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Expert Review

Bioadhesive Dosage Forms for Esophageal Drug Delivery

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The esophagus as a site for drug delivery has been much overlooked in comparison to the remainder of the gastrointestinal tract. The low permeability and transient nature of the esophagus means that it is unsuitable for delivery of drugs for systemic action. However, esophageal disorders including fungal infection, cancers, motility dysfunction, and damage due to gastric reflux may be treated using locally acting agents that offer benefits of reduced dosage and decreased side effects. Bioadhesive dosage forms that adhere to the esophageal mucosa and prolong contact have been investigated to improve the efficacy of locally acting agents. The rationale for local esophageal drug delivery and its limitations, the factors that determine adhesion to this organ, and the experimental models used in esophageal drug delivery research are reviewed.

KEY WORDS: bioadhesive; esophagus; retention; drug delivery.

INTRODUCTION

Esophageal drug delivery has mainly focused on drugs or "bandages" that protect the esophagus from gastric reflux, localized delivery of anticancer agents, or the delivery of drugs to treat local fungal infections. Historically, however, localized drug at the esophagus has been the result of tablets or capsules becoming lodged and often leading to local injury.

ANATOMY AND PHYSIOLOGY OF THE ESOPHAGUS

The esophagus is a muscular tube that connects the mouth to the stomach. In humans, the esophagus is approximately 25 cm long and has an internal diameter of 2 cm (1); thus its surface area is approximately 150–200 cm^2. The function of the esophagus is the effective transport of food, liquid, and drug formulations from the mouth to the stomach. The contact time of ingested materials with esophageal tissue is short in healthy individuals, however, it is increased when supine and in patients that have difficulty in swallowing. There are sphincters at either end of the esophagus; the upper esophageal sphincter and lower esophageal sphincter. The upper esophageal sphincter (UES) is an integral part of both the esophagus and the pharynx, which is closed except for the expulsion of air (belching) or during a swallow. The lower esophageal sphincter (LES) is a circle of muscle that seals the esophagus at the junction with the stomach. The LES relaxes in response to a swallow to allow the passage of food or drink from the esophagus into the stomach. Effective function of the LES prevents reflux of gastric contents into the esophagus.

The esophagus is lined with stratified squamous epithelium that is relatively impermeable to drug entities. The epithelial layer provides a tough, protective lining from the abrasive food boluses that pass through this organ and is lubricated by swallowed saliva that contains mucin and forms a coating over the epithelium of the esophagus. The pH within the esophagus is similar to that of saliva at about 6–7 (2), whereas the pH within the stomach is between 1.5 and 2 in the fasted state (3). At the junction between the esophagus and the stomach, the lower esophageal sphincter, the epithelial lining changes into stomach epithelium that is covered in a protective mucus layer, which is necessary to protect this tissue from the local acidic environment. For a full review of the histologic differences between esophageal and gastric epithelia the reader is referred to Kahrilas (4).

In the relaxed state, the esophagus is highly folded and expands as necessary upon swallowing. A swallow is a voluntary action that is associated with a peristaltic wave moving down the esophagus to clear food boluses or swallowed saliva. The speed of the peristaltic wave has been measured to be 2–6 cm per second (2). The typical transit time of dosage forms has been calculated to be 10–14 s (2). Secondary peristalsis is an involuntary action that occurs over the lower region of the esophagus. It is initiated in response to distension within the esophagus that may be caused by adherent food particles or refluxed gastric material.

LOCAL DISEASE STATES OF THE ESOPHAGUS

Esophageal disease is usually the result of esophageal malfunction. Esophageal blockage leads to an inability of the organ to function as a passage for the transport of food from the mouth to the stomach. Depending upon the nature of the blocking agent, the esophageal mucosa may also be susceptible to damage at the site of blockage. Lodging of solid dosage forms has been linked with local esophageal injury (5).

