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Novel Applications of Hot-Melt Extrusion Technology

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NOVEL APPLICATIONS OF HOT-MELT EXTRUSION TECHNOLOGY

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by

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ABSTRACT

Hot-melt extrusion, an adaptable technology, has established its position in a wide spectrum of manufacturing operations like amorphous solid dispersions, immediate and controlled oral formulations, implants, and taste masked products. In recent years the industrial focus has shifted towards continuous manufacturing, thus melt extrusion is being explored for new applications. The aim of this research work was to investigate the novel applications of hot-melt extrusion by carrying out an in depth study to understand the interplay between the process and the product.

The conventional techniques used for the preparation of ointments and nanostructured lipid carriers are multi-step and time consuming batch processes with low productivity. The low mixing efficiency coupled with high batch to batch variability makes these methods less industrial friendly. After optimization of screw configuration and process parameters, these formulations were successfully prepared using melt extrusion in a continuous fashion. The extruded ointment was similar to the conventionally prepared ointment with respect to flow characteristics, texture properties, and drug release profile, demonstrating the potential of hot-melt extrusion in preparation of topical semisolids. In an another study, extruded lidocaine loaded nanostructured lipid carriers were found to be stable for up to 60 days and the drug permeation from the carrier loaded gels was sustained as compared to control, thereby showing promising results for pain management in wounds.

In addition, investigating the impact of formulation composition on the product characteristics is of prime importance to understand melt extrusion process. With this goal, a response surface methodology was utilized to study influence of formulation variables on the extruded mucoadhesive films. It was observed that each independent variable influenced one or the other film characteristics either alone or in combination. It is only after such analysis that an optimized system with desired quality attributes could be formulated. The relationship between the process and formulation was elucidated and melt extrusion was found to be a viable approach for preparation of mucoadhesive films.

In summary, these successes associated/coupled with the versatility of HME, defines the future potential for this paradigm-changing technology.

DEDICATION

This work is dedicated to my parents, Moreshwar Bhagurkar and Jayashree Bhagurkar, my sister Priyanka Bhagurkar, and all my teachers.

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CHAPTER 1

INTRODUCTION: HOT-MELT EXTRUSION

Today most of the lead compounds, new chemical entities and marketed drugs have low intrinsic water solubility and high hydrophobicity. The reasons for such trend are difficult to understand and complex, however, some of the causes that contribute to this fact are use of high-throughput screening modalities that often use non-aqueous media, the inclination towards high drug potency and the realization that hydrophobic interactions play a role for drug receptor binding. Thus, such compounds with poor water solubility present a major challenge during the drug development program, as dissolution of drug in the aqueous environment is the pre-requisite for absorption and distribution process (Dahan et al. 2016; Williams et al. 2013). The various strategies used for improving drug solubility include salt formation, pH adjustment, co-crystals, co-solvents, surfactants, cyclodextrins, particle size reduction, amorphous solid dispersions, and lipid based formulations (Göke et al. 2017; Wen, Jung, and Li 2015; Alam et al. 2012).

Among these techniques, amorphous solid dispersion is a major technique used to obtain good physical stability along with improved dissolution and bio-availability. Amorphous solid dispersion refers to products containing drug either in amorphous form or as molecularly dispersed drug while dispersions containing amorphous carriers are known as glasses. Solid solutions (carrier is crystalline) and glass solutions (carrier is amorphous) have drug molecularly dispersed in the carrier. With the FDA's approval of several products in recent years (Baghel, Cathcart, and O'Reilly 2016; Sawicki et al. 2016), solid dispersions have become a prominent technique in the pharmaceutical industry for poorly water soluble drugs.

HME technology was primarily developed for improving the solubility and bioavailability of poorly water soluble drugs by preparing and manufacturing amorphous solid dispersions. This technique involves pumping of raw materials along with the API in a heated barrel with rotating screws to obtain a product of uniform shape and size from the die. The screws used inside the barrel and their unique blending geometry leads to high shear localized mixing, thus providing the necessary distributive and dispersive action. At the narrow space between the intermeshing screw elements and the screws and barrel wall, continuous thinning, deformation, and elongation processes occur, facilitating the dissolution/dispersion of the drug molecule in the thermoplastic polymer blend. HME is regarded as a green technology as it can be used for materials with high viscosity without any solvents. The technique is also amenable to continuous manufacturing and hence is an industrially feasible platform technology. Other advantages include shorter processing times, fewer unit operations, and relatively easy to scale up.

Hot-melt extrusion is a very flexible technology and there are numerous modifications that could be performed with the instrument to suit the formulator's needs. To start with, the feeding of the material could be performed in any of the multiple zones thus giving the formulator freedom with respect to the residence time of a specific material in the barrel. Some researchers have utilized this approach for thermolabile drugs, to expose such molecules to the high extrusion temperature for a shorter time. In addition, the screw configuration inside the barrel could be customized with a variety of designs and shear levels. One could have an intensive mixing zone to aid the conversion of drug from crystalline to amorphous form at high temperatures, in other cases the mixing zone could be tailored to retain the crystalline form of the drug. There are a lot of different screw elements and types, resulting into a specific mixing action. At the end of barrel is a die from which the material exits the barrel. The shape of the die could be spherical or flat to

obtain extrudates or films, respectively. Also, a suitable downstream auxiliary equipment could be connected to a melt extruder for example, a pelletizer or a roller to further process the extruded material. These modifications have been utilized by scientists to develop effective and a wide array of dosage forms, making HME a robust technology to prepare solid dispersions (Thiry et al. 2016; Vo et al. 2017), taste masked formulations (Pimparade et al. 2015), transdermal (Crowley et al. 2004), and topical (Bhagurkar et al. 2016; Repka and McGinity 2001) products. Furthermore, scientists are now exploring and investigating new applications of HME, so as to investigate this technique to its full potential. In recent years the increase in the number of patents and research articles showcases the wide spectrum of operations that could be performed using melt extrusion. The versatility and broad applicability has led to the emergence of HME as a technology leader in the pharmaceutical industry.

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CHAPTER 2

DEVELOPMENT OF AN OINTMENT FORMULATION USING HOT-MELT EXTRUSION TECHNOLOGY

2.1 INTRODUCTION

In the pharmaceutical industry, ointments are manufactured by melting oil and aqueous phases in two separate jacketed vessels with agitators for proper mixing. The two phases are transferred to the main ointment vessel through valves and pipes. The additional stirrers in the main vessel provide agitation ("Ointment Manufacturing Plant, Planetary Mixer, Tube Filling Machine," 2017). During the entire course of operation, uniform mixture of all the components (base + drug) is crucial. Formation of agglomerates and non-uniform distribution of drug in the base are the potential challenges encountered owing to inefficient mixing and improper design of the mixer. The content is not uniformly mixed in the dead spots of the vessel. Thus, additional steps are required for recirculation to avoid wastage of product accumulated at the dead spots (Inspection Guides-Topical Drug Products (7/94)).

Hot-melt extrusion (HME) is an established technology in the plastic, rubber, and food industries. Since the past few decades, this technique is known as a successful continuous and solvent-free process. Recently, this technology is under investigation for application in pharmaceutical research and industry. In HME process, rotating screws drive the physical mixture (drug + inactive excipients) above the glass transition temperature (Tg) and/or above the melting temperature (Tm) based on the type of material used in the formulation. Thus, uniform mixing of active pharmaceutical ingredient and thermoplastic binders, polymers, or both is achieved (Patil et al., 2016). Thus, HME technology is used to formulate granules, pellets, immediate and controlled release tablets, and transdermal and transmucosal drug delivery systems (Repka et al., 2008, 2012;

Shah and Repka, 2013). HME, a proven manufacturing process, complies with the goal of US FDA process analytical technology (PAT) scheme for designing, analyzing, and controlling the manufacturing process (Maniruzzaman et al., 2012). It improves the quality and efficacy of the manufactured products, and hence, it is being explored for numerous pharmaceutical applications (Maniruzzaman et al., 2012). In this study, we investigated a new application of HME technology in the field of production of topical semi-solids. HME provides many advantages over conventional methods of ointment preparation, such as reduced processing time since melting of the ingredients and mixing is a one-step process. Moreover, no additional agitators and scrapers are required since mixing action is performed by the screw elements in the barrel. The screw elements also aid in particle size reduction. Additionally, the processing parameters could be customized to obtain products with desired characteristics.

Lidocaine (melting point: 68°C) was used as a model drug. It is crystalline in nature and has a pKa of 7.8 (Gröningsson et al., 1985). Lidocaine acts as a local anesthetic by blocking the fast voltage-gated sodium channels in the cell membrane of postsynaptic neurons, thus preventing depolarization and inhibiting the generation and propagation of nerve impulses ("Lidocaine," 2017). Lidocaine ointment is used as an anesthetic for accessible mucous membranes of the oropharynx, as an anesthetic lubricant for intubation, and for temporary pain relief associated with minor burns ("DailyMed- lidocaine ointment"). In this study, polyethylene glycol (PEG) was selected as the base for the ointment. The PEG bases are water soluble, washable, possess good spreadability, and are stable ("The Pharmaceutics and Compounding Laboratory"). The ointment base composition of 50% *w*/*w* PEG 3350 and 50% *w*/*w* PEG 400 was selected, since this combination is recommended in the USP.

The main objective of this study was to investigate the potential use of the HME process in the continuous manufacturing of topical semi-solid products. Therefore, the characteristics of the product prepared by HME were compared with that of a reference product prepared by the fusion method.

2.2 MATERIALS AND METHODS

Materials

Lidocaine USP was purchased from Spectrum Chemical Mfg. Corp. (New Brunswick NJ, USA). Polyethylene glycol 3350 was purchased from Electron Microscopy Sciences (Hatfield PA, USA); Carbowax® PEG 400 NF was purchased from Fischer Scientific (NJ, USA). All other chemicals used were of analytical grade.

Preparation Methods

Preparation of Ointment Formulation

Conventional Ointment

The conventional method of fusion was used for the preparation of ointment. Mixture of lidocaine, PEG 3350, and PEG 400 was melted on a hot plate by heating it to 75°C. The mixture was then removed from the hot plate and was stirred continuously until it congealed ("The Pharmaceutics and Compounding Laboratory," n.d.).

Hot-Melt Extruded Ointment

A schematic illustration of preparation of ointment by HME is shown in Figure 2.1. Lidocaine base was blended with PEG 3350 at drug loading of 5% *w/w*. This binary mixture was fed into a co-rotating twin-screw extruder (11 mm Process 11™, Thermo Fischer Scientific, Karlsruhe, Germany) with a volumetric feeder. PEG 400 was introduced in the extruder barrel in zone 3, through an injection port using a peristaltic pump. The screw speed was set at 200 rpm, and the

barrel temperature was set to 75°C in the first five zones and 40°C in the remaining zones. A modified screw design as shown in Figure 2.2, with 3 mixing zones, was used for extrusion (Patil et al., 2014, 2015). The composition of the ointments is shown in Table 2.1.

Table 2.1 Composition of the ointment formulations.

Method of preparation	Lidocaine (% w/w)	Ointment base composition (% w/w)
1) Hot-melt extrusion	5%	50% PEG 400 + 50% PEG 3350
2) Conventional	5%	50% PEG 400 + 50% PEG 3350

Characterization of Raw Materials and Formulations

Differential Scanning Calorimetry

Physical characterization of lidocaine, PEG 3350 (melting range 53–57°C), and the ointment formulations was assessed using differential scanning calorimetry (DSC; Diamond DSC, Perkin Elmer) equipped with Pyris manager software. Samples of around 2–4 mg each were weighed and sealed in aluminum pans and analyzed at a heating rate of 10°C/min under an inert nitrogen atmosphere at a flow rate of 20 mL/min, over a temperature range of 30–150°C (Ahmed et al., 2011).

X-ray Diffraction

X-ray diffractograms were acquired for ointment formulations prepared using HME and conventional techniques. The studies were performed using SmartLab3 X-ray diffraction system (Rigaku, Japan) equipped with HyPix-400 2-D detector and SmartLab Studio II® software. Samples were filled into a glass sample holder and exposed to CuKα radiation (40 kV × 4 mA) to collect diffractogram over 2θ range of 4 to 40° with an increment of 0.0114 at 1 s per step.

pH Measurement

Weighed amount of ointment was dissolved in water so as to get final ointment concentrations of 1% *w*/*v*, 5% *w*/*v*, and 10% *w*/*v*. pH of these solutions was measured using the Mettler Toledo InLab®Micro pH probe (Electrolyte 3 mol/L KCl).

Uniformity of Drug Content

Predetermined amount of ointment formulation was taken from three different regions of an ointment jar and was dissolved in methanol. The samples were then subjected to centrifugal filtration. The supernatant was collected and directly injected into high performance liquid chromatography (HPLC) to measure the drug content.

Method of Analysis

The lidocaine content was analyzed using Waters HPLC-UV (Waters Corp) system. A Luna C18 Phenomenex column with dimensions of 250 × 4.6 mm (5 μ) was used for this study. The mobile phase used was methanol and 25 mM dibasic potassium phosphate (80:20% *v*/*v*) and the flow rate was adjusted to 1 mL/min. The injection volume was 20 μL and detection wavelength was 220 nm. The retention time of lidocaine was found to be 5.9 min. A calibration curve ($R^2 = 0.999$) was plotted after measuring the peak areas of the standard solutions of lidocaine. Drug concentration in the samples was determined by measuring the peak area of sample and comparing it with the peak area of the calibration curve (Repka et al., 2005).

Texture Profile Analysis of Ointment Formulation

Texture Analyzer model TA.XT2i (Texture Technologies Corp. /Stable Micro Systems) along with a 1-in. diameter (TA-3), acrylic, cylindrical probe, and a soft matter kit (TA-275) was used for the

determination of texture properties. The various set parameters for texture analysis are shown in Table 2.2.

Soft matter fixture was filled with the product, and it was placed below the texture analyzer's probe. The test was performed by lowering the probe at the pre-test speed to the product surface. The probe produced an additional deformation of 1 mm of the sample at the test speed of 0.50 mm/s after coming in contact with the surface and sensing the trigger force. The probe then withdrew from the sample at the speed of 5.00 mm/s. The same procedure was repeated for other samples after cleaning the probe and leveling the surface of the sample (Tai et al., 2014).

Table 2.2 The various set parameters for texture analysis.

Parameter	**Set value**
Test mode	Compression
Pre-test speed	0.50 mm/sec
Test speed	0.50 mm/sec
Post-test speed	5.00 mm/sec
Target mode	Distance
Distance	1 mm
Trigger type	Auto
Trigger force	5.0 g
Hold time	5.00 sec
Advanced options	Off
Temperature	Room temperature

Rheological Characterization

Rheological measurements were performed using TA instrument HR-2 rheometer. All experiments were conducted at room temperature (22°C) and using 25 mm parallel plate geometry. Adhesive backed sand papers (grit # 600 provided by Allied High Tech Products Inc.) were used for upper and lower plate in order to reduce slippage at the sample-plate interface. For each test, approximately 400 mg of sample was placed on the lower plate followed by slowly adjusting the upper plate to reach to a gap of 550 μm. After trimming off excess sample, the gap was set at 500 μm for rheological testing. Rheological characterization included four steps performed in sequence for each sample. Time sweep (at strain, γ_0, of 0.1% and frequency, ω, of 1 Hz) was conducted for 10 min to allow the sample to relax the stress the sample was subjected to during loading. It was followed by strain sweep test ($\gamma_0 = 0.05–50\%$, $\omega = 1$ Hz). Time sweep test for 10 min was then performed prior to steady-shear test by varying the shear rate from 0.002 to 100 s^{-1}. Rheological experiments were conducted in triplicate for each sample.

In Vitro Release Testing

Vertical Franz-type diffusion apparatus (Logan Instruments) maintained at 32 ± 1°C was used to study drug release profile across synthetic membranes (cuprophane membrane and silicone membrane thickness = 0.005"). Two hundred milligrams of the ointment formulation was applied to the membrane. The receiver compartment consisted of 5 mL phosphate buffer, pH 7.4. The active diffusion area of the membrane was 0.50 cm^2. During the course of the study, 0.5 mL of sample was collected from the receiver compartment at various time points and was subsequently replaced with fresh buffer. The collected samples were suitably diluted and analyzed using an HPLC-UV system (Waters Corp) (Brown et al., 2012; Food and Administration, 1997; Nallagundla et al., 2014; Olejnik et al., 2012; Shah et al., 1989, 1999; Thakker and Chern, 2003).

2.3 RESULTS AND DISCUSSION

Preparation of Ointment Formulation Using HME

Hot-melt extrusion technology is a continuous process of pumping raw materials at high temperature and pressure resulting in a product of uniform shape and density (Maniruzzaman et al., 2012). In hot-melt extrusion technology, various process parameters such as feed rate, screw design, screw speed, barrel temperature, and zone of liquid addition have a significant effect on the quality of the final dosage form. All of these parameters were optimized after intensive preliminary studies (Ahmed et al., 2011; Patil et al., 2015). The screw design was modified as shown in Figure 2.3, to obtain a uniform product. PEG 3350 and lidocaine (5% *w*/*w*) were fed into the barrel via a volumetric feeder. PEG 400, heated equivalent to the extrusion temperature, was injected into the barrel through zone 3 using a peristaltic pump equipped with an injection port. The temperature from zone 2 to zone 5 was set to 75°C to ensure complete melting of all the solids before reaching the zone of liquid addition. The first mixing zone helped in the proper mixing of the drug and PEG 3350. After the addition of PEG 400 in zone 3, the mixing zone 2 provided intense mixing action to ensure that all the components are uniformly mixed. The temperature from zone 6 to zone 8 was set to 40°C. The third mixing zone prevented the formation of agglomerates. The screw speed of 200 rpm was found to be optimum for this ointment. During the entire run, the torque values were found to be lower than 2%. The extruded mass gradually cooled down resulting in the final product.All the formulations were found to be smooth and devoid of any grittiness indicating uniform mixing of contents

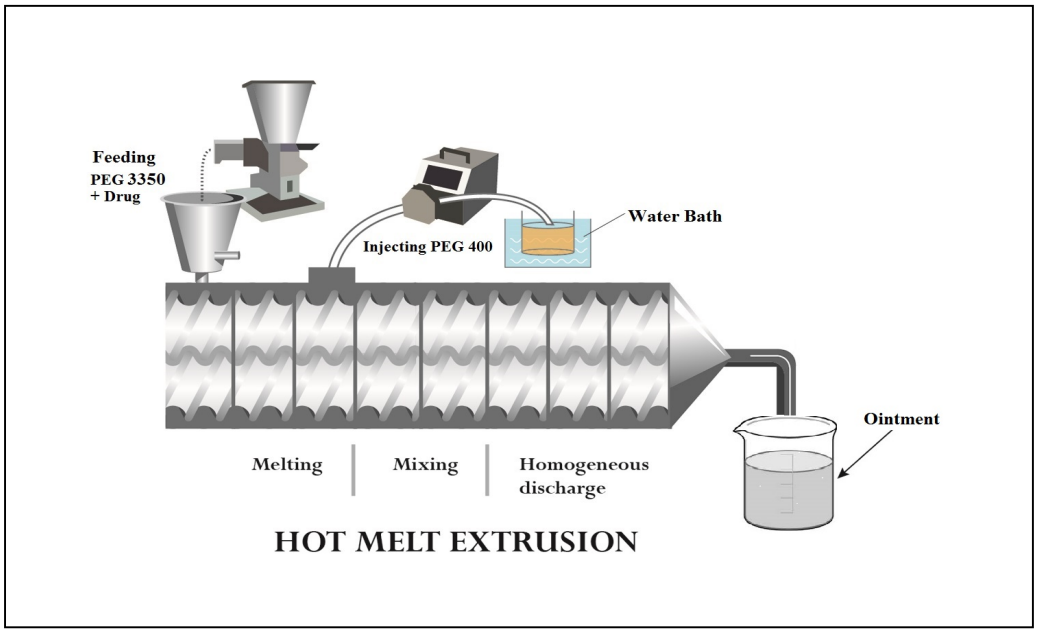

Figure 2.1 Schematic representation of preparation of ointment by hot-melt extrusion technology.

