RESEARCH PAPER

An Assessment and Comparison of Cilnidipine-Loaded Bovine Serum Albumin and Egg Albumin Microsphere Formulations.

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ABSTRACT

For medications that are poorly soluble, the cilnidipine microsphere created in this work provides an efficient drug delivery method. It is conceivable to conclude that Cilnidipine microspheres can effectively manage hypertension and assist obtain the full therapeutic advantage of calcium channel blockers in a clinical context. In this study, cilnidipine polymeric microspheres were made using the ionic gelation process. After that, polymeric microspheres were added to gellan gum gel and applied to the buccal cavity. The micromeritics properties, particle size, surface morphology characteristics, percentage drug entrapment efficiency, in-vitro drug release, and permeation studies of Cilnidipine-loaded polymeric microspheres were then evaluated. A comparative in-vitro drug release study was conducted using commercially available formulations of Cilacar and Dilnip tablets. Additionally, the appearance, pH, viscosity, refractive index, and spreadability of gellan gum were described.

To determine how different factors affected particle size, drug entrapment percentage, and drug release, optimization of drug-loaded polymeric microspheres was done. Consequently, it was shown that the biopolymeric carrier synthesized with BSA for the sustained release distribution of Cilnidipine had a sufficient drug entrapment efficiency of 96.7 percent w/v and a drug release rate of 93.3% w/v. Thus, the novel formulation of BSA-Cilnidipine offers a more recent extension of action that can be used to treat hypertension.

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INTRODUCTION

To optimize treatment efficacy and get around the drawbacks of traditional drug delivery techniques, a novel drug delivery system is created to get the medication to the right place [1][2]. Microspheres have become a successful carrier system among the many delivery methods created for the targeted and prolonged release of active medicinal components [3].

Microspheres are well known for their exceptional drug-carrying ability and small particle size. They are free-flowing powders with particle sizes ranging from 1 µm to 1000 µm, and are usually made of biodegradable natural or synthetic polymers. When distributed in a polymeric matrix, drugs that are integrated into these microspheres can be released under regulated circumstances. These systems, which enable prolonged drug action and decreased dose frequency, are typically made from synthetic polymers like polyesters, polyamides, or waxy compounds, or from naturally occurring biodegradable proteins [4][5][6][7]. Microspheres are sometimes also called microparticles [8][9].

Commonly used in the creation of microspheres include natural polymers including bovine serum albumin (BSA) [10][11][12], egg albumin [13][14][15], chitosan [16][17], starch [18][19], and poly dextran [20][21], as well as synthetic polymers such polylactic acid [22][23] and polyadipic anhydride [24]. The single emulsion technique [25][26], double emulsion technique [27][28], polymerization [29][30], phase separation coacervation [31][32], spray drying and spray congealing [33][34], and solvent extraction [35][36] are among the varieties of preparation techniques that are available.

A calcium channel blocker called cilnidipine is prescribed to treat hypertension [37][38][39]. In its early stages, hypertension is frequently asymptomatic and is defined by

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consistently high arterial blood pressure. It raises the risk of cardiovascular problems such heart failure, stroke, and coronary artery disease if treatment is not received [40]. Creating a sustained-release microsphere system with cilnidipine has a number of benefits, including as fewer dosage requirements, better patient adherence, fewer adverse effects, longer duration of medication action, and increased cost-effectiveness.

The research objective are explained as below

- To develop Cilnidipine-loaded microspheres using biodegradable polymers such as BSA and Egg Albumin.
- The study implements emulsification heat denaturation and glutaraldehyde cross-linking for effective microsphere formulation.
- For achieving sustained drug release and improved therapeutic performance of poorly soluble drugs.
- To evaluate the entrapment efficiency, drug release behavior, and overall performance of the formulated microspheres.
- The BSA-based formulation (F3) was identified as superior, demonstrating 96.7% entrapment efficiency and 93.3% drug release.
- For enhancing patient compliance and treatment effectiveness in hypertension management through controlled drug delivery.

This work aims to evaluate and compare Cilnidipine-loaded microspheres made with egg albumin and bovine serum albumin (BSA). The objective is to determine the optimal formulation that optimises the drug's bioavailability, thereby enhancing its effectiveness in the treatment of hypertension.

