Available online on 30.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Proteins and Peptide Drugs: Different Routes of Administration for Their Delivery

R. Santosh Kumar and R. Hemanth

GITAM Institute of Pharmacy, GITAM (Deemed To Be University) Rushikonda, Visakhapatnam-530045, Andhra Pradesh, India.

ABSTRACT

Proteins and peptides have the wide range of therapeutic agents emerged within and the administration is through needle and syringe i.e., parenteral delivery is the choice of route of administration, but it has drawn some drawback related to patient incompliance such as causing pain during administration, sterility and cost of the product though the bioavailability is 100%. The route of administration plays an important role as it have an impact on the therapeutic outcome of the drug, with the advancement in the branch of pharmaceutical biotechnology. Based on the biophysical and biochemical properties a delivery system was designed for protein and peptide based therapeutic and clinical application have come into existence through non-invasive delivery and in addition, this dosage form can be significantly self-administered by patients, manufacturing cost would be less compared to the injections. The main aim is to focus in this review article is the recent advances in the delivery of therapeutic proteins and peptides via different non-invasive routes and the barriers affecting the drug transportation, approaches, advantages, challenges.

Keywords: Non-invasive drug delivery, therapeutic proteins and peptides, non-invasive routes.

Article Info: Received 14 July 2019; Review Completed 10 Aug 2019; Accepted 23 Aug 2019; Available online 30 Aug 2019

Cite this article as:

Santosh Kumar R, Hemanth R, Proteins and Peptide Drugs: Different Routes of Administration for Their Delivery, Journal of Drug Delivery and Therapeutics. 2019; 9(4-A):815-819 http://dx.doi.org/10.22270/jddt.v9i4-A.3620

***Address for Correspondence:**

R. Santosh Kumar, GITAM Institute of Pharmacy, GITAM (Deemed to be University), Gandhinagar, Visakhapatnam-530045, Andhra Pradesh, INDIA.

INTRODUCTION

Proteins are the bio-polymers of amino acids, joined by peptide bonds. The amino acid sequence which is encoded by its gene determines a protein's structure and function. Proteins and peptides can be distinguished by the presence of number of amino acids. Proteins contain 50 and more amino acids whereas peptides contain less than 50 amino acids. The molecular weight greater than 10,000 are referred to as proteins and those which less than 10,000 are referred to as peptides.[1] Proteins have secondary and tertiary structures and their molecular size is greater than pharmaceuticals which leads to physical and chemical degradation. Proteins and peptides are very important in biological cells and lack of them causes diseases like diabetes mellitus, due to lack of protein called insulin. Hence, the US Food and Drug Administration in 1982, found the recombinant insulin and it became commercially available for patients suffering with diabetes mellitus.[2]

Many naturally occurring proteins and peptides were identified, and these often have vital roles in human physiology. All naturally occurring ones are not directly suitable for the therapeutic use, because they have intrinsic weakness, poor chemical and physical stability, short plasma half-life. These weaknesses have been successfully resolved through SWOT analysis. It is described below in the figure no.01. [3,4]

