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Development, Optimization and Evaluation of Ligand Bonded Microsphere of "Vitamin – E" for Skin Targeting

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ABSTRACT

The microsphere is one of the multi-particulate drug delivery systems & prepared to obtain prolonged, controlled drug delivery to improve bioavailability or stability & to target a drug to a specific site, which enhances the therapeutic efficacy of a drug. The microsphere is used in targeted drug delivery system we will improve the specificity of the drug, reduce the adverse effect, toxic effect & enhance the potency of a drug such as chemotherapeutic agents & various cytotoxic drugs, etc. Drugs can be targeted to a specific site in the body using a microsphere. The degree of targeting can be achieved by localization of a drug to a specific area in the body (for Ex. lung) to a particular group of the cell (for Ex. kuffer cell, tumor cell) & addition of site-specific ligand to the microsphere as a carrier. The main objective of the present investigation is to develop the targeted delivery system for skin. When the drug is applied topically, the duration of contact of the drug to the skin is very less, which requires more time for penetration of the skin layer. In a disease condition, the structural & physiological function of the cell is changed. They are opposed to the release of drugs as well as absorption. It may be minimized by adopting the targeted delivery system.

1. INTRODUCTION

Targeted drug delivery is a kind of smart drug delivery system which is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period to a targeted diseased area within the body *(Nirav R. Patel et al 2011).*

A conventional drug delivery system is done by the absorption of the drug across a biological membrane, whereas the targeted release system is that the drug is released in a dosage form *(Jain N.K.2001).* Targeted drug delivery systems are being prepared by considering the specific properties of target cells, the nature of markers or transport carriers or vehicles which convey drugs to specific receptors and ligands, and physically modulated components *(Kataria Sahil et al 2011).* It should have a controllable and predictable rate of drug release which should not affect the drug action. It should have the therapeutic amount of drug release and should have minimal drug leakage during transit *(Nirav R. Patel et al 2011).* Carriers used should be bio-degradable or readily eliminated from the body without any problem.

Microsphere, as the carrier for a drug, is one such approach that can be used in targeted delivery and sustained controlled release fashion. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). The range of techniques for the preparation of microspheres offers a variety of opportunities to control drug administration. This approach allows the accurate delivery of a small quantity of the potent drugs, reduced drug concentration at the site other than the target site, and the protection of the labile compound before and after the administration and before the site of action *(Alagusundaram. M et al 2009).* The microspheres can be produced by several methods utilizing an emulsion system (o/w, w/o, o/w/o, and w/o/w). The common emulsion system used oil-in-water (o/w), with microspheres being produced by the emulsion solvent evaporation method *(Anupama Singh et al 2012).* This relatively simple method enables the entrapment of a wide range of hydrophobic drugs. The behavior of the drugs in vivo can be changed when combining the drug with a carrier particle. The clearance kinetics, tissue distribution, metabolism i.e. kinetics, and cellular interaction of the drug are strongly influenced by the behavior of the carrier *(Harshad Parmar et al 2010).* When the change in pharmaco-dynamics behavior of microsphere may lead to enhance therapeutic efficiency and increase in selectivity of microsphere at the targeting site *(Saurabh Srivastava et al 2013).*

The main objective of the present study was to investigate the possibility of microspheres being utilized in targeted drug delivery systems for the skin. When the drug is applied

topically, the duration of contact of the drug to the skin is very less, which requires more time for penetration of skin layers. In a disease condition, the structural & physiological function of the cell is changed. They are opposed to the release of drugs as well as absorption. The potency will be improved & the release of the drug is regulated in a controlled way by using microspheres as a delivery system. Improved specificity & degree of targeting can be achieved by localization of a drug to a specific area in the body to the skin by addition of site-specific ligand into the microsphere as a carrier. Vitamin E is selected for the preparation of the microsphere. Vitamin E plays an important prophylactic role against some serious light-induced skin diseases such as erythrocyte photo-hemolysis, photo-erythema, photo-aging, and photo-carcinogenesis that are mediated by photo-oxidative damage to cell membranes.

2. MATERIALS AND METHODS

2.1. MATERIALS

Vitamin E was purchased from Sigma India Pvt. Ltd., New Delhi, India. Ethylcellulose was purchased from, and the Ethyl acetate was purchased from. Other reagents were obtained from Shri Rawatpura sarkar institute of pharmacy, Kumhari Laboratories of analytical grade.

