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Research Article

Development of Microparticles Based on Natural and Synthetic Pectin for the Encapsulation of Salicylic Acid in the Treatment of Acne Vulgaris

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Abstract

Acne is the leading cause of consultations for facial skin conditions. The aim of this study was to formulate and characterize pectin-based microparticles for the encapsulation of Salicylic Acid (SA), a keratolytic agent widely used in the treatment of acne vulgaris. Two types of pectin were evaluated: a natural pectin extracted from mango peel (*Mangifera indica*, «Amélie» variety), and a synthetic pectin. Ionotropic gelation was selected for its accessibility and its avoidance of organic solvents. Several formulations were tested by varying the pectin concentration (2% and 3%), the presence or absence of calcium chloride (0.2%), and the type of solvent (water or citrate buffer at pH 5). The microparticles were evaluated using macroscopic, microscopic, and granulometric analyses, as well as through the determination of encapsulation efficiency and yield. The results showed that synthetic pectin allowed the formation of smaller, more regular microparticles with a higher encapsulation efficiency (17.72%) compared to natural pectin (6.08%). Nevertheless, the latter demonstrated interesting potential despite morphological limitations. Both types of pectin showed acceptable encapsulation yields (> 78%). These results suggest that pectin-based microparticles are a promising option for a local delivery system of salicylic acid. Further optimizations, especially concerning the drying process and excipient ratios, could improve the performance of the formulations.

Keywords

Particulate System, Natural Biopolymer, Ionotropic Gelation, Keratolytic Agent, Acne

1. Introduction

Acne vulgaris is a common inflammatory skin condition, primarily affecting adolescents, but also present in adults. the pathophysiology of acne is an interplay of many factors such as hyperkeratinization of the hair follicle, excessive sebum production, proliferation of Cutibacterium acnes, and an inflammatory response [1]. Among the therapeutic agents used in acne management, salicylic acid (SA) holds a prominent place due to its keratolytic, comedolytic, anti-inflammatory, and antimicrobial properties. However, its use can lead to side effects such as skin irritation, excessive

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desquamation, or chemical instability depending on the area of the application [2]. This highlights the need for new dosage forms that enable controlled and targeted release of this active compound. In order to overcome the drawbacks of conventional forms, encapsulation of the active substance using naturally sourced polymers (pectin, gelatin, etc.) would be advantageous [3].

In this context, microparticles represent an innovative strategy to improve the stability, local bioavailability, and skin tolerance of active ingredients [3, 4]. They provide protection of the active compound against external conditions, reduce the frequency of application, and enhance therapeutic efficacy. Ionotropic gelation is one of the simplest and most eco-friendly techniques for producing microparticles, especially from natural polymers such as pectin [4, 5].

Pectin is a polysaccharide widely used in the pharmaceutical and food industries due to its biocompatibility, biodegradability, and gelling properties. It can be of natural or synthetic origin. Natural pectin, extracted from plant sources like citrus fruits or apples, is abundant and inexpensive. However, its composition varies depending on its source, which may affect its functional properties. Studies have shown that mango peel is a promising source of pectin [6, 7]. Synthetic pectin, on the other hand, offers better controlled composition, ensuring higher formulation reproducibility [6-8].

Objectives of the study

The present study aims to develop and characterize microparticles based on natural pectin extracted from mango peel (Mangifera indica, Amélie variety) and synthetic pectin, for the encapsulation of salicylic acid. The main objective is to evaluate the impact of the pectin type on the physicochemical characteristics, morphology, size, encapsulation efficiency and yield of the microparticles. The formulations were prepared using ionotropic gelation and subjected to various controls, with the perspective of their potential use in dermatological products intended for the treatment of acne vulgaris. This work is part of a strategy innovation, promoting local and natural resources in the development of skin delivery systems.

