



A REVIEW ON IMPACT OF POST COATING THERMAL TREATMENT ON THE QUALITY AND DRUG RELEASE OF FILM COATED TABLET (TRAMADOL)

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1. INTRODUCTION

Tablets are among the most convenient and preferred oral dosage forms because of their many advantages, including ease of administration, high patient compliance, and cost-effectiveness. Among the multiple steps in pharmaceutical manufacturing of tablets, coating is a critical process that is often used for functional and aesthetic reasons. Among three types of tablet-coating processes (sugar coating, film coating, and press coating), film coating is the most widely used approach to solve various issues encountered during manufacturing, transport, storage, and clinical use of drug products. For example, tablets containing active pharmaceutical ingredients (APIs) sensitive to light, oxidation, or moisture can be protected by film coating, leading to increased stability of drug products during manufacturing and storage.^[1,2]

In addition, film coating can control the drug release patterns of tablets in terms of site, rate, and time. Film coating is also applicable to mask taste and improve patient compliance. Accordingly, tablet film coating is widely used to achieve various pharmaceutical and therapeutic goals. Conventional solvent-based film coating involves deposition of a thin polymer film on the surface of the tablet core, typically using a spray method. The coating solution or suspension contains polymers and other ingredients such as pigments and plasticizers, which is sprayed onto a rotating tablet bed inside a pan. The drying process is accomplished by passing hot air through the tablet bed and permits removal of the solvent to leave a thin film on the surface of each tablet core.^[3,4]

Film formation depends on the physicochemical properties of polymers. Plasticizers are also used to reduce the glass transition temperature (T_g) and increase flexibility to avoid cracking and subsequent peel-off of polymer films. Many coating techniques have been developed for solvent-based or solvent free processes to improve the efficiency of the coating process. However, each method has its own advantages and disadvantages and may require continuous technical refinement. Tablet film coating is a technology-driven process, and the evolution of coated dosage forms depends on

advancements in coating technology, equipment, analytical techniques, and coating materials.^[5,6,7]

In film coating processes, the intra- and inter-batch coating uniformity of tablets is critical to ensure the quality of the final product. This is especially important for active film coating with an active pharmaceutical ingredient in the coating layer. Modeling approaches are also actively pursued to predict the influence of operation parameters on the quality of final products and optimize the process variables of tablet film coating. The concerted efforts of experiments and computational modeling can save time and cost to optimize the tablet coating process. This review covers a brief overview of tablet film coating technology and modeling approaches, with a focus on recent advancements in pharmaceutical applications.^[8,9,10]

Film Coating Methods

Organic solvent-based film coating: Although the use of organic solvent is not preferred, film coating with hydrophobic or lipophilic polymers requires the use of organic solvents due to the low aqueous solubility of coating materials.^[11,12]

The highly hydrophobic polymers are beneficial as moisture-protective coating polymers as they can reduce the water vapor permeability of the final film by preventing the movement of water molecules.^[13,14] In addition, coating process using organic solvents can also reduce drug degradation by hydrolysis. Therefore, organic solvent-based coating is useful for moisture sensitive drugs. The rate of evaporation of the solvent is crucial for the quality of final product and many variables including temperature, atmospheric pressure, and air movement should be adjusted to optimize the evaporation rate.^[15,16] Despite of pharmaceutical needs, organic solvent-based coating has many critical limitations because of potential toxicity of residual solvents, flammability, and environmental safety issues.^[17,18]

Even with a proper ventilation facility, it is difficult to completely remove organic solvent vapors from the coating room, increasing the risk of toxicity and explosion. Environmental and regulatory issues can increase the production costs. Aqueous film coating: Aqueous coating is a widely used film coating method in current pharmaceutical practice. It has many advantages over organic solvent-based coatings in terms of operator safety, environmental pollution, and risk of explosion.^[19,20]

Despite these benefits over organic solvent-based coating methods, aqueous coating also possesses certain drawbacks including energy- and time-consuming water evaporation process, longer processing time, validation of coating to control microbial presence, and potential activity loss of certain drugs caused by water or high coating temperature.^[21,22] In addition, preparation of an aqueous coating solution with water-insoluble polymers requires the addition of a suitable suspending agent or plasticizer for a homogeneous coating solution.^[23,24]

