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DESIGN AND EVALUATION OF GELATIN MICROSPHERES CONTAINING DICLOFENAC SODIUM

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ABSTRACT

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. The present study is aimed to formulate the Diclofenac Sodium (DFS) microspheres by using Co-acervation phase separation procedure to get better bioavailability of drug. In this study, we used DFS as a drug of choice since it has biological half-life of about 1-2 hrs. DFS microspheres were formulated by using different drug, gelatin and HPMC ratios. A total of 6 batches was F1, F2, F3, F4, F5 & F6 of varying concentrations of drug, gelatin and HPMC were prepared. DFS microspheres were evaluated by various tests like particle size analysis, angle of repose and bulk density. Further DFS Micro spheres were examined for in-vitro dissolution, by using phosphate buffer (PH 7.4) to make out the release of the drug. Results shown that microspheres with low amount of gelatin (F1), with high amount of HPMC (F4 & F5) has shown satisfactory prolonged action in invitro dissolution studies.

Key words: Diclofenac Sodium, Micro spheres, Gelatin, Formaldehyde.

INTRODUCTION

Alleviation of the problems faced in the conventional dosage forms and conventional therapy is achieved by designing as well structured controlled drug delivery system and also enhances the therapeutic efficacy of the drug of choice[1]. Maximum therapeutic efficacy can be accomplished when the drug delivered by the carrier to the target tissue in right amount in right period of time, in such a way that it could minimize toxicity and adverse effects [1,5].

Microspheres development is the one technique which elicits controlled release, transportability, reducing frequency of administration and safety. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. Micro sphere technology has been studied extensively for the sustained delivery of therapeutic agents [1-6].

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAIDs), commonly used in the long-term therapy for rheumatoid arthritis. The biological half-life of Diclofenac sodium is about 1-2 hours; therefore multiple dosing is required to maintain therapeutic drug blood level. The most frequently reported side effects of Diclofenac sodium on long-term administration are gastrointestinal disturbances, peptic ulceration and gastrointestinal bleeding. Diclofenac sodium is poorly soluble in water and has acidic pH (1-3) but is rapidly soluble in alkaline pH (5-8). Hence an attempt was made to formulate a sustained release formulation with increased patient compliance and decreased signs of adverse effects [2,7].

By taking the view of advantages microspheres and drug profile of DFS into consideration we have decided to carry out our work on DFS microspheres by coacervation phase separation method by using Gelatin.

Materials and Methods

Materials: Diclofenac Sodium (Finar chemicals), Gelatin IP grade (Qualis kems fine chem. Pvt Ltd), Hydroxy Propyl Methyl Cellulose (HPMC) (Qualis kems fine chem. Pvt Ltd), Formaldehyde, Isopropyl alcohol (Finar chemicals).

Method of Preparation:

Gelatin and Gelatin-HPMC mixture containing DFS Micro spheres were prepared by coacervation phase separation technique utilizing temperature change.

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Gelatin was dissolved in 10ml of water which was previously heated to 50˚ C, to this DFS was added and stirred approximately at 300 rpm with the help of magnetic stirrer for 15 mins to get a stable dispersion. The dispersion was poured drop wise into the 10ml of sunflower oil which was also previously heated to 50˚ C on a water bath. The mixture was stirred with a help of magnetic stirrer for 2 hrs at 300rpm at room temperature. At the end of 2 hrs, cross linking agent formaldehyde 0.5ml was added to the dispersion medium with continuous stirring for next 30 minutes. After that, the final dispersion was kept in refrigerator for 24 hrs to make sure the rigidization of Micro spheres. This Procedure was followed to prepare 6 batches of DFS Micro spheres with different ratios of gelatin and Gelatin-HPMC mixtures[1,8]. The core: coat ratio, amount of drug and polymers used were given in table-1

Result & Discussions:

Evaluation of Diclofenac Sodium Microspheres:

Particle size analysis:

The Particle size analysis was carried out by using optical microscopy. About 200 Micro spheres were selected randomly and their size was determined by using optical microscope fitted with standard micrometer scale [5]. The particle size of Micro spheres was given in table-2.

