

Chapter Four

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INTRODUCTION

The oesophagus serves to move boluses of food, drink or drug formulations from the buccal cavity, through the lower oesophageal sphincter and into the stomach. In normal healthy people, ingested materials have a very short contact time with oesophageal tissue, but this is slightly lengthened when individuals are supine due to the loss of the effect of gravity.

The appreciation that oesophageal transit of formulations could be the first stumbling block that orally administered solid drug formulations could encounter appears to stem from the introduction of wax-based matrix tablets of potassium chloride produced in the 1960's¹. Since this time there have been numerous reports in the literature of drugs that have the potential to cause damage to the mucosa. Although most of the injuries were self-limiting, with symptoms such as retrosternal pain and dysphagia, there were occasional instances of serious complications such as perforation and haemorrhage leading to death. Another significant consequence of retention of a formulation in the oesophagus is that it can reduce or delay absorption of the drug.

ANATOMY AND PHYSIOLOGY

Oesophagus

The oesophagus is a 25 cm long, 2 cm diameter muscular tube which joins the pharynx to the cardiac orifice of the stomach. The stratified squamous epithelium lining the buccal cavity continues through the pharynx and down the oesophagus. The lowest 2 cm or so of the oesophagus which lies within the abdominal cavity is normally lined with gastric mucosa and covered by peritoneum. The stratified squamous epithelium provides a tough impermeable lining resisting the abrasive nature of food boluses, whilst the gastric mucosal lining resists damage by gastric acid. The lumen of the oesophagus is highly folded in the relaxed state. The pH of the normal oesophageal lumen is usually between 6 and 7.

The oesophagus has four coats, a fibrous external layer, a muscular layer, a submucous or areolar layer and an internal or mucous layer (Figure 4.1).

- a) The fibrous coat consists of elastic fibres embedded in a layer of areolar tissue.
- b) The muscular layer is composed of circular muscle surrounded by longitudinal muscle. Smooth muscle is found in the lower third of the oesophagus, striated muscle in the upper part and both types are found in the middle section.
- c) The areolar or submucous coat contains the larger blood vessels, nerves and mucous glands. It loosely connects the mucous and muscular coats.
- d) The mucosal layer consists of a layer of stratified squamous epithelium, one of connective tissue, and a layer of longitudinal muscle fibres, the muscularis mucosae. It forms longitudinal folds in its resting state which disappear when distended.

Two types of secretory glands are found in the oesophagus. The majority of oesophageal glands are simple glands located in the lamina propria, but in the lower 5 cm of the oesophagus the glands are compound and identical to the cardiac glands of the stomach (Chapter 5) which secrete mucus rather than acid.

The oesophageal glands are distributed throughout the length of the oesophagus and are located in the submucosa. These are small racemose glands of the mucous type and each open into the lumen by a long duct which pierces the muscularis mucosae. There are probably no more than 300 in total, of which the majority lie in the proximal half of the oesophagus. The relatively few glands present make the oesophagus a moist rather than a wet environment with the majority of fluid coming from swallowed saliva (approximately 1 litre per day). The principal reason for secretion is to lubricate food and protect the lower part of the oesophagus from gastric acid damage.

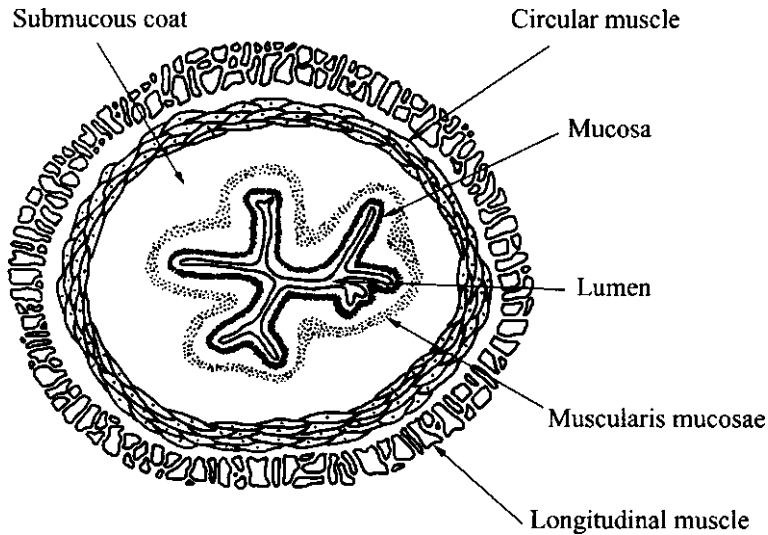


Figure 4.1 Cross section through the oesophagus

The oesophagus possesses both sympathetic and parasympathetic innervation. Extrinsic innervation consists of a supply from the vagus nerves and sympathetic fibres derived from the cervical and thoracic ganglia. The intrinsic supply is derived from the Auerbach and Meissner plexuses. Neurites are found in the circular muscle of the oesophagus. They also run over the surfaces of interstitial cells which are not present in the longitudinal layer. These cells are called interstitial cells of Cajal and they possess a round or oval nucleus and a long, flat broad process which extends between the muscle fibres. The precise function of these cells has not yet been discovered, but it is thought that they co-ordinate muscle contraction.

