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Development of Poloxamer Gel formulations via Hot-Melt Extrusion Technology

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Abstract

Poloxamer gels are conventionally prepared by the “hot” or the “cold” process. But these techniques have some disadvantages such as high energy consumption, requires expensive equipment and often have scale up issues. Therefore, the objective of this work was to develop poloxamer gels by hot-melt extrusion technology. The model drug selected was ketoprofen. The formulations developed were 30% and 40% poloxamer gels. Of these formulations, the 30% poloxamer gels were selected as ideal gels. DSC and XRD studies showed an amorphous nature of the drug after extrusion. It was observed from the permeation studies that with increasing poloxamer concentration, a decrease in drug permeation was obtained. Other studies conducted for the formulations included *in-vitro* release studies, texture analysis, rheological studies and pH measurements. In conclusion, the hot-melt extrusion technology could be successfully employed to develop poloxamer gels by overcoming the drawbacks associated with the conventional techniques.

Graphical abstract

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Declaration of interest

The authors report no conflicts of interest.

Keywords

poloxamer gels; hot-melt extrusion; *ex-vivo* permeation study; rheology study; *in-vitro* release study

1. Introduction

An essential component in topical gels are the gelling agents which when dissolved in a media form a three-dimensional network of particles that are responsible for the gel's viscosity and semisolid state. Some of the commonly used gelling agents are cellulose derivatives (methyl cellulose, hydroxyl propyl cellulose, etc.), carbomers, poloxamers, carboxy methyl cellulose, etc. Poloxamer gels have the potential to be in the liquid state at refrigerated temperatures of 4–5°C and convert into a gel at body temperature, thereby retarding the release of the drug from the gel. This unique property of the poloxamers is termed as “reverse thermal gelation” and has acquired great interest in liquid suppository systems, intramuscular drug delivery systems, ocular drug delivery systems, etc. Other properties of a poloxamer gel such as its capacity to take in a higher drug load, low toxicity, good solubilizing agent and its ability to stabilize proteins contribute to poloxamer gels being potential drug delivery systems (Gilbert et al., 1987; Dumortier et al., 2006).

Poloxamer gels are conventionally prepared by either the “hot process” or the “cold process”. The method of cold process is generally used for the active ingredients that are thermo labile. The main drawback associated with this method is its long processing time. As dissolving solid poloxamer in cold water, can be difficult, the processing times can vary from several hours to days thereby making the cold process method an ineffective method for preparing poloxamer gels. The hot method of preparation provides an intimate mixing between the poloxamer and the active ingredient that is poorly soluble in water, therefore solubilizing the poorly soluble active in the micelle. Both the methods require costly equipment (large refrigeration units, steam heating units, de-aeration equipment, etc.) as well as consume a great deal of energy to maintain the temperature and extend the duration of the mixing period (Chang et al., 2013; Schmolka et al., 1972). Another disadvantage associated with these methods is the scale up process. During the scale-up processes, the

