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FORMULATION AND EVALUATION OF CURCUMIN-LOADED POLYMERIC MICROSPHERES USING ETHYL CELLULOSE FOR PROLONGED DRUG RELEASE

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ABSTRACT :

Curcumin is a lipophilic phenolic compound, however its pharmaceutical applications are limited due to poor water solubility, stability and poor oral bioavailability. This study aimed to formulate and assess curcumin loaded ethyl cellulose microspheres for sustained delivery using an oil in water (O/W) solvent evaporation method. Nine different formulations (F1-F9) were formulated using three different ratios of curcumin to ethyl cellulose (1:1, 1:2, 1:3), three different stirring speeds (500, 1000, 1500 rpm) and 1% w/v Polyvinyl Alcohol (PVA) as a stabiliser. The organic phase was comprised of Dichloromethane and Ethanol (7:3). The microspheres were assessed for yield, particle size, drug loading, encapsulation efficiency, flowability, morphology, in-vitro release, release kinetics, reproducibility and accelerated stability. The formulations had a yield between 83.9-94.1%, particle size between 119.6-301.2 µm, drug loading between 24.95-48.63% and encapsulation efficiency between 80.5-94.0%. Formulation F5 (Drug to polymer ratio of 1:2 and 1000 rpm) had a high yield of 92.4%, particle size of 198.4 µm, drug loading of 33.12% and encapsulation efficiency of 91.8%. The microspheres released 93.6% of the drug after 12 hrs. The release data followed the Higuchi and Korsmeyer-Peppas model ($R2= R^2 = 0.999$). The results also show that the microspheres had a Peppas exponent value of $n = 0.649$, indicating anomalous/non-Fickian transport. When stored under accelerated conditions for six months (40 ± 2°C & 75 ± 5% RH) there were small changes in the formulation. Overall this indicates that ethyl cellulose microspheres can be used as a sustained delivery system in-vitro. Further confirmation and in-vivo studies would be required to confirm therapeutic benefits..

Keywords: Curcumin; ethyl cellulose; microspheres; solvent evaporation; sustained release; entrapment efficiency; release kinetics.

1. Introduction

Curcumin is a major polyphenolic compound found within Curcuma longa. It has been studied for many different biological activities such as antioxidant and anti-inflammatory properties. Its formulation into conventional dosage form is difficult due to its hydrophobic nature along with poor aqueous solubility, chemical instability and poor bioavailability.

Polymeric microspheres consist of a drug being dispersed or encapsulated within a polymer. If the correct polymer is used, it can provide protection to the encapsulated drug as well as providing control of the drug release by diffusion, swelling and/or erosion. Ethyl cellulose is a polymer with poor water solubility and can therefore be used as a hydrophobic, sustained release matrix system. The oil in water solvent evaporation method is a suitable method for the production of polymeric particles containing hydrophobic compounds. The drug and polymer can be added to an organic phase and then emulsified in a stabilising aqueous solution.

Previous studies have been carried out looking at curcumin delivery using polymeric microparticles, ethyl cellulose microspheres, gelatin systems and microfluidic microcapsules (as stated in the thesis). When formulating these systems factors such as drug/polymer ratios and agitation speeds should all be taken into consideration. In this investigation nine different ethyl cellulose microsphere formulations were produced containing curcumin. An optimised batch was chosen based on the overall physiochemical and release properties.

2. Aim and Objectives

To formulate curcumin loaded ethyl cellulose microspheres using the O/W solvent evaporation technique.
To determine the effect of varying drug:polymer ratios and stirring rates on formulation characteristics.
To characterise the formulated microspheres with respect to percentage yield, particle size, drug loading, entrapment efficiency, flow characteristics, morphology and in vitro drug release.

To determine the release kinetics of the microspheres using mathematical kinetic models and determine their reproducibility, and accelerated stability.