Determination of angle of repose:

The angle of repose was determined by funnel method, by using formula $\theta = \tan^{-1}(h/r)$ [9] .The angle of Micro spheres was given in table 3..

Determination of bulk density:

Bulk density was determined by transferring known quantity of Micro spheres to 50ml measuring cylinder and tapping 100 times from 1 inch at 2 sec interval [9]. The bulk density of Micro spheres was given in table 4.

Percentage yield:

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

Percentage yield = {the weight of microspheres / The weight of polymer + drug}*100 [9].

Encapsulation efficiency:

Encapsulation efficiency was determined for all batches using the following formulas. Values are expressed as percentage [5].

Encapsulation efficiency = {Actual weight of drug in sample/ Theoretical weight of drug} *100

In-vitro release study:

In-vitro release study was carried out by using basket method of dissolution at 50 rpm in 37º ± 0.5º C using phosphate buffer (PH 7.4) as dissolution medium. The samples were estimated at 264nm by using UV-visible spectrometer, the amount of drug released was interpreted from the calibration curve [7-11]. The results were given in table 5 & the plots were shown in fig 1.

Table 1 Composition of Diclofenac Sodium Microspheres

S.No	Formulation code	Core: coat ratio	Amount of drug (gm)	Amount of gelatin(gm)	Amount of HPMC(gm)
1	F1	1:1	1	1.0	-
2	F2	1:2	1	2.0	-
3	F3	1:3	1	3.0	-
4	F4	1:1	1	0.75	0.25
5	F5	1:1	1	0.50	0.50
6	F6	1:1	1	0.25	0.75

Table 2 The particle size of Diclofenac Sodium Microspheres

S.No	Formulation code	Average particle size (µm)
1	F1	65.2
2	F2	73.8
3	F3	80.4
4	F4	63.6
5	F5	67.3
6	F6	72.9

Table 3 The angle repose values of Diclofenac Sodium Microspheres

S.No	Formulation code	Angle of repose	Comments
1	F1	$26^{o}.58^{'}$	Good flow
2	F2	$28^{o}.44^{'}$	Good flow
3	F3	$28^{o}.61^{'}$	Good flow
4	F4	$24^{o}.57^{'}$	Good flow
5	F5	$26^{o}.41^{'}$	Good flow
6	F6	$26^{o}.62^{'}$	Good flow

Table 4 The bulk density of Diclofenac Sodium Micro spheres

S.No	Formulation code	Bulk density (gm/ml)
1	F1	0.71
2	F2	0.76
3	F3	0.86
4	F4	0.78
5	F5	0.88
6	F6	0.95

Table 5 The dissolution study of Diclofenac Sodium Microspheres

S.NO	Time intervals	Percentage release of drug					
		F1	F2	F3	F4	F5	F6
1	0.5	11.8	9.6	9.0	14.4	12.1	17.8
2	1	26.2	19.1	12.8	22.3	21.5	21.3
3	2	57.6	46.4	32.1	45.8	48.3	36.5
4	3	74.6	66.4	55.1	69.4	73.9	58.9
5	4	82.5	70.2	60.2	79.9	79.2	66.4
6	5	85.1	75.6	62.8	83.7	80.5	68.9
7	6	86.3	79.2	64.0	85.1	81.9	70.3
8	7	87.7	81.6	66.6	86.3	83.2	70.1
9	8	89.0	85.0	67.9	87.7	85.9	71.4

