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Article

In Vitro Release of Curcumin and Resveratrol from Polymeric Systems: Films and Hydrogel

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Abstract

Chronic wounds are a persistent clinical and public health challenge. Natural polyphenols such as curcumin and resveratrol, alongside mesenchymal stem cell (MSC) secretome, have demonstrated complementary anti-inflammatory, antioxidant, and pro-angiogenic properties with potential for wound healing. This study reports two complementary in vitro investigations evaluating the release profiles of curcumin and resveratrol from two polymeric platforms: poly(vinyl alcohol)/sodium alginate/carboxymethylcellulose films (Study 1) and an acrylate copolymer-based hydrogel incorporating MSC secretome (Study 2). UV-Vis spectrophotometric analysis confirmed analytical selectivity with no interference from excipients. In Study 1, films containing curcumin alone exhibited low structural stability and early disintegration in aqueous medium, whereas resveratrol-only films (2% w/w) demonstrated sustained and reproducible release profiles. Combined formulations showed that curcumin compromised polymer matrix integrity and reduced resveratrol release efficiency. In Study 2, resveratrol exhibited progressive and consistent release from the hydrogel, reaching 14.31 μg/mL (isolated control) and 12.60 μg/mL (combined with curcumin) at 120 min. Curcumin showed unsatisfactory release in both systems, attributed to its low aqueous solubility. These results support resveratrol-loaded polymeric matrices as promising sustained-release platforms for bioactive wound dressings and highlight the need for nanoencapsulation strategies to improve curcumin bioavailability.

Keywords: polymeric films; hydrogel; resveratrol

1. Introduction

Wound healing is a programmed physiological process comprising four sequential phases: hemostasis, inflammation, proliferation, and tissue remodeling. Under normal conditions, acute wounds complete this process within two to six weeks. Chronic wounds, however, remain stalled in the inflammatory phase, exhibiting elevated levels of pro-inflammatory cytokines, proteases, reactive oxygen species (ROS), and senescent cells, which collectively impair tissue repair. The most prevalent types include diabetic foot ulcers, venous leg ulcers, and pressure ulcers, all of which impose a substantial burden on healthcare systems worldwide [1].

The inflammatory phase is characterized by the predominance of phagocytic cells: neutrophils, which release ROS and proteases to prevent microbial contamination, and macrophages, which secrete growth factors and cytokines that recruit fibroblasts, endothelial cells, and keratinocytes to repair damaged blood vessels. The proliferation phase involves tissue granulation, angiogenesis, and epithelialization. Finally, the remodeling phase, which may last years, replaces the provisional matrix with organized collagen bundles [1]. Patients with chronic wounds experience reduced quality of life due to persistent pain, psychological distress, and the high financial cost of treatment [2,3]. The global

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wound care market was projected to reach USD 7.1 billion in 2019 [4], and recent industry estimates forecast growth of at least 11% per year through 2029 [5].

The development of bioactive formulations that promote rapid and complete healing of chronic wounds is, therefore, a scientific and clinical priority. Among the most extensively studied natural compounds, curcumin [1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione] and resveratrol (3,5,4′-trihydroxystilbene) stand out for their complementary mechanisms of action. Curcumin, the principal pigment of Curcuma longa L. rhizomes, has a topological polar surface area of 93.1 Å² and is practically insoluble in water. Resveratrol, a plant polyphenol found in high concentrations in red grapes, exists as cis-(Z) and trans-(E) isomers—the trans-form being more stable—with a water solubility of 3 mg/100 mL and UV absorption maxima at 218, 307, and 321 nm [6].

Both compounds inhibit the NF-κB signaling pathway, which is associated with prolonged inflammation, reduced angiogenesis, and impaired cell proliferation [7]. Their synergistic effects have been documented in cancer biology, hypertension, and inflammatory conditions through complementary mechanisms targeting multiple molecular pathways [8–11]. In fibroblast and keratinocyte cultures, both bioflavonoids stimulated cell division rates and scratch-wound closure without significant cytotoxicity [12]. In vivo, curcumin administered for 14 days in diabetic rats reduced NF-κB, TNF-α, and IL-6, while increasing re-epithelialization, wound closure, collagen deposition, and angiogenesis [13]; resveratrol produced analogous effects in a parallel model [14]. Both compounds also significantly increased collagen synthesis in the skin of healthy rats after chemical peeling [15], and in burn wounds, curcumin and resveratrol loaded in nanogels demonstrated in vivo healing efficacy [16].

