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Review Article

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, mucin 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 expul 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.

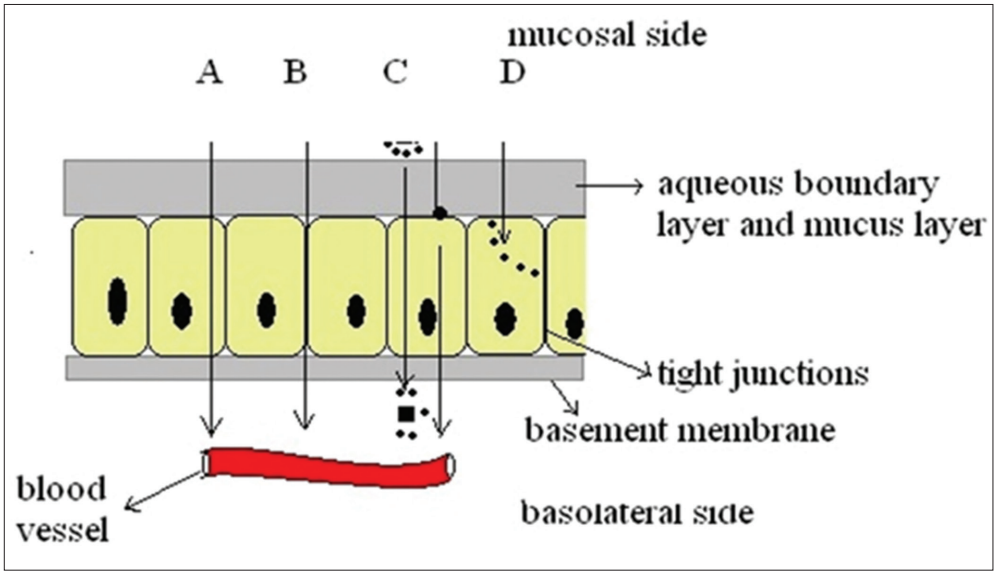

Fig. 1: A schematic illustration of potential mechanisms of transport across the cellular barrier in non-invasive routes of drug delivery systems. (A) Passive transcellular, (B) passive paracellular, (C) facilitated transcellular or active carrier mediated, (D) transcytosis

Table 1: Approaches to increase the oral bioavailability

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

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 epithelia followed by absorption by ocular tissue. 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 biovailabilty through corneal tissues [39-42].

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

Compound	Percentage of absorption	References
Dietary di- and tri-peptides	5-50	[7]
Aminocephalosporins	>50	[8]
Enalapril	>50	[9]
Dietary tetrapeptides	≈5	[10]
TRH analogs	≈5	[10]
Enkaphalins	<2	[10]
Bradykinin	<2	[10]

GI: Gastrointestinal

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

Table 3: Approaches for nasal delivery

Approach	Description	References
Nasal mucoadhesive	Ideal choice of delivery system increases the nasal residence time e.g.: 98% bioavailability was achieved for apomorphine by mucoadhesive polymers such as polyacrylic acid, carbopol, and CMC	[30]
Enhanced nasal blood flow	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_1, and beta-adrenergic agonists	[31]
Novel drug delivery systems 1. Microspheres 2. Vesicles	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	[32,33]
pH modification	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	[21]

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].

