FORMULATION AND CHARACTERISATION OF MUCOADHESIVE DENTAL APPLICATIONS CONTAINING BENZYDAMINE HYDROCHLORIDE

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Abstract

The aim of this research was to develop a bioadhesive film based on benzydamine hydrochloride incorporated into natural bioadhesive polymers with different quantities of chitosan and guar gum but utilising a plasticiser. The obtained gels were deaerated by sonification, formed and evaporated by hot air drying; then, the properties were evaluated. Guar gum had a great influence on mechanical properties of the films – dynamic viscosity, texture, elasticity, stretching robustness, swelling and blur time. The formulations were used to obtain mucoadhesive films containing 0.3% benzydamine hydrochloride; they were tested for the release of the model drug. The amount of chitosan added to the formulation reduced the quantity of released substance and slowed down the release. Fourier-transform infrared spectroscopy did not reveal the creation of new chemical structures. In conclusion, the ratio of chitosan to guar gum in the medium impacts the mechanical properties and release parameters of the drug. These findings should enable researchers to match the parameter values to receive the most beneficial therapeutic outcome.

Keywords: *chitosan, guar gum, benzydamine hydrochloride, mucoadhesive film, dressing, carries*

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1. Introduction

Due to the pain that they cause, inflammation of the oral cavity and the symptoms thereof – including ulcers, aphthous ulcers and oral thrush – constitute a major therapeutic problem. In recent years, researchers have focused on drug formulations that take advantage of the mucoadhesion phenomenon. Thanks to the new mucosal and local administration of antimicrobial, anti-inflammatory or local anaesthetic drugs, adverse effects can be prevented, and the drugs can be applied easily by patients and remain on the mucosa for a long time [1, 2].

Mucoadhesive systems in the form of small, thin and highly flexible films can provide comfort to patients and – due to their structure – limit the contact of the painful area with external factors, reducing the pain. The idea to create a natural, biodegradable film with proper physicochemical properties and a good level of mucoadhesion has inspired the concept of using chitosan as the main polymer of the hydrogel matrix in the presence of guar gum. Chitosan has adequate physicochemical properties, a good level of viscosity and it has been proven antibacterial and antifungal activity. Guar gum has good thickening and binding properties [3-5].

The aim of the study was to obtain an optimal qualitative and quantitative composition of the hydrogel film for the treatment of oral cavity inflammation as well as aphthous ulcers. Mucoadhesive dressings based on chitosan and guar gum could have significant advantages regarding drug application and accessibility to the affected area, prevent dilution of the drug dose by saliva, reduce rapid dilution of the swollen hydrogel and improve patient comfort. We incorporated benzydamine hydrochloride as a therapeutic substance with anti-inflammatory, analgesic and antimicrobial properties, on mucoadhesive carriers containing chitosan and guar gum in various quantitative ratios. The obtained dressings were tested with regard to their physicochemical properties and subjected to dissolution testing to distinguish the form of the drug with the best parameters [6, 7].

2. Materials and Methods

2.1. Materials

The study was performed with the use of benzydamine hydrochloride (BH), which was kindly to use by P.P.F. 'Fagron' S.A. (Poland). It incorporated into natural, highly purified high-molecular-weight chitosan, > 75% of which was 95% deacetylated and viscosity 800-2000 cP (Sigma-Aldrich); guar gum with viscosity 5000 cP (Sigma-Aldrich); and glacial acetic acid 99.5%-100.5% (United State Pharmacopeia, Food Chemical Codex, J.T. Baker, USA). We also used aqua purification according to to Farmakopea Polska XII (Poland). Other materials used in the study were of analytical grade.

2.2. Methods

2.2.1 Hydrogel Film Preparation Technology

Appropriate amounts of chitosan were dissolved in 1% acetic acid. Guar gum was dissolved in water. Benzydamine hydrochloride was dissolved in a specified amount of water. Polymer solutions were placed in the refrigerator for 24 h to enable complete dissolution and bulking of polymers. Subsequently, the drug solution and guar gum gel were added to the chitosan solution in batches, and then mixed at 40 rpm for 30 min until the components were completely combined. Then, an adequate amount of glycerol was added, and the mixing was continued for 10 min to obtain a homogenous gel.