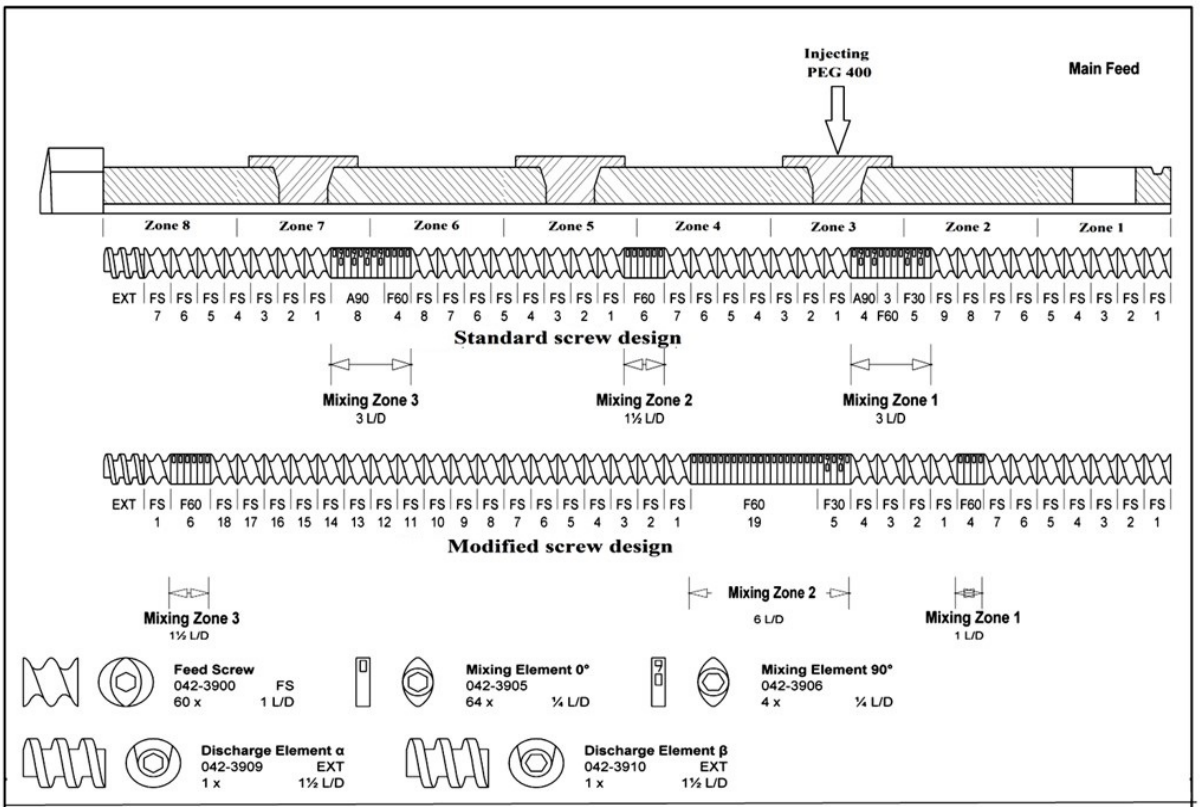

Figure 2.2 Modified screw design used for the preparation of an ointment.

Differential Scanning Calorimetry

The DSC thermogram shows that pure lidocaine base was characterized by a single endotherm peak representing its melting point at 69°C (Figure 2.3). PEG 3350 is a semi-crystalline polymer and was found to melt in the range of 60–70°C. The third component in the formulated ointment is PEG 400, which is a liquid. The DSC thermogram of the placebo ointment (ointment without the drug) shows two peaks, in the temperature range of 40–55°C (Figure 2.3). The same two peaks are observed in the formulations prepared by HME and conventional process. The absence of drug peak in these two formulations indicates that the crystal morphology of lidocaine is either

converted to amorphous nature or it has been solubilized during HME and conventional process.

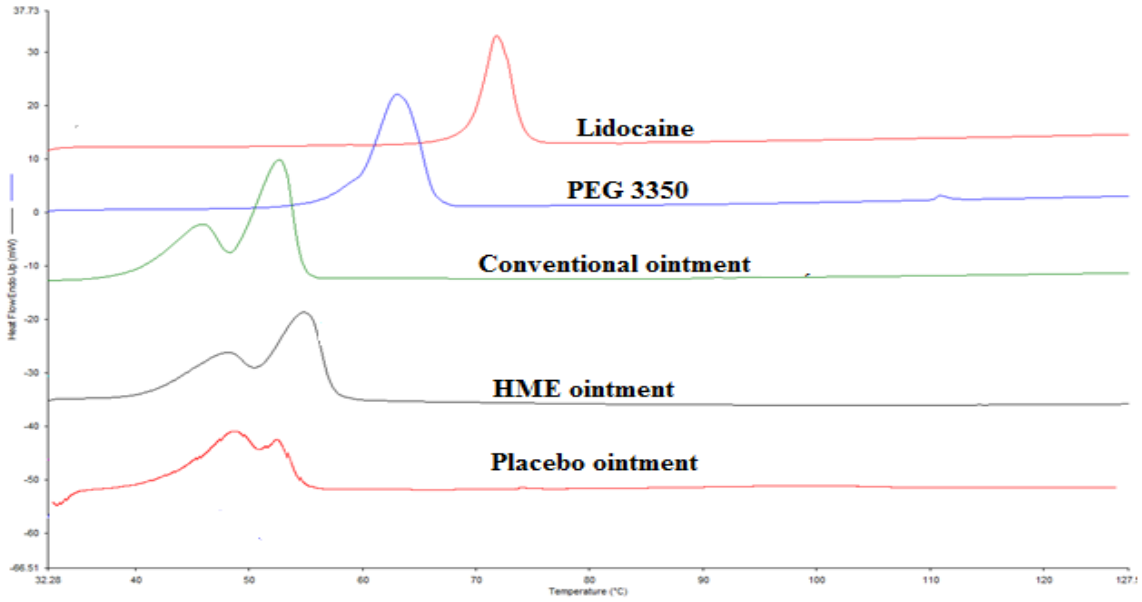

Figure 2.3 DSC thermogram of lidocaine, PEG 3350 and different ointment formulations.

X-ray Diffraction

The X-ray diffraction patterns of lidocaine API, placebo (ointment without the drug), HME, and conventional formulations are depicted in Figure 2.4. Lidocaine API is a highly crystalline solid and exhibited strong peaks at 2θ 10°, 12.5°, and 25°. However, diffractograms for both HME and conventional formulations lacked crystalline peaks characteristic for lidocaine and were identical to diffractogram of blank formulation (Figure 2.4). This study also suggests that the drug is either present in the amorphous form or has been completely solubilized in the ointment base. To further investigate the nature of drug in the formulation, the solubility of drug in PEG 400 was determined.

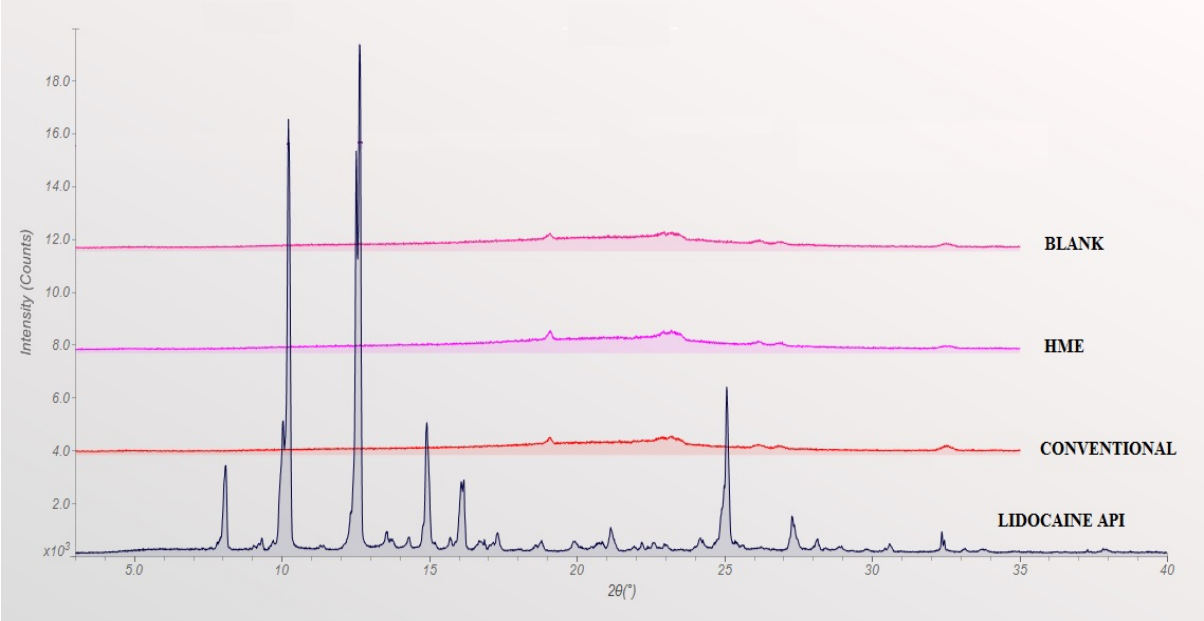

Figure 2.4 XRD data for the drug, conventional and HME formulation.

Solubility

In this study, the drug load in the formulation is 5% *w*/*w* and the concentration of PEG 400 is 50% *w*/*w*. Solubility studies revealed that lidocaine is highly soluble in PEG 400 (>250 mg/mL), which is many-fold higher than the concentration of drug in the formulation. Therefore, it is most likely that the drug exists in soluble form in the PEG ointment base.

Uniformity of Drug Content

As mentioned earlier, uniform mixing of the API with ointment base is one of the challenging tasks in manufacturing of topical semi-solids. Uniformity of drug content indicates the efficiency of mixing process. In this study, we found that the drug content in the hot-melt extruded ointment was 96.56 ± 5.21% and in the conventional ointment was 99.97 ± 4.36%. It is evident from the results that the modified screw configuration used in this study was effective resulting in a product with uniform drug content.

Formulation pH

pH measurement of non aqueous semi-solid bases is a challenge due to lack of compendial recommendations (Inoue et al., 2013; Ueda et al., 2009). Therefore, a method was developed to measure the pH of the ointment. The pH values (at 22°C) for the hot-melt extruded and the conventional formulation were found to be similar, 9.56 ± 0.19 and 9.31 ± 0.25, respectively. Also, it was found that the pH did not change significantly with incorporation of different amounts of ointment (1% *w*/*v*, 5% *w*/*v*, and 10% *w*/*v*) in water indicating absence of any acidic or alkaline impurities present in the excipients.

Firmness and Work of Adhesion of the Ointment

Texture parameters such as firmness and work of adhesion of semi-solids are important for product performance as well as for consumer acceptance. Firmness relates to the viscosity of the product and is denoted by the maximum value of force in the plot of force *versus* time (Figure 2.5). The work of adhesion relates to spreadability, and it is the area under the negative portion of the curve delimited by anchor 1 and 2 (Figure 2.5). The PEG polymers have a unique property as they add a silky feeling without greasiness to the semi-solid product. The higher firmness and work of adhesion values as shown in Table 2.3 indicate that the formulation is viscous and adhesive and thus it finds application as a local anesthetic for the mucous membranes.

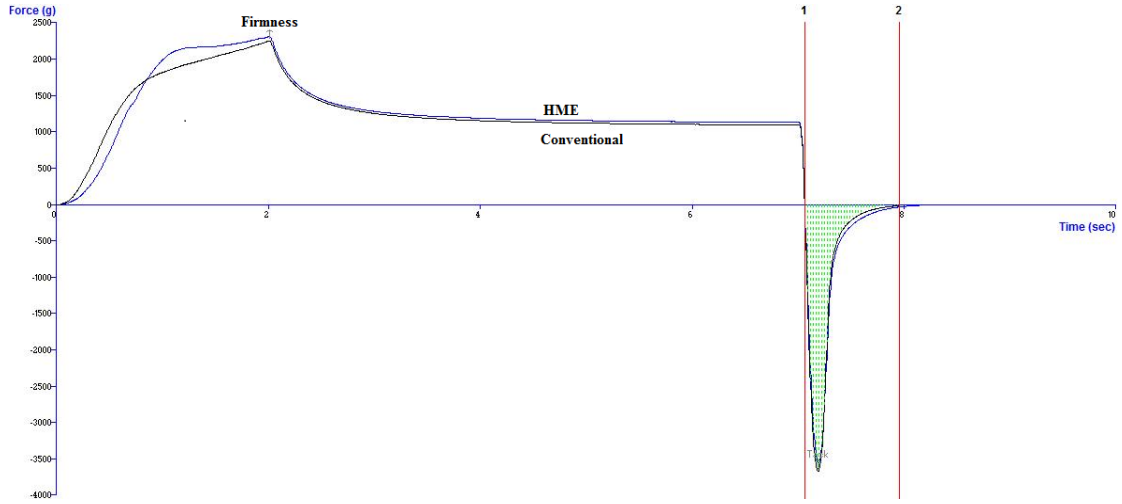

Figure 2.5 Representative picture of data of texture analysis of lidocaine ointments.

Table 2.3 Firmness and work of adhesion values for the formulations (n=3, ± S.D.)

Formulation	Firmness (g)	Work of adhesion (g sec)
HME	2271.71 ± 5.30	763.73 ± 10.50
Conventional	2324.81 ± 8.47	762.37 ± 32.14

Rheology

Dynamic oscillatory shear and shear flow are common rheological characterization protocol to characterize the stiffness, yield stress, and flow properties of viscoelastic materials, e.g., ointments, creams, and lotions (Krishnaiah et al., 2014). Figure 2.6a displays storage modulus, G', and loss modulus, G'', as a function of strain amplitude. For low-strain values, the storage modulus is an order of magnitude higher than loss modulus in small strain amplitude which is an indication of a soft solid-like behavior. However, with increasing strain, G' starts to decrease, and beyond a strain

amplitude (γ_0) of greater than 10%, a crossover between G' and G'' has been observed. Further, increasing strain resulted in G'' become higher than G', indicating a more fluid-like behavior.

Rheological results can be used to determine the yield stress of the samples (Adeyeye et al., 2002; "TA Instruments,"). The yield stress is defined as the stress required to initiate flow in the ointments, and it is related to the significant change in microstructure of the sample. To determine yield stress, elastic modulus for different samples was plotted as a function of shear stress in Figure 2.6b. The onset point, the stress in which elastic modulus (G') declines in a G' *versus* shear stress logarithmic plot, can be determined by applying tangents to the linear and nonlinear regime of the curve. The point where two tangents cross is estimated as the yield stress (σ_Y) of a material. The yield stress for the hot-melt extruded and conventional formulation was found to be 503 ± 80 Pa and 570 ± 70 Pa, respectively. It indicates that the HME and conventional formulations have relatively similar flowing properties. The effect of shear rate on material viscosity has been displayed in Figure 2.7. HME and conventional formulations have very similar viscosity profile. As it is observed, apart from the very low shear rate (less than 0.01), viscosity decrease with a constant slip for all samples with increasing shear rate. This type of trend is essential in ointments during their use performance to enhance better spreading of a material. The HME and conventional formulations exhibited similar stiffness (elastic modulus, G') for a similar concentration of polymers.

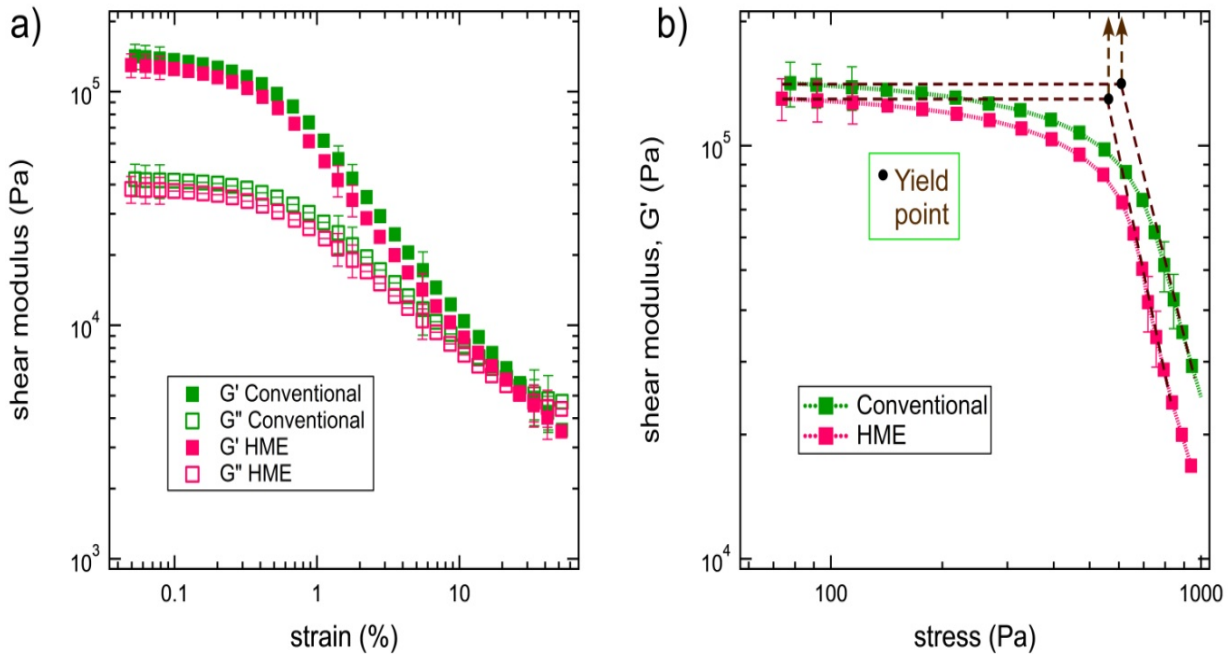

Figure 2.6 Rheological characterization: a) shear modulus (Pa) versus strain (%) b) shear modulus, G' (Pa) versus stress (Pa).

