NON-INVASIVE DELIVERY OF PROTEIN AND PEPTIDE DRUGS: A REVIEW

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ABSTRACT
The most common and improved bioavailable route for protein and peptide drugs is injectable route. These drugs are generally preferred to give in invasive route to get high bioavailability though possessing disadvantages and the major one is patient non-compliance. Hence, various non-invasive route of administration has been under research for these drugs to fetch more advantages. Although bioavailability is a major problem with non-invasive route such as oral, nasal, ocular, transdermal, rectal, colon, and vaginal route, these routes have been preferred compared to existing invasive one. Many researches have been conducted in this area, but achieving success is significantly challenging. The nasal delivery has been successfully exploited for vaccines compare to all other non-invasive drug delivery system. Currently, only molecule to reach market is oral cyclosporine. The present review aims to discuss the potential non-invasive routes of protein and peptide drug delivery. The factors which will affect drug permeation, and the bioavailability of proteins administered through these routes is also emphasized.

Key words: Protein and peptide, Non-invasive, Oral, Nasal, Rectal, Transdermal, Colonic, Vaginal.

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INTRODUCTION
In recent years, proteins and peptides have emerged as promising therapeutic agents. There are various problems associated with these agents. The problems are selecting a route of delivery and preparing a bioavailable formulation of these biopharmaceutical agents. Parenteral route is the common preferred route of delivery for parenteral drug delivery system. There are many disadvantages with this route of administration which is poor patient compliance and pain at the site of administration despite 100% bioavailable. Oral drug delivery of these drugs undergoes acid hydrolysis and extensive first-pass metabolism and degradation by enzymes. Hence, protein drugs other than parenteral route possess many disadvantages and very challenging for the pharmaceutical scientist to formulate a bioavailable non-invasive route for these drugs. The non-invasive routes under research are mucosal, transdermal, nasal, ocular, pulmonary, rectal, vaginal, buccal, and sublingual offer effective alternatives for systemic drug delivery.

Potential mechanisms of transport across cells are passive paracellular, passive transcellular, facilitated transcellular, active carrier-mediated, and transcytosis. The cellular barrier for each non-invasive delivery route is more complex, and a lot of manipulation is required to overcome the problems associated with permeation (Fig.1).

ORAL DELIVERY
Oral route is preferred over any other route because of good patient compliance and acceptance. This is the most preferred route for chronic ailments. Designing and formulating protein and peptide drug delivery system for the gastrointestinal (GI) route are a challenge because of the unfavorable conditions posed by it such as pre-systemic enzymatic degradation and poor membrane permeability.

Barriers for oral absorption
The barrier that prevents the entry of protein or peptide drugs into the systemic circulation is intestinal epithelial tight junctions. The major problems involved in oral delivery of proteins can be given as denaturation of proteins due to acidic environment in stomach, degradation of proteins in stomach and intestine due to proteolytic enzymes, intestinal wall which is impermeable to macromolecules, mucus barrier which is formed by mucus that is secreted by goblet cells, and intestinal transit time [1,2].

Enzymatic barriers
Most of the proteins are known not to be absorbed in humans as intact forms. They are usually broken down into amino acids or di- and tri-peptides first in the GI tract (GIT). The four peptidases secreted by the pancreas, that is, trypsin, chymotrypsin, carboxypeptidase, elastase, convert proteins, and polypeptides to oligopeptides [3]. Luminal degradation of proteins is up to 20% of the total degradation in the small intestine. The rest of the degradation occurs on contact with the brush border membrane or after entry into the cell. Brush border peptidases such as amino oligopeptidase, aminopeptidase, and dipeptidyl aminopeptidase then breakdown the oligopeptides to amino acids (up to 70%) and di- and tri-peptides (up to 30%) [3,4].

The above-mentioned enzymatic barriers must be overcome to improve oral absorption of protein and peptide drugs from the GIT. This may be possible to achieve to some extent using enzyme inhibitors or by chemical modification or by other approaches has been given in Table 1. GI absorption of peptides and peptide-like drugs is given in Table 2.

