Review

Sprinkle formulations—A review of commercially available products

Han Sol Lee\textsuperscript{a}, Jeong-Jun Lee\textsuperscript{a}, Myeong-Gyu Kim\textsuperscript{b}, Ki-Taek Kim\textsuperscript{c}, Cheong-Weon Cho\textsuperscript{a}, Dae-Duk Kim\textsuperscript{d}, Jae-Young Lee\textsuperscript{a,}\textsuperscript{*}

\textsuperscript{a}College of Pharmacy, Chungnam National University, Daejeon 34134, Republic of Korea
\textsuperscript{b}Graduate School of Clinical Pharmacy, CHA University, Pocheon 11160, Republic of Korea
\textsuperscript{c}College of Pharmacy and Natural Medicine Research Institute, Mokpo National University, Jeonnam 58554, Republic of Korea
\textsuperscript{d}College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 08826, Republic of Korea

\textbf{ARTICLE INFO}

Article history:
Received 19 November 2018
Revised 8 March 2019
Accepted 12 May 2019
Available online 8 July 2019

Keywords:
Sprinkle formulation
Soft food
Geriatric
Pediatric
Dysphagia
Guidance for industry

\textbf{ABSTRACT}

Currently, sixty-five original sprinkle drug products are available in various dosage forms including tablets, powders, immediate-release capsules, extended-release capsules, delayed-release capsules, and multiparticulate drug delivery systems. By sprinkling on soft food vehicles, these products provide dosing flexibility and convenience of administration, which potentially improve the compliance of patients with dysphagia. Due to these advantages, the growth of sprinkle products picked up since the 1990s, and several regulatory issues regarding this dosage form have been raised and documented. In this article, the types of sprinkle formulations were discussed by dividing them into seven categories, and the commercial products were summarized in terms of the drug substance, pharmaceutical excipients, storage conditions and administration methods. In addition, several US Food and Drug Administration guidelines related to the regulatory issues of sprinkle formulations were reviewed, which led to the conclusion that the future development of this promising dosage form demands integrated guidance for industry rather than scattered information in various documents.

© 2019 Shenyang Pharmaceutical University. Published by Elsevier B.V.
This is an open access article under the CC BY-NC-ND license.
(http://creativecommons.org/licenses/by-nc-nd/4.0/)

\textbf{1. Introduction}

Oral delivery is regarded as the most desirable route of administration, given its non-invasiveness and high patient acceptability [1]. Among the various types of oral formulations, solid dosage forms like capsules and tablets are preferred due to the dosing convenience, high physicochemical stability, and cost-effectiveness [2,3]. However, the large size of solid formulations is challenging for patients with dysphagia—often the elderly and children—to swallow, which in turn promoted the development of novel oral formulations, including sprinkle formulations [1,4–6].
Sprinkle formulations are drug-containing pellets or granules that can be mixed with soft food before administration (Fig. 1). These formulations provide almost the same dosing flexibility and ease of ingestion as liquid formulations when sprinkled on liquid or semi-solid vehicles, such as applesauce, pudding or yogurt [2,6]. The food taken together with the drug can also mask the unpleasant taste and smell of the drug substance, which potentially improves patient compliance [7]. Moreover, sprinkle formulations are available in tablet or capsule formulations for the convenience of handling and can be readily crushed or opened before being sprinkled on food, respectively [8]. Due to their solid state, sprinkle formulations guarantee the higher stability of loaded drugs than liquid formulations during storage [9].

Since the first product was approved by the US Food and Drug Administration (FDA) in the early 1940s, sixty-five original sprinkle formulations have been marketed in the US (Fig. 2). The commercially available sprinkle formulations can be classified into seven formulation types, consisting of tablets, powder, granules, immediate-release (IR) capsules, extended-release (ER) capsules, delayed-release (DR) capsules, and multiparticulate drug delivery system (MDDS). Tables 1–7 show the formulation types arranged by the date of approval in the US. This review aims to provide the information of each sprinkle product regarding its drug substance, pharmaceutical ingredients, storage condition, and administration method. In addition, FDA guidance articles related to sprinkle formulations were introduced for the future development of this formulation.

2. Types of sprinkle formulations

2.1. Method of collecting information on sprinkle drug products

Sixty-five New Drug Applications (NDAs) for sprinkle drug products were found in the FDA database (https://www.accessdata.fda.gov/scripts/cder/daf/; last accessed October 2018). The product list was compiled based on the labeling information of each product (Tables 1–7). Unless otherwise noted, the other information including generic name, drug substance, pharmaceutical ingredients, storage condition, and administration method was also adapted from each product labeling.

2.2. Tablets

The labeling of tablet formulations usually carries a warning that the product must not be crushed [10]. However, there are more than nine crushable tablet products commercially available. The administration of this sprinkle tablet is performed by carefully crushing the tablet and immediately

Fig. 1 – General administration methods for the sprinkle drug products in various dosage forms including tablets, powder, granules, immediate-release (IR) capsules, extended-release (ER) capsules, delayed-release (DR) capsules, and multiparticulate drug delivery system (MDDS).

