Control Release Effects of Binders Used in Pills of Traditional Chinese Medicine Herbs

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This research investigated the effects of control release of binders that are used in the pills of Chinese herbal medicine, namely, as processed honey, starch paste, beeswax, or mixtures thereof. Aspirin and baicalin were used as the active pharmaceutical ingredients (API). The processed honey was heated to 110 °C, 120 °C, or 130 °C. In these pills, the binders were the only excipients. The pills were prepared by the stir method using a mixer at 80 °C without pressure. The differential thermal analysis (DTA) showed that the melting points of aspirin and baicalin were changed by the binders. The Fourier Transform infrared spectra (FT-IR) of aspirin and baicalin suggest that there are different non-covalent molecular interactions between the API and the binders, such as C–H–π and hydrogen bond interaction. The dissolution profiles indicate that changing the ratio of the binders altered the patterns of dissolution of the API; thus, this ration may be used to control the release of API from the pills.

Key words traditional pill; control release; binder; honey; paste; beeswax

Control release techniques have been developed over during recent decades in pharmaceutical science, and there are still many problems in finding the all-pervading formulation for applying to most of the APIs. But, no one attended to has investigated the fact that the concept of control release had already mentioned was known and used by pharmacists in ancient China. In Chinese medicine, binders have been used in the pills to prolong the release of ingredients of the crude drug for treating chronic disorders; moreover, the pasted pills or waxed pills are especially used to prolong the release of toxic ingredients of the crude drug, *e.g.*, croton, nuxvomica, pinellia tuber, *etc.*[1,2)]

The most common manufactured dosage form of Chinese medicine herbs' products is honeyed pills, which are prepared on a large scale with mechanical equipments. There are many obstacles in the pharmaceutical industry to manufacture other solid dosage form for the herbs, such as tablets, capsules, granules *etc.*, because the products may contain a large quantity of natural herbs fiber. The excipients of the Traditional Chinese herbal pills have only one main excipient, the binder; and, they are classified into honeyed pills, pasted pills, and waxed pills according to the binder used.[3)] From the literatures of Chinese medicine and the properties of binders, these binders of the pills may be assumed to possessing the effects of control release of API. Today, few pills are prepared for using pure compounds as the active pharmaceutical ingredients (API) with mechanical equipment on large scale; moreover, almost no one pay any attention to uses the very ancient dosage forms for control release of the pure API; even though the preparation is not really more complex or higher cost than other solid dosage forms. In fact, the cost is lower, the operation is simpler, and it may be used to control the release of special APIs.

This research investigates the effect of using based on the facts of honeyed pills, pasted pills, and waxed pills as the products of Chinese herb medicine, using the binders of processed honey, starch paste, beeswax, and the mixtures of processed honey and beeswax in different ratios as binders to prepare the pills of the model drug aspirin and baicalin for the control release of API. The pills were prepared without pressure and other procedures factors, and no other excipients were used in order to insure that the results would directly reflect the reliability of control release effects of the binders. The effect of the binders and the states of model API aspirin and baicalin in the pills were speculated on determined by using differential thermal analysis (DTA) and Fourier transform infrared spectra (FT-IR). The release of aspirin and baicalin were evaluated according to the rules of dissolution test described in the pharmacopoeia of U.S.A.

Experimental

Materials Honey was purchased from Comvita New Zealand Ltd., New Zealand (Raw Multi Flora Honey, Raw New Zealand Honey). Soluble starch was purchased from Uni-Chem (UNI-CHEM®). Beeswax was refined yellow beeswax, purchased from Acros Organics. Aspirin (acetyl salicylic acid, 99%) was purchased from International Laboratory, U.S.A. Baicalin (baicalein-7-glucuronide) was obtained from YiKang Biotech Ltd. SiChuan, China. All other substances used were of analytical grade.

Preparation of Pills (1) Honeyed Pills: Honey was processed to evaporate moisture by heating to 110, 120 or 130 °C for primary processed honey (PPH), secondary processed honey (SPH), and tertiary processed honey (TPH), respectively.

The processed honeys were weighed and warmed to 80 °C, then equal quantities of the API (W/W) were added. The mixtures were stirred until uniform, then kneaded into gobbets. Finally, each gobbet was cut into 200 mg bits, and the bits were rolled into spherical form using a coating pan at 30 rpm.

(2) Pasted Pills: Soluble starch was added to water at a ratio of 1 : 4 (w/w). The suspension was then heated and stirred to pregelatinize the starch, forming a semitransparent paste. Then the API was added, mixed at 80 °C until uniform and kneaded into a gobbet. Finally, the gobbets were cut into bits, each containing within 100 mg API, and rolled into spherical form using a coating pan at 30 rpm.

(3) Waxed Pills: The yellow beeswax was warmed to 80 °C. When melted, the API was added, mixed until uniform and kneaded into a gobbet. Finally, the gobbets were cut into bits, each containing within 100 mg API, and rolled into spherical form using a coating pan at 30 rpm.

