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Characterization and Drug Behavior in Shellac Wax – Poloxamer Matrix Tablets Fabricated with Mold Technique

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Abstract

Shellac wax is a waste product from shellac manufacturing process and has not been reported to be used as pharmaceutical matrix base. This study was to prepared and characterized shellac wax–poloxamer 407 matrix tablet comprising hydrophilic or hydrophobic drug which were prepared by molten technique. The ratios of poloxamer 407: shellac wax was varied and subsequently loaded with the different drug content before characterized with differential scaning calorimetry (DSC), thermogravimetric analysis (TGA) and powder x-ray diffractometry (PXRD). Drug release study was also performed for 25 mg drug loaded matrix tablet in distilled water using dissolution apparatus II at 50 rpm, 37°C. Dissolution data were then fitted with five mathematic release equations by least square method to determine drug release kinetic. DSC and PXRD showed the solid dispersion for low content of hydrophobic drug in poloxamer 407. TGA showed no drug and other compound degraded during preparation. Drug release and drug release kinetic was dependent on content of poloxamer 407 and hydrophilicity of the model drug. Therefore shellac wax-poloxamer based could be used as matrix component for developing the controlled drug delivery systems in form of matrix tablet fabricated with mold technique.

Key words: Characterization, Matrix tablet, Shellac wax, Poloxamer 407

Introduction

Lipid or wax matrix was popularly used to sustain drug release due to their hydrophobic properties. However, some material, which is high hydrophobicity, might not allow drug release or its release could not be controlled at the desire range.[(1)] Adding hydrophilic polymer such as PEG or poloxamer could promote the drug release from the hydrophobic matrix. The hydrophilic polymer could promote pore on the matrix surface hence they could enhance the drug release.[(1, 2)] Shellac wax (S) is brownish wax obtained from manufacturing process as wasted product of shellac production,[(3, 4)] Poloxamers are non-ionic triblock copolymer between poly (ethylene oxide) and poly (propylene oxide) commonly used in pharmaceutical product as emulsifying agent and solubilizing agent[(5)]. Savolainen, *et. al*, 2003 and Jannin, *et. al*, 2006 reported the use of this polymer to enhance drug release from hydrophobic matrix.[(1, 2)] Propranolol hydrochloride (Pro) is non specific β-adrenergic blocker. This hydrophilic drug was indicated to treat cardio-vascular disease such as hypertension and cardiovasecular diseases.[(6)] Hydrochlorothiazide (HCT) is thiazide diuretic which could inhibit reabsorbtion of sodium and chloride at distal convoluted tubule. It was indicated to treat many diseases such as hypertension, diabetes insipidus and osteoporosis. This hydrophobic drug was commonly used together with the other drugs[(6)]. The marketed product of Pro and HCT combined formulation was named Inderide®[(6)]. Mechanism of drug release was mainly by two mechanism including drug dissolution and diffusion, and erosion of matrix tablet. However, many parameter could influence the drug release hence mathematic models was used to describe the mechanism of drug release[(7)]. The physicochemical properties of drug could affect the drug release and drug release kinetic since drug might be dispersed molecularly in matrix base or particularly dispersed[(8)]. The matrix base could also affect the drug release from base-base interaction. From the reason described above, physicochemical characterization of the matrix tablet should be also evaluated.

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This research prepared S- poloxamer (L) matrix tablet incorporated with a hydrophilic or hydrophobic model drug by molding technique. The physicochemical properties were characterized to observe the drug behavior in the matrix bases. Drug release study and drug release kinetic were also evaluated. The physicochemical properties of each drug in matrix bases was also used to describe the drug release behavior.

Materials and Experimental Procedures

Material

Pro was purchased from PC Drug Co., Ltd, Bangkok, Thailand. HCT was kindly gifted from Government of Pharmaceutical Organization, Bangkok, Thailand. S was purchased from Ake shellac Co.,Ltd., Lampang, Thailand. L was obtained from BASF, Ludwigshafen, Germany.