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Achalasia

Achalasia is an esophageal motor disorder of unknown etiology. It is an uncommon ailment with a reported incidence of 0.5–1 per 100,000 in the United States (6). The clinical result of achalasia is insufficient LES relaxation and ineffective peristalsis, which leads to an inability to clear material from within the esophagus. The main symptoms of achalasia are dysphagia and regurgitation of ingested food and drink. There is currently no cure for achalasia, therefore the goal of treatment is relief of patient symptoms and improved esophageal emptying. Pharmacological management of achalasia includes the use of nitrates (e.g., isosorbide dinitrate) and calcium channel blockers (e.g., nifedipine). These drugs are given either as a tablet for sublingual use or as conventional oral solid dosage forms, both for systemic uptake of the drugs. Both nitrates and calcium channel blockers relax smooth muscle, thus the esophageal body and LES relax, allowing the free passage of ingested materials. Systemic administration of these drugs is not recommended for long-term use as there are many associated side effects.

Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux occurs when the LES relaxes and allows the stomach's acidic contents to reflux back into the esophagus. This is a physiologic event that occurs in all of the population; however, reflux that causes symptoms or complications is called pathologic reflux and may lead to GERD (7). Clinical symptoms including heartburn are reported to occur in 20–30% of the general population within the Western world (8). Current therapy used in the treatment of GERD includes antacids to lower the pH within the stomach and reduce the corrosive nature of refluxed material; alginate-based preparations (e.g., Gaviscon Advance) that form a floating barrier on the top of the stomach's contents, providing physical protection against reflux; and proton pump inhibitors and histamine receptor antagonists that reduce gastric acid secretion thus raising gastric pH (e.g., omeprazole and cimetidine). Excessive contact of the acidic gastric contents with the esophageal mucosa leads to localized inflammation termed esophagitis.

Barrett Esophagus and Esophageal Adenocarcinoma

Barrett esophagus occurs when gastric columnar epithelial cells replace the squamous epithelial lining of the esophagus as a result of GERD. Dysplasia of epithelial type has been implicated as a precursor to esophageal adenocarcinoma, as in many patients the esophageal adenocarcinoma occurs within an area of dysplasia (9). Barrett esophagus cannot be cured by pharmacological intervention; however, proton pump inhibitors are used to relieve the symptoms and surgical procedures may be used to repair the damage. The incidence of Barrett esophagus has been suggested to be about 1% of the general population within the United States (10). In contrast to the declining rates of gastric cancer in developed countries, the incidence of esophageal cancer has been increasing over the past few decades in the United Kingdom; between 1971 and 1998, the age-standardized rate for esophageal cancer increased from 7.6 to 12.8 per 100,000 males and from 4.2 to 5.8 for females (11).

Infections Within the Esophagus

Infections of the esophagus are primarily associated with immunocompromised hosts, including patients undergoing cancer chemotherapy or those with HIV. *Candida* species, cytomegalovirus, and herpes simplex virus have been most frequently implicated with occasional reports of infection due to *Aspergillus* species, *Mycobacterium tuberculosis,* and both gram-negative and gram-positive bacteria (12). Available antifungals for the treatment of esophageal candidiasis include polyenes, azoles, nystatin, and amphotericin B. Therapy with these agents is not always successful due to the poor permeation of the esophagus and their low systemic availability.

The market share for drugs to treat esophageal diseases is largest for those linked to reflux disease. In 2003, three of the top twenty bestselling drugs in the United States were to treat gastroesophageal reflux with a total sales value of nearly $9 billion (13).

ADHESION WITHIN THE ESOPHAGUS

The esophageal transit time of a 10 ml liquid bolus in a normal subject in a supine position is less than 16 s (14). Tablets or capsules lodging in the esophagus leads to delayed absorption and therefore delayed onset of action, as the esophageal epithelial layer is impermeable to most drugs. In addition, adhesion at such a site may cause problems if localization of the drug or dosage form leads to irritation of the mucosa; this has been reported previously for solid dosage forms that have become lodged within the esophagus (5). Indeed, it has been postulated that oral dosage forms that become lodged in the esophagus may be a preliminary step or cause of esophagitis and dysphagia (7). Bioadhesive drug delivery systems have been targeted to many sites within the GI tract to increase the time available for absorption and therefore increase the overall bioavailability. Due to the poor blood supply and squamous epithelium of the esophagus, delivery of systemic drugs via this organ is not feasible. However, delivery of drugs that act directly on the esophageal epithelium may be beneficial in local disorders of the esophagus.