(4) Tertiary Processed Honey (TPH)-Waxed Pills: TPH and the beeswax were mixed in different ratios (W/W), and warmed to 80 °C. Due to the physical properties of honey and wax, uniformity in the mixtures requires stirring enough; thus, when melted, the API was added and stirred continuously as the mixtures were cooled to room temperature, each mixtures was; then, kneaded to a uniform gobbet; gobbets were cut into bits within 100 mg API, and bits were rolled into spherical form using a coating pan at 30 rpm.

The ratios of the pure binders to the API were different because of the properties of the binders and the APIs (Table 1).

Characterization Tests for the Pills (1) Dissolution Test: The API released from the pills was measured using a VanKel Total Solution-VK7025 dissolution tester (Varian Technologies Asia Ltd., Taiwan Branch).

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USP apparatus II (paddle) at 37±0.5 °C and 100 rpm. The API concentration was measured using a UV spectrophotometer Model Cary 50 Tablet UV-Visible system (Varian Technologies Asia Ltd., Taiwan Branch), at 295 nm for aspirin and at 276 nm for baicalin. The media used were purified water and 2nd fluid (pH 6.8). The 2nd fluid was prepared according to the Japanese Pharmacopoeia[4] by adding 250 ml of 0.2 mol/l potassium dihydrogenphosphate test solution and 118 ml of 0.2 mol/l sodium hydroxide test solution and water to make 1000 ml.

For each formulation and condition, dissolution rates of six individual pills were determined, and the means and standard deviation values were calculated.

(2) Fourier Transform Infrared Spectra (FT-IR): Infrared spectra of prepared pills and component samples dispersed in KBr were recorded on a FT-IR spectrometer (Spectrum One, Perkin-Elmer Inc., CT, U.S.A.). Spectra from 4000 to 700 cm^{-1} were collected in the reflectance mode, with resolution of 4 cm^{-1}, and the instrument's software was used to express the or dinate as absorbance.

(3) Differential Thermal Analysis (DTA): Differential thermal and thermogravimetric analysis were performed with an automatic thermal analyzer system (Thermogravimetric/Differential Thermal Analyzer, Pyris Diamond TG/DTA, Perkin Elmer instruments/Seiko Instruments Inc.). All samples were examined at a scanning rate of 5 °C/min, from 30 °C to 250 °C.

(4) Disintegration Test: The DST-3 disintegration tester (Logan Instruments Corp.; 19C School House Rd., Somerset. NJ 08873) is the apparatus used to determine the resistance or disintegration time of the pills. The media used were purified water for testing the aspirin pills and 2nd fluid (pH 6.8) for testing the baicalin pills. The 2nd fluid was prepared according to the Japanese Pharmacopoeia; and, the test procedure was strictly according to the Japanese Phrmacopoeia.[4] However, for investigating the relationship between the disintegration and the dissolution, the auxiliary disk were not used even the pills did not disintegrate.

Table 1. The Compositions (mg) of Each Honeyed or Pasted or Waxed Pill of Aspirin or Baicalin (with Binder Only)

	(TPH) Honeyed pills of		Pasted pills of		Waxed pills of	
	Aspirin	Baicalin	Aspirin	Baicalin	Aspirin	Baicalin
Binders	50	100	100	55	70	100
Drugs	100	100	100	100	100	100

The moisture content of TPH and paste are 10% and 80%, respectively.

Results and Discussion

Effects of the Binders on the Release of API Honey, paste, and beeswax are the typical binders used in Chinese herbal medicine pills, and they show different characteristic of release (Figs. 1, 2).

The honeyed pills of aspirin and baicalin were prepared only with the processed honeys and the API. The honeyed pills of aspirin and baicalin were the fastest pills to release

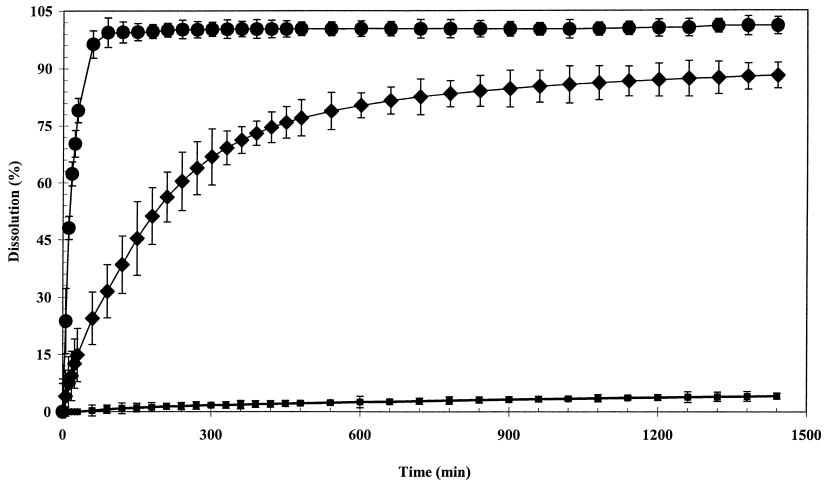

Fig. 1. The Dissolution Profiles of Aspirin in TPH Honeyed Pills (—●—), Pasted Pills (—◆—) and Waxed Pills (—■—)
The experiments represent mean±standard deviation of six independent pills (n=6).

