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REVIEW ARTICLE

Co-spray Drying Drugs with Aqueous Polymer Dispersions (APDs)—a Systematic Review

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Abstract

Aqueous colloidal dispersions of water-insoluble polymers (APDs) avoid hassles associated with the use of organic solvents and offer processing advantages related to their low viscosity and short processing times. Therefore, they became the main vehicle for pharmaceutical coating of tablets and multiparticulates, a process commonly employed using pan and fluidized-bed machinery. Another interesting although less common processing approach is co-spray drying APDs with drugs in aqueous systems. It enables the manufacture of capsule- and matrix-type microspheres with controllable size and improved processing characteristics in a single step. These microspheres can be further formulated into different dosage forms. This systematic review is based on published research articles and aims to highlight the applicability and opportunities of co-spray drying drugs with APDs in drug delivery.

KEY WORDS aqueous polymer dispersions · spray drying · agglomerates · biological drugs · modified release · taste masking

INTRODUCTION

In the last decade, guidelines for residual organic solvents have been issued restricting their use in pharmaceutical manufacturing processes, such as coating and wet granulation (1). Besides toxicity, organic solvents are costly, explosive, and environmentally hazardous. Instead, aqueous dispersions of water-insoluble polymers (APDs) are commonly employed in coating tablets and multiparticulates. APDs avoid the disadvantages of organic solvents and offer easy processability due to their low viscosity, adjustable polymer content, commercial availability for immediate application and hence reduced processing time (2–4). Moreover, they enable processing of biologicals (vaccines, peptides, and proteins) that may degrade in contact with organic solvents (5–10). In some cases, *e.g.*, enteric APDs, they can be easily transformed into aqueous solutions (11).

APDs may be prepared by emulsion polymerization of a monomer (latex) or by polymer emulsification (pseudolatex) (12). Commercially, they are available as ready-to-use dispersions or redispersible powders (12–15). The most commonly used APDs are summarized in Table I.

Although the primary application of APDs is through pan and fluid-bed (air-suspension) coating, co-processing with drugs *via* spray drying presents another interesting approach offering certain advantages.

Spray drying itself is a unique continuous one-step process producing powders with controllable particle size and round-shaped particles rendering them flowability, compactability, and feasibility for direct-compression tableting (31). It is a well-established co-processing technique that combines different ingredients dissolved or suspended in a liquid medium into composite particles.

Co-spray drying drug with APD produces composite microparticles that may follow different formulation lines. They might be formulated as a single-unit matrix system to construct a modified release product, which circumvents the risk and consequences of film rupture associated with

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Table I Aqueous Polymer Dispersions (APDs) That Are Currently Used for Extended Release, Delayed Release, and Taste Masking of Solid Dosage Forms

Application	APD	Polymer	Presentation	Reference
Extended release	Aquacoat® ECD	Ethylcellulose	Aqueous dispersion	(12, 15, 16)
	Surelease®	Ethylcellulose	Aqueous dispersion	(12, 15, 17)
	Eudragit® RS 30 D	Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1	Aqueous dispersion	(12, 15, 18)
	Eudragit® RL 30 D	Poly(ethyl acrylate, methyl methacrylate, trimethylammonio-ethyl methacrylate chloride) 1:2:0.2	Aqueous dispersion	(12, 15, 18)
	Eudragit® NE 30 D*	Poly(ethyl acrylate, methyl methacrylate) 2:1	Aqueous dispersion	(12, 15, 18)
	Eudragit® NE 40 D	Poly(ethyl acrylate, methyl methacrylate) 2:1	Aqueous dispersion	(15, 18)
	Eudragit® NM 30 D	Poly(ethyl acrylate, methyl methacrylate) 2:1	Aqueous dispersion	(12, 15, 18, 19)
	Kollicoat® SR 30 D	Polyvinyl acetate	Aqueous dispersion	(12, 20)
Delayed release	Aquacoat® CPD	Cellulose acetate phthalate	Aqueous dispersion	(15, 16)
	Eudragit® L 100-55	Poly(methacrylic acid, ethyl acrylate) 1:1	Redispersible powder	(15, 21)
	Eudragit® L 30 D 55**	Poly(methacrylic acid, ethyl acrylate) 1:1	Aqueous dispersion	(12, 15, 21)
	Eudragit® FL 30 D-55	Ethyl acrylate and methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer (1:1)	Aqueous dispersion	(22)
	Acryl-EZE®	Poly(methacrylic acid, ethyl acrylate) 1:1	Redispersible powder	(15, 23)
	Eastacryl® 30 D	Poly(methacrylic acid, ethyl acrylate) 1:1	Aqueous dispersion	(15)
	Kollicoat® MAE 30 D P	Poly(methacrylic acid, ethyl acrylate) 1:1	Aqueous dispersion	(15, 24)
	Kollicoat® MAE 100 P	Poly(methacrylic acid, ethyl acrylate) 1:1	Redispersible powder	(15, 25)
	Eudragit® FS 30 D	Poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1	Aqueous dispersion	(15, 21)
	AQOAT®	Hypromellose acetate succinate	Redispersible powder	(15, 26)
	Aquasolve®	Hypromellose acetate succinate	Redispersible powder	(12, 27)
	Sureteric®	Polyvinyl acetate phthalate	Redispersible powder	(15, 28)
Taste masking	Eudragit® E PO†	Poly(butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) 1:2:1	Redispersible powder	(15)
	Kollicoat® Smartseal 30 D	Methyl methacrylate and di(ethyl)aminoethyl methacrylate (7:3) copolymer	Aqueous dispersion	(29)

*Formerly known as Eudragit® E 30 D (30)

**Formerly known as Eudragit® L 30 D (30)

†Available also as a ready-to-use powder blend (ReadyMix®)

film coating (32–34) or as a multiple unit particulate system (MUPS) suitable for formulation in orally disintegrating tablets (35–38) and films (39). They have also been investigated for delivery *via* the skin through transdermal (40, 41), subcutaneous injection (41), and microneedle systems (42). Formulations targeting other routes such as nasal, rectal, and vaginal are also feasible but still understudied.

For all the above reasons, co-spray drying of drugs dissolved or dispersed in commercially available APDs appears to be attractive and suitable for the formulation of various dosage forms with different functionalities such as extended release, delayed release, and taste masking by selecting suitable ingredients and processing parameters.

This systematic review aims to provide a better understanding of the applicability and opportunities of co-spray drying with APDs in drug delivery.

METHODOLOGY

The review followed PRISMA guidelines (43). Scopus, EBSCOhost Web, and PubMed databases were exploited to search the literature published until the end of the year 2021 based on multiple search terms and combinations using Boolean operators, as shown in Table II. The criteria designated for the selection of the articles were (1) original research articles written in English and reporting pharmaceutical applications were used; (2) articles reporting applications based solely upon the use of organic solutions (*e.g.*, by dissolving redispersible powder products) were excluded since they do not realize the advantages of APDs. After screening, a secondary search within the references of selected articles was performed to check their relevancy.

Table II Multiple Search Terms and Combinations That Were Used to Screen Articles

Search terms	Search within
"spray drying" OR "spray-dried" OR "spray dryer" AND	Scopus: Article title, abstract, keywords EBSCOhost Web: Abstract PubMed: Title/abstract
"Aqueous dispersion" OR "aqueous polymer dispersion" OR "aqueous polymeric dispersion" OR Aquacoat OR AQOAT OR Smartseal OR Surelease OR Sureteric OR Acryl-EZE OR "Eudragit E PO" OR "L 100-55" OR "*30D" OR "*30 D" OR "*40 D" OR "*40D"	Scopus: Article title, abstract, keywords EBSCOhost Web: All text PubMed: Text word

There was a specific focus during the data extraction process on key information related to: (1) APD type, (2) loaded drug, (3) additives, (4) intended application/route of administration, (5) polymer/drug ratio, (6) processing parameters, (7) production yield, (8) solid state, (9) micromeritic properties, and (10) drug release pattern.

RESULTS

Literature Search Output

A rational flow of systematic searching followed in this work is presented in Fig. 1. The literature searches in Scopus, EBSCOhost Web, and PubMed resulted in 168, 192, and 47 records, respectively. Of these, titles and abstracts were first scanned and out-of-scope articles were excluded based on the criteria mentioned in the "METHODOLOGY" section. Then, a further scan of all fields of the remaining included articles was performed and the ruled-out articles were 130, 161, and 36 for Scopus, EBSCOhost Web, and PubMed, respectively. After removing duplicates found in the different databases, 49 relevant records remained. After a secondary search within the references of these relevant articles, seven additional articles were found raising the total to 56 articles that were utilized for data extraction. From Fig. 2, it clearly appears that the number of articles on co-spray drying with aqueous polymer dispersions (APDs) published after 1989 has increased remarkably in the last decade.

Processing and Formulation Parameters

For co-spray drying with APDs, the drug is either dissolved or dispersed in water in the case of poorly soluble drugs (40, 44–46) and then mixed with the aqueous polymer dispersion. The feed is atomized in a drying chamber where it is exposed to a current of drying air. In the cited articles, spray drying was investigated using a small-scale spray dryer except for one article where pilot-scale production is reported (35).

Inlet and Outlet Temperature

In Fig. 3, inlet and outlet temperatures that have been operated in spray drying experiments of biological and non-biological agents are presented as box plots (Fig. 3). For non-biological drugs, the inlet temperature varied from 60 to 275°C and the outlet from 35 to 108°C, whereas for biologicals, the corresponding ranges were from 45 to 160°C and 35 to 80°C. These results indicate that a wide range of processing temperatures have been applied for the co-spraying of the different types.

Types of Aqueous Polymer Dispersions (APDs)

The APD type plays an important role in the release profile and the drug solid state, micromeritic and other physicochemical properties of the produced microparticles. The dispersions that were used in the selected articles of this review were ethylcellulose (Aquacoat® ECD 30 D and Surelease®), polymethacrylates (Eudragit® L 30 D 55, Eudragit® RS 30 D, Eudragit® NE 30 D previously named as Eudragit® E 30 D, Eudragit® RL 30 D, Eudragit® FS 30 D, Eudragit® L30 D, and Eudragit® L100-55), PVAc-PVP (Kollicoat® SR 30 D), and HPMCAS AS-MF (AQOAT®). No publications were found reporting the polyvinyl acetate phthalate dispersion (Sureteric®) and the polymethacrylate dispersions Acryl-EZE®, Eudragit® NM 30 D, and Eudragit® FL 30 D-55 indicating that there is scope for further investigation. The outcomes of the selected articles were prolonged release (17 articles), delayed release (10 articles), protection of biologicals (23 articles), and taste masking (7 articles).

Polymer to Drug Ratio

The reported polymer to drug (P:D) ratio was up to 100:1 (47), which despite the high polymer content can be easily processed in the spray dryer due to the low feed viscosity.