Although aqueous film coating has some limitations, it can avoid the safety issues associated with organic solvent-based coating, and thus it is still widely used in the pharmaceutical industry. There are continuous efforts to reduce the processing time and improve productivity by process automation, process validation, and development of more efficient equipment, such as side-vented perforated coating pans and fluidized bed equipment. Solvent-free coating: The use of solvents and heat exposure in the coating process can increase product instability, processing cost, and risk of environmental and safety hazards. Therefore, solvent-free coating methods have been actively pursued to overcome the drawbacks of solvent-based coating.^[25,26]

Solvent-free coating can reduce the process time and cost by avoiding expensive and time-consuming processes of solvent disposal. Furthermore, since it does not require drying in most cases, solvent-free coating is applicable to heat-sensitive drugs. Solvent-free coating includes various technologies such as compression coating, dry

powder coating, electrostatic spray powder.^[27] coating, and photocuring coating. Recently, injection molding coating and hot melt coating have also been proposed as dry coating processes that do not require solvent.^[28]

In the injection molding coating process, the upper and lower surfaces of tablets are coated in two steps using a vertical injection molding unit. It is important to choose the right polymer because quality varies depending on workplace humidity and polymer properties. As high temperature (over 80°C) is used for coating, it is important to examine the surface conditions of coated tablets after cooling.^[29,30]

Hot-melt coating is also a dry coating method in which a lipid excipient is heated for melting and then sprayed onto the surface of tablets to form a coherent coating layer. This method has advantages including a short process time and no chemical interactions between the tablet ingredients and the inert coating materials. However, the high process temperatures depending on the melting point of coating materials may affect the stability of the tablet ingredients. Like injection mold coating, many variables may occur depending on excipient characteristics.^[31,32]

Spray congealing or spray cooling is also a melting-based method that transforms a melt into spherical solid particles. This method has advantages including the absence of solvent, low cost, applicability to hygroscopic and water-sensitive substances, and the ability to obtain spherical free-flowing microparticles for tableting or capsule filling without the need of other downstream processes.^[33] Spray congealing technology includes three steps (feed, atomization, and solidification stages). The first step involves the preparation of the fluid consisting of the molten carrier and drugs.^[34]

As drugs may be dissolved or dispersed into the molten carrier, it is important to keep the fluid homogeneous for a uniform drug loading. During the atomization step, the molten fluid stream breaks up into small droplets that are quickly solidified upon cooling to produce the solid microparticles. In this process, viscosity is a critical factor deciding the viability of spray congealing and the size of produced microparticles. In general, spray congealing is not suitable for highly viscous molten mixtures that may clog the feed tube or atomizer.^[35,36]

Although solvent-free coating may overcome some issues associated with solvent-based coating, the requirements for specific coating conditions, equipment, and coating materials limit wide application of solvent-free coating in the pharmaceutical industry. Process Parameters and Factors Affecting Film Coating Quality In the conventional solvent-based pan coating process, tablets are filled into the coater that is generally operated in batch mode and the batch size is determined by the mass of tablets from the compression unit operation. During the process operation, the rotating pan allows

tablets to circulate along the coater walls.^[37,38]

When tablets pass the spray zone, the droplets of coating solution are deposited on the surface of tablets to form a coating film. At each cycle, tablets pass the spray zone with different orientation and thus the surfaces of tablets facing to the spray gun are frequently changed, leading to the entire surface coating of tablets. After drying by a combination of hot airflow supplied from the upper region of the coater and conduction from the heated tablet bed, the obtained film must be smooth and uniform.^[39,40]

However, the complexity of the coating process often leads to the coating defects including bridging, cracking, and orange-peel roughness. These defects are mainly because process parameters are not satisfactory. Therefore, optimization of coating formulations (compositions), process variables, and equipment parameters are critical to obtain the uniform and smooth coating layer.^[41,42]

Some of process parameters and factors affecting film coating quality are discussed below. Spray air flow rate: An important step in the coating process is spraying the coating solution. High-pressure atomization air disintegrates the coating solution into droplets that are pushed through the spray nozzle. If spraying only with atomization air, coating solution droplets may move directly into a narrow area of the tablet surface, which may cause problems with coating uniformity.^[43,44]

