnataka

When applied topically, they have a greater ability to penetrate deeper into the skin than liposomes because they are made of more complex vesicles with extremely flexible and self-regulating membranes[2]. When compared to other formulations, these vesicles are widely used because of their low toxicity, biodegradation, capacity to encapsulate both hydrophilic and lipophilic molecules, and ability to extend the drug's duration in the systemic circulation[3]" by creating an "osmotic gradient" that allows the drug to enter the stratum corneum by the intracellular or transcellular route through evaporating water[4].

However, transdermal delivery has several advantages over traditional oral delivery[5], such as avoiding first-pass metabolism, minimizing side effects, stabilizing drug levels, enhancing physiological and pharmacological responses, and improving patient compliance. However, transdermal delivery shows many challenges when applied topically, so penetration enhancers are used to increase the drug's efficacy to penetrate across the skin. Some enhancers, like iontophoresis or sonophoresis, can cause itching, erythema, and local irritation[6].

The name transfersome is derived from the Latin word "transferre," which means "to carry across," and "some," which means "body."[2]Because transfersomes are more elastic than other carrier systems, it is appropriate for skin penetration and can be used for targeted and regulated drug administration[7]. Disadvantages of transfersomes include oxidative degradation and expense. Using the traditional rotary evaporation method, sonication methods are used to formulate the transfersome. It includes surfactants, phospholipids, and drugs. In this drug delivery system, edge activators like tween80, span80, sodium cholate, and sodium deoxycholate are often utilized to increase flexibility. Phospholipids such as soya phosphatidylcholine, egg lecithin, and cholesterol are used to produce vesicles. **Figure 1** schematically represents the transfersome.

The barrier properties of stratum corneum can be overcome using a vesicular system like transfersome, which are ultra-flexible, softer, adjustable membrane carriers that can deliver the drug to the systemic circulation by squeezing the intracellular sealing lipids of stratum corneum. They can penetrate both small and large molecules through the skin[8] Zeta potential, vesicle morphology, entrapment efficiency, drug content, turbidity measurement, degree of

deformability, or permeability measurement. Transfersomes can be assessed based on their penetrating ability, occlusion effect, surface charge, charge density, in vitro drug release, in vitro skin permeation investigations, and physical stability. It can be applied to transdermal immunization, target distribution to peripheral subcutaneous tissues, and controlled release of drugs. Transferosomal gel can enhance drug delivery to a particular site and extend drug release[5].

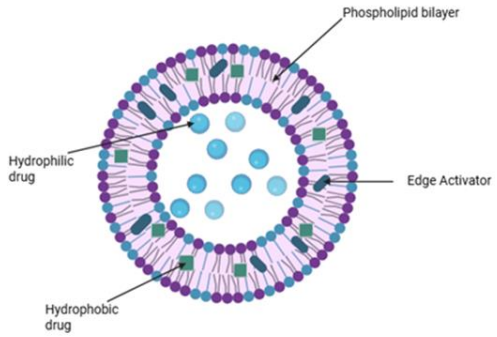

Figure 1. Schematic representation of a transfersomes.

Advantages of transfersome

- It consists of hydrophilic and hydrophobic moieties, which will increase the solubility of drugs and allow them to flow through narrow constrictions without the loss of drug[1].
- They can carry both low and large molecular weight medications, including corticosteroids, analgesics, and anaesthetics[1].
- It is biodegradable and biocompatible[1].
- It can prevent the degradation of encapsulated drugs compared to other carriers. Ex: protein[2].
- Herbal drugs can also be incorporated into transfersomes as they can penetrate the stratum corneum and supply nutrients locally to maintain their functioning[2].
- It has high entrapment efficiency[3].
- This can be easily deformable and permeate through the stratum corneum without the loss of drug than other carrier systems[3].

Disadvantages of transfersome

- Lipids in transfersomes formulations are unstable and prone to oxidative breakdown[1].
- These are highly expensive[1].
- It required a specialized technique for the formulation of transfersome[3].

