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EGG ALBUMIN MATRIX MICROSPHERES INCORPORATED WITH SOLID DISPERSION OF DICLOFENAC IN HPMC

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ABSTRACT

The present investigation concerned the development of extended release dosage form of diclofenac to achieve a slow, controlled and complete release of the drug. Solid dispersions of diclofenac sodium in HPMC were prepared by solvent evaporation technique with different drug to carrier ratio SD3 (1:05) SD2 (1:03), SD1 (1:02). The solid dispersions were evaluated for *in-vitro* release kinetics. Among the three drugs to carrier ratio SD3 (1:05) showed maximum drug dissolution in diclofenac- HPMC solid dispersion. The formulations were incorporated with egg albumin spheres by suspending the solid dispersions in phosphate buffer. To this suspensions egg albumin was added. Dried microspheres were microencapsulated. Different core: coat ratios were used. The prepared microcapsules were evaluated for morphological characters, drug content, drug release and various other parameters that may affect the flow properties were also studied. The microcapsules obtained were spherical, discrete free flowing & exhibited a slow, sustained and complete release of the drug from matrix type reservoir system over a period of 12 hours. The release depends on core: coat ratio and size of the microspheres. Whereas uncoated microspherules were found to be smooth and spherical in the liquid manufacturing vehicle. After drying the surface of the microspheres became rough & spherical. In the *In vitro* release study formulations ME1showed maximum drug release and found to be sustained.

Key Words: Diclofenac, Egg albumin, HPMC, Microspheres, Solid dispersion

INTRODUCTION

Controlled drug delivery is a topic of current interest in pharmaceutical technology and industry. In the last two decades, controlled release dosage forms have made significant progress in terms of clinical efficacy and potential compliance. Drugs administered orally in solid dosage form should dissolve in gastrointestinal fluids before they are absorbed. Drugs with united solubility in aqueous media may exhibit dissolution rate limited absorption profile.

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Thus the rate of dissolution of the drugs in the gastrointestinal fluids could influence the rate and extent of absorption. In the case of poorly soluble drug the dissolution rate always influences its absorption. Chiou and Riegelman, 1971 defined the term solid dispersion as "A dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method." Dispersions obtained through the fusion process are often called melts, and those obtained by the solvent method are frequently referred to as co-precipitates or co-evaporates, for example, sulfathiazole-povidone and reserpine-PVP.

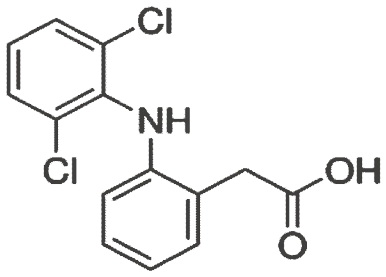
The two basic procedures used to prepare solid dispersions are the fusion and co solvent techniques. Modifications of these

methods and combinations of them have also been used.Although a very great number of polymers can be used, natural or semi-synthetic polysaccharides, such as celullose derivatives, play an important role in microencapsulation processes.[1]

Microspheres, loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol:dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C.The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. Diclofenac sodium (DS), is a potent drug in the NSAID group having non-steroidal, anti-inflammatory properties, and is widely used in the treatment of rheumatoid arthritis, osteoarthritis ankylosing spondylitis.

In the present work, solid dispersions of Diclofenac in HPMC were first prepared to enhance its dissolution rates and the suspensions were incorporated with egg albumin microspheres. Albumin microspheres can satisfactorily bind with high concentration of drugs. The polymer is biocompatible and stable after formulation and has a clinically acceptable shelf life.

All these criteria made egg albumin to be selected as an ideal matrix type reservoir to incorporate Diclofenac in HPMC solid dispersion. The purpose of the present work to investigate the feasibility of formulations of controlled release microspheres of reservoir type using egg albumin as core matrix and to coat the microspheres with ethyl cellulose.



IUPAC Name: 2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetic acid

The present investigation concerned the development of extended release dosage form of diclofenac microsphere using egg albumin incorporated with solid dispersion method by using HPMC polymer different proportions to achieve a slow, controlled and complete release of the drug.

MATERIALS AND METHODS:

Diclofenac was a gift sample from Karup PharmaPvt.Ltd, Hyderabad, Egg albumin was procured from Lobachemie Pvt.Ltd, Mumbai, HPMC was procured fromS.D. Fine Chem. Ltd., Mumbai. Chloroform was procured from Thermo electron LLS India Pvt.Ltd, Mumbai and All other materials used were of Pharmacopoeial grade.