equal distribution of all the components in the formulation as well as a proper balance in the physicochemical properties of the formulation is of utmost importance. On a small scale, the polymers can form a homogeneous solution with the media using the conventional methods of preparation. On a large scale, it would be difficult to uniformly disperse large amounts of the polymer in the media using these methods. Inconsistent addition of the polymer and insufficient mixing can therefore lead to poor hydration of the polymer (Garg et al., 2010). Hot-melt extrusion (HME) is defined as the process in which raw materials (polymers, drug and other excipients) are pumped into the feeder and subjected to mixing by the rotating screws at high temperatures which are then passed through a die to form products (films, granules, cylinders) of uniform size and shape (Mendonsa et al., 2017). The HME process has shown potential to develop products for application in the transdermal and topical drug delivery systems (McGinity and Repka, 2004; Crowley et al., 2013; Aitken-Nichol, 1996; Repka et al., 2004; Bhagurkar et al., 2016). Developing poloxamer gel formulations using the HME technology is a relatively short process and does not require any additional equipment for the removal of air bubbles or cooling units in comparison to the conventional methods of preparation, thereby making this process a cost-efficient process. As the final product obtained is a homogenous gel that does not have visible clumps of poloxamer in it, therefore the need to store the gels at lower temperatures after preparation is not required. The agitation provided by the mixing elements results in the de-aggregation of drug particles suspended in the molten polymer leading to a homogenous dispersion or a solid solution or both in the extruded product. This type of mixing on a molecular level could be useful in the scale up processes. Some of the other advantages of HME include a high product density, no significant downstream equipment, manufacturing dosage forms of API with poor compressibility index issues, solvent free technique, etc. (Tiwari et al., 2016) As the conventional methods of preparing poloxamer gels have several disadvantages, the objective of this novel study was to develop poloxamer gel formulations using the hot-melt extrusion technology. Poloxamer gels were also prepared using the conventional method (hot process method) (control gels) and the characteristic properties of both the gels were compared. Ketoprofen (KTP) is a non-steroidal anti-inflammatory drug which has been prescribed for the treatment of rheumatoid arthritis and other similar diseases. KTP when administered through the oral route results in upper abdominal pain and ulceration of the gastro-intestinal mucosa, thereby restricting its oral use. To avoid these adverse effects, KTP can be administered through the transdermal/topical route and was hence selected as a model drug for this study (Cho and Choi, 1998).

2. Materials and Methods

2.1. Materials

Ketoprofen (KTP) was purchased from Hawkins Pharmaceutical group (MN, USA). Poloxamer 407 (Kolliphor P407) was kindly gifted by BASF (Ludwigshafen, Germany). The other reagents used in this grade were of analytical grade.

2.2. Method of Preparation

2.2.1. Conventional Method—The composition of the control gels (i.e. the gels prepared by the conventional method) is shown in Table 1. Poloxamer and the drug were melted using

a hot plate set at 97°C with gentle stirring. Water was slowly added to the mixture with continuous stirring until a homogenous gel was obtained. The formulations were then stored at -4°C to achieve clear formulations (Chi and Jun, 1991).

2.2.2. Hot-Melt Extrusion Method—The composition of the extruded gels is shown in Table 1. A mixture of poloxamer and KTP were sieved through US# 35 mesh screen and blended using a V-shell blender (Maxiblend, Globe Pharma, New Brunswick, NJ). The mixture was fed through a volumetric feeder into a co-rotating twin screw extruder having an extrusion die of diameter 5.79 mm (Process 11, Thermo Fisher Scientific, Karlsruhe). Water was added into the extruder through an injection port with the aid of a peristaltic pump at zone 5. Figure 1 represents a schematic representation of the extrusion process. The temperatures from zones 2–4 were set at 97 °C, zone 5 at 90 °C, zones 6 and 7 at 80 °C and zone 8 and the die were set to 70 °C. Screw speed of 50 rpm was set. The pump speed was set to 0.83 rpm and the feeder speed was set to 3 rpm based upon the preliminary studies conducted. A modified screw design was used for extrusion that consisted of two mixing zones situated in zones 3 and 6 respectively as shown in Figure 2.

2.3. Characterization of Gel Formulations

2.3.1. Differential Scanning Calorimetry (DSC)—Pure drug, pure poloxamer, blank gel formulations (i.e. the gel formulations that did not contain any KTP) and drug loaded gel formulations were physically characterized using the Perkin Elmer Diamond DSC equipped with a Pyris software. Each of the samples were weighed and hermetically sealed into aluminum pans. The temperature range for the samples was from 30°C to 200°C at a heating rate of 10°C/min. The DSC studies were performed under an inert nitrogen atmosphere having a flow rate of 20 ml/min.

2.3.2. X-ray Diffraction (XRD)—XRD diffractograms were obtained for the pure drug, pure polymer, drug loaded and blank gel formulations. These studies were conducted on a Rigaku Miniflex600 (Rigaku Americas, The Woodlands, TX) equipped with a Cu-K α radiation source (and theta-2-theta diffractometer along with a Lynx-eye position sensitive detector) with a current of 15mA and a voltage of 40kV for the generator. A Si sample holder was used to spread the samples. The powder samples were scanned over a range of 5° to 33° 2 θ with a 0.05 step size at 1°/min. The gel samples were scanned over a range of 5° to 33° 2 θ with a step size of 0.02 at 2°/min.