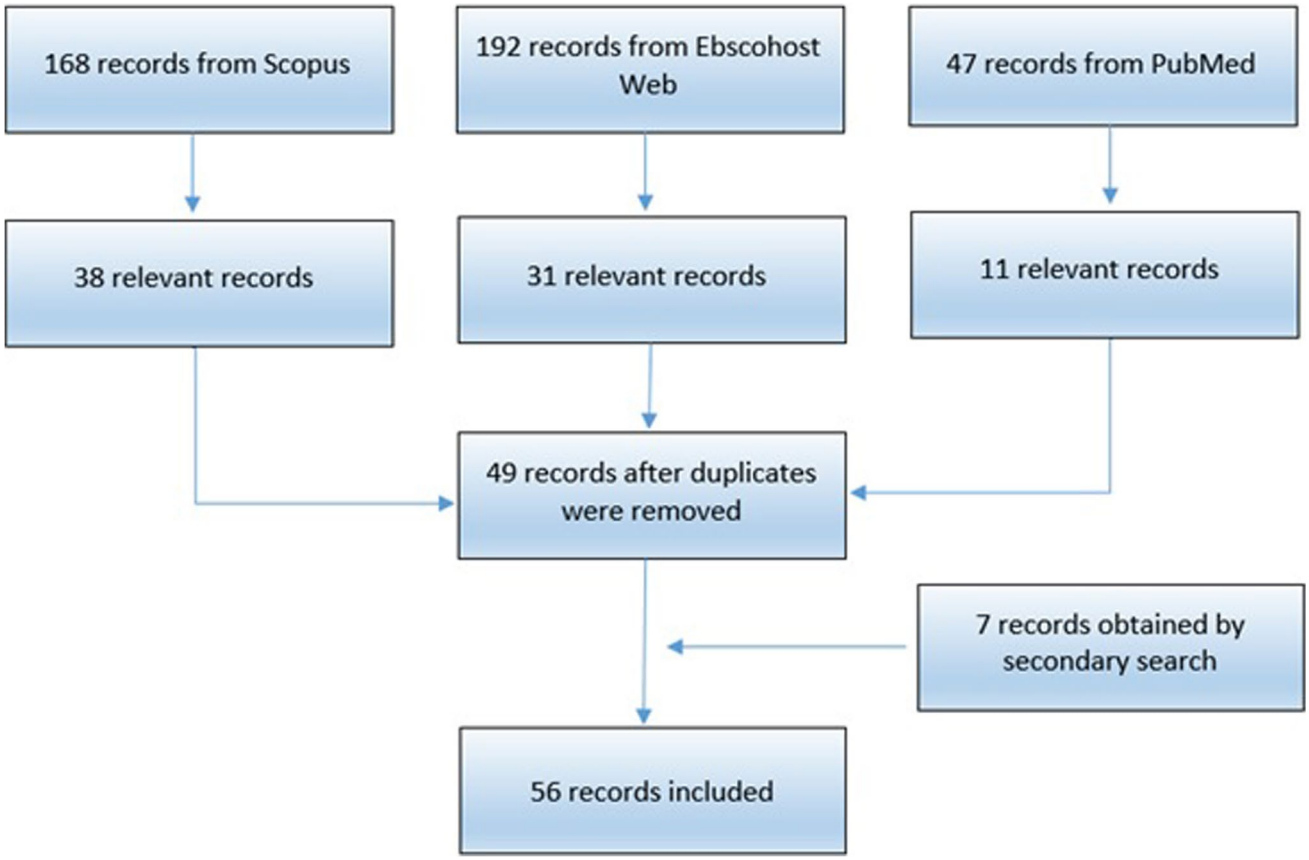

Fig. 1 Flowchart of records' search and selection strategy

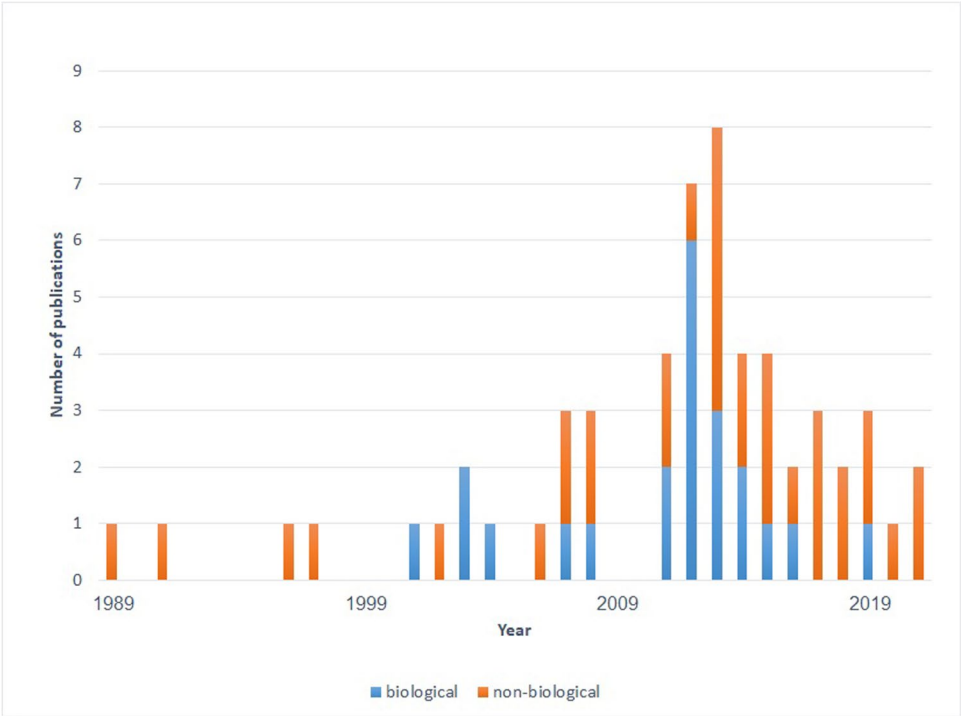

Fig. 2 Number of publications on co-spray drying with APDs included in this review over the years

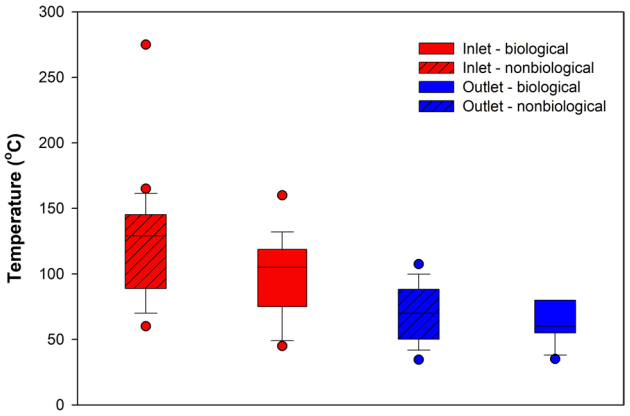

Fig. 3 Box plots for inlet and outlet temperatures applied in spray drying experiments for biological and non-biological drugs reported in the selected articles of this review

Such a high ratio is difficult to achieve by other approaches such as wet massing agglomeration because of the critical water content required to form liquid bridges and avoid overriding the capillary stage (48). Moreover, high drug content or low P:D ratio of the obtained particles is also possible by water dilution of the drug-APD dispersion and increasing the amount of dissolved drug in the feed solution, and the drug content of the produced particles.

Product Characteristics

Production Yield

Production yield in the selected studies varied between 7.2 and 93% (35, 49), the latter percentage achieved using a pilot-scale spray dryer. Lower than 100% yield is expected, especially when lab-scale spray dryers are used due to sticking of the droplets to the drying chamber and collecting cyclone walls or to the formation of fine particles that are exhausted by the aspirator (50). Besides the production scale, yield was found to depend on the type of polymer in the dispersion. For example, the yield was higher for buspirone HCl microparticles co-spray dried with Eudragit® RS 30 D than Kollicoat® SR 30 D (49). For metformin HCl microparticles, the yield was in decreasing order: Eudragit® RS 30 D > Eudragit® RL 30 D > Surelease® (51). These findings match the order of glass transition temperature (~55°C for Eudragit® RS 30 D (49, 52), ~41°C for Kollicoat® SR 30 D (49), and ~35°C for Surelease® (53)). APD polymers with low Tg are likely to be in the rubbery state during spray drying, causing sticking to the drying chamber wall. Since addition of plasticizers reduces the Tg, the same reason applies for the reduction of production yield found when plasticizer was added to Eudragit® RS 30 D (44).

In the case of buspirone HCl co-spray dried microparticles, the lower yield obtained with Kollicoat® SR 30 D, compared to Eudragit® RS 30 D, was attributed mainly to the increased viscosity and stickiness of the feed material due to the PVP present in Kollicoat® SR 30 D dispersion, besides the Tg difference. For the same reason, addition of alginates and Carbopol® was reported to decrease the yield of co-spray dried Aquacoat® cPD-cholera vaccine (8). High stickiness and low spray drying yield can also result from high feeding rate (11, 54). On the other hand, yield was increased by adding adsorbent powders Aerosil® to Eudragit® NE 30 D (55) and Starch 1500® to Eudragit® RS 30 D (37). Excipients of high adsorption capacity assist rapid drying of droplets and are commonly used to increase the spray drying yield (56–60).

Overall, high yield results from low P:D ratios (61) due to the decreased stickiness. However, the opposite has been reported for Eudragit® RS 30 D, which was probably associated with the formation of sticky amorphous drug solid dispersion as indicated by PXRD (44). In three further studies, yield was found to increase with inlet temperature (8, 11, 54). However, decrease with temperature due to stickiness of overheated droplets has also been reported (62), due to the induced rubbery state of the polymer. Therefore, there is a need to optimize the process parameters.

Regarding the effect of feed liquid, four studies compared co-spray drying from aqueous dispersions *vs*. organic solution (39, 63–65). No general conclusion could be made regarding production yield. In two of these studies comparing Eudragit® RS 30 D, Surelease® (APD of ethylcellulose) and Aquacoat® ECD (64, 65) with their corresponding organic solutions, the yield was higher from the aqueous dispersions. Conversely, in two other studies comparing Surelease® and Eudragit® EPO with the corresponding organic solutions of the polymers (39, 63), the organic solutions gave higher yield. The reason for the contradiction lies in the fact that organic solvents are more volatile than water facilitating drying, but organic polymer solutions are more viscous than aqueous dispersions and thus hamper crystallization.

Solid State of the Drug

Due to the rapid solidification and the presence of the polymer during co-spray drying drug crystallinity may be reduced. The solid state of the spray-dried particles was investigated mainly by XRD and by thermal analysis (DSC). Co-spray drying resulted either in crystallinity reduction (40, 47) or complete amorphization (11, 39, 66–68) of the drug at increased polymer content. This however is only a rough estimation, since there are instances where the drug retained its crystalline state (35, 38, 49, 51, 63, 65, 69).

The solid state of the drug is mainly influenced by the P:D ratio and drug type. For instance, when naproxen was

co-spray dried with ethylcellulose, drug crystallinity was reduced at high P:D ratios leading to complete amorphization at ratio 4:1 (40). However, high polymer content does not always promote amorphization. For example, buspirone HCl co-spray dried with Kollicoat® SR 30D or Eudragit® RS 30D retained its crystallinity even at high P:D ratio 9:1 (49). This suggests that besides P:D ratio, drug-polymer miscibility has also a key role in the resulting solid state of the drug.

Regarding studies comparing the effect of the type of feed liquid on drug solid state, there were no significant differences between aqueous dispersions and organic solutions. For instance, co-spray drying theophylline with Eudragit® RS or ethylcellulose from aqueous dispersions or organic solutions led in both cases to crystalline drug (63, 65). Also, co-spray drying prednisolone with Eudragit® E from aqueous dispersion or organic solution resulted in complete drug amorphization (39).

Morphology of Co-spray Dried Particles

The type of APD, the P:D ratio, and the presence of additives influence the micromeritic properties of the spray dried particles leading to different particle morphologies. In most cases, the final particles were round in shape with smooth surface (11, 35, 38, 40, 51, 69, 70). The effect of P:D ratio did not follow the same trend for all APDs, implying interaction between the effects of the two factors on the final particles' morphology. For instance, by co-spray drying buspirone HCl with Kollicoat® SR 30 D at P:D ratio 1:1, spherical and smooth particles were formed, whereas by increasing the P:D ratio, the particles became more shriveled. On the other hand, for Eudragit® RS 30 D at P:D ratio 1:1, less spherical particles were formed, whereas with increasing P:D ratio, sphericity increased. However, some doughnut-like particles and hollow spheres were also present (49).