A specific mass of the obtained gel was then poured into round moulds: 1 g for a mould with a 1.6-cm diameter and a surface area of approximately 2 cm^2 and 5 g for a mould with a 3.5-cm diameter and a surface area of 9.6 cm^2. They were then dried in an air dryer for 48 h at 45°. The films were 1.6 mm thick after drying.

Table 1. Qualitative and quantitative composition of hydrogel films

Formulation	Chitosan (%)	Guar gum (%)	Glycerol (%)	Benzydamine hydrochloride (%)
CH1+GG0.25+GL20+B	1.00	0.25	20	0.3
CH1+GG0.5+GL20+B	1.00	0.50	20	0.3
CH1+GG0.75+GL20+B	1.00	0.75	20	0.3
CH1+GG1+GL20+B	1.00	1.00	20	0.3
CH1.2+GG0.50+GL20+B	1.20	0.50	20	0.3

Note. In the first column, the number after each abbreviation indicates the per cent of that component in the film. Abbreviations: CH, chitosan; GG, guar gum; GL, glycerol; B, benzydamine hydrochloride.

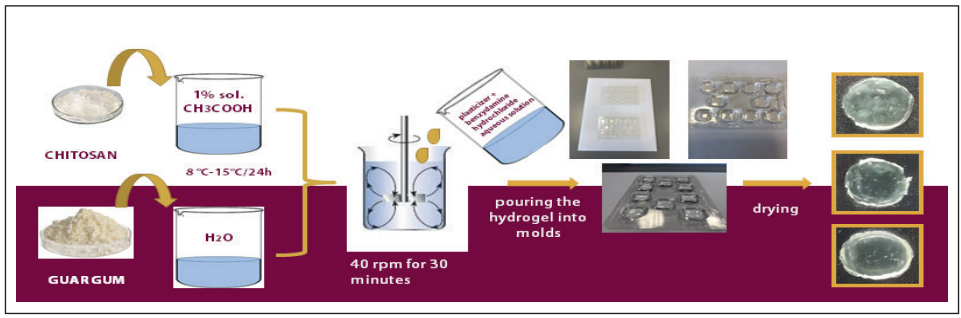

Figure 1. A schematic of hydrogel film preparation

The benzydamine hydrochloride content of all hydrogel dressings was 0.3%. The composition of the hydrogel films is presented in Table 1. Figure 1 presents a schematic of the technology used to prepared the formulation.

2.2.2. Dynamic Viscosity Test

The dynamic viscosity test was carried out using a Rheotest 2rotational viscosimeter (Medingen, Dresden, Germany). Determinations were performed in the Ia range on a K-1 cone with a diameter of 36 mm at 37°C. Values of shear stress and viscosity were calculated from the measurements.

2.2.3. Examination of Water Sorption by Hydrogel Carriers

The examined films were weighted on an analytical scale. They were placed at the bottom of a tared beaker, to which 20 ml of purified water, heated to 37°, was added. The samples were neither mixed nor shaken. After 3 min, the water was carefully removed, the walls of the beaker were dried and the beaker was weighed on an analytical scale together with the swollen dressing [8]. The average swelling coefficient of the tested complexes was calculated using the following formula:

$$W_p = \frac{m_w - m_s}{m_s} * 100,$$

where W_p is the swelling coefficient (%), m_w is the mass of lyophilisate with absorbed water (g) and m_s is the mass of dry lyophilisate (g).

2.2.4. Examination of Blur Time

Dressings measuring 1.6 cm in diameter were placed in beakers. Next, 30 ml of water that had been heated to 27°C was added, and the beakers were placed in a thermostatic shaker (Memmert, Germany) at the speed of 100 revolutions/min for 3 h. The blur times were then measured.