3. Materials and Methods

3.1 Materials

The following materials were used; curcumin as the model drug, ethyl cellulose as the matrix forming polymer, polyvinyl alcohol (PVA) as the stabiliser. An organic solvent system of dichloromethane:ethanol (7:3) was used. A phosphate buffer solution was used as a dissolution media (1% Tween 80, pH6.8). This was obtained from the given thesis, including the supplier information from lab notes.

3.2 Preparation

Microspheres were prepared using nine different formulations. Curcumin and ethyl cellulose were mixed together in an organic mixture of dichloromethane and ethanol (7:3). The organic phase was then added to an aqueous solution of PVA (1% w/v) and stirred. Different drug:polymer ratios (1:1, 1:2, 1:3) and stirring rates (500, 1000 and 1500 rpm) were investigated. The solution was left to stir to allow the solvent to diffuse/evaporate and the polymer to harden. The resulting microspheres were filtered, washed and dried. The exact amounts used in each batch and the time taken can be found in the original lab book.

Factor	Levels investigated
Curcumin:ethyl cellulose ratio	1:1; 1:2; 1:3
Stirring speed	500; 1000; 1500 rpm
Stabilizer	PVA, 1% w/v
Organic solvent	Dichloromethane:ethanol (7:3)

Table 1. Formulation and process variables reported in the thesis.

3.3 Evaluation parameters

The percentage yield was calculated by taking the mass of microspheres after drying and dividing by the mass of total solid substances. The drug content was calculated as the percentage of curcumin present within the microspheres. The drug encapsulation efficiency was also calculated to determine how much of the original drug was present in the microsphere. Particle size and morphology was determined using methods mentioned in this thesis. Flowability was determined using bulk/tapped density, angle of repose, Carr's index and Hausner ratio.

3.4 In-vitro drug release study

A dissolution study was conducted using a USP type II paddle system. 900ml of phosphate buffer (pH 6.8), with 1% Tween 80 was used at a temperature of 37+/-0.5oC and at a rotation speed of 50rpm. Microspheres equivalent to 50mg curcumin were used and analysed for 12 hours. At set time points, 5ml samples were removed from the dissolution media and replaced with the same volume of fresh medium. The samples were filtered and diluted and analysed using a spectrophotometer at 421nm. (see results section within this thesis).

3.5 Release kinetics, reproducibility and stability.

The release data for the optimised formulation (F5) was analysed using zero order, first order, Higuchi, Korsmeyer-Peppas and Hixson- Crowell kinetic models. To check the reproducibility, three separate batches of microspheres were created (batch F5). Accelerated stability testing was carried out in sealed amber containers at 40+/-2oC and a relative humidity of 75+/-5% for up to 6 months. Data has been taken from this thesis. No additional statistical calculations have been made for this article.

4. Results & Discussion

4.1 Yield, particle size, drug content and encapsulation efficiency.

Across all nine formulations the yield varied between 83.9% and 94.1%. Mean particle size varied between 119.6µm and 301.2µm. Drug content was between 24.95% and 48.63%. Encapsulation efficiency was between 80.5% and 94.0%. Overall the highest yield (94.1%) and encapsulation efficiency (94.0%) was obtained from formulation F8. Formulation F3 had the lowest particle size (119.6µm). The **microsphere** formulation F5 was chosen as the optimised formulation due to the balance of properties including yield, particle size, drug content, encapsulation efficiency and sustained release.

Batch	Yield (%)	Size (µm)	Drug loading (%)	Entrapment efficiency (%)
F1	84.2 ± 1.3	196.5 ± 8.4	47.80 ± 0.72	80.5 ± 1.4
F2	87.6 ± 1.1	155.8 ± 7.2	48.63 ± 0.65	85.2 ± 1.2
F3	83.9 ± 1.5	119.6 ± 5.8	48.45 ± 0.81	81.3 ± 1.5

