

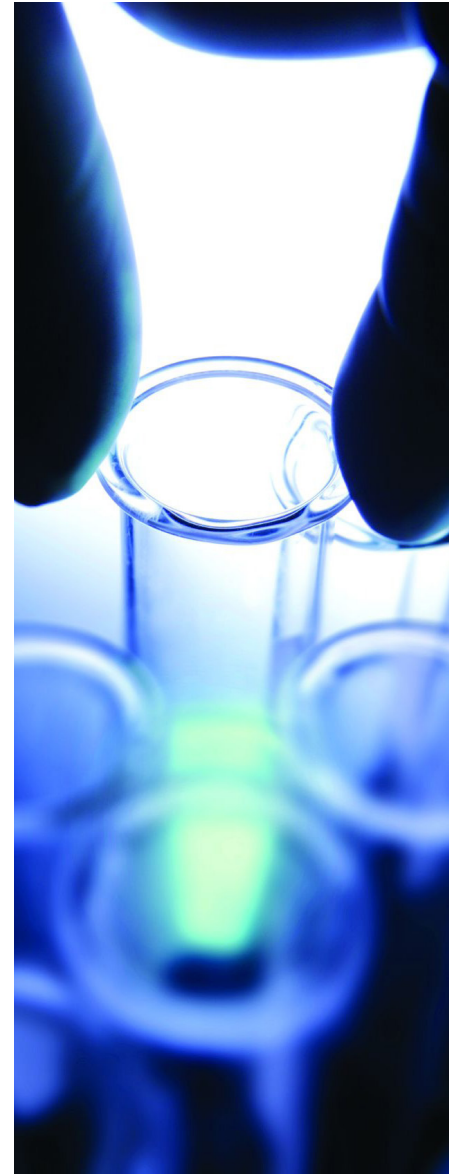
Choosing and Developing User-friendly Osmotic Laxatives for a More Patient-centric Portfolio

At least 1 in 10 people worldwide suffer from constipation at some point in their lives.^{1,2} It affects people of all ages and has many causes. The symptoms of constipation include pain in the lower abdomen and irregular and painful bowel movements. Laxatives are often needed in addition to dietary changes to treat constipation. There are many laxatives to choose from, each with different mechanisms of action and, consequently, different advantages and disadvantages. Here we look at the important role of osmotic laxatives, how they overcome many of the side effects and drawbacks of other constipation treatments, and the manufacturing expertise needed to make user-friendly laxatives part of a patient-centric product portfolio.

increases with age because of factors such as medicine use, underlying disease, change in drinking and diet habits, weakened pelvic floor muscles and long-term hospitalisation or institutionalisation. Women are twice as likely to be affected by constipation as men, especially during pregnancy where hormones influence bowel muscle movement.^{2,3}

For most people, constipation is caused by not drinking enough water or not eating enough fiber, but it is also a common side effect of taking certain medicines (e.g., opioids and diuretics), and can be associated with conditions such as anxiety or depression and gastrointestinal disease.

Some people experience acute constipation, which lasts for only a few hours and often results from lifestyle changes, such as travel or stress. For others, constipation becomes a chronic condition (obstipation) where symptoms persist for more than three months and have a significant impact on quality of life. They may not be able to pass stools at all, or they may pass stools that are hard, cause pain and lead to secondary



Constipation:

Prevalence, Causes and Treatment

Constipation affects many of us, but it is more common in older people, women and children.² The prevalence of constipation

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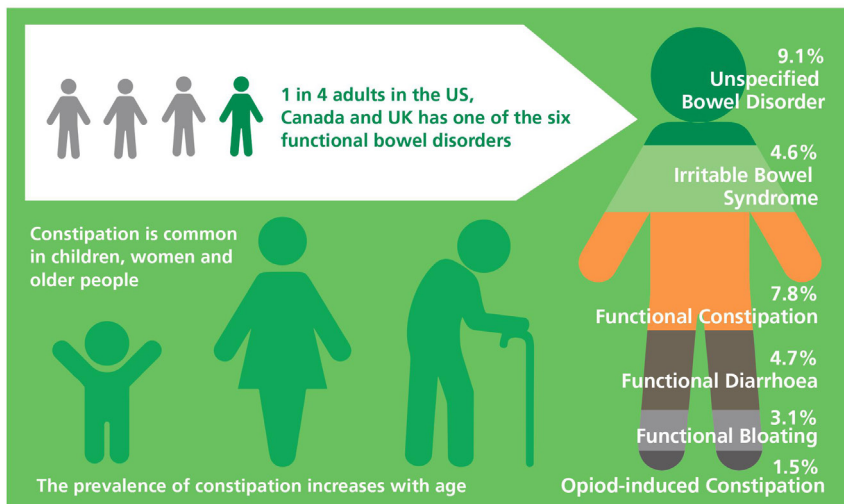