Bioavailability
Captopril, lisinopril, and enalapril have good oral bioavailability due to their low-molecular weight and their ability to inhibit tissue carboxyl peptidases [11]. Cyclosporine is a cyclic peptide with a number of methylated amino acid residues and is resistant to hydrolysis and therefore has good bioavailability [12]. Some protease inhibitors and absorption enhancers have been coadministered with peptide drugs to enhance their oral absorption. A good example is oral arginine-vasopressin. To produce a 50% reduction in urine flow, in the rat, an oral dose of about 3500 pmol was required. When the drug was
coadministered with aprotinin, a protease inhibitor, the oral dose was reduced to 1000 pmol [13].

**NASAL DELIVERY**

**Barriers for nasal absorption**

Nasal route provides advantages such as having larger surface area for absorption and almost closer to intravenous route of bioavailability is achievable. The lipophilicity of the molecule plays major role in absorption. The central nervous system can be targeted through this route with improved efficacy. For vaccines, nasal route is the most preferred route of delivery [14].

**Nasal mucosa and nasal epithelium**

The nasal epithelium consists of loosely packed cells with high permeability and vasculature. Passive diffusion, carrier-mediated transport, and transcytosis are the transportation mechanisms, through which nasal absorption is achieved [15,16]. Molecular weight plays a major role in reducing the absorption of compounds such as desmopressin, insulin, and human growth hormones. Low molecular weight compounds permeate at a faster rate. Pgp efflux transporters also another actor influences absorption through nasal epithelium [17-19].

**Mucociliary clearance**

The major barrier for nasal delivery is nasal mucociliary clearance (NMC). The residential time of many drugs has reduced to greater extent [20]. The NMC is a natural defense mechanism of the body to expel the foreign objects thus preventing the absorption of drug molecules. Antihistaminic drugs, beta blockers, general anesthetics, cocaine, etc., arrest the mucociliary clearance. Thus, NMC reduces the nasal bioavailability of drugs [21-29]. Various approaches for nasal delivery have been given in Table 3.

![Fig. 1: A schematic illustration of potential mechanisms of transport across the cellular barrier in non-invasive routes of drug delivery systems. (A) Passive transcellular, (B) passive paracellular, (C) facilitated transcellular or active carrier mediated, (D) transcytosis](image)

<table>
<thead>
<tr>
<th>Approach</th>
<th>Example</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption enhancers</td>
<td>Detergents, bile salts, fatty acids, chitosans, acylcarnitine, alkanoyl choline, N-acetylated α-amino acids, N-acetylated non-α-amino acids</td>
<td>Temporarily disturb intestinal barrier to improve the permeation</td>
<td>[5]</td>
</tr>
<tr>
<td>Enzyme inhibitors</td>
<td>Trypsin, chymotrypsin, carboxypeptidases, aprotinin, pancreatic inhibitors</td>
<td>Protects from degradation by enzymes in stomach and intestine</td>
<td>[1]</td>
</tr>
<tr>
<td>Chemical modification: Amino acid modification</td>
<td>Conjugation with polymer PEG or ligands like transferring 1, 3-dipalmitoylglycerol</td>
<td>Affects receptor binding capacity and decreases rate of clearance from systemic circulation Benefit to transcellular passive or active absorption</td>
<td>[1,5]</td>
</tr>
<tr>
<td>Lipidization</td>
<td>Types: Anionic, cationic, non-ionic, amphoteric, thiomres, dendrimers, synthetic glycol polymers, etc., ex: chitosan</td>
<td>Longer transit time and decreases diffusion barriers</td>
<td>[1]</td>
</tr>
<tr>
<td>Mucoadhesive polymer systems</td>
<td>S/O/W emulsion (surfactant - insulin complex is dispersed into oil phase) Microspheres of poly (methacrylic-g-ethylene glycol) Polystyrene, chitosan, PLA-PGA PEGylated liposomes, and mucin containing liposomes</td>
<td>Chemical and enzymatic breakdown protection in lumen Protects over the influence of the PH variability through the stomach to intestine Less sensitivity to enzymes Resistance against digestion by bile salts and stability in GIT</td>
<td>[5,6]</td>
</tr>
</tbody>
</table>

PEG: Polyethylene glycol
Drug metabolism

Even though nasal route provides low metabolic environment, metabolism of proteins and peptide molecules in nasal cavity is a major barrier for bioavailability [34-35]. The main enzymatic barrier present in the nasal mucosa is cytochrome P450 enzymes. Cytochrome P450 is present in both respiratory and olfactory mucosa, thus reducing both nose-to-blood and nose-to-brain transport of drugs[36]. Low bioavailability of protein and peptide drugs is obvious by the presence of various proteolytic enzymes such as exopeptidase (mono and diamino peptidase) and endopeptidase (serine, cysteine, and aspartic peptidase)[37].

