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Formulation and optimization of mucoadhesive simvastatin microspheres from natural and synthetic polymers

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ABSTRACT

The purpose of the present investigation was the formulation and characterization of mucoadhesive sustained release microsphere of antihyperlipidemic drug simvastatin that would adhere in mucosa and release continuously to provide long term effect. There was various formulations of simvastatin were prepared by solvent evaporation technique using hydroxypropyl methylcellulose (HPMC), Carbopol, Xanthan gum, Guar gum as a polymer. The prepared mucoadhesive microspheres were evaluated for particle size, surface morphology, drug entrapment efficiency, Drug content, buoyancy percentage and In-vitro drug release, In-vitro adhesion test and stability studies. The particle was found to be discrete and spherical with the average particle size in the range of 105.54-396.6μm. As the concentration of polymers increases it affects the various evaluation parameters like particle size, in-vitro drug release and In-vitro adhesion. The Mucoadhesive microspheres of optimized formulation exhibited the prolonged release of 88.28% in continuous manner up to 8 hrs. It is concluded that the optimized formulation of simvastatin mucoadhesive microspheres can be selected for sustained drug delivery system for improved bioavailability.

Keywords: mucoadhesive microspheres, simvastatin, *In-vitro* release, HPMC, Carbopol Xanthan and Guar gum etc.

INTRODUCTION

Over the decades mucoadhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site[1].

A bioadhesive system plays a major role, because of its potential. Furthermore acting as platforms for sustained release dosage forms, bioadhesive polymers can themselves apply some control over the rate and amount of drug release and thus contribute to the therapeutic efficacy of bioadhesive drug delivery systems. Bioadhesion is an interfacial marvel in which two materials, no less than one of which is biological, are held together by means of interfacial forces. The attachment could be between an simulated material and biological substrate, for example, the adhesion between polymer and /or copolymer and a biological membrane. On account of polymer attached to the mucin layer of mucosal tissue, the term “mucoadhesion” is employed[2].

Administration of the drug via the mucosal layer is a novel method that can render treatment more effective and safe, not only for the topical diseases but also for systemic ones. These unique dosage forms, which can be applied on a thick gel like structure known as mucin, therefore all bio-adhesives must collaborate with the mucin layer during the process of attachment, these depict the potential sites for attachment of any bioadhesive system wet

tissue, are developed by utilizing the adhesive properties of some water – dissolvable polymers. The mucosal layer lines a various regions of the body including the gastrointestinal tract, buccal cavity, aviation routes, ear, nose, eye, urogenital tract, vagina and rectum are covered[3,4].

Simvastatin is the treatment of choice in moderate to severe familial or non-familial hypercholesterolemia. Simvastatin [R-(R*,R*)]-2-(4-fluorophenyl)- b,d-dihydroxy-5-(1-methyl ethyl)-3-phenyl-4-[(phenyl amino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate, is a BCS class II drug used in the treatment of hypercholesterolemia. It acts by competitive inhibition of HMG-CoA reductase. Hence it prevents the conversion of HMG-CoA to mevalonate, an early rate-limiting step in the biosynthesis of cholesterol[5].

EXPERIMENTAL SECTION

The drug simvastatin was obtained from Heliox pharma ltd. Carbopol and HPMC $K_{15}M$ and xanthan gum, guar gum were acquired from Central drug house. All other chemicals/reagents used were of analytical grade and were used as received.

A UV/Vis spectrophotometer (UV-1800/Schimadzu) was used for drug analysis.

Preparation of microspheres

Mucoadhesive microspheres of simvastatin were prepared by emulsion solvent evaporation techniques[6]. Drug and polymer were accurately weighed and mixed properly. This mixture is mixed in the solvent (Acetone) at various ratios according to table no 1. This slurry introduced into 250 ml beaker containing 40 ml of liquid paraffin in presence of 0.2% SLS solution and subsequently stirred at ranging agitation speed for 2 hours to allow the volatile solvent to evaporate. The Mucoadhesive microspheres were collected by decantation, washed 3 times with n-hexane, dried overnight in oven at 40±2°c and stored in desiccators.

