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Formulation and Evaluation of Microsphere of Diclofenac Potassium along with Chitosan

Dinesh Chandra*[1], Santosh Kumar Singh[1], Jayant Kumar Maurya[1], Sarvesh Kumar Singh[1], Ashish Kumar[1]

1.Kamla Nehru Institute of Management and Technology, Sultanpur, India.

ABSTRACT

The aim of this study was to prepare Diclofenac potassium (DP) microspheres by using Double Emulsion-solvent evaporation method with ethyl cellulose (EC) and Eudragit polymers. An attempt was made to formulate a sustained release dosage form of diclofenac potassium, to minimize frequent dosing as well as reducing or eliminating local side effects by avoiding the drug release in the upper gastro-intestinal tract 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, six different formulations (F1, F2, F3, F4, F5, & F6) 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 96.24% loading efficiency for Eudragit and 82.34% 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. The formulations were found to be effective in providing controlled release of drug for a longer period of time.

Keywords: microsphere, diclofenac potassium, eudragit, ethyl cellulose, entrapment efficiency.

*Corresponding Author Email: santoshsingh399@gmail.com

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INTRODUCTION

Drug delivery through oral route is one of the most common and widely acceptable route through all over world and best route of administration since decades.

Microsphere:

Microsphere are defined as "monolithic sphere or therapeutic agent distributed throughout the matrix either of molecular dispersion of the particle or can be defined as the structure made of continuous phase of one or more miscible polymer in which drug particle are dispersed at the molecular or macroscopic level.

Now a days there are various slow release oral dosage form such as enteric coated/ double layered tablets which have ability to release a drug for 12-24 hours, therefore resulting in the inefficient systemic drug delivery and potential gastrointestinal irritation.

To overcome these problems the microencapsulation process for oral drug has been employed for the sustained release of drug and to reduce or eliminate the gastrointestinal irritation.[1]

By the process of microencapsulation we can modify and retard the release pattern of drug, since it has a very small particle size therefore these are widely distributed throughout the Gastrointestinal Tract (GIT), which improve the absorption of drug and minimizes or reduces the side effect of drug against the GIT mucosa.[2]

Microcapsule or microspheres have a very small particle size i.e. 1-1000 nm.[3]

Advantage of microsphere:[4]

1. Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.

2. Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.

3. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour.

4. The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in vivo.

5. Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intra-cellularly.

6. Blood flow determination.

Diclofenac potassium:

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. Gastrointestinal side effects such as bleeding, ulceration or perforation of intestinal wall are commonly seen. 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. Microencapsulation is one process used to control drug release and hence prolong therapeutic activity. 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.[5]

Chitosan:

Chitosan, a natural linear bio poly amino saccharide is obtained by alkaline deacetylation of chitin, which is the second abundant polysaccharide next to cellulose Chitin is the principal component of protective cuticles of crustaceans such as crabs, shrimps, prawns, lobsters and cell walls of some fungi such as *aspergillus* and *mucor*.

Chitin is a straight homopolymer composed of -(1,4)-linked *N*-acetyl-glucosamine units while chitosan comprises of copolymers of glucosamine and *N*-acetyl-glucosamine. Chitosan has one primary amino and two free hydroxyl groups for each C6 building Unit. Due to the easy availability of free amino groups in chitosan, it carries a positive charge and thus in turn reacts with many negatively charged surfaces/polymers and also undergoes chelation with metal ions like cobalt. Thus, it is utilized for separation of metals.

Chitosan is a weak base and is insoluble in water and organic solvents, however, it is soluble in dilute aqueous acidic solution (pH <6.5), which can convert the glucosamine units into a soluble form R–NH3.

It gets precipitated in alkaline solution or with polyanions and forms gel at lower pH. It also acts as flocculant for the treatment of waste water. Commercially, chitosan is available in the form of dry flakes, solution and fine powder.

Properties such as biodegradability, low toxicity and good biocompatibility make it suitable for use in biomedical and pharmaceutical formulations. It is used for hypobilirubinaemic and hypocholesterolemic effects antacid and antiulcer activities wound and burn healing properties immobilization of enzymes and living cell and in ophthalmology.[6]

Material and method:

Material:

Diclofenac potassium. I.P. was received as a gift sample from U.S. Vitamins Ltd, Gujarat India.

Chitosan and ethyl cellulose were purchased from S.D Fine Chemicals Mumbai. All other ingredients were used of analytical grade method.

Method:

The microsphere of diclofenac potassium was prepared by the double emulsion evaporation method.