Method

Sample Preparation

The samples were pure compound of each material in formulation, physical mixture and melted sample. For DSC and PXRD characterization, the physical mixture was prepared by varying L:S ratio at 0:10, 5:5 and 10:0. The 10, 20, 30, 40 and 50% w/w of a model drug was then added into the base. The mixtures were blended together by mortar and pestle. Melted samples were prepared with the same content of the physical mixture. The same content of drug was incorporated into the molten base and solidified at room temperature. The sample was grinded into fine powder by mortar and pestle before characterization. The pure compounds were the pure model drug which were Pro and HCT and the matrix base which were S, L and 5:5 ratio of L:S, respectively.

Matrix Tablet Preparation

Matrix tablets were prepared by varying L:S ratios at 0:10, 5:5 and 10:0. L and S were accurately weighed after deducted displacement value (D.V.) of each drug. The bases were melted by the order of melting point. The melting temperature was about 160°C in order to obtain the soft and pourable of the molten mixture. Pro and HCT were used as hydrophilic and hydrophobic model drug, respectively. The 25 mg drug was then incorporated into the molten mixtures and kept stirring until the drug and molten bases were mixed homogeneouslly. The drug loaded molten base was poured into 16 mm. diameter stainless steel mold (Figure 1) and kept at room temperature until the matrix tablet was solidified. The obtained tablets were withdrawn from the mold and were kept in the desiccator.

Thermogravimetric Analysis (TGA)

Thermogravimetric analysis has been performed to reveal the degradation temperature of each compound in formulation. S, L, HCT and Pro were analyzed with TGA (TG/DTA 6200, Seiko Instruments Inc., Japan**)**. The mixture of S and L at the ratio of 5:5 was also measured. The 5 mg of each compound was approximately weighed. The sample was placed in non-hermitically aluminium pan. The pan was then sealed and placed in TG. Heating rate was 10°C/min. The heating range was 30 – 400°C under 200 mL/min of nitrogen gas flow.

Differential Scanning Calorimetry (DSC)

DSC (DSC6200, Seiko Instruments Inc., Japan) was used to investigate the thermal properties of drug and other compounds in the formulation including pure compounds of model drugs and bases and mixed bases. Drug loaded matrices which were prepared by physical mixting and melting method were also tested. The test samples are shown in Table. 2. All samples were approximately weighed at about 5 mg then they were placed in non-hermitically aluminium pan. The pan was then sealed and placed in DSC chamber. The samples were investigated under 10°C/min of heating rate and the heating range was 30-350°C under 40 mL/min of nitrogen gas flow.

Figure 1. The 16 mm. diameter stainless steel mold

Powder X-ray Diffractometry (PXRD)

PXRD (MiniFlex II, Rigaku corp, Japan) was also performed to investigate the crystalline properties of the material used in this study. The result was used to describe the drugs and other compounds properties together with DSC results. The test samples as shown in table 2 were grinded into fine particle by mortar and pestle and loaded into PXRD disc. All samples were scanned in the degree of 2θ in the range of 0 to 30°2θ

Table 1. Test sample for DSC and PXRD analysis

Pure compound	Physical mixture (L:S)	Melted sample (L:S)
Drug[a]	10-50%w/w[c] drug in 10:0	10-50%w/w drug in 10:0
Matrix base[b]	10-50%w/w drug in 5:5	10-50%w/w drug in 5:5
	10-50%w/w drug in 0:10	10-50%w/w drug in 0:10

a: Model drug including Pro and HCT, b: Matrix base including pure of L (10:0), pure of S (0:10) and mixure of L and S (5:5), c: drug content was varied at 10, 20, 30, 40 and 50% w/w

Drug Release Study

Dissolution of the samples were studied using dissolution apparatus I (basket apparatus) (RC-6 , Minhua Pharmaceutical machinery Co., LTD., China**)** under 50 rpm of rotational speed in 900 mL distilled water which was used as dissolution medium. The medium was maintained at 37°C through the study. Samples were collected at specific time intervals at 5, 15, 30, 45 min, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7 and 8 hrs. The samples were examined by UV spectrophotometer at 289 and 271 nm to measure the amount of Pro and HCT release, respectively. The cumulative drug release of Pro or HCT were calculated and plotted against time.

