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Research Article

# PREPARATION AND EVALUATION OF ETHYL CELLULOSE AND EUDRAGIT BASED MICROSPHERES OF DICLOFENAC POTASSIUM USING DOUBLE EMULSION-SOLVENT EVAPORATION METHOD

**G.DINESH BABU*, B.VISHNU VARDHAN REDDY, S.RAJEEV CHANDRA, A.SUBHASH CHANDRA, VINOD KUMAR KH.**

**Department of pharmaceutics, MES College of pharmacy, Rajiv gandhi University of Health Science's, Aradeshahally gate, Bangalore, India.**
**Email: srivyshu.pharma@gmail.com, babu.dinesh89@live.in**

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**ABSTRACT**

Diclofenac potassium (DP) microspheres were prepared by using Double Emulsion-solvent evaporation method with ethyl cellulose (EC) and Eudragit polymers. Poly vinyl alcohol containing 2% (w/w) span 80 was the external phase and polymer -drug solution was the internal phase. EC and Eudragit were used to encapsulate diclofenac potassium. By using different formulation variables, eight different formulations (F1, F2, F3, F4, F5, F6, F7&F8) were prepared. The resulting microspheres obtained, were more spherical in shape and showed more entrapment efficiency. The size of the microspheres varied between 346-695 µm and as high as 96.48% loading efficiency for Eudragit and 77.36% for EC was obtained. In vitro release study was carried out in 0.1 N hydrochloric acid solution (pH 1.2) for first 2 hours followed by in phosphate buffer solution (pH 6.8) for next 4 hours. After first 2 hours of dissolution in 0.1 N hydrochloric acid, EC microspheres released 23% of drug and Eudragit released 7% of drug. After 4 hours of dissolution in phosphate buffer, 64.78% diclofenac potassium was released from EC microspheres and 92.35% of drug was released from Eudragit microspheres.

**Keyword:** Diclofenac potassium, Microspheres, Ethyl cellulose, Eudragit, PVA &Double emulsion.

## INTRODUCTION

Despite tremendous advancements in drug delivery, oral route remains the preferred route for the administration of therapeutic agents, low cost of therapy and ease of administration leads to higher levels of patient compliance. Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Microsphere[1] carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery[2]. Diclofenac exists in two forms known as Diclofenac Sodium and Diclofenac Potassium. The real difference lies in the fact that potassium salt of Diclofenac is more soluble in water than sodium salt. As far as response time is concerned, it is Diclofenac potassium that gets absorbed quickly and starts analgesic activity in a much quicker time than Diclofenac sodium. Both sodium and potassium salts of Diclofenac are different in nature and function and cannot be treated as equivalent though their dose may be same. Diclofenac potassium is immediate release, while Diclofenac sodium is delayed release. This implies that for acute and severe pain, it is better to take Diclofenac potassium than Diclofenac sodium.

Diclofenac potassium, a potent non-steroidal anti-inflammatory drug with pronounced analgesic properties, is used in the long term treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Its biological half-life has been reported as 1-2 hr[3]. Gastrointestinal side effects such as bleeding, ulceration or perforation of intestinal wall are commonly seen[4]. Due to short biological half life and associated adverse effects, it is considered as an ideal candidate for controlled drug delivery via sustained release matrix tablets, pellets and sustained release microspheres[3-5]. Microencapsulation is one process used to control drug release and hence prolong therapeutic activity[6]. In pharmaceutical sustained release preparations, the uniqueness of microcapsules lies in the wide distribution throughout the gastrointestinal tract. This potentially improves drug absorption and reduces side effects related to localized build-up of irritating drugs against the gastrointestinal mucosa[7].

The Double emulsion solvent evaporation method has been described in the literature, and has been applied to polymers like ethyl cellulose[8-9]and Eudragit. The purpose of this investigation was to prepare diclofenac potassium microspheres using ethyl cellulose and Eudragit as wall material by double emulsion solvent evaporation method.

