



RECENT ADVANCES IN DRUG DELIVERY SYSTEM

Dr. Swati Sharma^{1*} and Dr. Smriti Sharma²

¹Reader, Department of Preventive and Community Dentistry, School of Dental Sciences Sharda University, Greater Noida, UP.

²Senior Lecturer, Department of Oral Medicine & Radiology, Darshan Dental College, Udaipur, Rajasthan.

*** Corresponding Author: Dr. Swati Sharma**

Reader, Department of Preventive and Community Dentistry, School of Dental Sciences Sharda University, Greater Noida, UP.

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ABSTRACT

Evolution of an existing drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety, and efficacy. Presently, drug delivery companies are engaged in the development of multiple platform technologies to get competitive advantage, extend patent life, and increase market share of their products. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. This review article gives an overview of the recent advances in drug delivery system.

KEYWORDS: drug delivery system, transmucosal, transdermal.

INTRODUCTION

The method by which a drug is delivered can have a significant effect on its efficacy. Any drug delivery system may be defined as a system comprising of drug formulation, medical device or dosage form/technology to carry the drug inside the body, mechanism for the release. Conventional drug delivery involves the formulation of the drug into a suitable form, such as a compressed tablet for oral administration or a solution for intravenous administration.

A drug can be administered via many different routes to produce a systemic pharmacological effect. The most common method of drug administration is via per oral route in which the drug is swallowed and enters the systemic circulation primarily through the membrane of the small intestine. Other commonly used methods for drug administration in oral diseases are through pulmonary delivery in the form sprays, powders, transdermal drug delivery system, parenteral routes through intravenous, intramuscular & subcutaneous routes, trans- tissue systems in the form of gels, transmucosal system which includes buccal drug delivery system. Other approaches to drug delivery are focused on crossing particular physical barriers, such as the blood brain barrier, in order to better target the drug and improve its effectiveness; or on finding alternative and acceptable routes for the delivery of protein drugs other than via the gastro-intestinal tract, where degradation can occur.

NEWER DRUG DELIVERY SYSTEMS

Conventional drug delivery systems have been found to have serious limitations in terms of higher dosage required, lower effectiveness & toxicity. New drug delivery systems have been developed or are being developed to overcome these limitations of the conventional drug delivery systems. The therapeutic benefits of these new systems can be increased efficacy of the drug, site specific delivery, decreased toxicity/side effects, better patient compliance, increased convenience, shorter hospitalizations, viable treatments for previously incurable diseases, potential for prophylactic applications, lower healthcare costs - both short and long term.

The expected outcomes of these delivery systems with more precise localization and appropriate half-lives is to treat oral diseases such as caries and periodontal disease, oral mucositis and temporomandibular joint and muscle disorders and chronic pain.

VARIOUS DRUG DELIVERY SYSTEMS

The choice of a delivery route is driven by patient acceptability, the properties of the drug (such as its solubility), access to a disease location, or effectiveness in dealing with the specific disease.

1. Oral route

The most important drug delivery route is the peroral route. They offer the greatest potential for more effective

therapeutics, easy to administer, inexpensive, they are easily denatured or degraded.^[1] However, it has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract that prohibits oral administration of certain classes of drugs. They do not easily cross mucosal surfaces and biological membranes.

2. Chewing gums

Chewing gum is an obvious drug delivery system for local treatment of diseases in the oral cavity and in the throat, as sustaining the release of active substances may deliberately prolong exposure. Dry mouth is a side effect of many types of medicament (e.g. antidepressants) and it is also part of the symptomatology of several diseases (e.g. Sjögren's syndrome—an autoimmune disorder characterized by lymphocytic infiltration of the salivary and lacrimal glands). Chewing gum stimulates salivary secretion thereby decreasing dryness in the mouth (Xerostomia).^[2] Chewing gum freshens breath, whitens teeth by reducing stains and preventing stains from accumulating and reduces plaque.

As a drug delivery vehicle, chewing gum enables rapid drug absorption through the oral mucosa to achieve fast onset of action and bioavailability. It also has superior organoleptic properties compared with other dosage forms; it has a more attractive appeal and offers the patient active control over the treatment & its positive synergistic effect brought on by the chewing action boosts patient compliance.^[3]

Chewing sugared gum can lead to tooth decay, cavities and gum diseases. Frequent gum chewing can contribute to a condition known as Temporomandibular Joint Disorder (TMJ), which is caused by constant stress being placed on the jaws and its symptoms include severe facial pain and discomfort in the back of the neck. Frequent chewing over time can also result in the wearing down of tooth enamel.

3. Pulsatile drug delivery system

It aims to release drugs on a programmed pattern i.e.: at appropriate time and/or at appropriate site of action. It delivers a drug via the oral route at a rate different than constant, (i.e. zero order release).^[4-9] Ideally such systems match the drug release rate to a biological requirement of a given disease therapy and thus to manage the disease while minimizing treatment's side effects.

This system is characterized by at least two distinctive drug release phases following a predetermined lag time. Drug's release may be controlled by time, by site or a combination of the two parameters.

