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Effect of Stabilizing Solvent on the Preparation of Nimesulide Loaded Gelatin Microspheres

Rahisuddin*, Pramod Kumar Sharma, Garima Garg

Department of pharmaceutical technology, Meerut institute of Engineering and Technology, NH-58, Delhi-Roorkee Bypass road, Meerut (U.P.) – 250005, India.

ABSTRACT

In present work the effect of stabilizing solvent i.e. seasame oil, liquid paraffin, soybean oil on the preparation of nimesulide loaded gelatin microspheres was studied. The gelatin microspheres were prepared by using emulsion crosslinking technique with gluteraldehyde as crosslinking agent. The average particle size of the microspheres was in the following manner- liquid paraffin > soybean oil > seasame oil, where as the drug entrapment efficiency was in following order liquid paraffin > soybean oil > seasame oil. The shape of the microspheres obtained with seasame oil and soybean oil were nearly spherical, whereas the shape of the microspheres obtained liquid paraffin was irregular. In this study maximum release of nimesulide was observed with liquid paraffin.

Keywords: stabilizing agent, gelatin microsphere, microencapsulation crosslinking, Nimesulide.

Corresponding author

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INTRODUCTION

The main objective of nimesulide loaded gelatin microspheres is to avoid multiple dosing, side effects, improve patient compliance. Gelatin is a natural polymer that is extracted from collagen by alkaline or acidic pretreatment and thermal denaturation. Gelatin is used in pharmaceutics due to its biocompatibility and biodegradability properties. It can be utilized for the preparation of oral as well as injectable microspheres. Aldehyde derivatives such as formaldehyde, gluteraldehyde or other bifunctional reactants have been used to produce insoluble biodegradable gelatin microspheres. Gluteraldehyde is used as a cross-linking agent to obtain rigid microspheres. Gluteraldehyde produces cross-linking between gelatin molecules and thus reduces the rate of drug release from the microspheres. It is important to remove excess oil when emulsification crosslinking technique is used, by washing the microspheres with cold isopropyl alcohol. Otherwise, the oil retained on the surface of microspheres may cause aggregation and alter the morphological properties of the microspheres. This washing procedure is also important to remove excess of the cross-linking agent. Sustained release nimesulide loaded gelatin microspheres provide a prolonged dosing of the nimesulide by supplying an initial amount of loading dose, perhaps one-half of the total dose release, followed by a gradual and uniform release of the reminder of the drug over the desired time period. Nimesulide was introduced in 1985, is one of the most potent NSAIDs and useful for the various inflammatory condition. Nimesulide is 4-nitro-2-(phenoxy) methane sulfonanilide, a COX-2 inhibitor and inhibits synthesis of prostaglandins. Nimesulide is restricted in various countries due to gastric irritation and liver infection, for this reason a novel drug delivery system is required for administration of this drug. The present work is a part of research in that the effect of stabilizing agent on the preparation of nimesulide microspheres discussed [1-5].

EXPERIMENTAL

Materials

Nimesulide was a gift sample from Dr. Reddy, Hyderabad India., isopropyl alcohol was purchased from Rankem laboratory reagent New Delhi (India)., seasame oil, soybean oil were purchased from local market of Meerut (India)., liquid paraffin, gelatin, gluteraldehyde, NaOH, potassium dihydrogen phosphate, N-hexane, were purchased from CDH laboratory New Delhi.

Method

Microencapsulation crosslinking method [6]

A 5 ml solution (5% w/v) of gelatin in distilled water was prepared. 100 mg of nimesulide was added to the gelatin solution. The suspension of nimesulide in gelatin solution was homogenized using a magnetic stirrer. The suspension was then added gradually to 50 ml of stabilizing agent i.e. seasame oil, liquid paraffin, soybean oil, while stirred at 1000 rpm using mechanical stirrer (Yamato lab stirrer LT400). Then 2 ml of gluteraldehyde was added to the suspension/emulsion system. Stirring was continued for 4 h to allow the crosslinking of gelatin

microspheres to be completed. Microspheres were then filtered and washed with 30 ml of cold isopropyl alcohol at 5°C overnight. Microspheres were then dried at 37°C and stored in suitable containers.