Gastro-oesophageal junction or cardia

The distal or lower oesophageal sphincter, also called the cardia, represents the transition between the oesophagus and the stomach. As no definite anatomical sphincter exists, there are several definitions of the lower oesophageal sphincter:

- a) the junction of squamous and columnar epithelium,
- b) the point at which the oesophagus enters the stomach,
- c) the junction between the oesophageal inner muscle layer and the inner layer of oblique muscle of the stomach (Figure 4.2).

These features all occur in the human stomach within 1 cm of each other. The definition by manometry is a high pressure zone, 2 to 6 cm in length, with an intraluminal pressure of 15 to 40 mm Hg above intragastric pressure. This "sphincter" prevents gastrooesophageal reflux, i.e. acidic gastric contents from reaching stratified epithelia of the oesophagus, where it can cause inflammation and irritation.

MOTILITY OF THE OESOPHAGUS

Swallowing is a highly complex set of events controlled by a swallowing centre in the medulla. A normal adult swallows between 100 and 600 times per day, one-third of these accompany eating and drinking and the remaining events occur when breathing out. Relatively few swallows occur during sleep (<10%). The primary stimulus for swallowing food is provided by sensory stimuli originating from receptors located within the sensory

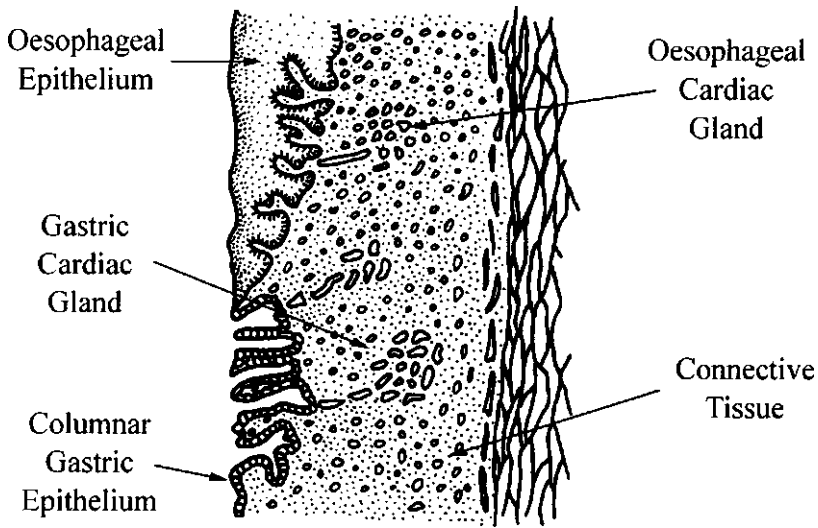


Figure 4.2 Transverse section through the cardia

fields of the mouth and pharynx. Non-prandial swallowing is driven by salivation and occurs without apparent cerebral participation

The resting pressure in the oesophagus reflects the changes due to breathing which cause cycles of positive and negative intrathoracic pressure between -5 to -10 mm Hg (Torr) during inspiration, to 0 to $+5$ mm Hg during expiration. On swallowing, the upper oesophageal sphincter relaxes for a period of about 1 second and then constricts. The swallow is associated with a transient decrease in pressure followed by a primary peristaltic wave of high pressure which travels towards the stomach at a speed of 2 to 6 cm s^{-1} in the proximal oesophagus, gradually becoming faster by the time it reaches the distal oesophagus (Figure 4.3). The lower oesophageal sphincter relaxes usually about 2 seconds after the initiation of swallowing for a period of 5 to 10 seconds allowing entry of the swallowed bolus.