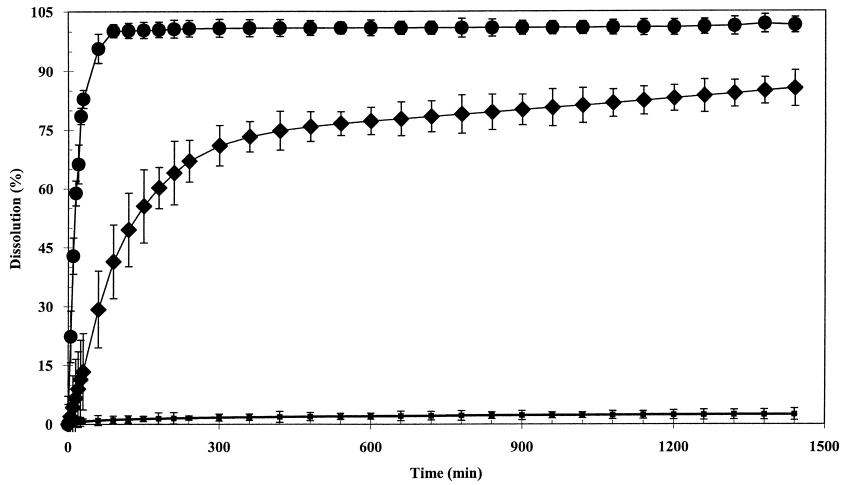

Fig. 2. The Dissolution Profiles of Baicalin in TPH Honeyed Pills (—●—), Pasted Pills (—◆—) and Waxed Pills (—■—)
The experiments represent mean±standard deviation of six independent pills (n=6).

the API. Starch paste also use as a binder in pasted pills of Chinese medicinal material. The main component of the paste is dextrin, which dissolves slowly in water under 40 °C but easily dissolves in boiling water. In 37 °C dissolution medium (*i.e.*, human body temperature), the pasted pills release aspirin and baicalin more slowly than did the honeyed pills; indeed, after as long as to 24 h, 10% API had not yet been released from the pasted pills. Therefore, abundant paste will form matrix, and the release of API must depend on the dissolution or degradation of the component of paste. In Chinese medicine, the beeswax is particularly use as a binder to prepare pills with toxic Chinese medicinal material, *e.g.*, the cinnabar, common threewingnut root. The dissolution test results indicate that the waxed pills release very little aspirin and baicalin into the water or buffer solution within 24 h. Beeswax demonstrates the property of holding the API in its matrix.

Effect of the Binders on the API Properties Table 2 shows the moisture contents, densities, and viscosities of processed honey (PPH, SPH, TPH), paste, and beeswax.

Honey is a mixed natural product. The constituents of honey are invert sugar (62—80%), sucrose (0 to 8%), and dextrin (0.26 to 7%). In contemporary Western pharmacy, honey is usually used as a sweetening agent[5]; but, in Chinese herbal medicine, honey is the most common binder used for manufacturing herbal pills. To be used in pills, the honey must be processed by heating to evaporate moisture; it is heated 110 °C, 120 °C or 130 °C to prepare the primary processed honey (PPH), secondary processed honey (SPH), and tertiary processed honey (TPH), respectively.

Table 2. The Properties of the Processed Honeys, Paste, and Beeswax

	PPH	SPH	TPH	Paste	Beeswax
Moisture content (%)	20	15	10	80	0
Density (g/ml, 80 °C)	1.35	1.38	1.41	1.13	0.94
Viscosity (cps, 80 °C)	686	7834	49216	121	23

The main component of the paste is dextrin. It dissolves in cold water (under 40 °C) very slowly, but dissolves in boiling water easily. The viscosity and density of the paste are much lower than processed honeys, but the moisture is 4—8 fold higher.

Yellow beeswax has the lowest viscosity and density, and the fewest excipients, of three binders. The physical properties of beeswax affect the dissolution of the API strongest. Essentially beeswax do not dissolve in water and 2nd fluid, and the very excellent ductility of beeswax is propitious to form the matrix sustaining the release and prolonging the dissolution of API.

The characteristic changes of honey during processing were investigated. Viscosity increases following heat processing because of dehydration. The IR spectra (Fig. 3) of honey should be mainly the superposed spectra of glucose and fructose because the predominant components of honey are invert sugar (an equimolecular mixture of glucose and fructose). Changes were observable in the region of 3800—3200 cm^{-1} corresponding to the absorption of the stretching vibrations hydroxyl groups and 1200—1150 cm^{-1} corresponding to the absorption of the stretching vibrations of C–O in carbohydrates. The density ratios between the bands at 3400 cm^{-1} were calculated with special positions at 2935 cm^{-1}, which corresponds to absorption of C–H, as reference baseline. The ratio value increase following the temperature and time of process suggests an increase in the number of hydroxyl groups *vis-a-vis* ethylene groups in differentiated processed honey because the water molecules also have a very broad absorption from 3800 cm^{-1} to 2700 cm^{-1}. Thus, the density ratio will increase following the processing of honey. The DTA curve (Fig. 4) of the honeys shows that TPH—the 130 °C processed honey—has almost no response following the increase of temperature, indicating that almost all of the moisture in the honey evaporated during processing. Comparing PPH, SPH, and TPH, the main