The secretome of mesenchymal stem cells (MSCs) constitutes a third promising component for wound-healing formulations. MSCs are multipotent adult stem cells found in bone marrow, adipose tissue, umbilical cord, and dental pulp, capable of differentiating into connective, skeletal muscle, and vascular tissues [17]. Their secretome—the collection of molecules and biological factors secreted into the extracellular space—exhibits pro-angiogenic, anti-fibrotic, anti-apoptotic, anti-inflammatory, and immunomodulatory properties [18]. Daily injections of secretome improved healing and angiogenesis in radiation-induced skin injuries in rats [19]; topical application accelerated wound closure in diabetic swine [20]; and its senolytic action promoted vascularization and reduced inflammation in diabetic wound beds [21]. Specifically, secretome derived from human deciduous tooth pulp-derived MSCs (hDP-MSCs) has been shown to promote keratinocyte migration, accelerate in vitro wound closure, and upregulate key regenerative genes including IL-1β, TGF-β1, and VEGFα, without cytotoxicity [22].

For the delivery of these active ingredients, polymeric film dressings and hydrogels have been widely explored. Films based on poly(vinyl alcohol) (PVA) [23,24], chitosan [25], sodium alginate [26], and crosslinked hydrogels [27], as well as acrylate copolymer-based hydrogels [28], have been developed with properties including biocompatibility, exudate control, and sustained active ingredient release. These platforms aim to overcome the poor bioavailability of compounds such as curcumin, which suffers from chemical instability, low aqueous solubility, and rapid metabolism.

The present work integrates two complementary undergraduate research projects evaluating the in vitro release of curcumin and resveratrol from two distinct polymeric systems: PVA/alginate/CMC films (Study 1) and an acrylate copolymer-based hydrogel (Study 2). In both cases, the formulation design includes future incorporation of MSC secretome, constituting an innovative multi-component approach with synergistic potential for the treatment of chronic wounds.

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2. Results and Discussion

2.1. Interference Analysis

Spectral scanning confirmed the selectivity of the UV-Vis method for the individual quantification of curcumin and resveratrol in both studies. The maximum absorbance wavelengths for all analyzed components are presented in Table 1. Glycerin, silicone oil, PVA, sodium alginate, CMC, and acrylate copolymer showed no appreciable absorption in the 200–800 nm range and did not interfere with active ingredient quantification.

Table 1. Maximum absorbance wavelengths of the analyzed components.

Substance	λmax (nm)	Absorbance
Curcumin	424.9	0.631
Resveratrol	305.0	0.504
Methylparaben	254.9	0.726
Propylparaben	260.0	0.883
Polysorbate 80	235.0	0.372
Acrylate copolymer	—	Not detectable

The wavelengths of curcumin (424.9 nm) and resveratrol (305.0 nm) are sufficiently distinct from all other components, confirming analytical selectivity.

2.2. Study 1—Evaluation of Polymeric Films

Formulations containing curcumin alone (D, and earlier formulations A and B) exhibited significant physicochemical problems: bubble formation, low mechanical resistance, high fragility, excessive adhesiveness, and rapid disintegration in aqueous medium, making release assays unfeasible. In contrast, resveratrol-only formulations (C, H, I) demonstrated greater structural stability. Formulation E was discarded due to fungal contamination after prolonged storage. Formulations F and G, containing both compounds, maintained integrity in aqueous medium but displayed irregular surface texture. Table 2 presents a consolidated summary of stability and release performance.

Table 2. Summary of stability and release profile of polymeric film formulations (Study 1).

Active ingredient	Stability	Release profile	Main observations
Curcumin 2%	Low	Irregular	Early disintegration; low solubility; unfeasible for release assay
Resveratrol 2%	High	Sustained	Progressive, stable, reproducible release
Curcumin + Resveratrol	Moderate	Unstable	Curcumin compromises matrix; reduces resveratrol release efficiency

2.3. Study 1—Release Profiles

Release assay results for Study 1 are presented in Tables 3 and 4. Resveratrol-only formulations (H and I) exhibited progressive and reproducible release profiles. In formulation H, maximum absorbance/g was reached at 90 min (0.2118 abs/g), with sustained release maintained up to 120 min

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(0.1954 abs/g). Formulation I confirmed the pattern with consistent values up to 0.1704 abs/g at 120 min. Curcumin in all film formulations showed low and inconsistent absorbance values throughout the entire release period.

Table 3. Release profile of resveratrol from film formulations H and I (PBS pH 6.5; 35.5 ± 1 °C).

