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Polymer Selection and Characterization for Hot Melt Extruded Formulations: A Review of Recent Advances and Challenges

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ABSTRACT

The purpose of this literature review is to investigate the selection and characterization of polymers for Hot Melt Extrusion (HME) formulations, a novel pharmaceutical manufacturing technology that improves the solubility and bioavailability of pharmaceuticals with low water solubility. Thermal processing of heat-sensitive drugs and polymers with undesirable properties is difficult. Creating superior HME formulations requires understanding these elements. In the pharmaceutical industry, studying starch thermal degradation and stability under different processing conditions is useful. The study examines how amylose and amylopectin ratios, starch modification, and processing environment affect starch-based materials, emphasizing the importance of chemical and thermal stability, drug-polymer interactions, drug loading, miscibility, and compatibility in HME formulations. Improved HME technology has improved medical formulations, especially abuse-deterrent formulations. The thermal properties of HME polymers have improved with the addition of high thermal conductivity nanofillers. HME product quality and productivity depend on process understanding and optimization. To translate laboratory-scale formulations to commercial production, scale-up methods for HME products have been extensively researched. The requirements, challenges, and opportunities of using HME technology in pharmaceutical manufacturing have been extensively studied.

Keywords: Hot Melt Extrusion, Thermal Processing, Pharmaceutical Formulations, Polymer selection, Drug-Polymer Interactions

1. Introduction

Hot melt extrusion (HME) is a novel pharmaceutical manufacturing technology that has several benefits compared to conventional processing techniques for creating solid dispersions, implants, and other drug delivery systems. HME allows for the uninterrupted manufacturing of pharmaceutical formulations, resulting in enhanced operational effectiveness, consistent product characteristics, and heightened oversight of essential quality features. (Patil and colleagues 2015). The method entails the process of liquefying and transporting a mixture via a cylindrical device called an extruder, utilizing mechanical cutting and high-temperature [1]

Nevertheless, the choice and analysis of polymers are essential factors in determining the effectiveness of HME formulations [2]. The majority of polymers are unsuitable for direct use in HME because to their elevated melt viscosity and susceptibility to thermal breakdown at the necessary processing temperatures[2,3]. Hence, it is crucial to conduct a thorough assessment of the chemical and thermal stability of polymers, together with their rheological and physicomechanical characteristics, to achieve effective product development in the field of HME [4]. The use of HME has been extensive in improving the solubility and bioavailability of pharmaceuticals that have low water solubility. This is achieved by creating amorphous solid dispersions [5]. The system has several benefits compared to traditional ways of creating solid dispersions, such as uninterrupted production, increased drug concentration, and enhanced process regulation [5]. However, obstacles exist in the thermal processing of heat-sensitive medicines and polymers with undesirable characteristics [6,7]

The dissolution enhancement and stability of HME products are greatly influenced by the physical state of the drug, drug loading, and drug-polymer interactions [8]. Therefore, the careful choice and analysis of polymers are crucial in maximizing the effectiveness of HME formulations [9]. Although HME has demonstrated efficacy in manufacturing several drug delivery systems [10], there are still difficulties in the thermal treatment of heat-sensitive medicines and polymers [11].

HME is a beneficial method for pharmaceutical manufacture. Nevertheless, meticulous polymer selection and characterisation are required for the development of superior HME formulations. The purpose of this literature review is to offer a thorough and detailed examination of the current progress and difficulties in choosing and characterising polymers for HME formulations.

2. Physicochemical factors in polymer selection

In the process of selecting and characterizing polymers for HME formulations, it is necessary to assess several physicochemical variables to guarantee the stability and effectiveness of the final products. These aspects are essential in the effective design and optimization of HME processes. Multiple research projects have enhanced our understanding of these physicochemical parameters, providing insights into their significance for the advancement and refinement of HME processes.