2.4. Method of Analysis

KTP content was determined using a Waters HPLC UV (Waters Corp, Milford, MA) system equipped with a dual λ absorbance detector. A Waters C18 (4.6 $\times$ 150 mm; 5 μ m particles) column was used. The mobile phase comprised of 20 mM phosphate buffer solution (pH 4.5) and acetonitrile in the ratio of 60:40 (%v/v). A 1ml/min flowrate and injection volume at 10 μ L was set. The UV detector was set to 256nm for KTP detection (Ashour et al., 2016).

2.5. pH Measurement

The gel formulations were first converted into the liquid form by storing them at -4°C . pH of the solutions was then measured using the Mettler Toledo InLab® Micro pH probe (Mettler Toledo, Columbus, OH) (Chi and Jun, 1991).

2.6. Uniformity of drug content

Accurately weighed amount of gel formulations were taken from different regions of the container and dissolved in suitable amounts of acetonitrile and sonicated. The samples were then analyzed by HPLC to determine the drug content.

2.7. Texture Analysis

The texture analysis for the formulations were conducted on a texture analyzer (Model TA.XT2i, Texture Technologies Corp. /Stable Micro Systems) using a 5 kg load cell. An acrylic cylindrical probe of 1 in. diameter (TA-3) and a soft matter kit (TA-275) were used. The gel was applied onto the soft matter fixture with the cylindrical probe attached to the arm of the texture analyzer. The surface of the sample was leveled before starting the experiment. The probe was lowered at a speed of 0.50 mm/sec till it touched the surface of the sample. On touching the surface of the sample and identifying a trigger force of 2.0 g, the probe produced a deformation of up to 1mm of the sample moving at a speed of 0.50 mm/sec. The probe was then removed from the sample at a speed of 5.0 mm/sec. Before the next sample was applied onto the soft matter fixture, the base of the probe was cleaned thoroughly (Tai et al., 2014).

2.8. Rheological Characterization

The rheological analysis for the formulations were conducted on a TA instrument DHR-2 rheometer. The study was conducted at 32°C and was controlled using a Peltier system. A parallel plate geometry (25 mm) was used and adhesive backed sand papers (grit number # 600, Allied High Tech Products) were attached to both upper and lower plates to reduce the sample slippage at the sample-rheometer plate interface. 400 mg of the sample was applied onto the lower plate and the upper plate was set to a gap of 550 μm . The gap was finally set at 500 μm after the excess sample was removed. A solvent trap was attached to the rheometer to minimize the water loss from the formulations that could occur during the testing. The study was performed in four steps. Firstly, a time sweep was done for 5 mins to let the sample relax from the stress it acquired during loading (at strain (γ_0) of 0.1% and frequency (ω) of 1 Hz). After the time sweep, the strain sweep test was conducted ($\gamma_0=0.05\text{--}50\%$, $\omega=1\text{Hz}$). The time sweep test was conducted again before the steady shear test was performed in the forward and the backward mode. In the forward mode, the shear rate was gradually increased to the maximum shear rate (100 s^{-1}) and in the backward direction, the shear rate was then decreased to the lowest shear-rate (0.001 s^{-1}) (Bhagurkar et al., 2016).

2.9. In-vitro Release Study

Vertical franz diffusion cells with an active diffusion area of 0.64 cm^2 (Logan Instruments, Somerset, NJ) were used to conduct the *in-vitro* release study. A non-porous hydrophobic

silicone membrane of thickness 0.005" (Speciality Manufacturing, Inc., Saginaw, MI) was used. Gel formulations weighing 100 mg were applied onto the membrane and was sandwiched between the donor and the receptor compartments. The receptor compartment consisted of phosphate buffer saline solution of pH 7.4 that simulated systemic conditions and was degassed before the experiment. A temperature of 32°C and constant stirring was provided to the cells. The cells were equilibrated for an hour prior to the study. At regular time intervals till the 10th hour, 0.2 ml of the samples were withdrawn and replaced with the same volume of PBS. The samples were then analyzed using the HPLC (Ueda et al., 2009).

