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# Design and characterization of bioadhesive microspheres prepared by double emulsion solvent evaporation method

**Nagda Chirag*[1], Chotai Narendra[2], Patel Sandip[1], Patel Upendra[4], Ahir Keyur[1], Nagda Dhruti[2]**

[1]Indukaka Ipcowala College of Pharmacy, New Vallabh Vidyanagar, Anand, Gujarat, India- 388121.
[2]A. R. College of Pharmacy, Vallabh Vidyanagr, Anand, Gujarat, India- 388120.
[3]Anand College of Pharmacy, Anand, Gujarat, India-388001.
[4]Arihant School of Pharmacy and Bioresearch institute, Gandhinagar, Gujarat, India- 382421.

## Abstract

Aceclofenac (ACE) is NSAIDs of a phenyl acetic acid class. It is indicated in arthritis and osteoarthritis, rheumatoid arthritis, ankylosing spondylitis. It has short elimination half life of 4 hours. The objective of the study is to design, characterize and evaluate bioadhesive microspheres of ACE employing polycarbophil as bioadhesive polymer. Bioadhesive microspheres of ACE were prepared by double emulsion solvent evaporation method. The prepared microspheres were free flowing and spherical in shape and characterized for drug loading, mucoadhesion test, infrared spectroscopy (IR), differential scanning colorimetry (DSC) and scanning electron microscopy (SEM). The *in-vitro* release studies were performed using pH 6.8 phosphate buffer. The drug loaded microspheres in a ratio of 1:5 showed 38 % of drug entrapment; percentage mucoadhesion was 79 % and 89 % release in 10 h. The infrared spectra and DSC showed stable character of aceclofenac in the drug loaded microspheres and revealed the absence of drug-polymer interactions. SEM studies showed that the microspheres are spherical and porous in nature. The in vitro release profiles from microspheres of different polymer-drug ratios followed Higuchi model.

**Key words:** Aceclofenac, bioadhesive, microspheres, polycarbophil, solvent evaporation method.

## Introduction

Bioadhesives can be defined as natural or synthetic materials capable of adhering to a biological substrate. Such materials can be incorporated in formulations to retain the dosage form at the absorbing epithelial membrane, thereby prolonging drug release and thus decreasing dosage frequency when compared to a conventional dosage form (Lim et al. 2000). Hence, bioadhesives have been incorporated in dosage forms administered via almost all accessible routes of drug absorption, including the eye, nose, mouth, rectum and vagina (Mathiowitz 1999). The bioadhesive properties of a wide range of materials have been evaluated over the last decade and synthetic polymers, such as carbopol and polycarbophil, display excellent adhesion when tested *in vitro* (Leung et al. 1988, Grabovac et al. 2005, Sandra et al. 2005).

Aceclofenac (ACE), phenyl acetic acid derivative 2-[(2,6-Dichlorophenyl)amino] phenyl

***Corresponding author:** cnagda@gmail.com

acetoxy acetic acid, is a novel NSAID indicated in the symptomatic treatment of pain and inflammation with a reduced side effect profile especially regarding gastrointestinal complications (Parfitt 1999, Brogden et al. 1996). Recommended dose is 200 mg daily in divided doses. The successful treatment of arthritis depends on the maintenance of effective drug concentration in the body for which a constant and uniform supply of drug is desired. Sustained release dosage forms deliver the drug at a slow release rate over an extended period of time and achieve this objective. The mean plasma elimination half life of aceclofenac is 4 h (Parfitt 1999). To reduce the dosing frequency and adverse effects during prolong treatment it is needed to formulate in long acting dosage form. Different workers have attempted to prepare sustained release oral formulations of aceclofenac like sustained release tablet, microparticulate system and microemulsion (Mutalik et al. 2007, Dashora et al. 2006, Lee et al. 2005). Our previous work has demonstrated that mucoadhesive microspheres prepared with carbopol and ethyl cellulose using solvent evaporation method give sustained release of aceclofenac (Nagda et al. 2008).

Preparation of bioadhesive microspheres would be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes (Patel et al. 2004). Polycarbophil (Noveon® AA1) selected as polymer in the production of bioadhesive microspheres due to its excellent bioadhesive properties (Carelli et al. 1997, Burjak et al. 2001, Cuna et al. 2001, Sandra et al. 2005). The purpose of present work was to design, characterize and evaluate bioadhesive microspheres of ACE employing polycarbophil (PL) as bioadhesive polymer by double emulsion solvent evaporation method.