2.2.5. Examination of Hydrogel Carrier Texture

A TA.XT Plus single-arm texture analyser (Stable Micro Systems, Texture Technologies Corporation, USA) with a maximum load of up to 50 kg as well as the Texture Exponent 32 software were used to assess the elasticity and brittleness of the films. An A/TGP measuring tip with two grips was used to stretch the films. The examination was performed using discs of prepared films with a 3.5-cm diameter and a surface area of 9,62 cm^2, which enabled stable fixing of the film between the handles that were placed 10 mm apart, with an applied force of 3.0 g and a stretching speed of 0.5 mm/s [9]. The elongation percentage at the time of the dressing rupture as well as the tensile resistance of the films were calculated using the following equations.

$$\text{Tensilestrength } [N/mm^2] = \frac{Force\ at\ break\ [N]}{Initial\ cross\ sectional\ area\ [mm^2]} \text{ and}$$

$$\text{Elongation at break } [\%] = \frac{increase\ in\ lengt\,h [mm]\ at\ break}{initial\ film\ lengt\,h\ [mm]} \times 100 \text{ [10].}$$

2.2.6. Dissolution of Benzydamine Hydrochloride From Bioadhesive Films

The dissolution of benzydamine hydrochloride from the films was examined in accordance with Polish Pharmacopoeia 12 using the paddle method [11] and the Vankel VK7035 device (Varian Medical Systems) with a Varian autosampler with a basket cap for releasing the medicinal substance from the films. The tests were conducted on films with an area of 9.62 cm^2 and a mean weight of 1.48 g with a 3.5-cm diameter; they were placed in the basket and dipped in chambers containing 500 ml of purified water at 37°C and mixed at 50 revolutions/min. The trial was continued for 130 min; 3-ml samples were collected at 13 time intervals: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 115, 130 minutes. The collected samples were filtered on filters with a 10-µm pore size.

The collected samples were diluted and then their content was evaluated with a JASCO V650 spectrophotometer a 1-cm cuvette at 307 nm against a reference of distilled water.

The drug concentration in samples and an average percentage of dissolved benzydamine hydrochloride were calculated using a linear regression equation for drug, $y = 0.0151x - 0.00346$, over the concentration range of 5-50 µg/ml. The correlation coefficient (R^2) for the calibration curve was 0.9999.

2.2.7. Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectra of polymers, benzydamine hydrochloride and selected films with different polymer contents were obtained using a Perkin-Elmer Spectrum Two FTIR spectrometer (Perkin Elmer). The spectra were collected in the range 400 to 4000 cm^1,

using the attenuated total reflection (ATR) sampling mode. An ATR device with a diamond crystal was used. Each FTIR spectrum was registered at room temperature in transmittance mode, by an accumulation of 32 scans with a resolution of 4 cm^{-1}. After scanning each sample, an air spectrum recording for the clean and dry ATR crystal was taken and subtracted automatically as background.

3. Results and Discussion

3.1. Comparison of the Impact of Viscosity and the Swelling Coefficient on the Blur Time of the Dressings

Table 2 shows the blur time of the dressings, their viscosity and capacity to swell.

At a shear rate of 4860 s^{-1}, the hydrogel with the lowest guar gum content (CH1+GG0.25+GL20) showed the lowest shear stress (τ), namely 708.05 N/m^2, and its viscosity (η) was 14.57 Pas. This viscosity was the lowest among all the tested gels. An increase in the guar gum content was accompanied by an increase in viscosity. At a shear rate of 4860 s^{-1}, the hydrogel with the highest content of guar gum (CH1+GG1+GL20) showed the highest shear stress (τ), 2351.95 N/m^2, and its viscosity (η) was 48.39 Pas.

Based on the above analysis, an increase in the concentration of guar gum in gel causes a marked increase in the values of the rheological parameters. Comparing gels composed of CH1+GG0.50+GL20+B and CH1.2+GG0.50+GL20+B, there was a slight difference in the values of their rheological parameters. When analysing gels with different contents of chitosan, the addition of chitosan slightly improved gel viscosity.