Regarding the impact of additives, shriveled L-alanyl-L-glutamine dipeptide particles were formed by co-spray drying with pectin and Surelease® at high pectin to Surelease® ratio. More spherical particles but with rough surfaces were obtained at lower pectin:Surelease® levels (66). Furthermore, more deformed and shriveled particles were obtained by adding silica nanoparticles to Eudragit® NE 30 D (68) and citric acid to Eudragit® L 30D 55 (54). On the other hand, addition of triethyl citrate (54) or lactose (68) improved particle morphology, resulting in both spherical and smooth particles. It is noteworthy that when Eudragit® S100 or RS 30D were co-spray dried alone with pantoprazole, hollow spheres and doughnut-like particles were formed. However, when a mixture of the two polymers was used, spherical and smooth particles formed (71).

In the cases of poorly water-soluble drugs, the particle size of the dispersed drug also seems to affect the morphology of spray-dried particles. Mizumoto *et al*. (35) reported that when famotidine was used as coarse powder, the particles were round with spiky crystals appearing on their surface. However, when pulverized drug was used instead, the particles had smooth surface.

Among the processing parameters, inlet temperature has been reported to impact particle morphology of co-spray dried APD microparticles. Liu *et al*. (72) designed uniform microencapsulates of vitamin B12 *via* microfluidic co-spray drying with APDs of Eudragit® L 30 D 55. Microparticles obtained at 146°C inlet temperature had more wrinkled morphologies, while those produced between 110 and 85°C had hollow pot-like shapes. In another study, Liao *et al*. (9) reported the effect of inlet temperature on the morphology of microspheres prepared by co-spray drying *Actinobacillus pleuropneumoniae* antigens and aqueous dispersions of ethylcellulose and HPMCAS. The shape of microparticles was spherical below 60°C but became irregular and doughnut-like at higher temperatures.

Comparison between aqueous dispersion with organic solutions showed that organic solutions produced more spherical and smooth particles (39, 65). However, when theophylline was co-spray dried with ethylcellulose, some shriveled particles were present from both aqueous and organic feeds (65).

Pharmaceutical Applications

The applications of co-spray drying with APDs in the reviewed articles were classified into four categories based on the primary objectives of the studies: (i) prolonged (PR) and (ii) delayed (DR) drug release, (iii) protection of biological drugs, and (iv) taste masking. The corresponding studies are summarized in Table III.

Prolonged Release

The application of APD in the formulation of prolonged release matrix type dosage forms by co-spray drying attracts interest for several reasons. First, the polymer in the APDs is in colloidal nanosized form, which controls more efficiently the drug release than larger sizes, due to the increased tortuosity and drug percolation threshold (93–96). Second, co-spray drying results in more intimate drug-polymer mixing than simple physical mixing (97, 98). Third, compaction of co-spray dried mixtures into tablets results in superior particle deformation and bonding (99) with lower matrix porosity and more effective release control.

Several types of aqueous dispersions were investigated for prolonging release from co-spray dried product. The most frequently explored are ethylcellulose-based dispersions (Aquacoat® ECD and Surelease®) followed by methacrylate-based (Eudragit® RS 30 D, Eudragit® NE 30 D, and

Table III Studies on Co-spray Drying Aqueous Polymer Dispersions for Prolonged and Delayed Drug Release, Protection and Delivery of Biological Drugs, and Taste Masking

APD	Co-spray dried excipients	Model drug	Particle size (μm)	Presentation	Reference
Prolonged drug release					
Aquacoat® ECD	Triethyl citrate	Mirabegron	< 200	Microparticles	(46)
Eudragit® RS 30 D	Propylene glycol	Sodium diclofenac	9.1–24.5	Microparticles	(73)
Surelease®	Talc Colloidal silicone dioxide Titanium dioxide		10.4–19.0		
Eudragit® RS 30 D	Talc	Metformin HCl	4.55–6.61	Microparticles	(51)
Eudragit® RL 30 D	Colloidal silicone dioxide		4.39–6.77		
Surelease®			4.41–6.53		
Kollicoat® SR 30 D	-------	Buspirone HCl	2–20*	Matrix tablets	(49)
Eudragit® RS 30 D	-------				
Surelease®	PVP Lactose Colloidal silicone dioxide	Theophylline	5–20	Matrix tablets	(74)
Eudragit® NE 30 D	Lactose	Vitamin B12	70.65–100.55	Microparticles	(68)
	Silica nanoparticles		98.10–114.81		
Surelease®	Pectin	L-Alanyl-L-glutamine dipeptide	1.77–2.52	Microparticles	(66)
Eudragit® NE 30 D	Talc Colloidal silicone dioxide	Diclofenac-sodium	10.5–12.9	Matrix tablets	(55)
Kollicoat® SR 30 D	PVP	Diltiazem HCl	9.68–23.14	Matrix tablets	(67)
Eudragit® RS 30 D	-------	Theophylline	38–46¶	Matrix tablets	(65)
-------	Eudragit® RS PO†		32–43¶		
Surelease®	-------	Theophylline	3–40	Matrix tablets	(63)
-------	Ethocel 20 cps†		1–25		
Eudragit® RS 30 D	PEG 6000 Starch 1500®	Ketoprofen	n.a.	Oral disintegrating tablets	(37)
Aquacoat® ECD	Triethyl citrate Colloidal silicone dioxide	Naproxen	10.8–14.7	Transdermal drug delivery system	(40)
Eudragit® E 30 D	Colloidal silicone dioxide	Theophylline	10.0–30.0	Matrix tablets	(75)
Eudragit® RS 30 D	-------	Chlorpheniramine maleate	n.a.	Matrix tablets	(44)
		Ibuprofen			
		Naproxen			
Eudragit® RS 30 D Eudragit® RL 30 D	Propylene glycol Titanium dioxide Talc Colloidal silicone dioxide	Ketoprofen	25.6±1.8**	Microparticles	(62)
Delayed release					
Eudragit® L 30 D Eudragit® L 100-55	PEG 6000 Colloidal silicone dioxide	Theophylline	10.0–30.0	Enteric matrix tablets	(75)
Eudragit® L 30 D	PEG 6000 Colloidal silicone dioxide Soluble starch Lactose	Sodium diclofenac	3.0–12.0 **	Enteric matrix tablets	(76)
-------	Eudragit® S 100	Pantoprazole sodium sesquihydrate	9.1 (span 1.55)	Microparticles	(71)
Eudragit® RS 30 D	-------		10.9 (span 1.69)		
Eudragit® RS 30 D	Eudragit® S 100		53.5 (span 3.60)		

Table III (continued)

APD	Co-spray dried excipients	Model drug	Particle size (μm)	Presentation	Reference
Eudragit® L 30 D- 55	-----	Vitamin B12	75.06–90.17	Microparticles	(72)
	Eudragit® NE 30 D		83.26–90.56		
	TEOS		91.01–94.37		
Eudragit® FS 30 D	Zein Gantrez® AN119	Curcumin	10.2–25.6	Microparticles	(70)
Eudragit® FS 30 D	-------	S-Nitrosoglutathione glutathione	5.0–7.0	Microparticles	(11)
Eudragit® L 30 D- 55	Triethyl citrate	Furosemide	24.1 ± 5.2	Microparticles	(77)
Eudragit® L 30 D- 55	Triethyl citrate	Furosemide	11.4–33.0	Microparticles	(69)
Eudragit® L 30 D- 55	Triethyl citrate	Allicin-rich extract phytosome	0.215–0.549	Microparticles	(78)
Eudragit® L 30 D- 55	Citric acid Triethyl citrate	Losartan potassium	1.3–7.3 **	Microparticles	(54)
Protection and delivery of biological drugs					
Eudragit® L30D-55 Eudragit® FS 30 D	-----	*Vibrio cholerae*	2.67–3.41	Microparticles for oral vaccine	(5)
Eudragit® L30D-55	-----	*Vibrio cholerae*	8.87 ± 0.04	Microparticles for oral vaccine	(6)
	Sodium alginate		8.92 ± 0.03		
	Carbopol®		7.64 ± 1.20		
Eudragit® L30D-55	Sodium alginate	*Vibrio cholerae*	7.55 ± 0.25	Microparticles for oral vaccine	(7)
	-----		8.93 ± 0.01		
Aquacoat® CPD	Sodium alginate	*Vibrio cholerae*	6.05–6.50	Microparticles for oral vaccine	(8)
HPMCAS-MF Aquacoat® ECD	Magnesium stearate	*Actinobacillus pleuropneumoniae* antigens	2–25*	Microparticles for oral vaccine	(9)
AQOAT® Aquacoat® ECD	Magnesium stearate	*Actinobacillus pleuropneumoniae* antigens	5.00–30.00	Microparticles for oral vaccine	(10)
HPMCAS-MF	-----	*Escherichia coli* antigen	3.00–30.0	Microparticles for oral vaccine	(79)
Aquacoat® ECD	-----				
-----	Ethylcellulose Aqualon™ ECN7, ECN14, ECN22, ECN50, ECN100				
Eudragit® L30D-55	Talc Glycerol	*Mycoplasma hyopneumoniae* antigens	n.a.	Microparticles for oral vaccine	(80)
Aquacoat® ECD AQOAT®	Bovine serum albumin	Extracellular antigen from B16 melanoma cells	2.55–5.50	Microparticles for oral vaccine	(81)
Aquacoat® ECD AQOAT®	β-Cyclodextrin Trehalose Tween 20	Whole cell lysate (4T07 antigen)	1.5	Microparticles for oral vaccine	(82)
AQOAT® Aquacoat® ECD	Bovine serum albumin	Whole cell lysate	0.47–2.03	Microparticles for oral vaccine	(83)
AQOAT® Eudragit® FS 30 D	Chitosan glycol	Mouse serum albumin	0.96–2.20	Microparticles for oral vaccine	(84)
Eudragit® FS 30D AQOAT®	β-Cyclodextrin Trehalose Tween 20	HBs antigen	0.63–1.40	Microparticles for oral vaccine	(85)
AQOAT® Eudragit® FS 30D	Chitosan glycol Trehalose Fluorescein isothiocyanate-albumin	Whole cell lysate	0.35–2.00	Microparticles for oral vaccine	(86)
Eudragit® FS30D AQOAT®	Chitosan glycol Trehalose Bovine serum albumin	Fluorescein isothiocyanate-albumin	1.51	Microparticles for oral vaccine	(87)

Table III (continued)

APD	Co-spray dried excipients	Model drug	Particle size (μm)	Presentation	Reference
Aquacoat® ECD AQOAT®	-----	Bovine serum albumin	0.63–1.40	Microparticles for transdermal vaccine	(88)
AQOAT® Eudragit® FS 30 D	Chitosan glycol	Mouse serum albumin	1.55–2.05	Microparticles for transdermal/subcutaneous vaccine	(41)
Aquacoat® ECD AQOAT®	β-Cyclodextrin Trehalose Tween 20	Whole cell lysate (4T07 antigen)	1.0–4.0	Microparticles for skin vaccine	(42)
Aquacoat® ECD AQOAT®	β-Cyclodextrin	Insulin	0.5–1.2	Microparticles for oral delivery	(47)
-----	-----	Lysozyme		Spray dried microparticles compared with freeze dried powder	(89)
-----	Copovidone		4–5*		
Kollicoat® MAE 30DP	-----		3–4*		
Eudragit® L100-55	-----	Bromophenol blue–loaded bovine serum albumin	2.48–8.74**	Enteric coated microparticles	(90)
Eudragit® FS 30 D	HPMC Chitosan glycol Eudragit® S100 Eudragit® L100	Bovine serum albumin	n.a.	Enteric coated microparticles	(91)
Taste masking					
Aquacoat® ECD & Eudragit® NE 30 D	-----	Famotidine	127**	Fast-disintegrating tablet	(35)
Aquacoat® ECD	Triacetin		121**		
Eudragit® L30D-55	-----	Roxithromycin	20–30*	Microparticles	(45)
Eudragit® E PO	-----	Prednisolone	5–60	Orodispersible tablet and orodispersible film	(39)
----- ‡	Eudragit® E 100		< 4.5		
-----†	Ethocel® Mannitol	Rupatadine fumarate	1.2–4.9	Microparticles	(64)
Aquacoat® ECD	-----		3.6 ± 0.5		
Surelease® E-7-19040	-----		3.2 ± 1.1		
Aquacoat® ECD	-----	Rupatadine fumarate	3.6 ± 1.5		
Surelease® E-7-19040	-----		3.2 ± 1.1	Orodispersible minitablets	(38)
Kollicoat® SmartSeal 30 D	-----	Cetirizine	13.1–64.5§	Microparticles	(61)
-----	Kollicoat® Protect		5.6–50.7§		
Kollicoat® SmartSeal 30 D	-----	Diphenhydramine HCl Ibuprofen lysine Phenylephrine HCl	2.2–2.9	Microparticles	(92)
Eudragit® E PO ReadyMix	-----				

TEOS Acid hydrolyzed tetraethoxysilane, *n.a.* Not available

*Range estimated from SEM images presented

**Reported for optimized formulation

¶Mean or median value

†Polymer was dissolved in 96% ethanol

‡Polymer was dissolved in organic solvent(s)

§Range reported based on optical microscopy

Eudragit® RL 30 D) (Fig. 4). The release studies were related to agglomerates and microparticles (40, 46, 51, 62, 66, 68, 73), matrix tablets (55, 67, 74, 75), or to both of them (37, 49, 63, 65). *In vivo* studies have also been performed to support the *in vitro* results (37, 46, 66).

