FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAIN RELESE MICROSPHERE

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ABSTRACT

The aim of present study was to formulate and evaluate the Haloperidol loaded Sustained release microspheres by solvent evaporation technique. sodium alginate, Hydroxypropyl methylcellulose, sodium carboxy methyl cellulose as polymer is used as the retardant material. The effects of process conditions such as drug loading, polymer type and solvent type on the characteristics of micro-spheres were investigated. The prepared microspheres were characterized for their particle size and drug loading and drug release. The in-vitro release studies were carried out in phosphate buffer at pH 7.4. The prepared microspheres were white, free flowing and spherical in shape. The maximum percentage yield was found 78.58±0.14. The drug entrapment efficacies of formulations were in range of 63.21±0.36 - 75.45±0.14% w/w.

Keywords: Microspheres, Haloperidol, Ethylcellulose, sodium alginate.

1. INTRODUCTION

The theories of micro particles were first observed in the 1960 when it was formulated on silicon rubber and polyethylene. The lack of degradability is the primary reason of its limited application and that leads to surgical removal of polymer from the system. Afterwards degradable polymers were used at random to coat the therapeutic agents. The process of applying relatively thin coating in different types of formulation like solids or droplets of liquid, dispersions and that should be in the size range of 1-1000μm is known as microencapsulation. This is a blend of deep knowledge of pure polymer science and emulsion technology with a proper implementation on drug stabilization. This technology involves entrapment of solids, liquid or gases in a suitable polymeric coating. This is a unique technology of converting liquids into solid with proper release profile inside the body. The

ultimate objectives of the microencapsulation drug delivery system is to extend and control the release of the active drug molecule from the coated particle without attempting to modify the normal biofate of the active drug molecule in the body after administration and adsorption.

2. MATERIAL AND METHOD

2.1 Preformulation Studies

A. Physical Evaluation

1.	Color	White to faintly yellowish, amorphous or micro-crystalline powder
2.	Odor	Odorless
3.	Appearance	Fine powder

B. Solubility

S. No.	Solvent used	Solubility
1.	Water	Insoluble
2.	Acetone	Freely soluble
3.	Benzene	Freely soluble
4.	Methanol	Freely soluble
5.	Chloroform	Freely soluble

C. Melting point: Melting point of Haloperidol was found 148°C -151.5 °C.

D. Identification test using FTIR spectroscopy

The IR spectrum of sample drug shows the peak values which are characteristics of the drug and the graph were exposed:
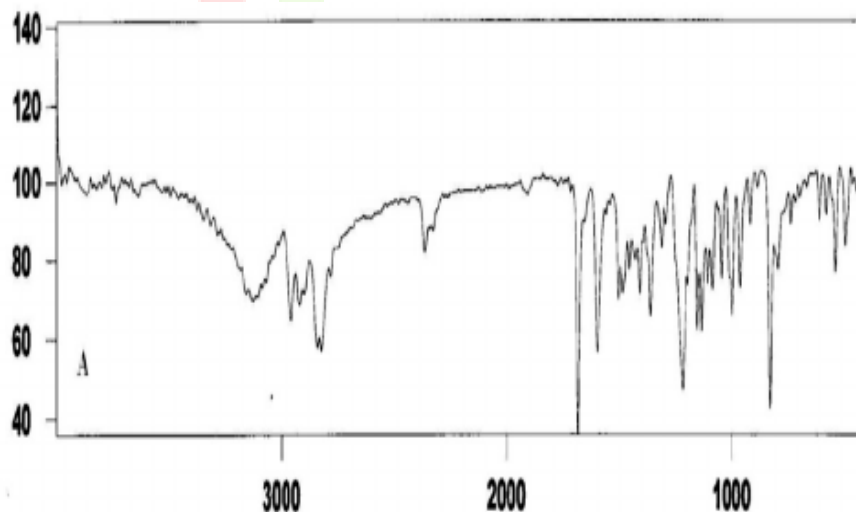
E. Loss of Drying: The percentage of loss on drying of Haloperidol was found 0.12 ±0.016.

