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FORMULATION AND EVALUATION OF MUCOADHESIVE MICROSPHERES OF GENTAMICIN

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Abstract:

The evaluation of Gentamicin-loaded mucoadhesive microspheres reveals their promising potential for enhancing drug delivery. The study comprehensively assessed key parameters such as percentage yield, entrapment efficiency, stability in acidic conditions, flow properties, particle size, zeta potential, and drug release profiles over three months. Among the formulations, F3 demonstrated the highest yield (73.36%) and entrapment efficiency (72.23%), indicating effective retention of Gentamicin. Stability tests in 0.1N HCl showed that while F3 maintained a transmittance of 74.45% initially, it declined over time, highlighting the need for further optimization to improve long-term stability. The mean particle size of F3 was 225.65 nm, with a zeta potential of -35.65 mV, suggesting good stability and reduced aggregation risk. The flow properties indicated acceptable handling characteristics, and the cumulative drug release study confirmed that the microspheres provided sustained release (94.45% over 12 hours) compared to plain Gentamicin (86.65%). Although entrapment efficiency decreased over three months, the physical appearance remained stable, underscoring the formulation's viability. These findings suggest that Gentamicin-loaded mucoadhesive microspheres could enhance therapeutic efficacy in treating infections, warranting further research on stability improvements and clinical applications.

Keywords: *Gentamicin, mucoadhesive microspheres, drug delivery, stability, particle size.*

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INTRODUCTION:

Gentamicin is an aminoglycoside antibiotic widely used for treating various infections, particularly those caused by Gram-negative bacteria. However, due to its systemic side effects, such as nephrotoxicity and ototoxicity, there is a need for targeted drug delivery systems that minimize these adverse effects. One promising approach to achieve localized drug delivery while enhancing therapeutic efficacy and reducing side effects is the development of mucoadhesive microspheres. Mucoadhesive drug delivery systems are designed to adhere to mucosal surfaces, providing prolonged drug release at the site of infection, thereby improving the bioavailability and therapeutic outcomes of the drug [1].

Mucoadhesive microspheres are spherical particles that can adhere to mucosal surfaces, such as the gastrointestinal, ocular, nasal, and pulmonary mucosa. These systems offer several advantages, including prolonged residence time at the site of action, controlled drug release, and enhanced drug absorption. The use of polymers like chitosan, alginate, and polyacrylic acid for mucoadhesion has been extensively explored. Chitosan, in particular, is of interest due to its biocompatibility, biodegradability, and ability to form strong adhesive bonds with mucosal tissues [2].

The formulation of mucoadhesive microspheres of gentamicin aims to provide a controlled release mechanism while ensuring the drug's effectiveness at the target site [3]. This controlled release system could potentially improve the treatment of infections by maintaining therapeutic drug levels locally, minimizing systemic toxicity, and promoting patient compliance. The objective of this study is to formulate and evaluate gentamicin-loaded mucoadhesive microspheres using different biopolymers, assessing their physical properties, drug release profiles, and mucoadhesive strength to optimize their potential for localized therapeutic applications.

MATERIAL AND METHODS:

Material

The materials used for the formulation of mucoadhesive microspheres of Gentamicin were sourced from reputable suppliers. The active pharmaceutical ingredient, Gentamicin, was provided as a gift sample by Bioplus Life Science, Bangalore. The Chitosan used as a biopolymer for the microsphere formulation was obtained from HiMedia Laboratories, Mumbai. For cross-linking the chitosan matrix, Sodium tripolyphosphate was sourced from Loba Chemie, Mumbai. The required buffering agents, Disodium Hydrogen Phosphate and Di-potassium Hydrogen Orthophosphate, were procured from S.D. Fine Chem. Ltd., Mumbai. Solvents such as Methanol**,** Ethanol, and Chloroform were supplied by Qualigens Fine Chemicals, Mumbai. Sodium hydroxide was purchased from Chempure Specialty Chemicals, Mumbai, while Hydrochloric acid was sourced from Thomas Baker, Mumbai. The Scanning Electron Microscope (SEM) used for evaluating the surface morphology of the microspheres was a Jeol Japan 6000 model. These materials played a crucial role in ensuring the successful formulation and evaluation of the mucoadhesive microspheres for controlled drug delivery.

