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Review Article

Application of Lipids in Hot Melt Extrusion Technology

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Abstract

Lipids are commonly used excipients in drug delivery for improving solubility of low soluble drugs, enhancing bioavailability through avoiding first pass metabolism through nanoparticulate approach, modifying the drug release, binders, permeation enhancers, transfection agents etc. Lipids alone or in combination of polymers are increasingly being used in hot melt extrusion (HME) technology for preparation of controlled release formulations, solid dispersions, self-emulsifying drug delivery systems, semi-solid formulations, solid lipid nanoparticles and others. Properties like low melting temperature, viscosity, ability to extrude at low temperature and ability to load high doses of drug favor use of lipids in HME technology. This review emphasizes the use of lipids for variety of applications in HME technology.

Keywords: Lipids, Hot melt extrusion, solubility, bioavailability, parameters.

Introduction

Researches in the recent decades have witnessed increased use of lipids as drug delivery systems such as micelles, liposomes, micro-emulsions etc. Lipids are chemically defined as fatty acids and their derivatives which can classified as polar and non-polar lipids. Polar lipids are those which interact with water to form aqueous phases and non-polar lipids are those which do not form aqueous phase. Lipids have the ability to resolve drug solubility issues, to improve stability of formulations, to control the drug release, target specific region by functionalization, etc.[1-2].

Lipids are generally used in drug delivery to improve solubility for those drug candidates which have poor oral bioavailability as a consequence of poor water solubility. Drugs need to enter into systemic circulation to elicit its action [3]. The three predominant mechanisms of lipids that influence drug absorption through oral route are by altering the composition of intestinal environment, enhancing absorption through lymphatic drug transport and by interacting with enterocyte based transport [4-10].

Hot melt extrusion technology has also gained importance in pharmaceutical industry due to the versatility in applications. Hot melt extrusion has advantages like continuous process thereby increase quality of pharmaceutical products, solvent-free process thereby environment friendly, easily scaled-up due to less variables involved in the manufacturing process, ability to integrate with process analytical technology, able to produce a wide variety of dosage forms and can manufacture at different production capacities [11-14].

Lipids conjointly with hot melt extrusion technology have a lot of potential to counter challenges associated with drug delivery and accelerate formulation development. This review tries to discuss the research on use of lipid in hot melt extrusion technology for solubility enhancement, controlled release, melt granulation, manufacturing semi-solids, protein drug delivery and nanoparticulate drug delivery [15-17].

Solubility Enhancement

Drugs administered orally need to be have sufficient solubility in the gastro-intestinal fluid to elicit its action systemically. Several approaches like amorphous solid dispersion, particle size reduction, chemical modification, complexation, surfactants, etc. are used to enhance solubility of poorly soluble drugs. Amorphous solid dispersions through HME technology has been one of the successful ways to improve solubility and thereby bioavailability of poorly soluble drugs [18-20].

Jaydip M. Vasoya et al. prepared solid dispersions of carvedilol using a combination of polyoxylglycerides (Acconon® C-50) and polymers model drug through HME technology. Kollidon ® VA64, hydroxypropyl methyl cellulose acetate succinate and Klucel™ EXF were the polymers selected for the study. Different solid dispersions were prepared with drug load ranging from 5-20%, Acconon C-50 ranging from 0-20% and remaining with Kollidon VA64. The solid dispersions were studied through characterization techniques like differential scanning calorimetry (DSC), powder X-ray diffraction analysis (PXRD) and dissolution studies. The data showed that drug release from formulations containing 20% drug increased with increase in polyoxylglyceride concentration and the

formulations were stable till 3 months when stored at 25ºC/60% RH [21].

In another study, amorphous solid dispersions were prepared by adsorbing lipid onto an adsorbent through HME technology. These lipids named designed lipid microdomains (DLMs) are disordered and can accommodate drug. Hydroxypropyl cellulose was selected as polymer, stearic acid as plasticizer and Neusilin US2 as adsorbent for the study. B-carotene was used as model drug for this study. Molecular interactions between Neusilin US2, stearic acid and polymer was confirmed by characterizing the ASDs using vibrational spectroscopy, X-ray powder diffraction, atomic force microscopy and electron microscopic imaging [22].

Controlled Release Formulations

Controlled release formulations are useful in reducing the frequency of dosing, avoiding erratic levels of drug in the blood stream thereby improving the safety and patient compliance to the treatment. Generally, polymers which degrade or swell with time when taken orally are used as rate-controlling polymers. Hot melt extrusion has been used tremendously in preparation of controlled release formulations [23-25].

In a study performed my Abdullah et al, sustained release formulations of Donepezil HCl were prepared by using hydrophobic carriers like Eudragit RS PO, ethyl cellulose N7, and Compritol 888 ATO with or without Mannitol as pore-forming agent through HME manufacturing technique. Screening was performed by using Compritol 888 ATO, ethyl cellulose N7 and Eudragit RS PO alone or in combination. The processing parameters were also studied by altering the processing temperature. DSC indicates that Donepezil hydrochloride remained as crystalline form in presence of lipid. The optimized formulation was compressed as tablets and the drug release profile was compared with marketed formulation, Aricept. The release profile of the prepared formulation matched with the release profile of Aricept [26].

