Polysaccharide Based Formulations for Mucosal Drug Delivery: A Review

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Abstract

There has been increased interest in novel drug delivery systems to be administered via mucosal routes as an alternative to the currently used traditional routes such as parenteral (injections) and oral routes of administration. This is due to the several advantages they offer including avoiding first pass metabolism in the liver for oral administration and local activity which avoids the need for high systemic doses. To achieve the foregoing objectives, bioadhesive vehicles are required that ensure prolonged residence time to achieve systemic bioavailability via substantial drug absorption or significant drug concentration for local action. The drug delivery system is also required to be non-deleterious to the site of application and be well tolerated by vulnerable groups such as paediatric and geriatric patients. These essential characteristics are mainly satisfied by naturally occurring polymers, including polysaccharide based polymers which have the advantage of biocompatibility, biodegradability and therefore safety. This review discusses various bioadhesive polymers of polysaccharide origin formulated into a variety of dosage forms for drug delivery via the body's mucosal (moist) surfaces including ocular, oral (buccal and sublingual), nasal, gastrointestinal and vaginal mucosa, as well as moist wound sites. The anatomy and / or physiology of each site, coupled with the unique challenges each poses, the strategies employed for ensuring therapeutic efficacy, as well as the current state of the art will also be covered.

Key words: Buccal, gastrointestinal, mucosal delivery, nasal, polysaccharides, ocular, vaginal, wounds.

1. Introduction

1.1 Overview

Drug delivery is most commonly achieved via oral administration of dosage forms such as tablets, capsules and liquids, representing about 70% of all pharmaceutical drug formulations. However, this is fraught with several problems including first pass metabolism in the liver, degradation in the gastrointestinal tract for acid labile drugs such as proteins and peptides and risk of poor uptake for children, the severely infirmed (e.g. comatose patients) and geriatric patients. The rejection rate of such oral dosage forms is higher than for other routes, due to factors such as unpleasant taste [1], difficulty in swallowing and the risk of choking. Though the alternative traditional parenteral route using injections is effective and avoids the above limitations, it presents several challenges as well, including pain, irritation at site of injection and the need for highly trained personnel for safe and effective administration. All these result in poor patient compliance with consequent poor clinical outcomes, which can be severe in certain diseases. There has been increased efforts in recent decades to develop novel alternative systems for drug delivery based on factors such as therapeutic concerns, biopharmaceutics and physico-chemical properties of the drug, such as poor solubility and instability via tradition routes.

These factors are important and are mainly aimed to improve safety, efficacy and patient compliance and ultimately help to increase product life cycle [1].

A major goal of novel drug delivery systems is appropriate targeting to direct the drug in question to its intended site of action, minimize drug degradation and loss, increase bioavailability, increase the fraction of drug accumulated at the site of action while preventing or limiting harmful and unwanted side effects.

One of the major areas of current interest, which addresses a significant number of the challenges highlighted above, is the development of bioadhesive (mucoadhesive) delivery systems for drug administration via one or more of the body's mucosal surfaces (routes). The characteristic features of transmucosal routes, such as large surface area and network of blood vessels, make such routes interesting sites for both systemic and local delivery of drugs. In addition, they provide the ability to bypass the hepatic first pass metabolism and degradation of drug in the stomach by delivering the drugs directly to the bloodstream thereby increasing bioavailability [2]. The transmucosal surfaces that have been under investigation for potential drug administration for systemic therapeutic action include the oral (buccal and sublingual) [3],

vaginal [4], nasal [5], ocular [6] and wound surfaces [7]. Apart from overcoming the limitations of oral (gastrointestinal) and parenteral administration, that is avoiding first pass metabolism and pain respectively, they are particularly advantageous in cases where only small doses are required at the local mucosal site, thus avoiding the need for unnecessarily high systemic doses, for example in local infections, where antibiotics are required [8, 9].

In order to achieve effective mucosal administration, the delivery matrix (system) needs to satisfy certain criteria, particularly being biocompatible, bioadhesive (mucoadhesive), biodegradable and easily processed into various dosage forms. Most of the above mentioned novel drug delivery systems can be prepared using such synthetic or biomaterial based polymers. However, the naturally occurring biomaterials have been used extensively due to their well-known biocompatibility and biodegradable nature, in addition to most of them being bioadhesive. A common group of such naturally occurring biomaterials is polysaccharide based polymers, ranging from common materials such as starch, to more complex examples such as chitosan and sodium alginate, obtained from various natural sources or in semi-synthetic form [10].

In this article, we review the current state of the art of mucosal delivery systems designed using polysaccharide based polymers with bio (muco) adhesive characteristics for an application via the various mucosal routes [buccal/sublingual, gastrointestinal (emphasis on colonic delivery), nasal, ocular and, vaginal as well as wounds surfaces due to the moist environment in a wound environment]). The molecular basis of bioadhesion and its importance are briefly discussed. Different formulation approaches, the unique challenges of each route (including barriers by their structural architecture and physiology), examples of systems available both in the literature and in some cases commercially, will be reviewed. Finally, the prospects of having such systems in routine clinical patient use, in the medium to long term future, are briefly discussed.

1.2 Bioadhesion (mucoadhesion)

The terms bioadhesion and mucoadhesion are sometimes used interchangeably, though they actually mean slightly different things. Bioadhesion defines adhesion between two materials where at least one material is of biological origin and is generally used when interaction occurs between adhesive polymers and an epithelial surface directly, such as a wound surface. Mucoadhesion on the other hand, involves adhesion with the mucus layer covering a biological tissue or membrane. The adhesion force/bond is dependent on parameters such as hydrophilicity (progress bioadhesion), stage of hydration and rate of

polymer erosion after being in contact with the hydrating surface. Apart from the function of increasing the retention time of the drug on the mucosal surface to enhance the bioavailability, some polymers can be used as enzyme inhibitors and penetration enhancers. It has been reported that the presence of polymers absorb water from the epithelial cells to widen the tight junction [11] and in the process allow easy penetration of drug molecules across the membrane into the systemic circulation.

In general, mucoadhesion and bioadhesion are described as bonding between polymers and mucosal tissues or any biological surface as shown in figure 1.

<**Figure 1 here**>

Mucoadhesion occurs because of various adhesive bonds at the interface between the mucosal membrane and the mucoadhesive agent [12, 13]. These bonds include (a) ionic bonds: where two oppositely charged ions attract each other via electrostatic interactions and form a strong bond; (b) covalent bonds: which are very strong bonds in which electrons are shared in space, between the bonded atoms in order to fill the orbitals; (c) hydrogen bonds: a hydrogen atom, when covalently bonded to an electronegative atom such as an oxygen, fluorine or nitrogen, carries a slightly positive charge and, hence, is attracted to electronegative atoms. The mucosal membrane and mucoadhesive material share the hydrogen atom, though this bond is usually weaker than ionic or covalent bonds; (d) van der Waals forces: these are some of the weakest forms of interaction that arise from dipole-dipole attractions in polar molecules, and dispersion forces with non-polar substances: (e) hydrophobic forces: give rise to a hydrophobic effect and occur when non-polar groups are present in an aqueous solution [12, 13].

1.2.1 Theories of bioadhesion

The mechanism of polymer attachment to a mucosal surface is not yet fully understood. However, certain theories of bioadhesion have been proposed suggesting that it might occur via physical entanglement and/or chemical interactions, such as electrostatic, hydrophobic, hydrogen bonding, and van der Waal's interactions [14]. A variety of factors affect the mucoadhesive properties of polymers, such as molecular weight, flexibility, hydrogen bonding capacity, cross-linking density, charge, concentration, hydration of a polymer and the environmental factors [15]. The processes involved in the formation of

bioadhesive bonds have been described in three steps – (a) wetting and swelling of polymer to permit intimate contact with biological tissue; (b) interpenetration (entanglement) of bioadhesive polymer chains with mucin chains and (c) formation of weak chemical bonds between the entangled chains [16]. The various theories proposed to explain the mechanisms of bio (muco) adhesion include electronic, adsorption, wetting, fracture and diffusion and the reader is referred to more extensive texts and reviews on the physico-chemical and biomechanical principles that underpin these proposed theories [13, 17, 18].

1.3 Mucoadhesive polymers

Mucoadhesive polymers include a large and diverse group of molecules covering biodegradable grafted co-polymers and thiolated polymers and are used in bioadhesive formulations either alone or in combination with others. These formulations are often water-soluble and when in dry form, they attract water from the biological surface and this water transfer results in a strong interaction [16]. The ideal mucoadhesive polymer should possess certain characteristics regarded as essential for effective function as a bioadhesive drug delivery system [19]. These include being non-toxic and non-irritant, possessing good spreading, swelling, solubility and biodegradable properties. In addition, they should possess adhesive properties both in the dry and liquid/gel state, be biocompatible and possess good viscoelastic, peel, tensile and shear strength properties as well as demonstrate local enzyme inhibition and penetration enhancement properties.

1.3.1 Classification

Bioadhesive polymers are classified as below depending upon various characteristics such as; (i) source: (natural and synthetic polymers), (ii) aqueous solubility (water soluble water and insoluble, (iii) first and second generation (cationic, anionic and non-ionic polymers), and (iv) potential bioadhesive forces (electrostatic interactions, hydrogen bonds and covalent bonds) [20]. Currently, bioadhesive (mucoadhesive) polymers are classified as ‘first and second generation’.

1.3.1.1 First generation polymers

The older generation of mucoadhesive polymers is referred to as ‘off-the-shelf’ polymers [21]. They lack specificity and targeting capability and adhere to mucus non-specifically, and suffer short retention times due to the high turnover rate of mucus. Examples

include anionic polymers such as sodium carboxymethylcellulose, alginate and carrageenan [23, 24, 25, 26], cationic polymers such as chitosan and its derivatives [27, 28].

1.3.1.2 Second generation polymers

The new generation of mucoadhesive polymers can adhere directly to the cell surface, rather than to mucus and they interact with the cell by means of specific receptor or covalent bonding instead of non-specific mechanism [22]. These include lectin-mediated bioadhesive polymers which are naturally occurring proteins that play a fundamental role in biological recognition phenomena involving cells and highly heterogeneous proteins [29]. This potential has been observed for materials such as polyacrylic acids in the dry state, wheat germ agglutinin and concanavalin A [30]. Such systems could offer duality of function in that lectin based platforms could not only allow targeted specific attachment, but also additionally offer a method of controlled drug delivery of macromolecular pharmaceuticals via active cell-mediated drug uptake [31]. The adhesive properties of bacterial cells, as a more complicated adhesion system, have recently been investigated. The ability of bacteria to adhere to a specific target is derived from particular cell-surface components or appendages, known as fimbriae that facilitate adhesion to other cells or inanimate surfaces [32].

1.3.1.3 Enzyme inhibiting polymers

It has been shown that some mucoadhesive polymers can act as enzyme inhibitors and important in delivering therapeutic compounds that are specifically prone to extensive enzymatic degradation, such as proteins and peptide drugs [33]. Investigations have demonstrated that polymers such as poly (acrylic acid), operate through a competitive mechanism with proteolytic enzymes. Circular dichroism studies suggest that Ca^{2+} depletion, mediated by the presence of some mucoadhesive polymers, causes the secondary structure of trypsin to change, and initiates a further auto degradation of the enzyme [34].

1.3.1.4 Thiolated polymers

Thiolated polymers are capable of forming disulphide bonds with cysteine-rich subdomains of mucus glycoproteins covering mucosal membranes. These are the special class of multifunctional polymers also called thiomers [35]. Thiomers are capable of forming intra- and inter chain disulphide bonds within the polymeric network leading to strongly improved cohesive properties and stability of drug delivery systems such as matrix tablets. These hydrophilic macromolecules exhibit free thiol groups on the polymeric backbone. These

functional groups have enabled various features of well-established polymeric excipients such as poly (acrylic acid) and chitosan to be significantly improved [36]. Due to the formation of strong covalent bonds with mucus glycoproteins, thiomers show the strongest mucoadhesive properties of all polymeric excipients via thiol-disulphide exchange reaction and an oxidation process [37].

1.3.2 Mucoadhesion measurement techniques

There are different approaches used to evaluate the mucoadhesive performance of polymers and polymeric dosage forms. These include texture analyser, [38-41], rheometric measurements [42] and attenuated total reflection-Fourier transform infrared spectroscopy [43, 44] methods. The texture analyser (TA) technique measures the maximum force required to separate the polymer or dosage form from the surface of a mucosal substrate after a specified contact time and applied force. This method evaluates stickiness, work of adhesion (WOA) and cohesiveness of dosage forms. Stickiness is the maximum force required to separate the probe attached to films and wafers from the given mucosal substrate such as mucin equilibrated gelatine substrate (i.e. maximum detachment force) whereas total amount of work or energy involved in the probe withdrawal from the substrate is calculated from the area under the forces versus distance curve and cohesiveness is the intermolecular attraction between the substrate and formulations and determined by the travel distance in mm on the force versus distance profile [38] (see figure 2). The rheometric method involves studying the extent of interpenetration of mucin (or moisture) with polymeric gels by measuring differences in the rheological parameters of polymeric gel and their mixture with mucin [42]. The attenuated total reflection-Fourier transform infrared spectroscopy (ATR-FTIR) approach involves the study of chain interpenetration or diffusion occurring between polymers or dosage forms (e.g. films and wafers) and mucosal fluid such as mucin solution [43] [44] or simulated wound fluid [40].

<**Figure 2 here**>

1.4 Polysaccharides

Polysaccharides are carbohydrates made up repeating monosaccharide or disaccharide units joined together by glycosidic bonds such as starch and glycogen. Most polysaccharides are

naturally occurring which make them attractive choices in traditional applications as food and pharmaceutical additives or in the form of excipients as binders, sweeteners, bulking agents, film coatings and suspending agents. Further, polysaccharides are abundantly present in nature, have wide availability, are inexpensive and are available in a variety of structures with varied properties [45]. They can easily be modified chemically and biochemically and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition biodegradable. These include naturally occurring polysaccharides obtained from plant (e.g. guar gum, inulin), animal (e.g. chitosan and chondroitin sulphate), algae (e.g. alginates, xanthan) or microorganism (e.g. dextran) origin as well as starch and certain cellulosic polymers mainly from plant sources. The most common polysaccharides used as mucoadhesive polymer can be further divided into positively charged and negatively charged polysaccharide based on their charge property. The most commonly used positively charged polysaccharide is chitosan while the most commonly used negatively charged polysaccharides are alginate, pectin and hyaluronic acid [46].

However, polysaccharides as well as other naturally occurring polymers also possess further unique functional characteristics such as swelling and hydration which control drug release but also impact on the mechanism of mucoadhesion. These two functional characteristics (swelling and mucoadhesion), coupled with their biocompatible properties have made them become commonly used polymers for various dosage forms used as drug delivery vehicles via the various mucosal surfaces outlined above. The rest of this review will cover each mucosal surface individually and the various polysaccharide and their corresponding dosage forms employed either alone or in combination to deliver drugs across these surfaces, either for systemic absorption or for local action within or around the mucosal environment.

2. Ocular drug delivery

The human eye is a very sensitive organ to exogenous materials such as debris, microorganisms and drugs [47] and therefore, formulations designed for ocular drug delivery should be simple, non-invasive (to prevent irritation, inflammation or infection, to maintain the visual clarity of the eye), as well as be able to penetrate the physiological eye barriers and reach the site of action. The eyeball has an approximate spherical shape and is situated in the orbit comprising three concentric: layers outer fibrous (sclera and cornea), the middle vascular (choroid, ciliary body and iris) and the inner nervous (retina)

layers [48]. The eye could also be divided into chambers i.e. the anterior chamber, the posterior chamber and the vitreous cavity [49].

The lachrymal film, is a dynamic fluid that is constantly renewed, therefore limiting the retention time of a drug on the eye surface [50] and protects the eye by acting as a defense against pathogens and a barrier against any drug penetration [51]. Another critical barrier in ocular therapeutics is the conjunctiva which is an epithelium about 100 times more permeable than the cornea for large hydrophilic compounds. Its role is to protect the eye and functions as a passive physical barrier [51].

2.1 Ocular conditions

Eye conditions can be classified as peri-ocular and intraocular. Peri-ocular conditions occur around the eye and can cause irritation to different parts of the eye, e.g. blepharitis, trachoma, conjunctivitis, and dry eye [52]. Intraocular conditions represent the infection of the inner parts of the eye and can affect the retina, the iris, the aqueous and the vitreous humour, with the most common being glaucoma. Glaucoma can be treated by application of topical drugs that constrict the pupil and tense the edge of the iris, which, in turn, make the surface more permeable to aqueous humour [49].

2.2 Polysaccharide-based ocular delivery systems

2.2.1 Topical ophthalmic preparations

The design of ocular drug delivery formulations is very challenging and requires an understanding of what can be tolerated by the eyes, of the physiology of the eyes and also of what the factors affecting ocular drug administration and absorption are (physiological and formulation factors (figure 3). It is very difficult in ocular therapeutics to achieve and to maintain an effective drug concentration at the site of action for a prolonged period of time to achieve the desired therapeutic response.

<**Figure 3 here**>

The available topical ophthalmic preparations include solutions, suspensions, ointments, gels and films to treat conditions such as inflammation, infection, allergy, glaucoma, dry eye as well for instilling local anaesthetics and diagnostic agents [53]. Liquid drops cannot be considered optimal in the treatment of ocular diseases because of their low bioavailability with only 5% of the instilled dose able to penetrate the cell membranes into the eye. Therefore frequent instillation of the dosage form in question is required which may lead to

systemic side effects and patient non-compliance [53]. As a result, current novel systems for drug delivery to the eye involve the use of bioadhesive polymers, including polysaccharides, that are not only safe but ensure prolonged residence time and controlled release of the drug to allow improved bioavailability and improved patient compliance due to reduced need for regular application. The commonly used polysaccharide polymers reported in the literature have been extensively evaluated by Ludwig [54] in his review paper. These include: chitosan [55-63], hyaluronic acid [64-73], polygalacturonic acid, xyloglucan, xanthan gum, pullulan, guar gum, scleroglucan [74-82] carrageenan [79, 83-84], gellan gum [85] and pectin [86, 87].

The factors that affect the formulation development of ophthalmic preparations include osmolality, pH, surface tension and viscosity and most of these are extensively discussed in other texts [53]. However, the viscosity is addressed here a bit more extensively, as it is directly affected by the type of polysaccharide polymer used and also affects other functional properties such as swelling and mucoadhesion. In many ophthalmic solutions viscosity-enhancing polymers are added to prolong drug retention time in the pre-corneal tear film and therefore to enhance drug absorption. The viscosity-enhancing polymers reduce drainage rate and increase the thickness of the pre-corneal tear film due to their ability to drag water and stabilize the aqueous layer.

Water-soluble hydrophilic polymers hydroxypropylmethylcellulose helps to increase viscosity from 400cps up to about 15,000cps as well as increasing lacrimal film stability which helps to increase residence time of drug in the cul-de-sac and thus helps increasing the absorption and eventual bioavailability [88, 89].

2.2.2 Ocular inserts (films)

Films are made of polymers that can be natural, synthetic or semi-synthetic and the drugs contained can be in the form of either dispersion or solution [90]. Acyclovir, phenylpherine, diclofenac sodium and natamicin are examples of drugs that can be contained within the ocular inserts. The ocular inserts can be either solid or semi-solid and biodegradable or non-biodegradable. The biodegradable films don't need to be removed, whereas the non-biodegradable films need to be removed after a given period of time [91]. Solvent cast composite ocular inserts combining polyvinylalcohol and sodium carboxymethylcellulose have been reported for ocular delivery of ciprofloxacillin for topical infections using a rabbit model [92]. In this study, esterification of the polymers was

confirmed by Fourier transform infra-red spectroscopy while surface smoothness of 7.3nm was obtained. Comparison of corneal penetration of the ocular insert with an eye drop solution using a model dye (fluorescein) showed higher penetration for the ocular insert which were also proved to be non-toxic from the *in vivo* study using albino rabbits.

Flurbiprofen loaded lipid based nanocarriers coated with chitosan oligosaccharides have been investigated for potential ocular drug delivery by Qiuhua and co-workers [93]. In their study, gamma scintigraphy was used to investigate the residence time of the coated nanoparticles which is proportional to bioadhesivity and showed that the clearance of the coated carriers was significantly reduced compared to the corresponding uncoated control carrier particles. Further, the coated formulations showed a 2.4 fold increase in corneal penetration. Both these results in the functional performance of coated carriers shows their potential as a possible ophthalmic drug delivery system and particularly, the importance of polysaccharides on effective bioadhesion and permeation after application.

