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Original Research Article

Development and Optimization of Carvedilol Microparticles

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Abstract:

The current study documents the formulation of Carvedilol-loaded microspheres, an antihypertensive drug, employing different cellulose derivative polymers. These microspheres were synthesized via the solvent evaporation method, employing cellulose derivative polymers. Carvedilol, a non-selective beta-blocker, is widely used in the treatment of hypertension and congestive heart failure. In the present study we have optimize the processing parameter and the various type of parameters were evaluated like microparticle yield, surface morphology, particle size analysis along with in-vitro drug release for prepared carvedilol microparticle. We have formulated six formulation of carvedilol microparticle out of which F2 showed the best result with production yield 75.31 % & drug encapsulation efficiency is 94.40 %.

Key Words: Carvedilol, microspheres, solvent evaporation, microparticle yield, in-vitro drug release.

Introduction

Microparticles are tiny particles ranging in size from 0.1 to 100 micrometers (µm) in diameter. They can be made from various materials including polymers, metals, ceramics, and lipids, and they find applications in a wide range of fields including medicine, environmental science, electronics, and cosmetics. [1,2]

Carvedilol is a widely used medication for the management of hypertension, congestive heart failure, and left ventricular dysfunction post-myocardial infarction. Despite its therapeutic efficacy, the short half-life of carvedilol necessitates frequent dosing, leading to fluctuations in plasma concentration and potential adverse effects. Various controlled release formulations of carvedilol microparticles were prepared using different techniques such as solvent evaporation, emulsion-solvent diffusion, and spray drying. Formulation parameters including polymer type, drug-to-polymer ratio, and particle size were optimized to achieve desired release profiles. [3,4]

Optimization of processing parameter:

Preliminary formulations were created with the aim of optimizing the process and other factors.

- **Homogenization speed's impact:**

To determine the optimal homogenization speed, we created formulations with several drug-polymer ratios and tested the resulting microspheres for size, shape, and yield percentage. [5]

- **Temperature's impact:**

microspheres were tested for size, shape, and yield percentage in order to determine the optimal temperature for the formulation, which was created with varying temperatures maintained in the continuous phase (1%PVA). [6]

- **The impact of surfactants:**

In order to find the optimal concentration of PVA, we tested several microspheres for size, shape, and yield percentage.

- **Effect of drug: polymer ratio:**

To find the optimal drug-to-polymer ratio, we created formulations f1–f6 with varying drug–to–polymer ratios and then tested the resulting microspheres for size, shape, and yield percentage. [7]

Characterization of prepared carvedilol microparticle:

- **Carvedilol Microparticle Yield:**

The following formula was used to determine the percentage yield of carvedilol microparticles:

$$\%\, Yield = \frac{Actual\ weight\ of\ product}{Total\ weight\ of\ drug\ and\ polymer} \times 100$$

- **Analysis of surface morphology using scanning electron microscopy:**

At various magnifications, the surface morphology of microspheres has been investigated to determine if the surface was smooth or rough.

Procedure: Microsphere surface morphology may be studied with the use of scanning electron microscopy, an effective analytical tool. By employing a scanning electron microscope (SEM) camera, the morphology characteristics of the specimens were determined. The microspheres were air-dried before being sputter-coated with platinum utilising auto fine coater ion sputter for 5-10 minutes. The samples were then inspected under a scanning electron microscope. To run the SEM, a low accelerating voltage of around 15 KV and a load current of around 80 MA were used. [8,9]

- **Particle size analysis:**

The particle size distribution (PSD) of a powder, granular material, or particles distributed in fluid is a representation of the proportions of particles at different sizes. PSD is a synonym for particle size distribution. The technique employed to ascertain PSD is referred to as particle size analysis, whereas the instrument used for this purpose is termed a particle size analyzer. The Power Spectral Density (PSD) of a substance plays a crucial role in comprehending its physical and chemical characteristics. The reactivity of solids involved in chemical processes is influenced by it, and it must be closely regulated in many industrial goods, such as the production of printer toner. [10,11]