Dissolution Profile Fitting

Mechanisms of drug release were evaluated by fitting of cumulative drug release data with mathematical release models. The models used in this experiment were zero order, first order, Higuchi's model, power law expression and Hixson-Crowell cube root equation. The experimental cumulative drug release data within the range of 5-80% were used to evaluate the kinetic of drug release by least square fitting method. The data were fitted with the mathematical equations by 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)[10] given below.

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

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

Results and Discussion

TGA

To ensure that the model drugs and matrix bases used in this experiment did not degrade at preparation temperature, 160°C, TGA was used to investigate the thermal degradation property. The minimum degradation temperature of each compound was approximately 350°C, 240°C, 215°C and 295°C for poloxamer, shellac wax, Pro and HCT, respectively (Table.2). Degradation temperature was 401.5°C, 355°C, 299.5°C and 335.8°C for poloxamer, shellac wax, Pro and HCT, respectively (Table.3). The results signified that drug and other compounds would not degrade during preparation.

Table 2. Minimum degradation temperature (MDT) and degradation temperature (DT) of each compound observed by TGA

Materials	MDT (°C)	DT (°C)
Poloxamer 407	350	401.5
Shellac wax	240	355.0
Propranolol HCl	215	299.5
Hydrochlorothiazide	295	335.8

DSC

Some research reported that shellac wax contained four main components including fatty

acid ester (70-82%), free alcohol (8-14%), free acid (1-4%) and aliphatic hydrocarbon (1-6%)[11].From the experiment, the DSC thermogram of S revealed only two endothermic peaks at 64.8ºC and 79.5º (data not shown). The two remaining peaks reported from the previous were not observed in this study due to a broad endothermic peak between the two sharp peaks.[11] L was found the sharp endothermic peak at 56.2ºC. In case of the model drugs, the sharp endothermic peak was found at 166.7 and 272.2ºC for Pro and HCT, respectively (data not shown). Physical mixture (PM) and melted sample (MS) of Pro in all matrix bases did not show any change of DSC thermogram of each individual matrix bases. It might be concluded that this drug might not interact or be solid dispersed in the matrix bases. On the other hand, the peak of HCT disappeared in PM and MS of 10, 20 and 30% HCT in L and also at 10 and 20% HCT in 5:5 of L:S, respectively. However, the small drug melting peak could be observed for higher drug loaded systems. Additionally, both 5:5 L:S loaded with HCT or Pro were observed the new broad peak of S at about 84.0°C. This might indicate the interaction between the two matrix bases. However, both drug and S peak was clearly observed when the drug was incorporated in S with both PM and MS. This might define the chemical reaction or solid dispersion of HCT could not occur in S. The data are shown in Figure 2.