Table no. 1 Batch specification of prepared mucoadesive microspheres

Code	Drug	Sodium alginate	HPMC	Guar gum	Carbopol	Xanthan gum
A1	1	1	1		1	
A2	1	1	1		2	
A3	1	1	1		3	
B1	1	1	2		1	
B2	1	1	3		1	
C1	1	1		1		1
C2	1	1		1		2
C3	1	1		1		3
D1	1	1	2			1
D2	1	1	3			1
E1	1	1	1			
E2	1	1	2			
E3	1	1	3			
F1	1	1		1		
F2	1	1		2		
F3	1	1		3		
G1	1	1			1	
G2	1	1			2	
G3	1	1			3	
H1	1	1				1
H2	1	1				2
H3	1	1				3
CF1	1	1	1	1	1	1
CF2	1	1	2	2	2	2

Characterization of mucoadhesive microspheres

Particle size analysis

The particle size was measured using an optical microscope, and the mean particle size was estimated by measuring 200 particles with the help of a calibrated ocular micrometer. A small amount of dry microspheres was suspended in purified water (10 ml). A small drop of suspension thus obtained was placed on a clean glass slide. The slide

containing microspheres was placed on the stage of the microscope and diameter of at least 100 particles was measured using a calibrated optical micrometer[7].

Drug content

The microspheres were powdered and suspended in phosphate buffer (pH 7.4) (Anand et al., 2004). The resultant dispersion was kept for 20 min on the sonicator bath for uniform mixing and filtered through whatman filter paper. The filtrate obtained was examined using a UV visible spectrophotometer at 250 nm[7,8].

Determination of incorporation efficiency

To determine the incorporation efficiency, 10 mg microspheres were thoroughly triturated and dissolved in minimum amount of methanol. The resulting solution was made up to 100 ml with 0.1 N HCl and filtered. Drug content was analyzed spectrophotometrically at 241.4 nm. The percentage incorporation efficiency and percentage drug loading were calculated using eq. 20 & 21 given below.

$$\%Drug\ loading = \frac{Calculated\ amount\ of\ drug}{Total\ weight\ of\ microspheres} \times 100$$

$$\%\ Incorporation\ efficiency = \frac{Actual\ drug\ content}{Theoritical\ content} \times 100$$

***In vitro* mucoadhesion test**

In the present study, the eggshell membrane was used to substitute the animal stomach mucosa in the mucoadhesion evaluation of microspheres, based on the similarity between the eggshell membrane and the stomach mucus with respect to its composition and thickness. The good correlation between *in vitro* data from the eggshell membrane and *in vivo* mucoadhesion studies demonstrated the potential of the eggshell membrane as substitute for the gastric mucosa.

The eggshell membranes were obtained from fresh chicken eggs. After emptying the egg of its substances , the external shell was uprooted, and the underlying membrane was isolated. A piece of egg membrane was tied on to a glass slide. Approximately 50 microspheres were spread onto the wet membrane and the prepared slide was hung on one the groves of a USP tablet disintegrating test assembly. The disintegrating test assembly was operated such that membrane specimen was given regular up and down movements in a beaker containing the simulated gastric fluid USP (pH 6.8). At the end of 1, 4 and 8h, the microspheres still adhering onto the membrane was counted[9].

***In-vitro* release of muchoadhesive microspheres**

The drug release rate from mucoadhesive microspheres was determined using USP XXIII basket type dissolution apparatus. A measured amount of mucoadhesive microspheres equivalent to 20 mg simvastatin was taken for dissolution study. Ph 7.4 buffer (900 ml) containing Tween 20 (0.02 w/v %) was used as the dissolution medium and maintained at 37^0C at a rotation speed of 100 rpm. 5 ml sample was withdrawn at 1 hr interval and analyzed spectrophotometrically at 247 nm to determine the concentration of drug present in the dissolution medium. The beginning volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal[10,11]

RESULTS AND DISCUSSION

Flow properties of mucoadhesive microspheres

the prepared microspheres of simvastatin were evaluated for different micromeritic properties such as angle of repose, bulk density, tapped density, car`s index, hausner`s ratio etc. and the results of these flow properties are shown in table no.2.