Therefore, both atomization and pattern air must act simultaneously to spray droplets homogeneously and widely. The ratio between atomization air and pattern air is an important parameter for coating efficiency. Atomization air and pattern air ratios closer to 1:1 correlate to smaller mean droplet size and better coating efficiency.^[45]

Along with the spray air, another important parameter that affects the coating process is spray rate. As spray rate increases, droplet size increases and droplet velocity decreases. Spray rate affects coating quality not only as an individual parameter but also as a composite parameter with atomization air and pattern air.^[46]

Because mean droplet size does not change significantly when the ratio of atomization air and spray rate is fixed, the atomization air/spray rate ratio is one of the most important parameters that affect droplet size and coating quality. In addition, droplet size determined by spray rate and atomization air is an important factor that determines the drying capacity in the coating process. Inlet air/Outlet air: Sprayed droplets of coating solution are transferred to the tablet surface and dried to form a coating film. Heat energy must be supplied to dry the coating pan via heated inlet air flow. The relative humidity of supplied inlet air can have a significant impact on the related humidity of the coating pan and outlet air, which in turn affects drying efficiency.^[47,48]

In cases of over-drying due to excessive inlet air supply, the coating droplet may be dried before it adheres to the tablet surface. This may generate a large number of polymer particles, resulting in a rough surface of the coated tablet. Conversely, if sufficient inlet air is not supplied for drying, twinning and tablet agglomeration may occur due to the viscosity of droplets on the wet tablet surface. Outlet air (exhausted air) temperature can indirectly indicate the temperature of the coating pan or tablet during the coating process. Generally, tablet temperature inside the coating pan is ~2–3°C lower than the outlet air temperature. Outlet air temperature should be changed according to the characteristics of the solvent or spray rate. Inlet and outlet air temperature can be controlled according to the coating machine brand.^[49,50]

Droplet size is highly affected by characteristics of the coating solution and process conditions. It also has a high correlation with coating efficiency. As the ratio of atomization air to pattern air approaches 1:1, droplet size becomes smaller and coating efficiency improves. In general, when droplet size decreases, a homogenous film layer is formed on the surface of tablets. Conversely, if the size of the droplet in contact with the tablet surface is too large, tablet surface roughness may increase. Droplet size is highly dependent on process conditions (spray air flow rate, spray rate, gun-to-bed distance, viscosity, etc.) and requires careful control.^[51,52]

Pharmaceutical Application of Film Coating

- Modified Drug Release
- Delayed Drug release
- Sustained Drug release
- Active film coating
- Improved Drug stability

TRAMADOL

Tramadol is a non-scheduled synthetic centrally acting opioid. It displays a dual action of being a μ -receptor agonist and weak inhibitor of norepinephrine and serotonin neuronal reuptake, which augments the efficacy of inhibitory spinal pathways. Tramadol is a racemic mixture of two enantiomers, with one enantiomer blocking norepinephrine reuptake and the other blocking serotonin reuptake.^[53] The effect of tramadol upon receptor reuptake contributes significantly to its analgesic properties. Its μ -receptor agonist properties occur primarily through its primary metabolite, *o*-desmethyltramadol.^[32] However, individuals with diminished capacity to metabolize tramadol still experience analgesia,^[33] and only approximately one third of analgesia from tramadol is reversible with the opioid receptor antagonist naxolone in healthy volunteers.^[54]

Preparations of tramadol are available for oral, rectal, intravenous, intramuscular, and subcutaneous administration. After oral administration, peak plasma concentration is achieved within 2 hours. However,

elimination is also rapid, with tramadol displaying a short elimination half-life of 5 to 6 hours.^[55] The consequent four-times-a-day dosing of tramadol limits its convenience of administration in the therapy of chronic pain. A sustained-released preparation of tramadol (tramadol ER) is now available utilizing a semipermeable membrane (Smartcoat; Biovail Corporation) that allows for the slow osmotic diffusion of the active ingredient in a pH-independent manner. Bioavailability of tramadol ER 200 mg is equivalent to tramadol immediate release 50 mg taken every 6 hours.^[56]

