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Review Article

Aqueous Film Coating the Current Trend

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Abstract

The presentation of this work aims to update professionals involved with aqueous film coating (AFC) of pharmaceuticals on facts associated with film coating (FC) based on aqueous solvent (AS). Initially sugar coating (SC) was the first choice of pharmaceutical industry and much time and efforts were spent in perfecting the techniques and processes of SC. Long processing time and demand for operator skill as in SC compelled them to develop FC. The FC of substrate is achieved by spraying solution of diverse polymer in AS or volatile organic solvent (VOS). Initially, use of VOS in the FC is preferred over AS, as latter inherits problems like sticking, picking, over-wetting, and many more. Momentum for using AS based FC and replacing the VOS based one with the aqua based one got accelerated from last few decade for reasons like safety, toxicity, stricter regulation on environmental pollution, and economy. Nowadays coating techniques & process relies mostly on AS due to its significant benefits over VOS. Functional properties of the film-coated pharmaceuticals depends greatly on film forming polymer (FFP) along with other factors like process, equipment, technology, additives, and many others. Summarised information on technical aspect of AFCs is rare, necessitating this work. Thus information gathered, summarised, studied, and hereby is attempting to be presented in a convenience way for enriching stakeholders in the pharmaceutical field. The presentation is for updating professionals in this regard.

Key words: Aqueous, dispersion, film-coating, latex, polymer.

INTRODUCTION

Till 1950, SC is the first preference and much effort was put on to perfect its techniques and processes [1-3]. However major cons are the longer processing time, and the operator-skill dependant productivity and quality [4-6]. Unavailability of skilled coating operator compels companies for rescheduling their production plans in many instances, a chief fact contributed for developing the FC process and technology [7-9].

To reduce processing time and overcoming requirement for skilled-operator, as in SC, developing is FC [10, 11]. Here coating of substrate is achieved by spraying solution of FFP in AS or VOS [11-13]. Furthermore the FC can improve stability by protecting substrate from humidity, temperature, and light; improve aesthetic property by masking obnoxious taste or odour, improving the appearance, facilitating swallowing; provide tablet identity; and modify or control release of the active [12-14]. The FC find applications for achieving release profile of the drug(s) that is either modified or conventional; accordingly the FC is either modified release FCs or conventional FCs [6-8]. Conventional FCs are for immediate release while the modified release FCs are for either enteric/delayed release or extended release, where the release is controlled by a membrane acts as barrier for drug release [7-9].

Initially, use of VOSs in the FC preferred over AS and used widely for avoiding possible degradation of drug(s) and diverse process linked problems of AS based coating systems like picking, over wetting, sticking, and may other [7-9]. While using VOSs none are concerned for problems like their toxic nature, their cost, coating associated toxic effects, pollution, and many more [7-9]. Follows are the major issues invokes from use of VOSs.

1. Venting of untreated VOS vapour into atmosphere: It is ecologically not acceptable and treatment of gaseous effluent is costly [7-9].
2. VOSs are safety hazard and fire hazard. As are flammable, toxic, and explosive, thus calls for building with explosive-proof and flame-proof facilities [7-9].
3. These are relatively costly, are likely to be costlier in future, and their storage cost is high [7-9].
4. For a given process, quantification of residual VOSs in film-coat is must [7-9].
5. Nowadays premium of insurance for manufacturing facility using VOSs is much higher [7-9].

Use of VOSs has continued, miserably, in order to achieve the rapid drying characteristics demanded by the process, especially when [7-9]:

- The coating process will not accommodate use of water (i.e., drying is poor) [7];
- The adhesion attained with aqua based system is not acceptable [9];

- Certain vital ingredients (i.e., film former) are water insoluble and unavailable as latex/ pseudo-latex system [8]; and
- Exposure to aqueous process will cause instability for candidate substrate [9].

However concerns on issues like safety of operator, environmental safety, and cost have provided momentum for utilisation of AFC as preferred option [7, 8]. Thus from last few decades AFC systems widely exploited as offer significant advantages over VOSs, are related to safety, environment, economy, residual solvent, etc [8, 9]. Available literature that summarises information relating processing and technical aspect of AFC is scare [9, 10]. Thus it was seemed necessary to study and summarise information and to present them for convenience and enrichment of professionals, working in pharmaceutical field. Presented information will be updating professionals in this field, and consequence is profit and productivity, ultimately benefit of mankind.

FILM COATING

In FC a thin layer/coat of a FFP is deposited surrounding the substrate, by spraying the same in the form of coating compositions, in liquid state, through one or more spray guns onto a small portion of rotating or fluidised bed of the substrates using panning equipment that is ether conventional or sophisticated one, to accomplish efficient drying, automation of higher degree, and reducing coating time [11-13]. Said composition of coating is either a solution or a suspension in a suitable liquid medium (a solvent either AS or VOSs), accordingly the FC process can be classed into two broader categories as follows [7-12]:

- AFC
- Non-AFC

The process basis involves spraying coating composition, in liquid state, on to the rotating/ fluidised bed of substrate using atomising/ spraying system [7, 9]. Spray-application process is to atomise bulk coating liquids as fine droplets and deliver them in such a state that they retain sufficient fluidity to wet the surface of substrate, spread out, and coalesce to form a film [7, 8]. The drying conditions permits solvent removal so as to leave a thin deposition of the coating material, usually between 20 and 200 µm, around each substrate core [8, 9]. High quality FC be uniform, smooth, adhere in satisfactory manner to surface of the substrate, and ensure physico-chemical stability of product [7, 10].

