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Bioadhesive hydrogels for cosmetic applications

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Synopsis

INTRODUCTION: The use of bioadhesive hydrogels for skin care presents important advantages such as long residence times on the application site and reduced product administration frequency.

OBJECT: The aim of the present work was to develop bioadhesive hydrogels for skin application, using caffeine as a model active ingredient.

METHODS: Eight hydrogels were formulated using binary combinations of a primary polymer (carbomer homopolymer type C (Carbopol® 980) or kappa carrageenan potassium salt (Gelcarin® GP-812 NF)) and a secondary polymer (carbomer copolymer type B (Pemulen™ TR-1), xanthan gum or guar gum). Hydrogels were characterized by means of physico-chemical (dynamic rheological measurements, spreadability and adhesion measurements) and sensory methods (projective mapping in combination with a check-all-that-apply (CATA) question). Caffeine hydrogels were formulated using two of the most promising formulations regarding adhesion properties and sensory characteristics. *In vitro* active ingredient release studies were carried out.

RESULTS: Hydrogel formulations showed a prevalently elastic rheological behaviour. Complex viscosity of carbomer homopolymer type C hydrogels was higher than that of the kappa carrageenan hydrogels. Besides, complex viscosity values were dependent on the secondary polymer present in the formulation. Significant differences among hydrogels were found in detachment force, work of adhesion and spreading diameter results. Association of projective mapping with CATA allowed to determine similarities and dissimilarities among samples. Cluster analysis associated the samples in two groups. Two hydrogels were selected to study the release of caffeine. Both hydrogels presented similar release profiles which were well described by the Higuchi model. Caffeine release was exclusively controlled by a diffusive process.

CONCLUSION: Physico-chemical and sensory techniques enabled the identification of bioadhesive hydrogel formulations with positive characteristics for cosmetic applications. Formulations which combined carbomer homopolymer type C with xanthan gum or with carbomer copolymer type B were the most promising for bioadhesive skin products. Caffeine release profiles of selected formulations were not statistically different. Both hydrogels gradually released the active ingredient, reaching approximately 80% within the first 5 h, and their profiles were well described by the Higuchi model. In this context, it could be concluded that the selected hydrogels are suitable bioadhesive hydrogel formulations for cosmetic application on the skin.

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Résumé

L'utilisation d'hydrogels bioadhésifs pour les soins de la peau présente des avantages importants tels que des temps de contacts longs sur le site d'application et la réduction de la fréquence de l'administration du produit.

OBJET: L'objectif de ce travail était de développer des hydrogels bioadhésifs pour l'application à la peau, en utilisant la caféine comme ingrédient actif de modèle.

MÉTHODES: Huit hydrogels ont été formulés en utilisant des combinaisons binaires d'un polymère primaire (carbomère type homopolymère de C (Carbopol® 980) ou sel kappa carraghénane de potassium (Gelcarin® GP-812 NF)) et un polymère secondaire (carbomère type copolymère B (PEMULEN™ TR -1), la gomme xanthane ou la gomme guar). Les hydrogels ont été caractérisés par des moyens physico-chimique (mesures rhéologiques dynamiques, étalement et mesures d'adhérence), des méthodes sensorielles (cartographie projective en combinaison avec un questionnaire du type (CATA) check-all-that-apply, i.e. cochez-tout-ce-qui-est-pertinent). Des hydrogels de caféine ont été formulés en utilisant deux des formulations les plus prometteuses en ce qui concerne les propriétés d'adhérence et les caractéristiques sensorielles. Des études *in vitro* de la libération de l'ingrédient actif ont été réalisées.

RÉSULTATS: Les formulations d'hydrogel ont montré un comportement rhéologique à prédominance élastique. La viscosité complexe des hydrogels du type carbomère homopolymère C était supérieure à celle des hydrogels de carraghénane kappa. En outre, des valeurs de viscosité complexe dépendaient du polymère secondaire présent dans la formulation. Des différences significatives entre les hydrogels ont été trouvées quant à la force de détachement, au travail d'adhésion et au diamètre d'étalement. L'association des cartographies projectives avec CATA a permis de déterminer les similitudes et les différences entre les échantillons. L'analyse typologique associe les échantillons en deux groupes. Deux hydrogels ont été choisis pour étudier la libération de la caféine. Les deux hydrogels présentent des profils de libération similaires qui ont été bien décrits par le modèle Higuchi. La libération de la caféine a été exclusivement contrôlée par un processus de diffusion.

