Polymers for Pharmaceutical Coating

Subjects: Pharmacology & Pharmacy

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Coating the solid dosage form, such as tablets, is considered common, but it is a critical process that provides different characteristics to tablets. It increases the value of solid dosage form, administered orally, and thus meets diverse clinical requirements. As tablet coating is a process driven by technology, it relies on advancements in coating techniques, equipment used for the coating process, evaluation of coated tablets, and coated material used. Although different techniques were employed for coating purposes, which may be based on the use of solvents or solvent-free, each of the methods used has its advantages and disadvantages, and the techniques need continued modification too. During the process of film coating, several inter-and intra-batch uniformity of coated material on the tablets is considered a critical point that ensures the worth of the final product, particularly for those drugs that contain an active medicament in the coating layer. Meanwhile, computational modeling and experimental evaluation were actively used to predict the impact of the operational parameters on the final product quality and optimize the variables in tablet coating. The efforts produced by computational modeling or experimental evaluation not only save cost in optimizing the coating process but also saves time.

solid dosage form | uniformity in coating process | Polymers

1. Introduction

Around 1500 BCE, the first reference to the term pill as a solid dosage form came into existence. The first source of pills in ancient Egypt was recorded to be written on papyruses. The pills were made from bread dough, grease, and honey. Pills were made of simple hand-using ingredients like spices or plant powders. In ancient Greece, medicines were termed katapotia [1]. Roman scholars termed Pills as pilula (little ball). In medieval times, pills were coated using slippery substances obtained from plants. By 1800, gelatin capsules were invented. William Brockedon made a machine that can formulate lozenges and pills with the help of pressure on suitable dies [1]. This device compresses the powder without using adhesive into tablets. Professor Brockedon, 1844 in England, developed the first compressed tablets. These tablets were hard, and no reference was found concerning their disintegration time and solubility. In 1871, Messrs Newbery had purchased Professor Brockedon's business.

The Brockedon method of tablet compression was used by Philadelphian Jacob Dunton to formulate tablets of different formulations, including quinine [2]. In 1872, two brothers, Mr. Henry Bower and John Wyeth built an advanced machine that was not only more advanced than the previous one but also reduced the cost of producing tablets. In 1878, Dr. Robert R. Fuller from New York, for the first time, suggested the concept of loading these molds with medicated milk sugar. Mr. Fraser, in 1883, started to fabricate molded tablets in a completely new concept that researchers use today. From the start of the 1940s to the 1990s, synthetic and semisynthetic

polymers were used for enteric coating. Dextroamphetamine sulfate was the first manufactured by Kline, Smith, and French as sustained release products using the Spansule method [2][3].

Drug carriers were used to incorporate nutraceutical, cosmeceutical, and pharmaceutical formulations. As per the report published in 2015, it was estimated that $178 million were spent on drug delivery systems, which could be increased to $310 billion by the year 2025.

By definition, the carrier means a system capable of incorporating a specific quantity of medicinal agents to increase their efficiency, selectivity, and bioavailability. The system's efficiency depends on how much the system could bear the protective barrier. The release of the medicinal agents from the carrier system depends upon the rate and shape of kinetics, the viscosity of the media, and the drug release profile. Lipid-based dosage forms, including microspheres and microcapsules, tend to avoid drug leakage after its administration.

One of the basic advantages of incorporating the drug into the carrier system is to protect the drug during its overall stay within the body, starting from its point of administration until it reaches a specific site of action. Dosage forms were designed according to their usage, specificity, and stimulus-based. Nanosystems were extensively employed to incorporate active constituents, including nanospheres, nanocapsules, niosomes, liposomes, and dendrimers.

With artificial variation in drug release profile, drug release at a specific site could be achieved. The use of the carrier system has successfully bypassed the traditional drug delivery system, which has strong gastrointestinal consequences (gastric irritant drugs). Another reason for using a drug carrier system is to prevent the drugs from biodegradation and increase the bioavailability of specific drugs in the target tissue [4].

By 1992, with the advancements in research, a new carrier system made of mesoporous material gained much attention. The system was further utilized for large pore volume, having increased surface area and a well-organized structure. For the first time in 1998, Zhao and their co-workers synthesized Santa Barbara Amorphous (SBA-15), mesoporous silica with a hexagonal arrangement with high thermal stability, pore size, and surface area. Co-condensation and direct synthesis were the two most commonly used methods for functionalization. Much recently, these mesoporous particles gained more attention as nanoparticles due to their small size ranging from 0.6–1 nm. NSAIDs are muco-irritant and were loaded (as an adsorption phenomenon), especially in SBA-15, due to their nanosized. Once SBA-15 [5] was treated with hydrophobic octadecyl chains using the Surface functionalization technique, the release of the drug from the delivery system becomes quicker than SBA-1 [6].