The coating liquid contains film former in a suited liquid medium along with plasticisers and other excipients like pigments [7, 8]. Furthermore, the coating fluid will be either be a aqueous solution or dispersion or be a non-aqueous solution or dispersion which in turn will change the overall process and processing requirement [9, 10], refer table-1.

Table 1: Processing requirement of FC, VOS versus AS [7-10].

VOS	AS
Coating solutions / suspensions are based on:	Coating suspension/ solution are based on:
VOSs: alcohols, methylene chloride.	AS only.
Hydroalcoholic solvents: Water and alcohol.	Suitable concentration: 12 to 15 % dispersion.
Suitable concentration:	Require highly efficient drying-air plant.
VOSs: 5-8 % dispersion	Takes longer processing time and can lead to mechanical harm as substrates tumbled for longer time period.
Hydroalcoholic solvents: 8-10 % dispersion.	Advances in drying efficiency have allowed AFC processes to be developing even for moisture labile products.
Rapid drying rate due to integral volatility.	No safety issues of operator (can allow for mobile vessels).
Can be utilised to moisture labile products.	Do not require modification to facility and equipment (intrinsically safe/ flame-proofing).
Safety issues of operator (cannot allow for mobile vessels).	Can release to atmosphere.
Requires modification to facility and equipment (intrinsically safe, flame-proofing, etc).	
Solvent recovery and environmentally creditworthy disposal is costly.	
Can impart odour/ taste to product.	

The processing requirement for dispersed system calls for cycling steps of spraying and distribution step and curing step, while that for solution system no curing step [8, 9]. The curing step is an intermediate step followed to spraying step, for allowing coalescence of deposited particles to form FC [15-18]. In nutshell a successful FC process calls for:

- Balance between and control of the delivery rate of coating composition and drying process [10],
- Uniform distribution of coating materials across surface of product being coated [7], and
- Optimisation of both visual and functional quality of final coated product [7, 10].

FORMULATION OF FC LIQUID

Film coating formulations (FCF), typically, has follow components [7-10].

A. Film former (Polymer)
1. Non-enteric polymers
a) Water soluble polymers
b) Water insoluble polymers
2. Enteric polymers

B. Plasticiser
a. Internal and
b. External
C. Colours/opacifiers

D. Other/auxiliary excipients
a) Surfactants,
b) Flavours,
c) Sweetening Agent,
d) Active pharmaceutical ingredient, and
e) Preservatives.
E. Solvent

FILM FORMERS (POLYMERS)

Film formers or FFP are usually the polymer substances are with high molar masses and are composed of many (large number) repeated subunits, called monomers, are joined sequentially by chemical reactions forming a chain [9]. Their function is to provide main structure and basic physical attributes and chemical/functional properties to film coat. Film formers, basing upon their molecular weight and viscosity grades, influence the substrate coating properties, to greater extent [9, 19]. Properties of an ideal FFP are follows [7-10, 20]:

1) Soluble in wider range of solvent systems, importantly solvent of choice for coating formulation.
2) Adequate solubility for the intended use, i.e., free water-solubility, slow water solubility or pH-dependent solubility.
3) Capacity to produce an elegant looking product.
4) Stable to the action of heat, light, moisture, air, and substrate.
5) Should be non-toxic, odourless, colourless, and tasteless.
6) Compatible with other ingredients and substrate.
7) No pharmacologic activity.
8) Capable to form continuous film having adequate mechanical properties.
9) Have capacity in producing an elegant product even in presence of additives.
10) Resistant to filling formation, bridging, cracking.
11) Easier be their application and ease of printing with high speed machines.

Basing on the chemical origin the polymers can be classed as follows [7-12, 19, 20]:

- ***Cellulosics***: Examples: Hydroxypropyl Methylcellulose (HPMC) [21-27], Hydroxyethyl Cellulose, Hydroxypropyl Cellulose (HPC), Methyl Cellulose, Sodium carboxymethyl cellulose (Sodium CMC), Methyl hydroxyethyl cellulose, Ethyl Cellulose (EC).
- ***Vinyl polymers***: Examples: Polyvinyl pyrrolidone, Polyvinyl alcohol, Polyvinyl pyrrolidone-polyvinyl acetate copolymers, Polyvinyl alcohol-poly ethylene glycol copolymers.
- ***Glycols***: Example, high molecular weight poly ethylene glycols.
- ***Acrylic acid polymers***: Examples: copolymer of Methacrylate aminoester, Ethacrylate methylmethacrylate copolymer, Eudragits® [28].
- ***Other carbohydrates***: Maltodextrin, Polydextrose. Starch acetate [29], Amylose corn-starch [30],

Non-enteric polymers (water soluble)

Since, water-soluble polymers do not influence therapeutic effect or drug release, thus widely employed in moisture-protective coating [31], while some could be used for taste-masking coating and can be easily used in AFC process [20]. The formed film-coat from water-soluble polymers have relatively shorter lifespan comparing to that from water-insoluble polymers, attributed from degradation of coating caused by ambient humidity during storage [8, 9]. Examples are presented with table-2.

Non-enteric polymers (water insoluble)

Water-insoluble polymers exploited mainly as coating materials for modifying and extending drug release to accomplish controlled or sustained release [8]. Some of them may form FC with low permeability, thus can also be used as coating materials for moisture protection [9]. Polymers include starch derivative like starch acetate [29], amylose corn-starch [30]; polyvinyl acetate [32]; cellulose esters like cellulose acetate and EC [33-37]; and acrylic esters like copolymers of ethyl acrylate–methyl methacrylate [9, 20]. Examples are presented with table-3.

Table 2: Aqua-soluble polymers for FC [9, 20].

