

VAGINAL MUCOADHESIVE DRUG DELIVERY SYSTEM

Abstract:

Mucoadhesive drug delivery systems are delivery systems which utilize the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time. Many of these delivery routes, particularly those through the nasal, ocular, reproductive and gastrointestinal system, involve contact with mucosal surfaces. The gastrointestinal route has been particularly popular among medical staff and patients alike. Although convenient, unfortunately, this route can be very inefficient for a number of reasons, including too rapid transit of the drug-containing delivery system Past the optimum site for absorption, which is normally the small intestine and to a lesser degree the stomach and colon. Mucoadhesive formulations use polymers as the adhesive component. Mucoadhesive drug delivery systems are available in the form of tablets, films, patches, and gels for oral, buccal, nasal, ocular, vaginal, rectal and topical routes for both systemic and local effects. This review article represents the various aspects of vaginal drug delivery system , bioadhesion mechanism, Theory of bioadhesion, factor affecting bioadhesion, various types of vaginal formulation etc.

Keywords: Bioadhesion, Vaginal Delivery, Vaginal formulation, Mucoadhesion Theory

Introduction: Mucoadhesive drug delivery systems are delivery systems which utilize the property of bioadhesion of certain polymers which become adhesive on hydration and hence

can be used for targeting a drug to a particular region of the body for extended periods of time. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane. In the case of polymer attached to the mucin layer of a mucosal tissue, the term “mucoadhesion” is used^{1,2}.

Mucoadhesive drug delivery systems can be delivered by various routes:-

Buccal Mucoadhesive Drug Delivery System

Oral Mucoadhesive Drug Delivery System

Vaginal Mucoadhesive Drug Delivery System

Rectal Mucoadhesive Drug Delivery System

Nasal Mucoadhesive Drug Delivery System

Ocular Mucoadhesive Drug Delivery System

The vaginal cavity is an important area of the reproductive tract and acts as a favourable site for drug administration due to avoidance of first pass effect, large permeation area, rich vascularization and relatively low enzymatic activity. In recent years, research has been focused on vaginal drug delivery systems as logical alternatives to oral or parenteral drug administration. Many studies have demonstrated the superiority of vaginal over oral drug administration in terms of minimizing general and gastrointestinal side effects. The search for non-invasive drug delivery systems continues due to poor patient compliance and acceptance, limited market size and drug uses, coupled with the high cost of disease management. The vaginal cavity has a potential for non-invasive, controlled transmucosal delivery of both local and systemic therapeutically active compounds. The vagina has a great potential for systemic delivery of a wide range of compounds including proteins and peptides. Formulation and delivery of microbicides is being developed as a new therapeutic approach to prevent HIV and other sexually transmitted diseases (STDs). The vaginal cavity is also an effective site for the uterine targeting of various therapeutic agents such as terbutaline, progesterone and danazol. Recently, the vagina has been studied as a novel route for the delivery of chemotherapeutic agents for treatment of all cancer. Creams, tablets, gels, suppositories, foams, ointments, tampons and inserts are commonly used as vaginal drug delivery systems. The currently available vaginal dosage forms have certain limitations such as messiness, leakage and low residence time, leading to poor patient compliance and loss of therapeutic efficacy. Therefore, novel concepts and dosage forms are needed. Extensive research is ongoing to develop better vaginal drug delivery systems that can full fill the user's

requirements. Some of the vaginal products recently introduced into the market and in various stage of development. This review highlights several recent advances in vaginal drug delivery^{3,4}.

Advantage of vaginal drug delivery

- a. The vagina may serve as a better route for the delivery of drugs due to the paucity of drug metabolism and the avoidance of the liver first-past effect.
- b. A reduction in hepatic side effects of steroids used in hormone replacement therapy or contraception period.
- c. Avoidance of the inconvenience caused by pain, tissue damage and risk of infections which are associated with parenteral routes.
- d. Ease of self-insertion and removal of the dosage form is possible.

