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A RECENT ADVANCES OF NANOPARTICLES FOR A MUCOSAL DRUG DELIVERY SYSTEM

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ABSTRACT

Delivery of drugs to the mucosal sites of the body may be beneficial for various reasons. Delivery of a mucosal drugs achieves a therapeutic effect as the permeation of sufficient amounts of a drug is permitted through the absorption membrane. The in-vitro and in-vivo models are required for the assessment of the delivery potential of such novel drug delivery systems, such as nanoparticles, and for explaining the mechanisms related to the drug delivery enhancement. This system exhibits various functions and features like mucoadhesive and protective activity, solubility improving, permeation and uptake enhancing, and drug release controlling properties. Drug delivery through mucosal surfaces including airways, gastrointestinal tract and the genital tract, represents a desirable delivery by injection. Administration of a drug by injection is expensive and is time consuming, and overall pain decreases the patient compliance.[1] The mucosal route is gaining attention for drug delivery via the oral, nasal, pulmonary or vaginal routes. It includes advantages, limitations of oral mucosal drug delivery system. Nanoparticles for mucosal drug delivery system have been found to be likely advantageous in terms of many features since they: a) decreases the dosing frequency, b) increase the bioavailability of anti-HIV drugs, c) enhance physicochemical properties of drugs such as less solubility as well as stability and d) decreases the adverse effects.

KEYWORDS: Nanoparticles, Mucoadhesive drug delivery system, Bioavailability.

INTRODUCTION

Drug delivery through mucosal surfaces including airways, gastrointestinal tract and the genital tract, represents a desirable delivery by injection. Administration of a drug by injection is expensive and is time consuming, and overall pain decreases the patient compliance.[1] The mucosal route is gaining attention for drug delivery via the oral, nasal, pulmonary or vaginal routes. Chitosan-based nanoparticle are particularly appropriate for the mucosal route, with their low toxicity, mucoadhesion and physical properties. Chitosan-based nanoparticles used for the treatment of cancer, gastrointestinal diseases, pulmonary diseases, drug delivery to the brain and ocular infections.[2]

Advantages of Oral Mucosal Drug Delivery system

Increases the bioavailability of orally administered drugs. Avoid hepatic first-pass metabolism. The drug is prevented from degradation due to pH and enzymes of the middle gastrointestinal tract.

Improved patient compliance due to the administration of drugs in unconscious patients; convenience of administration as compared to injections or oral medications.

Sustained drug delivery is suitable.

There is an increased in drug administration. Drug can be administered easily.

It is less permeable than the sublingual area, the buccal mucosa is vascularized properly.[3]

Limitations of Oral Mucosal Drug Delivery System

For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.

The drugs within saliva is not uniformly distributed, that means some areas of the oral cavity may not receive effective levels.

For both local and systemic action, patient compliance in terms of taste, irritancy and 'mouth feel' is an issue.[3]

Mucosal Delivery System

Most infections of pathogens occur through mucosal surfaces. Ideal vaccine can prevent the pathogen from initial attachment, colonization of the mucosal epithelium, and replication in the mucosa. Mucosal immunization having appropriate antigens can be able to induce both humoral and cellular immune responses throughout the body. For developing a mucosal vaccine targeting a definite system, an antigen delivery system must be needed.[4]

Induction of Mucosal Immunity

Organized inductive sites of mucosal immunity are situated in the areas where pathogens and commensal bacteria are mostly enter into the body.[6] The accumulation of mucosal lymphoid follicles are called mucosa-associated lymphoid tissue (MALT), which contains the mucosal immune system that can work as independently of the systemic immune system.[7] MALT is made up of bronchial-related lymphatic tissue (BALT) and intestinal-related lymphatic tissue (GALT).[6] The follicle-associated epithelium comprises M cells that produce transcytosis of antigens across the epithelium to underlying mucosal cells such as B cells and dendritic cells (DCs).[8] MALT consists of DCs, macrophages, T cells, and B cells.[9,10] These are the cells which are immunocompetent and are responsible for generating the antigen-specific immune response.[11,12] Antigen-presenting cells (APCs) process and present antigens to T cells in these lymphoid tissues.[13] IgA-generating plasma cells later generate dimeric or polymeric forms of IgA. Dimeric IgA becomes secretory IgA by attached to polymeric Ig receptors (pIgR) on the epithelial cells of the mucosal membranes and are discharge into the mucosal tract.[4]