CONCLUSION: Les techniques physico-chimiques et sensorielles ont permis l'identification des préparations d'hydrogels bioadhésifs avec des caractéristiques positives pour les applications cosmétiques. Les formulations qui combinent le carbomère type homopolymère C avec la gomme de xanthane ou de carbomère type copolymère B étaient les plus prometteuses pour les produits bioadhésifs de la peau. Les profils de libération de la caféine des formulations choisies n'étaient pas statistiquement différents. Les deux hydrogels libéraient progressivement l'ingrédient actif, atteignant environ 80% dans les cinq premières heures, et leurs profils ont été bien décrits par le modèle Higuchi. Dans ce contexte, on pourrait conclure que les hydrogels sélectionnés, sont des formulations hydrogels bioadhésifs appropriés pour application cosmétique sur la peau.

Introduction

Different strategies have been proposed to achieve efficient drug delivery systems for pharmaceutical or cosmetic topical cutaneous administration. Hydrogels [1] and bioadhesive hydrogels [2], in general, have been considered as good candidates. Hydrogels are three-dimensional, cross-linked networks of water-soluble polymers commonly used in cosmetic formulations for skin care. In particular, bioadhesive hydrogels show one important advantage over conventional hydrogels: they allow longer residence times on the application site, maintaining a high local concentration of active ingredient in the surrounding tissues over an extended period, which is important when a long dermal action and a reduced product administration frequency are desired. This might be advantageous for active ingredients intended for superficial action, as well as for those which should exert their action at deep layers of the skin.

Different polymers may be selected to formulate hydrogels. One of the most used gelling agents is carbomer, which is a high molecular weight polymer of acrylic acid. The polyacrylic acid derivatives have also been used for their bioadhesive properties, and a relevant amount of work has been carried out on their rheological and bioadhesive properties [3–6]. In addition, carrageenans are a family of naturally occurring and highly biocompatible polysaccharides, extracted from red seaweed, and used by the pharmaceutical industry for specific gelling, thickening and stabilizing applications [7–10].

Cellulite, or more correctly gynoid lipodystrophy (GLD), is a clinical syndrome mainly affecting women and rarely men and is considered to be a common aesthetic problem for many women. The combined effect of modifications and hypertrophy in adipose tissues, alterations in the fibrillar connective tissue and alterations in the microvascular venous network leads always to the presence of cellulite [11]. Active ingredients used to treat GLD should penetrate the deep layers of the skin. Treatment efficiency, then, will partly depend on the product residence time on the skin, the active ingredient release and its penetration up to the deep layers of the skin [12, 13]. Caffeine is widely used in cellulite treatment due to its lipolytic action over adipocytes and also has a stimulating effect on the cutaneous microcirculation [14].

Different characterization studies are commonly used during the development of bioadhesive hydrogels to select the best formulations for certain cosmetic purposes. Product spreadability is responsible for correct dosage transfer to the target site, ease of application on the substrate, extrudability from the package and most important, consumer preference [15]. The adhesive capacity in dermal administration is important to ensure retention at the site of application [2]. Active ingredient release is of main importance when its release from the cosmetic formulation is required to exert its action either at skin surface or at deeper layers. The skin sensory performance of personal care products is an important factor for the sales potential of any cosmetic product [16]. For this reason, sensory characterization may serve as a guide in the selection of formulations with sensory characteristics which can make them eligible for consumers, contributing to treatment compliance as well as enhancing its chances of success in the marketplace.

In this context, the aim of the present work was to develop bioadhesive hydrogels for skin application, based on carbomer homopolymer or carrageenan biopolymer and using caffeine as a model active ingredient.

Materials and methods

Materials

Carbopol® 980 (*Cb*) (Lubrizol, U.S.A.) and Pemulen™ TR-1 (*Pe*) (Lubrizol) are covalently cross-linked polyacrylic acids, but Pemulen™ TR-1 is hydrophobically modified by the incorporation of long-chain alkyl (C10-C30) acrylates [17]. Gelcarin® GP-812 NF (*Cg*) (FMC Corporation, U.S.A.) is a moderate potassium salt kappa carrageenan. Guar gum (*Gg*) (Chopra Gums, India) is a non-ionic polysaccharide commercially isolated from the seeds of several leguminous plants, whereas xanthan gum (*Xg*) (Weifang Ouchem, China) is an anionic polysaccharide commercially obtained by bacterial fermentation [18]. Caffeine *(Caf)* (BASF, Germany) was used as a model active ingredient.