Physiochemical characteristic of mucoadhesive microspheres

The physiochemical characteristics of the prepared mucoadhesive microspheres of simvastatin are shown in table no 3. The mucoadhesive microspheres were discrete and free flowing. The mean diameter varied between 105.5-396.6µm. The yield of mucoadhesive microspheres was in the range of 81.81-93.61% which shows that the yield increased with the increased polymer concentration while drug entrapment efficiency ranged from 54.11-96.44%.

Table 2: flow properties

Formulation	Bulk density (g/ml)*	Tapped density (g/ml)*	Carr's index*	Hausner's ratio*	Angle of repose*
A1	0.68±0.030	0.80±0.035	15±1.90	1.22±0.040	30.54±1.61
A2	0.68±0.030	0.81±0.026	18.07±1.56	1.17±0.025	30.96±2.00
A3	0.68±0.030	0.83±0.015	15±1.63	1.22±0.035	23.74±1.50
B1	0.68±0.030	0.86±0.035	18.07±1.58	1.22±0.050	23.74±0.72
B2	0.66±0.035	0.81±0.035	18.51±2.24	1.14±0.026	22.29±1.46
C1	0.71±0.020	0.78±0.026	12.34±1.87	1.11±0.040	25.17±1.42
C2	0.70±0.015	0.78±0.026	10.25±2.30	1.11±0.040	25.64±1.17
C3	0.68±0.015	0.74±0.026	10.52±2.17	1.15±0.030	26.56±1.41
D1	0.69±0.026	0.76±0.035	13.75±1.61	1.19±0.025	25.17±1.88
D2	0.68±0.030	0.80±0.015	16.04±1.86	1.16±0.041	27.02±1.64
E1	0.71±0.015	0.80±0.015	14.85±1.14	1.21±0.036	29.24±2.02
E2	0.71±0.015	0.80±0.020	17.44±1.89	1.19±0.036	29.24±2.02
E3	0.68±0.026	0.83±0.030	16±1.85	1.18±0.026	28.81±2.23
F1	0.66±0.035	0.85±0.051	15.38±1.16	1.14±0.035	25.17±2.04
F2	0.68±0.036	0.86±0.050	12.82±1.68	1.15±0.030	27.47±1.36
F3	0.64±0.020	0.80±0.040	13.51±1.67	1.15±0.030	27.47±0.92
G1	0.66±0.035	0.76±0.040	13.51±1.67	1.17±0.030	22.29±1.46
G2	0.73 ±0.015	0.80±0.035	15±1.11	1.14±0.035	23.26±2.23
G3	0.70±0.015	0.76±0.055	12.5±1.25	1.12±0.025	24.70±1.64
H1	0.71±0.015	0.81±0.035	11.25±1.13	1.16±0.020	25.17±1.54
H2	0.71±0.036	0.81±0.040	14.45±1.61	1.14±0.015	24.70±2.14
H3	0.74±0.036	0.86±0.040	12.94±1.60	1.16±0.026	25.64±2.24
Cf1	0.74±0.035	0.78±0.055	13.95±1.36	1.12±0.025	26.56±0.93
Cf2	0.71±0.051	0.76±0.051	11.25±2.07	1.15±0.035	27.92±1.65

Table no. 3 Particle size, % Yield and % Entrapment efficiency

Formulation	PARTICLE SIZE	% YIELD	% ENTRAPMENT EFFICIENCY
A1	105.54±1.14	81.81±0.04	83.06±1.21
A2	208.56±0.17	85.71±0.23	72.2±1.11
A3	396.6±0.64	93.75±0.84	68.8±0.68
B1	387.6±0.58	90.42±0.73	74.5±1.29
B2	413.5±0.67	89.52±0.61	60.23±0.76
C1	330.87±1.67	85.71±0.98	96.44±2.13
C2	359.61±0.78	93.75±0.74	78.54±1.04
C3	315.54±0.54	90.29±0.63	78.76±0.96
D1	149.57±0.77	87.82±1.02	77.4±0.95
D2	251.8±0.52	91.53±0.81	64.78±0.57
E1	249.5±0.32	90.42±0.73	70.53±0.74
E2	128.54±0.32	89.52±0.61	60.23±0.76
E3	181.59±0.49	93.84±0.74	54.11±0.59
F1	217.56±0.56	87.81±1.16	79.31±1.08
F2	208.95±0.67	85.71±0.98	79.06±1.14
F3	396.6±0.64	93.75±0.74	80.46±1.41
G1	387.6±0.58	85.71±0.98	85.71±1.54
G2	413.5±0.67	93.75±0.74	79.43±0.61
G3	210.6±0.52	88.29±0.63	74.5±1.29
H1	128.54±0.32	88.75±0.83	60.23±0.76
H2	181.59±0.49	93.61±0.84	54.11±0.59
H3	208.56±0.17	88.69±0.93	79.31±1.08
Cf1	396.6±0.64	92.69±0.63	79.06±1.14