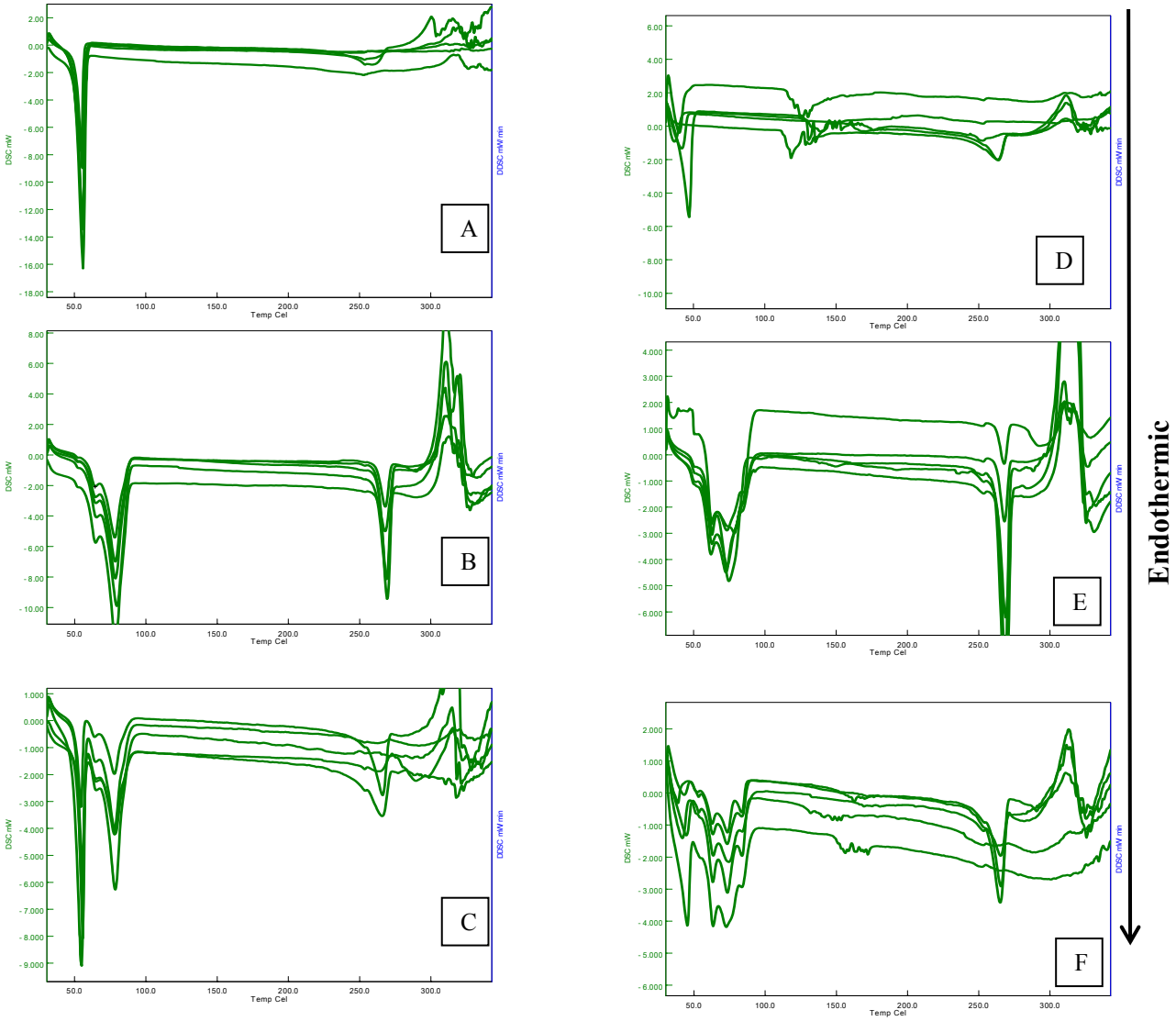

Figure 2. DSC thermograms of 10-50% w/w HCT in L - PM (A), 10-50% w/w HCT in S-PM (B), 10-50% w/w HCT in 5:5 - PM (C), 10-50% w/w HCT in L – MS (D), 10-50% w/w HCT in S-MS (E), 10-50% w/w HCT in 5:5 - MS (F).