Desired amount of diclofenac potassium will dissolved in distilled water. Polymer chitosan will dissolved separately in dichloromethane .Then the aqueous drug solution will gradually added to above prepared polymeric solution with constant stirring at req. rpm, stirring will continued for few minutes. Then the primary emulsion will added to PVA solution containing 2% span 80 stirring was continued up to 2 -4 hrs at a temperature of 60 ^{o}C in a 250 ml glass beaker. After 2-4 hours of stirring, hard, spherical microspheres was obtained. Microspheres was then washed three times with petroleum ether and vacuum-dried to obtain free flowing microspheres. The procedure will continued with Eudragit polymer also.

EVALUATION:

1. Particle size determination:

Microsphere (50 mg) was suspended in distilled water (5mL) containing 2%w/v of tween 80, To prevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size was expressed as volume mean diameter in micrometer.[7]

2. **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. A linear line was obtained while absorbance values were plotted against concentrations ($R^2 > 0.9997$).[8]

3. 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.

Drug-loading efficiency (%) = (Cp/Ct) × 100

Where, Cp and Ct is the actual and theoretical drug content in diclofenac potassium loaded microspheres, respectively.[9]

4. *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.[10]

RESULTS AND DISCUSSION:

Table 1 different formulation variables.

Formula	Amount of drug (mg)	Amount of polymer-Eudragit L 100	Amount of polymer-EC (mg)	Drug: polymer ratio	Qty. of Di chloromethane (ml)
F1	200	200	-	1:1	10
F2	200	400	-	1:2	10
F3	200	600	-	1:3	10
F4	200	-	200	1:1	10
F5	200	-	400	1:2	10
F6	200	-	600	1:3	10

Table 2: Mean particle size and drug entrapment efficiency of the microsphere prepared with Eudragit.

Formulation	Theoretical load of drug (mg)	Actual load of drug (mg)	Loading efficiency	Mean vol. diameter (±SD)
F1	50	48.12	96.23	885.65±2.54
F2	50	46.60	93.20	813.32±3.11
F3	50	44.40	88.80	425.34±1.65

Table 3: Mean particle size and drug entrapment efficiency of the microsphere prepared with ethyl cellulose.

Formulation	Theoretical load of drug. (mg)	Actual load of drug (mg)	Loading efficiency	Mean vol. diameter (±SD)
F4	50	44.06	88.12	656.65±1.46
F5	50	43.14	86.28	624.31±4.60
F6	50	41.17	82.34	595.34±1.98

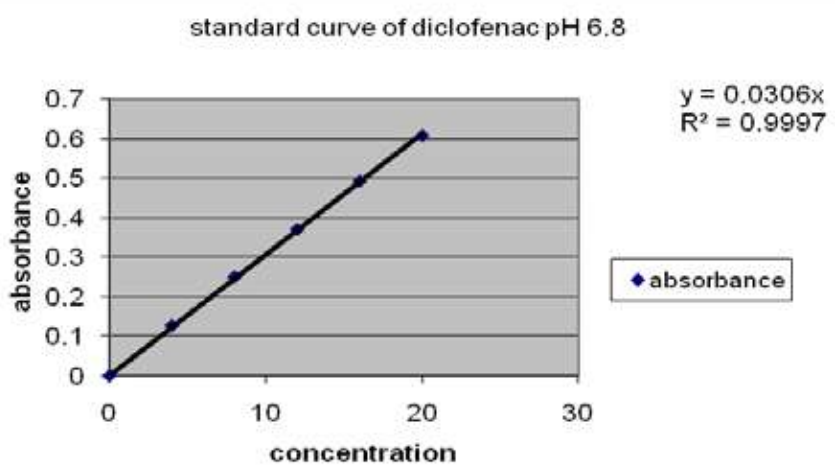


Figure.1: standard curve of diclofenac potassium at pH 6.8

Figure.2 FT-IR spectrum of pure drug

Figure.3 FT-IR spectrum of blank bead

Figure.4 FT-IR spectrum of drug loaded beads.

All the above mentioned graph indicate Comparative study of the FT-IR spectrum of pure drug, blank bead and the drug loaded beads.

