Indo Global Journal of Pharmaceutical Sciences, 2022; 12: 175-178

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Effect of Polymers in the Design and Characterization of Sustained Release Aceclofenac Microspheres

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Received: 21.04.2020
Accepted: 15.11.2020
Published: 23.04.2022
Keywords
Drug release; Emulsion solvent evaporation; Polymer; HPMC; EC.

ABSTRACT: **Purpose:** The aim of present work was to design and characterize sustained release Aceclofenac, model drug, microspheres by emulsion solvent evaporation technique. **Methods:** Aceclofenac microspheres were prepared by emulsion solvent evaporation process by using Ethyl cellulose and Hydroxy propyl methyl cellulose as polymers. The microspheres were evaluated by drug release study, drug content, drug loading and encapsulation efficiency, and determination of percentage yield. **Results:** The present study shows that as the polymer concentration increases the percentage encapsulation efficiency, and drug content in the microsphere formulation also increases. The microspheres of all the formulated batches were spherical, discrete and free flowing. Increasing the polymer concentration in microsphere formulation decreases the rate of drug release dramatically. **Conclusions:** It might be concluded that drug loaded microspheres appear to be a suitable delivery system for a model drug, Aceclofenac, and may help to reduce dose of drug and frequency of administration. Sustained release of Aceclofenac microspheres could be formulated by using ethyl cellulose and HPMC as a release retardant by emulsion solvent evaporation technique.

Cite this article as: Vaghela, P.D. Effect of Polymers in the Design and Characterization of Sustained Release Aceclofenac Microspheres. Indo Global J. Pharm. Sci., 2022; 12: 175-178. **DOI**: http://doi.org/10.35652/IGJPS.2022.12020 .

INTRODUCTION

Microspheres are one of the particulate delivery systems used to achieve sustained or controlled drug delivery, improve bioavailability and stability and target drug to specific sites [1]. Microspheres also offer advantages such as limiting fluctuation within a therapeutic range, reduction in side effects, decreased dose frequency and hence improved patient compliance [2]. The popular method for the encapsulation of drugs within water-insoluble polymers is the emulsion solvent evaporation method. This technique offers several advantages and is preferable to other preparation methods such as spray drying, sonication and homogenization because it requires only mild conditions such as ambient temperature and constant stirring. Thus, a stable emulsion can be formed without compromising the activity of the drugs [3].

The use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation [4,5]. High-viscosity grades of ethyl cellulose are used in drug microencapsulation. Aceclofenac is an orally absorbed non-steroidal anti-inflammatory drug with half-life 4 hours and hence owing to short half it was selected as model in this study, the usual oral dosage regimen is 100 mg per day. The present study was undertaken to prepare sustained release microspheres of aceclofenac using Ethyl cellulose and HPMC by the emulsion solvent evaporation method [6]. The factors affecting microsphere such as polymer concentration, type of polymer were investigated on particle size and drug release behavior of the microspheres [7].

MATERIALS AND METHODS

Materials

The materials used were aceclofenac (obtained as gift sample from Nectar Drugs Pvt. Ltd., Mumbai), Ethyl cellulose and HPMC (E. Merck Ltd, Mumbai, India), Acetone (Merck Ltd, Mumbai, India), Polyvinyl alcohol (Merck Ltd, Mumbai, India), tween80 (Loba chemicals Pvt. Ltd.). Other chemicals were of analytical grades.

Dose calculation

Daily dose of aceclofenac is 100mg. Here we required immediate release (IR) dose and total dose.

IR DOSE =(Css × V_d) / F(%) _____ (1)

= 24.11 mg

Where, Css is steady state concentration of drug (aceclofenac) = 434 ng/ml

Vd is volume of distribution = 25 litres.

F is bioavailability = 45%

And,

TOTAL DOSE = IR DOSE (1+0.693) × t / $t_{1/2}$ _____(2)

= 91 mg

Where, t is the time during which SR action is desired = 12 hours.

$t_{1/2}$ is half life of drug = 3 hours.

So, here we required amount of microsphere equivalent to 91 mg aceclofenac for sustained release up to 12 hours.

Formulation of Aceclofenac microsphere is shown in **Table 1**.

Methods

Preparation of Aceclofenac microspheres

Calculated quantity of polymers was dissolved in 18ml of acetone to form homogenous polymer solution. Then calculated quantity of drug was added to the polymer solution and mixed thoroughly. The resulting mixture was then added in a thin stream in 100 ml of aqueous solution of poly vinyl alcohol (PVA) containing 1% v/v tween 80, while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. The solvent, acetone was then removed by evaporation during continuous stirring at room temperature for 3 hours to produce spherical microspheres. Here acetone was used as polymer solvent, aqueous solution of PVA the microencapsulating vehicle, Tween 80 as the dispersing agent. During 3 hours stirring period, acetone was completely removed by evaporation. The microspheres were collected by simple filtration and washed repeatedly and dried at room temperature over a night to get free flowing microspheres. As shown in **Table 1**, by varying this drug: polymer ratio, five batches of microspheres were prepared [8,9].