F4	88.1 ± 1.2	245.3 ± 9.5	33.07 ± 0.54	87.4 ± 1.1
F5	92.4 ± 0.9	198.4 ± 7.8	33.12 ± 0.42	91.8 ± 0.8
F6	89.5 ± 1.0	149.7 ± 6.3	32.99 ± 0.49	88.6 ± 1.0
F7	90.3 ± 1.1	301.2 ± 10.6	25.14 ± 0.38	90.8 ± 0.9
F8	94.1 ± 0.8	242.6 ± 8.9	24.97 ± 0.31	94.0 ± 0.7
F9	91.7 ± 0.9	181.5 ± 7.1	24.95 ± 0.35	91.5 ± 0.8

Table 2. Physicochemical results for formulations F1–F9 (mean ± SD, as reported in the thesis).

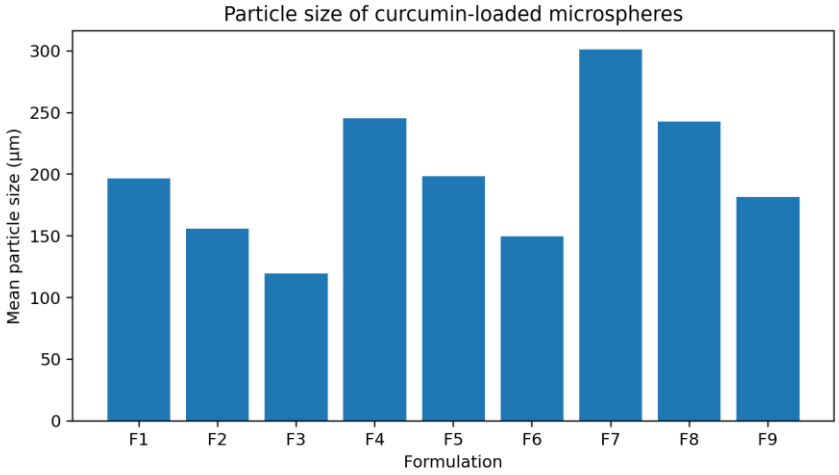


Figure 1. Mean particle size of formulations F1–F9.

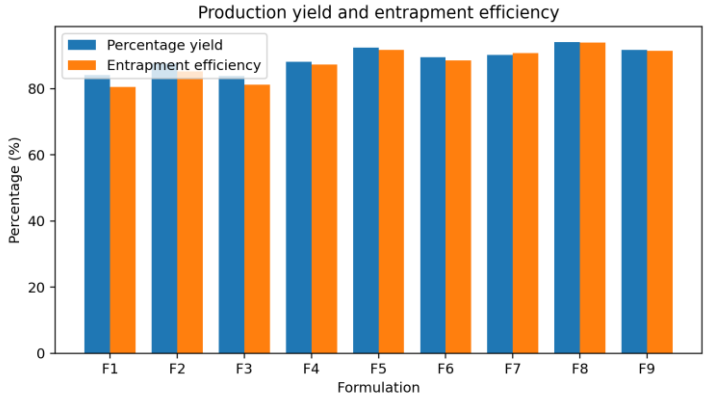


Figure 2. Percentage yield and entrapment efficiency of formulations F1–F9.

4.2 In-vitro drug release

Drug release varied with formulation composition. The 1:1 drug-to-polymer formulations released curcumin more rapidly, with F1–F3 reaching 100% release by 12 h and F2/F3 reaching approximately complete release by 10 h. Formulations with a 1:3 ratio released more slowly, consistent with a greater polymeric barrier to diffusion. F5 released 21.6% at 1 h, 52.7% at 4 h, 77.8% at 8 h and 93.6% at 12 h, providing a prolonged release profile while avoiding the near-complete early release seen in some formulations.