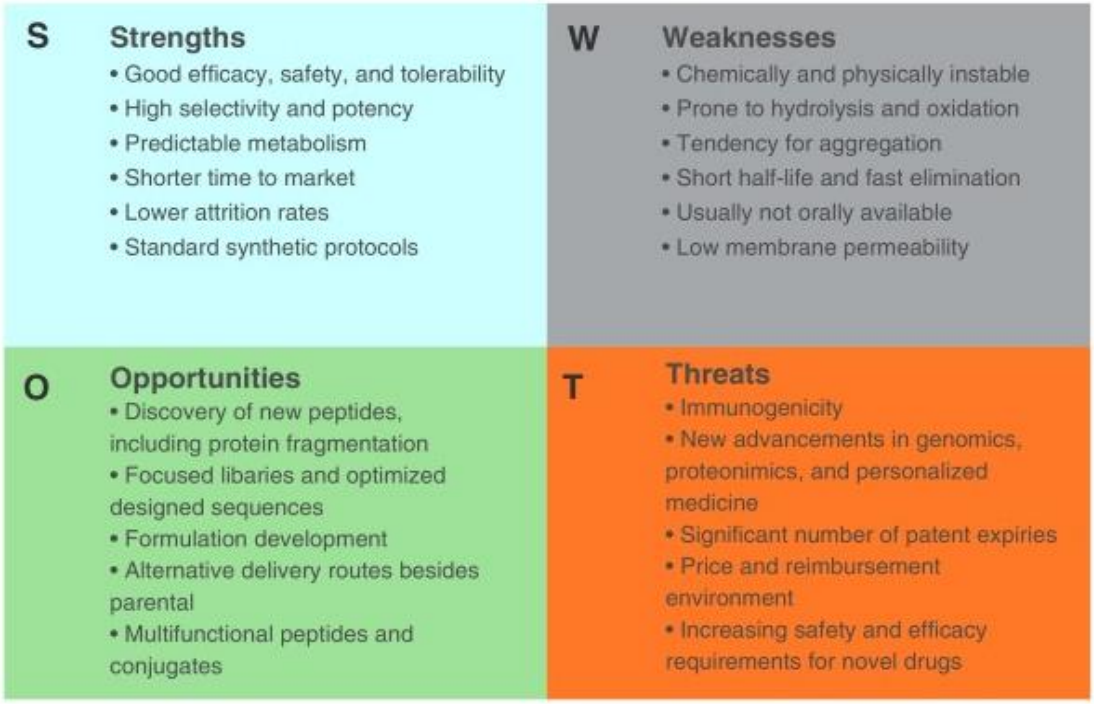

Fig no.01, SWOT analysis description

Prerequisite of Protein and Peptide Drug Delivery System [5-7]

- These are important in biological cells and organic molecules.
- Lack of these may be cause diseases like diabetes mellitus, which is caused due to lack of insulin protein.
- For the protein and peptide-based pharmaceuticals, hybridoma, r-DNA technologies are used.

Advantages of Protein and Peptide Drug Delivery System [8-14]

- Bradykinin, increases the peripheral circulation.
- Erythropoietin, used for production of RBC.
- Gonadotropin, induces ovulation.
- Insulin, maintains blood sugar level.
- Oxytocin, used in management of labour pain.
- Protein tissue, plasminogen, activator used for heart attack, stroke etc.
- Somatostatin, decreases bleeding in gastric ulcer.

Pharmaceutical Approaches [15-24]

The pharmaceutical approaches for protein and peptides are as follows,

I. Chemical modifications
II. Enzyme inhibitors
III. Penetration enhancers
IV. Formulation vehicle
V. Mucoadhesive polymeric system

Chemical modification

Proteins and peptides are modified chemically which plays an important role, in order to improve the enzymatic stability and membrane permeations. This type of modification can be applied to reduce immunogenicity.

Enzyme inhibitors

This modification is an enzymatic approach of protein and peptide drug delivery systems. Gastro-intestinal tract and liver involve in metabolization of protein and peptides into smaller fragments of amino acids.

Penetration enhancers:

These are most important components of protein and peptides, during formulation these are responsible for the disruption of the mucosal barriers and hence improve penetration of larger macromolecular substances.

Formulation vehicles:

The protein and peptide delivery systems can be administered through oral route successfully by the use of various carrier systems like;

1. Dry Emulsion
2. Microspheres
3. Liposomes
4. Nanoparticles

Mucoadhesive polymeric systems

These systems are important as they prevent the problem associated in pre-systemic metabolism at the site of action and also increases or decreases the drug clearance rate.

For the effective delivery system, the physiochemical and biological properties like molecular size, conformational stability, biological half-life, immunogenicity, sensitivity to heat and light, dose, chances of breakdown in both physical and biological environments, mechanism of transport etc., plays an important role as well as considered. [24] These can be delivered through parenteral route but led to an disadvantage as it is causing pain during delivery, cost of the product etc. The route of administration has an impact on therapeutic outcome of drug, recent advances in pharmaceutical biotechnology have made a specific route of delivery as well as delivery system which added importance in delivery of proteins and peptides, like transdermal, pulmonary routes, ophthalmic, buccal, rectal, intra-uterine, vaginal. [25,26]

Various routes of administration for protein and peptide drugs

The various routes of administration for proteins and peptide drugs are;

- Parenteral delivery system
- Non-parenteral delivery system

1. Oral route
2. Nasal route
3. Buccal route
4. Ocular route
5. Transdermal route
6. Pulmonary route
7. Rectal route

- **Parenteral delivery system**

The parenteral delivery system includes intravenous, intramuscular, subcutaneous, intraperitoneal and intrathecal. It used to be the major route of choice for administering the protein and peptides but due to high cost, pain during administration new delivery systems came into existence for better patient compliance. [27]

- **Non parenteral delivery systems**

1. Oral route, Oral route is better route over any other route because of good patient compliance and acceptance. Preparing and formulating protein and peptide drug delivery system for the gastrointestinal (GI) route is difficult because of its unfavourable conditions such as pre-systemic enzymatic degradation and poor membrane permeability.

