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β-cyclodextrin/curcumin inclusion complex-loaded hydrogels films based on biopolymers. Characterization and curcumin release kinetic study.

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Introduction:

- Curcumin has antibacterial, antioxidant, and anti-inflammatory activity. It was successfully used to treat dermatological diseases. The main drawback of using curcumin is its water insolubility and low bioavailability. The attenuation or elimination of these disadvantages has been attempted by preparing formulations based on micelles, liposomes, polymeric nanoparticles, complexes, emulsions. Polymer matrices can protect curcumin from adverse environmental conditions; improve the half-life of the bioactive compound, thus increasing its bioavailability both *in vitro* and *in vivo*.
- In this study, β-cyclodextrin inclusion complexes were prepared in order to increase the water solubility of curcumin. The inclusion complexes of curcumin/β-cyclodextrin were immobilized in hydrogels films based on biopolymers (gellan, albumin and pectin) obtained by ionic cross-linking and polyelectrolite complexation, in order to treat especially dermatological diseases

Experimental Methods

- The gellan/albumin (BSA) films containing the β-cyclodextrin/curcumin inclusion complex were obtained by ionic cross-linking with magnesium acetate at pH 7.8, being subsequently polyelectrolytically complexed with 1.5% (w/v) pectin solution.
- BSA was used in order to improve the hydrogel films biocompatibility, the immune response capacity and to increase the systemic level of glutathione.
- The effect of pH on the cross-linking degree was studied and it was observed that the BSA carboxylic groups from the gellan/BSA solution react at pH 7.8 with Mg^{2+} ions; the amino groups react at pH 3.5 with the pectin carboxylic groups leading to a polyelectrolyte complexed film.
- The films obtained were characterized by the swelling degree, SEM, FT-IR and the cytotoxicity was evaluated. The curcumin antioxidant activity within the films was evaluated and the protective role of the polymer matrix was proved. The release kinetics studies of curcumin from the biopolymer films were performed in two different pH media (5.5 and 7.4); higher release efficiency was observed at pH 7.4, in accordance with the swelling degree behavior.

Results:

Table 1: Experimental program:

Sample *	Quantity of gellan, mg	Quantity of BSA, mg	Quantity of pectin, mg	Magnesium acetate concentration%	Quantity of curcumin from inclusion complex, mg	Immobilization efficiency, %
P1	200	100	600	0.5		
P2	150	100				
P3	100	100				
P4	100	200				
P1C	200	100			25	60.48
P2C	150	100				84.91
P3C	100	100				97.78
P4C	100	200				89.05

**Gellan solution volume: 20 ml BSA solution volume: 5 ml*
Pectin solution volume: 60 ml Concentration of glycerine: 1% (w/w)
Magnesium acetate solution volume: 1 ml

Table 2. Influence of pH on polyelectrolyte complexation efficiency (Ef%) and BSA quantity that diffuse in pectin solution (1.5%, 60 ml, pH 3.5) from gellan/BSA films.

Sample	Quantity of BSA, mg-pH 6.5	Ef_{PE} % - pH 6.5	Quantity of BSA, mg-pH 7.4	Ef_{PE}% - pH 7.4	Quantity of BSA, mg-pH 7.8	Ef_{PE} % - pH 7.8	Quantity of BSA, mg-pH 8.5	Ef_{PE}% - pH 8.5
P1	30.2	69.8	63.48	36.52	7.84	92.16	52.24	47.76
P2	45	55	34.17	65.83	7.1	92.9	65.23	34.77
P3	21.9	78.1	27.02	72.98	3.93	96.07	68.82	31.18

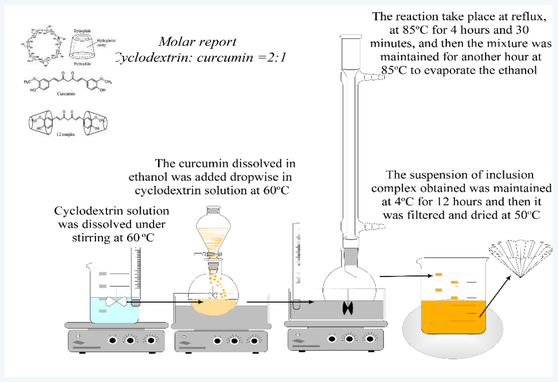

Figure 1. Method used for the preparation of inclusion complex of cyclodextrin with curcumin