The peak of the peristaltic wave is usually above 40 mm Hg, but there is considerable intra-subject variation. If a second swallow is taken before the peristaltic wave from the first swallow has reached the base of the oesophagus, then the initial peristaltic wave is

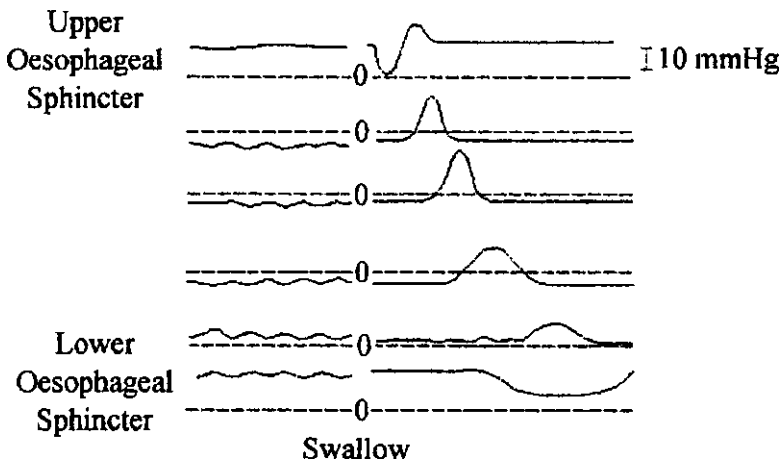


Figure 4.3 Progression of a peristaltic wave through the oesophagus

interrupted by the second peristaltic wave. When swallows are repeated in quick succession, then the contraction of the oesophagus is inhibited until the last swallow occurs; only the final peristaltic wave proceeds uninterrupted to the cardia carrying any food bolus or drug formulation with it.

If the subject is upright, gravity assists the movement of the swallowed material which may arrive at the lower oesophageal sphincter before relaxation has begun. This is especially true for non-viscous liquids whose entry in stomach may be slightly delayed until the lower oesophageal sphincter relaxes. Secondary peristaltic waves arise from distension of the oesophagus and serve to move sticky lumps of food or refluxed materials into the stomach. Initiation of secondary peristalsis is involuntary and is not normally sensed. Variation in the size of the bolus being swallowed leads to a variation in the amplitude of oesophageal contraction.

The pH of the oesophagus is between 6 and 7. After a meal, reflux of gastric acid is seen as sharp drops in pH which rapidly return to baseline. This is a normal physiological occurrence. Gastro-oesophageal reflux disease (heartburn) occurs when gastric acid damages the oesophageal mucosa either through prolonged contact or reduced resistance of the mucosa to damage.

OESOPHAGEAL TRANSIT OF DOSAGE FORMS

Measurement

Oesophageal transit is usually assessed clinically by x-ray study of a swallowed bolus of barium sulphate suspension. Very early studies also used barium to assess oesophageal transit of variety of substances such as gelatin cylinders², marshmallows^{3 4}, cotton pledgets, tablets^{5 6} and capsules⁷. However, later studies demonstrated that dense materials such as barium have faster transit than more physiological substances. In addition, X-ray contrast techniques are difficult to quantify and are associated with a significant radiation burden on the subjects. Consequently, gamma scintigraphy has become the method of choice to assess oesophageal transit. It has the advantages that any suitably labelled test material, food or dosage forms can be followed and radiation dosimetry is very small allowing repeat studies in individuals. It is a quantifiable technique since transit can be expressed as position of radioactivity against time (Figure 4.4).

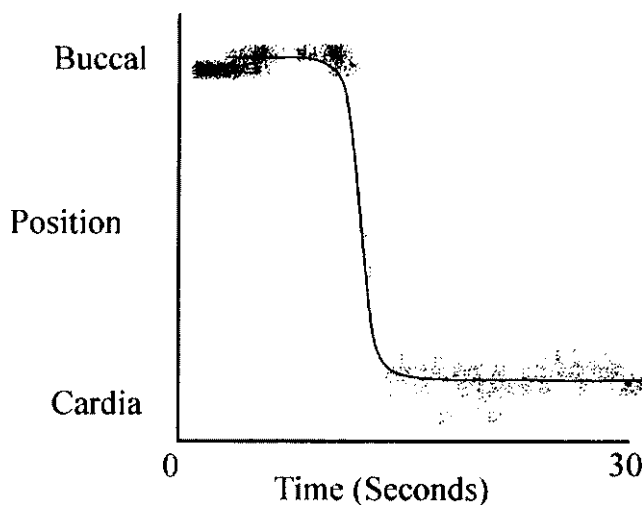


Figure 4.4 Plot of position of activity versus time for a swallow of technetium-99m—DTPA labelled water

Table 4.1 Typical transit times for various pharmaceutical dosage forms *ODT—Orally dissolving tablet