- ***In vitro* drug release study:**

A phosphate buffer solution with a pH of 6.8 (enzyme-free) was used for in vitro drug release experiments with various formulations. Half a milligrams of microspheres were dissolved in one milliliter of phosphate buffer solution and then placed within a dialysis membrane. Shaken at 100 rpm and maintained at 37^0C, the dialysis membrane sample was placed in a conical flask with 50 cc of phosphate buffer for dissolution. By taking out 10-milliliter portions at the predetermined intervals, we were able to calculate the medication release rate. The amount that was taken out was replaced with an equal amount of new. Using phosphate buffer as a blank, the samples were examined using a UV Spectrophotometer at a λmax value of 241nm. [12]

Result and Discussion

Optimization of processing parameter:

- **Effect of Homogenization speed:**

Emulsion droplet size is directly related to energy density, which is defined as energy applied per unit total volume. Particles can

be decreased in size to create microparticles by increasing the shear stress.

Consequently, the emulsification process was carried out at the same homogenization speeds of 1000 rpm for a duration of 15 minutes, with the organic phase evaporation period fixed at 3-4 hours.

- **Effect of temperature:**

Particles undergo changes if not maintained at normal temperature; for example, microparticles grow in size as temperatures rise and shrink as temperatures fall.

- **Effect of surfactant:**

For this study, the researchers settled on PVA as their surfactant of choice. The stable emulsion with particle sizes of 120-145 µm was noted to have been produced at a concentration of 1% PVA. Within a few hours of emulsification, phase separation occurred due to an unstable emulsion created by a shift in PVA concentration, leading to the formation of polymer aggregates.

- **Effect of drug: polymer ratio:**

The drug-to-polymer ratio had no effect on microparticles in this study. The effectiveness of microparticle encapsulation was influenced only by the polymer concentration. Encapsulation efficiency was shown to be positively correlated with polymer content.

Characterization of prepared carvedilol microparticle:

Production yield and Encapsulation efficiency

The encapsulation efficiency of microparticles made with ethyl cellulose (F1, F2) surpassed that of those made with cellulose acetate and hydroxyethyl cellulose (F3, F4, F5, F6), indicating ethyl cellulose's superior performance in encapsulating active materials. Table 1 illustrates the encapsulation efficiency and production yield of Carvedilol-loaded cellulose derivative microspheres, with all formulations (F1-F6) exhibiting high production yields and encapsulation efficiencies ranging from 44.11% to 75.31%. Carvedilol encapsulation within HEC, CA, and EC microspheres ranged from 46.16% to 94.40%, confirming cellulose derivatives as effective polymers for hydrophilic drug encapsulation. Variations in drug/polymer ratio and PVA concentration did not affect production yield or encapsulation efficiency. Increasing polymer concentration improved microsphere encapsulation efficiency, while PVA concentration had no effect. Overall, higher polymer percentages yielded better encapsulation efficiency

Table 1: Production Yield and Encapsulation Efficiency Results from Various Formulations

Formulation no.	Drug (mg)	Ethyl cellulose (mg)	Cellulose acetate (mg)	Hydroxy ethyl cellulose (mg)	PVA	Production Yield (%)	Encapsulation efficiency (%)
F1	10	200	-	-	1%	71.43%	75.58%
F2	10	400	-	-	1%	**75.31%**	**94.40%**
F3	10	-	200	-	1%	45.91%	73.75%
F4	10	-	400	-	1%	50.69%	80.03%
F5	10	-	-	200	1%	**44.11%**	**46.16%**
F6	10	-	-	400	1%	48.11%	52.23%

Scanning electron microscopy

Figure 1 displays the scanning electron micrograph of the Carvedilol-loaded cellulose derivatives microspheres from batch F2. The absence of drug crystals on the microsphere surface, together with their almost spherical shape and smooth surface, may be due to the uniform evaporation of the solvent, which ensures an equal distribution of polymer.