Characterization of microspheres

Drug Entrapment Efficiency [7,8]

The adequate quantity of microspheres were crushed and dissolved in 0.1 N NaOH solutions to get the stock solution, which was then filter and the filtrate was adequately diluted with 0.1 N NaOH solutions. Now the absorbance was taken at 392 with the help of UV- VIS spectrophotometer (Shimadzu-1700). The drug entrapment efficiency was determine by using the following formula-

$$\% \text{ drug entrapment efficiency} = \frac{\text{Actual amount of drug in microsphere} \times 100}{\text{Amount of drug added}}$$

Determination of Particle Size [9]

Particle size was determined by optical microscope with the help of ocular and stage micrometer calibration.

PARAMETER	A	B	C
YIELD (%)	69±1.63299	88±0.92631	90±1.4723
DEE (%)	50.226±0.79241	96±0.69317	85.37±0.59381
PARTICLE SIZE(µm)	22±0.57342	52±0.67479	27±0.47923

A: Seasame oil, **B:** Liquid paraffin, **C**: Soybean oil

Determination of *In-vitro* Release of Nimesulide from Microspheres [10,11]

In-vitro release studies of nimesulide loaded microspheres were carried out at 37±1 ^{o}C using phosphate buffer pH 7.4. Each batch of microspheres containing 50 mg of nimesulide was individually added to 900 ml of phosphate buffer pH 7.4 in flasks of paddle dissolution apparatus. The paddle was stirred at 100 rpm. 1 ml of samples was withdrawn at regular time intervals and same volume of phosphate buffer was replaced. Withdrawn sample was further diluted with 0.1 N NaOH solution and Absorbance was taken at 392 with the help of UV-VIS spectrophotometer (Shimadzu 1700).

% Release of nimesulide from different batch of microspheres

Time (hrs)	A	B	C
0.5	10.63	8.41	7.93
1	24.81	20.15	14.27
2	33.67	33.60	18.23
3	38.98	50.42	26.16
4	46.06	57.14	29.33
5	54.92	67.23	33.29
6	60.23	72.25	36.46

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% Remain of nimesulide in the microspheres of different batch

Time (hrs)	A	B	C
0.5	89.37	91.59	92.07
1	75.19	79.85	85.27
2	66.33	66.40	81.77
3	61.02	49.52	73.84
4	53.94	42.86	70.67
5	45.08	32.77	66.71
6	39.77	27.73	63.54