The resulting microspheres were subjected to study the effect of polymers (EC&Eudragit) on surface property, microspheres size and release profiles of the diclofenac potassium and to fit the data to various postulated drug release models.

## MATERIALS AND METHODS

The following chemicals were obtained from commercial sources and used as received: Diclofenac potassium (Hetero pharmaceuticals, Hyderabad.), Ethyl cellulose (SD fine chemicals, Mumbai), Eudragit (Karnataka fine chem, Bangalore), poly vinyl alcohol (SD fine chemicals, Mumbai), dichloromethane (SD fine chemicals, Mumbai), Span 80(SD fine chemicals, Mumbai), Hydrochloric acid (Karnataka fine chem, Bangalore), Petroleum ether of 40:60 grade (Karnataka fine chem, Bangalore).

### Preparation of Diclofenac potassium microspheres

Diclofenac potassium microspheres were prepared by different formulation variables as given in Table.No- 1. Desired amount of diclofenac potassium was dissolved in distilled water. Polymer (ethyl cellulose) was dissolved separately in dichloromethane .Then the aqueous drug solution was gradually added to above prepared polymeric solution with constant stirring at 600 rpm, stirring was continued for few minutes. Then the primary emulsion was added to PVA solution containing 2% span 80 stirring was continued up to 2 hrs at a temperature of 60°C in a 250 ml glass beaker. After 2 hours of stirring, hard, spherical microspheres were obtained. Microspheres were then washed three times with petroleum ether and vacuum-dried to obtain free flowing microspheres. The procedure was continued with Eudragit polymer also.

### Particle Size Analysis:

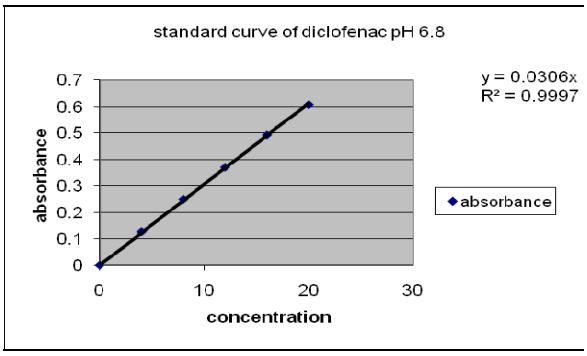
Size distribution of the microspheres was analyzed by scanning electron microscopy. Particle size distribution was measured by Dry Dispersion technique. Average particle size was expressed as volume mean diameter (D [4, 3]) and surface weighted mean diameter (D [3, 2]) in µm.

### Quantitative analysis of diclofenac potassium:

Aqueous solutions of diclofenac potassium (0 to 20 µg/ml) in phosphate buffer (pH 6.8) were prepared and the absorbance was measured at 276 nm by a Shimadzu UV-VIS Spectrophotometer (UVmini-1240, Shimadzu Corp., Kyoto, Japan). A linear line was obtained while absorbance values were plotted against concentrations (R2 > 0.9997).

**Table 1: Different formulation variables**

| Batch code | Amount of drug (mg) | Amount of polymer-Eudragit(mg) | Amount of polymer-EC (mg) | Drug: polymer ratio | Qty.of DCM (ml) |
|---|---|---|---|---|---|
| *F1* | *200* | - | *200* | *1:1* | *10* |
| *F2* | *200* | - | *400* | *1:2* | *10* |
| *F3* | *200* | - | *600* | *1:3* | *10* |
| *F4* | *200* | - | *800* | *1:4* | *10* |
| *F5* | *200* | *200* | - | *1:1* | *10* |
| *F6* | *200* | *400* | - | *1:2* | *10* |
| *F7* | *200* | *600* | - | *1:3* | *10* |
| *F8* | *200* | *800* | - | *1:4* | *10* |




**Drug-loading efficiency**

100 mg drug equivalent microspheres of each batch were finely powdered in a glass mortar. From that 50 mg powder was accurately weighed and taken in a volumetric flask. A clear solution was made using phosphate buffer after vigorous shaking on mechanical shaker .Then the solution was filtered through 0.45 µm filter and analyzed spectrophotometrically for drug content. The weight of diclofenac potassium theoretically contained in the microspheres was compared with the weight actually obtained from the drug content studies, i.e., the quantity loaded into the microspheres formulated, to get the diclofenac potassium loading efficiency.