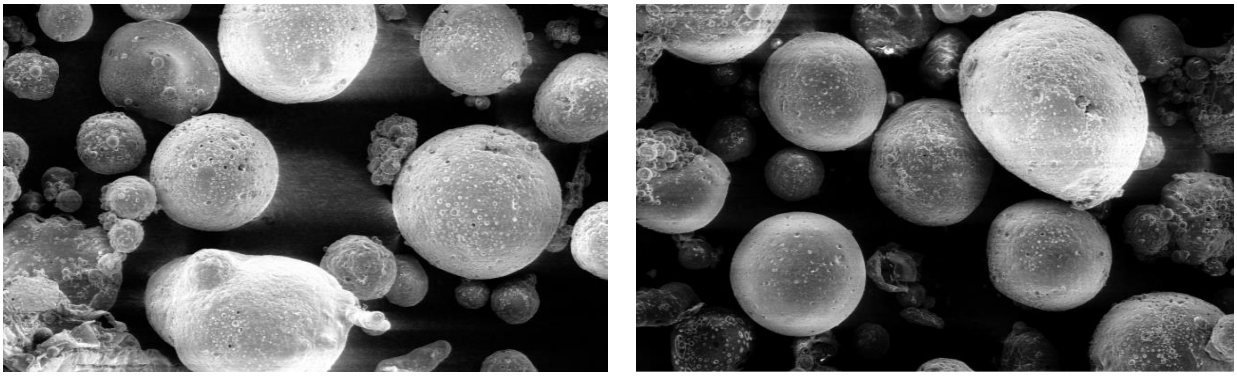

Figure 1: SEM of Carvedilol Microspheres prepared with Cellulose Derivatives

Analysis of particle size:

Figure 2 shows the size-distribution curve for typical formulations F2, while Table 2 shows the results of volume mean particle sizes of various formulations containing varied quantities of Carvedilol as well as Cellulose derivatives with standard errors. Microsphere size is proportional to polymer concentration. The internal phase gets thicker and larger particle size is produced by an increase in the polymer concentration.

Table 2: Results of Particle size for various formulations

Formulation no.	Drug	Ethyl cellulose	Cellulose acetate	Hydroxy ethyl cellulose	PVA	Particle size	Encapsulation efficiency (%)
F1	10	200	-	-	1%	120.81±8.64	75.58%
F2	10	400	-	-	1%	133.04±4.46	**94.40%**
F3	10	-	200	-	1%	126.73±9.93	73.75%
F4	10	-	400	-	1%	140.77±6.67	80.03%
F5	10	-	-	200	1%	131.34±9.87	**46.16%**
F6	10	-	-	400	1%	145.30±6.79	52.23%

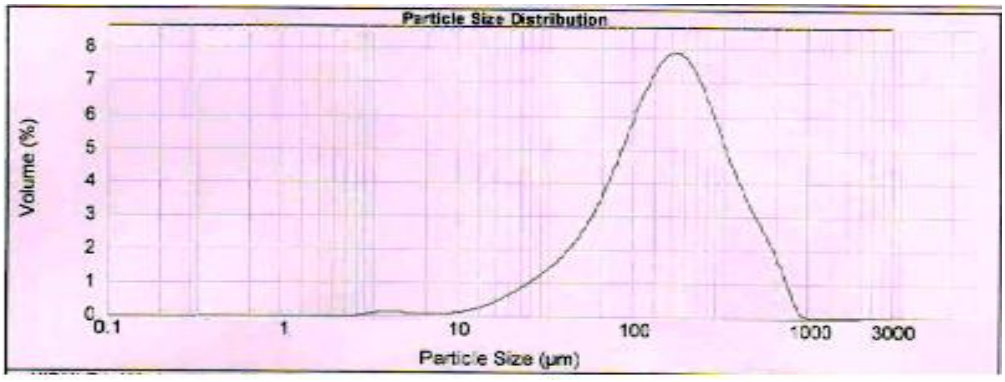

Figure 2: Particle size distribution of Carvedilol -loaded EC microspheres.