- **Barriers for oral absorption:** Intestinal epithelial tight junctions in the body prevent the entry of peptides and proteins into the systemic circulation. The major disadvantage in oral route is 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.

- **Enzymatic barriers:** When proteins are in intact form, they are not absorbed in humans in most of the cases. They get break down into amino acids or di- and tri-peptides first in the GI tract (GIT). Trypsin, chymotrypsin, carboxypeptidase, elastase, which are secreted from pancreas convert proteins, and polypeptides to oligopeptides. In small intestine when compared with the total degradation the luminal degradation is only up to 20%. After the entry of oligopeptides into the cell the rest of the degradation takes place by converting them into amino acids (up to 70%) and di- and tri- peptides (up to 30%) To improve oral absorption of protein and peptide drugs from the GIT, the above-mentioned barriers must be avoided. This may be possible to achieve to some extent using enzyme inhibitors or by chemical modification.

- **Bioavailability:** Captopril, Lisinopril, and enalapril have good oral bioavailability due to their low-molecular weight and their ability to inhibit tissue carboxyl peptidases. Cyclosporine is a cyclic peptide with a number of methylated amino acid residues and is resistant to hydrolysis and therefore has good bioavailability. Some protease inhibitors and absorption enhancers have been co-administered 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/mol was required. When the drug was co-administered with aprotinin, a protease inhibitor, the oral dose was reduced to 1000/mol.

2. Nasal route: It is a chief route for protein and peptide drug delivery next to the parenteral route for achieving systemic effect. Generally suitable for highly potent protein/peptide with low molecular weight.

- **Barriers for nasal absorption:** This route has more advantages like larger surface area for absorption. The lipophilicity of the molecule plays major role in absorption. By this route even the central nervous system can be targeted by having improved delivery rate. Vaccines are also delivered by this route.

- **Nasal mucosa and nasal epithelium:** Epithelium of nasal is loosely packed with high permeability and vasculature. This route delivers drugs by transport mechanisms like passive diffusion, carrier-mediated transport, and transcytosis. Compounds such as desmopressin, insulin, and human growth hormones have low absorption rate because of their molecular weight. Drugs by this route permeate at a faster rate when they have a low molecular weight.

- **Muco-ciliary clearance:** Nasal muco-ciliary clearance (NMC) plays a crucial role in delivering the drugs by this route. NMC has a natural defence mechanism in which can help in eliminating the foreign objects and improving the absorption of drug molecules. Antihistaminic drugs, beta blockers, general anaesthetics, cocaine, etc., arrest the muco-ciliary clearance.

- **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. The main enzymatic barrier present in the nasal mucosa is cytochrome P450 enzymes. It is present in both respiratory and olfactory mucosa, thus reducing both nose-to-blood and nose-to-brain transport of drugs. 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)

3. Buccal route: Buccal membrane has numerous elastic fibres in the dermis, which is another barrier for diffusion of drug across the buccal membrane.

- **The barriers for efficient drug absorption are**

✓ Mucus layer covering the oral epithelium.

✓ Epithelial barriers.

Peptidases in the saliva and the mucus layer and microbial flora. The buccal peptide absorption is assumed to be via passive absorption mechanism. The various parameters that influence the extent of buccal peptide absorption are molecular weight, polarity, conformation, dissociation and enzymatic and chemical stability.

4. Ocular route: Ocular route of delivery is useful in treating of ocular inflammation, corneal wounds, and glaucoma. The administration of biopharmaceuticals through eye is difficult because of its normal processes like blinking, tearing, and drainage from the eye which washes out the drugs when administered.

- **Drug absorption:** Cornea consists of three 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. A drug when administered topically on the precorneal area comes into contact with the corneal and conjunctival epithelia followed by absorption by ocular tissue. Then, it enters into the systemic circulation by various processes like corneal absorption. 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.

5.Transdermal route: Transdermal route has a lot of advantages because of its larger surface area which helps in improving the permeability of the drugs with the use of appropriate enhancers. The stratum corneum (SC) is the major barrier which avoids first-pass metabolism. This route has high patient compliance and at any time the drug action can be terminated.