Following equation was used for the calculation.

$$\text{Drug-loading efficiency (\%)} = (Cp/Ct) \times 100$$

Where, Cp and Ct were the actual and theoretical drug content in diclofenac sodium loaded microspheres, respectively.

***In vitro* dissolution study**

In-vitro dissolution was carried out in a USP dissolution testing apparatus TYPE -II (Paddle Apparatus) in 900 ml of 0.1 N HCl solution (pH 1.2) for 2 hours followed by in 900 ml of phosphate buffer (pH 6.8) for next 4 hours at 37±0.5ºC at a rotational speed of 50 rpm. Dissolution Samples were withdrawn at predetermined intervals and were filtered through 0.45 µm filters and proper sink conditions were maintained. The drug content was determined in the filtrate either directly or after appropriate dilution with the dissolution media.

**RESULTS AND DISCUSSION**

Diclofenac potassium microspheres were prepared by double emulsification-solvent evaporation technique with different polymeric concentrations of ethyl cellulose and Eudragit. Effect of different concentrations of EC&Eudragit-diclofenac potassium microspheres were successfully examined with respect to microcapsule size, surface characteristics, drug loading efficiency, and release kinetics.

**Morphology of the microspheres**

In Figure 1, significant differences in the surface characteristics were observed from batch to batch of different concentrations of EC polymer. While 1:1 EC was used, micro spheres shape was nearly spherical and surface was rough (Figure 1A). In contrast, while 1:2 EC was used, microsphere shape was more spherical and surface appeared more smooth (Figure 1B).

While 1:3 EC was used, microsphere shape was spherical and surface was smooth (Figure 1C). In contrast, while 1:4 EC was used, microsphere shape was more spherical and surface appeared very smooth (Figure 1D). This might be due to the less core load in the microspheres of the latter batch. A uniform wall was formed around each microsphere of the latter batch due to high polymeric content also.

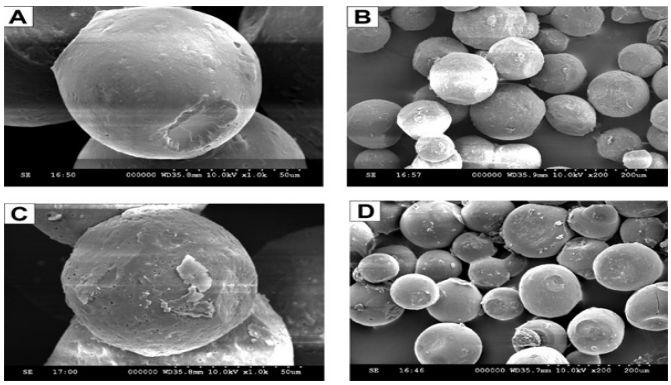



**Fig. I: Scanning electron micrograph of diclofenac sodium microspheres prepared with different concentration of EC;**

A = 1:1 ratio EC, B = 1:2 ratio EC. C=1:3 ratio EC and D=1:4 ratio EC.

