The Selection of Excipients for Oral Solid Dosage Forms

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Introduction

The preferred route of administration for most Active Pharmaceutical Ingredients (APIs) is orally due to ease of administration, improved patient adherence and reduced complexity required to manufacture oral solid dosage forms compared with alternative drug delivery systems. Factors which may preclude oral administration of APIs include poor bioavailability resulting from poor solubility and/or permeability, poor stability and degradation during gastric transit, as well as the therapeutic site and method of action. Examples of common oral solid dosage forms include tablets, capsules, beads, orally disintegrating tablets (ODTs) and lozenges, all of which involve compounding the required quantity of the API (the dose) with one or more excipients. The range of excipients available to the formulator is truly diverse; however, excipients are, in general, intended to be pharmacologically inert whilst conferring advantageous physical properties to the formulation, facilitating its ability to safely and reliably deliver the API to the therapeutic site of action. Excipients are only included within a formulation if there is suitable justification to do so. In general, the selection of an excipient is based on the dose, type of drug product, physicochemical properties, chemical compatibility with the API, route of delivery, administration frequency, interactions with other formulation components, method of manufacture, processability and the container or closure system.[1] This chapter aims to describe the scientific rationale behind the selection of common excipients used to manufacture oral solid dosage forms.

Excipients to enhance the flow of powders and granules

One of the most commonly identified critical quality attributes (CQAs) in the production of oral solid dosage forms is powder or granule flow. Modern tablet and capsule machines are designed to produce several hundred thousand units per hour and adequate flow of the final blend is essential to ensure that the resultant dosage form is consistent in terms of weight, composition and, for tablets, the degree of compaction it has received.

Flowability is not an inherent powder property but depends on four factors:

- Intrinsic properties such as particle size, density, shape and roughness.
- Bulk properties such as particle size distribution, cohesive and frictional interactions.
- External conditions such as temperature, humidity or state of compaction.
- Processing equipment design and settings, which affect the powder dynamics.

As such, it is impossible to adequately characterize flow using a single measurement technique. Although traditional, empirical tests such as compressibility or angle of repose may give a qualitative means of classifying or comparing powder behaviors, the data produced by more sophisticated techniques such as ring shear testing or powder rheometry enables a more complete characterization of powder flow and cohesion properties.[2]

APIs are often subjected to a particle size reduction process in order to ensure that the final dosage form meets the required standards of content uniformity and dissolution; thus they often contain a significant proportion of fine particles (e.g. with diameter <20 μm). These particles, by virtue of their high specific surface area, often exhibit high degrees of adhesion to other surfaces and cohesion to neighboring particles resulting in poor flow.[3] Certain morphologies of the API such as needle-shaped or acicular particles may also have a negative impact on flow due to mechanical locking. As a result, where the formulation contains a high percentage of API (e.g. $>10\%$) it may be possible to improve the overall blend flow by modifying either the particle shape or the particle size of the API present.

If the formulation composition is fixed, a preferred option for improving flow is to increase the particle size using a granulation process, which requires a degree of compactibility and moderately good flow for the purposes of roller compaction or the selection of an appropriate binder if wet granulation is adopted. If the formulation is open to modification, flow can be improved by switching excipient grades; many of the excipients used in solid dosage forms are marketed in a range of different particle size grades as shown in Table I. The benefits of increasing particle size must be weighed against the potential increased risk of API segregation from the other blend components, or the possible reduction in compactibility or dissolution rate. For example, one of the larger grades of microcrystalline cellulose (*Avicel PH-200*) has improved flow but has poorer compactibility than a smaller particle size grade (*Avicel PH-102*).[4]

The flow of both powders and granules can often be significantly improved by the addition of glidants, which are very finely divided powders that, by virtue of their small particle size (typically less than 50 nm), have a strong tendency to become adsorbed onto the surface of larger powder blend components. This process increases the minimal contact distance and reduces the contact area between the larger particles, resulting in the reduction of van der Waals forces and the tendency of powders to aggregate.[5,6] Additionally, glidants may increase flowability by absorbing moisture or rolling under stress.[5] Colloidal silica is one of the most effective glidants and is usually added at levels $<1\%$, but other materials such as maize starch or talc are often used in capsule formulations where compactibility is less crucial. A recently developed technique to improve flow known as 'nanocoating' involves comilling of colloidal silicon dioxide onto host pharmaceutical particles, prior to the addition of the remaining formulation components. This step has been shown to improve the flow of both APIs and active blends.[7]