***In vitro* drug release**

The drug release study from the prepared mucoadhesive microspheres was performed using USP type-II apparatus (rotating paddle) in 900 ml of 7.4 buffer dissolution media at 100 RPM at 37±0.5°C for 8 hours. The *in—vitro* release data of all the formulation of mucoadhesive microspheres are tabulated in table no.4

Table no. 4 Cumulative drug release profile

Formulation	% CDR 8 HRS
A1	79.3±1.03
A2	85.18±1.42
A3	82.86±1.59
B1	78.8±1.41
B2	82.6±1.39
C1	82.94±1.25
C2	85.27±1.18
C3	88.28±1.11
D1	81.3±1.12
D2	83.66±1.03
E1	85.03±1.15
E2	84.81±1.39
E3	85.75±1.25
F1	85.93±1.30
F2	84.76±1.41
F3	85.36±1.39
G1	85.24±1.25
G2	85.93±1.18
G3	86.46±1.11
H1	85.62±1.12
H2	85.47±1.03
H3	80.58±1.15
Cf1	82.4±1.39
Cf2	85.46±1.25

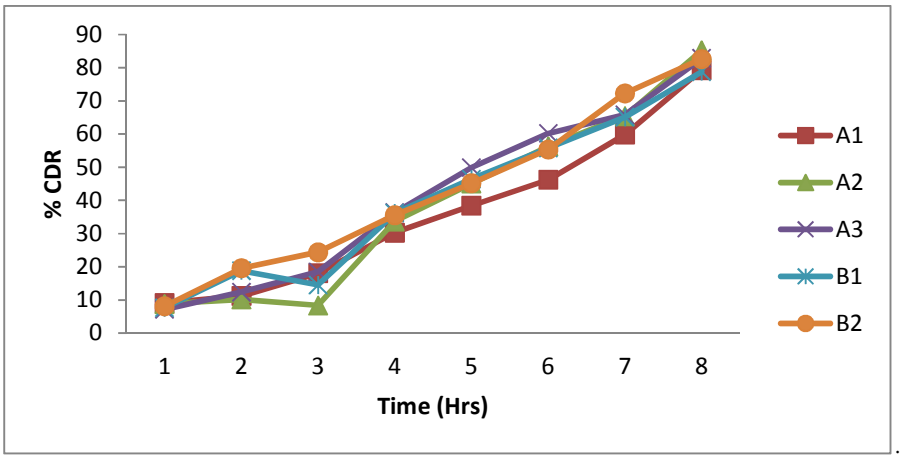

Figure 1: Comparative release profile of formulation

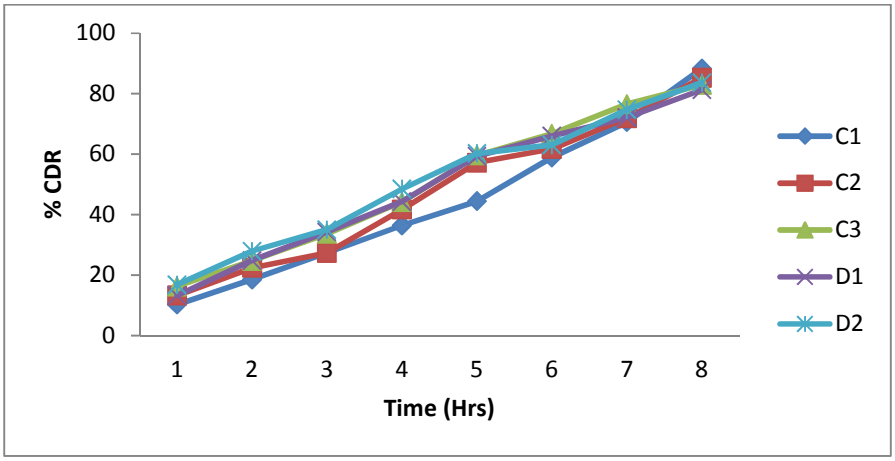

Figure 2: Comparative release profile of formulation

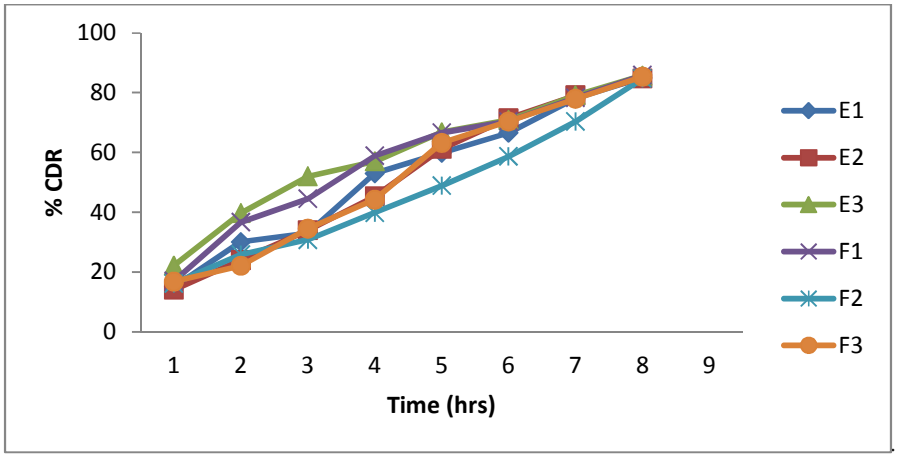

Figure 3: Comparative release profile of formulation

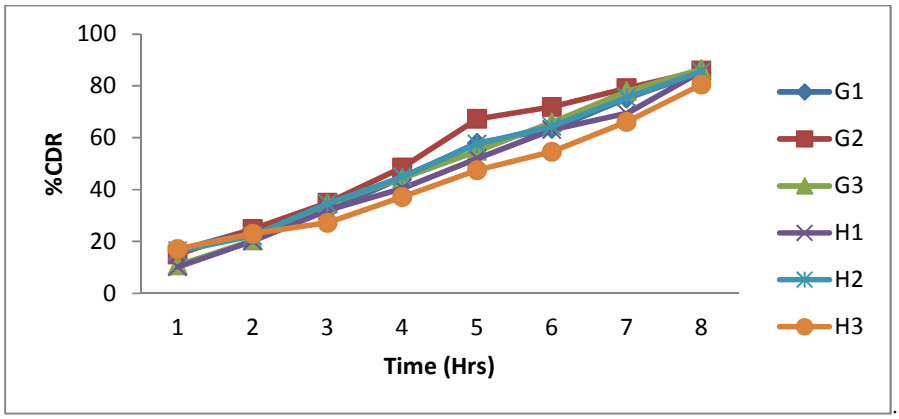

Figure 4: Comparative release profile of formulation

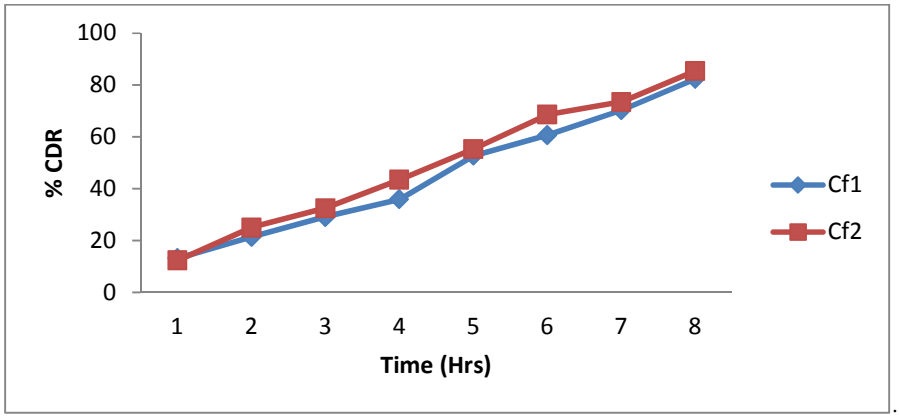

Figure 5: Comparative release profile of formulation

Mucoadhesion test