2.2. METHODS

Vitamin E microspheres were prepared based on the o/w emulsion solvent evaporation technique by using ethyl cellulose as a polymer. Formulations were prepared by dissolving the polymer and the drug in ethyl acetate (oil phase) and acetone as a solubilizer. This solution was poured slowly in the 300 ml of distilled water (aqueous phase) containing tween 80 as the emulsifying agent with continuous stirring on the propeller stirrer. The resultant mixture was emulsified at a speed of 500-1000 rpm for 4 hrs. The dispersed drug and polymer solution was immediately transformed into fine droplets, which subsequently solidified into rigid microspheres due to the solvent evaporation. The particles were collected by filtration, washed to remove excess oil by distilled water, dried in a hot air oven at 60˚C, and characterized. The microsphere was prepared by varying the Drug Polymer ratio and evaluated.

3. CONJUGATION OF MICROSPHERE WITH LIGANDS:

The surface modifications were performed through the adsorption process.

3.1. Ligand – I (Galactose): The Conjugation of ligand were performed on different ratio. 20mg, 10mg galactose, and 10mg, 20mg microsphere were added into the 100ml of Phosphate buffer at pH 5.2 respectively. The ligand and Microsphere ratio was (2:1, 1:2), then continuously stirred for 24hour.

3.2. Ligand – II (Sucrose)

20mg, 10mg Sucrose, and 10mg, 20mg microsphere were added into the 100 ml phosphate buffer at pH 5.2 respectively. The ligand and Microsphere ratio was (2:1, 1:2) then continuously stirred for 24 hours.

4. CHARACTERIZATION OF DELIVERY SYSTEM:

4.1. Percentage (%) yield:

The dried microspheres were weighed and the percentage yield of the prepared microspheres was calculated by using the following formula –

$$\% \text{ Yield } = \frac{\text{Weight of microsphere}}{Weight\ of Polymer + Drug} \times 100$$

4.2. Particle Size analysis:

The particle size of the microspheres was determined by optical microscopy. The eyepiece micrometer was calibrated with the help of a stage micrometer. The particle diameters of more than 50 microspheres were measured randomly. The average particle size was determined by using Edmondson's equation.

$$D = \frac{\sum nd}{\sum n}$$

Where n = Number of microspheres checked; D = Mean of the size range.

4.3. Drug Entrapment Efficiency:

10 mg Microspheres were crushed by using a mortar pestle then fined microspheres were suspended in 10ml of phosphate buffer at pH 6.8. After 24 hrs, the solution was filtered. 1 ml of the filtrate was pipette out and diluted up to 10 ml with Phosphate buffer then 1ml from the diluted solution was pipette out and diluted again up to 10 ml with phosphate buffer. The

drug contents were analyzed using UV Visible spectrophotometer at λ_{max} 295 nm. The drug entrapment efficiency was calculated by using the following formula:-

$$\% \textbf{ Drug Entrapment Efficiency} = \frac{(\textit{Practical Drug content})}{\textit{Theoritical Drug content}} \times 100$$

4.4. Fourier Transform Infrared Spectroscopy (FTIR) Studies:

The infrared (IR) spectra were recorded using an FTIR spectrophotometer by the KBr pellet method in the wavelength region between 400 and 4000 cm-1. The spectra obtained for Vitamin E and physical mixtures of vitamin E with polymers were compared to check the compatibility of the drug with polymers.

5. RESULT AND DISCUSSION

Microsphere was prepared by using ethyl cellulose by employing emulsification solvent evaporation technique. Vitamin E was used as a model drug to check the drug entrapment efficiency. The prepared microsphere was evaluated to check the effect of key parameters affecting the properties of the microsphere. For the present work, the composition of each formulation is shown in Table.4 Formulations F1, F2, F3, F4, F5 are designed to check the effect of the concentration of ethylcellulose, Effect of RPM on the characteristics of the microsphere.