ADHESION OF SOLID DOSAGE FORMS WITHIN THE ESOPHAGUS

Adhesion of solid dosage forms within the esophagus is relatively common; a study by Evans and Roberts demonstrated that approximately 20% of solid oral dosage forms adhere to the esophagus, yet only 3% of patients were aware that the tablet/capsule was stuck (15). The risk of a solid dosage form adhering to the esophagus increases to about 50% for people who take their medication while recumbent or with little or no water (16). Drug-induced esophageal injuries have been reported with many medications; tetracycline, doxycycline, and minocycline are among the most common medications implicated (5). Injuries include esophageal ulceration, perforation, strictures, and esophagitis (17–18). Adhesion of the dosage form leads to dehydration of the mucosal surface and the formation of a gel interface between the dosage form and the epithelium. The drug diffuses from the solid dosage form into the gel layer, forming a high concentration at the epithelial layer that is corrosive to the local tissue. Endoscopic examination of an esophagus following an

adhered dosage form has demonstrated erosion about the size of a small coin (19).

Techniques Used to Evaluate Adhesion of Solid Dosage Forms

Several workers have examined the factors that predispose esophageal adhesion of solid dosage forms. Marvola *et al.* introduced a novel test that measured the adhesion of solid dosage forms to the esophagus using *ex vivo* porcine esophageal tissue (17). This apparatus consisted of excised esophagus maintained in a vertical position at 37°C within oxygenated Tyrode's solution. The lower end of the esophagus was sealed, and the solid dosage attached to a copper wire was placed within the esophagus using a plastic tube as an applicator. The force required to withdraw the tablet from within the esophagus was measured, and this value was recorded as the force of detachment value. Experimental data revealed that the force of detachment was dependant upon the time for which the solid dosage form was left within the esophagus prior to removal, the surface area of the solid dosage form, and the natural variability between esophagi. This method was adapted by Al-Dujaili *et al.* who used strips of esophageal tissue mounted in a horizontal plane and measured the tensile force required to separate the solid dosage form from porcine esophageal tissue (18). Recently, Honkanen *et al.* (2002) have investigated *ex vivo* porcine models as a tool to evaluate the adhesive potential of capsules to the esophagus, in cases of capsules becoming lodged in the esophagus (20). The capsules were placed within the inner esophageal tube that was within a classic organ bath, and the force required to withdraw the capsule from the esophagus was measured.

The force required to detach a solid dosage form from esophageal mucosa has been the technique of choice in ranking the relative adhesive potential of solid dosage forms within the esophagus, and a summary of published data is presented in Table I.

It is interesting to note the trend of gelatin capsules showing the greatest adhesion followed by film-coated tablets (except Ref. 18), then uncoated tablets followed by sugar-coated tablets. The differences in values within each study is likely to be due to the differences in the parameters used to assess the force of detachment; factors such as equilibration time, attachment force, and speed of withdrawal of the probe will all influence the values obtained. A study by Mathias *et al.* examined the adhesive potential of formulation coatings using *ex vivo* porcine esophageal tissue (24); alginic acid demonstrated the greatest adhesion followed by hydroxypropylmethylcellulose (HPMC), pluronic surfactant, gelatin with polyethylene glycol, and paraffin wax having low values for the force of detachment.

The clinical implications of tablets lodging within the esophagus include ineffective therapy as well as potential localized injury and discomfort. Transit time of solid dosage forms was reviewed by Washington *et al.*, who suggested that size and shape of tablets was insignificant compared to the influence of subject posture (2). Table II summarizes the transit times of a variety of solid dosage forms that have been measured *in vivo*.

Transit times were found to be slower in supine compared to erect subjects, with more than 5 min for film-coated and uncoated tablets compared to under 10 s when patients remained erect (28). The extremely long transit time for the HPMC capsule is due to a high incidence (4 out of 12 subjects) of capsules lodging in the esophagus, leading to transit times of 22, 23, 101, and 143 min compared to the range of 7–24 s for those that did not stick (26). The long transit time of microcrystalline chitosan was the result of a single patient study where the chitosan adhered to the esophageal mucosa for 1.75 h (27). These *in vivo* studies have demonstrated that there is little correlation between the *in vivo* adhesion observed and the *in vitro* force of detachment tests (21).