Fig. 2 – The number of approved New Drug Applications (NDAs) for sprinkle drug products since 1941. A total of sixty-five original sprinkle products are available on the US pharmaceutical market.
| Brand/Generic names | Indications | Strength/Storage | Excipients | Manipulation | Company | Initial US approval |
|---------------------|-------------|------------------|------------|--------------|---------|---------------------|
| Doryx®/doxycycline hyclate | Treatment and prevention of bacterial infections | 50 and 200 mg Store at 20 to 25 °C in a tight and light-resistant container. | Lactose monohydrate; MCC; SLS; Sodium chloride; Talc; Anhydrous lactose; Corn starch; Crospovidone; Magnesium stearate; Celulose polymer coating | Carefully crush the tablet and must not be crush or damage of delayed-release pellets. Sprinkle the tablet fragments on a spoonful of applesauce. | Mylan | 1967 |
| Jadenu®/deferasirox | Treatment of chronic iron overload | 90, 180, and 360 mg Store at 20 to 25 °C and protect from moisture. | MCC; Crospovidone; Povidone K30; Magnesium stearate; Colloidal silicon dioxide; Poloxamer 188 | Carefully crush the tablet and sprinkle the tablet fragments on applesauce. | Novartis | 2005 |
| Kuvan®/sapropterin dihydrochloride | Tetrahydrobiopterin-responsive phenylketonuria | 100 mg Store below 25 °C and protect from moisture. | Ascorbic acid; Crospovidone;DBasic calcium phosphate; D-mannitol; Riboflavin; Sodium stearyl fumarate | Dissolve powder in 120 to 240 mL of water or apple juice, or in a small quantity of soft foods such as applesauce or pudding. Consume within 30 min of dissolution. For infants weighing less than 10 kg, dissolve powder in 5 mL of water or apple juice and administer this solution orally using a syringe. | BioMarin Pharmaceutical | 2007 |
| Xarelto®/rivaroxaban | Prevention and treatment of thromboembolism | 10, 15, and 20 mg Store at 25 °C or room temperature. | Croscarmellose sodium; HPMC; Lactose monohydrate; Magnesium stearate; MCC; SLS | Carefully crush the tablet and sprinkle the tablet fragments on applesauce. | Janssen | 2011 |
| Onf®/clorazam | Treatment of seizures | 10 and 20 mg Store at 20 to 25 °C. | Corn starch; Lactose monohydrate; Magnesium stearate; SD; Talc | Carefully crush the tablet and sprinkle the tablet fragments on applesauce. | Lundbeck | 2011 |
| Eliquis®/apixaban | Prevention and treatment of thromboembolism | 2.5 and 5 mg Store at 20 to 25 °C. | Anhydrous lactose; MCC; Croscarmellose sodium; SLS; Magnesium stearate | Carefully crush the tablet and sprinkle the tablet fragments on water, 5% dextrose in water, apple juice, or applesauce. | Bristol-Myers Squibb | 2012 |
| Savaya®/edoxaban | Prevention and treatment of thromboembolism | 15, 30, and 60 mg Store at 20 to 25 °C. | Mannitol; Pre-gelatinized starch; Crospovidone; HPC; Magnesium stearate; Talc; Carnauba wax | Carefully crush the tablet and sprinkle the tablet fragments on applesauce. | Daiichi Sankyo | 2015 |
| Emflaza™/deflazacort | Treatment of Duchenne muscular dystrophy | 6, 18, 30, and 36 mg Store at 20 to 25 °C. | Colloidal silicon dioxide; Lactose monohydrate; Magnesium stearate; Pre-gelatinized corn starch; Magnesium stearate; MCC | Carefully crush the tablet and sprinkle the tablet fragments on applesauce. | PTC Therapeutics | 2017 |
| Trulance®/plecanatide | Treatment of chronic idiopathic constipation | 3 mg Store at 20 to 25 °C in the original bottle and protect from moisture. | | Carefully crush the tablet and sprinkle the tablet fragments on applesauce. | Synergy Pharmaceuticals | 2017 |
| Brand/Generic Name                  | Indication                                           | Strength/Storage                  | Excipients                        | Manipulation                                                                 | Company                      | Initial US Approval |
|------------------------------------|------------------------------------------------------|-----------------------------------|----------------------------------|------------------------------------------------------------------------------|------------------------------|---------------------|
| Viread®/tenofovir disoproxil fumarate | Treatment of HIV-1 infection and chronic hepatitis B | 40 mg per 1 g powder Store at 25 °C in the original container. | Mannitol; HPC; EC; SD             | Sprinkle powder on soft food such as applesauce, baby food, or yogurt.       | Gilead Sciences           | 2001                |
| Reyataz®/atazanavir                  | Treatment of HIV-1 infection                         | 50 mg per packet Store at 25 °C.  | Aspartame; Sucrose                | Mix powder with soft food (applesauce or yogurt) or liquid (milk, infant formula, or water). If the vehicle is water, the patient must eat food immediately after taking Reyataz®. For infants less than 6 months, the powder should be mixed with infant formula and administered using an oral syringe. | Bristol-Myers Squibb        | 2003                |
| Fosrenol®/lanthanum carbonate       | Reduction of serum phosphate in patients with end-stage renal disease | 750 and 1000 mg Store at 25 °C and protect from moisture. | Colloidal silicon dioxide; Dextrates; Magnesium stearate | Sprinkle powder on a small amount of applesauce or other similar food and consume immediately. | Shire                      | 2004                |
| Kuvan®/sapropterin dihydrochloride  | Tetrahydrobiopterin-responsive phenylketonuria       | 100 and 500 mg Store below 25 °C and protect from moisture. | Ascorbic acid; d-mannitol; Potassium citrate; Sucralose | Dissolve powder in 120 to 240 mL of water or apple juice, or in a small quantity of soft foods such as applesauce or pudding. Consume within 30 min of dissolution. For infants weighing less than 10 kg, dissolve the powder in 5 mL of water or apple juice and administer this solution orally using a syringe. | BioMarin Pharmaceutical     | 2007                |
| Brand/Generic names                  | Indication                                                                 | Strength/Storage                   | Excipients                                                                 | Manipulation                                                                                                                                                                                                 | Company                        | Initial US approval |
|-------------------------------------|-----------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|---------------------|
| **Singulair®/montelukast sodium**   | Prophylaxis and chronic treatment of asthma, acute prevention of exercise-induced bronchoconstriction, and alleviation of allergic rhinitis | 4 mg Store at 15 to 30 °C in the original package and protect from moisture and light. | Mannitol; HPC; Magnesium stearate                                           | Dissolve granules in a teaspoonful of baby formula or breast milk, or mix with a spoonful of soft foods, only applesauce, carrots, rice, or ice cream. Do not dissolve granules in any liquid other than baby formula or breast milk for administration. Sprinkle granules on applesauce. Do not use other foods. Do not crush or chew the granules. | Merck                          | 1998                |
| **Protonix®/ pantoprazole sodium**  | Treatment of erosive esophagitis and pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome) | 40 mg Store at 20 to 25 °C.       | Crospovidone; HPMC; Methacrylic acid copolymer; MCC; Polysorbate 80; Povidone; Sodium carbonate; SLS; Talc; Titanium dioxide; Triethyl citrate; Yellow iron oxide | Sprinkle granules on soft food such as yogurt or applesauce.                                                                                                                                                | Pfizer                         | 2000                |
| **Jadenu® Sprinkle/deferasirox**    | Treatment of chronic iron overload                                           | 90, 180, and 360 mg Store at 20 to 25 °C and protect from moisture. | MCC; Crospovidone; Povidone K30; Magnesium stearate; Colloidal silicon dioxide; Poloxamer 188 | Sprinkle granules on soft food or liquid.                                                                                                                                                                    | Novartis                       | 2005                |
| **Kalydeco®/ivacaftor**             | Treatment of cystic fibrosis                                                 | 50 and 75 mg Store at 20 to 25 °C. | Colloidal silicon dioxide; Croscarmellose sodium; HPMC acetate-succinate; Lactose monohydrate; Magnesium stearate; Mannitol; Sucralose; SLS EC; HPMC; PEG | Sprinkle granules on soft food or liquid.                                                                                                                                                                    | Vertex Pharmaceuticals         | 2012                |
| **Xuriden®/uridine triacetate**     | Treatment of hereditary orotic aciduria                                       | 2 g per packet Store at 25 °C.   | Mannitol; Sucralose; SLS EC; HPMC; PEG                                       | Sprinkle granules on applesauce, pudding, or yogurt, or mix with milk or infant formula. Sprinkle granules on soft foods, such as applesauce, pudding, or yogurt, and ingest within 30 min. Do not chew the granules. | Wellstat Therapeutics Corporation | 2015                |
| **Vistogard®/uridine triacetate**   | Emergency treatment of overdose or severe adverse reactions of fluorouracil or capecitabine | 10 g per packet Store at 25 °C.  | EC; HPMC; PEG                                                               | Sprinkle granules on soft foods, such as applesauce, pudding, or yogurt, and ingest within 30 min. Do not chew the granules.                                                                                   | Wellstat Therapeutics Corporation | 2015                |
| **Solosec™/secnidazole**            | Treatment of bacterial vaginosis                                              | 2 g per packet Store at 20 to 25 °C. | Ethyl acrylate-methyl methacrylate copolymer; PEG4000; Povidone; Sugar spheres; Talc | Sprinkle granules on applesauce, yogurt, or pudding without chewing or crumbling the granules. Do not try to dissolve the granules in any liquid.                                                            | Lupin                          | 2017                |
| Brand/Generic names                  | Indication                                                                 | Strength/Storage                                      | Excipients                                                                                                                                  | Manipulation                                                                                   | Company                | Initial US approval |
|-------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------|---------------------|
| Chemet®/succimer                    | Treatment of lead, mercury, and arsenic poisoning                          | 100 mg<br>Store at 15 to 25 °C.                       | Povidone; Sodium starch glycolate; Starch; Sucrose                                                                                  | Carefully open the capsule and sprinkle the contents (beads) on a small amount of soft food or putting them in a spoon and following with fruit drink. | Recordati Rare       | 1991                |
| Sustiva®/efavirenz                  | Treatment of HIV-1 infection                                               | 50 and 200 mg<br>Store at 25 °C.                      | Lactose monohydrate; Magnesium stearate; Sodium starch glycolate                                                              | Carefully open the capsule and mix the contents with soft food, such as applesauce, grape jelly, or yogurt. For young infants who are not able to ingest solid foods, the contents can be administered with infant formula. | Bristol-Myers Squibb  | 1992                |
| Cystagon®/cysteamine bitartrate     | Treatment of nephropathic cystinosis                                       | 50 and 150 mg<br>Store at 20 to 25 °C and protect from light and moisture. | Colloidal silicon dioxide; Croscarmellose sodium; D&C yellow #10; FD&C blue #1; FD&C blue #2; FD&C red #40; Gelatin; Magnesium stearate; MCC; Pharmaceutical glaze; Pregelatinized starch; SLS; Black iron oxide; Titanium dioxide | Carefully open the capsule and sprinkle the contents on food to prevent choking.            | Mylan                  | 1995                |
| Topamax® Sprinkle Capsules/topiramate | Treatment of epilepsy and prevention of migraine                           | 15 and 25 mg<br>Store at or below 25 °C and protect from moisture. | Povidone; Cellulose acetate; SD SLS; Gelatin; Sorbitan monolaurate; Sugar spheres; Titanium dioxide | Carefully open the capsule and sprinkle the contents on soft food. Ingest the mixture immediately without chewing. | Janssen                | 1996                |
| Celebrex®/celecoxib                 | Treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain, and primary dysmenorrhea | 100 and 200 mg<br>Store at 20 to 25 °C.               | Colloidal silicon dioxide; Croscarmellose sodium; Gelatin Lactose monohydrate; Magnesium stearate; Povidone; SLS | Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture immediately with water. | GD Searle             | 1998                |
| Colazal™/balsalazide disodium       | Treatment of ulcerative colitis                                            | 750 mg<br>Store at 20 to 25 °C.                       | Colloidal silicon dioxide; Magnesium stearate                                                                                 | Carefully open the capsule and sprinkle the contents on applesauce. Chew or swallow the mixture immediately. | Valeant Pharms        | 2000                |
| Orfadin®/nitisinone                 | Treatment of hereditary tyrosinemia type 1                                 | 2, 5, 10, and 20 mg<br>Store refrigerated at 2 to 8 °C or store at room temperature up to 45 days. | HPMC; Glycerol; Polysorbate 80; Sodium benzoate; Citric acid monohydrate; Trisodium citrate dehydrate; Strawberry aroma | Carefully open the capsule and sprinkle the contents on water, formula, or applesauce immediately before use. | Swedish Orphan Biovitrum | 2002                |
| Tasigna®/nilotinib                  | Treatment of Philadelphia chromosome positive chronic myeloid leukemia     | 150 and 200 mg<br>Store at 25 °C.                     | Colloidal silicon dioxide; Crospovidone; Lactose monohydrate; Magnesium stearate; Poloxamer 188 d-mannitol; Magnesium stearate; Pre-gelatinized starch; SLS | Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture within 15 min. | Novartis              | 2007                |
| Rapafl®/silodosin                   | Treatment of the signs and symptoms of benign prostatic hyperplasia        | 4 and 8 mg<br>Store at 25 °C and protect from light and moisture. | Colloidal silicon dioxide; Crospovidone; Magnesium stearate; Pre-gelatinized starch; SLS | Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture within 5 min without chewing. | Allergan              | 2008                |
| Brand/Generic names       | Indication                                                                 | Strength/Storage                                                                 | Excipients                                                                 | Manipulation                                                                 | Company                     | Initial US Approval |
|--------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------|---------------------|
| Kadian®/morphine sulfate | Management of severe pain                                                  | 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, and 200 mg                           | HPMC;EC;Methacrylic acid copolymer;PEG;DEP;Talc;Corn starch;Sucrose         | Carefully open the capsule and sprinkle the contents on applesauce.           | Actavis                     | 1941                |
|                          |                                                                             | Store at 25 °C and protect from light and moisture.                               |                                                                            | Do not use other foods.                                                      |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Do not chew the granules.                                                   |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Carefully open a capsule and sprinkle the contents on applesauce, pudding, | Collegium Pharmaceutical  | 1950                |
|                          |                                                                             |                                                                                  |                                                                            | yogurt, ice cream or jam.                                                   |                            |                     |
| Xtampza® ER/oxycodeone   | Management of severe pain                                                  | 9, 13.5, 18, 27, and 36 mg                                                       | Myristic acid;Yellow beeswax;Carnauba wax;Gelucire 50/13,Magnesium        | Carefully open the capsule and sprinkle the contents on applesauce.           | Rhodes Pharmaceuticals      | 1955                |
|                          |                                                                             | Store at 25 °C in tight and light-light-resistant container.                     | stearate;Colloidal silicon dioxide |                                                                            |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Carefully open the capsule and sprinkle the contents on applesauce.         | Impax Laboratories         | 1975                |
|                          |                                                                             |                                                                                  |                                                                            | Ingest the mixture immediately                                                |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | without chewing.                                                            | Adamas Pharmaceuticals     | 1968                |
|                          |                                                                             |                                                                                  |                                                                            | Carefully open the capsule and sprinkle the contents on applesauce.         |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Ingest the mixture immediately                                                | Adamas Pharmaceuticals     | 1968                |
|                          |                                                                             |                                                                                  |                                                                            | without chewing.                                                            | Teva Pharmaceuticals       | 1977                |
|                          |                                                                             |                                                                                  |                                                                            | Carefully open the capsule and sprinkle the contents on applesauce.         |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Do not use other foods.                                                      | Recro Pharmaceuticals      | 1991                |
|                          |                                                                             |                                                                                  |                                                                            | Do not chew the granules.                                                   |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Carefully open the capsule and sprinkle the contents on applesauce that is  |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | not warm.                                                                   |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Ingest the mixture immediately                                                |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | without chewing.                                                            |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Carefully open the capsule and sprinkle the contents on applesauce.         |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Do not use other foods.                                                      |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Do not chew the granules.                                                   |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Carefully open the capsule and sprinkle the contents on applesauce that is  |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | not warm.                                                                   |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Ingest the mixture immediately                                                |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | without chewing.                                                            |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Carefully open the capsule and sprinkle the contents on applesace, pudding,|                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | yogurt, ice cream or jam.                                                   |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Carefully open the capsule and sprinkle the contents on applesace that is  |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | not warm.                                                                   |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Ingest the mixture within 60 min.                                           |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Carefully open the capsule and sprinkle the contents on applesace that is  |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | not warm.                                                                   |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Ingest the mixture within 60 min.                                           |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | Carefully open the capsule and sprinkle the contents on applesace that is  |                            |                     |
|                          |                                                                             |                                                                                  |                                                                            | not warm.                                                                   |                            |                     |