- **Barrier for transdermal delivery:** SC is the outer most layer which acts as a major layer for permeation. Drugs through skin permeate by passive diffusion. 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.
- **Skin barrier function:** The major barrier of skin is SC, which is the thin, outermost layer of the epidermis. 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 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 the continuity of the SC. Visualization of appendageal transport has been accomplished both for passive diffusion and for percutaneous transport enhanced by one means or another (e.g., iontophoresis). A third possible route across the SC is the transcellular path.
- **Approaches for transdermal delivery,** Several approaches have been explained which provides additional driving force in the form of electrical (iontophoresis) or ultrasound (sonophoresis) energies, structural perturbation of SC, penetration enhancers, or a combination of these strategies.

- **Iontophoresis,** To a few square centimetres 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 electro-repulsion and electroosmosis
- **Electro-repulsion,** 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.

6. Pulmonary route: Particles that reach the alveoli can be absorbed into the systemic circulation, avoiding first pass metabolism and the harsh conditions of the gut. The lung is, by necessity, a durable organ. An average person daily inhales air along with all the dust and all the particles floating in it. The safety issue pertaining to the pulmonary route for peptide/protein administration should be considered with regard to immunogenicity of peptide release. Most of the peptide/protein drugs require absorption enhancers to attain a reasonable level of absorption.

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

- **Barriers for rectal absorption,** The barriers of drug absorption are apical membrane, cell body, and tight junctions. The enzymatic barrier includes the presence of peptidases.
- **Approaches for rectal delivery,**

- Absorption enhancers play a major role in improving rectal absorption. The absorption enhancers, increases the membrane fluidity, 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.

- **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 in contrast 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 faecal 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 saccharides, which are not present in high amounts on the apical surfaces of epithelial cells in the rectal cavity.

8. Vaginal delivery: Vaginal administration of peptide and protein drugs which are used specifically for the treatment of female-related conditions is a favourable 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 micro-ridges covering the epithelial cell surface. In common with other mucosal routes, drugs administered vaginally will be transported across the vaginal membrane by a number of different mechanisms

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).

- **Approaches for vaginal administration**

1. Hydrogel slabs, The vaginal slabs are produced from polyethylene glycol -hexane tri-oldiisocyanate hydrogel and form a tri-dimensional lattice which swells when exposed to water and in this way it can be 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.

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.

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.

CONCLUSION

According to recent studies proteins and peptides are gaining a wide range of awareness in drug delivery. Through parental route delivering protein and peptide drugs contains a lot of disadvantages like patient incompliance. Non-invasive drug delivery is gaining importance. A 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. Because of the limitation of the current non-invasive route of protein and peptide drug delivery system but the continued research may help to enable the cost-effective, useful, and patient compliant biopharmaceuticals.

