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Review Article

Choosing a medication brand: Excipients, food intolerance and prescribing in older people

Amy Page*, Christopher Etherton-Beer

Western Australian Centre for Health and Ageing, University of Western Australia

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ABSTRACT

Multiple brands of the same active ingredient may be available for the same strength, administration route and dose form. Generic brands needs to demonstrate bioequivalence to the originator brand, but the appearance of the generic and originator brands are not required to match. This variation is possible because different brands may vary in the excipients used in the formulation. Excipients are inactive ingredients, and typically make up about 90% of the formulation of an individual medication. Individual preferences or requirements may affect tolerance of particular excipients, such as the use of animal products. The different appearance of brands can affect medication management for some people. This review discusses the potential for excipients to alter the individual response to or tolerance of a medication brand.

1. Introduction

Medications come in many different formulations, and multiple brands of the same active ingredient may be available in the same strength, administration route and dose form. Generic brands are required to demonstrate bioequivalence to the original brand prior to marketing authorisation [1]. Australian pharmacies, for example, are only permitted to substitute brands if the two brands are bioequivalent.

Bioequivalence does not mean that the brands are identical. While comparable plasma concentrations of the active ingredient(s) are achieved after healthy people take both brands, and the same clinical response can be expected, bioequivalent brands can differ substantially. The appearance – shape, colour, size – of the generic and originator brands are not required to match [2]. For example, tablet forms of the common antihypertensive ramipril are available in white, yellow, red and pink [3].

Such variation is possible because different pharmaceutical products vary in the excipients used in the formulation [1]. The inactive ingredients are excipients, which typically make up about 90% of the formulation of an individual medication [4]. The term encompasses all ingredients – except the active ingredient – found in pharmaceutical preparations. They are used to colour and flavour pharmaceutical preparations, and to enhance the product's performance. Binders hold all the ingredients together to provide structure and strength, diluents add bulk to allow small quantities to be measured accurately and disintegrants enhance dispersion of the dose-form in the gastro-intestinal tract (Table 1) [5,6]. Some common excipients and their function are listed in Table 2 [5,6].

The many different excipients included in a brand are available from the manufacturer [4]. Excipients generally are listed in the written information generally available online, namely the Product Information or Consumer Medicine Information leaflets [4]. In Australia, the manufacturer must declare the presence, but not the quantity, of specific ingredients including lactose, gluten and tartrazine [3,7]. This information must be on the label, except for prescription-only medications where it is an option to provide the information in the written information [3,7].

Excipients may affect individual responses to different brands. This concern can be linked to individual preference or requirements (such as for vegetarians or individuals with religious dietary restrictions) or physiological response (including adverse reactions and intolerances), as well as adherence which could be impacted by differences in the physical appearance of brands of active medicines. This review discusses the potential for excipients to alter the individual response or tolerance to a medication brand.

2. Methods

This paper examines the effect that excipients have on the choice of brand without respect to whether the formulation is the originator or generic brand. The emphasis is on the acceptability, safety and tolerability of the excipients themselves, and the effect that has on brand choice. Given the frequency of polypharmacy among older people [8], we have focused on the effect that excipients have on brand choice in

* Corresponding author.
E-mail address: amy.page@uwa.edu.au (A. Page).

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Table 1
Common reasons excipients are used during manufacturing medications.

Category	Function	Example excipients
Binders	Achieve the desired strength for the medication	Cellulose
	glues the powder together to form granules or tablets	Calcium carbonate
		Carbomers
		Gelatin
		Hydrogenated vegetable oil
		Lactose
Coatings and films	Protect medication from moisture	Hypromellose
	Assist to swallow medication	Beeswax, white
	Allow for medication release at a specific location in the gastrointestinal system	Calcium carbonate
		Carnauba wax
Colourants	Identify medication	Calcium
	Protect light-sensitive ingredients	Carmine
	Dies (water-soluble) and pigments (water-insoluble)	Iron oxide
		Quinoline yellow
		Tartrazide
		Titanium dioxide
Diluents	Provide bulk for the active ingredient;	Lactose
	improve properties such as cohesion	Simeticone
		Talc
		Cellulose, microcrystalline
		Calcium carbonate
Disintegrants	Promote dissolution in the gastrointestinal tract	Cellulose, microcrystalline
		Croscarmellose sodium
		Crospovidone
		Povidone
		Sodium starch glycolate
Glidants	Help powders to flow	Talc
		Starch
Lubricants	Prevents the product adhering to equipment during manufacturing or other surfaces	Castor oil, hydrogenated
		Vegetable oil, hydrogenated
		Macrogol
		Magnesium stearate
		Sodium benzoate
		Sodium lauryl sulfate
		Talc

older people.