2. Material and Methods

2.1. Materials

Cilnidipine is provided as a gift sample by Madras Pharmaceuticals Pvt. Ltd. in Chennai. Other necessary materials for study, including Bovine Serum Albumin (BSA) and Egg Albumin, are obtained from Southern India Scientific Corporation in Chennai. Chemicals such as Glutaraldehyde, Liquid Paraffin, Tween80, Span80, Potassium Dihydrogen Phosphate, Sodium Hydroxide, Ethanol, and Hydrochloric Acid are sourced from the local market for use in the formulation process.

2.2. Method for preparation of Cilnidipine loaded Bovine serum albumin (BSA) microspheres:[12]

Cilnidipine-containing bovine serum albumin (BSA) microspheres were manufactured via emulsification-cross-linking. In a beaker, the desired amount of drug (200 milligrammes) was weighed and dissolved in a 20% bovine serum albumin solution in water (2 ml). A dropwise stream of the drug-polymer mixture is introduced into a container containing 50 ml of liquid paraffin that is being stirred with a magnetic stirrer at an approximate speed of 2500rpm. As a surfactant, one percent wt./vol Span80 was introduced into the oil phase. Glutaraldehyde was introduced as a cross-linking agent after 15 minutes of stirring; stirring persisted for an additional 4-6 hours. Following the cessation of agitation, the albumin microspheres underwent filtration and n-hexane cleaning in order to eliminate any residual oil. Four samples of Cilnidipine-containing bovine serum albumin microspheres (F1, F2, F3, F4) were manufactured using varying concentrations of bovine serum albumin and Span80, as described in the preceding procedure. The formulations' compositions are detailed in Table 1.

2.3. Method of preparation of Cilnidipine loaded Egg albumin microspheres:[15]

Cilnidipine-containing egg albumin microspheres have been formulated via emulsification heat denaturation. The appropriate amount of the medication (0.5g) is measured and dissolved in 12.5ml of egg albumin solution in water. A volume of 50 mL of preheated liquid paraffin is treated with this solution at 60ºC. As an emulsifying agent, Tween80 is utilised, and the mixture is stirred for approximately one hour using a magnetic agitator. The temperature is then reduced to 40oC and maintained for 25 minutes to facilitate the hardening process. For approximately 15 minutes, the resultant microspheres are stabilised with a solution of glutaraldehyde (25%v/v). Following the collection of microspheres via decantation, they are rinsed with n-hexane and allowed to dry at room temperature.

Four samples of Cilnidipine-containing egg albumin microspheres (F5, F6, F7, F8) are produced using varying concentrations of egg albumin and Tween80 in accordance with the aforementioned procedure. Table 2 provides the composition for various formulations.

Table 1: Composition of Cilnidipine microspheres by using Bovine serum albumin

S.No	Batch. No	Core: Coat ratio	Amount of cross-linking agent(ml)	Amount of surfactant(ml)
1.	F1	1:2	1ml	1ml
2.	F2	1:2	1ml	2ml
3.	F3	1:4	1ml	1ml
4.	F4	1:4	1ml	2ml

Table 2: Composition of Cilnidipine microspheres by using Egg Albumin

S. No	Batch. No	Core:coat ratio	Amount of Glutaraldehyde(ml)	Amount of surfactant (ml)
1.	F5	1:1	1ml	1ml
2.	F6	1:1.5	1ml	2ml
3.	F7	1:2	1ml	1ml
4.	F8	1:2.5	1ml	2ml

2.4. Standard calibration curve of Cilnidipine

A precise 100mg of Cilnidipine was weighed and transferred to a 100ml standard vial, followed by the addition of a small amount of ethanol to solubilize the drug. The volume is then adjusted to 100 mL using ethanol. Thus, the default solution is produced. Phosphate buffer with a pH

of 6.8 is used to attenuate the aforementioned stock solution to the following concentrations: 5, 10, 15, 20, and 25µg/ml. The absorbance of the solution is then determined using a UV-visible spectrometer at 239nm, and a standard curve is generated by plotting a graph with concentration on the x-axis and absorbance on the y-axis. Utilising the standard curve, the amount of cilnidipine present in the current study is determined.

2.5. Evaluation of Cilnidipine microspheres

2.5.1. Particle size analysis:

The examination of particle size was performed utilising optical microscopy. A random selection of around 200 microspheres was made, and their dimensions were ascertained by utilising an optical microscope outfitted with a standard micrometre scale.