## Materials and Methods

*Materials*

Aceclofenac(ACE) was obtained as a gift sample from Torrent Pharmaceutical Limited (Ahmedabad, India). Noveon AA-1 (Polycarbophil, PL) was obtained as a gift sample from Lubrizol Advanced Materials Inc (Mumbai, India). All other reagents and solvent used were of analytical grade.

*Preparation of bioadhesive microspheres*

Bioadhesive microspheres were prepared by an oil-in water-in-oil (O/W/O) double-emulsion method (Sandra et al. 2005). Aqueous polymer solution was prepared and subsequently stored in sealed containers at 48 °C for 24 h prior to use. Polycarbophil (0.50 g) was dispersed in 50.0 g of deionized water and mixed by rapid vortexing; the pH was adjusted to 7 using dilute aqueous sodium hydroxide. Aceclofenac (ACE) was dissolved in dichloromethane.

For the first emulsion, ACE dissolved in dichloromethane was emulsified into 50.0 g of aqueous polymer solution. The concentrations and amounts applied are summarised in Table 1. The addition of 0.15 ml of Tween 80 aided the emulsification process. A Silverson homogenizer was used for rapid mixing of the emulsions for 15 min. The first emulsion (25 ml) was added drop wise to 250 ml light liquid paraffin containing 1% Span 80. The resultant double emulsion was stirred at 800 rpm. The samples were heated to 60-70 °C to promote evaporation of water. Solid polymer microspheres were subsequently separated from the oil by centrifugation, washed in hexane and dried in a vacuum oven at 40 °C for 24 h. For each polymer to drug ratio, three batches of microspheres were prepared in order to assess the reproducibility of drug loading by this method.

**Table 1.** Composition of bioadhesive microspheres formulations.

| Batch | Drug(g) | PL(g) | Dichloromethane (ml) | Span-80 (%) | Liquid paraffin light (ml) | n-Hexane (ml) |
|---|---|---|---|---|---|---|
| DEPL1 | 0.500 | 0.500 | 10 | 1.0 | 250 | 50 |
| DEPL2 | 0.500 | 1.000 | 10 | 1.0 | 250 | 50 |
| DEPL3 | 0.500 | 1.500 | 10 | 1.0 | 250 | 50 |
| DEPL4 | 0.500 | 2.000 | 10 | 1.0 | 250 | 50 |
| DEPL5 | 0.500 | 2.500 | 10 | 1.0 | 250 | 50 |
| DEPL6 | 0.500 | 3.000 | 10 | 1.0 | 250 | 50 |

*Encapsulation efficiency*

To determine encapsulation efficiency, 100 mg of accurately weighed drug loaded bioadhesive microspheres were added to 100 ml of methanol. The resulting mixture was kept shaking on a mechanical shaker for 24 h. Then, after the solution was filtered and 1 ml of this solution was appropriately diluted with methanol and analyzed with spectrophotometrically at 275 nm using a Shimazdu UV-1700 (UV/VIS double beam spectrophotometer, Kyoto, Japan). The drug encapsulation efficiency was calculated using the following formula: (Practical drug content/Theoretical Drug content) × 100.

*Particle Size*

A microscopical imaging analysis technique for determination of particle size distribution was used (Filipovic et al. 1996). Microsphere size and distribution were determined with an AXIOPALN microscope (Zeiss MPM400, Germany), equipped with a computer-controlled image analysis system (Zeiss, KS300, Germany).

*Swelling index*

The swelling ability of the microspheres in physiological media was determined by swelling them to their equilibrium (Jain et al. 2004). Accurately weighted amounts of microspheres were immersed in a little excess of Phosphate buffer (pH 6.8) and kept for 24 h. The following formula was used for calculation of percentage of swelling:

$$Ssw = (Ws\text{-}Wo/Ws) \times 100$$

Where, Ssw = Percentage swelling of microspheres, Wo=initial weight of microspheres, and Ws=weight of microspheres after swelling.

*Mucoadhesion*

Mucoadhesion of different microspheres system was assessed using the method reported by Jain et al. (2004) with little modification. A strip of rat intestinal mucosa was mounted on a glass slide and accurately weighed bioadhesive microspheres in dispersion form was placed on the mucosa of the intestine. This glass slide was incubated for 15 min in a desiccator at 90 % relative humidity to allow the polymer to interact with the membrane and finally placed in the cell that was attached to the outer assembly at an angle 45°. Phosphate buffer saline (pH 6.8), previously warmed to 37 ± 0.5 °C, was circulated to the cell over the microspheres and membrane at the rate of 1 ml/min. Washings were collected at different time intervals and microspheres were separated by centrifugation followed by drying at 50 °C. The weight of microspheres washed out was taken and percentage mucoadhesion was calculated by the following formula:

$$\text{Percentage mucoadhesion} = W_o - W_t / Wo \times 100$$

Where $W_o$ = weight of microspheres applied; $W_t$ = weight of microspheres leached out.

