

DR EMMA P HALMOS (Orcid ID : 0000-0002-6063-5118)

Article type : Review Article

**REVIEW ARTICLE: EMULSIFIERS IN THE FOOD SUPPLY AND IMPLICATIONS FOR
GASTROINTESTINAL DISEASE**

Emma P. Halmos¹, Alexandra Mack¹, Peter R. Gibson

Department of Gastroenterology, Alfred Hospital and Monash University

¹Equal first author

Correspondence to:

Dr Emma P. Halmos, Department of Gastroenterology, Alfred Hospital and Monash University,
99 Commercial Road, Melbourne, Victoria 3004 Australia

T: +61 3 99030270, E: Emma.Halmos@monash.edu

Short title: Emulsifiers and the gut

Word count: 4214 words

Acknowledgements: The authors thank Nerida Ivory for designing the figures.

Guarantor of the article: Prof Peter Gibson

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/APT.15045](https://doi.org/10.1111/APT.15045)

This article is protected by copyright. All rights reserved

Specific author contributions: All authors wrote, revised and approved the final version of the article

Funding: EPH received funding from 2017 GESA Ferring IBD Clinical Project Award.

Conflicts of interest: The authors have no perceived conflicts of interest.

SUMMARY

Background: Dietary emulsifiers are the latest food additives to be associated with intestinal, cardiovascular and metabolic health. Most recently, there are postulations around certain emulsifiers playing a role in the development of Crohn's disease.

Aim: To review the use of food-based emulsifiers, their content in the food supply and mechanisms by which they might exert potentially detrimental biological effects.

Methods: Information on emulsifiers and thickeners relevant to human health was critically examined.

Results: The term, 'emulsifier', has been used loosely and has included thickeners as well as agents that truly promote emulsions. These comprise of proteins, phospholipids and carbohydrates, alone or in combination, and play roles in optimising food appearance, texture and mouth-feel, delivering or disguising flavours and achieving palatable low-fat foods. Their presence in the food supply is common, but not 'ubiquitous' as frequently stated. Strict regulations limit the amount added to foods, but the lack of established methodologies to measure the actual food content of these diverse compounds limits our knowledge of consumption. Emulsifiers and thickeners have effects on gut microbiota, mucosal barrier and inflammatory pathways, and can induce disease in experimental models. However, differentiating pharmacological from physiological effects and translating findings in experimental animals to humans raise uncertainties about the relevance of such effects.

Conclusions: There is limited evidence to directly link emulsifiers and thickeners to human disease, but multiple potential pathogenic mechanisms. Knowledge of actual dietary intake and high-quality interventional studies are needed to enable risks associated with their intake to be understood.

Key words: thickeners, polysorbate, carboxymethylcellulose, Crohn's disease, diet

INTRODUCTION

The latest class of food additives to receive poor press is emulsifiers, due to the association of their ingestion with inflammatory bowel disease, specifically Crohn's disease, as well as cardiovascular and metabolic disease, as shown in epidemiological, animal and laboratory studies. For example, polysorbates affect permeability of cell lines in culture¹, promote translocation of *E. coli* across ileal epithelium and M cells *in vitro*², and induce intestinal inflammation and metabolic syndrome in susceptible mice³. An epidemiological study associated increased use of dishwashers, which would reduce residual detergent on utensils and plates, with falling cardiovascular disease in UK⁴. However, several difficulties arise in understanding the potential role of emulsifiers in disease pathogenesis. These include inconsistencies in what is called an 'emulsifier', limitations in our knowledge of the disposition and pharmacokinetics of emulsifiers after ingestion, and the commonly quoted statement that emulsifiers are 'ubiquitous' in our food supply. The current review attempts to address multiple issues of relevance to the understanding of potential links of emulsifiers with disease.

CONCEPT OF EMULSIONS AND THEIR VALUE IN FOOD

An emulsion describes a mixture of at least two immiscible liquids, in which small droplets of one liquid are dispersed within the other^{5,6}. Emulsions are an integral part of many foods eaten and the liquids typically involved are oil and water. There are different types of emulsions as illustrated in Figure 1. When oil droplets are dispersed (the 'dispersed' phase) into water (the 'continuous' phase), the emulsion is called an *oil-in-water* (O/W) emulsion; examples include milk, mayonnaise, cream, dressings, sauces and soups⁶. When water droplets are dispersed in oil, this is referred to as a *water-in-oil* (W/O) emulsion, with margarine and butter being common examples⁶. *Multiple emulsions* are produced by multi-layering, usually involving W/O/W in food (Figure 1).

The principles of generating and stabilising emulsions of two immiscible liquids is illustrated in Figure 1 with high-speed homogenisation, disruptive forces are applied to the liquids causing small droplets to form⁶. However, the droplets within emulsions are often different specific gravity to the continuous phase and can separate by gravitational forces leading to creaming or sedimentation. The drops are also constantly moving and colliding with one another, with a consequence that they can flocculate, a process of aggregation into three-dimensional structures, or they can coalesce with their neighbours (also called 'Ostwald ripening') (Figure 1). An example of the latter is the loss of creamy consistency of ice cream that has been frozen for a long time. It is, however, possible to form emulsions that will remain stable for an extended period of time by using substances known as *stabilisers*, a collective term describing agents with different modes of actions. Such agents include emulsifiers, texture modifiers and weighting agents, each of which increase the kinetic stability of emulsions via a different mechanism⁶ (Figure 1).

