EFFECT OF LUTROL® F GRADES (POLOXAMER) ON DISSOLUTION OF HOT-MELT EXTRUDED KOLLIDON® VA64-FELODIPINE MATRICES

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Abstract: The objective of this study was to assess the potential of Lutrol® F grades as polymeric surfactants for dissolution enhancement of Kollidon® VA64-drug matrices produced by hot-melt extrusion (HME). The poorly soluble model drug felodipine (FEL) with a medium melting point was selected for this study. Two different grades of Lutrol® F (also called Kolliphor® P grades) were added into the HME systems to investigate their influence on the drug-incorporated matrices. Two grades of Lutrols i.e., Lutrol® F 68 (Kolliphor® P 188) and Lutrol® F 127 (Kolliphor® P 407) were studied as polymeric solubilizers. FEL was mixed with Kollidon® VA64, with or without Lutrol® F (alone or in combination) at predetermined amounts which resulted in 8 different formulations. Each blend was melt-extruded at the same extrusion conditions. Differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) analyses were performed to evaluate their physicochemical properties. DSC and PXRD studies suggested the formation of amorphous solid dispersion for all extruded formulations. Dissolution studies revealed that the extrudates with Lutrol® F grades exhibited faster and higher release compared to formulations without Lutrol® F grades. Formulations with high drug loading, which did not include Lutrol® F grades, demonstrated low drug release profiles when compared with the same formulations containing Lutrol® F grades. Fourier transform infrared (FTIR) studies suggested that a stronger hydrogen bond has occurred between the (–NH) of FEL and (C=O) of the pyrrolidone group in Kollidon® VA 64. Overall, these studies suggested the potential of Lutrols in enhancing the dissolution rate of poorly soluble model drug FEL.

Keywords: Dissolution, Lutrol® F, Kollidon® VA 64, Hot-melt extrusion, Felodipine

Hot-melt extrusion (HME) technology has gathered attention in the field of the pharmaceutical industry due to its several advantages. The considerable advantages of HME over other traditional processing techniques are being a solvent-free and continuous process requiring fewer processing steps (1). Excipients such as plasticizers, surfactants, and antioxidants can be used if needed (2). The major candidates for HME are the poorly water-soluble active pharmaceutical ingredients (APIs) which are brought up by combinatorial chemistry and high throughput screening (3).

Poorly water-soluble APIs are classified according to the biopharmaceutical classification system (BCS). Solid drugs with BCS II and IV class are considered to have poor water solubility, and consequently a low bioavailability (4). Currently, the poorly water-soluble APIs represent 40% of marketed drugs and 80-90% of drug candidates in the R&D pipeline (5). Melt extrusion has been successfully applied to enhance solubility and therapeutic efficacy/bioavailability of poorly soluble drugs by developing a solid dispersion system (SDSs) (1, 6-8). A drug/polymer system is called an SDS when the drug is molecularly dissolved at the polymer matrix to form a single-phase system (9). SDSs work by converting the drug from the crystalline form into the amorphous form, or by the formation of a molecular dispersion/solid solution (10). The higher free energy of the amorphous form helps in increasing the apparent solubility and dissolution rate (11). Incorporation of polymeric surfactants like Lutrol® F grades in the HME process was found to improve the solubility and dissolution rate of poorly water-soluble APIs (12, 13).
In this study, Kollidon® VA 64 was used to produce the SDS of felodipine (FEL) via HME technology. Kollidon® VA64 is vinyl pyrrolidone—vinyl aceta te copolymer (Figure 1B) which is a water-soluble polymer. Different grades of Lutrol® F (Figure 1C; also called Kolliphor® P grades) were added into the HME systems to investigate their influence on the drug-incorporated matrices. FEL (Figure 1A) is a long-acting 1,4-dihydropyridine-calcium channel blocker that is used in the treatment of hypertension (14). It is a lipophilic drug (log P = 4.8) with a poor aqueous solubility (19.17 µg/mL) at 25°C and a melting point of 145°C (15, 16). Lutrol® F68 and Lutrol® F127 are block-copolymers, neutral surfactants which work as solubilizing agents and plasticizers in SDSs (17, 18). Lutrol® F68 has a melting point of 52°C and lower molecular weight than Lutrol® F127 which melts at 56°C (19). The main properties of Lutrol® are presented in Table 1 (20).