In a related study, Li and co-workers coated liposomes with low molecular weight chitosan and investigated them for potential ocular drug delivery application using diclofenac as a model drug [94]. Their results showed that coating with chitosan changed the surface charge, increased particle size but with no change in drug encapsulation efficiency. Furthermore, the chitosan coated liposomes showed prolonged drug release, improved physical and chemical stability, prolonged retention (bioadhesion) and enhanced drug penetration across the cornea compared to the non-coated formulation and pure drug solution (drops). Continuous application of the coated liposomes over a seven day period, showed no irritation or toxicity. Xu and co-workers developed injectable in situ hydrogels from crosslinking glycol chitosan and oxidised alginate for ocular delivery of the drug avastin which is used to treat age related macular degeneration and proliferative diabetic retinopathy [95]. They controlled the hydrogel degradation rate by varying the concentration of oxidised alginate whilst avastin encapsulated within the hydrogel showed a biphasic release with an initial burst release phase in four hours, followed by sustained release over three days.
Ilva and co-workers developed and compared various ion-activated in situ forming gels that form cross links with commonly available cations in tear fluid, with a resultant increase in corneal contact time, *in vitro*. In their study, gellan gum, xanthan gum, carrageenan and alginate, together with HPMC and chitosan, were characterised for gelling behaviour, rheological and textural characteristics, gel microstructure, contact angle and release of a model hydrophilic drug [96]. Their results showed that the systems exhibited physically entangled polymer networks that were able to disentangle upon shear stress, which

prolonged the release of the model hydrophilic drug, compared to a solution based dosage form. In addition, HPMC and chitosan gels showed no structural changes upon addition of cations, whilst gellan gum and carrageenan gels showed significant increase in viscosity, pseudoplasticity and hardness in the presence Ca^{2+} and K^{+} respectively. Solvent cast xyloglucan films have been employed for the delivery of ciprofloxacin with a percentage loading of 95.45% of expected dose and total cumulative release of 98.5% of the initial drug content following sustained type *in vitro* release, which was determined to follow anomalous transport release mechanism [97]. Miyazaki and co-authors reported on thermos-reversible in situ forming gels from enzyme hydrolysed xyloglucan for sustained ocular delivery of pilocarpine hydrochloride and showed a square root of time release kinetics over six hours [98].

Some of the commercially available mucoadhesive ocular products include Ocusert® (pilocarpine), BODI® (antibiotics), NyoGel ® (timolol) and Pilogel® (pilocarpine hydrochloride).

3. Intraoral mucosa delivery

There are various reasons for the formulation of drugs into appropriate oral mucosa dosage forms; one of which relates to accurate measurement of the dose. For example, in children, the dose required varies with age and weight and also differs significantly from the adult dose.

2.3.1 Sublingual and buccal mucosa drug delivery

The sublingual route of drug administration is widely studied and known to be relatively permeable compared to other oral mucosal surfaces. The sublingual route can provide rapid absorption and easy accessibility to the drug for systemic delivery, especially for quick-dissolving dosage forms [99, 100]. Currently available sublingual products have been developed for several purpose such as mental illness, in the cases where patient compliance is important for treating chronic conditions such as depression and schizophrenia [101].

The buccal mucosa refers to the membrane lining the inside of the cheek and has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa (figure 4), hence suitable for the administration of retentive dosage forms. It has relatively low enzyme activity compared to the gastro-intestinal tract, painless administration and easy dosage form withdrawal [102].

<**Figure 4 here**>

Buccal formulations have been developed to allow prolonged localised therapy and enhanced systemic delivery. The buccal mucosa, however, while avoiding first-pass effects, remains a significant barrier to drug absorption, especially for biopharmaceutical products [103, 104]. An important application of buccal drug delivery is in the areas of paediatric (and geriatric) drug administration due to the risk or fear of chocking [105, 106]. The size of the delivery system varies with the type of formulation, for example, a buccal tablet may be approximately 5–8mm in diameter, whereas a flexible buccal patch may be as large as 10–15cm^2 in area. The thickness of the delivery device is usually restricted to below 1 mm [14, 107]. Different types of buccal formulations such as; tablets, patches and films, semisolids and powders are used depending upon the desirable pharmacological action [108].

Buccal drug delivery systems present various advantages and limitations including bypassing of the gastrointestinal tract and hepatic portal system, thus increasing the bioavailability of orally administered drugs. The buccal mucosa provides improved patient compliance by avoiding pain associated with injections and extent of perfusion is aided by the rich supply of blood (2.0 ml/sec /cm^2). Further, a relatively rapid onset of action can be achieved compared to the gastrointestinal route and the formulation can be removed if therapy is required to be discontinued. In addition, buccal formulations can be used in cases of unconsciousness and less cooperative patients as these have difficulties in swallowing oral dosage form. Nausea and vomiting are avoided because medications do not interfere with the oesophagus and its functions whilst drugs which show poor bioavailability via the oral gastrointestinal route can be administered conveniently. For example, drugs such as pantoprazole sodium, which are unstable in the acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestine [109].

As far as limitations are concerned, drugs which irritate the oral mucosa, have a bitter taste, cause allergic reactions or discoloration of the teeth cannot be formulated for buccal delivery. If the formulation contains antimicrobial agents, it affects the natural microbes in the buccal cavity and patients can also not eat/drink/speak normally whilst the swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug. In addition, only those drugs which are absorbed by passive diffusion can be administered by this route and drugs which are unstable at buccal pH cannot be administered by this route. Finally, the buccal mucosa membrane has low permeability, when compared specifically to the sublingual membrane [110].

Because the buccal route is usually used in relatively more extended drug delivery compared to the sublingual route, bioadhesive formulations are more favoured. Bioadhesive polymers that have been used in buccal drug delivery to maintain formulations are hydrophilic macro molecules containing numerous hydrogen bonds [111].

Bioadhesive polymers require some important structural characteristics which include strong hydrogen bonding groups, strong anionic or cationic charges, high molecular weight, chain flexibility and surface energy properties [112, 113]. Some polysaccharide polymers achieve bioadhesion through a covalent attachment between a cysteine residues present in mucin and the polymer of choice [114, 115]. Regardless of the dosage form, the drug must be released from the delivery system and subsequently taken up by the oral mucosa. The drug release from the dosage is often retarded because of poor solubility and the introduction of cyclodextrin has been widely used to solubilise and increase the absorption of poorly water-soluble drugs delivered via the buccal mucosa [116].

3.2 Polysaccharide-based buccal delivery systems

The challenges encountered in the formulation development of mucoadhesive drug delivery systems have been discussed by Mizrahi and Domb [117] and Salamat-Miller [22]. The most frequently used mucoadhesive polysaccharide based polymers used in buccal mucosa drug delivery include sodium alginate, chitosan and its derivatives, pectin and carrageenan [118]. Various polysaccharide based formulations have been employed for delivery across the buccal and sublingual membranes for both small and macromolecules. These include gels films, tablets, wafers (xerogels), nano particles usually incorporated into gels, films. These are summarised in table below showing the type of polysaccharide, dosage form and the drug used for the study whilst selected references are reviewed in more detail.

Zeng and colleagues [119] developed buccal hydrogels that were sensitive to temperature for the delivery of salbutamol by combining poloxamer, xanthan gum and sodium chloride and characterising various functional characteristics such as gelation temperature, micellization temperature, gelation time, gel strength, in vitro release (using membrane-less and membrane based method). The above properties varied depending on the three main components mentioned above and showed potential clinical application for buccal delivery of salbutamol to achieve rapid systemic activity. Martin and co-workers synthesized

palmitoyl glycol chitosan hydrogels with different hydrophobicities by physical crosslinking and loaded them with a model hydrophobic drug (denbufylline) for buccal drug delivery [120]. Sodium glycodeoxycholate which is a soluble detergent was used as permeation enhancer. The resulting crosslinked hydrogels were characterised using H nuclear magnetic resonance spectroscopy, hydration, erosion, mucoadhesion, scanning electron microscopy and buccal absorption across rabbit buccal mucosa membrane (using carbopol, denbufylline and sodium glycodeoxycholate containing tablets as controls). Their results showed that denbufylline reduced the porosity, erosion and hydration of the gels while the permeation enhancer increased the hydration and erosion rates. Though the gels were all mucoadhesive this was comparable to the control tablets. The buccal absorption studies showed that the drug was detectable in the systemic circulation 30 minutes after administration for the most hydrophobic hydrogel and this was sustained over a 5 hour period. However, drug released from the control tablets was only detected after 60 minutes and the release was not sustained as was the case for the crosslinked hydrogels.

Nystatin loaded microspheres from alginate and chitosan coated were prepared by internal gelation method as antifungal delivery systems for the treatment of oral candidiasis, and characterised by size and size distribution, shape, encapsulation efficiency, Zeta potential, swelling, mucoadhesion, *in vitro* drug release and *in vivo* studies [121]. The microspheres were spherical in shape and ranged in size from 85 – 135 μm with negative potential (showing stability) and optimised encapsulation efficiency as well as swelling and mucoadhesive behaviour. The alginate and chitosan formulations both showed a concentration dependent release of the nystatin loaded within the microspheres and showed strong fungicidal activity against *Candida albicans* but with no tissue damage. Furthermore, the *in vivo* studies showed that the drug was not detectable in the systemic circulation, suggesting it did not cross the oral mucosa membrane but acted locally, implying safety and therefore reduced unwanted side effects.

Kassem and co-workers developed buccal adhesive tablets for sustained delivery of buspirone hydrochloride with the aim of improving systemic bioavailability [122]. The tablet formulation development involved the use of a 5 x 3 factorial design, setting polymer type (carbopol, hydroxypropylmethylcellulose, sodium alginate, sodium carboxymethylcellulose and guar gum) at five levels whilst polymer to drug ratios were set at three different levels (combinations) and various dependent variables (mucoadhesion force, *ex vivo* mucoadhesion time, percent drug release after 8 hours and time to release 50% of drug) employed. The tablets were characterised for content uniformity, weight variation, thickness, diameter,

hardness, friability, swelling index, surface pH, mucoadhesion strength / time and *in vitro* drug release. It was observed that the cup and core formulations adhered to the buccal mucosa for 8 hours, showed the highest percent drug release over the same time period with a zero order release profile. Further, pharmacokinetic experiments of the cup and core formula in human volunteers showed a 5.6 fold increase in drug bioavailability in comparison to oral commercial tablets with excellent *in vitro* and *in vivo* correlations.

Bilayered mucoadhesive tablets loaded with curcumin for unidirectional buccal delivery have been prepared using a natural buccoadhesive polymer from cashew nut tree gum with ethyl cellulose as an impermeable backing layer [123]. The tablets with mucoadhesive strength of 13.99 g were stable and released drug over 60 days at both high and low humidities and temperatures. Drug release was found to be via non-Fickian or anomalous diffusion kinetics and suggested as a potential buccal adhesive tablet for enhancing bioavailability of curcumin by avoiding first pass metabolism. Ameye and co, produced spray dried starch/carbopol mixtures in different proportions, for evaluation as potential bioadhesive tablets for buccal administration of miconazole [124]. They observed that all the spray-dried composite formulations showed a comparable or better bioadhesive capacity compared to a reference formulation with the spray drying procedure generally improving the bioadhesive performance. Further, the effect of modifying additive (carbopol) concentration on the *in vivo* adhesion time of placebo tablets and *in vitro* miconazole nitrate release were tested and showed that formulations containing the ratio starch / carbopol of 70/30 showed the longest *in vivo* adhesion time compared to very low and very high carbopol concentrations. Lower and higher carbopol concentrations had a shorter *in vivo* adhesion time. It was observed that the composite formulations containing between 15 and 30% of carbopol sustained the *in vitro* miconazole nitrate release over 20 hours whilst very high and and very low carbopol concentrations showed a faster *in vitro* miconazole release. Furthermore, *in vivo* studies in dogs using a different drug (testosterone) showed that the optimised spray dried mixture could be loaded with 60% of drug but still maintained the *in vivo* bioadhesion and pharmacokinetic profiles.

In an innovative application study, gum from the plant *Hakea gibbosa* (Hakea) was used to formulate and characterise sustained-release and mucoadhesive buccal tablets using rabbit buccal mucosa model with chlorpheniramine as model drug [125]. The plasm concentration of the drug was plotted against time following application of the tablets the buccal mucosa of rabbits. Further, mucoadhesive strength was determined by the force of detachment as a function of time. Their results showed that the force of detachment for the

mucoadhesive buccal tablets increased with increasing concentration of the Hakea gum between 5 and 90 minutes. On the contrary, it was also noted that the presence of additives such as sodium bicarbonate or tartaric acid or increasing the concentration of the drug did not impact on the mucoadhesive strength, suggesting that the mucoadhesive function was largely attributable to the gum content. They concluded that "the novel, natural gum, *Hakea gibbosa*, may not only be used to sustain the release of chlorpheniramine from a unidirectional-release buccal tablet, but also demonstrate that the tablets are sufficiently mucoadhesive for clinical application". Further, the mucoadhesion could be controlled by varying the content of the Hakea within the tablets and represents a viable approach for buccal drug administration as an alternative to the commonly used oral route.

Kianfar co-authors [25] have reported on novel solvent cast films comprising kappa carrageenan as film forming polymer and pluronic acid for buccal delivery of a model insoluble drug, ibuprofen. The films were physically characterized using texture analysis, hot stage microscopy, differential scanning calorimetry, thermogravimetric analysis, scanning electron microscopy, x-ray powder diffraction, and *in vitro* drug dissolution. Optimized films were obtained from gels containing 2.5% w/w of kappa carrageenan, 4% w/w poloxamer with polyethylene glycol as plasticiser, whilst only a maximum of 0.8% w/w ibuprofen could be incorporated into the gels to obtain films with optimum characteristics. Texture analysis confirmed that optimum film flexibility was achieved from gels containing 5.5% w/w and 6.5% w/w of PEG 600 for blank films and ibuprofen loaded films respectively. Thermogravimetric analysis showed residual water content of approximately 5% whilst differential scanning calorimetry showed glass transition for ibuprofen at −53.87°C, a unified melt peak for PEG 600/poloxamer mixture at 32.74°C and the existence of ibuprofen in amorphous form, which was confirmed by X-ray powder diffraction. *In vitro* drug dissolution studies showed that amorphous ibuprofen was released from the films at a faster rate than the pure crystalline drug, suggesting a successful formulation of a carrageenan and poloxamer based drug delivery system with potential for buccal delivery of an insoluble drug.

In a related follow up study, the functional performance of the optimised carrageenan / poloxamer films, loaded with two different drugs (hydrophilic and hydrophobic) having different solubilities were compared [126]. In this study, the authors aimed to formulate and characterize stable carrageenan based buccal films with desirable drug (paracetamol and indomethacin) loading capacity and characterized by texture analysis, thermogravimetric analysis, differential scanning calorimetry, scanning electron microscopy, X-ray powder diffraction, and *in vitro* drug release studies. In this case, optimized films were obtained from

aqueous gels comprising 2.5% w/w carrageenan, 4% w/w poloxamer and with maximum drug loading of 1.6% w/w and 0.8 % w/w respectively for paracetamol and indomethacin. Interestingly, the residual water content was approximately 5% similar to that observed for the ibuprofen loaded films previously described suggesting that this is largely dependent on the polymer rather than the drug content. In addition, differential scanning calorimetry showed glass transition peaks for both drugs suggesting the presence of amorphous forms of both drugs which was confirmed by X-ray powder diffraction, again, as was the case for ibuprofen. Finally, drug dissolution studies showed cumulative percent release of paracetamol up to 45% whilst indomethacin showed 57% interestingly, possibly due to the amorphous conversion.

With the aid of 9 (3 x 3) factorial design, tamarind seed xyloglucan bi-layer films were developed as novel mucoadhesive delivery system for buccal delivery of rizatriptan benzoate [127]. The drug loaded layer comprised xyloglucan and carbopol whilst the backing layer contained ethylcellulose. The independent variables employed were concentrations of the polysaccharide and added carbopol whilst three dependent variables of tensile strength, bioadhesion force and drug release were considered. Using differential scanning calorimetry, they showed that there were no interactions between rizatriptan and the two polymers. Drug diffusion and permeation were carried out using a Franz diffusion cell apparatus and bioadhesion of porcine buccal mucosa measured with the help of a texture analyser. The drug loaded film showed a cumulative diffusion of 93.45% through the porcine buccal mucosa, suggesting that xyloglucan polysaccharide has potential as mucoadhesive polymeric film for buccal delivery of the drug rizatriptan.

In an interesting set of experiments, Giovino and co-workers designed a novel mucoadhesive chitosan film incorporating insulin loaded nanoparticles for the buccal delivery of the peptide drug as an alternative to the traditional parenteral route [128]. The nanoparticles were prepared by double emulsion solvent evaporation method using polyethylene glycol-b-polylactide co-polymer in the presence of polyvinylalcohol and the optimised formulation loaded with the insulin at various concentrations (2, 5, 10 % relative to co-polymer weight). The initial results showed successful encapsulation of the insulin with high encapsulation efficiency (70% for particles loaded with 2% insulin), mono disperse (polydispersity index of 0.2) and spherical appropriate nanoparticles with average diameter > 300nm that were stable (negative zeta potential) and also released the encapsulated drug during in vitro dissolution studies in biphasic sustained fashion. Chitosan films incorporating 3 mg of insulin loaded nanoparticles were obtained by dissolving the polymer in dilute acetic acid to obtain gels into

which the drug loaded nanoparticles were dispersed and then subsequently dried to obtain the composite mucoadhesive films intended for buccal insulin administration.

In the follow up study, the selected optimised chitosan films embedded with insulin loaded nanoparticles were further characterised for functional characteristics including swelling, mucoadhesion (peak adhesive force, total work of adhesion and cohesiveness) using texture analyser, film erosion and nanoparticle release using dynamic laser scattering, insulin conformational stability using circular dichroism and Fourier transform infra-red spectroscopy and permeation through EpiOral^{TM} buccal tissue [129]. Their results showed that formulations containing 3mg of nanoparticles per film, produced optimised films with excellent mucoadhesion and swelling properties. Dynamic laser scattering measurements showed that the erosion of the chitosan backbone controlled the release of nanoparticles from the films, preceding insulin release from the films after 6 hours. Relative to the pure insulin, the chitosan films yielded a 1.8-fold enhancement of *ex vivo* insulin permeation via EpiOral^{TM} buccal tissue construct with flux and apparent permeation coefficient of 0.1 g/cm^2/hour and 4×10^{-2} cm^2/hour respectively for insulin released from chitosan films loaded with 3% of drug loaded nanoparticles. Circular dichroism and Fourier transform infra-red spectroscopy showed that the conformational structure of the insulin released from nanoparticles embedded within the chitosan films was maintained during formulation as well as during drug release.

In a recent study, Khan and co-authors reported on novel solvent cast films prepared various hydrophilic polymers including the polysaccharides sodium alginate and carrageenan as well as metolose, hydroxypropylmethylcellulose and methylcellulose equivalent for the paediatric buccal delivery of the proton pump inhibitor omeprazole used in treating peptic

ulcers [130]. Aqueous and ethanolic gels of both polymers were prepared and dried in an oven to obtain the films and the tensile properties determined to select optimum films for further analysis and drug loading. Preliminary observations showed only sodium alginate and metolose films satisfied expected ideal criteria and further tested. However, initial observations revealed the poor stability of omeprazole under aqueous environments and required the addition of L-arginine to stabilise the gels. The stabilised films were characterised to optimise plasticiser content and casting solvent, prior to drug loading using tensile testing with the help of a texture analyser. Further characterisation studies were performed using differential scanning calorimetry, thermogravimetric analysis X-ray diffraction, scanning electron microscopy. The differential scanning calorimetry and X-ray diffraction data suggested molecular dispersion of drug within the polymeric matrix whilst plasticised films prepared from ethanolic gels containing omeprazole: L-arginine 1: 2 were the most ideal in terms of transparency, ease of peeling and flexibility.

Composite dispersions combining the polysaccharide sodium alginate and the inorganic gum magnesium aluminium silicate have been used to prepare films incorporating nicotine for buccal delivery as a nicotine replacement therapy system [131]. The physicochemical properties, *in vitro* mucoadhesivity, drug content, drug release and permeation of nicotine released from the composite films were investigated. Nicotine which is basic was protonated under acid and neutral pH conditions thus interacting with the negatively charged magnesium aluminium silicate via an electrostatic interactions which resulted in the formation of nicotine magnesium aluminium silicate flocculates which acted as micro-reservoirs within the films and a pH of 5 was found to ensure minimal loss of nicotine during drying. The release of nicotine from the films and permeation across the model mucosal membrane was explained by a matrix diffusion controlled mechanism. In addition, the drug loaded composite films were bioadhesive and suggested as a potential means of buccal delivery of nicotine.

Shelider and co-workers have described a novel double layered adhesive patch for buccal delivery of zolmitriptan [132]. Three different polymers were employed; xanthan as mucoadhesive polymer, hydroxypropylmethylcellulose as film former and polyvinyl alcohol to improve tensile strength of the film patch. The effect of xanthan and polyvinyl alcohol concentrations on dependent variables such as *in vitro* drug release, *ex vivo* mucoadhesive strength and swelling index were investigated using a 3^2 factorial design. The *in vitro* drug release studies of optimized formulation showed rapid initial drug release of 43.15% within 15 minutes, followed by sustained drug release over a 5 hour period. Further, permeability of

drug was enhanced by 3.29 times with the addition of 4% dimethyl sulfoxide resulting in a total of 29.10% of drug crossing the membrane after 5 hours with no buccal mucosa tissue damage from histopathological studies.

