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New Coating Materials Based On Mixtures of Shellac and Pectin for Pharmaceutical Products

M. Kumpugdee-Vollrath, M. Tabatabaeifar, M. Helmis

***Abstract*—**Shellac is a natural polyester resin secreted by insects. Pectins are natural, non-toxic and water-soluble polysaccharides extracted from the peels of citrus fruits or the leftovers of apples. Both polymers are allowed for the use in the pharmaceutical industry and as a food additive. SSB Aquagold® is the aqueous solution of shellac and can be used for a coating process as an enteric or controlled drug release polymer. In this study, tablets containing 10 mg methylene blue as a model drug were prepared with a rotary press. Those tablets were coated with mixtures of shellac and one of the pectin different types (i.e. CU 201, CU 501, CU 701 and CU 020) mostly in a 2:1 ratio or with pure shellac in a small scale fluidized bed apparatus. A stable, simple and reproducible three-stage coating process was successfully developed. The drug contents of the coated tablets were determined using UV-VIS spectrophotometer. The characterization of the surface and the film thickness were performed with the scanning electron microscopy (SEM) and the light microscopy. Release studies were performed in a dissolution apparatus with a basket. Most of the formulations were enteric coated. The dissolution profiles showed a delayed or sustained release with a lagtime of at least 4 h. Dissolution profiles of coated tablets with pure shellac had a very long lagtime ranging from 13 to 17.9 h and the slopes were quite high. The duration of the lagtime and the slope of the dissolution profiles could be adjusted by adding the proper type of pectin to the shellac formulation and by variation of the coating amount. In order to apply a coating formulation as a colon delivery system, the prepared film should be resistant against gastric fluid for at least 2 h and against intestinal fluid for 4-6 h. The required delay time was gained with most of the shellac-pectin polymer mixtures. The release profiles were fitted with the modified model of the Korsmeyer-Peppas equation and the Hixson-Crowell model. A correlation coefficient (R^2)> 0.99 was obtained by Korsmeyer-Peppas equation.

***Keywords*—**Shellac, pectin, coating, fluidized bed, release, colon delivery system, kinetic, SEM, methylene blue.

I. Introduction

THE purpose of this research work was to develop new coating materials based on biopolymers i.e. shellac and pectins. Coatings were performed to obtain controlled release, sustained release, colon delivery, or enteric release. The coating process can be performed by different ways e.g. fluidized bed apparatus, coating pan [1]-[3]. The advantages of biopolymers are that they are nontoxic, biocompatible and biodegradable [1]. The biopolymer can be received from plants which are environmentally sustainable.

Shellac is natural, nontoxic, biocompatible and biodegradable polymer. It is a natural polyester resin secreted by insects. It is a mixture of different esters and carboxyl groups and is not soluble in neutral or acidic aqueous solution. Fig. 1 shows the chemical structure of shellac as ester or polyester. The commercial product of shellac is available as alkaline aqueous solution and is applied as enteric or sustained release coating polymer. Formally shellac was mostly used as alcoholic solution. However, it was a problem with products coated with this solution because the disintegration and dissolution profile changed after storage. An alternative product was developed and it is an alkaline aqueous solution called "SSB Aquagold®". Products coated with this aqueous coating solution did not have a problem with the release profile after storage. SSB Aquagold (SSB) was delivered at the 25% solid content and can be used as controlled release as well as enteric coating polymer. The SSB liquid stay stable if pH of the solution > 7. In contrast if pH < 7, the flocculation occurs [6].

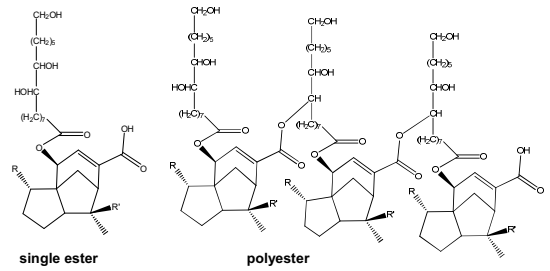

Fig. 1 Chemical structure of shellac as single and polyesters [5]

Pectins are biopolymer. They are nontoxic and water-soluble polysaccharides extracted from the peels of citrus fruits or the leftovers of apples. The chemical structure of pectins was shown in Fig. 2. Pectins can be used as gel formation substance, thickening agent, coating polymer or detoxication agent by forming complexation. Various types of pectins are available depending on the grade of esterification or/and amidation [7], [8]. Pectins occur as gel at pH < 2. If pH gets higher the viscosity and turbidity get lower [4].