F. Flow property of Haloperidol powder:

Bulk properties

Calculate the bulk density, in gm per ml gm/cc, by the formula:

$$\text{Bulk Density} = \frac{\text{Bulk Mass}}{\text{Bulk Volume}}$$

S. No.	Density	Result
1.	Untapped Density	0.261 g/cc
2.	Tapped Density (after 50 tapping)	0.347g/cc

Compressibility index

$$\text{C.I.} = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} \times 100$$

Result: The compressibility index of Haloperidol is **16.82%.**

Hausner ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk Density}}$$

G. Moisture content: The moisture content of was found 0.351%.

2.2 PREPARATION AND CHARACTERIZATION

Microspheres loaded with Haloperidol were prepared using solvent-evaporation method using HPMC and Eudragit RLPO in different ratio table. Drug and polymer in proportion of drug and polymers were dissolved in 1:2 mixture of solvent system of ethanol and dichloromethane. This clear solution was poured slowly in a thin stream into the aqueous solution of 1% polyvinyl alcohol. The emulsion was continuously stirred for 3 h at a speed of 500 rpm at 27±2°C. The microspheres were collected by decantation, while the non-floating microspheres were discarded. The microspheres were dried overnight at 40±2°C and stored in desicator .

Table 2.1 : Formulations of the microspheres prepared

S. No.	Formulation Code	Haloperidol (mg)	HPMC (mg)	Eudragit RLPO (mg)	Eudragit RSPO (mg)
1.	F1	5	25	25	-
2.	F2	5	25	50	-
3.	F3	5	25	100	-
4.	F4	5	25	-	25
5.	F5	5	25	-	50
6.	F6	5	25	-	100

2.3 Evaluation of microspheres

2.3.1 Percentage Yield

The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

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

2.3.2 Drug Entrapment

The various formulations of the microspheres were subjected for drug content. The percentage drug entrapment was calculated using calibration curve method.

2.3.3 Measurement of mean particle size

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer at a scattering angle of 90°.

2.3.4 Determination of zeta potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer by determining the electrophoretic mobility in a micro electrophoresis flow cell.

2.3.5 Shape and surface characterization of microspheres by scanning electron microscopy (SEM)

Microphotographs were taken on different magnification and higher magnification was used for surface morphology.

2.3.6 *In-vitro* release studies

The collected samples analyzed spectrophotometrically at 247 nm to determine the concentration of drug present in the dissolution medium. Several kinetic models have been proposed to describe the release characteristics of a drug from matrix.

8.3 Stability studies for optimized formulation

Three types of storage conditions are used i.e. long term, Accelerated and where appropriate, Intermediate.

Table 2.2: General guideline for stability study

Study	Storage conditions	Minimum time period covered by data at submission
Long term	25±2°C/60±5% RH or 30±2°C/65±5% RH	12 months
Intermediate	30±2°C/65±5% RH	6 months
Accelerated	40±2°C/75±5% RH	6 months

3. RESULTS AND DISCUSSION

3.1 Evaluation of Haloperidol microspheres

3.1 Percentage Yield

The percentage yield of different formulation was in range of 63.62±0.69%– 76.83±0.72%. The maximum percentage yield was found in formulation F4, 76.83±0.72%. as compare to all formulation.

Table 3.1: Percentage yield for different formulation

S. No.	Formulation	Percentage Yield
1.	F1	72.74±0.31
2.	F2	67.53±0.75
3.	F3	74.71±0.82
4.	F4	76.83±0.72
5.	F5	63.62±0.69
6.	F6	69.34±0.32

3.2 Drug Entrapment

The drug entrapment efficacies of different formulations were in range of 61.37±0.25- 72.87±0.14% w/w. Results demonstrated that increase in concentration of polymer increased the entrapment of the drug. The drug entrapment efficiency was found to be good in all the formulations. The maximum drug entrapment was found in formulation F-4 (72.87±0.14).