Water sorption tests presented in Table 2 revealed that alongside an increase in the added polymers (guar gum and chitosan), there was a decrease in water sorption of a given carrier. The swelling coefficient of the formulation with the lowest guar gum content (CH1+GG0.25+GL20) was 2.753, while the swelling coefficient of the formulation with the highest guar gum content (CH1+GG1+GL20) was 1.835, the lowest among all tested formulations. When more polymers are added to the formulations, the polymer network is thickened, a phenomenon that may be associated with a lower water sorption capacity. For technological reasons, it is preferable for the dressing to have a lower water sorption capacity.

Table 2. Hydrogel viscosity determined at 37°C and a shear rate of 4860 s^{-1}, swelling and blurring time of the films

Formulation	Shear stress (N/m^2)	Average viscosity of hydrogels (mPas)	Average swelling factor (W_p)	Blurring time Tav ± SD (min)
CH1+GG0.25+GL20+B	708.05	14.57	2.753	99 ± 1.73
CH1+GG0.50+GL20+B	1275.00	26.24	2.066	118 ± 5.00
CH1+GG0.75+GL20+B	1700.00	34.98	1.897	135 ± 2.65
CH1+GG1+GL20+B	2351.95	48.39	1.835	161 ± 7.55
CH1.2+GG0.50+GL20+B	1289.45	26.53	1.752	130 ± 1.00

Note. In the first column, the number after each abbreviation indicates the per cent of that component in the film. Abbreviations: CH, chitosan; GG, guar gum; GL, glycerol; B, benzydamine hydrochloride; SD, standard deviation.

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To determine the approximate duration of the activity of dressings on the oral mucosa, their blur time was investigated. As the guar gum content increased, the blur time increased. The film with the lowest guar gum content (CH1+GG0.25+GL20) had a blur time of 99 min, and this increased to 161 min for the formulation with the highest guar gum content (CH1+GG1+GL20). The CH1+GG0.50+GL20 carrier with a lower content of chitosan and the CH1.2+GG0.50+GL20 carrier with a greater content of chitosan had longer blur times. These data indicate that the addition of polymer strengthens the structure of the film and delays the process of hydrogen blurring. Overall, the swelling coefficient, blur time and viscosity were closely related and characterise the physicochemical properties of drug formulations. The increase in hydrogel viscosity as more polymer was added decreased the swelling coefficient and extended the blur time. The increase in the cross-linking of hydrogels increases their durability and makes it more difficult for them to blur in the area of application.

3.2. Effects of Guar Gum and Chitosan Addition on Texture Parameters of Hydrogel Dressings

The CH1+GG0.25+GL20 films showed low tensile strength and an unsatisfactory elongation percentage of < 20% (Table 3). Dressings with a greater content of guar gum in their composition (0.75% and 1%) showed high strength values – 30.330×10^{-4} and 41.994×10^{-4} N/mm^2, respectively – as well as satisfactory elasticity results, the elongation percentages of which were 24.086% and 25.914%, respectively. As the guar gum and chitosan contents increased, the tensile strength parameters and film elasticity also increased.

3.3. Benzydamine Hydrochloride Release from Mucoadhesive Films

The dissolution of benzydamine from the CH1+GG0.50+GL20+B, CH1+GG0.75+GL20+B, CH1+GG01+GL20+B and CH1+GG0.50+GL20+B films was

Table 3. Examination of the texture of hydrogel dressings

Formulation	Average force required to break (N)	Tensile strength ± SD (N/mm^2)	Average increase in dressing length (mm)	Average percentage of dressing elongation
CH1+GG0.25+GL20+B	0.169	1.736×10^{-4} ± 0.734×10^{-4}	6.225	17.786
CH1+GG0.5+GL20+B	0.913	9.488×10^{-4} ± 1.599×10^{-4}	7.00	20.000
CH1+GG0.75+GL20+B	2.918	30.330×10^{-4} ± 7.950×10^{-4}	8.43	24.086
CH1+GG1+GL20+B	4.040	41.994×10^{-4} ± 9.650×10^{-4}	9.07	25.914
CH1.2+GG0.50+GL20+B	0.929	9.661×10^{-4} ± 2.118×10^{-4}	8.20	23.429

Note. In the first column, the number after each abbreviation indicates the per cent of that component in the film. Abbreviations: CH, chitosan; GG, guar gum; GL, glycerol; B, benzydamine hydrochloride; SD, standard deviation.