2.5.2. Determination of drug content of microspheres:

Weigh out 50mg of the microspheres precisely, then pulverise them with a mortar and pestle. Crushed microspheres should be transferred to a 50 ml standard flask and dissolved in 0.1N hydrochloric acid. Add 50ml of water to the capacity. Using Whatman filter paper, strain the mixture. A 10 ml standard flask should hold 1 ml of the filtered solution. Dilute it with 0.1N hydrochloric acid to 10ml. Calculate the solution's absorbance at 240 nm. The absorbance of standard cilnidipine is then compared with this absorbance value for analysis.

2.5.3. Percentage of entrapment efficiency:

The following formula is used to determine the percentage of entrapment efficiency-

Percent entrapment efficiency= Entrapped drugTotal drug×100

2.5.4. Shape and Surface morphology:

Scanning electron microscopy (SEM) was used to evaluate the microspheres' shape and surface properties (roundness, smoothness, and forming aggregation), while optical microscopy was used to ascertain the microspheres' size distribution.

2.5.5. FTIR studies:

By analysing the infrared light absorption in a sample, Fourier-Transform Infrared (FTIR) spectroscopy can be used to determine the presence of functional groups and chemical bonds. It is performed to determine the interaction between the drug and polymer.

2.5.6. *In-Vitro* drug release studies of Cilnidipine loaded Bovine serum albumin and egg albumin microspheres:

Bovine serum albumin and egg albumin microspheres loaded with cilnidipine were tested for in vitro drug release. Utilising USP dissolving apparatus-I (Basket type) and 0.1N hydrochloric acid as the dissolution medium, the drug release study for microspheres was carried out. 900ml of the dissolution medium was used, and the dissolution was carried out at 100 rpm at 37± 0.5ºC. Microspheres weighing precisely 50 mg were extracted from each batch and placed within firm gelatin capsules. After putting these capsules in the basket, 900 millilitres of dissolving media were added. The dissolving process is completed after immersion. At predetermined intervals of one hour, five millilitres of the sample solution are removed from the dissolution device and replaced with an equal volume of brand-new 0.1N hydrochloric acid. This takes eight hours to complete. Using a UV-visible spectrophotometer, the content of cilnidipine in the withdrawn samples was measured at 240 nm, and the standard calibration curve was used to assess the amount of drug release. Plotting time versus drug release percentage allowed for the calculation of the percentage of drug released at different time intervals**.**

3. Results and Discussion

3.1. Standard Curve of Cilnidipine:

The standard curve of Cilnidipine fig. 1.

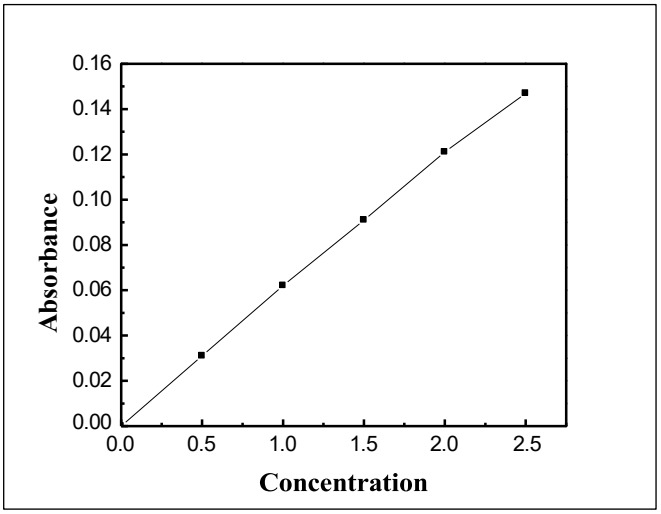
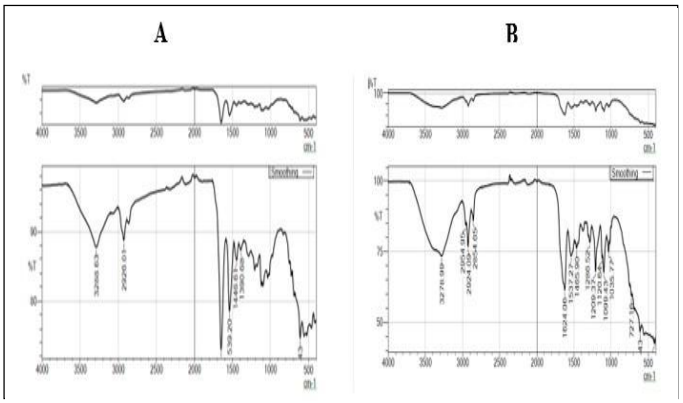