REFERENCES

1. SP Chaudhari, MP Ratnaparkhi, Peptides and proteins in pharmaceuticals, International Journal of Current Pharmaceutical Research, 2011, 3(2), 1-9.
2. PK Sharma, Sumedha Bansal, Arunabha Banik, Noninvasive Routes of Proteins and Peptides Drug Delivery, Indian Journal of Pharmaceutical Sciences, 2011, 73(4), 367-75.
3. A.A. Kaspar, J.M. Reichert, Future directions for peptide therapeutics development, Drug Discovery Today, 2013, 8, 807-17.
4. M.R. Rekha, C.P. Sharma, Oral delivery of therapeutic protein/peptide for diabetes—future perspectives, International Journal of Pharmaceutics, 2013, 440-48.
5. Maloney CM et al. The rectal administration of MS contin, clinical implications of use in end stage therapy cancer. Am. J. Hosp Care, 1989, 6(4), 34-35, 39.
6. Babul N, Drake Ac, Krishna Murthy TN, Pharmacokinetics of two novel rectal controlled release morphine formulations, Journal for Pain Symptom Management. 1992, 7(7), 400-5.
7. Warren DE, Practical use of rectal medications in palliative care, J. Pain Symptom Management, 1996, 11(6), 378-387.
8. Sarwar G, The protein digestibility-corrected amino acid score method overestimates quality of proteins containing antinutritional factors and of poorly digestible proteins supplemented with limiting amino acids in rats, Journal of Nutrition, 1997, 127, 758-64.
9. Schaafsma G, The protein digestibility-corrected amino acid score, Journal of Nutrition, 2000, 130, 1865S-1867S.
10. Sellmeyer, D.E., Stone, K.L., Sebastian, A. and Cummings, S.R. A high ratio of dietary animal to vegetable protein increases the rate of bone loss and risk of fracture in postmenopausal women, American Journal of Clinical Nutrition 2001, 73, 118-122.
11. St. Jeor, S.T., Howard, B.V., Prewitt, E., Bovee, V., Bazzarre, T. and Eckel, R.H. A statement for healthcare professionals from the nutrition committee of the council on nutrition, physical activity, and metabolism of the American Heart Association. Circulation, 2001, 104, 1869-74.
12. Tarnopolsky MA, Atkinson SA, MacDougall JD, Chesley A, Phillips, SM and Schwarcz H, Evaluation of protein requirements for trained strength athletes, Journal of Applied Physiology, 1992, 73, 1986-95.
13. Tarnolpolsky MA, MacDougall JD, and Atkinson SA, Influence of protein intake and training status on nitrogen balance and lean body mass, Journal of Applied Physiology 1988, 64, 187-93.
14. Tikkanen MJ, Wahala K, Ojala S, Vihma V, and Adlecrerutz H, Effect of soybean phytoestrogen intake on low-density lipoprotein oxidation resistance, Proclamations of the National Academy of Science 1998, 3106-10.
15. Okhamafe AO, Amsden B, Chu W and Goosen MFA, Madulation of protein release from chitosan-alginate microcapsules using the pH-sensitive polymer hydroxypropyl methylcellulose acetate succinate, Journal for Microencapsulation, 1996, 13, 497–508.
16. CO Tacket, MB Sztein, SS Wasserman, G Loson-sky and KL Kotloff, —Phase 2 Clinical Trial of Attenu-ated Salmonella Enterica Serovar Typhi Oral Live Vector Vaccine CVD 908-htrA in US Volunteers,‖ Infection and Immunity, 2000, 68(3), 1196-1201,2000.
17. GP Li, ZG Liu, B.Liao and NS Zhong, —Induction of Th1-Type Immune Response by Chitosan Nanoparti-cles Containing Plasmid DNA Encoding House Dust Mite Allergen Der p 2 for Oral Vaccination in Mice,‖ Cellular & Molecular Immunology, 2009, 6(1), 45-50.
18. IS Kim, SK Lee, YM Park, YB Lee and SC Shin, Physicochemical Characterization of Poly(L-lactic acid) and Poly(D,L-lactide-co-glycolide) Nanoparticles with Polyethylenimine as Gene Delivery Carrier,‖ International Journal of Pharmaceutics, 2005, 298(1), 255-62.
19. ANGELINI, —EPAXAL®—Vaccine for Active Immuni- sation against Hepatitis A,‖ 2011, http,//www,angelini,it/public/schedepharma/epaxal,htm
20. MR Kumar, U Bakowsky and CM Lehr, —Preparation and Characterization of Cationic PLGA Nanospheres as DNA Carriers, Biomaterials, 2004, 25(10), 1771-77.
21. Y Yue, F Jin, R, Deng J, Cai and Dai, —Revisit Com-plexation between DNA and Polyethylenimine Effect of Length of Free Polycationic Chains on Gene Transfection, Journal of Controlled Release, 2011, 152(1), 143-151.
22. JL Italia, A Sharp, KC Carter, P Warn and MNVR Kumar, Peroral Amphotericin B Polymer Nanoparti-cles Lead to Comparable or Superior in Vivo Antifungal Activity to That of Intravenous Ambisome® or Fungizone™, 2011, 6(10), 8.
23. R Rupp, SL Rosenthal and LR Stanberry, VivaGel (SPL7013 Gel), A Candidate Dendrimer—Microbicide for the Prevention of HIV and HSV Infection, International Journal of Nanomedicine, 2007, 2(4), 561-6.
24. Gary Gellerman, YosiGilad, Review Recent Innovations in Peptide Based Targeted Drug Delivery to Cancer Cells, Biomedicines, 2019, 4,2-24,
25. Moore JV, Dose-response curve after *in vivo* experimental chemotherapy, Influence of route of administration on biologicals outcomes, Cancer Chemotherapy in Pharmacology, 1985, 15-91.
26. Benet LZ, Effect of route of administration and distribution on drug action, Journal of Pharmacokinetics Biopharmaceutics, 1978, 6,559–85.
27. Jain A, Gulbake A, Peptide and protein delivery using new drug delivery systems, Critical Reviews in Therapeutic Drug Carrier Systems, PubMed 2013, 30, 293-329.