Drugs of Biopharmaceutical classification system II (BCS-II) that followed the problem of low solubility, but high permeability was resolved using techniques including solid dispersion techniques, use of the drug in amorphous form, and complexation techniques. With an increase in solubility, the bioavailability of the longer half-life drugs also increased, which results in the accumulation of drugs leading to drug toxicity. Mesoporous silica materials (MSM) and other mesoporous particles exhibit hexagonal structure (MCM-41) having an increased surface area used as a reservoir for drug release. HMS and MCM-41 both were used as drug carriers for drugs that exhibit low solubility [7][8].

2. Film Coating

It is a process in which a thin coat of a polymer material is coated with oral solid dosage forms, including particles, granules, and tablets. Coating thickness may range from 20 to 100 μm [9].

2.1. Organic Film Coating

Based on the material used for the coating perspective, the binding material can be changed accordingly. Organic film coating may include water-based paints, lacquers, and enamel [10].

2.2. Aqueous Film Coating

The disadvantages of SC have led to the development of aqueous FC methods. Previously, these methods employed organic solvents, but due to the safety issue of these solvents, a better and more cost-effective method was developed in which the solvent was switched by aqueous-based FC [11]. These are applied as a thin film on the surface of the dosage form to obtain numerous benefits, including modified release, environmental protection, and taste masking. The coating depends on several factors, including tablet shape, the liquid used for coating purposes, equipment used for coating, and characteristics of the tablet surface. The coated film must be smooth in appearance, stuck smoothly with the tablet's surface, and maintains physical and chemical stability. Based on the solubility of the water and the former film polymer used, the coating could be done by the solution or dispersion method [12].

3. Polymers Used in Pharmaceutical Coating

3.1. CAP

To achieve enteric coating or controlled release of tablets or capsules CAP, phthalate, Cellacefate, cellulose acetate, and cellulose esters were commonly used. To provide delayed action regarding drug absorption, CAP disintegrates at a pH greater than 6, producing it as a natural polymer used for enteric coating. Its properties determine that it is hygroscopic, which makes it vulnerable to solubility and penetration of moisture into GI fluid [13]. The molecular weight of CAP represents another parameter that affects the properties of the polymer. The properties of polymer vary with variations in the factors like viscosity, surface tension, conductivity, and rheology. A polymer with lower molecular weight yielded beads, while fibers with large diameters were yielded with a high molecular weight polymer. Polymers with high molecular weight were utilized for electrospinning to achieve formulation-based required viscosity. The viscosity of a solution directly reflects the chain entanglement of polymer chains. In contrast, processing electrospinning chain entanglement of the polymer depicts a vital role [14].

3.2. Cellulose Acetate Trimellitate (CAT)

Both CAP and CAT are similar other than the occurrence of the carboxylic group on the aromatic ring of CAT.. Manufacturers quoted a value of 22% for acetyl and 29% for timellityl correspondingly. This polymer proves its

enteric coating property by dissolving at pH 5.5 in the upper part of the intestine. Dissolution studies further demonstrated that both CAP and CAT exhibit similar solubility properties in organic solvents. Meanwhile, regarding aqueous solvents, studies have demonstrated that, while achieving full enteric properties, ammoniacal solutions of CAT were utilized with water. The plasticizers recommended to be used with aqueous solvents include acetylated monoglyceride, diethyl phthalate, and triacetin [15].

3.3. Methylcellulose (MC)

One of the most commonly and commercially used polymers is MC. The polymer is cellulose ether and has several industrial applications. It is the cellulose derivative with a structure comprising a methyl group followed by anhydrous-D-glucose moiety, which substitutes hydroxyl group (OH) at positions of C-2, 3, and 6. One of the most important esters of the methyl family is methyl cellulose (MC). Structurally it consists of a methoxy group that accounts for approximately 27.5–31.5% of the whole MC. An aqueous solution of MC showed heat-related gelling properties. It is soluble in water. Its average molecular weight ranges between 10,000–220,000 daltons. It is most commonly used as a coating agent, binder, and disintegrant in oral solid formulations. Furthermore, it is also used for sustaining the drug release [16].

