ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Shellac Wax-Lutrol F127 as Matrix Base for Hot Melt Extrusion

Thawatchai Phaechamud[1], Chanchai Thongpin[2] and Chai-ek Choncheewa[1]

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand 73000
[2]Department of Material Science and Engineering, Faculty of Engineering and Industrial Technology, Silpakorn University, Nakhon Pathom, Thailand 73000

ABSTRACT

Minitablet prepared from hot melt extrusion (HME) has many benefits such as increasing of bioavailability and reducing of dose dumping. This study aimed to prepare the minitablet using 3:7, 4:6, 6:4 and 7:3 shellac wax (SW):Lutrol F127 (Lut) as the matrix base. The 10, 20, 30 and 40% ibuprofen were incorporated into 7:3 SW:Lut to prepare the minitablet by HME. Each of them was then characterized their morphology, physico-chemical properties, drug release and release kinetic. Morphological characteristic revealed the larger drug crystals inside the lower drug-loaded matrix whereas the smaller drug crystals were found in higher drug-loaded matrix. Hot stage microscopy and FT-IR analysis signified the decreased melting temperature when drug was incorporated into the matrix base indicating the H-bonding formation between ibuprofen and Lut corresponding with the eutectic formation of these compounds. Almost drug release from 7:3 SW:Lut mini tablets trended to be first order release kinetic. From this study there was the feasibility of using the SW:Lut as matrix component for fabricating the minitablet prepared by HME to control the drug release.

Keywords: Ibuprofen, minitablet, lutrol F127, shellac wax, hot melt extrusion

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Hot melt extrusion (HME) is a process widely used in plastic manufacturing and, nowadays, interestingly applied in pharmaceutical process. HME has many advantages such as solvent free technique, less step of production process, no need many diluents or tableting compounds, homogeneous spreading and increasing for drug bioavailability [1,2]. Ibuprofen [Ibu] is non-steroidal anti-inflammatory drug (NSAID) indicating to be used as antipyretic, painkiller and anti-inflammatory. This drug is low aqueous solubility which solubilize less than 1 mg/ml at 25°C and its melting point is about 75-77°C whereas it can be degraded at about 252°C [3]. Shellac wax (SW) is a hydrophobic natural product obtained from the Lacciferalacca [4]. Poloxamer 407 or Lutrol F127 (Lut) composes of hydrophilic part, polyethylene, and hydrophobic part, polypropylene. It has popularly used in pharmaceuticals as surface active agent, emulsifying agent and solubilizing agent [5,6]. This study was to prepare the minitablet containing Ibu using the mixture of SW and Lut as matrix component with HME. Morphological characteristic, physico-chemical properties, drug release study and drug release kinetic were investigated.

MATERIALS AND METHODS

Materials

Ibuprofen [Ibu] and sodium hydroxide were purchased from PC Drug Co., Ltd., Bangkok, Thailand. Lutrol F127 [Lut] was obtained fromBASF, Ludwigshafen, Germany. Shellac wax [SW] was purchased from Ake shellac Co., Ltd., Lumpang, Thailand. Potassium dihydrogen phosphate was purchased from Ajax Finechem, New South Wales, Australia.

Methods

Matrix base selection and preparation of mini tablets

SW and Lut at various ratios (3:7, 4:6, 6:4 and 7:3 SW:Lut) were blended and mixed together by mortar and pestle to obtain the homogeneous powder mix. Each power mix base was extruded by HME. Morphology study was performed to select one of the homogeneous bases to be used as mini tablet base. The selected base was blended with drug to obtain 10, 20, 30 and 40% w/w Ibu powder mix. Each of them was extruded pass through HME. The extrudates were then cut into small pieces using the sharp knife which were approximately 0.5 mm lengthof each. The 400 mg Ibu mini tablets were filled into hard gelatin capsuleNo.1.

Physicochemical evaluation of the mini tablets

The prepared 10, 20, 30 and 40% Ibu matrix bases were characterized their hardness, thickness and diameter by hardness and thickness tester (ERWEKA® GmbH D-63150, Germany) and dinolite microscope (Shozen technology AM-413ZT, Thailand) was employed to observe the

ISSN: 0975-8585

extrudate surface. The topography was observed by scanning electron microscope (SEM)(Maxim 200 Camscan, Cambridge, England). Hot stage microscope (HSM) (Mettler Toledo FP900 Thermosystem, Mettler Toledo AG, Switzerland) and FT-IR spectrophotometer (Nicolet 4700, Thermo electron corporation, Madison, USA) were used to observe the physico-chemical properties of minitablet containing 10, 20, 30 and 40% Ibu and their physical mixtures.