Emulsifiers

In order to function as an emulsifier, a substance must have the ability to adsorb to the surface of droplets as they are formed during homogenisation and thereby protect them from aggregating with their neighbours^{6,7}. In an O/W emulsion, an emulsifier would need to have surface activity at the oil-water interface in order to have this functionality. Most emulsifiers are amphiphilic molecules (i.e., having both hydrophilic and hydrophobic parts) capable of adsorbing to an oil-water interface⁶. They not only enhance the stability of emulsions by protecting emulsion droplets from aggregation, but also assist in the formation of emulsions by reducing interfacial tension during homogenisation^{6,8}. Emulsifiers can be broadly divided into two subcategories⁶ – surfactants and amphiphilic biopolymers – and are described in Table 1:

- (a) *Surfactants*: They consist of a hydrophilic 'head' or polar group and a lipophilic 'tail' group⁸. The head group may be anionic, cationic, zwitterionic (i.e. amphoteric) or nonionic^{6,8}. Surfactant molecules adsorb to oil-water interfaces with the hydrophilic end located in the aqueous phase and the hydrophobic/lipophilic end located in the oil phase⁸. Surfactants help to prevent aggregation of droplets by producing repulsive force between droplets.

(b) *Amphiphilic biopolymers*: Some biopolymers are also surface-active as they are amphiphilic⁷, and may be proteins, polysaccharides, or protein-polysaccharide complexes. Naturally-occurring surface-active proteins (such as egg or casein) were the first emulsifiers utilised in the food industry⁸, and proteins extracted from milk, meat, fish, eggs or plants are all still commonly used in the food industry to this day⁶. There is controversy over polysaccharides as emulsifying agents. In general, polysaccharides are not surface-active, but stabilise emulsions via modifying texture. However, some have clear demonstration of surface activity whereas its origin in others, such as gum arabic and xanthan gum, may be from protein contaminants or proteins covalently bound to the polysaccharide backbone^{6,7}. Other polysaccharides, such as carrageenan, may be poorly surface-active when used alone⁹, but can be added to proteins to improve their emulsifying activity^{7,10}.

Texture modifiers

These stabilise emulsions by increasing the viscosity of the continuous (aqueous) phase, which reduces the rate at which particles sediment, cream, or form a gel. In that way, they can be even more effective than surfactants or proteins in conferring long-term stability on emulsions⁷. They can also alter the texture or mouth feels of food products⁶. These may be thickening agents that act via its large molecular dimension (see Table 1) or gelling agents that increase viscosity or form gels because of intermolecular cross-links.

Weighting agents

Weighting agents balance the densities of the dispersed and continuous phases. The most common agent used is sucrose acetate isobutyrate that increases the specific gravity of the flavouring oils used in citrus beverages and prevents those oils separating from other beverage components and rising to the surface.

Food value of emulsions

The production of stable emulsions in the food industry is important for many reasons, some of which are outlined in Table 2.

Gastrointestinal fate of emulsifiers and thickeners

Knowledge of the fate of emulsifiers and thickeners in the gastrointestinal tract is critical to understanding their possible role in disease pathogenesis.

Surfactant emulsifiers: Nearly all the surfactant-type emulsifiers have a fatty acid non-polar region with a hydrophilic head. Using polysorbates as the model for such emulsifiers, the fatty acid component is digested via the standard fat digestion mechanisms in the upper gut and the vast majority will be degraded. The polar head is released in an inert form and the vast majority of this will pass through the gastrointestinal tract without being absorbed or metabolised. However, this is not true for all surfactants. Choline released from digestion of phosphatidylcholine as part of lecithin is metabolised by intestinal bacteria to produce trimethylamine, which is absorbed (further discussed under Potential Mechanisms for Disease Pathogenesis). Data on the fate of many emulsifiers are not readily available.

Amphiphilic biopolymers: Proteins used as emulsifiers (such as whey or casein) will be digested via the proteolytic enzymatic mechanisms in the stomach and duodenum. The polysaccharide emulsifiers are generally indigestible (no suitable small intestinal hydrolases) and hence will be delivered to the colon largely intact. However, as outlined above, the surface activity of most may well reside in bound or contaminating proteins, which would also be subject to normal protein digestion. Thus, the emulsifying action would be destroyed in the small intestine.

Thickeners and gelling agents: Most thickening agents are non-starch polysaccharides (NSPs) that are indigestible. Some, such as guar gum, will be fermented by gut microbiota and others, such as carrageenan and modified celluloses, are not degraded and will remain present in the intestinal lumen throughout their gastrointestinal transit. These NSPs are likely to be able to enter the mucous layer, particularly those that are more readily hydrated. Carboxymethylcellulose (CMC) has received considerable attention because of this property and its consequent ability to alter functional properties of the mucus (discussed later). The

ability to make gels (i.e., gelling agents) is shared by proteins (such as gelatin), which will be digested in the proximal gastrointestinal tract, and some polysaccharides such as carageenan.

Weighting agents: Sucrose acetate isobutyrate has been used for decades in citrus beverages and has been studied in various animal models and humans. It is extensively metabolised within the gastrointestinal tract mostly to sucrose and acylated sucrose.

KNOWLEDGE OF STABILISERS IN THE FOOD SUPPLY

Stabilisers used

Emulsifiers and thickeners are naturally occurring in foods, as those found in eggs, meat and milk, but are also food additives. Recent evaluation of manufactured food in the USA have shown that the seven most commonly used additive emulsifiers and thickeners are: CMC, polysorbate 80, lecithin, mono- and diglycerides of fatty acids, stearyl lactylates, sucrose esters and polyglycerol polyricinoleate. Of these, lecithin and mono- and diglycerides are the two most widely used, with estimated intakes of 55 and 80 mg/kg/body weight (bw) day, respectively, compared to only 8 mg/kg/bw day of polysorbate 80¹¹. While it has not been formally assessed elsewhere, these also appear to be the most commonly found emulsifiers and thickeners in Australia and the UK. While it may be assumed that such consumption has increased with the influx of manufactured foods over the past century, the US dietary exposure seems not to have changed over the past 10 years¹¹.

