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Review Article

Formulation and Evaluation of Mucoadhesive Acarbose Microspheres

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Abstract

The purpose of the present investigation was the formulation and characterization of mucoadhesive sustained release microsphere of antidiabetic drug Acarbose that would adhere in mucosa and release continuously to provide long term effect. There was various formulations of Acarbose were prepared by solvent evaporation technique using hydroxypropyl methylcellulose (HPMC), Sodium Alginate, Carbopol, Xanthan gum, Guar gum as a polymer. The prepared mucoadhesive microspheres were evaluated for particle size, surface morphology, drug entrapment efficiency, Drug content 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 105.5 to 413.5 micrometer. 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 85.8% in continuous manner up to 12 hrs. It is concluded that the optimized formulation of Acarbose mucoadhesive microspheres can be selected for sustained drug delivery system for improved bioavailability.

Keywords: Mucoadhesive microspheres; Acarbose; Ethyl cellulose (EC); *In-vitro* release; Xanthan; Guar gum

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, due to its potential. Besides acting as platforms for sustained release dosage forms, bioadhesive polymers can

themselves exert 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 phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as the adhesion between polymer and/or copolymer and a biological membrane. In the case 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 tropical diseases but also for systemic ones. These unique dosage forms, which

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can be applied on a thick gel like structure known as mucin, therefore all bio-adhesives must interact with the mucin layer during the process of attachment, these represent the potential sites for attachment of any bioadhesive system wet tissue, are formulated by utilizing the adhesive properties of some water - soluble polymers. The mucosal layer lines a number of regions of the body including the gastrointestinal tract, buccal cavity, airways, ear, nose, eye, urogenital tract, vagina and rectum are covered [3].

Acarbose is an oral α -glucosidase inhibitor and used in the management of type II diabetes mellitus. Acarbose inhibits enzymes glycoside hydrolases needed to digest carbohydrates, specifically, α -glucosidase enzyme in the brush border of the small intestines and pancreatic α -amylase. Pancreatic α -amylase hydrolyzes complex starch to oligosaccharides in the lumen of the small intestine, whereas the membrane-bound intestinal α -glucosidases hydrolyze oligosaccharides, disaccharides and trisaccharides to glucose and other monosaccharides in the small intestine. Inhibition of these enzymes systems reduces the rate of digestion of complex carbohydrates [4].

Materials and Methods

The drug Acarbose was obtained from Amol Pharmaceutical Pvt. Ltd. Ethyl cellulose and HPMC K15M and xanthan gum, guar gums were obtained from Central drug house. All other chemicals/reagents used were of analytical grade and were used as received. A UV/Vis spectrophotometer (UV-1800/Schimidzu) was used for drug analysis.

Preparation of microspheres

Mucoadhesive microspheres of Acarbose were prepared by emulsion solvent evaporation techniques. Drug and polymer were accurately weighed and mixed properly. This mixture is mixed in the solvent (DCM: Methanol: 1:1) at various ratios according to Table 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 1 hr to allow the volatile solvent to evaporate. The floating microspheres were collected by decantation,

washed thrice with n-hexane, dried overnight in oven at $40 \pm 2^\circ\text{C}$ and stored in desiccators [5].

Characterization of mucoadhesive microspheres

Particle size analysis: The particle size was measured using an optical microscope, and the mean particle size was calculated 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 mounted on the stage of the microscope and diameter of at least 100 particles was measured using a calibrated optical micrometer.

Drug content

The microspheres were powdered and suspended in phosphate buffer (pH 7.4). 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 [6].

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 [7].

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

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

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

Table 1: Batch specification of prepared mucoadhesive microspheres.

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

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 content, the external shell was removed, 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 grooves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus 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, 5 and 10 h, the microspheres still adhering onto the membrane was counted [8].

microspheres

The drug release rate from mucoadhesive microspheres was determined using USP XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 20 mg Prazosin Hydrochloride was taken for dissolution study. Simulated gastric fluid (SGF, pH 0.1 N HCl) (900 ml) containing Tween 20 (0.02 w/v%) was used as the dissolution medium and maintained at 37°C 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 initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal [9].

In vitro release of mucoadhesive

Table 2: Flow properties.