Kasashima *et al*. (46) performed a proof-of-concept study comparing co-spray dried microparticles of a drug with drug solution. They encapsulated mirabegron lauryl sulfate (LS) salt/complex in ethylcellulose by co-spray drying with Aquacoat® ECD aiming for a sustained-release oral suspension.

The orally administered co-spray dried microparticles had lower C_{max} and reduced peak-trough fluctuation compared to mirabegron solution and gave slower release than the non-encapsulated lauryl sulfate salt/complex. Additional *in vivo* studies in dogs under fasted conditions confirmed the sustained-release profile of the oral suspension.

Further studies investigated the effects of formulation and process variables on release. The formulation parameters reported to impact prolonged release were the type of APD (49, 51, 73), drug solubility (44), addition and percentage of co-excipients (66–68, 74), and P:D ratio (44, 46, 49, 55, 74, 75). The important process parameter was the feed flow rate (73). Particle size also affected drug release from the uncompacted microparticles (73).

Comparing the release profiles of diclofenac sodium from different APDs, Rattes and Oliveira (73) found that release from microparticles co-spray dried with Surelease® was slightly slower than Eudragit® RS 30 D. Furthermore, microparticles obtained at high feeding rate gave significantly slower release due to the larger size of the resulting microparticles or lower specific surface area. The inlet air temperature did not have an effect on the drug release.

Kulkarni *et al*. (51) compared the effect of three APDs (Eudragit® RS 30 D, Eudragit® RL 30 D, and Surelease®) on the release control of the water-soluble metformin hydrochloride incorporated into spray dried microparticles. Prolongation and best control was achieved by co-spray drying with Eudragit® RS 30 D at high P:D ratio (11:1).

Al-Zoubi *et al*. (49) compared the release of buspirone HCl from agglomerated particles obtained by co-spray drying with Kollicoat® SR 30 D or Eudragit® RS 30 D. The release from non-compacted agglomerates decreased with increasing P:D ratio but the APDs had no significant influence. However, the release from matrix-tablets of particles co-spray dried with Kollicoat® SR 30 D was slower than those with Eudragit® RS 30 D, which was ascribed to the plasticity of the PVP present in the former APD and its binding action (49).

Hydrophilic additives such as lactose (68, 74) and pectin (66) increased drug release rate from APD-based matrix dosage forms. Lactose and silica nanoparticles were used by Liu *et al*. (68) as additives to Eudragit® NE 30 D to modify the release of vitamin B12. Lactose distributed itself homogeneously in the matrix resulting in faster release due to enhanced polymeric matrix swelling, whereas colloidal silica remained at the microparticle surface causing erosion and initial burst release. Also, diclofenac sodium/Eudragit® NE 30 D co-spray dried microparticles were prepared. Compacted matrices at polymer over drug 1.2:1 ratio gave prolonged release. Addition of silicon dioxide at about one-third of polymer reduced tackiness and improved yield of the spray-dried product but did not affect the drug release from tablets (55). Furthermore, addition of 5–10%PVP as co-excipient decreased the release rate of theophylline from matrix tablets prepared from microparticles of the drug co-spray dried with Surelease®. This was ascribed to the reduced porosity due to filling of pores with polymer leading to enhanced interparticle bonding, mechanical strength, and ultimately lower diffusion rate (74).

Al-Zoubi *et al*. studied co-spray drying of diltiazem HCl with Kollicoat® SR 30 D (67). They compared compacted matrices from co-spray dried products (CSD) and physical mixtures with Kollidon® SR (PM). Drug release was slower from CSD than PM matrices. This was ascribed to the lower PVP content in Kollicoat® SR 30 D dispersion compared to Kollidon® SR powder (9% and 19%, respectively) and was verified by dissolving extra PVP in the feed liquid to

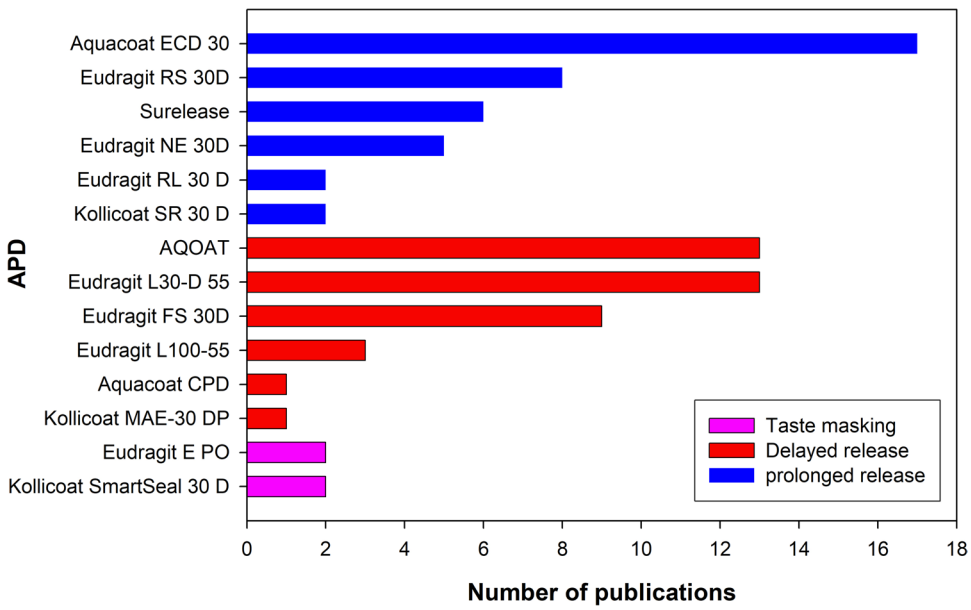

Fig. 4 Distribution by number of APDs in the selected articles for this review

make a spray dried product with the same PVP content as the PM. Then, the enriched Kollicoat SR 30 D feed and the PM showed similar release. From a manufacturing aspect, the co-spray dried particles compressed better than PM exhibiting higher work of compaction and tablet strength. Moreover, addition of PVP K30 to microparticles increased the drug release from the compacted powder mixture.

Nova *et al*. (66) developed L-alanyl-L-glutamine (AGP) sustained-release microparticles by co-spray drying with Surelease® and pectin. Increasing pectin content improved the *in vitro* release and the same effect had an increase in the pH of the dissolution medium. This result was also confirmed by *in vivo* studies which demonstrated slower release of AGP from microparticles with higher Surelease to pectin ratio. Thus, by adjusting the Surelease to pectin ratio, the desired *in vitro* release and *in vivo* activity can be achieved. From the above-cited works, it can be concluded that deliberate use of selected additives at the right proportions can provide fine-tuning of drug release profiles.

Garekani *et al*. (63, 65) compared microparticles of theophylline co-spray dried with APDs of Eudragit® RS 30 D (65) and Surelease (63), with ethanolic (96%) drug solutions co-spray dried with the same polymers. The release from microparticles obtained from organic solutions or from their compacted matrices was slower compared to release from APD-based microparticles or their compacted matrices. Also, the release was slower from matrices than from microparticles (63, 65).

Although in most studies co-spray dried microparticles are processed into matrix tablets, some studies reported different final dosage forms. Kasashima *et al*. (46) prepared a sustained-release oral suspension of mirabegron lauryl sulfate (LS) salt/complex. Wei *et al*. (37) prepared co-spray dried ketoprofen with Eudragit® RS 30 D, starch 1500®, and PEG 6000. The obtained microparticles were formulated into oral disintegrating sustained-release tablets which provided sustained release of ketoprofen for about 24 h after an initial rapid (30 s) disintegration. The sustained-release action was also confirmed by *in vivo* studies in beagles and there was *in vitro-in vivo* correlation. Arici *et al*. (40) prepared naproxen-ethyl cellulose microparticles by co-spray drying with Aquacoat® ECD. The microparticles were fixed onto textile fabrics to develop a transdermal drug delivery system. *In vitro* drug release exhibited biphasic profile with initial burst followed by very slow release. Skin permeation followed near zero-order release kinetics.

Results of several studies showed that the release profiles of compacted matrices followed Fickian diffusion (67, 74, 75), which is common for insoluble polymer matrices where matrix erosion is negligible. Addition of hydrophilic excipient favored shift towards zero-order kinetics (55, 67). On the other hand, release from microparticles was reported to follow anomalous transport (66).

Delayed Release

Co-spray drying of drugs with APDs has been employed to prepare delayed-release formulations, mainly with the aim of targeting the distal part of the GIT. These formulations offer improved efficacy and reduced side effects over conventional delivery systems. The number of articles published in this area is rather low and only ten articles are included in Table III that matched the searching criteria for delayed release. From these, six were exclusively devoted to targeting specific parts of the GIT, and two had a dual purpose, providing targeting besides sustained release. Two other studies addressed only process optimization. Polymers used exclusively for targeting were Eudragit® L 30 D 55 which dissolves above pH 5.5 and targets the duodenum, Eudragit® L 30 D which dissolves above pH 6.0 and targets the jejunum, and Eudragit® FS 30 D which dissolves above pH 7.0 and targets the ileum and colon. Co-spray dried systems for dual sustained/targeted action combine matrix-forming excipients (Eudragit® RS 30 D, NE 30 D, silicates) with enteric and pH-sensitive methacrylic polymers (Eudragit® L 30 D 55, L 30 D, FS 30 D, Eudragit® S100). Papers addressing the use of enteric APDs for gastroprotection of biological APIs are discussed in the next section.

Takeuchi *et al*. (75) prepared enteric and sustained-release theophylline tablets by co-spray drying with Eudragit® L 30 D, L100-55, and E 30 D. They reported complete enteric release with polymer to drug ratio of 3:1 using Eudragit® L 30 D and L100-55. Also, tablets formulated with 2–40% E 30 D showed sustained drug release which was independent of the pH of the dissolution media. The controlled release function was attributed to the homogeneous polymeric matrix formed by spray drying and to the subsequent compression.

Lin and Kao (76) prepared tablets of enteric coated microcapsules of sodium diclofenac by co-spray drying with Eudragit® L 30 D followed by mixing with microcrystalline cellulose (Neocel®) and pregelatinized starch (flo-starch®). The flowing properties of the spray-dried product were improved by mixing with Neocel® and flo-starch®. Both the spray-dried powder and the corresponding tablets exhibited enteric release.

Colomé *et al*. (71) prepared pantoprazole-loaded microparticles by co-spray drying with Eudragit® S100, Eudragit® RS 30 D, or a Eudragit® S100/RS 30 D blend. Microparticles containing the enteric Eudragit® S100 in combination with the APD of Eudragit® RS 30 D provided the best gastroprotection. *In vivo* tests showed that the orally administered microparticles were able to protect the rat stomach against ulceration induced by ethanol.