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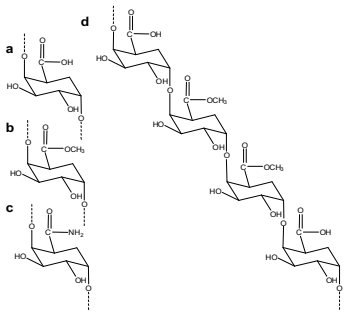

Fig. 2 Chemical structure of different functional groups a) carboxyl, b) ester and c) amide, and d) pectins [7]

Both polymers (shellac and pectins) are allowed for application in the pharmaceutical and food industries as an additive. Therefore they were applied in this project.

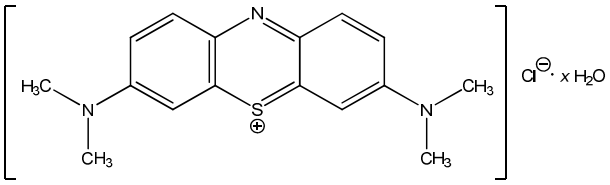

Fig. 3 Chemical structure of methylene blue [9]

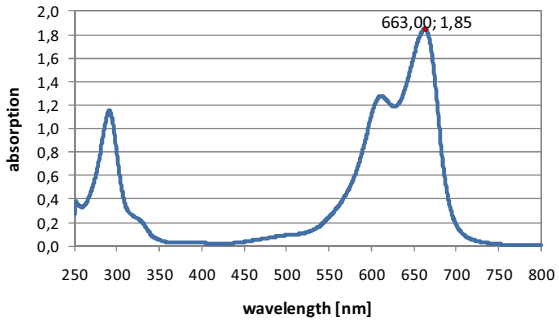

Fig. 4 UV-VIS spectrum of 10 mg/L methylene blue in phosphate buffer pH 6.8

Methylene blue (Fig. 3) was used in this project as model drug because of its water solubility and UV-VIS property. The pharmacological effect is not relevant to this project. Methylene blue is water soluble and can absorb UV-VIS as demonstrated in Fig. 4.

In order to obtain a deep knowledge of the release properties of each formulation the well-known different kinetic models i.e. Hixson-Crowell and Korsmeyer-Peppas [11]-[13] were applied.

II. Materials and Methods

A. Materials

Pectins (i.e. Pectin Classic CU501, 701, 201, Amid CU 020, Herbstreith & Fox, Neuenburg Fabrik, Germany), shellac (SSB Stroever, Bremen, Germany), glycerol 85% (Fagron, Barsbüttel, Germany), methylene blue (VWR International BVBA, Leuven, Belgium), Ludipress (BASF, Ludwigshafen, Germany), talc (Fagron, Barsbüttel, Germany), magnesium stearate (Fagron, Barsbüttel, Germany), Aerosil 200 (EvonikRöhm, Darmstadt, Germany). Sodium hydroxide, potassium phosphate and hydrochloric acid were purchased from Carl Roth, Karlsruhe, Germany.

B. Characterization of Powders and of Cores as Well as Coated Tablets

The angle of flow of the powder was measured by the method similar to that mentioned in the pharmacopoia [10]. The core tablets were prepared by mixing the different substances (5% methylene blue, 2.4% talc, 0.3% magnesium stearate, 0.3% Aerosol, 92% Ludipress) together. The powder mixtures were homogenized in two types of mixers, respectively (Turbula mixer and cubic mixer). The core tablets were prepared by rotating tablet press (Pressima, IMA Kilian, Köln, Germany). The tablets were characterized by a multifunctional semiautomatic Tablet Testing Instrument (PTB 311E, Pharmatest Apparatebau AG, Germany) to obtain details of the hardness, diameter and thickness. The disintegration (PTZ, Pharmatest, Germany) was performed after the method mentioned in the pharmacopoia [10]. The uniformity of mass was performed by weighing each tablet by an analytical balance. The mass of each tablet was controlled to be 200 mg and the hardness of about 70-90 N. The uniformity of content of methylene blue was measured in NaOH by the UV-VIS spectrometer (Jasco V-630, Japan).

C. Coating Process

Four types of pectins (i.e. Pectin Classic CU501, 701, 201, Amid CU 020) were applied. The solution of pectin in water was first prepared at the temperature of about 60-80°C. The concentration was controlled to be 5% and the pH of 8. The 25% solution of shellac was mixed with glycerol and the pH was controlled to be about 8. The two solutions were mixed together to receive different ratios of shellac to pectin (1:1, 2:1, 3:1) as mentioned in the Table I. The solid content of the coating liquid was controlled to be 9.81%.