Drug content

The various batches of the microspheres were subjected for drug content analysis. Accurately weighed microsphere samples (10 mg) were mechanically powdered. The powdered microspheres were dissolved in adequate quantity of methanol then filter (IP'10). The UV absorbance of the filtrate was measured using a UV spectrometer at 275 nm [8,9].

Drug loading and encapsulation efficiency

Drug loading and encapsulation efficiency was determined for all batches using the following formulas. Values are expressed as percentage [8,9].

Drug loading = Weight of drug in microspheres × 100/ Microspheres sample weight _____(3)

Encapsulation efficiency = Actual weight of drug in sample × 100 /Theoretical weight of drug. _____(4)

Percentage yield

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula [8,9],

$$\text{Percentage yield} = \frac{\text{The weight of microspheres} * 100}{\text{The weight of polymer + drug}}$$

____(5)

***In vitro* drug release**

Drug release studies were carried out using a USP type II Dissolution apparatus. The dissolution vessel was filled 900 ml of phosphate buffer PH 6.8 and the calculated amount of microsphere temperature was kept constant at 37±0.5 ºc. 100mg equivalent of aceclofenac containing EC/HPMC microsphere was filled in assembly. Samples were withdrawn at predetermined time intervals with the same volume of fresh medium being added after each withdrawal. The sample was suitably diluted and absorbance was measured at 275 nm [3-6].

RESULTS AND DISCUSSION

Percentage yield

The percentage yield of formulations are shown in **Table 2**. This higher percentage yields indicates that this method was very useful for adoption in the formulation of aceclofenac microsphere.

Drug content

The results of the determination of microsphere drug content for various polymer: Drug ratios are shown in **Table 2**.

Drug loading and encapsulation efficiency

The results of the variation in drug loading and encapsulation efficiency with polymer: Aceclofenac ratio is shown in **Table 2**.

The microscopic photographs of Aceclofenac microspheres of Batch M2, M3, M4, & M5 are shown in **Figure 1**.

***In vitro* drug release**

As per the data shown in **Table 2**, the Drug content, Percentage drug loading, Percentage encapsulation efficiency, and Percentage yield of batch M1 was very poor compared to the respective result of rest of the batches. Therefore, batch M1 would be excluded for further evaluation study.

The data of standard plot for Aceclofenac in Phosphate buffer pH 6.8 is shown **Table 3** and **Figure 2** while *In-vitro* drug release data is shown in **Table 4** while the profile is depicted in **Figure 3**.

The drug release data shown in **Table 4** & the profile depicted in **Figure 3** clearly shows that as the concentration of drug:polymer ratio is increased the drug release profile is decreased. Hence the microsphere formulation of batch-M2 having drug:polymer ratio of 1:2 showed decrease in drug release profile compared to batch-M3 & hence it would be

concluded that as the concentration of polymer increases, the drug release rate decreases.

Table 1. Formulation of Aceclofenac microsphere

Batch	Ratio (Drug to Polymer)	Drug(gm)	EC(gm)	HPMC (gm)	Acetone (ml)	PVA(ml)
M1	01:01	1	0.75	0.25	18	100
M2	01:02	1	0.75	0.25	18	100
M3	02:03	1	0.75	0.25	18	100
M4	01:01	1	1	-	18	100
M5	01:02	1	1	-	18	100

Table 2. Evaluation Data of prepared Formulation

BATCH	Drug content (mg)	Percentage Drug loading	Percentage incorporation efficiency	Percentage Yield
M1	258.44	35.90%	25.85%	21.00%
M2	525.76	53.00%	52.57%	49.60%
M3	441.67	42.00%	44.16%	51.00%
M4	399.5	38.70%	39.95%	30.70%
M5	450	40.57%	45.00%	39.60%

Table 3. Data of Standard plot for Aceclofenac in phosphate buffer pH 6.8

Sr. No.	Concentration (µg/ml)	Absorbance at 275 nm
1	0	0
2	10	0.292
3	20	0.497
4	30	0.707
5	40	1.015
6	50	1.265

Table 4. Drug release data of batch M2, M3, M4, M5

Time (Hours)	CPR (%)			
	M2	M3	M4	M5
0	0	0	0	0
1	10	21	9	8
2	22	30	14	12
3	25	35	21	17
4	36	42	25	21
5	38	50	30	26
6	40	58	33	29
7	45	64	38	32