Method of preparation of transfersome

1. Rotary film evaporation method

It is also called as Modified handshaking method, here API, lecithin, and edge activator are solubilized in a 1:1 mixture of chloroform with ethanol by manual shaking at a temperature higher than the lipid's transition temperature, and the resulting liquid is allowed to evaporate the organic solvent. The thin lipid coating is left to sit for 24 hours to help remove the organic solvent. Later, the film is hydrated by rotating round round-bottom flask at 60 rpm for around an hour at room temperature with a pH 6.5 phosphate buffer. Subsequent to hydration, the vesicles are permitted to swell for approximately two hours at room temperature. Finally, any leftover vesicles are sonicated at room temperature to yield smaller vesicles[6].

2. Reverse phase evaporation method

By nitrogen purging of aqueous medium containing edge activators, both lipids and organic solvents were mixed in a round-bottomed flask. The drug will either mix with hydrophilic or lipophilic materials, depending on the solubility. After sonication, the prepared material is allowed to sit for 30 minutes to achieve a homogenous mixture. The organic phase is eliminated by maintaining pressure, and the substance is collected and then subsequently formulated into a viscous gel[6].

3. Vortex or sonication method

Here, phospholipids and edge activators are combined and continuously swirled until they are fully dissolved in phosphate buffer. Before being extruded through polycarbonate membranes, the milky suspension is sonicated in a bath sonicator after it has formed[6].

4. Ethanol Injection Method

This method is more advantageous than another method of preparation, where medication and water solution are warmed up at a consistent temperature with continuous mixing. Phospholipids and edge activators are blended with an ethanolic solution in aqueous media until transfersome are formed[5].

5. Freeze-thaw method

This method consists of freezing the multi-lamellar vesicle suspension and consequently transferring it to a tube and dipping it in a nitrogen bath by maintaining the temperature of -300°C for 30 seconds. The obtained suspension has been frozen by being treated at a high temperature for 8-9 rounds[5].

Transferosomal Gel is prepared by using various hydrophilic polymers like Carbopol 934, polycarbophil, hydroxy propyl methyl cellulose or sodium alginate as a gelling agent. A specified quantity of these polymers is placed in a beaker containing purified water and allowed to soak for 12 hours (overnight). To this, transferosomal suspension can be added, and Glycerine or propylene glycol is slowly added

as permeation enhancers and moistening agent with gentle, continuous stirring until a homogeneous gel is formed[9].