Table I. A Summary of Data Collected that Measured the Force of Detachment Required to Separate Solid Dosage Forms from Esophageal Tissue

Dosage form	Detachment force (N)	Substrate	Ref.
Uncoated tablet (round)	0.164	Porcine	21
Uncoated tablet (oval)	0.245	Porcine	21
Film-coated tablet (oval)	0.407	Porcine	21
Gelatin capsule	1.232	Porcine	21
HPMC capsule	0.59	Porcine	20
Gelatin capsule	~1.5	Porcine	20
Sugar-coated and uncoated tablets	0.0005–0.0025	Porcine	18
Gelatin capsules	0.025–0.088	Porcine	18
Film-coated tablets	0.045–0.090	Porcine	18
Uncoated tablets	0.1–0.25[a]	Dog	22
Sugar-coated tablets	0.05[a]	Dog	22
Film-coated tablets	0.1–0.3[a]	Dog	22
Hard gelatin capsules	0.16–0.36[a]	Dog	22
Soft gelatin capsule	1.30	Porcine	23
Gelatin capsule	0.88	Porcine	23
Uncoated tablet	0.29	Porcine	17
Film-coated tablet	0.27–0.78	Porcine	17
Gelatin capsule	1.21	Porcine	17

HPMC, hydroxypropylmethylcellulose.
[a] Force converted from gram force to newtons (1 g-force = 0.01 N).

Table II. A Summary of Data Collected that Measured the Esophageal Transit Time of Solid Dosage Forms in Human Studies

Formulation	Transit time (s)	Volume of water	Position	Ref.
Film-coated tablet	3.2 ± 0.3	30 ml	Seated	25
Uncoated tablet	65 ± 33	30 ml	Seated	25
HPMC capsule	1445 ± 2840	180 ml	Seated	26
Microcrystalline chitosan	6300	180 ml	Seated	27
Large gelatin capsule (size 0)	3	15–30 ml	Erect	28
Small gelatin capsule (size 2)	9	15–30 ml	Erect	28
Uncoated tablet	10	15–30 ml	Erect	28
Film-coated tablet	3	15–30 ml	Erect	28
Large gelatin capsule (size 0)	45	15–30 ml	Supine	28
Small gelatin capsule (size 2)	80	15–30 ml	Supine	28
Uncoated tablet	>300	15–30 ml	Supine	28
Film-coated tablet	>300	15–30 ml	Supine	28

HPMC, hydroxypropylmethylcellulose.

ADHESION OF LIQUIDS WITHIN THE ESOPHAGUS

The transit time of liquids through the esophagus is less than 16 s even in a supine subject (14). Development of a liquid formulation that adheres to the esophagus has implications in both the protection of the epithelial surface from damage caused by reflux and as a vehicle to deliver drugs for local action within the esophagus.

Techniques Used to Evaluate Adhesion of Liquids

Ito *et al.* described an early technique used to measure the adhesion of a flowable system within the esophagus (29). This study examined the use of magnetic particles coated with a bioadhesive polymer for targeting to the esophagus via the use of an external magnet placed over the esophagus. Bioadhesive polymers were screened using a glass tube that was coated with an agar solution to mimic esophageal tissue. This tube was washed to mimic saliva flow, and adhesion of particles was measured via an incorporated blue dye and a colorimetric assay. A similar dynamic flow test was described by Vonarx *et al.* (1997) where gel formulations (that incorporated a red dye) were introduced into a horizontal flexible polyethylene tube and left to equilibrate for 10 min, after which the tube was placed in an upright position and washed at a rate of 7 ml/min with distilled water to mimic saliva flow (30). The retention of the formulations was quantified via a colorimetric assay; polycarbophil and xanthan both demonstrated excellent adhesive potential, whereas carmellose sodium and a thermosensitive poloxamer (Lutrol 407, BASF) demonstrated poor retention *in vitro* (30). This scenario was reversed (31), and microscope slides coated in agar were dipped into potential adhesive formulations, then was measured the adhesion of liquids to this agar substrate after washing that mimicked saliva flow; hydroxypropylmethylcellulose, Smart Hydrogel (a thermosensitive hydrogel of poloxomer covalently liked to polyacrylic acid), and Carbopol demonstrated adhesion of >80% after 10 min of washing.