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	17.2	19.6	22.1	14.8	13.8	16.0	11.5	12.4	14.1
1	28.0	31.0	34.0	23.0	21.6	25.0	18.0	19.5	21.8
2	45.0	49.0	53.0	38.0	34.9	40.0	29.0	31.2	34.5
4	68.0	73.0	77.0	58.0	52.7	60.0	44.0	47.5	51.2
6	83.0	87.0	90.0	72.0	66.4	74.0	56.0	59.8	63.5
8	94.0	97.0	99.0	83.0	77.8	84.5	66.0	70.5	74.2
10	99.0	100.0	100.0	91.0	86.5	91.8	75.0	79.3	82.6
12	100.0	100.0	100.0	96.0	93.6	96.8	83.0	87.4	90.1

Table 3. Cumulative percentage curcumin release from formulations F1–F9.

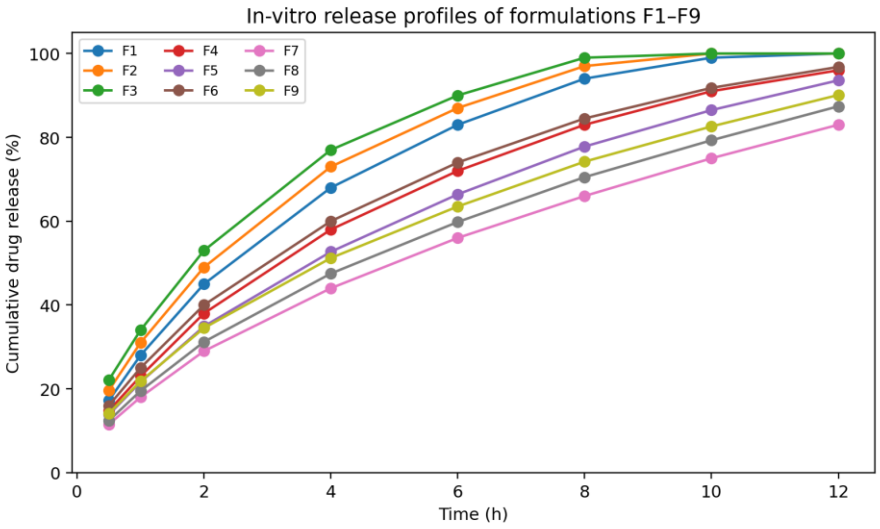


Figure 3. In-vitro cumulative drug-release profiles of F1–F9.

4.3 Release kinetics

Kinetic model	R^2	Reported parameter
Zero order	0.961	K_0 = 6.88 %/h
First order	0.979	K_1 = 0.212 h^{-1}
Higuchi	0.999	K_h = 29.54
Korsmeyer–Peppas	0.999	n = 0.649
Hixson–Crowell	0.998	KHC = 0.216

The highest reported coefficients of determination were obtained for the Higuchi and Korsmeyer–Peppas models (R^2 = 0.999). The Korsmeyer–Peppas exponent of 0.649 was interpreted in the thesis as indicating anomalous/non-Fickian transport, consistent with a combination of diffusion and polymer relaxation/erosion. This interpretation should be treated as indicative and depends on the geometry and fitting range used.

4.4 Flow properties and morphology

F5 demonstrated an angle of repose of 25.2°, Carr's index of 13.33% and Hausner ratio of 1.15, which were interpreted in the thesis as indicating acceptable flow behaviour. Scanning electron microscopy observations in the thesis described the optimized microspheres as spherical, discrete and relatively smooth. The original SEM micrograph should be inserted in the final journal submission if a high-resolution image is available.

4.5 Reproducibility and accelerated stability

Parameter	F5-A	F5-B	F5-C	Mean ± SD
Yield (%)	92.1	92.8	92.3	92.40 ± 0.36
Particle size (µm)	196.9	199.7	198.6	198.40 ± 1.41
Drug loading (%)	32.9	33.4	33.1	33.13 ± 0.25
Entrapment efficiency (%)	91.2	92.3	91.9	91.80 ± 0.56
Release at 12 h (%)	92.9	94.2	93.7	93.60 ± 0.66

Table 4. Reproducibility of optimized formulation F5.

