Thickening agents and thickened fluids: do they interact with medicines?

Prepared by a UK Medicines Information (UKMi) team for NHS healthcare professionals

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Background

Some people with dysphagia are unable to swallow thin liquids due to the risk of aspiration and require thickened fluids. The requirement for fluids to be thickened to the appropriate consistency also applies to medicines and any liquid used to swallow solid oral medication. These people are unable to safely swallow tablets and capsules with a glass of water (1).

Patients with dysphagia must be assessed by an appropriately trained health professional (a speech and language therapist) who will determine the appropriate fluid consistency, food texture and other swallowing recommendations for the individual (2-4). Fluid consistency and food texture is graded according to the International Dysphagia Diet Standardisation Initiative (IDDSI) framework; a continuum of eight levels with drinks graded from Level 0 ('thin' e.g. water) to Level 4 ('extremely thick' e.g. pureed food) and foods graded from Levels 3 to 7 (5). It is important that patients who require diet modification receive only food and fluids that are the correct IDDSI Level for them, to reduce the risk of aspiration or choking.

Patients need to be able to take their medicines safely. In most cases, patients requiring thickened fluids and unable to take medicines with water, will be able (and may prefer) to take solid medicines, typically crushed tablets or opened capsules, with a mouthful of food of the appropriate texture (6). In some cases, patients may prefer to take each medicine with a mouthful of thickened fluid (6). In a few cases, it may be necessary to consider thickening a liquid medicine (7).

Not all tablets and capsules are suitable for crushing or opening, or administering with food, and it is important to check beforehand. The Medicines Q&A *How can people who need thickened fluids take medicines?* describes options available.

This Medicines Q&A looks at drug interactions between solid oral dosage forms and thickened fluids, and at drug interactions between liquid oral medicines and thickening agents when prepared as a single dose immediately prior to administration. It does not look at thickening of liquid medicines in bulk, or at extemporaneous preparation of medicines prior to dispensing. It considers drug interactions between medicines and thickening agents used in adults, not children or infants.

This Medicines Q&A is complemented by two others: *How can people who need thickened fluids take medicines?* and *Thickening agents: what to consider when choosing a product?*

Answer

Thickening agents

There are two main types of thickening agent: starch-based and gum-based. In the UK, the majority of thickening agents for use in adults are based on modified maize starch or xanthan gum, with or without maltodextrin; many are listed in the BNF (8). For more detailed information, see the Medicines Q&A *Thickening agents: what to consider when choosing a product?* Starch and gum-based preparations act differently: starch molecules swell in contact with liquid to increase viscosity, whereas gums form 'meshes of entanglement' that trap liquid and increase viscosity (9). Xanthan gum is negatively charged whereas starch is without charge (9). Therefore interactions with medicines may be specific to one type of thickening agent or common to all.

Thickening agents are intended to be mixed with food and drinks, not medicines. Manufacturers of thickening agents generally do not have information on their use with medicines, although some advocate mixing the powder with liquid oral medicines, or using thickened liquids to take solid oral medicines only if advised by a pharmacist (10,11).

If patients use thickened fluids to take their medicines, or if liquid medicines are thickened, the potential for interactions between medicines and thickener needs to be considered. All liquids must be the appropriate IDDSI Level for the patient at the time of administration.

Macrogol 3350 laxatives (e.g. Movicol, Laxido) and starch-based thickening agents

Macrogol 3350 (also called polyethylene glycol 3350) laxatives are used to treat chronic constipation and faecal impaction, and for colonic lavage prior to colonoscopy or surgery. Brands in the UK include Movicol, Laxido, Cosmocol, Klean Prep and VistaPrep (12-17). All are available as sachets of powder that must be dissolved in water before administration, typically 125ml per sachet. Depending on the indication, patients are required to take between 125ml and four litres of fluid. Movicol is also available as a liquid and doses are diluted with 100mls of water before administration (18). For patients requiring thickened fluids, these laxatives must be the appropriate IDDSI Level for the patient at the time of administration.