Time (min)	Form. H – Absorbance	Form. H – Abs/g	Form. I – Absorbance	Form. I – Abs/g
10	0.1320	0.04125	0.1443	0.04655
30	0.4188	0.12770	0.2881	0.09293
60	0.2925	0.08310	0.4328	0.13872
90	0.8448	0.21180	0.5058	0.15468
120	0.7229	0.19540	0.4806	0.17042

Table 4. Release profile of formulation F (curcumin 2% + resveratrol 2%) in PBS, without and with polysorbate 80 (PBS pH 6.5; 35.5 ± 1 °C).

Time (min)	Resv. Abs/g (without PS80)	Curcu. Abs/g (without PS80)	Resv. Abs/g (with PS80)
10	0.1586	0.002121	0.001573
30	0.1642	0.000818	0.002757
60	0.2070	0.000157	0.008900
90	0.2575	0.001274	0.008050
120	0.2643	0.003227	0.010820

PS80: polysorbate 80; Resv.: resveratrol; Curcu.: curcumin.

2.4. Study 2—Release Profiles in Hydrogel

The complete release assay results for Study 2 are presented in Table 5. Resveratrol demonstrated progressive and consistent release in both control formulations—isolated and combined with curcumin. In the isolated resveratrol control, released concentration increased from zero at 10 min to 14.31 μg/mL at 120 min. In the combined formulation (resveratrol + curcumin), resveratrol release reached 12.60 μg/mL at 120 min. Curcumin absorbance values were below the linear range of the method (0.2–0.9) in the majority of time points, rendering quantitative results unreliable.

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Table 5. Release profile of resveratrol control formulations in the hydrogel system via Franz diffusion cell (PBS pH 6.5; 35.5 ± 1 °C).

	Time (min)	Absorbance	Concentration (μg/mL)	Released (%)
Resveratrol isolated	10	0.02136	0 ± 0	0
	30	0.03523	0.07 ± 0.00025	0.05
	60	0.25423	1.92 ± 0.00038	1.43
	90	0.36060	2.83 ± 0.00052	2.10
	120	0.87193	14.31 ± 0.00118	10.66
Resveratrol + Curcumin (resveratrol analysis)	10	0.05775	0.26 ± 0.00044	0.19
	30	0.16540	1.17 ± 0.00052	0.87
	60	0.72128	5.88 ± 0.00036	4.38
	90	0.96173	7.92 ± 0.00066	5.90
	120	0.77065	12.60 ± 0.00170	9.38

The results obtained in both studies converge consistently: resveratrol demonstrated a sustained and reproducible in vitro release profile across both evaluated polymeric platforms, as shown in Tables 3, 4, and 5, whereas curcumin exhibited unsatisfactory release, attributed primarily to its low aqueous solubility.

Confirmation of UV-Vis method selectivity by spectral scanning was an essential methodological step. Spectral overlapping is one of the main challenges of spectrophotometric methods applied to complex mixtures [32] and verifying that no excipient interfered with active ingredient quantification guaranteed the reliability of subsequent release assay results. With curcumin at 424.9 nm and resveratrol at 305.0 nm, and no excipient absorbing significantly at either wavelength, the method proved adequate for individual quantification of both compounds.

In Study 1, curcumin-only films showed behavior consistent with literature reports: the addition of curcumin to polymeric matrices reduces tensile strength and maximum elongation, indicating lower structural cohesion [33], which manifested as high fragility, excessive adhesiveness, and rapid disintegration in PBS. Resveratrol-only films (H and I), as shown in Table 3, conversely, exhibited satisfactory stability and an increasing, reproducible absorbance/g pattern over 120 min—consistent with a sustained-release system and desirable for chronic wound dressings, which require continuous antioxidant/anti-inflammatory supply over several hours.

In combined formulations (F and G), curcumin compromised matrix integrity, producing irregular surface texture and reduced resveratrol release efficiency. Nevertheless, formulation F, whose release data are presented in Table 4, with polysorbate 80 in the receptor medium yielded the highest resveratrol release percentages. The addition of a non-ionic surfactant to the receptor medium is a recognized strategy to increase the solubilization and diffusion of hydrophobic drugs in in vitro release assays [30], and the result reflects improved drug diffusivity in the receptor phase rather than an intrinsic change in formulation behavior.

In Study 2, the Franz diffusion cell methodology, the gold standard for in vitro release studies of semi-solid formulations [29,30,31]—enabled a more controlled and clinically comparable evaluation. As shown in Table 5, resveratrol incorporated into the acrylate copolymer hydrogel showed gradual and progressive release in both isolated and combined formulations, reaching concentrations above 14 μg/mL at 120 min. This behavior is attributed to resveratrol's hydrophobic nature: when embedded in the polymeric network, release is governed by diffusion through the matrix, avoiding a burst release and favoring maintenance of therapeutic concentrations over time. This characteristic is highly desirable for chronic wound management, where sustained antioxidants and anti-inflammatory activity is required.