In another study, controlled release formulation of carbamazepine was developed from hypromellose acetate succinate (HPMCAS) and Gelucire 50/13 using HME technique. Initially, binary formulation of carbamazepine and hypromellose were prepared using HME technology and the release from these extrudes was modified by using soluble excipients and Gelucire 50/13. It was observed that addition of excipients like crosscarmellose sodium, sodium starch glycolate, malodextrin and lactose led to increased porosity resulting in quicker erosion compared to extrudates composed only of HPMC AS and Gelucire 50/13. The results indicated that phase separated Gelucire was responsible in swelling of the extrudates and prolonging the drug release. Additionally, the swelling and drug release from the extrudates was evaluated using UV imaging technique [27].

Vithani et al. developed tablet from solid lipid matrices of diclofenac sodium through HME for sustaining the drug release. The extrudates were prepared with Compritol 888 ATO using cold, hot and pre-mixed approaches by varying the processing temperatures, drug loading (30:70, 40:60 and 50:50) and formulation composition. The processing temperature for cold, hot and pre-mixed approaches was selected based on the melting point of lipid which is 70ºC. A screw speed of 25 rpm and a feed rate of 0.7 kg/h was used for preparing the extrudates. The extrudates were evaluated for thermal analysis, powder-XRD, Energy Dispersive X-ray micro-analysis and in-vitro drug release. The results indicated through the drug was present in amorphous form, the drug release was sustained due to embedment in the lipid matrix [28].

Maniruzzaman et. al. evaluated polymer-lipid formulation developed through HME technique to control the drug release of indomethacin. The extrudates were prepared by processing drug, HPMCAS and stearoyl macrogol-32 glycerides-Gelucire 50/13 through twin screw extruder to produce solid dispersions. The amorphous nature of the extrudates was confirmed through XRD, DSC and hot stage microscopy. In addition, NIR spectroscopy was used to study interaction between polymer-lipid carriers through hydrogen bonding. The dissolution studies show a synergistic effect of polymer/lipid on the drug release of indomethacin at a pH more than 5.5 [29].

Melt Granulation

Often, high shear granulation and fluid bed granulation prepare granules by spraying aqueous binder solution or water. However, this technique of manufacturing granules is not suitable for actives which are susceptible to degradation by water. Melt granulation is suitable granulation technique for actives cannot be processed through high shear granulation and fluid bed granulation. Melt granulation is performed by injecting blend which consists of active, excipients and lipids through twin screw extruder. Lipids melt during the process due to temperature of barrel and mix with remaining blend forming granules when the barrel temperature is a below the melting point of lipids [30-31].

Jiping et al. investigated the properties of phenylpropanolamine hydrochloride tablets prepared by melt granulation. Either lipids, Precirol and Sterotex K were used as a thermal binder and also a retarding agent to achieve desired release characteristics of the tablets. Blend consisting of phenylpropanolamine hydrochloride, Precirol and other excipients were extruded using a single screw extruder. The melt extrudes were size reduced by passing through 14-mesh screen to form granules. In the formulations with Precirol, the drug release was highest from the tablets which used MCC as diluent followed by lactose and Emcompress. But in the tablets prepared using Sterotex K, tablets with lactose as diluent showed less release. The results showed that HME can be used successfully to prepare granules using melt granulation technique which can be compressed into tablets [32].

Sandeep et al. published his findings using Gelucire 48/16 as thermal binder to improve the solubility of poorly soluble drugs. Fenofibrate was used as model drug and Neusilin US2 was used as surface adsorbent. Different formulations were prepared by varying the ratios of Gelucire 48/16 and Neusilin US2. The drug release studies indicated that release of drug from the formulations was dependent on the Neusilin US2 concentration but not the Gelucire 48/16 levels. Increasing Neusilin US2 led to decreased drug release but improved the stability of tablets [33].

In a study performed by Rahamatullah et al., melt granulation was utilized to prepare co-crystals of theophylline and 4-aminobenzoic acid. Theophylline and 4-aminobenzoic acid were mixed in molar ratio of 1:1 with polyethylene glycol and passed through twin screw extruder. The mixture was run at 4 different trials by maintaining the six zones of barrel at different temperatures. The resulting products were analyzed through PXRD to identify co-crystal formation. Based on the results, co-crystals were observed at only one temperature profile. The product was characterized through other techniques like DSC, TGA, SEM, powder compaction and stability. The results indicated that co-crystals were stable at 50ºC/ 75%RH for 14 days [34].

Semi-solids

Semi-solids are prepared at industrial scale by using homogenizers, colloidal mills etc. In the recent past, the focus was turned towards continuous manufacturing of semi-solids using twin screw processor. Ability to maintain the temperature and create shear are key advantages to use twin screw processor for preparation of semi-solids [35-36].