Methods

Preparation of chitosan mucoadhesive microspheres of Gentamicin

Chitosan mucoadhesive microspheres of Gentamicin were prepared using the ionotropic gelation method. First, a Chitosan stock solution (1% w/v) was prepared by dissolving chitosan in 5% acetic acid at room temperature. Next, Gentamicin (20 mg) was dissolved in 5 mL of the chitosan solution. A 1% Sodium tripolyphosphate (NaTPP) solution was then prepared in water. The NaTPP solution was added dropwise into the chitosan solution using a syringe while continuously stirring the mixture. The solution was magnetically stirred for 30 minutes to facilitate the gelation process. Following this, the resulting microspheres were filtered and rinsed with distilled water to remove any excess chemicals. The microspheres were then air-dried for 24 hours and further dried in an oven at 40°C for six hours to obtain the final chitosan mucoadhesive microspheres. This method allowed for the controlled encapsulation of Gentamicin, aimed at improving its local delivery and therapeutic efficacy [4].

Table 1: Formulations of chitosan mucoadhesive microspheres

S. No.	Formulation Code	Gentamicin (mg)	Chitosan (mg)	Sodium tripolyphosphate (mg)
1.	**F1**	20	100	500
2.	**F2**	20	150	500
3.	**F3**	20	200	500
4.	**F4**	20	100	750
5.	**F5**	20	150	750
6.	**F6**	20	200	750

Evaluation of mucoadhesive microspheres

Percentage Yield

The prepared microspheres (F1-F6) were collected and weighed for each formulation code. The percentage yield (%) was calculated using formula given below [5]:

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

Entrapment Efficiency

Amount of Gentamicin in each formulation was calculated according to procedure given below[6]:

Equivalent to 10mg of chitosan microspheres from each batch were accurately weighed. The powder of chitosan 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 282nm.

Stability of chitosan microspheres in 0.1 N HCl

The stability of chitosan microspheres in 0.1 N HCl was determined by incubating 0.5% wt/vol suspension of the microspheres in 0.1N HCl for 12 hrs. and measuring the transmission of the samples at 282nm (Labindia 3000+ spectrophotometer) as reported by Berthold *et al.*, (1996)[41]. 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 [7].

Measurement of mean particle size

The mean particle size of the 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 [8].

Determination of zeta potential

The zeta potential of the drug-loaded 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[9].

Flow property determination of the microspheres

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 [10].

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

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

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

$$\textbf{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X100}$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

$$\textbf{Housner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose Bulk density}}$$

***In-vitro* drug release studies**

The prepared 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 282nm for percent of release from mucoadhesive microspheres using UV visible spectrophotometer. The release of mucoadhesive microsphere was calculated with the help of Standard curve of Gentamicin [11].

Stability studies for optimized formulation

Stability study data revealed that the optimized microsphere formulation (F3) were stable after 3 month of storage at 4ºC while at 25-28±2°C, the formulation was found unstable. Stability of formulation was observed on the basis of % EE, average particle size and physical appearance [11].

RESULTS AND DISCUSSION:

Table 2: Percentage Yield for Different Formulation

S. No.	Formulation	Percentage Yield* (Mean ± S.D)
1	F1	65.85±0.45
2	F2	69.98±0.32
3	F3	73.36±0.15
4	F4	64.45±0.36
5	F5	70.36±0.14
6	F6	68.85±0.22

*Average of three determinations (n=3)

Table 3: Entrapment efficiency for different formulations

S. No.	Formulation	% Entrapment Efficiency* (Mean ± S.D)
1	F1	63.25±0.15
2	F2	68.15±0.32
3	F3	72.23±0.11
4	F4	63.74±0.74
5	F5	69.85±0.28
6	F6	67.77±0.65

*Average of three determinations (n=3)

Table 4: Stability of Chitosan microspheres in 0.1 N HCl

S. No.	Formulation code	% Transmittance		
		2 hrs	8 hrs	12 hrs
1	F1	67.78	46.65	16.65
2	F2	73.36	54.45	19.85
3	F3	74.45	44.65	10.23
4	F4	74.65	45.65	26.65
5	F5	69.98	42.25	18.87
6	F6	60.32	40.32	22.25