Table 3.2: Drug Entrapment for Different formulations

| S. No.	Formulation	Drug entrapment (% w/w) of prepared microsphere
1.	F1	66.36±0.45
2.	F2	62.13±0.32
3.	F3	66.38±0.69
4.	F4	72.87±0.14
5.	F5	61.37±0.25
6.	F6	67.82±0.61

3.3 Particle size analysis

The results of measurement of mean particle size of optimized formulation F4 of floating microsphere was found to be 178.4 nm.

3.4 Zeta Potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate. Results of zeta potential of optimized formulation F4 of floating microsphere was found -16.6 mV.

3.5 Shape and Surface Characterization of Microspheres by Scanning Electron Microscopy (SEM)
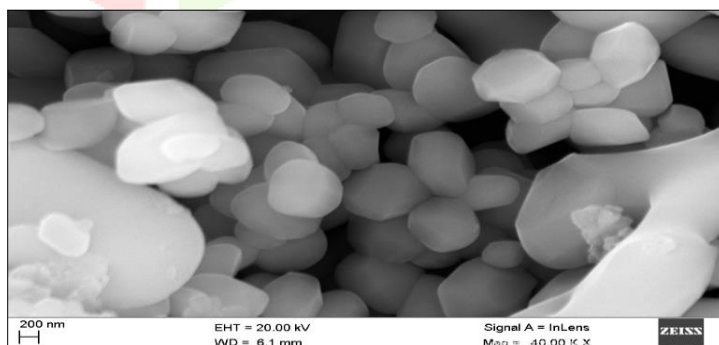
3.6 *In vitro* drug release study of Haloperidol loaded microsphere

Table 3.3: Comparative study of regression coefficient for selection of optimized Formulation F4

Release Kinetics	Zero order	First order	Higuchi	Korsmeyer peppas
R^2	0.998	0.815	0.937	0.981

3.7 Stability studies of final formulation

According to ICH guidelines, 3 months accelerated stability study at 40±2°C and 75±5% RH optimized formulations (F4) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference observed in the drug content between initial and formulations stored at 40±2°c & 75±5% RH for 3 months

CONCLUSION

Preformulation of drug was performed in which physiochemical properties and other parameters of drug were studied. Physiochemical parameters such determination of solubility, melting point, λ_{max} scan using UV-spectrophotometry, FT-IR spectrophotometry were performed in this study.

Color of Haloperidol was found White to faintly yellowish, amorphous or micro-crystalline powder and Odorless. It has been observed that Haloperidol was freely soluble in Acetone, methanol, Benzene, Chloroform and insoluble soluble in water. The melting point of Haloperidol was found 148°C -151.5 °C. The percentage of loss on drying of Haloperidol was found 0.12 ±0.016. Percentage yield of different formulation was determined by weighing the Microspheres after drying. The percentage yield of different formulation was in range of 65.58±0.41 to 78.58±0.14%. The maximum percentage yield was found in formulation F4, 78.58±0.14 as compare to all formulation.The drug entrapment efficacies of different formulations were in range of 63.21±0.36 - 75.45±0.14% w/w. Results demonstrated that increase in concentration of polymer increased the entrapment of the drug. The drug entrapment efficiency was found to be good in all the formulations. The maximum drug entrapment was found in formulation F-4 (75.45±0.14). The maximum percentage yield, drug entrapment, percentage buoyancy and floating lag time was found to be formulation F4 in microsphere. The optimized formulation of both batches subjected to further studies. The results of measurement of mean particle size of optimized formulation F4 of microsphere was found to be 178.4 nm. Results of zeta potential of optimized formulation F4 of microsphere was found -16.6 mV. The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, in order to determine the mechanism of drug release. When the regression coefficient values were compared, it was observed that an 'r' value of microsphere was maximum zero order i.e 0.998 hence indicating drug releases from formulations was found to follow zero order for microsphere.

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