Ayensu and co-authors have reported on the effect of membrane dialysis on the characteristics of chitosan based lyophilised wafers loaded with bovine serum albumin as model protein drug for buccal drug delivery and characterised by X-ray diffraction, attenuated total reflectance Fourier transform infra-red spectroscopy, circular dichroism, scanning electron microscopy, hydration capacity, *in vitro* mucoadhesivity and drug dissolution [137]. Their results showed that the dialysed wafers demonstrated enhanced mucoadhesion and drug release properties while newly formed sodium acetate in the undialysed wafers caused increased crystallinity with poor mucoadhesion and drug release properties. In a related study, both chitosan and thiolated chitosan based wafers loaded with bovine serum albumin were prepared by freeze-drying of aqueous gels and the effect of an annealing step during the freezing stage on functional characteristics determined with the help of analytical techniques including circular dichroism, infrared spectroscopy, X-ray diffraction and scanning electron microscopy as well as swelling and mucoadhesion [138]. Swelling capacities of 1110 ± 23.3% and 480 ± 18.2% were obtained for the chitosan and thiolated chitosan formulations respectively with thiolation showing a significant improvement in mucoadhesive performance of the wafers (xerogels). In vitro drug dissolution studies showed BSA release of 91.5 ± 3.7% and 94.4 ± 7.3% from the chitosan and thiolated-chitosan xerogels respectively which are very high and demonstrate the potential of lyophilised chitosan based wafers with optimised mucoadhesion characteristics for buccal mucosa delivery of protein based drugs.

Boateng and Araego [139] have developed a composite freeze-dried wafer for protein drug delivery via the buccal mucosa using two naturally occurring polysaccharides i.e. chitosan and sodium alginate and model protein drug in the form of bovine serum albumin.
Functional characterisation studies (swelling, mucoadhesion and in vitro drug dissolution) were performed together with physical characterisation (morphology and crystallinity) were performed using scanning electron microscopy and X-ray diffraction respectively. Following 2 hours of dissolution testing, the results showed that the release of BSA was dependent on both the sodium alginate and protein content. Further, the presence of chitosan acted as a suitable modifier to the mucoadhesion properties of sodium alginate and show the potential of developing a sustained delivery system for macromolecules by combining chitosan and sodium alginate for buccal mucosa drug delivery of macromolecules.

Table 1. Summary of published polysaccharide based systems used for buccal drug delivery

Polysaccharide(s)	Drug	Formulation	Year/Reference
Xanthan gum	Salbutamol	Gel	2014 [119]
Glycol chitosan	Denbufylline	Gel	2003 [120]
Alginate / chitosan	Nystatin	Gel	2015 [121]
Guar gum, sodium alginate	Buspirone	Tablet	2014 [122]
Anacardium occidentale gum	Curcumin	Tablet	2012 [123]
Starch/carbopol	Miconazole nitrate	Tablets	2005 [124]
Hakea	Chlorpheniramine maleate	Tablets	1999 [125]
Carrageenan	Ibuprofen	Film	2011 [25]
Carrageenan	Paracetamol, indomethacin	Film	2012 [126]
Xyloglucan	Rizatriptan benzoate	Film	2013 [127]
Chitosan	Insulin	Film	2012 [128]
Chitosan	Insulin	Film	2013 [129]
Carrageenan, sodium alginate	Omeprazole	Film	2015 [130]
Alginate-magnessium aluminium silicate	Nicotine	Film	2009 [131]
Xanthan gum	Zolmitriptan	Film	2014 [132]
Okra polymer	Zolmitriptan	Film	2014 [133]
Catechol-chitosan	Lidocaine	Patch	2015 [134]
Chitosan	BSA	Wafer	2012a [137]
Chitosan, thiolated chitosan	BSA	Xerogels	2012b [138]
Thiolated chitosan	BSA	Wafer	2012 [39]
Laminated thiolated chitosan	BSA	Wafer	2014 [135]
Chitosan	BSA	Wafer	2012 [136]
Thiolated chitosan	Insulin	Xerogels	2014 [141]
Carrageenan	Ibuprofen, paracetamol	Wafer	2014 [26]
Chitosan, sodium alginate	BSA	Wafer	2015 [139]

In an *in vitro* and *ex vivo* study, the mucoadhesive and drug release characteristics of buccal discs containing fluconazole, prepared by compressing gum cordia and lactose was studied [140]. Their results showed that bioadhesion was significantly dependent upon the concentration of gum cordia present within the buccal discs while the release of fluconazole from the buccal discs was significantly dependent on the pressure applied during compression. Kianfar and co-workers developed freeze-dried mucosal wafers using carrageenan and pluronic acid for potential buccal delivery of model soluble (paracetamol) and insoluble (ibuprofen) drugs [26]. Their results showed acceptable water content between 0.9 and 1.5% (thermogravimetric analysis) and amorphous conversion of original crystalline drugs into amorphous forms after the formulation process (differential scanning calorimetry and X-ray diffraction) which remained stable after 6 months. They also showed that the formulations exhibited ideal mechanical and mucoadhesion properties expected of a buccal mucosa delivery system and released both drugs in a sustained fashion over a two hour period.

Boateng and co-workers developed freeze-dried mucoadhesive xerogels from thiolated chitosan gels loaded with loaded with insulin for buccal mucosa delivery [141] in the presence of enzyme inhibitor (glutathione) and permeation enhancer (aprotinin) to enhance drug permeation. To ensure uni-directional release, the xerogels were coated on one side with an impermeable ethylcellulose film layer. The formulations were characterised for degree of deacetylation (nuclear magnetic resonance spectroscopy), amount of immobilised thiol groups (Ellman's reaction), molecular weight (gel permeation chromatography), stability (attenuated total reflectance Fourier transform infra-red spectroscopy and circular dichroism), in vitro and ex vivo permeation by means of EpiOral^{TM} and sheep buccal membrane. Their results showed that the insulin loaded xerogels showed a 1.7 fold increase in permeation through the EpiOral^{TM} buccal tissue in the presence of aprotinin when compared to the pure drug whilst the permeation decreased for formulations containing the enzyme inhibitor glutathione. The aprotinin also enhanced the permeation of insulin across sheep buccal membrane which was well correlated with the results from permeation through the EpiOral^{TM} tissue.

Commercialized buccal delivery systems available in the market include Zuplenz^{TM} (ondansetron), Benadryl^{TM} (diphenhydramine) and Gas-X (simethicone), Triaminic thin strips (phenylephrine, Pedia-lax Thin Strips (senna), Theraflu (diphenhydramine). In addition, insulin buccal spray or hydrocortisone buccal tablets are available on the market.

4. Nasal mucosa drug delivery

Drugs can be delivered directly to the circulatory system through the highly vascular mucosa surface of the nasal cavity thereby bypassing the hepatic first-pass effect and other degradation conditions in the intestines [142]. The major advantage of the nasal route over conventional parenteral route in terms of systemic delivery is based on patient compliance and its link to the brain via the putative pathway in the case of rapid crisis treatment. This provides more rapid and specific effect compared to the parenteral route [143]. However, nasal formulations are difficult to quantify and might result in overdose of drug [144] and can also be affected by mucocilliary clearance [145]. Over the years, nasal formulations such as sumatriptan, zolmitriptan and dihydroergotamine mesylate have been approved and commercially available for the treatment of migraine. Commercially available peptide drugs via nasal mucosal route include desmopressin, salmon calcitonin and nafarelin. Other available commercial products that exploit the advantages of the nasal mucosa as a systemic delivery route have also been developed especially in the treatment of pain, vaccination and erectile dysfunction [143].

4.1 Nasal physiology and anatomy

The vestibular, olfactory and the respiratory regions are the three different functional regions of the nasal cavity (figure 5). The nasal vestibule is found at the entrance of the nose and comprises features such as the nasal hairs and keratinised epithelial cells. The nasal vestibular region is less permeable as a result of the presence of keratinised cells. The olfactory region is located in the roof of the nasal cavity and contains specialized nerve cells which are sensitive to smell and is directly linked to the brain.

<**Figure 5 here**>

The region with the most drug absorption is the respiratory region containing the major part of the nasal cavity. The factors that contribute to its high drug absorption include high vascularity, large surface area, and high amount of nasal secretion [143, 146, 147]. Drug transport through the nasal mucosal membrane as with other membranes, can be achieved via the transcellular (i.e. transport across the cell) and paracellular (i.e. transport between cells) routes. Drugs transported via the transcellular route are usually lipophilic drugs while hydrophilic drugs are believed to be transported via the paracellular pathway [148].

4.2 Polysaccharide-based nasal delivery systems

Nasal formulations include gels, liquids, powdered particulates and pressurised metered dose inhalers [149] with powder and pressurised metered dose inhalers being the most common. Commercially available formulations for nasal delivery have been achieved using pectin polysaccharide for the delivery of fentanyl [150]. Nasal formulations can be enhanced for optimum absorption of drugs especially polar drugs with the use of both the bioadhesive effect of polysaccharides-based mucoadhesive polymers as well as absorption enhancers such as cyclodextrin (an oligosaccharide), surfactants, bile salts, fatty acids and phospholipids [148]. Cho and co-workers demonstrated use of hydroxypropyl-β-cyclodextrin combined with chitosan and poloxamer for enhanced absorption in the nasal cavity. Their studies showed an improved bioavailability of fexofenadine hydrochloride in animal model (i.e. rabbit) owing to the fact that chitosan and hydroxypropyl-β-cyclodextrin are permeation enhancers [151].

The nasal systemic route has gained interest in the delivery of vaccines given that it is the first portal of entry for inhaled pathogenic microorganisms, its richness in lymphoid tissue and its ability to initiate both mucosal and systemic immune response [143]. Lui and co-authors used of an ammonium salt chitosan polysaccharide in the preparation of ovalbumin/ N-trimethylaminoethylmethacrylate chitosan conjugates for nasal administration and demonstrated an induced systemic and mucosal response in mice with nasal administration of antigen conjugated trimethylaminoethylmethacrylate chitosan [152]. In a related study, a nasal Shigellosis vaccine was developed for inducing mucosal immune response [153] using chitosan nanofibers as the carrier. The antigen-containing chitosan nanofibrous membranes were obtained by electrospinning acidified chitosan solutions (using acetic acid) and directly administered to guinea pigs into their nasal cavity. Their results showed higher antibody responses in the guinea pigs immunised intra-nasally with evidence of protection against infection challenge with wild-type S flexneri 2a in a kerato-conjunctivitis Sereny test.

Starch nanoparticles, prepared by using different crosslinkers (epichlorohydrin vs $POCl_3$) and degree of crosslinking and different procedures (emulsion vs gelation) have been reported for trans-nasal delivery of insulin [154]. Their results showed that crosslinked nanoparticles prepared via the emulsion particles were smaller (351 nm) than those prepared by gel method (997 nm) and size further reduced for epichlorohydrin (194 nm) crosslinked particles compared to $POCl_3$ (810 nm). In vitro drug dissolution studies showed a size dependent burst release, more pronounced in the smaller nanoparticles with limited crosslinking. Hypoglycaemic effects in vivo were greater in particles with small size, lowest levels of crosslinking and those containing sodium glycholate as permeation enhancers. In a related study, pullulan based nanoparticles were prepared using polyelectrolyte complexation [155]. Pullulan was initially charged before complexation with chitosan and carrageenan to obtain positively charged nanoparticles for purposes of protein delivery via nasal mucosa, using BSA as model drug. The nanoparticles showed a burse release of 30% of BSA maintained over a 24 hour period. The study further showed stability of the protein following freeze-drying and showed acceptable toxicity via MTT assay.

Table 2, List of mucoadhesive polysaccharides used for nasal drug delivery.

Polysaccharide	**Drug**	**Formulation**	**Year / Reference**
Chitosan	Influenza vaccination	Nasal spray	2005 [156]
Chitosan	Carvedilol	Nasal insufflator	2010 [157]
Chitosan	Insulin	Nasal gel	2013 [158]
Chitosan	Leuprolide (peptide)	Nanoparticle solution	2012 [159]
Sodium alginate	Carvedilol	Nasal insufflator	2011 [160]
	Venlafaxine HCl	Nasal gel	2012 [161]
Pectin	Ondansetron HCl	Nasal powder	2012 [162]
	Tacrine HCl	Microparticle	2013 [163]
Hyaluronic acid	Ovalbumin	Nanoparticles	2011 [164]

5. Drug delivery through gastrointestinal mucosa

The gastrointestinal mucosa is the major barrier against the harsh environment of the lumen of the gastrointestinal tract which contains various microbial organisms, and toxic compounds which can be harmful to the body if absorbed in the systemic circulation. The key function of the gastrointestinal mucosa is to allow the transport of relevant compounds

including nutrients, drugs and water across the epithelial membrane whilst keeping out harmful materials including microorganisms.

5.1 Gastrointestinal anatomy

The gastrointestinal barrier comprises mainly two parts: (a) the intrinsic barrier (made up of epithelial cells which line the walls of the digestive tract, held together by very tight junctions) and (b) the extrinsic barrier (comprising secretions and other factors not physically part of the epithelium but contribute to the maintenance of their integrity towards its barrier function). These secretions include mucus, bicarbonates, hormones and cytokines, prostaglandins, growth factors, trefoil proteins, antibiotic peptides and antibodies and immunoglobulins. However, for purposes of this review, the mucus which forms part of the extrinsic gastrointestinal barrier will be the focus of attention and the reader is referred to more specific anatomical, physiological and biochemical sources of peer reviewed information for the other components outlined above [165].

<**Figure 6 here**>

5.2 Polysaccharide-based gastrointestinal mucosa delivery systems

As already noted, the environment within the gastrointestinal tract can be harsh to labile drugs including proteins and peptides and therefore these drugs have traditionally not been administered via the oral route, but rather via the parenteral injections. However, there has been recent attempts at delivering such drugs across the gastrointestinal mucosa barrier by use of various bioadhesive polymers including polysaccharides which either have intrinsic permeation enhancing properties or used to formulate delivery systems incorporating natural or synthetic permeation enhancers [166]. As is the case for the other mucosal routes, chitosan is the most common polysaccharide owing to its biocompatibility, its bioadhesivity and, permeation enhancing characteristics.

Guggi and co-workers prepared a delivery system for delivering calcitonin based on various chitosan derivatives in a composite system [167]. They synthesized chitosan–4-thiobutylamidine (as mucoadhesive fixer) conjugated to chitosan–pepstatin A (pepsin inhibitor conjugated to mucoadhesive chitosan), incorporated into mini-tablets and used for delivering the protein drug via the stomach mucosa. Protein permeation was further enhanced by use of glutathione as part of the formulation. Their results showed that the chitosan–pepsin inhibitor conjugate provided appropriate protection of the calcitonin.

However, the most common delivery system employed are encapsulated colloidal systems, usually in the form of nanoparticles, given their easy manipulation (e.g. pegylation) for targeting purposes and the extra protection afforded by encapsulating the target drug of interest [168]. Pullulan polysaccharide were combined with the enteric polymer Eudragit to prepare microparticles with gastric acid resistance as well as controlled drug release for oral delivery of risedronate [169]. The microparticles were prepared by spray drying and characterised for yield, size, encapsulating efficiency, morphology, moisture levels and in vitro dissolution characteristics. Their results showed suitable physical properties and most interestingly a 100 % encapsulation efficiency, resistant to simulated gastric fluid whilst showing prolonged release in intestinal fluid. Further, when the particles were compressed together with or without polyvinylpyrrolidone into tablets, they still maintained gastro resistance as well as prolonged release in intestinal medium and therefore provide great potential as an alternative oral delivery system.

Shina and Kumria [170] have reviewed several natural polysaccharides used either alone or in combination with other organic or inorganic components for colonic drug delivery and summarised in table 3.

Modified psyllium polysaccharide hydrogels have been proposed as potential drug delivery vehicles for methotrexate for the treatment of gastrointestinal tract cancer [209]. Swelling and drug release characterisation studies on the hydrogel formulations showed Fickian diffusion at different pH values suggesting the system can release the drug in different parts of the GIT in appropriate doses over a reasonable time frame in a controlled manner. In an *in vitro* study, composite calcium alginate and carboxymethylcellulose beads with pH responsive swelling and mucoadhesion behaviour as well as biodegradability induced by micro-organisms present in the colon, have been proposed for colon targeted delivery of 5-fluoro-uracil. Beads prepared by ionic gelation were physically characterized using scanning electron microscopy, X-ray diffraction, energy dispersive X-ray analysis (EDAX), differential scanning calorimetry and texture analysis which showed higher swelling and mucoadhesion within a simulated colonic environment. The composite beads also degraded slowly in simulated colonic fluid which was accelerated in the presence of microflora commonly present in the colon region. Further, *in vitro* drug release showed greater than 90% total drug release when colonic enzymes were present and carboxymethylcellulose modulated the drug release when analysed by fluorescence recovery after photo-bleaching. Testing of the drug loaded beads against colon adenocarcinoma cells suggested a potential application of these beads for colon specific drug delivery.

Table 3 Polysaccharides investigated for colon-specific drug delivery with their dosage forms and summary of the results obtained. Adapted from Shina and Kumria (2003) [170].

Polysaccharide	**Drug**	**Formulation**	**Year / Reference**
Chitosan	5-(6)-Carboxy fluorescein)	Enteric-coated capsules	1997 [171]
Chitosan	Insulin	Enteric-coated chitosan capsules	1997 [171]
Chitosan	R68070	Enteric-coated chitosan capsules	1999a [172]
Chitosan	Sodium diclofenac	Enteric-coated chitosan microspheres	1998 [173]
Chitosan	Acetaminophen	Cores coated with chitosan and phytin	1998[174]
Chitosan succinate / phthallate	Sodium diclofenac	Matrices	1999 [175]
Pectin (calcium salt)	Indomethacin	Matrices	1993 [176]
Pectin	Indomethacin	Compression coated/ matrix tablets	1995 [177]
Pectin	Insulin	Compression coated/ matrix tablets	1995 [177]
Pectin	Radioactive tracer	Enteric-coated matrix tablets	1997 [178]
Methoxylated pectinate	Radioactive tracer	Compression coat	1994 [179]
Amidated pectin	Paracetamol	Matrix tablets	1997 [180]
Amidated pectin	Indomethacin Sulphamethoxazole	Chitosan-coated amidated pectin beads	1997 [181]
Amidated pectin/ calcium pectinate	Ropivacaine	Matrix tablet	2000 [182]
Pectin	Paracetamol	Ethyl cellulose film coating	1996 [183]
Pectin	Theophylline	Mixed film with coating	2000a, 2000b [184, 185]
Pectin / chitosan	Technetium-99	Mixed film of pectin, chitosan and HPMC	1999a, 1999b [186, 187]
Pectin and chitosan	Indomethacin/ paracetamol	Compression coat	1998 [188]
Guar gum	Dexamethasone/ budesonide	Matrix tablet	1997 [189]
Guar gum	Dexamethasone	Matrix tablet (radio labelled)	1997 [190]
Guar gum	Indomethacin	Matrix tablet	1998 [191]
Guar gum	Technetium-99m-DTPA	Matrix tablet	1998 [192]

Guar gum	5-ASA	Compression coat	1999 [193]
Cross-linked guar	–	–	1995a [194]
Cross-linked guar	Hydrocortisone	Hydrogels	2000 [195]
Crosslinked dextran	–	Hydrogels	1995a [196]
pH-sensitive dextran	Bovine serum albumin (BSA)	Hydrogels	1999 [197]
Cross-linked dextran	Hydrocortisone	Capsules	1998 [198]
Dextran fatty acid esters	Theophylline	Films	1997 [199]
Inulin	–	Films	1996 [200]
Inulin	–	Hydrogels	1998 [201]
Cross-linked chondroitin	Indomethacin	Matrix tablet	1992a [202]
Amylose	5-ASA	Coated pellets	1996a [203]
Amylose/ethyl cellulose (1:4)	Glucose	Coated cores	1996 [204]
Amylose/ethylcellulose coating	5-ASA	Coated pellets	2000a [205]
Starch	Radioactive tracer	Enteric-coated capsules	2000 [206]
Calcium alginate	5-ASA	Double coated swellable beads	1992 [207]
Locust bean gum	Theophylline	Film	1995 [208]

In a related study, Feng and co-workers used chitosan based nanogels obtained by electrostatic interaction between chitosan and carboxy-methyl chitosan for delivering drugs against colorectal cancer and showed significant effect on cell viability owing to the improved mucoadhesion which allowed a higher accumulation of drug (doxorubicin) concentration within the cancer site [210].

pH responsive hydrogel beads obtained by grafting polyacrylamide onto kappa-carrageenan and sodium alginate (SA), for targeting ketoprofen to the intestine have been reported by Kulkarni and co [211]. The grafted polyacrylamide-carrageenan was synthesised by free-radical polymerization with alkaline hydrolysis whilst the drug loaded hydrogels were obtained by ionic gelation and covalent crosslinking and showed amorphous conversion of

the drug within the beads as analysed using differential scanning calorimetry and X-ray diffraction. The beads which were spherical in shape (scanning electron microscopy), exhibited pH sensitive swelling in a pulsatile fashion and showed that the drug release increased when pH changed from acid to alkaline conditions. Further *in vivo* studies in albino rats showed that the beads retarded the release of ketoprofen in the stomach (acidic pH) and therefore resulting in reduced ulceration, haemorrhage and gastric mucosa erosion associated with the drug. This finding is interesting and shows great potential for targeting such drugs to the small intestines for systemic absorption.