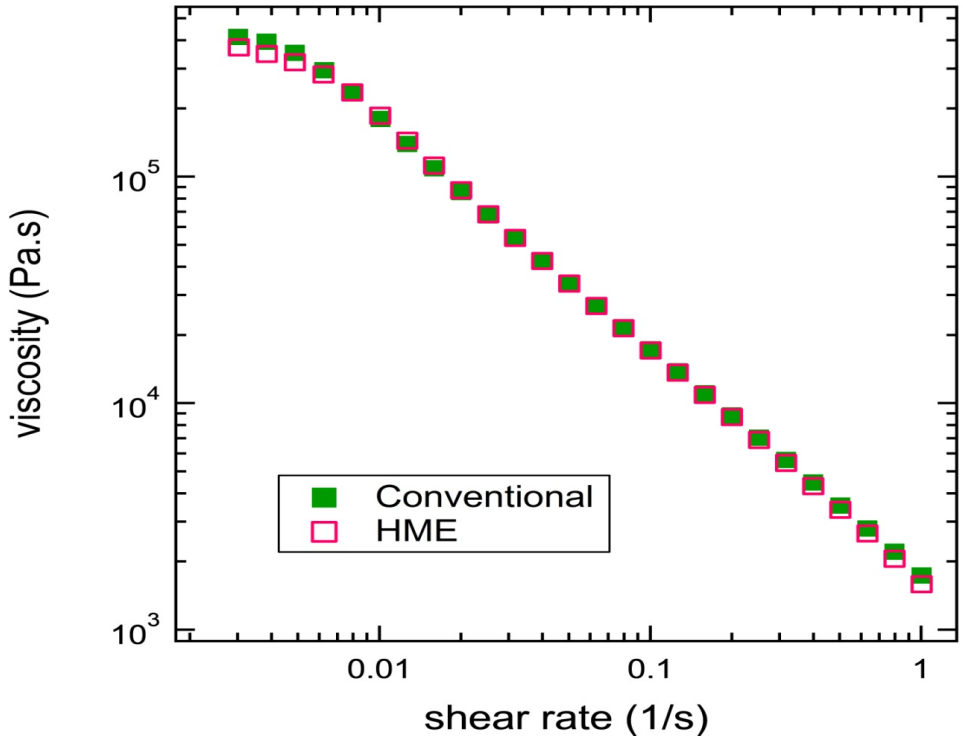

Figure 2.7 Plot of viscosity (Pa.s) versus shear rate (1/s).

In Vitro Release Testing

The use of Franz diffusion cell for *in vitro* release testing (IVRT) is a simple and reproducible method to evaluate the drug release profile from topical products. However, choosing an appropriate synthetic membrane is often deemed as the most challenging task in IVRT. In the present study, cuprophane membrane was chosen initially for determination of release profile. However, cuprophane being porous and hydrophilic in nature led to penetration of receptor media into the donor compartment owing to osmotic drive. Therefore, a non-porous hydrophobic silicone membrane was selected. To validate this membrane, ointments with different drug loads (2.5% *w*/*w*, 5% *w*/*w*, and 10% *w*/*w*, prepared by the fusion method) were subjected to IVRT. The rate of drug release from the ointment increased with the drug load as shown in Figure 2.8, indicating that the membrane was not controlling the rate of drug release. The release profile of the hot-melt extruded and the conventional ointment across silicone membrane was fit to Higuchi kinetic profile, and *K*-value was calculated. The release rate constant (hot-melt extruded ointment, $K = 405 \pm 41.59$ and conventional ointment, $K = 453.01 \pm 37.40$) was not significantly different between the two products (Figure 2.9).

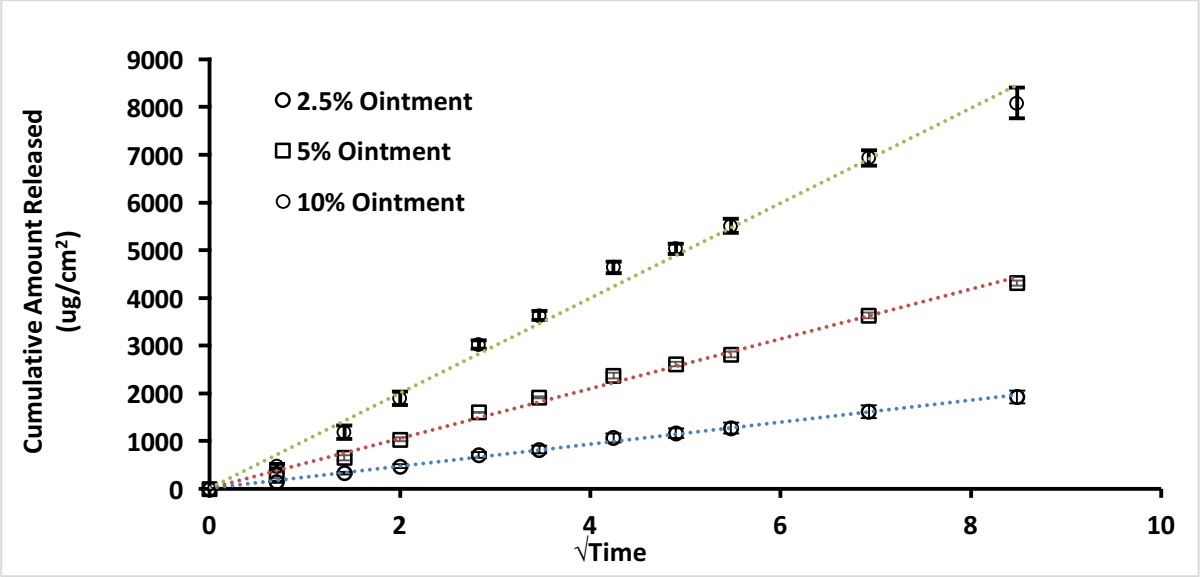

Figure 2.8 Plot of cumulative amount released (ug/cm^2) vs √Time for membrane validation studies.

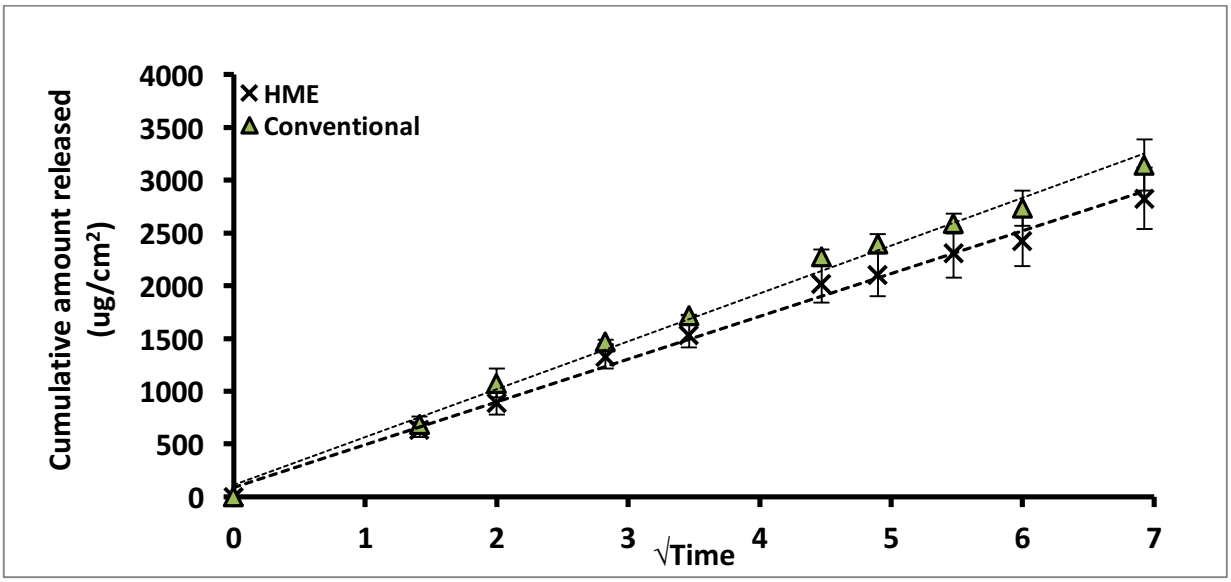

Figure 2.9 The *in-vitro* drug release profile of HME and conventional formulation.

2.4 CONCLUSION

The use of HME technology for development of a topical semi-solid product, reported in this study, is the first of its kind. Selection of suitable screw configuration ensures proper mixing of all the components of the formulation in HME. In the present study, the product prepared by HME and conventional processing was similar in terms of rheological properties, drug release profile, and texture characteristics, indicating the efficiency of HME technology to result in a semi-solid product which is similar in quality as that of the reference product. HME technology also provides many advantages over the conventional method of ointment preparation such as minimal processing steps (since melting and mixing is a one-step process), cost effectiveness, uniform product (owing to dispersive and distributive mixing), and shorter processing times. In addition, the different process parameters of HME technology such as feed rate, screw speed, and barrel temperature could be modified to impart desired characteristics to the product.

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CHAPTER 3

A NOVEL APPROACH FOR THE DEVELOPMENT OF A NANOSTRUCTURED LIPID CARRIER FORMULATION BY HOT-MELT EXTRUSION TECHNOLOGY

3.1 INTRODUCTION

Nanostructured lipid carriers (NLCs) are colloidal carriers with complex architecture, which confers them higher stability and drug loading capacity as compared to solid lipid nanoparticles. These carriers are composed of a solid lipid and an oil phase that is organized in nanocompartments inside the solid lipid matrix (Fang et al. 2008). According to some reports, the drug in the NLC remains in the liquid lipid surrounded by the solid lipid. This arrangement gives the drug some degree of mobility, offers stability to some extent even when the solid lipid undergoes polymorphic change (Pathak and Nagarsenker 2009). NLCs have numerous applications for drug delivery via oral, pulmonary, dermal and ocular route (Kovacevic, Savic et al. 2011, Beloqui, Solinis et al. 2016).

Microemulsification, solvent displacement and high pressure homogenization are some of the currently used methods for the preparation of NLCs (Pardeike, Hommoss et al. 2009). However, all of these methods are poorly energy efficient and involves multi-step processing. Additionally, in case of methods like microemulsification technique, there is potential for dilution of particle dispersion requiring to take the product through additional step to remove water (Montenegro, Lai et al. 2016). Methods like solvent displacement involves the use of organic solvent, which has to be removed from the product to ensure safety of the product. Although the high pressure homogenization (HPH) method is the preferred method for NLC preparation, this method involves the preparation of the lipid and the aqueous phase, melting the lipid phase, dispersing/dissolving the drug in the lipid phase, and finally mixing the two phases together to

prepare the pre-emulsion (Patil, Feng et al. 2015). The prepared pre-emulsion is further subjected to size reduction. Thus HPH process is associated with long processing time and frequent failures due to batch to batch variations (Puglia and Bonina 2012). Overall, the conventional methods are less industry friendly. Thus it would be required to develop an alternative method for NLC preparation, which will overcome most of the limitations of the conventional technologies.

Hot-melt extrusion (HME), involves pumping of raw materials (API and excipients) into a heated barrel at high pressure, so as to get a uniform product through a die. The active compound is usually embedded in a carrier, which comprises of a meltable substance/s and/or functional excipients. The chemical and physical properties of the carrier govern the release of drug from the formulation (Crowley, Zhang et al. 2007). The extensive industrial adaptability of HME, has established its position in the wide spectrum of manufacturing operations and pharmaceutical research (Maniruzzaman, Boateng et al. 2012). Shorter and efficient times to final product, non-solvent and a continuous process are some additional advantages of this technique (Repka, Battu et al. 2007, Douroumis 2012). This technique gained a lot of importance in the recent decade after the Food and Drug Administration (FDA) encouraged the use of continuous manufacturing processes (Langley, DiNunzio et al. 2013, Melocchi, Loreti et al. 2015). The hot-melt extruded materials have been used to prepare dosage forms like tablets, granules, transdermal systems and topical products (Bhagurkar, Angamuthu et al. 2016).

The main aim of this study was to investigate the feasibility of hot-melt extrusion technology in the preparation of NLCs and while doing so the various process parameters were optimized and the obtained product was characterized for various quality control attributes. Further, to investigate the applicability of the developed process, the NLC topical gel formulation incorporated with lidocaine, a local anesthetic was prepared. Lidocaine finds its application in the

pain management of wounds caused by burns and surgeries. Lidocaine inhibits the propagation of nerve impulses by binding to the voltage gated sodium channels, and thus it prevents the influx of sodium ions (Cummins 2007). There are therapeutic topical products available for the topical delivery of lidocaine. However, the conventional topical formulations are poorly efficient in retarding the clearance of drug from the affected region. It was hypothesized that the NLC formulation incorporated with lidocaine will lead to localization of the drug delivery system and controlled delivery of drug to the affected region for a prolonged therapeutic effect.

3.2 MATERIALS AND METHODS

Materials

Labrafac™ lipophile WL 1349 was kindly gifted by Gattefossé (Saint Priest, France). Cetyl esters wax NF, propylene glycol USP and carbomer 940 NF were purchased from PCCA (Houston, Texas, USA). Lidocaine USP was purchased from Spectrum Chemical Mfg. Corp. (New Brunswick NJ, USA). Tween™ 80 and potassium dihydrogen phosphate was purchased from Fischer Scientific (NJ, USA). All other chemicals and solvents (acetonitrile, methanol) used were of HPLC grade. DI water was used throughout the study.

Methods

Preparation of NLC Formulation

In this study, an HME technique was used to prepare the NLC. The preparation involved two main steps: First, formation of a pre-emulsion by pumping all the raw materials into the barrel and second, was size reduction of the pre-emulsion to obtain the nanocarriers. Thus NLC were prepared by making appropriate modification with screw design and using suitable downstream processing equipment. The composition of the NLC formulation is as shown in Table 3.1 (Khurana, Jain et al. 2013). The lipid components used in the formulation were reported to be safe, biocompatible and biodegradable. Extrusion was carried out on a 11 mm co-rotating twin screw extruder (11 mm Process 11™, ThermoFisher Scientific, Karlsruhe, Germany). Cetyl palmitate was passed through a sieve for size reduction, so as to improve its flowability. The drug was then

uniformly mixed with cetyl palmitate and introduced in the barrel using a volumetric feeder. Labrafac lipophile, heated to 75°C, was injected in zone 2 of the barrel using a peristaltic pump. A solution of polysorbate 80, propylene glycol and water was prepared and heated to 75°C. This solution was injected in zone 4 of the barrel using another peristaltic pump. The schematic representation of preparation of NLC by HME is shown in Figure 3.1. The feeding rates for the volumetric feeder and the peristaltic pumps were optimized. The screw configuration as shown in Figure 3.2, with a barrel temperature of 75°C was used for the extrusion process. Three screw speeds of 100, 200 and 300 rpm were used in the study to determine their influence on the product. The coarse-emulsion obtained was subjected to probe sonication (Vibra cell, Sonics and Material, Inc., Newtown, CT, USA) with amplitude of 70%, to obtain the NLC. The sonication time was varied from 1 to 3 min to investigate the influence of sonication time on the particle size of NLC.

Table 3.1 The composition of the NLC formulation.

Material	**Amount**
Lidocaine	11.3 mg (1% w/w)
Cetyl palmitate	65 mg
Labrafac™ lipophile	35 mg
Polysorbate 80	0.2 mL
Propylene glycol	0.1 mL
Carbopol 940	5 mg
Water	0.7 ml

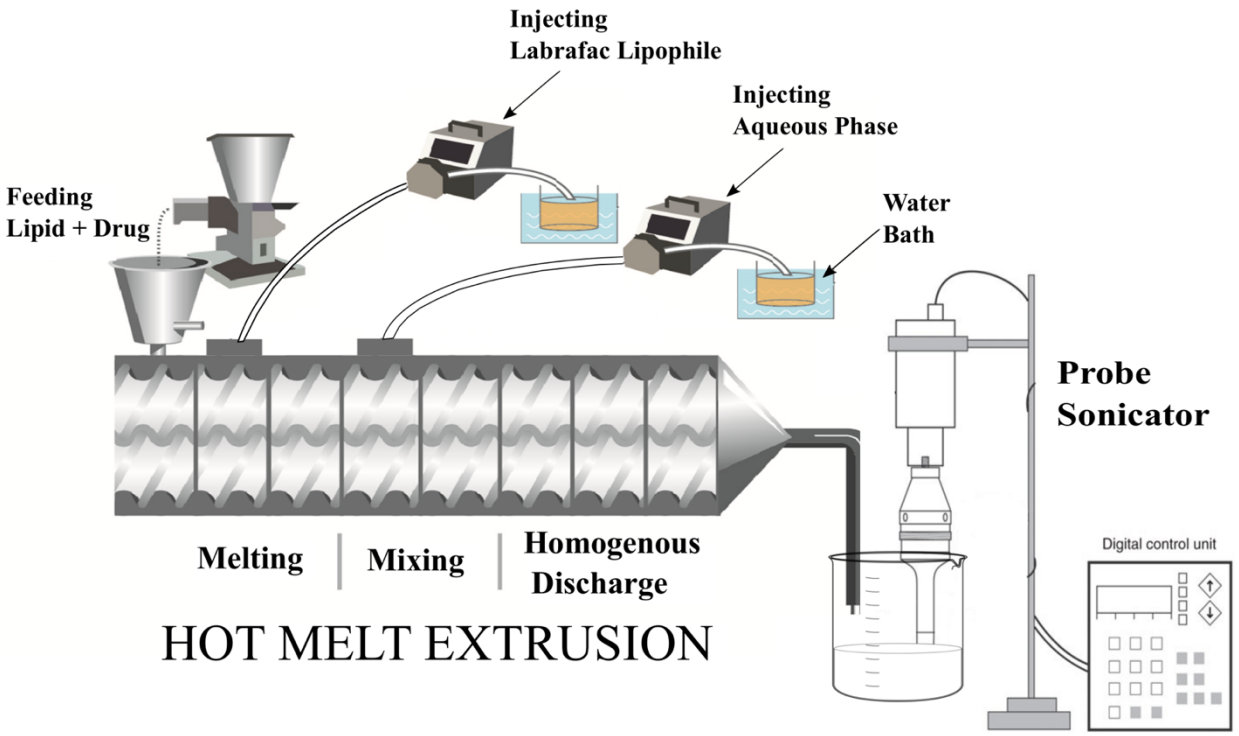

Figure 3.1 Schematic representation of preparation of NLC by conjugation of hot-melt extrusion and probe sonication. Adapted from "Continuous Production of Fenofibrate Solid Lipid Nanoparticles by Hot-Melt Extrusion Technology: A Systematic Study Based on a Quality by Design Approach," by Hemlata Patil et al. *The AAPS Journal* 17, no. 1 (January 2015): 194–205.

