Asian Journal of Pharmaceutical Sciences 15 (2020) 292–310

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/AJPS

Review

Sprinkle formulations—A review of commercially available products

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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

ABSTRACT

Currently, sixty-five original sprinkle drug products are available in various dosage forms including tablets, powders, granules, 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.

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].

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Peer review under responsibility of Shenyang Pharmaceutical University.

https://doi.org/10.1016/j.ajps.2019.05.003

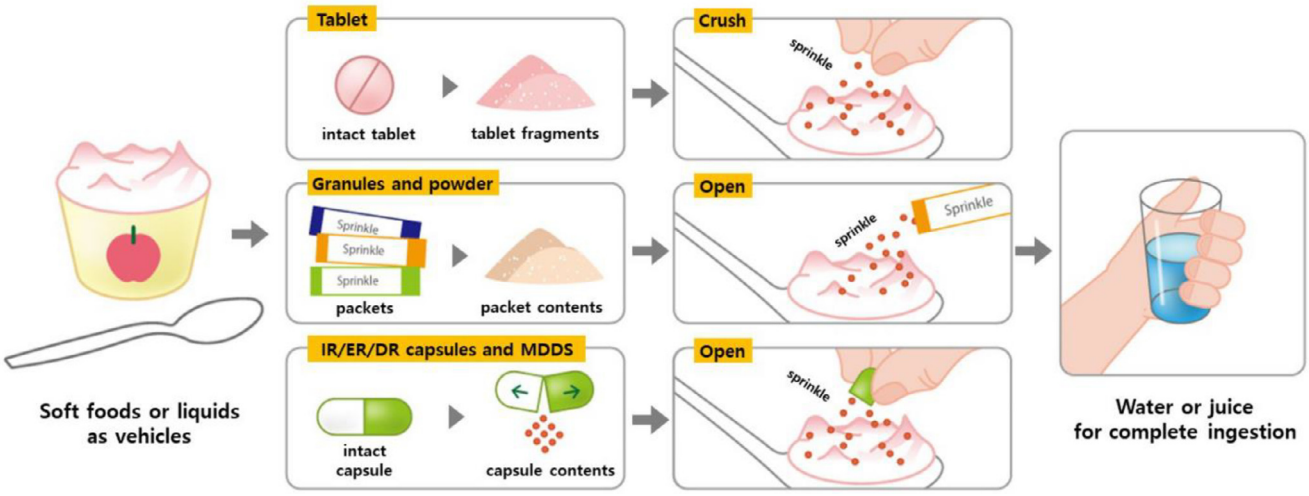

Fig. 1 – General administration methods for the sprinkle drug products in various dosage forms including tablets, powder, granules, immediate-release (IR) capsules, extended-release (ER) capsules, delayed-release (DR) capsules, and multiparticulate drug delivery system (MDDS).

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

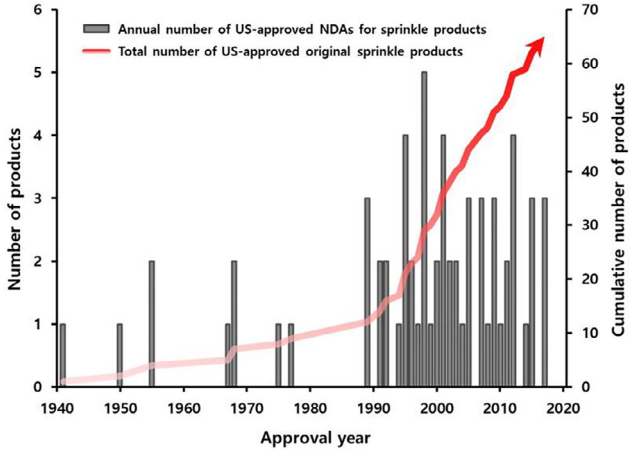

Fig. 2 – The number of approved New Drug Applications (NDAs) for sprinkle drug products since 1941. A total of sixty-five original sprinkle products are available on the US pharmaceutical market.

Table 1 – Commercially available sprinkle products – tablets.