2.10. Ex-Vivo Permeation Study

The *ex-vivo* permeation studies were conducted on vertical franz diffusion cells having a diffusion area of 0.64 cm² (Logan Instruments, Somerset, NJ). Freshly slaughtered porcine epidermis procured from domestic pigs from a local abattoir, were utilized for this study. The epidermis was stored in 8°C till further use. On the day of the experiment it was thawed at room temperature. Gel formulations weighing 20mg were evenly spread onto the epidermis and clamped between the donor and the receptor compartments. 5 ml of PBS at pH 7.4 was used as a receptor media and degassed prior to the experiment. The cells were maintained at 32°C with constant stirring. The system was kept for equilibration for an hour before the experiment. At predetermined time intervals till the 10th hour, 0.2ml of the sample was withdrawn from the cells and replaced with fresh PBS of the same volume. The samples were then subjected to analysis by the HPLC (enyi it et al., 2011).

2.11. Extraction of KTP from the Epidermis

At the end of the *ex-vivo* permeation study, the epidermis was washed several times with methanol and water. The active diffusion area was then removed using a biopsy punch and weighed. The epidermis was homogenized by adding appropriate amounts of NaOH (2N) to the epidermis and storing it at 50°C. Suitable dilutions were made with acetonitrile followed by vortexing and centrifuging the solutions. The supernatant was then analyzed for the drug content in the epidermis using HPLC (Maurya and Murthy, 2014).

2.12. Microscopic Studies

A thin film of the gel formulations (40%) was uniformly spread over a 1 cm² area on a microscopic slide to detect the presence of KTP crystals. The formulations were scanned under a microscope at predetermined time intervals till the 2nd hour with a 40× objective lens. Images were taken using a Zeiss, Axio Cam ICC1, Lab.A1 camera.

2.13. Statistical Data Analysis

The levels of statistical significance between formulations were evaluated using an unpaired t-test. The formulations were significantly different if the p-value obtained was less than 0.5. A mean of three readings was considered.

3. Results and Discussion

3.1. Methods of Preparation

The formulations were first conventionally prepared using different concentrations of poloxamer. The composition of poloxamer gel formulations constituted of 30%, 68%, 2% and 40%, 57% and 3% poloxamer, water and drug respectively. The control formulations eventually formed clear gels after refrigerating the poloxamer solutions for several days. Poloxamer gel formulations were also developed through the hot-melt extrusion method and the final product obtained were transparent gels devoid of air bubbles. Extrusion parameters such as screw speed, screw configuration, zone of water addition as well as feeding rate of the physical blend were optimized to provide minimum shear and torque. The first mixing zone consisted of 60° elements and was situated at zone three to break down agglomerates of the physical blend if any. The second mixing zone consisted of 90° elements and was situated at zone six to ensure that water and the binary mixture were uniformly mixed. In this way, a distributive and a dispersive mixing could be provided to the formulations. The temperature of zones 2–4 were set to 97°C to ensure that the drug and the polymer were completely melted. The temperature of the zones was gradually decreased to result in the final formulations. The water content of the extruded and the control gel formulations were determined through Thermogravimetric Analysis studies (TGA). The results of the studies indicated that the extruded and the control gel formulations contained the same amount of water (data not shown).