Liu *et al*. (72) designed uniform microencapsulates *via* microfluidic co-spray drying of vitamin B12 with Eudragit® L 30 D 55. The effect of incorporating in the formulations

acid hydrolyzed tetraethoxysilane (TEOS) and Eudragit® NE 30 D as water-based network-forming materials on the pH-responsiveness and controlled release enteric microparticles was studied. Addition of TEOS yielded a rigid porous interpenetrating network, while incorporation of Eudragit® NE formed a flexible dense entangled polymer network, which altered the swelling behavior of Eudragit® L polymer and modified the release rates. Overall, uniform microparticles with almost completely encapsulated active ingredient and tailored release properties could be made.

Blanco-García *et al*. (70) developed and evaluated *in vitro* a microparticulate system of curcumin (CRM) intended to heal inflammations in the intestine caused by inflammatory bowel diseases. Microspheres based on zein (ZN) and methyl vinyl ether and maleic acid copolymer (PVMMA) were prepared by co-spray drying and coated with Eudragit® FS 30 D in a second spray drying process. FTIR and DSC studies suggested the presence of a-helix structure for ZN and strong interaction between the components. The stabilization of a-helix by PVMMA or CRM was attributed to hydrogen bonding. Although encapsulation efficiency (EE) of CRM was high (89%) for ZN/PVMMA microspheres, coating with Eudragit® led to an EE decrease of 62%. Coating retained 20% of CRM within 6 h of release, despite a strong initial burst release. The anti-inflammatory activity of CRM-loaded microspheres was also studied using cell line RAW 264.7 and was found to inhibit significantly the pro-inflammatory cytokines (TNFa, IL-1b, NOS2, COX-2) in macrophages stimulated with lipopolysaccharide. In conclusion, the ZN/PVMMA microspheres present a serious alternative for delivering CRM to the intestine.

Shah *et al*. (11) reported formulation of co-spray dried microparticles of the pH-sensitive glutathione (GSH) and S-nitrosoglutathione (GSNO) with Eudragit® FS 30 D. Dissolution tests showed fast release at basic pH 7.4, sustained release at pH 6.8, but no release at acidic pHs of 1.2, 3.0, and 6.0. The optimized process parameters for particle size and shape were inlet temperature 120°C, pump rate 5 mL/min, and air flow 100%. Therefore, using Eudragit® FS 30 D as a gastroresistant rate-controlling polymer, GSNO could be targeted to the colon for further studies in the treatment of inflammatory bowel diseases including Crohn's disease.

Ostróżka-Cieślik *et al*. (77) analyzed the physical state of the drug and morphology of microspheres obtained by co-spray drying furosemide (FS) with Eudragit® L30 D 55. The optimized parameters were inlet temperature 140°C, pump rate 10%, and aspiration 80%. The release from microspheres was two steps. After 2 h in 0.1 HCl, only 28.68% FS was released, while the remaining drug was released within 30 min in pH 6.8 buffer.

Nining *et al*. (78) encapsulated allicin-rich extract phytosome (ArE-Ps) in Eudragit L 30D-55 by co-spray drying at three ArE-Ps:polymer ratios (1:1, 1:1.5, and 1:2). The three formulations showed no allicin release in acidic medium (pH 1.2 for 480 min), whereas in phosphate buffer, release reached between 55.23 and 61.26% after 45 min confirming enteric release of microparticles.

Protection and Delivery of Biological Drugs

Published research of co-spray dried biologicals with APDs is principally oriented towards release requirements. So far, contrary to previously described applications of the APDs and despite the considerable amount of research that has been done, there are no commercial APD products aimed specifically for the protection of orally administered biological drugs such as vaccines, proteins, and enzymes. Of great importance for their long-term storage is that proteinous products are moisture-free. Freeze drying has been applied for this purpose, but it is time and energy consuming as it requires a final break-down step of the aggregated freeze-dried mass into powder (89). Moreover, denaturing of biologicals has been reported (100, 101). For these reasons, spray drying could be an alternative for the production of moisture-free biologicals with good stability (100).

Most studies that matched the search criteria for co-spray drying APDs with biologicals (Table III) deal with the *in vitro* release, maintenance of biological activity, and *in vivo* performance. Less attention has been paid to the effects of processing parameters on product characteristics (9, 79, 91). In some studies, the process is not fully described.

Regarding the route of administration, the majority of the studies on biologicals in Table III (15 out of 22) report formulations of vaccine powders for oral administration and the primary function of APDs was to prepare gastroresistant microparticles and provide enteric release. For this reason, most studies utilized HPMCAS together with ethylcellulose (9 out of 22 studies) or with methacrylic acid copolymer (Eudragit® FS30D/ L30D-55) (5 out of 22 studies). Three studies (41, 42, 88) concern dermal application.

Preservation of the Activity of Orally Administered Vaccines Several studies have sought the co-spray drying with APDs to preserve the activity of vaccines against various infectious pathogens. Ano *et al*. (5) prepared a novel oral microencapsulated vaccine by spray-drying inactivated *Vibrio cholerae* (VC) with the methacrylic copolymers Eudragit® L 30 D 55, FS 30 D, or their blend (1:1) at bacteria/polymer ratio 1:10. The produced microparticles had a mean particle size of around 3.0 μm and became more irregular and shriveled with increasing temperature. *In vitro* release studies showed that after 2 h at pH 1.2, less than 5% of bacteria released, whereas after 24 h at pH 6.8, Eudragit® L 30 D 55 microparticles released 86% of bacteria, and FS 30 D microparticles released less than 30%. Rats inoculated with the Eudragit® L30D-55 microparticles exhibited

vibriocidal antibody titers reaching up to approximately 98% of the lipopolysaccharide (LPS) antigenicity of cellular standard, whereas for Eudragit® FS 30 D microparticles antigenicity was not maintained to the same extent (54–68% of the LPS antigenicity of cellular standard). Therefore, microencapsulation of inactivated VC by co-spray drying with Eudragit® L30D-55 was proposed for the formulation of controlled release oral vaccine.

In a further study by the same research group, Pastor *et al*. (6) prepared an oral vaccine of gastro-resistant VC microparticles by co-spray drying with Eudragit® L 30 D 55 alone or together with the mucoadhesives sodium alginate or Carbopol® (0.1% w/v) at polymer/bacteria ratio 10:1. The particle size varied from 7 to 9 μm and the combination with Carbopol gave even smaller particles. Antigenicity of the encapsulated VC was retained when Eudragit® L 30 D 55 was used alone or together with alginate, but it was reduced to 25% when Carbopol® was added. Stability study (25°C/60% RH for12 months and 30°C/75% RH for 6 months) showed a decrease in particle size, for both the Eudragit® and Eudragit®/alginate combination. However, gastroresistance was retained. *In vivo* experiments showed that the Eudragit®/alginate/*V. cholerae* microparticles induced stronger immune responses compared to free *V*C. Therefore, microencapsulation of VC by co-spray drying was proposed for a cold-chain free and effective oral vaccine. The toxicity of microspheres was investigated in another study by the same research group (7). Animals that received vaccination grew healthy. Hematological parameters, food and water intake, and body weight gain remained within physiological ranges, with no treatment-related differences or pathological anatomic alteration. Thus, VC-loaded MPs and VC-loaded alginate MPs have proved to be safe and effective in the assessed conditions.

Pastor *et al*. (8) also prepared an oral vaccine of gastro-resistant microparticles of VC by spray drying with cellulose acetate phthalate alone or together with alginate (0.1% w/v) at polymer/bacteria ratio 10:1. The resulting microparticles had 6-μm mean particle size and drug content 8.16–8.64%. Antigenicity was maintained and enteric release was achieved. *In vivo* study showed that alginate microparticles evoked immune responses similar to free VC. They concluded that the developed spray dried VC with cellulose acetate phthalate/alginate is a promising step towards a powder product for cholera vaccination.

Liao *et al*. (9) prepared oral vaccine microparticles of formalin-inactivated *A. pleuropneumoniae* antigens by co-spray drying with Aquacoat® ECD and AQOAT® separately or in combination (formula AQ6-AP). Enteric release was confirmed by *in vitro* dissolution, which showed 95% release of the *A. pleuropneumoniae* protein within 3 h at pH 7, but no release at pH 1.5. The release rate of proteins from the microparticles was pH dependent not only for the AQ6-AP formulation but also when antigens of *A. pleuropneumoniae* were replaced with porcine serum in the formulation. Scanning electron microscopy revealed that AQ6-AP microspheres became porous at neutral pH implying that *A. pleuropneumoniae* antigens were entrapped and protected in the AQ6 microspheres under acidic conditions. In a mouse model, oral immunization with AQ6-AP microspheres evoked systemic IgG and mucosal IgA responses against *A. pleuropneumoniae* antigens. In another *in vivo* study by the same research group (10), the percentage of pig survival ratio, lung lesion areas, and microscopic examinations indicated that the vaccine microparticles provided more protection than intramuscularly vaccinated pigs with AP-1 aluminum vaccine.

Lin *et al*. (80) prepared an oral vaccine of *Mycoplasma hyopneumoniae* antigens by co-spray drying with Eudragit® L30D-55. During the 3-h *in vitro* dissolution test, the microspheres released > 93% protein at pH 7.4, but almost none at pH 1.2. An SPF-swine model was used to evaluate the vaccination efficacy after oral administration and to evaluate related immune responses. The vaccinated groups' mean lesion score was significantly lower than the nonvaccinated groups. The study suggests that the developed oral vaccine microspheres prepared by co-spray drying provided effective protection against *M. hyopneumoniae* infection.

Other studies have also sought the co-spray drying with APDs for the preparation of vaccine to various types of cancers. Lai and D' Souza (81) prepared an oral vaccine of bovine serum albumin microparticles by spray drying with a blend of ethylcellulose Aquacoat® ECD and AQOAT® at drug/polymer ratio 4:1, for the treatment of melanoma. The microparticles demonstrated desirable particle size (2.55–5.50 μm), production yield (> 58%), and zeta potential (−40.63 to −51.22 mV). Furthermore, DSC and FTIR studies showed no significant degradation in microencapsulated extracellular antigen (ECA). In the challenge and efficacy studies, the oral vaccine group exhibited 25% greater survival compared to control.

Chablani *et al*. (82) prepared an oral vaccine of 4T07 antigen–loaded microparticles by spray drying with a blend of β-cyclodextrin, Aquacoat® ECD, and HMPCAS for breast cancer. The vaccine microparticles had an average size of 1.5 μm and showed gastro-resistance and sustained-release profile. Vaccinated animals showed a significant increase in serum antibody titers and number of CD4+ cells, and tumor challenge studies showed that vaccinated animals developed significantly smaller tumors. Therefore, the developed microparticles for oral breast cancer vaccination were effective in providing protective immune response in the murine model.

Tawde *et al*. (84) prepared an oral vaccine of mouse serum albumin microparticles by spray drying with a blend of AQOAT® and Eudragit® FS 30 D for the

treatment of ovarian cancer. The microparticles were targeted for uptake by the microfold cell (M-cell) in Peyer's patches of the small intestine using M-cell targeting ligand, *Aleuria aurantia* lectin. Recombinant murine interleukins, IL-2 and IL-12, were added to the vaccine formulation for further enhancement of the immune response. The produced particles had 1.58-μm mean diameter and 12.48-mV surface charge. Vaccinated mice showed around six-fold retardation of tumor growth compared to non-vaccinated animals after 3 weeks of tumor challenge. The serum IgG antibody levels, CD8+ T-cell, CD4+ T-cell, and B-cell populations in different lymphatic organs were elevated in the vaccinated mice. Therefore, orally administered whole cell lysate vaccine microparticles prepared by spray drying could trigger humoral and cellular immune responses.