Limitations of vaginal drug delivery

- a. This drug delivery system is gender specific.
- b. The vaginal route is less preferred because of inconvenience.
- c. The permeability of the vagina is strongly influenced by the estrogens concentration, which can influence the pharmacokinetics of drugs.
- d. The amount of vaginal fluid of an adult woman was reported to be in the range of 2–3 g (gram)/24 h (hour) and this amount is decreasing with increasing age which can affect the vaginal absorption of drugs.
- e. The pH of the vaginal fluid is also a factor which affects the drug absorption as the unionized drugs absorbed.

Ideal Characteristics of vaginal Drug Delivery System:^{5, 6}

- a. Component should melt at vaginal temperature i.e. at 36⁰C.
- b. Intra-vaginal drug delivery device should be non-toxic and non-irritating.
- c. It should not have any meta-stable form.
- d. The preparation should have high water number.
- e. The preparation should have wetting and emulsifying properties.
- f. The preparation should be non-sensitized on vaginal pH (i.e. 3.5-4.9)
- g. It should be stable on storage.
- h. The preparation should have small interval between melting and solidification point.
- i. The preparation should have proper viscosity, so avoid the leakage of preparation from vagina (in case of semisolid dosage form).
- j. The preparation should have proper bioadhesive/ mucoadhesive properties, so increase the contact time between the membrane and preparation

Basis of mucoadhesion:

Good defined 'Bioadhesion' as the state wherein two materials out of which at least one of biological origin, are held together for an extended period of time by interfacial forces. Alternatively it can also be defined as the ability of a material to adhere to biological tissue for an extended period of time. Scientist Peppas and Buri in 1985 defined Bioadhesion as "the attachment of synthetic or biological macromolecules to a biological tissue". When applied to a mucosal epithelium, bioadhesive interactions occur primarily with the mucus layer, and this phenomenon is referred to as 'mucoadhesion'⁷.

The mucoadhesive mucosa interaction:^{8,9}

For adhesion to occur, molecules must bond across the interface of mucus. These bonds can arise in the following ways:

Ionic bonds:

Two oppositely charged ions attract each other via electrostatic interactions to form a strong bond (e.g. in a salt crystal).

Covalent bonds:

Electrons are shared, in pairs, between the bonded atoms in order to fill the orbital in both. These are also strong bonds.

Hydrogen bonds:

A hydrogen atom, when covalently bonded to electronegative atoms such as oxygen, fluorine or nitrogen, carries a partial positive charge and is therefore attracted to other electronegative atoms. The bond formed is generally weaker than ionic or covalent bonds.

Van der-Waals bonds:

These are some of the weakest forms of interaction that arise from dipole-dipole and dipole-induced dipole attractions in polar molecules, and dispersion forces with non-polar substances.

Hydrophobic bonds:

More accurately described as the hydrophobic effect, these are indirect bonds (such groups only appear to be attracted to each other) that occur when non-polar groups are present in an aqueous solution. Water molecules adjacent to non-polar groups form hydrogen bonded structures, which lowers the system entropy. There is therefore an increase in the tendency of non-polar groups to associate with each other to minimize this effect.

Theories of Mucoadhesion:¹⁰

Several theories have been proposed to explain the fundamental mechanisms of adhesion.

a. Electronic Theory:

Electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of difference in the electronic structures. This results in the formation of electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer and inters diffusion of the two surfaces.

b. Adsorption Theory:

According to the adsorption theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms on the two surfaces.