Polymer	Brand Name	Manufacturer
HPC	Klucel™	Ashland, Covington USA.
HPMC	Methocel® E3/E5/E6/E15	Dow Chemical, Midland, USA.
	Walocel® HM 3 PA/ HM 5 PA/ HM 6 PA/ HM 15 PA	Dow Wolff Cellulosics, Mitterland, USA.
	Pharmacoat® 603/ 606/ 615/ 645	Shin-Etsu, Tokyo, Japan.
	Sepifilm® LP [21]	Seppic, Castres Cedex, France.
Hydroxyethyl cellulose	Natrosol, Oxycellulose	Ashland Aqualon, Covington, USA.
Methyl methacrylate and diethylamino–ethyl ethacrylate copolymer dispersion	Kollicoat®	BASF, Ludwigshafen, Germany.
Polyvinyl alcohol	Opadry® AMB [21]	Colorcon, Harleysville, USA.
Polyvinyl alcohol–poly ethylene glycol	AquaPolish®, Kollicoat® IR, Kollicoat® IR Protect	BASF. Ludwigshafen, Germany.

Table 3: Aqua-insoluble polymers for non-enteric FC [8, 9, 20].

Polymer	Brand Name	Manufacturer
Ammonio methacrylate	Eudragit® RS, Eudragit® RS PO, Eudragit® RL [38, 39]	Evonik, Essen, Germany.
Ammonio methacrylate copolymers (Type A & type B)	Aquapolish® R	Biogrund, Hünstetten, Germany.
Cellulose acetate	Eastman CA	Eastman, Rochester, USA.
EC	Auqacoat®	FMC, Philadelphia, USA.
	Surelease®	Colorcon, Harleysville, USA.
	Ethocel™	Dow Chemical, Mitterland, USA.
Poly (ethyl acrylate–co-methyl methacrylate) 2:1	Eudragit® NE Eudragit® NM	Evonik, Essen, Germany.
Polyvinyl acetate	Kollicoat®	BASF, Ludwigshafen, Germany.

Great interest in the FC has been shown in using aqueous-coating system termed aqueous polymeric dispersion (APD) for modified-release products [9, 20], refer table-4. These systems generally consist of aqueous dispersion of aqua-insoluble polymer(s) that form films by curing step [15-18], a coalescence process of submicron polymer particles with the aid of heat [8, 9, 20].

Table 4: Examples of APDs for non-enteric FC [8, 9, 20].

Polymer	Brand Name	Manufacturer
Ammonio methacrylate	Eudragit® RL 30 D, Eudragit® RS 30 D	Evonik, Essen, Germany.
EC	Auqacoat® ECD 30	FMC, Philadelphia, USA.
Poly (methyl methacrylate–co-ethyl acrylate)	Eudragit® NE 30 D Eudragit® NM 30 D	Evonik, Essen, Germany.
Polyvinyl acetate	Kollicoat® SR 30 D [40]	BASF, Ludwigshafen, Germany.

Sustained/ controlled release polymers

Drug release from products intended for sustained/controlled-release is moderated by FC that acts as a barrier-membrane which allows infusion of gastrointestinal fluids and outward diffusion of dissolved drug [8, 9], In some instance, release process can be increased by a coating which slowly dissolves (e.g. zein [41, 42], shellac), or subjects to enzymatic digestion (viz, waxes and fats) [8, 9, 20]. Examples are presented with table-5.

Table 5: Examples of coating material used in sustained release FC [8, 9, 20].

Coating material	Membrane characteristics
Acrylic esters	Permeable.
Cellulose esters (Example: Cellulose acetate)	Semipermeable.
EC	Permeable [33-37, 43].
Eudragit® NE [44], Eudragit® RL [38, 39], Eudragit® RS	Permeable.
Fats and waxes (Examples: beeswax, cetyl alcohol, carnauba wax, cetylstearyl alcohol)	Permeable and erodible.
HPMC [22-27]	Permeable and swellable,
Shellac	Permeable and soluble at higher pH.
Silicone elastomers	Permeable (when poly ethylene glycol is added).
Starch derivative like starch acetate [29], amylose corn-starch [30],	Permeable and swellable.
Zein	Permeable and soluble at higher pH [42].

As with other type of FC, great interest has showing in using AFC system for modified-release products [9], refer table-6. These systems usually consist of aqua dispersion [20, 32, 36, 37, 45] of aqua-insoluble polymer(s) that form films by the coalescence process of submicron polymer particles, termed curing [15-18].

Table 6: Examples of APDs for sustained release FC [8, 9, 20].

Polymer	Brand Name	Comments
EC	Surelease®	• APD, contain requisite plasticisers. • Addition of lake-colours be avoiding due to alkalinity of dispersion.
	Aquacoat®	• Pseudolatex dispersion. • Requires addition of plasticisers to facilitate coalescence of film.
Poly (ethylacrylate-co-methyl methacrylate) 2: 1.	Eudragit® NE 30 D	• Latex dispersion [44]. • No plasticisers required unless improved film flexibility is desired [44].
Poly (ethylacrylate-co-methyl methacrylate) triethyl ammonioethyl methacrylate chloride (1: 2: 0.2).	Eudragit® RL 30 D	• APD. • No plasticisers required unless improved film flexibility is desired.
Poly (ethylacrylate-co-methyl methaeryIate) triethyl ammonioethyl methacrylate chloride (1: 2: 0. 1).	Eudragit® RS 30 D	• APD. • No plasticisers required unless improved flexibility of film is desired [46].
Polyvinyl acetate.	Kollicoat® SR 30 D	• APD [40].