Figure 1: Standard calibration curve of Cilnidipine

3.1. FT-IR studies:

FT-IR analysis is used to collect data on drug compatibility (Cilnidipine) with polymers. We have identified the same peaks in the infrared spectra of Cilnidipine and other mixed samples from figure 2 (A, B, C, D, E, F, and G). The prepared microspheres did not reveal any sort of interactionbetween the medication and excipients, which shows there is no incompatibility between the drug and the polymers



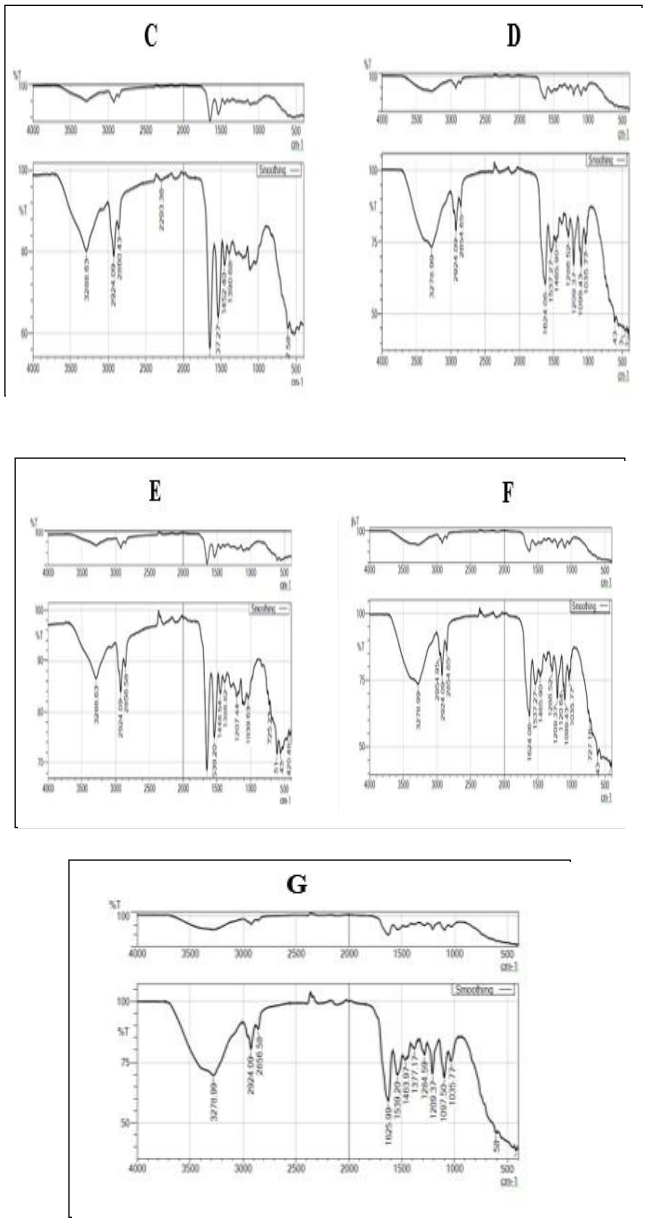


Figure 2: FT-IR spectra of (A) Cilnidipine (Pure Drug), (B) BSA (raw material), (C) Cilnidipine+ BSA (Raw Material), (D) Cilnidipine-BSA Microspheres, (E) Egg Albumin (Raw Material), (F) Cilnidipine+ Egg Albumin (Raw Material), (G)Cilnidipine- Egg Albumin Microspheres

3.2. Particle size analysis:

Using an optical microscope, the particle sizes of eight batches of Cilnidipine microspheres were measured; the findings are shown in Table 3. The developed microspheres' particle sizes were discovered to be between 50 and 75 µm. Table 3 displays the microparticles' distribution of particle sizes. The microparticles had a mean particle size of 50.05 ± 8.82 µm to 72.40 ± 10.43 µm (n = 50). The most tiny particle size is obtained from microparticles created using the F3 formulation, which contains BSA, but the egg albumin formulation yields larger particle sizes.