Two types of chemical bonds resulting from these forces can be distinguished:

- i.** Primary chemical bonds of covalent nature, which are undesirable in Bioadhesion because of their high strength, which may result in permanent bonds.
- ii.** Secondary chemical bonds having many different forces of attraction, including electrostatics forces, Van der Waals forces, and hydrogen or hydrophobic forces.

c. Wetting Theory:

Wetting theory is predominantly applicable to liquid bioadhesive systems. It analyzes adhesive and contact behavior in terms of the ability of a liquid or paste to spread over a biological system. Moderately wettable polymers have been shown to exhibit optimal adhesion to human endothelial cells.

d. Diffusion Theory:

Diffusion theory describes interpenetration of the mucoadhesive polymer to a sufficient depth to create a semi-permanent adhesive bond. Upon initial contact, diffusion of the bioadhesive polymer chain into the mucus network creates an entangled network between the two polymers. Sufficient polymer chain flexibility, adequate exposure for the surface contact of both polymers, similar chemical structures, and the diffusion coefficient of the bioadhesive polymer are among the factors which influence the inter-diffusion of the macromolecule network.

e. Fracture Theory:

Fracture theory attempts to relate the difficulty of separation of two surfaces after adhesion. This assumes that the failure of the adhesive bond occurs at the interface. However, failure normally occurs at the weakest component, which is typically a cohesive failure within one of the adhering surfaces.

Mechanism of tablet bioadhesion: ^{11, 12}

The mechanism by which the tablet can adhere to biological surface is, in fact, a succession of phenomena, and can be described in three stages as follows:

a. Contact stage

It is necessary to have intimate contact between the tablet and the mucosa. This is not too difficult to obtain with vaginal mucosa. In the vagina a good contact can be obtained by exerting a slight pressure on the tablet at the surface of the mucosa.

a. Moistening stage:

This stage lead to swelling of the Bioadhesive polymer, disentangling of the polymeric chains, leading to the interpenetration of the polymer and mucous chains.

b. Bonding stage:

The third phenomenon is the creation of interfacial bonds.

Vaginal Anatomy and Physiology With Respect To Drug Delivery

The vagina is a fibromuscular tube approximately 10 cm in length comprised of three distinct layers namely an outer adventitial layer, a middle muscularis layer and an innermost mucosal layer. The vaginal rugae and micro ridges on the epithelial cell surface permit the vagina to expand, allow the placement of vaginal formulations and increase the surface area of the vagina thus enhancing drug absorption. The vagina has remarkable features in terms of vaginal secretion, pH, enzyme activity and micro flora. These factors affect formulation spreading and retention as well as absorption and drug release in vagina¹³.

Vaginal Secretions: The vaginal discharge is a mixture of multiple secretions that collect in the vagina from peritoneal, follicular tubal, uterine, Bartholin's and Skene's glands. In presence of moisture, solid dosage formulations should ideally disperse in the vaginal canal immediately after insertion to avoid inconvenience to the users.

Enzyme Activity: The specific enzymatic activity of four different amino peptidases in vaginal homogenates decreases in the order: sheep > guinea pig > rabbit \geq human \geq rat. The human genital tract has lower enzymatic activity leading to less degradation of protein and peptide drugs in the vagina than the gastrointestinal tract.

Vaginal pH: The pH of the healthy female genital tract is acidic (pH 3.5–4.5) and is maintained within that range by bacterial conversion of glycogen from exfoliated epithelial cells to lactic acid.

Vaginal Routes of Drug Absorption: The drug is delivered in the vagina mainly via two routes: intravaginally to the vaginal epithelium or transvaginally through the vaginal mucosa to uterus and systemic circulation. Vagina has specific blood flow characteristics, either by a portal type circulation or by venous and lymphatic channels that allow bypassing the

gastrointestinal tract absorption and liver detoxification and permit preferential transport of drug molecules from the vagina to the uterus and systemic circulation. Several physical models have been devised to study the vaginal permeability of drugs. Many therapeutic compounds have been shown to be absorbed through the vaginal mucosa. Antifungal agents such as tioconazole, clotrimazole and miconazole are topically administered to treat vaginal yeast infections. On the basis of our knowledge of anatomical and physiological features of the vagina, it is likely that many other drugs will be formulated for vaginal administration in the future¹⁴.