2. Materials

Salicylic acid (Batch No. 10189209) was obtained from Alfa Aesar. low-methoxyl amidated pectin (ALMP) (Unipectine OF305C; DE = 25% and DA = 21%, Batch No. 1606365012. Sodium chloride (Batch No. 1665066), calcium chloride (Batch No. 0000456696), citric acid monohydrate (Batch No. A0388355), disodium citrate (Batch No. 23160), and sodium hydroxide (Batch No. 1866402).

All solvents, chemicals, and reagents used were of analytical grade. Osmosed water was obtained using a Thermo Fisher Scientific™ water purification system and was used as the preparation solvent throughout the study.

3. Methods

3.1. Microparticle Formulation

The ionotropic gelation technique was chosen. This method does not require organic solvents and is easy to implement, as it does not demand sophisticated equipment. It is based on the ability of polyelectrolytes to form an insoluble gel in the presence of divalent cations. It consists of extruding, through a nozzle or syringe needle, an aqueous polymer solution in which the active ingredient is dissolved, dispersed, or emulsified. The resulting droplets are received in a dispersing liquid phase and, following a chemical reaction, transform into spherical gel particles. Several 20 g batches of gel were prepared using citrate buffer at pH 5. This buffer was selected to mimic the natural skin pH, which varies between 4.5 and 5.5.

Two systems, ternary and quaternary were prepared by sequentially adding ingredients in different proportions to optimize the texture of the preparations and determine the most suitable formula. Ternary system: pectin (natural or synthetic) water + salicylic acid (SA) or pectin (natural or synthetic) + citrate buffer pH 5 + SA. Quaternary system: pectin (natural or synthetic) + citrate buffer pH 5 + $CaCl_2$ + SA.

The different formulations tested with natural and synthetic pectin are summarized in Table 1.

Table 1. *Different Microparticles Formulations.*

Formulation No (F).	Type of Pectin	% Pectin	Solvent	$CaCl_2$ (%)	SA (%)
F1	NP	2	Water	-	1
F2	NP	3	Water	-	1
F3	NP	2	Citrate buffer pH 5	0.2	1
F4	NP	3	Citrate buffer pH 5	0.2	1
F5	NP	3	Citrate buffer pH 5	-	1
F6	SP	2	Water	-	1
F7	SP	3	Water	-	1

Formulation No (F).	Type of Pectin	% Pectin	Solvent	$CaCl_2$ (%)	SA (%)
F8	SP	2	Citrate buffer pH 5	0.2	1
F9	SP	3	Citrate buffer pH 5	0.2	1
F10	SP	3	Citrate buffer pH 5	-	1

NP: Natural Pectin - SP: Synthetic Pectin - SA: Salicylic Acid - CB: Citrate Buffer

Depending on each formulation's proportions, the pectin was weighed and dissolved in the solvent under stirring at 500 rpm until homogenization. The mixture was then heated to 90 ℃ under continuous stirring for approximately 10 minutes. Salicylic acid was then weighed and gradually added to the pectin solution under continued agitation. Calcium chloride was weighed and dissolved in osmosis water to reach a 10% (w/v) $CaCl_2$ solution.

Microparticles were formed by dripping the polymer solution (pectin + active ingredient) into the $CaCl_2$ 10% (w/v) crosslinking bath under agitation at 300 rpm, using a 5 mL syringe, at a drop distance of approximately 5 cm. Stirring continued for 5 minutes after the final drop. The resulting microparticles were rinsed multiple times with distilled water to eliminate $CaCl_2$ crystals, then dried in a 35 ℃ oven for 24 to 48 hours.

A schematic representation of the microparticle preparation steps is provided in Figure 1.