Formulation	Weight & dimensions	Transit time Seconds	Posture
Tablet Round	100mg 6mm diameter	13	Supine ⁸
Tablet Oval	14mm x 9mm Film-coated	3	Erect ⁹
Tablet Oval	14mm x 9mm, Film-coated	>300	Supine ⁹
Tablet Oval	14mm x 9mm	>300	Supine ⁹
Tablets	Various sizes & shapes	8	Supine ¹⁰
Tablets	Various	4	Erect ¹¹
Capsule	Hard gelatin, Size 2	10	Supine ¹²
Capsule	Hard gelatin, Size 2 (0.59g)	10	Supine ¹¹
Capsule	Hard gelatin, Size 2 (1.2g)	80	Supine ⁹
Capsule	Hard gelatin, Size 2 (0.59g)	9	Erect ⁹
Capsule	Hard gelatin, Size 2 (1.2g)	3	Erect ⁹
Capsule	Hard gelatin, Size 0 (1.2g)	3	Erect ⁹
Capsule	Hard gelatin, Size 0 (1.2g)	45	Supine ⁹
Capsule	Hard gelatin, Size 0 (0.67g)	9	Erect ⁹
Capsule	Hard gelatin, Size 0 (1.2g)	9	Supine ⁹
Liquid	10 ml	9	Supine ¹²
Zydis™	12 mm diameter, 0.25 ml	14	Supine ¹²
Suspension	90 – 125 µm (5 mg)	9	Seated ¹⁴
Suspension	20 – 40 µm (5 mg)	7	Seated ¹⁴
ODT*	90 – 125 µm (5 mg resin)	35	Seated ¹⁴
ODT*	20 – 40 µm (5 mg resin)	39	Seated ¹⁴
Water	1.5 ml	8	Seated ¹⁴

Typical transit times

Normally, the oesophageal transit of dose forms is extremely rapid, usually of the order of 10 to 14 seconds. Typical transit times for various pharmaceutical dosage forms are shown in Table 4.1

These data suggest that large oval tablets have a shorter oesophageal transit than large round tablets, but the influence of size and shape of formulations on oesophageal transit is insignificant when compared to the influence of the posture of the subject. Oesophageal transit is slower in supine patients than upright ones. Although studies are often carried out in supine patients to eliminate the effects of gravity, the differences in oesophageal transit produced with varying size and shape of a tablet are only observed in upright subjects and not supine ones. Interestingly, the transit of a heavy capsule is significantly faster than a light capsule in erect subjects, but the order is reversed in supine subjects¹⁵. The transit of large but not small capsules is significantly faster than plain oval tablets in both erect and supine volunteers¹⁵.

Bolus composition can markedly affect transit. Liquids clear rapidly, with one swallow regardless of whether the subjects were supine or seated, but capsules or liver cubes when ingested without water, frequently remained in the oesophagus up to 2 hours after administration, without the subject being aware of their presence¹³.

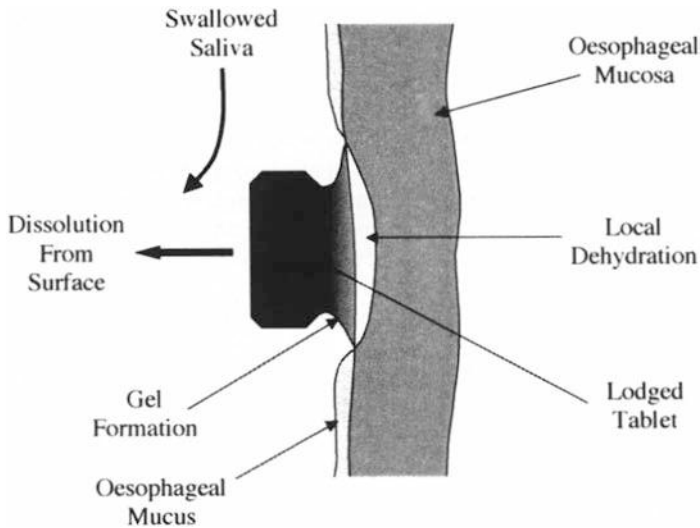


Figure 4.5 Mechanism of adhesion of a dosage form

OESOPHAGEAL ADHESION OF DOSAGE FORMS

There are normal anatomic narrowings of the oesophagus located at the cricopharyngeus, aortic arch and left main stem bronchus which increase the contact time of a bolus and hence are potential sites for adhesion in healthy subjects. It is well recognised that there is approximately a 20% incidence of adhesion of dosage forms to the oesophagus, particularly for tablets or capsules. Only 3% of patients are aware that the tablet/ capsule has stuck in the oesophagus¹⁶. The risk of adhesion of dosage forms to the oesophagus is increased to about 50% for people who take their medication whilst recumbent or semi-recumbent and/ or who take formulations with little or no water. If patients sleep whilst the dose form is lodged in the oesophagus, disintegration will be very slow since saliva production is greatly reduced compared to waking levels.

The recommended method of taking tablets and capsules to avoid oesophageal retention is upright, with a sip of water before the dose form and then at least 100 ml of water with the medication. Hospital dosing cups in particular should be marked with a minimum fill line for water to assist staff to give the correct amount when dosing patients, particularly since they are likely to be recumbent or semi-recumbent.