The SDSs of FEL has been prepared using a variety of technologies such as spray drying, solvent evaporation, solvent shift, solvent wetting, physical mixing, kneading, HME, melt quench, and supercritical antisolvent methods using a variety of polymeric carriers in order to improve its solubility/dissolution and bioavailability (21-30). In addition, Kollidon®VA64-FEL amorphous SDSs have also been prepared using HME technology (31). Nevertheless, the influence of two different grades of Lutrol (Lutrol® F68 and Lutrol® F127) on the dissolution behavior of Kollidon®VA64-FEL matrices using HME technology has not been studied yet in literature. Hence, the objective of this study was to assess the potential of Lutrol® F68 and Lutrol® F127 as polymeric surfactants for dissolution enhancement of Kollidon®VA64-FEL matrices produced by HME technology.

**MATERIALS AND METHODS**

**Materials**

High purity FEL was procured from Ria International LLC (East Hanover, NJ, USA). Kollidon® VA64, Lutrol® F 68 and Lutrol® F 127 were donated as kind gift samples by BASF Chemical Co. (Ludwigshafen, Germany). All the organic solvents and water were of high-performance liquid chromatography (HPLC) grade.

**HME technology**

Model drug FEL was selected due to its poor solubility in water. Two different grades of Lutrols i.e., Lutrol® F 68 (Kolliphor® P 188) and Lutrol® F 127 (Kolliphor® P 407) were studied.

|                  | Molecular weight (g/mol) | % of Polyethylene–glycol polymers | HLB | Melting point (°C) |
|------------------|--------------------------|----------------------------------|-----|-------------------|
| Lutrol® F68      | 8436                     | 81.8 ± 1.9                       | 29  | 52                |
| Lutrol® F127     | 12330                    | 73.2 ± 1.7                       | 18-23 | 53-57             |
as polymeric solubilizers. FEL was mixed with Kollidon®VA64 with or without Lutrol®F (alone or in combination) at predetermined amounts which resulted in 8 different formulations. The composition of each formulation is summarized in Table 2. The physical mixtures were initially sieved with USP 60 mesh and mixed in a V-cone blender (MaxiBlend™, GlobePharma, North Brunswick, NJ, USA) at 50 rpm for 15 min. Each blend was evaluated for blend uniformity using HPLC and then melt extruded using a twin-screw extruder (Process 11 mm Prism EuroLab, ThermoScientific, Waltham, MA, USA).

### Differential scanning calorimetry

A Perkin Elmer Hyper Differential Scanning Calorimeter (DSC) (PerkinElmer Life and analytical sciences, 710 Bridgeport Ave., Connecticut, USA) was utilized to detect the physical state of FEL inside the milled extrudate. 3–4 mg of the samples was weighed in an aluminum pan and the heating rate was 10°C/min. The melting points (T_m) were calculated from the obtained thermogram by Pyris™ manager software. The crystallinity of different drugs inside different matrices was also evaluated similarly.

### Powder X-ray diffraction (PXRD)

PXRD studies were performed on a powder X-ray diffraction apparatus (Bruker AXS, Madison, WI) using CuKα radiation at 40 mA and 40 kV. The samples of interest were analyzed in the diffraction angles range of 5–40° (2θ) at a scan rate of 2°/min and step size of 0.02°.

### HPLC method for FEL analysis

A Waters 600 binary pump, Waters 2489 UV/ detector, and Waters 717 plus autosampler (Waters Technologies Corporation, 34 Maple St, Milford MA0157) were the components of the HPLC. The stationary phase of the column was a Waters Symmetry shield C18 (250X4.6mm, 5 μm particle size) reverse phase. The mobile phase was 85: 15 (% v/v) methanol-water. The mobile phase flow rate was maintained at 1.0 mL/min. FEL was detected at 238 nm. The powder of physical mixtures and milled extrudate were analyzed by dissolving weighed samples in 20 mL of respective mobile phases and filtering through a 0.45 μm membrane to extract the drug prior to HPLC injection. All studies were performed as replicates of three and injected at 20 μL volume.

### In vitro dissolution studies

Milled extrudates containing FEL equivalent to 5 mg were filled into hard gelatin capsule shells (Capsugel, Morristown, NJ, USA) and subjected to dissolution studies using a Hanson SR8-Plus dissolution test system. The dissolution medium of FEL was 900 mL water which was maintained at 37 ± 0.5°C and operated at 100 rpm paddle speed. The solubility of FEL in water at 25°C has been reported as 19.17 µg/mL (16). If the highest amount of FEL i.e., 5 mg will be released into the dissolution media (900 mL of water), the maximum concentration of FEL in dissolution media will be 5.55 µg/mL. The solubility of FEL in water (19.17 µg/mL) was 3.45 times higher than its maximum concentration in dissolution media and hence sink conditions were maintained throughout the dissolution studies using water as a dissolution media. Hence, water was used as a dissolution media in this study. 1.5 mL samples were collected precisely at pre-determined intervals and replaced with equal amounts of fresh dissolution medium. The replacement was taken into consideration for the calculation of dissolution profiles. The withdrawn samples were immediately filtered through 13 mm PTFE membrane filters (Whatman, Piscataway, NJ, USA) with a pore size of 0.2 µm and
analyzed for FEL content using the HPLC method described above. A model-independent similarity factor \( f_2 \) values were calculated to compare the dissolution profiles using Equation (1) (32):

