Pharmaceutical Studies on Certain Drug Delivery Systems for the Treatment of Periodontal Diseases

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دراسة صيدلانية على بعض أنظمة الدواء المستخدمة لعلاج أمراض التهاب الفم

رسالة مقدمة من

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Abstract

Pharmaceutical Studies on Certain Drug Delivery Systems for the Treatment of Periodontal Diseases

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Periodontal diseases are group of inflammatory conditions affecting the supportive structures of the teeth, the gingiva, the periodontal ligament, and the alveolar bone and can eventually cause tooth loss. Tetracyclines and metronidazole were reported to be effective for the treatment of periodontal diseases. Among the group of tetracyclines, doxycycline hydrochloride proved its effectiveness against periodontopathic microorganisms.

Secnidazole is structurally related to the commonly used ٥-nitroimidazoles metronidazole and as other members of ٥-nitroimidazole drugs; secnidazole has a spectrum of activity against anaerobic microorganisms. However, secnidazole has a longer terminal elimination half-life than commonly used drugs in this class.

Local delivery of antibiotics has been shown to be effective in reducing periodontopathic microorganisms Thus, it was desired to formulate doxycycline hydrochloride and secnidazole each alone or both in combination together into gels and liquid implants that could be used in the field of dentistry. Gels were prepared using different mucoadhesive polymers, while biodegradable polymers as poly (lactide) and poly (lactide-co-glycolide) were used to prepare liquid implants.

Gels were evaluated in terms of rheology, *in-vitro* release, in addition to mucoadhesion properties. Increasing the concentration of

each polymer increased the viscosity, mucoadhesion and the time required for ٣٠٪, ٥٠٪ release of the original mass of secnidazole or doxycycline hydrochloride from gels.

Increasing the concentration of poly (lactide) and poly (lactide-co-glycolide) in liquid implants increased the viscosity and decreased the percent of secnidazole or doxycycline hydrochloride released after ٢٤ hours. Also the effect of combination of the two drugs on the previous parameters was studied, in which no significant change in these parameters was observed.

Finally, isolation, identification of the periodontopathic microorganisms from patients was done and the antibacterial activity of the selected formulations against these microorganisms was tested. Formulations selected for microbiological evaluation were chosen on the basis of a compromise between a slow release profile, a good mucoadhesive behavior and an acceptable rheology. Microbiological studies on selected gels showed better release of the two drugs (expressed as inhibition zones) than the commercial products of chlorhexidine gel (Elugel®) and miconazole nitrate emulgel (Miconaz®). Also, the antimicrobial activity of liquid implants was compared with the antimicrobial activity of ١٠٪ doxycycline hyclate in the Atrigel® Delivery System (Atridox®). Results revealed that ٢٥٪ poly (lactide-co-glycolide) implant containing both drugs showed a satisfactory antimicrobial activity in comparison to Atridox®.

Key words: Periodontal diseases, Doxycycline hydrochloride, Secnidazole, Mucoadhesive polymers, Biodegradable polymers, Antibacterial activity.

General Introduction

The oral cavity is an attractive target for administration of several drugs, it provides several patterns of drug delivery, however drug delivery via the membranes of the oral cavity can be subdivided as follows: [١, ٢]

a) Sublingual delivery, which is the administration of drug via the sublingual mucosa (the membrane of the ventral surface of the tongue and the floor of the mouth) to the systemic circulation. The thin and highly permeable membrane of the sublingual tissue is a perfect target if a prompt onset is desired. Considerable surface area and high blood flow to this region provide a means for rapid access to the systemic circulation. [٣]

b) Buccal delivery, which is the administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation. Sustained-release systems, which are able to provide sustained drug concentrations in the systemic circulation due to delayed release of the drug from the formulation, are suitable dosage forms for the buccal region of the oral cavity. The lower permeability of the buccal region compared to the sublingual site is ideal for controlled-release systems. Additionally, drug delivery via this site avoids extensive enzyme degradation and first-pass metabolism seen with oral administration, which is desired outcomes for the delivery of therapeutic proteins and peptides [٣]. However, the low permeability of this site is not always an attractive feature and, depending on the choice of drug, can be a major limitation. Use of sub-toxic levels of penetration enhancers and targeted delivery may potentially overcome this problem in the buccal region of the oral cavity. [٤]

c) Local delivery in the oral cavity had particular applications in the treatment of toothache [٥], periodontal diseases, [٦-٩] dental caries, [١٠]

bacterial infections, [١١] fungal infections [١٢] and aphthous stomatitis [١٣] However, because of its specificity, local delivery does not have the broad range of applications that sublingual and buccal drug administration provides.[١] Indeed, salivary flow is probably even more important an issue in the context of local delivery than in the sublingual or buccal delivery.