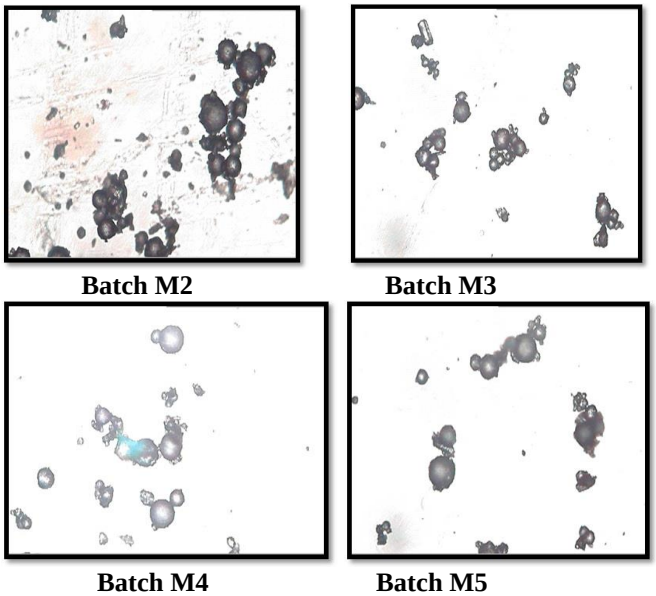

Figure 1. Microscopic Photograph of Aceclofenac Microspheres of Batch M2, M3, M4, M5

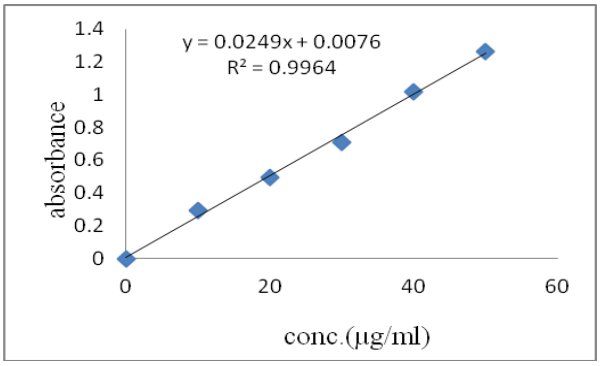

Figure 2. Standard plot of aceclofenac

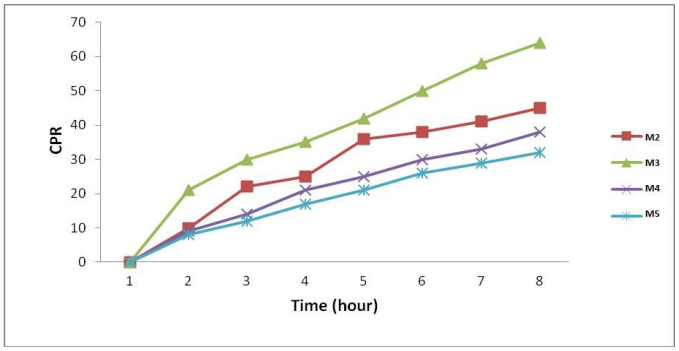

Figure 3. *In vitro* drug release profile of Batch M2, M3, M4 and M5

CONCLUSION

The present study concluded that the batch-M2 gives better percentage encapsulation efficiency, and drug content while the drug release profile is retarded. As polymer concentration is increase, the percentage encapsulation efficiency and drug content is also increase. It might be concluded that the drug loaded microspheres appear to be a suitable delivery system for aceclofenac and may help to reduce dose of drug and frequency of administration. Sustained release of Aceclofenac microspheres could be formulated by using ethyl cellulose and HPMC as a release retardant by emulsion solvent evaporation technique. The microspheres of all the formulated batches were spherical, discrete and free flowing. Increasing the polymer concentration in microsphere formulation decreases the rate of drug release dramatically.

ACKNOWLEDGEMENT

The author greatly acknowledge the Nectar Drugs Pvt. Ltd., Mumbai for providing the gift sample of Aceclofenac, and Merck Ltd, Mumbai, India for providing the gift samples of Ethyl cellulose, HPMC, Acetone, and Polyvinyl alcohol, and Loba chemicals Pvt. Ltd. for providing gift sample of tween80. Author also extend the sincere gratitude to the Principal, B. K. Mody Government Pharmacy College, Rajkot and the HOD, Department of Pharmaceutical Sciences, Rajkot for assistance in the present research work by providing various instrumental facilities.

AUTHOR CONTRIBUTION

All the authors have equally contributed in conceiving this research and designing of experiments; all authors have participated in the design and interpretation of the data; experiments and analysis; writing the paper and participated in the revisions of it. All authors read and approved the final manuscript.

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issue.

DATA AVAILABILITY

The data used to support the research are included in the article.

FUNDING

None

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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