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Research Article

Preparation of Cephalexin Microspheres Using Eudragit E 100

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ABSTRACT
Cephalexin is semisynthetic first generation cephalosporin having activity against gram positive and gram negative bacteria. As it is bitter drug work has been undertaken to prepare taste- masked mouth dissolving tablets of cephalexin by incorporation of drug encapsulated microspheres into the tablets for use in pediatrics and also in patients experiencing difficulty in swallowing like geriatrics. Microspheres of cephalexin were prepared by solvent evaporation method using Eudragit E 100 and were characterized with regard to percentage yield, drug content and percentage entrapment, particle size, surface features, in-vitro drug release and taste. The microspheres of cephalexin having a drug: polymer ratio of 1:0.5 are tasteless, free flowing and spherical in shape.
Keywords: Cephalexin, Eudragit, Solvent evaporation, Microspheres

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INTRODUCTION
Despite the availability and use of effective vaccines and antibiotics, infectious diseases remain an important cause of death in India and worldwide. Cephalosporins are class of β-lactam antibiotics originally derived from Acremonium, which was previously known as "cephalosporium"[1]. Cephalosporins are bactericidal and have the same mode of action as other β-lactam antibiotics (penicillin) but are less susceptible to penicillinases are used for the treatment against infections. Cephalexin is very active against gram positive cocci, such as pneumococci, streptococci and staphylococci. As cephalexin is bitter in taste so taste masking is essential to ensure patient compliance as bitter drugs are unpalatable for the pediatrics. Various methods are available to mask undesirable taste of the drugs out of which Microspheres is the best choice of preparation for oral or parental delivery. Microencapsulation as a process to prepare microspheres has been defined by as a means of applying relatively thin coating to small particles of solid, droplets of liquid and dispersion[2]. This process can be used for masking of bitter tasting drugs microencapsulating drug particles with various coating agents. Cephalexin Microspheres were prepared by solvent evaporation method using Eudragit E 100.

MATERIALS AND METHODS
Cephalexin was obtained as a gift sample from Ajanta Pharma, Charkop, Mumbai. Eudragit E 100 was procured from Sigma-Aldrich Chemical Co. Ltd. Acetone, liquid paraffin, n-hexane, Span-60 and all other chemicals used were of analytical grade and double distilled water was used throughout the experiments.

METHOD OF PREPERATION
Solvent evaporation techniques are carried out in a liquid manufacturing vehicle (O/W emulsion) which is prepared by agitation of two immiscible liquids. The process involves dissolving microcapsule coating (polymer) in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase[3]. A core material (drug) to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core-coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain appropriate size microcapsules. Accurately weighed but varying amounts of Eudragit E 100 were dissolved in 10ml of

acetone over a cyclomixer and 250mg of accurately weighed cephalexin was added in the polymer solution. This organic phase was poured drop wise to 25ml of 1:1 mixture of heavy and light liquid paraffin with vigorous stirring over a mechanical stirrer[4]. High stirring rates of approximately 3000rpm were employed to obtain microspheres of smaller size. Stirring was continued for 3 hrs[5]. Then 20ml of hexane was added to the stirred contents. The suspension was filtered and microspheres were washed thrice with hexane, 10ml each, to remove any adhering liquid paraffin from the surface[6]. Finally prepared microspheres were washed with distilled water to remove any unentrapped drug from the surface of the microspheres. This was followed by vacuum drying of the microspheres overnight at room temperature (Fig.1). Several batches of microspheres were prepared by varying drug-polymer ratio, keeping all other formulation factors constant.