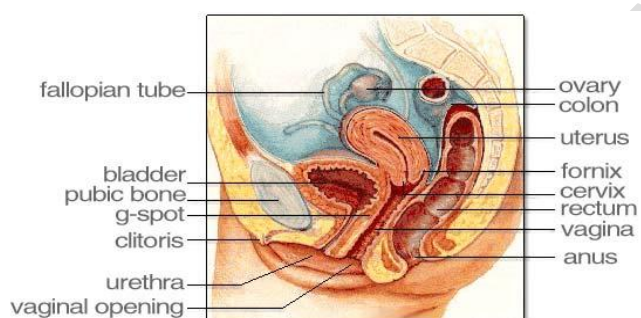


Figure 1: Female reproductive system

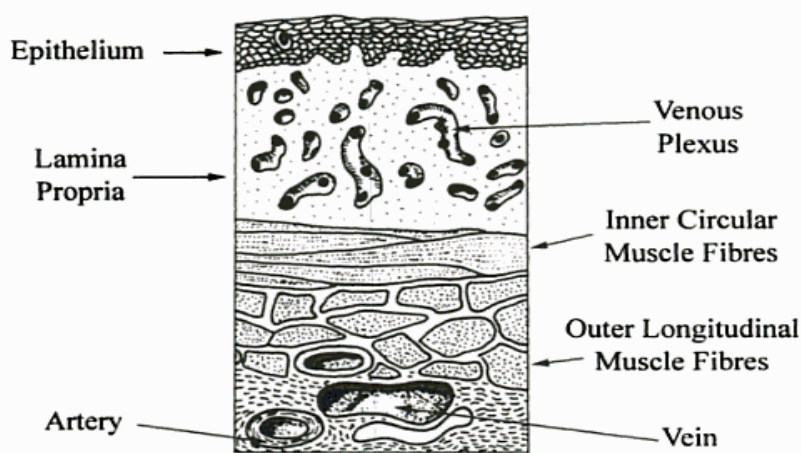


Figure 2: Schematic illustration of the vaginal wall .

Factors affecting mucoadhesion ¹⁵

Polymer related factors:

- a) **Molecular weight:** In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 100000 because entanglements are favored in high molecular weight polymers.

- b) Flexibility: Bioadhesion starts with the diffusion of the polymer chains in the interfacial region. Therefore, it is important that the polymer chains contain substantial degree of flexibility in order to achieve the desired entanglement with the mucus.
- c) Concentration of active polymer: For solid dosage forms such as tablets, the higher the concentration of polymer, the stronger the bioadhesion force.
- d) Spatial Conformation: Bioadhesive force is also dependent on the conformation of polymers, i.e., helical or linear. The helical conformation of polymers may shield many active groups, primarily responsible for adhesion, thus reducing the mucoadhesive strength of the polymer.
- e) Charge: Peppas and Buri have been demonstrated that strong anionic charge is one of the required characteristics for mucoadhesion. Cationic polymer bind more efficiently than non anionic polymer.

Environmental – Related Factors¹⁶

- a) pH: pH influences the charge on the surface of both mucus and polymers. Mucus will have different charge density depending on pH, because of difference in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which may affect adhesion.
- b) Applied strength: To place a solid bioadhesive system, it is necessary to apply a defined strength. Whichever the polymer may be the adhesion strength of those polymers increases with the increase in the applied strength.
- c) Initial contact time: The initial contact time between bioadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. The bioadhesive strength increases as the initial contact time increases.
- d) Selection of the model substrate surface: The handling and treatment of biological substrates during the testing of bioadhesive is an important factor, since physical and biological changes may occurs in the mucus gels or tissues under the experimental conditions.
- e) Swelling: The swelling characteristic is related to the polymer itself, and also to its environment. Interpenetration of chains is easier as polymer chains are disentangled and free of interactions. Swelling depends both on polymer concentration and on water presence. When swelling is too great, a decrease in bioadhesion occurs; such a phenomenon must not occur too early, in order to lead to a sufficient action of the bioadhesive system. Its appearance allows easy detachment of the bioadhesive system after the discharge of the active ingredient.

Physiological variables¹⁷

Mucin turnover and disease state of mucus layer are physiological variables, which may affect bioadhesion.