Mucosal Administration Route

The traditional mucosal administration routes are oral and nasal routes, and the immune induction sites differ with respect to the immunization route.[4] Oral immunization is efficient in producing the immune response in the gastrointestinal tract, salivary glands, and mammary glands, while intranasal immunization is efficient in the respiratory, gastric, and genital tracts.[14,15] These broad recognition systems are called the "common mucosal immune system".[16,17,18] The generation of IgA upregulates the explanation of sticking molecules for definite tissues and chemokine receptors that can activate and acuminate lymphocytes back to mucosa all over the body.[4,19,20]

Nanoparticles

Nansoparticles are colloidal particles can produce the drug to the target sites in the body and sustained drug release for prolong period. Nanoparticles have also been formulated for developing the effectiveness of drugs with physicochemical problems and for targeted delivery of antiretroviral drugs to HIV-infected cells and to get prolong drug release kinetics. The nanoparticle drug delivery systems have several benefits such as developed effectiveness, dosage minimization, decline drug resistance and reduction in systemic toxicity.[5]

Controlled and sustained administration by oral route

The oral route of drug delivery is the most common process of drug administration into the body, due to patient acceptance. The tablet form is the mostly accepted among all oral dosage formulations because of the ease of application and the manufacturing on the industrial scale. The maximum oral tablet formulations are immediate release formulations. But the immediate release tablet formulations are usually related with some disadvantages such as repeated administration, toxic side effects, low water solubility, drug fluctuations and poor bioavailability. Therefore, to overcome these limitations of conventional oral dosage forms, controlled and sustained release tablet formulations have been mature with respect to increase the overall therapeutic advantage of antiHIV drugs and to get effective therapy for various drugs. Various types of controlled release tablet have developed e.g. extended release tablets, sustained release tablets, bilayered tablets, floating tablets, Bioadhesive tablets, etc. The sustained release tablets reduces the repeated dosing, increase therapeutic effectiveness and stay away from the side effects related with conventional tablets. Floating tablets extend the gastric residence time of drug, thereby increasing its duration of action and its bioavailability. Bioadhesive drug delivery systems are fabricated for sticking on the mucosa by interrelating with mucin with respect to provide drug absorption for a longer period of time. Oral controlled release formulations for antiretroviral drugs are easily available in the market e.g. Retrovir, Epivir.[5]

Polymers used and their advancements

Polymers are made up of monomers or monomeric units which have a large number of molecular masses. Polymers are a compressed form of large repeating units which are known as monomers. At present times, drug administration is supported through nanoparticles has become a platform to increase as well as repair many properties of drug-like a modification of solubility, improvement of its half-life and its release characteristics thereby, increasing the pharmacodynamic as well as pharmacokinetic parameters of the biopharmaceutical formulations. Polymeric nanoparticles hold most of the share in it. Polymers play a vital role in this regard. To make polymeric nanoparticles, enough knowledge of polymers is very much important. The stability and compatibility problem of the drug and excipients with the polymer has been a major matter of concern during the manufacturing of the formulation. Polymers work as inert carriers in which the drugs are assembled so that the polymer can work as a vehicle to carry or take the drug molecule to the targeted site. Polymers can be both synthetic as well as natural in nature. Naturally existing polymers can be cellulose, proteins, latex, and starches whereas, on the other hand, synthetic polymers are manufactured in large scale in laboratory.[21]

Chitosan

Chitosan is a deacetylated chitin derivative and is a natural polymer. Chitosan is a modified natural carbohydrate-based derivative obtained from insects, fungi, animals or other marine invertebrates. Chitosan has a big role in the biomedical field. Chitosan has been used as a polymer in many fields like agriculture, biomedical, etc. It is among the highly rich natural polymer and can be easily made into various forms like threads, matrix, beads, nanoparticles, etc. Mostly

chitosan is used as chitosan sponges, chitosan beads, chitosan film, chitosan nanoparticles and chitosan microbeads (microspheres) in a targeted drug delivery system. Since chitosan is a natural polymer, it is biocompatible and biodegradable as well. Chitosan is freely soluble in acidic solution and produces a free amino group and grow positive charge over the polymeric chain. Chitosan have poor solubility at pH above 6.5. Normally, the chitosan nanoparticle can be made by including a polyanion like TPP (tripolyphosphate) into the chitosan with continuous stirring.[22] Usually, Chitosan nanoparticles can be used for drug delivery, anticancer activity, gene therapy, etc.