A study, conducted a thorough assessment of various aspects related to extrudates, including their chemical and thermal stability, solid physical state, potential interactions between drugs and polymers, the miscibility and solubility of drug-polymer systems, the rheological properties of extrudates, and the physicomechanical properties of films produced through HME. This article provides the physicomechanical properties of films produced through HME. This article provides a thorough examination of the physicochemical variables that must be explored while developing and refining a HME process [4]. The process involved in the hotmelt extrusion of pharmaceuticals is shown in Figure 1. The evaluation of the solid physical state of extrudates, including whether they are amorphous, crystalline, or partially amorphous, provides critical information on product stability during shelf life, crystallization propensity, drug dissolution, and drug bioavailability, as well as

process efficiency. Additionally, the miscibility/solubility of the drug-polymer system is essential for understanding the dissolution behavior and bioavailability of the drug. The rheological properties of extrudates play a crucial role in determining the processability and manufacturability of HME products, while the physicomechanical properties of films produced by HME are essential for ensuring the integrity and performance of the final dosage form. Furthermore, the drug-polymer interactions and the thermal stability of the extrudates are critical factors that influence the stability, bioavailability, and performance of the final pharmaceutical product. In the future, the insights gained from the evaluation of these physicochemical factors will contribute to the development of innovative pharmaceutical products and drug delivery systems. The optimization of HME processes based on a comprehensive understanding of these factors will lead to the development of high-quality, effective, and stable pharmaceutical formulations. This will open up new opportunities for the pharmaceutical industry to address the challenges associated with drug solubility, bioavailability, and stability, ultimately leading to the development of improved drug products for patient care [4].

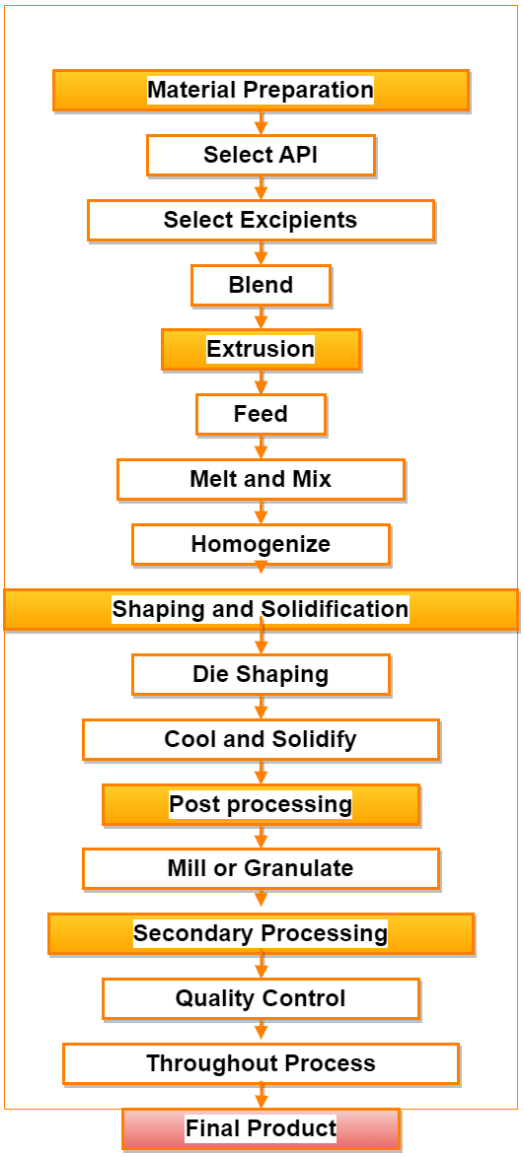

Figure 1: A flow chart of the steps involved in the hot melt extrusion process of pharmaceuticals.[12,13]

The study by Liu et al. provides valuable insights into the process of thermal degradation and stability of starch under various processing circumstances, particularly focusing on the impact of the ratios of amylose and amylopectin on the thermal stability of extrudates made from starch. This study enhances our comprehension of how the mix of polymers affects the stability of HME products. The authors examined the thermal degradation and stability of starch and starch-based materials, including the effect of amylose/amylopectin contents, starch modification, and the effect of processing environment, such as in open or sealed systems, and shear less or shear stress conditions. The study sheds light on the fundamental sciences and various detecting techniques related to starch thermal degradation and stability, providing a comprehensive understanding of the impact of processing conditions on the properties of starch-based materials[14]. The findings of this study have significant implications for the pharmaceutical industry, particularly in the development and optimization of HME processes. Understanding the thermal degradation and stability of starch under different processing conditions is crucial for ensuring the quality and performance of HME products. The insights gained from this study can contribute to the improvement of HME processes in the pharmaceutical industry. Critical evaluation parameters for HME products are given in Table 1.

