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FORMULATION AND EVALUATION OF ENTERIC COATED MICROSPHERES OF ATORVASTATIN CALCIUM

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Abstract: Aim of the present research work is to prepare enteric coated microspheres of Atorvastatin to bypass first pass metabolism. Morphology of microsphere permits a controllable variability in degradation and drug release. Enteric coated microspheres of Atorvastatin using Sodium alginate and HPMC K100M were successfully prepared by solvent evaporation method. The percent yield of core microspheres was found in range from 79.52-91.11% and for coated microspheres range from 85.84 to 90.21%. The entrapment efficiency was found in range of 89.83±2.69 to 94.44±0.55%. The particle size of core microspheres was found in range from 627.51±1.17 to 632.01±1.29 µm and for coated microspheres range from 871.22±0.81 to 881.95±1.80 µm.

Keywords: Enteric coated microspheres, Atorvastatin, Solvent evaporation method.

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INTRODUCTION

Microspheres can be described as small particles (in 1-1000 µm size range) for use as carriers of drugs and other therapeutic agents. The term microspheres describe a monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles. They can also be defined as a structure made up of continuous phase of one or more miscible polymers in which the particulate drug is dispersed at the macroscopic or molecular level. Microsphere based drug delivery systems have received considerable attention in recent years[1].

Advantage[2]

1. Microspheres provide constant and prolonged therapeutic effect.

2. Reduces the dosing frequency and thereby improve the patient compliance.

3. They could be injected into the body due to the spherical shape and smaller size.

4. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.

5. Microsphere morphology allows a controllable variability in degradation and drug release

Limitation of Microsphere[3]

1. The release from the formulations may get modified.

2. The release rate may vary from a variety of factors like food and the rate of transit though gut, mucin turnover rate etc.

3. Differences in the release rate can be found from one dose to another.

4. Any loss of integrity in release pattern of the dosage form may lead to potential toxicity.

5. These kinds of dosage forms cannot be crushed or chewed.

Experimental work:

Materials

Atorvastatin calcium was obtained from Heliox pharma, India. The other chemicals were obtained from authenticated manufacturer like Sodium alginate was obtained from National scientific (Guntur), Ethanol, Acetone, Methanol was obtained from Changsu yangyuan chemical, china. HPMC K100m was obtained from Cental drug house (P) Ltd, Delhi. Dichloromethane, Light paraffin liquid was obtained from Finar chemical Ltd., Ahemdabad and Eudragit RS – 100 was obtained from Evonik industries AG, Germany. All chemicals used were of analytical grade.

Formulation of microspheres:

Emulsion Solvent Evaporation Technique[4]:

Microspheres were prepared by water in oil emulsification solvent evaporation technique. Drug and polymers were dispersed in acetone and then the solution poured into 200 ml of light liquid paraffin containing 0.5% span 20 as an emulsifying agent. The aqueous phase was emulsified in oily phase by stirring the system in a 500ml beaker. Constant stirring at 500- 1000 rpm was carried out using magnetic stirrer. The beaker and its content were heated at 50ºC, stirring and heating were maintained for 4.5 hrs. The aqueous phase was evaporated. The microspheres were washed with n-hexane, separated and dried at room temperature.

Coating of microspheres[5]:

The previously formulated microspheres were dispersed in the organic phase (methanol : dichloromethane 1:4). Atorvastatin and the second polymer eudragit RS 100 were dissolved in the same organic phase. The resulting organic phase solution was emulsified in liquid paraffin. 1% span 80 solutions were used as emulsifying agent. Above emulsion was stirred at 500-1000 rpm for 4 hrs for complete evaporation of the organic solution. After complete evaporation of the organic solution the double walled microspheres were collected by vacuum filtration and washed with 3-4 times with n-hexane. The resulted double walled microspheres were freeze dried for 24 hrs.