\[
f_2 = 50 \times \log \left( \left[ 1 + \frac{1}{n} \sum_{k=1}^{n} ((R_t - T_t)^2)^{-0.5} \times 100 \right] \right)
\]

where, \( R_t \) and \( T_t \) are the percentages of FEL dissolved at time \( t \) for the reference and the test formulation, respectively. All-time points were considered for the calculation of the \( f_2 \) value.

**FTIR analysis**

Fourier transform infrared (FTIR) analysis was conducted in the spectral range of 4000-650 cm\(^{-1}\) using Cary 620 FTIR Microscopes (Agilent Technologies, Santa Clara, CA, USA). The bench was equipped with a MIRacle ATR (Pike Technologies, Fitchburg, WI, USA), that was fitted with a single-bounce, diamond-coated ZnSe internal reflection element. FTIR samples were studied before and after physical blending and melt extrusion to study intermolecular interactions before and after applying high shear forces and elevated temperatures.

**RESULTS AND DISCUSSION**

**Drug content**

The results of drug content analysis are presented in Figure 2. The percentage of drug contents of all formulations was found in the range of 95-105%, suggested good loading of FEL in all formulations.

**DSC analysis**

The DSC thermograms of FEL along with SDs are reported in Figure 3. The pure FEL had a distinct melting peak at 145°C, which suggested the melting point of FEL. The endothermic peaks of FEL were found to disappear in all of the melt extrudates suggesting the formation of amorphous SD of FEL.

**PXRD analysis**

The PXRD spectra of pure FEL and different SDs are reported in Figure 4. PXRD spectra exhibited sharp crystalline peaks of pure FEL which represents the crystal form for the pure FEL. However, the milled extrudates
showed a halo effect with no intense crystalline peaks (Figure 4). The results confirmed the DSC finding that FEL transferred to an amorphous state after the extrusion process.

**Effect of Lutrol® F grades**

Lutrol® F68 and Lutrol® F127 (Poloxamers) exist individually as monomolecular micelles. They form multimolecular aggregates when their concentration in the system increases. Lutrols are block-copolymers consisting of polypropylene oxide (PPO) and polyethylene oxide (PEO) units. PPO usually forms central hydrophobic cores, wherein methyl groups interact via Van der Waals forces with the substance undergoing solubilization. PEO block causes water solubility due to the hydrogen bonding interactions of ether oxygen with water molecules. As a result of these interactions, Lutrols are readily soluble in polar and nonpolar solvents (19, 33). Lutrol® F68 is composed of more hydrophilic PEO than Lutrol® F127 (Table 1). This leads to a higher HLB value and as a result, it has a great tendency to solubilize in water. On the other hand, Lutrol® F127 is less water-soluble and more swellable in water than Lutrol® F68. The swelling of hydrophilic polymers is well known to allow more drug release from dense polymer matrices by creating a porous matrix (34, 35).

**In vitro dissolution studies**

The DSC and PXRD studies confirmed the amorphous state of the FEL in all formulations. The amorphous state of the FEL offers a lower thermodynamic barrier to dissolution media where the drug is molecularly dispersed into the polymer. The amorphous drugs are structurally disordered with no lattice energy which needs to be overcome. This results in an enhanced dissolution rate (36, 37). The significant differences in the dissolution profiles between the matrices are due to the difference in the solubility and dissolution nature of polymers, as well as surfactants in the dissolution media. Dissolution of the different drugs in Kollidon® VA 64 alone is governed by the polymer itself, whereas in the case of Kollidon® VA 64-surfactant systems, the dissolution rate is governed by solubilization of the polymer to create a hydrotrropic environment for the poorly water-soluble drugs (12). Dissolution studies revealed that the extrudates with Lutrol® F grades exhibited faster and higher releases than without Lutrol® F grades, leaving the drug as a fine particles in a dissolved state. The significant improvement of dissolution rate is attributed to drug-polymer molecular intermixing at a micro-level. The drug loading has a clear effect on the release profile, and enhanced dissolution was generated in all FEL formulations. The higher drug-loaded formulations with Lutrol® F grades had lower drug release profiles compared to lower drug-loaded formulations.