Illustration 1: The prevalence of constipation

issues such as anal tears (fissures) or even fainting or heart attacks in the elderly.²

Treatment for adults usually involves increasing water and fiber intake as well as upping exercise levels, and laxatives may be offered if symptoms don't improve. In children, laxatives are usually offered as first-line standard care because constipation can worsen quickly.

Types of Laxatives

There are many different laxatives available, each varying in their mechanisms of action, ease of administration and the side effects they can cause:

Type of laxative	Mechanism of action	Examples	Considerations/restrictions on use
Contact stimulant laxatives	<p>Increase fluid secretion into the bowel and prevent resorption of water</p> <p>Stimulate nerves in the bowel muscles, which increases bowel movement (peristalsis)</p>	<p>Bisacodyl (available as oral tablets and as suppositories)</p> <p>Sodium picosulfate (given as oral tablets often before a colonoscopy or bowel surgery)</p> <p>Anthraquinones found in plants such as Senna</p>	<p>Side effects include irritation of the bowel lining and gastrointestinal spasms</p> <p>Can cause heart dysfunction</p> <p>May not be suitable for diabetics as they reduce the effectiveness of insulin</p>
Softeners and emollients	Lubricate the intestine wall and soften stools to make them easier to pass	<p>Paraffin</p> <p>Glycerol</p> <p>Sorbitol</p>	<p>Can lead to steatorrhea (fatty stools) and diarrhea</p> <p>Can reduce absorption of fat-soluble vitamins, such as vitamin K</p> <p>Some (e.g., glycerol) need to be administered as suppository or clysta (enema) so are fast-acting but only work within the rectum and not the large bowel</p> <p>In some countries, paraffin is not recommended for use in children under 18 or during pregnancy</p>
Bulk-forming laxatives	<p>Contain non-digestible substances that add bulk to stool</p> <p>Absorb water to increase the volume of stools</p> <p>Larger, softer stools stretch the internal bowel wall and trigger bowel movements</p>	<p>Psyllium husk (taken as a drink)</p> <p>Flaxseed</p>	<p>Additional stool bulk can cause bloating and abdominal pain</p> <p>Essential to drink plenty of water to avoid risk of bowel obstruction</p>
Osmotic laxatives	<p>Facilitate the drawing and retention of water into the gut, increasing stool volume and softness and triggering bowel movement</p> <p>Different types of osmotic laxatives stimulate water release into the gut in different ways</p>	<p>Lactulose</p> <p>Sugar alcohols</p> <p>Saline laxatives</p> <p>Macrogols</p>	<p>Some osmotic laxatives are metabolised, and others are not, leading to differences in side effects</p> <p>Most are given orally, but some are also available as enemas</p>

Table 1. Types of laxatives and considerations for use

In the rest of this article, we will look more closely at osmotic laxatives and discuss why these are considered one of the most patient-friendly and effective treatments for constipation in all age groups.

Osmotic Laxatives – A Patient-friendly Solution

Osmotic laxatives can be further divided into four groups: lactulose, sugar alcohols, saline laxatives and macrogols (polyethylene glycol).

- **Lactulose** is a non-absorbable disaccharide that is metabolised in the

gut. The metabolites bind water and draw it into the colon, softening stools.

- **Sugar alcohols** work in a similar way to lactulose: they are metabolised by intestinal bacteria to form acids which stimulate peristalsis, and the metabolites draw water from the gut mucosa, softening stools.
- **Saline laxatives** contain magnesium or potassium and work primarily by drawing water into the bowel and making stools softer and easier to pass.

- **Macrogols** (polyethylene glycol) work by binding the water they are consumed with to make stools slightly larger (which stimulates bowel movements) and softer (which makes stools easier to pass). There are different types of macrogols available, characterised by their mean chain-length. Macrogol 3350 and Macrogol 4000, which are mainly used, have approximately 3350 and 4000 ethylene units respectively, and they have virtually the same properties.