EXPERIMENTAL WORK

1. Preparation of solid dispersion:

Solvent evaporation method was implemented in the preparation of solid dispersion of Diclofenac in HPMC. Different drug: carrier ratios SD1 (1:02), SD2 (1:03), SD3 (1:05) were employed. The carrier first dissolved in chloroform (30ml) with the help of magnetic stirrer. The Diclofenac was transferred in to this polymer-chloroform solution part by part while stirring. The solvent was removed by evaporation at 40 ^{0}C under vacuum. The mass obtained was dried in a desiccators for 72 hrs, crushed, pulverized and shifted through mesh no 80.

2. Preparation of egg albumin microspheres:

Solid dispersion(1:05) of Diclofenac sodium in HPMC which showed good dissolution rate profile was adopted for incorporating in the preparation of microspheres in different drug to carrier ratios MC1(1:3), MC2(2:2), MC3(3:1) were employed. Solid dispersion equivalent to 200mg of Diclofenac was taken and suspended in 2ml of phosphate buffer. To this suspension 200mg of egg albumin was added. This was added at a constant rate drop wise to 240ml of coconut oil and stirred with three blade remi-motor stirrer at 800 rpm. After 15min 2ml of formaldehyde was added and stirring was continued for one hour .oil phase was separated and microspheres were washed thrice with n-hexan.

Dried microspheres were passed through sieve no.85 and stored in glass vials at 25^0c.Drug release of microspheres was shown in (fig2).

3. Encapsulation of microspheres

Dried microsphere which shows high drug dissolution rates MC3 (3:1) were taken into 100ml hot solution of ethyl cellulose in cyclohexane. The system was stirred at 50 rpm. The contents were slowly cooled to room temperature. The microspheres were then separated through filtration through 85 mesh sieve and dried in a dessicator. Two different core: coat ratios 2:1 and 1:2 were used, referred as ME1 and ME2.Drug release of encapsulated microspheres was shown in (fig3).

EVALUATION:

1. PARTICLE SIZE ANALYSIS

Particle size distribution analysis using method of microscopic measurement for not less than 50 microspheres was performed and shown in table 1.

2. DRUG CONTENT UNIFORMITY

Encapsulated microspheres equivalent to 200mg of diclofenac were taken and grounded. This was dissolved and filtered and the diclofenac was estimated spectrophotometrically at 230 nm and was shown in table 2.

3. DISSOLUTION RATE STUDIES ON SOLID DISPERSION

Dissolution studies of all samples were performed using USP XXIII apparatus. SDs(1:05 which has been shown good drug release characteristics) equivalent to 100 mg of the drug were added to the dissolution medium (900 ml of phosphate buffer pH 7.4 at a temperature of 37°C ± 0.5°C), which was stirred with a rotating paddle at 50 rpm. At suitable time intervals, 5 ml samples were withdrawn, filtered (0.22 µm), diluted and analyze at 230 nm using UV spectrophotometer. Equal volume of fresh medium prewarmed at the same temperature was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test. Each test was performed in triplicate and calculated mean values of cumulative drug release were used while plotting the release curves. Which have been shown in table 4, 5, 6 and Fig 1.

4. DISSOLUTION RATE STUDIES ON MICROSPHERES:

Dissolution studies of all samples were performed using USP XXIII apparatus type 1 for 12 h. Samples of pure Diclofenac equivalent to 100 mg of the drug from MC3 (3:1) which shown good dissolution profile were added to the dissolution medium (900 ml of phosphate buffer pH 7.4 at a temperature of 37°C ± 0.5°C), which was stirred with a rotating paddle at 50 rpm. At suitable time intervals, 5 ml samples were withdrawn, filtered (0.22 µm), diluted and analyzed at 230 nm using UV spectrophotometer. Equal volume of fresh medium pre warmed at the same temperature was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test. Each test was performed in triplicate and calculated mean values of cumulative drug release were used while plotting the release curves. Which have been shown in table 7, 8, 9 and Fig 2.

5. DISSOLUTION RATE STUDIES ON ENCAPSULATED MICROSPHERULES

All the batches of uncoated ME1 and ME2 were subjected to dissolution studies. Then encapsulated microspheres equivalent to 100mg of Diclofenac were taken and grounded. This was dissolved and filtered and the Diclofenc was estimated spectrophotometrically at 276nm.Which has been shown in fig 3.