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Curcumin results were unsatisfactory in both systems. Despite imparting its characteristic yellow-orange color to the receptor medium, its absorbance values were systematically outside the analytical method's linear range, preventing reliable quantification. This is consistent with the well-documented low bioavailability of curcumin due to its poor aqueous solubility, chemical instability (photodegradation, alkaline hydrolysis), and rapid metabolism [34,35]. Comparative studies have shown that hydrogel-based systems tend to retain curcumin within the matrix, resulting in lower release rates compared to nanoparticle systems [34,35]. Nanoencapsulation strategies, particularly liposomes, can encapsulate both hydrophilic and hydrophobic compounds within phospholipid bilayer membranes [36,37] and polymeric nanoparticles [13] have demonstrated improved curcumin solubility, stability, and bioavailability. Reformulation of curcumin using nanotechnology therefore represents the logical next step to enable its incorporation into the proposed bioactive wound dressing.

The MSC secretome component, incorporated into the Study 2 test formulation, was not quantitatively evaluated in the present work due to the high cost of cytokine and growth factor assay kits. However, secretome components are predominantly water-soluble, which would favor their release into the aqueous wound environment. Payão et al. [22] demonstrated that hDP-MSC secretome accelerates keratinocyte migration and in vitro wound closure, modulates key regenerative genes (IL-1β, TGF-β1, VEGFα) in a time-dependent manner, and configures a promising cell-free therapy approach for impaired healing contexts. The combination of resveratrol—with proven antioxidant, anti-inflammatory, and pro-angiogenic activity [7,15]—and MSC secretome in a single polymeric platform represents an innovative and potentially synergistic strategy.

This study has limitations inherent to its exploratory and preliminary character. Formal validation of the analytical method (linearity, precision, accuracy, detection and quantification limits) is planned for subsequent research stages. In Study 1, the absence of calibration curves precluded expression of results in μg/mL, limiting direct quantitative comparison with Study 2. The adapted release apparatus and variation in film drying conditions may have introduced uncontrolled variability. The limited number of replicates restricts statistical power. Furthermore, all experiments were conducted in vitro using PBS as the receptor medium, which only partially simulates the complex chronic wound microenvironment (enzymes, variable pH, plasma proteins, possible biofilm). The clinical relevance of the observed release profiles remains to be confirmed in cellular and preclinical in vivo models.

3. Conclusions

Both studies converge to demonstrate that resveratrol at 2% (w/w) exhibits progressive, sustained, and reproducible in vitro release profiles from PVA/alginate/CMC polymeric films and an acrylate copolymer-based hydrogel, supporting the viability of these matrices as sustained-release platforms for bioactive wound dressings. Formulations H and I (Study 1) and the resveratrol control (Study 2) are recommended for continuation as the most suitable for further development.

Curcumin demonstrated unsatisfactory release in both platforms, attributed to its low aqueous solubility. Nanoencapsulation strategies, particularly liposomes and polymeric nanoparticles, are recommended to overcome this limitation and enable its inclusion in the proposed formulation.

The association of resveratrol with MSC secretome from deciduous tooth pulp in a single polymeric platform represents an innovative multi-component approach with high therapeutic potential for chronic wound healing, warranting further investigation in cellular and in vivo preclinical models, including quantitative secretome release profiling.

4. Materials and Methods

4.1. Study Design

Two in vitro experimental studies were conducted at the School of Pharmaceutical Sciences, PUC-Campinas. Study 1 evaluated polymeric films as drug delivery systems; Study 2 evaluated an

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acrylate copolymer-based hydrogel using Franz diffusion cells. Both studies followed the same active ingredients and release quantification methodology, enabling comparative analysis.

4.2. Study 1—Polymeric Films

4.2.1. Formulation Preparation

All materials were of pharmaceutical grade. Polymeric films were prepared with poly(vinyl alcohol) (PVA), sodium alginate, carboxymethylcellulose (CMC), glycerin, silicone oil, methylparaben, and deionized water, incorporating curcumin and/or resveratrol at 2% (w/w). A 15% (w/v) PVA stock solution was prepared under controlled heating (60 °C) with constant magnetic stirring until complete dissolution. CMC was hydrated in a water bath at 40 °C for 1 h. Sodium alginate was dissolved under heating below 50 °C. Active ingredients were dispersed in glycerin and added to the PVA solution. After homogenization of all components, pH was adjusted to 5.8 with 10% (w/v) acetic acid. Formulations were poured into circular silicone molds, dried in an oven at 50 °C, and subsequently stored in a desiccator. The compositions of the main evaluated formulations are presented in Table 6.