3.2. Physicochemical Characterization of the Formulations and the Raw Materials

3.2.1 DSC Thermogram—DSC studies were conducted to determine the compatibility between the drug and the polymer involved. DSC thermograms of the formulations, pure drug and polymer are shown in Figure 3. Pure KTP showed a sharp melting peak at 97.21°C. Pure poloxamer also exhibited a melting peak at 58.21°C indicating a crystalline nature of the polymer. DSC studies were also conducted for the blank (i.e. gel formulation that did not contain any KTP, data not shown) and drug loaded gel formulations. The results for the blank gel formulation indicated a single endothermic peak in the temperature range of 100–110°C. This peak could be attributed to the loss of water in the formulations that takes place during the heating cycle of the DSC study. To confirm this hypothesis, DSC studies of the blank gel formulations were also conducted in hermetically sealed aluminum pinhole pans wherein a similar endothermic peak was observed. Two peaks were observed in the drug loaded formulations. The first peak obtained was in the temperature range of 50–70°C which could be attributed to the presence of poloxamer. The second peak obtained for the formulations was in the same temperature range as the peak obtained for the blank gel formulation. The absence of drug peak in the formulations indicated that the crystalline drug had either converted to an amorphous form or was present in the soluble form in the polymer matrix after preparation. Solubility studies of the drug in pure poloxamer were conducted to determine the nature of the drug after preparation. The drug load and the poloxamer content in the formulation was 2% and 30% respectively. From the solubility studies, it was determined that the solubility of KTP in poloxamer was much higher (0.375 mg/mg) than the drug load in the formulation and therefore all the KTP incorporated existed in a soluble form in the polymer matrix.

3.2.2. X-Ray Diffraction—X-Ray Diffraction studies were conducted for pure drug, polymer, blank gel formulation and drug loaded gel formulations. The results of the XRD studies are shown in Figure 4. KTP was in the crystalline form which was indicated by the presence of strong peaks observed at 2θ 19° and 23° . Strong crystalline peaks were also observed for pure poloxamer at 2θ 18° and 23° . The blank gel (data not shown) and the drug loaded gel formulations showed no peak corresponding to KTP indicating the absence of drug after the gel preparation. The results of the XRD studies performed therefore supported the results obtained in the DSC studies.

3.3. Texture Analysis Study

A texture analysis study investigates the textural characteristics of gel formulations (such as its hardness, consistency, work of adhesion, etc.) through which additional information about the properties of the gel such as its spreadability, viscosity, mucoadhesion, strength, etc. can be determined. The force vs. distance profile for the 30% poloxamer formulations is shown in Figure 5. Firmness or hardness refers to the amount of work required to remove the gel from the container and apply it to the desired site. With respect to the force vs. distance profile, it is defined as the maximum peak force obtained during the compression cycle (Gilbert et al., 1986). From Figure 5, the firmness obtained for the extruded formulation was 75.38 ± 11.62 g and for the control formulation was 83.95 ± 6.81 g. Firmness is directly proportional to the consistency of the sample which is indicated by the negative region of the graph. The consistency obtained for the extruded formulations is 35.6 ± 8.67 g.sec and for the control formulations is 45.02 ± 2.88 g.sec. The work of adhesion (WOA) refers to the spreadability of the gels and from the figure, it is indicated by the ratio of the area under the second curve (AUC_2) to the area under the first curve (AUC_1). WOA obtained for the extruded formulations was 96.4 ± 22.8 g.sec and for the control formulations was 66.1 ± 8.3 g.sec. The firmness, consistency and WOA results represent the mean ($n=3$). The p-value obtained from the t test for the formulations were as follows – 0.560 for the firmness, 0.148 for the consistency and 0.097 for the work of adhesion. Therefore, it could be concluded that as the p-values obtained were > 0.05 , the formulations were not statistically significant for the texture analysis study and thus had similar textural properties (Ricci et al., 2005).

3.4. Rheology Study

The rheology of semi-solid products relies on the product's microstructure that could be affected by process conditions. Therefore, it is important to conduct a rheology study to investigate the effects of processing conditions on the rheological properties such as viscoelastic behavior, yield stress and the effect of shear rate on the product's viscosity. Figures 6 and 7 A. (extruded and control gels respectively) depict the plot of storage modulus (G') and loss modulus (G'') against strain where G' represents the elasticity of the product and G'' represents the viscous behavior of the product. As can be seen from the figures, G' of the formulations continued to remain constant up to 1% strain (approximately), after which a decrease in G' was observed. The region in which the G' remains constant with increase in strain is termed as linear viscoelastic region in which the product can recover quickly upon any disturbance. From the figures, it can also be observed that G' is significantly higher than G'' . This indicates that the microstructure of the semi-solid product is organized and is controlled by the cohesive forces. Till the strain of 1%, the