Characterization of the NLC

Particle Size, Polydispersity Index and Zeta Potential Analysis

The particle size, polydispersity index (PDI) and zeta potential of the NLC formulations were analyzed using a Malvern Nanosizer ZS (Nano ZS, Malvern Instruments, UK). The formulations were suitably diluted with distilled water prior to measurements. All the measurements were carried out at a scattering angle of 90° at 25°C.

Entrapment Efficiency

The entrapment efficiency was determined by calculating the entrapped drug after removal of un-entrapped drug using a Amicon centrifugal filter (MWCO 100 KD) units centrifuged at 13,200 rpm for 40 min. The filtrate was diluted appropriately with methanol and analyzed using a suitable HPLC method. The following formula was used to calculate the % entrapment efficiency:

$$\% \text{ Entrapment efficiency} = \frac{\text{Amount of lidocaine entrapped}}{\text{Amount of lidocaine added in the formulation}} \times 100$$

Transmission Electron Microscopy (TEM)

TEM was used to observe the morphology of the NLC dispersions. The nanoparticles suspension was stained with 0.5% phosphotungstic acid and the stained grid was air dried and examined under Zeiss Auriga 40.

Formulation of Topical Gel of NLC

The fact that NLCs remain stable in hydrogel has been studied by Yang et al (Yang, Corona et al. 2014). In this project, the NLC were loaded in a hydrogel vehicle for convenient topical application. Measured quantity of carbopol 940 was slowly added to the NLC dispersion with stirring. The carbopol was allowed to swell overnight with intermittent stirring. Later, triethanolamine was added dropwise to the mixture, so as to raise the pH to 7-7.5. A gel without lipids, having composition as shown in Table 3.1, was prepared, to serve as control.

In-vitro Drug Release Study

The amount of drug released from the lidocaine NLC gel was studied using a vertical Franz diffusion apparatus (Logan Instruments, NJ, USA). The dialysis membrane (MWCO 10 kDa) was mounted between the donor and receiver compartment and the active diffusion area was 0.64 cm^2. The receptor compartment consisted of 5 mL phosphate buffer, pH 7.4. Gel formulations equivalent to 2 mg of lidocaine was applied on the membrane and 0.5 mL of samples were withdrawn at various time intervals. The samples were further analyzed using a HPLC-UV system.

Ex Vivo Permeation Studies

The permeation of lidocaine from the NLC gel was evaluated using abdominal porcine skin epidermis. Before using the epidermis, it was thawed at room temperature for 1h and was then placed on the vertical Franz diffusion cells with the stratum corneum (SC) facing the donor side. The integrity of the epidermis was confirmed by measuring the resistance at a frequency of 10 Hz and voltage of 100 mV. Only the epidermis having resistance values greater than 20 $K\Omega/cm^2$ were used in the study (Maurya and Murthy 2014). The receptor compartment consisted of 5 mL phosphate buffer, pH 7.4. The experiment was carried out at 37°C. Gel formulations equivalent to 2 mg of lidocaine was applied on the epidermis and 0.5 mL of samples were withdrawn at predetermined time points and analyzed by an HPLC- UV system.

Mechanistic Studies

Drug Retention in the Cutaneous Tissue

Abdominal porcine skin was used for this study. The hairs were removed using a trimmer and then the excess fat from the dermal side was removed. The skin was soaked in phosphate buffer for 1 h and later, it was allowed to air dry. The stratum corneum was removed from rest of the layers of

the skin by tape stripping using Transpore® adhesive tape (3M, St. Paul, MN, USA). The skin with intact stratum corneum was used as control. The vertical Franz diffusion cells were used to perform the studies (Logan Instruments, NJ, USA). The receptor media consisted of 5 mL of phosphate buffer of pH 7.4. The formulations were allowed to stay for 24 h, after which the skin was rinsed with water and dried. Later, the drug was extracted into acetonitrile using a suitable method and analyzed with HPLC.

Analytical Method

The amount of lidocaine base was determined using a HPLC-UV system (Waters Corp). A Luna C18 Phenomenex column with dimensions of 250×4.6 mm (5 μ) was used. The mobile phase consisted of a mixture of (14/86 v/v) of acetonitrile and potassium dihydrogen phosphate 0.05 M (pH adjusted to 4.0). Flow rate of 1.2 mL/min and detection wavelength of 216 nm was used for analysis (Murthy, Sammeta et al. 2010).

3.3 RESULTS AND DISCUSSION

Preparation of Nanostructured Lipid Carrier

The screw extruder mainly comprises of three parts: a conveying system, which helps in the transport and efficient mixing, a die system at the end of the barrel, and downstream auxiliary equipment which can serve the purpose of cutting or collecting the product for further processing. The screw configuration plays a vital role in HME and it affects the characteristics of final product to a great extent (Shah, Maddineni et al. 2013, Alsulays, Park et al. 2015, Morott, Pimparade et al. 2015). The screw configuration (Figure 3.2) was devised by taking into consideration the zones of material addition. The 1st mixing zone was placed with the aim of mixing the melted lipid and drug with Labrafac lipophile. The intensive 2nd mixing zone ensured the efficient mixing of the oil and water phase and facilitated the formation of pre-emulsion. The pre-emulsion from the die was collected in a beaker which was connected to a probe sonicator. The parameters for the probe sonication were optimized and the NLCs were successfully obtained after sonication. During the entire run, the torque values were found to be lower than 10%.

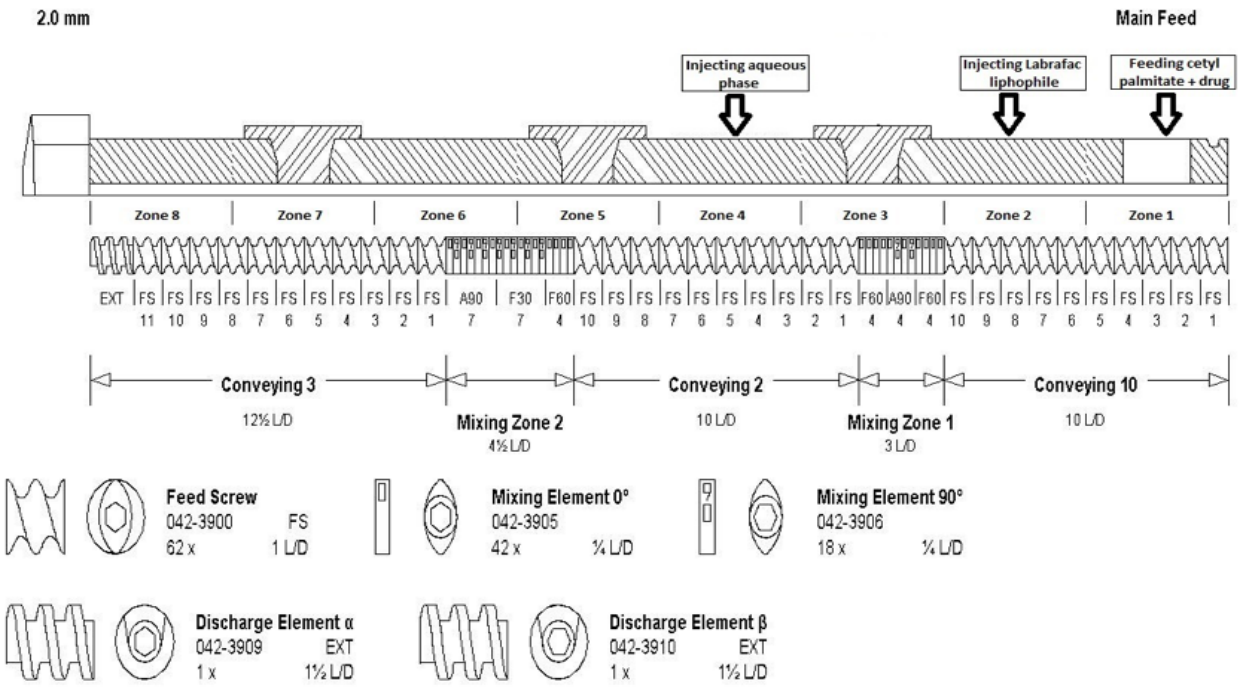

Figure 3.2 Modified screw configuration used for extrusion.

Characterization of the Prepared NLC

The particle size, PDI and zeta potential for the various formulations is as shown in Table 3.2. Usually with longer sonication time, it is reasonable to expect decrease in the size of the particles (Das, Ng et al. 2012). However, it can be seen from the particle size data on day 0, that the different screw speeds and the sonication times did not significantly influence the particle size of the NLC. But analyzing the particle size on day 60 revealed that the particle size for the formulations prepared with 200 and 300 rpm of screw speed, increased in contrast to 100 rpm. One of the reasons for the increase in the particle size at 200 and 300 rpm is likely due to the higher shear in the system at higher screw speeds in contrast to 100 rpm screw speeds. In general, with higher screw speeds, the residence time within the barrel decreases, but the shear in the system increases, which is likely to affect the quality of the coarse emulsion prepared, thus influencing the stability of the NLCs. The reason for higher particle size for formulation F-7 is unknown at this point. Moreover,

it can be observed that on day 60, the PDI for the formulations with 100 rpm did remain consistent as compared to other manufacturing screw speeds indicating the formation of a thermodynamically stable dispersion of uniformly sized nanocarriers (Ghate, Lewis et al. 2016). No specific correlation was found between zeta potential and sonication time or screw speed. Thus it can be concluded that in this case, the screw speed of 100 rpm was found to be optimum for the NLC, with the sonication time having little influence over the size. Hence the formulations with 100 rpm screw speed (F-1, F-2, and F-3) were selected for further studies.

Entrapment Efficiency and pH

The % entrapment efficiency for the formulations is as shown in Table 3.3. The lower values for % entrapment for the formulations is mainly due to partitioning of the drug between the oil and aqueous phase. Since lidocaine has fairly good solubility in the surfactants and solubilizers used (more than 25 mg/mL of lidocaine was soluble in the aqueous phase, which is about 2-folds more than the amount of drug added in the formulation), it is pulled out from the oil phase leading to low entrapment values (Joshi and Patravale 2008). Also, it was observed that as the sonication time increased, the % entrapment efficiency decreased. The reason for this might be the leakage of the drug from the lipid due expansion of nanolipid structures due to increase in the temperature, *in situ*. The pH of the NLC loaded with lidocaine is shown in Table 3.3. The pH was found to be within 4.0-8.0, which is the acceptable range for topical application.

Table 3.2 The particle size, PDI and zeta potential of the NLCs prepared using hot-melt extrusion.

Formulation	Processing		Particle size (nm)		PDI		Zeta potential (mV)	
	Screw speed (rpm)	Sonication time (min)	Day 0	Day 60	Day 0	Day 60	Day 0	Day 60
F-1*	100	1	12.97 ± 0.18	18.93 ± 0.16	0.31 ± 0.01	0.33 ± 0.01	-12.53 ± 5.37	-14 ± 3.89
F-2*	100	2	13.23 ± 0.81	16.28 ± 0.23	0.22 ± 0.02	0.23 ± 0.01	-16.3 ± 7.17	-15 ± 5.18
F-3*	100	3	23.76 ± 9.26	28.44 ± 4.82	0.24 ± 0.09	0.25 ± 0.03	-19.7 ± 3.80	-16.5 ± 6.58
F-4	200	1	14.44 ± 0.19	38.39 ± 0.24	0.19 ± 0.03	0.22 ± 0.01	-20.4 ± 7.73	-12.8 ± 3.4
F-5	200	2	13.49 ± 0.11	39.45 ± 0.07	0.12 ± 0.01	0.20 ± 0.01	-10.7 ± 12.1	-16.1 ± 3.6
F-6	200	3	12.86 ± 0.02	38.59 ± 0.21	0.10 ± 0.01	0.22 ± 0.01	-17.5 ± 21.6	-14.5 ± 3.75
F-7	300	1	62.36 ± 0.41	80.72 ± 1.60	0.67 ± 0.00	0.35 ± 0.05	-22.9 ± 4.75	-15.3 ± 3.78
F-8	300	2	13.52 ± 0.09	42.03 ± 0.31	0.13 ± 0.00	0.20 ± 0.01	-4.67 ± 10.7	-11.7 ± 4.11
F-9	300	3	12.50 ± 0.01	39.36 ± 0.32	0.09 ± 0.01	0.23 ± 0.01	-5.74 ± 5.87	-10.9 ± 5.24

* Formulations selected for further studies.

Table 3.3 The % entrapment efficiency and pH for the NLCs.

Formulation	% entrapment efficiency	pH
F-1	73.89 ± 1.39	6.96 ± 0.00
F-2	70.51 ± 0.97	6.14 ± 0.04
F-3	39.39 ± 1.51	6.68 ± 0.02

Transmission Electron Microscopy

Scanning transmission electron microscopy (STEM) studies were performed so as to understand the shape and morphology of the NLCs prepared at 100 rpm screw speed and sonicated for 2 min (F-2). The images were taken in freshly prepared and aged (2 months) formulations. It can be observed as shown in Figure 3.3 (after 2 months of storage), the NLCs were found to be spherical. The particle size observed by TEM image, was found to be in agreement with the data obtained from the dynamic light scattering.

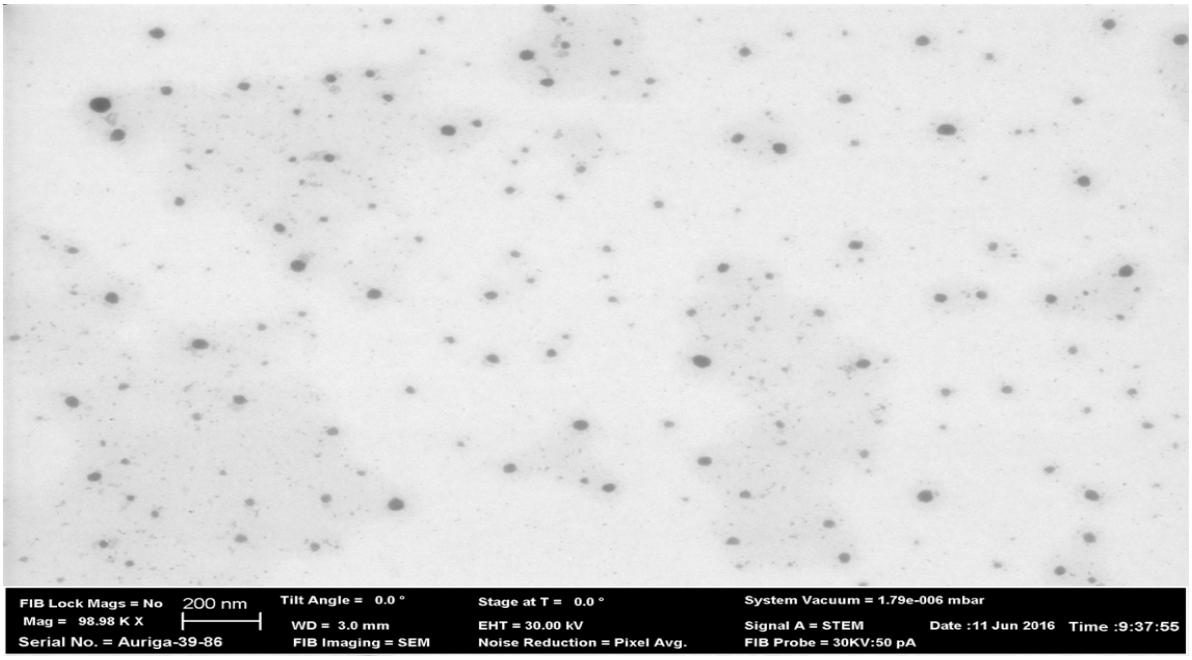

Figure 3.3 STEM image for F-2 NLC formulation

In Vitro Drug Release

The release profile of lidocaine from the lidocaine loaded NLC gel and gel without lipids is shown in Figure 3.4a and 3.4b. It can be observed that the rate of drug release from the NLC loaded gel was lower as compared to the gel without lipids indicating that lipid carriers play a predominant role in sustaining the drug release. The drug release data was fitted with Higuchi model (Figure 3.4a). The release rate constant (K) for F-2 formulation was 42.06, while it was 363.51, for the gel without lipids. However, there was no significant difference between the drug release rate between the three different NLC-loaded gel formulations.

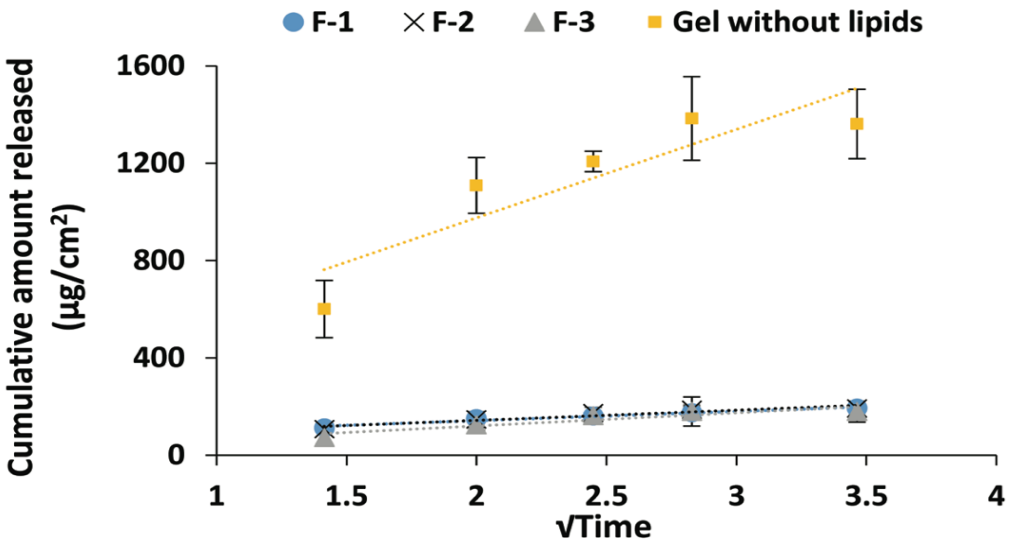

Figure 3.4a The *in-vitro* drug release profile for NLC loaded gel and gel without lipids (n=3).