Dobrozi *et al.* (1999) used everted rat esophagus to measure the retention of liquid sucralfate formulations; Carbopol was used as a positive control and three commercially available sucralfate formulations were tested (32). Sucralfate gel suspension (Gastrogel) was retained to a greater extent than non-gel formulations (Antepsin, Ulcogant). Key features of the everted rat esophagus model include the ability of the model to test flowable systems with a wide range of viscosities, the rapid testing time, and the physiologic similarity to *in vivo* studies.

Batchelor *et al.* (33) described in detail the dynamic flow model that has also been used in other studies (34–36). This model used *ex vivo* porcine esophagus strips that leave the epithelial surface exposed and maintained at physiologic temperature and humidity. Liquid or semisolid formulations were labeled using either fluorescent or radiochemical markers prior to dispensing onto the tissue surface, which allowed quantification of their retention on this surface. The tissue surface was inclined to a fixed angle and bathed in fluid to mimic saliva flow over the tissue surface. At designated time points, the eluate was collected and analysis revealed the percentage of the original dose retained on the tissue surface over time. A summary of the bioadhesive potential of liquid formulations using techniques that model esophageal adhesion is presented in Table III.

The differences observed in the retention of similar materials is likely to be due to the variations in apparatus used to measure the retention of these formulations. Recent work performed within the author's laboratory has demonstrated that the retention of a wide range of liquids may be quantified using a single, dynamic flow method (33), and the results are shown in Fig. 1. This model used a noncovalently bound radioactive label, technetium tin colloid, to label each liquid. 1 ml of each formulation was dispensed over an area of 10 × 80 mm *ex vivo* porcine esophageal tissue and washed at a rate of 1 ml per minute using distilled water to mimic saliva flow. Water was used as a control to observe the retention of the label, and glycerol was also used as a control as it is not adhesive yet has a viscosity greater than water. The results show that there was a great deal of variability within the model, yet this method was suitable to screen potential esophageal adhesives.

In vitro esophageal adhesion test systems are advanta-

Table III. The Percentage of the Applied Dose that Was Adhered at 10 Min. Measured Using a Variety of Techniques to Model Adhesion Within the Esophagus

Liquid	% Retained[a]	Substrate	Ref.
1% m/v Noveon AA1	~90	Polyethylene tube	30
2% m/v xanthan gum	~83	Polyethylene tube	30
10% m/v carmellose sodium	~20	Polyethylene tube	30
15.5% m/v poloxamer 407 (thermogelling)	~40	Polyethylene tube	30
Smart hydrogel (concentration not reported)	83.5	Agar substrate	31
Carbopol 934P (concentration not reported)	92.9	Agar substrate	31
HPMC (concentration not reported)	89.7	Agar substrate	31
4% m/v Carbopol 934P	64–73%	Rat esophagus	32
Antepsin	~5	Rat esophagus	32
Gastrogel	~50	Rat esophagus	32
Ulcogant	~5	Rat esophagus	32
2% m/v sodium alginate (medium MW)	23	Porcine esophagus	33
2% m/v sodium alginate (medium MW)	10	Cellulose acetate membrane	33
5% m/v polyacrylic acid (high MW)	~43	Porcine esophagus	36
5% m/v polyacrylic acid (low MW)	~23	Porcine esophagus	36

HPMC, hydroxypropylmethylcellulose; MW, molecular weight.
[a] The percentage of an applied dose retained at 10 min.

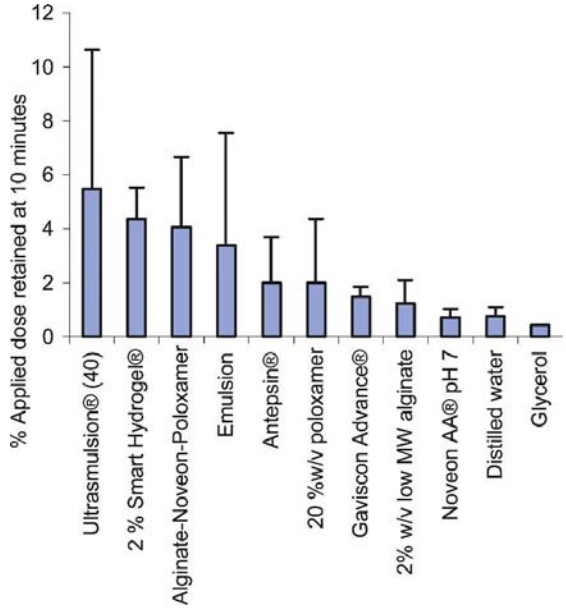

Fig. 1. Comparison of the retention of a range of liquids using a single model.

geous in that they provide a rapid screening program for wide ranging formulations that may be targeted to the esophagus. However, they are limited as they do not account for the presence of food, motility, and digestive enzymes.

