Journal of the Serbian Chemical Society
JSCS@tmf.bg.ac.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *89* (4) 521–537 (2024)
JSCS–5737
Original scientific paper
Published 15 April 2024

Thermoanalytical and spectroscopic studies on medicated jellies with perphenazine

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(Received 2 April, revised 1 July, accepted 10 October 2023)

Abstract: Medicated jellies are widely used by a large part of patients, especially by people with swallowing difficulties. Preformulation studies play an essential role in the development of new pharmaceutical formulations. The present study aimed to formulate and evaluate medicated jellies containing perphenazine, an antipsychotic drug from the group of phenothiazine compounds used to treat schizophrenia and other mental disorders. Typical gelling agents such as sodium alginate (Alg), gelatine (Gel), and pectin (Pec) were used to develop the medicated jellies. In addition to the biopolymers, components such as benzoic acid (BenzAc), citric acid (CitAc), sodium citrate (NaCit), sorbitol (Sorb) and xylitol (Xyl) were also used. Before preparing the jellies, the moist binary mixture between each component of the jelly and the active substance was analysed to investigate the compatibility of the substances. The active substance, moist binary mixture, and medicated jellies were analysed by FTIR_UATR spectroscopy, UV–Vis spectroscopy and thermogravimetry.

Keywords: antipsychotic drug; pharmaceutical formulations; thermal properties; biocompatible polymers; biopolymers; gelling agents.

INTRODUCTION

Oral medicated jellies (OMJs) are appreciated by a large part of the population, especially by people with swallowing difficulties. These pharmaceutical formulations are used in psychiatry and for patients with Parkinson's, motion sickness and multiple sclerosis.[1] Commercial oral medicated jelly products of donepezil hydrochloride and alendronate are available in some countries.[2] Dysphasia (difficulty swallowing) has been reported to be common in all age groups, especially in children, geriatric patients, standardized patients, psychiatric patients, and patients with nausea, vomiting and motion sickness. Dysphasia is com-

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https://doi.org/10.2298/JSC230402077B

mon in all age groups and is observed in approximately 35 % of the general population, up to 60 % of the elderly institutionalized people and 18–22 % of all patients in long-term care facilities. OMJs with good taste and flavour increase the acceptability of bitter medications in different populations.[3] Children prefer jelly when administering medications compared to oral liquids or tablets. Nowadays, jelly candies are popular among children because they like to chew the jelly and can use it as an alternative to solid and liquid dosage forms as a preferred method of drug administration. Medicated jelly can be used for the local treatment of oral cavity ailments and also for the treatment of systemic diseases. Medications with an unpleasant taste, such as erythromycin, paracetamol, aspirin, ibuprofen, antacids, minerals, and vitamin preparations, can be formulated as soft, chewable dosage forms.

According to the USP, medicated jellies are found under the name of chewable gels. Chewing gels are used to deliver drugs or dietary supplement ingredients orally. Chewable gels may consist of any or all of the following: gelling agents, sugars, water, sweeteners and flavourings. The sweeteners and flavouring agents are intended to increase consumer acceptance and mask the taste of the drug or dietary supplement being administered. Chewable gels maintain their shape, are elastic and yield when chewed. They are intended to be chewed before swallowing. Chewable gels are also known as "gummies" in the confectionery and dietary supplement industries, but this term is not used in official article titles.[4]

Chewable dosage forms are more convenient when administering medications for dysphagia patients and offer easier handling compared to liquid and powder formulations. The chewable formulation has a high drug delivery capacity and requires a smaller amount of super-disintegrants. The soft chewable system's esthetic appearance and pleasant taste easily attract children.[5]

Oral medicated jellies, developed as early as the 20th century, remain popular with consumers and continue to be commercially produced.

According to the 17th edition of the Japanese Pharmacopeia, jellies are specific, non-flowable preparations in gelatinous form with a particular size and shape intended for oral administration. Jellies can be defined as transparent or translucent, non-greasy, semi-solid preparations designed for both external and internal use. There are three types of jellies: medicated jelly, lubricating jelly, and other miscellaneous jelly.[3]

Phenothiazines are a group of drugs used in the treatment of mental illness.[6] Perphenazine (Per, 4-[3-(2-chlorophenothiazin-10-yl)propyl]-1-piperazineethanol, Fig. 1)[7] is an antipsychotic drug from the group of phenothiazine compounds used in the treatment of schizophrenia and other mental disorders.[8]

The bioavailability of drugs depends on the physicochemical properties, dosage form, metabolites, various enzymes, restriction by the intestinal barrier and glycoproteins.[9]

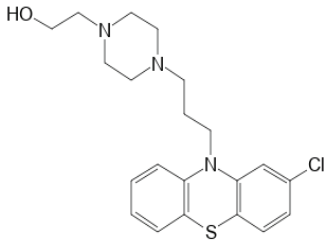

Fig. 1. Chemical structure of Per.