Bhomwik *et al*. (85) prepared an oral vaccine of microparticles containing plasmid DNA encoding hepatitis-B surface antigen (HBsAg) by spray drying with a blend of bovine serum albumin (BSA), AQOAT®, and Eudragit® FS 30 D. The microparticles could protect HBsAg DNA from nuclease degradation. Oral immunization with the plasmidic DNA/HBsAg microparticles gave significantly higher IgA and IgG titer levels after 9 and 34 weeks respectively. Therefore, augmentation of both cellular and humoral immune responses was observed for prolonged periods after immunization with the developed microparticles.

Alkakotkar *et al*. (86) prepared an oral vaccine of fluorescein isothiocyanate albumin–loaded microparticles for the treatment of prostate cancer by spray drying with AQOAT® and Eudragit® FS 30 D. The serum IgG levels of vaccinated animals were higher compared to those of controls. Moreover, the tumor growth was retarded significantly in the vaccinated mice.

Chablani *et al*. (87) prepared an oral vaccine of albumin microparticles by spray drying with Eudragit® FS 30 D and HPMCAS at different polymer ratios. The produced microparticles had average size of 1.51 μm and surface charge of 15.7 mV. Moreover, they provided prolonged release over a period of 8 h, which ensures M-cell uptake of intact particles by antigen. This was further supported by *in vivo* experiments, which proved particle uptake in Peyer's patches of the small intestine during an 8-h observation. Thus, the microparticles can be used as a vehicle for efficient oral vaccine delivery.

D' Souza *et al*. (91) prepared an oral vaccine of albumin-loaded microparticles by co-spray drying with a blend of APDs at drug/ethylcellulose/HPMCAS ratios 14:3:1. Oral vaccination effectively protected mice from subcutaneously injected tumor cells. They reported that ligand-loaded microparticles may have potential for targeting antigens to M-cells.

Delivery of Vaccines Trans- and Intra-dermally Bhowmik *et al*. (88) prepared a novel microparticulate transdermal vaccine by co-spray drying bovine serum albumin (BSA) with a blend of Aquacoat® ECD and AQOAT® (3:1) at a polymer/drug ratio 1:4, for the treatment of melanoma. Smooth and spherical microparticles with size around 1 μm were produced. After transdermal administration, the microparticles were taken up by antigen-presenting cells which demonstrated a strong 930 μg/mL IgG titer in serum samples. The immunogenicity of vaccine was increased by incorporating the antigen into an albumin matrix of around 0.63–1.4 μm particle size.

Akalkotkar *et al*. (41) developed a transdermal and subcutaneous vaccine of microparticles of mouse serum albumin by spray drying with a AQOAT®/Eudragit® FS 30 D blend at polymer/drug ratio 1:1 for the treatment of prostate cancer. They reported significant increase of humoral responses determined by the IgG titers and of cellular responses determined by the T- and B-cells in spleen samples and delayed tumor growth. Transdermally administered vaccine microparticles induced only a Th2-mediated immune response, whereas subcutaneous administration induced a mixed Th1 and Th2 response. The developed microparticles present a promising alternative for prostate cancer treatment.

Chablani *et al*. (42) prepared a vaccine of 4T07 antigen–loaded microparticles by spray drying with a blend of β-cyclodextrin/Aquacoat® ECD/AQOAT® for breast cancer by administration through the skin. Microparticles of average size of 1.5 μm were produced. The particulate vaccine was administered intradermally *via* commercially available metal microneedles. Results showed that microneedles created aqueous conduits of 50 ± 10 μm to deliver the microparticulate vaccine to the skin layers. Further *in vivo* comparison of immune response showed a significantly higher concentration of serum IgG, IgG2a, and B- and T-cell (CD4+ and CD8+) populations in the vaccinated compared to control animals. Upon challenge with live murine breast cancer cells, the vaccinated animals showed five times greater tumor suppression than the control, confirming immune response activation and protection.

Preservation of Activity of Orally Admisistered Peptides *via* Gastroprotection D'Souza *et al*. (47) developed insulin microparticles for oral administration by spray drying with β-cyclodextrin and a blend of Aquacoat® ECD/AQOAT® at polymer/drug ratio 100:1. They studied the hypoglycemic effect of the microparticles in diabetic rats after oral administration. Insulin-loaded microparticles had a mean size of 0.8 ± 0.25 μm, zeta potential of 3.57 + 0.62 mV, and insulin of 94.9 ± 2.77%. In cytotoxic analysis of insulin formulation, RAW macrophage cells showed more than 80% viability after 24-h incubation with insulin and blank microparticles. An *in vitro* study showed no significant release

in gastric fluid, followed by only 50% release in intestinal fluid in the first 8 h. This was correlated with the *in vivo* data where 50% glucose inhibition occurred 8 h after oral administration in diabetic rats. Therefore, the developed oral insulin microparticles were able to reduce glucose levels and might be considered for oral administration, as an alternative to subcutaneous injection.

Haj-Ahmad *et al*. (89) prepared lysozyme microparticles by spray drying with either copovidone or Kollicoat® MAE 30 DP and compared their stability and biological activity with freeze-dried particles. Copovidone successfully preserved integrity and biological activity before and after storage in both spray-dried and freeze-dried forms, especially when added at high concentration. Furthermore, it gave smooth and spherical spray dried lysozyme microparticles which were smaller than those prepared with Kollicoat MAE 30DP. However, copovidone reduced the production yield due to the formation of fine particles, which were exhausted by the aspirator.

Bejugam *et al*. (90) prepared enteric coated bromophenol blue–loaded albumin microspheres by co-spray drying with Eudragit® L100-55. First, microspheres were prepared by cross-linking bromophenol blue with albumin using glutaraldehyde (25% in water) at different concentrations and time periods. Then a suspension of the optimal microspheres was spray-dried on a benchtop spray-dryer to obtain enteric coated microspheres. Coating efficiency was tested in simulated gastric fluid. Compared to uncoated microspheres, the cumulative drug amount released in gastric fluid after 3 h from the coated ones was significantly lower, indicating effective surface coating.

Shastri *et al*. (91) developed enteric albumin-loaded microparticles by co-spray drying with Eudragit® FS 30 D, L100, and S100, which in a second step were co-spray dried with HPMC and chitosan. The optimal formulation contained 70% Eudragit® S100, 25% HPMC, and 5% chitosan and showed < 5% protein release at pH 1.2. After 6 h at pH 6.8, the selected microparticles released about 25% less protein than those containing only Eudragit® S100. Addition of HPMC in the formulation matrix resulted in production yield reduction from 77.99 to 71.56% due to polymer adhesiveness. Better gastroprotection was obtained with Eudragit® S100, whereas the combined use of HPMC with Eudragit® S100 promoted sustained release.

Taste Masking

Taste masking of bitter drugs incorporated into polymeric particles by spray drying is an important application of APDs. However, only seven papers have matched the searching criteria for taste masking and only two of them used APDs dedicated for taste masking, while the others used APDs dedicated for DR or PR action. To achieve taste masking of a pharmaceutical product is a complex task. Besides the type of APD polymer and liquid feed (organic solution or aqueous dispersion), spray drying process variables such as drying temperature, feeding rate, polymer content, and atomizer rotation speed that influence drug encapsulation also influence taste masking efficacy.

For drugs that are insoluble in the feed dispersion, their particle size was found to affect the characteristics of the spray-dried particles and the effectiveness of taste masking. As it was shown by Mizumoto *et al*. (35), uniform round shape and fine particle size distribution of the added drug are important. Incomplete coating of famotidine co-spray dried with ethylcellulose-Eudragit® NE 30 D mix resulted when drug was added as needle-shaped crystals with broad size distribution between 3.4 and 344 μm. Conversely, when pulverized drug was used, excellent taste masking was achieved (35). Therefore, uniform and complete coating of the bitter drug particles and hence prevention of contact with taste buds is a prerequisite for the achievement of taste masking (45).

Several other parameters including polymer/plasticizer ratio, atomizer rotation speed, solid concentration in the spray suspension, and amount of added coating require optimization to obtain microparticles with satisfactory characteristics. While some factors such as atomizer rotation speed could be optimized and fixed independently, other factors could not. For the ethylcellulose-Eudragit® NE 30 D mix, polymer/plasticizer ratio of 6:4, 50% solid content, and 50% of coating were found to be optimal. On the other hand, for ethylcellulose-triacetin, the optimized parameters were 8:2 ratio, 40% solid content, and 56% coating material (35).

Regarding the type of feed liquid, two striking examples have been reported. Brniak and coworkers (39) compared an aqueous dispersion of Eudragit® E PO and a solution of Eudragit® E 100 in acetone-isopropanol solution (1:2) as feeding polymer liquids for masking prednisolone's taste. Fine (mean diameter 4.5 μm) and spherical spray-dried microparticles were produced from the organic Eudragit® E 100 solution that imparted satisfactory taste masking. Conversely, irregular agglomerates between 5 and 60 μm were produced with the aqueous dispersion of Eudragit® E PO failing taste masking.

Wasilewska and coworkers (64) compared organic solutions and aqueous dispersions of ethyl cellulose for taste masking and release of the bitter drug rupatadine fumarate from co-spray dried microparticles. In the first part of their work, drug was dissolved in a solution of ethyl cellulose in ethanol (96% v/v) and mannitol was added as a flavor enhancer. The levels of five factors—inlet temperature, spray rate, mannitol concentration, polymer concentration,

and polymer/drug ratio—were optimized for maximum production yield and encapsulation efficiency, minimum moisture content, uniform particle size distribution, and spherical particle shape. Taste masking efficacy of the microparticles was varied from slightly bitter to very bitter. Electron microscopy revealed that the microparticles were collapsed, wrinkled aggregates releasing > 30% drug in half a minute. In the second part of the work, two microparticle formulations were prepared using dispersions of drug in either Surelease® or Aquacoat® ethylcellulose APDs. The particle size of the microparticles was similar with that from the drug/ethylcellulose organic solution, but the size distribution was uniform, particle shape was smooth and spherical, and bitterness was eradicated as confirmed by electronic tongue. About 6% and 30% drug was released after 3 min from the Surelease® and Aquacoat® microparticles, respectively (64).

In another study, spray dried microparticles of rupatadine fumarate with aqueous ethylcellulose dispersions were processed into orodispersible minitablets (ODMT) (38). Taste masking of microparticles' ODMT formulations was compared with ODMT formulations containing unprocessed drug. Evaluation was performed by human taste panel, *in vitro* drug dissolution, and "electronic tongue". All three methods confirmed that the developed formulations provided satisfactory taste masking rate and in particular drug formulation prepared with Pearlitol® Flash and Surelease® microparticles had the lowest bitterness score.

Wesoły *et al*. (61) used co-spray drying to prepare microparticles of the bitter drug cetirizine with two coating agents either Kollicoat SmartSeal 30 D or Kollicoat Protect for taste masking. Taste masking efficacy was found to be dependent on the type of microencapsulating polymer used and the polymer/drug ratio. Assessment of bitterness was made by a human taste panel and chemical images recorded by an electronic tongue. Good correlation was found between the two methods. For the Kollicoat® SmartSeal 30 D microparticles, about 40 to 60% drug was released in the first minute. Kollicoat® Protect microparticles gave even faster release of about 55–80% in the first minute (61).

Muoka *et al*. (92) evaluated the taste masking effectiveness of Kollicoat Smartseal® 30 D and Eudragit® E PO ReadyMix on three bitter active ingredients: diphenhydramine HCl, ibuprofen lysine, and phenylephrine HCl. The drugs were co-spray dried with the APDs at 10–20% loading and taste was evaluated *in vivo* using human test panel. Noticeable reduction of drug bitterness was found at all loadings compared to the unprocessed drug substances.

CONCLUSION

Aqueous polymer dispersions offer processing advantages related to low viscosity and shorter processing time. The approach of co-spray drying with APDs has received increasing interest in the last decade as an alternative to conventional coating for modified-release drug delivery, taste masking, and delivery of biologicals. Different APDs have been investigated offering different functionalities. The process and formulation parameters can be widely varied and optimized for better product yield and properties. The obtained microparticles can be used "as is" or formulated into different dosage forms such as matrix tablets, oral disintegration tablets, transdermal patches, and injections.