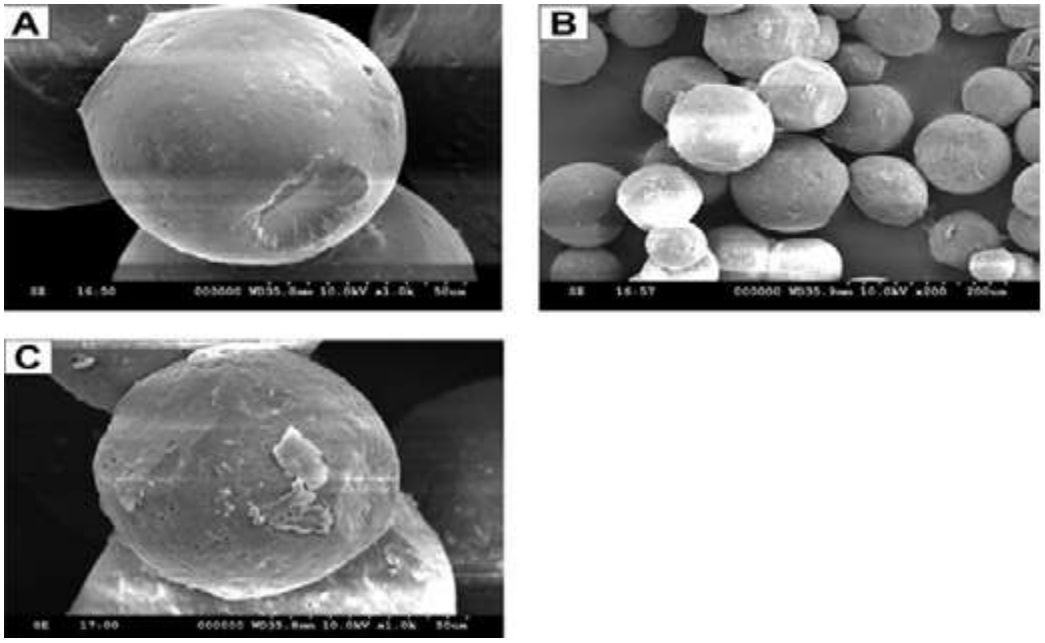


Figure. 5: Scanning electron micrograph of diclofenac sodium microspheres prepared with different concentration of EC;

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

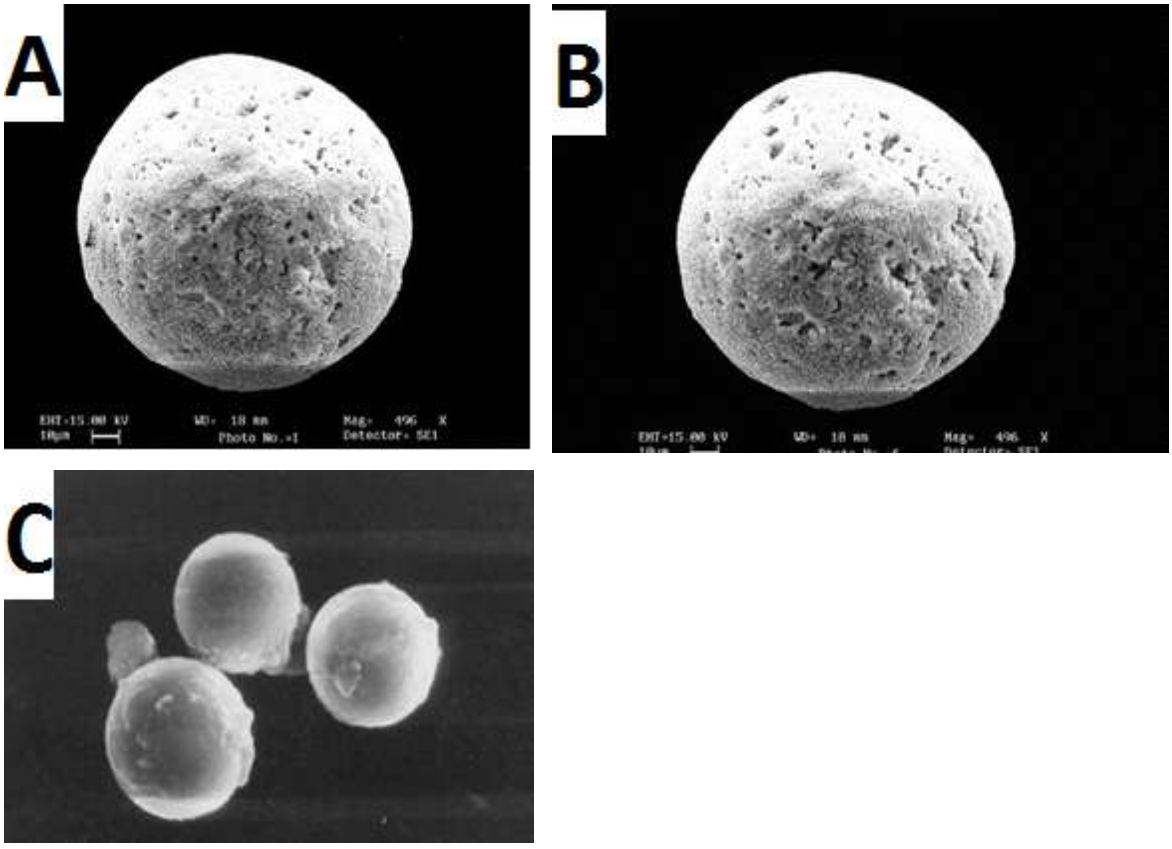
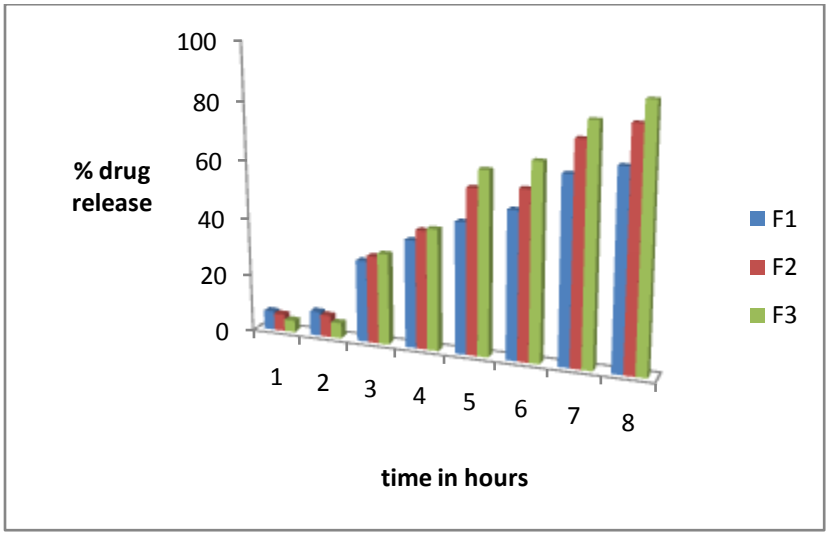