Table no. 5 - *In vitro* mucoadhesion test

S.No.	Time (Hr)	No. of microsphere adhere			% Mucodhesion		
		A1	C1	CF2	A1	C1	CF2
1	0	50	50	50	100	100	100
2	4	35	40	45	70	80	90
3	8	4	7	7	8	14	14

The table shows that some of microspheres were adhere to the membrane even after 8hrs. The highest percentage mucoadhesion was found 14% in formulation

Drug release kinetics study

It was found that drug release rate fluctuated by changing the ratio of polymers in the formulation. Kinetics and mechanism of drug release from all formulations was evaluated on the basis of zero order, first order, higuchi equation and kesmeyer peppas model.

formulation	Zero order		First order		Higuchi		Korsmeyer peppas	
	R^2	K_0(-) (1/S)	R^2	K_1(-) M/L.S	R^2	K_H	R^2	N
A1	0.959	9.845	0.034	0.096	0.959	26.37	0.846	0.232
A2	0.945	11.5	0.041	0.106	0.945	30.12	0.849	0.276
A3	0.982	11.13	0.077	0.143	0.982	29.29	0.841	0.267
B1	0.968	10.28	0.041	0.104	0.968	26.1	0.761	0.256
B2	0.986	10.56	0.04	0.103	0.986	29.2	0.767	0.296
C1	0.990	10.37	0.03	0.084	0.991	29.33	0.788	0.302
C2	0.988	10.36	0.032	0.090	0.988	30.29	0.776	0.335
C3	0.992	10.44	0.043	0.104	0.995	29.31	0.724	0.331
D1	0.989	9.796	0.037	0.094	0.989	28.76	0.680	0.318
D2	0.991	9.497	0.028	0.081	0.991	29.58	0.692	0.348
E1	0.962	9.963	0.019	0.069	0.962	30.07	0.655	0.351