In-vitro drug release

Formulations F1 to F6, utilizing various cellulose derivatives at different polymer concentrations, were assessed for in vitro cumulative release. In F1 & F2, with EC concentrations of 1% and 2% w/w, drug entrapment was 75.58% and 94.41%, respectively, with microspheres buoyant after 48 hours; increasing polymer concentration led to higher drug release rates. Similarly, in F3 & F4, CA concentrations at 1% and 2% w/w resulted in drug entrapment of 73.74% and 80.03%, respectively, with microspheres buoyant after 24 hours. In F5 & F6, utilizing HEC at 1% and 2% w/w, drug entrapment was 46.16% and 52.23%, respectively, with microspheres buoyant after 12 hours; increasing polymer concentration increased drug release rates. The maximum drug release was observed in F2 with EC, releasing for 24 hours, while the minimum was in F5 & F6 with HEC, releasing for 12 hours. The in vitro release profiles are detailed in Table 3, and Figure 3 illustrates these profiles.

Table 3: In-vitro cumulative % release

Time	F1	F2	F3	F4	F5	F6
1	5.98519	3.14614	4.38219	4.30494	1.00236	1.09893
3	10.9047	6.38894	9.56319	10.1228	4.90922	7.1501
6	15.4651	12.6046	15.584	18.0202	14.0137	15.8228
9	20.7632	18.1593	24.3013	29.6093	30.892	35.2798
12	26.9033	25.9829	34.1693	39.331	**46.1641**	52.2371
15	32.2271	31.8041	43.1817	48.0647		
18	39.0262	38.0799	53.3845	58.9877		
21	45.0336	45.5888	65.0507	70.4352		
24	52.4637	55.0504	73.7498	80.0307		
30	58.2129	65.3337				
36	63.7607	74.0328				
42	68.8374	86.3493				
48	75.582	**94.4058**				