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examined. The average percentage of the drug dose released from CH1+GG1+GL20+B was the highest among the tested samples (77.51%). With a constant chitosan content but variable guar gum content, the average percentage of the released drug dose was 77.44% for a guar gum content of 0.50%, 76.91% for a guar gum content of 0.75% and 77.51% for a guar gum content of 1% after 130 min (Figure 2). There were no significant differences among the films. When the films had a constant guar gum content but a variable chitosan content, the release of benzydamine hydrochloride decreased as the chitosan content increased. The average percentage of the drug dose released from a film containing 1% chitosan was 77.44%, while in the case of films containing 1.2% chitosan it was 61.88% (Figure 2).

Based on these results, changes in the quantitative ratio of guar gum in films did not affect the kinetics of benzydamine hydrochloride release from bioadhesive dressings. However, changes in the amount of chitosan in formulations had a significant impact on the pharmaceutical availability of drugs, which results in the extension of the release time and better therapeutic effects of mucoadhesive films.

3.4. Analysis of FT-IR Spectra of Chitosan, Guar Gum and Their Combinations

The FT-IR spectra for chitosan, gum, benzydamine hydrochloride and their combinations are presented in Figure 3. The FT-IR spectrum of chitosan presents a broad absorption band at 3,300 cm^{-1}, which illustrates stretching vibrations between N-H and O-H. The absorption band at 2,900 cm^{-1} corresponds to stretching vibrations of C-H bonds in the pyranose ring. The peak visible at 1,650 cm^{-1} originates from C=O bond vibrations in the amide group, and the one visible at 1,580 cm^{-1} illustrates vibrations of N-H in the amine group. The intense band at 1,150 cm^{-1} can be attributed to the glycosidic bonds in