PXRD

Characteristic drug peak of Pro could be clearly observed in both PM and MS of 0:10, 5:5 and 10:0 L:S. The result was as same as in DSC which clearly observed the pro endothermic peak in those bases, hence it might be concluded that solid dispersion or molecular interaction might not occur between this drug and the matrix bases. In case of HCT, it could be observed a sharp diffractogram at about 19 º2θ and small peak at 28.5º2θ (Figure 3A). Unfortunately, there was coincident diffractogram between HCT and L at about 19º2θ. However, there was still a characteristic peak at 28.5º2θ. The melting peak of 10% w/w HCT was disappeared in both PM and MS when mixed with 10:0 (L) as shown in Figure 3C and 3D. Higher drug loaded system showed more clearly intense of drug melting peak. In case of HCT incorporated in 0:10 (S) and 5:5 (L: S), a small drug melting peak was still observed from both bases (data not shown). The decrement of L amount in the formulation affected the solid dispersion or molecular interaction of HCT. The results from PXRD was not the same with DSC since DSC was studied by heating the samples to temperature that over the melting temperature of each base and that HCT could be more dissolved in the molten base. Therefore, HCT endothermic peak could not be observed at the content higher than 10% w/w of HCT in L because the drug could dissolve in that molten base. In contrast with PXRD, the disappearance of PXRD diffractogram of HCT in L could found only at the content 10% w/w of HCT because the drug could not dissolve in the base during characterizing. From the reason described above, it might conclude that the 10% in L could found only at the content 10% w/w of HCT because the drug could not dissolve in HCT could solid dispersed or molecular interacted with L whereas at higher drug loaded or the utilization of the other bases the drug was only dispersed particulately in those bases.

Drug Release

Both drugs could not release from matrix tablet made from S owing to the high hydrophobic nature of this wax (Figure 4). On the other hand, these drugs could release completely within 180 min from L matrix tablet. This might be described by the hydrophilic nature and surface active property of L[5] which could enhance the drug release. In case of hydrophobic drug like HCT, the drug might be dispersed in molecular level in L matrix.[8] Drug release from 5:5 L:S matrix tablet was different for two model drugs. Pro could be completely released within 480 min but HCT could be released only a half. This is due to the different for hydrophilicity nature of the drug. In case of hydrophilic drug like Pro, drug release might occur from both drug diffusion and matrix erosion. For HCT which is hydrophobic drug, the drug could release similar to that of Pro but with apparently slower. DSC and PXRD results, indicated the solid dispersion formation of this drug in 5:5 L:S but