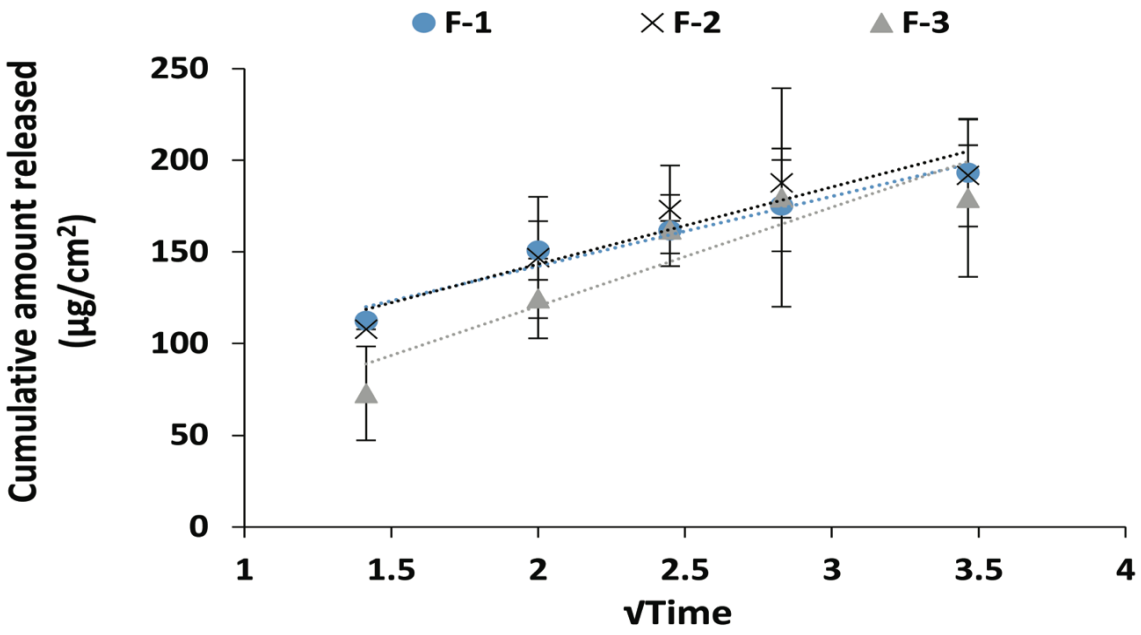

Figure 3.4b The *in-vitro* drug release profile for NLC loaded gel (n=3).

Ex Vivo Permeation Studies

The cumulative amount of drug permeated at the end of 36 h for F-1, F-2 and F-3 formulations was found to be 2.19 ± 1.11 µg/cm^2, 4.32 ± 1.05 µg/cm^2, and 8.44 ± 2.60 µg/cm^2 (Figure 3.5a and 3.5b), respectively. On the other hand, 23.79 ± 0.67 µg/cm^2 of lidocaine permeated through the epidermis from the gel without lipids. It is evident from the data that there was a significant difference in the amount of drug permeated across the epidermis from the gel devoid of NLCs and the gel loaded with NLCs. It clearly shows that the the controlled release of drug from the NLCs predominates over the inherent rate of drug permeation across the intact stratum corneum from the gel. However, this study did not demonstrate the ability of NLCs to localize in the tissue and control the release of drug in a skin that is devoid of stratum corneum barrier, such as skin ulcers and wounds. Therefore, to investigate the workability of NLC in wounds, mechanistic studies were performed using skin without SC.

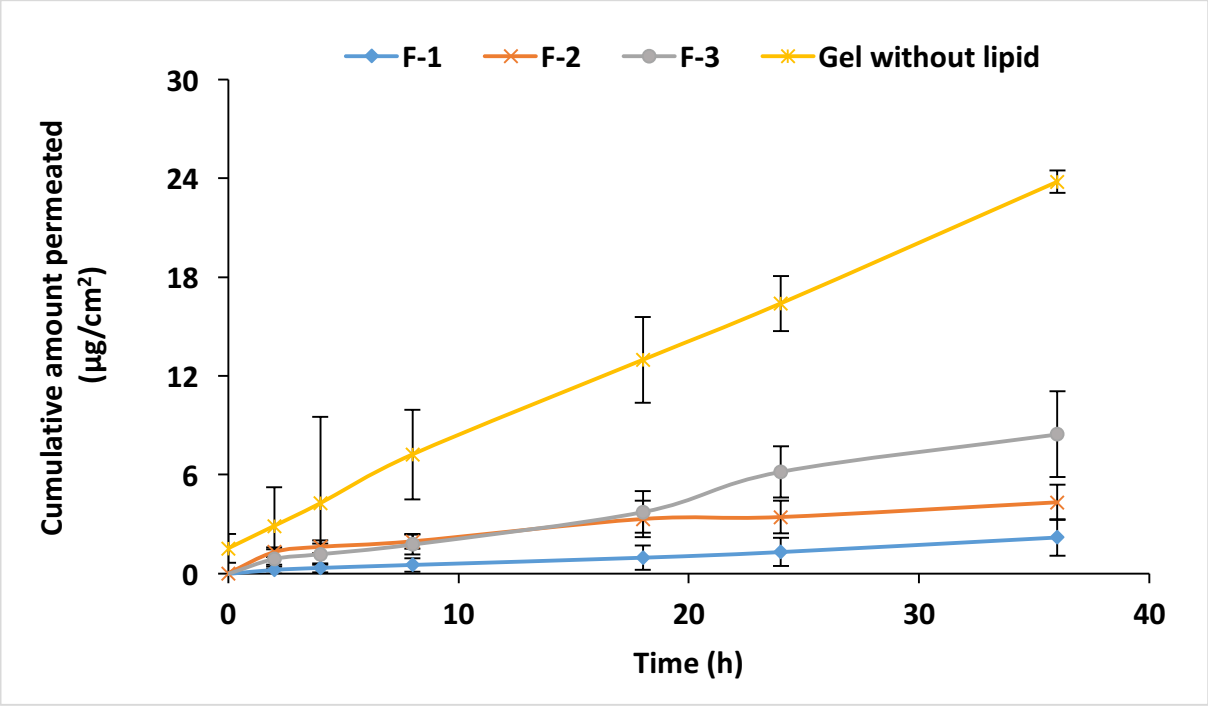

Figure 3.5a The *ex-vivo* drug permeation profile for the NLC loaded gels and gel without lipids (n-3).

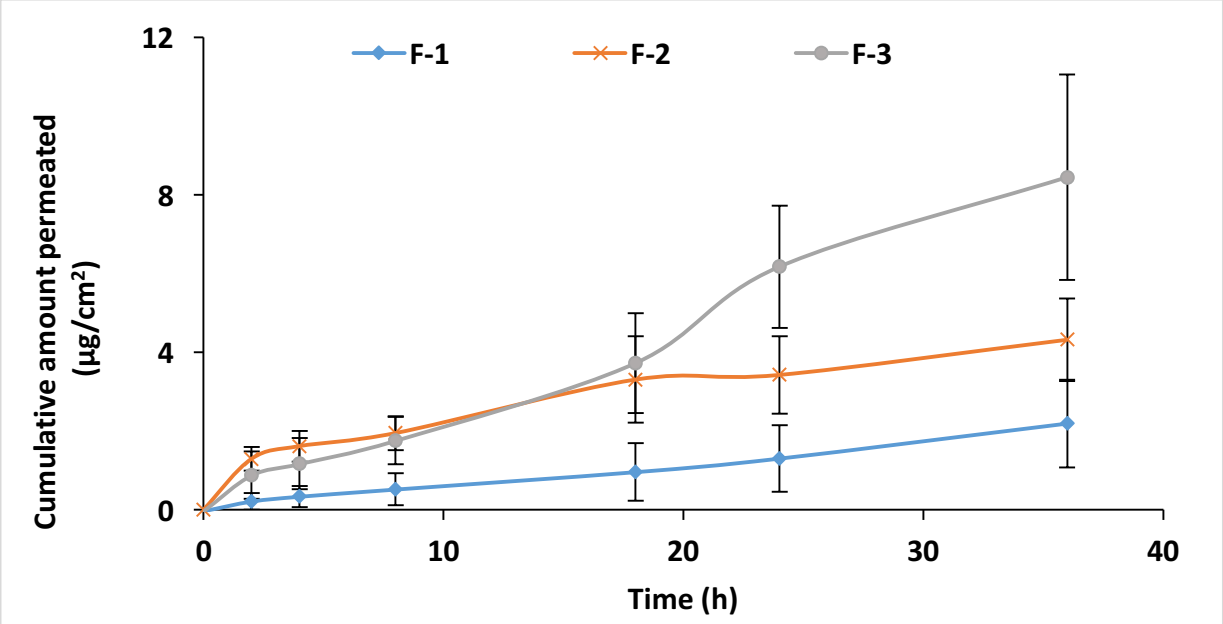

Figure 3.5b The *ex-vivo* drug permeation profile for the NLC loaded gels (n=3).

Mechanistic Studies

The barrier function of the skin is highly disrupted in cases when skin suffers burns, cuts and other mechanical injuries. Therefore, regional delivery of antibiotics, pain management drugs and wound healing agents, to treat such wounds and injuries would become highly challenging owing to poor retainability of drug in and rapid clearance of drug from the applied region. Therefore, to assess the hypothesis that drug loaded NLCs would offer longer retentivity in the skin and controlled drug release, the formulations were applied to intact skin and tape stripped skin. Figure 3.6, represents the amount of drug that was delivered into the skin from different formulations. It was observed that significantly higher amounts of drug penetrated into the intact as well as the tape stripped skin from the gel without lipids as compared to the NLC loaded gels. However, for all the NLC loaded gels, no significant difference was observed for lidocaine penetration between the intact and tape stripped skin. This study clearly confirmed that the predominant release controlling step was the release of drug from the NLCs rather than viscosity of the gel or stratum corneum barrier. Therefore, it is plausible to use NLCs for formulation of drug delivery systems for regional prolonged delivery of drugs in the treatment of skin conditions in which the stratum corneum barrier is compromised completely or partially. This would enable regional therapy of wounds and injuries, more safely and effectively as compared to systemic therapy.

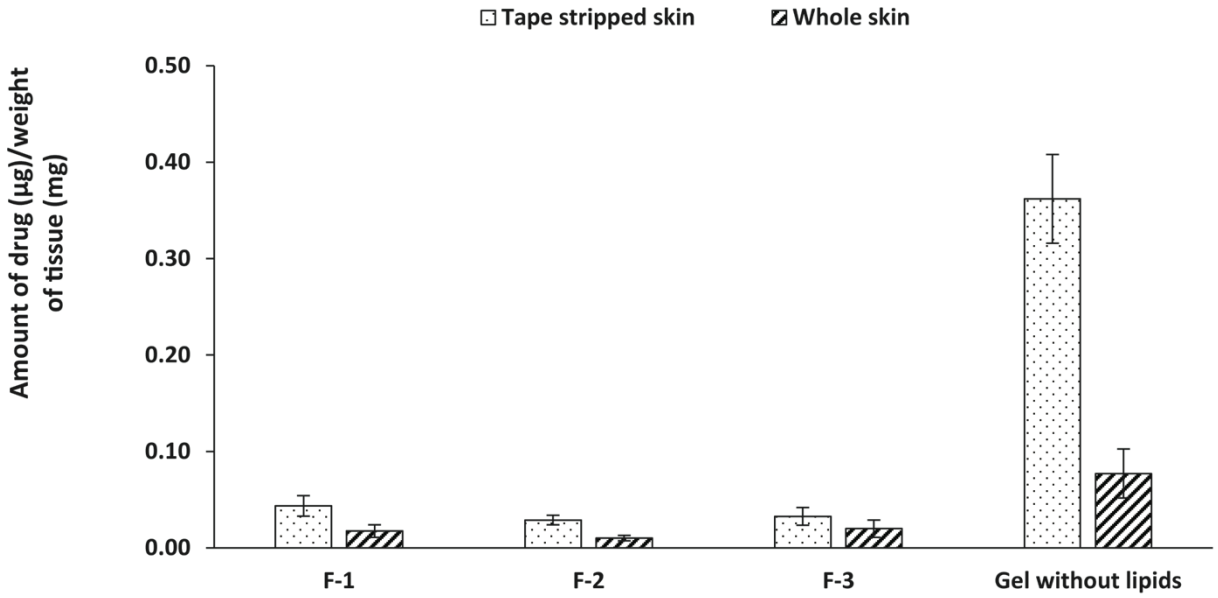

Figure 3.6 Graphical representation of data obtained from drug retention studies (n=3).

3.4 CONCLUSION

This work opens up a new application for hot-melt extrusion techniques in the field of nanotechnology. Hot-melt extrusion technology along with probe sonication was successfully utilized to prepare nanostructured lipid carrier formulations. The various parameters for HME such as screw speed, screw design, barrel temperature and feeding rate could be varied as to obtain a desired product. Also, this process provides many advantages over the conventional methods of NLC preparation like shorter processing times, fewer unit operations, a continuous process, which makes the process more suitable for the industry. The permeation and mechanistic studies indicate that the formulated NLCs are expected to provide a prolonged delivery of lidocaine at the affected local site and confirmed the main release controlling step to be release of the drug from the nanocarriers. The formulation thus has potential for pain management in wounds and other injuries.

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CHAPTER 4

EFFECTS OF FORMULATION COMPOSITION ON THE CHARACTERISTICS OF MUCOADHESIVE FILMS PREPARED BY HOT-MELT EXTRUSION TECHNOLOGY

4.1 INTRODUCTION

Over the last few years, the US Food and Drug Administration has encouraged the use of QbD principle in drug product development, manufacturing and regulation. The International Conference on Harmonisation (ICH) Quality Guidelines defines QbD as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" (Food et al., 2011). Prior knowledge, mechanistic models, risk analysis, design of experiment (DoE), data analysis and process analytical technology (PAT) are integral parts of QbD. Some of the goals for QbD include improving process capability, reducing product variability and defects, enhancing the product development and manufacturing efficiencies (Yu et al., 2014). While applying a DoE to a pharmaceutical system, the input factors are raw material attributes, process and formulation parameters and the output factors are the critical quality attributes (CQAs). Further more, the effect of process and formulation parameters on the product's CQA are studied and a controlled design space is established (Patwardhan et al., 2015).

Response Surface Methodology (RSM) is a collection of statistical and mathematical techniques utilized for developing, improving and optimizing processes in which the response of interest is influenced by several variables and the aim is optimizing this response (Baş and Boyacı, 2007). Using this technique, we can establish relationship between the response and the independent variables. The effect of independent variable, alone or in combination, on the process

can be studied. Reduced process variability, higher percentage yields and less treatment time are additional advantages of RSM (Pawar et al., 2016).

Mucoadhesive films are dosage forms that remain in intimate contact with the oral mucosa and release the drug for prolonged period either for local or systemic action. The release of drug can either be in the direction of oral mucosa or towards the oral cavity (Silva et al., 2015). The bioavailability of drugs that undergo extensive first pass metabolism after oral administration could be improved by formulating it as a mucoadhesive film. These dosage forms are particularly advantageous for pediatric and geriatric populations as they are easy to administer and danger of choking is minimal.

Currently, solvent casting (Vuddanda et al., 2017; Wang et al., 2016), printing (Buanz et al., 2015; Jamróz et al., 2017), compression (Garrido et al., 2016) and hot-melt extrusion (Albarahmieh et al., 2016; Repka et al., 2005) are the various techniques used for preparation of films. Although, solvent casting is the most commonly used technique for film preparation, it has many disadvantages, like multistep process, batch to batch variations, air entrapment and removal of solvent from the product is time consuming and tedious (Pimparade et al., 2017). On the contrary, hot-melt extrusion (HME), is solvent free, adaptable to continuous manufacturing and an economical process. Hot-melt extrusion involves heating the mixture of polymer blend and drug in a barrel and forcing it through a die to obtain granules or films. The heat and the shear via the mixing elements ensure the mixing of all the components uniformly. However, very few scientific articles demonstrating the manufacturing of mucoadhesive oral films by HME have been reported. These published articles primarily focus on development and characterization of mucoadhesive films. However, interaction between formulation variables and the HME process needs to be studied, to help the formulation scientists in designing quality products.

The aim of this study was to investigate the effects of formulation variables on the physico-chemical and drug release characteristics of mucoadhesive films prepared by melt extrusion technique, using the DoE approach. Salbutamol sulphate, an anti-asthmatic drug (pKa 9.2) was incorporated in the mucoadhesive film, containing hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC) as the film forming and drug retarding polymer, respectively. PEG 4500 was used as the plasticizer to aid the extrusion process.

4.2 MATERIALS AND METHODS

Materials

Salbutamol sulphate was purchased from Shreeji Pharma International, Vadodara, India. Klucel™ hydroxypropylcellulose EF and Benecel™ hydroxypropylmethylcellulose K15M were received as gift samples from Ashland, USA. Polyethylene glycol (PEG) 4500 was purchased from Professional Compounding Centers of America, Inc (PCCA). Avicel® PH 101 was purchased from FMC Health and Nutrition, USA. All other chemicals used were of analytical grade.

Methods

Design of experiments

The effect of formulation composition on the physico-chemical and drug release properties of films was studied using the response surface methodology (Type IV-Optimal). The experimental design and data analysis was carried out using a Design-Expert® software version 8. Fifteen runs with three independent factors, each with 3 levels, were designed using the DOE software. Table 4.1 enlists the independent and dependent variables used for the study. The responses were fitted to a full quadratic model and p-values for each of the factors were used to determine their significance ($p < 0.05$) on the film characteristics.

Analysis of variance (ANOVA) was conducted to test the significance ($p < 0.05$) of the model and factor coefficients (Table 4.5). Further, stepwise selection procedure was applied to eliminate

insignificant predictors and improve the model. Simple effect analysis was conducted for the predictors of the model that had a significant interaction term.

Table 4.1 Experimental factors and their levels for RSM study

Independent factors	**Levels**		
	Low (-1)	**Medium (0)**	**High (+1)**
HPC EF (x_1)	40	60	80
HPMC K15 (x_2)	0	10	20
PEG 4500 (x_3)	20	30	40
Dependent factors	Torque (y_1), stiffness (y_2), swelling index (y_3), disintegration time (y_4), % drug release at 4 h (y_5)		

Thermogravimetric analysis (TGA)

The thermal stability of drug and all excipients was verified using a Perkin-Elmer Pyris 1 TGA instrument. Samples of 10-15 mg, each weighed in a platinum pan, were heated from 50-250°C at a linear heating rate of 20°C/min and nitrogen purge of 20 mL/min. Data was collected and analyzed using Pyris manager software.