**Ocular delivery**

Ocular route is mainly used for the treatment of ocular inflammation, corneal wounds, and glaucoma. The administration of biopharmaceuticals through eye is complicated by the normal processes of blinking, tearing, and drainage from the eye which wash out the drugs which are administered.

**Drug absorption**

The cornea is composed of three major layers: Two boundary cellular layers, the epithelium, the endothelium, and the stroma (a thick connective tissue) in between. The corneal epithelium is a non-keratinized stratified squamous epithelium, 5-6 cell layers in thickness (Fig.2).

The conjunctiva consists of a stratified squamous epithelium, overlying a loose, highly vascular connective tissue, and the substantia propria [38]. The conjunctival epithelium is continuous with the corneal epithelium at the corneoscleral limbus. A drug administered topically on the percorneal area comes into contact with the corneal and conjunctival epithelium followed by absorption by ocular tissues. This absorbed drug enters into the systemic circulation by various processes like corneal absorption which is through adjacent ocular tissues because it is avascular Conjunctiva is highly perfused and most of the absorbed drug enters to the systemic circulation. The nasolacrimal secretion also another process through which drug is lost. The enzymes such as neutral protease and aminopeptidase also cause destruction of proteins and peptides. Some novel approaches such as cyclodextrin complexes of cyclosporin have increased the bioavailability through corneal tissues [39-42].

**Transdermal delivery**

Transdermal drug delivery provides lot of advantages due to large surface area which can enhance the flux of the drugs with the use of appropriate enhancers. The stratum corneum (SC) is the major barrier. It also avoids first-pass metabolism. This route high patient compliant route and any time the drug action can be terminated [43].

**Barrier for transdermal delivery**

The major barrier of skin permeation is SC the outer most layer. Skin allows only passive diffusion of drugs. There are ideal properties of a drug to possess to permeate through the skin. The ideal log P, molecular weight, melting point, solubility, and dose of the drug influences the permeation through skin. Chemical permeation enhancers play major role as passive enhancement of drugs through skin[44].

**Skin barrier function**

SC and routes of passive permeation: The major barrier is SC, the thin, outermost layer of the epidermis [45]. The SC consists of several layers of protein-filled corneocytes (i.e., terminally differentiated keratinocytes) embedded in an extracellular lipid matrix. Passive permeation across the SC is believed to occur primarily through the intercellular lipid pathway (Fig. 3a) which constitutes the only continuous phase through the SC, appendageal transport through hair follicles, and sweat glands is another potential route, these structures offering “shunt” pathways across

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Table 2: GI absorption of peptides and peptide-like drugs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Percentage of absorption</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary di- and tri-peptides</td>
<td>5-50</td>
<td>[7]</td>
</tr>
<tr>
<td>Aminocephalosporins</td>
<td>&gt;50</td>
<td>[8]</td>
</tr>
<tr>
<td>Enalapril</td>
<td>&gt;50</td>
<td>[9]</td>
</tr>
<tr>
<td>Dietary tetrapeptides</td>
<td>≈5</td>
<td>[10]</td>
</tr>
<tr>
<td>TRH analogs</td>
<td>≈5</td>
<td>[10]</td>
</tr>
<tr>
<td>Enkaphalins</td>
<td>&lt;2</td>
<td>[10]</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>&lt;2</td>
<td>[10]</td>
</tr>
</tbody>
</table>