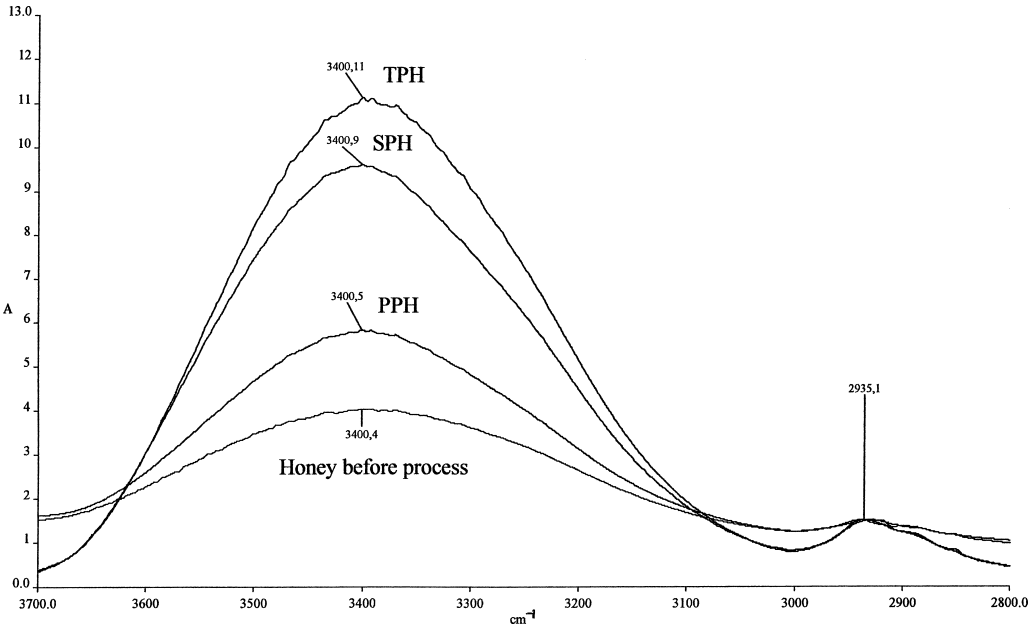

Fig. 3. The IR Spectra of TPH, SPH, PPH and the Honey before Process

The illuminations gradation of the peaks are arranged according to the peak intensity.

change in physical properties is increase in viscosity. This increase prolonged the dissolution of API slightly (Figs. 5, 6). That is, the dissolution profiles show that PPH pills release the API a little faster than the SPH pills, and the TPH pills are slowest in releasing to release the API. Nevertheless, after 60 min, the API had been almost totally released from all of the honeyed pills. Therefore, honeyed pills (composed of only processed honey) do not prolong API release because even the highest viscosity TPH dissolves into water and buffer solutions quickly; and within the range of the solubility of API, these honeyed pills release 100% of API in less than 60 min.

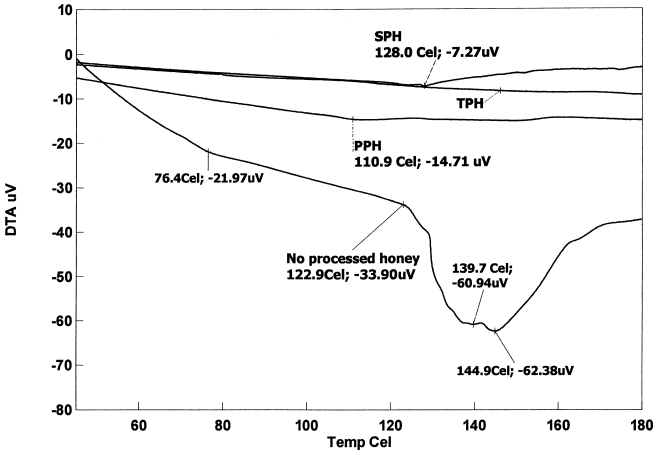

Fig. 4. The DTA Curves of TPH, SPH, PPH and the Honey before Process

The IR spectra of aspirin and baicalin were taken before and after they were prepared as the honeyed, pasted, and waxed pills (Figs. 7, 8).