product behaves like a solid. On further increasing the strain, both G' and G'' decrease wherein G'' exceeds G' and the product now behaves like a liquid (Krishnaiah et al., 2014). Yield stress is defined as the stress that is needed to initiate the flow in a product and corresponds to changes to the microstructure of the products. In the Figures 6 and 7 B., a plot of G' vs. stress is shown. The yield stress or otherwise known as onset point (σ_Y) can be determined from the figures as the point where the two tangents (from the linear and the non-linear portion of the curve) intersect. The yield stress for the extruded gel is 900 ± 80 Pa and that for the control gel was 1000 ± 70 Pa. The results obtained for the yield stress for the 30% extruded and the control gel indicate similar flow properties. From the Figures 6 and 7 C., it can be seen that at low shear values, the viscosity of the products is high, thereby providing good firmness to the products. As the shear values increase, the viscosity of the formulations decreases rapidly, thereby allowing the products to easily spread over a large surface area.

3.5. In-Vitro Release Study

A non-porous hydrophobic silicone membrane was selected for this study. Such membranes are inert and only permit the lipophilic drug to pass through, thereby separating the receptor media from the formulation. In doing so, the dissolution of the poloxamer into the receptor media can be prevented (Dumortier et al., 2006). The amount of drug released from the extruded gels was 40.73 ± 6 ug/cm² and from the control gels was 35.80 ± 5 ug/cm². Poloxamer gels comprise of micelles and aqueous channels and it is from these aqueous channels that the drug is released. Some of the factors affecting drug release from the poloxamer gels include the viscosity of the gels, the size of aqueous channels and the dispersal of the drug in the micellar and aqueous regions. As poloxamer 407 forms viscous isotropic liquid crystal gels that mainly comprise of micelles, therefore it was likely that the drug was released by a diffusion mechanism via the extra micellar water channels of the gel. The release of KTP from the poloxamer gel gave a best fit to the Higuchi equation as from the plot of Q vs. T , the release of the drug increased with increase in time ($r > 0.98$) (Figure 8). The Higuchi equation is given by

$$Q_t = K_h * t_{1/2}$$

where, Q_t is the amount of drug released in time ' t ' and K_h is the Higuchi diffusion rate constant (Gilbert et al., 1986; Ricci et al., 2005; Bentley et al., 1999; Nair and Panchagnula, 2003; Su and Miller, 1990; Patil et al. 2015). The rate constant calculated from the plot of Q vs. T for the extruded formulation was 11.98 ± 1.74 and that for the control formulation was 11.12 ± 1.07 . The p-value obtained from the t-test was 0.57 for the formulations. As the p value obtained was greater than 0.05, therefore for the release study, the two formulations were not considered to be statistically significant.

3.6. Ex-Vivo Permeation Study

Several alternatives to the human skin such as rodents, monkeys, pigs, etc. are used for *ex-vivo* permeation studies but porcine epidermis is preferred as it can be easily obtained and is the closest alternative to the human skin based on its morphological characteristics. The

results of the *ex-vivo* permeation studies for the 30% poloxamer gels are shown in Figure 9. For 30% poloxamer gels, the amount of drug permeated from the extruded gel was $4.082 \pm 1.1 \mu\text{g}/\text{cm}^2$ and from the control gel was $3.979 \pm 1.2 \mu\text{g}/\text{cm}^2$. The p-value obtained from the t-test for the formulations of 30% poloxamer gels was 0.90. As the p-value obtained was greater than 0.05 for the 30% gel formulations, therefore the two formulations were not statistically significant for the permeation study. Based on the results of the *in-vitro* release study and the *ex-vivo* permeation study, for the 30% poloxamer gels, no significant difference was obtained between the extruded and the conventional gels which was confirmed from the results of the statistical t-test conducted on the formulations.