Polymer exhibits exceptional amphiphilic and physicochemical properties. Solubility of the polymer shifts from water-soluble towards organo-soluble, which depends upon the placement of the OH group upon its substitution from three to zero. Meanwhile, by increasing the temperature of the polymer towards a critical temperature, Singular thermal behavior was observed, which reduces the viscosity and produces an aqueous solution. With a constant rise in temperature, the lowest critical solution temperature (LCST) of the polymer MC was observed that produced a thermoreversible gel with augmented viscosity. Below LCST temperature MC is highly water soluble, while the polymer becomes insoluble at temperatures exceeding LCST. That could be the possible reason that the saturated solution of the polymer converts to a solid state upon heating [17].

3.4. Ethylcellulose (EC)

Directly, EC is water insoluble; it is further made water and fluid soluble after addition with other additives like HPMC. It is a partial derivative of cellulose ether (*O*-ethylated). EC is available in various molecular grades, which vary in viscosity. With the structural combination of alkali cellulose and ethyl chloride EC was prepared. The substitution of ethoxy groups was controlled throughout this reaction. In pharmaceutical formulations, EC is used as a binder, taste masking agent, and modified release agent [18].

The polymer is non-toxic, colorless, and tasteless and is widely used in organic solvents. EC can resist drug release. EC can also be used to incorporate materials by employing direct compression or wet granulation. Different microencapsulation techniques were used for the encapsulation of EC microparticles. It is one of the most widely used polymers for coating solid dosage forms that are water-insoluble [19]. Colorectal capecitabine-based microspheres were developed by Kumbhar et al. with the help of natural polysaccharide polymers to enhance cost-effectiveness. Microspheres were developed using single emulsification technology using calcium chloride ($CaCl_2$)

loaded with pectin, which was further coated with EC using the solvent evaporation technique. Furthermore, characterization of the microspheres was done, which includes particle size, Fourier-transform infrared spectroscopy (FTIR), surface electron microscopy (SEM), differential scanning calorimetry (DSC), drug release, and entrapment efficiency. Drug release studies observed that less than 20% of the drug was released in an acidic medium. An initial burst of drug release was observed, but at the end of the 12th hour, a total drug release of 85.33–95.55% was observed due to coating with EC. It was concluded that capecitabine-based microspheres loaded with pectin and coated with CE were also used effectively in the treatment of colon cancer and can replace conventional therapy [20].

3.5. Hydroxyethyl Cellulose (HEC)

It is a cellulose-based polymer used for gelling and thickening properties. HEC is further used in the hydrophilization process, which increases the solubility profiling of drugs within GI fluids. HEC has a molecular weight of 90 kDa, improved water solubility and neutral nature, making it an excellent candidate for drug carrier systems. Regarding its demand, its high biocompatibility, chemical stability, and exceptional thickening property make it a good candidate for pharmaceutical formulations. Before the formulation of a carrier system, the characteristics of both the drug and the carrier must be examined carefully [21].

It is further used as cleaning solutions, household products, and cosmetics due to its water-soluble and non-ionic abilities. HEC produces crystal-clear gels and solidifies the water phase of cosmetic emulsions. This polymer has a big disadvantage: it forms agglomerates or lumps when it first gets moistened with water. One of the grades of HEC, termed as R grade, is used for solution formation because no lumps were formed as it comes in contact with moisture and ultimately enhances solubility and processing time of the reaction [22]. Chowdary et al. developed a bilayer film-coated tablet of paliperidone. The tablet was further characterized for in vitro drug release studies. The tablet core was formulated with varying concentrations of polyox. An enteric coating optimized the coating with cellulose acetate and a sub-coating using HEC. Different influencing factors like the composition of tablet core and ingredients of the coating were investigated. The formulations were optimized by comparing the results of in vitro drug release studies [23].

3.6. Hydroxypropyl Methylcellulose (HPMC)

HPMC is a synthetic alteration of natural polymer. It is white to slightly off-white, odorless, and tasteless. It is a water-soluble polymer and can also be used in the controlled release delivery of tablets. It is also used for coated and uncoated matrix tablets. Upon hydration of the matrix with water, the polymeric chains disentangled [24]. Drug releases from drugs follow a two-way mechanism; in the first step, the drug is diffused from the gel layer of the polymer, while in the second mechanism, the release of the drug is followed by erosion of the swollen layer. As a result of the presence of cellulose ether, it is possibly used for the controlled release of oral drug delivery. HPMC can further be used for aqueous and solvent film coating. Matrix-based tablets could be developed using wet granulation or direct compression [25]. In another study conducted by Ifat Katzhendler et al., the release of naproxen and naproxen sodium was studied by varying the molecular weight of HPMC. It was concluded from the

results that when used alone, naproxen decreases the drug's solubility while naproxen sodium increases the system's pH and ultimately increases drug loading; hence, drug release also increases [24].