Author Contribution Nizar Al-Zoubi: conceptualization, methodology and investigation, data curation, writing—original draft preparation, writing—review and editing, visualization, project administration. Ioannis Partheniadis: writing—original draft preparation, writing—review and editing. Ahmad Aljaberi: writing—original draft preparation, writing—review and editing. Ioannis Nikolakakis: writing—original draft preparation, writing—review and editing.

Declarations

Conflict of Interest The authors declare no competing interests.

References

1. International Community of Harmonization (ICH). Impurities: Guideline for Residual Solvents Q3C (R6). Int Conf Harmon Tech Requir Regist Pharm Hum Use. 2011;44:29.
2. Yang Z, Craig DQM. Monitoring film coalescence from aqueous polymeric dispersions using atomic force microscopy: surface topographic and nano-adhesion studies. Asian J Pharm Sci. 2020;15:104–11.
3. Lecomte F, Siepmann J, Walther M, MacRae RJ, Bodmeier R. Polymer blends used for the coating of multiparticulates: comparison of aqueous and organic coating techniques. Pharm Res. 2004;21:882–90.
4. Felton LA, Porter SC. An update on pharmaceutical film coating for drug delivery. Expert Opin Drug Deliv. 2013;10:421–35.
5. Año G, Esquisabel A, Pastor M, Talavera A, Cedré B, Fernández S, *et al*. A new oral vaccine candidate based on the microencapsulation by spray-drying of inactivated Vibrio cholerae. Vaccine. 2011;29:5758–64.
6. Pastor M, Esquisabel A, Talavera A, Año G, Fernández S, Cedré B, *et al*. An approach to a cold chain free oral cholera vaccine: in vitro and in vivo characterization of Vibrio cholerae gastroresistant microparticles. Int J Pharm. 2013;448:247–58.
7. López Y, Pastor M, Infante JF, Díaz D, Oliva R, Fernández S, *et al*. Repeated dose toxicity study of Vibrio cholerae-loaded gastro-resistant microparticles. J Microencapsul. 2014;31:86–92.
8. Pastor M, Esquisabel A, Marquínez I, Talavera A, Pedraz JL. Cellulose acetate phthalate microparticles containing Vibrio cholerae: steps toward an oral cholera vaccine. J Drug Target. 2014;22:478–87.

9. Liao CW, Cheng IC, Yeh KS, Lin FY, Weng CN. Release characteristics of microspheres prepared by co-spray drying Actinobacillus pleuropneumoniae antigens and aqueous ethyl-cellulose dispersion. J Microencapsul. 2001;18:285–97.
10. Liao CW, Chiou HY, Yeh KS, Chen JR, Weng CN. Oral immunization using formalin-inactivated Actinobacillus pleuropneumoniae antigens entrapped in microspheres with aqueous dispersion polymers prepared using a co-spray drying process. Prev Vet Med. 2003;61:1–15.
11. Shah SU, Socha M, Sejil C, Gibaud S. Spray-dried microparticles of glutathione and S-nitrosoglutathione based on Eudragit® FS 30D polymer. Ann Pharm Françaises. Académie Nationale de Pharmacie; 2017;75:95–104.
12. Ahmed AR, Mota JP, Shahba AA-W, Irfan M. Aqueous polymeric coatings: new opportunities in drug delivery systems [Internet]. Drug Deliv. Asp. Elsevier Inc.; 2020. Available from: https://doi.org/10.1016/B978-0-12-821222-6.00003-8.
13. Miller DA, McGinity JW. Aqueous polymeric film coating. Pharm Dos Forms Tablets, Third Ed Vol 1 Unit Oper Mech Prop. 2008.
14. Skalsky B, Petereit H-U. Chemistry and application properties of poly(meth)acrylate systems. In: Felton L, editor. Aqueous Polym Coatings Pharm Dos Forms. 4th ed. New York: CRC Press; 2017. p. 207–46.
15. Sheskey P, Cook W, Cable C, editors. Handbook of pharmaceutical excipients. 8th ed. Washington: Pharmceutical Press; 2017.
16. Aquacoat® [Internet]. [cited 2021 Mar 12]. Available from: https://www.pharma.dupont.com/pharmaceutical-brands/aquacoatr.html
17. Colorcon® | Surelease® aqueous ethylcellulose dispersions [Internet]. [cited 2021 Mar 12]. Available from: https://www.colorcon.com/products-formulation/all-products/film-coatings/sustained-release/surelease
18. EUDRAGIT® Functional Polymers for Sustained Release - Evonik Industries [Internet]. [cited 2021 Mar 12]. Available from: https://healthcare.evonik.com/en/pharmaceuticals/oral-drug-delivery/oral-excipients/eudragit-portfolio/sustained-release
19. Dvořácková K, Kaledaite R, Gajdziok J, Rabišková M, Bajerová M, Muselík J, *et al*. The development of Eudragit® NM-based controlled-release matrix tablets. Med. 2012;48:28.
20. Kollicoat® SR 30 D [Internet]. [cited 2021 Mar 12]. Available from: https://pharmaceutical.basf.com/global/en/drug-formulation/products/kollicoat-sr-30-d.html
21. The Global Market Leader for Enteric Release Coatings - Evonik Industries [Internet]. [cited 2021 Mar 12]. Available from: https://healthcare.evonik.com/en/pharmaceuticals/oral-drug-delivery/oral-excipients/eudragit-portfolio/delayed-release
22. Evonik launches EUDRAGIT® FL 30 D-55, an advanced combination polymer that sets a new benchmark for enteric coatings - Evonik Industries [Internet]. [cited 2021 Apr 2]. Available from: https://corporate.evonik.com/en/media/press-releases/nutrition-and-care/evonik-launches-eudragit-fl-30-d-55-an-advanced-combination-polymer-that-sets-a-new-benchmark-for-en-106222.html
23. Colorcon® | Acryl-EZE® Aqueous Acrylic Enteric System [Internet]. [cited 2021 Mar 12]. Available from: https://www.colorcon.com/products-formulation/all-products/film-coatings/enteric-release/acryl-eze
24. Kollicoat® MAE 30 DP [Internet]. [cited 2021 Mar 12]. Available from: https://pharmaceutical.basf.com/global/en/drug-formulation/products/kollicoat-mae-30dp.html
25. Kollicoat® MAE 100 P [Internet]. [cited 2021 Mar 12]. Available from: https://pharmaceutical.basf.com/global/en/drug-formulation/products/kollicoat-mae-100p.html
26. Shin-Etsu AQOAT® - For Pharmaceutical : Shin-Etsu Cellulose [Internet]. [cited 2021 Mar 12]. Available from: https://www.metolose.jp/en/pharmaceutical/aqoat.html
27. AquasolveTM hydroxypropylmethylcellulose acetate succinate-physical and chemical properties handbook [Internet]. [cited 2021 Mar 12]. Available from: https://www.ashland.com/file_source/Ashland/Industries/Pharmaceutical/Links/PC-12624.6_AquaSolve_HPMCAS_Physical_Chemical_Properties.pdf
28. Colorcon® | Sureteric® Aqueous Enteric Coating System [Internet]. [cited 2021 Mar 12]. Available from: https://www.colorcon.com/products-formulation/all-products/film-coatings/enteric-release/sureteric
29. Kollicoat® Smartseal 30 D [Internet]. [cited 2021 Mar 12]. Available from: https://pharmaceutical.basf.com/global/en/drug-formulation/products/kollicoat-smartseal30d.html
30. Thakral S, Thakral NK, Majumdar DK. Eudragit®: a technology evaluation. Expert Opin Drug Deliv. 2013;10:131–49.
31. Al-Zoubi N, Gharaibeh S, Aljaberi A, Nikolakakis I. Spray drying for direct compression of pharmaceuticals. Processes. 2021;9:267.
32. Jedinger N, Khinast J, Roblegg E. The design of controlled-release formulations resistant to alcohol-induced dose dumping - a review. Eur J Pharm Biopharm. 2014;87:217–26.
33. Al-Zoubi N, Al-Rusasi A, Sallam AS. Ethanol effect on acid resistance of selected enteric polymers. Pharm Dev Technol. Taylor and Francis Ltd; 2019;24:24–34.
34. Lazzari A, Kleinebudde P, Knop K. Xanthan gum as a rate-controlling polymer for the development of alcohol resistant matrix tablets and mini-tablets. Int J Pharm. Elsevier; 2018;536:440–449.
35. Mizumoto T, Tamura T, Kawai H, Kajiyama A, Itai S. Formulation design of taste-masked particles, including famotidine, for an oral fast-disintegrating dosage form. Chem Pharm Bull. 2008;56:530–5.
36. Kim JY, An SH, Rhee YS, Park CW, Park ES. A comparative study between spray-drying and fluidized bed coating processes for the preparation of pramipexole controlled-release microparticles for orally disintegrating tablets. Dry Technol. 2014;32:935–45.
37. Wei Q, Yang F, Luan L. Preparation and in vitro/in vivo evaluation of a ketoprofen orally disintegrating/sustained release tablet. Drug Dev Ind Pharm. 2013;39:928–34.
38. Wasilewska K, Ciosek-Skibińska P, Lenik J, Srčič S, Basa A, Winnicka K. Utilization of ethylcellulose microparticles with rupatadine fumarate in designing orodispersible minitablets with taste masking effect. Materials (Basel). 2020;13:1–22.
39. Brniak W, Mašlak E, Jachowicz R. Orodispersible films and tablets with prednisolone microparticles. Eur J Pharm Sci. 2015;75:81–90.
40. Arici M, Topbas O, Karavana SY, Ertan G, Sariisik M, Ozturk C. Preparation of naproxen-ethyl cellulose microparticles by spray-drying technique and their application to textile materials. J Microencapsul. 2014;31:654–66.
41. Akalkotkar A, Chablani L, Tawde SA, Dsouza C, Dsouza MJ. Development of a microparticulate prostate cancer vaccine and evaluating the effect of route of administration on its efficacy via the skin. J Microencapsul. 2015;32:281–9.
42. Chablani L, Tawde SA, Akalkotkar A, D'Souza MJ. Evaluation of a particulate breast cancer vaccine delivered via skin. AAPS J. 2019;21:1–11.
43. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10.
44. Quo X, Bodmeier R. Polymeric microparticles prepared by spray-drying a drugcontaining, aqueous colloidal acrylic polymer dispersion, Eudragit RS30D. STP Pharma Sci. 1997;7:521–8.