The two main problems associated with oral cavity dosage form include:

(i) Discontinuation of required drug concentration in the saliva.

(ii) Potential side effects derived from high amounts of swallowed drug.[١٤]

The simplest and probably the most widely used delivery systems for local delivery to the oral mucosa are conventional mouthwashes, oral suspensions and lozenges. The duration of action of a drug can be improved somewhat by the use of ointments or creams which can be applied to the oral mucosa. More recently mucoadhesive drug delivery systems have attracted considerable interest because of their sustained drug release profile at the absorption site and increased drug bioavailability due to the intimate contact with the absorbing tissue. [١٥] These include mucoadhesive lozenges or denture based delivery systems which provide sustained drug levels within a particular tissue or region of the oral cavity, such systems have applications in the treatment of periodontal disease and aphthae in particular. [١]

Several alternative mucosal drug delivery systems have been designed; most of the systems were controlled release products, which include bioadhesive systems in the form of adhesive tablets, [١٦, ١٧] adhesive films, [١٨, ١٩] patches, [٢٠] and buccal gels. [٢١, ٢٢]

Mucosal adhesive dosage forms are new types of external preparations that may make treatment more effective and safe, not only

for topical diseases, but also for systemic ones. Adhesion to the mucosa, or sometimes called bioadhesion, is an interfacial phenomenon in which two materials, one of which is of biological nature are held together for extended period of times. [٢٣]

There are many kinds of bioadhesive polymers; in general, bioadhesive polymers can be classified as synthetic/natural, water-soluble/water insoluble, and charged/uncharged polymers as shown in Table (I).

Natural bioadhesive macromolecules share similar structural properties with the synthetic polymers. They are generally linear polymers with high molecular weight, contain a substantial number of hydrophilic, negatively charged functional groups, and form three-dimensional expanded networks. [٢٤] In the class of synthetic polymers, poly (acrylic acid), cellulose ester derivatives, and polymethacrylate derivatives are the current choices. Chitosan and examples of various gums, such as guar and hakea (from Hakea gibbosa), are classified as semi-natural/natural bioadhesive polymers. Poly(acrylic acid), a linear or random polymer, and polycarbophil, a swellable polymer, represent water-soluble and water-insoluble polymers, respectively. The charged polymers are divided into cationic and anionic polymers, such as chitosan and polycarbophil, respectively, while hydroxypropylcellulose is an example of uncharged bioadhesive polymers. [٢٥]

Also, Hydrogels (hydrophilic polymer gels) are hydrophilic natural or synthetic crosslinked polymers that have the ability to swell in an aqueous environment without dissolution. [٢٦, ٢٧] The capacity of these macromolecular networks to absorb water invariably arises from hydrophilic functional groups attached to the polymeric network, while their inability to dissolve arises from crosslinks between polymer chains.

When drugs are loaded into these hydrogels, as water is absorbed into the matrix, chain relaxation occurs and drug molecules are released through the spaces or channels within the hydrogel network. These 'pseudo-hydrogels' swell infinitely and the component molecules dissolve from the surface of the matrix. Drug release would then occur through the spaces or channels within the network as well as through the dissolution and/or the disintegration of the matrix.

Many properties of hydrogels make them suitable for biomedical applications, which sometimes require contact with living tissue. The ability of these materials to absorb and retain aqueous solutions and their consequent permeability to small molecules such as oxygen, nutrients and metabolites render them as candidates for replacing living tissues. The soft rubbery state of swollen hydrogels minimizes frictional irritation of surrounding cells and tissues. [٢٨]

Some hydrogels are able to adhere to biological tissues or the mucus layer of the tissue (i.e. bio/mucoadhesive hydrogels). Polymer adhesion to tissues permits intimacy of contact to improve drug absorption, localization of drug delivery system in case of preferential of a drug in a specific region. [٢٩] The common hydrogel polymers includes, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, sodium carboxy methylcellulose, polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyacrylic acid (PAA or carbopol), and polyhydroxy ethyl methacrylate (PHEMA). [٣٠]

Nagai *et al.* [٣١] studied the applicability of hydroxypropyl cellulose (HPC) as a mucoadhesive agent; they found that the high viscosity grade of HPC was a suitable adhesive for topical mucus membranes. They reported that the combination of HPC and carbopol ٩٣٤P (CP) produced a preferable material for mucoadhesive dosage forms.