(continued on next page)
| Brand/Generic names | Indication | Strength/Storage | Excipients | Manipulation | Company | Initial US Approval |
|---------------------|------------|------------------|------------|--------------|---------|-------------------|
| Qudexy® XR/ topiramate | Treatment of seizures associated with epilepsy or Lennox-Gastaut syndrome and prevention of migraine | 25, 50, 100, 150, and 200 mg Store at 20 to 25 °C and protect from moisture. | MCC, HPMC 2910; EC, DEP; Titanium dioxide; Black iron oxide; Red iron oxide; Yellow iron oxide | Carefully open the capsule and sprinkle the contents on soft food. Ingest the mixture immediately without chewing or crushing. | Upsher-Smith Laboratories | 1996 |
| Effexor XR®/ venlafaxine | Treatment of major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder | 37.5, 75, and 150 mg Store at 20 to 25 °C. | Cellulose; EC; Gelatin; HPMC; Iron oxide; Titanium dioxide | Carefully open the capsule and sprinkle the contents on soft foods, such as applesauce or pudding. Ingest the mixture immediately without chewing. | Wyeth | 1997 |
| Klor-Con® Sprinkle/potassium chloride | Treatment of or prevention of hypokalemia | 600 and 750 mg Store at 20 to 25 °C and protect from light and moisture. | EC; Talc; Gelatin; Titanium dioxide | Carefully open the capsule and sprinkle the contents on soft foods. | Upsher-Smith Laboratories | 1998 |
| Adderall XR®/dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate | Treatment of ADHD | 5, 10, 15, 20, 25, and 30 mg Store at 25 °C. | HPMC; Methacrylic acid copolymer; Opadry beige; Sugar spheres; Talc; Triethyl citrate | Carefully open the capsule and sprinkle the contents on soft foods. | Shire | 2001 |
| Namenda XR™/memantine hydrochloride | Treatment of moderate to severe dementia of the Alzheimer's type | 7, 14, 21, and 28 mg Store at 25 °C. | Sugar spheres; PVP; HPMC; Talc; PEG; EC; Ammonium hydroxide; Oleic acid; Medium chain triglycerides Talc; Ammonio methacrylate copolymer; Sugar spheres; EC; Sodium chloride; PEG; HPC; DBS; Methacrylic acid copolymer DEP; Magnesium stearate; SLS; Ascorbic acid | Carefully open the capsule and sprinkle the contents on soft foods. | Forest | 2003 |
| Embeda™/morphine sulfate and naltrexone hydrochloride | Management of moderate to severe pain | 20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, and 100/4 mg morphine sulfate/mg naltrexone hydrochloride Store at 25 °C and protect from light. | Talc; Ammonio methacrylate copolymer; Sugar spheres; EC; Sodium chloride; PEG; HPC; DBS; Methacrylic acid copolymer DEP; Magnesium stearate; SLS; Ascorbic acid | Carefully open the capsule and sprinkle the contents on soft foods. Do not use other foods. Do not chew the granules. | Alpharma Pharmaceuticals | 2009 |
| Namzaric®/memantine hydrochloride and donepezil hydrochloride | Treatment of moderate to severe dementia of the Alzheimer's type | 14/10 and 28/10 mg memantine hydrochloride/mg donepezil hydrochloride Store at 25 °C and protect from light. | Sugar spheres; Povidone; Talc; HPMC; PEG; EC; Oleic acid; Medium chain triglycerides; Lactose monohydrate; MCC; Corn starch; Colloidal silicon dioxide; Magnesium stearate | Carefully open the capsule and sprinkle the contents on soft foods. Ingest the mixture without chewing. | Allergan | 2014 |
Table 6 – Commercially available sprinkle products – DR capsules.