Formulation Code	Bulk density (g/ml)*	Tapped density (g/ml)*	Carr's index*	Hausner's ratio*	Angle of repose*
A1	0.66 ± 0.020	0.80 ± 0.035	17.5 ± 1.63	1.21 ± 0.035	30.11 ± 1.11
A2	0.68 ± 0.030	0.80 ± 0.035	15 ± 1.90	1.17 ± 0.025	27.47 ± 1.76
A3	0.68 ± 0.030	0.83 ± 0.030	18.07 ± 1.56	1.22 ± 0.040	30.54 ± 1.13
B1	0.68 ± 0.030	0.80 ± 0.020	15 ± 1.63	1.17 ± 0.025	29.68 ± 1.60
B2	0.68 ± 0.030	0.83 ± 0.030	18.07 ± 1.58	1.22 ± 0.035	30.54 ± 1.61
C1	0.66 ± 0.035	0.81 ± 0.030	18.51 ± 2.24	1.22 ± 0.050	30.96 ± 2.00
C2	0.71 ± 0.020	0.81 ± 0.015	12.34 ± 1.87	1.14 ± 0.026	23.74 ± 1.50
C3	0.70 ± 0.015	0.78 ± 0.025	10.25 ± 2.30	1.11 ± 0.040	23.74 ± 0.72
D1	0.68 ± 0.015	0.76 ± 0.036	10.52 ± 2.17	1.11 ± 0.040	22.29 ± 1.46
D2	0.69 ± 0.026	0.80 ± 0.035	13.75 ± 1.61	1.15 ± 0.030	25.17 ± 1.42
E1	0.68 ± 0.030	0.81 ± 0.026	16.04 ± 1.86	1.19 ± 0.025	25.64 ± 1.17
E2	0.71 ± 0.015	0.83 ± 0.015	14.85 ± 1.14	1.16 ± 0.041	26.56 ± 1.41
E3	0.71 ± 0.015	0.86 ± 0.035	17.44 ± 1.89	1.21 ± 0.036	25.17 ± 1.88
F1	0.68 ± 0.026	0.81 ± 0.035	16 ± 1.85	1.19 ± 0.036	27.02 ± 1.64
F2	0.66 ± 0.035	0.78 ± 0.026	15.38 ± 1.16	1.18 ± 0.026	29.24 ± 2.02
F3	0.68 ± 0.036	0.78 ± 0.026	12.82 ± 1.68	1.14 ± 0.035	29.24 ± 2.02
G1	0.64 ± 0.020	0.74 ± 0.026	13.51 ± 1.67	1.15 ± 0.030	28.81 ± 2.23
G2	0.66 ± 0.035	0.76 ± 0.035	13.51 ± 1.67	1.15 ± 0.030	25.17 ± 2.04
G3	0.68 ± 0.015	0.80 ± 0.015	15 ± 1.11	1.17 ± 0.030	27.47 ± 1.36
H1	0.70 ± 0.015	0.80 ± 0.015	12.5 ± 1.25	1.14 ± 0.035	27.47 ± 0.92
H2	0.71 ± 0.015	0.80 ± 0.020	11.25 ± 1.13	1.12 ± 0.025	22.29 ± 1.46
H3	0.71 ± 0.036	0.83 ± 0.030	14.45 ± 1.61	1.16 ± 0.020	23.26 ± 2.23

*All the values are expressed as ± standard deviation

Results

Flow properties of Acarbose mucoadhesive microspheres

The prepared microspheres of Acarbose 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 2.

Physiochemical characteristic of mucoadhesive microspheres

The physiochemical characteristics of the prepared mucoadhesive microspheres of Acarbose are shown in Table 3. The mucoadhesive microspheres were discrete and free flowing. The mean diameter varied between 105.5 to 413.5 µm. The yield of mucoadhesive microspheres was in the range of 63.5 to 83.2% which shows that the yield increased with the increased polymer concentration while drug entrapment efficiency

ranged from 64.8 to 96.44%.

In vitro drug release

The drug release study from the prepared floating microspheres was performed using USP type-II apparatus (rotating paddle) in 900 ml of 0.1 N HCl dissolution media at 100 RPM at 37 ± 0.5°C for 12 hours. The *in vitro* release data of all the formulation of floating microspheres are tabulated in Tables 4-7.

In vitro mucoadhesion test

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

Conclusion

In the above study the mucoadhesive microspheres of Acarbose were prepared by emulsion solvent

Table 3: Physiochemical Properties of mucoadhesive microsphere.

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	96.44 ± 2.13
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	219.87 ± 1.67	85.71 ± 0.98	78.76 ± 0.96
C2	359.61 ± 0.78	93.75 ± 0.74	72.22 ± 0.79
C3	131.54 ± 0.54	88.29 ± 0.63	78.54 ± 1.04
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

*All the values are expressed as ± standard deviation

Table 4: *In vitro* drug release profile.