RESULTS AND DISCUSSION

Table 1: Particle size analysis

S. No	Particle size	S. No	Particle Size	S. No	Particle size
1	1.37	1	0.82	1	4.020
2	1.37	2	1.03	2	2.16
3	0.82	3	1.44	3	1.85
4	2.06	4	1.88	4	1.03
5	0.92	5	3.09	5	1.95
6	1.23	6	4.32	6	3.27
7	1.54	7	1.13	7	1.85
8	1.75	8	1.34	8	4.32
9	0.61	9	1.54	9	3.29
10	0.82	10	1.34	10	1.97
11	1.23	11	2.06	11	1.113
12	1.44	12	2.16	12	1.34
13	2.16	13	2.47	13	2.47
14	1.95	14	2.68	14	3.09
15	2.57	15	2.98	15	2.98
16	2.47	16	3.09	16	2.88
17	1.44	17	0.82	17	1.44
18	1.23	18	1.64	18	1.23
19	2.37	19	1.88	19	0.82
20	2.98	20	1.95	20	0.95
21	3.09	21	2.26	21	2.25
22	3.29	22	0.92	22	4.02
23	3.30	23	1.13	23	1.85
24	2.57	24	1.88	24	2.06
25	4.02	25	2.37	25	2.22
26	1.85	26	4.2	26	2.57
27	2.16	27	4.43	27	4.12
28	2.26	28	2.98	28	4.32
29	2.37	*29*	3.09	29	5.05
30	2.57	30	3.19	30	2.16
31	3.19	31	2.98	31	2.47
32	1.99	32	3.09	32	2.66
33	2.06	33	0.61	33	3.29
34	1.85	34	0.82	34	2.98
35	0.26	35	1.44	35	1.85
36	2.37	36	1.95	36	1.95
37	4.12	37	2.06	37	2.31
38	4.63	38	1.88	38	3.19
39	1.85	39	2.16	39	0.732
40	5.64	40	2.78	40	1.44
41	5.15	41	2.88	41	2.15
42	5.25	42	1.44	42	2.78
43	5.05	43	1.75	43	2.98

Particle size (mc3)=108.566/43=2.524
Particle size (mc1)=103.941/43=2.4172
Particle size (mc2)=93.50319/43=2.1744

Table 2: Drug content uniformity

S. No	Formulation	% Yield	Drug content
1	SD3	88.5%	90%
2	SD2	90%	77%
3	SD3	88%	83%

Table 3: *In vitro* dissolution studies of solid dispersion of diclofenac sample (1:02)

Time	Abs	conc.(mcg/ml)	conc.(mg/ml)	D.F	Amt (5ml)	Amt (900ml)	CR	%CR
0	0	0	0	0	0	0	0	0
1	0.2	6.91	0.0069	10	0.34	62.25	62.25	20.75
2	0.232	9.58	0.0095	10	0.47	86.25	86.59	28.86
3	0.248	10.9	0.0109	10	0.54	98.25	99.07	33.02
4	0.267	12.5	0.0125	10	0.62	112.51	113.87	37.95
6	0.282	13.75	0.0137	10	0.68	123.75	125.74	41.91
8	0.296	14.91	0.0149	10	0.74	134.25	136.93	45.64
10	0.345	19.01	0.019	10	0.95	171.01	173.68	57.89
12	0.372	21.25	0.0212	10	1.06	191.25	195.62	65.20

Table 4: *In vitro* dissolution studies of solid dispersion of diclofenac sample (1:03)

Time	Abs	conc.(mcg/ml)	conc.(mg/ml)	D.F	Amt (5ml)	Amt (900ml)	CR	%CR
0	0	0	0	0	0	0	0	0
1	0.245	10.66	0.010	10	0.53	96.03	96.03	24.11
2	0.276	13.25	0.013	10	0.66	119.25	119.78	29.94
3	0.285	14.01	0.014	10	0.72	126	127.19	31.79
4	0.298	15.08	0.015	10	0.75	135.75	137.64	34.41
6	0.343	18.83	0.018	10	0.94	169.5	172.15	43.03
8	0.423	25.51	0.025	10	1.27	229.5	233.09	58.27
10	0.456	28.25	0.028	10	1.41	254.25	259.11	64.77
12	0.519	33.52	0.033	10	1.67	301.5	307.77	76.94

Table no 5: *In vitro* dissolution studies of solid dispersion of diclofenac sample (1:05)

Time	Abs	conc.(mcg/ml)	conc.(mg/ml)	D.F	Amt (5ml)	Amt (900ml)	CR	%CR
0	0	0	0	0	0	0	0	0
1	0.342	18.75	0.018	10	0.93	168.5	168.75	28.12
2	0.393	23	0.023	10	1.15	207.1	207.93	34.65
3	0.454	28.08	0.028	10	1.40	252.7	254.83	42.47
4	0.563	37.16	0.037	10	1.85	334.5	337.99	56.33
6	0.589	39.33	0.039	10	1.96	354.3	359.35	59.89
8	0.675	46.5	0.046	10	2.32	418.5	425.81	70.96
10	0.723	50.5	0.050	10	2.52	454.5	464.14	77.35
12	0.818	58.41	0.058	10	2.92	525.75	537.91	89.65