Although the outer surface of many dosage forms will rapidly disintegrate when placed in fluid under sink conditions, the small amount of fluid available in the oesophagus will only moisten the surface. If this quickly becomes sticky, then the dosage form has the potential to adhere, a problem that is exacerbated by the highly folded nature of the oesophageal lumen in the resting state which will press the sticky dosage form against the mucosa. The mucosa will partly dehydrate at the site of contact as the unit hydrates, resulting in formation of a gel between the formulation and the mucosa (Figure 4.5). The unit then disintegrates from its non-contact side. Disintegration of the lodged formulation is slow, firstly because the amount of dissolution fluid available is low, being dependent on the volume of swallowed saliva and secondly due to the reduced surface area available for dissolution.

In some patients, solid dosage forms will still adhere to the oesophagus even when reasonable volumes of water are taken, these patients may have reduced peristaltic pressures or have cardiac pathologies in which the left side of the heart is enlarged. In these patients

liquid preparations should be used or alternative routes of drug administration should be explored to avoid oesophageal damage by delivery of high concentration of drug to a small area of mucosa.

Factors predisposing formulations to adhere

There have been many studies carried out examining the potential for various dosage forms to adhere in the oesophagus. The main discrepancies in the literature arise from whether the data is derived from *in vitro* preparations of animal oesophagus or human studies. *In vitro* studies often use isolated porcine mucosa. Here the formulations are moistened, placed in contact with the mucosa and the force required to detach them is measured. *In vivo* studies generally measure transit in humans using fluoroscopy or gamma scintigraphy. In the transit studies all the factors which influence the tendency of a formulation to adhere e.g. shape, size, density etc are measured, whereas the *in vitro* experiments only study the tendency of the surface layer to adhere.

Tablets are often coated to render them more acceptable to the patient or to protect the drug from gastric acid etc., but the coatings themselves may affect the tendency for formulations to adhere. *In vitro* studies using isolated oesophageal preparations have concluded that hard gelatin capsules had the greatest tendency to adhere, followed by film coated tablets, uncoated tablets, with sugar coated tablets demonstrating the least adhesion^{17 18}. It was estimated that hard gelatin capsules have 6 times the tendency to adhere than that of sugar coated tablets and 1.5 times that of soft gelatin capsules when calculated per unit area. The difference between hard and soft gelatin capsules in their tendency to adhere is not borne out in human studies¹⁶. Although coated tablets have significantly shorter oesophageal transit times than plain tablets, if they do lodge, they take longer to disintegrate. Coatings made from cellulose acetate phthalate, shellac, methacrylate copolymer and a copolymer composed from vinyl acetate and crotonic acid all have a low tendency to adhere. The tendency of hydroxypropylmethylcellulose to adhere can be altered by incorporation of sucrose which reduces surface stickiness; conversely addition of lactose or titanium oxide and talc increases the tendency to adhere. In contrast, polyethylene glycol 6000 coating demonstrated the greatest tendency to adhere.

A variety of studies in humans have demonstrated that capsules lodge in the oesophagus with a much higher incidence than tablets^{10-12 19}. If the passage through the oesophagus of a hard gelatin capsule is delayed for more than two minutes, it can absorb sufficient water to become adherent to the mucosa. Apart from gelatin, other materials which become sticky as they hydrate are cellulose derivatives and guar gum. Recently it was reported that guar gum, formulated into a slimming product, hydrated and formed a large viscous mass which was sufficient to cause oesophageal obstruction²⁰. A further report of an anhydrous protein health food tablet, which adhered to the oesophagus so firmly that it had to be removed at endoscopy, shows that it is not only pharmaceutical dosage forms which have potential to stick, but now nutraceuticals also have to be evaluated for this possible hazard²¹.

Dosage forms are being developed which can be swallowed with little or no water. There has been some concern that material from these dose forms is retained in the mouth and oesophagus since they rely on saliva for clearance. The Zydis[®] formulation (Scherer DDS Ltd) is an examples of rapidly disintegrating solid dosage forms which can be taken without water. The general pattern of buccal clearance of the fast dissolving dosage form was either to dissolve rapidly in the mouth and hence clear with several swallows, or to pass intact through the oesophagus (Figure 4.6)¹².