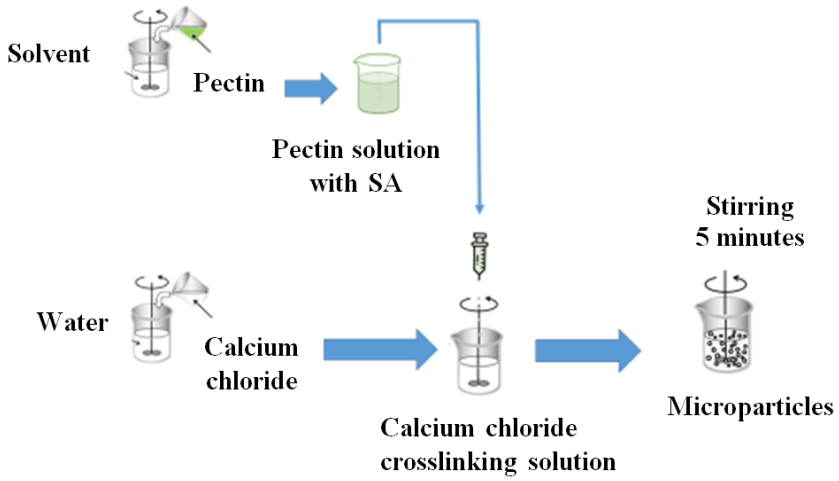

Figure 1. *Schematic procedure for microparticle formulation.*

3.2. Macroscopic Examination of Microparticles

The shape and color of the microparticles were evaluated visually.

3.3. Microscopic Examination of Microparticles

A microscope (Optika Vision Pro) connected to a computer was used to assess microparticle size and shape under magnifications x40. 300 particles were observed. D10 (10% of particles), D90 (90% of particles), and the interdecile ratio (D90/D10) were calculated.

3.4. Determination of Encapsulation Yield

The amount of SA encapsulated was measured by dispersing 25 mg of microparticles in 50 mL of absolute ethanol in a sealed volumetric flask, under magnetic stirring at 460 rpm for 24 hours at room temperature. A 1 mL sample of this solution was withdrawn, filtered, and diluted 10-fold in the same solvent. Absorbance was then measured using a UV-visible spectrophotometer (JENWAY™ 7315, Thermo Fisher Scientific™) at 260 nm (maximum absorption wavelength of SA in absolute ethanol). Each formulation was analyzed in triplicate.

The amount of SA was determined using the standard calibration curve for salicylic acid in ethanol (0.00002 to 0.00016 mol/L). The regression equation obtained was:

$y = 4234.5x + 0.0008$ ($R^2 = 0.999$), where y = Absorbance at 260 nm, and x = SA concentration in mg/L. Ethanol was used as the blank. All experiments were conducted in triplicate.

Encapsulation parameters were calculated as follows.

Encapsulation Efficiency (EE, %) = (Q1 / Q0) × 100 where Q1 = Actual quantity of SA found in dry microparticles (mg), and Q0 = Theoretical quantity of SA used in formulation (mg) [6].

Encapsulation Yield (EY, %) = (Q1 / QBT) × 100 where Q1 = Quantity of SA in the dry microparticles (g), and QBT = Total weight of dried microparticles obtained (g).

4. Results

4.1. Formulated Microparticles

The organoleptic characteristics of the formulated microparticles are presented in Tables 2 and 3.

Table 2. *Microparticles Formulated with Natural Pectin.*

Formulation	Solvent	Results
F1 (2% P + 1% SA)	Water	No microparticles formed
F2 (3% P + 1% SA)	Water	-
F3 (2% P + 1% SA + 0.2% $CaCl_2$)	Citrate buffer pH 5	Flattened particles that burst
F4 (3% P + 1% SA + 0.2% $CaCl_2$)	Citrate buffer pH 5	Moderately rounded particles
F5 (3% P + 1% SA)	Citrate buffer pH 5	Flattened and deformed particles

With water as the solvent, no microparticles were formed due to lack of gelation. Using citrate buffer, particles were obtained, with shape depending on the pectin concentration.

The selected formulation for natural pectin microparticles was F4 (3% pectin, 0.2% $CaCl_2$, 1% salicylic acid in citrate buffer), as it provided particles with acceptable shape.