According to the literature, Per's systemic availability appears variable and poor via the oral route.[10,11] Several studies have investigated different oral dosage forms with Per, such as disintegrating tablets, to overcome this disadvantage of low bioavailability.[12]

OMJs have gained acceptance as a drug delivery system and were included in the 16th edition of the Japanese Pharmacopeia, in 2011, as a type of dosage form.[13] These pharmaceutical formulations improve the bioavailability of the drug and provide a much earlier onset of action.[14] Other advantages include ease of administration for psychiatric patients and pleasant taste.[5] In addition, numerous studies have been conducted on OMJs to improve the bioavailability of some active pharmaceutical ingredients.[15,16]

The polymers used in manufacturing are inexpensive, safe, environmentally friendly, biodegradable, biocompatible, locally available, and well tolerated by patients.[17]

Preformulation studies play an essential role in the development of new pharmaceutical formulations. The study of compatibility between the active pharmaceutical ingredient and excipients is a fundamental part of the preformulation data. Chemical and physical interactions between the active ingredient and excipients can influence stability, bioavailability, and therapeutic safety. Thermal analysis such as thermogravimetry, differential thermal analysis, or differential scanning calorimetry is usually used in the physicochemical characterization of pharmaceutical materials. Complementary methods such as FTIR, UV–Vis and others are often used to study pharmaceutical formulations.[18]

Our study aims to develop and characterize a new pharmaceutical formulation containing Per. For this purpose, we use common natural polymers such as sodium alginate (Alg), gelatin (Gel) and pectin (Pec), which can be easily administered to patients with dysphagia, people with esophageal problems, children or psychiatric patients. In addition, we use a fast and accurate method to select the optimal excipients and the best jelly base for a stable medicated jelly. Alg is a biomaterial with several properties that make it helpful in formulation aid, especially in polymeric-controlled drug delivery.[19] Gel is traditionally used to prepare jellies and also serves as a gelling ingredient in vitamin capsules or other pharmaceutical preparations.[20,21] Pec is a natural polymer recognized as a viscosity-

-enhancing agent, approved by the United States Food and Drug Administration, and is officially in the United States Pharmacopeia.[22]

In addition to the biopolymers, components such as the preservative benzoic acid (BenzAc), stabilizers such as citric acid (CitAc) and sodium citrate (NaCit), and sweeteners such as sorbitol (Sorb) and xylitol (Xyl) were also used.

The compatibility between the active ingredient and each component used in the jelly bases was investigated on a moist 1:1 binary mixture using FTIR spectroscopy and thermal analysis, TG/DTG/HF.

To investigate the possible interactions, the processes of jelly synthesis were followed. For this purpose, active substances' solubilization and recrystallization were carried out to investigate the changes during the jelly synthesis. Therefore, we will highlight the Per in the moist binary mixture and medicated jellies.

This paper presents the thermal and spectroscopic analysis results of Per, moist binary mixtures and OMJs. The presence of the active ingredient in these pharmaceutical formulations was also confirmed by UV–Vis analysis.

EXPERIMENTAL

The active substance perphenazine Per (SA, see Fig. 1) was received from Stada Hemofarm Timisoara, Romania; alginic acid sodium salt powder (Alg) from Sigma–Aldrich, Lot# MKCN7477, product of Norway; gelatine (Gel) from Sigma–Aldrich, CAS Number 9000-70-8; pectin (Pec) from Sigma–Aldrich, lot# BCCD1493, product of China; benzoic acid (BenzAc) from Sigma–Aldrich, CAS Number 65-85-0; citric acid (CitAc) from Merck, K93661307 743; xylitol (Xyl), Ref: M-1290, Lot: 75499, Denmark; sorbitol (Sorb) Sigma–Aldrich, CAS Number 50-70-4; sodium citrate (NaCit) from Merck, AM1005848 647.

The binary physical mixtures with Per and the components used in the jelly bases consisted of equal masses of Per and each component. They were prepared by mixing the two substances in an agate mortar with a pestle for a few minutes, moistened by about 5 %, and then dried to 50 °C. The mass ratio of 1:1 was chosen to maximize the probability of observing the interactions between the components studied.

Preparation of medicated jellies

The 40 g/L polymers for Pec and Gel were dissolved in purified water and heated to approximately 50–60 °C. After complete solubilization of the gelling agent, BenzAc, CitAc, and sweeteners was added, the solution was stirred for 30 min, and NaCit was added. The resulting solution was stirred for another 10 min after complete solubilization of all ingredients, resulting in the jelly base. For Alg-based jelly, a prepared alginate solution of 1 % was used (Table S-I of the Supplementary material to this paper). Ingredients were calculated on the basis mass %.

The active substance was dissolved in ethanol and mixed with the jelly base in a 1:4 ratio. The solution was stirred for 10 min and then transferred to a matrix.

Pec-based jelly and Gel-based jelly were stored in air at room temperature for 24 h and then stored in polyethylene bags for analysis. Alg-based jelly was stored in air at room temperature for 48 h and then stored in polyethylene bags for analysis.

Formulations with a relatively high composition of Per were chosen to highlight the thermal behaviour of the active substance and, thus, the possible interactions with the components present in the jelly bases.

The ingredients of the formulated jellies were selected considering their use in the literature and previous studies conducted by our research group in other research as follows: BenzAc is recognized in the literature as a preservative[23] while NaCit and CitAc are recognized as stabilizers and where reported previously in the literature as proper ingredients for medicated jellies with ambroxol,[24] cyproheptadine HCl[25] preparation being recommended as ingredients for oral drug delivery platforms in pediatrics.[3]

Methods

FTIR_UATR spectra. FTIR_UATR spectroscopy data were collected using a Perkin Elmer Spectrum 100 instrument and employing the universal attenuated total reflectance (U--ATR) technique. Data were collected after eight consecutive recordings at a resolution of 4 cm^{-1} on the spectral range 4000–650 cm^{-1}.