4. Oral transmucosal system

Oral transmucosal systems address the need for a convenient noninvasive drug delivery vehicle that provides rapid onset of therapeutic action and allows the

patient to control drug administration until the desired effect is achieved. The drug is released in the mouth, allowing rapid absorption through the oral mucosal tissues. Various drug delivery systems which use the oral mucosa as a drug delivery site such as – buccal delivery, fast dissolving tablets, orodissolving films, fast caps, buccoadhesive film and tablets.

(a) Buccal drug delivery—Buccal delivery specifically refers to the delivery of drugs within/through the mucosa lining the inner cheeks. Local delivery to tissues of the oral cavity has a number of applications, including treatment of local conditions such as toothaches^[10], periodontal disease^[11,12], bacterial and fungal infections^[13], aphthous & dental stomatitis.^[14] Compared with other mucosal tissues, buccal mucosa is more tolerant to potential allergens and has a lesser tendency to irreversible damage. Additionally, it is a well-vascularized, relatively immobile tissue and has relatively lower enzymatic activity. Buccal mucosa allows drug delivery for both local and systemic therapies. Similar to any other mucosal membrane, the buccal mucosa as a site for drug delivery has limitations as well.

One of the major disadvantages associated with buccal drug delivery are the low flux which results in low drug bioavailability^[15] & the lack of dosage form retention at the site of absorption. Consequently, bioadhesive polymers have extensively been employed in buccal drug delivery systems. Bioadhesive polymers are defined as polymers that can adhere onto a biological substrate.^[16]

(b) Fast Dissolving Tablet (FDT): These tablets can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth.^[17] Recently fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery system, because they are easy to administer and lead to better patient compliance. They also impart unique product differentiation thus enabling use as line extension for existing commercial products. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms.^[18-20]

However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are travelling or have little access to water are similarly affected.^[21-23]

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Orally Disintegrating Tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take with water & also, there are disadvantages like fast dissolving tablets are

hygroscopic in nature so must be kept in dry place & FDT requires special packaging for proper stabilization & safety of stable product.

(c) Fast Dissolving Films: It consists of a very thin oral strip, which releases the active ingredient immediately after uptake into the oral cavity. The novel natural polymer chitosan is also utilized as a polymeric matrix in the form of film enriched with taurine (antioxidant agent). Taurine enhances the wound healing ability of chitosan and could be considered beneficial in tissue repair in destructive diseases like periodontitis.^[24]

Rapid film combines all the advantages of tablets (precise dosage, easy application) with those of liquid dosage forms (easy swallowing, rapid bioavailability). FDFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices. A far more widely used form of intra-pocket delivery device has been in the shape of film. The advantages of such a device include ease of insertion, dimensions that conform well with the dimensions of the periodontal pocket and minimum pain on insertion.

(d) Fast Caps. A new type of fast dissolving drug delivery system based on gelatin capsules was developed. In contrast to conventional hard capsules, the fast caps consist of gelation of low bloom strength and various additives to improve the mechanical and dissolution properties of the capsule shell. The advantage of these fast disintegrating capsules are high drug loading, possible solid and liquid filling, no compression of coated taste-masked or extended release drug particles/pellets, good mechanical properties, simple manufacturing, mechanical stability and requirement of special packaging.

(e) Buccoadhesive Film and Tablets: These are useful for the systemic delivery of drugs as well as for local targeting of drug to a particular region of the body. Films based on synthetic biodegradable polymers such as poly (lactide-co-glycolide) (PLGA) containing tetracycline have been developed for modulated-release of drug in the periodontal pocket as slab like device.^[25] Water soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparations due to their susceptibility to "dose dumping phenomena". Attempts have been made to regulate their release process by use of mucoadhesive polymers in order to achieve a once-a-day dose treatment. Sustained release devices composed of cross-linked fish gelatin (bycoprotein) containing chlorhexidine diacetate or chlorhexidine hydrochloride have been developed by Steinberg. Release of drugs from these preparations involves initial burst of activity, whose level rapidly declines to subtherapeutic concentrations.^[26] Thus, systemic antifungals such as fluconazole are usually preferred for treating oral candidiasis.

The various advantages of buccoadhesive films & tablets are ease of administration and can be removed from the site of application, permits localized and systemic action of the drug to the oral cavity for longer period of time, a significant reduction in dose can be achieved, thereby, reducing dose dependent side effects, increased bioavailability, can be administered to unconscious patients, offers excellent route for systemic delivery of drugs with high first pass metabolism, thereby offering greater bioavailability.

Besides all the advantages, this system has some limitations also like only those drugs with small dose requirements & which are absorbed by passive diffusion can be administered by this route, eating and drinking may become restricted, drugs which irritate the mucosa or having bitter and unpleasant taste or odour cannot be administered, possibility that the patient may swallow the tablet, drugs contained in the swallowed saliva leads to the loss of drug.