*Scanning electron microscope (SEM)*

A scanning electron microscope (ESEM TMP with EDAX, Philips, Holland) was used to characterize the surface topography of the microscope. The microspheres were placed on a metallic support with a

thin adhesive tape and microspheres were coated with gold under vacuum. The surface was scanned and photographs were taken at 30kV accelerating voltage for the drug loaded microspheres.

*Fourier transform infrared spectroscopy (FTIR)*

The spectra were recorded for pure drug, drug loaded microspheres and blank microspheres using FTIR (Perkin-Elmer, Spectrum GX, USA). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400 – 4000 $cm^{-1}$ and the resolution was 2 $cm^{-1}$.

*Differential scanning calorimetry (DSC)*

Differential scanning calorimetry (DSC) scans of aceclofenac, blank microspheres and drug loaded microspheres were performed using DSC-PYRIS-1(Perkin-Elmer, USA). The samples were heated from 50- 300°C and a rate of 10 °C $min^{-1}$.

*Drug release study*

The drug release study was performed using USP XXIV basket apparatus (Electrolab, TDT-06T, Mumbai, India) at 37 °C and at 50 rpm using 900 mL of phosphate buffer (pH 6.8) as a dissolution medium up to 10 h (Mutalik et al. 2007, Soni et al. 2008). Microspheres equivalent to 100 mg of Aceclofenac were used for the test. Five ml of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 mm membrane filter, diluted suitably, and analyzed spectrophotometrically. An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved at different time intervals was calculated using the Lambert-Beer's equation.

*Release kinetics*

In order to understand the mechanism and kinetics of drug release, the results of the in vitro drug release study were fitted with various kinetic equations namely zero order (% release vs t), first order (log% unrelease vs t) , Higuchi matrix (% release vs square root of time), (Yadav et al. 2007). In order to define a model which will represent a better fit for the formulation, drug release data further analysed by Peppas equation, $Mt/M\infty=kt^n$, where Mt is the amount of drug released at time t and $M\infty$ is the amount released at time $\infty$, the $Mt/M\infty$ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent, a measure of the primary mechanism of drug release. Regression co-efficient ($r^2$) values were calculated for the linear curves obtained by regression analysis of the above plots.

## Results and Discussion

*Effect of experimental variables on particle size*

The processing variables such as drug to polymer ratio, stirring speed, stabilizer concentration affect the particle size of microspheres. The drug to polymer ratio appeared to influence on particle size distribution of microspheres (Table 2).

When drug to polymer ratio was increased from 1:1 to 1:6, the proportion of larger particles formed became higher, which may be due to increase in viscosity of the solvent with increase in polymer to drug ratio. The mean particle size ranged from 23.40 to 53.60 μm. The minimum concentration of span 80 required to form stable emulsion was found to be 1%. Changing the stirring speed during emulsification process seems to influence the mean particle size of the microspheres. When the stirring speed was kept below 800 rpm, the mean particle size of the microspheres was increased and they became large and aggregated. When the speed was kept above 800 rpm, the size of the microspheres was smaller and irregular in shape. We found optimal temperature at 70 °C as at higher temperature; it might affect polymer stability and increased aggregation at lower temperature.

**Table 2.** Mean particle size, encapsulation efficiency.

| Batch | Theoritical drug content | Practical drug content | Encapsulation efficiency* (%) | Mean Particle size* (μm) |
|---|---|---|---|---|
| DEPL1 | 50 | 16.28 | 26.81± 1.35 | 23.40±1.10 |
| DEPL2 | 33.5 | 12.98 | 36.47± 0.98 | 29.82±2.54 |
| DEPL3 | 25 | 8.57 | 31.25± 2.13 | 33.53±1.76 |
| DEPL4 | 20 | 8.15 | 37.79± 1.15 | 40.55±1.87 |
| DEPL5 | 16.5 | 7.81 | 32.46± 1.75 | 44.23±0.85 |
| DEPL6 | 14.4 | 5.44 | 30.72± 2.04 | 53.60± 1.92 |

* Each observation is the mean (±SD) of three determinations

*Encapsulation efficiency*

The drug entrapment efficiency within microspheres produced using the solvent evaporation method is of fundamental importance as failure to achieve acceptable drug loadings may preclude the use of this method for economic reasons (Jones et al. 1995). The entrapment efficiency of various formulations was found to be in the range of 26.81 to 37.79 % as shown in Table 2. The low entrapment efficiency may be due to solubility of the drug in the solvent, the drug may be migrated to the processing medium during extraction and evaporation process of dichloromethane.