Table 3. *Microparticles Formulated with Synthetic Pectin.*

Formulation	Solvent	Results
F6 (2% P + 1% SA)	Water	Flattened particles that burst
F7 (3% P + 1% SA)	Water	Regular and rounded particles
F8 (2% P + 1% SA + 0.2% $CaCl_2$)	Citrate buffer pH 5	Flattened particles
F9 (3% P + 1% SA + 0.2% $CaCl_2$)	Citrate buffer pH 5	Irregular, elongated particles
F10 (3% P + 1% SA)	Citrate buffer pH 5	-

Microparticles were successfully obtained with formulation F7 (3% synthetic pectin and 1% salicylic acid in osmosis water). In citrate buffer, particles were irregular or unstable when pectin concentration was low (2%).

4.2. Organoleptic Characteristics

The humid natural pectin microparticles were of varying shapes, elongated or more or less rounded and flattened (Figure 2). After drying in an oven at 35 ℃, they had elongated and clumped together (Figure 3).

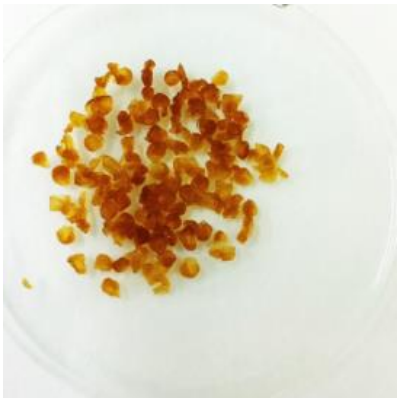

Figure 2. *Humid natural pectin microparticles.*

Figure 3. *Dry natural pectin microparticles.*

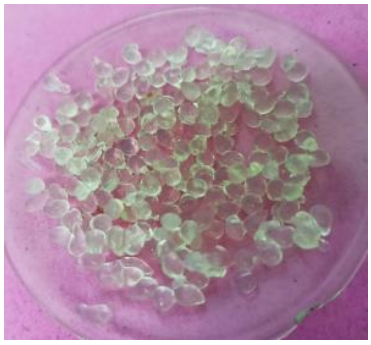

Figure 4. *Humid synthetic pectin microparticles.*

Figure 5. *Dry synthetic pectin microparticles.*

With synthetic pectin, the microparticles were white, rounded, and of uniform size (Figure 4). After drying in an oven at 35 ℃, they were beige in color with varying shapes (Figure 5).

4.3. Particle size analysis

Figures 6 and 7 showed dry microparticles of natural and synthetic pectin under optical microscopy at magnifications x40.

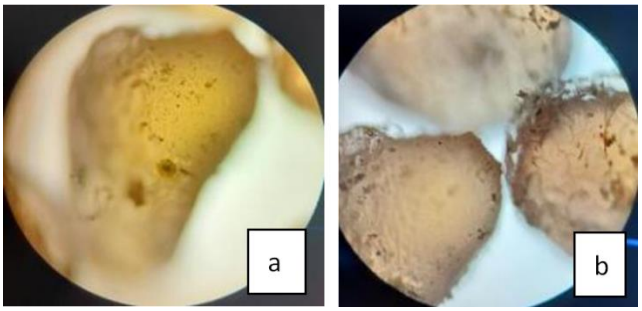

Figure 6. *Dry natural pectin microparticles.*

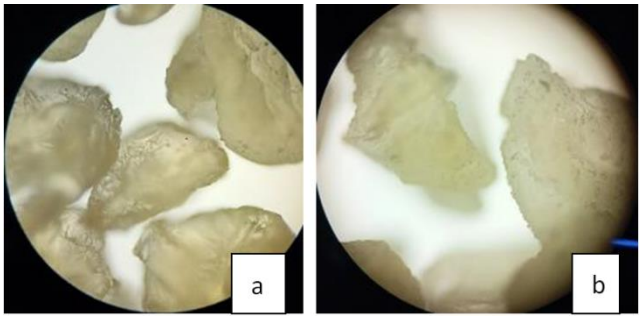

Figure 7. *Dry synthetic pectin microparticles.*

The microparticles exhibited diverse morphologies: elongated or pear-shaped or ovoid and flattened. They were of varying size (Table 4).