Fig 1: *In vitro* dissolution studies of solid dispersions of Diclofenac

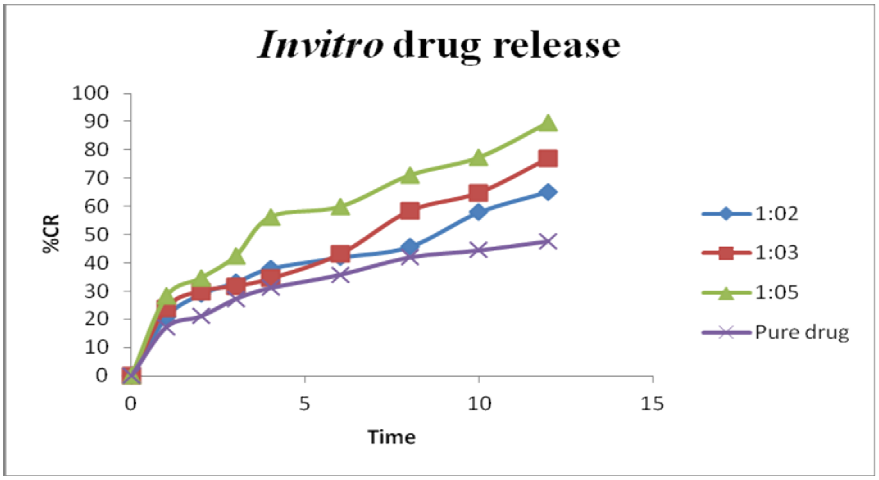


Table 6*: In vitro* dissolution study of microspheres: drug: MC1 (1:3)

Time	Absorbance	Con.cug/ml	amt dg mg/ml	cum /900	%Cdr
0	0.168	2.16	0.02	19.47	0
10	0.176	2.27	0.02	20.48	10.24
20	0.198	2.57	0.02	23.22	11.61
30	0.208	2.71	0.02	24.48	12.24
45	0.239	3.13	0.03	28.33	14.16
60	0.309	4.09	0.04	36.99	18.49
120	0.389	5.19	0.05	46.89	23.44
180	0.456	6.10	0.06	55.20	27.60
240	0.498	6.68	0.06	60.44	30.22
300	0.542	7.28	0.07	65.58	32.79
360	0.586	7.89	0.07	71.43	35.71
480	0.657	8.86	0.08	80.26	40.13
600	0.698	9.42	0.09	85.41	42.70
720	0.754	10.19	0.10	92.41	46.20

Table no 7*: In vitro* dissolution study of microspheres: drug: MC2 (2:2)

Time	Absorbance	Concug/ml	Amtdrugmg/ml	cu*900	%Cdr
0	0.234	3.06	0.03	27.61	0
10	0.298	3.94	0.03	35.50	17.75
20	0.345	4.58	0.04	41.30	20.65
30	0.396	5.28	0.05	47.58	23.79
45	0.467	6.26	0.06	56.34	28.17
60	0.497	6.67	0.06	60.04	30.02
120	0.499	6.69	0.06	60.28	30.14
180	0.523	7.02	0.07	63.24	31.62
240	0.678	9.15	0.09	82.35	41.17
300	0.789	10.67	0.10	96.04	48.02
360	0.798	10.79	0.10	97.15	48.57
480	0.876	11.86	0.11	106.76	53.38
600	0.893	12.09	0.12	108.88	54.43
720	1.09	14.79	0.14	133.15	66.57

Table 8: *In vitro* dissolution study of microspheres: drug: MC3 (3:1)

Time	absorbance	Con. ug/ml	amt mg/ml	amt*900	%cdr
0	0.21	2.80	0.02	20.34	0
10	0.23	3.06	0.03	27.63	13.81
20	0.29	3.94	0.03	35.56	17.78
30	0.34	4.58	0.04	41.39	20.69
45	0.39	5.30	0.05	47.85	23.92
60	0.49	6.68	0.06	60.35	30.17
120	0.54	7.30	0.07	65.97	32.98
180	0.76	10.38	0.10	93.78	46.89
240	0.87	11.86	0.11	107.52	53.76
300	0.95	12.93	0.12	116.93	58.46
360	0.99	13.54	0.13	122.61	61.30
480	1.07	14.52	0.14	131.50	65.75
600	1.16	15.75	0.15	142.74	71.37
720	1.23	16.71	0.16	151.53	75.76