The specific peaks in the IR spectra of aspirin are 1753 cm^{-1} (ester carbonyl), 1692 cm^{-1} (acid carbonyl); and 1605 cm^{-1} (aromatic C=C), 1575 cm^{-1} (aromatic C=C connected to the non-covalent electron pair directly), and 1458 cm^{-1} (aromatic C=C). The IR spectra of aspirin and its pills overlapped and were normalized on the basis of ring C=C band (1605 cm^{-1}). The aspirin pills IR data suggest that molecular interaction may occur between aspirin and the main component of honey and paste. The ratio of the intensity at 1754 and 1692 cm^{-1} (the carbonyl absorption) to at 1605 cm^{-1} (the aromatic ring absorption) are increased by the processed honey—TPH, in the pills. Therefore, honey

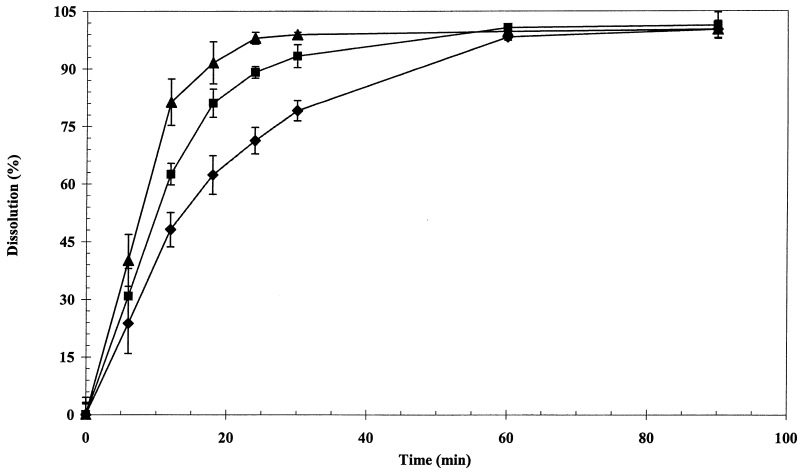

Fig. 5. The Dissolution Profiles of Aspirin from TPH (—◆—), SPH (—■—) and PPH (—▲—) Honeyed Pills
The experiments represent mean±standard deviation of six independent pills (n=6).

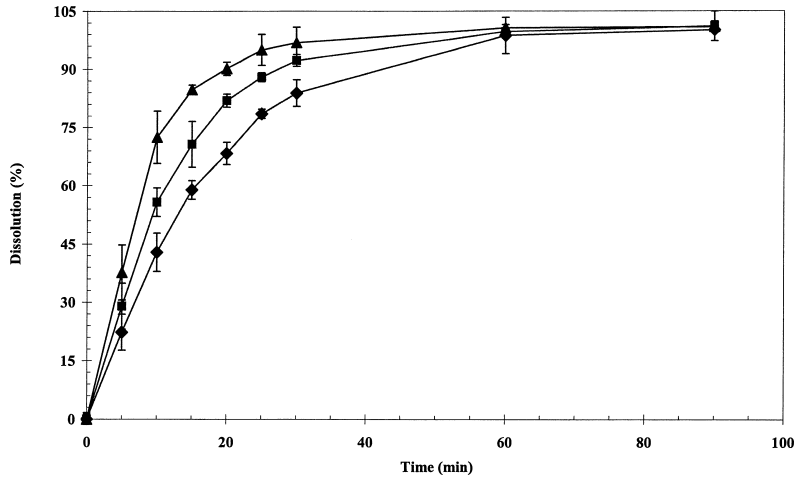

Fig. 6. The Dissolution Profiles of Baicalin from TPH (—◆—), SPH (—■—) and PPH (—▲—) Honeyed Pills
The experiments represent mean±standard deviation of six independent pills (n=6).

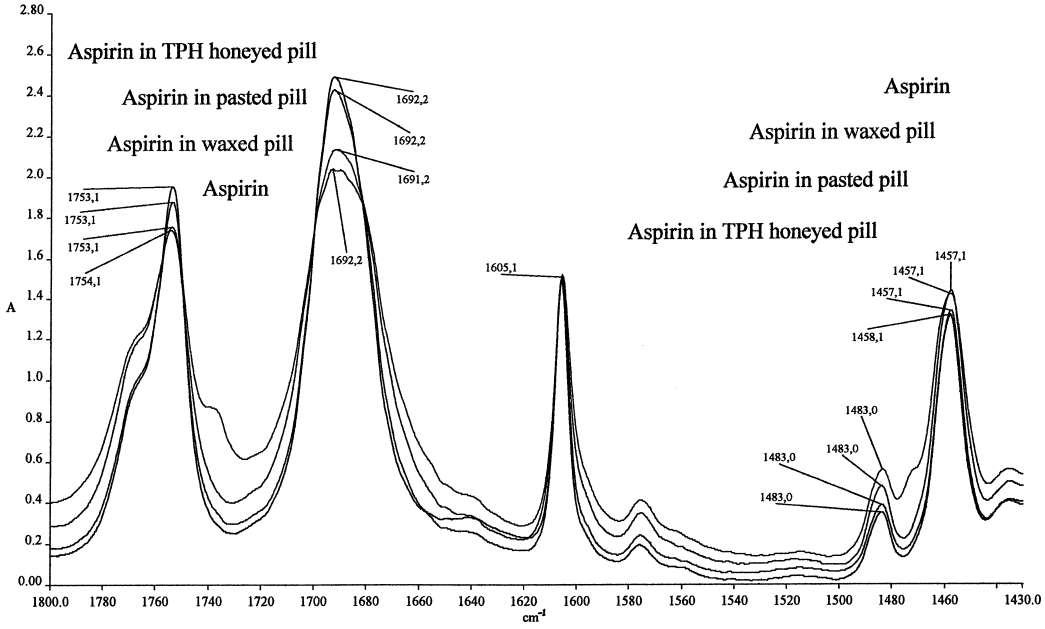

Fig. 7. The IR Spectra of Aspirin and Its Pills

The illuminations gradation of the peaks are arranged according to the peak intensity.