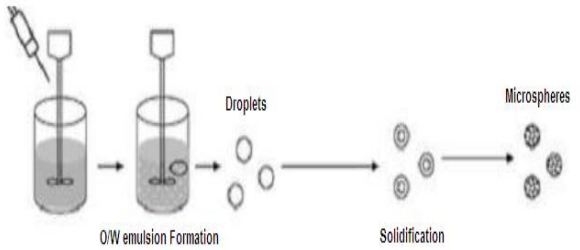

Fig. 1: Method of formulation of cephalexin Microspheres

RESULTS AND DISCUSSION

Particle size analysis

The particle size characterization of microspheres is an important study to ensure that particle size of the formulation lies in the optimal range. The size of microspheres was determined by dynamic light scattering (Nano ZS 3600, Microtrac- X100) with varying duration greater than 20 s. The dispersant used was water having RI (1.33), viscosity (0.8872 cP)[7]. Disposable sizing cuvette was used for determination. High yields of free flowing, non- aggregated microspheres were obtained with all the ratios of drug: polymer investigated[8]. The percentage yield obtained for the taste masked microspheres prepared by solvent evaporation method were 93%±5, 96%±0.3, 91%±5.2 and 90%±3.6 respectively for varying ratios of drug : Eudragit E100 1:0.5, 1:1, 1:2, 1:3. The highest yield was obtained with the ratio of 1:2. The mean particle size was influenced by the concentration of polymer, stirring speed, and surfactant concentrations.

Determination of drug content

About 100 mg equivalent of cephalexin microspheres was dissolved in 100 ml of isopropyl alcohol: water (50:50) solution. Then 1 ml of the above solution was diluted to 25 ml with distilled water and measured at 262nm under UV spectrophotometer[9]. The percentage drug content in the microspheres was calculated from the equation shown below:

$$\% \text{ Drug content} = \frac{\text{Analyzed weight of the drug in microspheres}}{\text{Theoretical weight of the drug loaded in the system}} \times 100$$

The drug content obtained for the taste- masked microspheres were 84%±4.5, 97%±6.08, 93%±5.0 and 92%±3.6 respectively. The highest drug content was obtained with the ratio of 1:2.

Entrapment Efficiency

About 100 mg equivalent cephalexin microspheres was washed with 10ml of water and filtered using Whatmann filter paper (#1). The residue was then dissolved in 100 ml of isopropyl alcohol: water solution (50:50). Then 1 ml of the above solution was diluted to 10ml with distilled water and measured at 262 nm in UV Spectrophotometer[10]. The percentage entrapment for the formulation was calculated by the following equation:

$$\text{Entrapment Efficiency} = \frac{\text{Weight of the drug in the microspheres}}{\text{Total drug content}} \times 100$$

The encapsulation efficiency of drug was found to be increasing with increase in concentration of polymer in a fixed volume of organic solvent i.e 78.8%±0.28, 81.1%±0.4, 92.9%±0.2, 96.7%±0.3respectively. After the preliminary studies the 1:0.5 ratio of drug:polymer is selected as it produces tasteless microspheres with entrapment efficiency of (78.8%) along with satisfactory results for other parameters.

In-vitro dissolution study

In vitro drug release studies were carried out using USP dissolution apparatus II (Model, TDT-06T, Electrolab, Mumbai, India). Accurately weighed equivalent to 125mg of drug microspheres were added to the medium under test[11]. The tests were carried out in pH 1.2 buffer (900ml) and pH 6.8 buffer (900ml) equilibrated at 37°C ± 0.5°C. The paddles were rotated at 75rpm. At specific times, 5 ml aliquots of the dissolution medium were withdrawn and replaced with 5 ml of fresh dissolution medium. The collected samples were analyzed spectrophotometrically at 262nm. The dissolution profile of these studies is given in figure 2. Eudragit E 100 is soluble in acid environment by formation of salts. Therefore, the drug is released from the microspheres very rapidly in pH 1.2 medium. Approximately 81% of the drug was released within 15min. Drug release in pH 6.8 buffer was 61% within 30mins

which is comparatively slower than that in pH 1.2 medium. Therefore, it is expected that as soon as the polymer dissolves in the acidic content of the stomach, the drug will release in the stomach and then absorbed by the gastrointestinal tract.