Thickening agents have been used to thicken macrogol laxatives, either by dissolving the macrogol in water first and then thickening, or by dissolving the macrogol powder in thickened fluid (10,19-22). In 2019, the Institute for Safe Medication Practices (ISMP) in Canada shared an incident where a patient who had received macrogol laxative powder mixed in a starch-based pre-thickened juice, died following suspected aspiration (19). The macrogol-starch mixture had resulted in a thin, watery liquid, essentially undoing the act of thickening. This interaction was also seen when macrogol powder was added to thickened apple juice, thickened water or thickened coffee, resulting in a reduction in the viscosity of the combined mixture (20).

Viscosity was not reduced when macrogol was added to fluids thickened with xanthan gum-based thickening agents (20). However, not all gum-based thickening agents are the same, and it appears that thickening agents based on carob gum (also called locust bean gum) are not suitable for thickening macrogol laxatives (21).

In practice

If a macrogol laxative is required, starch-based thickening agents must not be used to thicken the dose required, as the resulting mixture is thin and watery.

Xanthan gum-based thickening agents can be used to thicken macrogol laxatives; it is not clear if other gum-based laxatives are suitable. Some brands of xanthan gum-based thickener are promoted as being suitable for mixing with macrogol laxatives, and provide information on how they should be mixed, for example Swalloweze Clear and Thick & Easy Clear (10,22).

Product information for starch-based thickening agents does not warn against use with macrogol laxatives. In order to reduce the risk of inadvertently administering a thin fluid, it is good practice to visually check the consistency of all fluids before they are taken or administered (19).

There may be issues with patient compliance given the volume of thickened fluid needed to take a macrogol laxative. An alternative laxative may be preferred.

Amitriptyline, tamoxifen and verapamil with xanthan gum-based thickening agents

Amitriptyline, tamoxifen and verapamil are documented in several textbooks as being incompatible with xanthan gum (23-25). This dates back to a UKCPA symposium in 1986 where it was reported that most drugs extemporaneously mixed with a new thickening agent called Keltrol (xanthan gum)

remained physically stable for at least six weeks (26). The author noted “only a small number of drugs (including tamoxifen, verapamil and amitriptyline) have been found to be incompatible”.

There is no further information regarding the nature of the incompatibility and no case reports of incompatibility in practice.

In practice

There is no requirement for these medicines to be given on an empty stomach so it may be preferable to administer a tablet of amitriptyline, tamoxifen or verapamil with a spoonful of food, rather than with a thickened fluid (27-29). It has been suggested that amitriptyline absorption can be affected by food, but that taking the medicine at the same time each day in relation to food would reduce any variation in absorption (30).

It is not known if a clinically significant interaction occurs if amitriptyline, tamoxifen or verapamil is mixed with a spoonful of thickened fluid immediately prior to administration. It may be prudent to avoid thickening liquid preparations of these drugs with xanthan gum-based thickening agents. If any liquid medicine is thickened, it must be checked to ensure it is the correct consistency for the patient at the time of administration.

Reduced drug absorption of various medicines with thickeners

There is some evidence that thickeners can reduce or delay drug dissolution (the rate and extent to which the drug forms a solution in body fluids, used as a marker for drug bioavailability), particularly when used at the thickest level. Dissolution is reduced more in thicker fluids, and the effect is greater with negatively charged xanthan gum-based thickeners than starch-based thickeners which have no charge (6). Indeed, xanthan, guar and other gum-based thickeners are used to slow drug dissolution in modified-release preparations (23,31,32). However, there are few data, and no *in vivo* studies in people with swallowing difficulties regarding the effects of thickened fluids on the bioavailability of medicines.

A 2014 *in vitro* study compared the dissolution of crushed amlodipine, atenolol, carbamazepine and warfarin tablets when mixed with water, thickened water (thickened with a xanthan gum and maltodextrin thickening agent to “extremely thick”, equivalent to IDDSI Level 4) and various foods (orange juice, honey, yoghurt and jam) (32). For all the drugs tested, drug dissolution in thickened water was significantly delayed compared to dissolution in unthickened water and all the foods tested.