TABLE I
Different Formulations of Polymer Coating Liquid

Amount of 25% SSB solution (g)	Amount of pectin (g)	Pectin type	Ratio of shellac to pectin	Glycerol 85% (g)	Water (g)
95.25	-	-	-	5.66	192.5
43.88	10.88	CU 501	1:1	5.16	208.4
57.65	7.21	CU 501	2:1	5.09	136.9
64.86	5.41	CU 501	3:1	5.09	102.7
57.50	7.19	CU 701	2:1	5.07	194.1
51.50	6.44	CU 501	2:1	4.54	173.8
51.52	6.44	CU 201	2:1	4.55	173.8
51.55	6.44	CU 020	2:1	4.51	171.4

The polymer mixture was used to coat the core tablets containing methylene blue by a coating apparatus (Air Coater IAC 025, Innojet, Germany). The coating parameters were as follows:

Air volume: 75-80% of the maximum volume
Inlet air temperature (°C): 40
Outlet air temperature (°C): 36-38
Spraying pressure (bar): 1
Spraying rate (g/min): 0.6-0.7
Total weight of core tablets (g): 75

The tablets of about 40 pieces were taken during the coating process in order to receive the coated tablets with the weight gain of about 10-20%.

D.Release Studies

The UV-VIS absorptions of the model drug methylene blue in the different solvents (0.1N NaOH, HCl pH 1.2, phosphate buffer pH 6.8 and pH 7.4) were determined by the UV-VIS spectrometer (Jasco V-630, Japan). The calibration curves of the model drug were obtained by measuring the solutions in various dilutions with the spectrometer at the maximum absorption. The releases were studied by using an automatic dissolution apparatus with baskets defined after pharmacopoia [10] (PT-DT70 Pharmatest, Germany, UV-VIS Spectrometer Cecil 3021, England, WinDiss32). The basket rotation was set at 100 rpm. Different dissolution media (i.e. HCl pH 1.2, phosphate buffer pH 6.8 and pH 7.4) were used as a medium to mimic the enteric or intestinal fluid at the temperature of 37 °C ± 0.5 °C. At first the tablets were tested in HCl for 2 h, afterwards the same tablets were tested in buffer until the end of the time. The release kinetics were described by two typical mathematic models. The Korsmeyer-Peppas (1) equation modified after Harland et al [13] was applied. The equation is shown in (2).

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

$$\frac{M_{(t-t_{lag})}}{M_\infty} = k(t - t_{lag})^n \quad (2)$$

where
M_t/M_∞= fraction of the released drug at the release time t
t_{lag} = lagtime
k = release constant corresponding to the kinetic characteristic of drug/polymer system
n = release exponent, influenced by the drug release mechanism and shape of tablet

The Hixson-Crowell equation was shown in (3).

$$(1 - f_t)^{1/3} = 1 - K_\beta t \quad (3)$$

where f_t is the amount of the model drug at the time „t“ with the Hixson-Crowell constant "K_β".

E. Morphologies and Thickness of Films

The morphology of the coated tablets was observed by a digital microscope (Traveller, Aldi, Germany). The pictures of the samples were taken without any treatment. Furthermore the scanning electron microscope (SEM, DSM950, Carl Zeiss, Oberkochen, Germany) was applied at the voltage of 10 kV to determine the inner structure and of the thicknesses of the coating. The samples were cut into two pieces for determination of thickness and one of them was fixed onto the holder for coating with a thin layer of gold-Pd (Vacuum sputter, SCD 040, Balzers Union, Lichtenstein) prior to the measurement.

III. Results and Discussion

A. Calibration Curves

The calibration curves were demonstrated in Table II. By application of the suitable calibration, the amount of the model drug methylene blue can be calculated. The maximum wavelengths (λ) at different media were also mentioned.

TABLE II
Summary of Calibration of Methylene Blue in Different Media

Type of medium	λ (nm)	Calibration's Equation	R^2
buffer pH 6.8	663.0	Y=0.175x+0.113	0.996
0.1N HCl	663.5	Y=0..171x+0.174	0.996
buffer pH 7.4	663.5	Y=0.164x+0.150	0.999
0.1 N NaOH	611.0	Y=0.079x-0.026	0.996

B. Characterization of Products

The powder mixtures had an angle of flow of about 26°. This means excellent flow ability. Most of the particles of the powder mixtures (> 90%) were smaller than 400 µm. The uniformity of mass of all formulations (Fig. 5) has a deviation < 3.2%, which is in the accepted level mentioned in the pharmacopoia. The hardnesses of the pure shellac coated tablets were lower than that with the mixture of shellac and pectins. However, there was almost no significant difference between pectin types (Fig. 6).

There was a linear correlation between the spraying time and weight increase (Fig. 7). The deviation of hardness of the coated tablets was lower than 10% except those tablets coated with pure shellac which had a value of about 20%. However, these values can still be accepted. Fig. 8 shows a linear correlation between the hardness and the weight increase of polymer (10-30%) except those tablets coated with pure shellac. The interesting phenomenon can be observed with tablets coated with shellac: CU 501 3:1 at 20-30% weight increase because the tablets were not broken under the test but they were deformed to be seen in Fig. 9. Core tablets disintegrated within 5 min. However, coated tablets did not disintegrate so quickly. The disintegrating times can be taken from Table III.