Other excipients used were propylene glycol, methylparaben, sorbic acid, FD&C blue n°1 colourant, sodium hydroxide or hydrochloride acid and deionized water.

Preparation of hydrogels

Eight bioadhesive hydrogels were formulated using carbomer homopolymer type C or kappa carrageenan in binary combination either with carbomer copolymer type B, guar gum or xanthan gum as a secondary bioadhesive agent. Compositions are given in

Table 1 Formulation of the hydrogels considered in the study

		Primary polymer		Secondary polymer (%)		
Hydrogel		Type	%	Carbomer copolymer type B	Guar gum	Xanthan gum
1	*CbPe0.5*		0.4	0.5	–	–
2	*CbGg1.0*	Carbomer	0.4	–	1.0	–
3	*CbGg2.0*	homopolymer	0.4	–	2.0	–
4	*CbXg1.0*	type C	0.4	–	–	1.0
5	*CbXg1.5*		0.4	–	–	1.5
6	*CgPe0.5*		0.5	0.5	–	–
7	*CgXg1.0*	Kappa carrageenan	0.5	–	–	1.0
8	*CgXg1.5*		0.5	–	–	1.5

Other components: 5.0% propylene glycol, 0.2% methylparaben and 0.1% sorbic acid, 0.001% colorant blue FD&C no. 1, 10% NaOH or 2% HCl solution and deionised water up to 100% (500 g).

Table I. Based on results of a previous work, in which hydrogels developed using the same polymers were characterized using rheological and spreadability measurements [19], the combination of *Cg* and *Gg* was not included in the present work.

Hydrogels 1 and 5 (*CbPeO.5* and *CbXg1.5*) were also formulated including 2% of caffeine to perform active release studies. Colourant was not included in these formulations.

Hydrogels were prepared dispersing each pair of polymers by mechanical stirring (Servodyne 50003-45; Cole-Parmer Instrument Co., Vernon Hill, U.S.A.) in hot water (70 ± 5°C) in the presence of propylene glycol, preservatives and colourant. Acid or basic solution was added up to make the final pH 5, and hydrogel final weight was completed with water.

Characterization of hydrogels

Rheological characteristics

Dynamic rheological measurements were performed using a controlled stress Paar Physica MCR 301 rheometer (Anton Paar, Graz, Austria). Rheological data were collected using RheoPlus software version 3.21 (Anton Paar).

Stress sweeps were run at a frequency of 1 Hz at 37.0 ± 0.5°C. Elastic or storage modulus (G′) and viscous or loss modulus (G″) were plotted in logarithmic scale, and complex viscosity (η^*) was determined.

Adhesion properties

Texture analysers are widely used to study bioadhesion [20, 21]. These equipments are capable of measuring detachment force (maximum force registered) and work of adhesion (work required to detach the sample from the probe), which are parameters used as indicators of the adhesive potential of the products tested. However, work of adhesion has been reported to be more reliable and reproducible than detachment force when adhesion properties are being evaluated [22].

Adhesion properties were evaluated at 37 ± 1°C using a TA-XT Plus Texture Analyser (Stable Micro Systems, Godalming, U.K.) with a load cell of 30 Kg and set in 'Adhesive mode'. Samples were placed in cylindrical containers sticked to the base of the analyser with double-sided adhesive tape. The probe (cylindrical, 40 mm diameter) was lowered to the surface of each sample at a speed of 1.0 mm s^{-1}, and after reaching the trigger force (0.049 N), intimate contact between probe surface and hydrogel was assured by means of a constant downward force of 0.5 N applied by the probe during 60 s. Afterwards, the probe was brought back through a return distance of 20 mm at a speed of 1.0 mm s^{-1}. Detachment force and work of adhesion were measured automatically by the texture analyser software, Texture Exponent 32 (Stable Micro Systems, Godalming, U.K). In the case of caffeine hydrogels, adhesion properties were studied at 32 ± 1°C.

Spreadability test

This test was based on a method proposed by Bachhav and Patravale [23]. Briefly, 1 g of sample at 37 ± 1°C was loaded on a glass plate placed over squared paper (in millimetres). A second glass plate was placed over the sample, and a weight of 100 g was allowed to rest on the upper glass plate for 1 min. The diameter after spreading of the hydrogel was measured.

All the above-mentioned tests were performed in duplicate, and average results are presented.

