

Unit 3: Gastro-Retentive and Buccal Drug Delivery Systems

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3.1 Gastro-retentive systems: principle and concepts

A gastro-retentive drug delivery system (GRDDS) is designed to stay in the stomach for a prolonged, predictable time instead of emptying with the normal gastric contents. Normal gastric residence of a dosage form is short and variable, often under 2 to 3 hours, and is decided by the migrating myoelectric complex, the housekeeper waves that sweep the fasted stomach roughly every 90 to 120 minutes.

Why retain a form in the stomach at all? Four clear reasons:

- The drug has an **absorption window** in the stomach or upper small intestine (for example levodopa, furosemide, riboflavin, many weak bases) and is lost if the form travels beyond it.
- The drug **acts locally in the stomach** (antacids, and antibiotics against *Helicobacter pylori* such as amoxicillin and clarithromycin combinations).
- The drug is **more soluble or more stable in acid** and dissolves better if released slowly into gastric fluid (weak bases that precipitate at intestinal pH).
- **Sustained local supply** to the upper gut smooths the plasma profile for short half life drugs absorbed mainly from that region.

Basic physiological facts the design must respect: gastric fluid volume is small at rest (about 25 to 50 mL) and rises with food and fluid intake; a fed stomach empties solids slowly over hours, while the fasted stomach clears even large objects in the next housekeeper wave; objects larger than the pyloric opening (about 12 to 15 mm in the fed state) are retained longer; posture, age, sex and disease (diabetic gastroparesis, for example) all shift emptying.

Advantages: better bioavailability for window absorbed drugs, reduced dosing frequency, local action at a controlled rate, and less drug wasted in the colon. **Disadvantages:** retention is never guaranteed in the fasted state, large single units can be uncomfortable and carry a small risk of obstruction in narrowed stomachs, drugs that irritate the gastric mucosa or are unstable in acid are excluded, and food dependence makes performance differ between patients and days.

3.2 Modulation of GI transit time: approaches to extend GI transit

The recognised approaches, which are also the formulation methods for GRDDS:

Gastro-Retentive Floating System

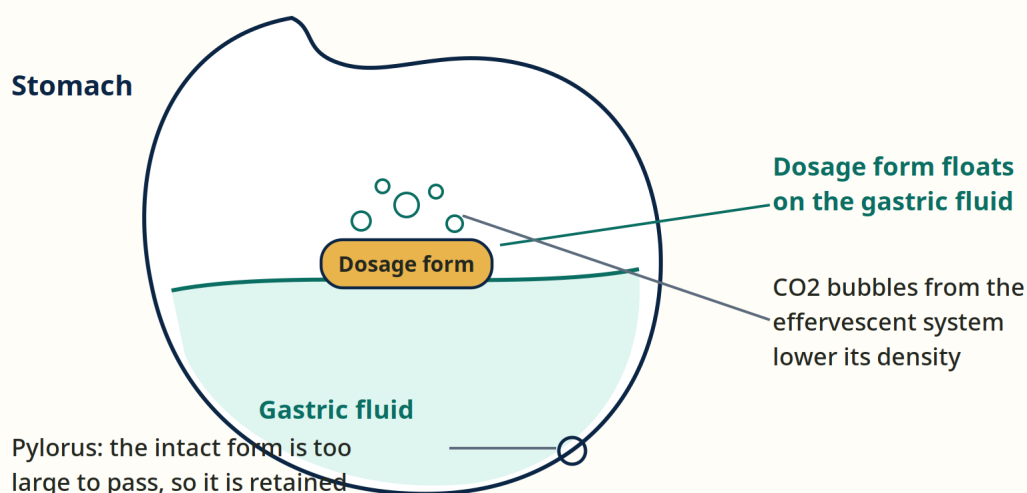


Figure: A floating gastro-retentive system stays buoyant on the gastric contents and is too large to pass the pylorus while intact.