Enteric polymers

Enteric polymers or entero-soluble polymer are the polymer that resists its degradation in the gastric (acidic) pH while gets degraded in the intestinal fluid (alkaline) and are incorporated in the formulations of enteric FCs to [8, 9, 20, 47, 48]:

- Protect acid-labile drug from the action of gastric fluid.
- Deliver drug(s) to intestine for optimal absorption or local action.
- Provides delayed release components for a repeat action.

Enteric polymers refer table-7 and table-8 for examples, often referred as polyacids, contains ionisable functional groups which makes polymer aqua-soluble, at and above a specific pH value [9, 48], refer table-7. Many of them are esters, can be subject to hydrolytic degradation at elevated humidity condition and temperature thus can result substantial changes in their enteric properties [48]. Follows are the properties of an ideal enteric polymer.

- Resistance to gastric fluid (acidic pH) [9].
- Should dissolve or become permeable near and above pH 5.0 [48].
- Compatible with other components of coating liquid [9].
- Non-toxic and have no therapeutic and pharmacologic activity [48].
- Formation of continuous and flexible film [48].
- Be stable, alone and in the coating liquid [9].
- The properties of resulted coat should remain unchanged with aging [48], and
- Ease of printing with high speed machines and easier be their application [9].

Table 7: Examples of entero-soluble polymers for FC, along with their dissolution pH [8, 9, 48].

Polymer	Dissolution pH
Cellulose acetate phthalate [49, 50].	6.2
Cellulose acetate trimellitate.	5.0
Hydroxypropyl methylcellulose acetate succinate (HPMC-AS). HPMC-AS-L HPMC-AS-M HPMC-AS-H	5.0 - 7,0 5.0 5.5 6.5
Hydroxypropyl Methyl Cellulose Phthalate (HPMCP). HPMCP 55 HPMCP 50 HPMCP 55S (higher viscosity grade). HPMCP 55F (fine particle grade).	4.5-5.5 ≥5.5 ≥5.0 ≥5.5 ≥5.5
Poly (methacrylic acid-co-methyl methacrylates).	5.5-7.0
Polyvinyl acetate phthalate.	5.0
Shellac	7.0

Table 8: Examples of entero-soluble polymers for FC [8, 9, 48].

Polymer	Brand Name	Manufacturer
Amino diethyl–methacrylate copolymer.	Kollicoat®	BASF. Ludwigshafen, Germany.
Amino dimethyl methacrylate copolymer.	Eudragit® E / E PO [21]	Evonik, Essen, Germany.
Acrylic acid copolymer,	Aquapolish® E	Biogrund, Hünstetten, Germany.
Carboxymethyl cellulose.	Akucell	Ashland Aqualon, Kentucky, USA.
Cellulose acetate phthalate.	Aquacoat®	FMC, Philadelphia, USA.
	Eastman C-A-P NF	Eastman, Rochester, USA.
Cellulose acetate butyrate.	CAB Eastman	Eastman, Rochester, USA.
Methacrylic acid copolymer, Type A.	Eudragit® L 100-55 [51, 52]	Evonik, Essen, Germany.
	Kollicoat® MAE 100 P [53]	BASF, Ludwigshafen, Germany.
Methacrylic acid copolymer, Type B.	Eudragit® L 100 [54]	Evonik, Essen, Germany.
Methacrylic acid copolymer, Type C.	Eudragit® S 100 [55]	Evonik, Essen, Germany.
Shellac	SSB 55 Pharma	Chineway, Shanghai, China.
Sodium alginate.	Keltone LV CR	FMC, Philadelphia, USA.

The special aqueous solubility requirements for an entero-soluble polymer have delayed the routine employment of aqueous coating system for enteric release products. More recently, APD systems for aqueous based enteric coating [48] processes had been introduced as diverse one; refer table-9 for examples. Many of them (coating systems) are available as dry powders [9]. The coating liquid is prepared shortly before their use by dispersing them in water [53]. Supplying them as dry powder is to overcome problems of low stability of polymer, due to hydrolysis, when they are exposed to aqua for extended periods [9].

Table 9: Examples of APDs for enteric FC [9, 48]**.**

Polymer	Brand Name	Manufacturer
Cellulose acetate butyrate	CAB Eastman	Eastman, Rochester, USA.
Methacrylic acid copolymer, Type A	Eudragit® L 30 D-55 [21, 51]	Evonik, Essen, Germany.
	Eastacryl 30 D NF	Eastman, Rochester, USA.
	Kollicoat® MAE 30 DP	BASF, Ludwigshafen, Germany.
Cellulose acetate phthalate	Aquacoat® CPD [50]	FMC, Philadelphia, USA.
EC	Aquacoat® ECD 30 [45]	DuPont, West Point, USA.
	Surelease®	Colorcon, West Point, USA.
Methacrylic acid copolymer	Eudragit® FS 30 D	Evonik, Essen, Germany.
Amino diethyl–methacrylate copolymer	Smartseal 30 D	BASF, Ludwigshafen, Germany.
Polyvinyl acetate phthalate	Sureteric®	Colorcon, West Point, USA.

Table 10: Plasticisers commonly used in conventional FC [8, 9].

Class	Examples
Acetate esters	Glyceryl triacetate (Triacetin), Triethyl citrate [37], Acetyl triethyl citrate.
Glycerides	Acetylated monoglycerides like Glyceryl monostearate.
Oils	Castor oil, Mineral oil.
Organic esters	Triethyl citrate, Acetyltributyl citrate, Acetyltriethyl citrate, Tributyl citrate, etc.
Phthalate esters	Diethyl phthalate, Dibutyl phthalate [46].
Polyhydric alcohols	Glycerol, Propylene glycol, Poly ethylene glycols (200 – 6000 grades).
Water-soluble	Polyethylene glycols, Glycerol, Triacetin, Propylene glycol.
Organic-soluble	Fractionated coconut oils, Castor-oil, and Spans.