Thermogravimetric analysis. The thermal behaviour was determined using an aluminium crucible on TG/DTA Diamond thermal analyser produced by Perkin Elmer. Analyses were performed in a dynamic air atmosphere (synthetic air 5.0 Linde Gas with flow 100 $mL \cdot min^{-1}$) at a heating rate, β = 10 $°C \cdot min^{-1}$, in the temperature range of 30–500 °C for Per and temperature range 30–400 °C for moist binary mixtures and medicated jellies. All analysed samples had a mass between 8 and 12 mg.

UV–Vis spectrophotometry. UV–Vis spectra were measured with the T90 + UV–Vis spectrophotometer with a double beam in the photometric range of 190–900 nm. All absorbance measurements were performed in a 10 mm UV–Vis spectroscopy cell at room temperature, using distilled water as a blank. They were executed for the standard active ingredient and medicated jellies. The studies were performed for qualitative purposes. The presence of Per in medicated jellies was detected by UV–Vis spectrophotometric method. The concentration of the standards was 5 mg/mL. The amount used for the jellies was chosen to retain about 0.1 mg/mL of the active ingredient. Since the active substance is soluble in ethyl alcohol and the jelly is not soluble in alcohol, the solutions used for UV–Vis analysis were prepared by the following procedure: The active substance was dissolved in alcohol, and the solution was then diluted with water. The ratio of alcohol: water was 1:2, and for the jellies, the initial solubilization of the jellies were performed in water, and the solution was supplemented with alcohol to achieve the same ratio of alcohol: to water as in the case of Per.

Physical examination

The medicinal jellies were examined for their appearance, texture, consistency, transparency and gumminess, as described in the literature.[26]

Stickiness and grittiness

Formulated jellies were examined in terms of the stickiness and grittiness by mildly rubbing the jelly between fingers.[27]

RESULTS AND DISCUSSION

FTIR_UATR study – FTIR_UATR spectra of the active substance

The spectroscopic study of the initial active substance Per (SA) and the recrystallized active substance Per (D) was performed to highlight the active substance's characteristic bands. Therefore, these spectra are used for comparison with the spectra of moist binary mixtures and with the spectra of medicinal jellies based on Alg, Gel and Pec to investigate the compatibility between the com-

pounds. To observe the changes of the active compound in the phase of jelly synthesis, it was moistened with 5 % water and then dried. The spectra of Per (SA) and Per (D) are shown in Fig. S-1 of the Supplementary material.

The spectrum of Per (SA) and Per (D) shows an absorption band at 3440 cm^{-1} corresponding to the stretching vibration of the bond OH. At the same time, other sharp bands at 1455, 1564 and 1590 cm^{-1} (specific bands for aromatic stretching of C=C bond), bands at 2877 and 2938 cm^{-1} (specific stretching of C–C bond due to CH_2 group), the bands at 2800 cm^{-1} (specific C–H stretching due to a CH_2–N group), the vibrations in the range 1200–1000 cm^{-1} (specific to the C–N stretching of the tertiary amine) and the band at 755 cm^{-1} indicating the C–Cl stretching are highlighted.

From a spectral point of view, it should be noted that solubilization and subsequent drying of the active substance do not lead to changes in the spectrum of Per (D). Thus, all bands are seen equally in both spectra.

FTIR_UATR study of binary mixtures–active substances: Jellies components

The FTIR_UATR study for the moist binary mixtures was performed to observe possible interactions between the active substance and the components of medicated jellies. It was investigated if there are relevant shifts and if there are specific peaks for the active substance. In addition, the presence of –Cl, which attached to the phenothiazine ring enhances the antipsychotic activity,[28] is investigated.

In the case of the moist binary mixture Per_Xyl, Fig. 2, most of the peaks characteristic of the active substance are highlighted so that the bond OH is present through the peak at 3422 cm^{-1}. The bands specific for the stretching of the C–C bond of the CH_2 group are observed at 2943 cm^{-1} at higher wavelengths than in the case of the pure active substance. The specific bands for the C–H stretching of the CH_2N group at 2875 cm^{-1} were also highlighted, as in the case of the pure active substance. The specific bands for the stretching of the C=C bond in aromatic compounds are at 1455 and 1565 cm^{-1}. The tertiary amine is argued by the presence of bands from 1200–1000 cm^{-1}. The band specific for the bond with halogen is also at the same wavelength as in the active substance at 745 cm^{-1}, with a small shift. So, we can say that the active substance is present in this mixture.

The FTIR spectrum of the moist binary mixture of Per_Sorb shows several characteristic bands in the range 3400–2400 cm^{-1}, which are hidden or absent. One can observe the specific bands for the stretching of the C–C bond of the CH_2 group at 2985, 2970 and 2932 cm^{-1}. The specific bands for the C–H stretching of the CH_2N group are also not visible. The specific bands for stretching of the C=C bond in aromatic compounds are found at 1415 and 1564 cm^{-1}. Tertiary amine is argued by the presence of bands in the range 1200–1000 cm^{-1}, and C–Cl specific

band is also not visible. Thus, it can be said that the active ingredient is not completely visible in the FTIR spectrum of the mixture.