Parameter	Initial	1 month	3 months	6 months
Particle size (µm)	198.4 ± 7.8	199.1 ± 8.0	200.3 ± 8.2	201.8 ± 8.4
Drug content (%)	99.1 ± 0.6	98.8 ± 0.7	98.3 ± 0.8	97.8 ± 0.9
Entrapment efficiency (%)	91.8 ± 0.8	91.5 ± 0.9	90.9 ± 0.9	90.4 ± 1.0
Release at 8 h (%)	77.8 ± 1.6	77.3 ± 1.5	76.5 ± 1.7	75.8 ± 1.8
Release at 12 h (%)	93.6 ± 1.4	93.1 ± 1.5	92.4 ± 1.5	91.7 ± 1.7

Table 5. Accelerated stability of F5 at 40 ± 2°C/75 ± 5% RH.

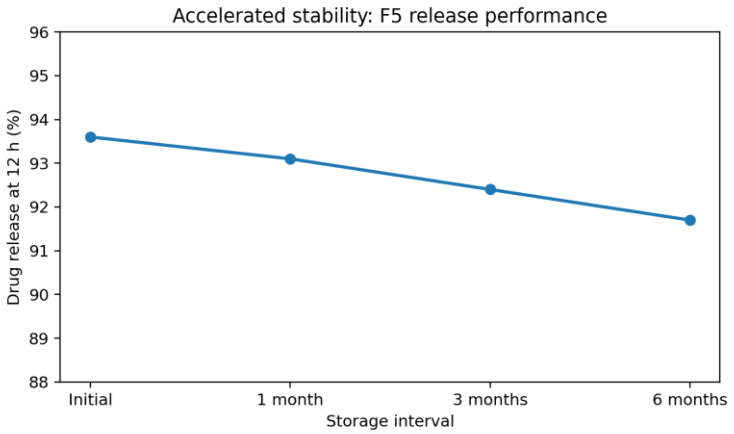


Figure 4. Change in 12-h release of F5 during accelerated storage.

There was a small amount of variability between the three batches. Throughout the six month accelerated stability testing there was a slight increase in particle size and a small decrease in the drug content, entrapment efficiency and release. There was no aggregation. This suggests that the samples have good stability when stored under these conditions. However, it should be ensured that there are defined acceptance criteria and the full data should be checked prior to publishing.

5. Conclusion

Ethyl cellulose microspheres loaded with curcumin were successfully produced using the O/W solvent evaporation method. Nine formulations were assessed, however the optimal batch was F5 (Curcumin: Ethyl Cellulose ratio 1:2, 1000rpm). This had a high yield of 92.4%, average particle size of 198.4µm, drug loading of 33.12%, entrapment efficiency of 91.8% and cumulative release of 93.6% after 12h. The release kinetics were best fit by the Higuchi model and Korsmeyer-Peppas model. The calculated exponent was 0.649 suggesting non-Fickian diffusion. The microsphere batches displayed good reproducibility and the accelerated stability was promising. It would be beneficial to ensure the method of analysis is valid, the levels of residual solvents are low and the statistical analysis is expanded. Further work is required to ensure the microspheres perform well in-vivo before any claims can be made regarding enhanced bioavailability or therapeutic efficacy.

6. Limitations and further work

- The article is based on results obtained from the provided thesis, therefore the data from the experiment has not been independently validated.
- The information on the suppliers, amounts used per batch, time taken during processing and validation of analysis should be checked from the lab records.
- The thesis contains a discrepancy in the wavelength used throughout. In this article 421nm has been used as it was stated in the dissolution results. Ensure the correct wavelength for analysis is being used before submitting.The article does not claim clinical efficacy or improved oral bioavailability because no new in-vivo data are presented in this manuscript.
- Full bibliographic details for the literature cited in the thesis must be checked against the original publications before journal submission.

References

The thesis literature review names the following studies, but complete bibliographic details (full author lists, article titles, journal names, volume/pages and DOI) were not available in the extracted material used to prepare this draft. Verify each citation against the original publication and replace these provisional entries with complete references before submission.

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