Similarly, Prezotti and co-workers [212] obtained circular beads containing gellan gum and pectin by ionotropic gelation, but using Al^{3+} as crosslinker, with high yield and entrapment efficiencies and sizes ranging between 728.95 and 924.56 μm but increased with higher polymer and crosslinker concentrations. Thermal analysis and Fourier transform infra-red spectroscopy showed the absence of drug–polymers interactions but high mucoadhesion both *in vitro* and *ex vivo*. Further, the beads showed high erosion under acidic pH whilst swelling was enhanced at pH of 7.4, suggesting pH depended drug (ketoprofen) release characteristics which was determined to be via a super case 2 type sustained release over a 6 hour period at pH 7.4.

Different commercial products incorporating 5 amino salicylic acid are marketed under different brand names (Pentasa, Asacol, Salofalk, Lialda, and Mezavant). Lipfen®, is a flurbiprofen liquid suppository containing HP-beta-CD. Chronotropic™ is a "two-pulse" colonic device for oral delivery of insulin and consists of an inner swellable/erodible hydroxylpropylmethylcellulose (HPMC) layer surrounding a tablet core as well as an another HPMC external coating on the exterior. Other products include Desmopressin containing antidiuretic hormone and Sandimmune® Soft Gelatin Capsules containing cyclosporin

6. Vaginal mucosa drug delivery

The vaginal route of drug administration is an excellent route for systemic drug delivery considering its large mucosal surface area and high blood vessel network, a common feature in other mucosa sites. Challenges of vaginal mucosa drug delivery include vaginal irritation, sexual activity and menstrual cycle, urination, hygiene of the individual and cultural background [213].

6.1 Vaginal physiology and anatomy

The vagina is made up of muscles with an elastic lining that provide lubrication and sensation, and links the uterus to the external genitalia called the vulva. Its diameter range from 2.1 to 5.0cm whiles its length range from 8.4 to 11.3cm. The walls of the vagina consist of three layers: the stratified squamous epithelial layer, the lamina propria, the muscular layer and the tunica adventitia made up areolar connective tissues [214, 215] (figure 7). Although the mucosal surface of the vagina does not have glands, it is usually composed of fluid which are secreted by other components such as endometrial and tubal, cervical mucus, exfoliating epithelial cells, Bartholin's and Skene's glands and transudation of leukocytes and vaginal cells from blood vessels [216].

<**Figure 7 here**>

The normal microbial flora of the vagina such as *Lactobacillus acidophilus* helps in regulating and maintaining the pH of the vagina by producing lactic acid with pH 3.8 and 4.2. However, the pH of the vagina is usually altered as a result of menstruation and sexual intercourse due to the alkalinity of semen and vaginal transudates. Absorption of drugs administered via transmucosal routes are usually by transcellular (i.e. transport across the cell) and paracellular (i.e. transport between cells). Dissolution of drugs in the vaginal lumen and penetration of the membrane are important processes in the absorption of drugs from a designed vaginal drug delivery system. Physiological factors such as change in hormonal levels vaginal secretion volume and composition, pH and sexual activities could affect the release and absorption of drug [213, 216].

6.2 Polysaccharide-based vaginal mucoadhesive systems

The different dosage forms of the vaginal route include solutions, suppositories, gels, foams, vaginal rings, tampons, sponges, creams, ointments, doushes, pessaries, soft gelatin capsules and tablets [215]. Recently, polymeric films have been considered as a novel dosage form in vaginal mucosal delivery. Research focus of films has been aimed at solving genital problems such as contraceptives and microbicides [217]. Mucosal delivery of drugs in the vagina can either be systemic or locally. Local mucosal delivery involves the delivery of drug to the tissues of the vaginal cavity as is the case in the treatment of vaginitis. In other to achieve optimum characteristics such as bioadhesion, retention, distribution and release, formulation of vaginal drug delivery system will require the use of a mucoadhesive

system [216]. There have been commercially available polysaccharide based mucoadhesive formulations as shown in table 4. Chitosan, alginate, pectin and hyaluronic acid have been investigated in vaginal delivery as polysaccharide based mucoadhesive polymers (table 5). Nowak and co-workers demonstrated the potential use of hyaluronic acid in the development of a mucoadhesive drug delivery system [218].

Table 4. Polysaccharide based commercial vaginal delivery products available on the market (www.medicines.org.uk Accessed 9 March 2015)

Commercial name	**Drug**	**Polysaccharide**	**Use**	**Formulation**	**Source**
Postin® E2	Dinoprostone	Microcrystalline cellulose, corn starch	Induce labour	Tablet	Pfizer
Medabon	Misoprostol, milfepristone	Microcrystalline cellulose, corn starch	Pregnancy termination	Tablet	Sun Pharmaceuticals

Table 5. Polysaccharides under investigation for vaginal delivery.

Polysaccharide	**Drug**	**Use**	**Formulation**	**Year / Reference**
Chitosan	Chlorhexidine	Vaginitis	Insert	2014 [219]
Chitosan	Econazole	Vaginitis	Solution	2013 [220]
Chitosan	Nile red	-	Gel	2014 [221]
Chitosan	Curcumin	Cancer	Solution	2014 [222]
Chitosan	Tenofovir	HIV	Solution	2011 [223]
Chitosan/alginate	Chlorhexidine digluconate	Vaginitis	Insert	2012 [224]
Alginate, chitosan	Nystatin	Vaginitis	Gel	2013 [225]
Alginate	siRNA	Viral infection	Insert	2011 [226]
Pectin	Ornidazole	Vaginitis	Tablet	2006 [227]
Hyaluronic acid	-	-	Tablets	2014 [218]
Hyaluronic acid	-	-	Gel	2014 [228]
Hyaluronic acid	Estroldiol	Vaginitis	Tablet	2011 [229]

6.3 Prevention of human immune deficiency (HIV) virus infection

One of the most productive fields of research in terms of vaginal delivery is in the use of topical microbicides in the prevention of HIV transmission. The microbicides prevent early transmission of the virus at the mucosal level and contiguous side when administered to the vaginal mucosa. The most common anti-HIV microbicides approved molecules are tenofovir and dapivirine. Meng and co-workers designed a polysaccharide based formulation loaded with tenofovir using chitosan based nanoparticles. Chitosan was used as an adhesive component to improve retention time of the formulation. The result of their research demonstrate chitosan nanoparticle as a potential microbicide delivery system with a safe bioadhesive and control release properties [223]. In another approach, Belletti and co-workers investigated tenofovir loaded nanoparticle of chitosan and/or poly-(d,l-lactide-co-glycolide) (PLGA). They also investigated the strategies at which the nanoparticles were prepared for more efficient drug loading. In their findings it was concluded that PLGA/chitosan nanoparticles could be an effective and attractive tenofovir antiretroviral carrier [230].

6.4 Vaginal infections

Vaginal infections are known to cause vaginitis (inflammation of the vagina) which is highly prevalent in women within reproductive age. The most common cause of vaginitis is vaginal candidiasis caused by fungi such as *Candida albicans*. Other causes of vaginitis are known to include aerobic vaginitis caused by the disruption of *Lactobacillus spp* followed by signs of inflammation and the manifestation of a predominantly aerobic microflora such as *Escherichia coli* and *Streptococcus agalactiae* [231, 232]. The management of vaginitis is usually by the administration of antifungal azoles and antibacterial small molecules such as imidazoles (for candidiasis) and quinolone (for aerobic vaginitis). These molecules are known to hinder the activities of abnormal and invasive microorganisms however, they exhibit poor local pharmacokinetics with commercially available products associated to safety issues [233].

Abruzzo and co-workers demonstrated the use of polysaccharide complexes of chitosan and alginate in the development of vaginal insert loaded with chlorhexidine digluconate for local vaginal delivery. The use of chitosan and alginate polysaccharides in the reported formulation was to obtain a good mucoadhesion between the insert and the mucosal surface of the vaginal cavity [224]. Other polysaccharides such as pectin have been studied as a mucoadhesive polymer in the treatment of vaginitis. Baloglu and colleagues demonstrated

the use of various polymers including pectin as mucoadhesive polysaccharide in the development of vaginal tablets loaded with ornidazole. The formulation containing pectin demonstrate enhanced mucoadhesive properties, controlled release and non-toxic characteristics [227].

6.5 Delivery of nucleic acids

Another field of study in vaginal mucosal delivery in terms of viral infections responsible for diseases such as HIV, genital herpes and cervical cancer is the use of nucleic acids such as small interfering RNA (siRNA) or plasmid DNA. siRNA can be used to target both viral and host gene or combined together. The vaginal route offers self-administration as well as low toxicity in terms of siRNA delivery against sexually transmitted diseases. However, siRNAs are susceptible to vaginal degradation, less likely to internalise into the cell and when they do, their ability to escape the endosome is low. There is therefore need for delivery systems that can transport siRNA via transcellular and paracellular pathways [234]. To achieve this, there are two categories of vectors used in the transport of therapeutic siRNA; viral and non-viral vectors. The viral vectors involve the use of viruses such as retrovirus, lentivirus and adenovirus, while non-viral vectors include liposome-based cationic transfection reagent [235], macromolecular conjugation [236], and polymeric nanoparticles [234].

Mucoadhesive polymeric formulation can be used to improve the delivery of designed vectors by decreasing the effect of the physiological factors that affect absorption of vector as well as increasing the retention time of the vector on the mucosal surface. Alginate polysaccharide has been under investigation in the development of an alginate scaffold system for the delivery of siRNA through the vaginal mucosal. Wu and co, developed a PEGylated lipoplex-entrapped alginate scaffolds (PLAS) using alginate polysaccharides. Their studies demonstrated a significant improvement in the delivery siRNA via intravaginal route by entrapping PEGylated lipoplexes in a negatively charged alginate scaffold system compared to conventional lipoplexes [237].

7. Drug delivery in the context of wound therapy

A wound can be defined as an injury or disruption to anatomical structure and function resulting from simple or sever break in the skin, extending into regions such as the subcutaneous tissue. The damage can extend to other tissues such as muscles, tendons, nerves, vessels and even the bone [7, 238, 239]. It has been suggested that wound healing

involves a series of overlapping molecular events requiring extensive communication between cells and various physiological processes (figure 8). These comprise haemostasis and inflammatory phase, proliferative phase, remodelling and scar maturation phase [7, 240].

A wide range of wound dressings are available for a variety of wound types including foam dressings, alginates, films, hydrocolloids and hydrogels. These have absorbent properties and their main aim is to form gels upon contact with the wound exudate. Most of these dressings provide and maintain a moist wound environment and are recognised for optimal healing. However, many factors may delay the phase of healing process, because not all dressings have the contents required for an ideal property of a dressing for optimal healing of the wound. As a result, many wound dressings have been extensively studied as drug delivery systems which take active part to improve wound healing [241, 242]. These are usually prepared using various natural and synthetic polymers including hydrocolloids, hydrogels and polysaccharides such as xanthan gum, alginates, chitosan and its derivatives, carrageenan, hyaluronic acid and collagen. The latter group (polysaccharides) have attracted significant interest due to their hydrophilicity, bioadhesion, biocompatibility and biodegradability.

<**Figure 8 here**>

7.2 Polysaccharide-based wound delivery systems

Bioactive composite films comprising the polysaccharide carrageenan combined with polyethylene oxide have been reported for use in chronic wounds. The films were loaded with streptomycin to target bacterial infections and diclofenac to target the inflammatory phase of wound healing [241, 244]. In a parallel study, freeze-dried wafers comprising carrageenan and polyethylene oxide or sodium alginate and polyethylene oxide loaded with the above two drugs were also prepared and characterised [242]. In both type of formulations (films and wafers), the results showed sustained release of both drugs over a 72 hour period whilst antibacterial studies showed synergistic antibacterial action of the two drugs against three main infection causative bacteria which were *Staphyloccocus* aureus, *Pseudomonas aeruginosa* and *Escherichia coli* when compared to the streptomycin on its own. The results were interesting as they suggest the possibility of targeting more than one phase of wound healing by treating infection and preventing reinfection over a three day period whilst at the same time reducing swelling and pain associated with inflammation. In addition, the synergistic action between the two drugs allowed the use of a lower dose of the streptomycin

which is advantageous in terms of lowering the exposure of newly formed cells to high doses of both drugs, and therefore reduce the chances of toxicity. Furthermore, the release of drug over three days due to high swelling and moisture holding capacity which controlled high exudate levels will reduce the need for too frequent dressing changes which is a major cause of patient non-compliance that can result in serious complications, especially for chronic wounds.

Lyophilized wafers prepared from karaya gum were formulated and loaded with four different antimicrobial agents (neomycin, povidone iodine, chlorhexidine and silver sulphadiazine) as potential therapeutic dressings for exuding wounds against methicillin-resistant Staphylococcus aureus [245]. They showed that the wafers swelled in simulated wound fluid and released the compounds to different extents, with povidone iodine and chlorhexidine being effective in the absence of proteins whilst neomycin was enhanced by the presence protein in the form of bovine serum albumin with silver sulfadiazine showing the lowest antibacterial potency. In a related study, the same group tested the effect of chlorhexidine digluconate loaded polysaccharide based wafers against *Pseudomonas aeruginosa* [246]. They produced different formulations containing the drug and functionally characterized for simulated wound fluid absorption and holding capacity, rheological characteristics of hydrated gels and *in vitro* efficacy against the bacteria in question and the results of the different formulations compared. Their results showed that the drug reduced the absorption of the simulated wound fluid by a factor between 11 – 50% and reduced the rheological consistency of gels containing no sodium alginate by 10-65%. The drug dissolution results showed that wafers containing karaya gum exhibited sustained release of the drug within 24 hours with the highest amount released significantly higher the minimum inhibitory concentration against the bacteria. The fitting of the release data to Korsmeyer Peppas equation showed an anomalous diffusion mechanism for most of the wafers except those containing xanthan.

In a further follow up study, Labovitiadi and co-workers investigated the effect of gamma irradiation as an alternative sterilization technique to autoclaving, on lyophilized wafers prepared from gels of guar gum, karaya gum, sodium alginate and xanthan gum, loaded with chlorhexidine digluconate [247]. They determined the rheological (flow properties) behaviour of irradiated wafers compared to non - irradiated controls as well as *in vitro* activity against Pseudomonas aeruginosa using disc diffusion test and in vitro drug dissolution studies by means of a diffusion cell set up. Their results showed a significant reduction in consistency, yield stress or efficacy for the irradiated wafers compared to the

control, with the exception of xanthan gum. This is significant as the performance of an intended drug delivery dressings is expected to remain consistent throughout formulation, sterilization, handling and application to ensure its therapeutic wound healing effect. In the case of a wound healing, any dressing or medicated dressing (delivery system) is expected to be sterile since it makes direct contact with blood capillaries and in some cases with veins and arteries with risk of direct entry of toxins or bacterial infection into the systemic circulation. Since moist heat autoclaving is not possible with most polymeric dressings, gamma radiation is one of the major sources of rendering wound management products sterile. However, gamma radiation, because of the high energy it transmits, also has the ability to degrade such polymers by interfering with the polymer chain integrity. It is therefore vital to ensure that the appropriate dose is selected that removes all microbial contamination whilst maintaining dressing structural integrity and therefore functional performance in terms of exudate absorption capacity, swelling, viscosity and eventual control of drug release.

Fibrous alginate hydrogel dressings loaded with tetracycline as an anti-bacterial drug have been prepared [248]. The dressings were prepared with three dimensional plotting by varying different processing conditions (parameters) including air pressure, nozzle diameter, layer increment, calcium concentration, alginate concentration and speed of the nozzle along x and y coordinates and compared with standard film controls. The dressings were then characterized for fibre size, porosity, tensile characteristics, degradation, swelling capacity, drug release, water vapour transmission rate and bacterial inhibition based on the different variables noted above. The results showed the fibres had larger fibre size, lower porosity, higher elastic modulus and tensile strength, reduced degradation and lower swelling capacity which were all significant when compared to the control samples. Further, the drug release and antibacterial activity were not significantly different from those of the control films, whilst the water vapour transmission rates were only slightly different than the commercial control dressings. They concluded that the fibrous samples absorbed fluid faster, were more flexible which allowed better conformation around the wound contours whilst also providing better sustained release of the model antibiotic drug. Composite freeze-dried wafers comprising sodium alginate and gelatin have been reported for the delivery of the antimicrobial drug silver sulphadiazine [249]. The combination of both alginate and gelatin were observed to improve functional characteristics of the dressing such as swelling, mucoadhesion and drug release, compared to those containing only one polymer [249]

Singh and Pal [250] reported on the synthesis and characterisation of Sterculia polysaccharide crosslinked polyvinylalcohol based hydrogel film dressings for prolonged delivery of an antibacterial drug. The films were characterised for tensile, mucoadhesion, permeability, blood compatibility, surface morphology, in vitro drug release and antimicrobial activity. The films absorbed between 4.80 and 6.32 gram fluid per gram of /g of gel with swelling occurring via a Case II diffusion mechanism whilst the drug release followed non-Fickian and Case II diffusion mechanisms depending on the type of poly vinyl alcohol. The polymeric films were permeable to oxygen and water vapour but not permeable to micro-organisms Further, Sterculia–PVA hydrogel wound dressing showed better blood compatibility as compared to Sterculia-PVA-AAm.

Carboxybutylchitosan and agarose based films and foam type wound dressings loaded with quercetin and thymol as anti-inflammatory and anaesthetic respectively have been prepared using supercritical solvent impregnation by means of supercritical carbon dioxide [251]. The formulations were characterised for sustained release and fluid handling characteristics. The results showed that the drug loading amounts increased at higher pressures and temperatures and showed that the relative amounts quercetin and thymol loaded can be “tuned” by changing the operational pressure-temperature conditions. They also showed that quercetin was released in a more sustained fashion owing to its higher molecular volume, lower water solubility and favoured interactions with the carboxybutylchitosan. Furthermore, the dressings exhibited ideal fluid and water vapour absorption capacities coupled with adequate water vapour transmission rates expected for an ideal [7] wound dressing.

Ribeiro and co-authors have developed hydrogel dressings combining dextran incorporating chitosan microparticles encapsulating growth factors for wound healing of skin burns using both in vitro and in vivo characterisation [252]. In their study, the dressings were characterised for morphology using scanning electron microscopy, cytotoxicity profile and degradation by-products as well as application onto burn skin wounds using an animal model. The growth factor loaded dressings showed appropriately rapid wound healing within the expected time period whilst histological analysis showed the absence of reactive or granulomatous inflammatory reaction in skin lesions. Further, the dressing components and degradation by-products were biocompatible and contributed to restoration of skin architecture.

In a recent article, Mohandas and co-workers reported on development of composite chitosan and hyaluronic acid based sponges loaded with fibrin nanoparticles incorporating

vascular endothelial growth factor to target multiple phases of wound healing for accelerated therapeutic action in diabetic wounds [253]. They characterised the dressings for porosity, swelling, biodegradation, mechanical properties and haemostatic potential of the sponges whilst release of the growth factor from the sponges were evaluated using ELISA. Further, cell viability and attachment of the composite sponges were evaluated using human dermal fibroblast cells and human umbilical vein endothelial cells and observed capillary like tube formation for the growth factor loaded dressings when compared with blank control sponges.

Apart from the above systems, other drugs delivered to wound sites using polysaccharide polymers include antioxidants [254], debriding agents [255] and peptides [256, 257]. However, a detailed and extensive evaluation is not provided here as this falls outside the scope of the current review and the reader is encouraged to consult more specific literature on these.

The main polysaccharide based wound dressings available commercially fall under three main categories; hydrocolloid (mainly carboxymethylcellulose, pectin or gelatin) dressings, alginate (sodium or calcium alginate) dressings and biomaterials (collagen/hyaluronic acid) based tissue engineered matrices and are summarised in the table below. To avoid any conflicts of interest and inadvertent product endorsements, the company names are not provided and the reader is invited to find these out if of interest. Each of these dressings can be used alone in passive wound healing or loaded with various active ingredients such as antimicrobial or debriding agents where they act as drug delivery systems. For extensive read about these products, the reader should please refer to the review by Boateng et al [7]

Table 6 Polysaccharide based commercial dressings available on the market

Hydrocolloid dressing	**Alginate dressing**	**Biomaterial dressing**
Granuflex™	Algisite® M	Alloskin
Aquacel™	Algosteril®	Biobrane®
Comfeel™	Kaltocarb®	Apligraf®
Tegasorb™	Seasorb®	Dermagraft®
	Sorbalgon®	
	Kaltostat ®	
	Sorbsan®	

8 Chemically modified polysaccharide polymers

An important strategy for improving mucoadhesive performance to enhance formulation retention time at the target absorption site and ultimate improvement is bioavailability is the use of derivatives of naturally occurring bioadhesive polymers. These include thiolated chitosan [35, 36, 37], carboxybutylchitosan [251], thiolated pectin, [258, 259] and caboxymethyl xanthan [260, 261, 262]. The reader is referred to the references provided for more in depth evaluation of the unique characteristics of these chemically modified natural polysaccharides and their use as drug delivery systems for drug delivery across the various mucosal routes as discussed above.