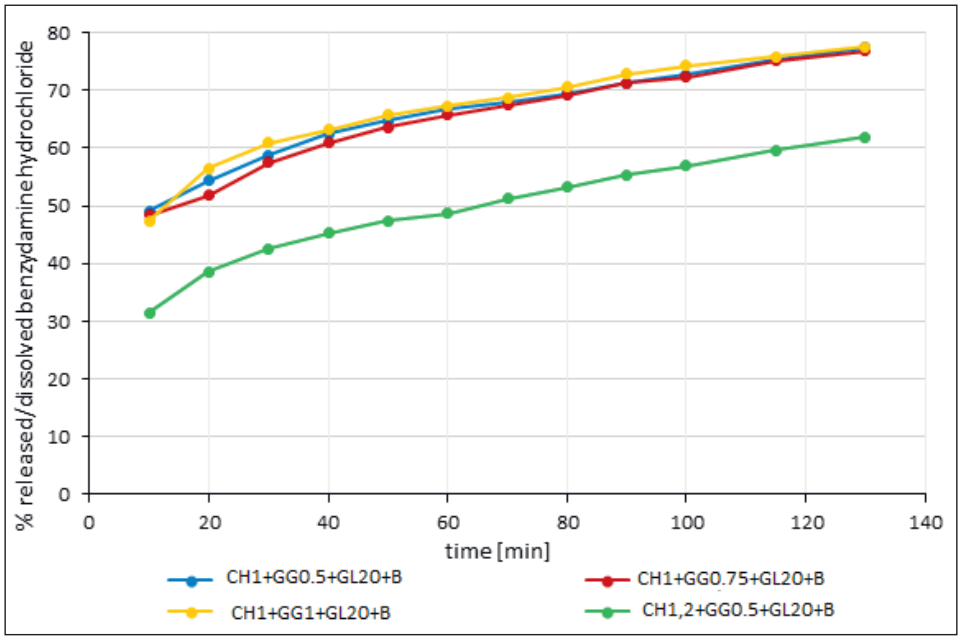

Figure 2. Benzydamine hydrochloride release from hydrogel films. The number after each abbreviation indicates the per cent of that component in the film.
Abbreviations: CH, chitosan; GG, guar gum; GL, glycerol; B, benzydamine hydrochloride

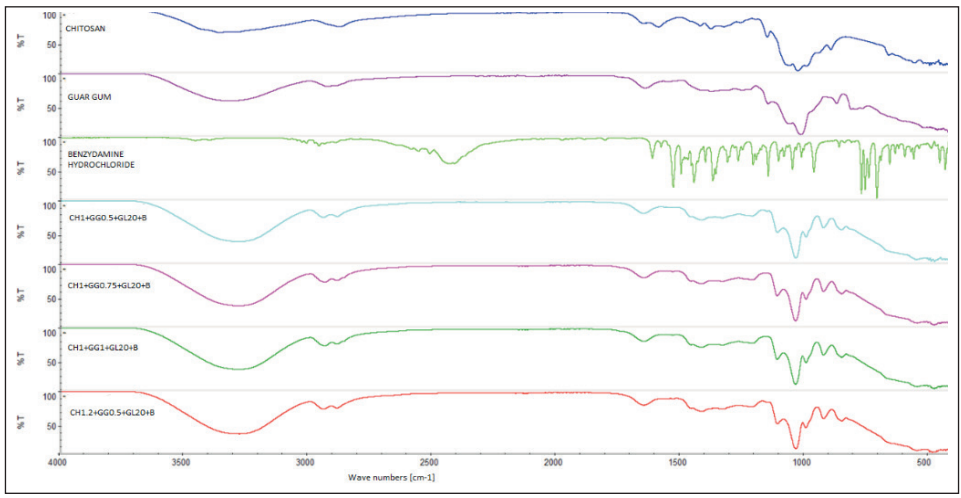

Figure 3. Fourier-transform infrared spectra of chitosan, guar gum, benzydamine hydrochloride and selected films with different polymer contents. The number after each abbreviation indicates the per cent of that component in the film.
Abbreviations: CH, chitosan; GG, guar gum; GL, glycerol; B, benzydamine hydrochloride

the molecule [12]. The guar gum spectrum is characterised by a broad band at 3,300 cm^{-1}, which corresponds to stretching vibrations of the O-H bond. The peak at approximately 2,950 cm^{-1} is responsible for the vibration of C-H bonds. The distinct peak at wave number 1,000 cm^{-1} indicates the presence of C-O-C bonds in the molecule [13]. The FT-IR spectrum of benzydamine hydrochloride presents a band at 2,380 cm^{-1} and is characteristic of this medicinal substance. In the spectra of films containing polymers and benzydamine hydrochloride, the intensity of the peak characteristic of the medicinal product is low, which may stem from a lower content of the drug in the film compared with the content of polymers and compared with pure benzydamine. The peaks characteristic of guar gum and chitosan increase as the amount of these polymers in the film composition increases. The FTIR spectra of films did not show additional unidentified peaks that could indicate the emergence of interactions and formation of new chemical structures.

4. Conclusions

The film containing 1% chitosan and 1% guar gum exhibited the best strength and elasticity parameters of mucoadhesive dressings. The film containing 1.2% chitosan and 0.5% guar gum had the best pharmacokinetic parameters. Guar gum had a significant impact on increasing the mechanical resistance of carriers, while chitosan impacts the texturometric properties and pharmaceutical availability of benzydamine hydrochloride. Analysis of the FT-IR spectra of the prepared films did not reveal any new chemical structures in dressings.

5. Acknowledgements

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6. Literature

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