Differential scanning calorimetry (DSC)

DSC studies were performed using TA Instruments, the Discovery series DSC 25 equipped with TRIOS software to assess the nature of drug in extruded films. Approximately 2-10 mg of pure drug, polymers and extruded formulations were hermetically sealed in Tzero aluminum pans and exposed to temperature range of 25-200°C at a ramp of 10°C/min and nitrogen gas at 50 mL/min. DSC studies were repeated after 6 months to check the stability and change in nature of drug in the formulations.

Preparation of mucoadhesive buccal films using HME

Mucoadhesive buccal films were prepared using the co-rotating twin-screw extruder (16 mm Prism Euro Lab Thermo Fisher™ Scientific). The composition of each film formulation is as shown in Table 4.4. All the film formulations had 20% w/w salbutamol sulphate and 10% w/w Avicel PH 101 (filler). The physical mixture of each respective formulation was sieved, and hand blended to acquire a homogenous mixture. Extrusion was carried out at 130°C with a feed rate of 0.58 kg/h and screw speed of 50 rpm. A standard screw design with three mixing zones was used. The die opening of 1.5 mm thickness was attached to obtain uniformly thick films. Torque observed during extrusion of each formulation was noted and considered as one of the response variables in DOE. Films of each formulation were collected in rolls, labeled and sealed in polyethylene bags.

Thickness, weight and surface pH determination

Thickness was determined using a Thermo Fischer™ Scientific 0-150 mm Digital Caliper and each film was measured at three, randomly selected positions and an average value was considered. For determining the weight and surface pH of each formulation, films were cut into 1cm×1cm pieces. Weight of each film piece was measured on an electronic balance. Each piece of the respective formulation was soaked in 3 mL solution of phosphate buffered saline (PBS) pH 7.4 ± 0.1, in a petri dish. The glass electrode was brought in contact with the surface of the film, equilibrated for 1min to measure the surface pH using Mettler Toledo InLab® Micro pH probe (Reference Electrolyte 3 mol/L KCl).

Uniformity of drug content

Three films of each formulation were randomly selected and cut into 1cm×1cm pieces and weighed using an electronic balance. Addition of 10 mL of water, followed by sonication for 15 min was performed to dissolve the drug. Appropriate amount of sample was withdrawn and suitable dilutions were made. The amount of salbutamol sulphate present was determined using a HPLC-UV method at wavelength of 276 nm.

Swelling index (S.I.) and disintegration time (D.T.)

The procedure followed for determining swelling index and disintegration time was same. Films were cut into 1cm×1cm pieces, weighed and placed in a petri dish containing 3 mL of PBS solution, pH 7.4 ± 0.1. S.I. studies for each sample were carried out up to 9h. At specific time points, excess PBS on the sides of the sample was carefully absorbed using tissue paper and reweighed. After noting the wet weight, 3 mL of fresh solvent was introduced into the petri dish and procedure was repeated for each reading. S.I. was calculated using the following equation:

$$\text{Swelling Index (\%)} = \frac{\text{Wet weight} - \text{Original dry weight}}{\text{Original dry weight}} X\ 100$$

Simultaneously, each sample was visually checked periodically to note the D.T. Time when the film completely disintegrated was recorded.

Physical characterization

TA.XT2i Texture Analyzer Stable Micro Systems equipped with Texture Expert™ software was used to study stiffness and bioadhesion properties of each formulation.

Table 4.2 Test parameters for stiffness and bioadhesion studies.

Test	Stiffness		Bioadhesion	
Fixture	TA-108s5i Indexable Film Extensibility Rig		A-MUC SMS Mucoadhesive Rig	
Probe	TA-8 1/4" dia. Ball, SS		TA-57R 7mm dia., 1" radius, SS	
Load	5kg		5kg	
Process Parameters	Pre-test speed	2.0 mm/s	Pre-test speed	1.0 mm/s
	Test speed	1.0 mm/s	Test speed	0.1 mm/s
	Post-test speed	10.0 mm/s	Post-test speed	0.5 mm/s
	Distance	10.0 mm	Applied Force	3.5 N
	Trigger Force	10.0 g	Contact time	60.0s
	Break Sensitivity	50.0 g		

Stiffness studies were performed by placing an appropriate size of film of each formulation individually on the base plate and the screws are tightened such that the film does not move from its position. The stainless-steel ball probe was used to break through each film piece and the amount of work required to break it was recorded (Table 4.2).

Evaluation of bioadhesive property of the films was done using rabbit buccal mucosa purchased from Pel-Freeze® Biologicals, Arkansas, USA, with the parameters as mentioned in Table 4.2. The tissue was thawed in PBS solution pH 7.4 ± 0.1, for 1h and placed on the lower base plate, fixed using heavy hold-down brass fixture. The films were wetted with PBS solution pH 7.4 ± 0.1, for 60s and mounted onto the probe using a cyanoacrylate adhesive. The work of adhesion and detachment force were considered to evaluate the bioadhesive property of films.

Scanning electron microscope (SEM)

The surface morphology of the films was studied using SEM. The samples were placed on an aluminum base using an adhesive carbon tape. Hummer 6.2 Sputter Coater Ladd Research Industries, Williston, VT was used to sputter coat the samples with gold in a high vacuum evaporator. Images of these coated samples were captured using JEOL JSM-5600 SEM at an accelerating voltage of 10kV.

In vitro drug release

Drug release studies were carried out using Hanson SR8 Plus USP Apparatus 5 paddle over disk method with 500 mL of phosphate buffer pH 6.8, at speed of 50 rpm and at 37±0.5°C. The films of 1cm×1cm were cut, weighed and fixed on a watch glass using a cyanoacrylate adhesive, leaving the other side open. The films were positioned against the watch glass, such that the drug release is unidirectional and films were retained with the 17 mesh film retainer screen. 1 mL aliquots were withdrawn from the vessel at predetermined time intervals of 0, 1, 2, 4, 6, 8, 10 and 12h and replenished with equal volume of phosphate buffer pH 6.8. The samples were analyzed using a suitable HPLC-UV method.

Analytical Method

The salbutamol sulphate content in each formulation and analysis of drug release was performed using a Waters HPLC system with a Waters 2489 UV detector utilizing a Luna C18, 250×4.6mm (5µ) Phenomenex column. The mobile phase composition of 0.08 mol/L sodium dihydrogen phosphate solution (pH adjustment to 3.10 ± 0.05 using o-phosphoric acid) – methanol (85:15 v/v), flow rate of 1 mL/min, injection volume of 20 µL and detection wavelength of 276 nm was used for analysis.

4.3 RESULTS AND DISCUSSION

Thermal analysis

During hot-melt extrusion, the drugs and polymers are heated to high temperature and it is necessary to ensure all the components are stable at the employed processing condition. TGA analysis (Figure 4.1) revealed all the ingredients were stable at 130°C (no weight change seen), which was the extrusion temperature for the formulation. DSC scan of pure salbutamol sulphate (melting point- 180°C) did not show a melting peak (Figure 4.2), indicating the amorphous form of drug. The amorphous form of drug was retained even after extrusion. However, pharmaceutical systems containing amorphous drugs have tendency to revert to the crystalline form as it is the thermodynamically favored form. But in this case, DSC thermogram (Figure 4.2) for samples stored for 6 months at 25°C, did not show any crystalline peak confirming the stability of the amorphous system for up to 6 months.

Preparation of Films by Hot-Melt Extrusion

Preliminary extrusion studies were carried out at 150°C, with this temperature a yellow discoloration of the drug was observed. Thus, it was necessary to reduce the extrusion temperature to prevent drug discoloration. Plasticizers are commonly utilized in HME, as they lower the glass transition temperature of polymers by weakening the intermolecular forces that hold the polymer chains together and thus improve the processability at lower temperature (Thumma et al., 2008). PEG 4500 was the plasticizer used in this study to extrude the films at 130°C. All the 15

formulations were successfully extruded at the processing conditions mentioned above and no drug discoloration was observed.

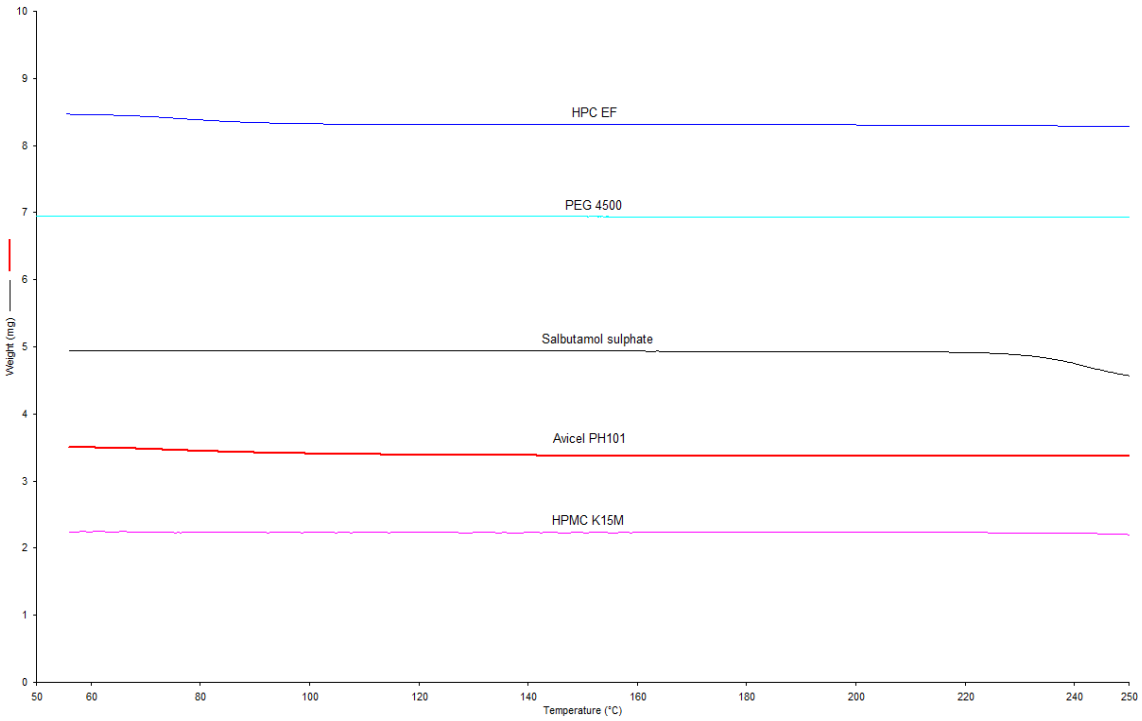


Figure 4.1 Thermogravimetric analysis for the formulation ingredients

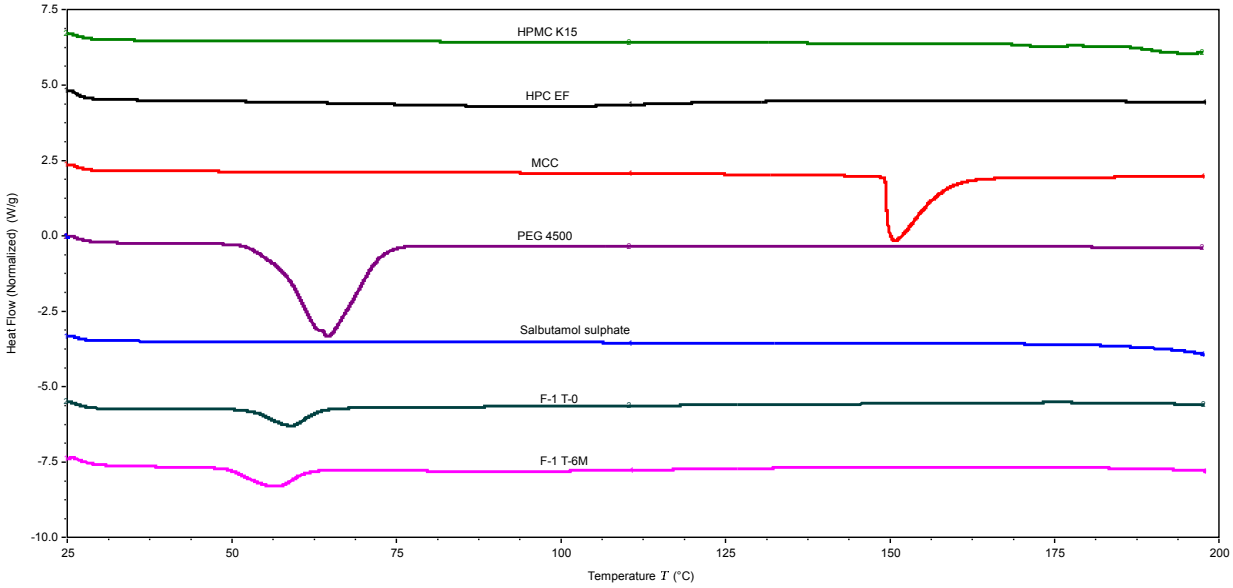


Figure 4.2 DSC thermogram for the film ingredients and extruded films (F-1 T-0 and F-1 T-6M refers to film formulation at time 0 and 6 months, respectively)

Characterization of films

The weight and thickness of 1cm x 1cm films was found to be in the range of 113.63 - 132.50 mg and 0.90 – 1.11 mm, respectively (Table 4.3). Surface pH was in the range of 7.06 – 7.32. The drug content was found to vary from 91.33% to 98.53% (Table 4.3). In addition, the standard deviation for drug content for each formulation was less than 4%, thus demonstrating uniformity of drug content.

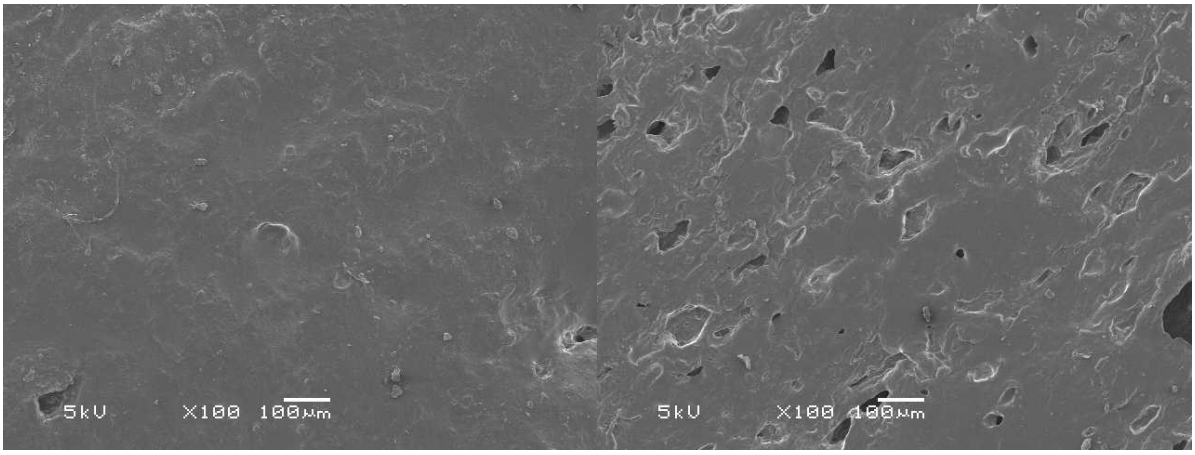
Table 4.3 Characterization of extruded films

Formulation no.	Weight (mg)	Thickness (mm)	Surface pH	Drug Content (%)
F-1	126.60 ± 1.47	1.03 ± 0.01	7.26 ± 0.11	94.04 ± 0.51
F-2	131.53 ± 0.96	1.04 ± 0.02	7.21 ± 0.06	93.66 ± 0.54
F-3	128.87 ± 1.20	1.06 ± 0.03	7.12 ± 0.07	94.05 ± 1.74
F-4	128.87 ± 0.86	1.08 ± 0.03	7.24 ± 0.13	91.33 ± 2.45
F-5	127.47 ± 0.85	1.06 ± 0.05	7.22 ± 0.09	91.36 ± 1.02
F-6	129.23 ± 0.45	0.92 ± 0.05	7.29 ± 0.10	94.51 ± 0.97
F-7	127.13 ± 0.59	1.00 ± 0.05	7.18 ± 0.14	94.32 ± 2.27
F-8	127.47 ± 0.60	1.06 ± 0.03	7.23 ± 0.13	93.25 ± 0.63
F-9	132.50 ± 1.28	1.11 ± 0.03	7.18 ± 0.10	98.53 ± 3.66
F-10	128.20 ± 1.81	1.06 ± 0.04	7.16 ± 0.07	93.43 ± 3.2
F-11	121.17 ± 1.15	1.10 ± 0.03	7.25 ± 0.19	94.64 ± 1.77
F-12	114.00 ± 0.35	0.97 ± 0.02	7.32 ± 0.11	93.4 ± 1.53
F-13	113.63 ± 0.78	0.90 ± 0.04	7.09 ± 0.07	93.06 ± 0.73
F-14	127.93 ± 0.32	1.07 ± 0.03	7.06 ± 0.09	92.33 ± 1.22
F-15	126.67 ± 1.62	1.10 ± 0.01	7.28 ± 0.10	92.62 ± 0.95

Scanning electron microscopy

SEM was performed to study the surface morphology of the extruded films. A variation in the surface characteristics as shown in Figure 4.3, was observed for the films with varying composition. F-6 and F-7 formulation had same composition except the concentration of film forming polymer (HPC). Films containing higher amounts of HPC (F-6) were found to have a smooth surface, while those containing lower amount of HPC (F-7) were found to be porous. No

crystals of salbutamol sulphate were observed, supporting the DSC finding of amorphous drug in the formulation.



(a) (b)

Figure 4.3 Surface morphology analyzed using SEM. a) Formulation F-6. b) Formulation F-7

Bioadhesion studies

Bioadhesion can be defined as the ability of a biological substrate or synthetic material to stick to the human epidermis or a mucous membrane (Repka and McGinity, 2001). Bioadhesion is a complex process and various mechanisms like hydrogen bonding, polymer chain inter-penetration, surface energy and contact angle measurement and swelling rate of the polymer have been studied and proposed for bioadhesion. In this study, peak force and work of adhesion were evaluated to study the bioadhesion of films. Peak force (adhesive strength) is the maximum force required to detach the film from the biological substrate, while work of adhesion is the area under the curve (plot of force versus time). Peak force and work of adhesion were found to be in the range of 0.09 - 0.28 N and 0.32 - 0.71 N-s, respectively (Figure 4.4). Hydration of polymers, followed by physical entanglement and interpenetration of the polymer chains with the mucin and hydrogen

bonding have been reported as the mechanisms for bioadhesion of HPMC and HPC (Repka et al., 2005). This study demonstrated the low to moderate adhesive potential of the cellulose polymers used.