Alginate

Alginate is a natural polymer and is biodegradable and biocompatible in nature. Alginate is usually a copolymer of (1, 4) linked β-D mannuronate and α-l-glucoronate. It is water soluble in nature and a linear polysaccharide. Most of the alginates are used as hydrogels, porous scaffolds, microparticle, and nanoparticle. Normally, alginate nanoparticle is develop by processes like ionic gelation, emulsion, covalent cross-linking, complexation method, and self-assembly method. Among all the method of preparation, ionic gelation and complexation are commonly used method to prepare alginate nanoparticles.[21] Alginate nanoparticles can be used for the administration of drugs like an anti-tumor drug, an anticancer drug, proteins, insulin, etc. The alginate nanoparticles are controllable and are pH-sensitive.

Synthesis methodologies of nanoparticles

The manufacturing of Nanoparticles needs development of different preparation parameters based on different uses for which the polymeric nanoparticles are to be used. The choice of the drug and the polymer is very important, in a same way, the method of preparation also plays a important role in achieving the properties of interest. A broad range of polymers is used for the preparation of polymeric nanoparticles. The combination of the various polymeric systems with the nanostructures has helped to develop a sustained release drug delivery system. There are different ways of preparation of Polymeric Nanoparticles.[21]

Nanoprecipitation

It is the method of preparation of polymeric nanoparticles which also known as interfacial deposition or solvent displacement method. This technique was first introduced by Fessi. This is an encapsulation technique which associate precipitation of polymers followed by solidification. The solidification of polymers happen due to the interfacial disposition of the polymers. The interfacial disposition of polymers takes place by displacement of a semi-polar solvent miscible with water, which was at first present in a lipophilic solution.

In this preparation process, first, a favourable organic solvent is chosen. The organic solvent should be water-miscible by nature. The required drug and the polymer should be mixed in the organic solvent. Then, finally, the aqueous phase which contains a stabilizer is added with continuously stirring. Due to reduction in the interfacial tension between the aqueous phase and the organic phase, the diffusion of organic solvent into the aqueous phase takes place very quickly. This quick diffusion and the flow of solvent forms and characterizes well-defined droplets of nanoparticles. Then finally the nanosuspension is obtained after freeze-drying the suspension with the help of 5% mannitol as cryoprotectant.[23,24]

Solvent evaporation

It is one of the most widely used technique for the preparation of polymeric nanoparticles. Mostly, in this technique of preparation of polymeric nanoparticles, such as an organic solvent is chose into which drug will get dissolved and dispersed. Then, in this solution of an organic solvent which having the dispersed drug, the polymer is also mixed. Then, the resultant organic phase which having the drug and the polymer is then added to the aqueous phase. The aqueous phase having surfactant like poloxamer 188, Polysorbate 80, PVA, etc. The organic phase and the aqueous phase are mixed by highspeed homogenization, which outcomes in the formation of a stable emulsion. After the emulsion is formed, the emulsion is changed into nanoparticle suspension. Under highly increased temperature and reduced pressure, the evaporation of the solvent takes place. In general, the single emulsions or double emulsions are prepared by ultra-sonication or high-speed homogenization. Finally, ultracentrifugation is convey out to achieve the solidified nanoparticles.[25]

Salting out

It is the modification of solvent diffusion or emulsification. It is the modified version of the emulsion method. In this method, drug and polymer are dissolved in an organic solvent which is miscible in water. Then, the resulting solution formed is mixed with the aqueous match of the solution which already had the salting-out agent in it. Thus, the organic phase which already having the surfactant is mixed with the aqueous solution which contained the salting-out agent and the stabilizer, by continuous stirring. The salting-out agents, like magnesium and calcium chloride mostly avert the miscibility of the aqueous phase with the organic phase resulting in the formation of an emulsion. When the emulsion is diluted, a reverse salting-out effect is noticed which results in the precipitation of the polymer. The precipitated polymer matrix having the encapsulated drug prime to the formation of nanoparticles.[26]

Supercritical fluid technology

It prevents the use of organic solvents for the preparation of polymeric nanoparticles. Drug and polymer are dissolved in an environmental friendly solvent which have ability in producing polymeric nanoparticles. The drug and polymer together are changed to a solution with the supercritical fluid. This solution extends rapidly

throughout the capillary nozzle into the ambient air. A high degree of supersaturation go alongwith the fast expansion of the solution results homogeneous nucleation and finely dispersed nanoparticles.[27–29]

Dialysis

It is a technique similar to the nanoprecipitation technique. But the only difference is that the polymers having the drug dissolved in the water-miscible organic solvent are put inside a dialysis membrane. The organic phase comes into the aqueous phase by diffusing out across the dialysis tube. The diffusion decreases the interfacial tension between the two phases. Afterwards, inside the membrane, there is displacement of the solvent. This episode is come behind by loss solubility of the polymer which results to the continuous aggregation of the polymer.[30]