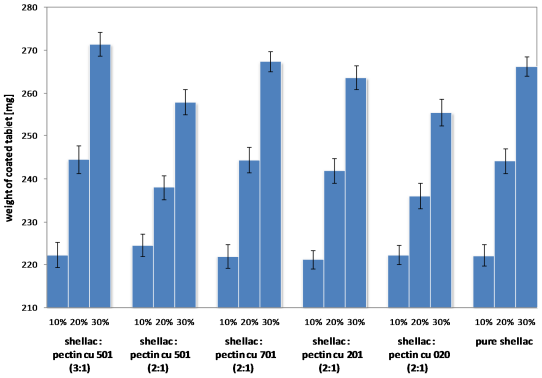

Fig. 5 Mass of tablets coated with pure shellac or with the mixture of shellac and pectins showing standard deviation as bars

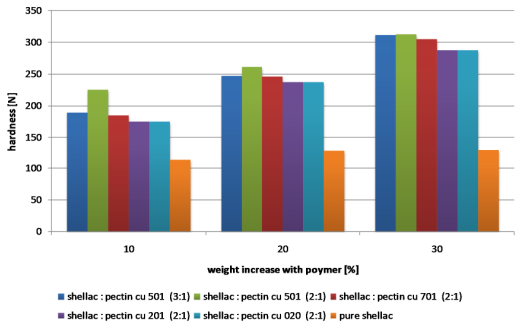

Fig. 6 Correlation of weight increase of polymer (10-30%) and the hardness of tablets coated with pure shellac or with the mixture of shellac and pectins

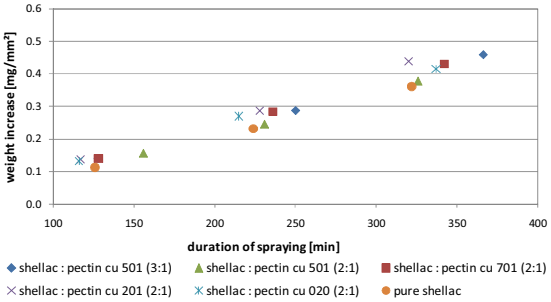

Fig. 7 Correlation of spraying time and weight increase of the coated tablets (mg/mm^2)

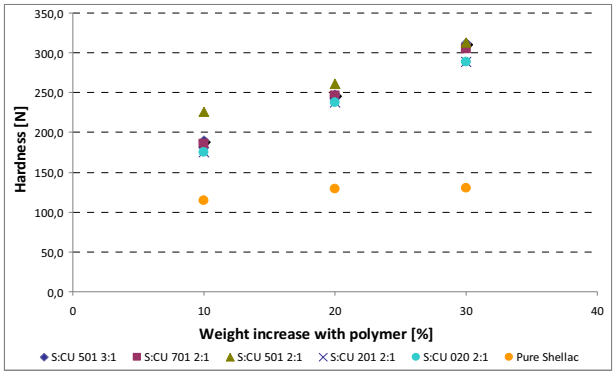

Fig. 8 Correlation of weight increase of polymer (10-30%) and the hardness of tablets coated with pure shellac or with the mixture of shellac and pectins

(a) (b)

Fig. 9 Photographs of tablets coated with shellac: pectin CU 501 3:1 at the weight increase (a) 20% and (b) 30% after hardness test showing deformation

TABLE III
DISINTEGRATION TIME OF CORES AND COATED TABLETS

Formulation	Coating level (%)	Disintegration Time (min)	Remark
Core tablet	0	4-5	
S:CU 501 3:1	10	< 60	nf
S:CU 501 3:1	20-30	-	nd
S:CU 701 2:1	10-30	< 60	
S:CU 501 2:1	10	20-30	
S:CU 501 2:1	20	< 60	
S:CU 501 2:1	30	-	nf
S:CU 201 2:1	10	< 60	
S:CU 201 2:1	20	< 60	nf
S:CU 201 2:1	30	> 60	nf
S:CU 020 2:1	10	15-20	
S:CU 020 2:1	20	<60	ad
S:CU 020 2:1	30	-	nd
Pure Shellac	10-30	-	nc

nf = did not fully disintegrate, nd = did not disintegrate at all
ad = almost fully disintegrated, nc= tablet did not change

All tablets contained the model drug methylene blue as theoretically expected content i.e. about 10%. Table IV shows some data. The deviation was in the accepted level mentioned in pharmacopoia.

TABLE IV
CONTENT UNIFORMITY OF SOME COATED TABLETS IN 0.1 M NAOH

Formulation	Content (mg)	Mean of content (mg)
S:CU 501 2:1 30%	10.20	
S:CU 501 2:1 30%	9.83	10.03
S:CU 501 2:1 30%	10.06	
S:CU 501 3:1 30%	10.63	
S:CU 501 3:1 30%	10.12	10.13
S:CU 501 3:1 30%	9.63	

C. Morphology and Film Thickness

Optical determination was performed with a digital camera. The results are shown in Fig. 10. The roughness can be clearly detected with the tablets coated with S:CU501 3:1 (Fig. 10 (a)). In contrast tablets coated with pure shellac or other mixtures seemed to have smooth surface.