3.3. Percentage yield:

The formulations exhibit a range of percentage yields, varying from 72% to 88%. Notably, the F3 formulation achieves the highest yield of 88%. The data displayed in Table 1 indicate a significant percentage yield of microparticles. Of particular significance is the batch that achieved the greatest yield of 88%. This took place within microspheres that contained BSA

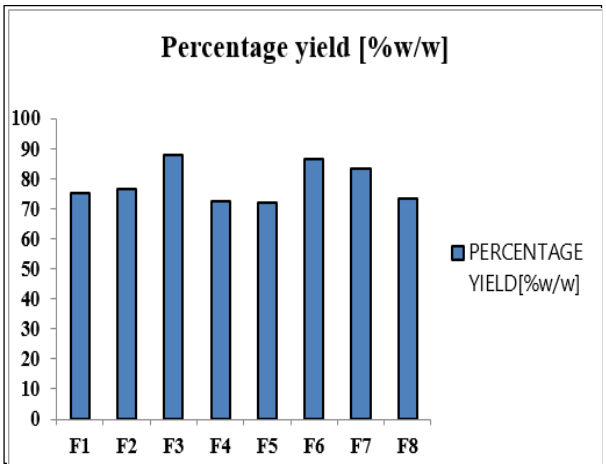


Figure 3: Percentage Yield

3.4. Percentage of Drug Entrapment Efficiency

The entrapment efficiency of Cilnidipine loaded BSA and Egg albumin microspheres can be found in Table 3 and Figure 4 and 5, respectively. For BSA formulations, F3 has the highest level of entrapment efficacy. Conversely, for Egg albumin formulations, F6 demonstrates the maximum entrapment efficacy, reaching 86.7%. However, when comparing these two formulations, it is shown that the F3 formulation, which contains BSA, has the highest entrapment efficacy, reaching approximately 97.7%. Drug entrapment exhibited a consistent trend of decline as the amount of BSA utilised in the preparation of the microspheres increased.

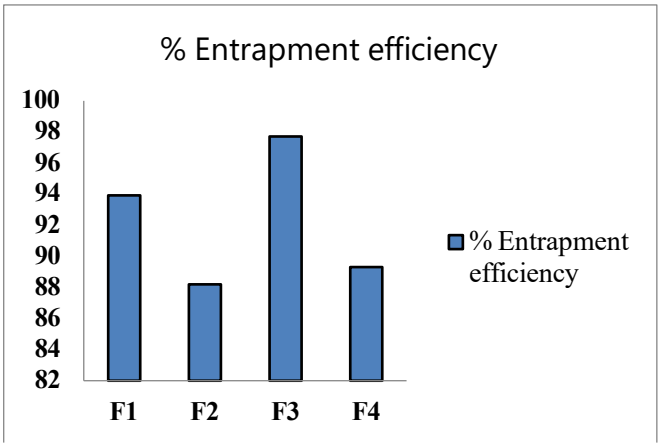


Figure 4: Entrapment efficiency of Cilnidipine loaded BSA microspheres

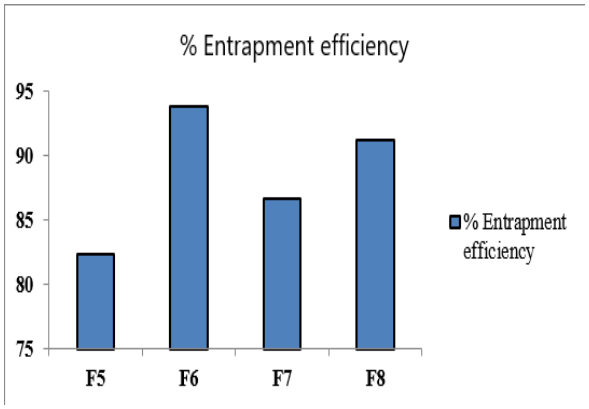


Figure 5: Entrapment efficiency of Cilnidipine loaded Egg Albumin microspheres

3.5. *In-Vitro* Release Studies for Cilnidipine Microspheres by Using Bovine Serum Albumin and Egg Albumin