Identification and safety of stabilisers

In Europe, UK, Australia and New Zealand, food additives are designated a number by the International Numbering System, which is defined by the Codex Alimentarius. These numbers may be used in place of the actual food additive name on food packaging. Most stabilisers are allocated an International Numbering System number 400-499, with some exceptions that sit outside that range, including lecithins (examples in Table 1). While food additive descriptions are stipulated by this European numbering system, each national regulatory agency use their own method of enforcing additive identification on labels and assessment of safety. For

example, in many European countries, food manufacturers may use a previously unused food additive until the appropriate regulatory agency assesses its safety and determines whether it is to be placed on a 'banned list'. In contrast, Food Standards Australia New Zealand (FSANZ) must approve additives before use and generally follows the safety assessments completed by the Joint FAO/WHO Expert Committee on Food Additives, although may also complete their own assessments. In USA, the Food and Drug Administration (FDA) regulate food additives independently and all food additives must obtain their premarket approval. The only exemptions are additives termed 'Generally Recognised As Safe' (GRAS), a list of food substances established in 1958 and deemed as such by an expert committee. Both CMC and lecithin are GRAS, but additives have been removed from the list if subsequently shown to be unsafe. Regulatory agencies require that the minimum amount of substance that is necessary to achieve the technical effect is used, although it is unclear how this is determined for each additive. In Australia, identification of emulsifiers is compulsory, except if present within a compound ingredient (i.e., an ingredient made up of at least two ingredients) that constitute less than 5% of the final product and does not provide a technological function, as decided by the manufacturing company. US and European standards are very similar. Hence, additive emulsifiers present as a small ingredient may not be identified on ingredients lists. An example of this is the case of the aforementioned citrus soft drinks that use stabilisers as a weighting agent. Indeed, many citrus soft drinks do not have additive stabilisers listed on their ingredients lists, yet the flavour remains stable and evenly dispersed through the bottle.

Most emulsifiers and thickeners have no defined level of toxicity, because the highest dose required to produce an adverse effect is above the level experimental animals can reasonably consume. Acceptance of safety has been thrown into question following the recent publication by Chassaing et al., in which polysorbate 80 and CMC both induced colitis in genetically predisposed mice³. Past data investigating the safety of CMC and polysorbate 80 have not indicated any adverse effects, other than diarrhoea and weight loss in rats fed polysorbate 80 for two years¹²⁻¹⁵. These rodents were not genetically predisposed to disease, so it is likely that toxicity levels are different for select populations and re-evaluation of emulsifiers previously

considered to be safe is required. Mono- and diglycerides have been assessed in animal studies, showing that ingestion of levels of 15% of the diet showed liver enlargement but no significant histopathological change¹⁶. In humans, it is thought that the likely unwanted effects of mono- and diglycerides are from increasing long-chain saturated fatty acids¹⁶. For lecithin, no adverse effects have been seen in acute toxicity studies in animals provided both orally or parentally¹⁶. No human studies have been conducted as it is considered that the clinical experience of lecithin is sufficient proof of safety. The weighting agent, sucrose acetate isobutyrate, has been studied in detail and no known toxicity, although, in dogs, has reversible hepatic effects not found in humans¹⁷.

Food composition of stabilisers

Various stabilisers may be used in food depending on their characteristics. For example, they may be used to keep the oil mixed in salad dressings and nut butters, or to help incorporate fat into the dough of baked goods. Emulsifiers and thickeners are added to many manufactured foods, but the six main food categories where they are generally present include breads and other baked goods, fat spreads, mayonnaises and salad dressings, ice creams and other dairy desserts, confectionery and beverages. Some foods, such as ice cream, will always contain emulsifiers. However, there is generally considerable inconsistency in the presence and type of stabilisers used in manufactured foods, as illustrated in Figure 2. Table 2 describes the common applications of stabilisers within the six food categories.

METHODOLOGIES FOR MEASUREMENT OF STABILISERS

The measurement of the concentration of emulsifiers and thickeners in foods is needed for the purposes of regulation (to ensure compliance to safe limits) and food safety (e.g., to ensure degradation products are not present). However, for the purposes of the clinical evaluation of safety during everyday dietary consumption, it is a basic principle that the actual concentration of food substances and the amount being consumed are measured, particularly if the clinical or biological effects of those substances is being assessed. An example of the importance of

accurate food characterisation is the analysis of FODMAP content in food, as such data have been critical to the design and subsequent success of a therapeutic diet.

Unfortunately, measurement is difficult. The first step involves extraction of fat and the emulsifiers from food, with use of various solvents. Separation of non-lipid emulsifiers within complex matrices, initial separation will also be required using, for example, enzymatic digestion⁸. For polysaccharide thickeners like CMC, extraction involves enzymatic digestion of associated protein followed by a 'clean-up' process to separate from other gums like carrageenan¹⁸.

Multiple detection and quantification methodologies have been applied depending upon the nature of the emulsifier or thickener⁸, but gaining a quantitative catalogue of contents is near impossible for reasons of their diversity, of the methodological challenges associated with individual additives in both their extraction and quantification, and the variability and changeability of their use in the food industry. As an alternative, a specific agent identified in the food label of a food can be assumed to be found at the upper level of its usual range as dictated by safety limits. This method was applied by the Food Drug Administration in one of the few estimates of population intake of specific emulsifiers and thickeners¹¹. This imprecise method of estimation is dictated by regulatory limits, which will confound examination of, for example, dose-dependent effects in clinical intervention studies.

POTENTIAL MECHANISMS FOR DISEASE PATHOGENESIS

Four broad mechanisms for disease pathogenesis associated with emulsifying and thickening agents have been described. These are illustrated in Figure 3.

Alteration of intestinal mucosal barrier function

The intestinal barrier has multiple components. These include the mucosa-associated microbiota, mucus and its associated anti-microbial contents such as IgA and defensins, the epithelium with its tight junctions, and cellular components of both innate and acquired

immune system arranged in the intraepithelial compartment, the lamina propria and the mucosa-associated lymphoid tissue. All components are potentially affected by the presence of dietary emulsifiers and thickeners, but dissecting which change is cause and which is effect is challenging.