Articles were included that discussed the effect of excipients on acceptability, tolerance, safety or adherence. We only included oral preparations. For relevance to current practice, we excluded reports where concerns about an individual excipient has led to a re-formulation of the product. An example of this issue were compounding incompatibilities between an excipient and an active ingredient caused effected the performance or stability of the product, which led to a re-formulation so that the issue is not a current concern.

We conducted a search in the Medline, Scopus, and Google Scholar databases using a combination of search terms including “excipient”, “brand” and specific excipient names. Articles were included if they were in English. Reference lists of identified papers were scanned for relevant studies.

3. Adverse reactions to excipients

An allergen is a substance that is harmless for most people but can produce an immune-mediated response which triggers symptoms that can range from mild to life-threatening [9] in allergic individuals. Theoretically, any dietary protein can be a potential allergen [10]. Intolerances can mimic allergic symptoms but are not immune-mediated and include responses to a broad range of triggers [11].

Adverse reactions to excipients are thought to be uncommon [12], however numerous case reports that outline patient sensitivity to a specific excipient describe allergic reactions [13–19]. The nature of these papers suggests such responses are rare but serious, though did not report fatalities. Authors generally report that their investigations determined the adverse events were confirmed allergic reactions mediated by an immune system response [18,20–26]. These reported adverse events varied from skin reactions to severe allergic reactions with documented anaphylaxis [18,20–26].

Individual reactions to excipients may go unnoticed, and thus unreported, if mild or not identified as being due to an excipient [21]. Those referenced above were typically only identified after the person experienced the same or a similar adverse effect to multiple medications, or reacted to one brand but not another [21]. Suspected reactions were generally confirmed by patch or intradermal testing [18,20–26].

3.1. Specific excipients

Colouring agents are added to medications for reasons that include ease of identification, improved acceptability and stabilising light-sensitive ingredients [4]. Many different agents may be used to produce the same or similar colours, and numerous case reports exist of allergies to colouring agents such as the yellow dye tartrazine [19]. Little research has been done to confirm the potential for pharmacological activity of these excipients. Tartrazine allergy, was not found in 26 people with atopic allergies in a pilot double-blind randomised controlled trial [17]. However, allergic responses to excipients that are intended to be inert, are likely to be rare, and thus difficult to detect in clinical trials.

Gluten triggers an immune response that causes chronic inflammation in the small intestine of people with coeliac disease which can lead to malabsorption. The exact quantity of ingested gluten that triggers an adverse effect is uncertain and may vary between people, though it may be as little as 10 mg in a day and “gluten-free” is defined by the American Food and Drug Administration (FDA) as 20 parts per million (ppm) of gluten or less [27].

Starch is used in oral formulations as a binder and disintegrant [4]. It is derived from plant sources such as wheat, corn and potato, so concerns have been expressed about the possible gluten content in wheat-derived starch. However, wheat starch is so highly processed that it is unlikely to have any remaining gluten content. In Australia and the UK, manufacturers must declare if they have used wheat starch in their printed materials [3,28,29].

Lactose is a disaccharide sugar present in milk and used as a binder and a diluent in pharmaceutical products. The lactase enzyme in the small intestine metabolises lactose into two smaller sugars, glucose and galactose, that are absorbed into the blood stream [30]. Some people have reduced or absent lactase activity so cannot completely metabolise all the lactose in the small intestine, which means some lactose reaches the large intestine [30]. The presence of lactose in the large intestine can trigger the symptoms of lactose intolerance [30] when bacteria metabolise lactose, producing gases that cause symptoms including abdominal cramps, bloating and flatulence. Lactose intolerance is distinct from a milk allergy, which is an immune reaction to milk proteins [30].

The lactose volume required to cause symptoms is variable, and can change with age [31]. It is suggested that lactose intolerant people can consume 12 g in a single dose with either no effect or only minor symptoms [32]. Oral preparations that contain lactose may range from 4 mg to 600 mg [31] so it is unlikely that a single tablet or capsule would contain sufficient lactose to cause symptoms [32]. No significant difference in symptoms after eight hours was found with 400 mg lactose compared to placebo in a blinded crossover RCT with 77 lactose-

Table 2
Selected excipients that are commonly used in oral medications*.