Tramadol is an atypical synthetic analgesic which has tremendous use in acute pain, dental pain, labor pain, chronic pain, cancer pain mostly due to its dual mechanism of action. Tramadol can interact with other drugs that share the same metabolic pathway and utilizes same enzymes, thus use of tramadol should be carefully monitored in the patients to avoid its misuse and associated adverse effects. However, tramadol has many side effects and thus the tramadol should be chosen carefully to treat the patients outlining the risk to benefits ratio and the patients must be monitored carefully for any possible side effects.^[57,58]

To avoid adverse effects newer drugs are needed and we propose tramadol-based derivatives for future and this review will give better insights to design them with lesser side effects and potent therapeutic activity with minimum side effects.^[59,60]

4. Mechanism of action (MOA)

Tramadol shows very good analgesic activity by its action on central nervous system. The racemic mixture of (+) dextro and (-) levo enantiomer of tramadol has synergistic analgesic effect. It acts by various pathways such as a weak MOR agonist or as a serotonin and norepinephrine reuptake inhibitors for the nociception. O-desmethyl tramadol metabolite (M1) of tramadol also shows analgesic action by acting as weak MOR agonist. The (+) enantiomer of tramadol acts as a MOR agonist and by inhibition of the reuptake of serotonin, whereas (-) enantiomer inhibits noradrenalin reuptake. Opioid receptors are G-protein coupled receptor and are of four types. The most commonly used opioids analgesic act on μ opioid receptor. The (+) Dextro enantiomer of Tramadol showed μ (μ) opioid receptor agonistic activity and enhance the activation of central dopamine.^[61,62,63]

1. IMPACT OF POST COATING THERMAL TREATMENT ON THE QUALITY AND DRUG RELEASE OF FILM COATED TABLET (TRAMADOL)

1. Investigation of the Drug Release and Surface Morphological Properties of Film-Coated Pellets, and Physical, Thermal and Mechanical Properties of Free Films as a Function of Various Curing Conditions

The purpose of the present investigation was to elucidate

the influence of curing on different physical properties of Eudragit® NE and RS coating systems. Increased curing times resulted in decreased drug release rates from Eudragit® NE-coated beads. However, an increase in drug release rates was noticed at longer curing times and higher temperatures for the Eudragit® RS coating system. The surface morphological changes of the film-coated beads revealed that there were no visible macroscopic changes as a result of curing. The absence of any ibuprofen melting peak in the DSC thermograms of cured NE and RS coated beads confirmed that there was no surface crystallization of ibuprofen. These results indicated that the increase in drug release rates from RS coated pellets, when subjected to long curing times, resulted from loss of plasticizer. Free films of Eudragit® NE exhibited an increase in tensile strength with increased curing times, whereas Eudragit® RS free films showed a decrease in tensile strength beyond 4 h of curing at 70 and 90 °C. The film thicknesses and weights of free films of Eudragit® RS prepared with triethyl citrate plasticizer were found to change more dramatically with curing than did free films of Eudragit® RS prepared with ibuprofen as the plasticizer. An increase in pore volume was also observed with increased curing times for Eudragit® RS free films. Such changes with curing were shown to be due to the loss of plasticizer molecules, leading to the formation of molecular-scale voids and channels.^[64]

2. Effect of thermal curing of the ethyl cellulose film on the rapidity

Coated pellets controlling drug release are a very popular dosage form which is widely used in medical practice. At present the coatings of water-insoluble polymers formed from aqueous dispersions are preferred. However, film formation from an aqueous polymeric dispersion is different from that from their organic solutions. A stable film on the pellets surface is produced by coalesces of discrete latex particles at an optimum temperature. The present experimental paper studied the changes of diclofenac sodium dissolution profiles from coated pellets, when their coatings from an aqueous polymeric dispersion of ethyl cellulose were cured for different time periods (1-72 hours) and a temperature of 60 degrees C. Drug release rate was decreasing with the increasing time of the layer curing up to 24 hours. At this time the dissolution curve was similar to a straight line. When the curing time further increased, the drug release was again faster. All prepared samples (with or without seal coat, cured for a period of 24 hour or uncured) were filled into hard gelatine capsules and stored in blisters in three different stability boxes (25 degrees C/60% RH, 30 degrees C/65% RH, 40 degrees C/75% RH) for 6 or 12 months. The best drug dissolution profile and stability were observed for the pellets with the seal coat and ethyl cellulose coating cured for 24 hours.^[65]