The mini tablets comprising 10, 20, 30 and 40% w/w drug in the selected base containing 400 mg Ibu, and 400 mg Ibu powder were tested for their drug dissolution. The dissolution was tested under 8 hours in 900 ml phosphate buffer pH 7.2 at 25 °C (n=6) using dissolution apparatus I (Minhua Pharmaceutical Machinery Co., Ltd. China) at 100 rpm. The 5 ml of dissolution medium were taken as sample then 5 ml of phosphate buffer pH 7.2 was added to the dissolution pool to retain the sink condition. The samples were taken at specific time interval and determined the drug concentration by UV-spectrophotometry (Agilent Technology 8453E,USA) at 264 nm.

Drug release profiles were fitted with mathematic drug release models including zero order, first order and Higuchi's. Least squares fitting of the experimental dissolution data (cumulative drug release>10% and up to 80%) to the mentioned mathematical equations was performed using a nonlinear computer programme, Scientist for Windows, version 2.1 (MicroMath Scientific Software, Salt Lake City, UT, USA). The coefficient of determination (r^2) was used to indicate the degree of curve fitting. Goodness-of-fit was also evaluated using the Model Selection Criterion (MSC) [7], given below.

$$MSC = \ln\left\{\frac{\sum_{i=1}^{n} w_i \left(Y_{obs_i} - \bar{Y}_{obs}\right)^2}{\sum_{i=1}^{n} w_i \left(Y_{obs_i} - Y_{cal_i}\right)^2}\right\} - \frac{2p}{n}$$

Where Y_{obsi} and Y_{cali} are observed and calculated values of the i-th point, respectively, and w_i is the weight that applies to the i-th point, n is the number of points and p is the number of parameters.

RESULTS AND DISCUSSION

Matrix base selection and preparation of mini tablets:

According to morphology of the matrix extrudates (Fig. 1), the 7:3 SW:Lut was chosen as selected base because there was the smallest gap in the base with homogeneous texture and hence it might sustain the drug release more effectively than the other ratios. The gap was enlarged when Lut was increased since the surface active property of Lut which could produce many bubbles during the production process. The 7:3 was then selected and mixed with 10, 20, 30 and 40% w/w Ibu and extruded using HME. The obtained extrudates were cut into a small

ISSN: 0975-8585

pieces and filled in the capsule No.1 (Fig. 2). SEMs of top and side views of 7:3 SW:Lut mini tablets are shown in Fig. 3.

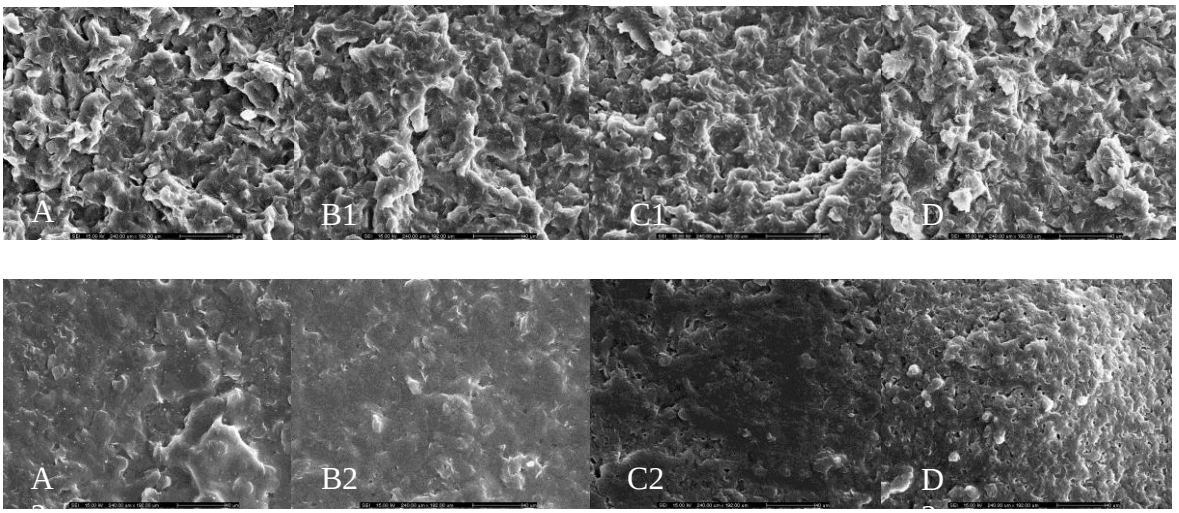

Fig. 1 Morphology of SW:Lut at various ratios 3:7 (A), 4:6 (B), 6:4(C), 7:3 (D) at magnification of 500X. The No. 1 was the surface of the bases and No. 2 was the cross-section of the bases.