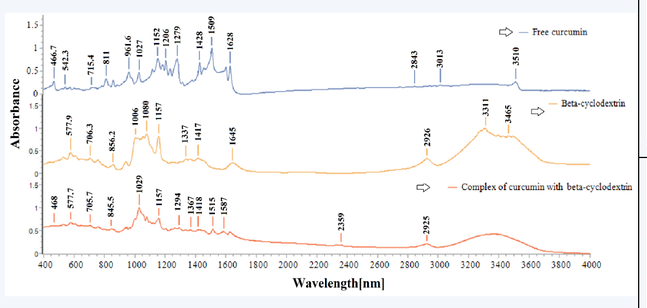

Figure 2. FT-IR spectrum of curcumin, β-cyclodextrin inclusion complex of curcumin/cyclodextrin

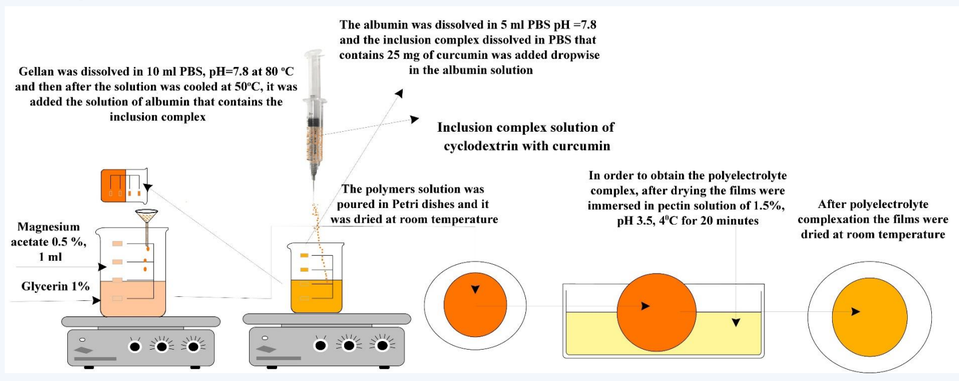

Figure 3. Preparation of the hydrogel films based on biopolymers with inclusion complex of cyclodextrin with curcumin loaded

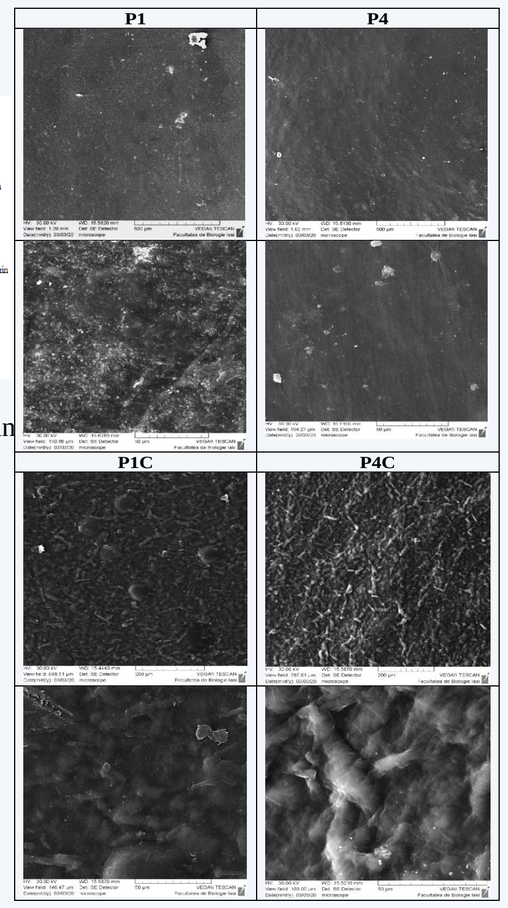

Figure 4. SEM micrographs for P1, P4, P1C and P4C samples.