Various core formulations using HPMC and Sod. Alginate polymer

S.No.	Formulation code	Drug (w/w)	HPMC (w/w)	Sod. alginate(w/w)
1	A1	1	1	1
2	A2	1	1	2
3	A3	1	1	3
4	A4	1	2	1
5	A5	1	2	2
6	A6	1	2	3
7	**A7**	**1**	**3**	**1**
8	A8	1	3	2
9	A9	1	3	3

Various formulations of Coated Microspheres

S.No.	Formulation code	Core to coat ratio(w/w)
1	C1	1:0.75
2	C2	1:1
3	C3	1:1.25
4	C4	1:1.50

Evaluation of entric coated microspheres:

Particle size analysis of microsphere:[6,7]

Particle size analysis of drug loaded microspheres was determined by optical microscopic method using a compound microscope. At least 100 microspheres were analyzed for each preparation and the mean particle size was determined by using Edmondson's equation

$$D \text{ mean} = \Sigma nd/\Sigma n,$$

Where n= number of microspheres observed and d= mean size range

Calculations:

Scale length of stage micrometer = 1mm =1000µ

1mm = 100 divisions = 1000µ

No. of divisions of stage micrometer = 100 divisions

100 divisions of stage micrometer = 1000µ

Therefore length of each division of stage micrometer equal to 100 divisions = 1000µ

1 division = 1000/100 = 10µ = 0.01mm

Determination of Entrapment Efficiency:[6,7]

To determine the drug entrapment efficiency or incorporation efficiency the microspheres were crushed in glass mortar and powered, then suspended in 10 ml of methanol. The percent encapsulation efficiency is calculated using following equation-

% Entrapment = (Actual content/Theoretical content) * 100

Determination of percent yield of microspheres:[8]

Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was then calculated using the formula given below-

% yield = (Mass of microspheres obtained/ Total weight of drug and polymer used) * 100

Flow properties:[8]

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method. A funnel was secured with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Microspheres were carefully poured through a funnel until the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$\theta = \tan^{-1}(h/r)$

Where, θ = angle of repose, h = height of pile, r = radius of the base of the pile.

***In vitro* release studies:** [9,10]

In vitro dissolution studies were performed using (USP type II dissolution apparatus). The rotating basket method. The microspheres were weighed and tied in the muslin bag and placed in the basket. The dissolution medium (900ml) consisted of 0.1N hydrochloric acid for the first 2 hours and then changed to phosphate buffer pH 7.4 from the 3rd hour. The temperature was maintained at 37°C. An aliquot of (1ml) sample was withdrawn at specified time interval and replaced with an equivalent volume of dissolution fluid. Drug content was determined by UV-Visible spectrophotometer at 241 nm. The release studies were conducted in triplicate.

RESULT AND DISCUSSION:

Determination of percent yield of microspheres

S.No.	Formulation code	% Production yield
1	A1	79.52
2	A2	83.16
3	A3	79.46
4	A4	84.92
5	A5	82.34
6	A6	88.45
7	A7	90.32

8	**A8**	**91.11**
9	A9	90.24
10	C1	89.74
11	**C2**	**90.21**
12	C3	86.74
13	C4	85.84

Percentage yield was found in range of 79.46% - 91.11%. The best formulation was found A8.

Determination of particle size

S.No.	Formulation code	Particle size (µm)			Average % ±SD (µm)
1	A1	629.58	626.13	627.84	627.85±1.72
2	A2	627.19	628.82	626.54	627.51±1.17
3	A3	629.79	627.51	627.24	628.18±1.40
4	A4	628.4	628.2	630.94	629.18±1.52
5	A5	629.0	630.9	628.64	629.51±1.21
6	A6	629.23	631.38	629.47	630.02±1.17
7	A7	631.2	628.96	630.12	630.09±1.12
8	A8	629.98	630.64	628.41	629.67±1.14
9	**A9**	**630.65**	**633.23**	**632.17**	**632.01±1.29**
10	C1	870.36	871.33	871.98	871.22±0.81
11	C2	876.42	877.33	875.98	876.57±0.68
12	C3	879.48	878.33	878.98	878.93±0.57
13	**C4**	**880.54**	**881.33**	**883.98**	**881.95±1.80**

Particle size was found in range of 627.85 – 881.95.