A B C

Fig. 2 The obtained extrudates (A) with close up surface (B) and filled in the capsule No. 1(C)

A B

Fig. 3 SEM image for top (A) and side (B) views of 7:3 SW:Lut base at magnification of 10.

Physical properties and morphology of the mini tablets

ISSN: 0975-8585

Hardness was not significantly depended on the ratio of SW: Lut (data not shown). Addition of drug trended to lower the hardness of extrudate. Thickness of each extrudates prepared from different base ratios was not much different, but addition of drug could cause a little increasing of the thickness about 1 mm at 10% drug loaded. Increasing of drug could lower the thickness. Diameter was not different in each base ratio which was less than 0.5 mm. Addition of drug could increase the base diameteras same as that of the thickness (data not shown).

Morphology of drug loaded base was shown in Fig. 4. The Ibu crystals were observed in all prepared extrudates. Increasing of drug could cause apparently lowering of crystal size due to high concentration of drug which could produce much more crystal nuclei and hence lowered of drug crystal size. Typically, the crystallization consists of two different processes, nucleation and crystal growth, usually occurring simultaneously in a supersaturated solution. When the supersaturation in a target solution is high so is its crystallization rate. When lowering the supersaturation, it will eventually reach a concentration where nucleation ceases whereas the crystal growth continues [8]. Therefore the drug crystals dispersed in the prepared extrudates was apparently smaller in the case of lower drug loading as presented in Fig. 4.

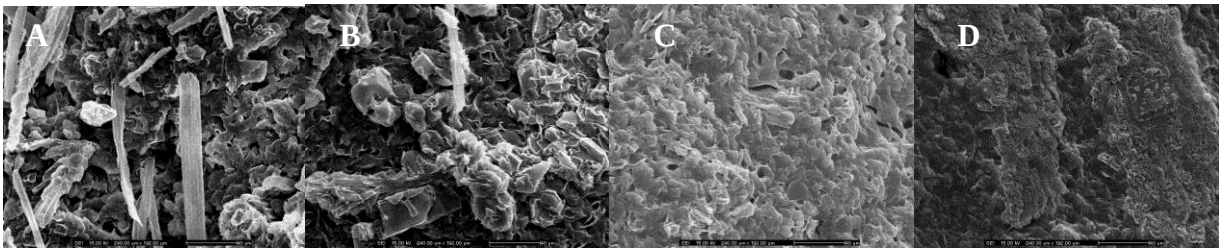

Fig. 4 SEM image of 10% (A), 20% (B), 30% (C) and 40% w/w (D) Ibu-loaded 7:3 Sw:Lut extrudates at magnification of 500.

Physico-chemical properties study of the mini tablets

HSM could demonstrate the melting temperature of pure compounds which were 76.0, 86.3 and 55.7 °C for Ibu, SW and Lut, respectively. The physical mixture (PM) of SW and Lut did not alter the melting temperature of each other (data not shown). For PM and HME of drug in the 7:3 SW:Lut base, the melting of the mixed component was apparently lower than that of each pure compounds (Table.1). FT-IR spectra indicated the shift of carbonyl stretching at wavenumber about 1700 cm^{-1} (data not shown) which signified that Ibu could form H-bonding with Lut and the formation of eutectic mixture was evident which this behavior was beneficial for lowering the HME processing temperature. The carbonyl stretching vibration of the ibuprofen dimer shifted to higher wavenumber in the FT-IR spectra indicating disruption of the ibuprofen dimer concomitant with hydrogen bond formation between Ibu and Lut as claimed previously [9,10]. HMS analysis of Ibu and Lut systems suggested that a eutectic system was formed depending on degree of drug loading. For higher drug loading, there might be other forms of solid dispersions co-exist with the solid solutions, including eutectic systems and

microcrystalline drug in the used carriers. The tendency of lowering the onset of melting point (Table 1) was corresponded with the morphological change since the more homogeneous was evident for the higher drug loaded extrudates (Fig. 4).