Table

1 represents few drugs and carrier lipids investigated as

Table 1. Transfersome carrier system and drugs

Drug and Drug carrier system	Excipients	Preparation method
Lornoxicam transfersomal gel[10]	*Lipids:* Phosphatidylcholine, phospholipon®90G *Surfactants:* Tween 80, Sodium deoxycholate *Solvents:* Chloroform: Methanol (2:1) *Gelling agents:* Hydroxypropyl cellulose (15 % w/v), Hydroxypropyl methyl cellulose (HPMC) (2.5 %w/v), Sodium carboxymethyl cellulose (2 %w/v), Carbopol 934, Sodium alginate (3% w/v)	Thin film hydration method Hydrating solvent: phosphate buffer pH 6.8
Piroxicam transfersomal gel [11]	*Lipids:* Soy phosphatidylcholine, Cholesterol *Surfactants:* Span80, Tween 80 *Solvents:* Chloroform: Methanol (3:1) *Gelling agents:* Carbopol 914, pH adjusted with triethanolamine	Rotary evaporation method Hydrating solvent: 10 % v/v hydroethanolic solution of drug.
Ivabradine HCL transfersomal film[12]	*Lipids:* Soy lecithin, *Surfactant:* Tween80, Sodium Lauryl Sulphate, Cetrimide *Solvents:* Sorenson phosphate buffer pH7.4, anhydrous ethanol *Film forming polymer:* Starch: HPMC (1:1) *Plasticizer:* Propylene Glycol (300 mg)	Ethanol injection technique
Proanthocyanidin transfersomal gel[13]	*Lipid:* Phospholipid 90 G *Surfactant:* Tween 80 *Solvents:* Chloroform *Gelling agent:* Methyl cellulose (4 5 w/v)	Thin film hydration method Hydrating solvent: phosphate buffer saline (PBS) pH 7.4
Famciclovir transfersomal gel[14]	*Lipid:* Phospholipid and Cholesterol *Surfactants:* Tween 80 *Gelling agent:* Carbopol 940	Thin film hydration method
Itraconazole transfersomal Hydrogel [15]	*Lipids:* Phospholipid 90 H *Surfactants:* Sodium deoxycholate, sodium lauryl sulphate *Gelling agent:* HPMC	Thin lipid film hydration method
Voriconazole -clove oil Nano Transferosomal *in situ* nasal gel [16]	*Lipid:* Soybean lecithin, *Surfactant:* Tween 80 *Gelling agent:* Gallen gum	Thin layer evaporation technique
Genistein transfersomal Hydrogel[17]	*Lipid:* Phospholipon® 90 G *Surfactant:* Span 60, D α tocopherol polyethylene glycol 1000 succinate *Solvent:* drug in Absolute Ethyl alcohol; lipids and surfactants in chloroform *Gelling agent:* 2 % low MW Chitosan in 1% glacial acetic acid, Carbopol 940 (0.5% w/v)	Thin film hydration method Hydrating solvent: 10ml deionised water containing glycerine
Rasagiline mesylate transfersomal gel[18]	*Lipid:* Phosphatidylcholine, cholesterol *Surfactant as edge activators:* Span 60, Sodium deoxycholate, Sodium cholate, Pluronic® F-68, Pluronic® L-35, Pluronic® L-31 Solvent: Ethanol	Thin film hydration technique Hydrating solvent: PBS 7.4
Ebastine transfersomal Oral films[19]	*Lipid:* Phospholipon® 90 H *Edge activators:* Tween80, Span 20 *Solvents:* chloroform: methanol (2:1) *Gelling agent:* HPMC K 15M (2-3%w/v) *Plasticizer:* Glycerol (4-8%)	Thin film hydration method Hydrating solvent: PBS pH 7.4
Silymarin transfersomal gel[20]	*Lipid:* Phospholipone® H 100, *Surfactants:* Span 80, Tween 80, *Solvent:* Chloroform: methanol (1:1) Gelling agent: HPMC (4% w/v) in PBS	Rotary flask evaporation sonication technique Hydrating solvent: PBS pH 7.4 with 0.02 % sodium azide

transfersome along with various methods of preparation. Evaluation parameters are viscosity, pH, drug content, and homogeneity.

Transferosomal films are prepared by the solvent casting method and evaluated for drug content, weight and thickness variation, pH, folding endurance, tensile strength, and moisture content.

Characterization of transfersome

Transfersomes are characterized for Particle size and Poly dispersity index (PDI), Zeta potential, Drug Entrapment efficiency, SEM or TEM, FTIR, DSC, XRD. They are evaluated for *in vitro* release, *ex vivo* permeation, *in vivo* preclinical studies.

Particle Size (PS), Poly dispersity Index (PDI) and Zeta Potential (ZP)

Photon correlation spectroscopy measures PS, PDI and ZP at an angle of 90° with water as dispersant. The light scattering method is used to determine the optimised formulation's size distribution, and vesicle size. In an study Ibuprofen transfersomes vesicle's average diameter was measured as 632.5nm with a PDI of 0.796 in an reported study[21].

Entrapment efficiency (%EE)

The entrapped efficiency of transfersome can be detected by direct or indirect method. In the direct method the sediment (entrapped drug) whereas in the indirect method the supernatant (unentrapped drug) is considered for estimation. A study detected 83% EE with 297nm particle size. The researchers employed thin film hydration technique for transfersome of Ibuprofen by utilizing oleic acid, cholesterol, Span 80, Tween 80, methanol and chloroform[22].

%Entrapment Efficiency= Amount of drug entrapped/ Total Drug×100

Morphology

Morphology of transfersomes can be explored by Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM). In a dermal delivery for transfersomes vesicle of combined drugs meloxicam and dexamethasone, SEM images revealed distinct, almost spherical vesicles with a clear outline. The image showed that developed vesicles are of colloidal dimensions. The outline and core of vesicles confirmed vesicular characteristics, indicating the integrity of closed structures[23]. Transfersomes vesicle of flurbiprofen illustrates smooth spherical-shaped discrete particles appearing in SEM, whereas, in TEM, it was observed that the vesicles were irregular, spherical in the nanoscale range of 500-100nm[24].