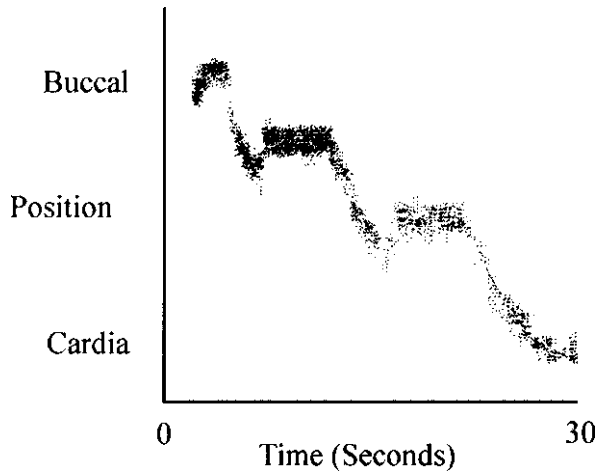


Figure 4.6 Clearance of a fast-dissolving dosage form from the oesophagus

CONSEQUENCES OF ADHESION OF DOSAGE FORMS

Delay in drug absorption

Retention of the dosage form in the oesophagus can delay drug absorption and consequently the onset of action (Figure 4.7)²². Drugs cannot easily pass through the stratified squamous epithelium of the oesophageal mucosa. Passage of the drug into the stomach and through to the small intestine where they are absorbed will be dependent upon the disintegration time of the unit in the oesophagus.

Oesophageal damage

If a dosage form adheres to the oesophagus, a very concentrated solution of drug is presented to an extremely small area of the mucosa and it is not surprising that oesophageal injury can occur. Repeated insult to the mucosa can result in dysphagia and even stricture formation, both of which exacerbate the original problem. Drugs which are irritant to the gastric mucosa are often given as enteric coated formulations; however, failure of these coatings may result if units lodge in the oesophagus where the pH is near 7.

Medication induced oesophageal injury was first reported in 1970¹, and was reviewed 1983²³. During the period between 1960 and 1983, 221 cases were reported due to 26 different medications, and since then there have been numerous reports in the literature^{24 25}. Antibiotics account for half the reported cases regardless of brand, although it has been reported for numerous other drugs including emepronium bromide, theophylline, doxycycline monohydrate and bisphosphonates²⁶. This may reflect the various proportions of drugs which are prescribed, but this has not been studied. Endoscopic surveillance in healthy volunteer studies has shown that oesophagitis is detectable in 20% of subjects taking non-steroidal anti-inflammatories (NSAIDs)²⁷. NSAIDs are also believed to have a causative role in oesophageal stricture in patients with gastro-oesophageal reflux²⁸.

Drugs can cause local injury by a range of mechanisms including caustic or acidic effects, hyperosmotic effect, heat production, gastro-oesophageal reflux, impaired oesophageal clearance of acid and accumulation within the basal layer of the epithelium, in addition to any specific toxic effects caused by the drug.

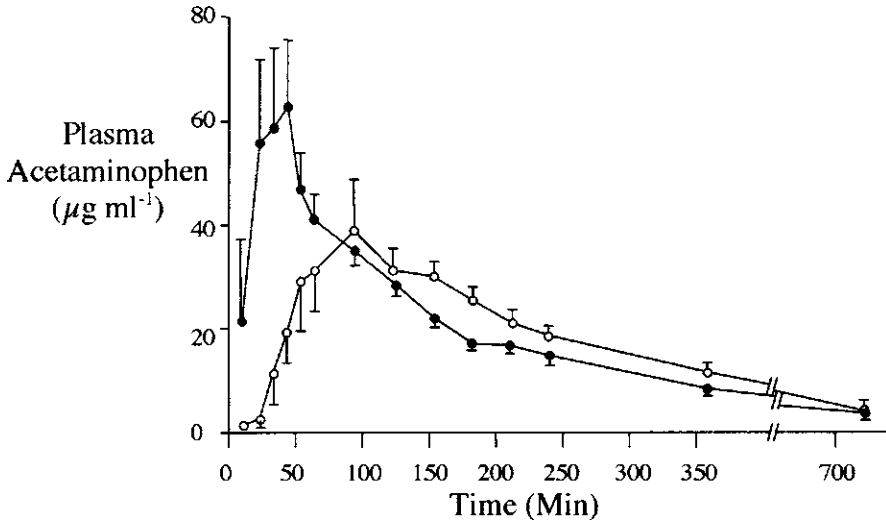


Figure 4.7 Plasma concentrations of 400 mg acetaminophen in patients with delayed oesophageal transit (○) and normal transit (●)²³

Endoscopy demonstrates a redness and friability of the mucosa, an erosion about the size of a coin, or a deep ulcer²⁹. Occasionally particles of drug may be seen to be adhered to the mucosa. The majority of lesions are located at the level of the aortic arch or slightly above it (Figure 4.8). Less commonly lesions can be seen higher in the oesophagus, particularly in bedridden patients. Lesions have also been reported in the lower third of the oesophagus, just above the gastro-oesophageal junction. In severe cases, stricture may result. Most patients are apparently healthy people who are suddenly hit by symptoms of oesophageal injury. Men and women alike are affected and patients between 9 and 98 years of age have been reported in the literature. A single dosage form can cause problems, particularly if the patient takes the tablets/capsules immediately before retiring to bed and without water. The patient wakes up a few hours later, or in the morning with severe retrosternal pain which is not relieved by drinking or eating. The patient avoids swallowing as it is painful. If medical attention is sought, a doctor will rule out heart disease and prescribe an analgesic or antacid. The pain can persist for days and will only resolve when the patient alters his method of taking medication.