Anders and Merkle [٣٢] developed and evaluated adhesive patches for buccal administration, consisting of two-ply laminates of an impermeable backing layer and a hydrocolloid polymer layer containing the drug. The polymers used HPC, HEC, PVP, and PVA. The integrity of the laminate was based on adhesive bonds between the hydrocolloid layer and an agarose layer grafted to one side of the backing layer sheet. Their work showed that among the cellulose ethers studied HEC and HPC possessed superior mucosal adhesion.

Watanabe *et al.* [٣٣] reported on hydrogels formed by the combination of natural gums, xantham gum, and locust bean gum, which are applicable in buccal delivery systems. Locust bean gum and xantham gum alone cannot form a hydrogel. However, when a mixture of these gums is dissolved in a neutral medium at ٩٠°C and then cooled with ice for ٣٠ min, a clear, strong hydrogel is formed. The mechanism of gel formation was reported to be the formation of a three dimensional network by interaction between the double helix structure of xantham gum and the straight molecular chain of locust bean gum. The gel strength of the hydrogels was affected by the mixing ratio of the gums, and the addition of sucrose improved the sustained release properties of the hydrogels. The hydrogel consisting of xantham gum and locust bean gum showed only a low mucoadhesion, but it can be applied to a buccal delivery system because of its safety, gel strength, sustained release properties and good feel in the mouth.

Collins and Deasy [٣٤] prepared a tri-layered tablet made of carbopol and hydroxypropyl cellulose for local delivery of cetyl pyridinium chloride. Also Scherlund *et al* [٣٥] have used non-ionic cellulose ethers with great success as potential drug delivery systems for periodontal anesthesia.

Johnson and Johnson have described [٣٦] an extruded buccal

adhesive system, either single or multilayered for the delivery of local medication such as antifungals, corticosteroid or anaesthetics. The bioadhesion is achieved in a typical multiple layered system by a mixture of hydroxypropylcellulose and polyethylene oxide polymer (high molecular weight). Drug is contained in a mixed cellulose ether reservoir layer and there can be a protective barrier layer, primarily of ethyl cellulose. This limits leaching of drug into the saliva. Nippon Soda has also described cast film systems based on cellulose ethers. [٣٧]

Bottenberg and his colleagues [١٠] researched the possibility of using various bioadhesive polymers as fluoride containing, slow release tablets for oral use, especially in the war against dental caries. Modified starch, poly(acrylic acid) (PAA), poly(ethylene glycol) (PEG) and sodium carboxymethylcellulose were the bioadhesive polymers investigated.

For local drug delivery, the vehicle must be adhesive to the site of application. Bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time [٢٣]. For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The surface can be epithelial tissue, or it can be the mucous coat on the surface of the tissue, if the adhesive attachment is to a mucous coat, the phenomenon is referred to as mucoadhesion.[٢٤]

Table (I): Mucoadhesive polymers in buccal delivery

Criteria	Categories	Examples
Semi-natural/natural		Agarose, chitosan, gelatin, Hyaluronic acid Various gums (guar, hakea , xanthan, gellan, carragenan, pectin, and sodium alginate)
Synthetic	Cellulose derivatives	[CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methylhydroxyethylcellulose]
	Poly(acrylic acid)-based polymers	[CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(٢-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly(methacrylate),poly(alkylcyanoacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG]
	Others	Poly(N-٢-hydroxypropyl methacrylamide) (PHPMAm), polyoxyethylene, PVA, PVP, thiolated polymers
Aqueous solubility	Water-soluble	CP, HEC, HPC (water < ٣٨ ˚C), HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, dimethylaminoethyl (DEAE)- dextran, trimethylated chitosan
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan
Potential bioadhesive forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA
	Elesctrostsatic interaction	Chitosan