GI: Gastrointestinal

Table 3: Approaches for nasal delivery

<table>
<thead>
<tr>
<th>Approach</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal mucoadhesive</td>
<td>Ideal choice of delivery system increases the nasal residence time e.g.: 90% bioavailability was achieved for apomorphine by mucoadhesive polymers such as polyacrylic acid, carbopol, and CMC</td>
<td>[30]</td>
</tr>
<tr>
<td>Enhanced nasal blood flow</td>
<td>By increasing the concentration gradient for passive diffusion of peptide drugs Nasal blood flow can be increased by vasoactive agents such as histamine, prostaglandin E, and beta-adrenergic agonists</td>
<td>[31]</td>
</tr>
<tr>
<td>Novel drug delivery systems</td>
<td>Absorb water into the sphere matrix, resulting in swelling and gel formation, this increase the residential time of the drug in the mucosa Materials used to construct microspheres include starch, dextran, albumin, hyaluronic acid, carbopol, and chitosan For example: Dextran used for insulin, octreotide, and nicotine The amphiphilic nature of liposomes is well characterized for favorable permeation of drugs through biological membranes The comparative pharmacokinetics in rats showed high permeability of liposome pre-treated with permeation enhancer than solution form containing the same quantity of permeation enhancer</td>
<td>[32,33]</td>
</tr>
<tr>
<td>pH modification</td>
<td>At isoelectric point proteins and peptides usually have less solubility; by adjusting pH its solubility can be increased For example: DDAVP exhibits good solubility at pH 4.0</td>
<td>[21]</td>
</tr>
</tbody>
</table>
the continuity of the SC (Fig. 3b). Visualization of appendageal transport has been accomplished both for passive diffusion and for percutaneous transport enhanced by one means or another (e.g., iontophoresis) [46,47]. A third possible route across the SC is the transcellular path (Fig. 3c).

**Approaches for transdermal delivery**

Several approaches have been explored that provide additional driving force in the form of electrical (iontophoresis) [48] or ultrasound (sonophoresis) [49] energies, structural perturbation of SC (e.g., electroporation, thermal microporation, microneedles), [50] penetration enhancers, [51,52] or a combination of these strategies.

**Iontophoresis**

To a few square centimeters of skin, a small amount of physiologically accepted current is applied to drive drug molecules into and across the skin. Iontophoretic delivery is achieved by 2 ways of electrorepulsion and electroosmosis [44].

**Electrorepulsion**

Delivery of charged molecule across the skin is possible due to repulsion between same charges, when a charged molecule is placed under an electrode of same polarity.

**Electroosmosis**

Skin is negatively charged; transport of positively charged drugs is possible. Under the influence of electric current, net flow of water from anode to cathode occurs which is called electroosmosis.

Iontophoretic study of some of harmones such as LHRH showed increased permeation following SC injection [53-55].
Table 4: Approaches for colonic delivery

<table>
<thead>
<tr>
<th>Polymeric approach</th>
<th>Mechanism</th>
<th>Polymers used</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric coating polymers</td>
<td>Dissolve in the pH range 4.8-7.0</td>
<td>Eudragit L100 &amp; S 100, HPMC pthalate</td>
<td>[64]</td>
</tr>
<tr>
<td>Timed release polymers</td>
<td>Retard the release of drug long enough to reach large intestine</td>
<td>HPMC, polysaccharides such as pectin and calcium pectinate, ethyl cellulose, natural polymers</td>
<td>[65]</td>
</tr>
<tr>
<td>Biodegradable polymers</td>
<td>Azo reduction causes degradation of polymer</td>
<td>Copolymers of styrene and hydroxyethyl methacrylate cross-linked with divinilbenzene derivative, Polyactic acid, polyglycolic acid</td>
<td></td>
</tr>
<tr>
<td>Saccharidic polymers</td>
<td>Increase in the porosity of the film as a result of enzymatic degradation</td>
<td>Mono-, di-, or oligo saccharides are treated with synthetic polymers eg; Guar gum - alactomannans+ Eudragit, dextran hydrogels cross-linked with disocyanate</td>
<td>[66]</td>
</tr>
</tbody>
</table>