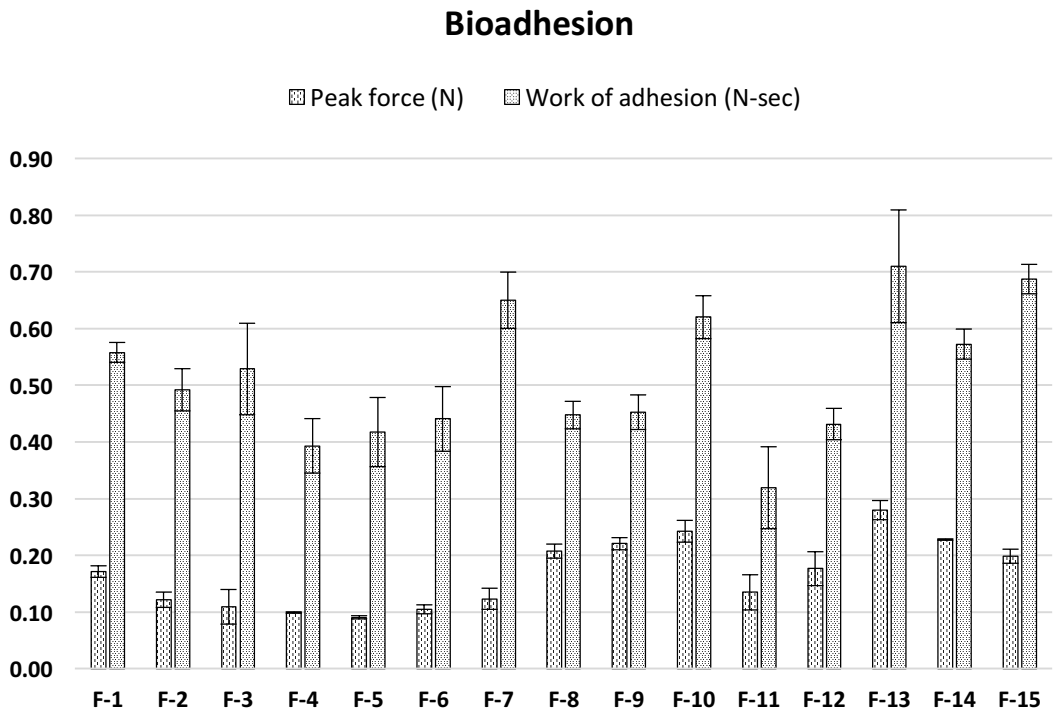


Figure 4.4 Bioadhesion studies performed for the film formulations

Table 4.4 The design of RSM: Factors and Responses

Run	Factor x_1: HPC-EF (g)	Factor x_2: HPMC K-15 (g)	Factor x_3: PEG 4500 (g)	Response y_1: Torque (%)	Response y_2: Stiffness (g/s)	Response y_3: Swelling index	Response y_4: Disintegration time (min)	Response y_5: % drug release
F-1	80	20	40	23	1024	27.76	210.67	69.21
F-2	80	10	40	20	616	23	130	80.56
F-3	60	10	40	17	746	19.36	149.67	80.23
F-4	40	20	20	32	1782	75.48	540	71.5
F-5	60	0	30	18	1309	0	131.33	86.28
F-6	80	10	30	28	856	58.49	75	73.2
F-7	60	10	30	19	948	31.58	135	81.55
F-8	40	10	20	25	1301	40.33	190	75.4
F-9	40	0	40	8	1036	0	136	72.31
F-10	60	20	20	29	1094	59.67	380.33	69.36
F-11	60	0	30	17	851	0	135.33	89.47
F-12	80	0	40	17	1295	0	130.33	84.64
F-13	80	0	20	32	1132	0	152	83
F-14	40	20	30	18	1262	105.35	290	70.54
F-15	60	10	30	17	782	46.37	132.67	71.64

Table 4.5 Analysis of variance (ANOVA) for all responses

Source	Torque		Stiffness		Swelling index		Disintegration time		% drug release	
	f-value	p-value	f-value	p-value	f-value	p-value	f-value	p-value	f-value	p-value
Model	24.29	<0.0001	5.45	0.0139	22.33	0.0001	37.28	<0.0001	18.49	0.0009
x_1	22.84	0.0006	3.72	0.0859	4.96	0.0565	20.95	0.0026	-	-
x_2	10.06	0.0089	0.48	0.5071	81.03	<0.0001	84.75	<0.0001	18.49	0.0009
x_3	50.34	<0.0001	5.12	0.0499	0.16	0.6960	2.64	0.1484	-	-
x_1x_2	-	-	-	-	4.77	0.0605	8.51	0.0224	-	-
x_1x_3	-	-	5.71	0.0406	-	-	-	-	-	-
x_2x_3	-	-	-	-	-	-	-	-	-	-
x_1^2	-	-	-	-	5.21	0.0519	8.68	0.0215	-	-
x_2^2	-	-	10.26	0.0108	-	-	36.34	0.0005	-	-
x_3^2	-	-	-	-	14.57	0.0051	27.14	0.0012	-	-

Note: Stepwise selection procedure was applied to improve the model

Torque

Parameters like screw speed and throughput can be set individually, while torque is a resulting value which represents the resistance of the material to move forward in the barrel. In other words, it indicates how much energy is conveyed from motor to the screw to process a formulation. Torque is one of the most relevant practical response as it measures how the process reacts to a given input (Lowinger 2011). Generally, polymers that are difficult to extrude or the ones that have very high glass transition temperature show higher torque values during extrusion. Thus plasticizers are added to the polymer blend to improve the processability of such mixtures, either by lowering the processing temperature or by decreasing the melt viscosity. For this study, torque values during extrusion were in the range of 8-32%. The equation representing the effect of independent variables on torque is shown below:

$$y_1 = 25.49 + 0.23x_1 + 0.30x_2 - 0.70x_3$$

The positive coefficient for HPC EF and HPMC K15 indicates that an increase in the concentration of these polymers results in higher torque values (Figure 4.5). However, an increase in the concentration of PEG 4500 results in lower torque values (Figure 4.6), this can be attributed to the plasticizing effect provided by PEG. Thus our hypothesis of reduction in torque with an increase in the amount of plasticizer was confirmed in this study. Similar effects of plasticizer on torque values have been observed in few other studies (Desai et al., 2017; Grymonpré et al., 2017).

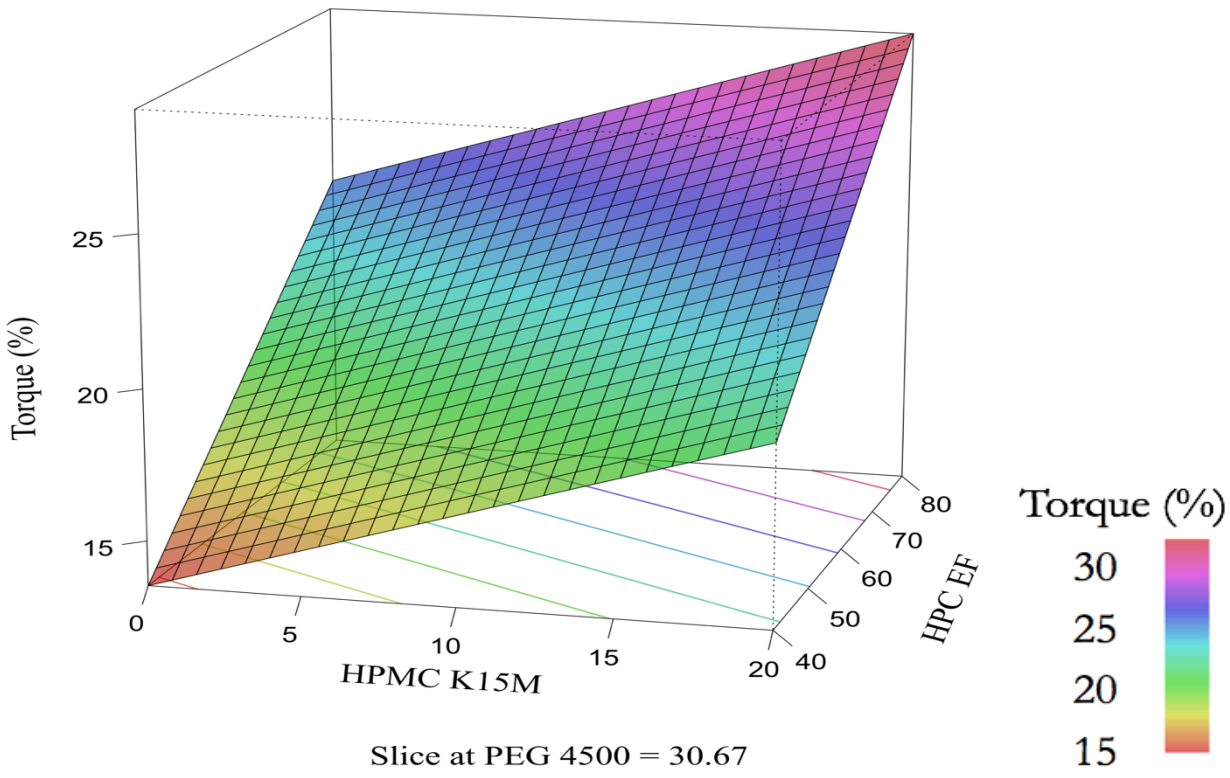


Figure 4.5 Response surface 3D plot showing effect of different levels of HPC EF (g) and HPMC K15M (g) on torque values.

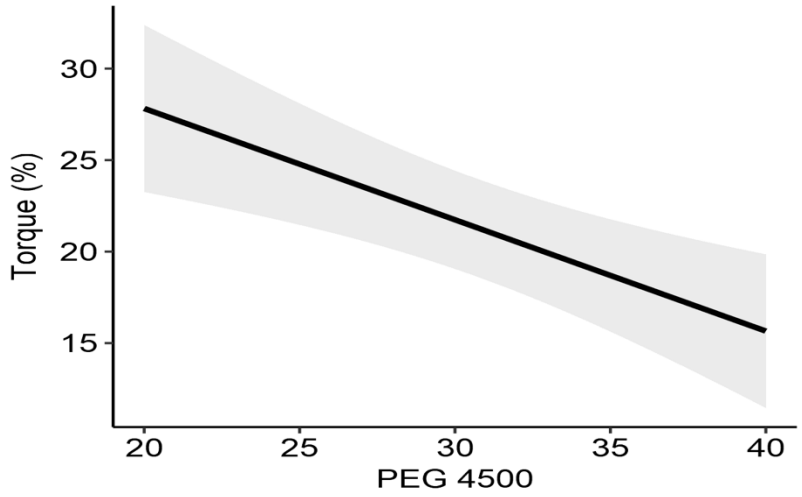


Figure 4.6 The effect of PEG 4500 concentration (g) on torque values

Stiffness

Mechanical properties are important quality attributes of films and they affect the quality and elegance of the product. Mechanical properties like stiffness need to be considered while optimizing a film formulation, so as to ensure it can withstand the stress during transport and patient handling. Different factors like film forming agent, type and amount of plasticizer, type of manufacturing process and type and amount of API have an impact on the mechanical properties of films (Preis et al., 2014). The stiffness of extruded films was in the range of 616 - 1782 g/s. The equation below shows the effect of independent variables on stiffness of films.

$$y_2 = 3860.39 - 36.44x_1 - 68.15x_2 - 75.11x_3 + 3.16x_2^2 + 0.99x_1.x_3$$

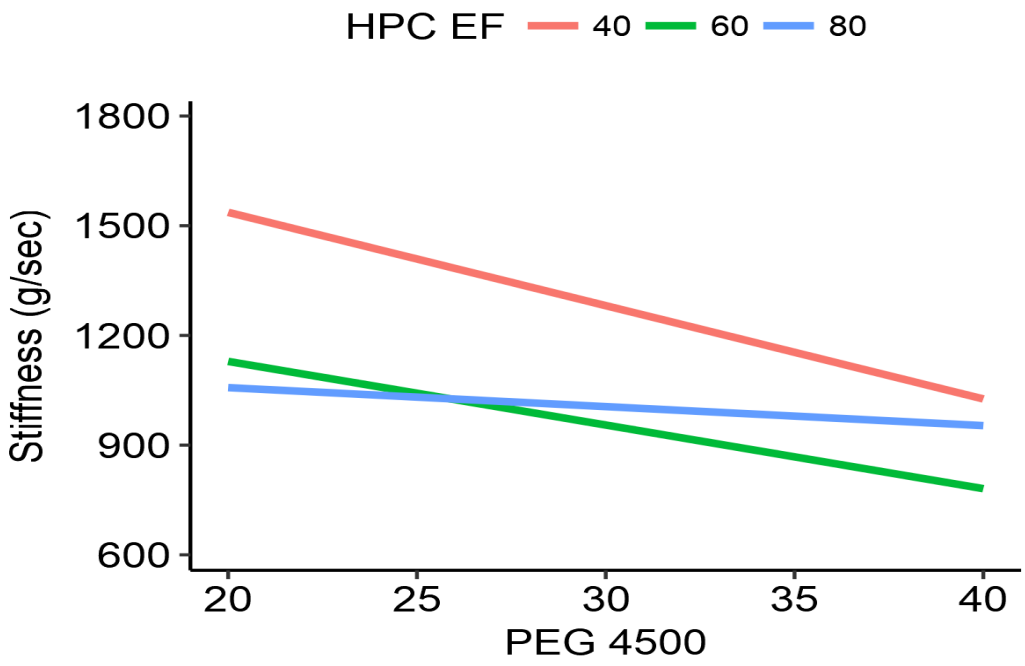


Figure 4.7 The effect of PEG 4500 and HPC EF concentration (g) on stiffness of films

It was observed that amount of plasticizer had a significant influence on stiffness of films and this effect was qualified by the amount of film forming polymer. At a constant amount of HPC EF

(40 g and 60 g), an increase in the amount of PEG 4500 caused a significant decrease in the stiffness of the films (Figure 4.7). However, at HPC level of 80 g, plasticizer did not have a significant effect on stiffness. Thus, the plasticizing effect by PEG 4500 negatively influenced the mechanical properties of the film at HPC concentration of 40 g and 60 g. In a study conducted by Visser et al., on orally disintegrating films, higher percentage of glycerol (plasticizer) corresponded to decreased tensile strength, further supporting our results (Visser et al., 2015). Another finding from this study was that as the concentration of HPMC increased from low to medium level, there was a decrease in stiffness, however, a further increase in the concentration of HPMC (from 10 g to 20 g) resulted in an increase in stiffness values. It might be possible that at low level of HPMC, it is the other factors that have a pronounced effect on stiffness, but as the concentration of HPMC increase, its influence on stiffness is observed. However, further investigation is necessary to find out the exact mechanism for such a trend. Similar behaviour was observed for HPMC E5 films that were plastcized by PEG 4000, and prepared using sraying technique, in a study conducted by Heinämäki et al.

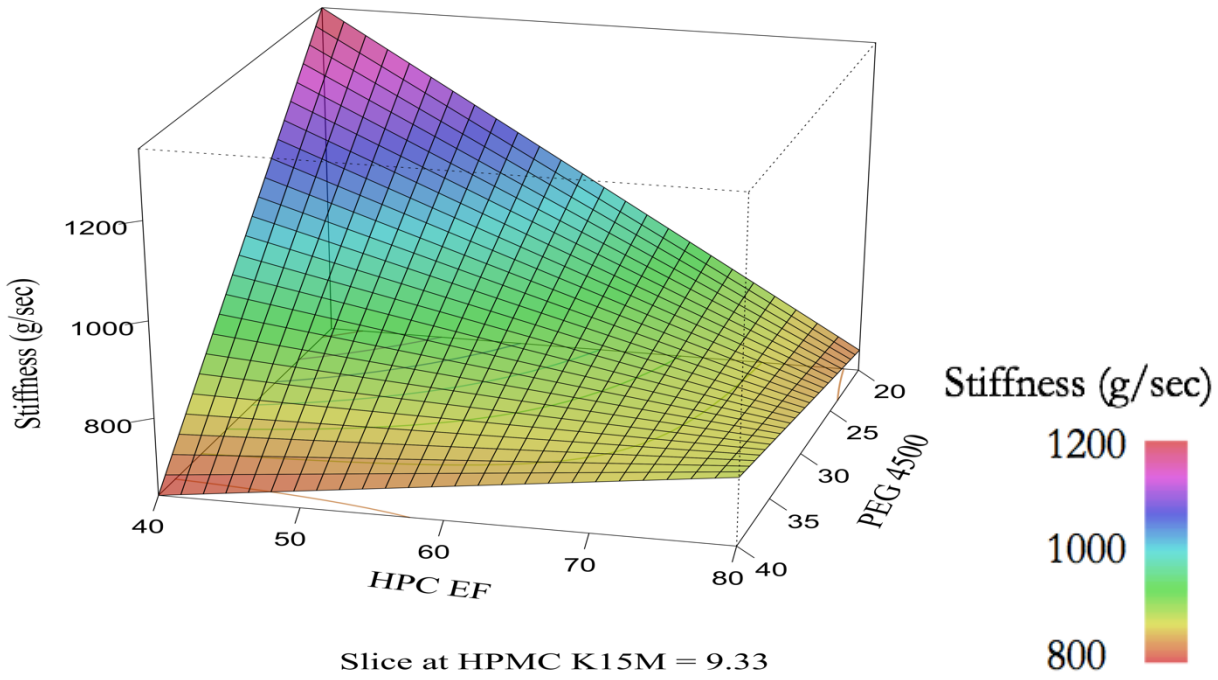


Figure 4.8 Response surface 3D plot showing the interactive effect of concentration of HPC EF (g) and PEG 4500 (g) on stiffness of films.

Swelling index

Swelling index represents the water retaining/holding capacity of polymers (Sharma et al., 2016). Mucoadhesive polymers undergo hydration to form a macromolecular mesh, leading to mobility in the polymer chains and enhancing the interpenetration between polymer and mucin (Costa et al., 2014). A progressive change from the glassy to the rubbery state leads to the swelling process. Determining the swelling index for the formulation is thus a good indicator of the adhesion properties of films. The equation below shows the effect of independent variables on swelling index of films.

$$y_3 = -74.97 - 4.10x_1 + 6.42x_2 + 13.59x_3 + 0.035x_1^2 - 0.229x_3^2 - 0.053x_1.x_2$$

A significant interaction between the concentration of HPMC K15M and HPC EF was seen for swelling index (Figure 4.9). Very high swelling index was seen with high amounts of HPMC

K15M and at low levels of HPC EF, as shown in Figure 4.9. HPMC K15M and HPC EF have average molecular weight of 575,000 Da and 80,000 Da, respectively. The high molecular weight HPMC polymers are hydrophilic swellable polymers that form a viscous gel layer upon hydration (Conti et al., 2007). Thus an increase in the amount of such polymer in a film, leads to an increase in the swelling behavior as seen in Figure 4.9. The dissolution of HPC polymers occurs via a swelling and erosion driven mechanism, which is dependent upon chain length. The lower molecular weight grades like Klucel EF undergo a faster erosion and show a lower swelling index (Mohammed et al., 2012), thereby confirming our results. Interestingly, it was observed that swelling index increased as the PEG concentration increased from low to medium levels but further increase in concentration to high levels, reduced the swelling index.