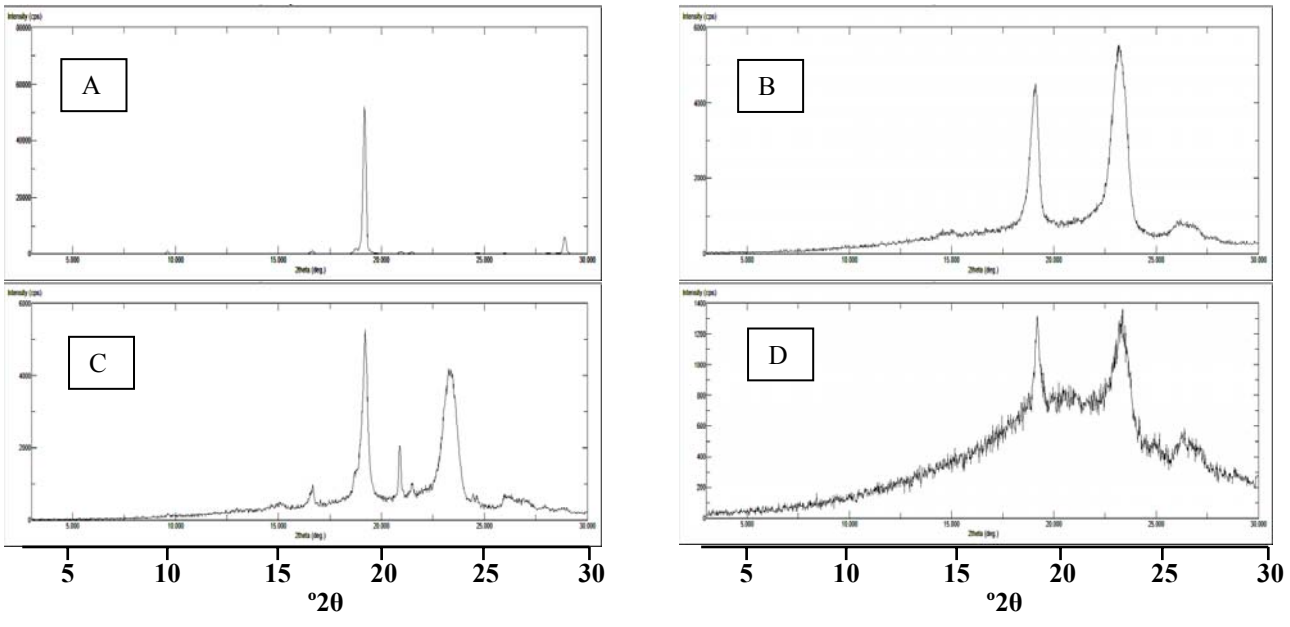

Figure 3. Powder X-ray diffractogram of HCT (A), Lutrol F127 (B), 10% HCT in L-PM (C), 10% HCT in L-MS (D)

some of them was not dispersed or molecular interacted with the bases and it would be gradually dissolved and released from the matrix base. According to the result, The HCT release rate was slower than Pro from 5:5 bases ratio.

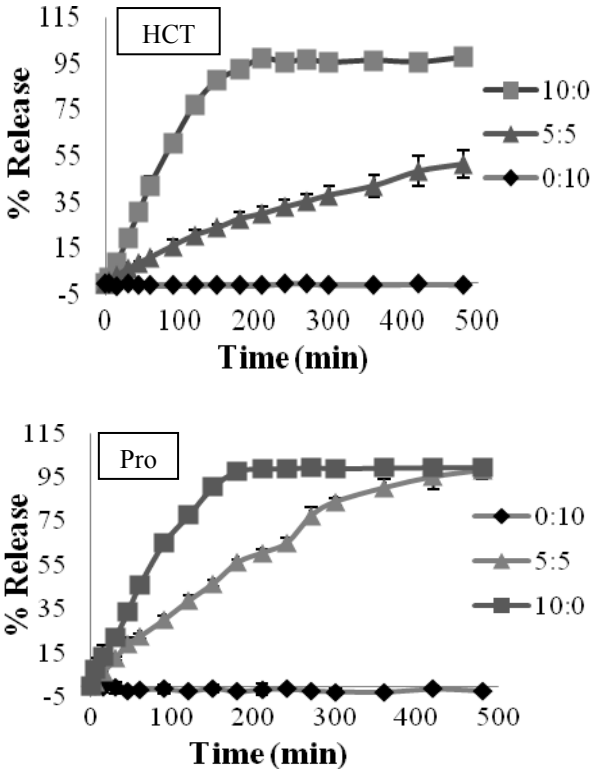

Figure 4. Release of HCT and Pro from L: S matrix tablets; pure L (10:0), mixture of L and S (5:5) and pure S (0:10).