Drug content of core microspheres

S.No.	Formulation code	% drug content
1	A1	90.02±2.95
2	A2	91.25±1.79
3	A3	89.83±2.69
4	A4	90.18±2.27
5	A5	90.69±3.52
6	A6	92.99±0.72
7	**A7**	**94.44±0.55**
8	A8	93.81±0.96
9	A9	92.39±0.50

Drug content was found in range of 89.83% - 94.44%. The best formulation was found A7 with 94.44 ±0.55.

Flow properties:

Angle of repose of optimized formulation C1.

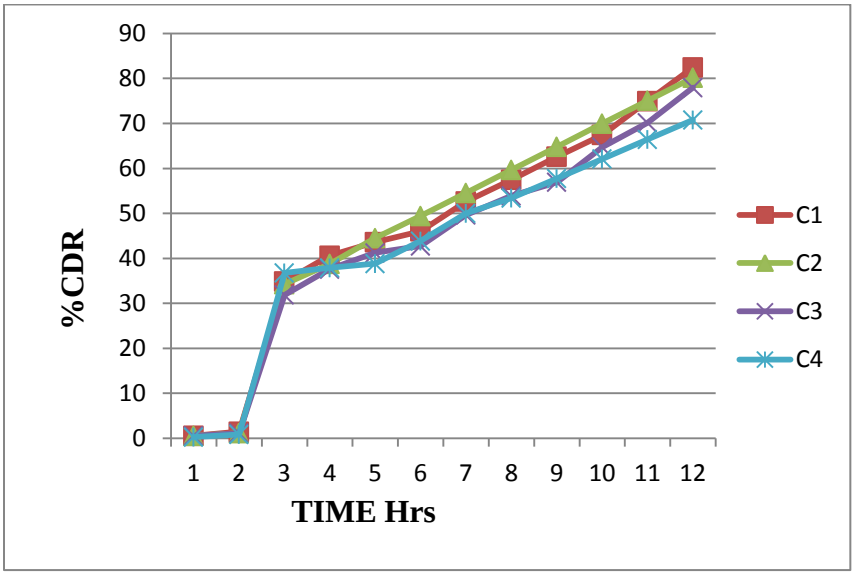
S.No.	Height of pile (cm)		Radius of the base of the pile (cm)		Angle of repose
1	h_1=0.6	Average height =0.56cm	r_1 = 0.7	Average radius =0.76cm	36^0
2	h_2=0.5		r_2= 0.8		
3	h_3=0.6		r_3 = 0.8		

Angle of repose 36^0 shows that the microspheres fell in passable range and the angle of repose greater than 40° indicate poor flow of material.

***In vitro* release studies:**

Percentage cumulative drug release.

S.No.	Time (hrs)	% CDR of coated formulations			
		C1	C2	C3	C4
1	1	0.56	0.56	0.56	0.26
2	2	1.46	1.16	1.16	0.86
3	3	34.87	34.2	31.89	36.78
4	4	40.58	38.7	37.59	37.90
5	5	43.61	44.50	41.22	38.83
6	6	46.04	49.42	42.75	43.85
7	7	52.66	54.55	49.66	50.01
8	8	57.49	59.68	53.89	53.41
9	9	62.63	64.82	56.94	57.77
10	10	67.47	69.96	64.76	62.12
11	11	74.96	75.07	70.16	66.45
12	12	82.46	80.18	77.95	70.78



Percentage cumulative drug release.

CONCLUSION:

In this present study enteric coated microspheres of Atorvastatin using Sodium alginate and HPMC K100M were successfully prepared by solvent evaporation method. On the basis of experimental results of particle size determination, percentage yield and entrapment efficiency the formulation was found upto the mark and A7 was found the best formulation on the basis of percentage yield and entrapment efficiency. A7 contents ratio of (Drug : HPMC : Sod. Alginate) 1:3:1.

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