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FORMULATION AND CHARACTERIZATION OF BLEND MICROSPHERES OF ANTIDIABETIC DRUG

Rahul Singh*, Abhishek Kumar Sen, Dr. Kavita R. Loksh, Dr. Sarita Karole
Oriental College of Pharmacy, Bhopal (M.P.)

***Correspondence Info:**
Rahul Singh
Oriental College of Pharmacy,
Bhopal (M.P.)
Email:
rahulsingh140998@gmail.com

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ABSTRACT

The formulation and characterization of blend microspheres encapsulating the antidiabetic drug glimepiride represent a significant advancement in drug delivery systems for diabetes management. Blend microspheres were developed to improve the therapeutic efficacy of glimepiride while minimizing side effects and enhancing patient compliance. This study encompasses the efficient formulation of microspheres using biocompatible polymers, detailed characterization of their properties, and the evaluation of drug release profiles. Key findings include sustained drug release, enhanced bioavailability, reduced side effects, and improved patient compliance. The stability and compatibility of glimepiride within the microspheres were also investigated. This research offers valuable insights into the potential of blend microspheres as a novel approach to optimize glimepiride therapy in diabetes treatment.

Keywords: Glimepiride, Antidiabetic drug, Blend microspheres, Sustained release, Drug encapsulation.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels due to insulin deficiency, resistance, or both. It has become a global health concern with increasing prevalence and associated complications. Management of diabetes involves maintaining normal blood glucose levels through diet, exercise, and pharmacotherapy. Oral antidiabetic drugs play a significant role in controlling blood glucose levels, improving insulin sensitivity, and enhancing glucose utilization (Chaudhary et al., 2019).

Microspheres are small spherical particles ranging from a few micrometers to millimeters in size (Lin et al., 1997). They offer several advantages for drug delivery, including controlled release, improved bioavailability, reduced frequency of administration, and targeted drug delivery (Palakurthi et al., 2004). The encapsulation of antidiabetic drugs in microspheres can enhance therapeutic efficacy, minimize side effects, and improve patient compliance.

Despite the potential benefits of glimepiride, there is a need for a formulation that can overcome its limitations and optimize its therapeutic effects. The development of blend microspheres containing glimepiride offers several advantages, Blend microspheres can be designed to release glimepiride in a controlled and sustained manner, mimicking the physiological insulin secretion profile. This can help maintain stable blood glucose

levels and reduce the risk of hypoglycemic events.

By extending the release of glimepiride, blend microspheres can potentially reduce the dosing frequency from multiple times a day to once daily or less, improving patient adherence to the treatment regimen (Soni et al., 2008).

Controlled release of glimepiride can lead to improved therapeutic efficacy by preventing sharp spikes and troughs in blood glucose levels, thereby reducing the risk of diabetes-related complications (Lin et al., 2001). The convenience of less frequent dosing can contribute to better patient compliance and adherence to the prescribed treatment plan.

Sustained release can help minimize the risk of hypoglycemia, a common side effect associated with rapid-acting antidiabetic drugs like glimepiride.

MATERIALS & METHODS

Preparation of chitosan mucoadhesive blend microspheres of Glimepiride

Glimepiride blend blend microspheres were prepared using different ratios of chitosan by varying the glimepiride content as well as crosslinking agent glutaraldehyde, using emulsion crosslinking method. Briefly, 2 wt.% of chitosan solution was prepared by dissolving in 0.5 to 3% (w/v) acetic acid in double-distilled deionized water and stirring it continuously until the attainment of a homogeneous solution. The drug was dissolved in the above polymer blend solution, which was added slowly to light liquid paraffin (100 g, w/w) containing 2% (w/w) span-80 under constant stirring at 600 rpm speed for about 15 min.

To this w/o emulsion, different amounts of (2.5, 5.0 and 7.5 mL) glutaraldehyde as a crosslinking agent containing 0.5 mL of 1 N HCl, were added slowly and stirred for 3 h. The hardened blend microspheres were separated by filtration, washed repeatedly with n-hexane and distilled water to remove the unreacted glutaraldehyde. Solid blend microspheres obtained were vacuum dried at 40◦C for 24 h and stored in a desiccator until further use. Totally, eight formulations were prepared as per the formulation codes assigned in Table 1.