Figure. 6: Scanning electron micrograph of diclofenac sodium microspheres prepared with different concentration of EC



A = 1:1 ratio Eudragit, B = 1:2 ratio Eudragit. C=1:3 ratio Eudragit

Figure.7: Cumulative % drug release of F1, F2 and F3 formulation

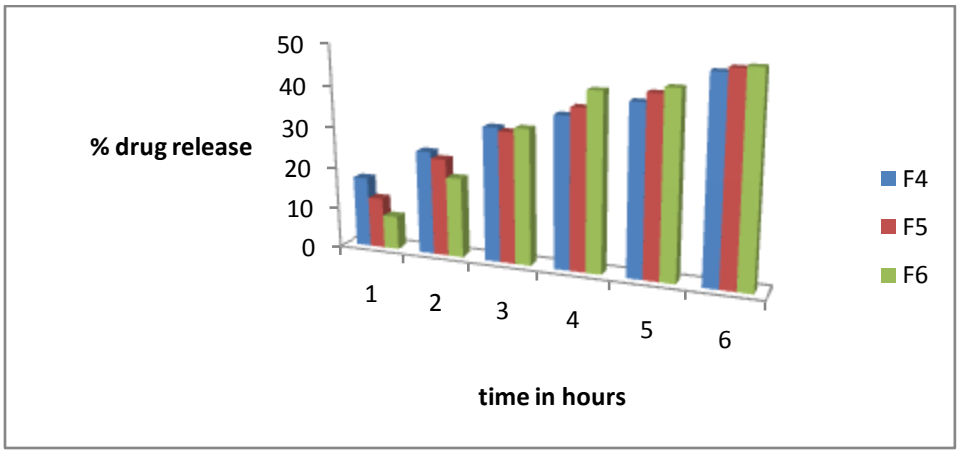


Figure.8: Cumulative % drug release of F4, F5 and F6 formulation.

In this experimental case the microsphere of diclofenac potassium along with chitosan-eudragit formulation the % drug release data were F1 is 67.70 at 8 hours, F2 is 81.25 at hours and F3 is 88.73 at 8 hours. Where as in other case ethyl cellulose microsphere formulation the % drug release data were found to be F4 is 48.20 at 6 hours, F5 is 49.16 at 6 hours and F6 is 49.61 at 6 hours.

CONCLUSION:

In this experiment, we have prepared six 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 F4 was found to be more, and the in-vitro drug release profile of both F3&F6 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 they 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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