PLASTICISER

Plasticisers are comparatively low molecular weight material that added to FCFs for modifying the basic mechanical properties of polymer [8, 46]. General postulation on mechanism of their action is plasticiser molecules interpose themselves in-between individual polymer strands thereby breaking down polymer-polymer interactions hence converting into more pliable materials [9, 46]. These have high affinity for polymer(s) thus is also called non-volatile solvents [8, 46]. When the plasticisers are used in correct concentration they confer flexibility by relieving molecular rigidity and/or weakening intermolecular attraction between polymer chains, and facilitate coalescence of discrete polymeric spheres of aqueous dispersion during film formation [9, 46]. Increased film flexibility reduces residual stresses within the coating as it shrinks around the core during drying [8, 46]. Have ability to decrease film brittleness, polymer-polymer interactions, reduce glass transition temperature (*Tg*) of the amorphous polymers [46], and impart flexibility [8, 9]. They modify plasticity of FFP by follow two ways [8, 9].

- Internal plasticising
- External plasticising

Internal plasticising involves chemical modification, which is brought in polymer chain that alters their physical properties i.e. elastic modulus [9, 46]. External plasticising involves use of other substances as plasticiser in formulations [8]. External and internal plasticisers are used at 1-50% of the polymer concentration, but commonly at 10% [8, 9]. Examples of commonly used plasticiser are presented with table-10.

For HPMCs, Poly ethylene glycols are most effective plasticisers whose effectiveness is inversely proportional to their molecular weight [8]. Polyethylene glycols being hygroscopic facilitate plasticisation process by assisting amount of moisture retention in polymeric-film. Triacetin as plasticiser in aqueous coating formulations is less popular but have certain advantages while trying to improve coating's moisture barrier properties [9].

COLOURANTS AND OPACIFIERS

Inclusion of colourants in many FCFs is for enabling product identification, improving product appearance, modifying gas permeability of the film, and decreasing risk of counterfeit product [8]. Whereas inclusion of the opacifiers for protecting product from deleterious effect of light. In addition, the colourants protect the active ingredients from the action of light by optimising opacifying properties of the pigment [9]. The preferred level of colourants in FCF for light shade is 0.01% w/w while for dark shade is >2.0% w/w [8, 9]. Colourants and opacifiers complying regulations promulgated by national legislation of the country where the products are to be marketed, must be using, refer table-11 for examples.

Colours may be water-soluble (known as dyes or supras) or water-insoluble (known as pigments or lakes). Pigments are preferred in FCFs due to follow facts [8, 9].

- Exhibit better light stability [8].
- Provide better opacity and covering power [9].
- Provide a means of optimising moisture barrier properties of applied FCs [8].
- Do not suffer from the disadvantageous phenomenon of mottling (as may be observed with spurs, caused by solute migration) [9].

Table 11: Colourants and opacifiers used in FCFs [8, 9].

Class	Examples
Water soluble dyes (Supras)	FD&C Blue #2, FD&C Yellow #5.
FD&C lakes	FD&C Blue #2 Lake, FD&C Yellow #5 Lake.
D&C lakes	D&C Yellow #10 Lake, D&C Red #30 Lake.
Inorganic pigments	Iron oxides, Titanium dioxide,
Natural colourants	Riboflavin, Beta-carotene, Carmine lake

MISCELLANEOUS ADDITIVES

Other materials may be included in FCFs, occasionally, in very low concentrations for conferring specific attributes to film-coat and/or FCFs [8, 9], and are as follows.

Active pharmaceutical ingredient(s): The FC itself may contain, in rare instances, active or drug [9].

Flavours and sweeteners: These may be added for masking unpleasant odour of some drug and/or to improve palatability. For example, diverse fruit spirits, aqua soluble pineapple flavour, aspartame, etc [8, 9].

Dissolution enhancers or Surfactants: Polyoxyethylene sorbitan derivatives might be added to emulsify aqua-insoluble plasticisers, improve substrate wettability, stabilise dispersion, and fasten spreadability of film during coating application, etc [8, 9].

Antioxidants: These are incorporated for stabilising a dye system from oxidative degradation and colour change. Examples: phenols, oximes, etc [8, 9].

Preservative/ antimicrobials: Some aqua cellulosic FCFs are prone to microbial growth, thus antimicrobials are included to protect FC from such degradation. Examples are carbamates, alkylisothiazloinone, benzothiazoles, and many others [8, 9].

Adhesion enhancers: Adhesion enhancer improves the adhesion property of sprayed droplets and film onto the substrate surface. Examples are maltodextrin, polydextrose, and lactose [8, 9].

Antifoaming agents: These are the surfactants included for preventing the foam formation during the stirring operation of the FCFs, example dimethylpolysiloxane [8, 9].

Pore forming agents: Their inclusion in FCF results in formation of pores or channels of micron size within film

coat, as to control the diffusion/release of drug(s) from substrate core. For instance sodium chloride or sucrose with EC-coated tablets of salicylic acid [56, 57].

Waxes: In some cases the waxes are used for imparting glossiness to film coat. For example bees wax, carnauba wax [8, 9],

Solvents/ Vehicles: Solvents used for dissolving or dispersing materials of FCF and deliver them onto surface of substrate core, here water [8, 9].