Sensory characterization

Projective mapping, also known as Napping® [24], is a methodology for sensory characterization based on the quantification of individual perception of overall similarity and dissimilarity among products. Participants are asked to provide a two dimensional representation of a group of samples, according to their own criteria. In order to understand the similarities and dissimilarities among samples, a description phase is usually added to the projective mapping task. When assessors are not trained, they might find it difficult to provide an objective description of the sensory characteristics of the samples. Therefore, to make the description phase easier, check-all-that-apply (CATA) question can be used after the projective mapping task [25–30].

In the present work, samples were placed in 30-mL odourless plastic containers at 25 ± 2°C, identified with three-digit random numbers and presented to 21 untrained assessors in a single session, following a complete balanced design (William's Latin square).

Assessors were asked to apply the hydrogels on their forearm skin and to locate the samples on a 60 × 40 cm sheet of paper, according to the similarities or dissimilarities among them. After completing the projective mapping task, assessors completed a CATA question for describing each sample. The question included 19 terms associated to appearance, consistency when taken in the hand, sensations when being applied on the skin and sensations once the product was already on the skin (fluid, gloss, difficult to take for application, difficult to spread, irregular film, fresh, flattens, no gloss, heavy, easy to spread, sticky, soft sensation, leaves residue, retains shape, light, easy to take for application, uniform film, fast absorbed, can be applied in a well defined area).

The testing was carried out in a sensory laboratory that was designed in accordance with ISO 8589 [31]. Evaluations were performed under artificial daylight-type illumination, temperature control (between 22 and 24°C) and air circulation.

In vitro release studies

In vitro release method for topical semisolid products is based on a diffusion cell system such as a Franz cell system, fitted usually with a synthetic membrane. Release is theoretically proportional to the square root of time when the formulation in question is in control of the release process because the release is from a receding boundary [32].

Caffeine release studies were performed by triplicate on two of the most promising hydrogel formulations, using jacketed Franz diffusion cells. The volume of the receptor compartments was 17 mL, and the average diffusion area was 1.3 ± 0.2 cm^2. Cellulose acetate membranes (12 kDa, Dialysis tubing cellulose membrane, Sigma®, St. Louis, U.S.A.) were placed between the donor and the receptor compartments. Membranes were embedded in receptor fluid for 24 h before using them. Receptor fluid was phosphate-buffered saline (PBS, pH = 5.8 ± 0.1), as skin surface pH is known to be between 5.4 and 5.9 [33]. The experiments were carried out for 24 h at 32 ± 1°C, accepted value for skin temperature [34]. Samples were withdrawn at appropriate time intervals and analysed by UV spectrophotometry (UV-1603, Shimadzu, Kyoto, Japan) at the wavelength of 273 nm. After each withdrawal, receptor compartment was refilled with fresh receptor fluid.

Data analysis

Analysis of variance (ANOVA) was performed on spreading diameter, rheological parameters, detachment force, work of adhesion data and caffeine release results, considering either sample or primary polymer as fixed source of variation. Honestly, significant

differences for a significance level of 0.05 were calculated using Tukey's test.

Multiple Factor Analysis (MFA) was also used for analysis of physico-chemical data. MFA is a factorial technique that enables working with several groups of variables (numerical and/or categorical) evaluated on the same samples. The core of MFA is a principal component analysis applied to the whole set of variables in which each group of variables is weighted, rendering possible the analysis of different points of view by taking them equally into account [35]. In the present work, eight samples and seven variables divided into three groups were taken into account to perform MFA. The variables included in each group were as follows:

Group 1 – stress sweep variables: storage modulus (G′1 Pa) and loss modulus (G″1 Pa) at 1 Pa, and storage modulus (G′10 Pa) and loss modulus (G″10 Pa) at 10 Pa.
Group 2 – spreading diameter (Spread).
Group 3 – adhesion: detachment force (Detach F) and work of adhesion (Adh W).

Frequency of use of each of the terms of the CATA question was determined by counting the number of assessors that used each term to describe the hydrogels. Cochran's Q test was carried out for each option in order to determine whether the CATA question allowed to establish differences among samples. Cochran's Q test is a nonparametric statistical test used in the analysis of two-way randomized block designs to determine whether k treatments have identical effects when the response variable is binary [36].

Multiple Factor Analysis of projective mapping data was performed [37]. For this purpose, *X* and *Y* values of each assessor were considered as active variables, whereas the frequency table from CATA question was considered as supplementary variables. This means that CATA data are not taken into account in the construction of the MFA factors, but they were represented in the same space.