3. Characterization of the film formation of the dry coating process

As the film formation of the dry coating process differs

completely from conventional coating methods it is of certain interest to define a parameter like the minimum film formation temperature (MFT) used for aqueous dispersion-based processes in order to describe an efficient film formation. Film formation occurs mainly during the curing step following the coating phase. Therefore, the film formation of the dry coating process was analyzed with regard to the two process parameters influencing film formation, namely curing temperature and time. Theophylline pellets were coated using the enteric polymer HPMCAS and TEC/Myvacet as plasticizer composition. The polymer and the plasticizer were applied to the pellets simultaneously, except for the beginning of the coating step when the plasticizer has been sprayed 30 s before powder feeding was started. The coated pellets were cured for five different time periods at eight different temperatures. Drug release was determined in 0.1 N HCl. Their surface and cross-sectional morphologies were examined by scanning electron microscopy. The glass transition temperature of the obtained films as well as of the polymer plasticizer mixture obtained by casting a film using an organic solution of the coating components was determined by thermomechanical analysis. At higher curing temperature and/or extended curing time an enhancement of acid resistance is observed. The glass transition temperature of the coating mixture was determined to be 51.7 $\pm$ 3.3 degrees C. It is close to the temperature needed for film formation. Enteric resistant pellets are obtained after curing for 0.75 h at 55 degrees C. However, enteric resistance was achieved as well slightly below the glass transition temperature at 45 degrees C applying long curing periods of at least 12 h. This may be caused by the plasticizer gradient along the coat which is caused by spraying the plasticizer 30 s before starting powder feeding. This results in a higher plasticizer concentration of the inner layers of the coat relatively to the outer ones. Due to this film formation starts at the inner layers even below the glass transition temperature. As the plasticizer diffuses to the outer layers during curing according to the plasticizer gradient, film formation proceeds.^[66]

4. Influence of curing on the adhesive and thermomechanical properties of an applied acrylic polymer

The objective of the current study was to investigate the relationship between polymer adhesion and post-coating thermal treatment. A novel adhesion technique was used to quantify the adhesive properties of applied acrylic films. Differential scanning calorimetry was used to determine the glass transition temperature of the applied polymer. Post-coating thermal treatment, or curing, was found to significantly influence the adhesive and thermomechanical properties of the applied film coating. Adhesion of triethyl citrate-plasticized films to tablets increased during storage at elevated temperatures, equilibrating within four hours. The glass transition temperature of the applied triethyl citrate-plasticized coatings also increased during curing. Equilibration of polymer properties was found to be dependent on the

hydrophobicity of the plasticizer incorporated into the coating formulation, with longer curing times required for films containing the hydrophobic plasticizer tributyl citrate. The curing temperature was shown to influence polymer properties, with stronger film-tablet adhesion and higher glass transition temperatures resulting when the coated tablets were stored at higher temperatures. Substrate hydrophobicity was also found to influence the curing process, suggesting that the mechanisms involved in film formation and polymer-substrate adhesion may contribute to the internal stresses within the film.^[67]

5. Effect of thermal gelation on dissolution from coated tablets

Tablets with a methylcellulose coating were found to exhibit lower dissolution profiles than those coated with a hydroxypropyl methylcellulose coating at 37 degrees, and the cause was investigated. The differences are attributed to thermal gelation of the methylcellulose at temperatures near 37 degrees, which creates a barrier to the dissolution process and essentially changes the dissolution mechanism. This mechanism is substantiated by the fact that at temperatures below the gel point and at increased agitation, the effect disappears. The retarded dissolution effect is not peculiar to the drug involved.^[68]