45. Sollohub K, Janczyk M, Kutyla A, Wosicka H, Ciosek P, Cal K. Taste masking of roxithromycin by spray drying technique. Acta Pol Pharm Drug Res. 2011;68:601–4.
46. Kasashima Y, Uchida S, Yoshihara K, Yasuji T, Sako K, Namiki N. Oral sustained-release suspension based on a lauryl sulfate salt/complex. Int J Pharm. 2016;515:677–83.
47. D'Souza B, Bhowmik T, Uddin MN, Oettinger C, D'Souza M. Development of β-cyclodextrin-based sustained release microparticles for oral insulin delivery. Drug Dev Ind Pharm. 2015;41:1288–93.
48. Parikh D, editor. Handbook of pharmaceutical granulation technology. Second. New York: Taylor & Francis; 2005. p. 191–228.
49. Al-Zoubi N, AlKhatib HS, Bustanji Y, Aiedeh K, Malamataris S. Sustained-release of buspirone HCl by co spray-drying with aqueous polymeric dispersions. Eur J Pharm Biopharm. 2008;69:735–42.
50. Al-Zoubi N, Odeh F, Nikolakakis I. Co-spray drying of metformin hydrochloride with polymers to improve compaction behavior. Powder Technol. 2017;307:163–74.
51. Kulkarni NB, Wakte PS, Naik JB. Metformin hydrochloride microparticles for oral controlled release: effect of formulation variables. Int J Pharm Pharm Sci. 2013;5:135–44.
52. Wu C, McGinity JW. Influence of ibuprofen as a solid-state plasticizer in Eudragit® RS 30 D on the physicochemical properties of coated beads. AAPS PharmSciTech. 2001;2:35–43.
53. Parikh NH, Porter SC, Rohera BD. Aqueous ethylcellulose dispersion of ethylcellulose. I. Evaluation of coating process variables. Pharm Res. 1993;10:525–34.
54. Jankowski A, Balwiarz R, Marciniak D, Łukowiec D, Pluta J. Influence of spray drying manufacturing parameters on quality of losartan potassium microspheres. Acta Pol Pharm. 2014;71:833–41.
55. Thakare M, Singh KK. Preparation and evaluation of diclofenac sodium controlled release tablets using spray-drying technology in aqueous system. Indian J Pharm Sci. 2006;68:530–2.
56. Lee YC, McNevin M, Ikeda C, Chouzouri G, Moser J, Harris D, *et al*. Combination of colloidal silicon dioxide with spray-dried solid dispersion to facilitate discharge from an agitated dryer. AAPS PharmSciTech. 2019;20:1–7.
57. Ambike AA, Mahadik KR, Paradkar A. Spray-dried amorphous solid dispersions of simvastatin, a low Tg drug: in vitro and in vivo evaluations. Pharm Res. 2005;22:990–8.
58. Surti N, Mahajan AN, Patel D, Patel A, Surti Z. Spray dried solid dispersion of repaglinide using hypromellose acetate succinate: in vitro and in vivo characterization. Drug Dev Ind Pharm. 2020;46:1622–31.
59. Chandralekha A, Rani A, Tavanandi HA, Amrutha N, Hebbar U, Raghavarao KSMS. Role of carrier material in encapsulation of yeast (Saccharomyces cerevisiae) by spray drying. Dry Technol. 2017;35:1029–42.
60. Lee JKM, Taip FS, Abdulla HZ. Effectiveness of additives in spray drying performance: a review. Food Res. 2018;2:486–99.
61. Wesoły M, Zabadaj M, Amelian A, Winnicka K, Wróblewski W, Ciosek P. Tasting cetirizine-based microspheres with an electronic tongue. Sensors Actuators B Chem. 2017;238:1190–8.
62. Souza CRF, Oliveira WP. Microencapsulation of ketoprofen in blends of acrylic resins by spray drying. Dry Technol. 2012;30:263–75.
63. Garekani HA, Sedighi S, Sadeghi F. Surelease or organic solution of ethylcellulose in preparation of sustained release theophylline micromatrices or matrices using spray drying technique. Pharm Dev Technol. 2015;20:204–10.
64. Wasilewska K, Szekalska M, Ciosek-Skibinska P, Lenik J, Basa A, Jacyna J, *et al*. Ethylcellulose in organic solution or aqueous dispersion form in designing taste-masked microparticles by the spray drying technique with a model bitter drug: rupatadine fumarate. Polymers (Basel). 2019;11:1–17.
65. Garekani HA, Moghaddam ZF, Sadeghi F. Organic solution versus aqueous dispersion of Eudragit RS in preparation of sustained release microparticles of theophylline using spray drying. Colloids Surfaces B Biointerfaces [Internet]. Elsevier B.V.; 2013;108:374–9. Available from: https://doi.org/10.1016/j.colsurfb.2013.03.012.
66. Nova MV, Nothnagel L, Thurn M, Travassos PB, Herculano LS, Bittencourt PRS, *et al*. Development study of pectin/Surelease® solid microparticles for the delivery of L-alanyl-L-glutamine dipeptide. Food Hydrocoll [Internet]. Elsevier Ltd; 2019;89:921–32. Available from: https://doi.org/10.1016/j.foodhyd.2018.11.038.
67. Al-Zoubi N, Al-obaidi G, Tashtoush B, Malamataris S. Sustained release of diltiazem HCl tableted after co-spray drying and physical mixing with PVAc and PVP. Drug Dev Ind Pharm [Internet]. Informa Healthcare USA, Inc; 2016;42:270–9. Available from: https://doi.org/10.3109/03639045.2015.1047848.
68. Liu W, Wu WD, Selomulya C, Chen XD. On designing particulate carriers for encapsulation and controlled release applications. Powder Technol. Elsevier B.V.; 2013;236:188–96.
69. Ostrøka-Cieslik A, Sarecka-Hujar B, Krzykawski T, Karcz J, Banys A, Jankowski A. Application of selected diffractive and microscopic methods to evaluate the physical state of drug and morphology of microspheres obtained by spray drying of furosemide with eudragit L30 D-55. Acta Pol Pharm. 2018;75:759-65.
70. Blanco-García E, Otero-Espinar FJ, Blanco-Méndez J, Leiro-Vidal JM, Luzardo-Álvarez A. Development and characterization of anti-inflammatory activity of curcumin-loaded biodegradable microspheres with potential use in intestinal inflammatory disorders. Int J Pharm. 2017;518:86–104.
71. Colomé LM, Raffin RP, Jornada DS, Pohlmann AR, Guterres SS. Pantoprazole-loaded Eudragit blended microparticles: preparation, characterization, in vitro gastro-resistance and in vivo antiulcer evaluation. J Drug Deliv Sci Technol. 2007;17:113–8.
72. Liu W, Selomulya C, Chen XD. Design of polymeric microparticles for pH-responsive and time-sustained drug release. Biochem Eng J. 2013;81:177–86.
73. Rattes ALR, Oliveira WP. Spray drying conditions and encapsulating composition effects on formation and properties of sodium diclofenac microparticles. Powder Technol. 2007;171:7–14.
74. Kulvanich P, Leesawat P, Patomchaiviwat V. Release characteristics of the matrices prepared from co-spray-dried powders of theophylline and ethylcellulose. Drug Dev Ind Pharm. 2002;28:727–39.
75. Takeuchi H, Handa T, Kawashima Y. Controlled release theophylline tablet with acrylic polymers prepared by spray-drying technique in aqueous system. Drug Dev Ind Pharm. 1989;15:1999–2016.
76. Lin SY, Kao YH. Tablet formulation study of spray-dried sodium diclofenac enteric-coated microcapsules. Pharm Res. 1991;8:919–24.
77. Ostrózka-Cieślik A, Sarecka-Hujar B, Jankowski A. Physicochemical characteristics of furosemide incorporated eudragit microspheres formulated by spray drying. Acta Pol Pharm. 2018;75:1369–76.
78. Nining N, Srifiana Y, Fadlianty EM. Preparation and characterization of enteric-coated delayed-release microsphere of phytosome loading allicin-rich extract. Int J Appl Pharm. 2021;13:71–5.
79. Liao CW, Lin SH, Lin PY, Chiou HY, Chang WF, Weng CN. Orally administrable enterotoxigenic Escherichia coli vaccine encapsulated by ethylcellulose powder dispersion. Appl Microbiol Biotechnol. 2004;65:295–300.

80. Lin JH, Weng CN, Liao CW, Yeh KS, Pan MJ. Protective effects of oral microencapsulated mycoplasma hyopneumoniae vaccine prepared by co-spray drying method. J Vet Med Sci. 2003;65:69–74.
81. Lai YH, D'Souza M. Formulation and evaluation of an oral melanoma vaccine. J Microencapsul. 2007;24:235–52.
82. Chablani L, Tawde SA, Akalkotkar A, D'Souza C, Selvaraj P, D'Souza MJ. Formulation and evaluation of a particulate oral breast cancer vaccine. J Pharm Sci. 2012;101:3661–71.
83. D'Souza B, Bhowmik T, Shashidharamurthy R, Oettinger C, Selvaraj P, D'Souza M. Oral microparticulate vaccine for melanoma using M-cell targeting. J Drug Target. 2012;20:166–73.
84. Tawde SA, Chablani L, Akalkotkar A, D'Souza C, Chiriva-Internati M, Selvaraj P, *et al*. Formulation and evaluation of oral microparticulate ovarian cancer vaccines. Vaccine. 2012;30:5675–81.
85. Bhowmik T, D'Souza B, Uddin MN, D'Souza MJ. Oral delivery of microparticles containing plasmid DNA encoding hepatitis-B surface antigen. J Drug Target. 2012;20:364–71.
86. Akalkotkar A, Tawde SA, Chablani L, D'Souza MJ. Oral delivery of particulate prostate cancer vaccine: in vitro and in vivo evaluation. J Drug Target. 2012;20:338–46.
87. Chablani L, Tawde SA, D'Souza MJ. Spray-dried microparticles: a potential vehicle for oral delivery of vaccines. J Microencapsul. 2012;29:388–97.
88. Bhowmik T, D'souza B, Shashidharamurthy R, Oettinger C, Selvaraj P, D'Souza MJ. A novel microparticulate vaccine for melanoma cancer using transdermal delivery. J Microencapsul. 2011;28:294–300.
89. Haj-Ahmad RR, Mamayusupov M, Elkordy EA, Elkordy AA. Influences of copolymers (copovidone, Eudragit RL PO and Kollicoat MAE 30 DP) on stability and bioactivity of spray-dried and freeze-dried lysozyme. Drug Dev Ind Pharm. 2016;42:2086–96.
90. Bejugam NK, Uddin AN, Gayakwad SG, D'Souza MJ. Formulation and evaluation of albumin microspheres and its enteric coating using a spray-dryer. J Microencapsul. 2008;25:577–83.
91. Shastri PN, Ubale RV, D'Souza MJ. Implementation of mixture design for formulation of albumin containing enteric-coated spray-dried microparticles. Drug Dev Ind Pharm. 2013;39:164–75.
92. Muoka LC, Ross SA, Mithu MSH, Nandi U, Douroumis D. Comparative taste-masking evaluation of microencapsulated bitter drugs using Smartseal 30D and ReadyMix for paediatric dosage forms. AAPS PharmSciTech. AAPS PharmSciTech. 2021;22:1–9.
93. Crowley MM, Schroeder B, Fredersdorf A, Obara S, Talarico M, Kucera S, *et al*. Physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot-melt extrusion. Int J Pharm. 2004;269:509–22.
94. Millán M, Caraballo I, Rabasco AM. The role of the drug/excipient particle size ratio in the percolation model for tablets. Pharm Res. 1998;15:216–20.
95. Agrawal AM, Neau SH, Bonate PL. Wet granulation fine particle ethylcellulose tablets: effect of production variables and mathematical modeling of drug release. AAPS PharmSci. 2003;5:48–60.
96. Obeidat WM, Alzoubi NM. Controlled-release cellulose esters matrices for water-soluble diclofenac sodium: compression and dissolution studies. Pharmazie. 2014;69:96–103.
97. Al-Zoubi NM, Alkhatib HS, Obeidat WM. Evaluation of hydrophilic matrix tablets based on Carbopol ® 971P and low-viscosity sodium alginate for pH-independent controlled drug release. Drug Dev Ind Pharm. 2011;37:798–808.
98. Chen R, Okamoto H, Danjo K. Preparation of functional composite particles of salbutamol sulfate using a 4-fluid nozzle spray-drying technique. Chem Pharm Bull. 2008;56:254–9.
99. Sakhnini N, Al-Zoubi N, Al-Obaidi GH, Ardakani A. Sustained release matrix tablets prepared from cospray dried mixtures with starch hydrophobic esters. Pharmazie. 2015;70:177–82.
100. Ziaee A, Albadarin AB, Padrela L, Femmer T, O'Reilly E, Walker G. Spray drying of pharmaceuticals and biopharmaceuticals: critical parameters and experimental process optimization approaches. Eur J Pharm Sci. 2019;127:300–18.
101. Preston KB, Randolph TW. Stability of lyophilized and spray dried vaccine formulations. Adv Drug Deliv Rev. 2021;171:50–61.