Cluster analysis was performed to identify groups of samples with different characteristics. This analysis was performed on samples' coordinates in the first and second dimensions of the MFA of projective mapping data, considering Euclidean distances and Ward's aggregation criterion [38].

All data analyses were performed using R language [39, 40].

Results and discussion

Physico-chemical hydrogel characterization

Rheological characteristics

Hydrogel formulations showed a prevalently elastic rheological behaviour, as G′ moduli were higher than G″ moduli.

As shown in Fig. 1, complex viscosity of carbomer homopolymer type C hydrogels was higher than that of the carrageenan hydrogels. Complex viscosity values were dependent on the secondary polymer present in the formulation. In carbomer hydrogels, η^* increased in the presence of the secondary polymer according to the sequence: *Gg* > *Pe* > *Xg*. In the case of carrageenan hydrogels, the sequence was *Xg* > *Pe*.

Adhesion properties and spreadability

All of the hydrogel formulations studied in the present work presented values of $G' < 10^5$ Pa. Dahlquish criterion, which is commonly used to evaluate adhesive properties of materials, considers that an elastic modulus (G′) of less than 10^5 Pa corresponds with good adhesive properties. However, not all polymer gels which meet Dahlquist criterion are necessarily good adhesives [41].

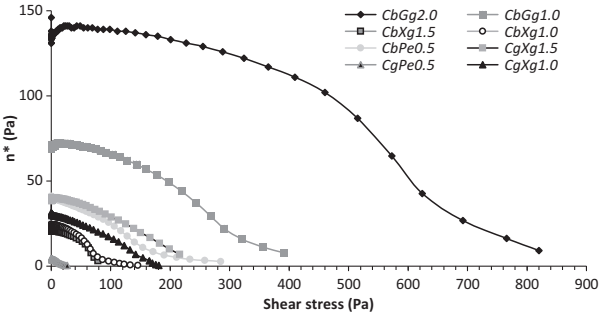

Figure 1 Complex viscosity (n*) of kappa carrageenan and carbomer homopolymer type C hydrogels as a function of shear stress.

Figure 2 shows adhesion properties of two of the hydrogels: detachment force (peak height) and work of adhesion (area under curve), measured with texture analyser.

Hydrogels spreading diameter, detachment force and work of adhesion results are shown in Table II. Significant differences among samples were found in detachment force, work of adhesion and spreading diameter results.

Carbomer homopolymer type C hydrogels presented higher adhesion and lower spreadability results than the correspondent carrageenan formulations.

When carbomer was combined with xanthan gum or with the lowest guar gum percentage, the hydrogels (*CbXg1.0*, *CbXg1.5* and *CbGg1.0*) showed the highest work of adhesion results and intermediate spreading diameter values. The binary combination of the two carbomers (*CbPe0.5*) showed intermediate spreadability and adhesion results. In carbomer formulations including guar gum, spreadability and adhesion properties revealed a significant dependency on the secondary polymer concentration in the hydrogel, with *CbGg2.0* showing the lowest work of adhesion together with *CgPe0.5*, the least adhesive of carrageenan formulations.

MFA of physico-chemical properties

The first two dimensions of the MFA explained 94% of the variance of the physico-chemical data obtained. The groups of variables are plotted in Fig. 3. As observed, spreading diameters and rheological measurements were located close to each other on the graph, indicating that they provided similar information.

The representation of the variables in the first and second dimensions of the MFA is shown in Fig. 4. Oscillatory rheological parameters were positively correlated with the first dimension, whereas spreading diameter was negatively correlated with this dimension. Finally, adhesion properties were positively correlated with dimension 2.

Spreadability was negatively correlated with stress sweep variables (Fig. 4). Inverse correlation between spreading diameter and G″ can probably be explained considering that spreadability decreased as viscosity increased. The higher the G″ value, the more pronounced the viscous properties of the sample [42].

Multiple Factor Analysis revealed other trends as well. As the percentage of guar gum in hydrogel compositions increased, the hydrogels moved towards higher values of the first dimension, which corresponded to a decrease in Spread, and an increase in G′ and G″ (Fig. 5).