IN VIVO LIQUID RETENTION WITHIN THE ESOPHAGUS

Historically, esophageal transit has been measured using barium to label a variety of substances including gelatin cylinders, marshmallows, tablets, and capsules with X-ray analysis to visualize their motion (2). However, gamma scintigraphy has been the technique of choice when examining bioadhesion within the esophagus. Studies performed (25–27) have used gamma scintigraphy to observe the transit of dosage forms within the esophagus of human volunteers. McCargar *et al.* compared an *ex vivo* porcine model to human gamma scintigraphy work and discovered that the porcine adhesion model was not predictive of esophageal transit *in vivo* (21). The retention of a thermosensitive hydrogel (Smart Hydrogel) using gamma scintigraphy demonstrated that 13% of the applied 5-ml formulation was retained at 10 min, whereas an agar model showed that 83% of the dose was retained at the same time point (31). Potts *et al.* used magnetic resonance imaging (MRI) to visualize the esophageal retention of three potential bioadhesive agents; this technique provided a noninvasive means of obtaining *in vivo* information on esophageal transit yet it did not allow quantification of retention and it was therefore less useful than gamma scintigraphy for human *in vivo* studies (37). The lack of correlation previously noted between *in vitro* models to measure adhesion and *in vivo* studies using gamma scintigraphy may be due to the design of the *in vitro* test apparatus. Where forces of detachment methods are used, the presence of saliva as a washing medium is not accounted for and neither is the postural position of the subject. Mortazavi and Smart discussed how experimental factors influence the assessment of bioadhesion with reference to force of detachment methods (38). Esophageal retention models that have measured the adhesive profile of a liquid formulation on ex vivo esophageal tissue in the presence of washing to mimic saliva flow offer a more physiologically relevant technique; however, they do not account for peristalsis. Recent work performed (39) uses an entire porcine esophageal tube maintained at 37°C and high humidity; the dose was introduced at the upper end of the tube followed by five "peristaltic" waves performed by controlled motion of a roller along the length of the esophageal tube. Saliva flow was also mimicked via introduction of 30 × 1 ml aliquots of artificial saliva with each followed by a peristaltic wave. The retention of the formulation of the esophageal surface was quantified by measurement of the removed adhered formulation at the end of the procedure.

DRUG DELIVERY TO THE ESOPHAGUS

Liquid formulations that adhere to esophageal tissue may be used to deliver drugs to the esophageal mucosa as well as to provide a protective bandage to defend the esophageal epithelium from damage caused by gastric reflux. Many patents have been granted that propose formulations that are able to deliver drugs to the esophagus, Table IV lists some of these.

Barrett's esophagus is characterized by a replacement of normal esophageal mucosa with metaplastic columnar epithelium that is more like the epithelium within the stomach. This alteration is linked to increased incidence of adenocarcinoma of the esophagus. Photodynamic therapy is commonly used in the treatment of esophageal cancer, although its efficacy would greatly be increased if the photosensitizer was applied topically to the site of action. Iooss *et al.* investigated the retention and drug release of δ-5-aminolevulinic acid in combination with polycarbophil (Noveon AA1, BF Goodrich)

Table IV. Examples of Recent Patents that Describe Formulations that Deliver Drugs to the Esophagus

Formulation	Example	Ref.
Ultramulsion (silicone-based emulsion)	Liquid antacid to provide relief from symptoms of GERD	40
Long-acting GI and esophageal protectant (water in oil emulsion)	Liquid antacid to provide relief from symptoms of GERD	41
Nondissolvable formulations for transmucosal delivery	Liquid antacid to provide relief from symptoms of GERD	42
End-modified thermal responsive hydrogels	Liquid antacid to provide relief from symptoms of GERD	43
Aqueous liquid with 2–50% by weight colloidal titanium dioxide	Liquid antacid and sucralfate dispersion	44
Aqueous mix of polymers from alginate, xanthan gum, carageenan, glucomannan, and galactomannan	Liquid antacid to provide relief from symptoms of GERD	45
Effervescent drug delivery for oral administration	General drug delivery to the esophagus	46