Excipients to enhance the compaction of oral solid dosage forms

Compaction can be defined as the transformation of a powder or granules into a coherent dosage form of defined shape through the process of compression[8] and is the fundamental concept behind successful tablet production. A degree of compactibility is also important for capsule formulations, as successful capsule filling depends on the production of robust and uniform powder plugs at forces much lower than those used in tablet production.[9]

distribution is prescribed. Manufacturers have developed sodium polystyrene sulfonate powders meeting a wide range of particle size distributions in order to meet specific customer's requirements. For example:

AMBERLITE IRP69 (Dow Chemical Co.): Fine (10–25% of the powder is retained on a 75 µm sieve);

AMBERLITE IRP70 (Dow Chemical Co.): Middle (52-70% of the powder is retained on a 75 µm sieve);

AMBERLITE IRP476 (Dow Chemical Co.): Coarse (not less than 95% of the powder is retained on a 75 µm sieve);

AMBERLITE IRP469 (Dow Chemical Co.): Coarse (not less than 90% of the powder is retained on a 50 µm sieve);

AMBERLITE IR69F (Dow Chemical Co.): Spherical beads of 0.2–1.2 mm (intermediate).

Sodium polystyrene sulfonate is used as an API to treat hyperkalemia,[9] and is included as an active ingredient in a number of approved drug products worldwide including USA, UK, Canada and France.

The UNII code for sodium polystyrene sulfonate is 1699G8679Z.

19 Specific References

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2 The Dow Chemical Company. Applications for *Amberlite* & *Duolite* ion exchange resins. http://pharmaandfood.dow.com/en/pharma-solutions/products/amberlite-and-duolite/applications (accessed 20 April 2016).

3 Drugs.com. Product information: *Codeprex*, June 2004. http://www.drugs.com/pro/codeprex.html (accessed November 26, 2015).

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8 The Dow Chemical Company. MSDS USA: *AMBERLITE IRP69*, Sodium Polystyrene Sulfonate USP, Sept 2014.

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21 Author

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Sodium Propionate

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1 Nonproprietary Names

BP: Sodium Propionate

PhEur: Sodium Propionate

USP–NF: Sodium Propionate

2 Synonyms

E281; ethyl formic acid, sodium salt; methylacetic acid, sodium salt; napropion; natrii propionas; prophyllin; sodium propanoate.

3 Chemical Name and CAS Registry Number

Propionic acid, sodium salt, hydrate [6700-17-0]

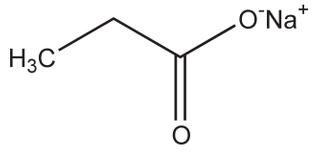
Propionic acid, sodium salt, anhydrous [137-40-6]

4 Empirical Formula and Molecular Weight

$C_3H_5NaO_2 \cdot xH_2O$ 114.06 (for monohydrate)

$C_3H_5NaO_2$ 96.06 (for anhydrous)

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Sodium propionate is used in oral pharmaceutical formulations as an antimicrobial preservative. Like propionic acid, sodium propionate and other propionic acid salts are fungistatic and bacteriostatic against a number of Gram-positive cocci. Propionates are more active against molds than sodium benzoate, but have essentially no activity against yeasts; *see* Section 10. Sodium propionate has also been used as a preservative in eye drops.[1]

8 Description

Sodium propionate occurs as colorless transparent crystals or as a granular, free-flowing, crystalline powder. It is odorless, or has a slight characteristic odor, and is deliquescent in moist air. Sodium propionate has a characteristic, slightly cheeselike taste, although by itself it is unpalatable.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium propionate.