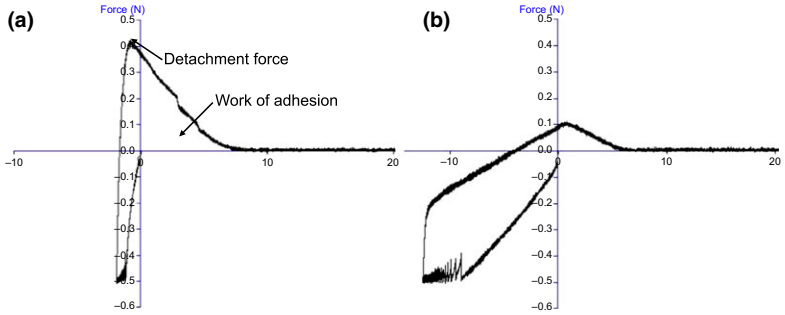

Figure 2 Force (N) vs. distance (mm) plot for formulations: a) *CbPe0.5*, b) *CgPe0.5*.

Table II Spreading diameter, work of adhesion and detachment force of kappa carrageenan and carbomer homopolymer type C hydrogels

Hydrogel	Spreading diameter (mm)	Detachment force (N)	Work of adhesion (Nmm)
CbPe0.5	47.8^{b}	0.48^{d}	1.67^{c}
CbGg1.0	53.8^{c}	0.64^{e}	2.34^{d}
CbGg2.0	32.0^{a}	0.30^{b}	0.74^{a}
CbXg1.0	58.8^{c,d}	0.61^{e}	2.68^{d}
CbXg1.5	62.5^{d}	0.45^{c,d}	2.83^{d}
CgPe0.5	83.3^{e}	0.11^{a}	0.72^{a}
CgXg1.0	64.0^{d}	0.40^{b,c,d}	1.35^{b,c}
CgXg1.5	58.8^{c,d}	0.35^{b,c}	1.08^{a,b}

Different superscripts within a column imply significant differences ($p < 0.05$) when hydrogel sample was taken as source of variation.

Carrageenan samples (lower left side of the plot) presented high spreading diameters, low elastic and viscous moduli and the lowest work of adhesion values, whereas showed higher adhesion properties when formulated with xanthan gum.

Results of carbomer homopolymer type C samples were more dependent on the secondary polymer used in the formulation than those of carrageenan. Hydrogels including guar gum or carbomer copolymer type B were located more to the right of the plot than those including xanthan gum. Moreover, carbomer homopolymer type C samples – with the only exception of *CbG2.0* – were all located in the upper portion of the plot, corresponding to higher values of adhesion properties.

Sensory characterization

The first two dimensions of the MFA performed on projective mapping data explained 64% of the inertia. The representation of samples in the first two dimensions of the MFA is presented in Fig. 6.

Carbomer copolymer type B-containing samples plus carbomer homopolymer type C and xanthan gum-containing samples were located on the left of the plot, whereas guar gum-containing samples and carrageenan samples – with the only exception of *CgPe0.5* – were located on the right. Cluster analysis associated with the samples in the same groups. Therefore, *Cluster 1* included *CbXg1.5, CbXg1.0, CbPe0.5* and *CgPe0.5*, and *Cluster 2* included *CbGg1.0, CbGg2, CgXg1.0* and *CgXg1.5.*

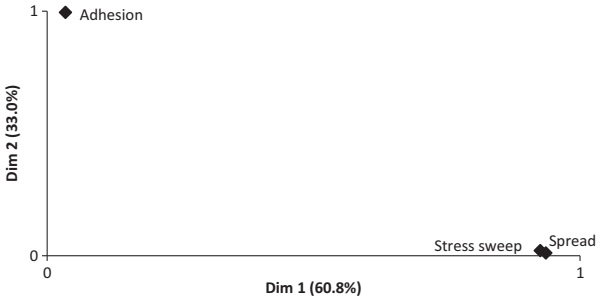

Figure 3 Representation of the groups of variables in the first two dimensions of the MFA.

Assessors used between 2 and 12 CATA terms to characterize the gels. The most frequently used terms were gloss, easy to take for application, fresh, can be applied in well defined area, and the less frequently applied terms were flattens, no gloss, heavy.

Significant differences were found in the frequency of use of 18 of the 19 terms by Cochran's Q test: difficult to take for application, difficult to spread, irregular film, fresh, flattens, no gloss, heavy, easy to spread, sticky, soft sensation, leaves residue, light, easy to take for application, uniform film, fast absorbed, can be applied in a well defined area.

Projection of the terms of the CATA question in the first two dimensions of the multiple factor analysis of projective mapping data are shown in Fig. 7.