| Brand/Generic names                      | Indication                                                                 | Strength/Storage          | Excipients                                                                                                           | Manipulation                                                                                      | Company       | Initial US approval |
|------------------------------------------|------------------------------------------------------------------------------|---------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------|---------------------|
| Depakote® Sprinkle Capsules/divalproex sodium | Treatment of epilepsy                                                       | 125 mg                    | Cellulosic polymers, Iron oxide, Magnesium stearate, Silica gel, Titanium dioxide, Triethyl citrate                  | Carefully open the capsule and sprinkle the contents on soft foods, such as applesauce or pudding. Ingest the mixture immediately without chewing. | AbbVie        | 1989                |
| Esomeprazole Strontium Delayed-Release Capsules/esomeprazole strontium | Treatment of GERD, gastric ulcer, and pathological hypersecretory conditions, and eradication of Helicobacter pylori. | 49.3 mg Store at 20 to 25 °C. | Calcium carbonate, HPMC, Methacrylic acid copolymer, Mono and diglycerides, Polysorbate 80, Sugar spheres, Talc, Triethyl citrate | The capsule contents should only be sprinkled on applesauce, as the other soft foods has not been tested. Ingest the mixture immediately without chewing. | R2 Pharma     | 1989                |
| Nexium®/esomeprazole magnesium           | Treatment of GERD and pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome), and eradication of Helicobacter pylori. | 20 and 40 mg Store at 25 °C. | Glyceryl monostearate 40–55, HPC, HPMC, Magnesium stearate, MCC, Polysorbate 80, Sugar spheres, Talc, Triethyl citrate | Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture immediately without chewing. | AstraZeneca   | 1989                |
| Procysbi®/cysteamine bitartrate          | Treatment of nephropathic cystinosis                                         | 25 and 75 mg Store at 2 to 8 °C and at 20 to 25 °C before and after dispensing, respectively, and protect from light and moisture. | Eudragit L 30 d-55, HPMC, Talc, Triethyl citrate, SLS. | Carefully open the capsule and sprinkle the contents on applesauce, berry jelly, or fruit juice. Do not use grapefruit juice. Ingest the mixture within 30 min without chewing. | Horizon       | 1994                |

(continued on next page)
| Brand/Generic names                  | Indication                                                                 | Strength/Storage | Excipients                                                                 | Manipulation                                                                                       | Company   | Initial US approval |
|-------------------------------------|-----------------------------------------------------------------------------|------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------|---------------------|
| Dexilant®/dexlansoprazole            | Treatment of erosive esophagitis and GERD                                   | 30 and 60 mg     | Sugar spheres, Magnesium carbonate, Sucrose, L-HPC, Titanium dioxide, HPC, HPMC 2910, Talc, Methacrylic acid copolymers, PEG 8000, Triethyl citrate, Polysorbate 80, Colloidal silicon dioxide | Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture immediately without chewing. | Takeda    | 1995                |
| Prevacid®/lansoprazole               | Treatment of gastric/duodenal ulcer, GERD, erosive esophagitis, and pathological hypersecretory conditions, and eradication of *Helicobacter pylori*. | 15 and 30 mg     | HPC, L-HPC, Colloidal silicon dioxide, Magnesium carbonate, Methacrylic acid copolymer, Starch, Talc, Sugar sphere, Sucrose, PEG, Polysorbate 80, Titanium dioxide | Carefully open the capsule and sprinkle the contents on applesauce, Ensure, pudding, cottage cheese, yogurt, strained pears, apple juice, orange juice, or tomato juice. Ingest the mixture immediately. | Takeda    | 1995                |
| Aciphex®/sprinkle™/rabeprazole sodium | Treatment of GERD                                                           | 5 and 10 mg      | Colloidal silicon dioxide, Diacetylated monoglycerides, EC, HPC, HPMCP, Magnesium oxide, Magnesium stearate, Mannitol, Talc, Titanium dioxide, Carrageenan, Potassium chloride | Carefully open the capsule and sprinkle the contents on applesauce, fruit- or vegetable-based baby food, yogurt, infant formula, apple juice, or pediatric electrolyte solution. Ingest the mixture within 15 min without chewing. | Cerecor   | 1999                |
| Brand/Generic names | Indication | Strength/Storage | Excipients | Manipulation | Company | Initial US approval |
|---------------------|------------|------------------|------------|--------------|---------|--------------------|
| Creon®/pancrelipase | Treatment of exocrine pancreatic insufficiency | 3/9.5/15, 6/19/30, 12/38/60, 24/76/120, and 36/114/180 × 10³ USP units of lipase/protease/amylase | Cetyl alcohol Dimethicone HPMC PEG Triethyl citrate | For infants, administer the capsule contents before breast-feeding. Contents should not be mixed directly into infant formula or breast milk. For children and adults, carefully open the capsule and sprinkle the contents on acidic soft food with a pH of 4.5 or less, such as applesauce, at room temperature. Ingest the mixture immediately without chewing. Ensure that no drug is retained in the mouth. | AbbVie | 2009 |
| Zenpep®/pancrelipase | Treatment of exocrine pancreatic insufficiency | 3/10/14, 5/17/24, 10/32/42, 15/47/63, 20/63/84, 25/79/105, and 40/126/168 × 10³ USP units of lipase/protease | Colloidal silicon dioxide Croscarmellose sodium Hydrogenated castor oil HPMC Magnesium stearate MCC Talc Triethyl citrate | For infants, administer the capsule contents before breast-feeding. Contents should not be mixed directly into infant formula or breast milk. For children and adults, carefully open the capsule and sprinkle the contents on acidic soft food with a pH of 4.5 or less, such as applesauce, at room temperature. Ingest the mixture immediately without chewing. Ensure that no drug is retained in the mouth. | Forest | 2009 |
| Pancreaze®/pancrelipase | Treatment of exocrine pancreatic insufficiency | 2.6/6.2/10.85, 4.2/14.2/24.6, 10.5/35.5/61.5, 16.8/56.8/98.4 and 21/54.7/83.9 × 10³ USP units of lipase/protease/amylase | Cellulose; Colloidal anhydrous silica Crospovidone Magnesium stearate Methacrylic acid-ethyl acrylate copolymer Montan glycol wax Simethicone emulsion Talc Triethyl citrate | For infants, administer the capsule contents before breast-feeding. Contents should not be mixed directly into infant formula or breast milk as this may compromise efficacy. For children and adults, carefully open the capsule and sprinkle the contents on acidic soft food with a pH of 4.5 or less, such as applesauce, at room temperature. Ingest the mixture immediately without chewing. Ensure that no drug is retained in the mouth. | Vivus | 2010 |
Table 6 (continued)