In a study, voriconazole oil in PEG cream was prepared using twin screw processor. Either PEG 1450, PEG 2000, PEG 3350 and PEG 4500 grades were used in combination with PEG 400 which constituted the one phase. Mineral oil and Labrafil M1944 CS were used as oil phase of the cream. Tefose 63 and Transcutol P were used as emulsifier and permeation enhancer for voriconazole respectively. Different creams were prepared by altering the composition of non-oily phase and oil phase. All the formulations were run by maintaining 70ºC at the feed zone and 40ºC at zone 2. The screw speed was maintained 200 rpm. The prepared creams were tested for viscosity, in-vitro drug release and permeation. The results indicated that voriconazole oil in PEG cream was successfully prepared through twin screw processor and Transcutol P was successful in enhancing permeation of voriconazole [37].

Nanoparticulate Drug Delivery

Nanoparticles are advantageous as drug carriers due to their capability to enhance solubility, passive targeting, active targeting, improve bioavailability etc. Solid lipid nanoparticles (SLNs) are nanoparticles in the size range of 50-1000 nm with a lipid core. HME is being used to develop SLNs as the preparation technique is a solvent free process and also a continuous process unlike hot homogenization or cold homogenization technique which involve use of organic solvents [38-39].

Hemlata et al. explored use of HME technique and high pressure homogenization for continuous preparation of SLNs. In this study, effect of process parameters like zone of liquid addition, screw speed, liquid temperature, screw design and lipid concentration were optimized for preparation of SLNs. Glyceryl behenate (Compritol 888 ATO) was used as lipid which was fed into the extruder along with 1.5%w/w Tween 80 using peristaltic pump. The resulting emulsion from the extruder was passed through high pressure homogenizer at 75ºC and 1000 bar for size reduction. The particle size of the SLNs were determined using photon correlation spectroscopy. The impact of process variables on the size and zeta potential of the SLNs was also studied. The results indicate that a low screw speeds led to particles of less than 200nm with narrow PDI [40].

In another study, a solid lipid nanoparticulate topical gel of ibuprofen was produced by HME technique. Glyceryl behenate (Compritol 888 ATO), Precirol ATO 5 (glycerol distearate (type I) EP), geleol mono and diglyceride NF, and glyceryl monostearate were the lipids studied, Kolliphor RH40 was used as emulsifier. The mixture of drug, lipid and emulsifier was processed at different temperature conditions ranging from 90 - 120ºC. Screw design with a D_o/D_i of 1.21, 1.55 and 1.71 were explored for this study. The different SLN manufactured by altering the processing and formulation variables were characterized and the final formulation was made into gel with the help of 1% carbopol 981A. The gel formulation was subjected to anti-inflammatory activity in Sprague Dawley rats. The results indicate that there was d 40.17 ± 2.41% edema inhibition compared to 20.08 ± 3.23% edema inhibition control formulation [41].

Protein Drug Delivery

Preserving the native nature of the proteins is important to retain therapeutic activity as intended. Proteins on exposure to extreme stresses lead to instability due to denaturation [42-43]. Sustained protein delivery through lipid extrusion was explored by Moritz et al. A depot preparation of monoclonal antibody was prepared using lipids (Dynasan D118 and H12) through extrusion technique. Dynasan D118 has a melting point of 70.2ºC consisting of tristearin and Dyansin H12 has a melting point of 42.4 ºC consisting of trilaurin, trimyristin and tripalmitin. A lipid matrix of H12 and D118 were prepared by varying the ratios from 30-70%. Final composition consisted of 10% protein lyophilizate. Formulations were prepared by feeding lyophilizate and sieved triglyceride powder in mini-extruder ZE-5 by varying the extrusion temperature between 33-42 ºC and screw speed between 40-80 rpm.

Extrudates were prepared by double extrusion through three approaches. In the first approach, extrudates were prepared by extruding 10% protein lyophilizate and lipids consisting of 50:50 of D118 and H12 at 35 ºC. These strand were milled and extruded for the second time at either of the temperatures 33ºC,35ºC or 37ºC. In the second technique, initial extrudate was prepared by extruding 20% lyophilizate and 80% D118 at 65 ºC. The extrudates were ground and diluted with H12 to get a final concentration of 50:50 (D118:H12). In the third technique, extrudates were prepared in a similar way like second technique but the protein lyophilizate was initially diluted with H12 and later diluted with D118.

The implants were evaluated for protein release in a 2.0 centrifuge tubes with 1 mL of pH 7.4 PBS buffer in a horizontal shaker. The implants were also evaluated for mechanical properties and SEM. The results indicate that release of monoclonal antibody was slowed down by half by use of double extrusion technique [44].

Conclusion

Lipids has widespread applicability in drug delivery as they are utilized in preparation of solid nanoparticles, SEDDS, semi-solids etc. Hot melt extrusion technique is gaining its presence in pharmaceutical industry due to inherent advantages like continuous process, solvent-free technique, ability to replicate functions of equipment like granulator, mill etc. Lipids are used in preparation of various dosage forms through hot melt extrusion for various purposes like solubility enhancement, controlled release etc. Increased research on utilization of lipids in HME can resolve some of the current unmet needs in pharmaceutical industry.

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Author Contribution

Concept, literature, writing, review, supervision – A.K.G.; Writing, reviewing, literature – M.R.L.K.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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