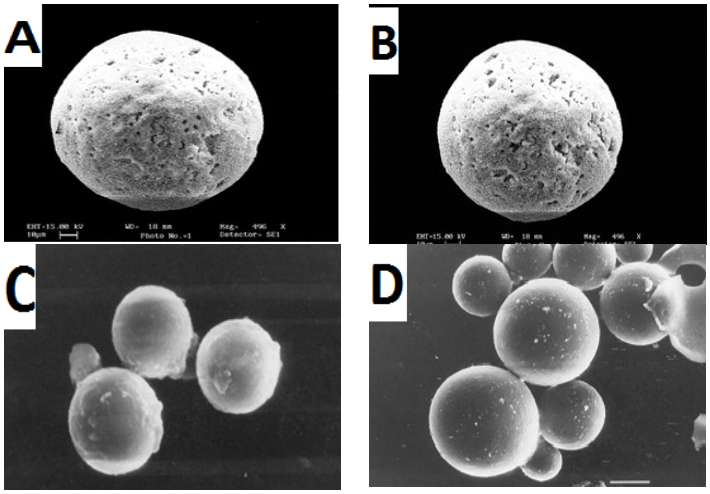



**Fig. II: Scanning electron micrograph of diclofenac sodium microspheres prepared with different concentration of EC;**
A = 1:1 ratio Eudragit, B = 1:2 ratio Eudragit. C=1:3 ratio Eudragit and D=1:4 ratio.

In Figure- II, significant differences in the surface characteristics were observed from batch to batch of different concentrations of Eudragit polymer. While 1:1 Edragit was used, micro spheres shape was nearly spherical and surface was rough (Figure 1A).

In contrast, while 1:2 Eudragit was used, microsphere shape was more spherical and surface appeared more smooth (Figure 1B). While 1:3 Eudragit was used, microsphere shape was spherical and surface was smooth (Figure 1C). In contrast, while 1:4 Eudragit was used, microsphere shape was more spherical and surface appeared very smooth (Figure 1D).

Theoretically, more DP crystals should be present on the microsphere surface as the formulation contained relatively larger amount of the drug. But figuratively, a surface embedded with fewer amounts of DP and containing large holes were seen**.**

**Particle size distribution analysis**

Increased amount of polymeric material resulted in increased particle size (see Table 2). Mean particle size was 885.65 (±2.54) µm for 80% EC and 523.91 (±4.21) µm for 20% EC. As the polymeric amount was increased, fusion between semi formed microparticles was increased which ultimately produced larger microcapsules[10-11] (Figure 3).

Whereas microspheres, formulated with lesser polymeric materials, were comparatively smaller. Presence of insufficient polymeric material might be attributed to this. And this resulted in the formation of small volume of smaller particles along with the large volume larger particles.

**Loading Efficiency**

Maximum drug load for EC was 88.24% (F1) and 96.48% for Eudragit ( F5) and minimum drug load for EC was 77.36%(F4) and for Eudragit 83.96% ( F8). Generally encapsulation efficiency of a drug depends on the solubility of the drug in the organic solvent and continuous phase.

But, an increase in the concentration of polymer in a fixed volume of organic solvent also results in an increase in encapsulation efficiency[12].

**Drug Release Profile**

Figure-III shows the percentage release of diclofenac potassium from the different formulations of microspheres formulated with EC and Eudragit. Percentage amount of drug release was found to be decreased significantly with increase amount of EC. However, gradual decrease in drug release rate with increased amount of polymer is a very common phenomenon.

This can be explained by a decreased amount of drug present close to the surface and also by the fact that the amount of uncoated drug decreases with higher polymer concentration.[13-14].

**Table 2: Mean particle size and Drug entrapment efficiency of the microspheres prepared with ethyl cellulose.**

| Batch | Theoretical load of DP(mg) | Actual load of DP(mg) | Loading Efficiency (%) | Mean population diameter µm (±SD)[a] | Mean volume diameter µm (±SD)[a] | SSA (m2/g X 10-2)[b] |
|---|---|---|---|---|---|---|
| F1 | 50 | 44.12 | 88.24 | 545.22 ± 3.45 | 657.65 ± 1.46 | 0.67 |
| F2 | 50 | 43.20 | 86.40 | 412.65 ± 1.87 | 621.31 ± 4.6 | 0.94 |
| F3 | 50 | 41.23 | 82.46 | 398.43 ± 2.6 | 595.34 ± 1.98 | 1.25 |
| F4 | 50 | 38.68 | 77.36 | 346.76 ± 2.48 | 523.91 ± 7.39 | 1.46 |