The drug release profile of Cilnidipine loaded BSA formulations (F1 to F4) and Egg albumin formulations (F5 to F8) are presented in Table 8, Figure 12, and Figure 13. When examining the drug release in a controlled environment, the F3 formulation of BSA showed the highest release rate of 93.3% after 8 hours. Similarly, for Egg albumin microspheres, the F6 formulation exhibited the highest release rate of 85.4% after 8 hours. Figure12 clearly demonstrates that F3 BSA formulation exhibited the highest in-vitro drug release when compared to F6 Egg albumin formulation. The optimised formulation of F3, consisting of BSA polymer, has a composition with a core-to-coat ratio of 1:4 and a surfactant-to-crosslinking agent ratio of 1:1. The graphical representation of the release characteristics of Cilnidipine from the microspheres may be observed in Figures 12 and 13. The majority of the microspheres exhibited a continuous and controlled release of the medication. Nevertheless, there was an immediate and fast discharge of Cilnidipine from the F3 BSA formulation and F6 Egg albumin formulation within a span of 2 hours. The release profile of F3 BSA formulation and F6 Egg albumin formulation batches exhibit a biphasic pattern of release, which is a distinguishing feature.

Table 3: Evaluation of Microspheres

S.N	Batch No	Average particle size(µm)	Percentage yield[%w/w]	% Entrapment efficiency	In-vitro drug release studies
1.	F1	55.2±10.55	75.3± 1.35	93.9±4.55	91.3± 1.41
2.	F2	54.1±11.50	76.67±3.08	88.2±3.58	84.7± 2.52
3.	F3	61.3±5.55	88.0± 2.55	97.7±1.50	93.3±1.87
4.	F4	72.4±9.55	72.6± 1.02	89.3±3.55	87.8±2.04
5.	F5	60.3±8.34	72.0±2.08	82.4±1.04	81.3±3.55
6.	F6	59.7±6.50	86.4± 5.42	83.8±1.57	85.4±5.44
7.	F7	51.8±12.05	83.2± 1.58	86.7±3.59	85.7±2.46
8.	F8	57.5±10.46	73.2± 1.25	8 1.2±1.44	79.9±2.33

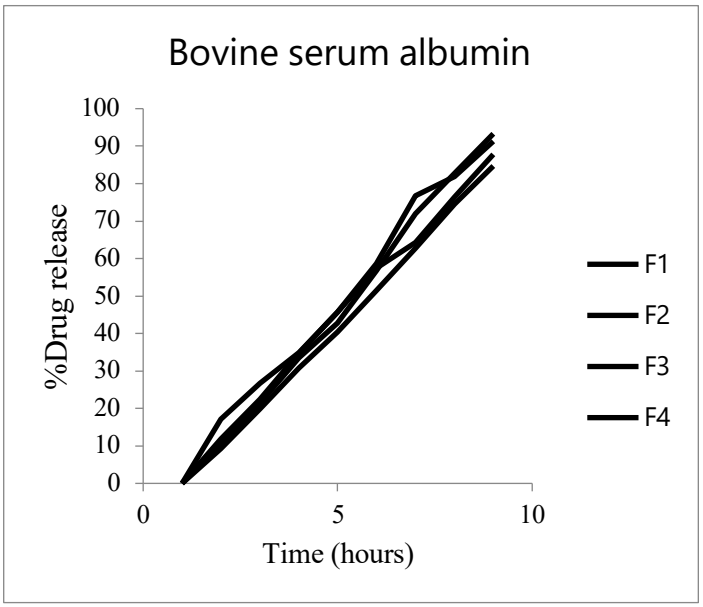


Figure 6*: In- vitro* drug release profile of Cilnidipine loaded BSA microspheres

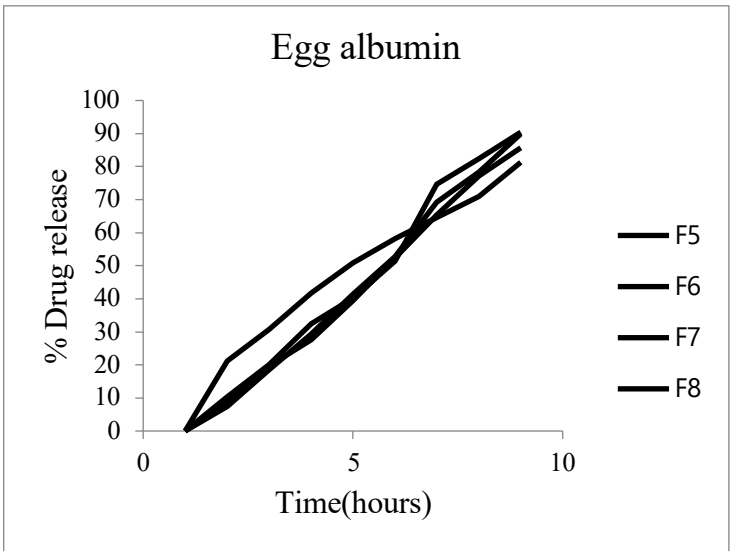


Figure 7:*In- vitro* drug release profile of Cilnidipine loaded Egg albumin microspheres