The ability of the mucous layer to inhibit the movement of molecules and bacteria from the lumen to the epithelium may be reduced by emulsifiers and thickeners. The absorption of phytochemicals such as curcumin can be markedly enhanced by their presentation in micellar form using polysorbate 80¹⁹⁻²¹. Likewise, the absorption of furosemide can be enhanced by the concomitant use of emulsifiers²². The thickener, CMC, integrates into the mucous layer by virtue of its very high water-holding capacity. Its other properties of being non-fermentable and not binding bile acids or cholesterol have led to the belief that CMC is harmless in the GI tract^{23, 24}. However, CMC does appear to support the encroachment of bacteria into the mucous layer as shown by closer proximity of bacteria to the epithelium, small intestinal bacterial overgrowth and mucosal inflammation in genetically susceptible mice^{3, 25}. Reasons for such effects appear to be a combination of effects on the bacteria (described later) and the microenvironment within which it sits (i.e., the mucous layer).

Emulsifiers might also have effects on the cell membranes of the epithelium. Indeed, M cells generated *in vitro* permitted a marked increase in translocation of *E. coli* across them when exposed to low concentrations of polysorbate 80, as did follicular-associated epithelium when human ileal biopsies mounted in Ussing chambers². Whether this represented an effect of the emulsifier on the epithelial cells or on the behaviour of the bacteria was not investigated in this study.

Alteration of the functional characteristics of gut microbiota

The effects of the emulsifiers on cell membranes of bacteria or the provision of specific nutrient groups by thickeners might alter the pathogenicity of specific bacteria and/or change the compositional structure of the microbiota. In the mucosal simulator of the human intestinal

microbial ecosystem (M-SHIME), CMC and polysorbate 80 induce increased expression of bioactive flagellin, which increases the ability of the bacteria to penetrate the mucus²⁶. CMC seems to do this directly and, therefore, must not be quite as inert as originally thought. While CMC is not fermented by bacteria, it may still provide carbohydrates to support bacterial growth and/or functional change. This is consistent with the promotion of growth of *Neisseria gonorrhoea* in tampons impregnated with CMC²⁷. Polysorbate 80 appears to have a similar effect on flagellin, but does so in conjunction with other changes to microbial composition²⁶.

Induction of mucosal inflammation

It is presumed that the mucosal inflammation that is associated with the exposure of emulsifiers and thickening agents in animal models is a direct consequence of the alteration of barrier function and of increased aggressiveness of bacteria with greater translocation. However, some proteins with strong emulsifier activity, such as egg-yolk phovitin, have direct effects on a macrophage-like cell line by increasing nitric oxide production and increasing phagocytosis in a dose-dependent manner²⁸. The *in vivo* significance of this is unknown. Soybean lecithin, but not milk lecithin, induces increased adiposity and inflammation in mice fed high-fat diets^{29, 30}. The underlying mechanism of this phenomenon is not understood, but may involve barrier dysfunction since the stimulation by milk lecithin of goblet cells to release mucus is not evident for soybean lecithin. Interestingly, the pro-inflammatory effect of a high fat diet may relate to the emulsifier content of the fats used³⁰.

Effects of metabolic products of the agents

The metabolism of polar groups on emulsifying agents potentially may lead to pathogenic molecules that can be absorbed. The known example is lecithin (phosphatidylcholine), which is digested by intestinal lipases to choline-containing nutrients. These can be further metabolised by intestinal microbiota to trimethylamine, a molecule that is readily absorbed and oxidised in the liver to trimethylamine-N-oxide (TMAO). There is now strong evidence for the direct atherogenic, thrombotic, renotoxic and other effects of TMAO, and its circulating levels are associated with cardiac and metabolic diseases³¹. Such levels are related to the dietary intake of

choline-contain nutrients, which in turn influence the functional ability and composition of the microbiota to metabolise choline to trimethylamine. While these may be components of essential nutrients (such as L-carnitine in red meat), this example does illustrate the pathogenic potential of metabolites of emulsifiers.

CAVEATS TO CONSIDER

Hypothetical issues that require consideration in the pathogenic capabilities of emulsifying and thickening agents include the following:

- ***The actual amount of emulsifiers and thickeners ingested in the diet is poorly documented:*** The content of emulsifiers and thickeners in food is not quantified (see discussion above under ‘Methodologies for measurement of emulsifiers and thickeners’), but must, by law, be restricted to ‘safe’ concentrations. They are used in food processing to achieve the desired organoleptic effect. One of the few reports of actual dietary intake of common emulsifiers quantified daily intake by assuming food containing emulsifiers had ‘maximum-use levels’¹¹. In other words, the published results of daily intake represented the worse-case-scenario if the emulsifier concentrations were indeed within the legal limits. Emulsifiers and thickeners are also not always used alone in any one food product and meals usually involve ingestion of multiple food types. Furthermore, the relationship of the amounts fed to mice or concentrations exposed to cells *in vitro* in experimental studies to actual exposure is uncertain. The risk that pharmacological rather than physiological effects are being reported has to be seriously considered. Thus, there is a real need for methods to be developed and applied to their accurate quantification within food.
- ***There is no information of the effects of multiple emulsifiers and thickeners:*** They may have additive, synergistic or even antagonistic effects, especially given their wide variation of structure of type and differing mechanisms of action.
- ***The behaviour of the agent when ingested independently of an emulsion may be different to that when ingested as an emulsion:*** In animal and *in vitro* studies, emulsifiers or thickeners are given or exposed to cells/tissue other than in an emulsion – usually in the drinking water or dissolved in the culture medium. *In vivo*, the fate of the agent used and its

behaviour in the gastrointestinal tract may be quite different when ingested in the context of food. A surfactant provided alone will seek lipid and hydrophilic substrates that it would not have had access to if ingested in its bound form. This may be less relevant to thickening agents since their mode of actions in emulsions is very different.

- ***The likely concentration of the agent at sites of potential pathogenicity must be considered:*** Most emulsifiers are effectively destroyed by digestive processes in the proximal small intestine and would be unlikely to be present in concentrations that would be pathogenic locally in the more distal intestine. This is particularly the case in the terminal ileum regarding development of Crohn's disease. Thickening agents like CMC and carrageenan are different in that they are not apparently metabolised and so have the potential to have effects all along the gastrointestinal tract.