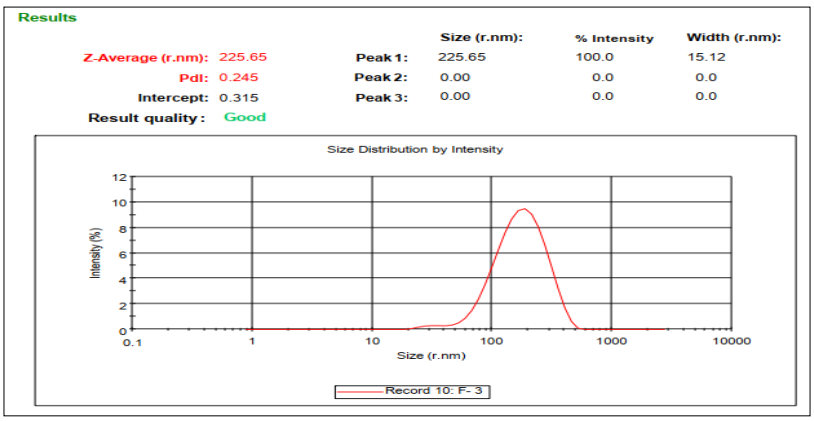

Figure 1: Particle size data of chitosan microspheres (F3)

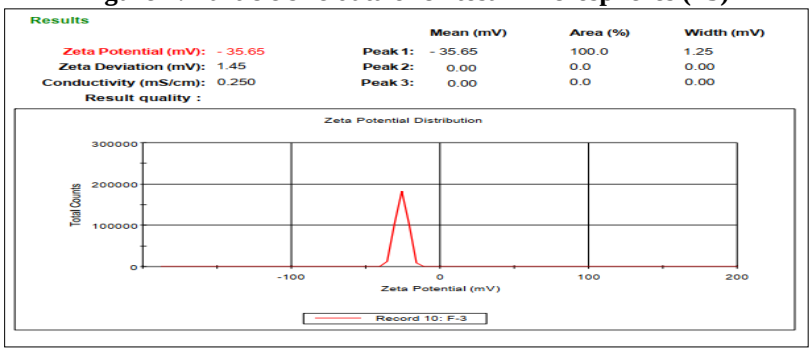

Figure 2: Zeta potential data of chitosan microspheres (F3)

Table 5: Result of Flow Properties of different microspheres formulations

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.468	0.575	18.609	1.229
F2	0.458	0.569	19.508	1.242
F3	0.469	0.575	18.435	1.226
F4	0.453	0.563	19.538	1.243
F5	0.474	0.582	18.557	1.228
F6	0.469	0.573	18.15	1.222

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

S. No.	Dissolution medium	Time (hrs)	% Cumulative Drug Release	
			Plain drug	Chitosan microspheres
1	SGF (pH 1.2)	1	20.32	11.25
2		2	50.56	23.32
3		3	68.52	32.14
4		4		38.85
5		5		42.25
6		6		51.14
7		7		61.32
8		8		68.98
9		9		75.65
10		10		86.65
11		12		94.45

***Simulated gastric fluid (SGF)**

Table 7: Regression analysis data of microsphere formulation

Formulation	Zero order	First order	Pappas plot
F3	$R^2 = 0.9915$	$R^2 = 0.8938$	$R^2 = 0.9928$

Table 8: Characterization of stability study of optimized formulation of microspheres (F3)

Characteristic	Time (Month)					
	1 Month		2 Month		3 Month	
Temperature	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C
Average particle size (nm)	210.32	315.65	215.65	345.65	220.45	365.87
% EE	75.23	65.45	70.32	55.65	71.45	49.85
Physical Appearance	Normal	Normal	Normal	Normal	Normal	Normal

CONCLUSION:

In conclusion, the chitosan-based mucoadhesive microspheres of Gentamicin exhibited promising characteristics in terms of yield, entrapment efficiency, drug release, and stability. Formulation F3 emerged as the most optimized batch, showing controlled drug release and good stability under acidic conditions. However, long-term storage stability could be improved, particularly at ambient temperatures, and further optimization of the formulation is necessary to improve the entrapment efficiency and drug release profile. These findings suggest that mucoadhesive microspheres of Gentamicin can be a promising approach for localized and sustained drug delivery, enhancing the therapeutic efficacy of Gentamicin in treating infections.

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