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; Cellulosic 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;Dibasic 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
Onfi®/clobazam	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
Savaysa®/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;	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.	Magnesium stearate; MCC	Carefully crush the tablet and sprinkle the tablet fragments on applesauce.	Synergy Pharmaceuticals	2017

Table 2 – Commercially available sprinkle products – powder.

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

Table 3 – Commercially available sprinkle products – granules.

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.	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 applesauce. Do not use other foods. Do not crush or chew the granules.	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 such as yogurt or applesauce.	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	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.	EC; HPMC; PEG	Sprinkle granules on applesauce, pudding, or yogurt, or mix with milk or infant formula.	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 crunching the granules. Do not try to dissolve the granules in any liquid.	Lupin	2017

Table 4 – Commercially available sprinkle products – IR capsules.

Brand/Generic names	Indication	Strength/Storage	Excipients	Manipulation	Company	Initial US approval
Chemet®/succimer	Treatment of lead, mercury, and arsenic poisoning	100 mg 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 Store at 25 °C.	Lactose monohydrate;Magnesium stearate;SLS;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 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	For children under the age of six, 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 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 Store at 20 to 25 °C.	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 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 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 Store at 25 °C.	Colloidal silicon dioxide;Crospovidone;Lactose monohydrate;Magnesium stearate;Poloxamer 188	Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture within 15 min.	Novartis	2007
Rapaflo®/silodosin	Treatment of the signs and symptoms of benign prostatic hyperplasia	4 and 8 mg Store at 25 °C and protect from light and moisture.	D-mannitol;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

Table 5 – Commercially available sprinkle products – ER capsules.

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 Store at 25 °C and protect from light and moisture.	HPMC;EC;Methacrylic acid copolymer;PEG;DEP;Talc;Corn starch;Sucrose	Carefully open the capsule and sprinkle the contents on applesauce. Do not use other foods. Do not chew the granules.	Actavis	1941
Xtampza® ER/ oxycodone	Management of severe pain	9, 13.5, 18, 27, and 36 mg Store at 25 °C in tight and light-resistant container.	Myristic acid;Yellow beeswax;Carnauba wax;Gelucire 50/13;Magnesium stearate;Colloidal silicon dioxide	Carefully open a capsule and sprinkle the contents on applesauce, pudding, yogurt, ice cream or jam.	Collegium Pharmaceutical	1950
Aptensio XR™/ methylphenidate hydrochloride	Treatment of ADHD	10, 15, 20, 30, 40, 50, and 60 mg Store at 20 to 25 °C and protect from moisture.	Sugar spheres;HPMC;PEG;Ammonio methacrylate copolymer;Triethyl citrate;Talc;Colloidal silicon dioxide;Titanium oxide;Gelatin	Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture immediately without chewing.	Rhodes Pharmaceuticals	1955
Rytary™/carbidopa and levodopa	Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism caused by carbon monoxide or manganese intoxication	23.75/95, 36.25/145, 48.75/195, and 61.25/245 mg carbidopa/mg levodopa Store at 25 °C and protect from light and moisture.	MCC;Mannitol;Tartaric acid;Ethyl cellulose;HPMC;Sodium starch glycolate;SLS;Povidone;Talc; Methacrylic acid copolymer;Triethyl citrate;Croscarmellose sodium;Magnesium stearate	Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture immediately.	Impax Laboratories	1975
Gocovri™/ amantadine	Treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy	68.5 and 137 mg Store at 20 to 25 °C.	Copovidone;EC;HPMC;Magnesium stearate;Medium chain triglycerides;MCC;Povidone;Talc	Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture immediately without chewing.	Adamas Pharmaceuticals	1968
Amrix®/ cyclobenzaprine hydrochloride	Relief of muscle spasm associated with acute, painful musculoskeletal conditions	15 and 30 mg Store at 25 °C and protect from light.	DEP;EC;Gelatin;Opadry Clear YS-1-7006 Sugar spheres (20–25 mesh);Titanium dioxide	Carefully open the capsule and sprinkle the contents on applesauce. Do not use other foods. Do not chew the granules.	Teva Pharmaceuticals	1977
Verelan®/ verapamil hydrochloride	Treatment of hypertension	120, 180, 240, and 360 mg Store at 20 to 25 °C and protect from light and moisture.	Fumaric acid;Talc;Sugar spheres;Povidone;Shellac; Gelatin;FD&C red #40;Yellow iron oxide;Titanium dioxide;Methylparaben;Propylparaben; SD;SLS	Carefully open the capsule and sprinkle the contents on applesauce that is not warm. Ingest the mixture immediately without chewing.	Recro Gainesville	1991
Kapspargo™ Sprinkle/ metoprolol succinate	Treatment of hypertension, angina pectoris, and heart failure	25, 50, 100, and 200 mg Store at 20 to 25 °C.	EC;HPMC;PEG400;PEG6000;Sugar spheres;Talc;Triethyl citrate	Carefully open the capsule and sprinkle the contents on applesauce, pudding, or yogurt. Ingest the mixture within 60 min.	Sun Pharmaceutical	1992
Coreg® CR/ carvedilol phosphate	Treatment of mild to chronic heart failure, left ventricular dysfunction following myocardial infarction, and hypertension	10, 20, 40, and 80 mg Store at 25 °C and protect from light.	Crospovidone;Hydrogenated castor oil;Hydrogenated vegetable oil;Magnesium stearate;Methacrylic acid copolymer;MCC;Povidone	Carefully open the capsule and sprinkle the contents on applesauce that is not warm.	GlaxoSmithKline	1995