3.6. Scanning Electron Microscopy

The SEM-JEOL, JSM-840 instrument was used to analyse the SEM images of microspheres F3 and F6. Upon conducting a comparison, it was noticed that the F3 formulation, which includes Bovine Serum Albumin (BSA), displayed a more spherical and smoother morphology. This property implies that the F3 formulation can be regarded as the optimised formulation.

SEM photomicrographs of the F3 BSA formulation and F6 Egg Albumin formulation exhibited microspheres that were predominantly brownish and spherical in shape. Nevertheless, it is important to mention that several batches displayed indications of hydration and uneven forms, suggesting inconsistency within the F6 formulation. Based on the overall research, it can be concluded that F3, which

is made with BSA, has a more homogeneous and optimised structure in comparison to F6.

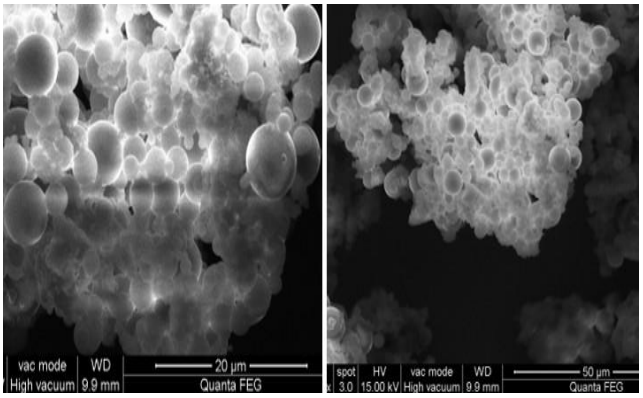


Figure 8: SEM photomicrograph of F3 & F6

Table 4: Particle size

Formulation Code (F)	Conc. of Sodium Alginate (%w/v)	Conc. of Calcium Chloride (%w/v)	Speed (rpm)	Particle Size (µm)
F1	8	20	990	254
F2	5	25	1620	174
F3	4	40	1980	102
F4	2.5	40	2100	77

The optimization of cilnidipine-loaded microspheres with different calcium chloride, sodium alginate, and stirring speed concentrations is displayed in the table 4. The microspheres' particle size dramatically shrank as the concentration of sodium alginate dropped and the concentration of calcium chloride and stirring speed rose. Formulation F1 produced the biggest particle size (254 µm), whereas F4 produced the smallest size (77 µm). This suggests that smaller particles are more likely to develop when the polymer content is lower and cross-linking and agitation are higher.

Table 5: % Drug Entrapment Efficiency of Cilnidipine Microspheres

Formulation Code (F)	Conc. of Sodium Alginate (%w/v)	Conc. of Calcium Chloride (%w/v)	% Entrapment Efficiency
F1	8	20	22
F2	5	25	42
F3	4	40	54
F4	2.5	40	95

As calcium chloride concentration rose and sodium alginate content decreased, the entrapment effectiveness of Cilnidipine-loaded microspheres increased noticeably. Entrapment efficiency was highest in Formulation F4 (95%), and lowest in Formulation F1 (22%) which is shown in table 5. According to this, improved drug entrapment within the microspheres is made possible by a lower polymer content and a greater availability of cross-linkers.

Table 6: Parameters and their values

Parameters	Observation
Appearance	Transparent
Consistency	Thick
pH	7.1
Viscosity	31.66 cps
Refractive Index	0.33

Gellan gum's chemical and physical properties were shown in table 6. Its thick consistency and translucent appearance suggested that it might work well as a gel-forming agent. With a pH of 7.1, it was neutral and in line with physiological circumstances. Its stability and homogeneity for use in pharmaceutical formulations were confirmed by the viscosity measurement of 31.66 cps and the refractive index of 0.33.