Excipient	Synonyms (or 'E number' if applicable)	Functions, examples	Notes or reactions (theoretical, attributed or confirmed reactions)	Source, if animal
Beeswax, white	Wax, white	Film; Alter absorption.	Generally considered nontoxic and nonirritant. Rare hypersensitivity reactions have been reported.	Prepared from yellow beeswax
Beeswax, yellow	Refined wax (E901)	Modified released agent; Stiffening agent; Stabiliser;	Generally considered nontoxic and nonirritant. Rare hypersensitivity reactions have been reported.	Bees
Calcium carbonate	Precipitated calcium carbonate	Buffer; Coating; Colourant; Binder; Diluent.	Large quantities are used therapeutically	
Carbomers	Acrylic acid polymer, polyacrylic acid	Binder; Emulsifier; Modified release agent; Stabiliser.	Considered nontoxic and nonirritant orally as it is not absorbed.	
Carmine	Cochineal carmine	Colourant.	It has been associated with hypersensitivity reactions, with at least 35 cases reported to the Food and Drug Administration.	Prepared from cochineal, which is derived from insects
Carnauba wax	Brazil wax	Coating agent.	Considered nontoxic and nonirritant for oral medications. 7 mg/kg of body weight is considered an acceptable daily intake	
Carrageenan	Chondrus extract; irish moss extract	Emulsifer; Stabiliser; Suspending agent; Modified release agent.	Relatively nontoxic and nonirritant when used orally Known to induce inflammation in laboratory animals	
Castor oil	Virgin caster oil, oleum ricini, richinus oil	Emulsifier Solvent	Considered nontoxic and nonirritant Large quantities are used therapeutically	
Castor oil, hydrogenated	Castor wax	Lubricant; Stiffening agent; Modified release agent.	Considered nontoxic and nonirritant	
Cellulose, microcrystalline	Cellulose gel; crystalline cellulose (E460)	Adsorbant; Suspending agent; Binder; Diluent; Disintegrant.	Relatively nontoxic and nonirritant when used orally as not absorbed systemically Larger quantities may have a laxative effect, unlikely to be relevant when used as an excipient	
Colloidal anhydrous silica	Colloidal silica; Colloidal silicon dioxide		Generally considered nontoxic and nonirritant for oral medications	
Croscarmellose sodium	Modified cellulose gum	Disintegrant.	Considered nontoxic and nonirritant Large quantities may have a laxative effect, unlikely to be relevant for solid oral medications	
Crospovidone	Crospovidonum; Crosslinked povidone (E1202)	Disintegrant.	Generally regarded as nontoxic and nonirritant, but limited available data	
Fumaric acid	Allomaleic acid; allomalenic acid; boletic acid; butenedioic acid.	Acidulant; Antioxidant; Flavouring.	Generally regarded as relatively nontoxic and nonirritant. Acute renal failure and other adverse reactions have occurred following use for skin conditions. Also linked to liver function disturbances, gastrointestinal effects and flushing.	
Gelatin	Gelatine.	Film; Coating; Gelling agent; Binder.	Generally regarded as nontoxic and nonirritant. Rare reports of local irritation in the oesophagus if the casule adheres.	Multiple possible sources. Can be prepared from bovine or porcine collagen.

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Table 2 (*continued*)