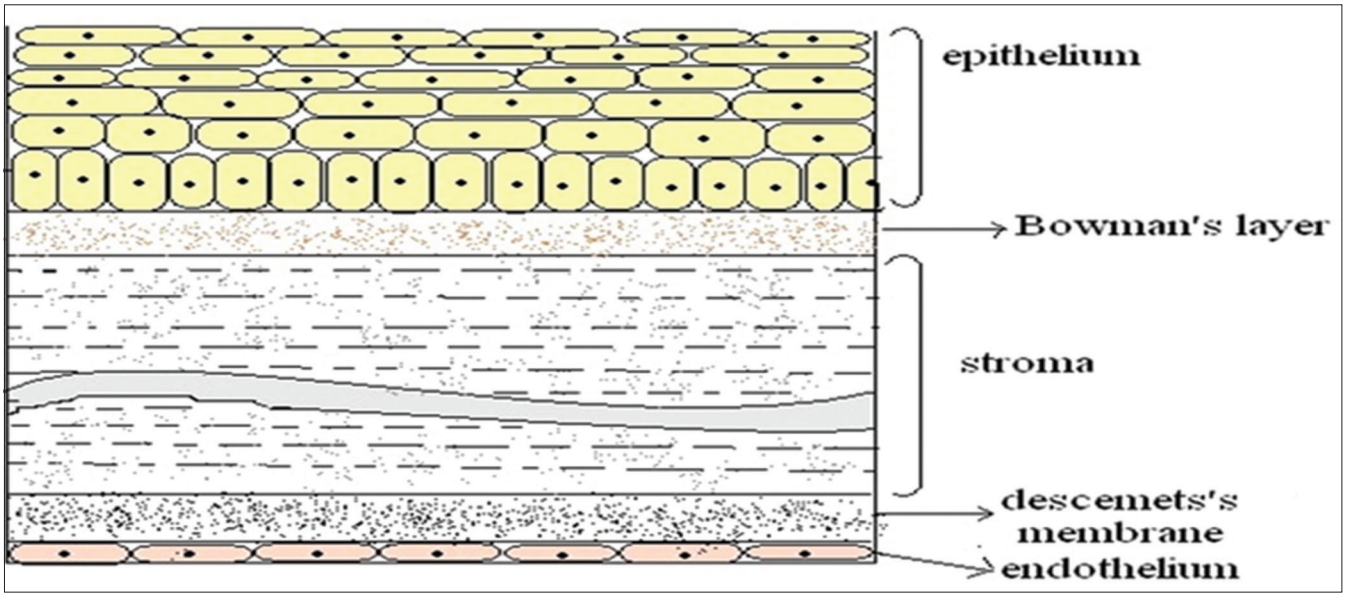

Fig. 2: Diagrammatic representation of cross section of cornea

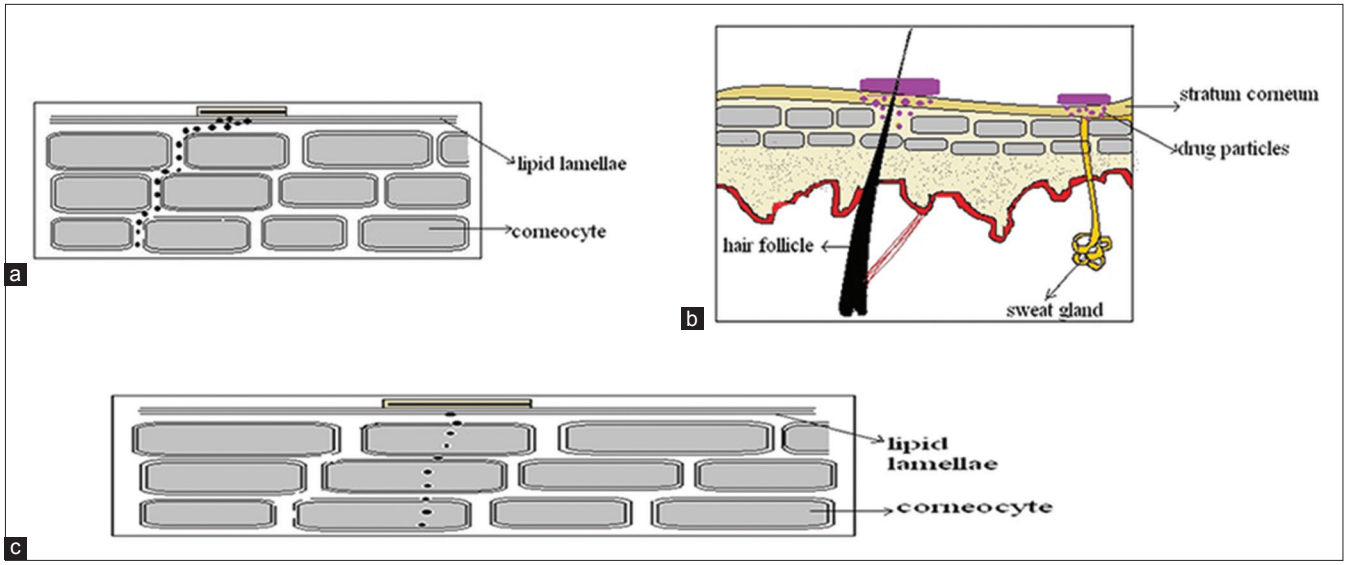

Fig. 3: Routes of passive permeation across the stratum corneum. (A) Intercellular lipid pathway, (B) appendageal transport, (C) transcellular path

Table 4: Approaches for colonic delivery

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

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

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

Electroporation

Application of 100-1000 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. Piezoelectric 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 ultradeformable 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 polypeptides 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

Colonic 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 drag and possibly improved drag 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):

i. By diffusion through the cell due to a concentration gradient (transcellular route);
ii. By a vesicular or receptor-mediated transport mechanism; or
iii. 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 cyclic 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 trioldiisocyanate hydrogel and form a tridimensional lattice which swells when exposed to water and in this way it can be