Polymerization

It is a technique where there is the polymerization of two monomers. When the two monomers are there in two different interfaces, then the process is known as an interfacial polymerization. When a single or multiple emulsions are used for the encapsulation of drugs, then the process is single/ double emulsion technique. Polymeric micelles are frequently formed by the process of polymerization. The basic principle behind all these processes is the polymerization of the monomeric units. There could be intermolecular cross-linking occured by the polymerization reaction. The limitation of the polymerization process is that there could be unreacted monomers, toxic substances may be generated from the chemical reactions, unreacted toxic by-products may also obtained from monomeric reactions, etc.[31,32]

Application of polymeric nanoparticles

Treatment of vaginal diseases

The vagina is the main route of administration to get local effect or systemic effect and this route can also bypass the hepatic first-pass metabolism. This route can also be used to treat the sexually transmitted disease or infections. But delivering the drug through vaginal route is not easy and has many disadvantages. The abundant mucus released by the vagina is the main barrier for the conventional dosage form and because of this conventional drug does not show sustained and targeted action. It is because of these disadvantages that modified release dosage form for vagina was introduced. The polymeric nanoparticles have been introduced to control the physiological barrier and has certain benefits like mucoadhesiveness, easy penetration to mucosa as well as a sustained and targeted release of the drug. Both biodegradable and non-biodegradable polymer of natural and synthetic start has obtained immense purpose.[33]

Cancer treatment

Cancer is one of the serious diseases nowadays. Cancer is one of the fatal diseases worldwide. Chemotherapy and surgical processes were the only methods of treatment of cancer in ancient times. The idea of encapsulation of the drug came into existence for effective targeting as well as treatment of cancer cells. The biggest limitation of the conventional method is that chemotherapy and other techniques of radiation cannot differentiate between the self and non-self cells. This incapacity of bias of self and non-self cells source a vast and extensive amount of side-effects, thereby causing hurt to even healthy cells. The concept of encapsulation of drug came into existence for systematic, specific and targeted delivery of drug with decreased side-effects. The nature of the polymer also decide a lot of things connected to the formulation.[33]

Formulations which are used currently

Most of the novel formulations have been improved to many stages of development and acceptance and have met with various producing and marketing successes.

Tablets

For medications like nitroglycerin and fentanyl, lozenges, troches, and tablets for systemic delivery through the oral mucosa are already commercially available.[34] Solid formulations, such as tablets and lozenges, dissolve in saliva and absorb through the entire surface area of the mouth cavity. Variation in saliva production and sucking intensity, unintentional swallowing, and a limited exposure time of not more than 30 minutes are all disadvantages of tablets and lozenges.[34] Mucoadhesive tablet formulations are preferable in this regard since they cling to the mucosa, extending the length of exposure. A mucoadhesive pill currently in development has been proven to transmit therapeutic amounts of flurbiprofen to the saliva for 12 hours.[35] This mucoadhesive tablet enables patients to eat and speak freely without irritation, foul taste, or pain.[35]

Sprays

For angina treatment, glyceryl trinitrate is a tiny molecule that can be quickly given across the sublingual oral mucosa via a spray. The Generex Biotechnology Corporation has created a RapidMistTM spray that can transfer big molecules over the oral mucosa, such as insulin.[36,37] To promote medication permeability across the buccal epithelium, the Generex Oral-lynTM spray employs micelles and widely recognised as safe GRAS-like surfactants as permeability enhancers.[38,39] The product is now available for purchase in India and Ecuador, and it is pending regulatory approval in other countries. Vaccination against influenza and malignancies, pain treatment, and weight loss are among the other applications of the RapidMistTM system in development.

Mouthwashes

The current literature on mouthwashes and oral rinses focuses mostly on their application in antibacterial local administration. Chlorhexidine gluconate is one such antibacterial, with research supporting its use in the treatment of gingival and periodontal disease, caries[40,41], and oral candidiasis prophylaxis in immunocompromised

patients.[42] The substantivity of the mouth rinse provides for a considerable antibacterial impact up to 7 hours after use.[43] Several naturally occurring antimicrobials, including lactoperoxidases, lysozymes, and lactoferrin, have also been studied in mouthwash form and have recently been reviewed elsewhere.[44] The antioxidant characteristics of antimicrobial mouthwashes containing essential oils are assumed to be related to their efficiency[45], with current data revealing varying levels of effectiveness.[46,47] Antimicrobial mouthwashes have also become more popular in recent years.