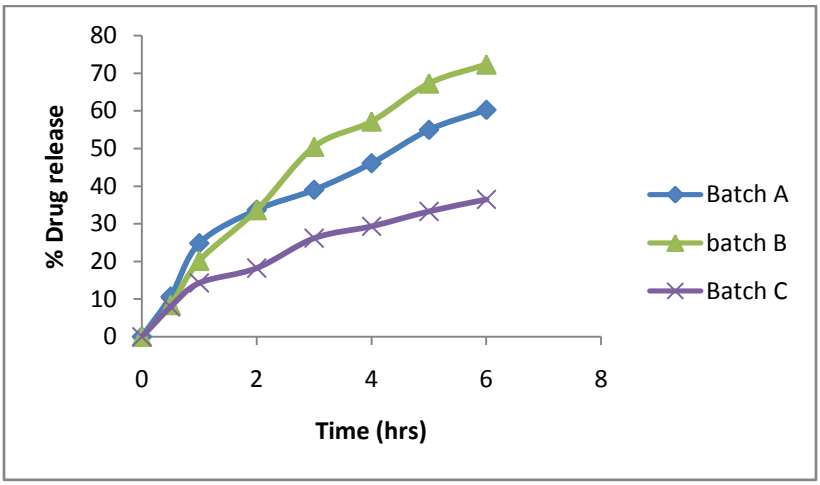

Fig1. In-vitro nimesulide release from the microspheres prepared in this study

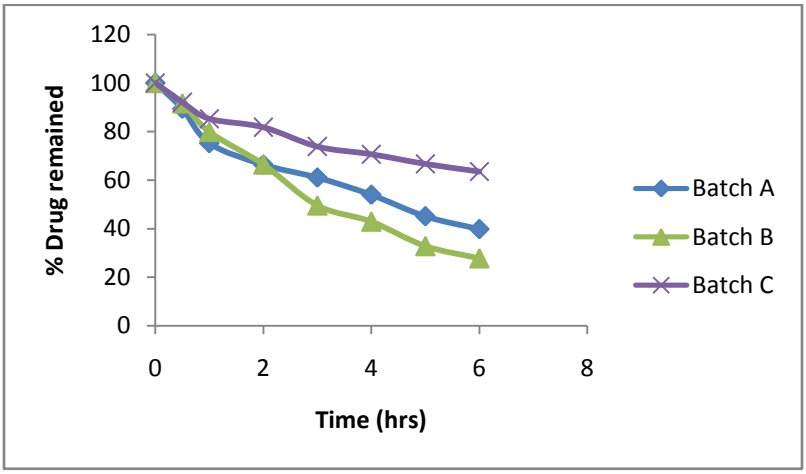

Fig2. In-vitro nimesulide remained in the microspheres prepared in this study

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% Log released of nimesulide from different batch

Time (hrs)	A	B	C
0.5	1.0265	0.9247	0.8992
1	1.3946	1.3042	1.1544
2	1.5272	1.5263	1.2607
3	1.5908	1.7026	1.4176
4	1.6633	1.7569	1.4673
5	1.7397	1.8275	1.5223
6	1.7798	1.8588	1.5618

% Log of nimesulide remained in the microspheres of different batch

Time (hrs)	A	B	C
0.5	1.9511	1.9618	1.9641
1	1.8761	1.9022	1.9307
2	1.8217	1.8221	1.9125
3	1.7854	1.6947	1.8682
4	1.7319	1.632	1.8492
5	1.6539	1.5154	1.8241
6	1.5995	1.4429	1.803