SEM of the surface and of the cross section of an example of the coating prepared from the mixture of shellac and pectin was shown in Fig. 11. There is some roughness on the surface. Small air bubbles inside the films can be observed, but these films can still hinder the release of the model drug from the coated formulation as the delayed release can be detected.

D.Release Studies

The release profiles of methylene blue from core tablets in HCl and phosphate buffer pH 7.4 were demonstrated in Fig. 12. It can be seen that after a short time the release was fast and reached almost 100% after 10 min. Fig. 13 shows the release of methylene blue from tablets coated with a mixture of shellac and pectin CU501 (3:1) at different polymer level (10-30%). In 0.1 N HCl the drug was not released at all. The release in buffer pH 7.4 was depending on the thickness of the film. At the higher thickness the release was smaller. The maximum release amount did not reach 100%, which may be due to the adsorption of methylelne blue at the film layer. The delayed release to maximum 30% can be monitored over 24h, especially at 30% polymer level. This formulation (both 20% and 30% polymer level) can be also used as colon delivery because the delayed release and lagtime was more than 6h, which was required for this purpose.

By reduction of the shellac amount i.e. S:CU (2:1) (Fig. 14) the total release amount was smaller than that at 3:1. The increase of the film thickness (20% to 30%) did not significantly affect the release profile. This implied that the effect of the mixture shellac and pectin has an optimum point. The mixture of S.CU501 at 2:1 at 20-30% polymer level can be used as colon delivery as well.

Tablets coated with the mixture of S:CU701 2:1 at 10-20% were not resistant against gastric fluid. Only at 30%, the tablets did not release methylene blue to the medium HCl (Fig. 15). The degree of esterification of Pectin CU701 was 38%, which was low compared to that of CU501 or 201. Pectin CU701 contained more ionized carboxylic groups and therefore has more hydrophilicity. This may cause a faster release of the model drug. Moreover, the molecular weight of Pectin CU701 was lower than other types of pectin used in this study. The low molecular weight will cause the non stable gel or swelling layer. Therefore the mixture of S:CU701 at 2:1 cannot be used as colon delivery.

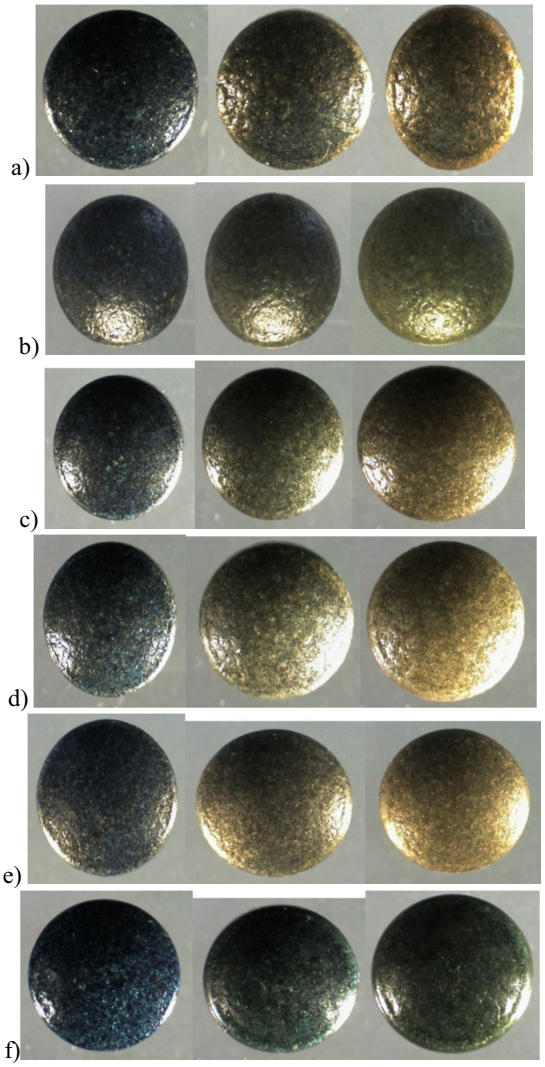

Fig. 10 Photographs of tablets coated with different polymers (a) S:CU501 3:1 10-30%, (b) S:CU501 2:1 10-30%, (c) S:CU701 2:1 10-30%, (d) S:CU201 2:1 10-30%, (e) S:CU020 2:1 10-30%, (f) pure shellac 10-30% (from left to right)