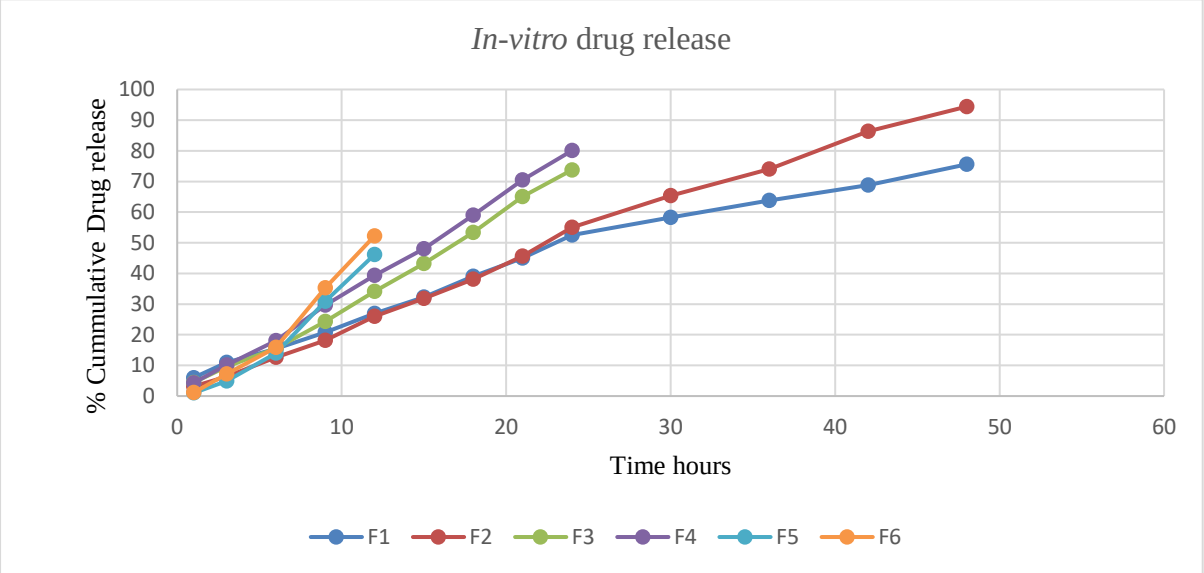

Figure 3: *in-vitro* graph of formulation F1 – F6

Conclusion

Carvedilol-loaded microspheres with different cellulose derivative polymers were developed in this work. Microspheres were made by solvent evaporation method with cellulose derivative polymer. High yield and encapsulation efficiency were achieved for all microsphere formulations (F1-F6). Production yield was 44.11–75.31 percent. The encapsulation efficiency of Carvedilol in HEC, CA, and EC microspheres was 46.16-94.40%. It is obvious that polymer concentration enhances Carvedilol microsphere encapsulation efficiency. Ethyl cellulose microparticles had greater encapsulation effectiveness (F1, F2) than cellulose acetate and Hydroxy ethyl cellulose microparticles (F3, F4, F5, F6). Figure 1 shows batch F2 Carvedilol-loaded cellulose derivative microsphere SEM. Microspheres have smooth, nearly spherical surfaces. No drug crystals were observed on the microsphere surface, perhaps due to solvent evaporation for equal polymer dispersion.

References

1. Gupta , Y., Sharma, A., Sain, S. K., Sharma, Y., & Jangir , S. (2023). An Overview on Microparticle Drug Delivery Systems. International Journal of Health Advancement and Clinical Research (tz), 1(4), 65–70.
2. Siepmann, J. and Siepmann, F., Microparticles used as drug delivery systems. In Smart colloidal materials, Springer Berlin Heidelberg, 2006; 15-21.
3. Chen-Scarabelli, C., Saravolatz, L., Murad, Y., Shieh, W.S., Qureshi, W., Di Rezze, J., Abrencillo, R., Gardin, T., Gidwani, U.K., Saravolatz, L. and Faggian, G., A critical review of the use of carvedilol in ischemic heart disease. American Journal of Cardiovascular Drugs, 2012;12:391-401.
4. Beattie, K., Phadke, G. and Novakovic, J., 2013. Carvedilol. Profiles of drug substances, excipients and related methodology, 38, pp.113-157.
5. Varde, N.K. and Pack, D.W., Microspheres for controlled release drug delivery. Expert opinion on biological therapy, 2004; 4(1):35-51.
6. Nila, M.V., Sudhir, M.R., Cinu, T.A., Aleykutty, N.A. and Jose, S., Floating microspheres of carvedilol as gastro retentive drug delivery system: 32 full factorial design and in vitro evaluation. Drug delivery, 2014; 21(2):110-117.
7. Patil, R., Pande, V. and Sonawane, R., Nano and microparticulate chitosan-based system for formulation of carvedilol rapid melt tablet. Advanced Pharmaceutical Bulletin, 2015;5(2):169.
8. Patel, S., Dubey, N., Gajbhiye, A. and Patil, S., Floating microspheres encapsulating carvedilol for the effective management of hypertension. Pharmaceutical and Biomedical Research, 2019; 5(2): 17.
9. Singh V, Bansal M, Gupta R.K, Sharma A, Preparation and Evaluation of Eperisone Hydrochloride Resinate Beads. International Journal of Health Advancement and Clinical Research (tz), 2023;1(1): 12-18.
10. Gurung, B.D. and Kakar, S., 2020. An overview on microspheres. Int J Health Clin Res, 2020; 3(1): 11-24.
11. Herring, J.M., McMichael, M.A. and Smith, S.A., 2013. Microparticles in health and disease. Journal of veterinary internal medicine, 2013; 27(5):1020-1033.
12. Singhvi, G. and Singh, M., 2011. In-vitro drug release characterization models. Int J Pharm Stud Res,2011; 2(1):77-84.