Considering the projection of the terms of the CATA question on the first and second dimensions of the MFA, it can be concluded that hydrogels grouped in the first cluster presented the following characteristics: gloss, fluid, light, flattens, easy to spread, easy to take for application, uniform film, fast absorbed, fresh and soft sensation, retains shape and can be applied in a well defined area. Meanwhile, hydrogels grouped in the second cluster presented characteristics, such as difficult to take for application, heavy, leaves residue, irregular film, sticky.

Association of projective mapping with CATA allowed to determine similarities and dissimilarities among samples, as well as their main sensory characteristics.

Characterization of caffeine hydrogels

Two hydrogels, *CbXg1.5 and CbPe0.5*, were selected to study the release of caffeine. Both formulations presented intermediate

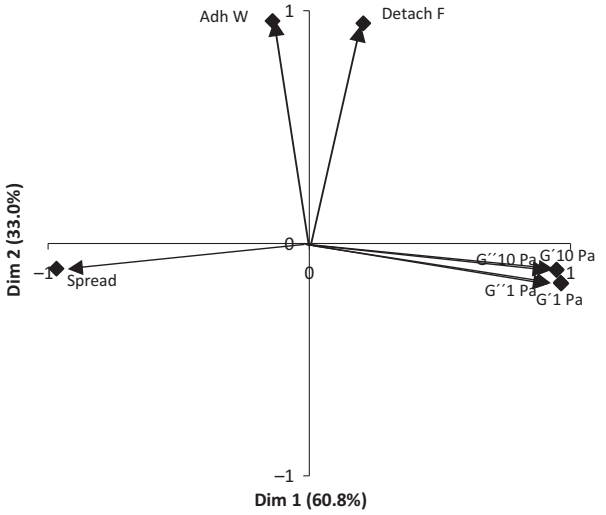

Figure 4 Representation of the variables in the first and second dimensions of the MFA [storage modulus (G'1Pa) and loss modulus (G"1Pa) at 1 Pa, storage modulus (G'10Pa) and loss modulus (G"10Pa) at 10 Pa, spreading diameter (Spread), detachment force (Detach F) and work of adhesion (Adh W)].

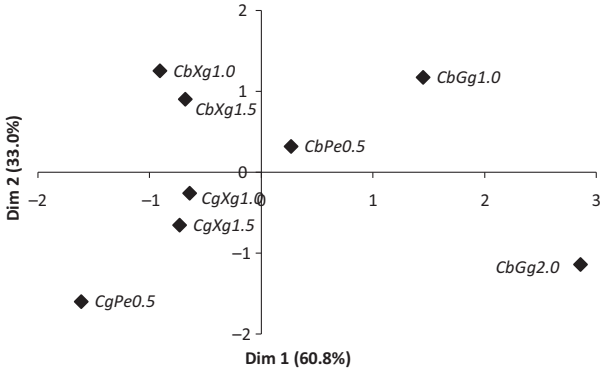

Figure 5 Representation of hydrogels in the first and second dimensions of the MFA.

spreading diameter and good adhesion properties, as well as desirable sensory characteristics such as fluid, light, easy to take for application, uniform film, fast absorbed, soft sensation and can be applied in a well defined area. Their adhesion properties were verified at 32 ± 1°C after inclusion of the active ingredient. ANOVA showed significant differences on their work of adhesion values; *CbXg1.5* presented the highest of the two results.

Guar gum-containing samples were not selected as they presented low spreadability values and undesirable sensory characteristics. *CbGg2.0* also presented low adhesion results. Carrageenan samples were not selected either, as they showed low adhesion results. Moreover, *CgXg1.0* and *CgXg1.5* presented undesirable sensory characteristics.

In vitro caffeine release studies

Active ingredient release profiles are presented in Fig. 8, where each data point represents the average of three determinations. A

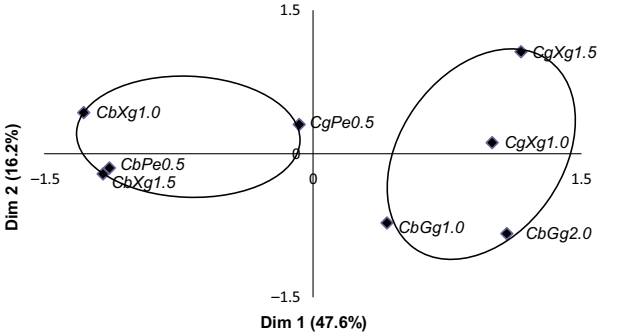

Figure 6 Representation of samples on the first and second dimensions of the multiple factor analysis of projective mapping data.