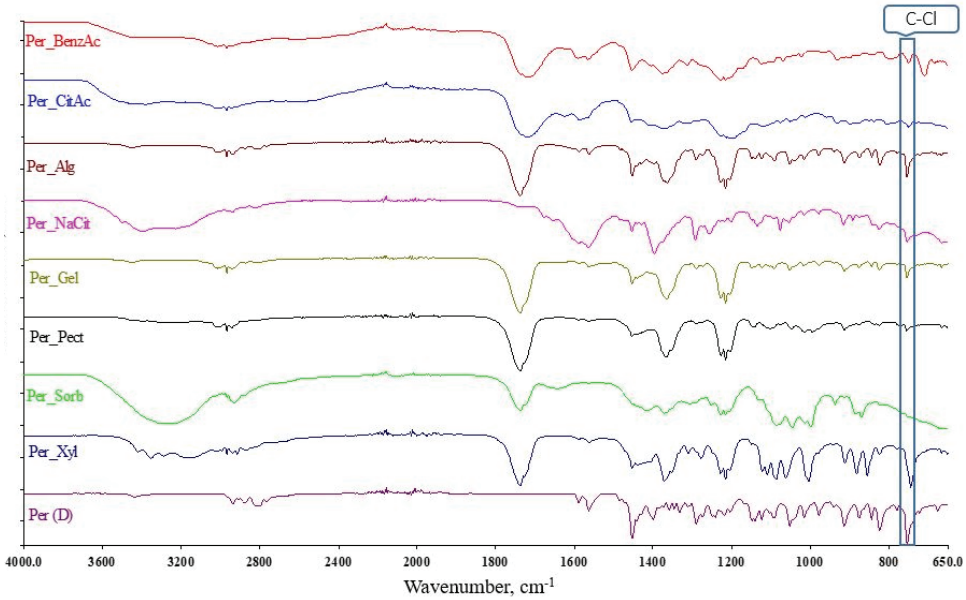

Fig. 2. FTIR spectra for Per (D) compared to binary mixtures of the active substance with the components used in jellies synthesis (1:1) for the spectral region 4000–650 cm^{-1}.

For the moist binary mixture obtained for Per_Pec, the following peaks characteristic of the active substance were highlighted, such as the peak at 3255 cm^{-1} for the bond OH, but much less highlighted. The specific bands of the C–C bond stretching of the CH_2 group appeared at 2944 cm^{-1}. The specific bands for the C–H stretching of the CH_2N group at 2830 cm^{-1} were also highlighted, as in the case of the pure active substance. The specific bands for the stretching of the C=C bond in aromatic compounds are at 1454 and 1565 cm^{-1}. The presence of a tertiary amine is confirmed by the bands in the range 1200–1000 cm^{-1}. The C–Cl specific band is also at the same wavelength as in the active substance at 755 cm^{-1}. We can thus say that the active compound is present in this mixture.

The FTIR spectrum of the moist binary mixture Per_Gel also contains most of the important bands of the active substance, so the presence of the bond OH can be observed by the vibration at 3454 cm^{-1}. The C–C bond by vibrations at 2943 and 2970 cm^{-1}, the characteristic bands of C–H stretching of the CH_2N group at 2823 cm^{-1}, and the aromatic C=C bond at 1454 and 1565 cm^{-1}. Tertiary amine is also present at the same wavelengths as in the case of the active substance. C–Cl bond at 755 cm^{-1} as in the case of the pure substance. Thus, this mixture also contains an intact active substance.

FTIR analysis of the moist binary mixture Per_NaCit shows the specific vibration of the bond OH at 3400 cm^{-1}, which corresponds to the stretching vibration of the bond OH. At the same time, other bands specific for the stretching of the C–C bond of the CH_2 group were highlighted at 2941 cm^{-1}, at shorter wavelengths than in the case of the pure active substance. The bands specific for the C–H stretching of the CH_2N group at 2825 cm^{-1} were also highlighted. Tertiary amine is confirmed by the presence of bands at 1295, 1258 and 1055 cm^{-1}. The specific band for the bond with the halogen is also present at the same wavelength as in the active substance at 755 cm^{-1}. At the same time, other sharp bands were highlighted at 1455 and 1565 cm^{-1} (specific bands for the aromatic stretching of the C=C bond).

Alg, like Gel, does not interact with the active substance in the binary mixture. It shows all the characteristic bands in the FTIR spectrum of the mixture, namely the bond OH (3445 cm^{-1}), C–C bond (2876, 2822 cm^{-1}), C=C bond (1590, 1564 and 1454 cm^{-1}), C–H bond (2942 cm^{-1}), tertiary amine (1200–1000 cm^{-1}) and C–Cl bond (755 cm^{-1}). Thus, it can be said that Alg can be used as a jelly base to deliver active ingredient.

In the case of the moist binary mixture Per_CitAc, it is observed that some characteristic bands in the range 3400–2400 cm^{-1} are hidden or absent in the spectrum of the binary mixture. The vibration of the bond OH is further observed at a lower wavelength, namely at 3400 cm^{-1}. The specific bands for the stretching of the C–C bond of the CH_2 group are at 2970 and 2942 cm^{-1}. The specific bands for the C–H stretching of the CH_2N group at 2876 and 2823 cm^{-1}, which are slightly changed compared to the pure active substance, were also highlighted. The specific bands for the stretching of the C=C bond in aromatic compounds are found at 1454 and 1588 cm^{-1}. The presence of a tertiary amine is proved by the bands in the range of 1200–1000 cm^{-1}. The specific C–Cl band is also at the same wavelength as in the active substance at 750 cm^{-1}. Thus, we can say that the active substance is present in this mixture.

The FTIR spectrum of the binary mixture Per_BenzAc shows that some characteristic bands in the range 3400–2400 cm^{-1} are hidden or absent, as in the case of the Per_CitAc mixture. The vibration of the bond OH can still be observed at a lower wavelength, 3387 cm^{-1}. The specific bands for the stretching of the C–C bond of the CH_2 group are at 2970 and 2946 cm^{-1}. The specific bands for the stretching of the C=C bond in aromatic compounds are at 1455 and 1566 cm^{-1}. The tertiary amine is present through the bands in the range 1200–1000 cm^{-1}. The specific C–Cl band is also present at the same wavelength as in the active substance at 751 cm^{-1}.