| Brand/Generic names | Indication                        | Strength/Storage                                                                 | Excipients                          | Manipulation                                                                 | Company       | Initial US approval |
|---------------------|-----------------------------------|----------------------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------------|---------------|---------------------|
| Pertzye<sup>®</sup>/pancrelipase | Treatment of exocrine pancreatic insufficiency | 4/14.375/15.125, 8/28.75/30.25, and 16/57.5/60.5 × 10<sup>3</sup> USP units of lipase/protease | Sodium bicarbonate, Sodium carbonate, Cellulose acetate phthalate, Sodium starch glycolate, DEP, Ursodiol, PVP, Talc | For infants, administer the capsule contents before breast-feeding. Contents should not be mixed directly into infant formula or breast milk as this may diminish efficacy. For children and adults, carefully open the capsule and sprinkle the contents on acidic soft food with a pH of 4.5 or less, such as applesauce, at room temperature. Ingest the mixture immediately without chewing. Ensure that no drug is retained in the mouth. | Digestive Care | 2012                |
| Ultresa<sup>TM</sup>/pancrelipase | Treatment of exocrine pancreatic insufficiency | 4/8/8, 13.8/27.6/27.6, 20.7/41.4/41.4, and 23/46/46 × 10<sup>3</sup> USP units of lipase/protease/amylase | Colloidal silicon dioxide, Croscarmellose sodium, Hydrogenated castor oil, HPMCP, Magnesium stearate, MCC, Talc, Triethyl citrate | For infants, administer the capsule contents before breast-feeding. Contents should not be mixed directly into infant formula or breast milk as this may reduce efficacy. For children and adults, carefully open the capsule and sprinkle the contents on acidic soft food with a pH of 4.5 or less, such as applesauce, at room temperature. Ingest the mixture immediately without chewing. Ensure that no drug is retained in the mouth. | Forest       | 2012                |
| Brand/Generic Names                        | Indication                      | Strength/Storage          | Excipients                                                                 | Manipulation                                                                 | Company          | Initial US Approval |
|-------------------------------------------|---------------------------------|---------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------|---------------------|
| Jornay PM/methylphenidate hydrochloride   | Treatment of ADHD               | 20, 40, 60, 80, and 100 mg Store at 20 to 25 °C and protect from moisture. | DBS;EC;HPC;HPMC;Magnesium stearate;Methacrylic acid copolymer;MCC;Mono and diglycerides;Polysorbate 80;Talc | Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture immediately. | Ironshore Pharmaceuticals | 1955                |
| Equetro®/carbamazepine                    | Treatment of acute manic or mixed episodes associated with bipolar I disorder, pain associated with trigeminal neuralgia, and epilepsy | 100, 200, and 300 mg Store at 25 °C and protect from light and moisture. | Citric acid;Colloidal silicon dioxide;Lactose monohydrate;MCC;PEG;Povidone;SLS;Talc;Triethyl citrate | Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture without chewing. | Validus Pharmaceuticals | 1968                |
| Carbatrol®/carbamazepine                  | Treatment of pain associated with trigeminal neuralgia and epilepsy | 100, 200, and 300 mg Store at 25 °C and protect from light and moisture. | Citric acid;Colloidal silicon dioxide;Lactose monohydrate;MCC;PEG;Povidone;SLS;Talc;Triethyl citrate | Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture without chewing. | Shire            | 1998                |
| Verelan® PM/verapamil hydrochloride       | Management of essential hypertension | 100, 200, and 300 mg Store at 25 °C and protect from moisture. | Fumaric acid;Povidone;Shells;SD;SLS;Starch;Sugar spheres;Talc;Titanium dioxide | Carefully open the capsule and sprinkle the contents on applesauce. | Recro Gainesville | 1998                |
| Metadate CD®/methylphenidate hydrochloride| Treatment of ADHD               | 10, 20, 30, and 40 mg Store at 15 to 30 °C and protect from moisture. | Sugar spheres;Povidone;HPMC;PEG;EC;DBS;Gelatin;Titanium dioxide | Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture immediately without chewing. | UCB              | 2001                |
| Mydayis®/dextroamphetamine sulfate, amphetamine sulfate, dextroamphetamine saccharate, and amphetamine aspartate monohydrate | Treatment of ADHD               | 12.5, 25, 37.5, and 50 mg Store at 20 to 25 °C | EC;HPMC;Methacrylic acid copolymer;Methyl acrylate;Methyl methacrylate;Opadry beige;Sugar spheres;Talc;Triethyl citrate | Carefully open the capsule and sprinkle the contents on applesauce. | Shire            | 2001                |
| Ritalin LA®/methylphenidate hydrochloride | Treatment of ADHD               | 10, 20, 30, and 40 mg Store at 25 °C. | Ammonio methacrylate copolymer;Black iron oxide (10 and 40 mg strengths);Gelatin;Methacrylic acid copolymer;PEG;Red iron oxide (10 and 40 mg strengths);Sugar spheres;Talc;Titanium dioxide;Triethyl citrate;Yellow iron oxide (10, 30, and 40 mg strengths) | Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture immediately without chewing. | Novartis         | 2002                |
| Focalin XR®/dexamethasphenidate hydrochloride | Treatment of ADHD               | 5, 10, 15, 20, 25, 30, 35, and 40 mg Store at 25 °C. | Ammonio methacrylate copolymer;FD&C Blue #2 (5, 15, 25, 35, and 40 mg strengths); Yellow iron oxide (10, 15, 30, 35, and 40 mg strengths);Gelatin;Ink Tan SW-8010;Methacrylic acid copolymer;PEG;Sugar spheres Talc;Titanium dioxide;Triethyl citrate | Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture immediately. | Novartis         | 2005                |
sprinkling the fragments on soft food so that the patients can easily swallow them with food.

Doryx® (doxycycline hyclate; Mylan) is used to treat or prevent infections that are caused by bacteria [11]. Doryx® tablets contain coated pellets of doxycycline hyclate in a DR formulation. The tablet of 50/200 mg dose contains lactose, microcrystalline cellulose (MCC), povidone, starch wheat, magnesium stearate, and cellulose polymer coating. After crushed, the obtained Doryx® pellets can be sprinkled on applesauce and administered. The extent of absorption of doxycycline does not change with concomitant water, but the absorption rate increases slightly.

Jadenu® (deferasirox; Novartis) is an iron chelator agent indicated for the treatment of chronic iron overload caused by blood transfusions. Jadenu® includes 90, 180, and 360 mg deferasirox. Inactive ingredients include MCC, crospovidone, povidone K30, magnesium stearate, colloidal silicon dioxide and poloxamer 188. The instruction for manipulation is to carefully crush the tablet and immediately sprinkle the contents on applesauce. Commercial grinders with serrated surfaces should be avoided when crushing the 90 mg tablet. Sprinkled tablets should be consumed immediately and completely.

Xarelto® (rivaroxaban; Janssen) is an anticoagulant or blood-thinner to reduce the risk of pulmonary embolism, deep vein thrombosis, and stroke systemic embolism. It is available in 10, 15, and 20 mg tablets, and contains croscarmellose sodium, hydroxymethyl (HPMC), lactose monohydrate, magnesium stearate, MCC, and sodium lauryl sulfate (SLS). Crushed Xarelto® is stable in applesauce and water for up to 4 h. A crushed Xarelto® tablet showed a comparable relative bioavailability compared with an intact tablet [12].

Savaysa® (edoxaban; Daiichi Sankyo) is a factor Xa inhibitor to reduce the risk of systemic embolism and stroke in patients with nonvalvular atrial fibrillation. The product comes in 15, 30, and 60 mg strengths, and contains mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose (HPC), magnesium stearate, talc, and carnauba wax. The total systemic exposure of edoxaban is not affected by food. Administration of a crushed tablet mixed with soft food or suspended in water and given via a nasogastric tube showed similar absorption with the administration of an intact tablet.

Emflaza™ (deflazacort; PTC Therapeutics) is a corticosteroid used to treat Duchenne muscular dystrophy. It is available in 6, 18, 30, and 36 mg tablets, and contains colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and pre-gelatinized corn starch. Crushing and sprinkling of Emflaza™ on applesauce did not influence the bioavailability of deflazacort.

2.3. Powders

Powder is much easier to administer with food or drink to elderly and pediatric patients compared with tablets or capsules. The powder formulations usually have fine bead-like morphology. The powder is typically 0.1 to 10 μm in size [13]. Commercially, there are more than four products of sprinkle powder.

Viread® (tenofovir disoproxil fumarate; Gilead Sciences) is a nucleotide analog that acts as reverse transcriptase inhibitor for human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus. In a bioequivalence study conducted under non-fasting conditions, the average maximum plasma concentration (Cmax) of tenofovir was 26.9% lower for the oral powder compared with the tablet formulation. According to the FDA review document, this difference can be attributed to the taste-masking technology used in Viread® [14]. However, the mean values of total area under the plasma concentration-time curve (AUC) of tenofovir were similar between the powder and the tablet.