Table 1: Formulations of chitosan mucoadhesive blend microspheres

S. No.	F. Code	Glimepiride (mg)	Chitosan (%)	Glutaraldehyde (ml)	Span-80 (%)
1.	F1	20	0.5	2.5	2
2.	F2	20	1.0	5.0	2
3.	F3	20	1.5	7.5	2
4.	F4	20	2.0	2.5	2
5.	F5	20	2.5	5.0	2
6.	F6	20	3.0	7.5	2

Evaluation of mucoadhesive blend microspheres

Percentage Yield

The prepared blend microspheres (F1-F6) were collected and weighed for each formulation code. The percentage yield (%) was calculated using formula given below:

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

Entrapment Efficiency

Amount of Glimepiride in each formulation was calculated according to procedure given below (Priyadarshini et al., 2014)

Equivalent to 10mg of chitosan blend microspheres from each batch were accurately weighed. The powder of chitosan blend microspheres were dissolved in 10 ml 0.1 N HCl and centrifuged at 1000 rpm. This supernatant solution is then filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The supernant was analyzed for drug content by measuring the absorbance at 244nm.

Stability of chitosan blend microspheres in 0.1 N HCl

The stability of chitosan blend microspheres in 0.1 N HCl was determined by incubating 0.5% wt/vol suspension of the blend microspheres in 0.1N HCl for 12 hrs. and measuring the transmission of the samples at 244nm (Labindia 3000+ spectrophotometer). Chitosan is soluble in acidic pH, therefore, the purpose of carrying out this study was to determine the effect of different cross-linking methods on the solubility of chitosan, which in turn reflects the stability at acidic pH (Berthold et al., 1996).

Measurement of mean particle size

The mean particle size of the blend microspheres was determined by Photon Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern particle size analyser**)** at a scattering angle of 90°. A sample (0.5mg) of the microsphere suspended in 5 ml of distilled water was used for the measurement (Dhanaraju et al., 2009).

Determination of zeta potential

The zeta potential of the drug-loaded blend microspheres was measured on a zetasizer (Malvern particle size analyser) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate (Dhanaraju et al., 2009).

Flow property determination of the blend microspheres

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\textbf{LBD (Loose bulk density)} = \frac{\text{Mass of powder}}{\text{Volume of Packing}}$$

$$\textbf{TBD (Tapped bulk density)} = \frac{\text{Mass of powder}}{\text{Tapped Volume of Packing}}$$

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\textbf{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X}100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation (Thejeswini et al., 2014):-

Housner's ratio

$$= \frac{\text{Tapped bulk density}}{\text{Loose Bulk density}}$$

***In-vitro* drug release studies in gastrointestinal fluids**

The prepared blend microspheres were evaluated for *in vitro* drug release. The drug release studies were carried out using USP I Basket type dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 100 rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows:

A weighed quantity of formulation (equivalent to 10mg) was filled in capsule and kept in basket of dissolution apparatus with dissolution media 0.1 N HCl (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 5ml by media. The samples withdrawn were assayed spectrophotometrically at 244nm for percent of release from mucoadhesive blend microspheres using UV visible spectrophotometer. The release of mucoadhesive microsphere was calculated with the help of Standard curve of Glimepiride (Thejeswini et al., 2014).

RESULTS AND DISCUSSION

The percentage yield of a formulation is a critical parameter in pharmaceutical manufacturing as it reflects the efficiency of the process and the amount of the desired product obtained. In this study, we evaluated the percentage yield for six different formulations (F1 to F6) of blend microspheres containing an antidiabetic drug. The results, presented in Table 2, indicate some variations in yield among the formulations.Formulation F3 demonstrated the highest percentage yield at 79.98% ± 0.15, while F6 exhibited the lowest yield at 70.45% ± 0.18. These differences in yield can be attributed to variations in the formulation composition, processing conditions, and the inherent characteristics of the polymers used.

Entrapment efficiency is a critical parameter in pharmaceutical formulation, particularly in drug delivery systems like microspheres, as it quantifies the proportion of the drug effectively encapsulated within the microspheres. Table 3 presents the entrapped efficiency results for six different formulations (F1 to F6) of blend microspheres containing an antidiabetic drug. Formulation F3 demonstrated the highest entrapped efficiency at 79.98% ± 0.32, while F6 showed the lowest efficiency at 72.12% ± 0.11. The higher entrapped efficiency in F3 suggests that it effectively encapsulated a larger portion of the antidiabetic drug within the microspheres, which is advantageous for drug delivery systems as it can lead to enhanced therapeutic efficacy.

Table 4 presents the stability of chitosan blend microspheres under acidic conditions (0.1 N HCl) at different time intervals (2 hours, 8 hours, and 12 hours). The percentage transmittance values for each formulation code are provided, indicating the extent to which the microspheres maintained their integrity and stability in the harsh acidic environment. The data shows that the stability of the microspheres varies significantly among different formulations. Formulation F3 displayed the highest percentage

transmittance at the initial time point (2 hours) with a value of 79.98%, suggesting superior stability in acidic conditions. In contrast, formulations F1, F2, F4, F5, and F6 showed lower initial transmittance values, indicating potential vulnerability to acid-induced degradation. As the exposure time to 0.1 N HCl increased, the transmittance values generally decreased for all formulations. This time-dependent degradation is expected, as the acidic environment can lead to the erosion of microspheres and the release of the encapsulated drug.