9. Summary conclusion

This review has covered various polysaccharides used for mucosal drug delivery as an alternative to the traditionally used oral and parenteral routes. It is apparent that polysaccharides possess most of the ideal characteristics expected for effective drug administration via mucosal membranes, including biocompatibility (safety), bioadhesion, hydration and swelling, ease of formulation, including water solubility and biodegradability. In addition, some polysaccharides such as chitosan have smart properties which allow modulation of drug release based on external stimuli, such as pH and temperature. In addition, chitosan possesses, various reactive functionalities which allow easy manipulation to produce versatile derivatives with enhanced ideal properties such as bioadhesion, controlled drug release as well as permeation enhancement. Furthermore, these polysaccharides can be formulated into a wide range of dosage forms ranging from simple solutions, swollen gels, tablets, films and patches, particulate systems and wafers (xerogels). It is also interesting to note that these various polysaccharides and the different dosage forms have been used to deliver a wide range of active pharmaceutical agents including small molecules, large macromolecules, biological agents for a variety of disease conditions that locally affect the various mucosal routes, as well as for absorption into the systemic circulation to exert the required therapeutic effect.

Other approaches such as bladder tumors and intravesical drug delivery are also an important routes of administration for polysaccharide based carriers for active molecules. However, these fall outside the scope of the current review and the reader is referred to the relevant texts which discuss these in much more detail.

With the above in mind, it is expected that more sophisticated and novel formulations for drug administration across these mucosal routes will be reported in the near to medium

term, which should ultimately result in new commercial products on the market. One such area is the delivery of recombinant and vaccine products, with the latter providing a viable option for achieving mucosal immunization. It is hoped that such systems will continue to advance and hopefully move from bench to bedside for patient use in the long term.

Conflict of interest

The authors report no conflicts of interest

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REFERENCES

[1] Panda BP, Dey NS, Rao MEB. Development of innovative orally fast disintegrating film dosage forms: A review. Int J Pharm Sci Nanotech. 2012; 5(2): 1666–74.

[2] Patel V, Desai T, Chavda B, Katira R. Extemporaneous dosage form for Oral liquids. Pharmacophore. 2011; 2(2): 86-103.

[3] Satter M, Sayed OM, Lane ME. Oral transmucosal drug delivery – Current status and future prospects. Int J Pharm. 2014; 471: 498-06.

[4] Hussain A, Ahsan F. The vagina as a route for systemic drug delivery. J Contr Rel. 2005; 103(2): 301-13.

[5] Hussain A, Majumder QH, Ahsan F. Inhaled insulin is better absorbed when administered as a dry powder compared to solution in the presence or absence of alkylglycosides. Pharm Res. 2006; 23(1): 138-47.

[6] Nargarwal RC, Kant S, Singh PN, Maiti P, Pandit JK. Polymeric nanoparticulate system: A potential approach for ocular drug delivery. J Contr Rel. 2009; 136)1): 2-13.

[7] Boateng JS, Matthews KH, Stevens HNE, Eccleston GM. Wound healing dressings and drug delivery systems: A review. J Pharm Sci. 2008; 97(8): 2892-923.

[8] Suzuki Y, Tanihara M, Nishimura Y, Suzuki K, Kakimaru Y, Shimizu Y. A new drug delivery system with controlled release of antibiotic only in the presence of infection. J Biomed Mater Res. 1998; 42(1): 112-6.

[9] Aubyn L, Boateng J. Formulation, Design and Functional Characterization of a Novel Vaginal Mucosa Drug Delivery System. Proceedings of American Association of Pharmaceutical Scientists (AAPS 2013), R6221, San Antonio, Texas, USA.

[10] Jana S, Ghandi A, Sen KK, Basu SK. Natural polymers and their application in drug delivery and biomedical field. J PharmSciTech. 2011; 1(1): 16-27.

[11] Patel V, Liu F, Brown M. Modeling the oral cavity: In vitro and in vivo evaluations of buccal drug delivery systems. J Contr Rel. 2012; 161(1): 746-56.

[12] Gupta SK, Singhvi IJ, Shirsati M, Karwani G, Agarwal A, Agarwak A. Buccal Adhesive Drug Delivery System: A Review. Asian J Biochem Pharm Res. 2011; 2(1): 105-14.

[13] Smart JD. Theories of Mucoadhesion in Khutoryanskiy VV (Ed). Mucoadhesive Materials and Drug Delivery Systems. 2014; Chapter 7 pp John Wiley and Sons Ltd, West Sussex, UK.

[14] Bobade NN, Atram SC, Wankhade VP, Pande SD, Tapar KK. A Review on Buccal Drug Delivery System. Int J Pharm Pharm Sci Res. 2013; 3(1): 35-40.

[15] Roy S, Prabhakar B. Bioadhesive Polymeric Platforms for Transmucosal Drug Delivery Systems – a Review. Trop J Pharm Res. 2010; 9(1): 91-104.

[16] Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery – a promising option for orally less efficient drugs. J Contr Rel. 2006; 114(1): 15-40.

[17] Tangri P, Khurana S, Madhav S. Muchoadhesive drug delivery: Mechanism and methods of evaluation. Int J Pharma Bio Sci. 2011; 2(1): 458-67.

[18] Junginger H, Hoogstraate J, Verhoef C. 1999. Recent advances in buccal drug delivery and absorption - in vitro and in vivo studies. J Contr Rel. 1999; 62(1-2): 149-59.

[19] Punitha S, Girish Y. 2010. Polymers in mucoadhesive buccal drug delivery system – A review. Int J Res Pharm Sci. 2010; 1(2): 170-86.

[20] Alexander A, Swarna A, Tripathi D. Polymers and Permeation Enhancers: Specialized Components of Mucoadhesives. Stamford J Pharm Sci. 2011; 4(1): 91-95.

[21] Kalani M, Yunus R. 2011. Application of supercritical antisolvent method in drug encapsulation: a review. Int J Nanomed. 2011; 6(1): 1429-42.

[22] Salamaat-Miller N, Chittchang M, Johnson T. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Del Rev. 2005; 57: 1666-91.

[23] Abruzzo A, Bigucci F, Cerchiara T, Cruciani F, Vitali B, Luppi B. Mucoadhesive chitosan/gelatin films for buccal delivery of propranolol hydrochloride. Carbo Polym, 2012; 87(1): 581-88.

[24] Rossi S, Bonferoni MC, Ferrari F, Bertoni M, Caramella C. Characterization of mucin interaction with three viscosity grades of sodium carboxymethylcellulose. Comparison between rheological and tensile testing. Eur J Pharm Sci. 1996; 4(3): 189–96.

[25] Kianfar F, Chowdhry BZ, Antonijevic M, Boateng JS. Formulation development of a carrageenan based delivery system for buccal drug delivery using ibuprofen as a model drug. J Biomater Nano Biotech. 2011; 2(5A), 582-95.

[26] Kianfar F, Antonijevic M, Chowdhry BZ, Boateng JS. Lyophilized wafers comprising κ-carrageenan & pluronic acid for buccal drug delivery using model soluble and insoluble drugs. Coll Surf B: Biointerf. 2013; 103: 99– 106.

[27] Le Brun P, Fox P, De Vries M, Bodde H. In vitro penetration of some β-adrenoreceptor blocking drugs through porcine buccal mucosa. Int J Pharm. 1989; 49(2): 141-45.

[28] Andrews G, Laverty T, Jones D. Mucoadhesive polymeric platforms for controlled drug delivery. Eur J Pharm Biopharm. 2009; 71(3): 505-18.

[29] Arya A, Chandra A, Sharma V, Pathak K. Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form. Int J ChemTech Res. 2010; 2(1): 576-83.

[30] Dojo M, Azuma T, Saito T, Ohtani M, Muramatsu A, Kuriyama M. 2001. Effects of CYP2C19 gene polymorphism on cure rates for Helicobacter pylori infection by triple therapy with proton pump inhibitor (omeprazole or rabeprazole), amoxycillin and clarithromycin in Japan. Digestive Liver Dis. 2001; 33(8): 671-75.

[31] Lehr C. 2000. lectin-mediated drug delivery: the second generation of bioadhesives. J Contr Rel. 2000; 65: 19-29.

[32] Nibha K, Pancholi S. An Overview on: Sublingual Route for Systemic Drug Delivery. Int J Res Pharm Biomed Sci. 2012; 3(2): 913-23.

[33] Jeng-Lin H. Role of proton pump inhibitors in the management of peptic ulcer bleeding. World J Gastrointest Pharmacol Ther. 2010; 1(2): 51-53.

[34] Khairnar GA, Sayyad FJ. Development of buccal drug delivery system based on mucoadhesive polymers. Int J PharmTech Res. 2010; 2(2): 719-35.

[35] Schirm, E. Tobi H, de Vries TW, Choonara I, De Jong-van den Berg LT. Lack of appropriate formulations of medicines for children in the community. Acta Paediatrica. 2003; 92(3): 1486-89.

[36] Bemkop A. Thiomers: A new generation of mucoadhesive polymers. Adv Drug Del Rev. 2005; 57(11): 1569-82.

[37] Punitha S, Girish Y. Polymers in mucoadhesive buccal drug delivery system – A review. Int J Res Pharm Sci. 2010; 1(2): 170-186.

[38] Thirawong N, Nunthanid J, Puttipipatkhachorn S, Sriamornsak P. (2007) 'Mucoadhesive properties of various pectins on gastrointestinal mucosa: An in vitro evaluation using texture analyzer', Eur J Pharm Biopharm. 2007; 67(1): 132-40.

[39] Ayensu I, Boateng JS. Development and evaluation of lyophilized thiolated-chitosan wafers for buccal delivery of protein. J Sci Tech. 2012; 32 (2): 46-55.

[40] Boateng JS, Pawar HV, Tetteh J. 2013. Polyox and carrageenan based composite film dressing containing anti-microbial and anti-inflammatory drugs for effective wound healing. Int J Pharm. 2013; 441(1-2):181-91.

[41] Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Del Rev. 2005; 57(11):1556-68.

[42] Tamburic S, Craig DQM. A comparison of different in vitro methods for measuring mucoadhesive performance. Eur J Pharm Biopharm. 1997; 44(2): 159-67.

[43] Saiano F, Pitarresi G, Cavallaro G, Licciardi M, Giammona G. (2002) Evaluation of mucoadhesive properties of alpha,beta-poly(N-hydroxyethyl)-DL-aspartamide and alpha,beta-poly(aspartylhydrazide) using ATR-FTIR spectroscopy, Polymer, 2002; 43(23): 6281-86.

[44] Jabbari E, Wisniewski N, Peppas NA. Evidence of mucoadhesion by chain interpenetration at a poly(acrylic acid)/mucin interface using ATR-FTIR spectroscopy. J Contr Rel. 1993; 26(2): 99-108.

[45] Hovgaard L, Brøndsted H. Current applications of polysaccharides in colon targeting. Crit Rev Ther Drug Carrier Syst. 1996; 13(3-4): 185-23.

[46] Liu Z, Jiao Y, Wang Y, Zhou C, Zhang Z. Polysaccharides-based nanoparticles as drug delivery systems. Adv Drug Del Rev. 2008; 60(15): 1650–62.

[47] Lai S, Wang Y, Hanes J. Mucus-penetrating nano particles for drug and gene delivery to mucosal tissues.

Adv Drug Del Rev. 2009; 61(2): 158–71.

[48] Cristescu D, Salavastru C, Voiculescu B, Niculescu C. Carmaciu R. Biologie. 1st ed. Bucuresti: Corint. 2008; pp.44-48.

[49] Martini F, Nath, J, Batrholomew E. Fundamentals of anatomy & physiology. 9th ed. San Francisco, CA: Pearson Benjamin Cummings. 2012; pp.556-74.

[50] De la Fuente M, Raviña M, Paolicelli P, Sanchez A, Seijo B, Alonso M. Chitosan-based nanostructures: a delivery platform for ocular therapeutics. Adv Drug Del Rev. 2010; 62(1): 100 - 17.

[51] Ye T, Yuan K, Zhang W, Song S, Chen F, Yang X, Wang S, Bi J, Pan W. Prodrugs incorporated into nanotechnology-based drug delivery systems for possible improvement in bioavailability of ocular drugs delivery. Asian J Pharm Sci. 2013; 8(4): 207-17.

[52] Pflugfelder S, Karpecki P, Perez V. Treatment of Blepharitis: Recent Clinical Trials. The Ocular Surf. 2014; 12(4): 273-84.

[53] Aulton M. Pharmaceutics, The science of dosage form design. 4th ed. Edinburgh: Churchill Livingstone. 2013.

[54] Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. Adv Drug Del Rev. 2005; 57: 1595– 1639.

[55] Felt O, Furrer P, Mayer JM, Plazonnet B, Buri P, Gurny R. Topical use of chitosan in ophthalmology: tolerance, assessment and evaluation of precorneal retention. Int J Pharm. 1999; 180: 185–93.

[56] Rossi S, Ferrari F, Bonferoni MC, Caramella C. Characterization of chitosan hydrochloride–mucin rheological interaction: influence of polymer concentration and polymer: mucin weight ratio. Eur J Pharm Sci. 2001; 12: 479–85.

[57] Alonso MJ, Sanchez A, The potential of chitosan in ocular drug delivery. J Pharm Pharmacol. 2003; 55: 1451– 63.

[58] Artursson P, Lindmark T, Davis SS, Illum L. Effect of chitosan on the permeability of monolayers of intestinal epithelial cells (Caco-2). Pharm Res. 1994; 11: 1358–61.

[59] Dodane V, Khan MA, Mervin JR. Effect of chitosan on epithelial permeability and structure, Int J Pharm. 1999; 182: 21– 32.

[60] Di Colo G, Zambito Y, Burgalassi S, Saettone MF. Effects of chitosan and of its N-trimethyl and N-carboxymethyl derivatives on the ocular pharmacokinetics of ofloxacin in rabbits. Proceedings 30th Int Symp Contr Rel Bioact Mater. (Glasgow), 2003.

[61] Genta I, Conti B, Prugini P, Pavanetto F, Spadaro A, Puglisi P. Bioadhesive microspheres for ophthalmic administration of acyclovir. J Pharm Pharmacol. 1997; 49: 737–42.

[62] Ferrari F, Rossi S, Bonferoni M, Caramella C, Karlsen J. Characterisation of rheological and mucoadhesive properties of three grades of chitosan hydrochloride. Farmaco1. 997; 52: 493– 97.

[63] Li J, Xu Z. Physical characterisation of a chitosan-based hydrogel delivery system. J Pharm Sci. 2002; 91: 1669–77.

[64] Donabedian DH, Martin L, Eng DJ. Compositions comprising cationic polysaccharides and cationic drugs. EP 0 888 770 A1 (1999).

[65] Hartmann V, Keipert S. Physico-chemical, in vitro and in vivo characterisation of polymers for ocular use. Pharmazie. 2000; 55: 440–43.

[66] Gurny R, Ibrahim H, Aebi A, Buri P, Wilson CG, Washington N, Edman P, Camber O. Design and evaluation of controlled release systems for the eye. J Contr Rel. 1987; 6: 367–73.

[67] Camber O, Edman P. Sodium hyaluronate as an ophthalmic vehicle: some factors governing its effect on the ocular absorption of pilocarpine. Curr Eye Res. 1989; 6: 563–67.

[68] Saettone MF, Giannaccini B, Chetoni P, Torracca MT, Monti D. Evaluation of high- and low-molecular-weight fractions of sodium hyaluronate and an ionic complex as adjuvants for topical ophthalmic vehicles containing pilocarpine. Int J Pharm. 1991; 72: 131–39.

[69] Durrani AM, Farr SJ, Kellaway IW. Influence of molecular weight and formulation pH on the precorneal clearance rate of hyaluronic acid in the rabbit eye. Int J Pham. 1995; 118: 243–50.

[70] Bucolo C, Spadaro A, Mangiafico S. Pharmacological evaluation of a new timolol/pilocarpine formulation. Ophthalm Res. 1998; 30: 101–8.

[71] Herrero-Vanrell R, Fernandez-Carballido A, Frutos G, Cadorniga R. Enhancement of the mydriatic response to tropicamide by bioadhesive polymers. J Ocul Pharmacol Ther. 2000; 16: 419–28.

[72] Camber O, Lundgren P. Diffusion of some low molecular weight compounds in sodium hyaluronate. Acta Pharm Suec. 1985; 22: 315–20.

[73] Kyyro¨nen K, Hume L, Benedetti L, Urtti A, Topp E, Stella V. Methylprednisolone esters of hyaluronic acid in ophthalmic drug delivery: in vitro and in vivo release. Int J. Pharm. 1992; 80: 161–69.

[74] Greaves JL, Wilson CG. Treatment of diseases of the eye with mucoadhesive delivery systems. Adv. Drug Deliv Rev. 1993; 11: 349–83.

[75] Sintzel MB, Bernatchez SF, Tabatabay C, Gurny R. Biomaterials in ophthalmic drug delivery. Eur J Pharm Biopharm. 1996; 42: 358–74.

[76] Madsen F, Eberth K, Smart JD. A rheological examination of the mucoadhesive/mucus interaction: the effect of mucoadhesive type and concentration. J Control Rel. 1998; 50: 167–78.

[77] Meseguer G, Gurny R, Buri P, Rozier A, Plazonnet B. Gamma scintigraphic study of precorneal drainage and assessment of miotic response in rabbits of various ophthalmic formulations containing pilocarpine. Int J Pharm. 1993; 95: 229–34.

[78] Burgalassi S, Chetoni P, Saettone MF. Hydrogels for ocular delivery of pilocarpine: preliminary evaluation in rabbits of the influence of viscosity and of drug solubility. Eur J Pharm. 1996; 42: 385–92.

[79] Saettone MF, Monti D, Torracca MT, Chetoni P. Mucoadhesive ophthalmic vehicles: evaluation of polymeric lowviscosity formulations. J Ocul Pharmacol 1994; 10: 83–92.

[80] Burgalassi S, Panichi P, Chetoni P, Saettone MF, Boldrini E. Development of a simple dry eye model in the albino rabbit and evaluation of some tear substitutes. Ophthalm. Res. 1999; 31: 229–35.

[81] Albasini M, Ludwig A. Evaluation of polysaccharides intended for ophthalmic use in ocular dosage forms. Farmaco. 1995; 50: 633–42.

[82] D'Amico M, Di Filippo C, Lampa E, Boldrini E, Rossi F, Ruggiero A, Filippelli A. Effects of timolol and timolol with tamarind seed polysaccharide on intraocular pressure in rabbits. Pharm Pharmacol Commun. 1999; 5: 361–64.

[83] Verschueren E, Van Santvliet L, Ludwig A. Evaluation of various carrageenans as ophthalmic viscolysers. S.T.P. Pharma Sci. 1996; 6: 203–10.

[84] Saettone MF, Monti D, Giannaccini B, Salminen L, Huupponen R. Macromolecular ionic complexes of cyclopentolate for topical ocular administration. Preparation and preliminary evaluation in albino rabbits. S.T.P. Pharma Sci. 1992; 2: 68–75.

[85] Burgalassi S, Chetoni P, Panichi L, Boldrini E, Saettone MF. Xyloglucan as a novel vehicle for timolol: pharmacokinetics and pressure lowering activity in rabbits. J Ocul Pharmacol Ther. 2000; 16: 497–509.

[86] Giannavola C, Bucolo C, Maltese A, Paolino D, Vandelli MA, Puglisi G, Lee VHL, Fresta M. Influence of preparations on acyclovir-loaded poly-d,l-lactic acid nanospheres and effect of PEG coating on ocular drug bioavailability. Pharm Res 2003; 20: 584–90.

[87] Giunchedi, Conte U, Chetoni P, Saettone MF. Pectin microspheres as ophthalmic carriers for piroxicam: evaluation in vitro and in vivo in albino rabbits. Eur J Pharm Sci. 1999; 9: 1–7.

[88] Liu Z, Li J, Nie S, Liu H, Ding P, Pan W. Study of an alginate/HPMC-based in situ gelling ophthalmic delivery system for gatifloxacin. Int J Pharm. 2006; 315(5): P12-7.

[89] Pygall SR, Kujawinski S, Timmins P, Melia CD. The suitability of tris(hydroxylmethyl) aminomethane (THAM) as a buffering system for hydroxypropyl methylcellulose (HPMC) hydrophilic matrices containing a weak acid drug. Int J Pharm. 2010; 387(5): P93-102.

[90] Gupta S, Songara R and Lokwani P. Ocular inserts: An overview. Int J Pharm Res Dev. 2011; 3(6): 141-48.

[91] Kumari A, Sharma P, Garg V, Garg G. Ocular inserts - Advancement in therapy of eye diseases. J Adv Pharm Tech Res. 2010; 1(3): 291.

[92] Jain D, Carvalho E, Banerjee R. Biodegradable hybrid polymeric membranes for ocular drug delivery. Acta Biomater. 2010; 6(4): 1370-79.