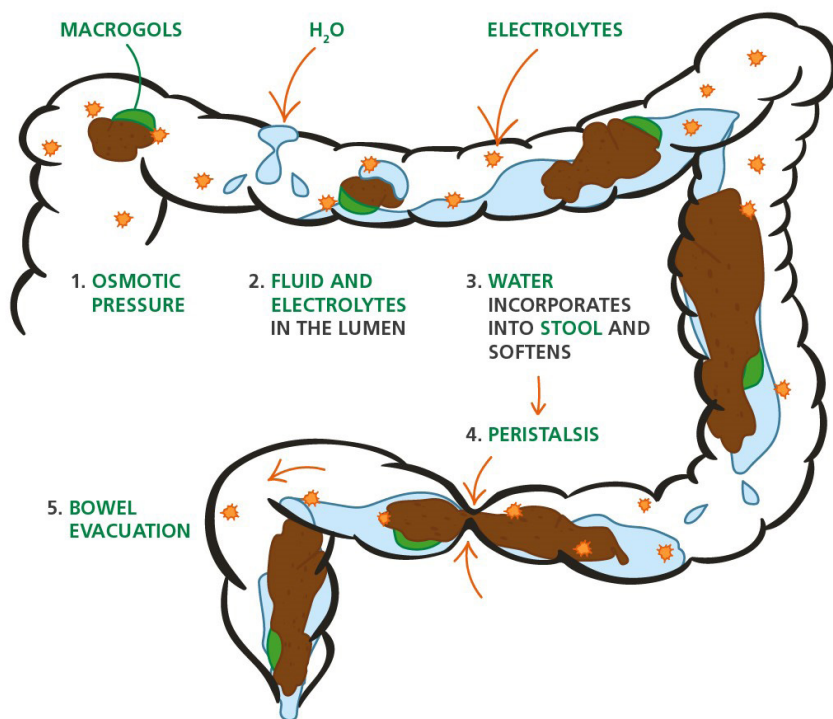


Illustration 2: Mechanism of action of macrogols in the large intestine

need to take more laxatives. In addition, when stools are hard, the body sends fewer reflexes to go to the toilet, which further worsens constipation. Thus, the patient needs greater laxative levels to achieve a bowel movement and the vicious cycle continues.

Some laxatives include salts to mitigate for this issue but taking these can be problematic for patients who have cardiovascular or renal disease and need to be on a low potassium or sodium diet. The impact of losing salts is also much worse for these patients. For example, in someone with cardiovascular disease, the heart already has a high workload, but an electrolyte imbalance requires it to work even harder.

Because macrogols have only a physical mode of action they avoid this issue with salt loss. Some macrogol products do contain electrolytes, but these are added in such a way as to balance the electrolyte

These four different classes of osmotic laxatives have different advantages and disadvantages, as summarised in Table 2.

	Ease of administration	Causes bloating	Causes abdominal pain	Affects microbiome or nutrient uptake	Safe for children?	Safe for those with renal impairment or diabetes?	Safe and effective for long-term use?
Lactulose	Oral	Y	Y	Y	Y*	N	N**
Sugar alcohols	Oral or rectal	Y	Y	Y	Y*	N	N
Saline laxatives	Oral or rectal	Y	Y	Y	N	N	N
Macrogols	Oral (as a drink)	N	N	N	Y	Y	Y

* For short term use only ** Although lactulose is often used long-term with patients in retirement/care homes.

Table 2. Advantages and disadvantages of osmotic laxatives.

From Table 2, macrogols stand out as the osmotic laxative that can be most widely used and that causes the fewest side-effects. They are easy to take as an oral solution and are also available as a dosage strength that is suitable for children from 6 months to 14 years. Further, they do not cause fermentation in the gut, so they avoid bloating and abdominal pain. Unlike softeners and emollients, macrogols do not affect the uptake of nutrients and, because they don't cause any changes to the gut microbiome, they can be taken long-term.

Macrogols can be classed as either a medicine or a medical device in the EU because it only has a physical mode of action and is non-resorbable. This makes it faster and easier for such products to be registered in Europe as the process

is centralised rather than being country specific. For the patient, the benefit comes through a simple physical mechanism of action that also ensures there is no loss of effectiveness over time. It is easy to add other substances to macrogol-containing products such as electrolytes to maintain salt balance, or prebiotics such as inulin, citrus fibers, or partially hydrolysed guar gum (PHGG) to improve intestinal flora, all of which contributes to improving bowel function long-term.