Fosrenol® (lanthanum carbonate; Shire) is a phosphate binder for reducing serum phosphate level in patients with the end-stage renal disease. This product is available in 750 or 1000 mg strength and contains colloidal silicon dioxide, dextrates, and magnesium stearate as excipients. It is recommended to sprinkle Fosrenol® on a small quantity of applesauce or other similar food, rather than to mix with liquid vehicles due to its poor solubility.

Kuvan® (sapropterin dihydrochloride; BioMarin Pharmaceutical) can decrease blood phenylalanine levels. Kuvan® is available in unit capacity packets of 100 or 200 mg of sapropterin dihydrochloride. Each unit dose packet contains ascorbic acid, D-mannitol, potassium citrate, and sucralose. For infants weighing less than 10 kg, dissolve powder in 5 ml of water or apple juice. Some of this solution can be administered orally via a syringe. Kuvan® powder is bioequivalent to the same dose of Kuvan® tablet. Before administration, the packet content needs to be dissolved in 120–240 ml of water or apple juice; or sprinkled on a small amount of soft food such as applesauce or pudding. However, administration with high-fat/high-calorie meal caused 1.84- and 1.87-fold increase in the mean Cmax and AUC values of sapropterin, respectively, with extensive individual variability.

2.4. Granules

Granules are large and free-flowing particles, which are commonly prepared by the agglomeration of powder. There are three types of granulations as dry granulation, wet granulation and fluid bed granulation. Dry granulation is made by crushing large masses of powder mixture into small pieces, and wet granules are made by adding a liquid binder or adhesive. Fluid bed granulation is made by spraying a granulating solution onto the particles [13]. Their size ranges from 0.85 mm (sieve No. 20) to 4.75 mm (sieve No. 4). The shape of granules is generally irregular [13]. There are more than seven sprinkle granule products commercially available, which can be sprinkled on liquid or soft foods and swallowed without chewing.

Singulair® (montelukast sodium; Merck) is a leukotriene receptor antagonist for prophylaxis and chronic treatment of asthma, acute prevention of exercise-induced bronchoconstriction, and alleviation of allergic rhinitis. The product is available in 4mg dose, and the inactive ingredients include mannitol, HPC, and magnesium stearate. Singulair® granules can be administered by dissolving in a teaspoonful of baby formula or breast milk or mixing with a
spoonful of soft food such as applesauce, carrots, rice or ice cream.

Jadenu® Sprinkle (deferisox; Novartis) is used for chronic iron overload caused by blood transfusion. Jadenu® Sprinkle granules contain 90, 180, and 360 mg deferisox. MCC, povidone K30, magnesium stearate, colloidal silicon dioxide, and poloxamer 188 are included as excipients. The bioavailability (as AUC) of granules was 52% higher than tablets, and the mean Cmax increased by 34% in the fasted state, although the results were not clinically relevant. When sprinkle granules were taken with low-calorie food (approximately 450 calories with a fat content around 30% of total calories), AUC and Cmax were similar to those under fasting condition. However, when administered with high-calorie food (approximately 1000 calories with a fat content higher than 50% of total calories), AUC increased by 18% without changes in Cmax.

Xuriden® (uridine triacetate; Wellstat Therapeutics Co.) is a pyrimidine analog for the therapy of hereditary orotic aciduria. Xuriden® 2 g packet contains ethylcellulose (EC), HPMC, and polyethylene glycol (PEG) as inactive ingredients. The granules can be sprinkled on applesauce, pudding, or yogurt; or may be mixed with milk or infant formula. The food effect on uridine pharmacokinetics was negligible, showing no difference in total urinary exposure and range.

Solosec™ (secnidazole; Lupin) is a nitroimidazole antimicrobial for the treatment of bacterial vaginosis in adult women. Yellowish granules (4.8 g), which contain 2 g of secnidazole, are packed in a foil packet that is difficult for children to open. The other ingredients are ethyl acrylate-methyl methacrylate copolymer, PEG4000, povidone, sugar spheres, and talc. Solosec™ exhibited no significant difference in Cmax and AUC values when administered under fasting conditions (mixed with applesauce) or with high-calorie foods. Administration of Solosec™ with pudding or yogurt showed no difference either.

2.5. Immediate-release capsules

Most oral formulations such as tablets, powder, granules, and capsules are designed to release the drug immediately after oral administration [15]. IR products generally provide fast absorption of the drug and consequent rapid onset of the pharmacokinetic effects. There are at least nine sprinkle IR capsule products available commercially. Sprinkle IR capsules should be opened carefully, and the contents sprinkled on soft foods need to be swallowed immediately without chewing.

Sustiva® (efavirenz; Bristol-Myers Squibb), a non-nucleoside reverse transcriptase inhibitor, is used in combination with other antiretroviral agents for the treatment of HIV-1 infection. Sustiva® contains 50 or 200 mg of efavirenz and lactose monohydrate, magnesium, stearate, SLS, and sodium starch glycolate as inactive ingredients. This product should be administered orally once daily on an empty stomach, preferably at bedtime. The AUC value of Sustiva® sprinkled on applesauce was bioequivalent to that of the intact Sustiva® capsule when administered in the fasted state.

Topamax® Sprinkle Capsules (topiramate; Janssen) are used for the treatment of epileptic convulsions and migraine in adults and children. Topamax® sprinkle capsules include 15 or 25 mg of topiramate-coated beads in a hard gelatin capsule. Cellulose acetate, gelatin, povidone, SLS, sorbitan monolaurate, sugar spheres, and titanium dioxide are added as excipients. Topamax® Sprinkle Capsules are bioequivalent to the immediate-release tablet. Food does not affect the bioavailability of topiramate.

Colazal™ (balsalazide disodium; Valeant Pharma) is a locally acting aminosalicylate to treat mild to active ulcerative colitis. The 750 mg capsules have colloidal silicon dioxide and magnesium stearate as inactive ingredients. The systemic absorption of Colazal™ exhibited high variability in Cmax and AUC values when administered as sprinkles and intact capsules. However, its ingestion with high-fat meal markedly delayed the time to reach Cmax (Tmax) compared with administration in the fasted state.

Tasigna® (nilotinib; Novartis) is a kinase inhibitor used to treat patients with Philadelphia chromosome-positive chronic myeloid leukemia. Tasigna® contains 150 or 200 mg nilotinib with colloidal silicon dioxide, crosnopovidone, lactose monohydrate, magnesium stearate, and poloxamer 188. Tasigna® sprinkled on applesauce and administered within 15 min is bioequivalent to the intact capsule.

Rapafloro® (silodosin; Allergan) was developed for the treatment of benign prostatic hyperplasia. Rapafloro® capsules include 4 or 8 mg of silodosin with D-mannitol, magnesium stearate, pre-gelatinized starch, and SLS. The bioequivalent AUC and Cmax values were observed when the capsule was administrated intact or with the capsule content sprinkled on applesauce.

2.6. Extended-release capsules

ER drug products can reduce the frequency of dosing more than two-fold compared with IR (conventional) products [15]. ER dosage forms are divided into two types: sustained-release (SR) and controlled-release (CR) types. SR type releases cargo molecules over a sustained period, but not at a constant rate, whereas CR type releases the drug at a nearly constant rate [16]. More than twenty products are listed as ER sprinkle capsules in the FDA database. The method of administration of ER capsules is the same as that of IR capsules.

Kadian® (morphine sulfate; Actavis) is an opioid agonist for the management of severe pain. Kadian® contains 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, or 200 mg of morphine sulfate with HPMC, EC, methacrylic acid copolymer, PEG, DEP, talc, corn starch, and sucrose. Capsule contents of Kadian® can be administered by sprinkling on applesauce, which is bioequivalent to the intact capsule.

Rytary™ (carbidopa and levodopa; Impax Laboratories) is indicated for the treatment of Parkinson’s disease. Rytary™ comes in 23.75/95, 36.25/145, 48.75/195, and 61.25/245 mg strengths (carbidopa/levodopa). The inactive ingredients are MCC, mannitol, tartaric acid, ethyl cellulose, HPMC, sodium starch glycolate, SLS, povidone, talc, methacrylic acid copolymer, triethyl citrate, croscarmellose sodium, and magnesium stearate.