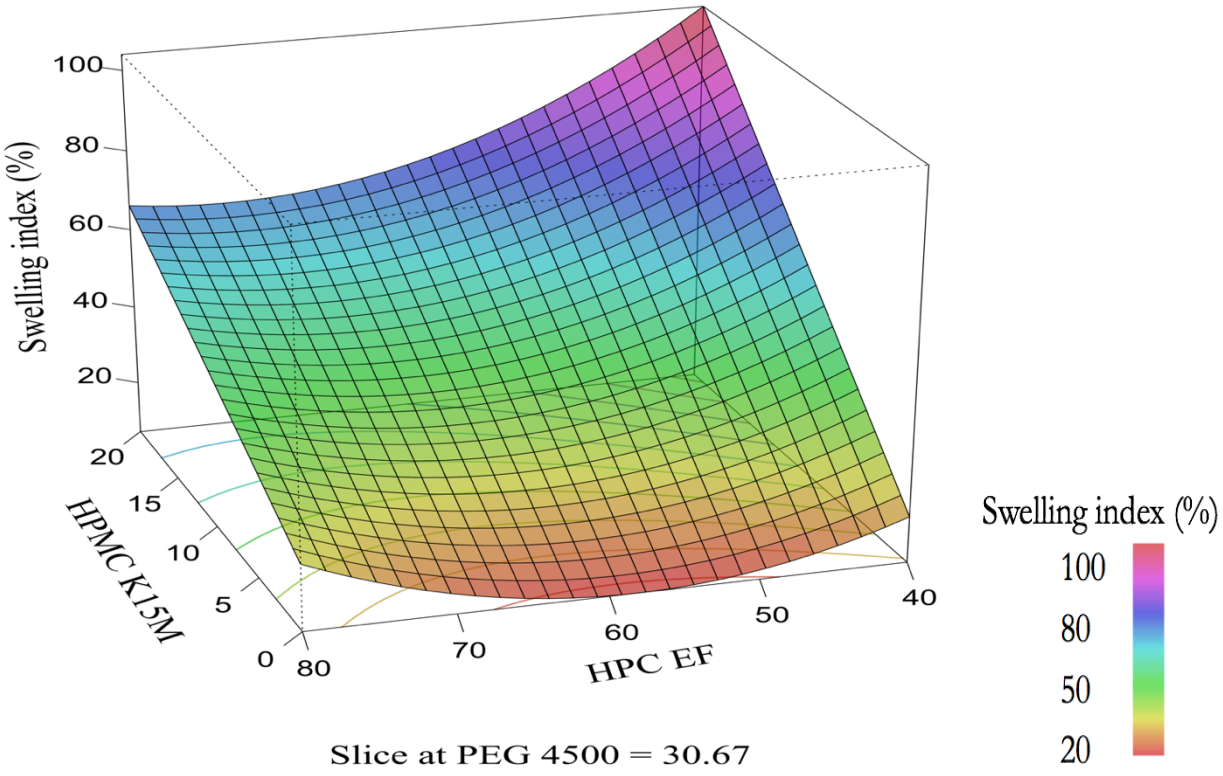


Figure 4.9 Response surface 3D plot showing the interactive effect of concentration of HPMC K15M (g) and HPC EF (g) on swelling index.

Disintegration time

Disintegration time of mucoadhesive films has been co-related with their swelling index because swelling of films is followed by eventual disintegration (Garsuch and Breitkreutz, 2009). The disintegration time was found to vary from 75 min to 540 min. Interactions between the independent variables (HPMC K15M and HPC EF) as seen for swelling index were observed for disintegration time (Figure 4.10). Film formulation with low level of HPC EF (40 g) and PEG 4500 (20 g), and high level of HPMC K15 demonstrated the longest disintegration time because HPC EF and PEG 4500 are water soluble and erode quickly while, HPMC K15M is a swellable polymer undergoing slow erosion. The equation below demonstrates the effect of independent variables on disintegration time.

$$\ln(y_4) = 6.5 + 0.06x_1 + 0.01x_2 - 0.22x_3 - 0.0005x_2^2 + 0.003x_3^2 - 0.0008x_1x_2$$

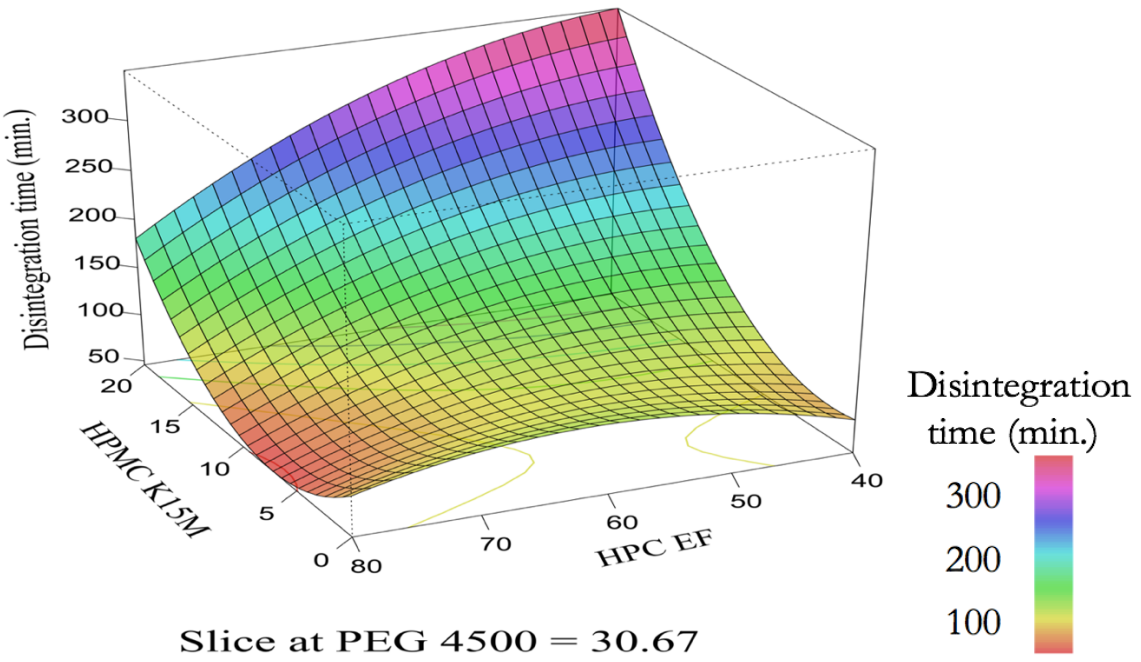


Figure 4.10 Response surface 3D plot showing the interactive effect of concentration of HPC EF (g) and HPMC K15M (g) on the disintegration time.

Drug release (Dissolution)

At 4 h time point, drug release from the films varied from 69.21% to 89.47% (Figure 4.12). Drug release from the polymeric films was found to be significantly affected by the concentration of HPMC K15M in the formulation (Figure 4.11). The equation below represents the effect of HPMC on the % drug release.

$$y_5 = 83.30 - 0.65x_2$$

The negative coefficient for HPMC indicates that as the amount of this polymer is increased, the % drug release decreases significantly.

Higuchi model was not suitable for this study because few of the assumptions of this model as mentioned below, did not apply to this investigation (Siepmann and Peppas, 2012).

1) The initial drug concentration in the system is much higher than the drug solubility.

2) Drug diffusion is one-dimensional, making edge effects negligible.

3) Swelling or dissolution of the polymer carrier can be neglected.

Korsmeyer-Peppas model was used to analyze the in vitro drug release mechanism. The release exponent (n) for the film formulations ranged from 0.6675 to 0.9297 (Table 4.6), indicating anomalous drug transport as the drug release mechanism(Avachat et al., 2013; Costa and Sousa Lobo, 2001). Thus diffusion as well as erosion were responsible for drug release. HPC EF undergoes dissolution by the mechanism of erosion and diffusion, while HPMC K15M swells and dissolves, thus explaining to some extent the reason for anomalous drug transport.

Table 4.6 R^2 and n values for Korsmeyer-Peppas model

Formulation	R^2	n
F-1	0.98615	0.8831
F-2	0.98814	0.8188
F-3	0.98593	0.7935
F-4	0.98207	0.8174
F-5	0.97198	0.8255
F-6	0.97987	0.8147
F-7	0.98401	0.7852
F-8	0.97633	0.7434
F-9	0.98508	0.8485
F-10	0.99352	0.6675
F-11	0.9466	0.8648
F-12	0.97899	0.8129
F-13	0.97994	0.8605
F-14	0.97904	0.8827
F-15	0.97527	0.9297

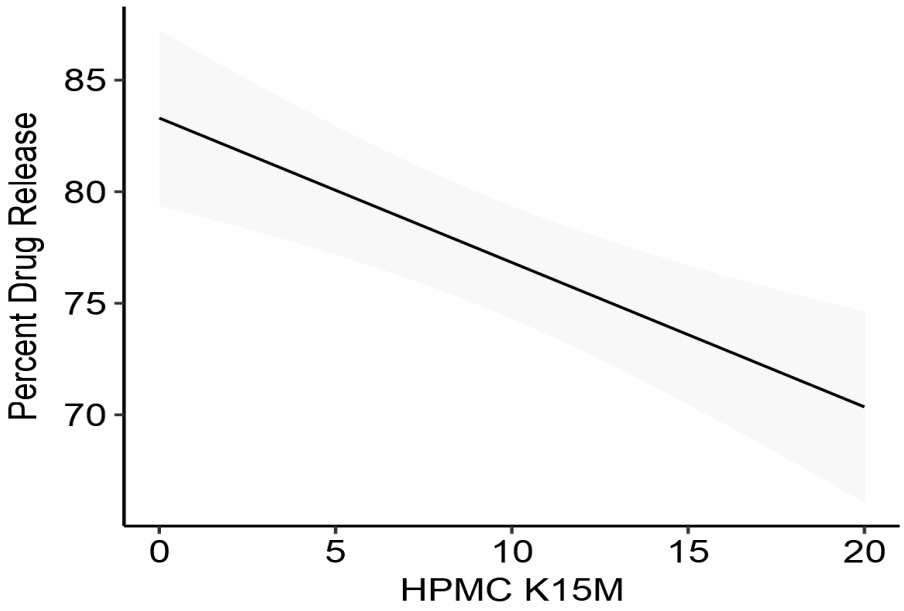


Figure 4.11 The effect of concentration of HPMC (g) on percent drug release of mucoadhesive films.

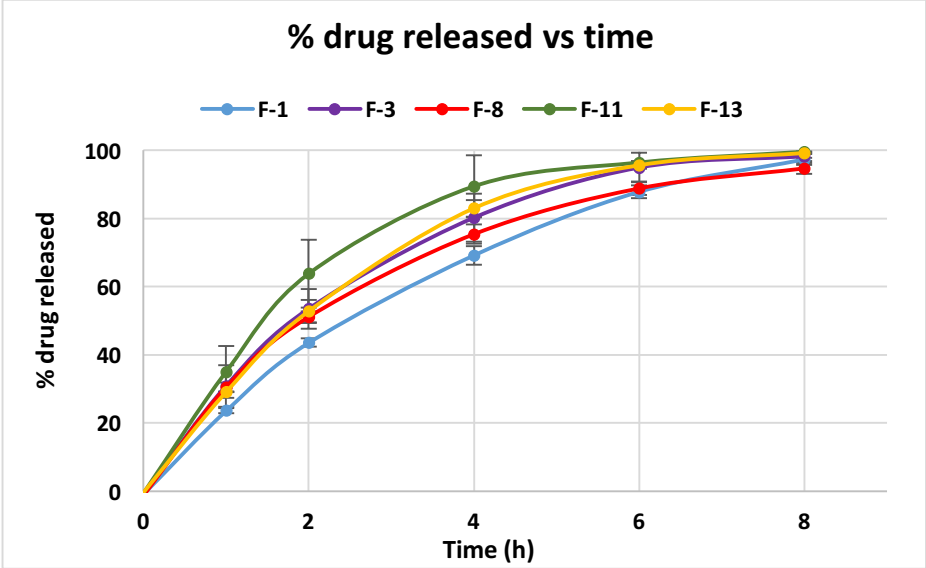


Figure 4.12 Few extruded films with significant difference in the drug release profile.

4.4 CONCLUSION

Films were successfully extruded using melt extrusion technique. Response surface methodology provided a clear picture of impact of formulation composition on the physico-chemical and drug release properties of films. It was observed that HPC EF, HPMC K15M and PEG 4500 all influenced one or the other film characteristics either alone or in combination. It is of utmost importance to understand how interactions between factors affect a specific response. It is only after such analysis that an optimized system with desired properties could be formulated. Thus, this study provides a valuable insight for selection of formulation composition for hot melt extruded mucoadhesive films. The relationship between formulation composition and product performance was elucidated, thus demonstrating the use of melt extrusion technology as a viable approach for preparation of films with desired quality attributes.

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SUMMARY:

- Highly motivated and goal oriented researcher with a broad experience in formulation development of solid orals, topical semisolids, and nanocarriers, resulting in 3 publications and 5+ collaborative grants.
- Three years of experience in process development and optimization of hot-melt extrusion technology along with strong analytical characterization skills.
- Excellent laboratory and communication skills showcased through teaching formulation lab techniques to 120+ Pharm.D. students and by instructing the pre-formulation lab for the post graduate course in tablet technology.
- Demonstrated leadership and managerial skills by serving as the Chair of the AAPS Students' Chapter and the editor of the annual college magazine.

WORK EXPERIENCE:

Graduate Research Assistant, Oxford, MS
Aug 2014 – Present, The University of Mississippi

- Independently designed and executed formulation development projects and elucidated the relationship between hot-melt extrusion and drug product characteristics.
- Displayed innovative thinking by establishing a new platform for the preparation of semisolids and nanocarriers using melt extrusion.

Intern, Celgene Corporation, Summit, NJ
May 2017 – Aug 2017, Biologics Drug Product Development

- Late phase in-use stability testing for lyophilized recombinant fusion protein product, along with aseptic handling and vial filling for product.
- Formulation screening along with biophysical characterization of liquid protein product, thus laying a strong foundation for future work.

Intern, Meyer Organics, Mumbai, India
May 2013 – Jun 2013, Tablet and Capsule Manufacturing Section
Tablet and Capsule Manufacturing Section

- Got an exposure of the various pharmaceutical unit operations like tablet press, fluid bed dryer, capsule filling machin

EDUCATION:

The University of Mississippi, Oxford, MS
Academic Advisor: Dr. Michael Repka
Doctor of Philosophy (Ph.D.) Pharmaceutical Sciences, GPA: 3.98
Dissertation: Novel Applications of Hot-Melt Extrusion Technology

The University of Mumbai, India
Bachelor of Science (B.S) in Pharmacy, May 2014

HONORS:

- Winner of Podium Presentation at the 7th Annual Research Symposium (Mar 2017)
- Winner of the 3-Minute Thesis Competition at the University of Mississippi (Nov 2016)
- AAPS Travelship award from the Manufacturing Science and Engineering section (Nov 2016 and Oct 2015)
- Research grant awarded by the Graduate School (May 2016 and May 2015)
- Inducted in Phi Kappa Phi Academic Honor Society (Apr 2017) and Rho Chi, Pharmacy's Academic Honor Society (Apr 2016)

TECHNICAL SKILLS:

- Design of Experiments, Hot Melt Extruder, High-Shear Granulator, Pan Coater, Fluid Bed Dryer, Extrusion-Spheronization, Tablet Press
- DSC, TGA, SEM, Texture Analyzer, HIAC
- RP-HPLC, Size Exclusion Chromatography, Dynamic Light Scattering, Differential Scanning Fluorimetry, UV Spectrophotometer, Franz Diffusion Apparatus, Dissolution

PUBLICATIONS:

- Repka, Michael A., et al. "Melt extrusion with poorly soluble drugs-An integrated review." *International Journal of Pharmaceutics* 535.1-2 (2017): 68.
- Bhagurkar, Ajinkya., et al. "A Novel Approach for the Development of a Nanostructured Lipid Carrier Formulation by Hot-Melt Extrusion Technology." *Journal of Pharmaceutical Sciences* 106.4 (2016): 1085-1091
- Bhagurkar, Ajinkya M., et al. "Development of an ointment formulation using hot-melt extrusion technology." *AAPS PharmSciTech* 17.1 (2016): 158-166

PROFESSIONAL AFFILIATIONS:

- Chair of AAPS-UM student chapter
- American Association of Pharmaceutical Scientists
- Indian Pharmaceutical Association

PROFESSIONAL EXPERIENCE:

- Podium and poster presentation at the Graduate Research Association of Student in Pharmacy Conference, Atlanta, Georgia (Jun 2015) and at the AAPS Annual Meeting (Oct 2015, Nov 2016, Nov 2017)
- Completed a post graduate course in Hands on Course in Tablet Technology (Mar 2015)

POSTER PRESENTATIONS:

- AAPS Annual Meeting, San Diego, Nov 2017- Development and Characterization of Mucoadhesive Buccal Films by Hot-Melt Extrusion Technology using a Design of Experiment Approach
- AAPS Annual Meeting, San Diego, Nov 2017- Development of a Cyclodextrin Based Dry Syrup Formulation Using Hot-Melt Extrusion Technology
- AAPS Annual Meeting, Denver, Nov 2016- Modified Release Characteristics of a Water Soluble Drug Using Ethyl Cellulose and Polyethylene Glycol via Hot-Melt Extrusion Technology
- AAPS Annual Meeting, Denver, Nov 2016- Nanostructured Lipid Carriers (NLC) for Controlled Delivery of Lidocaine for Pain Management in Wounds
- AAPS Annual Meeting, Denver Nov 2016- Development of a Nanostructured Lipid Carrier (NLC) Formulation for Topical Drug Delivery, using Hot-Melt Extrusion Technology
- School of Pharmacy, Ole Miss, Oct 2016- Development of a Nanostructured Lipid Carrier (NLC) Formulation for Topical Drug Delivery, using Hot-Melt Extrusion Technology
- GSC Poster Session, Ole Miss, Apr 2016- Influence of Hydrophilic Polymers on the Release Characteristics of Ethyl Cellulose Extrudates Produced by Hot-Melt Extrusion Technology
- AAPS Annual Meeting, Orlando, Oct 2015- Formulation and Processing of a Topical Ointment Prepared via Hot-Melt Extrusion Technology
- School of Pharmacy, Ole Miss, Oct 2014- Formulation and Processing of a Topical Ointment Prepared via Hot-Melt Extrusion Technology
- GRASP Conference, Atlanta, June 2014- Development of an ointment formulation by a novel technique of Hot-Melt Extrusion