Avoiding Electrolyte Loss

A key general drawback with laxatives is the vicious cycle that occurs when they are used over a long time. Many laxatives cause electrolyte loss from the body into the stool, and this can cause stools to thicken. In turn, this leads to increased constipation and a

levels in the body and in the stool. This reduces the risk that electrolytes move from the body into the stool and keeps the patient in control of their condition.

The fact that these products are also classed as medical devices rather than medicines indicates that the notified bodies accept that the electrolytes are not absorbed by the body but simply balance electrolyte levels and have no pharmacological effect.

And that's Not All

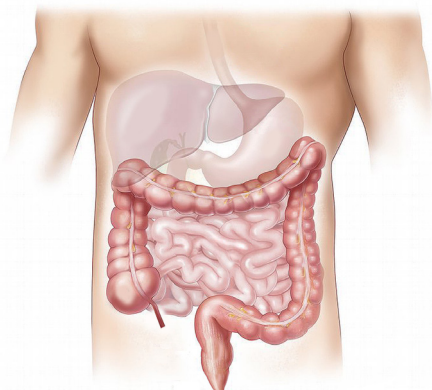
Beyond constipation, a physical laxative has several other applications. They can be used to empty the intestine before surgery, to induce labor when babies are overdue, and to flush the system ready for colonoscopy. The doses used will vary depending on the objective of treatment. For constipation and

stool softening, a daily dosage of around 10g for adults is sufficient. To clear the bowel before a colonoscopy, a dosage of around 40g is used.

Overcoming Formulation and Manufacturing Hurdles

Despite their many advantages for the patient, user-friendly macrogol products can be challenging to create, requiring a thorough understanding of the product and its components, as well as deep technical expertise in manufacturing and formulation. Product development should focus on end-product homogeneity and content uniformity. Specifically, the particle size distributions of macrogol and other ingredients must match to ensure good blend homogeneity. Even minor variability in particle size distribution can lead to dust formation, which compromises proper sachet sealing and risks ingress of moisture. Resultant product agglomeration can then create poor dissolution characteristics when mixed with water, or a change in the product's appearance when still in the sachet. Products suffering from such issues risk not meeting patient expectations, compromising brand reputation.

Flavoring macrogol products is not straightforward either, primarily because the large volume of macrogol dominates product composition. Creating a palatable and enjoyable product that patients are happy to buy repeatedly thus requires deep expertise in flavoring. For example, in macrogol products containing inulin or PHGG, which are generally included in the composition at doses above 500 mg, knowledge of which flavors will work optimally can avoid unnecessary trial and error, and accelerate product development and time to market.



Macrogol is also incompatible with several excipients, as they can cause the formation of formaldehyde upon storage, impacting product quality, reducing shelf life, and necessitating inconvenient storage restrictions (storing below 25°C, for example). Knowledge of these incompatibilities not only reduces product development time but also eliminates the need for additional storage restrictions, offering better convenience for the patient and additional selling points to differentiate from competing products.

To obtain high product quality, managing excellent supplier relations can't be overstated. Access to the right, high-quality raw materials and excipients, as well as reliable and consistent delivery performance, must be secured in order to deliver On Time and In Full (OTIF) – reducing the chances of being impacted by stock shortage.

Conclusion

Of the many types of laxatives available to treat constipation, osmotic laxatives are some of the easiest to use by virtue of their easy route of administration. Within this class, there are options that avoid the side effects that are common with other types of constipation treatment – namely, bloating, abdominal pain, and flatulence.

We know that patients are more likely to use laxatives if they are user-friendly: easy to take and avoid the discomfort and embarrassment of these common side effects, especially when they are needed for long term use.

As an example, macrogol is an easy-to-use alternative available in a range of formulations and doses that are safe for children as young as six months, and for older adults, including those with long-term health complications such as heart and renal conditions, and diabetes. It's wide applicability to all patients with constipation and the ability to register as a medical device rather than a medicinal product in the EU makes it a straightforward and patient-friendly addition to any company's portfolio of constipation treatments.

Although easy to use, macrogols are challenging to formulate, and so technical expertise in their formulation and manufacturing is key to ensuring they are effective, user-friendly and purchased again and again.

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