Excipient	Synonyms (or 'E number' if applicable)	Functions, examples	Notes or reactions (theoretical, attributed or confirmed reactions)	Source, if animal
Glycerin	Glycerol; Glycerine.	Solvent; Emollient; Sweetener; Plasticiser.	Generally regarded nontoxic and nonirritant for oral medications. May have a mild laxative effect. Large doses may cause headache, thirst, nausea and hyperglycaemia.	Multiple possible source. Glycerin occurs naturally in animal and vegetable fats. Can be sourced as a by-product from oils and fats in manufacture of soaps and fatty acids
Hydrogenated vegetable oil	Hydrogenated oil	Lubricant; Binder.	Considered nontoxic	
Hypromellose	Methylcellulose propylene glycol ether; Methyl hydroxypropylcellulose (E464)	Coating agent; Modified release agent; Emulsifier; Film; Binder; Stabiliser.	Generally considered nontoxic and nonirritant Large quantities may have a laxative effect.	
Iron oxide	Iron oxide black; Iron oxide red; Iron oxide yellow.	Colourant.	Generally considered nontoxic and nonirritant. Some countries limit iron oxide colouring intake to 5 mg elemental iron daily.	
Lactose	Lactose hydrate; lactose monohydrate.	Diluent; Filler; Binder.	For lactose intolerant people, it may cause symptoms of lactose intolerance	Whey of cows' milk
Macrogols	Polyethylene glycol	Plasticiser; Solvent; Lubricant.	Generally regarded as nontoxic and nonirritant. Adverse effects have been reported, which are more common with those with lower molecular weights than greater weights.	
Magnesium stearate	Stearic acid.	Lubricant.	Considered nontoxic. Large quantities may have a laxative effect or mucosal irritant.	Multiple possible source. Can be prepared using stearic acid from bovine, porcine or ovine sources.
Povidine	(E1201)	Disintegrant; Dissolution; Enhancer Suspending agent; Binder.	Considered nontoxic and nonirritant orally as it is not absorbed.	
Quinoline yellow	(E104)	Colourant	Reported suspected severe urticarial reaction	
Simeticone	Simethicone	Antifoam; Diluent; Water-repellent agent.	Considered nontoxic and nonirritant. Large quantities are used therapeutically	
Sodium benzoate	(E211)	Antimicrobial preservative; Lubricant.	Well tolerated Sensitivities reported of both side effects and allergic reactions	
Sodium lauryl sulfate	Lauryl sodium sulfate	Surfactant; Detergent; Emulsifier; Lubricant.	Contact to mucus membranes including the stomach can cause acute irritation	
Sodium starch glycolate	Carboxymethyl starch	Disintegrant.	Considered nontoxic and nonirritant. Large quantities may be harmful	
Starch	Maize starch; Potato starch; Rice starch; Tapioca starch; Pea starch; Wheat starch	Diluent; Disintegrant; Binder.	Regarded as essentially nontoxic and nonirritant. Rare allergic reactions to starch, and these may not be experienced with starch from an alternative vegetable. Wheat proteins (gluten) may be problematic for people with coeliac disease.	
Talc	Purified talc; powdered talc; hydrous magnesium silicate; (E553b)	Anticaking agent; Glidant; Diluent; Lubricant.	Not absorbed systemically so consisted nontoxic	

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Table 2 (*continued*)

Excipient	Synonyms (or 'E number' if applicable)	Functions, examples	Notes or reactions (theoretical, attributed or confirmed reactions)	Source, if animal
Tartrazine	Food yellow 4, (E171)	Colourant.	Sensitivities reported of both side effects and allergic reactions	
Titanium dioxide		Colourant. Opaque.	Considered nontoxic and nonirritant.	
Tributyl citrate	Citric acid	Plasticizer.	Considered nontoxic and nonirritant. Large quantities may be harmful	
Triethyl citrate	Citric acid ethyl ester	Plasticizer; Solvent.	Considered nontoxic and nonirritant. Large quantities may be harmful	

*Tolerabilities vary for some excipients if prepared for other routes of administration, therefore, comments here apply only to the oral route of administration.
References compiled from multiple source, primarily:

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- Rowe, R. C., et al. [5]. Handbook of Pharmaceutical Excipients. London UK and Washington DC, Pharmaceutical Press and American Pharmacists Association.

intolerant participants [32].

Written material from the manufacturer declares only the presence of lactose, but not the volume, which can change considerably between active ingredients and between brands. American pharmaceuticals can contain up to 1020 mg lactose as an inert ingredient [33]. When lactose is present, an average 300 mg immediate release tablet was found to contain 240 mg lactose (80% of its weight) [33]. The lactose content is variable as laboratory testing showed that, for example, maximum daily dose of loperamide, codeine and omeprazole would result in consuming 1000 mg, 368 mg and 8 mg lactose respectively [31]. People who take many lactose-containing medications at the same time may risk a cumulative lactose content that could trigger symptoms. The quantity of lactose in medications may be inconsequential for people only taking a few medications. The risk may be greater in older people as medication use often increases with age with estimates that three-quarters of older people take five or more medications every day [34]. For people with severe lactose intolerance and take many medications, medications could be considered as a source of hidden lactose if symptoms occur [31].