Table 5: An overview of non-invasive protein and peptide drug delivery

<table>
<thead>
<tr>
<th>Route</th>
<th>Enzymatic activity level</th>
<th>Barriers</th>
<th>Examples of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Less</td>
<td>Enzymes, rapid post-absorptive clearance, physical instabilities such as adsorption and aggregation</td>
<td>Cyclosporine, enalapril</td>
</tr>
<tr>
<td>Colonic</td>
<td>More</td>
<td>High concentration of anaerobic bacteria and absence of villi and microvilli</td>
<td>Tissue necrosis factor, proleukin, and epidermal growth factor</td>
</tr>
<tr>
<td>Nasal</td>
<td>Less</td>
<td>Mucus secretions, mucociliary clearance, extent of absorption varies with mucus secretions, rhinitis</td>
<td>Enkephalins, epidermal growth factor, Insulin, salson calcitonin, LHRH</td>
</tr>
<tr>
<td>Ocular</td>
<td>Less</td>
<td>Enzymatic degradation by neutral protease and aminopeptidase, nasalocular secretions, and hydrophilicity</td>
<td>Ens</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Less</td>
<td>Lipophilicity of SC, low permeation for proteins due to large mol. wt. and hydrophilicity</td>
<td>Insulin, enkephalin, salmon calcitonin, and recombiant</td>
</tr>
<tr>
<td>Vaginal</td>
<td>Less</td>
<td>Changes in thickness and porosity of the vaginal epithelium, presence of thick cervical mucus due to menstruation cycle</td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>Relatively less</td>
<td>Villi and microvilli are not present, intercellular junctional complexes are tighter</td>
<td></td>
</tr>
</tbody>
</table>

**Electroporation**
Application of 1000-1000 V to enhance the permeability of drugs through skin opens the pathway for aqueous route. Movement of ions followed by enhanced diffusion and electrodiffusion is the possible mechanism to enhance the delivery through skin.

**Sonophoresis**
Use of low-frequency ultrasound in the range of 1-3 MHz for delivery of molecules across the skin is called sonophoresis. Piezo electric crystal which is made of lead zirconate is the main component of equipment, will convert the electrical energy into mechanical energy giving raise to acoustic waves or ultra sounds [56].

**Formulation approaches**
To enhance the skin permeability of protein and peptides, novel strategies are followed. Use of protease inhibitors, or formulations such as liposomes, niosomes found to enhance the skin permeation. These studies were conducted only on animals and not done on human models. Vesicular drug delivery systems such as ultra deformable vesicles like transfersomes can enhance the creation of hydrophilic pathways. Stearylamine and sodium cholate are used as edge activators. This approach has also been successfully demonstrated with other poly peptides such as interferons a, b, and g, calcitonin, and superoxide dismutase in pre-clinical experiments [57-59].

**COLONIC DELIVERY**
The colon has received considerable attention as a possible delivery site for protein and peptide drug delivery compared to other possible oral routes because enzyme activities are significantly lower when compared to small intestine, the residence time in colon is longer; the bacteria present in colon secrete many enzymes which act as triggers for colon-specific drug delivery, and the microflora degradation mechanism has been used as a tool for the site-targeted delivery of peptide and protein drugs.

**Barrier for colonic absorption**
Colon absorption of protein and peptide drugs administered orally are seriously restrained by diffusional barriers (unstirred layers and mucosal permeability) as in the case of small intestine, but more importantly the inhibition is due to metabolism which occurs in the lumen, brush border, and at the cytosol level [60].

**Colonic absorption**
The lack of organic nutrient transporters may limit the potential for drug design with respect to carrier-mediated transport across the colon. The active transport pathways of the colon have been reviewed [61]. The transmucosal and membrane potential differences may be significant in the absorption of ionized or ionizable drugs [62]. Colon offers less barrier to macromolecules than small intestine, therefore, it is suitable for both protein and peptide absorption. The bulk water absorption in this region of the intestine provides scope for solvent drug and possibly improved drug and possibly improved drug absorption [63].

**Approaches for colonic delivery**
Peptide and protein drugs are coated with azoaromatic groups to form an impermeable film to protect them from digestion in the stomach and small intestine. When the polymer-coated peptide and protein drugs reach the colon, the colonic bacteria cleave the azo bonds and break the polymer film, releasing the drugs into the lumen of the colon for absorption. This polymeric system was demonstrated to protect and deliver orally administered insulin and vasopressin in rats [13]. Other approaches for colonic delivery have been given in Table 4.
Drug metabolism

Drug metabolism in the colon is caused by the host enzymes in the epithelial cells or by the microbial enzymes in the gut flora. Metabolic activities in the wall of the colon can be attributed to enzymes such as cytochrome P450, esterases, amidases, and various transferases [67]. The colonic mucosa resembles the small intestinal mucosa with respect to the spectrum of metabolizing enzymes. However, the total metabolic capacity of the colonic wall is inferior, because the mucosal mass in the lower part of the intestine is several times smaller than that in the upper part.