Gocovri™ (amantadine; Adamas Pharmaceuticals) is used to treat dyskinesia in patients with Parkinson’s
disease. Each amantadine capsule (68.5 or 137 mg dose) contains copovidone, EC, HPMC, magnesium stearate, medium chain triglyceride, MCC, povidone, and talc as excipients. Administration of Gocovri™ as sprinkles on applesauce exerted no significant effect on the plasma pharmacokinetics of amantadine compared with the intact capsule administration. In addition, concomitant high-calorie food also did not affect the amantadine pharmacokinetics.

Amrix® (cyclobenzaprine hydrochloride; Teva Pharmaceuticals) is a muscle relaxant to be used as an adjunct to rest and physical therapy. Amrix® comes in 15 and 30 mg capsules, and the inactive ingredients include diethyl phthalate(DEP), EC, gelatin, Opadry® Clear YS-1-7006, sugar spheres NF (20–25 mesh), and titanium dioxide. Bioequivalence of Amrix® capsules administered as sprinkles on applesauce compared with the intact capsule was proved.

Verelan® (verapamil hydrochloride; Recro Gainesville) is used for the management of essential hypertension. This product contains 100, 200, or 300 mg of verapamil hydrochloride and fumaric acid, povidone, shellac, SD, SLS, starch, sugar spheres, talc, and titanium dioxide as inactive ingredients. When Verelan® capsule was administered by sprinkling on applesauce, the rate and extent of verapamil absorption were bioequivalent to those of the intact capsule with the same dose.

Adderall XR® (dextroamphetamine sulfate; Shire) is used for the treatment of attention deficit hyperactivity disorder (ADHD). While the conventional Adderall tablets are designed for IR type drug release, Adderall XR® capsules, which contains two types of drug-containing beads, provide double-pulsed delivery of amphetamine. The inactive ingredients in 5, 10, and 15 mg Adderall XR® capsules include HPMC, methacrylic acid copolymer, Opadry® beige, sugar spheres, talc, and triethyl citrate. Adderall XR® capsules administered as an intact capsule and sprinkles on applesauce were bioequivalent in the fasted condition. Moreover, Adderall IR tablets (twice a day) can be replaced with the same dose of Adderall XR® capsules (once a day).

Namzaric® ER capsules (memantine hydrochloride and donepezil hydrochloride; Allergan) are indicated for the treatment of moderate to severe dementia of the Alzheimer type. Namzaric® contains 14/10 mg or 28/10 mg of memantine hydrochloride/donepezil hydrochloride in each capsule. The other components are sugar spheres, povidone, talc, HPMC, PEG, EC, oleic acid, medium chain triglycerides, lactose monohydrate, MCC, corn starch, colloidal silicon dioxide, and magnesium stearate. Cmax and AUC values of Namzaric® in the fed and fasted conditions were similar. Moreover, no significant difference in the absorption of memantine hydrochloride was observed when the capsule was administrated intact or with its contents sprinkled on applesauce.

2.7 Delayed-release capsules

In general, DR dosage forms refer to enteric-coated formulations, of which drug release begins after a predetermined delay [13]. More than twelve products are listed as DR sprinkle capsules. The administration method of the DR capsule is the same as those of the IR and ER capsules. However, in most cases, DR and ER products are not interchangeable due to the difference in release pattern.

Depakote® sprinkle capsule (divalproex sodium; AbbVie) is used as monotherapy or adjuvant therapy for complex partial seizures of adult and pediatric patients (ten years of age and older) [17]. The coated beads of divalproex sodium are contained in a hard gelatin capsule. Cellulosics polymers, iron oxide, magnesium stearate, silica gel, titanium dioxide, and triethyl citrate are added as inactive ingredients. Depakote® sprinkle capsule should not be used as a substitute for Depakote® ER tablet, as these products have different pharmacokinetic properties.

Esomeprazole Strontium Delayed-Release Capsules (esomeprazole strontium; R2 Pharma) are used for gastroesophageal reflux disease (GERD), gastric and duodenal ulcer, and pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome) in adults. This product comes in 49.3 mg dose and contains calcium carbonate, HPMC, methacrylic acid copolymer, mono and diglycerides, polysorbate 80, sugar spheres, talc, and triethyl citrate. When administered after a high fat meal, AUC value was reduced by 52% compared with fasting condition.

Aciphex® Sprinkle™ (rabeprazole sodium; FSC Laboratories) is a proton-pump inhibitor (PPI) for GERD. This product contains granules of 5 or 10 mg of rabeprazole sodium in a hard hyromellose capsule. The inactive ingredients are colloidal silicon dioxide, dicylated monoglycerides, EC, HPC, hyromellose phthalate (HPMCP), magnesium oxide, magnesium stearate, mannitol, talc, titanium dioxide, carrageenan, and potassium chloride. Aciphex® administered with high-fat meal exhibited reduced Cmax and AUC (by 55% and 33%, respectively) as well as delayed median Tmax (from 2.5 to 4.5 h) compared with that with applesauce under fasted condition. The type of soft food (e.g., applesauce, yogurt, and liquid infant formula) did not significantly change Tmax, Cmax, and AUC of rabeprazole.

2.8 Multiparticulate drug delivery system (MDDS)

The MDDS oral dosage form consists of small individual subunits (e.g., beads or microencapsulated drugs) that exhibit different properties [18]. These subunits can be compressed into a tablet or packed into a capsule [19]. Most of the MDDS sprinkle products are designed based on the spherical oral drug absorption system (SODAS®) or chronotherapeutic oral drug absorption system (CODAS®) technologies.

Metadate CD® (methylphenidate hydrochloride; UCB) is a central nervous system stimulant for the treatment of ADHD. Metadate CD® has a biphasic release pattern, which is attributed from the IR (30% of dose) and ER (70% of dose) beads included in the capsule. Metadate CD® contains 10, 20, 30, 40, 50 or 60 mg of methylphenidate hydrochloride. The other components are sugar spheres, povidone, HPMC, PEG, EC aqueous dispersion, dibutyl sebacate (DBS), gelatin, and titanium dioxide. Metadate CD® administered as sprinkles on applesauce showed bioequivalent systemic exposure (as Cmax and AUC) of methylphenidate compared with the intact capsule.

Ritalin LA® (methylphenidate; Novartis) and Focalin™ XR (dexmethylphenidate; Novartis) are also used to treat
ADHD. Ritalin LA® and Focalin™ XR are designed based on SODAS® technology, with which uniform spherical beads of approximately 1 to 2 mm in diameter can be produced. The schematic illustration of SODAS® is shown in Fig. 3. The spherical bead has a multilayered structure of a drug/excipients core and release-controlling polymer coatings [20,21]. The polymers in the coating layers can be water soluble, insoluble, or even pH-responsive. Their physicochemical properties directly affect the release pattern of the final product [2]. Additionally, by compounding beads with different coatings, a customized drug-release profile can be achieved, which makes SODAS® a versatile oral drug delivery system [2].

Verelan® PM (verapamil hydrochloride; Schwarz Pharma) is used for the management of essential hypertension. Verelan® PM administered at bedtime shows a 4 to 5 h of delay in drug release. This product contains DR beads of CODAS®, of which release-controlling polymer layer consists of both water-soluble and insoluble polymers. When contacted with water in the gastrointestinal tract, the water-soluble polymer in the coating gradually dissolves forming drug-releasing pores. The water-insoluble polymer acts as a barrier to control the release of the drug [22]. The release rate of Verelan® PM is independent of pH and concomitant food. Moreover, Verelan® PM administered as sprinkles on applesauce was bioequivalent to the intact capsule.

3. FDA guidance of sprinkle formulations

A practical guidance that contains assessment criteria for manufacturing and quality control of sprinkle formulations has been needed. The FDA guidance on tablet scoring is related to this issue to a certain degree [23]. (1) The split tablet portion should not have a lower amount of drug than the minimum dose indicated on the approved labeling. (2) Modified-release products, of which drug release can be changed by splitting, should not be pre-scored. (3) The split tablet should be stable for 90 d under ambient condition. (4) The split tablet portions should meet the same criteria of finished-product testing as for a whole-tablet product of equivalent strength. However, this information is not directly applicable to sprinkle dosage forms.