Mechanism of Mucoadhesion As stated, mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following mechanism

1. Intimate contact between a Mucoadhesive and a membrane(wetting or swelling phenomenon)
2. Penetration of the mucoadhesive into the tissue or into the surface of the mucous membrane(interpenetration).

Characteristics of Mucoadhesive Polymer

1. Cationic and anionic polymers bind more effectively than neutral polymers.

Poly-anions are better than polycations in terms of binding/ potential toxicity, and further, that water-insoluble polymers give greater flexibility in dosage form design compared with rapidly or slowly dissolving water-soluble polymers.

3. Anionic polymers with sulfate groups bind more effectively than those with carboxylic groups.
4. Degree of binding is proportional to the charge density on the polymer.
5. Highly binding polymers include carboxyl methyl cellulose, gelatin, hyaluronic acid, carbopol and polycarbophyl.

Classification of dosage Form of Mucoadhesive

1. Mucoadhesive Gel Formulations: Mucoadhesive semi-solid formulations are able to facilitate intimate contact with the underlying absorption surface and improve the bioavailability of drugs. Rheological properties of gels are important for their retention on the vaginal surface, which are fundamental to their efficacy. The remarkable elastic character and the improvement of the rheological properties of the mucoadhesive gel prolong the residence time at the application site. For these kinds of formulations, selection of correct viscosity of the formulation is important in order to provide adequate retention and distribution in the vagina.

2. Mucoadhesive Tablet Formulations: Vaginal mucoadhesive tablet formulations are important alternatives to conventional vaginal formulations and are particularly useful for the therapy of insistent vaginal infections as they reduce the required dose frequency, provide easy application and therefore increase patient compliance. Chitosan is used in mucoadhesive

tablets for vaginal delivery of metronidazole. The polymer matrix containing a mixture of chitosan, Carrageenan, xanthan gum, polyox WSR 303, Hydroxypropylmethyl cellulose, magnesium stearate, microcrystalline cellulose provides an adequate release of metronidazole for 8 h and maximum adhesion was also obtained with minimum pressure applied.

3. Mucoadhesive Suppositories: Among the solid vaginal preparations, suppositories have advantages as they facilitate the application due to their slippery and smooth surface. To provide a long term therapeutic concentration of miconazole following a single dose, hydrogel based suppositories were prepared with polyvinyl alcohol and the effect of the time of the freezing and thawing cycles was investigated vis-a-vis the swelling property of the hydrogels outcome. It was observed that an increase in the number of freeze-thaw cycles reduced the equilibrium swelling of polyvinyl alcohol hydrogel. This reduction in equilibrium swelling was due to an increase in the degree of crystallinity of the hydrogel. The release of the drug was continued beyond three days and the Fickian diffusion mechanism of release was found predominant.

4. Mucoadhesive Particulate Formulations: Although several studies have focused on mucoadhesive drug delivery systems in the form of tablets, films, patches, and gels for mucosal routes, very few reports on mucoadhesive microparticles are available. Hyaluronan esters (HYAFF) have opened new avenues for mucoadhesive vaginal formulations. Due to their biocompatibility and controllable degradation rate HYAFF microspheres have been used for localized drug delivery of steroids, analgesics, antiinflammatory and anti-infectives. Recent studies have indicated that a number of polymeric delivery systems such as mucoadhesive microspheres possess significant potential for the development of vaginally administered vaccines.

5. Mucoadhesive Film Formulations: Thin films have been found to be suitable physical forms for vaginal drugs and peptide delivery. To develop an efficient female controlled drug delivery system against sexually transmitted diseases, polymeric films containing sodium dodecyl sulfate were prepared with various compositions of Carbopol 934 P, hydroxypropylmethylcellulose and polyethyleneglycol. It was demonstrated that the films made of Carbopol, hydroxypropylmethylcellulose and polyethyleneglycol were colorless, thin and soft, also had sufficient strength to withstand mechanical damage during production, handling and application for a female controlled drug delivery system. An increase in Carbopol content elevated the tensile strength and swelling ratio of the films but decreased the contact angle, erosion rate and sodium dodecyl sulfate release rate from the films. The

films containing 0.25% (w/v) polyethyleneglycol as well as 0.75% (w/v) of Carbopol/ Hydroxypropyl methylcellulose remained on the vaginal tissue for up to 6 hours¹⁸.