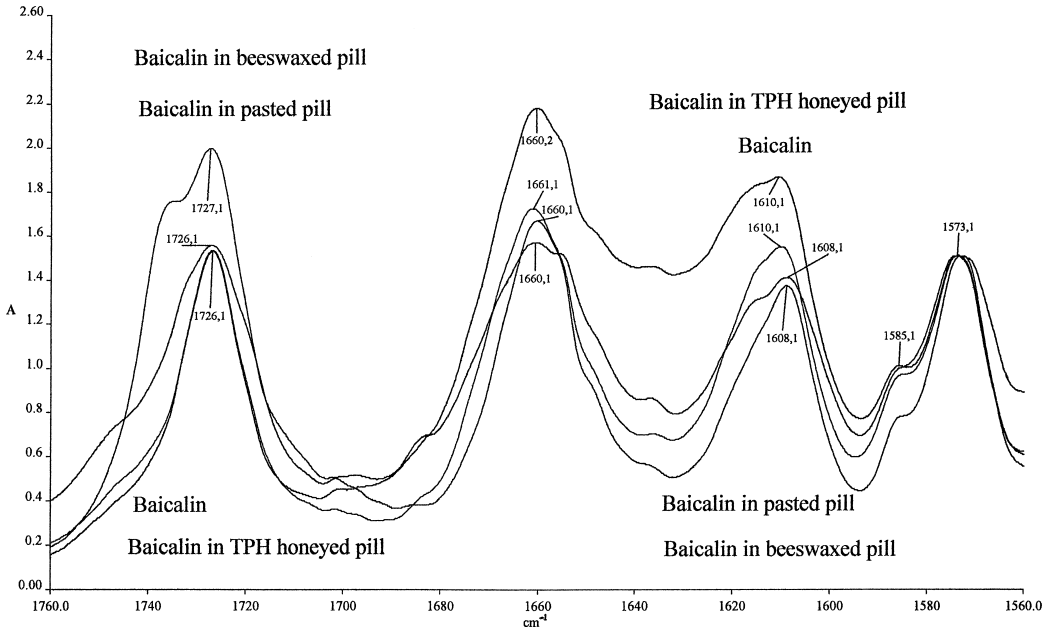

Fig. 8. The IR Spectra of Baicalin and Its Pills.

The illuminations gradation of the peaks are arranged according to the peak intensity.

and paste can be ratiocinated to interact on carbonyl of acid party because the consideration of the molecular structures of the main component of the binders and the intensity of IR absorption increased along with the polarity of the carbonyl group in the molecular.[6] On the other hand, beeswax may interact with the aromatic C=C connected to the non-covalent electron pair directly because at 1575 cm^{-1} the absorption of the aromatic C=C of aspirin in the waxed pills is stronger than the absorption of the pure aspirin. The IR also suggest that the paste and beeswax interact with aspirin in a way similar to how they interact with honey. The absorption bands of pure aspirin's acid carbonyl group bifurcate at 1692 and 1687 cm^{-1}; after preparation as pills, the bifurcations disappear. This suggests that aspirin's crystal lattice did not exist as integrally in pills as it did in the pure state.

The specific peaks in the IR spectra of baicalin are 1726 cm^{-1} (aglycone carbonyl), 1661 cm^{-1} (glucuronide carbonyl); and 1608 cm^{-1} (aromatic C=C), 1573 cm^{-1} (aromatic C=C connected to the non-covalent electron pair directly). The IR spectra of baicalin and its pills overlapped and were normalized on the basis of band of C=C of aromatic connected to non-covalent electron pair directly (1573 cm^{-1}). The IR data suggest that honey and paste interact with the carbonyl of the glucuronide of baicalin; for both TPH and paste pills, the absorption at 1661 cm^{-1} decrease, and an appeared shoulder at 1654 cm^{-1}, that means the