EFFECT OF AGEING

Impairment of the ability to swallow with advancing age has been identified as a major healthcare problem in an ageing population. Radiological studies of an asymptomatic group of 56 patients with a mean age 83 years showed that a normal pattern of deglutition was present in only 16% of individuals³⁰. Oral abnormalities, which included difficulty in controlling and delivering a bolus to the oesophagus following ingestion, was noted in 63% of cases. Structural abnormalities capable of causing oesophageal dysphagia include neoplasms, strictures and diverticula although only minor changes of structure and function are associated directly with ageing. The difficulty appears therefore to relate to neurological mechanisms associated with the coordination of tongue, oropharynx and upper oesophagus during a swallow.

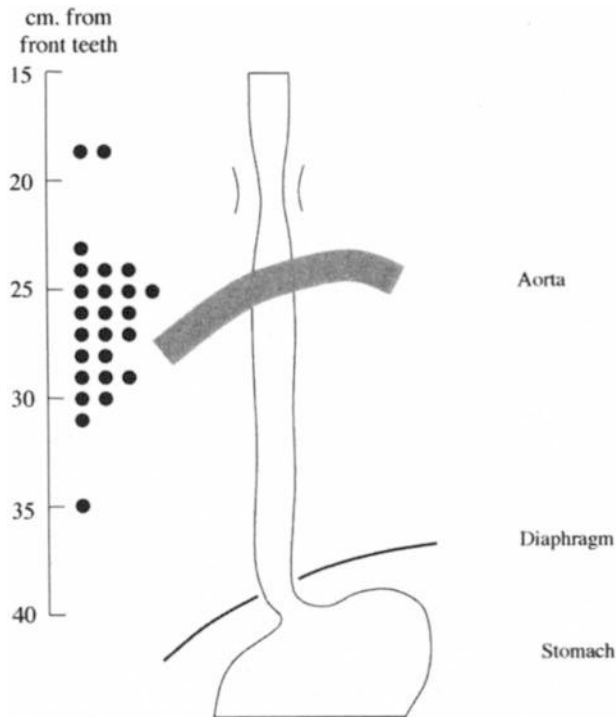


Figure 4.8 Location of twenty five drug induced ulcers, (scale on the left hand side indicates distance of the lesions from the teeth²⁹)

Impaired swallowing in the elderly will result in even small tablets (4 mm) adhering to the oesophagus³¹. Low dose tablets, including the aminobisphosphonates used to inhibit bone resorption, have been reported to cause ulceration³². This has led to a FDA recommendation that these medications be consumed with 240 ml water, the subject to remain erect for 30 minutes after administration. Dosage forms which float on the co-administered water may also present problems to the elderly by sticking to the roof of the oropharynx.

PATIENT PREFERENCE AND EASE OF SWALLOWING

Patients prefer taking capsules to large oval or round tablets, partly due to the smooth surface and the shape which assists swallowing. The difficulty in swallowing large round tablets increases over the age of 60 years when up to 60% of healthy subjects may report a problem. There is a tendency amongst these patients to chew the tablets and capsules or to open the capsule and disperse the pellets in food or a drink. This can lead to an unknown loss of a proportion of the dose. Chewing formulations will destroy the integrity of any surface coating and it is a particular problem for sustained or controlled release formulations that are designed to be swallowed intact. Chewing will destroy matrix structures and increase the surface area available for drug dissolution.