Table 1: Composition of Ethyl Cellulose Microspheres

S.N.	Ingredient	F1	F2	F3	F4	F5
1.	Vitamin E (mg)	**250**	**250**	**250**	**250**	**250**
2.	Ethyl Cellulose (mg)	**500**	**750**	**1000**	**1250**	**1500**
3.	Ethyl Acetate (ml)	**20**	**20**	**20**	**20**	**20**
4.	Acetone (ml)	**10**	**10**	**10**	**10**	**10**
5.	Tween 80(ml)	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**
6.	Distilled Water (ml)	**300**	**300**	**300**	**300**	**300**
7.	Stirring Rate (rpm)	**500**	**800**	**1000**	**1000**	**1500**

*F1, F2, F3, F4, F5 is formulation code.

5.1. Percentage Yield

The percentage yield of all formulations was ranging from 12.62 to 38.08%. There was no significant difference observed by solvent mixture on % yield but the concentration of polymer and stirring rate affected the % yield of the prepared microsphere. The data is represented in Table No.2 below.

5.2. Particle size and Particle size Distribution

The particle size of the vitamin E-loaded microsphere was analyzed by optical microscopy. All the formulations of microspheres show uniform size distribution. The average particle size of microspheres was found to be in the range of 3.2 to 8.7 µm. From the results were shown in Table 5, it was observed that the particle size of the microspheres increased as the drug: polymer ratio was increased. The increase in the size of the microspheres may be attributed to an increase in viscosity of polymer solution with increasing concentration, which resulted in the formation of larger emulsion droplets and finally greater size of microspheres. As the stirring rate was increased, the particle size of the microspheres was decreased. This may be due to the formation of small size droplets at a higher stirring rate. The concentration of acetone has significantly affected the size of the prepared microsphere. The concentration of acetone in comparison to ethyl acetate was increased, the size of the microsphere was decreased. The data is represented in Table No.2 below.

5.3. Percentage Drug Entrapment

The results are shown in Table 5 which suggests that when the drug: polymer ratio increased, the entrapment efficiency was increased. As the stirring rate was increased, the entrapment efficiency was decreased. This may be due to the formation of small size microspheres with increased surface area and a higher stirring rate was enhanced the diffusion of the drug from such microspheres to aqueous solvent. However, the results shown in table 5 indicate that the change in the concentration of acetone does not affect the entrapment efficiency of the microspheres. The data is represented in Table No.2 below.

Table 2: Physical Evaluation of Ethyl Cellulose Microspheres

SN	Parameter	F1	F2	F3	F4	F5
1.	% Yield	**23.46%**	**28.9**	**38.08%**	**19.06%**	**12.62%**
2.	Particle Size (µm)	**3.2µm**	**5.1 µm**	**6.6 µm**	**7.4 µm**	**8.7 µm**
3.	Entrapment Efficiency (%)	**2.4%**	**22%**	**29.29%**	**16.99%**	**13.99%**

*F1, F2, F3, F4, F5 is formulation code.