3.6.1 Development and ex-vivo permeation studies of 40% poloxamer gel formulations

—As the extruded and the control 30% poloxamer gel formulations had similar characteristic properties, therefore another set of gel formulations were developed that consisted of a higher concentration of poloxamer content and characteristic studies were conducted on them. During the extrusion of the 40% poloxamer gels, minimum torque was maintained and the end product was a clear gel formulation devoid of air bubbles. Therefore, the melt extrusion technology could be successfully employed to prepare 40% poloxamer gels. *Ex-vivo* permeation studies were conducted for these gels. For 40% poloxamer gels, the amount of drug permeated from the extruded gel was $2.86 \pm 0.31 \mu\text{g}/\text{cm}^2$ and from the control gel was $1.54 \pm 0.27 \mu\text{g}/\text{cm}^2$. As the concentration of poloxamer in the gel increases, the amount of drug permeated from the formulation decreases as can be seen from Figure 10. The gel structure behaves as a barrier to drug diffusion and the resistance of the drug to diffuse out of the formulation increases as the poloxamer concentration increases. This could be attributed to the decrease in the number and dimensions of the water channels with an increase in the number of micelles that occurs when the poloxamer concentration increases (thereby resulting in an increase in the solubility of the drug) (Sin et al., 1999; Chen-Chow and Frank, 1981; Moore et al, 2000). The Fickian equation explains the passive permeation of a permeant across the stratum corneum and is defined as the amount of drug entering a membrane equal to the amount of drug leaving a membrane and is given by the following equation –

$$J_{ss} = K_p \cdot C_{veh}$$

where, J_{ss} is the steady-state flux ($\text{ng h}^{-1}.\text{cm}^{-2}$) across a membrane of thickness 'h' cm, C_{veh} is the drug concentration (mg cm^{-3}) in the vehicle, and K_p is the formulation dependent permeability coefficient of the drug (Naik et al., 2000). From the permeation figures (Figures 9 and 10), the flux was calculated as the slope of the linear part of the curve. The flux obtained for the 30% extruded and the control formulations were $0.46 \pm 0.10 \mu\text{g h}^{-1}.\text{cm}^{-2}$ and $0.41 \pm 0.11 \mu\text{g h}^{-1}.\text{cm}^{-2}$ respectively. For the 40% extruded and the control formulations, the flux values were $0.266 \pm 0.018 \mu\text{g h}^{-1}.\text{cm}^{-2}$ and $0.116 \pm 0.025 \mu\text{g h}^{-1}.\text{cm}^{-2}$. For the 30% extruded and the control formulations, the drug retained in the epidermis was $4.38 \pm 1.29 \mu\text{g}$ of drug/mg of skin and $3.42 \pm 1.1 \mu\text{g}$ of drug/mg of skin respectively. For the 40% extruded and the control formulations, the drug retained in the epidermis was $3.05 \pm 1.39 \mu\text{g}$ of drug/mg of skin and $2.27 \pm 0.56 \mu\text{g}$ of drug/mg of skin. The results for flux and the drug retained represent the mean of three values. From these results, we observe that the

drug retained in the epidermis decreased with increasing concentration of poloxamer, thereby relating well with the flux values. The p-value obtained from the t-test for the 40% poloxamer gels was 0.027. As the p-values obtained were less than 0.05 for the 40% gel formulations, therefore the extruded and control 40% gel formulations were considered to be statistically significant for the permeation studies.

3.7. Microscopic Studies

From the results, unlike in case of 30% gel formulations, a significant difference in the permeation of the drug was observed between the 40% poloxamer extruded and control gels. To investigate the cause for the significant difference in permeation, a microscopic study was carried out for the formulations. The differences in performance can be due to the differences in the post application changes to the product. To investigate the effect of the post application using an applicator on a slide to create a thin film. The products on the slides were observed under the microscope for changes. The images shown in the figures depict the gel formulations examined under the microscope for drug crystals at different time intervals (0, 1 and 2 hr). The authors speculate that the crystallization could be induced due to the loss of significant amounts of water from the gel leading to concentrated or supersaturated zones causing nucleation and crystallization. The other speculation could be that complete drying of water in some of the regions on the applied area would lead to complete precipitation of drug. The presence of large amount of drug crystals (image C.) as shown in Figure 11 indicate that KTP crystals started appearing from the 2nd hour for the extruded gel. On the contrary, drug crystals started to show from the 1st hour (image D.) for the control gel as shown in Figure 11. This difference in the presence of the drug crystals at different times could be attributed to the difference in the drying rate of the gels. The extruded gel had a slower drying rate in comparison to the control gel. Thus, KTP stayed in the solubilized form in the extruded formulation longer than in the control formulation. This difference in drying rate explained why more amount of drug could permeate in the extruded gel as compared to the control gel. However, at this point it is not clear why HME processed gels are relatively superior in retaining water as compared to gel prepared by the conventional method.