Gels

Gels have been investigated as a means of controlled drug delivery since the 1980s. The primary goal of bioadhesive controlled drug delivery is to localise a delivery device within the body to enhance the drug absorption process in a site-specific manner. Bioadhesion is affected by the synergistic action of the biological environment, the properties of the polymeric controlled release device, and the presence of the drug itself.[54] Overall, more than half of the therapeutic agents and vehicles being formulated are in the development stage (bioavailability, distribution, safety and adherence stages). Others are at the stage of animal or ex-vivo studies. Few clinical trials have been performed and those that have are often small in size. None-the-less, gels applied to the oral mucosa have been trialled for the delivery of systemic analgesics[55–58], anti-hypertensives and drugs for treating cardiovascular disease[59–61] as well as topical delivery of antifungal agents[34,62], anti-inflammatories[63] and mucoprotective agents[64] to the oral mucosa.

Pastes

Most current work focuses on the intra-canal distribution of antimicrobial pastes in endodontics, however this is beyond the scope of this review. Both as a solution and in a paste formulation, liposomes have been studied as drug delivery carriers.[65] Pastes have been used to administer antimicrobial agents for enhanced extraction socket healing following tooth extractions in HIV patients[68] and to deliver controlled release triclosan in oral care formulations.[69] In the treatment of periodontal disease, pastes are also being employed for the local administration and retention of slow release minocycline in the gingival crevice around teeth.[70] Allen et al.[71] looked into the topical administration of an antiviral drug in the form of a paste. Topically, the medication was applied to oral and genital lesions. Only the genital lesion reaction was studied, and it was discovered to have some influence. For the treatment of oral HSV lesions, topical oral administration may be considered.

Patches

Several different patch systems for drug delivery that attach to the oral mucosa have been developed. Oro-adhesive patches can be divided into three categories:

(1) Drug administration to the oral cavity via patches with a dissolvable matrix. These patches are more effective than solid forms such as tablets and lozenges in treating oral candidiasis and mucositis because they last longer.[32] During use, they gently and totally disintegrate, leaving no residue to clean up. However, the oral cavity will lose a large proportion of the medicine. As a result, they are better suited to delivering medications into the oral cavity as a whole than to the specific oral mucosa to which they are placed.

(2) Non-dissolvable backing patch methods for systemic drug distribution that provide saliva protection. For 10–15 hours, the patches release a concentrated amount of the medication into the oral mucosa. The patch can only distribute to a small area of the mucosa, limiting the dose that can be provided, and the patient must remove the patch after the dose has been delivered.

(3) Patches having a dissolvable impermeable backing that dissolves the entire patch into the oral cavity over time. These patches administer drugs directly into the mucosa without requiring the patch to be removed at the conclusion of treatment. As wound dressings, mucoadhesive patches offer therapeutic potential in and of themselves, even without the addition of drugs. Several products to cover and heal oral aphthous ulcers have been created, albeit many are no longer available. In the treatment of herpes labialis, an occlusive hydrocolloid patch devoid of any drug has recently been found to be equally effective as topical acyclovir.[73]

CONCLUSION

Conventional drug delivery associated in antiretroviral, like compressed tablet for oral delivery or a solution for intravenous administration, such dosage form have many disadvantages such as requirement of high dosage, dose frequency, less affectivity, high adverse effects. In the last decades various novel and controlled drug delivery systems are being look over to control the disadvantages of the conventional drug delivery, to reduce drug degradation, to reduce the adverse-effects and to make better drug bioavailability. Many drug delivery and drug targeting systems are presently under development to increase the effective delivery of antiretroviral drugs for HIV prevention and therapy. As a conclusion of this review paper introduce the most recent approaches of novel drug delivery system for antiHIV drugs, (nanoparticles) that have been found to be likely advantageous in terms of many features since they: a) decreases the dosing frequency, b) increase the bioavailability of anti-HIV drugs, c) enhance physicochemical properties of drugs such as less solubility as well as stability and d) decreases the adverse effects.

List of abbreviations

HIV:Human Immunodeficiency Virus; IgA:Immunoglobulin A; MALT:Mucosa-Associated Lymphoid Tissue; BALT:Bronchial-related lymphatic tissue; GALT:Intestinal-related lymphatic tissue; DCs:Dendritic Cells; APCs:Antigen presenting cells; pIgR: polymeric Ig Receptors; PVA:Polyvinyl Alcohol;

GRAS:Generally Recognized as Safe; HSV:Herpes simplex virus.

Authors' contributions
All authors have read and approved the final manuscript. US Author participated in study conception and writing a manuscript. CB Author participated to draft the manuscript. SSR Author give final approval of the version to be submitted and any revised version.

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