VAGINAL DELIVERY

Vaginal administration of peptide and protein drugs which are used specifically for the treatment of female-related conditions is a favorable alternative to parenteral administration.

Vaginal barrier for absorption

The vaginal wall consists of three main layers: an outer fibrous layer, a middle muscular layer, and an epithelial layer. The vaginal epithelium is a stratified, squamous epithelium which rests on a lamina propria. The surface area of the vagina is increased by numerous folds in the epithelium and by microridges covering the epithelial cell surface [68].

In common with other mucosal routes, drugs administered vaginally will be transported across the vaginal membrane by a number of different mechanisms (Fig. 4):

- By diffusion through the cell due to a concentration gradient (transcellular route);
- By a vesicular or receptor-mediated transport mechanism; or
- By diffusion between the cells through the tight junctions (intercellular route).

Advantages

Despite traditionally being a site for the delivery of locally acting drugs, the vagina has great potential for the systemic absorption of drugs due to its large surface area, rich blood supply, and permeability to a wide range of compounds, including peptides and proteins [69]. This route provides avoidance of first-pass metabolism, GI effects, side effects at GIT. Steroids used in hormone replacement therapy or for contraception have been administered vaginally to reduce the possibility of hepatic side-effects, associated with oral route [70]. Another advantage is the possible self-insertion and removal of the dosage form [71].

Disadvantages

The main disadvantages include the gender specificity, personal hygiene, local irritation, sexual intercourse, and cultural sensitivity.

Factors affecting the vaginal absorption of drugs

The thickness and porosity of vaginal epithelium may affect vaginal absorption. Menstrual cycle changes may be one of the reasons for this. The presence of moisture helps in absorption. The major barrier for absorption is thick cervical mucous and also the pH of the secretion [71].

Drug absorption

Animal studies have shown changes in the intravaginal absorption of insulin and TSH which may be due to menstrual cycle. Insulin being a hydrophilic in nature may have enhanced absorption due to thinness of epithelium. Absorption enhancers may help in enhancing the absorption [72-74].

Initial work with leuprolide found greater potency in rats through vaginal administration over rectal, nasal, and oral administration [75]. Enhancement of absorption by organic acids (citric, succinic, tartaric, and glycocholic) increased bioavailability by 20%.

Good absorption of some of the protein drugs such as estradiol and progesterone found due to thin atrophic vaginal epithelium [76].

Approaches for vaginal administration

1. Hydrogel slabs: The vaginal slabs are produced from polyethylene glycol-hexane triol diisocyanate hydrogel and form a tridimensional lattice which swells when exposed to water and in this way it can be...
Table 6: Brands names of marketed protein or peptide drugs

<table>
<thead>
<tr>
<th>Oral</th>
<th>Nasal</th>
<th>Ocular</th>
<th>Transdermal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril Brand: Capoten</td>
<td>Calcitonin-salmon brand: Miacalcin, fortical</td>
<td>Cyclosporin Brand: Retasis</td>
<td>Insulin Brand: Dermionic U-strips</td>
</tr>
</tbody>
</table>

An overview of non-invasive protein and peptide drug delivery is given Table 5 and the available marketed formulations are given in Table 6.

CONCLUSION

With the advent of newer molecules in pipeline, large number of proteins and peptides are to be available in coming years. Injectable protein and peptide drugs possess a lot of disadvantages and non-invasive drug delivery become choice of the day. Although lot of intricacies involved in understanding the non-invasive delivery routes, scientists have started devising a novel technology to administer these drugs with improved bioavailability. Although there is a limitation of the current non-invasive route of protein and peptide drug delivery system, continued research may enable the cost-effective, useful, and patient compliant biopharmaceuticals.

REFERENCES