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Table 5 (*continued*)

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 applesauce. Ingest the mixture immediately without chewing.	Wyeth	1997
Klor-Con® Sprinkle/potassium chloride	Treatment 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, such as applesauce or pudding. Ingest the mixture immediately without chewing.	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 applesauce. Ingest the mixture immediately without chewing.	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	Carefully open the capsule and sprinkle the contents on applesauce.	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 applesauce. 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 applesauce. 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 Store below 25 °C.	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.	MCC 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

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Table 6 (*continued*)

Brand/Generic names	Indication	Strength/Storage	Excipients	Manipulation	Company	Initial US approval
Dexilant®/dexlansoprazole	Treatment of erosive esophagitis and GERD	30 and 60 mg Store at 20 to 25 °C.	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 Store at 25 °C.	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 Store at 25 °C and protect from moisture.	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

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Table 6 (*continued*)

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 × 10^3 USP units of lipase/protease/amylase Store below 25 °C and protect from moisture.	Cetyl alcohol Dimethicone HPMCP 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 × 10^3 USP units of lipase/protease Store at 25 °C and protect from moisture.	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. 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 and commercially available preparations of bananas or pears. 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 × 10^3 USP units of lipase/protease/amylase Store below 25 °C in the original container and protect from moisture.	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

(*continued on next page*)

Table 6 (*continued*)

Brand/Generic names	Indication	Strength/Storage	Excipients	Manipulation	Company	Initial US approval
Pertzye®/pancrelipase	Treatment of exocrine pancreatic insufficiency	4/14.375/15.125, 8/28.75/30.25, and 16/57.5/60.5 × 10^3 USP units of lipase/protease Store at 20 to 25 °C and protect from moisture.	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™/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 × 10^3 USP units of lipase/protease/amylase Store at 20 to 25 °C and protect from moisture.	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

Table 7 – Commercially available sprinkle products – MDDS.

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.	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;Shellac;SD;SLS; Starch;Sugar spheres;Talc;Titanium dioxide	Carefully open the capsule and sprinkle the contents on applesauce. Ingest the mixture immediately without chewing.	Recro Gainesville	1998
Metadate CD®/methylphenidate hydrochloride	Treatment of ADHD	10, 20, 30, 40 and 60 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®/dexmethylphenidate 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 cellulosic 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, hypromellose (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 (C_{max}) 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 500 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 C_{max} 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 4 mg 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 (deferasirox; Novartis) is used for chronic iron overload caused by blood transfusion. Jadenu® Sprinkle granules contain 90, 180, and 360 mg deferasirox. 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 C_{max} 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 C_{max} 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 C_{max}.