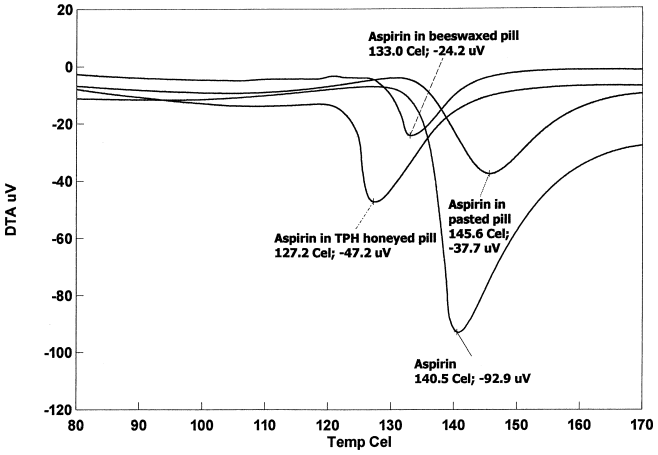

Fig. 9. The DTA Curves of Aspirin and Its Pills

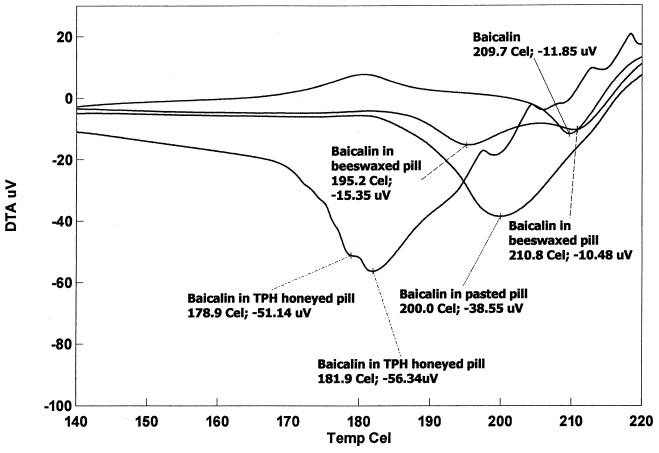

Fig. 10. The DTA Curves of Baicalin and Its Pills

Table 3. The Compositions (mg) of TPH-Waxed Pill of Aspirin or Baicalin

Ratio (w/w)	TPH/beeswax=8/1		TPH/beeswax=4/1		TPH/beeswax=2/1		TPH/beeswax=1/1	
	Aspirin	Baicalin	Aspirin	Baicalin	Aspirin	Baicalin	Aspirin	Baicalin
Binders	100	100	100	100	100	100	100	100
Drugs	100	100	100	100	100	100	100	100

honey and paste decreased the polarity of the acid carbonyl group. When baicalin was prepared as a beeswax pill, the IR absorption band of aglycone carbonyl of baicalin, which normally appears around 1726 cm^{-1} appeared at 1735 cm^{-1}. This suggests that beeswax interact with the carbonyl group in the aglycone of baicalin, increasing its polarity.

DTA curves (Figs. 9, 10) of aspirin and baicalin were taken before and after preparation as honeyed, pasted, and waxed pills. The DTA curves indicate that honey and beeswax decrease the melting points of aspirin and baicalin. In contrast, paste decreases the melting point of baicalin from 209.7 to 200.0 °C, but increases the melting point of aspirin from 140.5 to 146.6 °C. These phenomena may be because the melting points of beeswax and honey are lower than aspirin and baicalin, but the melting point of dextrin, the main component of paste, is about 178 °C, between the melting point of aspirin (145.6 °C) and baicalin (209.7 °C). The IR and DTA results validate honey, paste and beeswax as the binders of pills, affecting the properties of API in the pills by molecular interaction; thereby, the properties of the binders can determine the release of API from the pills to dissolve into the dissolution test mediums.

Aforementioned discussion explained the mechanisms of processed honey do not prolong API release because it dissolves in the dissolution test mediums. Paste dissolves and/or disperses into the mediums slower than the processed honey, and it prolong the release of API. Beeswax do not dissolve into the mediums, nor disperse into the medium, it forms a very stable matrix for API, and almost do not release the API. The IR and DTA results validate honey, paste and beeswax as binders of pills. In all three cases, interaction between the binders and the API affect release of the API into test mediums. So, it is assumed that the mixed binders may control the release the API.

The Application of the Binders on the Control Release Effects The previous discussion explained the mechanisms of how processed honey function that is, as paste and beeswax as the binders—excipients affecting the release of API from pills. In addition, the binders themselves may be mixed to control the release of the API. Considering the difference of the moisture content and the solubility of processed honey paste and beeswax, the TPH were chosen as the honey to be used in preparing pills made of honey and beeswax. The ratio of TPH to beeswax and the API used for preparing the TPH-waxed pills are in show Table 3.

The dissolution profiles of the pills show that mixing beeswax and TPH in different ratio can be used to control the release of the API. Figures 11 and 12 indicate there is similarity in the way dissolution aspirin dissolves in water and baicalin dissolves into 2nd solution of the pharmacopeia when the ratio of TPH to beeswax changed. However, the dissolution of baicalin in the 2nd solution is a little faster than the dissolution of aspirin in the water. So, even though the release of API from the pills depends on the solubility and dissolving speeds of the API and on the properties of the dissolution mediums, THP and the beeswax can be used to control the release of API.