5. Pulmonary drug delivery system

Pulmonary delivery is also important and is effected in a variety of ways - via aerosols, metered dose inhaler systems (MDIs), powders (dry powder inhalers, DPIs) and solutions (nebulizers), all of which may contain nanostructures such as liposomes, micelles, nanoparticles and dendrimers. As an intranasal spray lidocaine can be used as a treatment for migraine headaches and trigeminal neuralgia.^[27]

In this system, drugs are absorbed quickly, there is systemic as well as local effect & it is good in emergencies. But in spite of all these advantages, patient can have an unpleasant taste & can irritate the mouth, there may be difficulty in administering the correct dose & can cause hyperactivity & restlessness.

6. Transdermal drug delivery system

Transdermal drug delivery systems (TDDS) deliver drugs through the skin into the systemic circulation at a predetermined rate, thereby avoiding metabolism in the GI tract and liver. Therefore, the amount of active ingredient required for transdermal delivery can be significantly less than that for oral systems.

Transdermal patch is a medicated adhesive pad that is placed on the skin to deliver a time-release dose of medication through the skin into the bloodstream. It is also called skin patch. Skin patches are used as an alternative way of getting medicines into the body. Drugs administered through skin patches include lidocaine to relieve the pain of shingles (herpes zoster). Lidocaine patches can also be used as a treatment for other types of neuropathic pain, as well as fibromyalgia and myofascial trigger points^[28] but these patches are not effective in an emergency, sometimes may irritate the skin & absorption of dose may be affected by skin condition & circulation.

7. Trans-tissue drug delivery system

Trans-tissue and local delivery systems require to be tightly fixed to resected tissues during surgery. The aim is to produce an elevated pharmacological effect, while minimizing systemic, administration-associated toxicity. Trans-tissue systems include: drug-loaded gelatinous gels, which are formed in-situ and adhere to resected tissues, releasing drugs, proteins or gene-encoding adenoviruses. Isolated severe ulcers may be treated with a one-time local injection of steroid (eg, triamcinolone) in the submucosal tissue after application of a topical anesthetic. The most effective treatment for myofascial pain caused by trigger points is injecting lidocaine or another local anaesthetic directly into it. These injections are effective for temporomandibular pain (TMJ/TMD) as well.^[29] High-potency corticosteroids applied locally 2-4 times daily may be successful in promoting healing and shortening the course of recurrent aphthous ulcers (canker sores), especially if applied early in the development of the lesions. Topical lidocaine, in the form of Lidoderm patches or lidocaine cream/gel, is most commonly used for postherpetic neuralgia (pain caused by shingles).^[30]

Polyvinylpyrrolidone-sodium hyaluronate gel (Gelclair) is used (off-label) primarily for relief of oral mucositis associated with cancer chemotherapy or irradiation, and may be effective for pain control in severe, refractory recurrent aphthous ulcers (canker sores).^[31] Topical preparations such as mouthwash or gels are preferred because they limit the amount of medication delivered and thus reduce systemic adverse effects.

Parenteral routes (intravenous, intramuscular, subcutaneous) are very important. The only nanosystems presently in the market (liposomes) are administered intravenously. Nanoscale drug carriers have a great potential for improving the delivery of drugs.

Some other less well-defined factors, such as the presence of a 3D mucus network, presence of bacteria, salivary flow rate, foods and involuntary swallowing, result in drug losses from the site of absorption. Injuries and disease states, where the mucosa is seriously damaged, would be expected to increase permeability (e.g., in conditions that result in erosion of the oral mucosa such as lichen planus, pemphigus, viral infections and allergic reactions).

RECENT DEVELOPMENTS

While there are a number of other delivery systems being developed, such as chewables and transmucosals, advances in nanotechnology have in recent times provided better improvements in drug delivery system. Nanoparticles are made from biocompatible and biodegradable materials such as polymers, either natural (e.g., gelatin, albumin) or synthetic (e.g., polyglactides, polyalkylcyanoacrylates), or solid lipids. Chen *et al.* took advantage of these latest developments in the area of nanotechnology to mimic the natural biomineralization

process to create the hardest tissue in the human body, dental enamel (bio-mimicry). In oral tissue, nanoparticles play an important role in induction of anesthesia, major tooth repair, renaturalization procedures, dentin hypersensitivity, tooth repositioning, tooth durability and appearance, salivary diagnostics.

FUTURE DIRECTIONS AND CONCLUSIONS

As discussed in this article, drugs can be delivered to a patient by many different delivery systems, including oral, transdermal, injection, implants, etc. Most of the drugs are amenable to these types of delivery systems. The routes of administration will be dictated by the drug, disease state, and desired site of action. Some sites are easy to reach such as the nose, the mouth. Others sites are more challenging to access, such as the brain. Gene therapy is also likely to be one of the most exciting growth sectors as biotech companies become involved in drug delivery. In conclusion, the market for drug delivery systems has come a long way and will continue to grow at an impressive rate. Today's drug delivery technologies enable the incorporation of drug molecules into new delivery systems, thus providing numerous therapeutic and commercial advantages.

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