Approaches to extend gastric residence time

Floating systems	-> density below gastric fluid, form floats on contents
- effervescent (gas generating) and non effervescent (swelling gel) types	
High density systems	-> density about 2.5 g per mL or more, form sinks and is held in the antrum folds
Expandable / swelling systems	-> form swells or unfolds larger than the pylorus after swallowing, shrinks later for exit
Mucoadhesive systems	-> form sticks to the gastric mucosa
Magnetic systems	-> internal magnet in the form, external magnet on skin
Raft forming systems	-> viscous gel raft floats on gastric contents (the alginate raft principle of antacid products)

- **Floating systems:** the dosage form has an overall density below that of gastric fluid (1.004 to 1.01 g per mL). Effervescent systems generate carbon dioxide inside a polymer matrix (sodium bicarbonate plus citric or tartaric acid with a hydrocolloid such as HPMC); the gas is trapped and the form floats, releasing drug by diffusion and erosion. Non effervescent systems swell into a gel that traps air. Evaluation must report floating lag time and total floating duration.
- **High density systems:** pellets or tablets made dense with inert heavy materials (barium sulphate, iron powder, zinc oxide, titanium dioxide) sink to the bottom of the stomach and resist the housekeeper waves in the antral folds.
- **Expandable and unfoldable systems:** a capsule sized form that, once in the stomach, swells (superporous hydrogels) or unfolds (spring like or geometric shapes of biodegradable polymer film) to a size the pylorus cannot pass, then degrades or softens after the release period so it can leave safely. The safety rule is absolute: the exit mechanism must be as reliable as the retention mechanism.
- **Mucoadhesive systems:** polymers such as carbopol, chitosan and HPMC hydrate and bond to gastric mucin (mechanism in Section 3.4). Gastric mucus turns over quickly, which limits how long adhesion alone can retain the form.
- **Magnetic systems:** a small magnet inside the form and an external magnet worn over the stomach hold the form in place; effective in studies, limited in practice by patient acceptance.
- **Evaluation of GRDDS in general:** buoyancy tests for floating forms (lag time, duration), swelling index for expandable forms, in vitro release in simulated gastric fluid, mucoadhesive strength where relevant, and in vivo confirmation by gamma scintigraphy or X ray with radio opaque markers, because in vitro retention claims are meaningless without imaging in humans.

3.3 Buccal drug delivery: the route and its logic

The buccal route delivers drug across the lining of the cheek into the systemic circulation. The buccal mucosa is relatively immobile, well supplied with blood, heals quickly after minor injury, and drains into the jugular vein, so the drug **avoids first pass metabolism and avoids the acid and enzymes of the stomach**. It suits potent drugs with heavy first pass loss, drugs destroyed in the gut, and situations where a patient cannot swallow or oral dosing is impractical (nausea, unconsciousness risk groups under supervision). Marketed logic examples: buccal and sublingual nitroglycerin for rapid angina relief, fentanyl buccal products for breakthrough pain, buccal midazolam for acute seizures, prochlorperazine buccal tablets for nausea.

Advantages: rapid onset, bypass of first pass and gut degradation, easy termination (the form can be removed), good patient acceptance compared with injections, and usefulness in emergencies.

Disadvantages: small surface area (the buccal surface is only about 50 cm²) and low total fluid volume limit the dose and dissolution; saliva flow washes the form and the drug away and causes swallowing of part of the dose; taste, mouth feel and irritation restrict candidates; eating, drinking and talking must be managed while the form is in place; only small, potent, moderately lipophilic drugs qualify.

3.4 Principle of mucoadhesion

Mucoadhesion is the attachment of a polymer based dosage form to a mucosal surface. It happens in two stages: first the **contact stage**, in which the polymer wets, swells and makes intimate contact with the mucus layer; then the **consolidation stage**, in which polymer chains interpenetrate the mucin chains and weak bonds (hydrogen bonds, van der Waals forces, electrostatic attraction) build a durable joint.

The theories used to explain it, any two of which may be asked:

- **Wetting theory:** the polymer spreads over the mucus like a liquid adhesive; good spreading (low contact angle) means good adhesion.
- **Diffusion or interpenetration theory:** polymer and mucin chains diffuse into each other to a depth of about 0.2 to 0.5 micrometres and entangle; needs similar solubility character and flexible chains.
- **Adsorption theory:** surface forces, mainly hydrogen bonding and van der Waals attraction, hold the joint; the most widely used explanation for dry polymer systems.
- **Electronic theory:** electron transfer between polymer and mucus creates an electrical double layer that attracts; applies to charged polymers such as cationic chitosan against negatively charged mucin.
- **Fracture theory:** adhesion is judged by the force needed to break the joint, which is the basis of detachment force measurement in evaluation.

Polymers used: carbopol (polycarbophil family) is the benchmark anionic mucoadhesive; chitosan is the main cationic one and also opens tight junctions slightly; HPMC, hydroxypropyl cellulose, sodium carboxymethyl cellulose, sodium alginate, pectin and xanthan are common partners, often blended to balance adhesion, release rate and comfort. Second generation ideas (thiolated polymers forming disulphide bonds with mucin, and lectin based targeting) increase bond strength but belong to advanced discussion, one line is enough at this level.