For FEL formulations, the total percent of 5 mg of pure FEL released in 120 min did not exceed 1.6% in water media, while after extrusion, all extruded formulations released a larger percentage of the FEL into the media within 120 min. A 10% FEL-loaded formulation with Lutrol® F 68 showed the maximum release, compared to all other formulations (Figure 5a). This can be attributed to the fact that Lutrol® F 68 has a higher HLB value and as a result, it has a greater tendency to solubilize the drug in water. The formulation with combinations of Lutrol® F grades 68 and 127 showed more drug release in the medium than the formulation with only Lutrol F 127. This clearly shows that the amount of
Lutrol® F 68 is the leading factor in solubilizing the drug. Due to the maximum release of FEL from 10% FEL-loaded formulations, these formulations can possibly be administered to the patients after filling them into hard gelatin capsule shells. Formulations without Lutrol® had the lowest release amount. The polymer alone was not able to increase the dissolution of the 10% drug-loaded formations in the absence of surfactants. The same release behavior of 10% FEL-loaded formulations was obtained with 30% FEL-loaded formulations (Figure 5b), but the increased drug loading has the clear effect of the decreasing amount of drug released in the media. The possible reason for the decreased dissolution in the case of 30% FEL-loaded formulations could be recrystallization or precipitation of FEL in dissolution media compared with 10% FEL-loaded formulation. Qualitative evaluation of DSC results suggested that all formulations (10% and 30% FEL) showed the formation of solid dispersions as the crystalline peak of FEL was disappeared in all formulations (Figure 3). However, the degree of amorphization was not possible to determine using DSC data. In addition, the glass transition was not detected in any formulation studied.

**Dissolution profiles comparison using f2 values**

Release kinetics were compared using f2 values to assess the similarity of release profiles between Lutrol® F included formulations and Lutrol® F non-included formulations. If the f2 value is between 50 and 100, that suggests that the two release profiles are similar (32). For 10% FEL drug-loaded formulation, f2 values for formulations containing Lutrol® F 68, Lutrol® F 127, and the combination were found as 12, 24, and 18, respectively using the formulation containing 10% drug with no Lutrol® F as a reference product. For 30% FEL drug-loaded formulations, f2 values for formulations containing Lutrol® F 68, Lutrol® F 127, and the combination were found as 1, 11, and 4, respectively, using a formulation containing 30% drug with no Lutrol® F as a reference product. From the above results for 10% and 30% drug-loaded FEL formulations, it is clearly seen that dissolution profiles are not similar and incorporation of Lutrol® F grades helped to dramatically enhance the saturation solubility of FEL.

**FTIR analysis**

FTIR spectroscopy is one of the most widely used techniques to characterize the intermolecular interactions in SDSs (32). FTIR spectra of pure FEL and extrudates are presented in Figure 6. Extruded formulations containing 30% w/w FEL were studied for clarity and showed stronger absorption arising from a higher concentration of FEL. The Lutrol® F 68 showed characteristic peaks at 2886 and 1102 cm⁻¹ arising from stretching of C-H, and C-O groups (38). Kollidon® VA 64 spectra exhibited two stretching peaks of (-COO) at 1734 cm⁻¹ which belongs to vinyl acetate monomer (39) and at 1666 cm⁻¹ which belongs to the vinyl pyrrolidone monomer (10).

FEL was reported to be able to form hydrogen bonding with several types of polymers containing a hydrogen acceptor group while FEL itself functions as a donor (26-29). FT-IR spectra illustrated the characteristic peaks for FEL (Figure 6). N-H stretching band at 3366 cm⁻¹ had disappeared from the extrudate and was clearly seen in the physical mixture. This indicates that a stronger hydrogen bond has occurred between the (–NH) of FEL and the (C=O) of the pyrrolidone group in Kollidon® VA 64. There was
a considerable shift in (C=O) band of Kollidon® in 30% drug-loaded extrudates due to the formation of solid dispersions.

CONCLUSION

HME technology was able to successfully produce amorphous SD formulations for FEL with Kollidon®VA64. DSC and PXRD data verified the formation of amorphous SDSs of FEL which were extruded at the same extrusion conditions. Dissolution studies revealed that the extrudates with Lutrol® F grades exhibited faster and higher releases than without Lutrol® F grades. Polymer melt extrudates of Kollidon®VA64 incorporated with Lutrol® F grades demonstrated a promising role in enhancing the release of FEL. Additionally, the enhancement of dissolution/release was correlated with the grade of Lutrol® F. Overall, Lutrols have a great influence on the dissolution enhancement of poorly water-soluble drugs such as FEL.

Conflict of interest

Authors report no conflict of interest associated with this manuscript.

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