Table 4. *Microscopic analysis of natural and synthetic pectin microparticles.*

Parameters	Natural Pectin (µm)	Synthetic Pectin (µm)
Average size	137.70 ± 25.15	85.19 ± 14.33
D10 (10% of particles ≤)	104.00 ± 0.8	66.00 ± 0.5
D90 (90% of particles ≤)	173.00 ± 0.13	103.00 ± 0.6
Interdecile ratio (D90/D10)	1.66 ± 0.2	1.56 ± 0.4

Analysis size distribution of the dry microparticles showed that synthetic pectin microparticles were smaller than those made with

natural pectin. For natural pectin, 10% of particles had a diameter inferior or equal to 104 µm and 90% were less than or equal to 173 µm. For synthetic pectin, 10% of particles were inferior or egal to 66 µm and 90% were less than or equal to 103 µm.

4.4. Encapsulation Yield and Efficiency

The encapsulation efficiency and yield for dry microparticles are shown in Table 5.

Table 5. *Encapsulation Yield and Efficiency of Dry Microparticles.*

Parameters	Natural Pectin (%)	Synthetic Pectin (%)
Encapsulation efficiency	6.08 ±0.3 (standard deviation)	17.72 ±0.5 (standard deviation)
Encapsulation yield	78.5 ±0.2 (standard deviation)	88 ±0.16 (standard deviation)

The encapsulation efficiencies of dry microparticles of natural pectin and synthetic pectin were 6.08% and 17.72%, respectively. Encapsulation efficiency of synthetic pectin microparticles was nearly three times higher than that of natural pectin microparticles. However, encapsulation yields were relatively similar between the two types: 78.5% for natural pectin and 88% for synthetic pectin.

5. Discussion

Pectin is an important natural polymer derived from various plants, widely used in the food industry, pharmaceuticals, and many other sectors due to its excellent gelling, thickening, and stabilizing properties. Although pectin is present in most plants, sources for commercial pectin production remain limited. Indeed, studies have shown that the gelling properties of pectin can vary depending on its origin [9, 10]. Mango is one of the most appreciated and valuable fruits in tropical and subtropical regions. Mango peel has been identified as a promising source of pectin, especially for its film-forming properties [7]. The objective of this work was to develop and characterize microparticles based on natural pectin extracted from mango peel (Mangifera indica, variety Amélie) and synthetic pectin, for the encapsulation of salicylic acid with a view to topical application in the treatment of acne vulgaris.

Several formulations were prepared by varying parameters such as the pectin concentration (2% and 3%), the solvent (osmosis water or citrate buffer pH 5), and the presence or absence of $CaCl_2$. At the end of the formulation trials, the selected formulas were F4 (3% natural pectin + 0.2% $CaCl_2$ + 1% salicylic acid in citrate buffer pH 5) and F7 (3% synthetic pectin + 1% salicylic acid in osmosis water).

The choice of ionotropic gelation as the encapsulation method was justified by its simplicity, low toxicity, and the absence of organic solvents, as reported by Chan et *al.* who consider this method particularly suitable for encapsulating substances sensitive to heat or organic solvents [11].

Wet microparticles made from synthetic pectin (F7) were spherical and light brown in color. In contrast, those made from natural pectin (F4) were slightly flattened and dark brown. Oven drying at 35 ℃ caused visible deformation of the microparticles, particularly those based on natural pectin. This deformation may be due to the drying technique used. Morita et *al.* suggested that freeze-drying microparticles after formulation would preserve their initial spherical morphology [12].