5.4. Fourier Transform Infrared Spectroscopy

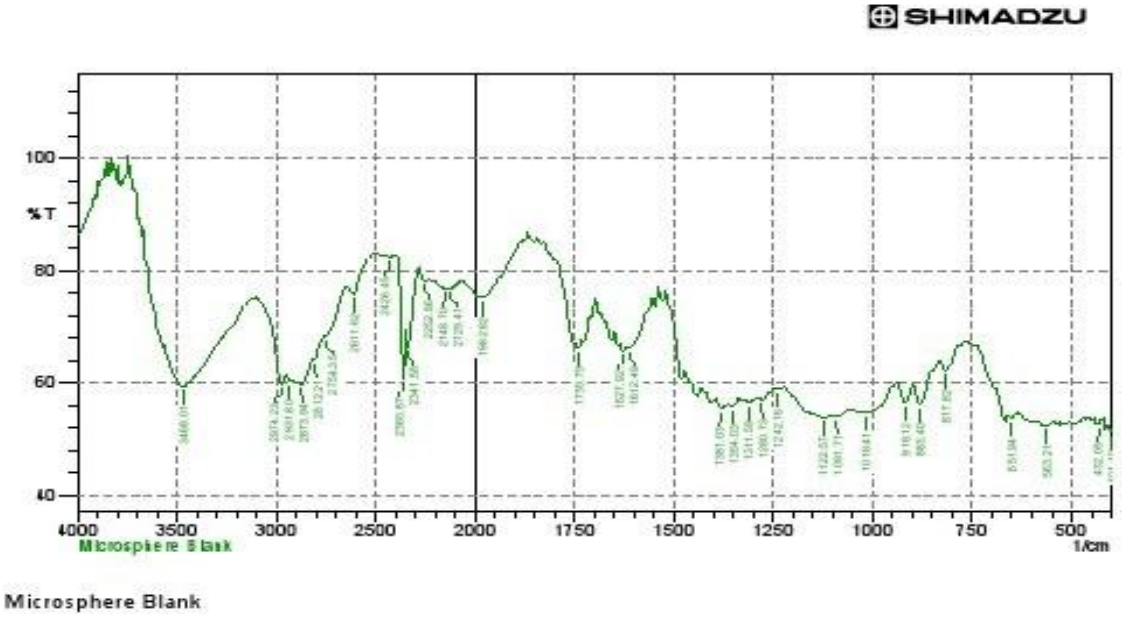

Figure 1: IR Scanning of Blank Microsphere

The infrared (IR) spectra were recorded using an FTIR spectrophotometer by the KBr pellet method where the wavelength region was between 400 and 4000 cm-1. The spectra obtained for Vitamin E and physical mixtures of vitamin E with polymers were compared to check the compatibility of the drug with polymers. The IR Scanning shows the polymer does not affect the chemical properties of vitamin E, which means they are compatible with each other.

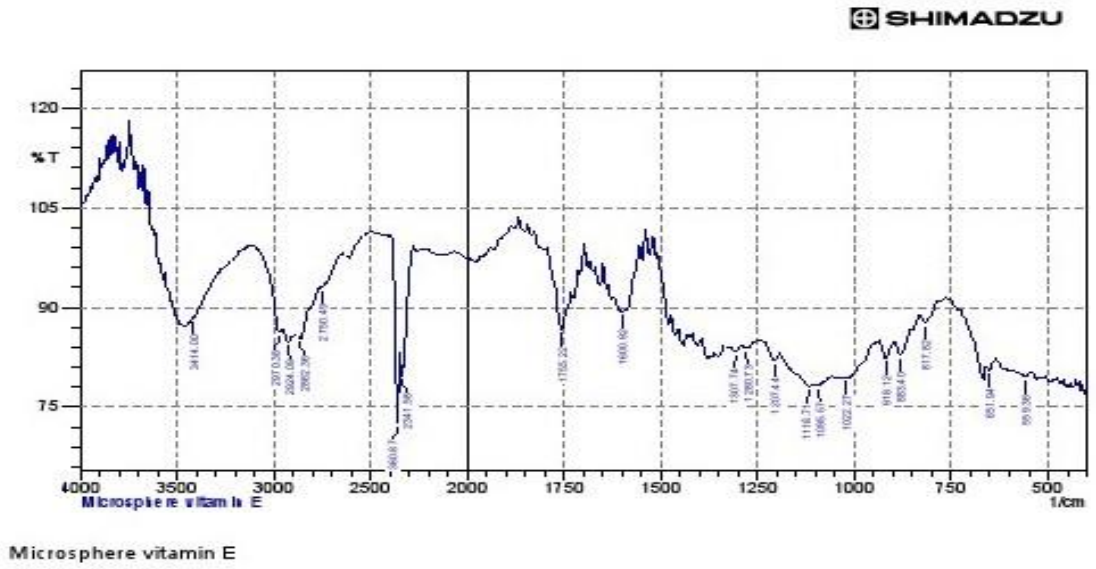

Figure 2:IR Scanning of Vitamin Microsphere

6. CONCLUSION

The ligand bonded ethyl cellulose microspheres of Vitamin E were successfully prepared by emulsification solvent evaporation technique and confirmed that it is the best method for preparing microspheres in terms of size uniformity and spherical shape. A higher percentage of drug loading was obtained by increasing the concentration of the polymer. The particle size of a microsphere was determined by optical microscopy and all the batches of microspheres show uniform size distribution. The average particle size was found to be in the range of 3.2 to 8.7µm. The various parameters such as solvent mixture, composition, and speed of stirring have found a significant effect on microsphere size, drug loading capacity.

The conjugation of the prepared microsphere with ligand dose not significantly affect the properties of vitamin E.

7. CONFLICT OF INTEREST: None

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