In May 2012, the US FDA released a brief guideline on the products labeled for sprinkle, where the following three recommendations are listed [24]. The first is the maximum bead size of sprinkle drug products. The agency recommends a target bead size up to 2.5 mm with less than 10% variation and a maximum size of 2.8 mm to avoid inadvertent chewing. The unintentional chewing of beads may compromise the safety and efficacy of the loaded drug. For example, a burst or an early release of the drug may occur for the ER or DR beads, respectively, and the unpleasant taste of released drug may lead to poor compliance with the oral administration. Indeed, the labeling of most sprinkle beads states that the contents should not be crushed, chewed, split, or dissolved. The second topic of the guidance is the administration of the sprinkle products via the enteral feeding tube. According to these recommendations, the sprinkle drug products need to be delivered through an enteral feeding tube without loss of dose, crushing of beads, and tube occlusions. Also, the manufacturer should display special instructions on the product labeling regarding the information on this alternative delivery method. The third part of guidance contains the recommendations related to the bioequivalence and bioavailability studies. For the labeling to state that the drug product can be sprinkled, the information on the bioavailability or bioequivalence of the sprinkled formulation versus its intact form (for new drug applications, NDAs) or reference listed drug (for abbreviated new drug applications, ANDAs) should be included, respectively. Regarding the IR sprinkle products, the bioequivalence study is not necessary because their pharmacokinetic properties are expected to be similar compared with the IR product of reference listed drug.

Recently in July 2018, the US FDA released a draft guidance on the use of liquids and/or soft foods as vehicles for drug administration [25]. This article encompasses not only general considerations for soft food vehicles but also methodologies for assessing the impact of the vehicles on the drug product quality. The general considerations and recommendations part focuses on the compatibility and suitability for selecting soft foods, possible impacts of vehicles on the drug product, and patient adherence and acceptance in terms of palatability and swallowability. According to this part, the compatibility of commonly used soft foods with sprinkle formulations should be informed to ensure the efficacy and safety. Moreover, the product labeling needs to contain more than one example of soft food, because the limited types of food are inconvenient for patients with allergy or intolerances.

When evaluating the compatibility and suitability, not only the properties of drug substance or drug product but also those of foods, such as acidity and drug-binding/chelating characteristics, should be taken into account. Approximate pH ranges of commonly used soft foods and liquids are provided in this guidance (Fig. 4). In addition, the age of the target
population needs to be considered when selecting the flavor, texture, and mouthfeel of the food vehicles, as the age-related responses to these properties are different. For example, some vehicles with grainy texture may cause inadvertent chewing in young patients, and soft food vehicles are discouraged for infants who are able to ingest only the liquid foods.

The guideline also provides methods for handling and dosing the mixture of the drug product and soft foods. The in vitro methods recommended for assessing impact of a vehicle on product quality attributes part presents a standardized methodology for evaluating the integrity and dose uniformity of drug products as well as the potency and stability of drug substance in the soft food vehicles. Moreover, this part provides general recommendations for dissolution testing of the mixture of the drug product and soft food.

4. Conclusions

Sprinkle formulations can improve compliance of patients with dysphagia. Indeed, more than 75% and 93% of children preferred sprinkle dosage form to syrup and oral drops, respectively [26,27]. This preference spurred the growth of sprinkle products since the early 1990s as can be seen in Fig. 1. However, the product number is still small; there have been only sixty-five NDA approvals. The limited kinds of sprinkle products compromise their flexibility and convenience of administration. In the complex medication regimen where both sprinkle and other dosage forms are mixed, patients would experience inconvenience due to the difference in administration methods. Considering this unmet need and the market trend, it is expected that more and more sprinkle products will be launched in the future. Nonetheless, this promising dosage form does not have comprehensive guidance for industry. Compilation and reinforcement of scattered information regarding sprinkle formulations in various regulatory documents would further accelerate their development and consequently provide higher therapeutic benefit for patients.

Conflicts of interest

The authors declare that there is no conflicts of interest.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Ministry of Science and ICT (No. NRF-2018R1C1B6005379).

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajps.2019.05.003.

REFERENCES

[1] Sastry SV, Nyshadham JR, Fix JA. Recent technological advances in oral drug delivery - a review. Pharm Sci Technol Today 2000;3(4):138–45.
[2] Strickley RG, Iwata Q, Wu S, Dahl TC. Pediatric drugs–a review of commercially available oral formulations. J Pharm Sci 2008;97(5):1731–74.
[3] Tahaineh L, Wazaify M. Difficulties in swallowing oral medications in Jordan. Int J Clin Pharm 2017;39(2):373–9.
[4] Lau ETL, Steadman KJ, Mak M, Cichero JAY, Nissen LM. Prevalence of swallowing difficulties and medication modification in customers of community pharmacists. J Pharm Pract Res 2015;45(1):18–23.
[5] Logrippo S, Ricci G, Sestili M, Cespi M, Ferrara L, Palmieri GF, et al. Oral drug therapy in elderly with dysphagia: between a rock and a hard place! Clin Interv Aging 2017;12:241–51.
[6] Lopez FL, Ernest TB, Tuleu C, Gil MO. Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms. Expert Opin Drug Delivery 2015;12(11):1727–40.
[7] Nunn T, Williams J. Formulation of medicines for children. Br J Clin Pharmacol 2005;59(6):674–6.
[8] Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: recent developments and approaches. Drug Dev Ind Pharm 2004;30(5):429–48.
[9] Nokhodchi A, Javadzadeh Y. The effect of storage conditions on the physical stability of tablets. Pharm Technol Eur 2007;19(1):20–6.
[10] Wright D. Swallowing difficulties protocol: medication administration. Nurs Stand 2002;17(14–15):43–5.
[11] Phaechamud T, Praphanwittaya P, Laotaweesub K. Solvent effect on fluid characteristics of doxycycline hyclate-loaded bleached shellac in situ-forming gel and -microsphere formulations. J Pharm Investig 2018;48(3):409–19.
[12] Moore KT, Krook MA, Vaidyanathan S, Sarich TC, Damaraju C, Fields LE. Rivaroxaban crushed tablet suspension characteristics and relative bioavailability in healthy adults when administered orally or via nasogastric tube. Clin Pharmacol Drug Dev 2014;3(4):321–7.
[13] Kunji D, Levenspiel O. Fluidization engineering. 2nd ed. New York: John Wiley & Sons; 1991.
[14] US Department of Health and Human Services, Food and
Drug Administration. Office of clinical pharmacology review of viread®. 2011. Available at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM292364.pdf

[15] Shargel L, Andrew B, Wu-Pong S. Applied biopharmaceutics & pharmacokinetics. 6th ed. New York: McGraw-Hill; 1999.

[16] Yvonne P, Thomas R. Pharmaceutics–drug delivery and targeting. 2nd ed. London: Fastrack, Pharmaceutical Press; 2010.

[17] Feas DA, Igartúa DE, Calienni M, Martinez CS, Pifano M, Chiaramoni NS, et al. Nutraceutical emulsion containing valproic acid (NE-VPA): a drug delivery system for reversion of seizures in zebrafish larvae epilepsy model. J Pharm Investig 2017;47(5):429–37.

[18] Dey N, Majumdar S, Rao M. Multiparticulate drug delivery systems for controlled release. Trop J Pharm Res 2008;7(3):1067–75.

[19] Patwekar SL, Baramade MK. Controlled release approach to novel multiparticulate drug delivery system. Int J Pharm Pharm Sci 2012;4(3):757–63.

[20] Bodmeier R. Tableting of coated pellets. Eur J Pharm Biopharm 1997;43(1):1–8.

[21] Devane J.G., Stark P, Fanning N.M. Multiparticulate modified release composition. US Patent No. 6228398B1.

[22] Youan B. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery? J Control Rel 2004;98(3):337–53.

[23] US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: tablet scoring: nomenclature, labeling, and data for evaluation. 2013. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm269921.pdf

[24] US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: size of beads in drug products labeled for sprinkle. 2012. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm240243.pdf

[25] US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: use of liquids and/or soft foods as vehicles for drug administration: general considerations for selection and in vitro methods for product quality assessments. 2018. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM614401.pdf

[26] Cloyd JC, Kriel RL, Jones-Saete CM, Ong BY, Jancik JT, Remmel RP. Comparison of sprinkle versus syrup formulations of valproate for bioavailability, tolerance and preference. J Pediatr 1992;120(4):634–8.

[27] Zlotkin S, Antwi KY, Schauer C, Yeung G. Use of microencapsulated iron (II) fumarate sprinkles to prevent recurrence of anaemia in infants and young children at high risk. Bull World Health Organ 2003;81:108–15.