*Swelling index*

The most promising approach to achieving gastro retention is that of creating a swelling or expanding system *in situ* (Davis 2005). Figure 1 depicts the percentage swelling of microspheres. It is evident from the Figure that all prepared batches of microspheres rapidly swelled in phosphate buffer pH 6.8. The high swelling property of PL (294%, DEPL4) could be attributed to high molecular weight and their ionized ability to uncoil polymer into an extended structure.

*Mucoadhesion*

In the mucoadhesion process, it is necessary for swelling and expansion of the polymer chain since interpenetration and entanglement of the polymers and the mucous networks are considered to be responsible for adhesion (Ponchel et al. 1997). Therefore, bioadhesives should swell and expand rapidly when they come in contact with water. A high percentage of adhesion indicates that microspheres have excellent mucoadhesion to mucosal tissue. Percentages of muoadhesion are given in Figure 2.

It can be seen that the microspheres had good mucoadhesive properties and could adequately adhere to intestinal mucosa. The results also showed that with change in polymer to drug ratio, the % mucoadhesion also varies. The maximum and prolonged mucoadhesion (81.46%) was observed with the batch DEPL6.

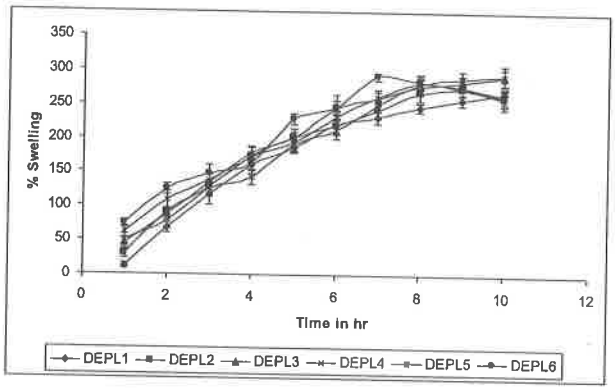


**Figure 1.** The Profiles of percentage swelling with time of microspheres.

* Each observation is the mean (±SD) of three determinations

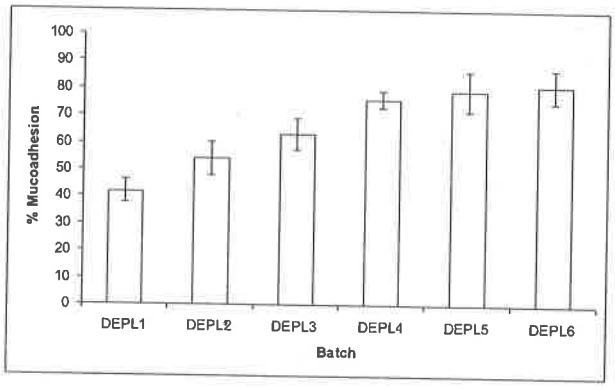


**Figure 2.** Percentage mucoadhesion of microspheres.

* Each observation is the mean (±SD) of three determinations

*Scanning Electron Microscopy*

Surface morphology of microspheres and the morphological changes produced through polymer degradation can be investigated and documented using scanning electron microscopy (SEM). From SEM study, it was found that microspheres were spherical and rough as shown in Figure 3. The study of drug loaded microspheres shows the presence of drug particles on the surface, which may be responsible for an initial burst release of the drug during dissolution.

*Infrared Spectroscopy*

The IR spectra of pure aceclofenac, drug loaded microsphere and blank microsphere are shown in the Figure 4. The peak at 3319 nm indicating the –NH stretching, two peaks at 1771 nm and 1717 nm for the –C=O stretching of –COO and –COOH group respectively. The peaks at 1589 nm, 1281 nm, and 749 nm show as major peaks for drug. All the above peaks are present in drug loaded microspheres that confirms the presence of drug in the polymer without any interaction.