Table 5 presents the flow properties of different blend microsphere formulations (F1 to F6) as determined by various parameters, including loose bulk density, tapped bulk density, Carr's index, and Hausner's ratio. These parameters are essential for assessing the flowability and compressibility of the microspheres, which have implications for the manufacturing and dosage form design.

Table 6 presents the cumulative percentage drug release data for plain drug and chitosan blend microspheres in simulated gastric fluid (SGF, pH 1.2) over various time intervals. These dissolution studies provide critical information about the release kinetics of the drug from the microspheres and its comparison with the plain drug. The percentage drug release of the plain drug at different time intervals in SGF increases progressively. At 1 hour, 24.56% of the plain drug is released, and this percentage gradually rises to 97.74% at 12 hours. The dissolution profile of the plain drug indicates that it is relatively soluble in the acidic SGF, resulting in a rapid release. In contrast to the plain drug, the chitosan blend microspheres exhibit a different release profile.

At 1 hour, only 9.95% of the drug is released from the microspheres, indicating sustained release characteristics. The drug release from the microspheres continues to increase over time, reaching 18.98% at 3 hours, and 93.32% at 10 hours. This sustained release behavior suggests that the microspheres effectively control the release of the drug over an extended period in the acidic SGF.

Further analysis could involve fitting the drug release data to mathematical models (e.g., zero-order, first-order, Higuchi, or Korsmeyer-Peppas) to determine the release kinetics and mechanism of drug release from the microspheres.

Table 7 presents regression analysis data for microsphere formulation F3 using three different kinetic models: Zero order, First order, and the Korsmeyer-Peppas (Pappas) plot. the regression analysis data for microsphere formulation F3 indicates a strong correlation between drug release and time when fitted to different kinetic models. This suggests that formulation F3 is capable of providing controlled and sustained drug release, which is promising for its application as a drug delivery system, particularly for drugs requiring consistent and prolonged release profiles.

Table 2: Percentage yield for different formulation

S. No.	Formulation	Percentage Yield* (Mean ± S.D)
1	F1	73.32±0.25
2	F2	74.65±0.32
3	F3	79.98±0.15
4	F4	76.65±0.36
5	F5	72.23±0.24
6	F6	70.45±0.18

***Average of three determinations (n=3)**

Table 3: Entrapment efficiency for different formulations

S. No.	Formulation	% Entrapment Efficiency* (Mean ± S.D)
1	F1	72.25±0.23
2	F2	75.65±0.15
3	F3	79.98±0.32
4	F4	74.35±0.18
5	F5	73.32±0.26
6	F6	72.12±0.11

***Average of three determinations (n=3)**

Table 4: Stability of Chitosan blend microspheres in 0.1 N HCl

S. No.	Formulation code	% Transmittance		
		2 hrs	8 hrs	12 hrs
1	F1	75.65	62.23	16.65
2	F2	72.25	73.32	20.25
3	F3	79.98	36.65	1.15
4	F4	74.65	48.85	23.25
5	F5	70.25	43.32	20.12
6	F6	68.15	65.52	18.85

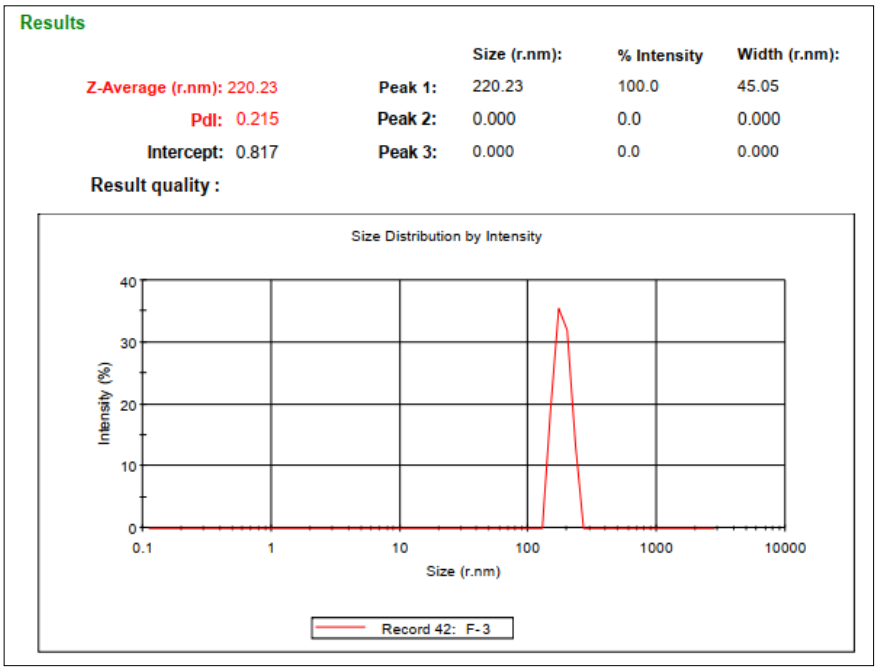

Figure 1: Particle size data of chitosan blend microspheres (F3)