This study also compared the dissolution of crushed atenolol tablets mixed with five different thickened fluids (using different brands of thickening agents) at three thickness levels: water thickened to “mildly thick” (equivalent to IDDSI Level 2), “moderately thick” (IDDSI Level 3) and “extremely thick” (IDDSI Level 4) (32). Terminology used to describe the level of thickness in this Australian study predates the introduction of IDDSI Levels, therefore these have been determined from the conversion of old levels (33). Dissolution was not reduced by either starch-based or xanthan gum-based thickened fluid at the “mildly thick” level but was reduced by the xanthan-based thickened fluid at the “moderately thick” level and by both starch-based and xanthan gum-based thickened fluids at the “extremely thick” level (32).

The authors concluded that, of the vehicles tested, yoghurt was the most appropriate as it aided drug delivery (so long as the consistency is appropriate for the patient) without severely affecting drug dissolution (32).

A further *in vitro* study compared the dissolution of paracetamol from various dosage forms (crushed immediate release tablets mixed with water, effervescent tablets mixed with water, elixir and suspension) thickened with a xanthan gum and maltodextrin thickening agent to “extremely thick” (equivalent to IDDSI Level 4), and found considerably reduced drug dissolution in all cases (34). In some cases, paracetamol release at 30 minutes was less than the pharmacopoeial standard for

immediate release medicines, which could lead to a reduced or delayed effect. Three different methods of mixing the thickened water and crushed paracetamol were studied (adding a crushed tablet to thickened water, adding thickener powder to a crushed tablet in water, and adding water to a crushed tablet mixed with thickener powder); the authors concluded that dissolution was not improved by changing the order or by mixing mechanically rather than manually.

An *in vivo* study in 20 healthy volunteers found drug release from crushed paracetamol tablets was retarded in thickened fluids but concluded the difference was unlikely to be clinically relevant. The study compared crushed paracetamol tablets mixed with water, thickened water (thickened with a xanthan gum and maltodextrin thickening agent to “extremely thick”, equivalent to IDDSI Level 4) or jam, and whole paracetamol tablets with water (35). An attempt to correlate *in vitro* and *in vivo* data was not successful (35). The author noted that *in vivo* drug delivery is affected by a number of factors such as action of the tongue. Forces exerted during swallowing may be expected to break up thickened fluid globules and increase drug release (6). Pharmacokinetic studies of patients with swallowing difficulties could give more relevant data than studies in healthy volunteers (35).

In practice

Unless there is a relevant drug-food interaction, administering medicines with food rather than with thickened fluids is likely to be preferred.

If crushed tablets or opened capsules are administered with thickened fluids, bear in mind the potential for reduced dissolution, particularly with very thick fluids (IDDSI Level 4). If a moderately thickened fluid is required, interaction may be less likely with a starch-based than a gum-based thickener.

For most medicines, the therapeutic range is wide and a change in bioavailability would not be clinically relevant. It is potentially more significant for drugs with a narrow therapeutic range or where a fast therapeutic action is needed, e.g. for pain relief. For such drugs it would be advisable to monitor clinically, for example by monitoring blood levels of the drug (e.g. for phenytoin) or the intended effect such a blood pressure or pain relief and adjusting the dose accordingly. Ensure the drug is given in the same way, with regard to food or thickener, each time to avoid variation in absorption.

Summary

This Medicines Q&A considers interactions between medicines and thickening agents or thickened fluids.

- Thickening agents can be starch- or gum-based. Some drug interactions are specific to a type of thickener; some are common to all.
- Macrogol laxatives must not be mixed with starch-based thickening agents, as macrogol opposes the thickening effect of the starch, resulting in a thin liquid. This interaction has been implicated in a patient death. However, macrogol laxatives can be mixed with xanthan gum-based thickening agents.
- Thickened fluids may delay or reduce the absorption of medicines, particularly when very thick. This may be more problematic with xanthan gum-based than starch-based thickeners, but available data are limited.
- Where medicines have a wide therapeutic range, changes in absorption when mixed with thickened fluid immediately before administration are unlikely to be clinically relevant.
- Where medicines have a narrow therapeutic range, if the patient is consistent in the way they take the medicine, with regards to the food or thickener used to achieve the desired consistency, changes in absorption may be managed by clinical monitoring for effect and dose adjustment if necessary.