FTIR_UATR study of synthesized jellies

Since in the composition of jellies, the amount of active ingredient is much lower, namely the ratio of the solid mass of the jelly base: as in the mass of the

active ingredient it is 1:4, we expect that the active ingredient will not be as visible in the FTIR spectrum of medicated jellies, Fig. 3. It will be looked for the representative bands, namely the group OH, which is undoubtedly covered by the water spectrum, the C–C, C=C and C–H bonds, and the C–Cl bond. The tertiary amine will also be followed in the spectra.

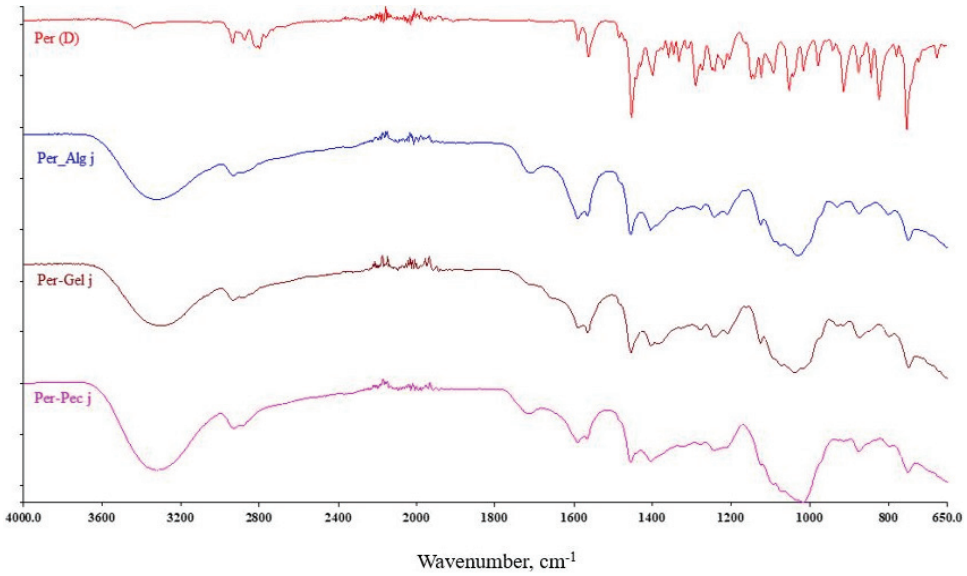

Fig. 3. FTIR spectra for Per (D) and jellies based on Alg, Gel and Pec.

The FTIR spectra of the Alg, Gel and Pec–based jellies are very similar, highlighting the specific bands of the C–C and C–H bonds. Thus, the bands are present at 2930, 1566 and 1455 cm^{-1}. The tertiary amine is also present in the 1200–1000 cm^{-1} range, and the C–Cl bond is visible through the vibrations at 750 cm^{-1}. The same intense bands as in the case of the active substance or the binary mixtures are not visible, but this is justified by the composition of the active substance of the jellies.

Thus, the active ingredient is completely present in the jellies. Although some jelly components have raised question marks, the final jellies suggest that they can be used to administer Per.

Thermal analysis – Thermogravimetric study of the recrystallized active substance

The recrystallized active substance Per (D) and the initial active substance Per (SA) have the same thermal behaviour. The present paper shows the thermoanalytical curves obtained in the case of Per (D), Fig. 4, because this is used as a benchmark. The thermogravimetric study allows us to justify the presence of the

active substance in the jellies and to identify possible interactions with the components of the jellies. To determine the thermal behaviour of the active substance, the analysis was performed in the temperature range of 30–500 °C. To determine the possible interactions in moist binary mixtures and medicated jellies, the thermal behaviour was determined in the temperature range of 30–400 °C. Above this temperature, no significant processes take place, and the last process of the active substance is not completed at the end of the temperature range of the analysis.

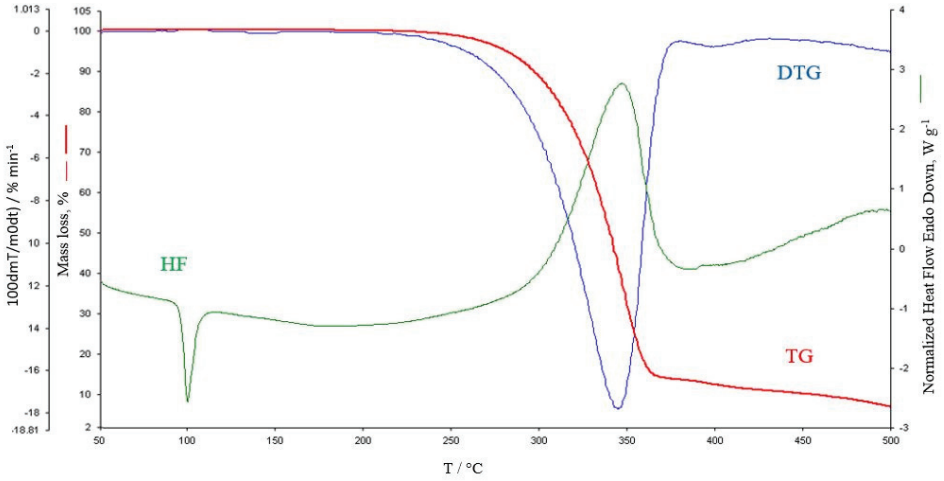

Fig. 4. Thermoanalytical curves obtained for active substance – Per (D), obtained at a heating rate of 10 °C min^{-1} – 500°C in air atmosphere.