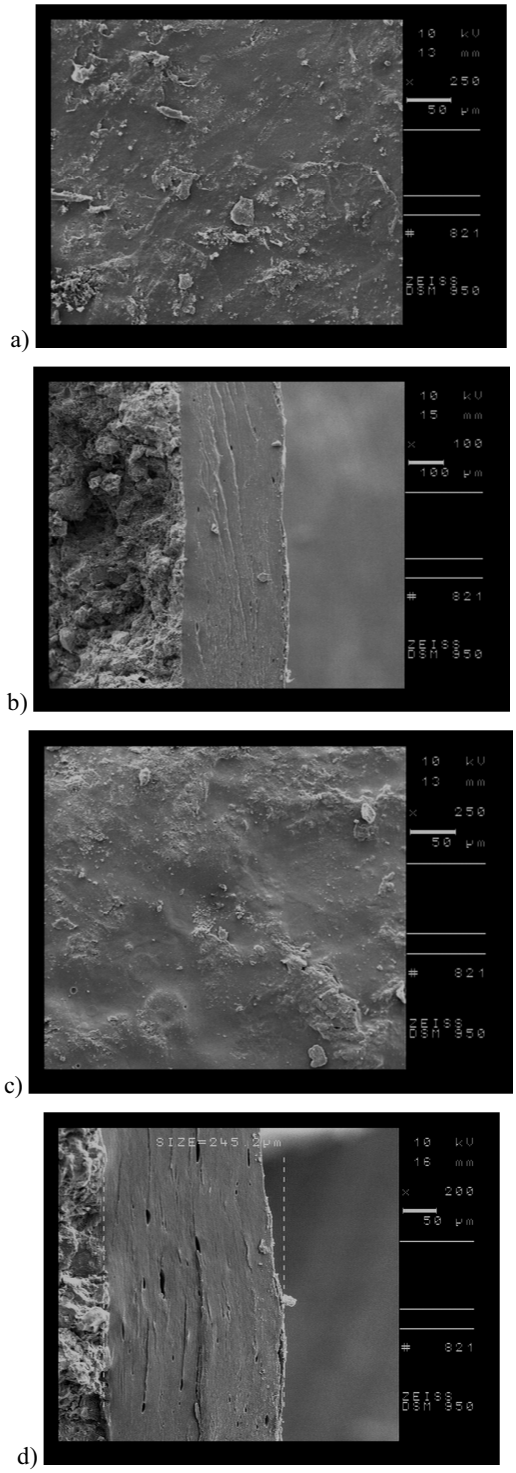

Fig. 11 SEM of tablets coated with shellac and pectins (a) surface at 30% S:CU501 3:1, (b) cross-section S:CU501 3:1, (c) surface at 30% S:CU501 2:1, (d) cross-section S:CU501 2:1

TABLE V
FILM THICKNESSES AND SPRAYING TIME OF TABLETS COATED WITH DIFFERENT POLYMER OR WITH POLYMER MIXTURE AT VARIOUS COATING LEVELS (10-30%)

Formulation	Coating Level (%)	Thickness (µm)	Spraying time (min)
S:CU 501 3:1	10	110.7	128
S:CU 501 3:1	20	234.3	250
S:CU 501 3:1	30	357.0	366
S:CU 501 2:1	10	147.0	156
S:CU 501 2:1	20	219.5	231
S:CU 501 2:1	30	306.0	326
S:CU 701 2:1	10	127.0	128
S:CU 701 2:1	20	248.0	236
S:CU 701 2:1	30	371.0	342
S:CU 201 2:1	10	125.3	117
S:CU 201 2:1	20	260.0	228
S:CU 201 2:1	30	353.5	320
S:CU 020 2:1	10	113.5	116
S:CU 020 2:1	20	259.3	215
S:CU 020 2:1	30	337.0	337
Pure Shellac	10	109.0	126
Pure Shellac	20	222.0	224
Pure Shellac	30	314.0	322

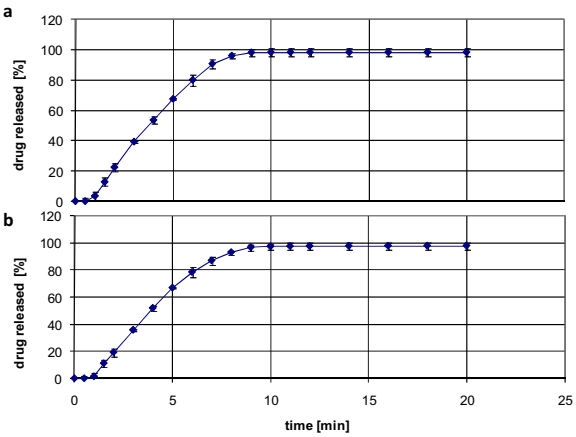

Fig. 12 Drug release of uncoated tablets in (a) 0.1 M HCl and in (b) phosphate buffer pH 6.8 (n=3)