Limitations

- This Medicines Q&A offers pragmatic advice and is the opinion of the authors.
- It considers interactions between medicines and thickener when prepared as a single dose immediately prior to administration.
- It does not look at thickening of liquid medicines in bulk, or at extemporaneous preparation of medicines prior to dispensing.
- It considers drug interactions between medicines and thickening agents used in adults, not children or infants.

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Quality Assurance

Prepared by

Karoline Brennan, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool, and
Claire King, Medicines Information Pharmacist, Regional Medicines and Poisons Information Service Belfast.

Date Prepared

June 2020

Checked by

Helen Edmondson, Medicines Information Technician, Jaskiran McPhail and Joanne McEntee, Senior Medicines Information Pharmacists, North West Medicines Information Centre, 70 Pembroke Place, Liverpool, L69 3GF

Date of check

September-October 2020

Contact

nwmedinfo@nhs.net and clairez.king@belfasttrust.hscni.net

Search strategy

1. Embase via NICE Evidence

   ("GUAR GUM"/it) (exp XANTHAN/ + AMITRIPTYLINE/) (exp XANTHAN /+ TAMOXIFEN/) (exp XANTHAN/ + VERAPAMIL/) (XANTHAN/it), (STARCH/it) ("GUAR GUM"/it), ("THICKENING AGENT"/ + exp "DRUG INTERACTION"/) ("THICKENING AGENT"/po) ("THICKENING AGENT" + exp "DRUG INTERACTION"/) ("THICKENING AGENT"/ + "DRUG INTERACTION"/ + DYSPHAGIA) ("THICKENING AGENT"/ + "DRUG INTERACTION"/ + "FOOD DRUG INTERACTION") (XANTHAN/ + exp "DRUG INTERACTION"/) (DYSPHAGIA/ + "THICKENING AGENT"/) (exp DYSPHAGIA/ + "THICKENING AGENT"/) (exp DYSPHAGIA/ + exp "THICKENING AGENT"/), (exp *DYSPHAGIA/ + *"ORAL DRUG ADMINISTRATION"/)

2. Medline via NICE Evidence

   (xanthan.ti,ab + AMITRIPTYLINE/) (xanthan.ti,ab + TAMOXIFEN/) (xanthan.ti,ab + VERAPAMIL/) (xanthan.ti,ab + "DRUG INTERACTIONS"/) (guar.ti,ab + exp DRUG INTERACTIONS"/) (thicken*ti.ab + exp "DRUG INTERACTIONS"/) (thicken*ti.ab + exp "DRUG INTERACTIONS"/ + "DEGLUTITION DISORDERS"/) (thicken*ti.ab +"DEGLUTITION DISORDERS"/) (STARCH/ + exp "DRUG INTERACTIONS"/) ("DEGLUTITION DISORDERS"/ + *"ADMINISTRATION, ORAL"/) ("ADMINISTRATION, ORAL"/ + "DEGLUTITION DISORDERS"/ + "PHARMACEUTICAL PREPARATIONS"/) ("DEGLUTITION DISORDERS"/ + medication.ti,ab + thickened liquid.ti,ab) (medication.ti,ab + thickened liquid.ti,ab) ("DEGLUTITION DISORDERS"/ + VISCOSITY/) (thickened liquid.ti,ab + dysphagia.ti,ab) (thickeners.ti,ab + medication.ti,ab) (DEGLUTITION DISORDERS/ + thickeners.ti,ab)

3. In-house database/ resources

4. Manufacturers:
   (a) Abbott Laboratories. Communication by email on 05/06/2020.
   (b) Aymes International Ltd. Communication by email on 05/06/2020.
   (c) Fresenius Kabi. Communication by email on 03/06/2020.

(d) Nestle Health Science. Communication by email on 03/06/2020.
(e) Nualtra. Communication by email on 02/06/2020.
(f) Nutricia. Communication by email on 17/06/2020.

5. Internet search (Google; thicken movicol, thicken laxido, speech and language therapy IDDSI, dysphagia guidance UK, stroke guidance UK, use of thickening agents with medicines, administering medicines to patients with dysphagia, crushing medication and giving with thickened fluids)