TIME (hr)	A1	A2	A3	B1	B2	C1
1	10.41	8.4	12.45	9.48	10.6	13.6
2	16.41	18.3	17.18	18.25	20.65	17.28
3	19.85	24.28	23.21	20.65	22.63	20.48
4	27.18	22.61	23.58	24.28	26.35	30.91
5	30.83	26.61	31.5	30.0	33.21	33.66
6	40.83	39.8	40.55	38.75	39.76	40.56
7	47.91	49.49	47.81	40.96	54.76	48.45
8	58.31	57.31	57.98	56.28	60.3	53.65

Table 5: *In vitro* drug release profile.

TIME (hr)	C2	C3	D1	D2	E1	E2
1	15.68	13.95	23.63	15.5	9.0	22.15
2	16.29	18.76	26.68	16.5	15.68	20.2
3	15.98	27.13	31.57	30.33	30.8	29.65
4	20.2	32.35	28.81	24.63	28.87	30.16
5	22.75	34.68	33.01	30.16	34.68	34.68
6	30.92	39.39	39.92	32.51	40.73	35.73
7	38.61	48.25	43.07	39.03	46.75	42.23
8	44.04	51.3	49.17	43.73	55.8	52.78

Table 6: *In vitro* drug release profile.

Time(hr)	E3	F1	F2	F3	G1	G2
1	11.75	10.65	12.18	16.56	13.81	12.18
2	14.31	15.16	16.41	19.86	15.76	21.8
3	19.65	20.63	24.68	23.41	20.5	23.68
4	21.41	24.6	22.6	31.57	29.11	31.08
5	30.96	29.43	30.35	33.16	41.55	39.4
6	35.75	33.98	35.65	35.9	43.98	45.1
7	42.3	40.48	43.03	42.8	48.7	49.81
8	55.36	51.41	53.6	52.86	56.03	56.9

Table 7: *In vitro* drug release profile.

Time(hr)	G3	H1	H2	H3
1	11.75	10.65	12.18	16.56
2	21.41	24.6	22.6	31.57
5	22.75	34.68	33.01	30.16
6	30.92	39.39	39.92	32.51
4	21.41	24.6	22.6	31.57
5	30.96	29.43	30.35	33.16
3	19.85	24.28	23.21	20.65
4	27.18	22.61	23.58	24.28

Table 8: *In vitro* mucoadhesion drug profile.

S.No.	Time (Hr)	No. of microsphere adhere			% Mucodhesion		
		A1	C2	CF2	A1	C2	CF2
1	0	50	50	50	100	100	100
2	4	35	32	45	70	64	90
3	8	4	2	7	8	4	14

evaporation technique by using natural and natural polymers. It showed a high percentage of mucoadhesion and entrapment efficiency. The optimized formulation (C1) of Acarbose 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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Table 9: Drug release kinetics profile.

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	0.831	6.832	0.120	0.124	0.856	22.56	0.890	0.67
A2	0.903	7.279	0.075	0.099	0.913	24.14	0.877	0.63
A3	0.928	6.494	0.142	0.140	0.895	20.97	0.927	0.70
B1	0.885	6.717	0.120	0.124	0.910	22.57	0.868	0.64
B2	0.907	7.720	0.022	0.052	0.935	26.24	0.842	0.58
C1	0.915	5.933	0.176	0.158	0.896	19.39	0.918	0.71
C2	0.970	5.120	0.120	0.177	0.887	17.79	0.936	0.72
C3	0.984	4.445	0.237	0.191	0.908	16.23	0.878	0.71
D1	0.978	4.397	0.247	0.195	0.911	14.66	0.945	0.79
D2	0.974	4.840	0.214	0.181	0.876	17.79	0.886	0.69
E1	0.980	4.938	0.215	0.179	0.922	17.80	0.877	0.70
E2	0.993	3.902	0.261	0.202	0.903	13.08	0.957	0.82
E3	0.977	5.333	0.189	0.168	0.897	19.36	0.885	0.67
F1	0.974	4.841	0.214	0.181	0.875	17.79	0.886	0.69
F2	0.980	4.628	0.231	0.188	0.876	16.21	0.948	0.74
F3	0.962	5.634	0.185	0.161	0.964	16.20	0.837	0.67
G1	0.996	5.005	0.211	0.179	0.906	17.79	0.894	0.70
G2	0.992	5.254	0.202	0.177	0.851	17.77	0.976	0.72
G3	0.992	5.254	0.202	0.177	0.851	17.77	0.976	0.72
H1	0.960	3.178	0.285	0.216	0.794	10.97	0.937	0.85
H2	1.000	2.718	0.300	0.223	0.906	9.42	0.953	0.90
H3	0.995	5.225	0.204	0.175	0.920	17.80	0.901	0.71

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