Microscopic observation revealed that microparticles made from natural pectin were more flattened and of very irregular shape. This heterogeneity may be explained by the composition variability inherent to natural polymers, particularly plant-derived polysaccharides such as natural pectin, which may contain other elements (ions, chemical compounds) interfering with the formation of well-defined microparticles [13]. This author noted that the purity, degree of esterification, and presence of impurities such as metallic ions or proteins can alter the formation of a gel network in the presence of divalent cations.

Granulometric analysis showed that the average size of the microparticles varied depending on the type of pectin used. Dry microparticles from natural pectin had an average size of 137.70 ±25.15 µm, whereas those from synthetic pectin had a smaller average size of 85.19 ± 14.33 µm. These results confirm that synthetic pectin tends to produce smaller particles, consistent with observations by Anselmi et *al.* who demonstrated that using highly homogeneous polymers allowed better control over particle size [14]. Thus, the nature of pectin may influence microparticle size. The interdecile ratios were 1.66 for natural pectin and 1.56 for synthetic pectin. Since these values are close to 1, they suggest a relatively uniform particle size distribution, which is important for ensuring the reproducibility of formulations.

The encapsulation efficiencies of dry microparticles from natural and synthetic pectin were 6.08% and 17.72%, respectively. These efficiencies remain relatively low, likely due to the encapsulation method used. Indeed, Richard et *al.* reported that encapsulation efficiencies for ionotropic gelation generally range from 10% to 30%, due to rapid diffusion of the hydrosoluble active ingredient into the crosslinking bath [15]. The low encapsulation observed in this study may also be explained by the high solubility of salicylic acid in the

crosslinking solvent (water or citrate buffer), favoring its loss before the polymer network stabilizes. Additionally, the matrix nature and its composition may have contributed. Mehida et *al.* reported salicylic acid encapsulation efficiencies ranging from 10.76% to 39.42% depending on the matrix used. They concluded that the nature and composition of the encapsulating matrix had a significant impact on drug content, yield, and particle size [16]. According to Mehida et *al.* the density of free carboxyl groups and the degree of pectin methylation strongly influence its gelling properties, and consequently, the quality of the microparticles formed [16].

Nonetheless, synthetic pectin-based microparticles had clearly superior encapsulation efficiency compared to those based on natural pectin, while the encapsulation yields of both types were relatively similar.

Still, the natural mango pectin («Amélie» variety) demonstrated its ability to encapsulate salicylic acid, opening the way for future optimization of these formulations, particularly through calibration of the encapsulation process and drying method.

6. Conclusion

This study successfully developed and characterized salicylic acid-loaded microparticles using two types of pectin: a natural pectin extracted from mango peel (Mangifera indica, Amélie variety) and a synthetic pectin. The ionotropic gelation technique proved suitable for encapsulating salicylic acid with both types of pectin. The microparticles were used for further experiments. The results demonstrated that the type of pectin significantly influences the quality of the microparticles obtained. Synthetic pectin produced smaller, more regular microparticles (85.19 ± 14.33 µm) with a higher encapsulation efficiency (17.72%) compared to natural pectin (6.08%). These differences are likely due to the more homogeneous chemical composition of synthetic pectin, which promotes efficient ionic crosslinking. In contrast, although natural pectin showed the ability to form microparticles, it presented considerable morphological variability, probably due to the presence of impurities and a non-standardized degree of esterification. Overall, these results confirm the feasibility of developing a topical delivery system based on locally sourced natural polymers. However, they also underline the need to optimize formulation parameters to improve both the galenic performance and therapeutic effectiveness. This work contributes to the valorization of local plant resources and the development of innovative, accessible, and eco-friendly pharmaceutical forms.

Abbreviations

ALMP	Low-Methoxyl Amidated Pectin
CB	Citrate Buffer
F	Formulation
NP	Natural Pectin
SA	Salicylic Acid
SP	Synthetic Pectin

Conflicts of Interest

The authors declare no conflicts of interest.

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