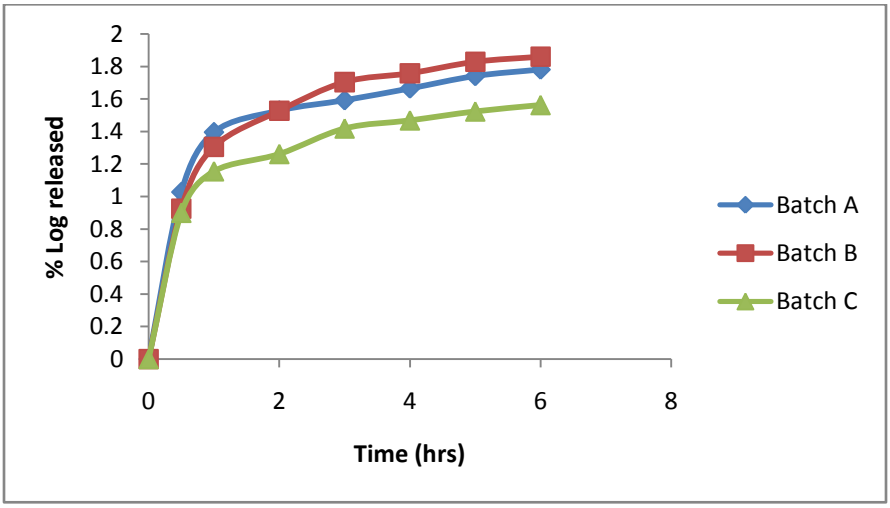

Fig 3 % Log released of nimesulide from different batch

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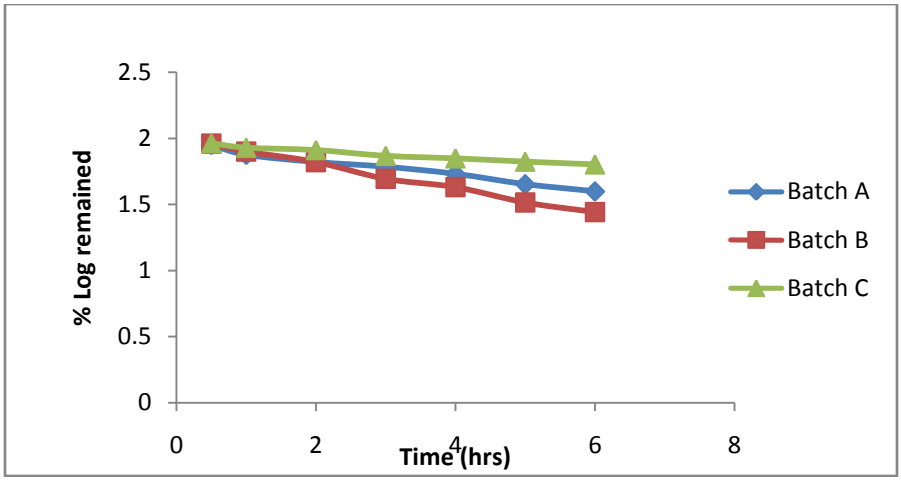

Fig 4 % Log remained of nimesulide in the microspheres of different batch

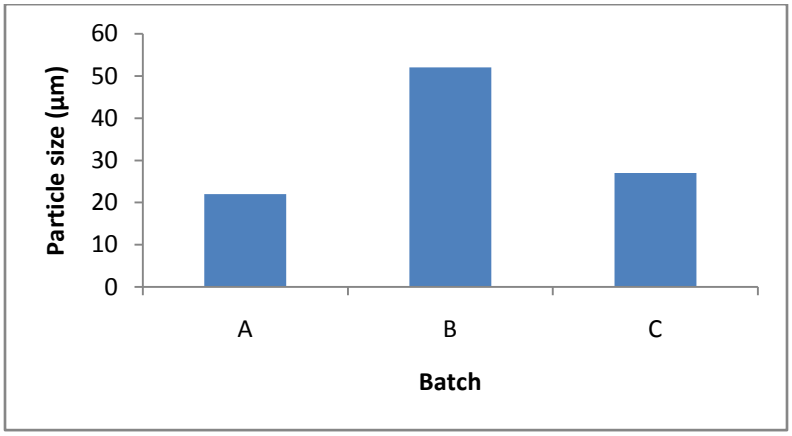

Fig5. Particle size of the microspheres prepared in the present study

The Phase Contrast Studies Of The All Batch (A, B, C ,) Of Microspheres Prepared In This Study Are Shown Below:

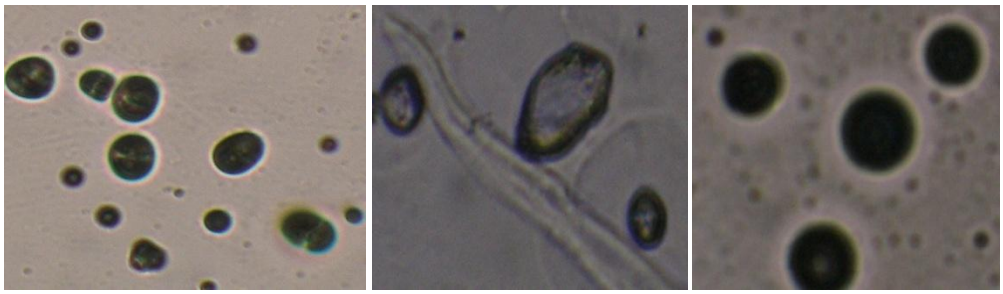

Fig 6 Fig 7 Fig 8

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RESULT AND DISCUSSION

In present investigation it was observed that the microspheres prepared with seasame oil and soybean oil are nearly spherical as shown in Fig 6 and Fig 8 respectively. The microsphere prepared with liquid paraffin was irregular in shape as shown in Fig 7. The average particle size of the microspheres prepared in the present study are 7, 17, 15 for the seasame oil, liquid paraffin, soybean oil respectively as shown in figure 5. The releases of nimesulide from microspheres of different batch are shown in figure 1 that indicate the release about 60.23%, 72.25%, 36.46% for seasame oil, liquid paraffin, soybean oil respectively. So we conclude that liquid paraffin is one of the stabilizing agent that give maximum release of nimesulide from the prepared microspheres in this study which may be due to the irregular in shape and the drug may leakage from the microspheres.

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