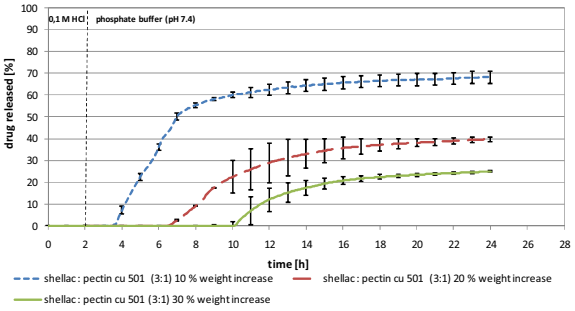

Fig. 13 Drug release of tablets coated with shellac:pectin CU501 (3:1) in phosphate buffer (pH 7.4) after two hours exposure in 0.1 M HCl (n=2)

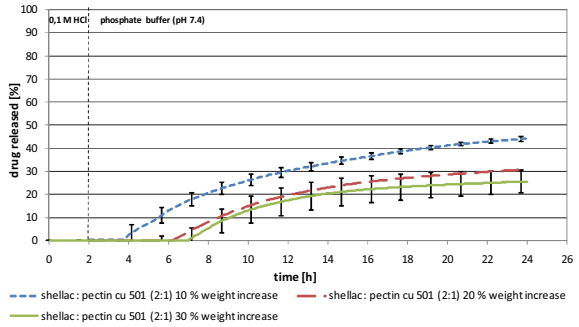

Fig. 14 Drug release of tablets coated with shellac:pectin CU501 (2:1) in phosphate buffer pH 7.4 after two hours exposure in 0.1 M HCl (n=1-2)

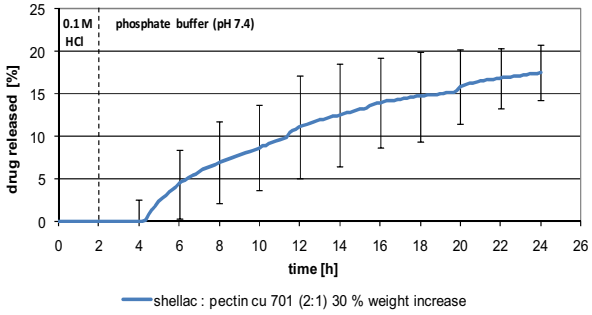

Fig. 15 Drug release of tablets coated with shellac:pectin CU701 (2:1) 30% in 0.1 M HCl and phosphate buffer pH 7.4 (n=2)

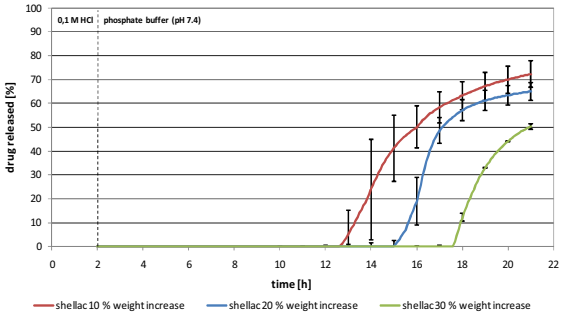

Fig. 16 Drug release of tablets coated with pure shellac in phosphate buffer pH 7.4 after two hours exposure in 0.1 M HCl (n=2)

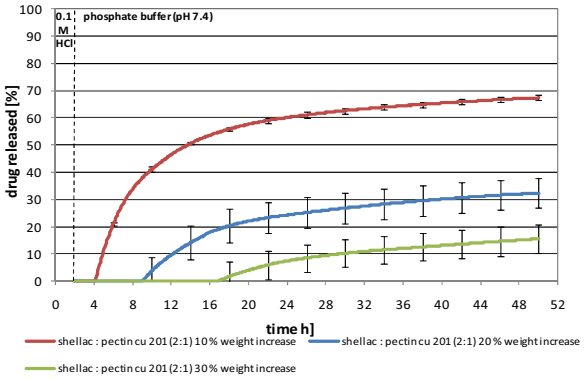

Fig. 17 Drug release of tablets coated with shellac:pectin CU201 (2:1) in 0.1 M HCl and phosphate buffer pH 7.4 (n=2)

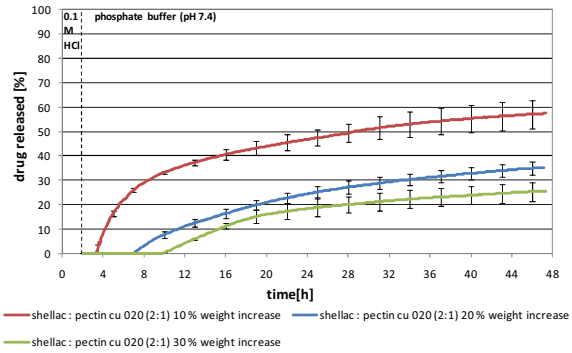

Fig. 18 Drug release of tablets coated with shellac:pectin CU020 (2:1) in 0.1 M HCl and phosphate buffer pH (n=2)