Table 1: An overview of critical evaluation parameters of Hot Melt Extruded pharmaceutical products

Evaluation Parameters	Description
Drug Content Uniformity	Ensuring consistent drug concentration throughout the extrudate[15,16]
Particle Size Distribution	Measuring the size range of particles within the extrudate[1,17]
Melting Point	Determining the temperature at which the extrudate melts[18]
Crystallinity	Assessing the crystalline structure of the drug within the extrudate[19]
Tensile Strength	Measuring the extrudate's resistance to breaking under tension[20]
Elasticity	Evaluating the ability of the extrudate to return to its original shape[21]
Thermal Stability	Assessing the stability of the extrudate when exposed to heat[22,23]
Dissolution Rate	Determining the rate at which the extrudate dissolves in a solvent[23]
Drug Release Profile	Analyzing the pattern of drug release from the extrudate over time[24]
Manufacturability	Considering the ease and efficiency of manufacturing the final dosage form[25]
Stability	Assessing the long-term stability of the extrudate under various conditions[26]

A study addressing the challenges in precisely determining the specific molecular interactions and binding patterns between drugs and polymeric inhibitors in solid form. The authors emphasize the significance of comprehending the molecular interactions between drugs and polymers to create stable amorphous solid dispersions. This study enhances our comprehension of how the mix of polymers affects the stability of HME products. The authors examined the molecular interactions and binding patterns between drugs and polymeric inhibitors, shedding light on the complexities of creating stable amorphous solid dispersions. The study provides valuable insights into the impact of polymer-drug interactions on the stability and performance of HME products, offering a deeper understanding of the molecular mechanisms underlying the formation and stability of amorphous solid dispersions.[27]

The findings of this study have significant implications for the pharmaceutical industry, particularly in the development and optimization of HME processes. Understanding the specific molecular interactions and binding patterns between drugs and polymeric inhibitors is crucial for ensuring the quality and stability of amorphous solid dispersions. The insights gained from this study can contribute to the improvement of HME processes in the pharmaceutical industry, leading to the development of high-quality, stable, and effective pharmaceutical formulations.

A study that investigated the interaction between drugs, polymers, and water, and its impact on the ability of amorphous solid dispersions to dissolve. The research provides valuable information about the physical and chemical properties involved in drug-polymer-water interaction and how they relate to the dissolution performance of amorphous solid dispersions. The study explores the drug crystallization tendency in aqueous medium, drug-polymer interaction before and after moisture exposure, supersaturation of drug in the presence of polymer, and polymer dissolution kinetics. These characteristics were characterized and correlated with the dissolution performance of amorphous solid dispersions at different doses and drug/polymer ratios[28] . The findings of this study have significant implications for pharmaceutical formulation development, particularly in the design and optimization of amorphous solid dispersions. Understanding the drug-polymer-water interaction and its influence on dissolution performance is crucial for ensuring the efficacy and stability of pharmaceutical products. The insights gained from this research can contribute to the improvement of drug delivery systems, leading to the development of high-quality, stable, and effective pharmaceutical formulations.

These studies emphasize the importance of assessing the chemical and thermal stability of extrudates, comprehending drug-polymer interactions, and taking into account the effects of drug loading, drug-polymer miscibility, and drug-polymer compatibility on the stability and performance of HME products. A thorough grasp of these aspects is vital for selecting and characterizing polymers for HME formulations. It is necessary for the effective development and optimization of HME procedures.

3. Novel Applications and Challenges

Recent advancements in HME technology have led to significant advances in the development of medical formulations via polymer selection. The thermal conductivity of carbon nanotubes and their polymer nanocomposites was investigated, stressing the current focus on increasing the thermal conductivity of polymers by utilizing nanofillers with high thermal conductivity.[29,30] This advancement has offered the potential to increase the thermal properties of polymers used in HME formulations.[31]

The study provides a summary of the application of HME technology in the development of abuse-deterrent formulations (ADFs). The authors highlight the innovative application of scalable and uninterrupted manufacturing methods, such as HME, to improve the development and manufacture of ADF. This underscores the significance of HME in addressing the pharmacological challenges linked to abuse-deterrent formulations. The study sheds light on the potential of HME technology to meet the growing needs of the pharmaceutical sector, particularly in the development of abuse-deterrent medicine formulations.