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 C_{max} 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 Pharms) 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 C_{max} and AUC values when administered as sprinkles and intact capsules. However, its ingestion with high-fat meal markedly delayed the time to reach C_{max} (T_{max}) 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, crospovidone, lactose monohydrate, magnesium stearate, and poloxamer 188. Tasigna® sprinkled on applesauce and administered within 15 min is bioequivalent to the intact capsule.

Rapaflo® (silodosin; Allergan) was developed for the treatment of benign prostatic hyperplasia. Rapaflo® capsules include 4 or 8 mg of silodosin with D-mannitol, magnesium stearate, pre-gelatinized starch, and SLS. The bioequivalent AUC and C_{max} 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. C_{max} 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. Cellulosic 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 hypromellose capsule. The inactive ingredients are colloidal silicon dioxide, diacetylated monoglycerides, EC, HPC, hypromellose phthalate (HPMCP), magnesium oxide, magnesium stearate, mannitol, talc, titanium dioxide, carrageenan, and potassium chloride. Aciphex® administered with high-fat meal exhibited reduced C_{max} and AUC (by 55% and 33%, respectively) as well as delayed median T_{max} (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 T_{max}, C_{max}, 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 spheroidal 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 C_{max} and AUC) of methylphenidate compared with the intact capsule.

Ritalin LA® (methylphenidate; Novartis) and Focalin™ XR (dexmethylphenidate; Novartis) are also used to treat

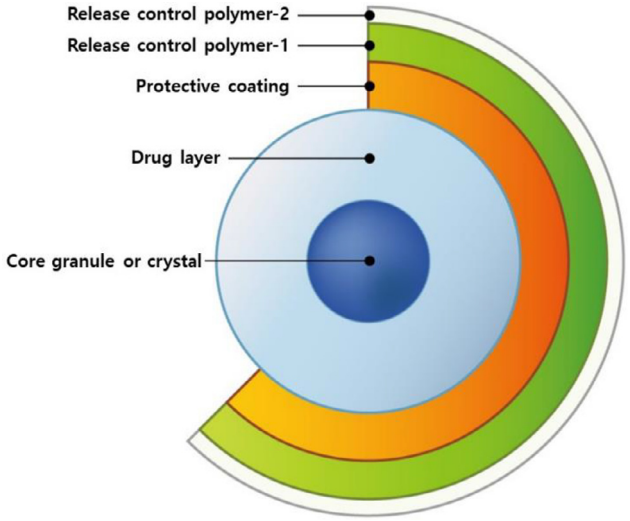

Fig. 3 – Schematic illustration of SODAS® technology. The spherical bead has a multilayered structure, of which the drug-containing core is coated with the layers of release-controlling polymers.

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 intolerance.

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

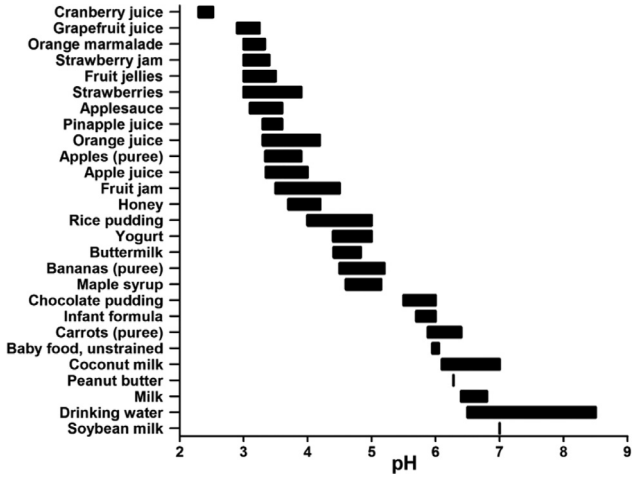

Fig. 4 – Approximate pH ranges of commonly used soft foods and liquids.(Adapted from Appendix A of Ref. [25].

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.

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