Table 6 Percentage yield of Diclofenac Sodium Microspheres

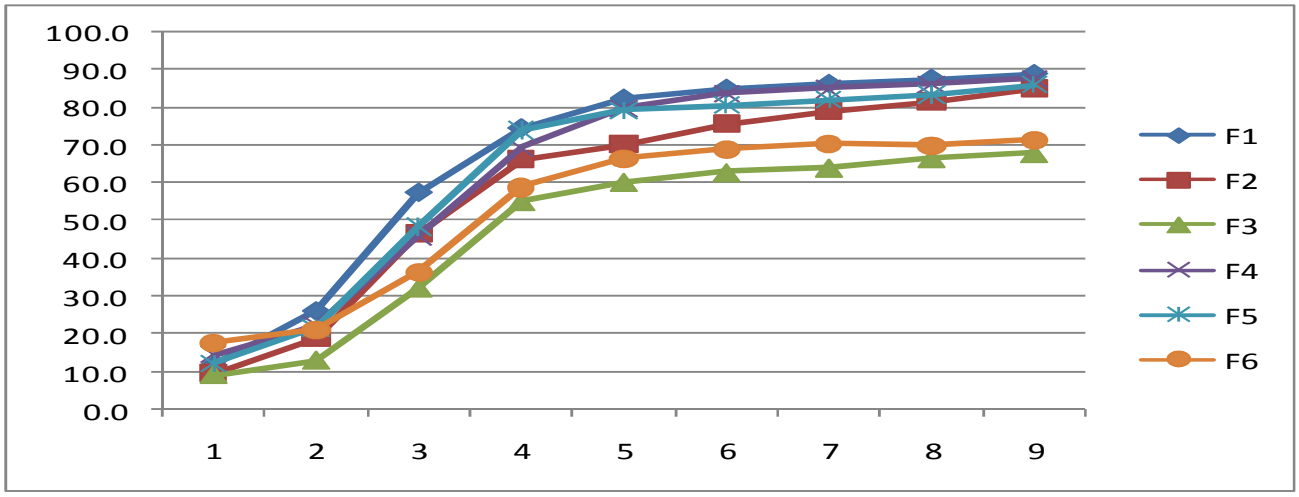
S.No	Formulation code	Core: coat ratio	Amount of drug (gm)	Amount of gelatin(gm)	Amount of HPMC(gm)	% Yield
1	F1	1:1	1	1.0	-	70.0
2	F2	1:2	1	2.0	-	81.7
3	F3	1:3	1	3.0	-	83.8
4	F4	1:1	1	0.75	0.25	77.5
5	F5	1:1	1	0.50	0.50	82.0
6	F6	1:1	1	0.25	0.75	84.5

Table 7 Percentage encapsulation efficiency of Diclofenac Sodium Microspheres

S.No	Formulation code	Theoretical weight in gms	Actual Weight in gms	% encapsulation
1	F1	0.200	0.136	68
2	F2	0.200	0.152	76
3	F3	0.200	0.164	82
4	F4	0.200	0.148	74
5	F5	0.200	0.162	81

6	F6	0.200	0.174	87

Fig 1 Dissolution Profile of DFS Micro spheres at 37°C in Phosphate buffer (PH 7.4).



DISCUSSION

The particle size distribution range of the prepared Micro spheres was found in the range between 65.2µm-85.4µm.It was mentioned in table2. The flow properties of the DFS Micro spheres were estimated by determining angle of repose, which indicated good flowability. The results were shown in table 3. Bulk density test and its results given in table 4 designated good packing properties. The in-vitro dissolution profile of gelatin containing DFS Micro spheres in Phosphate buffer PH7.4 showed that Micro spheres with low amount of gelatin released 89.0%(F1) of DFS after 8hrs while Micro spheres prepared with high amount of gelatin released only 67.9%(F3) of DFS. The in-vitro dissolution profile of gelatin-HPMC containing DFS Micro spheres in Phosphate buffer PH7.4 showed that Micro spheres with high amount of HPMC were most effective in showing down the drug release 71.4%(F6),while the Micro spheres containing high amount of gelatin were released 87.7%(F4) of DFS.

CONCLUSION

The Micro encapsulation of DFS with gelatin and gelatin –HPMC by co-acervation phase separation by temperature change technique and cross linking with formaldehyde, was shown successfully the sustaining of the drug release. The invitro studies revealed that F1, F4 and F5 were the best sustained release formulations among the total six formulations, the other formulations have also depicted longer duration of action. These studies compared the release behaviour of gelatin and gelatin –HPMC controlled release system of DFS.

Microspheres formulated with formula 1 i.e.F1 illustrated a prominent sustained release effect within 8 hours period of time. At the same time the formulations F4 and F5 also reveled substantial continuous release and similar pattern of release of the drug like F1. Formulation F2 has shown ample ability of sustainability. Modest prolonged release was presented by the formulations F3 and F6 in comparison with other formulations. Overall it was found that all the microspheres were able to regulate the release of the drug.

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