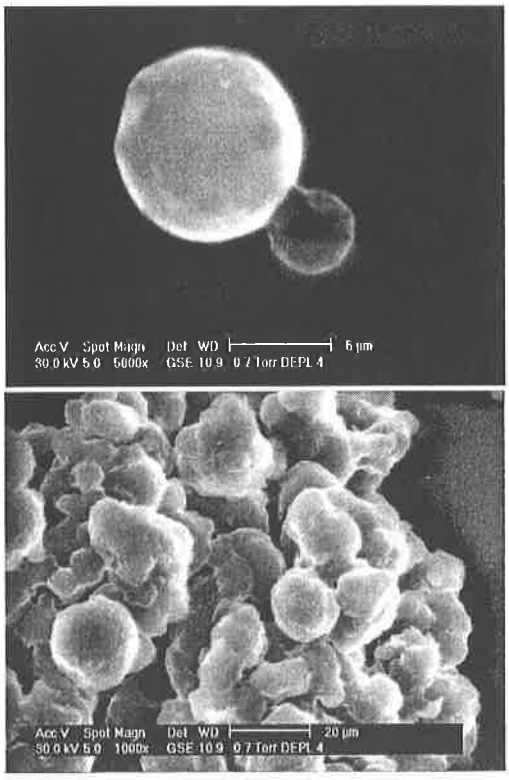


**Figure 3.** SEM photographs of microspheres.

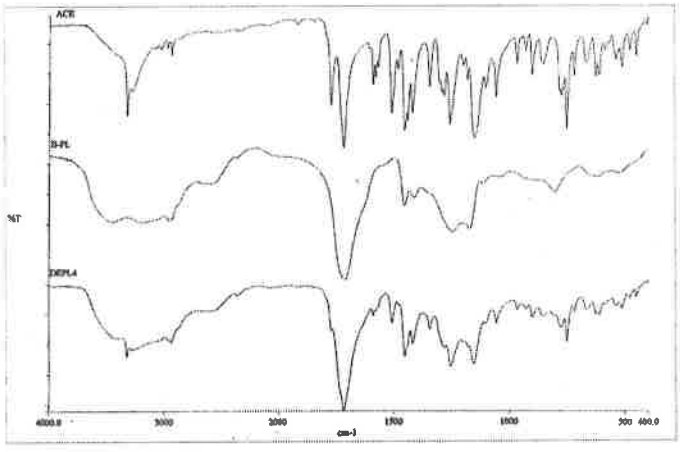


**Figure 4.** Comparative IR spectra of ACE, Blank PL microsphere (B-PL), and Drug loaded microspheres (DEPL4).

*Differential Scanning Colorimetry study*

The results of DSC study are given in Figure 5. DSC thermograms showed endothermic peak of ACE at 155°C, which corresponded to its melting point. Thermograms of blank

microspheres showed at 79.40 °C and drug loaded microspheres showed peak at 153.39 °C, indicating absence of interaction between drug and polymer.

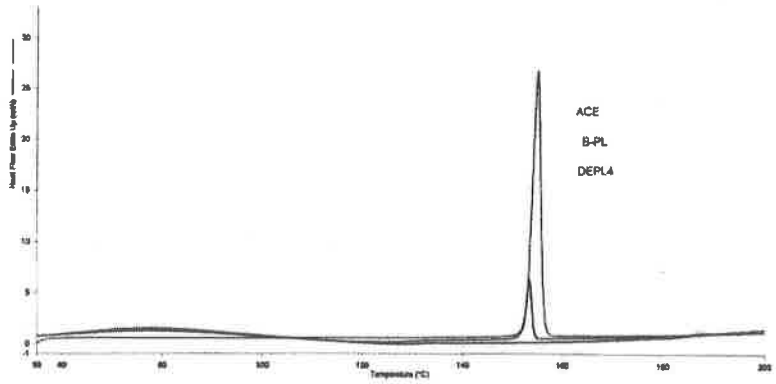


**Figure 5.** Comparative DSC spectra of ACE, Blank microsphere (B-PL), and Drug loaded microspheres (DEPL4).

*In-Vitro release study*

*In vitro* release profiles of prepared microspheres bathces are shown in Figure 6.