TABLE VI
SUMMARY OF FITTING RESULTS BY MATHEMATICAL MODELS HIXSON-CROWELL AND KORSMEYER–PEPPAS

Formulation		Hixson-Crowell			Korsmeyer-Peppas			
		R^2	K_β ($h^{-1/3}$)	t_{lag}(h)	R^2	k	n (h^{-n})	t_{lag}(h)
Pure shellac	10%	0.993	1054.84	13.6	0.997	2.548	0.58	13.2
	20%	0.992	1248.07	15.7	0.992	4.892	0.50	15.6
	30%	0.993	726.92	17.9	0.997	3.898	0.49	17.9
S:CU 501 3:1	10%	0.924	421.67	3.9	0.983	3.692	0.49	4.3
	20%	0.987	89.37	7.6	0.990	5.282	0.30	7.7
	30%	0.994	26.28	10.5	0.991	4.465	0.26	11.0
S:CU 501 2:1	10%	0.987	68.73	5.4	0.995	2.677	0.40	5.1
	20%	0.989	27.49	7.8	0.993	2.172	0.39	7.2
	30%	0.991	16.77	7.9	0.992	2.688	0.33	7.7
S:CU 201 2:1	10%	0.951	175.23	4.4	0.992	6.107	0.33	5.0
	20%	0.993	18.38	10.1	0.994	3.106	0.30	10.8
	30%	0.990	2.12	18.5	0.999	0.494	0.46	17.8
S:CU 020 2:1	10%	0.994	95.78	3.9	0.996	5.860	0.30	3.9
	20%	0.983	20.57	9.1	0.997	0.977	0.47	8.4
	30%	0.992	9.68	11.8	0.995	1.477	0.38	11.6
S:CU 701 2:1	30%	0.975	5.10	5.5	0.998	0.451	0.52	4.8

S = Shellac
R^2= correlation coefficient

The highest delayed release was received with tablets coated with pure shellac (Fig. 16). The lagtime can be increased up to 17.9 h if pure shellac at 30% weight increase was applied. The total amount of drug release was however higher than that with the mixture of shellac and pectins. This confirmed the hypothesis that methylene blue cannot release from the tablets coated with the mixture because the model drug adsorbed at the films prepared from formulations containing pectins. Shellac alone was not suitable to be used as colon delivery because the delayed release was very high (at 10% weight increase, lagtime ~ 13h).

Pectin CU201 has a higher degree of esterification (70%) and therefore can affect the delayed release. This was also demonstrated by application of pectin CU201 as matrix formation [14]-[16]. The optimal mixture between shellac and pectin CU201 at 2:1 e.g. at 15% weight increase will cause a colon delivery system (Fig. 17). It is however necessary to be careful to make use of a higher polymer amount because the release may delay too much.

The highest sustained release can be received by the mixture of shellac and pectin CU020 (Fig. 18). This pectin has amidation in the structure. The sustained release can reach 48h, which showed the release of model drug lower than 40% at 20% weight increase.

The Hixson-Crowell model [12] is mostly suitable for the globular shape dosage form. f_t is the drug released fraction at the release time t, K_β is the Hixson-Crowell-constant. Another mathematic model to describe release profiles is Korsmeyer-Peppas [11], with M_t/M_∞ for drug released fraction at release time t. k is a constant corresponding to the kinetic characteristic of drug/polymer system and n is the release exponent, which is influenced by the drug release mechanism and shape of the tablet. Harland et al. [13] modified the Korsmeyer-Peppas-Model to implicate lagtime t_{lag}. Table VI shows the summary of the fitting results by the two mathematical models. It's seems that the suitable mathematical model for our coated tablets is the modified Korsmeyer-Peppas-Model because the R^2 was higher (almost 0.99) than that from Hixson-Crowell. This may be also due to the form of the tablets, which was cylindrical and not globular.

IV. CONCLUSION

It is possible to develop new coating materials based on biopolymers i.e. shellac and pectins. The suitable ratio of shellac and pectin seems to be 2:1. The morphology of the films was smoother than that at 3:1. The drug release of 2:1 was more sustainable than that at 3:1. Every formulations were resistant against gastric fluid except the mixture of S:CU701 at 2:1 and 10-20% weight gain. The release rate was reduced if the film thickness increased. The highest sustained release was reached by the mixture of S:CU020 at 2:1. This may be because of the amidation of the pectin polymer. The pure shellac can give the highest delayed release with the lagtime up to 17.9 h. The modification of the release profile in the slope, lagtime and the duration can be performed by an addition of pectin and by varying the coating amount. The new coating formulation can be used for delayed release, sustained release, colon delivery, or enteric release. The suitable formulation must be respectively chosen. The release profile can be better fitted by the kinetic model of modified Korsmeyer-Peppas.

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