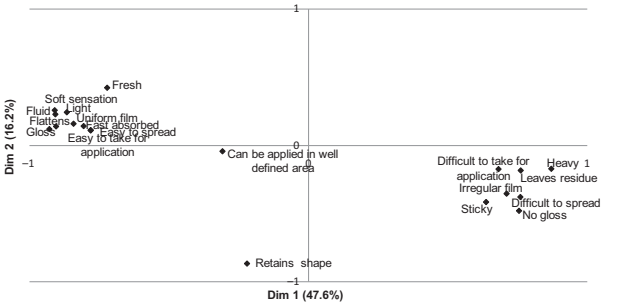

Figure 7 Projection of the terms included in the CATA question on the first and second dimensions of the multiple factor analysis of projective mapping data.

gradual and extended release of caffeine from both hydrogels was observed. The amount released reached approximately 80% of the active ingredient present in the hydrogels in less than 5 h.

According to ANOVA, the differences in the formulations did not affect caffeine release profile. As the aim was to develop bioadhesive products, which prolong retention time on the application site, it is of interest that these hydrogel formulations release the active ingredient gradually.

By plotting amount of drug released by surface area vs. the squared root of time, it was found that active ingredient release from both of the evaluated formulations was well described by the Higuchi model (Fig. 9). This suggested a matrix-type control of caffeine release from the hydrogels [43], which means the release is exclusively controlled by a diffusive process.

The *in vitro* tests revealed that cosmetic active ingredient release from the selected hydrogels was appropriate, both in terms of magnitude and velocity [44].

Conclusions

Physico-chemical (dynamic rheological, spreadability and adhesion measurements) and sensory techniques (association of projective mapping with a CATA question) enabled the identification of bioadhesive hydrogel formulations with positive characteristics for cosmetic applications.

Association of projective mapping with CATA question did not require trained assesors to perform the sensory characterization

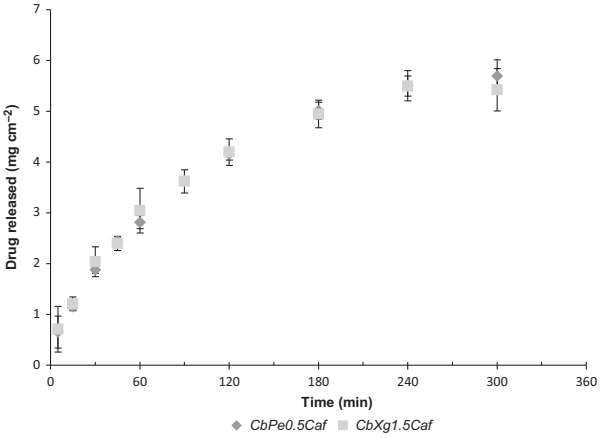

Figure 8 *In vitro* caffeine release profiles from two bioadhesive hydrogel formulations.

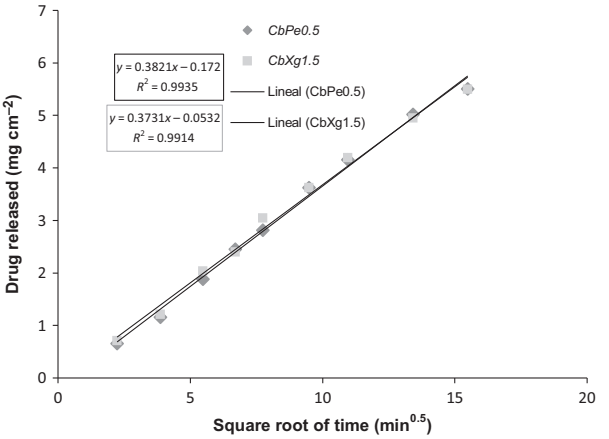

Figure 9 Fit of caffeine release profiles from two bioadhesive hydrogel formulations to Higuchi model.

task, which allowed a profitable work time reduction. These methodologies can provide information about the sensory characteristics of products which can contribute to the development of cosmetics that meet consumer demands.

Formulations which combined carbomer homopolymer type C with xanthan gum or with carbomer copolymer type B were the most promising for bioadhesive skin products.

Caffeine release profiles of *CbXg1.5Caf* and *CbPeO.5Caf* were not statistically different. Both hydrogels gradually released the active ingredient, reaching approximately 80% within the first 5 h, and their profiles were well described by the Higuchi model.

In this context, it could be concluded that both *CbXg1.5* and *CbPeO.5* are suitable bioadhesive hydrogel formulations for cosmetic application on the skin.

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