Evaluation of Vaginal Mucoadhesive Drug Delivery System^{19,20}

a. Swelling index

From each formulation, single tablet was taken and weighed, individually [designated as W_1] and placed separately in petridish containing 5 ml of acetate buffer PH 4.6. The petridish were kept at room temperature for 30 minutes, then vaginal tablets were removed from petridish and excess of water was removed carefully by using filter paper. The swollen vaginal tablets were weighed [W_2]. Percentage swelling index was calculated, each experiment was performed in triplicate, and average reading was taken.

$$\% \text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 100$$

Where, W_1 Initial weight
 W_2 Final weight

b. Surface pH Study

The surface pH of the vaginal tablets was determined in order to investigate the possibility of any side effects *in-vivo*. As more acidic or alkaline pH may cause discomfort to the vaginal mucosa, the pH was maintained to weak acid as closely as possible. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of acetate buffer (pH 4.4 ± 0.05) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 ml acetate buffer (pH 4.4 ± 0.05) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min.

c. Matrix erosion test

After swelling study, the swollen tablets were dried at 60°C for 24 h in an oven and kept in desiccator for 48 h and reweighed (W_3). Matrix erosion was calculated using following formula.

$$\% \text{ Matrix erosion} = \frac{(W_1 - W_3)}{W_3} \times 100$$

d. Bioadhesion strength

Bioadhesive strength of the vaginal tablets was measured on the "Modified Physical Balance method". The method used sheep vaginal membrane as the model mucosal membrane. The fresh sheep vaginal mucosa was cut into pieces and washed with acetate buffer pH 4.6. A piece

of mucosa was tied to the glass slide which was moistened with acetate buffer pH 4.6. The tablet was stuck to the lower side of another glass slide with glue. The both pans were balanced by adding an appropriate weight on the left- hand pan. The glass slide with mucosa was placed with appropriate support, so that the tablet touches the mucosa. Previously weighed beaker was placed on the right hand pan and powder (equivalent to weight) was added slowly to it until the tablet detach from the mucosal surface. The weight required to detach the tablet from the mucosal surface gave the bioadhesive strength. The experiment was performed in triplicate and average value was calculated. Bioadhesive strength was assessed in terms of weight [gm.] required to detach from membrane. Bioadhesion strength which was measured as force of adhesion in Newton by using formula.

$$\text{Force of adhesion (N)} = \text{Mucoadhesive strength} / 100 \times 9.81$$

e. Bioadhesion time determination

The *ex-vivo* mucoadhesion time was examined after application of the vaginal tablet on freshly cut sheep vaginal mucosa. The fresh sheep vaginal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of acetate buffer pH 4.6 and pasted to the sheep vaginal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 4.6 and kept at $37 \pm 1^\circ\text{C}$. After 2 minutes, stirring was applied slowly to simulate the vaginal cavity environment, and tablet adhesion was monitored for 12 hr. The time for the tablet to detach from the sheep vaginal mucosa was recorded as the mucoadhesion time.

f. In-vitro dissolution study

The release rate of formulation from Bioadhesive tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml pH 4.6 acetate buffer, at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. The absorbance of these solutions was measured at specific nm^{20,21}.

Conclusion

Vaginal mucoadhesive drug delivery provides tremendous advantages over other conventional dosage form. It provides intimate contact of dosage form at the site of vaginal cavity which offers prolonged drug release. Mucoadhesive polymers are mainly used for this purpose which can also avoid hepatic first pass elimination. For evaluation of this dosage

form both in vivo and in vitro methods have been developed. Recently researchers facing many more challenges in development of such formulation and it requires a multidisciplinary approach.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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