[93] Luo Q, Zhao J, Zhang X, Pan W. Nanostructured lipid carrier (NLC) coated with Chitosan Oligosaccharides and its potential use in ocular drug delivery system. Int J Pharm. 2011; 403(2): 185–91.

[94] Li N, Zhuang C, Wang M, Sun X, Nie S, Pan W. Liposome coated with low molecular weight chitosan and its potential use in ocular drug delivery. Int J Pharm. 2009; 379(1): 131–38.

[95] Xu X, Weng Y, Xu L, Chen H. Sustained release of avastin® from polysaccharides cross-linked hydrogels for ocular drug delivery. Int J Biol Macromol. 2013; 60: 272– 76.

[96] Rupenthal ID, Green CR, Alany RG. Comparison of ion-activated in situ gelling systems for ocular drug delivery. Part 1: physicochemical characterisation and in vitro release. Int J Pharm. 2011; 411(1): 69-77.

[97] Mahajan HS, Deshmukh SR. Development and evaluation of gel-forming ocular films based on xyloglucan. Carbo Polym. 2015; 122: 243–47.

[98] Miyazaki S, Suzuki S, Kawasaki N, Endo K, Takahashi A, Attwood D. In situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. Int J Pharm. 2001; 229(2): 29–36.

[99] Kurosaki Y, Takatori T, Nishimura H, Nakayama T, Kimura T. Regional variation in oral mucosal drug absorption permeability and degree of keratinization in hamster oral cavity. Pharm Res. 1991; 8: 1297-1301.

[100] Narang N, Sharma J. Sublingual mucosa as a route for systemic drug delivery. Int J Pharm Pharm Sci. 2011; 3(2): 18-22.

[101] Ghosh TK, Chatterjee DJ, Pfister WR. Quick dissolving oral dosage forms: Scientific and regulatory considerations from a clinical pharmacology and biopharmaceutical perspective. In: Ghosh TK and Pfister WR (Eds). Drug Delivery to the Oral Cavity Molecules to Market. NY, USA: CRC Press. 2005: 337-356.

[102] Verma N, Chattopadhyay. Polymeric platform for mucoadhesive buccal drug delivery system: A Review. Int J Curr Pharm Res. 2011; 3(3): 3-8.

[103] Aggrawal J, Gurpeet S, Saini S, Rana A. Fast dissolving films: A novel Approach to oral drug delivery. International Research Journal of Pharmacy. 2011; 2(12): 69-74.

[104] Shojaie AH. Buccal mucosa as a route for systemic drug delivery: A review. J Pharm Pharm Sci 1998; 1(1): 15-30.

[105] Chul J, Tordoff J, Kennedy J. Relth D. Trends in accessibility to medicines for children in New Zealand: 1998–2002. Brit J Clin Pharmacol. 2004; 57(3): 322-27.

[106] Liu F, Ranmal S, Batchelor HK, Orlu-Gul M, Ernest TB, Thomas IW, Flanagan T, Tuleu C. Patient-Centred Pharmaceutical Design to Improve Acceptability of Medicines: Similarities and Differences in Paediatric and Geriatric Populations. Drugs. 2014; 74(16): 1871–89.

[107] Boateng JS, Stevens HN, Eccleston GM, Auffret AD, Humphrey MJ, Matthews KH. Development and mechanical characterization of solvent-cast polymeric films as potential drug delivery systems to mucosal surfaces. Drug Dev Ind Pharm. 2009; 35(8): 986-96.

[108] Senel S, Ikinci G, Kas S, Yousefi-Rad A, Hincal A. Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery. Int J Pharm. 2000; 193: 197–203.

[109] Reddy PC, Chaitanya KSC, Rao YM., A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. Daru J Pharm Sci. 2011; 19(6): 385-403.

[110] Neelagiri R, Reddy M, Rao N. Buccal patch as drug delivery system: An overview. Int J Curr Pharm Res. 2013; 5(2): 40-7.

[111] Caon T, Jin L, Simões CMO, Norton RS, Nicolazzo JA. Enhancing the Buccal Mucosal Delivery of Peptide and Protein Therapeutics. Pharm Res. 2014; 32(1): 1485-91.

[112] Peppas NA, Buri PA. Surface interfacial and molecular aspects of polymer bioadhesion on soft tissues. J Contr Rel. 1985; 2: 257-76.

[113] Boddupalli BM, Mohammed ZNK, Nath RA, Banji D. Mucoadhesive drug delivery system: An overview. J Adv Pharm Technol Res. 2010; 1(4):381-7.

[114] Wagh MP, Joshi OU, Patel JS, Jain VR. Thiomers: A new generation of Mucoadhesive Polymers. Res J Pharm Tech. 2009; 2(2): 250-5.

[115] Prabaharan M, Gong S. Novel thiolated carboxymethyl chitosan-g-β-cyclodextrin as mucoadhesive hydrophobic drug delivery carriers. Carb Polym. 2008; 73: 117–25.

[116] Jug M, Becirevic-Lacan M, Bengez S. Novel cyclodextrin-based film formulation intended for buccal delivery of atenolol. Drug Dev Ind Pharm. 2009; 35: 796-807.

[117] Mizrahi B, Domb AJ. Mucoadhesive polymers for delivery of drugs to the oral cavity. Recent Pat Drug Del Formul. 2008; 2(2): 108-19.

[118] Chopra S, Mahdi S, Kaur J, Iqbal Z, Talegaonkar S, Ahmad FJ. Advances and potential applications of chitosan derivatives as mucoadhesive biomaterials in modern drug delivery. J Pharm Pharmacol. 2006;

58(8): 1021-32.

[119] Zeng N, Dumortier G, Maury M, Mignet N, Boudy V. Influence of additives on a thermosensitive hydrogel for buccal delivery of salbutamol: Relation between micellization, gelation, mechanic and release properties. Int J Pharm. 2014; 467(2): 70-83.

[120] Martin L, Wilson CG, Koosha F, Uchegbu IF. Sustained buccal delivery of the hydrophobic drug denbufylline using physically cross-linked palmitoyl glycol chitosan hydrogels. Eur J Pharm Biopharm. 2003; 55(1): 35–45.

[121] Martín MJ, Calpena AC, Fernández F, Mallandrich M, Gálvez P, Clares B. Development of alginate microspheres as nystatin carriers for oral mucosa drug delivery. Carb Polym. 2015; 117: 140–49.

[122] Kassem MAA, ElMeshad AN, Fares AR. Enhanced bioavailability of buspirone hydrochloride via cup and core buccal tablets: Formulation and in vitro / in vivo evaluation. Int J Pharm. 2014; 463(1): 68–80.

[123] Jawahar KN, Wake P, Jain K, Sood S. Development of buccal tablets for curcumin using ANACARDIUM OCCIDENTALE gum. Carb Polym. 2012; 88(4): 1177–83.

[124] Ameye D, Mus D, Foreman P, Remon JP. Spray-dried Amioca starch/Carbopol 974P mixtures as buccal bioadhesive carriers. Int J Pharm. 2005; 301(1-2): 170-80.

[125] Alur HH, Pather SI, Mitra AK, Johnston TP. Transmucosal sustained-delivery of chlorpheniramine maleate in rabbits using a novel, natural mucoadhesive gum as an excipient in buccal tablets. Int J Pharm. 1999; 188(1): 1-10.

[126] Kianfar F, Chowdhry BZ, Antonijevic MD, Boateng JS. Novel films for drug delivery via the buccal mucosa using model soluble and insoluble drugs. Drug Dev Ind Pharm. 2012; 38(10): 1207-20.

[127] Avachat AM, Gujar KN, Wagh KV. Development and evaluation of tamarind seed xyloglucan-based mucoadhesive buccal films of rizatriptan benzoate. Carbo Polym. 2013; 91(2): 537–42.

[128] Giovino C, Ayensu I, Tetteh J, Boateng JS. Development and characterisation of chitosan films impregnated with insulin loaded PEG-b-PLA nanoparticles (NPs): a potential approach for buccal delivery of macromolecules. Int J Pharm. 2012; 428(1-2): 143-51.

[129] Giovino C, Ayensu I, Tetteh J, Boateng J. An integrated buccal delivery system combining chitosan films impregnated with peptide loaded PEG-b-PLA nanoparticles. Coll Surf B: Biointerf. 2013; 112: 9-15.

[130] Khan S, Boateng J, Trivedi V, Mitchell J. Formulation, Characterisation and Stabilisation of Buccal Films for Paediatric Drug Delivery of Omeprazole. AAPS PharmTech. 2015; DOI: 10.1208/s12249-014-0268-7.

[131] Pongjanyakul T, Suksri H. Alginate-magnesium aluminum silicate films for buccal delivery of nicotine. Coll Surf B: Biointerf. 2009; 74(1): 103–13.

[132] Shiledar RR, Tagalpallewar AA, Kokare CR. Formulation and in vitro evaluation of xanthan gum-based bilayered mucoadhesive buccal patches of zolmitriptan. Carb Polym. 2014; 101: 1234-42.

[133] Kaur G, Singh D, Brar V. Bioadhesive okra polymer based buccal patches as platform for controlled drug delivery. Int J Biol Macromol. 2014; 70: 408–19.

[134] Xu J, Strandman S, Zhu JXX, Barralet J, Cerruti M. Genipin-crosslinked catechol-chitosan mucoadhesive hydrogels for buccal drug delivery. Biomater. 2015; 37: 395–404.

[135] Boateng J, Ayensu I. Preparation and characterisation of laminated thiolated chitosan-based freeze-dried wafers for potential buccal delivery of macromolecules. Drug Dev Ind Pharm. 2014; 40(5): 611-18.

[136] Ayensu I, Mitchell JC, Boateng JS. Development and physico-mechanical characterisation of lyophilised chitosan wafers as potential protein drug delivery systems via the buccal mucosa. Coll Surf B. Biointerf. 2012; 91: 258–265.

[137] Ayensu I, Mitchell JC, Boateng JS. Effect of membrane dialysis on characteristics of lyophilised chitosan wafers for potential buccal delivery of proteins. Int J Biol Macromol. 2012; 50: 905-09.

[138] Ayensu I, Mitchell JC, Boateng JS. In-vitro characterisation of thiolated chitosan based lyophilized formulations for buccal mucosa delivery of proteins. Carbo Polym. 2012; 89: 935-41.

[139] Boateng J, Areago D. Composite sodium alginate and chitosan based wafers for buccal delivery of macromolecules. Austin J Anal Pharm Chem. 2014; 1(5): 1022.

[140] Ahuja M, Kumar S, Kumar A. Evaluation of mucoadhesive potential of gum cordia, an anionic polysaccharide. Int J Biol Macromol. 2013; 55: 109–12.

[141] Boateng J, Mitchell J, Pawar H, Ayensu I. Functional characterisation and permeation studies of lyophilized thiolated chitosan xerogels for buccal delivery of insulin. Pept Prot Lett. 2014; 21(11): 1163-75.

[142] Chang SF, Chien YW. Intranasal drug administration for systemic medication. Pharm Int. 1984; 5(12): 287-8.

[143] Illum L. Nasal drug delivery—possibilities, problems and solutions. J Contr Rel. 2003; 87(1–3): 187-98.

[144] Patel RS, McGarry GW. Most patients overdose on topical nasal corticosteroid drops: An accurate delivery device is required. J Laryngol Otol. 2001; 115(8): 633-35.

[145] Soane RJ, Frier M, Perkins AC, Jones NS, Davis SS, Illum L. Evaluation of the clearance characteristics of bioadhesive systems in humans. Int J Pharm. 1999; 178(1): 55-65.

[146] Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery, Drug Discov Today. 2002a; 7(18): 967-75.

[147] Türker S, Onur E, Ózer Y. Nasal route and drug delivery systems. Pharm World Sci. 2004; 26(3): 137-42.

[148] Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drug Discov Today. 2002b; 7(18): 967-75.

[149] Kublik H, Vidgren MT. Nasal delivery systems and their effect on deposition and absorption. Adv Drug Del Rev. 1998; 29(1–2): 157-77.

[150] Watts P, Smith A, Perelman M. Nasal delivery of fentanyl. Drug Del Trans Res. 2013; 3(1): 75-83.

[151] Cho HJ, Balakrishnan P, Park EK, Song KW, Hong SS, Jang TY, Kim KS, Chung SK, Shim CK, Kim DD. Poloxamer/cyclodextrin/chitosan-based thermoreversible gel for intranasal delivery of fexofenadine hydrochloride. J Pharm Sci. 2011; 100(2): 381-91.

[152] Liu Z, Jiao Y, Wang Y, Zhou C, Zhang Z. Polysaccharides-based nanoparticles as drug delivery systems. Adv Drug Del Rev. 2008; 60(15): 1650-62.

[153] Jahantigh D, Saadati M, Ramandi MF, Mousavi M, Zand AM. Novel Intranasal Vaccine Delivery System by Chitosan Nanofibrous Membrane Containing N-Terminal Region of Ipad Antigen as a Nasal Shigellosis Vaccine, Studies in Guinea Pigs. J Drug Del Sci Tech. 2014; 24(1): 33–9.

[154] Jain AK, Khar RK, Ahmed FJ, Diwan PV. Effective insulin delivery using starch nanoparticles as a potential trans-nasal mucoadhesive carrier. Eur J Pharm Biopharm. 2008; 69(2): 426–35.

[155] Dionísio M, Cordeiro C, Remuñán-López C, Seijo B, Rosa da Costa AM, Grenha A. Pullulan-based nanoparticles as carriers for transmucosal protein delivery. Eur J Pharm Sci. 2013; 50(1): 102–13.

[156] Read RC, Naylor SC, Potter CW, Bond J, Jabbal-Gill I, Fisher A, Illum L, Jennings R. Effective nasal influenza vaccine delivery using chitosan. Vaccine. 2005; 23(35): 4367-74.

[157] Patil S, Babbar A, Mathur R, Mishra A, Sawant K. Mucoadhesive chitosan microspheres of carvedilol for nasal administration. J Drug Target. 2010; 18(4): 321-31.

[158] Nazar H, Caliceti P, Carpenter B, El-Mallah AI, Fatouros DG, Roldo M, van der Merwe SM, Tsibouklis J. A once-a-day dosage form for the delivery of insulin through the nasal route: in vitro assessment and in vivo evaluation. Biomater Sci. 2013; 1(3): 306-14.

[159] Shahnaz G, Vetter A, Barthelmes J, Rahmat D, Laffleur F, Iqbal J, Perera G, Schlocker W, Dünnhaput S, Augustijns P. Thiolated chitosan nanoparticles for the nasal administration of leuprolide: bioavailability and pharmacokinetic characterization. Int J Pharm. 2012; 428(1): 164-170.

[160] Patil SB, Kaul A, Babbar A, Mathur R, Mishra A, Sawant KK. In vivo evaluation of alginate microspheres of carvedilol for nasal delivery. J Biomed Mater Res Part B: Appl Biomater. 2012; 100B (1): 249-55.

[161] Basu S, Maity S. Preparation and characterisation of mucoadhesive nasal gel of venlafaxine hydrochloride for treatment of anxiety disorders. Indian J Pharm Sci. 2012; 74(5): 428.

[162] Mahajan HS, Tatiya BV, Nerkar PP. Ondansetron loaded pectin based microspheres for nasal administration: In vitro and in vivo studies. Powder Tech. 2012; 221: 168-76.

[163] Saladini B, Bigucci F, Cerchiara T, Gallucci MC, Luppi B. Microparticles based on chitosan/pectin polyelectrolyte complexes for nasal delivery of tacrine hydrochloride. Drug Del Trans Res. 2013; 3(1): 33-41.

[164] Verheul RJ, Slütter B, Bal SM, Bouwstra JA, Jiskoot W, Hennink WE. Covalently stabilized trimethyl chitosan-hyaluronic acid nanoparticles for nasal and intradermal vaccination. J Contr Rel. 2011; 156(1): 46-52.

[165] http://www.vivo.colostate.edu/hbooks/pathphys/digestion/stomach/gibarrier.html- Accessed 1 March 2015.

[166] Singh D, Sharma PK, Sara UVS. Development, optimization and evaluation of solid dosage form of Thiocolchicoside by using absorption enhancers. Der Pharmacia Lettre. 2013; 5(3): 405-14.

[167] Guggi D, Krauland AH, Schnurch AB. Systemic peptide delivery via the stomach: in vivo evaluation of an oral dosage form for salmon calcitonin. J Contr Rel. 2003; 92: 125–35.

[168] Pawar VK, Meher JG, Singh Y, Chaurasia M, Reddy BS, Chourasia MK. Targeting of gastrointestinal tract for amended delivery of protein/peptide therapeutics: Strategies and industrial perspectives. J Contr Rel. 2014; 168–83.

[169] de Arce Velasquez A, Ferreira LM, Stangarlin MFL, de Bona da Silva C, Rolim CMB, Cruz L. Novel Pullulan–Eudragit® S100 blend microparticles for oral delivery of risedronate: Formulation, in vitro evaluation and tableting of blend microparticles. Mater Sci Eng: C. 2014; 38: 212–17.

[170] Sinha VR, Kumria R. Microbially triggered drug delivery to the colon. Eur J Pharm Sci. 2003; 18(1): 3–18.

[171] Tozaki H, Komoike J, Tada C, Maruyama T, Terabe A, Suzuki T, Wakerly Z,. An investigation into citrus pectins for colonic drug specific drug delivery: Improvement of insulin absorption from the rat Wakerly, Z., Fell, J.T., Attwood, D., Parkins, D., 1996. Pectin / ethylcellulcolon. J Pharm Sci. 1995; 86: 1016–21.

[172] Tozaki H, Fujita T, Odoriba T, Terabe A, Suzuki T, Tanaka C, Okabe S, Shoo Muranishi S, Yamamoto A. Colon specific delivery of R68070, a new thromboxane synthase inhibitor, using chitosan capsules: Therapeutic effects against 2,4,6-trinitrobenzene sulfonic acid-induced ulcerative colitis in rats. Life Sci. 1999a; 64: 1155–62.

[173] Lorenzo-Lamosa ML, Remunan-Lopez C, Vila-Jato JL, Alonson MJ. Design of microencapsulated chitosan microspheres for colonic drug delivery. J Contr Rel. 1998; 52: 109–18.

[174] Tominaga S, Takaizawa T, Yamada M. Colon drug delivery system. J Pol Appl. 1998; 10: 642.

[175] Aiedeh K, Taha MO. Synthesis of chitosan succinate and chitosan phthalate and their evaluation as suggested matrices in orally administered, colon specific drug delivery system. Arch. Pharm (Weinheim). 1999; 332: 103–7.

[176] Rubinstein A, Radai R, Ezra M, Pathak S, Rokem JS. In vitro evaluation of calcium pectinate: A potential colon-specific drug delivery carrier. Pharm Res. 1993; 10: 258–63.

[177] Rubinstein A, Radai R. In vitro and in vivo analysis of colon specificity of calcium pectinate formulations. Eur J Pharm Biopharm. 1995; 41: 291–95.

[178] Adkin AD, Kenyon CJ, Lerner EI, Landau I, Strauss E, Caron D, Penhasi A, Rubinstein A, Wilding IR. The use of scintigraphy to provide ‘proof of concept’ for novel polysaccharide preparation designed for colonic drug delivery. Pharm Res 1997; 14: 103–7.

[179] Ashford M, Fell JT, Attwood D, Sharma HL, Woodhead PJ. Studies on pectin formulation for colonic drug delivery. J Control Rel. 1994; 30: 225–32.

[180] Wakerly Z, Fell J, Attwood D, Parkins D. Studies on amidated pectins as potential carriers in colonic drug delivery. J Pharm Pharmacol. 1997; 49: 622–25.

[181] Munjeri O, Collett JH, Fell JT. Hydrogel beads based on amidated pectins for colon-specific drug delivery: the role of chitosan in modifying drug release. J Control Rel. 1997; 46: 273–78.

[182] Ahrabi SF, Madsen G, Dyrstad K, Sande SA, Graffner C. Development of pectin matrix tablets for colonic delivery of model drug ropivacaine. Eur J Pharm Sci 2000; 10: 43–52.

[183] Wakerly Z, Fell JT, Attwood D, Parkins D. Pectin / ethylcelluose film coating formulations for colonic drug delivery. Pharm Res. 1996; 13: 1210–12.

[184] Semde R, Amighi K, Devleeschouwe MJ, Moes AJ. Effect of pectinolytic enzymes on the theophylline release from pellets coated with water insoluble polymers containing pectin HM or calcium pectinate. Int J Pharm. 2000a; 197: 169–79.

[185] Semde R, Amighi K, Devleeschouwe MJ, Moes AJ. Studies of pectin HM/Eudragit RL/Eudragit NE film coating formulations intended for colonic drug delivery. Int J Pharm. 2000b; 197: 181–92.

[186] MacLeod GS, Fell JT, Collett JH, Sharma HL, Smith AM. Selective drug delivery to the colon using pectin:chitosan:hydroxypropyl methylcellulose film coated tablets. Int J Pharm. 1999a; 187: 251–57.