TRANSLATION TO THE COMMUNITY

Multiple individual food components may have deleterious effects on the gastrointestinal tract when they are tested under experimental conditions outside the context of actual food, as illustrated with emulsifiers and thickeners. This offers the opportunity to utilise such information falsely as scientific proof of their toxicity (i.e., so-called pseudoscience) to support campaigns of fear to change eating habits. This approach is concerning but unfortunately common³². On the evidence to date, our messages to the community should remain vague and non-specific due to our limited knowledge of food composition, relevance of various emulsifiers and thickeners on pathogenesis of disease and their role in prevention and therapy. 'Common sense' messages that are in line with current recommendations for healthy eating, such as limiting manufactured foods containing additives, will continue to be our general advice until the evidence base for a pathogenic contribution of emulsifiers and thickeners to illness is established and the development of targeted therapeutic diets and subsequently controlled trials performed to better direct us.

CONCLUSIONS

The term, 'emulsifier', has been used loosely and has included thickeners as well as agents that truly do promote emulsions. Their presence in the food supply is common, but not 'ubiquitous' as frequently stated. Emulsifiers and thickeners comprise a broad range of molecules that include protein, phospholipid and carbohydrates alone or in combination. These agents play important roles in optimising food appearance, texture and mouth-feel not only for foods with the need to prevent overt separation of lipid and water components like mayonnaise, but also for the optimal delivery of flavours and nutrients, and for achieving palatable low-fat foods. There are strict regulations that limit relative content in foods, but the lack of established methodologies to measure the actual food content of these diverse compounds limits the understanding of how much is being consumed within a population or by an individual. There are multiple mechanisms by which emulsifiers and thickeners modulate the biology of the gut microbiota and physiological processes of the human and experimental models in which they induce disease. However, differentiation between pharmacological and physiological effects, and uncertainties of translating phenomena in experimental animals to humans raise uncertainties about the relevance of such effects. Addressing such uncertainties will require better knowledge of actual exposure, an understanding of interactions between individual emulsifiers and thickeners, and interventional studies where they are delivered in the real-world context of food examining their physiological and pathophysiological effects in humans.

References:

1. Dimitrijevic D, Shaw AJ, Florence AT. Effects of some non-ionic surfactants on transepithelial permeability in Caco-2 cells. *J Pharm Pharmacol.* 2000;52(2):157-62.
2. Roberts CL, Keita AV, Duncan SH, et al. Translocation of Crohn's disease *Escherichia coli* across M-cells: contrasting effects of soluble plant fibres and emulsifiers. *Gut.* 2010;59(10):1331-9.
3. Chassaing B, Koren O, Goodrich JK, et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature.* 2015;519(7541):92-6.
4. Rhodes JM. Dietary exposure to emulsifiers and detergents and the prevalence of cardiovascular disease. *QJM.* 2018;111(5):283-86.

5. Kralova I, Sjöblom J. Surfactants used in food industry: a review. *J Disper Sci Technol*. 2009;30(9):1363-83.
6. McClements DJ. *Food Emulsions Principles, Practices, and Techniques*. Third ed. Boca Raton, FL: CRC Press; Taylor & Francis Group; 2015.
7. Dickinson E. Hydrocolloids at interfaces and the influence on the properties of dispersed systems. *Food Hydrocoll*. 2003;17(1):25-39.
8. Hasenhuettl GL. *Food emulsifiers and their applications*. New York, NY: Springer Science + Business Media; 2008.
9. Huang X, Kakuda Y, Cui W. Hydrocolloids in emulsions: particle size distribution and interfacial activity. *Food Hydrocoll*. 2001;15(4-6):533-42.
10. Uruakpa FO, Arntfield SD. Emulsifying characteristics of commercial canola protein -hydrocolloid systems. *Food Res Int*. 2005;38(6):659-72.
11. Shah R, Kolanos R, DiNovi MJ, et al. Dietary exposures for the safety assessment of seven emulsifiers commonly added to foods in the United States and implications for safety. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. 2017;34(6):905-17.
12. McElligott TF, Hurst EW. Long-term feeding studies of methyl ethyl cellulose ('Edifas' A) and sodium carboxy-methyl cellulose ('Edifas' B) in rats and mice. *Food Cosmet Toxicol*. 1968;6:449-60.
13. Oser BL, Oser M. Nutritional studies on rats on diets containing high levels of partial ester emulsifiers. I. General plan and procedures; growth and food utilization. *J Nutr*. 1956;60:367-90.
14. Shelanski HA, Clark AM. Physiological action of sodium carboxymethylcellulose on laboratory animals and humans. *Food Res*. 1948;13:29-35.
15. Anderson DMW, Eastwood MA, Brydon WG. The dietary effects of sodium carboxymethylcellulose in man. *Food Hydrocoll*. 1986;1(37-44).
16. Joint FAO/WHO Expert Committee on Food Additives. Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. Geneva 1974.
17. Reynolds RC. Metabolism and pharmacokinetics of sucrose acetate isobutyrate (SAIB) and sucrose octaisobutyrate (SOIB) in rats, dogs, monkeys or humans: a review. *Food Chem Toxicol*. 1998;36(2):95-9.
18. Zorba M, Ova G. An improved method for the quantitative determination of carboxymethyl cellulose in food products. *Food Hydrocoll*. 1999;13(1):73-6.