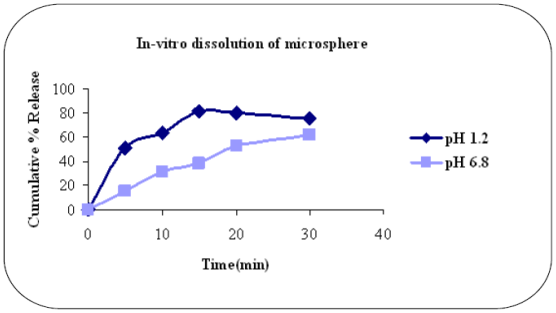

Figure 2: Dissolution of prepared Microspheres

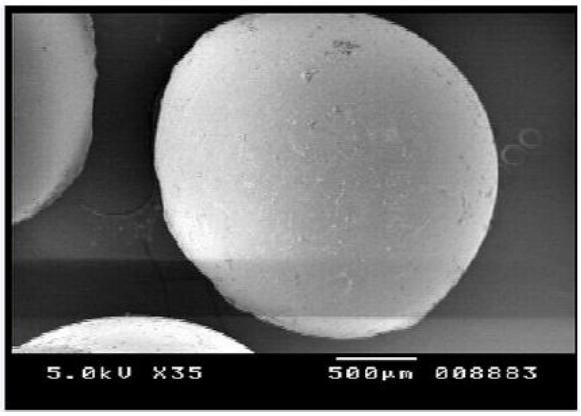

Figure 3: SEM of Prepared Microspheres

Scanning electron microscopy

Scanning Electron microscopy (SEM) studies were carried out for pure drug, Eudragit E100 and microspheres[12]. The pictures showed the crystalline shape of cephalexin particles, Eudragit E 100 showed the small spherical shape particles and cephalexin microspheres were free flowing, smooth and spherical in shape shown in figure 3.

Table 1: Percentage yield, Drug content, Entrapment efficiency and Particle size

Serial No	Drug:Polymer ratio	Yield (%)	%Drug content	% Entrapment	Particle Size (µm)
1	1:0.5	93±5.0000	84±4.5388	78.8±0.2645	507
2	1:1	96±0.3000	97±6.0827	81.1±0.4582	526
3	1:2	91±5.2915	93±5.0000	92.9±0.2645	580
4	1:3	90±3.6055	92±3.6055	96.7±0.3000	587

Stability study

The prepared microspheres were kept at 40°C/ 75% RH for 3 months as per ICH guidelines[13]. The samples were characterized for percentage drug content; drug entrapment and *invitro* drug release were performed in two different media of pH 1.2 and pH 6.8. The microspheres remain stable for the period of three months as shown in Table 2.

Table 2: Stability Study of Prepared Microspheres

Storage conditions 45°C/ 75% RH				
Serial No.	**Time**	**Appearance**	**%Drug content**	**% Entrapment**
1	0 month	no change	94.31± 0.128	78.21±0.041
2	1month	no change	86.32±0.042	74.53±0.032
3	2 month	no change	87.04±0.061	77.17±0.058
4	3 month	no change	84.75±0.054	77. 67±0.022

CONLUSION

Cephalexin is a semi-synthetic first generation having activity against gram positive bacteria like Staphylococcus aureas and Streptococci, which are the most frequent causes of the community, acquired skin and soft tissues infections. Microspheres of cephalexin were prepared by solvent evaporation method using acetone as a solvent, Eudragit E 100 as taste masking polymer, span 60 as a surfactant, light liquid paraffin as encapsulating medium and n-hexane was used to rigidize the microspheres and to accelerate settling. Analysis of microspheres has shown that microspheres are within acceptable size range with smooth surface and spherical shape. The in-vitro dissolution study of microspheres has shown that drug release in pH 6.8 media was comparatively slower than that in pH 1.2 media as Eudragit E 100 is insoluble in water but it swells and is permeable in water above pH 5. .Eudragit E 100 is soluble in acid environment by formation of salts. Therefore, the drug is released from the microspheres very rapidly in pH 1.2 medium. Approximately 81% of the drug was released within 15min. Drug release in pH 6.8 buffer was 61% within 30mins which is comparatively slower than that in pH 1.2 medium. Therefore, it is expected that as soon as the polymer dissolves in the acidic content of the stomach, the drug will release in the stomach and then absorbed by the gastrointestinal tract. After preliminary studies it is confirmed that cephalexin containing microspheres in the ratio of 1:0.5 are tasteless and these may be used for any oral drug delivery formulation.

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