4. Personal preferences and values

The source of excipients can be a contentious issue for some consumers: excipients can be synthetic or sourced from animals or plants. The avoidance of animal-derived excipients often relates to a personal preference rather than a safety concern. Safety concerns from animal-derived excipients have included prion-related diseases, so extracted excipients are further refined and tested to reduce the risk of contaminated products [35]. The USA and Australia, for example, have limited some animal-derived excipients to those sourced from specified listed countries to address infection concerns [36]. Some authors have argued that all medications should be suitable for vegetarians or vegans, or at least adequately labelled as safe for vegans or vegetarians [37]. However, there are practical considerations for the source of excipients. For example, phospholipids can be derived either natural or synthetic sources, with natural phospholipids sourced from vegetables (e.g soybeans or flax seed) or animal materials (eg. egg yolk, milk or krill) [35]. Preference is given to sourcing phospholipids from natural sources as it is more sustainable and less expensive [35].

Religious beliefs can include dietary restrictions on certain animal products. These dietary restrictions can extend to excipients. Hinduism restricts bovine products, while Judaism and Islam restrict porcine products [38]. The extent to which an individual adheres to these religious restrictions varies, and provisions within some religious groups allow for therapeutic use depending on the therapeutic need. A statement arose from a World Health Organisation seminar which declared the gelatin in pharmaceutical products to be halal, and thus acceptable for consumption by Muslims [39]. Most Muslims are able to use other medications with porcine-derived excipients (e.g. some anticoagulants such as pancreatic enzymes) if no alternative therapy is available as the preservation of human life is considered to take precedence over dietary laws [40]. Several reports exist of religious believers choosing not to use medications based on a religious aversion to an excipient [41,42].

Gelatin is usually derived from either bovine or porcine bones, and can be problematic for vegetarians and observant members of some religions [43]. Most capsules (50–80%) contain gelatine, which means that, for strict vegetarians, the brand of capsules need to be carefully selected [40]. For example, there are 14 brands of omeprazole, a proton pump inhibitor to reduce gastric acid, available in Denmark; 10 out of 12 contain porcine-derived gelatin and the other two contain gelatin from an alternative source [40]. A similar report from the UK found that 20 out of 100 common medications contained gelatin, of which eight stated it was animal-derived but did not identify the animal [37]. In Australia, the origin of gelatin is not stated in the manufacturer's written information but may be available from the Medical Information department of the pharmaceutical company.

Vegetarians avoid the consumption of meat products, which may include animal-derived excipients. Vegans additionally avoid animal products such as honey, eggs and dairy. The extent to which an individual adheres to a vegetarian diet varies. For strict vegetarians or vegans, the presence of animal-derived excipients can interfere with their willingness to take a pharmaceutical product [38]. The presence of animal-derived excipients in commonly dispensed medications in the UK vary, with up to one-third of 100 common medication brands containing animal products and only one-quarter clearly identified as definitely not containing animal-derived excipients [37].

5. Effect on adherence for older people

Generally, research indicates that whether a brand is generic or originator, per se, has little effect on adherence to therapy [44]. A Dutch study investigated 1028 people (age 60 ± 14 years) with hypertension who continued to take the originator brand compared to those who were substituted to a generic brand [45]. Compliance was similar in the two groups, and so were hospital admissions. [45] Other research has suggested that the reduced cost of the generic brand compared to the originator brand can improve compliance [46].

The variable appearance of pharmaceutical products means that frequent brand substitution may negatively impact patients' ability to self-manage their medications [2]. For older people, particularly those with cognitive impairment or managing many medications, the changed appearance of the packaging or medication can cause confusion [2,47]. This confusion can lead to unintentional non-adherence or incorrect dosing [2,47]. People who identify their medications primarily by size and colour – "I take the little blue pill in the morning" – may struggle if unable to also confidently identify names of the active ingredient and brands [47]. Consistency in a medicine's appearance, regardless of which excipients are used to produce it, supports this group to manage their medications, regardless of whether it is the generic or originator brand.

6. Conclusion

All brands for a single active ingredient are tested for bioequivalence, but do not need to be identical in appearance or contain the same excipients. The included excipients may vary between brands: an allergy or an objection to an individual excipient may mean that excipients help determine the choice of brand. The origin of excipients is not always clear, and it is important that information on all ingredients, including excipients, is available for consumers and carers from a source such as the written Product Information.

Older people and their carers who manage complex medication regimens, have low health literacy or have cognitive impairment may benefit from a consistent choice of brand to avoid the appearance of their medications changing.

Contributors

Both authors designed the review. Amy Page drafted the paper. Both authors critically reviewed the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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