Fourier-transform infrared (FTIR) spectroscopy

It is carried out to check the purity of the drug and drug excipient compatibility. Pure drug and physical mixture of drug with excipients were combined separately with infrared (IR) grade KBr in a ratio of 1:100. Pellets were developed by applying 15,000 lb of pressure using a hydraulic press, followed by scanning using a FTIR spectrophotometer. The overall results of a study revealed chemical compatibility between model drugs meloxicam and dexamethasone with vesicular ingredients (raw materials) since there were no changes in band spectra when compared with each separate spectrum of the pure drug [23].

Differential scanning calorimetry (DSC)

DSC is an analytical technique used to measure thermal properties, such as temperature, heat flow, and enthalpy change. It is used to study the flexible lipid bubbles transfersome, which are used to improve drug delivery through the skin. DSC can also be used to determine how a drug molecule is arranged within a transfersomes, and how the lipid layers behave within and outside the transfersomes, which could help create more effective platforms for improved drug delivery. Cyclosporine A transfersomes prepared with Linoleic acid, Tween 80 and span 80 was studies for its thermal behaviour. The thermogram of bilayers of pure lipids often illustrates the temperature at which the lipid transitions from gel to liquid crystalline[25]. DSC was performed to determine the compatibility between formulation components. The phase transition temperature of roughly 111 °C demonstrated the thermodynamic behaviour of the gel[26].

X-ray Diffraction (XRD)

The XRD technique is used to analyse the structure of crystalline substances. It works by beaming X-rays onto a powdered sample and measuring their diffraction pattern. XRD is used to study the structure of transfersomes, particularly the structure of their membranes and the crystalline form of drugs present inside them, and to understand their effectiveness. Swroop K et al. have studied the crystalline nature of gefitinib transfersomes[27]. PXRD studies of pure drug and TF of the ebastine film were conducted using a diffractometer, D8-Advance (Bruker Corporation, Billerica, MA, USA). The samples were measured at angles of 5 to 50° at 2θ. The spectra of pure drug revealed numerous diffraction peaks with high intensities reflecting its crystalline nature; however, XRD patterns of Ebastine TF film were completely different from those of pure drug, which could be attributed to its conversion into amorphous form in transfersome, and a few minor peaks were found that could be attributed to film polymers. The absence of large diffractogram peaks indicates that either ebastine was converted into an amorphous form or completely enclosed in HPMC film[28].

Transferosomal gel is characterized by homogeneity, viscosity, pH, and drug content

Homogeneity

Homogeneity of gel is visually inspected. Researchers created a transfersome-based gel for the simultaneous dermal delivery of meloxicam and dexamethasone, which demonstrated good homogeneity with no lumps or aggregates and was clear and transparent[23].

Viscosity

Viscosity of transferosomal gel is determined at room temperature using various viscometers. Brookfield digital viscometer, along with various spindles, is often used to measure the viscosity. Suitable viscosity is desirable for suitable spreadability.

pH

The electrode is directly placed in contact with the gel, pH is directly read and displayed by the calibrated pH meter. pH of the gel or film in the range of skin pH confirms non-irritancy.

Drug Content

The most important factor in transferosomal gel is drug content. Content uniformity is determined in the case of film. Weighed quantity of gel or a suitable size of film is often placed overnight with agitation in a suitable solvent, and the drug content is determined spectrophotometrically or chromatographically after suitable dilutions. Previously, a calibration curve is constructed. It was found to be 83.06 to 94.12 %, which shows the good capacity of the formulation to hold the drug, which is Ibuprofen. The maximum drug content was found in formulation IG-3 (94.12 %)[21]. The drug content (mefenamic acid) of plain gel (PG) and nano-based gels (T10G) formulations was analyzed. The percent of drug content in PG and T10G formulations was determined to be 94.2% and 91%, respectively, indicating that the T10G formulation had the highest drug content of 91%[29].