EFFECT OF DISEASED STATES ON TRANSIT

Oesophageal transit may be influenced by diseased states such as oropharyngeal dysphagia or achalasia. Oral pharyngeal dysphagia is a common problem particularly in the elderly which carries a significant morbidity and mortality³³. Oral-pharyngeal dysphagia could be

Table 4.2 Potential risk factors for stricture development in subjects with pill-induced oesophageal damage³⁸

Risk factor	Pill-induced oesophageal damage without stricture	Pill induced oesophageal stricture
Age (years, mean \pm s.d)	36 \pm 19	60 \pm 16
Sex (M:F)	43:95	18:17
Number taking sustained release formulations	14/155 (9%)	17/33 (52%)
Number in reclining position	60/121 (50%)	18/25 (72%)
Number with left atrial engorgement	11/119 (9%)	15/25 (63%)
Number with pre-existing oesophageal disease	1/120 (1%)	5/32 (16%)

caused by neurogenic dysfunction, with stroke being the commonest cause, but could also be due to local structural lesions³⁴. Achalasia is caused by local structural lesions in which transit is impaired by an oesophageal stricture or inability of the lower oesophageal sphincter to relax. Oesophageal retention of food results. Additionally, abnormalities in oesophageal function can occur as a result of a variety of diseased states such as diabetes mellitus, chronic alcoholism and scleroderma, although an abnormality of the oesophagus is not a prerequisite for adhesion of dosage forms. Oesophageal dysfunction has been shown to be more common in asthmatics than normal subjects³⁵, so drugs such as theophylline may show an increased incidence of adhesion³⁶.

Reflux of gastric contents can cause injury to the oesophageal mucosa and the oesophagitis produced can lead to stricture. The acid reflux may actually exacerbate the oesophageal damage produced by some drugs such as doxycycline monohydrate which are poorly water soluble and should produce little damage under normal conditions. If gastrooesophageal reflux of acid occurs, the monohydrate may be converted to the highly ulcerogenic hydrochloride. In humans, this problem would be compounded since delayed transit is associated with hiatus hernia and gastro-oesophageal reflux with typical clearance times of 50 s compared to 9.5 s in normals³⁷.

Where there is an existing stricture due to reflux or previous 'pill-induced' damage, the likely hood of further damage is increased. Risk factors associated with age, posture and formulation for stricture and non-stricture groups illustrated in Table 4.2³⁸.

TARGETING THE OESOPHAGUS

In the past attention has been focused on reproducible smooth and rapid oesophageal transit. In some instances, for example in the treatment of oesophageal damage from gastrooesophageal reflux or oesophageal cancer, delivery of drugs to the oesophageal mucosa would be desirable. In 1990, the use of ultrafine ferrite (γ -Fe₂O₃), utilising a dye and polymer as an adhesion/release controlling delivery system was reported for the delivery of drugs to treat oesophageal cancer³⁹. More recently, poly (oxyethylene-b-oxypropylene-b-oxyethylene)-g-poly (acrylic acid) which is composed of polyacrylic acid and a block copolymer of ethylene oxide and propylene oxide has been explored for this use. The material shows strong mucoadhesive properties and undergoes reverse thermal gelation at body temperature⁴⁰. Approximately ten percent of the formulation was observed to remain in the oesophagus 10 minutes after administration (Figure 4.9).

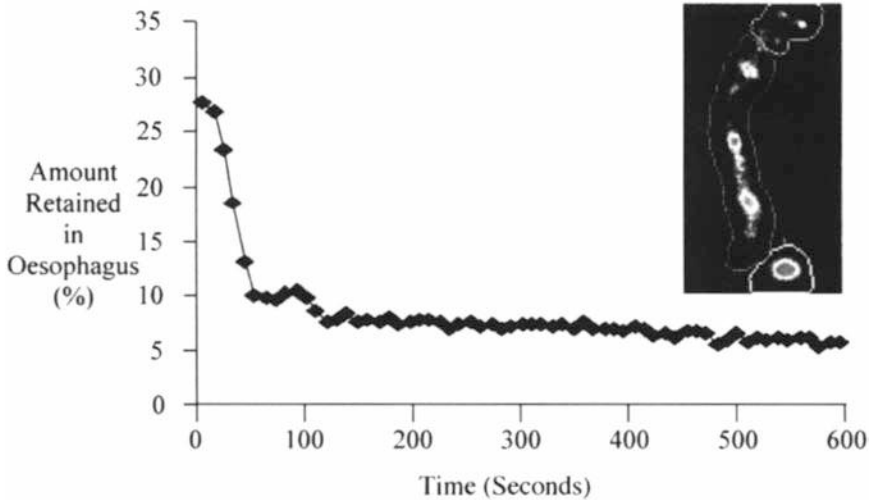


Figure 4.9 Distribution of smart hydrogel

CONCLUSIONS

Oesophageal adhesion of dosage forms is surprisingly common and can cause problems of local ulceration or delayed drug absorption. In general, there are several factors which predispose a formulation to adhere: a) shape of dosage form, b) size of dosage form, c) position of subject, d) volume of water with which the dosage form is administered, e) surface characteristic of the dosage form. It is important to emphasise the correct method of swallowing tablets, particularly in high risk groups. New technologies are emerging which can locally delivery drugs to treat disorders of the oesophagus.

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