19. Kocher A, Schiborr C, Behnam D, Frank J. The oral bioavailability of curcuminoids in healthy humans is markedly enhanced by micellar solubilisation but not further improved by simultaneous ingestion of sesamin, ferulic acid, naringenin, and xanthohumol. *J Funct Foods*. 2015;14(183-91).
20. Schiborr C, Kocher A, Behnam D, et al. The oral bioavailability of curcumin from micronized powder and liquid micelles is significantly increased in healthy humans and differs between sexes. *Mol Nutr Food Res*. 2014;58(3):516-27.
21. Zou L, Lui W, Lui C, et al. Designing excipient emulsions to increase nutraceutical bioavailability: emulsifier type influences curcumin stability and bioaccessibility by altering gastrointestinal fate. *Food Funct*. 2015;6(8):2475-86.
22. Valizadeh H, Fahimfar H, Ghanbarzadeh S, et al. Effect of anionic macromolecules on intestinal permeability of furosemide. *Drug Dev Ind Pharm*. 2015;41(2):190-3.
23. Adiotomre J, Eastwood MA, Edwards CA, Brydon WG. Dietary fiber: in vitro methods that anticipate nutrition and metabolic activity in humans. *Am J Clin Nutr*. 1990;52(1):128-34.
24. Bliss DZ, Weimer PJ, Jung HJ, Savik K. In vitro degradation and fermentation of three dietary fiber sources by human colonic bacteria. *J Agric Food Chem*. 2013;61(19):4614-21.
25. Swidsinski A, Ung V, Sydora BC, et al. Bacterial overgrowth and inflammation of small intestine after carboxymethylcellulose ingestion in genetically susceptible mice. *Inflamm Bowel Dis*. 2009;15(3):359-64.
26. Chassaing B, Van de Wiele T, De Bodt J, et al. Dietary emulsifiers directly alter human microbiota composition and gene expression ex vivo potentiating intestinal inflammation. *Gut*. 2017;66(8):1414-27.
27. Arko RJ, Wong KH, Finley-Price KG, Rasheed JK. Effects of tampon components on growth and dissemination of *Neisseria gonorrhoeae*. *Br J Vener Dis*. 1982;52(2):105-8.
28. Lee JH, Moon SH, Kim HS, et al. Immune-enhancing activity of phosvitin by stimulating the production of pro-inflammatory mediator. *Poult Sci*. 2017;96(11):3872-78.
29. Lecomte M, Couëdelo L, Meugnier E, et al. Dietary emulsifiers from milk and soybean differently impact adiposity and inflammation in association with modulation of colonic goblet cells in high-fat fed mice. *Mol Nutr Food Res*. 2016;60(3):609-20.
30. Lecomte M, Couëdelo L, Meugnier E, et al. Soybean polar lipids differently impact adipose tissue inflammation and the endotoxin transporters LBP and sCD14 in flaxseed vs. palm oil-rich diets. *J Nutr Biochem*. 2017;43:116-24.

31. Tang WH, Hazen SL. Microbiome, trimethylamine N-oxide, and cardiometabolic disease. *Transl Res.* 2017;179:108-15.
32. Levinovitz A. *The Gluten Lie: And Other Myths About What You Eat* Regan Arts; 2015.
33. Dickinson E, Narhan SK, Stainsby G. Stability of cream liqueurs containing low-molecular-weight surfactants. *J Food Sci.* 1989;54(1):77-81.

Author Manuscript

Table 1. Substances commonly used to stabilise emulsions in food and beverages

Substance	Class	Description	Examples	E Number
Emulsifiers - surfactants	Non-ionic	No charge at its hydrophilic head	• Mono- and di-glycerides of fatty acids	• 471
			• Monoglycerides esters (acetic acid, lactic acid, succinic acid)	• 472a, 472b, 472f, 363
			• FA esters (polyglycerol, propylene glycol, sucrose)	• 473, 475, 476, 1520
			• Ethoxylated sorbitan esters (polysorbates (Tween) 20, 60, 65, 80)	• 432, 433, 435, 436
	Anionic	Contains negatively charged functional group at the hydrophilic head	• Sorbitan esters (Span)	• 491-495
			• FA salts - sodium stearyl lactylate, calcium stearyl lactylate	• 481, 482
			• MG esters - citric acid diacetyl tartaric acid	• 472c, 472e
			• Lauroyl arginate	• 243
	Cationic	Contains positively charged functional group at the hydrophilic head		
	Zwitterionic (amphoteric)	Contains a hydrophilic head with 2 oppositely charged groups	• Lecithin	• 322
			• Lysolecithin	• No E number
Emulsifiers - amphiphilic biopolymers	Proteins	Forming viscoelastic absorbed layer	• Milk (casein, whey)	-
			• Meat and fish (e.g. gelatin)	
			• Egg	

			<ul style="list-style-type: none"> Plants (e.g., soy protein) 	
	Protein-polysaccharide complexes	Protein-polysaccharide ratio forms viscoelastic properties	<ul style="list-style-type: none"> Gum arabic Xanthan gum 	<ul style="list-style-type: none"> 414 415
	Polysaccharides*	High viscosity & prevents oil droplets from coalescing	<ul style="list-style-type: none"> Some pectins (e.g. acetylated pectin from sugar beet, depolymerised citrus pectin) Galactomannans (e.g. guar gum) Modified starches Modified celluloses (e.g. methylcellulose) 	<ul style="list-style-type: none"> 440 412 1400-1500 460-469
Texture modifiers	Thickening & gelling agents	Increases viscosity by reducing rate of sedimentation or forming a gel	<ul style="list-style-type: none"> Modified celluloses* e.g. carboxymethylcellulose, hydroxypropyl, methylcellulose, hydroxypropyl cellulose Pectin*†, guar gum*†, xanthan gum*† Agar, gelatin†, casein† Carrageenan 	<ul style="list-style-type: none"> 466, 463, 464 440, 412, 415 406 407
Weighting agents		Increases the specific gravity of oils to prevent separating from other components, usually in non-alcoholic beverages	<ul style="list-style-type: none"> Sucrose acetate isobutyrate 	<ul style="list-style-type: none"> 444

* Surface activity may be due to presence of protein contaminants

†Can be classified as both texture modifiers and emulsifiers^{6,7}

Table 2. Some uses and techniques in which emulsions are of value in the food industry

Technique of using emulsions	Food value
Enhance the appearance of the product by avoiding separation and other manifestations of instability	A mayonnaise in which the oil and water separate would be unattractive to buy and use in food preparation. Shelf-life may be enhanced
Improve the organoleptic characteristics (i.e., taste, colour, odour and mouth feel) of food	An essential part of the food experience
Use multiple emulsion techniques to control the release of or protect labile ingredients	Encapsulate unpleasant aroma Encapsulate bioactive compounds and sensitive food components to improve nutritional value
Replace O/W emulsions with W/O/W so that the oil content is reduced without affecting the physical characteristics of the product	Produce low-fat emulsions without affecting the mouth feel of the full-fat equivalent