E2	0.988	10.7	0.028	0.081	0.988	29.99	0.647	0.328
E3	0.962	8.433	0.022	0.074	0.962	30.32	0.703	0.388
F1	0.96	9.237	0.044	0.106	0.96	30.39	0.565	0.327
F2	0.985	9.461	0.019	0.069	0.985	29.97	0.642	0.360
F3	0.983	10.54	0.030	0.085	0.983	30.18	0.675	0.339
G1	0.994	10.01	0.044	0.106	0.994	30.14	0.691	0.35
G2	0.976	10.68	0.019	0.069	0.976	30.39	0.651	0.337
G3	0.998	10.96	0.032	0.09	0.998	30.5	0.692	0.324
H1	0.995	10.45	0.027	0.083	0.995	30.28	0.741	0.323
H2	0.996	10.15	0.066	0.129	0.996	30.22	0.689	0.35
H3	0.978	8.956	0.044	0.106	0.978	28.49	0.680	0.343
CF1	0.990	9.999	0.027	0.083	0.99	29.14	0.726	0.327
CF2	0.995	10.40	0.024	0.76	0.995	30.24	0.711	0.335

CONCLUSION

In the above study the mucoadhesive microspheres of simvastatin were prepared by emulsion solvent evaporation technique by using natural and natural polymers. it showed a high percentage of mucoadhesion and entrapment efficiency. The optimized formulation(C1) of simvastatin mucoadhesive microsphere prepared by natural polymer showed maximum drug release than the synthetic polymers and followed Higuchi release. Other evaluation parameters for natural polymer based mucoadhesive microsphere are higher than the synthetic.

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