6. Effect of heat on characteristics of chitosan film coated

The effect of heat on the characteristics of chitosan film coated on theophylline tablets was studied. Chitosan of high viscosity grade with molecular weight in the range of 800,000-1,000,000, 80-85% degree of deacetylation was used as a film former by dissolving in 1% v/v acetic acid solution. The coated tablets had been cured at 40, 60, and 100 degrees C for 6, 12, and 24 hr. The morphology of the film at the edge and surface of coated tablets was investigated using scanning electron microscopy. Film cracking was increased and clearly observed in the coated tablets cured at 100 degrees C for 24 hr. As a result, more water could be absorbed into the tablets, followed by faster disintegration and faster drug release. The evidence of partial conversion of chitosonium acetate to chitin in the ¹³C nuclear magnetic resonance (NMR) spectra of chitosan films cured at 40, 60, and 100 degrees C was observed, but it had no effect on drug release behavior. Theophylline tablets coated with chitosan films gave sustained release behavior in various media, i.e., distilled water, 0.1 N hydrochloric acid, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. In addition, the film coating temperature at 55-60 degrees C and curing process at 40 and 60 degrees C had no effect on the drug release from theophylline tablets coated with chitosan polymer. Finally, it might be concluded that both the physical and chemical properties of chitosan films were affected by heat.^[69]

7. Curing of aqueous polymeric film coatings: Importance of the coating level and type of plasticizer

The aim of this study was to better understand the effects

of the curing conditions on the resulting drug release patterns from pellets coated with aqueous polymer dispersions. Diltiazem HCl was used as model drug, ethylcellulose as polymer, triethyl citrate (TEC), dibutyl sebacate (DBS), and distilled acetylated monoglycerides (Myvacet) as plasticizers. Interestingly, the effects of the curing conditions strongly depended on the coating level and the type of plasticizer: in the case of TEC, the drug release rate monotonically decreased with increasing harshness of the curing conditions (time, temperature, and relative humidity), irrespective of the coating level. In contrast, in the case of DBS and Myvacet, this type of relationship was only observed at low coating levels (5%). At intermediate coating levels (around 7.5%), the curing conditions had virtually no effect on drug release. At high coating levels (10%), the release rate initially increased and then decreased with increasing harshness of the curing conditions. This more complex behavior might be attributable to the superposition of two competing phenomena: improved film formation and drug migration into the polymeric membrane. Furthermore, it could be shown that the type of plasticizer had a major effect on drug release in not fully coalesced and equilibrated film coatings, whereas the release profiles were similar for all plasticizers in the case of completely formed and equilibrated film coatings. Importantly, the latter systems were stable for long term even during storage under stress conditions.^[70]

8. Modulation of Tramadol Release from a Hydrophobic Matrix: Implications of Formulations and Processing Variables

In the present investigation, hydrogenated cottonseed oil (HCSO) was evaluated as a sustained release matrix for a freely soluble drug, tramadol. Hydrophobic matrix tablets of tramadol was evaluated by compression of physical mixture of drug and wax, dispersion of drug in HCSO by hot fusion or solubilisation techniques. The method of preparation of tablet had a significant effect on drug release with higher release observed from direct compression matrices and slower release from matrix prepared by dispersion (hot-fused matrices). Influence of addition of hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, polyethylene glycol 4000 and surfactants like sodium lauryl sulphate and polysorbate 20 to HCSO matrix on drug release was investigated. The added excipients exhibited a propensity to enhance drug release from the HCSO matrix. NaCMC was effective at a lower ratio (<10% w/w) and when incorporated at higher level made HCSO matrix to erode and disintegrate in a short period.^[71]

9. Hot-Melt Extrusion: from Theory to Application in Pharmaceutical Formulation

Hot-melt extrusion (HME) is a promising technology for the production of new chemical entities in the developmental pipeline and for improving products already on the market. In drug discovery and development, industry estimates that more than 50% of active pharmaceutical ingredients currently used belong