Thermal analysis of the recrystallized active substance was carried out in the range of 50–500 °C with a heating rate of 10 °C/min in the dynamic atmosphere of synthetic air. Analysing the TG and DTG curves, it was found that two decomposition processes occur in the studied temperature range, namely the first process in the range 230–373 °C, where a continuous loss of 85.42 % of the mass of the sample occurs. This process is accompanied by an exothermic process with a maximum of 347 °C and a ΔH = –796.33 J/g. The last process is not yet completed at 500 °C and is accompanied by an exothermic process. On the curve HF, a small endothermic process can be seen at 100.23 °C, which can be attributed to the melting of the active substance.

Thermal analysis of Per binary mixtures with the components used in the synthesis of three types of jellies

Regarding the thermal behaviour of the binary mixture Per_Sorb, the active substance;s primary decomposition process partially overlaps with Sorb's primary decomposition process. However, it can still be argued that the first decom-

position of **Per** occurs considering the enthalpy associated with this process in a narrower correlation with that of the active substance, Fig. 5.

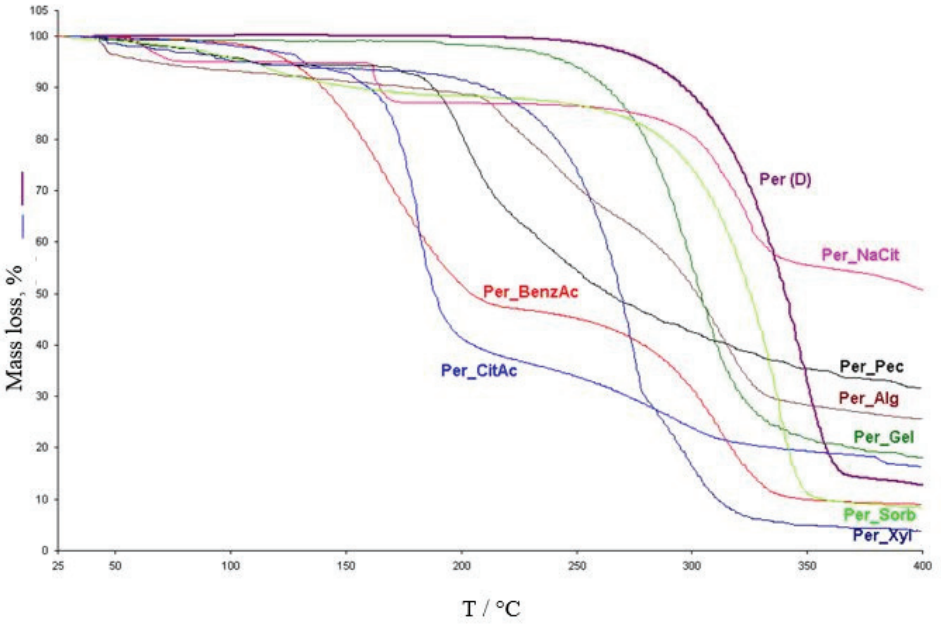

Fig. 5. TG curves obtained for Pec (D) and the moist binary mixture obtained at a heating rate of 10 °C min^{-1} – 400 °C.

The thermogravimetric study of the binary mixture Per_BenzAc reveals the main decomposition processes of the two components of the mixture. Thus, it is found that the decomposition process of BenzAc takes place before the degradation of the active ingredient. The degradation of Per takes place in the range of 220–330 ℃. It is accompanied by an exothermic process, Fig. 6,with a mass loss of about 40 % of the sample's total mass, closely correlated with the amount of the active substance in the mixture and the mass loss of pure active ingredient.

The binary mixture Per_Pec does not show the thermal behaviour of the active substance within the mixture, which would lead us to the idea of a thermally induced interaction between the two components. We will correlate these data with those from spectroscopic investigations.

In the air atmosphere, the thermal analysis carried out on the binary mixture Per_Gel shows the decomposition of the active substance in the same decomposition interval as that of Gel. The integrity of the active substance is also demonstrated by the melting process's presence with a maximum of 100 ℃. The total mass loss of the mixture correlates closely with the masses and mass losses

of the components of the binary mixture. Therefore, the fact that Gel can be used in medicated jellies can be supported.

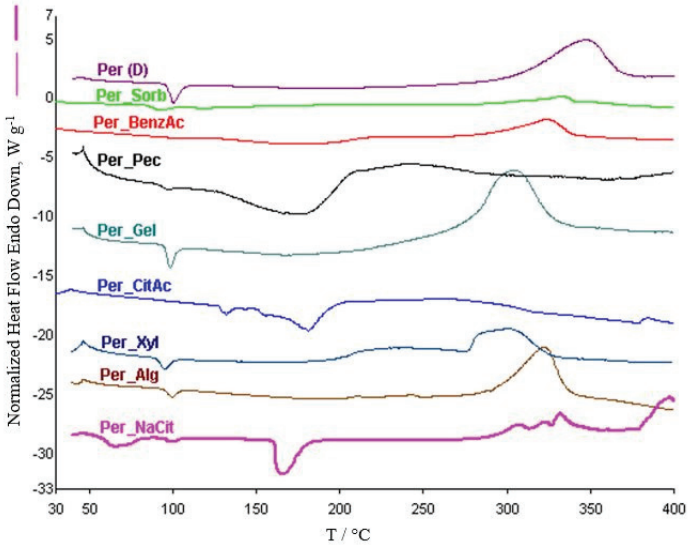

Fig. 6. Heat flow (HF) curves obtained for Per (D) and the moist binary mixture obtained at a heating rate of 10 °C min^{-1} – 400 °C in air atmosphere.