The industry's commitment to addressing significant pharmacological issues is seen in the innovative application of HME in developing abuse-deterrent formulations. Pharmaceutical companies may enhance the research and production of abuse-deterrent formulations (ADFs) by utilising scalable and continuous manufacturing methods, hence promoting the progress of abuse-resistant medicine products. This exemplifies the capacity of HME technology to foster innovation and tackle significant pharmacological challenges in the pharmaceutical industry.[32] The successful formulation of pharmaceuticals or active pharmaceutical ingredients (APIs) using HME with diverse polymers or excipients has demonstrated the versatility and usefulness of this technology. For example, to address the issue of insufficient drug breakdown and bioavailability, we investigated the function of functional excipients in solid oral dosage forms. The authors underlined the formulation approaches explored, such as melt extrusion/granulation, creation of solid dispersions,

and synthesis of inclusion complexes, which illustrate the wide variety of applications of HME in the development of pharmaceutical formulations.[33] A study was also conducted on the creation of aripiprazole-loaded pH-modulated solid dispersions utilising HME technology. Their study looked into the usage of acidifiers in solid dispersions as well as the use of HME technology in the production of solid dispersions. These tactics were proven to be effective in increasing medication release and bioavailability. This demonstrates the successful creation of aripiprazole using HME, demonstrating its capacity to increase medicine administration and therapeutic effects.[34] A recent study also highlighted the problems in thermal processing and formulation processes. The problems and procedures involved in the thermal processing of amorphous solid dispersions were examined, stressing the continuous importance of thermal processing in the pharmaceutical sector for amorphous solid dispersions. This underscores the importance of developing novel approaches to address the issues associated with thermal processing in HME formulations.[7]

To recap, recent advancements in HME technology addressing the selection of polymers, as well as the successful production of medications and APIs using HME, have demonstrated the efficacy of this technology in overcoming pharmaceutical challenges. Nonetheless, the field of HME still has challenges in thermal processing and formulation processes, which are being actively researched. This emphasizes the significance of continual innovation and improvement in this field of study.

4. Characterization Techniques

Characterization techniques are essential for assessing the physical and chemical features of HME products. These techniques offer valuable information on the solid physical state, drug distribution, and rheological aspects of the products. A variety of sophisticated methods have been utilised to analyse HME formulations, aiding in the thorough comprehension of their characteristics and behaviour.

Terahertz Raman imaging, spectroscopy, and microscopy are now important techniques for studying the physical properties and distribution of APIs in HME formulations. Terahertz Raman imaging was used to confirm the appropriateness of distinguishing distinct solid physical states of APIs inside a polymer matrix and visualising their distribution in Hot Melt Extrudates. This method allows for the direct observation of the distribution of APIs, providing vital information on their spatial arrangement inside the formulations [35]. Investigations on the rheology of polymer blends in HME formulations have played a crucial role in comprehending the flow characteristics and mechanical attributes of HME products.[36] Performed rheological analyses to assist in the informed determination of the optimal processing temperature for the production of copovidone-nifedipine amorphous solid dispersions using HME. Their research emphasized the importance of rheological characterization in optimising the processing parameters for preparing amorphous solid dispersions, highlighting the function of rheology in formulation development.[37]

It is crucial to compare the benefits and drawbacks of various characterization approaches in order to assess the physical and chemical features of HME products. This comparison is necessary to choose the most appropriate methods for characterization. Explored different methods, such as differential scanning calorimetry, Fourier transform infrared spectroscopy, near-infrared spectroscopy, Raman spectroscopy, solid-state nuclear magnetic resonance, and polarised light microscopy, and their individual strengths and weaknesses in distinguishing between crystalline and amorphous states of an API.[38] This comparative analysis offers significant insights into the strengths and limits of various characterization approaches, assisting researchers in choosing suitable methods for characterizing HME products.[39] Furthermore, chemical imaging methods, such as confocal Raman spectroscopy and broadband coherent anti-Stokes Raman scattering (BCARS)

microscopy, have been used to evaluate the qualitative and quantitative properties of complex drug formulations. This study compared the capabilities of BCARS microscopy with spontaneous Raman microscopy in evaluating multicomponent medicines. The findings shed light on the possibilities of chemical imaging methods for characterising pharmaceuticals.[40]