[187] MacLeod GS, Fell JT, Collett JH. An in vitro investigation into the potential for biomodal drug release from pectin / chitosan HPMC-coated tablets. Int J Pharm. 1999b; 188: 11–8.

[188] Fernandez-Hervas MJ, Fell JT. Pectin / chitosan mixtures as coatings for colon-specific drug delivery: an in vitro evaluation. Int J Pharm. 1998; 169: 115–19.

[189] Wong D, Larrabeo S, Clifford K, Tremblay J, Friend DR. USP dissolution apparatus III (reciprocating cylinder) for screening of guar-based colonic delivery formulation. J Contr. Rel. 1997; 47: 173–79.

[190] Kenyon CJ, Nardi RV, Wong D, Hooper G, Wilding IR, Friend DR. Colonic delivery of dexamethasone: a pharmacoscintig- raphic evaluation. Aliment Pharmacol Ther. 1997; 11: 205–13.

[191] Rama Prasad YV, Krishnaiah YS, Satyanarayana S. In vitro evaluation of guar gum as a carrier for colon-specific drug delivery. J Contr. Rel. 1998; 51: 281–87.

[192] Krishnaiah YSR, Satyanarayana S, Rama Prasad YV, Narasimha Rao S. Gamma scintigraphic studies on guar gum matrix tablets for colonic drug delivery in healthy human volunteers. J Contr Rel. 1998; 55: 245–52.

[193] Krishnaiah YSR, Satyanaryana S, Rama Prasad YV. Studies of guar gum compression-coated 5-aminosalicylic acid tablets for colon- specific drug delivery. Drug Dev Ind Pharm. 1999; 25: 651–57.

[194] Rubinstein A, Gliko-Kabir I. Synthesis and swelling dependent enzymatic degradation of borax modified guar gum for colonic delivery purpose. STP Pharm Sci. 1995a; 5: 41–6.

[195] Gliko-Kabir I, Yagen B, Baluom M, Rubinstein A. Phosphated cross-linked guar for colon-specific drug delivery. II. In vitro and in vivo evaluation in the rat. J Contr Rel 2000; 63: 129–34.

[196] Brondsted H, Hovgaard L, Simonsen L. Dextran hydrogels for colon specific drug delivery. III. In vitro and in vivo degradation. STP Pharm. 1995a; 5: 60–4.

[197] Chiu HC, Hsiue GH, Lee YP, Huang LW. Synthesis and characterization of pH-sensitive dextran hydrogels as a potential colon-specific drug delivery system. J Biomater Sci Polym. 1999; 10: 591–608.

[198] Brondsted H, Andersen C, Hovgaard L. Cross linked dextran-a new capsule material for colon targeting of drug. J Contr Rel. 1998; 53: 7–13.

[199] Hirsch S, Binder V, Kolter K, Kesselhut JF, Bauer KH. Lauroyldextran as a coating material for site-specific drug delivery to pectinthe colon: in vitro dissolution of coated tablets. Proc Int Symp Contr Rel Bioact Mater 1997; 24: 379–80.

[200] Vervoort L, Kinget R. In vitro degradation by colonic bacteria of inulin HP incorporated in Eudragit films. Int J Pharm. 1996; 129: 185–90.

[201] Vervoort L, Rambant P, Van den Mooter G, Augustijns P, Kinget R. Inulin hydrogels. II. In vitro degradation study. Int J Pharm. 1998; 172: 137–45.

[202] Rubinstein A, Nakar D, Sintov A. Chondroitin sulphate: A potential biodegradable carrier for colon-specific drug delivery. Int J Pharm. 1992a; 84: 141–50.

[203] Milojevic S, Newton JM, Cummings JH, Gibson GR, Botham RL, Ring SG, Stockham M, Allwood MC. Amylose as a coating for drug delivery to the colon: Preparation and in vitro evaluation using 5-aminosalicylic acid pellets. J Contr Rel 1996a; 38: 75–84.

[204] Cummings JH, Milojevic S, Harding M, Coward WA, Gibson GR, Botham RL, Ring SG, Wraight EP, Stockham MA, Alwood MC, Newton JM. In vivo studies of amylose- and ethylcel- lulose-coated [13C] glucose microspheres as a model for drug delivery to the colon. J Contr Rel. 1996; 40: 123–31.

[205] Siew LF, Basit AW, Newton JM. The properties of amylose-ethylcellulose films cast from organic based solvents as potential coatings for colonic drug delivery. Eur J Pharm Sci. 2000a; 11: 133–39.

[206] Vilivalam VD, Illum L, Iqbal K. Starch capsules: an alternative system for oral drug delivery. Pharm Sci Technol. Today 2000; 3: 64–9.

[207] Shun YL, Ayres JW. Calcium alginate beads as core carriers of 5-aminosalicylic acid. Pharm Res. 1992; 9: 1128-31.

[208] Bauer KH, Kesselhut JF. Novel pharmaceutical excipients for colon targeting. STP Pharm Sci. 1995; 5: 54–9.

[209] Singh B, Bala R. Polysaccharide based hydrogels as controlled drug delivery system for GIT cancer. Int J Biol Macromol. 2014; 65: 524–33.

[210] Feng C, Li J, Kong M, Liu Y, Cheng XJ, Li Y, Park HJ, Chen XG. Surface charge effect on mucoadhesion of chitosan based nanogels for local anti-colorectal cancer drug delivery. Coll Surf B: Biointerf. 2015; (In Press).

[211] Kulkarni RV, Boppana R, Mohan GK, Mutalik S, Kalyane NV. pH-responsive interpenetrating network hydrogel beads of poly(acrylamide)-G-carrageenan and sodium alginate for intestinal targeted drug delivery: Synthesis, in vitro and in vivo evaluation. J Coll Interf Sci. 2012; 367(1): 509–17.

[212] Prezotti FG, Cury BSF, Evangelista RC. Mucoadhesive beads of gellan gum/pectin intended to controlled delivery of drugs. Carbo Polym. 2014; 113: 286–95.

[213] Hussain A, Ahsan F. The vagina as a route for systemic drug delivery. J Contr Rel. 2005; 103(2): 301-13.

[214] das Neves J, Bahia MF. Gels as vaginal drug delivery systems. Int J Pharm. 2006; 318(1–2): 1-14.

[215] de Araújo Pereira RR, Bruschi ML. Vaginal mucoadhesive drug delivery systems. Drug Dev Ind Pharm. 2012; 38(6): 643-52.

[216] Vermani K, Garg S. The scope and potential of vaginal drug delivery. Pharm Sci Tech Today. 2000; 3(10): 359-64.

[217] Machado RM, Palmeira-De-Oliveira A, Martinez-De-Oliveira J, Palmeira-De-Oliveira R. Vaginal films for drug delivery. J Pharm Sci. 2013; 102(7): 2069-81.

[218] Nowak J, Laffleur F, Bernkop-Schnürch A. Preactivated hyaluronic acid: A potential mucoadhesive polymer for vaginal drug delivery. Int J Pharm. 2014; 478(1): 383-89.

[219] Bigucci F, Abruzzo A, Vitali B, Saladini B, Cerchiara, T, Gallucci MC Luppi B. Vaginal inserts based on chitosan and carboxymethylcellulose complexes for local delivery of chlorhexidine: Preparation, characterization and antimicrobial activity, Int J Pharm. 2015; 478(2): 456-63.

[220] Parodi B, Russo E, Caviglioli G, Baldassari S, Gaglianone N, Schito AM, Cafaggi S. A chitosan lactate/poloxamer 407-based matrix containing Eudragit RS microparticles for vaginal delivery of econazole: Design and in vitro evaluation. Drug Dev Ind Pharm. 2013; 39(12): 1911-20.

[221] Frank LA, Sandri G, D'Autilia F, Contri RV, Bonferoni MC, Caramella C, Frank AG, Pohlmann AR Guterres SS. Chitosan gel containing polymeric nanocapsules: a new formulation for vaginal drug delivery. Int J Nanomed. 2014; 9: 3151.

[222] Berginc K, Suljaković S, Škalko-Basnet N, Kristl A. Mucoadhesive liposomes as new formulation for vaginal delivery of curcumin. Eur J Pharm Biopharm. 2014; 87(1): 40-6.

[223] Meng J, Sturgis TF, Youan BBC. Engineering tenofovir loaded chitosan nanoparticles to maximize microbicide mucoadhesion. Eur J Pharm Sci. 2011; 44(1–2): 57-67.

[224] Abruzzo A, Bigucci F, Cerchiara T, Saladini B, Gallucci MC, Cruciani F, Vitali B, Luppi B. Chitosan/alginate complexes for vaginal delivery of chlorhexidine digluconate. Carbo Polym. 2013; 91(2): 651-58.

[225] Martín-Villena MJ, Fernández-Campos F, Calpena-Campmany AC, Bozal-de Febrer N, Ruiz-Martínez MA, Clares-Naveros B. Novel microparticulate systems for the vaginal delivery of nystatin: Development and characterization. Carbo Polym. 2013; 94(1): 1-11.

[226] Wu SY, Chang HI, Burgess M, McMillan NAJ. Vaginal delivery of siRNA using a novel PEGylated lipoplex-entrapped alginate scaffold system. J Contr Rel. 2011; 155(3): 418-26.

[227] Baloğlu E, Özyazıcı M, Hızarcıoğlu SY, Şenyiğit T, Özyurt D, Pekçetin C. Bioadhesive controlled release systems of ornidazole for vaginal delivery. Pharm Dev Tech. 2006; 11(4): 477-84.

[228] Liu SB, Liu SL, Gan XL, Zhou Q, Hu LN. The effects of hyaluronic acid vaginal gel on the vaginal epithelium of ovariectomized rats. Gynecol Endocrinol. 2014; (0): 1-6.

[229] Ekin M, Yaşar L, Savan K, Temur M, Uhri M, Gencer I, Kıvanç E. The comparison of hyaluronic acid vaginal tablets with estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. Archives Gynecol Obstet. 2011; 283(3): 539-43.

[230] Belletti D, Tosi G, Forni F, Gamberini MC, Baraldi C, Vandelli MA Ruozi B. Chemico-physical investigation of tenofovir loaded polymeric nanoparticles. Int J Pharm. 2012; 436(1-2): 753-63.

[231] Sobel JD. Genital candidiasis, Medicine. 2005; 33(10): 62-5.

[232] Donders GGG, Bellen G, Rezeberga D. Aerobic vaginitis in pregnancy. BJOG: An Int J Obstet Gynaecol. 2011; 118(10): 1163-70.

[233] Das Neves J, Pinto E, Teixeira B, Dias G, Rocha P, Cunha T, Santos B, Amaral MH, Bahia MF. Local treatment of vulvovaginal candidosis: General and practical considerations. Drugs. 2008; 68(13): 1787-802.

[234] Yang S, Chen Y, Ahmadie R, Ho EA. Advancements in the field of intravaginal siRNA delivery. J Contr Rel. 2013; 167(1): 29-39.

[235] Palliser D, Chowdhury D, Wang QY, Lee SJ, Bronson RT, Knipe DM, Lieberman J. An siRNA-based microbicide protects mice from lethal herpes simplex virus 2 infection. Nature. 2006; 439(7072): 89-94.

[236] Wu Y, Navarro F, Lal A, Basar E, Pandey RK, Manoharan M, Feng Y, Lee SJ, Lieberman J, Palliser D. Durable protection from Herpes Simplex Virus-2 transmission following intravaginal application of siRNAs targeting both a viral and host gene. Cell Host Microb. 2009; 5(1): 84-94.

[237] Wu SY, Chang HI, Burgess M, McMillan NAJ. Vaginal delivery of siRNA using a novel PEGylated lipoplex-entrapped alginate scaffold system. J Contr Rel 2011; 155(3): 418-26.

[238] Velnar T, Bailey T, Smrkolj V. The wound healing process: an overview of the cellular and molecular mechanics. The J Int Med Res. 2009; 37: 1528-42.

[239] Thu HE, Zulfakar MH, Ng SF. Alginate based bilayer hydrocolloid films as potential slow-release modern wound dressing. Int J Pharm. 2012; 434(1): 375-83.

[240] Guo S, Dipietro LA. Factors affecting wound healing. J Dent Res. 2010; 89(3): 219-29.

[241] Pawar H, Tetteh J, Boateng J. Preparation and characterization of novel wound healing film dressings loaded with streptomycin and diclofenac. Coll Suf B: Biointerf. 2013; 102: 102–10.

[242] Pawar HV, Boateng JS, Ayensu I, Tetteh J. Multifunctional medicated lyophilised wafer dressing for effective chronic wound healing. J Pharm Sci. 2014; 103(6): 1720-33.

[243] Beanes RS, Dang C, Soo C, Ting K. Skin repair and scar formation: the central role of TGF-[beta]. Exp Rev Mol Med. 2003; 5: 1-22.

[244] Boateng JS, Pawar HV, Tetteh J. Polyox and carrageenan based composite film dressing containing anti-microbial and anti-inflammatory drugs for effective wound healing. Int J Pharm. 2013; 441(1): 181-91.

[245] Labovitiadi O, Lamb AJ, Matthews KH. In vitro efficacy of antimicrobial wafers against methicillin-resistant Staphylococcus aureus. Ther Deliv. 2012; 3(4): 443-55.

[246] Labovitiadi O, Lamb AJ, Matthews KH. Lyophilised wafers as vehicles for the topical release of chlorhexidine digluconate—Release kinetics and efficacy against Pseudomonas aeruginosa. Int J Pharm. 2012; 439(1): 157-64.

[247] Labovitiadi O, O'Driscoll NH, Lamb AJ, Matthews KH. Rheological properties of gamma-irradiated antimicrobial wafers and in vitro efficacy against Pseudomonas aeruginosa. Int J Pharm. 2013; 453(2): 462-72.

[248] Peng CW, Lin HY, Wang HW, Wu WW. The influence of operating parameters on the drug release and anti-bacterial performances of alginate wound dressings prepared by three-dimensional plotting. Mater Sci Eng: C. 2012; 32(8): 2491-500.

[249] Boateng JS, Burgos-Amador R, Okeke O, Pawar HV. Composite alginate and gelatin based bio-polymeric wafers containing silver sulfadiazine for wound healing. Int J Biol Macromol. 2015; 79: 63-71.

[250] Baljit S, Lok P. Sterculia crosslinked PVA and PVA-poly(AAm) hydrogel wound dressings for slow drug delivery: Mechanical, mucoadhesive, biocompatible and permeability properties. J Mech Behav Biomed Mater. 2012; 9: 9–21.

[251] Dias AMA, Braga MEM, Seabra IJ, Ferreira P, Gil MH, de Sousa HC. Development of natural-based wound dressings impregnated with bioactive compounds and using supercritical carbon dioxide. Int J Pharm. 2011; 408(1–2): 9–19.

[252] Ribeiro MP, Morgado PI, Miguel SP, Coutinho P, Correia IJ. Dextran-based hydrogel containing chitosan microparticles loaded with growth factors (epidermal growth factor and vascular endothelial growth factor) to be used in wound healing. Mater Sci Eng: C. 2013; 33(5): 2958–66.

[253] Mohandas A, Anisha BS, Chennazhi KP, Jayakumar R. Chitosan–hyaluronic acid/VEGF loaded fibrin nanoparticles composite sponges for enhancing angiogenesis in wounds. Coll Surf B: Biointerf. 2015; 127: 105-13.

[254] Eroğlu İ, Gökçe EH, Tsapis N, Tanrıverdi ST, Gökçe G, Fattal E, Özer Ö. Evaluation of characteristics and in vitro antioxidant properties of RSV loaded hyaluronic acid–DPPC microparticles as a wound healing system. Coll Surf B: Biointerf. 2015; 126: 50-7.

[255] Singh D, Singh R. Papain incorporated chitin dressings for wound debridement sterilized by gamma radiation. Radiation Phys Chem. 2012; 81(11): 1781-85.

[256] Moura LI, Dias AM, Leal EC, Carvalho L, de Sousa HC, Carvalho E. Chitosan-based dressings loaded with neurotensin—An efficient strategy to improve early diabetic wound healing. Acta Biomater. 2014; 10(2): 843-57.

[257] Moura LI, Dias AM, Suesca E, Casadiegos S, Leal EC, Fontanilla MR, Carvalho L, de Sousa HC, Carvalho E. Neurotensin-loaded collagen dressings reduce inflammation and improve wound healing in diabetic mice. Biochimi et Biophys Acta (BBA)-Mol Basis Dis. 2014; 1842(1): 32-43.

[258] Hintzen F, Haupstein S, Perera G, Bernkop-Schnürch A. Synthesis and IN VITRO characterization of entirely S-protected thiolated pectin for drug delivery. Eur J Pharm Biopharm. 2013; 85(3):1266-73.

[259] Sharma R, Ahuja M. Thiolated pectin: Synthesis, characterization and evaluation as a mucoadhesive polymer. Carb Polym. 2011; 85(3): 658-63.

[260] Maity S, Sa B. Ca-carboxymethyl xanthan gum mini matrices: Swelling, erosion and their impact on drug release mechanism. Int J Biol Macromol. 2014; 68: 78-85.

[261] Maiti S, Mukherjee S. Controlled drug delivery attributes of co-polymer micelles and xathan-O-carboxymethyl hydrogel particles. Int J Biol Macromol. 2014; 70: 37-43.

[262] Ahuja M, Kumar A, Singh K. Synthesis, characterization and in vitro release behaviour of carboxymethyl xanthan. Int J Biol Macromol. 2012; 51(5): 1086-90.

FIGURES

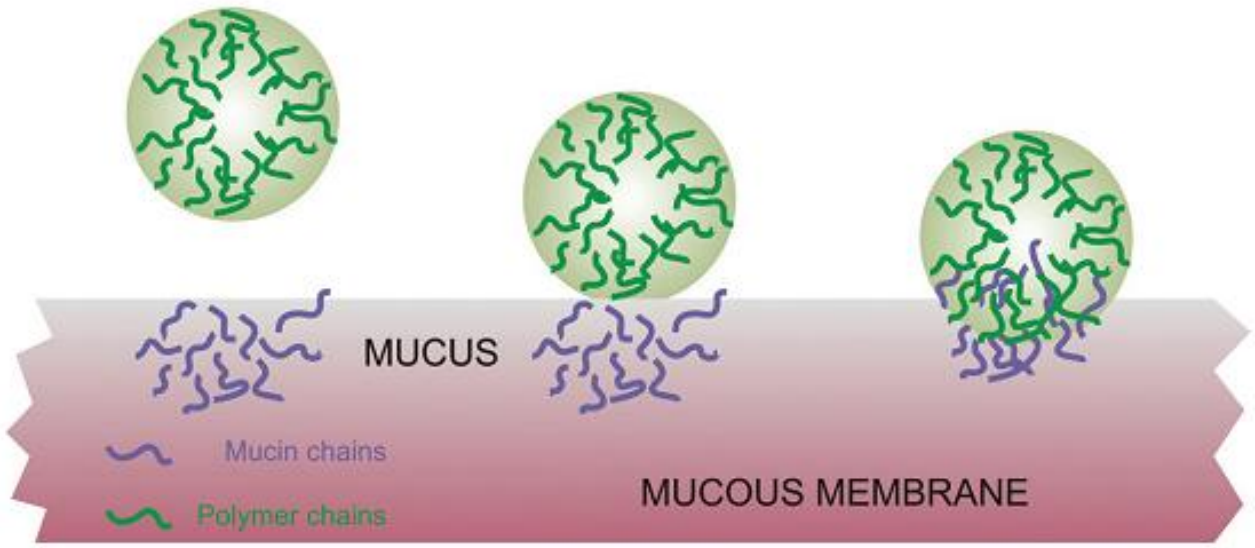

Figure 1 Adhesion process between polymer and mucous membrane (Reproduced with permission from [12].