GERD, gastroesophageal reflux disease.

and demonstrated excellent adhesion using an *in vitro* model (47). Vonarx *et al.* also investigated the development of a δ-5-aminolevulinic acid bioadhesive gel that could be administered orally for action within the esophagus (30). Ito *et al.* introduced the use of magnetic particles as a means of local targeting of therapeutic agents to the esophagus following oral administration (29). A study that continued this work found that the retention of the formulation (bleomycin in hydroxypropylcellulose:Carbopol 3:2 ratio) on the esophagus was not of sufficient duration for effective therapy using a rabbit model; it was concluded that a stronger bioadhesive agent may aid the retention of the particles at the desired site of action (48). Batchelor *et al.* investigated liquid alginates as potential drug delivery vehicles targeted to the esophagus (49). Previous work has demonstrated that alginates adhere to the esophageal mucosa *in vitro* for periods of up to 60 min (33); the incorporation of drugs into such an adhesive layer would allow localized therapy acting at the esophageal epithelium.

Esophageal candidiasis is an increasingly common clinical condition associated mainly with immunocompromised patients; effective topical therapy would minimize the amount of drug used and reduce the many unwanted side effects associated with systemic therapy. Vandergam *et al.* reported a 63-fold increase in saliva concentrations of fluconazole using an orally dissolving tablet compared to a conventional tablet (50). This increase in concentration of dissolved drug within the esophagus was suggested to account for the improved efficacy of such a formulation in treating esophageal candidiasis. Incorporation of antifungal agents into a formulation that coated the esophagus and provided drug at the site of action has been investigated (51); the study suggested that a topical formulation delivered orally to treat esophageal candidiasis was feasible.

Sublingual nitroglycerin has demonstrated a clinical effect on local esophageal smooth muscle in humans, as previously reported (52). This study measured the esophageal response to long-acting nitrates to measure the effect these may have on the smooth muscle and the lower esophageal sphincter, greater action was noted for sublingual nitrates that was attributed to the local action within the esophagus.

Drug delivery to the esophagus was achieved in rabbits using magnetic particles in conjunction with hydroxypropyl cellulose and carboxyvinyl polymer as bioadhesive excipients (48). However, this formulation did not adhere for an adequate duration to deliver bleomycin to esophageal cancers, and it was concluded that the formulation could be improved by employing alternative bioadhesive polymers.

Strategies for delivery of drugs to the esophagus include producing high levels of drug dissolved within the saliva for a local and prolonged contact with the esophageal mucosa; formulations including lozenges and chewing gums can provide this. However, saliva flows through the esophagus rapidly, and thus the time for drug action is short. A combination of readily soluble drug within an adhesive formulation would be ideally suited for drug delivery to the esophageal epithelium.

Esophageal Bandages

Many of the patents listed in Table IV postulate the idea of a protective coat that lines the esophagus and prevents refluxed material from contact with the esophageal epithelium. Incorporation of antacids into such coatings further protects the esophagus via neutralization of the corrosive acid component within the refluxed material. The term "esophageal bandage" was introduced by Potts *et al.* (53), who investigated thermosensitive polymers as potential formulations that could coat the esophagus. Recent work by Tang *et al.* has looked not only at the adhesive potential of formulations targeted as esophageal bandages but also at their ability to protect the underlying epithelium; this study demonstrated that the presence of an alginate layer reduced the diffusion of both acid (hydrogen ions) and pepsin (54).

THE FUTURE OF DRUG DELIVERY TO THE ESOPHAGUS

Esophageal adhesion of solid dosage forms is common, and this phenomenon, as well as the injuries that result from tablets and capsules lodging within the esophagus, has widely been reported. In some instances, for example in the treatment of esophageal cancer, fungal infections within the esophagus, and esophageal motility disorders, delivery of drugs directly to the esophagus is desirable. Novel formulations are being designed that can deliver drugs directly to the esophageal mucosa after oral administration.

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