Figure 2: *In vitro* drug release studies of microspheres: Drug: MC

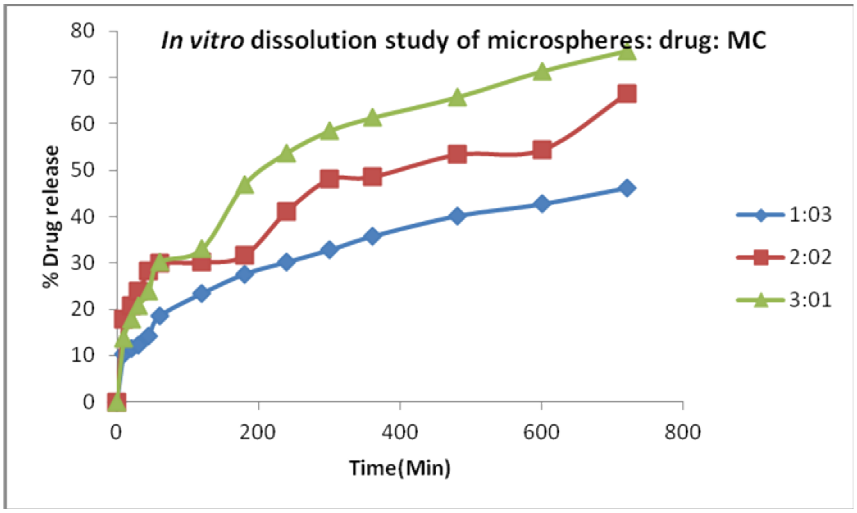


Figure 3: *In vitro* drug release studies of microcapsules: ME1 & ME2

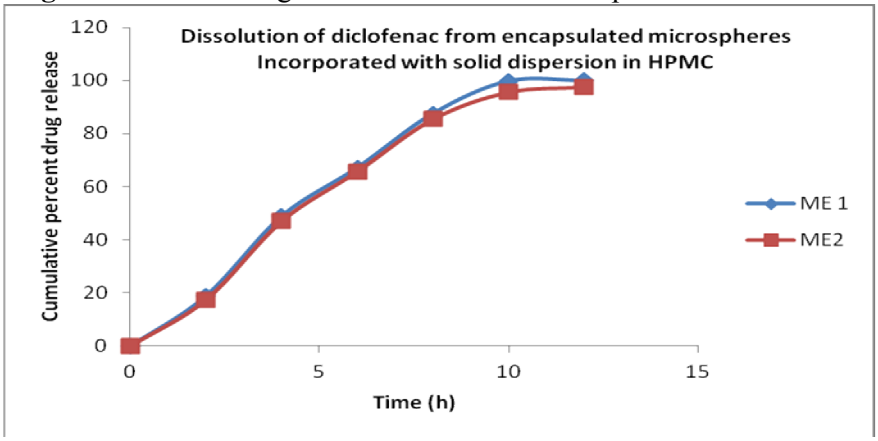


Table 9: Dissolution of diclofenac from encapsulated microspheres incorporated with solid dispersion in HPMC

TIME (h)	(CORE :COAT)	
	ME1(2:1)	ME2(1:2)
0	0	0
2	18.89	17.45
4	48.87	47015
6	67.16	65.73
8	87.54	85.43
10	99.78	95.62
12	100	100

DISCUSSION

Solid dispersions of Diclofenac in HPMC prepared by solvent evaporation method were formed to be fine and free flowing .Dissolution rate increased in Diclofenac – HPMC solid dispersion (SD3) shown in fig 1.The microspheres and its encapsulated products at different core :coat ratios (ME1-ME2) were found to be discrete free flowing and nearly spherical.

Dissolution rate studies indicate encapsulated microspheres ME1 and ME2 gave sustained action up to 10 h and 12 h respectively as shown in fig 3. When amount released was plotted against square root of time, a straight line was obtained indicating that the release may be of diffusion type. In encapsulated microspheres, the release was extended since the rate limiting step was determined by the coated membrane over the microspheres. Encapsulated microspheres were found to have slow, controlled and complete release of Diclofenac may be due to the molecular micronization that the drug undergoes which deposits on HPMC.

CONCLUSION

The encapsulated microcapsules of an egg albumin matrix reservoir type system containing solid dispersion of diclofenac with ME1 gave a maximum slow, Sustained and complete release of the drug from matrix type reservoir system over a period of 12 h. Release rate can be altered by the core: coat ratio of microspheres.

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