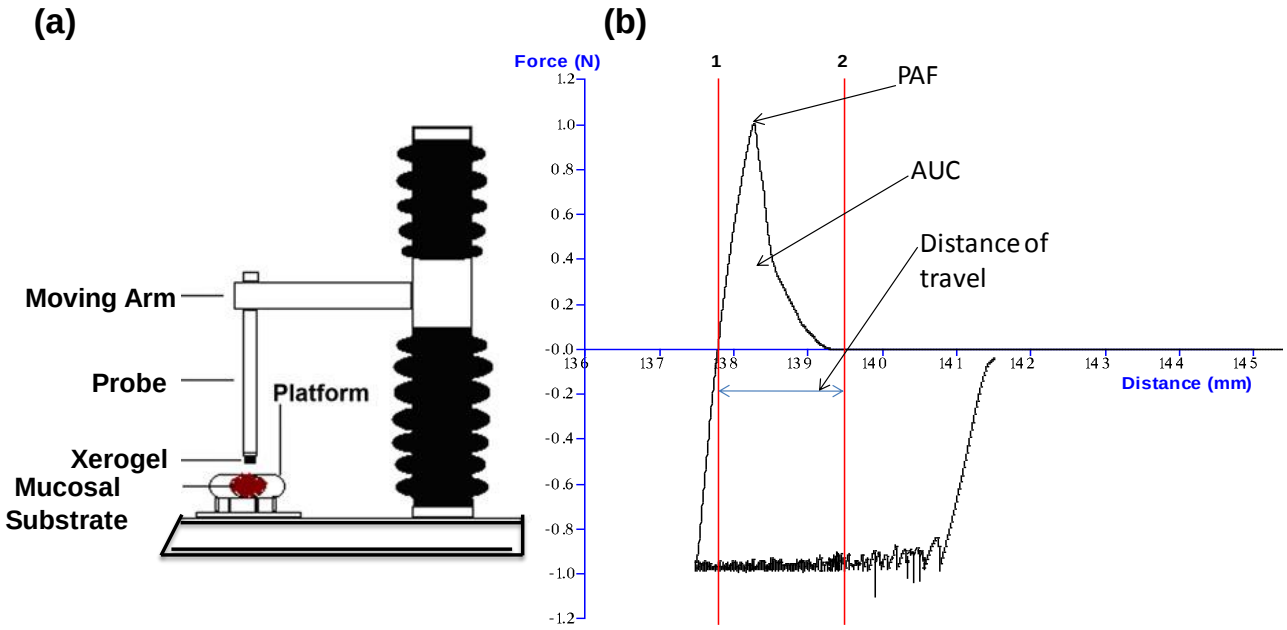

Figure 2 (a) Schematic diagram of texture analyser with xerogel attached to the probe and the mucosal substrate on the platform (b) Typical texture analysis force-distance plot (Ayensu, 2012 PhD Thesis, University of Greenwich). (Reproduced with permission)

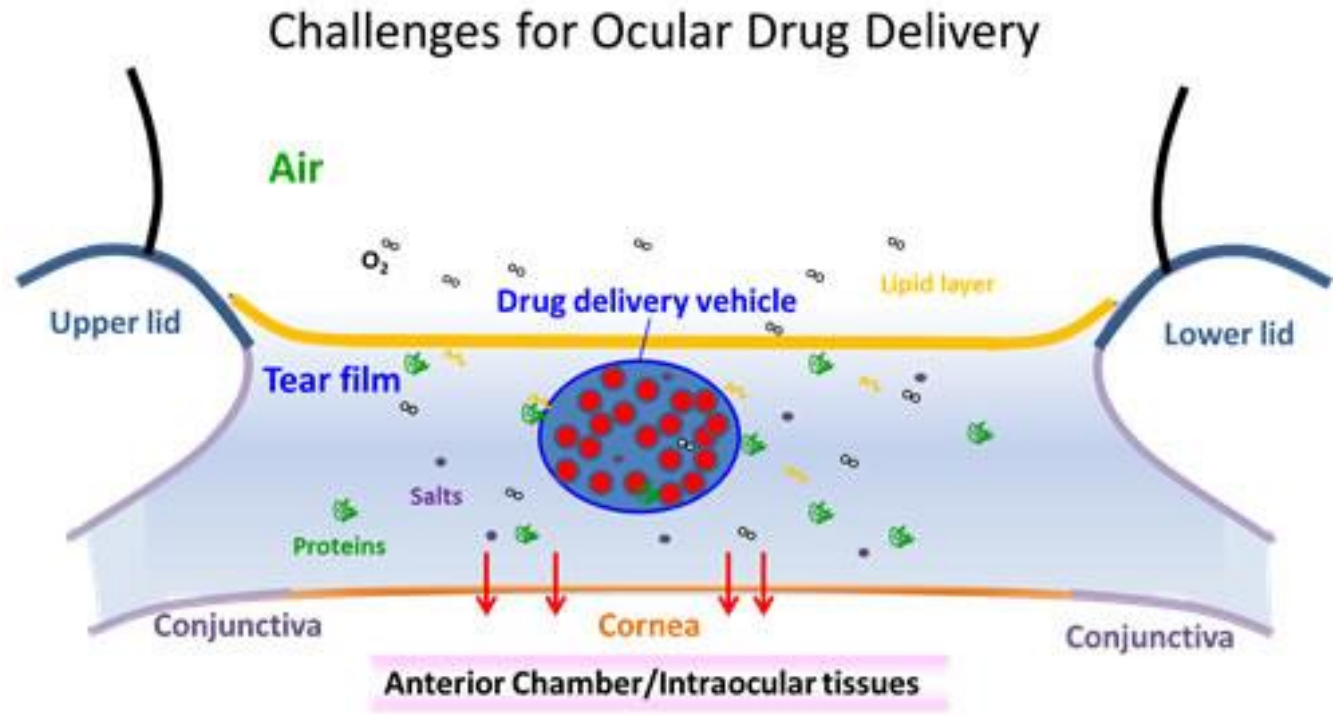

Figure 3 Cartoon showing cross section of the eye and illustrating the challenges of ocular delivery including the various routes via which drugs can be effectively delivered across the ocular barriers. (Available at: http://www.cchem.berkeley.edu/cjrgrp/group/peng.html - Accessed 16 March 2015) Reproduced with permission.

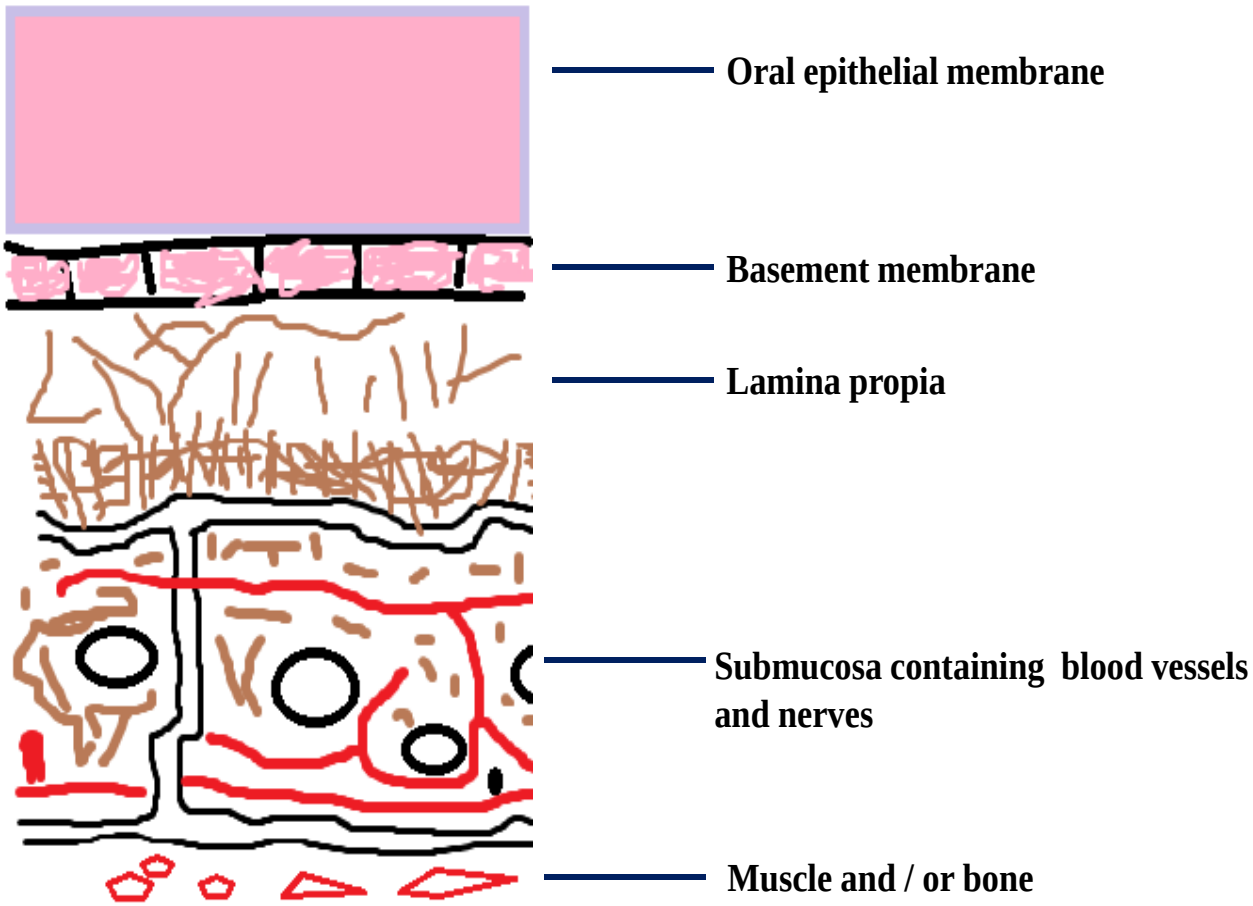

Figure 4 A drawn schematic cross section of the buccal mucosa showing the various layers requiring penetration to reach the systemic circulation.

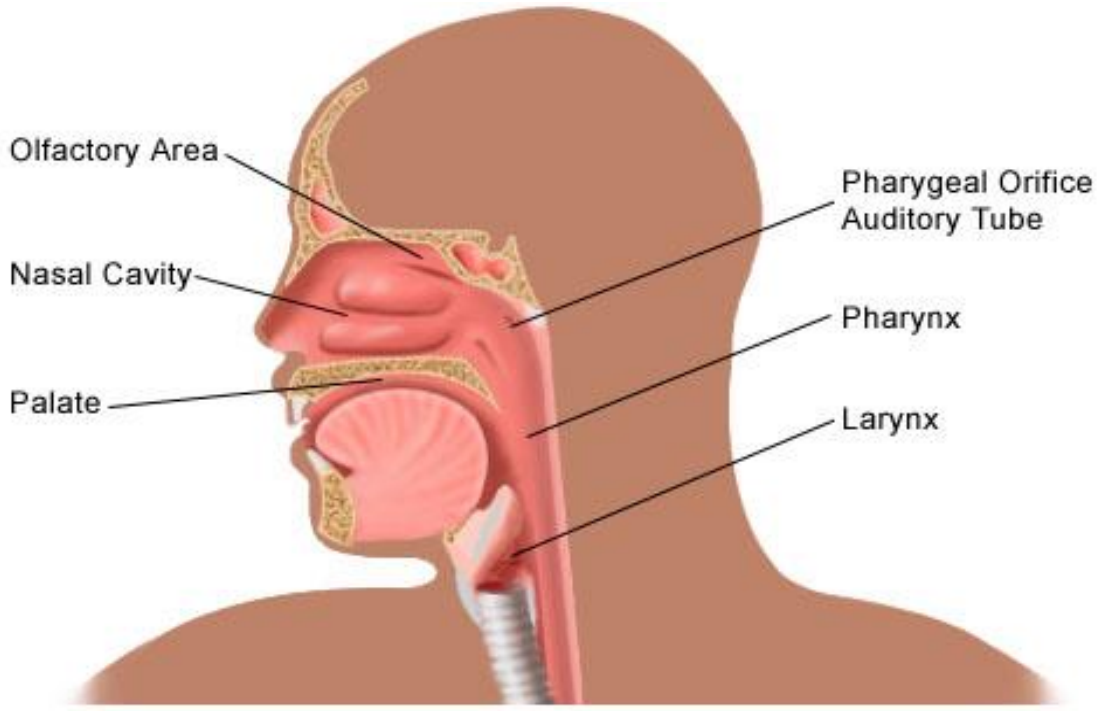

Figure 5 The main regions of the nasal – pharyngeal cortex for potential drug delivery (Available at: http://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=90&ContentID=P02027) (Accessed 16 March 2015). Reproduced with permission.

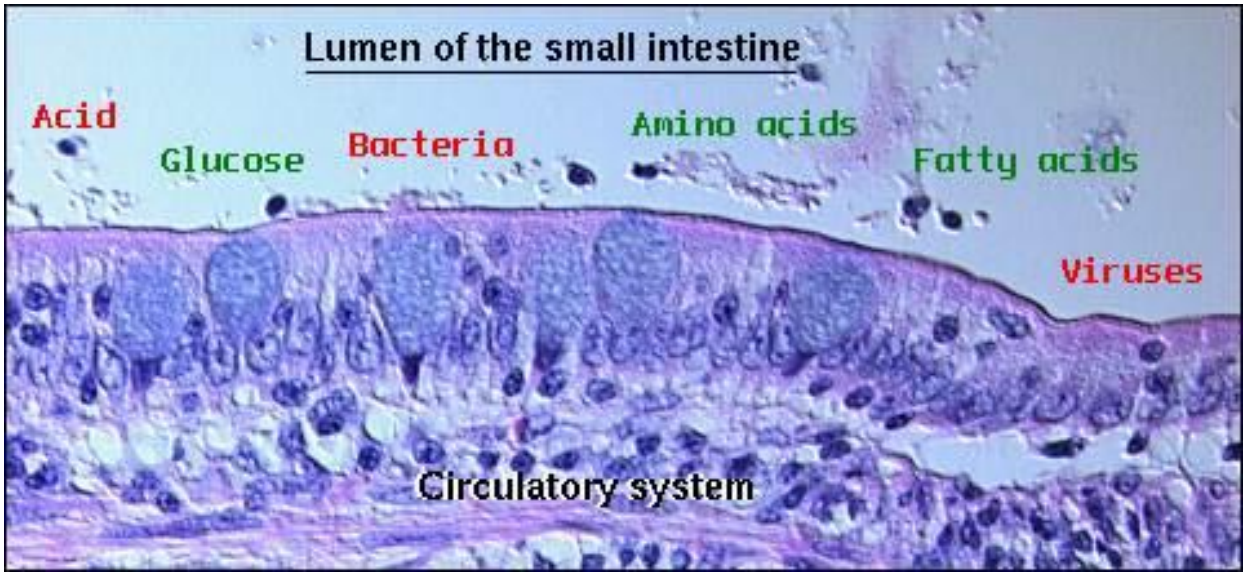

Figure 6 Cross section of the lumen of the small intestines, showing the various components within the lumen and on the mucosa lining. Reproduced with permission from [165].

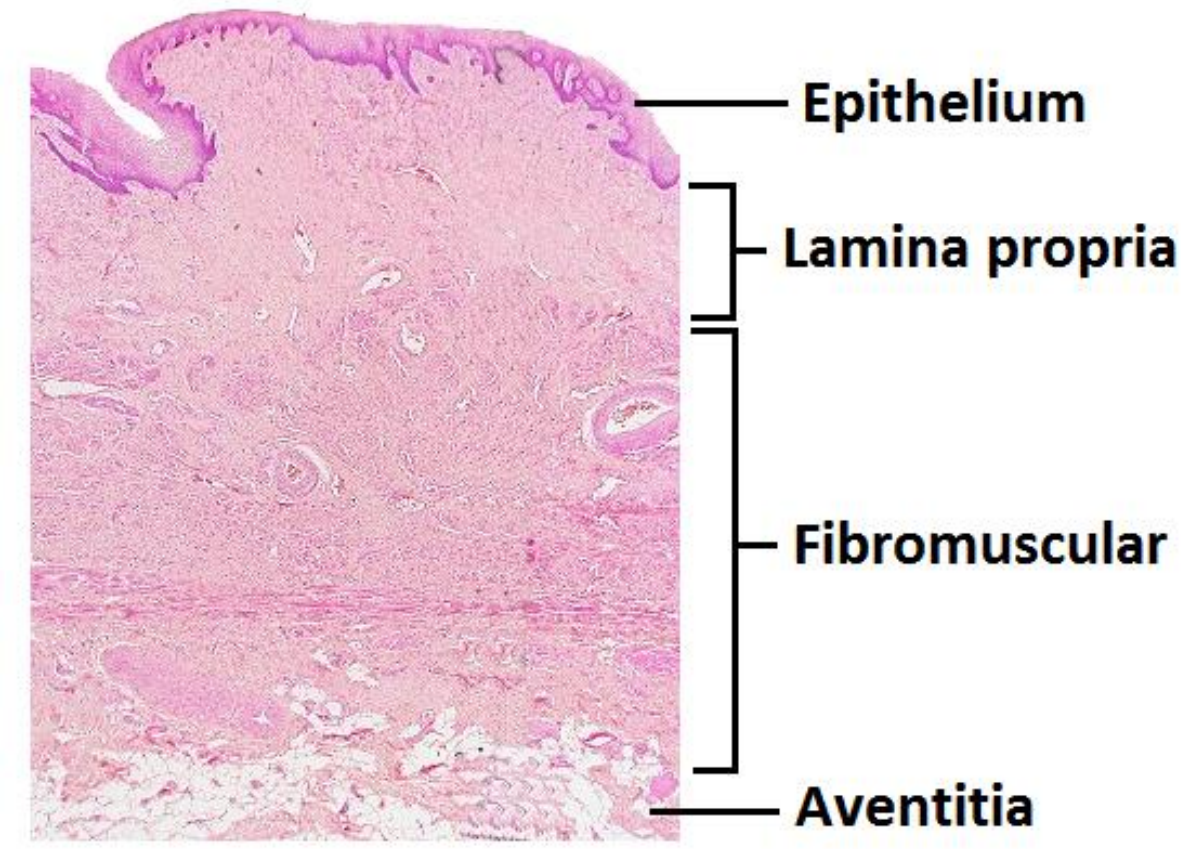

Figure 7 Structure of the walls of the vaginal wall including the mucosal epithelium. Available at http://teachmeanatomy.info/wp-content/uploads/Histological-Layers-of-the-Vagina-TeachMeAnatomy.png (Accessed on 19 March 2015). Reproduced with permission

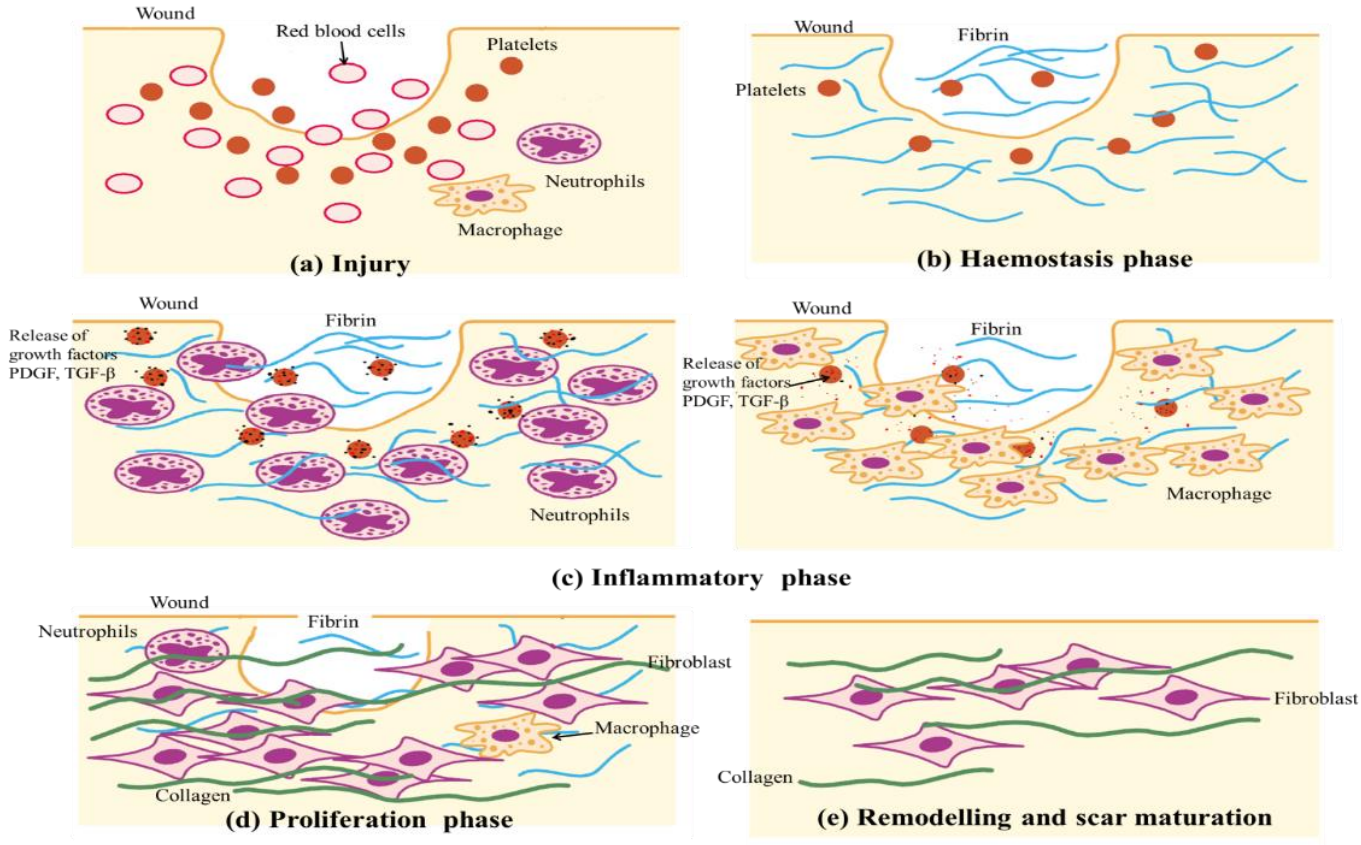

Figure 8 Schematic representation of different stages involved in the wound healing process (a) wound or injury (b) haemostasis (c) inflammatory phase (d) proliferation (e) remodelling and scar maturation. Reproduced with permission [243].