The Relationship between Disintegration and Dissolution The disintegration tests of the pills show that the disintegration time of honeyed pills are all less than 10 min regardless of the honey as the binder is TPH, SPH or PPH and the API is aspirin or baicalin. Contrastively, the aspirin pasted pills disintegrate less than 15 min, and the baicalin pasted pills disintegrate between 55 to 65 min. However, the waxed pills and do not disintegrate. On the other hand, there is no difference between the aspirin and baicalin TPH-waxed pills, while the disintegration time is prolonged with the increase of the beeswax in the pills; the times are 35—45 and 55—65 min corresponding to the ratios of TPH honey to the

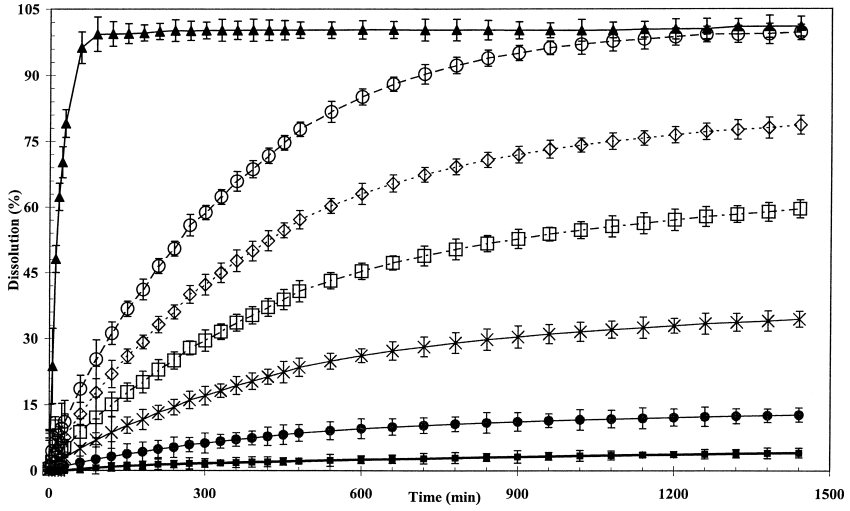

Fig. 11. The Dissolution Profiles of Aspirin TPH-Waxed Pills

The ratios of the TPH honey to the beeswax: TPH honeyed pills (—▲—), TPH honey/beeswax=8 (—○—), TPH honey/beeswax=4 (—◇—), TPH honey/beeswax=3 (—□—), TPH honey/beeswax=2 (—×—), TPH honey/beeswax=1 (—●—), beeswaxed pills (—■—); the experiments represent mean±standard deviation of six independent pills (n=6).

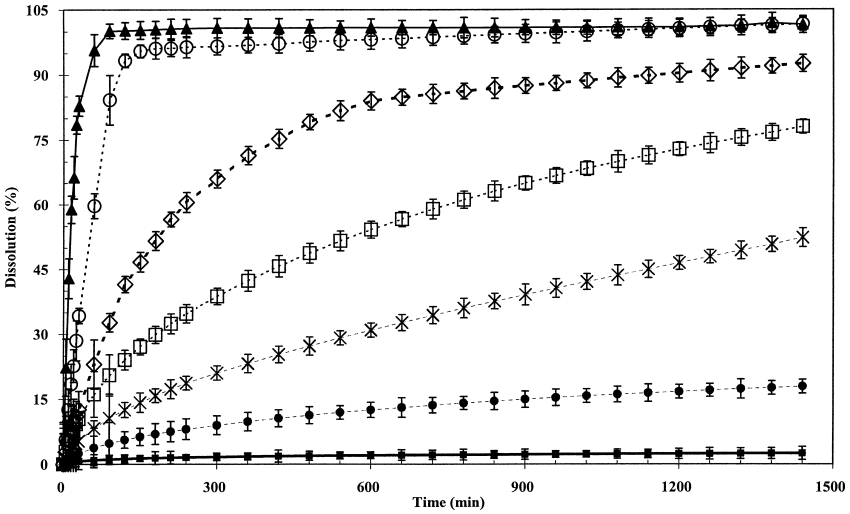

Fig. 12. The Dissolution Profiles of Baicalin TPH-Waxed Pills, Which Ratios of the TPH Honey to the Beeswax Are Different as the Legends

The ratios of the TPH honey to the beeswax: TPH honeyed pills (—▲—), TPH honey/beeswax=8 (—○—), TPH honey/beeswax=4 (—◇—), TPH honey/beeswax=3 (—□—), TPH honey/beeswax=2 (—×—), TPH honey/beeswax=1 (—●—), beeswaxed pills (—■—); the experiments represent mean±standard deviation of six independent pills (n=6).

beeswax 8 and 4; and when the ratio are 3, 2 and 1, the TPH-waxed pills do not disintegrate. The results of the disintegration test and the dissolution test show that the dissolution of the APIs from the pills somewhat related to the disintegration; the dissolution may be faster following the disintegration faster; but, the relationship cannot be described in continuous function.

Conclusion

Processed honey, paste, and beeswax as binders are the only excipients used in the preparation of traditional Chinese herbal medicine pills. The type of binder can be used to control the pure API release because there is a very weak molecular interaction between binder and API. Preparing the traditional pills of Chinese medicine is a very simple manufacturing process, usually with only one (or two) excipients. Thus, this research provides a clue to approach the simplest formulation and the easiest manufacture process for control release pharmaceutical products in the range of API's solubility. Moreover, honey, paste, and beeswax are all of the natural products, using these binders not only contribute to the control release of solid dosage form for oral administration, but may also ameliorate the relationship of pharmaceutical industry and natural environment, save the energy in pharmaceutical manufacture, and reduce the cost of pharmaceutical production.

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