**Table 3: Mean particle size and Drug entrapment efficiency of the microspheres prepared with Eudragit.**

| Batch | Theoretical load of DP(mg) | Actual load of DP(mg) | Loading Efficiency (%) | Mean population diameter µm (±SD)[a] | Mean volume diameter µm (±SD) | SSA (m2/g X 10-2)[b] |
|---|---|---|---|---|---|---|
| F5 | 50 | 48.24 | 96.48 | 695.22 ± 2.14 | 885.65 ± 2.54 | 0.98 |
| F6 | 50 | 46.82 | 93.64 | 667.87± 3.58 | 813.32 ± 3.11 | 1.23 |
| F7 | 50 | 44.62 | 89.24 | 623.54 ± 2.82 | 725.34 ± 1.65 | 1.67 |
| F8 | 50 | 41.98 | 83.96 | 596.98 ± 7.13 | 623.98 ± 4.21 | 1.76 |

All the mean microcapsule sizes are the geometric mean and geometric standard deviation (SD) respectively.

a Geometric mean and geometric standard deviation (SD)

b SSA = Specific surface area of microcapsules

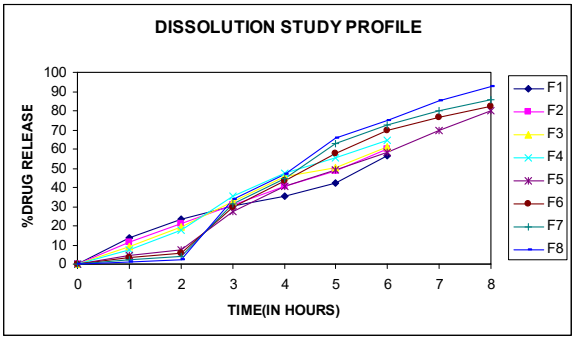



**Fig. III: Drug release profile**

In this case, release data were F1-56.65% at 6hrs, F2-59.88% at 6 hrs, F3-60.98% at 6 hrs and F4-64.78% at 6 hrs from EC microspheres. EC has a pH independent solubility profile where it shows a good solubility in polar solvents[15]. And in case of Eudragit coated microspheres release data were F5-79.87% at 8 hrs,F6-82.32% at 8 hrs,F7-85.67% at 8 hrs,F8-92.35% at 8 hrs.

The Eudragit is a enteric coating polymer ( pH dependent solubility), it will not release the drug in acidic medium, so, it will release the drug in a sustained manner for 8 hrs. This pH non dependent solubility of EC caused dissolution of DP in both acidic and neutral media. Due to this reason, no significant variation in release rate of DP was observed between acidic and neutral dissolution media. These findings indicated that the internal structure of the EC microspheres was a polymeric matrix containing dispersed drug. Drug release from dosage forms, coated with ethyl cellulose, is a function of wall thickness and surface area. This will also reduce the gastrointestinal toxicity of diclofenac potassium associated with excess amount of it in the GI tract.

## CONCLUSION

In this experiment, we have prepared eight different formulations of diclofenac potassium-ethyl cellulose, Eudragit microspheres by using double emulsion solvent evaporation technique. In conclusion, Eudragit microspheres showed good batch to batch reproducibility with respect to yield, particle size and entrapment efficiency when compared to Ethyl cellulose microspheres. The volume of the internal phase of the primary emulsion and the volume of the external phase of the secondary emulsion are the area of concentration and which affects significantly, the characteristic of microspheres. The entrapment efficiency of both F1 and F5 was found to be more, and the in-vitro drug release profile of both F4&F8 was more when compared to remaining formulations. The physicochemical properties of ethyl cellulose, mainly its aqueous solubility and film forming capacity, allowed the easy production of microspheres but it is non pH dependent polymer, so the will release and degrade in acidic medium and the Eudragit is a enteric coating polymer it will not release DP in acidic medium, and there by avoids GI irritation and produce sustained action for prolonged time. Thus the polymer Eudragit could be used to prepare sustained release diclofenac potassium microspheres.

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