Application of Hydroxypropyl Cellulose to Solubility Enhancement of Poorly Soluble Drugs

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ABSTRACT SUMMARY
Low viscosity grade of hydroxypropyl cellulose (HPC) is a versatile pharmaceutical excipient which can be used for solubility enhancement of poorly soluble drugs. In this study, HPC-SL and HPC-SSL were found to improve the dissolution rate of BCS class II drugs by using various pharmaceutical techniques.

INTRODUCTION
The percentage of new chemical entities with poorly soluble properties is increasing, and researchers in the pharmaceutical industry and academia are trying various approaches in order to improve the solubility of poorly soluble drugs. The solid dispersion (SD) of such drugs into polymeric carriers using hot melt and solvent methods has gained much attention in the pharmaceutical industry. Hot melt extrusion (HME) is an attractive technology for manufacturing SDs that involves heating, softening and mixing of drug, thermoplastic polymers, and other components followed by extrusion of the molten mass through a die in the shape of cylinders or films.

Hydroxypropyl cellulose is a semi-crystalline polymer with amorphous domains of very low Tg along with the crystalline domains. Thus, HPC depicts higher molecular mobility and plasticity due to a high degree of amorphous content with a low Tg. It may cause melting point (Tm) depression of high melting drugs. The amorphous conversion of poorly soluble drugs as well as size reduction of their crystalline form along with intimate mixing and dispersion in hydrophilic polymers can also be achieved using solvent evaporation or particle size reduction techniques in order to improve their solubility.

In this study, the utility of HPC-SL and HPC-SSL polymers was assessed as HME excipients for solubility enhancement. Two BCS Class II drugs with high Tm and different ionic properties have been selected. Carbamazepine (CBZ) is a neutral drug and phenytoin (PHT) is a weak acid. Processibility and dissolution enhancement efficiency of SDs manufactured by hot melt mixing (HMM) of these drugs with non-ionic HPC polymers HPC-SL and HPC-SSL was evaluated. Also, other pharmaceutical processes such as solvent evaporation and ball milling were investigated for solubility enhancement of very high melting drug PHT using HPC-SSL.

EXPERIMENTAL METHODS

Materials
CBZ and PHT were purchased from Sigma Aldrich. HPC-SL and HPC-SSL were donated by Nippon Soda Co., Ltd. All other chemicals and reagents were purchased from Fisher Scientific and were of analytical grade. Melting point of CBZ and PHT is 205 °C and 296 °C respectively.

Preparation of Physical Mixture (PM)
PM were prepared by mixing each drug with HPC-SL at a 25:75 drug:polymer ratio (w/w) for 5 min, followed by mixing in a Tubular blender for 15 min. The blended PM were compacted (Carver press), milled (twin-blade rotary mill) and sieved (US mesh nos. 40 and 60 (420-250 µm)).

Preparation of Hot Melt Mixing (HMM)
PMs were mixed at 150 rpm for 5 min using a Brabender hot melt mixer. PM containing CBZ and PHT were heated up to 150°C and 180°C respectively, milled and sieved (US mesh nos. 40 and 60), obtaining HMM formulations.

Preparation of Ball Milling (BM)
PMs were loaded into the bowl of a planetary mill and BM was performed for 30 min at 400 rpm. The ball milled product was compacted (Carver press) at 4000-psi for 30 sec, milled and sieved (US mesh nos. 40 and 60).

Preparation of Solvent Evaporation (SE)
PMs were dissolved in methanol and evaporated in vacuo afterwards for 30 min. The resulting SD was dried in vacuum oven for 12 hours at 40°C, milled using a twin-blade rotary mill and sieved (US mesh nos. 40 and 60).
Evaluation Method

Amorphous transformation was investigated using differential scanning calorimetry (DSC) and polarized light microscopy (PLM). Milled SDs were filled into capsules for dissolution studies, which were carried at 37 ± 0.5°C and 50 rpm using 900 ml 50 mM phosphate buffer (pH 6.8) as the dissolution medium.

RESULTS AND DISCUSSION

1. DSC and PLM studies

As a result of DSC study, melting point depression of CBZ was observed in its PMs formulated with HPC-SL and HPC-SSL. On the other hand, the melting endotherm of CBZ was not detected in HMMs. This is indicating crystalline drug was converted into a state of amorphous by HMM.

The birefringence of crystalline drug observed in the PLM images of PMs was significantly reduced in the HMMs for CBZ melted with HPC polymers.

2. Dissolution Study

Dissolution of CBZ was significantly improved by HMM and complete recovery could be obtained within 5 hours. Compared to PM, the dissolution rate and extent of CBZ was found to be significantly higher in the case of HMM. Both HPC-SL and HPC-SSL showed significant enhancement of dissolution of CBZ. This could be owing to amorphous conversion of drug by HMM process. (Fig.1)

On the other hand, the dissolution rate and extent of PHT was slightly enhanced by, perhaps due to the formation of crystalline solid dispersions of the drug in HPC by HMM process. Since the melting point of PHT is very high (290-300°C), it was estimated that the drug could not be mixed and dispersed thoroughly during HMM process at the operating temperature of 180 °C. (Fig.2)

Fig.3: Dissolution profiles of PM, HMM, BM and SE of PHT:HPC-SSL compared to pure drug.

The enhancement in dissolution rate of PHT was in the order of SE, BM, HMM, and then PM compared to the pure drug. The better performance of SE and BM products could be owing to better mixing and dispersing compared to HMM, as well as to the formation of much smaller drug particles during mechanical milling by BM process. (Fig.3)

CONCLUSION

HPC-SL and HPC–SSL could be used to convert carbamazepine, which has relatively high melting point, into a state of amorphous using HMM process. Also, dissolution could be improved significantly.

Although dissolution rate of phenytoin, which has very high melting point, could not be improved by HMM, it could be significantly improved by manufacturing its crystalline dispersions in HPC-SSL using other techniques such as BM and SE.

REFERENCES