AQUEOUS FILM COATING

Increasing degree of understanding on toxicities of VOSs with concomitant worldwide tightening of Food & Drug regulations, industrial hygiene rules, and exposure of workers to VOSs is limiting their use. [8-10] Furthermore in today's competitive environment of business any cost-cutting will improve market viability of any product thus its success [9-11]. Existing stringent regulatory control along with concern regarding the increasing cost of VOSs, and market viability of any product thus its success [10-12, 58]; therefore as alternative to counterfeit these adverse situation requirement is reverting back to aqua as medium/solvent for coating of substrate [58, 59].

Initially, AFC processes were seeing with skepticism for facts of lengthy processing time and inferior appearance of coated product [8-10]. Research along with experience of industry has revealed that decomposition of active and possible difficulties of coating are not serious issues in practical application [12] as these problems can be addressing through scientific evaluation of reasons with significant advancement in process technology and equipment design [9-11]. Most of them could be categorised as related to material, coating process, and coating instrument/equipment [58, 59].

The development of latex and pseudo-latex system followed by introduction of these materials side-by-side improvements in designs of equipment has broadened spectrum of AFC [9-11]. With correct setting of processing conditions and proper selection of equipment, now is possible to perform AFC of smaller particles without their agglomeration [11, 12] or of tablets that contains superdisintegrants without dissolution of their surface and core penetration [8-10]. Formulations of aqua enteric coating system is advancement from the traditional solvent system, as latter one require separate inclusion of plasticisers, pigments, detackifiers, and other process additives and aids [12, 58, 59].

Thus from many years AFC systems are widely exploited [8-10]. The performance of dispersed system can be significantly affected by the conditions set in coating process, as variable results (relating ultimate drug-release features) can often attributing significantly to the choice of incompatible processing parameters or lack of control on coating process rather than to any variance in aqua dispersion used [11, 12, 20].

AQUEOUS POLYMERIC DISPERSIONS

The advantage of APDs is that they permit the aqueous processing of otherwise water-insoluble polymers, with the consequent benefits of aqueous processing. Industrially, specialised dispersions of aqua-insoluble polymers like EC and ammonium methacrylate copolymers for use in the aqueous media are frequently encountered in the FC of beads and granules for use in modified-release preparations [8-12, 60].

Eudragit® RL 30 D/ RS 30 D [46]/ NM 30 D/ NE 30 D [44]/ NE 40 D is preferred for AFC to have sustained/controlled release profile. The Eudragit® FS 30 D and Eudragit® L 30 D-55 [21, 51] is preferred for enteric AFC [8, 9].

Sureteric®, an aqueous dispersion of Polyvinyl acetate phthalate, and ammoniacal solution of Cellulose acetate trimellitate in water for enteric FCs. Aquacoat® and Surelease® are the pseudo latexes of EC [8, 9].

Preparation Aqueous Polymer Dispersions

Aqua dispersion system based coating liquids, from the method of preparation aspect, are of two types:

True dispersions/latexes

These are very fine dispersions of polymer in an aqueous phase and are characterised by a particle size range of between 10 and 1000 nm [8-10]. Particle size is crucial in stability and use of these materials as they have tendency to sediment [9, 10]. This tendency is counter-balanced by Brownian movement of particles which is aided by the micro-convection currents found in body of liquid [9-11]. The greatest particle diameter which can be tolerating in these systems without sedimentation can be determining by Stokes equation [10-12]. Dispersions, in which degree of fineness of particle approaches size range that is characteristic of the colloidal particles, are almost clear and are just opaque to the light [11, 12].

Emulsion polymerisation is one of chief methodology for producing latex dispersions [8, 9]. Said processes start with monomer that after purification is emulsified as internal phase using suitable surfactant [8, 9]. Then the polymerisation is activating by addition of an initiator that controls rate and extent of reaction [8, 9]. The reaction is to be quenched when particle size of polymer is within the range of 50–200 nm [8, 9]. Common practice is to purge the system with nitrogen for removing atmospheric oxygen that may leads to side reactions [8, 9]. Examples are Eudragit® NE 30 D [44] and Eudragit® L 100–55 [51, 52].

For preparing Polyvinyl acetate phthalate based coating liquid, polymer is dispersed in solvent, alongside other dispersed ingredient [8, 9].

In case of aqua soluble cellulosics (HPMC, HPC, Sodium CMC), and zein [41, 42] solubility is slow due to sudden gelling while adding to water, thus it is either [9]:

- Let it for overnight standing and soaking, thereby formed gel dissolves slowly in aqua [9], or
- Disperse it in portion of the hot water, not less than 80 ^{0}C, and then adding rest amount of water (in cold state) [9].

If the plasticiser and/or the colour are aqua soluble, it must be adding directly to polymer solution. If a detackifier and/or a lakes or pigment exist, it must be homogenised externally, then be adding to polymer solution with uninterrupted stirring [8-10]. Throughout coating process continue stirring so that air entrapment in coating liquid is avoided or minimised at least [10-12].

Important measures in preparation of true dispersions: The FFP would be last ingredient in addition process; care must take upon stirring for avoiding air entrapment [8, 9]. Generally, stirring have to be efficient and be continuing for long time period to maintain homogenous dispersity of the coating ingredients, specifically the film former in solvent [8, 9]. In case of the enteric FFPs, most of them need addition of an alkali for facilitating homogeneity of dispersion and avoiding coagulation of polymer particles [8, 9], as in the case of Eudragit® L 100-55 [51, 52]. Polymers with higher deviation in the surface tension value comparing that of aqua should be admixed with a surfactant for facilitating [8, 9]:

- Dispersing of polymer.
- Wetting of substrate by coating formulation (dispersion).
- Coalescence of polymer particle if the film coat upon drying.