3.7. Polyvinyl Pyrrolidone (PVP)

It is a water-soluble polymer; its molecular weight ranges between 40,000 to 600,000 Daltons and can be distinguished into different grades. PVP is manufactured by polymerizing vinyl pyrrolidone in isopropyl alcohol or water (the chemical structure of which is represented. Due to the presence of the polar amide group and hydrophobic alkyl group, and the polar amide, it is highly water-soluble. Due to Its high degree of compatibility, it is an excellent candidate for a drug carrier system. PVP is a non-carcinogen, non-toxic, and temperature stable polymer. PVP exhibits a superior drug carrier system [26].

Different grades of PVP were used to enhance the bioavailability of poorly water-soluble drugs. In essence, it is used in tablet manufacturing as a binder. Granules produced by wet granulation using this polymer exhibit greater binding strength, low friability, and good flowability compared to other binders [27].

Tang et al. prepared paliperidone tablets using simple manufacturing and then coated them to produce a sustained effect. Tablets were evaluated and investigated for their in-vitro drug release behavior. Tablets were coated using a highly viscous HPMC K 100M and HPC coat. The in-vitro drug release parameters were evaluated considering different factors that include the core tablet composites, the material used for FC, and the formulation parameters. Gravimetric analysis was used to determine the drug release mechanism. The data obtained from drug release profiling were then put into the Peppas model. Drug releases at different intervals were then plotted in graphical form; the drug release was represented in the form of a slope at various time points. The results showed that the preparation could achieve better ascending drug release once the weight relation of paliperidone was 5:1 (core: layer). The fraction of HPMC and HPC was 33%. The ascending drug release was probably due to the penetration of solvent into the coated paliperidone tablets with the subsequent dissolution of the drug from the viscous polymer HPMC and HPC due to erosion of the matrix. Both erosion and diffusion mechanism of drug release was followed. It is concluded that coated tablets prepared by compression possibly are used for ascending control drug release over 24 h [28].

3.8. Shellac

Due to structural novelty, shellac was considered to have unique properties. It is composed of an ester complex with polyhydroxy polybasic acids. Shellac has various applications, including adhesiveness, insulator, film forming agent, and thermoplastic agent. As shellac is obtained from animal origin and is completely different from other polymers, the unavailability of resins, aromatic compounds, resumes, phenolic compounds, oxidized polyterpenic acids, and resinotannols give it unique properties [29].

Shellac consists of an acidic group with a high acidic dissociation value. Due to this, it is not easy for the group to dissociate in a gastric environment, which causes a decreased dissolution effect in the stomach (pH 2). With the modification of shellac chemical structure with the addition of sodium carbonate (alkaline group) performance of

shellac in the stomach was enhanced. In one study, nanoparticles and nanofibers of ketoprofen were formulated, incorporated with shellac, and done with its characterization (SEM, XRD, FTIR [30]). Results showed that nanocomposites were suitable for the controlled release of ketoprofen [31].

3.9. Sodium Carboxymethylcellulose (SCMC)

It has a further polynomial cross-linked form known as croscarmellose sodium. It has excellent swelling properties, hydrophilic with excellent absorbing properties. Commercially SCMC is available with varying degrees of substitution (DS) ranging from 0.7 to 1.2, with a subsequent amount of sodium content of 6.5–12% of total weight. SCMC is extremely hygroscopic in nature and absorbs more than 50% of water content. Tablets formulated by using SCMC tend to harden with time [18].

Croscarmellose sodium enhances the bioavailability of numerous formulations, giving excellent disintegration and dissolution characteristics. In oral formulations, croscarmellose sodium is used as a disintegrant. While related to the pharmaceutical industry, it is used to develop tablets with direct compassion and as an insecticide employed in the paper and textile industries. It behaves as a protective colloid to prevent water loss [32]. Shinde et al. tried to develop sustained swellable matrix release tablets using diltiazem hydrochloride as a model drug. The purpose of the dosage form was to improve the dissolution profile of the drug as the drug is more soluble in the upper part of the GI tract [33].