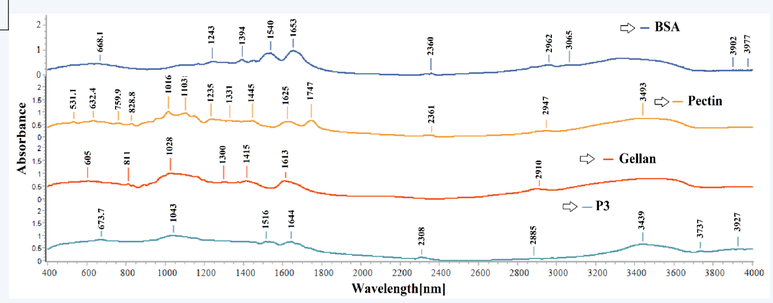

Figure 4. FT-IR spectrum of gellan, BSA, pectin and P3 sample.

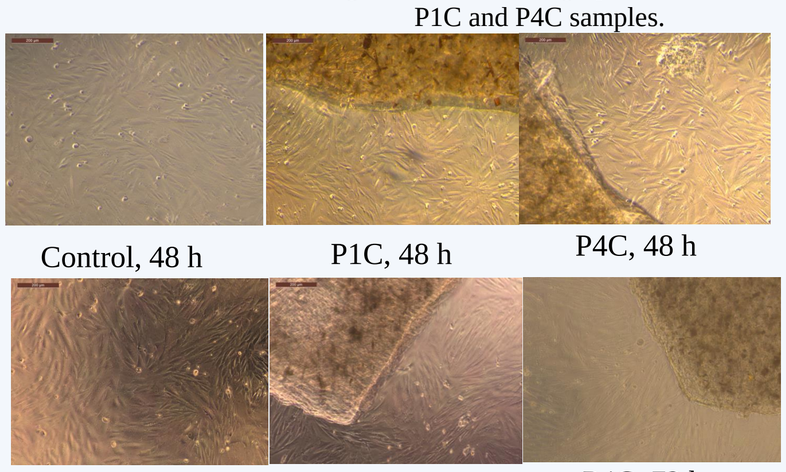

Figure 8. Phase contrast images of cells (fibroblast)

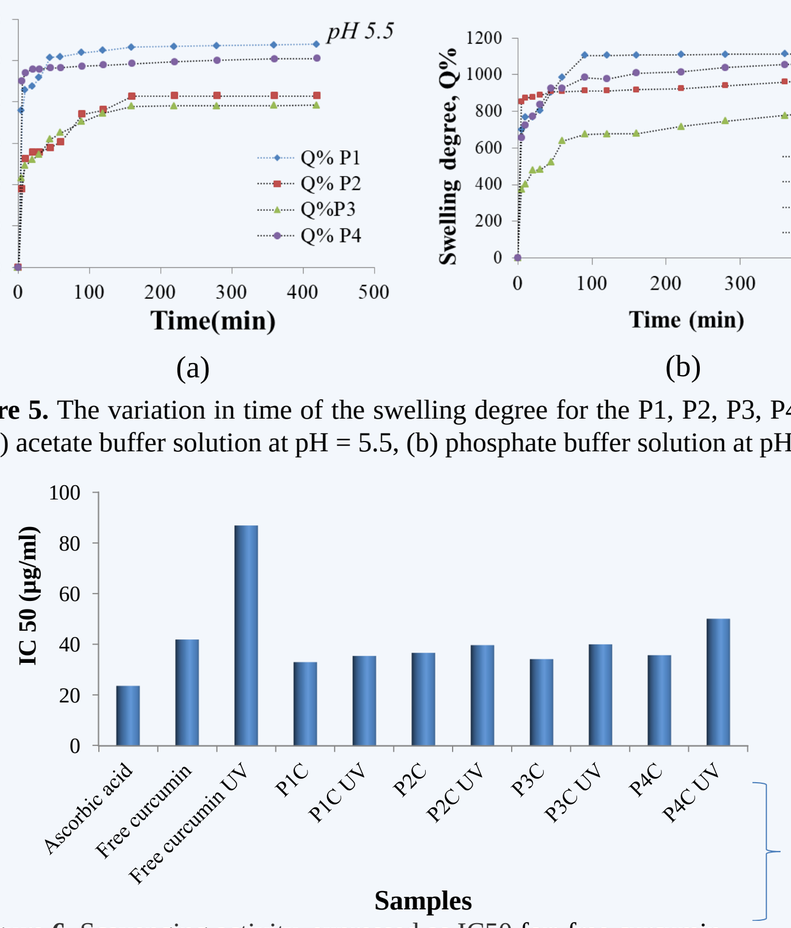

Figure 5. The variation in time of the swelling degree for the P1, P2, P3, P4 samples in: (a) acetate buffer solution at pH = 5.5, (b) phosphate buffer solution at pH = 7.4.