Test	PhEur 10.2	USP 43–NF 38 S1
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Alkalinity	—	+
pH	7.8–9.2	—
Water	—	≤1.0%
Related substances	+	—
Readily oxidizable substances	+	—
Iron	≤10 ppm	—
Loss on drying	0.5%	—
Assay (dried basis)	99.0–101.0%	99.0–100.5%

10 Typical Properties

Antimicrobial activity Sodium propionate, propionic acid, and other propionates possess mainly antifungal activity and are used as preservatives primarily against molds; they exhibit essentially no activity against yeasts. Although, in general, propionates exhibit little activity against bacteria, sodium propionate is effective against *Bacillus mesenterium*, the organism that causes 'rope' in bread. Antimicrobial activity is largely dependent upon the presence of the free acid and hence propionates exhibit optimum activity at acidic pH, notably at less than pH 5. Synergistic effects occur between propionates and carbon dioxide or sorbic acid. *See also* Propionic acid.

Melting point 285°C

Solubility Soluble 1 in 24 of ethanol (95%), 1 in 1 of water, and 1 in 0.65 of boiling water; practically insoluble in chloroform, ether, and methylene chloride.

Spectroscopy

IR spectrum *see* Figure 1.

NIR spectrum *see* Figure 2.

Raman spectrum *see* Figure 3.

11 Stability and Storage Conditions

Sodium propionate is deliquescent and should therefore be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Incompatibilities for sodium propionate are similar to those of other weak organic acids.

13 Method of Manufacture

Sodium propionate is prepared by the reaction of propionic acid with sodium carbonate or sodium hydroxide.

14 Safety

Sodium propionate and other propionates are used in oral pharmaceutical formulations, food products, and cosmetics. The free acid, propionic acid, occurs naturally at levels up to 1% w/w in certain cheeses.

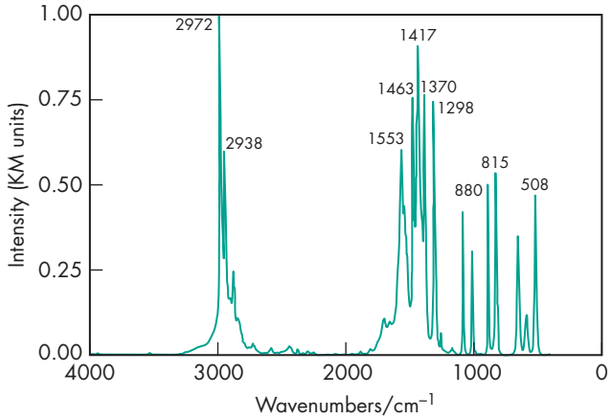


Figure 1: Infrared spectrum of sodium propionate (anhydrous) measured by diffuse reflectance. Adapted with permission of Informa Healthcare.

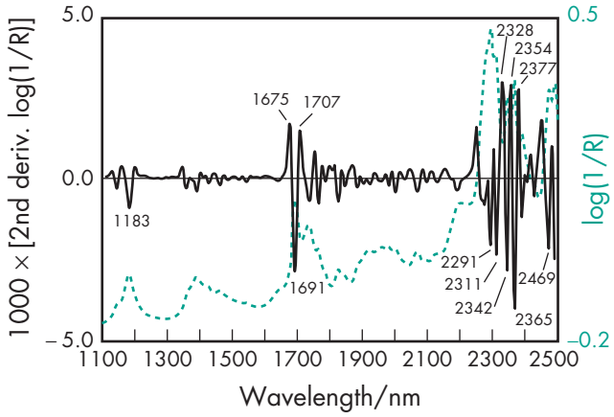


Figure 2: Near-infrared spectrum of sodium propionate measured by reflectance.

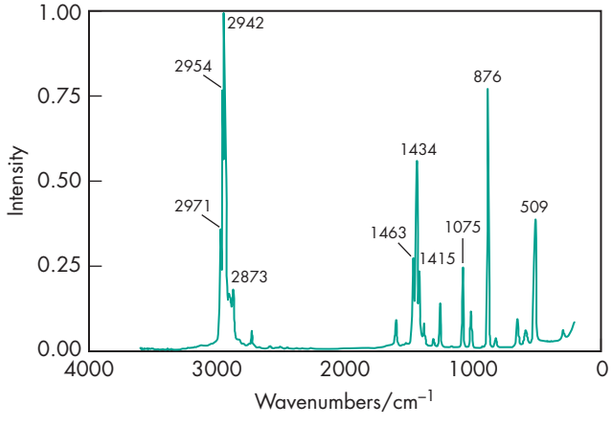


Figure 3: Raman spectrum of sodium propionate (anhydrous) measured in the 180° reflectance mode. Adapted with permission of Informa Healthcare.