To summarise, the use of advanced methods for analysing HME formulations, such as terahertz Raman imaging, rheological studies, and chemical imaging, has greatly enhanced our understanding of their physical and chemical properties.[41,42]

5. Process Understanding and Optimization

The understanding and optimization of HME processes are essential for ensuring the quality and productivity of HME products. Advanced process monitoring and visualization solutions have been instrumental in gaining insights into material behavior in the extrusion barrel. implemented a Raman probe in each section of the barrel to visualize the material behavior in the extrusion barrel, providing valuable insights into the process understanding of a laboratory-scale extrusion process [43]. Similarly, elucidated and visualized solid-state transformation and mixing in a pharmaceutical mini HME process using in-line Raman spectroscopy, demonstrating the potential of in-line Raman spectroscopy for process understanding and optimization.[44]

The influence of extrusion speed, temperature, feed rate, screw configuration, and die geometry on the quality and productivity of HME products has been a subject of active research. highlighted the considerable variation in product quality based on extruder type, screw configuration, feed moisture, and temperature profile in the barrel session, screw speed, and feed rate. This emphasizes the need for a comprehensive understanding of the influence of process parameters on the quality and productivity of HME products.[45]

Cleaning-in-place (CIP) strategies for pharmaceutical HME have been essential for maintaining the integrity and cleanliness of the extrusion equipment. discussed novel CIP strategies for pharmaceutical HME, emphasizing the importance of efficient cleaning strategies to ensure the quality and safety of HME products.[46] Furthermore, highlighted the challenges in eliminating established biofilms during CIP procedures, underscoring the need for robust CIP strategies to maintain equipment cleanliness and product quality.[47]

In addition, in-line monitoring and process analytical technology (PAT) have been instrumental in optimizing HME processes. used in-line near-infrared (NIR) spectroscopy for the understanding of polymer-drug interaction during pharmaceutical hot-melt extrusion, demonstrating the potential of in-line spectroscopic monitoring for process optimization.[43] Similarly, utilized in-line UV-Vis spectroscopy as a fast-working PAT during early phase development of a hot-melt extrusion process, highlighting its potential for process understanding and control.[48]

6. Scale-Up and In-Vivo Assessment of HME Products

The scale-up methods for the preparation of HME products have been a focus of extensive research to facilitate the translation of laboratory-scale formulations to commercial production. A study provided a comprehensive review of the scale-up process for HME, highlighting the challenges and opportunities associated with transitioning from small-scale to large-scale production. This review emphasized the importance of process optimization and scale-up strategies to ensure the successful commercialization of HME products. Additionally, Repka et al. discussed different scale-up strategies for HME, including power scale-up, volumetric scale-up, and heat transfer scale-up, providing valuable insights into the process [1,15].

A fast-track roadmap for developing HME-based drug products, providing a comprehensive workflow from concept to clinical batch in less than a year was demonstrated in a study. The study focused on the scale-up process for HME, emphasizing the challenges and opportunities associated with transitioning from small-scale to large-scale production. By implementing a rational workflow, the researchers successfully developed enabling formulations, such as amorphous solid dispersions, via HME. This exemplifies the efficient translation of laboratory-scale formulations to commercial production, highlighting the importance of process optimization and scale-up strategies to ensure the successful commercialization of HME products [49]

In-vitro and in-vivo taste assessment of bitter drugs has been a critical aspect of pharmaceutical development, particularly in the context of pediatric formulations. Two authors discussed the taste-masking mechanism of chitosan at the molecular level for bitter drugs, providing insights into the potential of taste-masking technologies for improving the palatability of bitter drugs [50,51]. Additionally. A study conducted in-vivo characterization of bitter taste thresholds in chickens, demonstrating the application of in-vivo taste assessment in animal models for understanding taste perception [52]. In their study, researchers investigated the taste-masking mechanism of chitosan at the molecular level for bitter drugs, providing insights into the potential of taste-masking technologies for improving the palatability of bitter drugs. The study focused on the in-vitro and in-vivo taste assessment of bitter drugs, particularly in the context of pediatric formulations. By elucidating the taste-masking mechanism of chitosan, the researchers aimed to enhance the palatability of bitter drugs [1,51].