Pseudo-dispersions/latexes:

Manufacturing of the pseudo-latexes starts with polymer itself and not with the monomer, as in the case of true-latexes [8-10]. Here particle size of the FFP is reducing by a physical process followed by producing an aqueous dispersion [9-11]. Characteristics of pseudolatex dispersions are significantly similar to true-latex, including considerations on the particle size, however are free from traces of initiator and monomer residue, etc [10-12].

In usual practice, FFP dissolved in solvent, and dispersed phase results from insoluble detackifier and/or the insoluble pigments or lakes. Examples are coating liquid based on HPMC, Eudragit® E 30 D, Aquacoat® ECD 30 [45], etc [9].

Commercially there two main products are available namely Aquacoat® and Surelease®. EC is the FFP in both product but are manufactured quite differently and their application method also differs to significant extent [8-10]. Aquacoat® is the earliest one, manufactured by dissolving FFP in VOS to have EC solution that then emulsified in a continuous phase of aqua [9-11]. The VOS is finally removed by vacuum distillation, thereby leaving a fine dispersion of FFP particles in aqueous phase [10-12]. Food grade antifoaming agent, sodium lauryl sulphate, and cetyl alcohol are included latter on that act as surfactants/stabilisers during the later stages of production [8, 11, 12].

Surelease® is the newer one, manufactured using the process, patented one, basing on the phase inversion technology [8, 9]. The EC is heated in presence of oleic acid and dibutyl sebacate (coconut oil that is fractionated is the alternate for dibutyl sebacate), and the mixture then is introduced into required quantity of ammoniated water for having phase inversion [9, 10]. Result of phase inversion gives rise to fine dispersion of polymer particles in the continuous phase of aqua, thus sits dibutyl sebacate (alternately coconut oil, fractionated one) in the EC fraction while ammonia and oleic acid together effectively stabilise dispersed phase in continuous phase [10, 11]. This siting of oleic acid and dibutyl sebacate is important which confer it as an effectual coating agent, as both acts as plasticisers [11, 12]. Such physical-siting; of them in Surelease® system that keep them in intimate contact with polymer, enables them to function almost effectively [8, 11, 12].

Aquacoat® have moisture content near 70% w/w and solid content near 30% w/w, solids being composing EC 87% w/w, sodium lauryl sulphate 4% w/w and cetyl alcohol 9% w/w [8, 9]. Surelease® has nominal solid content of 25% w/w and does not requires further addition of plasticiser, unlike Aquacoat® [10, 11]. Furthermore Surelease® contains required quantity of fumed silica that acts as antitacking agent during coating process [11, 12].

Important measures required in preparation of pseudo-dispersions: Generally, coating medium prepared using the high-shear mixer that is equipped with a homogenising device. Stirring is most important measure needs consideration, where entrapment of air is most hazardous factor. If external plasticiser and/or detackifier are required, inclusion must be done with extreme care, while stirring, in order to avoid any disturbance in pseudolatex structure. Example: Eudragit® E 30 D [45], Aquacoat® ECD 30 [45].

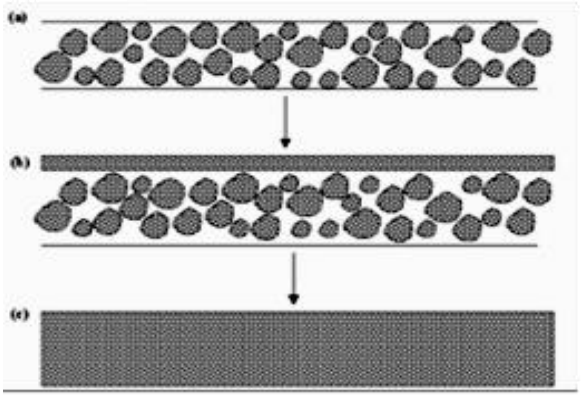

Figure 1: Mechanism of the film formation from polymeric dispersion (Latex) [9, 15].

FUNDAMENTALS AND MECHANISM OF THE FILM FORMATION IN FC

Coating liquid prepared containing film former, by either dissolving or dispersing the FFP in a solvent system, is atomised as small droplets and delivered onto surface of pre-warmed substrate [10-12]. Upon touching substrate the atomised droplets spread across surface of substrate [9, 10]. Then solvent may penetrate into substrate core, causing dissolution of the surface and their physical mixing at film-substrate interface [11, 12]. As solvent starts to evaporate, either polymer chain approaches each other to form polymeric film or polymer particles thickly pack on surface of substrate then the polymer particle coalesces under appropriate condition to form polymeric film [11, 15]. Generally coating equipment is equipped to apply heat for facilitating evaporation of solvent and film formation [12, 15].

Mechanism of film formation is basically different while using APDs comparing to that with organic polymeric solutions [8]. Following spraying of the organic polymeric solutions onto substrate surface; solvent evaporates, polymer chains approaches each other and then finally form a FC that is continuous and homogeneous [9, 10]. Whilst upon spraying of APDs onto substrate surface, the water evaporates; polymer particle approaches each other then under appropriate processing conditions (particularly temperature, presence of plasticisers and/or water in sufficient quantity) coalesce to form continuous and homogeneous FC [8, 11, 12].

Dispersed system requires coalescence of polymer particles into a continuous film [8], refer figure-1. The water removal process by drying of these systems is often quite fast, whilst coalescence can be much slower process, which extends to weeks even months if an appropriate formulation and/or

processing parameters are not using [9, 10]. Coalescence of polymer particle from the aqueous dispersion that deposited on surface of the substrate into a continuous film is initiated by evaporation of water [11, 12].