Sodium propionate is moderately toxic by skin contact and subcutaneous routes.[2]

Following oral consumption, propionate is metabolized in mammals in a manner similar to that of fatty acids. Toxicity studies in animals have shown sodium propionate and other propionates to be relatively nontoxic materials.[3,4] In veterinary medicine, sodium propionate is used as a therapeutic agent for cattle and sheep.[5]

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In humans, 6 g of oral sodium propionate has been administered daily without harm.[3] However, allergic reactions to propionates can occur.

LD_{50} (mouse, oral): 6.33 g/kg[2]
LD_{50} (mouse, SC): 2.1 g/kg[2]
LD_{50} (rabbit, skin): 1.64 g/kg[2]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium propionate may be irritant to the eyes and skin. Gloves, eye protection, and a dust-mask are recommended. When heated to decomposition, sodium propionate emits toxic fumes of sodium monoxide, Na_2O.

In the UK, the workplace exposure limits for propionic acid are 31 mg/m^3 (10 ppm), long-term (8-hour TWA) and 46 mg/m^3 (15 ppm) short-term.[6]

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (oral capsules, powders, solutions, suspensions, syrups, tablets and other oral preparations). Included in the Substances Added to Food (formerly EAFUS) list compiled by the FDA. Accepted for use as a food additive in Europe. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Calcium propionate; potassium propionate; propionic acid; zinc propionate.

Calcium propionate

Empirical formula $C_6H_{10}O_4Ca$
Molecular weight 186.22
CAS number [4075-81-4]
Synonyms Calcium dipropionate; E282; propanoic acid, calcium salt; propionic acid, calcium salt.
Appearance White crystalline powder.
Solubility Soluble in water; slightly soluble in ethanol (95%) and methanol; practically insoluble in acetone and benzene.
Method of manufacture Prepared by the reaction of propionic acid and calcium hydroxide.
Comments Occurs as the monohydrate or trihydrate.

Potassium propionate

Empirical formula $C_3H_5O_2K$
Molecular weight 112.17
CAS number [327-62-8]
Synonyms E283; propanoic acid, potassium salt; propionic acid, potassium salt.
Appearance White crystalline powder.
Comments Occurs as the anhydrous form and the monohydrate. Decomposes in moist air to give off propionic acid.

Zinc propionate

Empirical formula $C_6H_{10}O_4Zn$
Molecular weight 211.52
CAS number [557-28-8]
Synonyms Propanoic acid, zinc salt; propionic acid, zinc salt.
Appearance White platelets or needlelike crystals (for the monohydrate).
Solubility The anhydrous form is soluble 1 in 36 of ethanol (95%) at 15°C, 1 in 6 of boiling ethanol (95%), and 1 in 3 of water at 15°C.
Method of manufacture Prepared by dissolving zinc oxide in dilute propionic acid solution.
Comments Occurs as the anhydrous form and the monohydrate. Decomposes in moist air to give off propionic acid.

18 Comments

Propionate salts are used as antimicrobial preservatives in preference to propionic acid since they are less corrosive.

In food processes, particularly baking, sodium propionate is used as an antifungal agent; it may also be used as a flavoring agent in food products. In cheese products, propionates are limited to 0.3% w/w concentration; a limit of 0.32% w/w is applied in flour and white bread rolls, while a limit of 0.38% w/w is applied in whole wheat products.

Therapeutically, sodium propionate has been used topically in concentrations up to 10% w/w alone or in combination with other propionates, caprylates, or other antifungal agents, in the form of ointments or solutions for the treatment of dermatophyte infections. However, the therapeutic use of sodium propionate in topical antifungal preparations has largely been superseded by a new generation of antifungal drugs.

In veterinary medicine, sodium propionate is used therapeutically as a glucogenic substance in ruminants.[5]

A specification for sodium propionate is contained in the *Food Chemicals Codex* (FCC).[7]

The EINECS number for sodium propionate is 205-290-4. The PubChem Compound ID (CID) for sodium propionate is 23663426.

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