The pharmaceutical applications of HME have been the subject of extensive research, with a focus on the requirements, challenges, and opportunities associated with the implementation of HME in pharmaceutical manufacturing. An update on the contribution of HME technology to novel drug delivery, highlighting the requirements and challenges associated with the implementation of HME in pharmaceutical manufacturing was reported[53]. This review emphasized the opportunities for leveraging HME technology to develop innovative pharmaceutical products and drug delivery systems. The challenges associated with HME technology include the selection of suitable pharmaceutical-grade polymers and excipients, achieving consistent and reproducible product quality at a larger scale, and meeting regulatory requirements for continuous manufacturing via HME. These challenges require careful material selection, process optimization, and compliance with regulatory guidelines to ensure the successful implementation of HME in pharmaceutical manufacturing. On the other hand, the opportunities presented by HME technology include the development of novel drug delivery systems, intellectual property generation, and the potential for continuous manufacturing processes[54]. HME offers opportunities for the development of controlled-release formulations, multiparticulate systems, and personalized drug delivery devices. Additionally, the increasing number of patents and publications related to HME technology presents opportunities for intellectual property generation and innovation in pharmaceutical formulations.[55]

Continuous manufacturing via HME has emerged as a promising alternative for achieving efficient and cost-effective pharmaceutical production.[56,57] Authors discussed the regulatory matters associated with continuous manufacturing via HME, emphasizing the potential of this approach to meet the evolving regulatory requirements and quality standards in pharmaceutical manufacturing. This review highlighted the advantages of continuous manufacturing processes, such as reduced cost, increased safety, lower processing time, improved efficiency, and consistent quality. The authors also emphasized the potential of HME as a promising strategy for this application, given its ability to ensure high quality and efficacy with less batch-to-batch variations of pharmaceutical products. Continuous manufacturing offers several advantages, including reduced cost, increased

safety, lower processing time, improved efficiency, and consistent quality. By implementing continuous manufacturing processes, pharmaceutical manufacturers can achieve high-quality products with less batch-to-batch variation.[58,59] This approach aligns with the evolving regulatory requirements and quality standards in pharmaceutical manufacturing, making it a promising alternative for achieving efficient and cost-effective pharmaceutical production. The potential of HME as a continuous manufacturing strategy is underscored by its ability to ensure high quality and efficacy with fewer batch-to-batch variations of pharmaceutical products. This aligns with the evolving regulatory requirements and quality standards in pharmaceutical manufacturing, making continuous manufacturing via HME a promising alternative for achieving efficient and cost-effective pharmaceutical production.[60]

Conclusion

In conclusion, the review paper on HME has provided a comprehensive overview of recent advances and challenges in polymer selection and characterization for HME formulations. The review has highlighted the significant contributions of HME technology to novel drug delivery, emphasizing its potential applications in the pharmaceutical industry. The authors have discussed the potential of HME to address the evolving regulatory requirements and quality standards in pharmaceutical manufacturing, positioning it as a promising alternative for achieving efficient and cost-effective pharmaceutical production. The review has shed light on the opportunities presented by HME technology, including the development of novel drug delivery systems, intellectual property generation, and the potential for continuous manufacturing processes. It has also emphasized the challenges associated with material selection, process optimization, and regulatory compliance, underscoring the need for careful consideration of these factors to leverage the potential of HME technology for the development of innovative pharmaceutical products and drug delivery systems. Overall, the review has provided valuable insights into the advancements and challenges in HME technology, offering future perspectives on its potential applications in the pharmaceutical industry. The comprehensive understanding of the requirements, challenges, and opportunities associated with HME technology will be instrumental in driving further innovation and development in the field of pharmaceutical manufacturing.

List of abbreviations

HME - Hot melt extrusion; API - Active pharmaceutical ingredient; ADF- abuse-deterrent formulations

Conflict of Interest

There is no conflict of interest.

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