to the biopharmaceutical classification system II (BCS class II), which are characterized as poorly water-soluble compounds and result in formulations with low bioavailability. Therefore, there is a critical need for the pharmaceutical industry to develop formulations that will enhance the solubility and ultimately the bioavailability of these compounds. HME technology also offers an opportunity to earn intellectual property, which is evident from an increasing number of patents and publications that have included it as a novel pharmaceutical formulation technology over the past decades. This review had a threefold objective. First, it sought to provide an overview of HME principles and present detailed engineered extrusion equipment designs. Second, it included a number of published reports on the application of HME techniques that covered the fields of solid dispersions, microencapsulation, taste masking, targeted drug delivery systems, sustained release, films, nanotechnology, floating drug delivery systems, implants, and continuous manufacturing using the wet granulation process. Lastly, this review discussed the importance of using the quality by design approach in drug development, evaluated the process analytical technology used in pharmaceutical HME monitoring and control, discussed techniques used in HME, and emphasized the potential for monitoring and controlling hot-melt technology.^[72]

10. Strategies to improve the stability of amorphous solid dispersions in view of the hot melt extrusion (HME) method

Oral administration of drugs is preferred over other routes for several reasons: it is non-invasive, easy to administer, and easy to store. However, drug formulation for oral administration is often hindered by the drug's poor solubility, which limits its bioavailability and reduces its commercial value. As a solution, amorphous solid dispersion (ASD) was introduced as a drug formulation method that improves drug solubility by changing the molecular structure of the drugs from crystalline to amorphous. The hot melt extrusion (HME) method is emerging in the pharmaceutical industry as an alternative to manufacture ASD. However, despite solving solubility issues, ASD also exposes the drug to a high risk of crystallisation, either during processing or storage. Formulating a successful oral administration drug using ASD requires optimisation of the formulation, polymers, and HME manufacturing processes applied. This review presents some important considerations in ASD formulation, including strategies to improve the stability of the final product using HME to allow more new drugs to be formulated using this method.^[73]

11. Quality-by-design in hot melt extrusion based amorphous solid dispersions: An industrial perspective on product development

An industrially feasible approach to overcome the solubility and bioavailability limitations of poorly soluble active pharmaceutical ingredients is the development of amorphous solid dispersions (ASDs)

using hot-melt extrusion (HME) technique. The application of Quality by Design (QbD) had a profound impact on the development of HME-based ASDs. The formulation and process optimization of ASDs manufactured via HME techniques require an understanding of critical quality attributes, critical material attributes, critical process parameters, risk assessment tools, and experimental designs. The knowledge gained from each of these QbD elements helps ensure the consistency of product quality. The selection and implementation of appropriate Design of Experiments (DoE) methodology to screen and optimize the formulation and process variables remain a major challenge. This review provides a comprehensive overview on QbD concepts in HME-based ASDs with an emphasis on DoE methodologies. Further, the information provided in this review can assist researchers in selecting a suitable design with optimal experimental conditions. Specifically, this review has focused on the prediction of drug-polymer miscibility, the elements and sequence of QbD, and various screening and optimization designs, to provide insights into the formulation and process variables that are encountered routinely in the production of HME-based ASDs.^[74]

2. CONCLUSION

Post-coating thermal treatment, also known as curing, plays an important role in determining the quality, stability, mechanical properties, and drug release characteristics of film-coated tablets. The literature reviewed indicates that curing temperature and duration, polymer type, plasticizer composition, and coating thickness significantly influence film formation, adhesion, porosity, and dissolution behavior. Appropriate thermal treatment can improve polymer coalescence, enhance film integrity, and provide more consistent drug release. However, excessive temperature or prolonged curing may cause plasticizer loss, film cracking, changes in polymer properties, and undesirable variations in drug release.

In the case of tramadol tablets, controlling drug release is particularly important for achieving the intended therapeutic effect and maintaining consistent product performance. Although the reviewed studies provide useful insights into the effects of thermal treatment on different pharmaceutical coating systems and the release of tramadol from hydrophobic matrices, direct evidence specifically evaluating post-coating thermal treatment in film-coated tramadol tablets remains limited in the reviewed literature. Therefore, further experimental studies are required to establish the optimum curing temperature and duration for tramadol film-coated tablets. Such studies should include dissolution testing, surface morphology analysis, thermal characterization, mechanical strength evaluation, and stability studies. Overall, careful optimization of post-coating thermal treatment can contribute to improved film-coated tablet quality, reliable drug release, and consistent pharmaceutical product performance.

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