Figure 6. Scavenging activity, expressed as IC50 for: free curcumin, curcumin extracted from P1C, P2C, P3C, P4C films. The films were exposed to UV light at 364 nm for 30 minutes and the antioxidant activity of curcumin within the films was measured. Lower IC50 values indicates a higher radical scavenging activity.

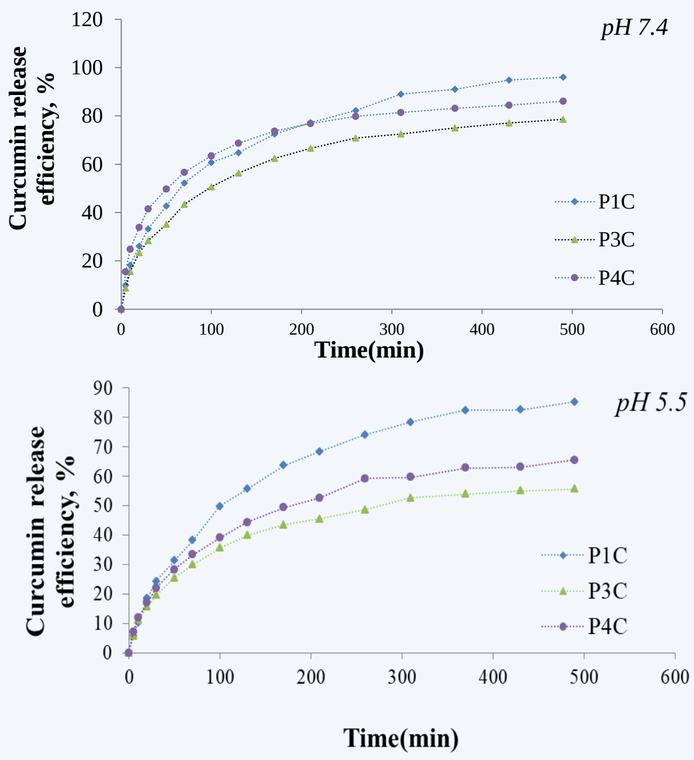

Figure 7. Curcumin release kinetics from biopolymers films P1C, P3C and P4C in phosphate buffer solution at pH = 7.4 and in acetate buffer solution with pH = 5.5.

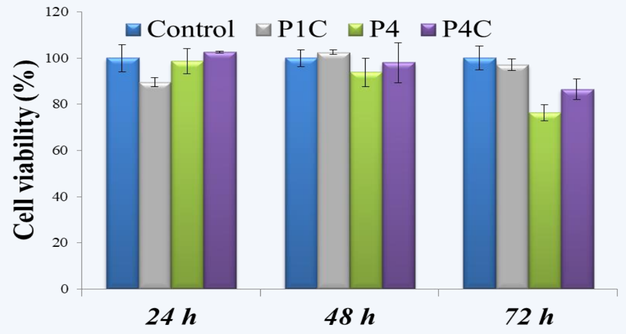

Figure 9. Cell viability on biopolymers films by MTT assay.

Table 3. Permeability of curcumin through skin and the exponential factor from Ritger Peppas diffusion model

Proba	PH	P, µg/cm²/h	n	R^2
P1C	5.5	5.71	0.5614	0.9927
P2C		4.9	0.7643	0.9938
P4C		5.1	0.7664	0.9893
P1C	7.4	7.3	0.7159	0.9667
P2C		5.8	0.5992	0.99
P4C		5.8	0.6704	0.9858

Conclusions

(a) curcumin allows to obtain complexes with with β- cyclodextrin, thus improving its water solubility; (b) curcumin complexes can be immobilized successfully in films with hydrogel character based on gellan/BSA/pectin leading to systems with increased bioavailability; (c) the polymeric matrix of the films has a protective role for curcumin against UV degradation and improved the antioxidant activity of curcumin;(d) the swelling degree value are high and depends on the BSA quantity within the films and of the biopolymer concentration; (e) higher release efficiency was observed at pH 7.4, in accordance with the swelling degree behavior; (f) the citotoxicity test shows that the films maintain cell viability which increases for P1C sample after 72 h probable because the curcumin release is improved compared with P4C sample.