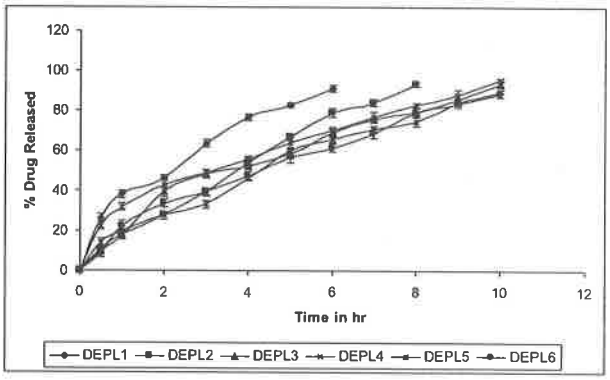


**Figure 6.** Cumulative percent release of aceclofenac (n=3) from different mucoadhesive microspheres prepared with different drug: polymer ratio.

The release profiles of the formulations appear to be slow release with negligible burst effect. The burst effect corresponds to the release of the drug located on or near surface of the microspheres or release of poorly entrapped drug. The rate of release of drug from the bioadhesive microspheres was slow and found to further decrease with increase in drug to polymer ratio. In order to achieve near to complete release, the formulations were prepared by increasing the concentration of polycarbophil. DEPL1 showed a cumulative release of 91% within 6 h. Further increasing the concentration of polycarbophil (DEPL4, DEPL5 and DEPL6), the release rate decreased to 88%. This decrease in dissolution rate can be explained based on the viscous gel formation by polycarbophil at higher concentration; where as at lower concentration, easy solubilization of polycarbophil may aid increased dissolution rate. It was observed that the polymeric gel might have act as a barrier to penetration of the medium,

may be due to the medium being diffused in the polymer matrix and the drug diffusing out of the microspheres.

*Release kinetics*

The *in-vitro* release profile was analyzed by various kinetic models. The kinetic models used were Higuchi, zero order, first order and Krosmeyer Peppas equations (Table 3). The release constants were calculated from the slope of the respective plots. Higher correlation was observed in the Higuchi equation. For planer geometry, the value of n=0.5 indicates a Fickian diffusion mechanism, for 0.5<n<1.0, indicates anomalous (non-fickian) transport, and n=1 implies case II (relaxation controlled) transport. In the present systems, the value for n was found to be in the range of 0.469 to 0.802 indicating that the release mechanisms followed fickian diffusion and anomalous (non-fickian) transport. The batch DEPL4 was having n=0.469, indicating that the release mechanism followed is fickian diffusion controlled mechanism.

**Table 3.** Various parameters of the model equations on the *in vitro* release kinetics.

| Batch | Higuchi model | | Zero order | | First order | | Krosemeyer peppes model | |
|---|---|---|---|---|---|---|---|---|
| | $r^2$ | $K_h$ | $R^2$ | $K_0$ | $r^2$ | $K_1$ | $R^2$ | n |
| DEPL1 | 0.987 | 37.79 | 0.976 | 11.78 | 0.973 | -0.16 | 0.986 | 0.503 |
| DEPL2 | 0.979 | 40.61 | 0.991 | 11.35 | 0.930 | -0.138 | 0.994 | 0.802 |
| DEPL3 | 0.990 | 32.94 | 0.954 | 8.14 | 0.939 | -0.101 | 0.975 | 0.728 |
| DEPL4 | 0.993 | 28.72 | 0.985 | 7.20 | 0.901 | -0.107 | 0.994 | 0.469 |
| DEPL5 | 0.978 | 31.97 | 0.983 | 8.07 | 0.955 | -0.090 | 0.981 | 0.643 |
| DEPL6 | 0.990 | 31.57 | 0.978 | 7.90 | 0.962 | -0.087 | 0.971 | 0.714 |

The batch (formulation code: DEPL4) demonstrated a satisfactory encapsulation efficiency, mucoadhesion and drug release property from among all the formulated microspheres and were chosen for in vivo trials. It is revealed from Figure 6, the release of ACE from the said batch at the end of $4^{th}$ and $9^{th}$ h was found to be ~50% and 85%, respectively.

The multiple emulsion method (O/W/O) proposed for the preparation of polycarbophil microspheres was found to be a good technique to encapsulate hydrophobic drug in hydrophilic polymer. The polycarbophil microspheres prepared showed, reasonable drug entrapment, suitable size and relatively slow release of the drug. FT-IR and DSC studies did not reveal any significant drug interactions. The release profiles of microsphere formulations prepared by double emulsion solvent evaporation showed that microspheres provided release upto 10 h. The prepared microspheres exhibited a significant bioadhesive property and could potentially be used as bioadhesive microspheres for controlled and sustained delivery of ACE. Further, the desired goals can be obtained by systemic evaluation of bioadhesive microsphers in animals and/or human volunteers.

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