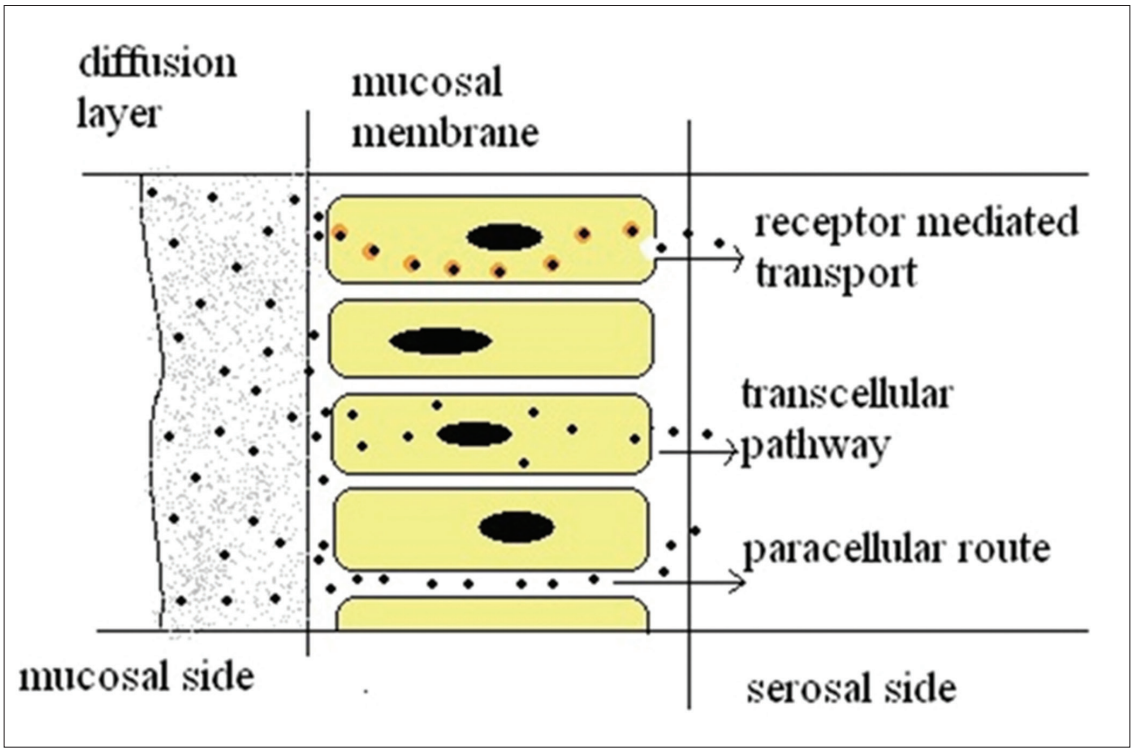

Fig. 4: Schematic representation of vaginal membrane as transport barrier

Table 6: Brands names of marketed protein or peptide drugs

Oral	Nasal	Ocular	Transdermal
Captopril Brand: Capoten	Calcitonin-salmon brand: Miacalcin, fortical	Cyclosporin Brand: Retasis	Insulin Brand: Dermisonic U-strips

loaded with drug. After drying, the drug is trapped in the hydrogel matrix in a near dry state which results in increased stability of the drug. The hydrogel swells and the drug is released, after vaginal administration [76].

2. Microbicidal gel: Microbicidal gel containing monoclonal human antibodies is used for topical immunization, for protecting genital skin, and epithelia from HIV and STIs pathogens [69].
3. Mucoadhesive delivery systems: Polycarbophil, hydroxypropyl cellulose, and polyacrylic acid are the bio-adhesive polymers employed for intravaginal formulations. Hyaluronic acid-based intravaginal delivery of calcitonin, a polypeptide used in the treatment of post-menopausal osteoporosis, has shown promise for intravaginal administration of drugs for systemic effect [69].

RECTAL ROUTE

Rectal delivery of peptide and protein drugs is another very active area of research.

Advantages of rectal protein and peptide drug delivery

Rectal route has less protease activity, partially avoids first-pass metabolism. This route also facilitates potential for absorption through lymphatic system. This route can be exploited for controlled release drug delivery system because of its relatively large surface area [77,78].

Barriers for rectal absorption

The barriers of drug absortion are apical membrane, cell body, and tight junctions. The enzymatic barrier includes the presence of peptidases [79].

Approaches for rectal delivery

Absorption enhancers play a major role in improving rectal absorption. The absorption enhancers, increases the membrane fluidiry, increases the size of the intercellular space, and enhances the solubility of mucosal membrane thereby increasing the water penetration. This also reduced the viscosity of mucus layer.

The various absorption enhancers include sodiumtaurodihydrofusidate, sodium 5-methoxy salicylate, enamine derivatives, and sodium caprate. Some of the protease inhibitors are also can be used as enzyme inhibitors, which includes aprotinin, trypsin inhibitors, bacitracin, puromycin, bestatin, and bile salts [80].

Drug absorption

Although extensive villi and microvilli are not present in the rectum tissue, sufficient surface area is present to allow absorption of readily permeable drugs. There is an extensive motility small intestine incontrast to rectum enables high concentration gradient.

Together with a limited fluid volume in the lower colon, typically 2-3 ml of inert mucous fluid in the absence of fecal material, the static environment of the rectum and lower colon provides an area for maintaining significantly higher drug concentrations than is readily achievable in the small intestine.

Significant rectal absorptions of growth hormone have also been demonstrated with the help of absorption enhancing agents. The apical membranes of the small intestine epithelial cell layer express high levels of membrane-associated or membrane-bound enzymes, such as peptidases and saccharidases, which are not present in high amounts on the apical surfaces of epithelial cells in the rectal cavity [81-84].

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.

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