3.5 Mechanism of drug permeation across the buccal mucosa

The buccal epithelium is a stratified squamous, non keratinised lining about 500 to 800 micrometres thick. Drug crosses by:

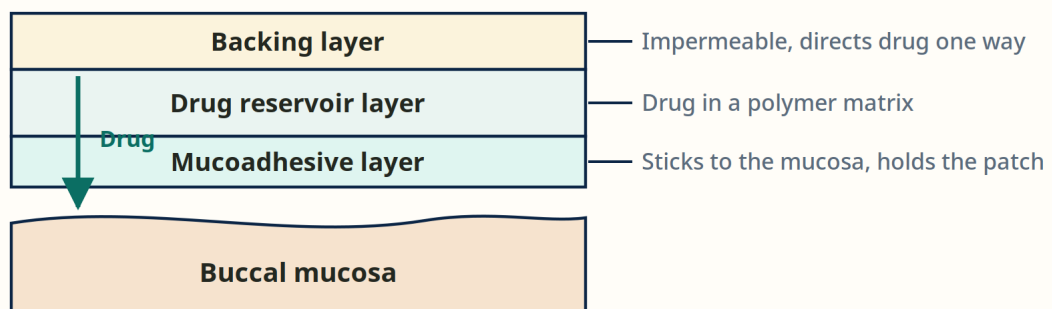
- **Transcellular route:** through the cells; favoured by lipophilic drugs that partition into cell membranes, crossing many lipid bilayers in series.
- **Paracellular route:** between the cells through the intercellular spaces; favoured by small hydrophilic drugs, limited by the lipid material extruded between the upper cell layers, which is the main permeability barrier of the buccal mucosa.
- The barrier is therefore lipid in nature but the tissue is far more permeable than skin (no stratum corneum) and far less enzymatic than the gut, though saliva and mucosal enzymes (esterases, peptidases) still degrade sensitive drugs, which matters for peptides.
- **Permeation enhancers** used in research and some products: bile salts, fatty acids (oleic acid), surfactants, chelators and chitosan; each raises permeability by disturbing intercellular lipids or tight junctions, and each must pass irritation and reversibility checks.

Only the unionised, moderately lipophilic fraction crosses well, so buccal pH (about 6.2 to 7.4 in saliva) and drug pKa decide the absorbed fraction, the same pH partition logic as the gut.

3.6 Methods of formulation of buccal systems

- **Buccal tablets:** small flat tablets, often bilayer, with drug and mucoadhesive polymer, and an impermeable backing layer (for example ethyl cellulose) so the drug is released towards the mucosa only, not into saliva. Made by direct compression.
- **Buccal films and patches:** thin flexible films cast or hot melt extruded from film forming polymers with plasticiser; they conform to the cheek, are discreet, and are the most comfortable modern form. Multilayer films add a backing and a separate drug layer for unidirectional release.

Buccal Patch: Layer Structure



Drug crosses the mucosa into its rich blood supply, reaching the systemic circulation and avoiding first pass metabolism in the liver

Figure: Layers of a buccal patch, from the impermeable backing to the mucoadhesive layer that holds it on the mucosa.

- **Buccal gels, ointments and pastes:** semi solids with mucoadhesive gel bases; easier to apply over a larger area but shorter residence and less dose accuracy.
- **Sprays and liquids:** metered sprays coat the mucosa for rapid absorption of potent drugs; residence is short, so they suit rapid onset more than sustained action.
- **Wafers and lyophilised forms:** fast dissolving porous wafers for rapid release on the mucosa.

3.7 Evaluation of buccal systems

The standard evaluation set for a buccal formulation in practical and exam work:

- **Physical tests:** weight and thickness uniformity, surface pH (must sit near saliva pH to avoid irritation), folding endurance for films, swelling index.
- **Mucoadhesive strength:** measured as the force needed to detach the form from a mucosal surface (modified balance or texture analyser, using excised animal mucosa such as porcine or sheep buccal mucosa), and residence time in vitro and in volunteers.
- **In vitro release and permeation:** release into simulated saliva in a dissolution setup, and permeation across excised buccal mucosa in a Franz diffusion cell to get flux and permeability coefficient.
- **In vivo checks:** residence time, irritation and acceptability in volunteers, and pharmacokinetic comparison against the reference route to prove the first pass advantage.
- **Stability:** drug and adhesive performance after storage, since a polymer that loses tack or a film that turns brittle fails the whole concept.