Table 3. Description of foods commonly containing emulsifiers and the emulsifier properties

Food category	Food type	Commonly added emulsifier (E number)	Property of stabiliser
Baked goods	Bread	471, 472e, 481, 482	• strengthening and softening dough for crumb-structure
	Biscuits	472e, 473	• retaining moisture for freshness
	Cakes	472b, 475	
Fat-based spreads	Margarines	322, 471, 472c, 472b, 475, 476	• providing stability
			• improving spreadability, particularly in low fat varieties
	Nut butters	471	• optimising whipping
	Shortening (solid vegetable-based fat)	322, 471, 472b, 475	• reducing water content to prevent splattering • reducing splattering when brought to a high temperature
Dairy desserts	Ice cream	471, 432-436, 473	• enabling aeration of fat, protein, sugars and gum and provide smooth, creamy and fine texture
	Other desserts	472a, 472b, 477	• reducing rate of melting and reducing freezing time • incorporating air bubbles into aerated desserts and providing a fine, regular and highly stable air structure that does not collapse • thickening, gelling and improving mouth-feel
Mayonnaises and		405, 415, 322, 471,	• stabilising the product in place of egg yolk

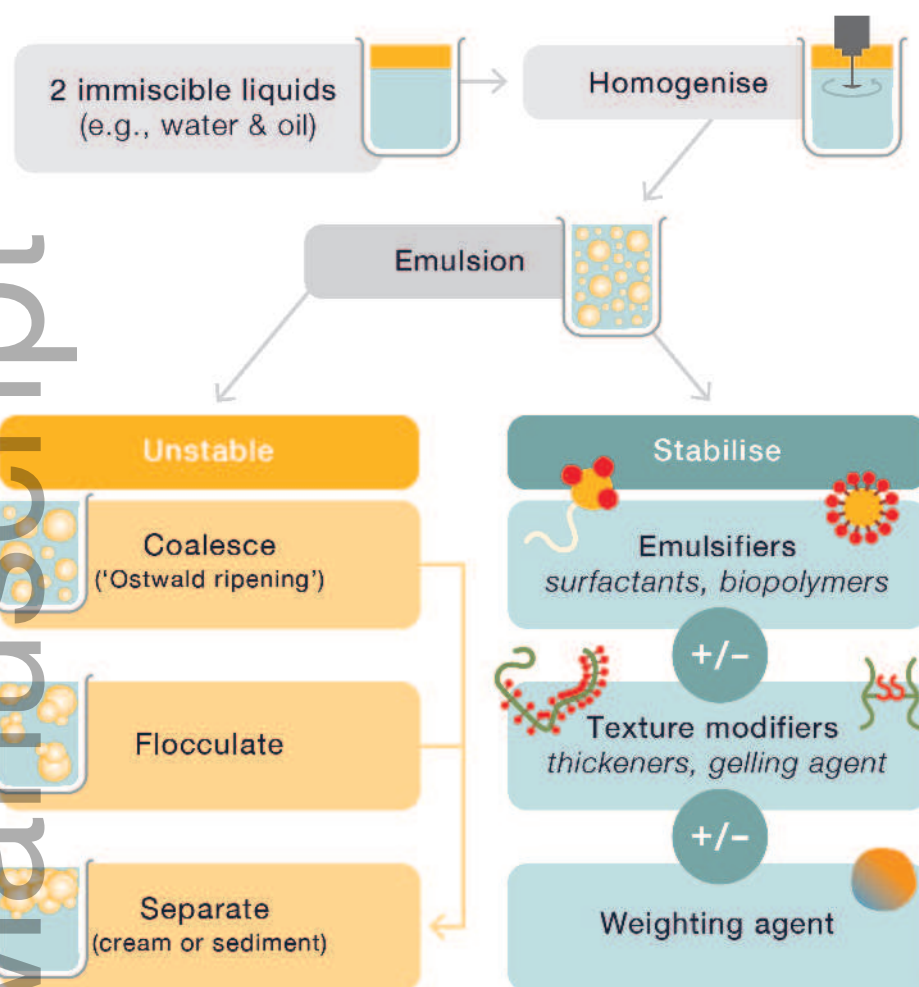
salad dressings		472e	
Confectionery	Caramels, toffees, gummy lollies	471, 473	<ul style="list-style-type: none"> controlling stickiness and improve flavour release delaying 'bloom', which describes the white spots on the surface of chocolate that commonly develops with time or with temperature fluctuations
	Chocolate	322, 476, 472c, 442, 492	
Beverages	Soft drinks	444	<ul style="list-style-type: none"> Contributing to flavour of citrus and kola drinks that remain stable and uniform during varying storage temperatures
	Wine	466	
	Spirits	481, 477	<ul style="list-style-type: none"> stabilising potassium bitartrate (KHT) stabilisation (tartaric acid crystallisation) lengthening shelf life and increasing stability of cream-based liqueurs³³

Figure legend:

Figure 1. Schematic of the creation and fate of emulsions. Most emulsions are unstable, leading to coalesce, flocculate or separate. Emulsions can be stabilised by addition of emulsifiers, texture modifiers and/or weighting agents. Emulsifiers adsorb to droplet surface and stop aggregation, texture modifiers increase viscosity, and weighting agents set oil droplets to the same specific gravity as water.