Drug release is shown in Fig. 5. Ibu powder which is hydrophobic drug rapidly dissolved within an hour because phosphate buffer pH 7.4 had pH higher than the pKa of this drug therefore the Ibu powder completely dissolved. Incorporation of drug into Lut and SW could sustain drug release. All formula could sustain the drug release when compared with Ibu powder. The 30% Ibu minitablet showed the slowest release. The low content of the base also lowered the Lut content which is the surface active agent. The fastest release was evident for 10% Ibu loaded-minitablet. Minitablet comprising 10% Ibu contained the highest content of Lut therefore it could rapidly dissolve which was faster than the other mini tablets. In the other hand the drug release from 40% Ibu loaded mini tablet was not slowest since almost of the drug could not be completely bounded with Lut in the 7:3 base thereafter the unbound drug dissolved immediately and hence the drug release was faster than 30% Ibu loaded-minitablet. The hydrophilic and lipophilic balance of SW-Lut matrix can be adjusted by changing its ratio which this strategy should modify the drug release behavior. From coefficient of determination (r^2) and model selection criteria (MSC) of curve fitting, the drug release of all prepared mini tablets obeyed the first order release kinetic as presented in Table 2. The applications of shellac wax as electrets or fruit coating material have been reported previously [11,12]. The thermal analysis of shellac wax signified that DSC was qualitatively and quantitatively available for analysis of insect waxes such as shellac wax and these insect waxes were good in thermal stability [13]. There was less investigations for characterization and application of shellac wax. This study showed the opportunity or possibility for applying this component system, especially, shellac wax as the materials used in other pharmaceutical dosage forms development.

Table 1: Onset and end point of melting temperature obtained from HMS (n=3).

Sample	Melting temperature (Cº)	
	Onset	End point
Ibu	76.00±0.00	79.00±0.00
SW	80.33±1.15	85.00±0.00
Lut	55.67±0.58	57.00±0.00
10% Ibu PM	44.67±0.58	67.33±4.16
20% Ibu PM	43.33±0.58	80.00±3.46
30% Ibu PM	44.33±0.58	76.33±0.58
40% Ibu PM	43.00±3.00	80.67±3.06
10% Ibu minitablet	47.33±3.79	77.33±2.08
20% Ibu minitablet	42.33±2.52	75.33±2.08
30% Ibu minitablet	43.00±2.00	76.67±3.06
40% Ibu minitablet	41.00±1.73	72.67±1.53