Drug Release Kinetic

Many mathematic models could be applied to describe the mechanism of drug release. Zero order kinetic described the system with the drug release rate did not depend on time. First order kinetic was expressed for the release with the drug concentration dependent. Higuchi's model was explained the diffusion of drug through the matrix system. Power law model was popularly used because it could be determined many kinetic by n exponent value. Cube root law was evaluated to describe the release of drug from the erosion of matrix system which geometrical constant [9]. Release kinetic of both Pro and HCT incorporated in L were fitted well with the cube root law. Theoretically, Pro should release from the matrix tablet from both erosion and diffusion control which could be explained by first order. However, the erosion rate of L might faster than the dissolution and diffusion of the drug from the matrix hence Pro in the tablet made from L mainly released by erosion of the base which could maintain the constant geometric shape through the dissolution time. Pro dispersed in 5:5 L:S matrix tablet released by first order kinetic which could be confirmed by the n exponent from power law expression. This hydrophilic drug could easily dissolve and diffuse from the matrix tablet simultaneously with the erosion of the matrix tablet. The matrix tablet made from L has high erosion rate which could completely release the entire drug within 180 min. However, in case of 5:5 L:S matrix tablet, the erosion rate was deducted by S hence the release was not mainly by the erosion of L but the release occurred from both diffusion control and erosion control which could be the best described by first order release kinetic. In the other hand, HCT incorporated in 5:5 L:S matrix system was the best described by zero order kinetic which could be confirmed by n exponent value of power law model. Generally, the surface area was gradually decreased as dissolution time increased, resulted in the decrement of drug release. In case of 5:5 L:S matrix system surface area of tablet was gradually decreased because of the barrier property of S which could obstruct the water penetration into the matrix tablet. As described previously, HCT was not completely dispersed or molecular interacted in 5:5. When dissolution medium penetrated into the matrix tablet, the matrix was gradually eroded simultaneously with the dissolution of dispersed drug. In the other hand, the non-dispersed drug was gradually dissolved and diffused out from the pore of the eroded surface. Some of them might appear at the eroded surface and gradually release into the dissolution medium. The non-dispersed component could compensate the drug release from the decrement of surface area. The balance between matrix erosion and drug dissolution might result in the zero order release kinetic. For both drugs in S (0:10), they could not release from the matrix system therefore the release kinetics could not be determined. The r^2 and msc values from dissolution profile fitting for the other systems are shown in Table. 3.

Table 3. Pro and HCT release kinetic from 10:0, 5:5 and 0:10 ratios of L: S

Pro											
L:S	Zero order		First order		Higuchi's		Cube root		Power law		
	r^2	msc	r^2	msc	r^2	msc	r^2	msc	r^2	msc	n
10:00	0.9851	3.64	0.9799	3.34	0.9564	2.56	0.9941	4.56	0.995	4.44	0.72
5:5	0.9525	2.74	0.9958	5.17	0.9950	4.99	0.9932	4.70	0.9956	4.96	0.47
10:00	-	-	-	-	-	-	-	-	-	-	-
HCT											
L:S	Zero order		First order		Higuchi's		Cube root		Power law		
	r^2	msc	r^2	msc	r^2	msc	r^2	msc	r^2	msc	n
10:00	0.9857	3.58	0.987	3.68	0.9829	3.40	0.9981	5.61	0.9979	5.18	0.64
5:5	0.9943	4.81	0.9573	2.79	0.9260	2.24	0.9736	3.30	0.9945	4.66	1.07
10:00	-	-	-	-	-	-	-	-	-	-	-

Conclusion

The materials (S, L, Pro and HCT) used in this experiment were not degraded at the preparation temperature. DSC and PXRD showed that L influenced the properties of S by interacting with some fatty compounds in S therefore the hidden peaks which were crowded by those peaks were revealed. Moreover, the solid dispersion or molecular interaction between HCT and L might be occurred and some of HCT might disperse in molecular level in L. From drug release study, increment of L could enhance the drug release from S matrix tablet. The release of two model drugs incorporated in L was best described by cube root law. Drug in S could not release due to the hydrophobic properties of S. For the 5:5 L:S matrix tablet, the release of two model drugs were different due to the hydrophilic-hydrophobic properties of drugs. The hydrophilic drug, Pro, could release pass through matrix tablet via two mechanism, dissolution and diffusion of drug from the matrix and erosion of the matrix system. The hydrophobic drug, HCT, the release could occur mainly by erosion of the matrix system hence the dissolution was slower. The release kinetic of Pro in 5:5 was best described by first order release kinetic. The release of HCT in 5:5 was best fit with zero order kinetic from the reason described above. Therefore, shellac wax-poloxamer based could be used as matrix component for the developing controlled drug delivery systems in form of matrix tablet fabricated with mold technique.

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