Figure 2. Examples of ingredients lists of emulsifier-containing and emulsifier-free food products

Figure 3. Potential pathogenic mechanisms associated with emulsifiers and thickeners



apt_15045_f1.jpg

Bread 1

Wheat Flour, Water, Mixed Grains (23%) (Kibbled Purple Wheat, Barley, Wheat Flakes), Wheat Gluten, Yeast, Iodised Salt, Vinegar, Vegetable Oil, Soy Flour, **Vegetable Emulsifiers (481, 471, 472e)**, Mineral Salt (Calcium Carbonate), Vitamins (Thiamin, Folic Acid)

Bread 2

Water, Wheat Flour, Kibbled Rye and/or Triticale (16%), Wheat Gluten, Wholemeal Rye Flour (5%), Canola Oil, Corn Starch, Baker's Yeast, Barley Malt Flour (1%), Vinegar, Iodised Salt, Cultured Whey, Vitamins (Thiamin, Folate)



Biscuit 1

Wheat Flour, Sugar, Cocoa Mass, Vegetable Oil (Contains Soy), Milk Solids, Cocoa Butter, Golden Syrup, **Emulsifiers (Soy Lecithin, E476)**, Salt, Baking Powder, Flavour, Food Acid (Citric Acid)



Biscuit 2

Wheat Flour, Sugar, Oats, Desiccated Coconut [Preservative (233(Sulphites))], Golden Syrup, Butter [Cream (from Milk) Salt], Vegetable Oil & Fats [Antioxidant (307b (from Soy))], Brown Sugar, Raising Agent (500), Salt

Peanut butter 1

Freshly Roasted Peanuts (90%), Sugar, Vegetable Oils, Salt, **Stabiliser (Mono and Diglycerides)**

Peanut butter 2

Roasted Peanuts (85%), Vegetable Oils (Contains Antioxidant (320)), Sugar, Salt



Chocolate 1

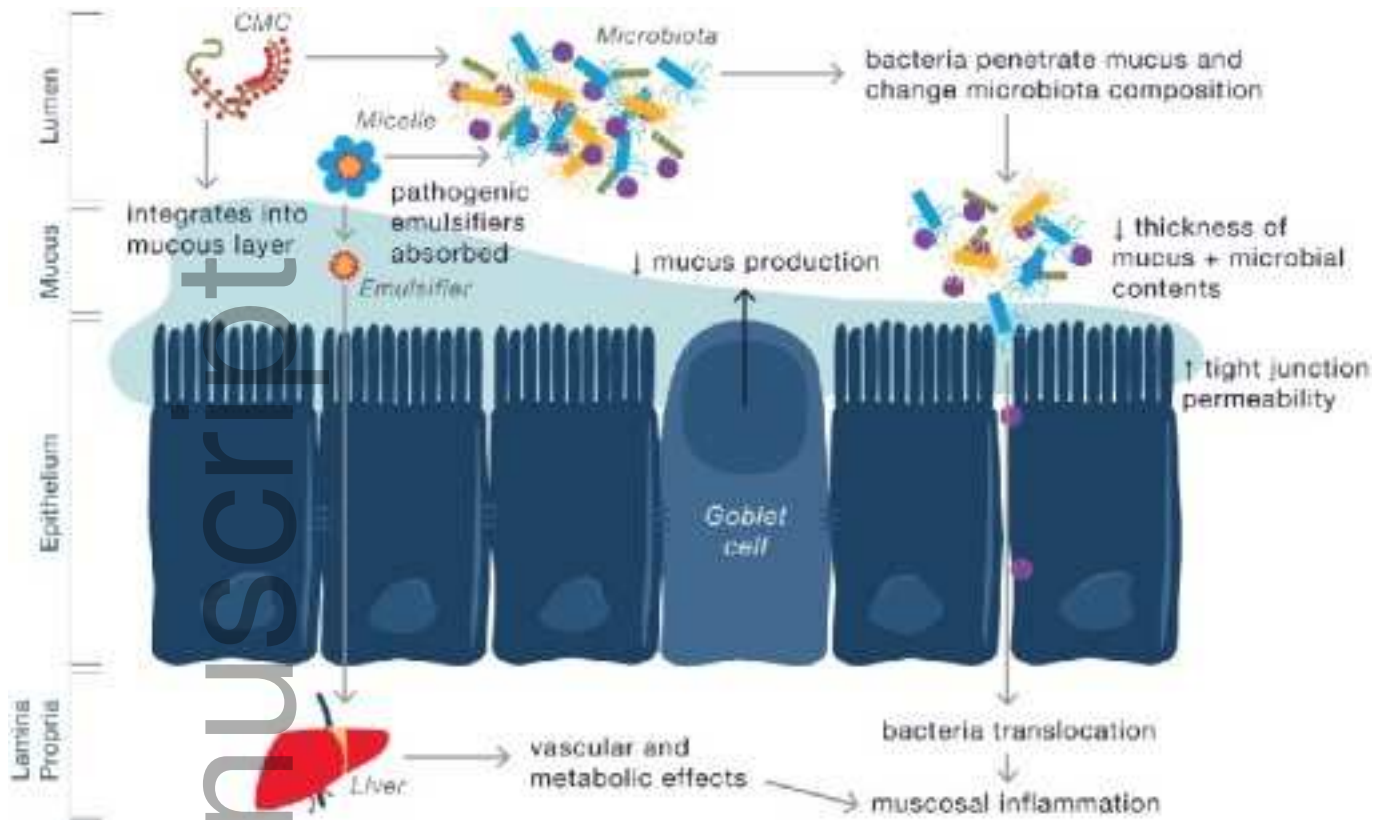
Full Cream Milk, Sugar, Cocoa Butter, Cocoa Mass, Milk Solids, **Emulsifiers (Soy Lecithin, 476)**, Flavours

Chocolate 2

Cocoa Mass, Sugar, Cocoa Butter, Natural Bourbon Vanilla Bean



apt_15045_f2.jpg



apt_15045_f3.jpg



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Halmos, EP;Mack, A;Gibson, PR

Title:

Review article: emulsifiers in the food supply and implications for gastrointestinal disease.

Date:

2019-01

Citation:

Halmos, E. P., Mack, A. & Gibson, P. R. (2019). Review article: emulsifiers in the food supply and implications for gastrointestinal disease.. Aliment Pharmacol Ther, 49 (1), pp.41-50.
<https://doi.org/10.1111/apt.15045>.

Persistent Link:

<http://hdl.handle.net/11343/284881>