Table 6. Composition of the main polymeric film formulations evaluated in Study 1.

Component	D	E	F	G	H/I
PVA stock solution	26.7 g	26.7 g	22.0 g	22.0 g	22.0 g
Sodium alginate	0.60 g	0.60 g	0.60 g	0.60 g	0.60 g
CMC	0.15 g	0.15 g	0.15 g	0.15 g	0.15 g
Curcumin	2 g (2%)	—	2 g (2%)	0.67 g (0.67%)	—
Resveratrol	—	2 g (2%)	2 g (2%)	2 g (2%)	2 g (2%)
Glycerin	10 mL	10 mL	15 mL	15 mL	15 mL
Silicone oil	2 drops	2 drops	2 drops	2 drops	2 drops
Methylparaben	0.15 g	0.15 g	0.15 g	0.15 g	0.15 g
Deionized water	q.s. 100 g	q.s. 100 g	q.s. 100 g	q.s. 100 g	q.s. 100 g

CMC: carboxymethylcellulose; PVA: poly(vinyl alcohol); q.s.: quantum satis.

4.2.2. Release Assays—Study 1

In vitro release profiles were evaluated using phosphate-buffered saline (PBS, pH 6.5; 35.5 ± 1 °C) as the receptor medium, which partially simulates the wound microenvironment [29,30]. Films were positioned either on semi-permeable cellulose acetate membranes (diameter 47 mm; porosity ~4500 Å) pre-soaked in the receptor medium, or directly immersed in the receptor medium, in 80 mL hermetic flasks. Aliquots were collected at 10, 30, 60, 90, and 120 min for UV-Vis spectrophotometric quantification. For formulation F, additional assays were performed with polysorbate 80 added to the receptor medium to improve curcumin solubilization. The corresponding release results are presented in Tables 3 and 4.

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4.3. Study 2—Hydrogel

4.3.1. Formulation

The test formulation was a hydrogel of simplified composition, developed focusing on formulation simplicity and excipient safety for application on chronic wounds. The final composition comprised acrylate copolymer (1.8%), preservative (0.8%), emulsifying agent (0.2%), curcumin (2%), resveratrol (2%), MSC secretome (0.2%), and purified water to 100%. The secretome was obtained from MSCs derived from deciduous tooth pulp, collected from pediatric patients treated at the Pediatric Dentistry Clinic of PUC-Campinas, as described by Payão et al. [22]. For release assays, control formulations were also prepared: placebo (blank), curcumin-only control, resveratrol-only control, and curcumin + resveratrol combined (without secretome).

4.3.2. Release Assays—Study 2

Release assays were conducted using Franz diffusion cells [29,30,31], with 74.5 mL of PBS (pH 6.5) as the receptor medium, maintained at 35.5 ± 1 °C. Exactly 0.5 g of each formulation was weighed and uniformly distributed over cellulose acetate semi-permeable membranes (47 mm, 4500 Å, Kasvi, São José dos Pinhais, Brazil). Individual apparatus were assembled for each collection time point (10, 30, 60, 90, and 120 min) and maintained in a thermostated ultrasonic bath at 35.5 ± 1 °C throughout the assay. At each time point, a 3 mL aliquot of the receptor medium was collected for quantification of released curcumin and/or resveratrol by UV-Vis spectrophotometry at 425 nm and 305 nm, respectively.

4.3.3. Calibration Curves

For curcumin quantification, stock solutions were prepared in PBS (pH 6.5) with a few drops of Tween 80 to promote aqueous dissolution. Final calibration concentrations were: 25, 37.5, 50, 62.5, and 75 μg/mL. For resveratrol, stock solutions were prepared in PBS (pH 6.5), with final calibration concentrations of 1, 2, 3, 4, 5, and 6 μg/mL. Linear regression equations and correlation coefficients (r^2) were calculated for each compound.

4.4. Interference Analysis

In both studies, individual spectral scanning of each formulation component was performed in the range of 200–800 nm to confirm the absence of overlapping absorbance bands that could interfere with active ingredient quantification [32]. This step was essential to establish the selectivity of the UV-Vis method prior to release assays.

4.5. Statistical Analysis

Results were organized in tables and figures. Descriptive statistical analyses (means and standard deviations) were performed using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA).

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protocol approved by the Ethics Committee of PUC-Campinas (see Payão et al. [22]).**Informed Consent Statement:** Not applicable.

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Abbreviations

The following abbreviations are used in this manuscript:

CMC	sodium alginate, carboxymethylcellulose
MSC	alongside mesenchymal stem cell
PVA	poly(vinyl alcohol
ROS	reactive oxygen species

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