Weight and thickness variation

An electronic balance is used to check the weight of each film, whereas digital slide callipers are used for thickness determination[28].

Folding endurance

Suitable size of the transferosomal film is repeatedly bent along the same line to evaluate the resistance to breaking and tearing[28].

Tensile strength and elongation

Tensile strength tester provides an estimate of the forces required for breaking and maximum stretching without breaking, calculated as tensile strength and elongation, respectively. These parameters are useful for the flexibility, elasticity, and durability of films[28].

***In vitro* release study**

The dialysis bag approach is used for *in vitro* release studies of transfersome, while the Franz diffusion cell method is used for transferosomal gels.

Dialysis bag technique

Briefly, around two ml of the transferosomal suspension is loaded into the dialysis bag, tied at both ends, and dipped in a beaker containing a suitable buffer.

Franz diffusion cell method

The gel is applied to the donor cell facing the skin, covered by a synthetic semipermeable dialysis membrane. Phosphate buffer is added to the receptor chamber.

Samples are withdrawn at set intervals from the beaker/ receptor compartment, each sample replaced by an equal volume of dissolution medium at a constant temperature. Drug release is measured spectrophotometrically or chromatographically. In vitro drug permeation studies of the transferosomal transdermal patch were performed by Franz diffusion cell. In a study, the in vitro drug permeation of Aceclofenac TF patch was studied for 24 h. Aceclofenac 84.6% was permeated at 24h, which indicates Aceclofenac-loaded transferosomal patches have greater permeation of the drug than a normal patch of Aceclofenac[30]. Mefenamic acid TF gel was evaluated for *in vitro* diffusion using the Franz diffusion cell for a period of 12 h. The cumulative drug release of PG and TF gel was found to be 97.8% and 89.4%, respectively, after 5 h and 12 h. TF gel exhibited a more sustained release compared which can be attributed to the higher drug content and greater entrapment efficiency[29].

***Ex vivo* study**

Ex vivo study is carried out with natural membranes as permeation barrier across Franz diffusion cell. One of the studies reported *ex vivo* permeation with abdominal skin of Wister rat[31]. Animals were sacrificed, the dermal part was cleaned, saturated in isopropanol, and soaked into phosphate buffer pH 7.4 for six hours, to equilibrate the membrane just before starting the experiment. Additionally, the skin was placed over one open-ended glass tube. Tubes were placed in a glass beaker containing phosphate buffer and kept in a vertical position, so the membrane was just under the surface of the solution. The tube (donor) compartment was filled with the tested sample and at different time intervals samples were withdrawn from the receptor compartment, the same amount of buffer was replaced in the receptor cell, subsequently the sample was analyzed spectrophotometrically. Another study described *ex vivo* permeation with porcine ear skin as a model membrane because of its similarity to human skin in lipid content and permeability. Piroxicam transfersomes gel release was demonstrated in a sustained manner compared to conventional gels. Piroxicam prolonged release being related to high entrapment efficiency and better drug loading[32]. Researchers have also experimented flurbiprofen loaded transethosomal gel permeation across porcine ear pinna skin in comparison with Hydroethanolic drug solution and marketed gel, permeation at the end of 24 h was found to be 26.06±0.83 µg $h^{-1}cm^{-2}$, 14.29±0.12 µg $h^{-1}cm^{-2}$and 39.11±0.04 µg $h^{-1}cm^{-2}$ respectively which demonstrates that transethosomal gel has better *ex vivo* permeation than the other two because of the integrating effect of phospholipid and edge activator Tween 80 of transethosomes[24]. Yet another research work documented *ex vivo* skin permeation studies performed through the hairless skin of a rat using a Franz diffusion cell. The results revealed that the maximum percentage of meloxicam released was 90% and 81% of dexamethasone from the same transferosomal gel after six hours. The difference in drug release at the same time from the same gel may be attributed to the variable in the percentage of entrapped medications in the vesicles[23].