In the case of the binary mixture Per_CitAc, the thermal behaviour of the active substance is hardly visible. A decomposition process is observed in the range of 210–331 °C, similar to the range highlighted in the active substance. Still, it does not closely correlate with the amount of active substance in the mixture. These results do not clearly indicate whether or not the active substance interacted with CitAc, which is known for its properties. The thermogravimetric data must be correlated with the spectroscopic data or the data obtained after dosing the active substance.

The thermal analysis of the binary mixture Per_Xyl shows a destabilization of the active substance in the mixture. It can be observed that the main decomposition process starts faster at a temperature of 50 °C than in the thermal analysis of the pure active substance. The melting point of the active substance is seen on the HF curve at 95 °C, which can be explained by the fact that it is present in a mixture.

The case of the moist binary mixture Per_Alg is an example of a thermal analysis that argues the absence of interactions between the two components of the mixture. Thus, the thermal behaviour of the two components can be observed as they exhibit decomposition stages at different temperatures. On the HF curve of the mixture, even the melting point of the active ingredient can be seen at 100 °C, indicating that the Alg does not prevent the crystallization of the active sub-

stance. The main decomposition process of Per is observed in the same temperature range, and the mass loss is closely correlated with its concentration in the mixture.

The thermogravimetric study of the binary mixture Per_NaCit showed several clearly separated stages of decomposition in the same temperature range. The first two processes, namely one in the range 39–82 °C with a mass loss of 4.86 % and the next in the range 157.4 and 182 °C with a mass loss of 7.69 %, can be attributed to moisture loss and, respectively, to the decomposition of NaCit. The last two stages are due to the decomposition of the active substance, which occurs in the same interval as in the thermal analysis of the individual component. The active substance accumulates a mass loss of 30 % of the mass of the mixture, which is in close correlation with the data obtained for the active substance.

Thermal analysis of jellies with an active substance

The thermal analysis of the Alg-based jelly with Per showed the thermal behaviour of the active ingredient in the same temperature range and with a weight that correlates closely with the primary degradation process of the active ingredient and the other components within the jelly, Fig. 7. The composition and thermal behaviour highlighted in the studies on the binary mixtures were considered.

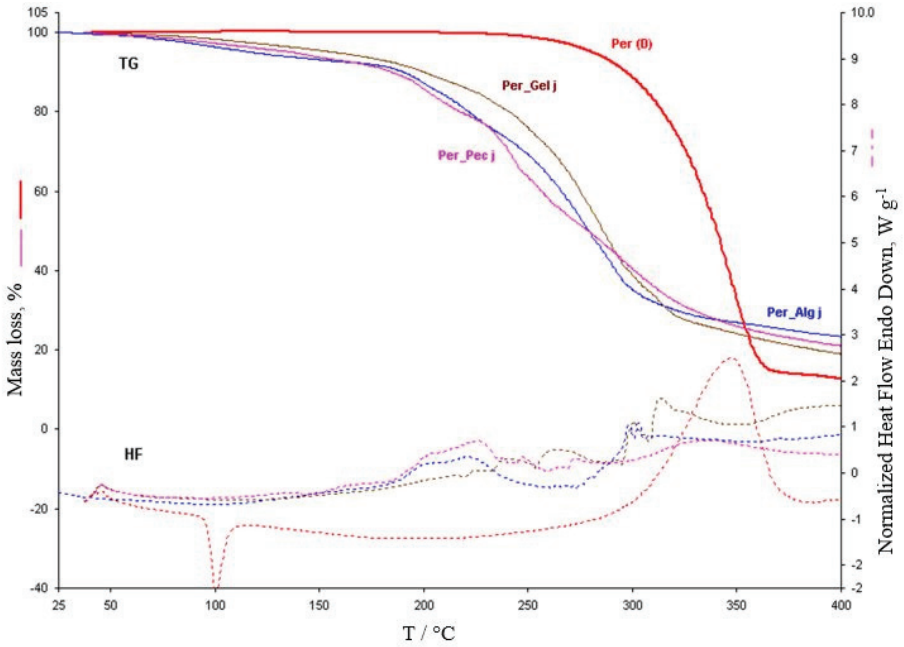

Fig. 7. Comparative of TG and HF for Pec (D) and medicated jellies based on Alg, Gel and Pec obtained at a heating rate of 10 °C min^{-1} – 400 °C.

In the case of Gel-based jelly, good agreement is observed with the thermogravimetric data obtained in the case of the binary mixture Per_Gel. Also, in the case of this jelly, it is observed that the Gel and the active substance have the main degradation process in the same temperature range, but it can be said that the mass loss is in close correlation with the degradation of the constituent components. In this case, more clear results will be obtained in the dissolution studies.

Thermal analysis of jelly based on Pec with active substance shows a variety of decomposition stages that are difficult to separate. The decomposition stage of the active substance is not visible on the thermogravimetric curve of the jelly. In the case of this jelly, confirmation of the presence of the active substance also requires dissolution studies or other UV–Vis spectroscopy studies. The conclusions are correlated with the FTIR spectroscopy studies.