3.10. Zein

It is a natural polymer derived from plant origin and is more beneficial than synthetic polymers. It has applications for controlled drug release and biomedical purposes. Zein is highly nutritive due to the presence of numerous components, which include proteins. It comprises 50% corn protein and 6 to 12% protein according to its dry weight. About 25% of this protein is present between the bran and germ, while 75% of this protein is present in endosperm tissues. Zein is also used in vaccines, tissue engineering, and gene delivery. It is used as a biopolymer due to its two basic properties: biodegradability and biocompatibility [34]. A complete illustration of zein structure was not discovered until now, but with the help of chromatographic techniques, some of its characteristics were discovered in the 80s. With the help of the small-angle X-ray scattering (SAXS) technique, the helical structure (with ten successive folds) of zein was revealed [35]. Zein was obtained in α-, β-, δ-, and γ forms depending on the molecular weight and extraction method used. It was further used in various industrial fields, including adhesives, ink, food industry, ceramics, ink, chewing gums, candy formation, plastic packaging materials, and adhesives. Initially, zein was used as protective material on coated materials because it is more resistant to humidity, abrasion, and heat tolerable. Due to its low cost, it was also used as a taste-enhancing agent in an immediate release dosage form. It was concluded from a study that there appeared to be no influence of the coating process on the hardness of the core. However, tablets coated with zein (FC) showed a high strength compared to HPMC and CAP [35].

Zein exhibits excellent physical characteristics, which is why it is used in different formulations, including gels, fibers, films, nanoparticles, and for the controlled release of drugs in tablets. Products prepared using zein have improved shelf life because zein is resistant to water, heat, and abrasion [15]. Van et al. inspected zein as a coating material by preparing prednisolone for colon-specific drug delivery. A suitable proportion of zein and Kollicoat MAE 100P were prepared and tested to confirm the strengthening capacity of zein films. It becomes evident from the specific dosage form of the colon that zein exhibited an immediate release of the drug substance immediately as it reaches the basic medium of the intestine. Furthermore, the formulations were characterized by FTIR, and it was evident that different ratios of zein and Kollicoat MAE 100P experience physical interactions [36].

3.11. Eudragit L-100-55

It is a copolymer obtained from the esters of methacrylic acid and acrylic acid, where the functional group (R) is responsible for its physicochemical properties. Eudragit is anionic, white in color, and has free-flowing properties. It is used for entering coating purposes and dissolves at a pH of 5.5 or more [37]. One of the pharmaceutical industry's most commonly used pH-sensitive polymers is Eudragit because of their soluble nature at various pH ranges. At a pH higher than 5.5, Eudragit L100-55 controlled the release of the pharmaceutically active ingredient. There appeared a difference in Eudragit L100 and Eudragit L100-55 by substituting a methyl group rather than an ethyl group. The difference in the functional groups eventually imparts a change in the dissolution profile of both polymers at different pH values [38].

Alsulays et al. developed enteric coated tablets of lansoprazole to improve their physical and chemical properties by using a new technique named hot-melt extrusion. Kollidon 12PF was used as polymer, Lutrol F68 was used as a plasticizer, and magnesium oxide (MgO) as an alkalizing agent. An amorphous state of lansoprazole appeared and presented a better drug release when it was extruded with Kollidon 12 and Lutrol F68. At the same time, incorporating MgO improved the extrudability of lansoprazole and its release, resulting in more than 80% of drug release within the buffer zone [39].

3.12. Other Additives

Plasticizer

These are low molecular materials that were added to enhance the mechanical strength of a polymer [40]. Plasticizers weaken the intermolecular forces of the polymers, thereby reducing their rigidity and improving their coalescence properties while making films [40]. They can reduce the glass transition temperature of amorphous polymers, decrease the interactions of different polymers, and reduce the brittleness of films [40]. They alter the plasticity of film-forming polymers (FFP) in two basic ways, external and internal plasticizing. External plasticizing involves the use of plasticizers, while internal plasticizing appears to be due to a modification in chemical structure that ultimately changes its physical properties. External or internal plasticizers were used in an optimum range, which ranges from 1–50%, but most commonly 10% plasticizers were used. Polyethylene glycol and HPMC were the polymers most commonly and effectively used. Triacetin, a less commonly used plasticizer, protects the aqueous coating by creating a moisture barrier against the coat and protects the formulation [41].

Colorants and Opacifiers

To improve product identification, enhance the appearance of products, and decrease the risk of counterfeit products, colorants were added to the formulations. Opacifiers were used in those products that were damaged by light. The ideal concentration of colorants used in film coating formulations (FCF) ranges from more than 2% *w*/*w* for dark shade and 0.01% *w*/*w* for light shade.

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