***In vivo* studies**

In vivo studies carried out with transferosomal gel have proven to exhibit better results when compared to PG. In a study of combined anti-inflammatory activity of meloxicam and dexamethasone carried out by the carrageenan-induced hind paw edema method in Albino rats, the percent inhibition was found to be greater for transferosomal gel (50.57% after 5 h) as compared to PG, which exhibited a mean percentage edema inhibition of 47.42%, after 5 hours[23]. Another study

with transferosomal gel of piroxicam, the anti-inflammatory activity was evaluated by the carrageenan-induced rat paw edema volume model. IC50 value indicative of the concentration of the drug that is required to elicit 50% of the proposed activity was 95.34 ± 12 µg/ml for piroxicam TF gel, whereas PG showed an IC50 value of 140.4. ± 33 µg/ml. Thus, TF gel showed better inhibition of lipid peroxidation and reduction of edema. In other words, almost double the quantity of plain piroxicam is required to elicit the same response as that produced by TF gel[32].

Skin irritation study

Since the transferosomal gel/patch is applied topically the skin irritation is also studied. In a reported work, to study any irritant effect, patches loaded with transfersomes of ibuprofen were applied on the skin and observed for 24 hours under normal conditions. There was no itching, redness, oedema, or erythema at the conclusion of the research. This shows no irritation of the transferosomal patch. Thus, prepared compositions can be administered on the skin[22].

CONCLUSION

Transfersome are specialized vesicles designed to optimize drug delivery across biological barriers, particularly the skin. Their ability to undergo rapid and energetically efficient shape transformations in response to external stress makes them highly effective for drug transport. These deformable particles can navigate through extremely small pores—up to 100 micrometers—almost as easily as water, which is significantly smaller in size. This remarkable capability allows drug-laden transfersome to deliver considerable amounts of medication across the skin at rates of up to 100 µg/cm²/h.

The transdermal drug delivery system is favoured due to its numerous benefits compared to other routes; however, the stratum corneum poses a significant barrier that limits drug penetration. This limitation becomes even more pronounced when it comes to larger molecules, which transfersome are specifically designed to address. By employing a vesicular system, transfersomes can deform and squeeze through pore openings in the skin, enhancing the efficiency and safety of drug delivery.

Additionally, transfersome provides the advantage of controlled drug release, allowing for tailored therapeutic effects according to patient needs. This innovative approach effectively resolves challenges often faced in traditional drug delivery methods, presenting a promising solution for enhancing transdermal drug administration.

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Conflict of interest

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Ms Nayana D N is an 2nd year M pharm student (Pharmaceutics) under the guidance of Dr Nidhi Malviya (Asst Professor), Rajiv Gandhi University of Health Sciences Bengaluru. She pursuing masters by secured first class and attended Seven Seminars and Nine National Webinars.

Dr. Nidhi Malviya, M Pharm (Pharmaceutics) earned PhD from Rajiv Gandhi University of Health Sciences, Bangalore under the guidance of Dr. Vijaya G Joshi, Professor and Principal, Government College of Pharmacy, Bangalore. She has 11 years of teaching and 16 years of research experience. She has qualified and received the AICTE GATE scholarship. Her research as Principal investigator in areas of novel drug delivery systems received grants from Department of Science and Technology, New Delhi, Indian Pharmaceutical Association, Mumbai, and Council of Scientific and Medical research, New Delhi amounting to more than two million Rupees along with scientist mentors Dr Vemula Kusum Devi, Professor and Principal NITTE, College of Pharmacy, Bangalore, and Dr Somisetty Kusum Valli, Professor and HOD (Endodontics), Rajiv Dental College, Bangalore. Along with the same coauthors she won special recognition award and cash prize for poster presentation at Bangalore India Bio (2013) and best oral presentation award at Indian Pharmaceutical Congress, Chennai (2012). She has attended two international conferences and 21 national conference/workshop/seminar. She has publications with h-index 3, i10-index 4 and 333 citations in google scholar. She is a coauthor in an Indian Patent for Bakuchi oil collagen Nanoemulgel. She is reviewer of various journals and subject expert for paper setting in various universities. She is a registered KSPC and APTI member.