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Boateng, Joshua S. and Okeke, Obinna (2014) Chitosan-based films for the sustained release of peptides: a new era in buccal delivery? *Therapeutic Delivery*, 5 (5). pp. 497-500. ISSN 2041-5990 (doi:10.4155/TDE.14.21)

*Publisher's version available at:*

<http://dx.doi.org/10.4155/TDE.14.21>

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Available at: <http://gala.gre.ac.uk/12399/>

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*<http://dx.doi.org/10.4155/TDE.14.21>*

*Citation: Boateng, Joshua S. and Okeke, Obinna (2014) [Chitosan-based films for the sustained release of peptides: a new era in buccal delivery?](#) *Therapeutic Delivery*, 5 (5). pp. 497-500.*

*ISSN 2041-5990 doi:[10.4155/TDE.14.21](https://doi.org/10.4155/TDE.14.21)*

# Chitosan-based films for the sustained release of peptides: a new era in buccal delivery?

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In recent years, peptide-based drugs have received significant attention from researchers in academia as well as pharmaceutical and biotechnological industries. This has been fuelled in part by the availability of recombinant technology, allowing high throughput production of such therapeutic peptides. In 2012, six peptides were approved in the US; five of which were also approved in the EU [1]. One of the most common peptide drugs is insulin, used in the treatment of diabetes. Another peptide carfilzomib is available to treat pituitary and gastrointestinal tumours and multiple myelomas [2,3].

Compared to small molecules peptides still present with many challenges such as low permeability, poor bioavailability, stability and potency. According to Aoki and co-workers, about 95% of peptide based drugs face these challenges and therefore usually discarded during pre-clinical and/or clinical trials. One major way of overcoming these challenges is the development of suitable peptide delivery systems [2]. The parenteral route has traditionally been used to deliver peptides. Compared to the gastrointestinal route, this route delivers peptides directly into the bloodstream, thereby avoiding denaturing by stomach acid and peptidase enzymes present in the digestive tract [4] as well as bypassing first pass liver metabolism. However, peptides have relatively short half-lives and therefore require repeat injections which are invasive and painful leading to poor patient compliance. In addition, parenteral injections generally require trained personnel for effective and safe administration. It is our view that traditional (parenteral injections) means of delivering large molecules such as peptide drugs will most likely disappear or at best used in emergency situations such as comatose patients, once cheaper and efficient alternatives become available routinely available. Chitosan based films, for sustained buccal drug delivery presents such a unique opportunity for achieving this objective and therefore represents a new era in peptide therapeutics.

Though the transdermal route has the advantages of the parenteral route and does not need trained personnel, it can cause localized irritation, itching, oedema, and erythema [4]. In our opinion, if there is one route that is robust in providing sustained peptide drug delivery to achieve a relatively rapid systemic bioavailability in a controlled way, it is the buccal mucosa. The oral mucosa presents more advantages than the transdermal route in the delivery of peptides, providing a more comfortable route of administration with better patient compliance. Compared to other mucosal sites (i.e. intestinal, rectal and nasal); the oral

mucosa possesses higher vascularity, less enzyme activity and are less susceptible to irritation and damage.

The oral mucosa route can be employed for both local and systemic administration of drugs. Systemic administration of drugs (including peptides) can be administered by either buccal or sublingual routes of administration. These routes exhibit different modes of delivery with the sublingual providing more rapid penetration across the mucosa while the buccal mucosa can be utilized to achieve a more sustained release profile. As a result, the buccal mucosa has been extensively investigated as an important route for delivery of high molecular weight drugs such as peptides. Therefore, the buccal mucosa has become a major alternative to parenteral route in the administration and delivery of peptide drugs [5]. Obviously any successful drug administration via a particular route requires a suitable drug delivery matrix which we believe can be found in chitosan. Here, we focus on chitosan based films as a suitable matrix and which we suggest represents a potential new era of sustained delivery of peptide based drugs. The question is whether such a system provides significant novelty at least in matching the performance of parenteral injections and be robust enough to use various age groups spanning paediatric, young adult, adult and geriatric populations. We believe it does and though uptake by the industry and regulatory authorities remain slow, this could be achieved in the not too distant future.