Table 7: Comparative In-Vitro Permeation Study of Optimized Microspheres (F4) and Marketed Formulations (Cilacar and Dilnip)

Time (min)	F4	Cilacar	Dilnip
0	0	0	0
15	18.65	25.87	22.65
30	23.45	35.17	33.13
45	33.09	42.16	40.09
60	44.201	51.18	47.15
120	47.54	59.98	57.23
180	51.98	54.23	59.98
240	54.32	53.18	61.24
300	58.04	56.18	56.34
360	62.13	61.67	53.21
480	70.12	49.90	51.17
Time (min)	F4	Cilacar	Dilnip

The release profile of the optimized Cilnidipine microsphere formulation (F4) is compared to those of two commercially available products, Cilacar and Dilnip, in the in-vitro permeation research is shown in table 7. The commercially available formulations first displayed quicker drug release. But after 120 minutes, F4 showed a more regulated and prolonged release, outperforming the commercially available drugs by 480 minutes with 70.12% penetration, as opposed to 49.90% for Cilacar and 51.17% for Dilnip. This suggests that F4 is a good option for long-term antihypertensive treatment since it offers prolonged medication release.

4. DISCUSSION

All of the microsphere diameters fell within the micrometre range, proving that the production method was successful in reaching the desired result. It seems that as the amount of cross-linking agent and polymers used grew, so did the microspheres' average size. The microspheres made with egg albumin, in particular, were bigger than those made with bovine serum albumin in the other batches. Particle size would affect the rate of drug release and then pharmacokinetics in this investigation of microspheres meant for oral delivery. The excellent yield of microspheres suggests that the formulation procedure used was dependable. The amount of cross-linking agent utilised in the microsphere formulation did not appear to be correlated with the microsphere yield. The cross-linking time and cross-linking agent concentration are two factors that affect the swelling of swellable polymers made by the crosslinking process. Implicitly, Cilnidipine encapsulation in BSA cross-linked span80 microspheres would result in a minor release of the medication in the stomach and improve its targeting to the intestine, where the intended sustained release effects would be realised. This might be the ideal cross-linking agent concentration required to create microspheres for a sustained release dosage form. When evaluating the drug loading capacity of microspheres and their drug release profiles, the drug entrapment effectiveness is a crucial factor that indicates the amount of drug that will be released gradually. After the initial quick hydration and swelling, the unentrapped drug may have leached out and adhered to the surface of the microspheres, causing a burst effect that may have contributed to the rapid release of Cilnidipine from batches F3 and F6 in the first 30 minutes. Dosage formulations with a biphasic release pattern due to burst release may be used therapeutically. This has been noted in microspheres made with albumin from cows. However, in this instance, it would be advantageous because it would result in a high blood concentration of the medication at first and a slow release of the remaining medication. This suggests that drug release becomes diffusion regulated once the medication clinging to the microspheric surface has leached. based on the findings that the Cilnidipine-formulated microspheres might be physiologically safe, widely accepted, and able to display long-lasting characteristics.

5. CONCLUSION

Emulsification heat de-naturation method was used to successfully manufacture cilnidipine-loaded microspheres from egg albumin microspheres and bovine serum albumin (BSA) microspheres via emulsification cross linking technology. The cross-linking agent in this investigation is glutaraldehyde saturated toluene. The goal of the current study was to compare Cilnidipine microspheres made with various biodegradable polymers in order to determine the optimal formulation. Compared to the F6 formulation made with egg albumin, the F3 formulation made with BSA is the superior formulation, according to the data. Widespread acceptance of the Cilnidipine-formulated microsphere was possible, and the physiologically acceptable polymers were able to demonstrate sustained release qualities. In conclusion, it was demonstrated that the Cilnidipine microsphere developed in this work is an effective drug delivery system for poorly soluble medicines. It is possible to draw the conclusion that using Cilnidipine microspheres in a clinical setting can help achieve the full therapeutic benefit of calcium channel blockers and successfully manage hypertension. Therefore, it was determined that the biopolymeric carrier synthesised with BSA for the sustained release distribution of cilnidipine produced a drug release rate of 93.3% w/v and an adequate drug entrapment efficiency of 96.7 percent w/v. Therefore, a newer extension of action that can be employed to treat hypertension is provided by the innovative formulation of BSA-Cilnidipine..

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