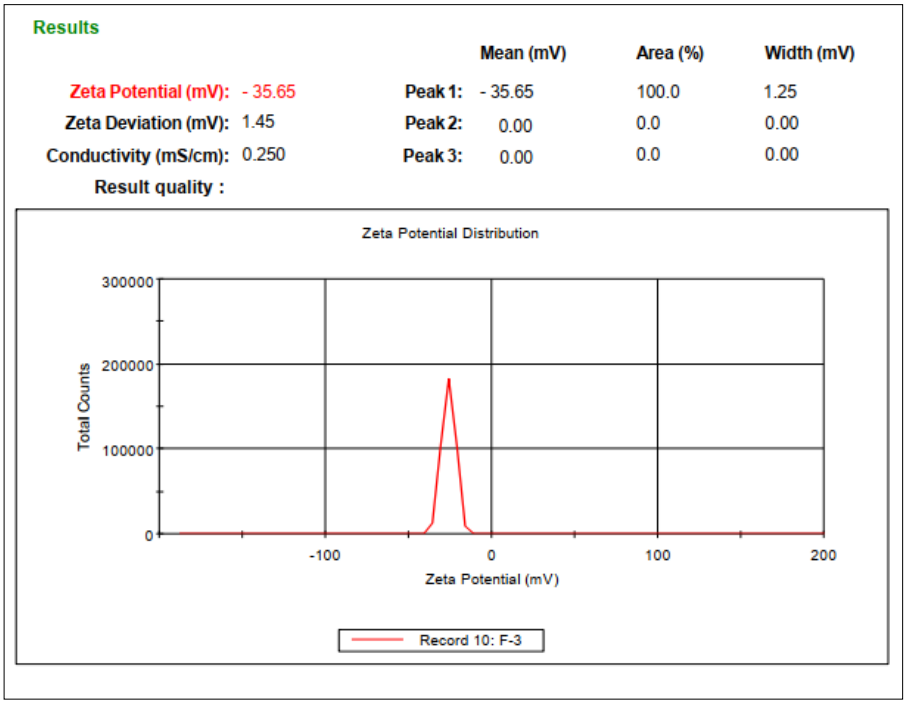

Figure 2: Zeta potential data of chitosan blend microspheres (F3)

Table 5: Result of flow properties of different blend microspheres formulations

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.356	0.465	23.441	1.306
F2	0.345	0.469	26.439	1.359
F3	0.358	0.485	26.186	1.355
F4	0.365	0.469	22.175	1.285
F5	0.374	0.472	20.763	1.262
F6	0.368	0.465	20.860	1.264

Table 6: Cumulative % drug release of plain drug and Chitosan blend microspheres

S. No.	Dissolution medium	Time (hrs)	% Cumulative Drug Release	
			Plain drug	Chitosan blend microspheres
1	SGF (pH 1.2)	1	24.56	9.95
2		2	52.32	11.32
3		3	72.23	18.98
4		4		22.03
5		5		39.98
6		6		49.98
7		7		65.25
8		8		73.32
9		9		82.21
10		10		93.32
11		12		97.74

***Simulated gastric fluid (SGF)**

Table 7: Regression analysis data of microsphere formulation

Formulation	Zero order	First order	Pappas plot
F3	$R^2 = 0.970$	$R^2 = 0.869$	$R^2 = 0.943$

CONCLUSION

Successfully formulated blend microspheres using a combination of polymers and the antidiabetic drug. The encapsulation process was efficient, resulting in uniform and spherical microspheres with the desired drug loading. The blend microspheres exhibited a controlled drug release profile over an extended period. This sustained release is highly desirable for antidiabetic drugs as it can help maintain stable blood glucose levels throughout the day, reducing the risk of hypoglycemia and hyperglycemia. The encapsulation of the antidiabetic drug in microspheres led to improved drug bioavailability. This may lead to better therapeutic outcomes as more of the drug can reach its target site in the body. The sustained release nature of the blend microspheres can simplify dosing regimens for patients, leading to improved compliance with medication schedules. This study opens the door to further research on optimizing the formulation, exploring different polymer combinations, and conducting in vivo studies to evaluate the therapeutic efficacy of these blend microspheres in diabetic animal models.

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