Upon further evaporation of solvent, coalescence of particles occurs, a process flow together of particles due to cohesive forces between polymeric droplets [8]. Prevailing conditions of processing vaporises solvent molecules thus gets lost, thereupon polymer particles will be increase in proximity to one another, a process that is greatly assisted by the capillary action of solvent-film that surrounds the particles [9, 10]. When adjacent polymer particles are capable to mutually diffuse into each other, occurring is their complete coalescence [11, 12].

In wet state the polymer is present as numerous discrete particles. These particles have to approach each other in close proximity, deform, coalesce, and at last fuses together to form discrete film [8, 9]. During processing, the surface of substrate should be wetted with diluted dispersion [10, 11]. In practice, it often hard task for assuring complete the film formation during coating process thus generally curing (a thermo after-treatment) [15-18, 49] is performed. For this reason general practice is following the completion of coating process, the coated substrate are immediately stored at a temperature that is above the *Tg* of the polymer for promoting further coalescence of the film (discrete one) and ensuring plasticiser's homogeneous distribution [10-12].

Formation of films from polymeric solutions

The film formation from a polymeric solution occurs via a series of stages [8, 9]. When a polymeric solution is sprayed onto the surface of substrate, cohesion forces built bond between polymer molecules [10]. Thus cohesive strength of polymer molecules should be relatively high and uninterrupted surface of film material must be coalescence [11, 12].

Formation of films from polymeric dispersions

The aqua solvent based coating process comprise of first spraying aqua coating dispersion composed of fine particles of FFP(s) and other additives, such as pigments and plasticisers, onto the substrate surface, followed by the curing step [15-18, 49] for allowing coalescence deposited particles to form the film coat [8-12, 20].

Actual mechanism of the film formation from an APD is rather complex that can be briefed as follows [9-12, 15].

a) Rapid evaporation of water, causing polymer particles of dispersion to be brought into close contact with one another. At this stage, dispersed polymer particles are pushed into a densely packed ordered array and water fills the voids [8, 9].

b) After the polymer particle comes into close proximity of one another, they should deform then fuses into a film by coalescence [8, 9].

c) Coalescence will be occurring when promoting forces exceeds resistive forces of polymer particles [8]. Development of capillary pressures (air-water interfacial tension) along with air-particle and water-particle interfacial tension overcomes repulsive forces between particles and cause deformation of polymer particles [9].

d) Gradual coalescence of polymer particles, results viscous flow and mobility of the polymer molecules across particle-particle interfaces [8, 9].

e) Coalescence of the polymer particles are complemented further by inter-diffusion or auto-adhesion of polymer chains that is occurring across particle interfaces, thus making more homogeneous film [8, 9].

f) Coalescences of latex particles are much more dependent on the free volume that influences movement of the polymer molecules amongst individual latex particles [8, 9].

Minimum Film-Forming Temperature

This is minimum temperature above which the film formation happen applying individually defined conditions. It is largely dependent on *Tg* of the FFP, a key characteristic of the polymers that have profound effect on properties of the polymer which can influence film formation, specifically in case of APDs. *Tg* is the temperature where hard glassy form of largely amorphous or an amorphous polymer changes to a softer and more rubbery consistency [9-12, 15].

ISSUES IN THE AQUEOUS FILM COATING

The film forming process from APD is very sensitive to the composition of coating liquid and the process conditions [61, 62], most importantly temperature and humidity [63]. The FC must be processed at a temperature above the *Tg* of polymer [15-18]. Furthermore, the quality and quantity of the pigment, and quality and quantity of plasticiser [64] in the coating formulation influences, to greatest extent, the pharmaceutical attributes of film coat like mechanical properties, physicochemical properties, barrier properties, and many others, refer table-12. Thus, the APDs have optimum processing conditions across a narrow temperature range. This is reason of tackiness, a common problem noticed in the process of FC with APDs [9, 15].

Table 12: General effects of pigments and plasticiser on the properties of the FCs [8, 9].

Property of film	Effect of increase in the concentration of	
	Pigment	**Plasticiser**
Tensile strength	Reduced, but the effect can be minimised by effective dispersal of the pigment in film.	Reduced.
Elastic modulus	Increased.	Reduced.
Film adhesion	Generally little effect.	Variable, but increases under optimal use conditions.
Viscosity of the coating liquid	Increased but usually not substantially.	Usually increased, but effect is greater as plasticiser molecular weight increased.
Film permeability	Reduced, unless pigment volume concentration exceeds critical level.	Variable, depending on physicochemical properties of plasticiser [46].
Glass transition temperature	Generally little or no effect.	Reduced, with magnitude of effect being influenced by compatibility with polymer.
Hiding power	Increased, but the result is dependent on light absorption characteristic and refractive index of the pigment.	Generally little or no effect.

CONCLUSION

AFC technology and process remains main option for the oral solid dosage form(s), regardless of purposes of the FC applications that is conventional (immediate) release and modified-release for enteric/delayed release or for extended release. Film formers be selecting basing upon their chemical nature and physical parameter of grade (that determined by viscosity grades and molecular weight), having influence on substrate's coating properties, to greater extent. Polymer chosen be comply the prevailing relevant pharmacopoeial and regulatory requirements, in the proposed marketing area.

Continued popularity of AFC process are mainly for environmental limitations on use of VOSs, recent progresses in formulation of AFC materials, and major improvements held with coating machines and their ancillaries.

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