3.8. pH Measurements

The pH of a semisolid product affects the stability and solubility of the active ingredient in the formulation. The pH obtained for the extruded formulations was 3.88 ± 0.078 and that for the control formulations was 3.98 ± 0.26 . Several authors who have developed poloxamer gel formulations have also reported the pH of the poloxamer gels in this range (Chi and Jun, 1991; Shin et al., 1999; Suh and Jun, 1996).

3.9. Uniformity of Drug Content

As mentioned above, the mixing that is provided by the hot-melt extruder results in the drug being uniformly distributed in the polymer matrix which is one of the key factors to be taken into consideration while developing gel formulations. The drug content obtained for the extruded formulations was $100.9 \pm 0.7\%$ and for the control formulations was $97.22 \pm 5.23\%$. As a lower standard deviation was obtained for the extruded gel (0.7%) as compared to the standard deviation obtained for the control gel (5.23%), therefore the results

from the drug content analysis indicate that the optimized screw configuration provided sufficient mixing to the formulation resulting in a homogenous distribution of the drug in the polymer matrix.

4. Conclusions

In this study, topical semisolid gels were prepared by the HME technology as well as the conventional technique and characteristic properties were compared between the formulations. The results from the *in-vitro* release study showed the drug release from the polymer matrix was governed by a diffusion process. *Ex-vivo* permeation studies were conducted for 30% and 40% poloxamer gels. It was observed that as the concentration of poloxamer increased in the formulation, the viscosity of the gel increased and therefore the amount of drug permeated from the gel decreased. A texture analysis and a rheology study were also conducted for the 30% poloxamer gels. The textural and the rheological values obtained were similar for the extruded and the control gels. In conclusion, the HME technology could be successfully used to develop poloxamer gels. In the development of the gel formulations, the advantages of the HME technology such as short processing times, cost efficient process and uniform mixing can overcome the disadvantages associated with the conventional methods of preparation.

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Glossary

HME	Hot melt extrusion
KTP	Ketoprofen
DSC	Differential Scanning Calorimetry
XRD	X-ray Diffraction
WOA	Work of Adhesion
AUC	Area under the curve

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Figure 1.
Schematic representation of the hot-melt extrusion process of the gel formulations.

Figure 2.
Modified Screw Configuration.

Figure 3.
DSC thermograms of pure drug, polymer and gel formulations.

Figure 4.
XRD diffractograms of pure drug, polymer and gel formulations.

Figure 5.
Force vs. Distance profile for (A) Extruded Gel and (B) Control Gel

Figure 6.

Rheological characterization plots of 30% extruded gel (A) modulus vs. strain %, (B) storage modulus vs. stress, (C) viscosity vs. shear rate. Each value represents the mean (n=3).

Figure 7. Rheological characterization plots of 30% control gel (A) modulus vs. strain %, (B) storage modulus vs. stress, (C) viscosity vs. shear rate. Each value represents the mean ($n=3$).

Figure 8. Plot of Q vs. $\sqrt{T}$ for the calculation of Higuchi diffusion rate constant. Each value represents the mean $\pm$ S.D. (n=3).

Figure 9. Cumulative amount of KTP permeated vs. time from 30% poloxamer gels. Each value represents the mean $\pm$ S.D. (n=3).

Figure 10.
Cumulative amount of KTP permeated vs. time from 40% poloxamer gels. Each value represents the mean $\pm$ S.D. (n=3).

Figure 11. Microscopic images of 40% extruded gel at (A) 0 hr (B) 1 hr and (C) 2 hr and control gel at (D) 0 hr (E) 1 hr and (F) 2 hr.

Table 1

Composition of the extruded and control gel formulations (in percentile).

Poloxamer 407	Water	Drug
30	68	2
40	57	3