Formulation of conventional dosage forms for buccal drug delivery is affected by physiological challenges of the oral cavity. These challenges include the washing effect of saliva and poor retention of the formulations on the mucosa surface resulting in unexpected drug distribution and less contact period. To achieve better performance, the formulation must be optimised to ensure prolonged residence in the buccal area as well as improved drug permeation which ensures increased bioavailability. This can be achieved by introducing different additives such as mucoadhesive polymers, penetration enhancers and enzyme inhibitors [5,6]. These agents are incorporated to help maintain prolonged contact with the site of absorption, optimize permeation of drug and inhibit enzyme activities. Generally, buccal dosage forms can be divided into four groups; liquids [7]; semi-solids [8]; solids such as tablets [9], wafers [10-13], films [14], nano-particulates embedded within films [15,16], and sprays [6].

Buccal films are novel relevant solid pharmaceutical formulations based on their versatility (both local and systemic drug administration). Their size and thin nature allow ease of handling and application, potentially promoting patient compliance. Since they are normally prepared from film forming mucoadhesive polymers which attach to the mucosa of the buccal region, they can be designed to release drugs (peptides) with a predictable controlled (sustained) release profile. Polymers used in the formulation of buccal films are mainly hydrophilic which interact with mucin found on the buccal mucosa when swollen. These polymers include; chitosan, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose and poly (vinyl pyrrolidone) [17]. Based on their surface charge, mucoadhesive polymers can be classified as anionic, cationic and non-ionic polymers, with anionic and cationic polymers showing better mucoadhesive performance than non-ionic counterparts [6].

Before exploring this further, it is important to note that a novel buccal delivery system for systemic effect of a therapeutic peptide is required to make intimate contact with the buccal mucosa, to assure prolonged residence, overcome local peptidase activity and eventual drug permeation and bioavailability. Is there a delivery system that is uniquely placed to achieve such multi-faceted objective? It is our firm belief that a solution could be found in chitosan based films.

Chitosan is a non-toxic biodegradable polymer that is extensively used in the pharmaceutical, food and clinical context. It is a cationic polysaccharide formed by the de-acetylation of chitin [6], which is the major component of the shells of organisms such as prawns and cell walls of fungi such as aspergillus. Chitin is made up of  $\beta$ -(1,4)-linked N-acetyl-glucosamine homopolymer units whereas chitosan is made up of glucosamine and N-acetyl-glucosamine copolymers. Chitosan derives its cationic nature the free amino group, which allows reaction with many anionic polymers. Different researchers have demonstrated the use of chitosan and its derivatives to formulate matrices for buccal delivery of peptides and proteins [10 -13] and been found to enhance drug absorption through mucosae without damaging the biological system. The pH sensitivity, coupled with the reactivity of the primary amine group of chitosans allows easy functionalization which can be tailored for specific applications including sustained drug delivery via the buccal mucosa [18]. The amino group of chitosan contributes to functional characteristics such as controlled drug release, mucoadhesion, penetration enhancement, transfection efflux pump inhibition and in situ gelation [19].

Chitosan formulations, including films, have therefore attracted significant attention as novel drug delivery systems.

We propose that the unique and functional properties of chitosan, coupled with its matrix forming ability can be utilized in formulating buccal (matrix) films for the controlled (sustained) release of peptides. In our informed opinion, this is significant given the fact that though the buccal mucosa represents a suitable alternative to parenteral injections, certain inherent factors limit the absorption of drugs. These challenges include the limited absorption area compared to the skin, barrier properties (especially to large molecules such as peptides), involuntary swallowing of dosage forms and continuous dilution of dissolved drugs by saliva.

Chitosan films [20] may be prepared from either solvent casting [14] or hot melt extrusion technique [17] with the former being the most common due to ease of preparation and low cost of production. It has been shown that increased chitosan amounts in chitosan/gelatine films allowed the lowest percent water-uptake ability and the highest in vivo residence time in the buccal cavity [21]. Cui et al., [22] showed the potential of chitosan based films to deliver insulin through the buccal mucosa route and they reported a high bioavailability of 17% within 5 hours compared with subcutaneous insulin. Giovino and co-workers demonstrated the use of insulin loaded nanoparticles incorporated into chitosan based films for sustained release of the peptide [15]. The use of chitosan films yielded a 1.8-fold enhancement of ex vivo insulin permeation via EpiOral<sup>TM</sup> buccal tissue construct relative to the pure drug [16].

In looking into the near future, the desire for a simple but efficient formulation that can deliver peptides in a sustained manner without the pain of injections will be a key driving force for developing novel peptide delivery systems. It is our view that chitosan based films for administration via the buccal mucosa fulfils this criteria and represents a new era in buccal drug delivery. This must be keenly followed, though much remains to be achieved to enable their routine use in patient care.

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