UV–Vis spectrophotometry

All absorbance measurements were performed in a 10 mm UV–Vis spectroscopy cell at room temperature, using water as a blank. The standard active substance and medicated jellies were investigated. The concentration of the standards was 5 $mg \cdot mL^{-1}$, and the amount used for the jellies was chosen to retain approximately 0.1 $mg \cdot mL^{-1}$. The study conducted at UV–Vis considers a qualitative relevance at about 300 nm. The jellies based on Alg, Gel and Pec were analysed using UV–Vis.

The active substance Per (Fig. 8) is visible in all samples and has a maximum at 300 nm. After UV–Vis spectroscopy analysis, the active substance in the synthesized medicated jellies is found in all cases.

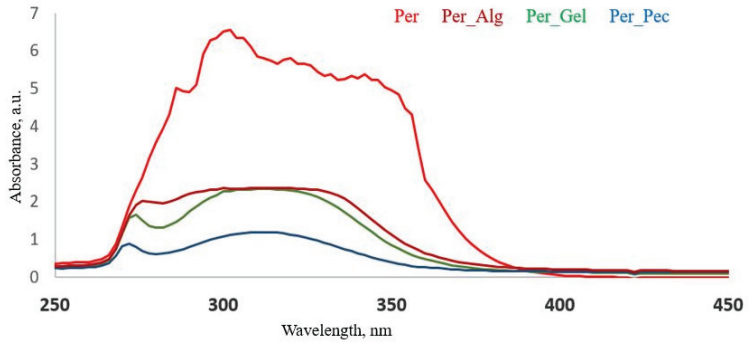

Fig. 8. The UV–Vis spectra for Per, Per-Alg, Per-Gel and Per-Pec, medicated jelly in the range 250–450 nm.

Physical examination

All medicinal jellies prepared presented a smooth texture, a clear appearance. Medicated jellies prepared with Pec and Alg presented a very thick consistency while jelly prepared with Gel presented a moderately thick consistency.

Stickiness and grittiness

The stickiness and grittiness of the jellies prepared with Pec and Alg were non-sticky and non-gritty, while the ones prepared with Gel were slightly sticky and non-gritty.

After thermal analysis, the rest of the prepared jellies were stored in polyethylene bags at room temperature to be re-examined after one and three months. In the physical examination after one month, no change in the jellies' appearance, texture, or stickiness and grittiness was observed. At the final three-month inspection, a slight change in the texture of the jellies prepared with Gel and increased stickiness was observed.

According to the literature, the protocol for stability testing may differ for the same product if it is to be distributed or marketed in other regions, such as in ASEAN regulations which belong to the hot and humid climate zone (zone IV).[29]

CONCLUSION

In this study, we presented spectroscopy and thermal analysis of Per, an antidepressant drug, moist binary mixtures, and medicated jellies based on the common gelling agents: alginate (Alg), pectin (Pec) and gelatin (Gel). Our work aimed to formulate and investigate new pharmaceutical formulations that can be more easily administered to patients with conditions that make other forms of a drug challenging to administer.

The FTIR spectra of the medicated jellies indicate that all components are compatible for use in the formulations.

The thermogravimetric study of a moist binary mixture shows that components such as BenzAc, Sorb, Xyl, NaCit, Gel and Alg are compatible with the active substance Per and CitAc, which should be used in small amounts. The results obtained for the moist binary mixtures also show that Pec can lead to possible interactions with the active ingredient Per.

Thermal analysis of the medicinal jellies with Per showed that the Alg-based jelly is the only jelly in which the contribution of the active substance is visible. In the other Gel and Pec-based jellies, the thermal analysis contains a variety of decomposition processes that are more difficult to separate, with overlapping decomposition stages, leading to the conclusion that only the thermogravimetric study does not allow definite conclusions.

Thus, by combining the FTIR and UV–Vis spectroscopy results with thermogravimetric analysis, it was possible to obtain motivated confirmations of the presence of the active substance in the studied medicated jellies.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12343, or from the corresponding author on request.

ИЗВОД

ТЕРМОАНАЛИТИЧКА И СПЕКТРОСКОПСКА ИСПИТИВАЊА МЕДИЦИНСКИХ ГЕЛОВА СА ПЕРФЕНАЗИНОМ

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Употреба медицинских гелова је широко распрострањена међу великим бројем пацијената, посебно оних са потешкоћама при гутању. Студије преформулација играју есенцијалну улогу у развоју нових фармацеутских формулација. Циљ овог испитивања је да се формулишу и оцене медицински гелови који садрже перфеназин, антипсихотични лек из групе фенотиазин једињења који се користи при лечењу шизофреније и других менталних поремећаја. Типични агенси за гелирање као што су натријум-алгинат (Alg), желатин (Gel) и пектин (Pec) су коришћени за развој медицинских гелова. Као додатак биополимерима, компоненте попут бензоеве киселине (BenzAc), лимунске киселине (CitAc), натријум-цитрата (NaCit), сорбитола (Sorb) и ксилитола (Xyl). Пре припреме гелова, влажне бинарне смеше сваке компоненте гела и активне супстанце су анализиране да би се испитала комаптибилност супстанци. Активна супстанца, влажна бинарна смеша, и медицински гелови су анализирани FTIR_UATR спектроскопијом, UV–Vis спектроскопијом и термогравиметријом (TGA).

(Примљено 2. априла, ревидирано 1. јула, прихваћено 10. октобра 2023)

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