ISSN: 0975-8585

*PM=physical mixture

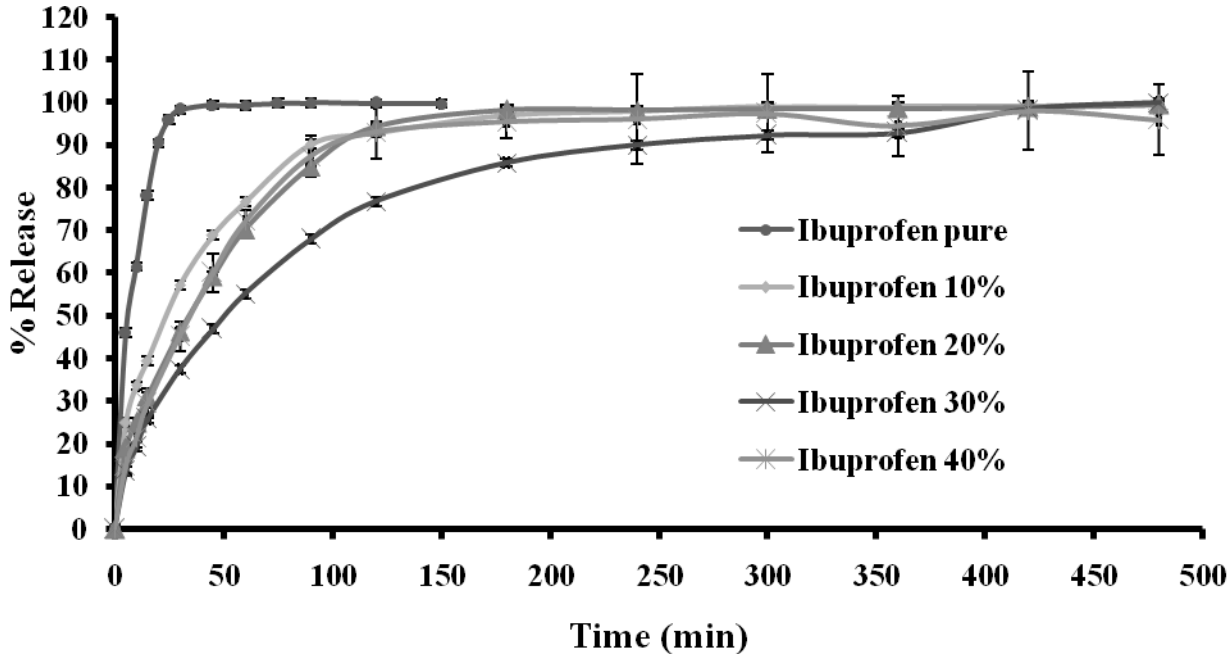

Fig 5: Drug release profiles of Ibu powder, mini tablets containing 10, 20, 30 and 40% w/w Ibu.

Table 2: Comparison for degree of goodness of fit from drug release data fitting with different equations.

Ibu minitablet	Zero order		First order		Higuchi's	
	r^2	MSC	r^2	MSC	r^2	MSC
Ibu powder	0.9960	4.51	0.9712	2.55	0.9929	3.95
10%	0.9474	2.37	0.9987	6.05	0.9943	4.60
20%	0.9741	3.08	0.9969	5.20	0.9956	4.85
30%	0.8623	1.58	0.9957	5.05	0.9679	3.04
40%	0.9689	2.90	0.9956	4.85	0.9907	4.11

CONCLUSION

Ibu mini tablet could be prepared with HME technique using 7:3 SW:Lut as matrix base. Eutectic mixture was evident for combination of this drug with Lut which this behavior was beneficial for lowering the HME processing temperature. Dissolution profile fitting showed the first order release kinetic therefore the drug liberation depended on the content of drug in the mini tablet. All results indicated that Ibu mini tablet could be prepared from HME and could prolong the drug release using SW combined with Lut as matrix component.

ISSN: 0975-8585

ACKNOWLEDGEMENTS

This research project specially thanks to Department of Pharmaceutical Technology, Faculty of Pharmacy, and Department of Material Science and Engineering, Faculty of Engineering and Industrial Technology, Silpakorn University, Thailand for their support and facilities. Miss Jongjan Mahadlek, Miss Phatthamon Laphanuwat, Miss Patcharaporn Hengjumrut, Mr. Nuttawat Ittiponkangwan and Mr. Thanachai Rutnumnoi are acknowledged for their valuable assistance on this work.

REFERENCES

[1] Zgney I, Shuwisitkul D, Bodmeier R. Eur J Pharm Biopharm 2009; 73:140-5.
[2] Verhoeven E. Hot-melt extrusion as processing technique for multiparticulate dosage forms containing lipophilic and hydrophilic polymers. [Thesis]. Ghent Univ 2008.
[3] Pignatello R, Bucolo C, Feeara P. et al. Eur J Pharm Sci 2002; 16:53-61.
[4] Kuebler WR, Gregory PI. US. Patent No. 2,985,642. May 23, 1961.
[5] Ali W, William AC, Rawlinson CF. Int J Pharm 2010; 391:162-68.
[6] Dumortier G. Grossiord JL, Agnely F, Chaumeil JC. Pharm Res 2006; 23:709-28.
[7] MicroMath Scientist Handbook Rev. 7EEF, MicroMath: Salt Lake City 1995; 467.
[8] Lindfors L, Forssén S, Westergren J, Olsson U. J Colloid Interface Sci 2008; 325:404-13.
[9] Newa M, Bhandari KH, Li DX, Kwon TX, Kim JA, Yoo BK et al. Int J Pharm 2007; 343:228-37.
[10] Ali W, Williams AC, Rawlinson CF. Inter J Pharm 2010; 391:162-8.
[11] Pillai PK, Jain K, Jain VK. Phys Lett A 1971; 35:403-4.
[12] Hugues K, Kouassi S, Bajji M, Jijakli H. Postharvest Bio Technol 2012;73:122-8.
[13] Ruguo Z, Hua Z, Hong Z, Ying F, Kun F, Wenwen Z. Procedia Eng 2011;18:101-6.