www.ijrps.pharmascope.org

ISSN: 0975-7538
Research Article

Preparation and evaluation of mucoadhesive microcapsules of Nimodipne

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ABSTRACT

Mucoadhesive drug delivery systems are delivery systems which utilized the property of bioadhesion of certain polymers which become adhesive on hydration. Nimodipine is an effective calcium channel blocker, used in the treatment of subarachnoid hemorrhage, migraine and angina. It has short biological half life of 1-2hrs, and eliminated rapidly and its activity lost only a few hours. Therefore, sustained release is needed for Nimodipine to give a prolonged action and reduction of usage frequency. Microcapsules of Nimodipine employing various Mucoadhesive polymers like Hydropropyl Methyl Cellulose, Methyl Cellulose, Carbopol 934, Sodium Carboxy Methyl Cellulose and Sodium Alginate. Data of *in-vitro* release from microcapsules were fit to different equations and kinetic models to explain release profiles. Kinetic models used were zero and first-order equations, Higuchi, and Korsmeyer-Peppas models. The correlation coefficient value (r) indicates the kinetic of drug release was zero order. The formulation was found to be right and suitable candidate for the formulation of Mucoadhesive microcapsules of Nimodipine for therapeutic use.

Keywords: Nimodipine; mucoadhesive micro capsule; *in vitro* release studies; zero order.

INTRODUCTION

Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs. Over the last two decades mucoadhesion becomes of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (with in gastro intestinal tract) or systemic delivery (Smart JD et al., 2005), by retaining a formulation in intimate contact with absorption site. Mucoadhesion may be defined as a state in which two materials, one of which mucus or a mucous membrane, is held together for extended period of time[1]. The mucosa is relatively permeable with a rich blood supply. The oral transmucosal drug delivery bypasses liver and avoids presystemic elimination in the gastro intestinal tract and liver (IJM 2004). These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. During the last two and half decades an extensive research work has been carried out on mucoadhesive drug delivery systems for various routes of drug administration. As such mucoadhesive dosage forms are developed for other routes of drug administration such as buccal, nasal and vaginal routes which avoid the disadvantages of oral route. The bioavailability and duration of action of drugs administered by these routes are increased by use of the principle of mucoadhesion. Nimodipine is well absorbed upon oral administration. Peak blood levels occur in about one hour and protein binding is over 95 %. Nimodipine is eliminated bin urine (less than 1 % unchanged.) Elimination of metabolites is less effective than parent compound. The present investigation highlights the formulation and evaluation of mucoadhesive microcapsules of Nimodipine. The Microcapsules of Nimodipine with a coat consisting of Sodium Alginate and Mucoadhesive polymers namely sodium CMC, methylcellulose, HPMC and Carbopol in 1:1 and 1:2 ratios were prepared by the Orifice-ionic gelation process.

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Received on: 15-03-2010
Revised on: 16-03-2010
Accepted on: 24-04-2010

MATERIALS AND METHODS

Nimodipine was procured from Micro Labs Ltd., Bangalore India. Sodium Carboxy Methyl Cellulose (Ainely et al., 1994)′ Sodium Alginate (Ainely et al., 1994)′ Hydropropyl Methyl Cellulose(Chien Y.W et al., 1991), Methyl Cellulose(Udupa et al., 1995) and (Colorncon Asia Pvt ltd, Goa, India), Carbopol-934 and Calcium Chloride (Karnataka fine chem. industries, Bangalore, India). All other chemicals were of analytical grade and procured from S.D fine chemicals, Mumbai, India. The Concentrations of Nimodipine were measured with UV-VIS Spectrometer Labomed, Inc, USA. (Model No: 2602).

Orifice-Ionic gelation process (syringe Method)

Orifice-ionic gelation process (Kondo., 1979, Kim CK et al., 1992, Hari PC et al., 1996), is also been successfully used to prepare large sized alginate beads. In this method Microcapsules are prepared by employing sodium

Table 1: Preparation of mucoadhesive Microcapsules

S.No	Ingredients	Quantity used in Formulations (gms)							
		MH1	MH2	MS1	MS2	MC1	MC2	MM1	MM2
1	Nimodipine	2	1	2	1	2	1	2	1
2	HPMC	1	1	-	-	-	-	-	-
3	SCMC	-	-	1	1	-	-	-	-
4	Carbopol-934	-	-	-	-	1	1	-	-
5	Methyl Cellulose	-	-	-	-	-	-	1	1
6	Sod. Alginate	1	1	1	1	1	1	1	1
7	Total Weight	4	3	4	3	4	3	4	3
8	Drug: Polymer	1:1	1:2	1:1	1:2	1:1	1:2	1:1	1:2

Table 2: Assay of Prepared Micro Capsules

Sl. No	Formulations	D/P ratio	% drug content	% drug entrapment
1	MH1	1:1	34.79	51.18
2	MH2	1:2	26.57	56.92
3	MS1	1:1	33.02	64.89
4	MS2	1:2	21.86	62.82
5	MC1	1:1	38.49	76.44
6	MC2	1:2	24.93	66.18
7	MM1	1:1	37.43	72.25
8	MM2	1:2	25.01	67.82

Table 3: Sieve Analysis of Micro Capsules

Sl. No	Sieve No	Size range (μm)	Formulation (% weight retained)							
			MH1	MH2	*MS1*	MS2	MC1	MC2	MM1	MM2
1	Below 36	425	6.96	7.74	4.31	7.92	6.54	5.84	5.74	7.55
2	25/36	425-600	61.46	53.42	57.96	48.47	63.53	59.72	55.53	53.24
3	16/25	600-1000	22.46	28.34	27.24	33.23	18.82	23.54	20.03	22.15
4	Above 16	1000	9.11s	10.40	10.49	10.38	11.10	10.80	18.70	13.16

Table 4: Micro Encapsulation Efficiency of Micro Capsules

Sl. No	Formulations	Weight taken (mg)	Theoretical drug content (mg)	Practical drug content (mg±SD)*	Encapsulation efficiency (%)	Weight of micro capsules equivalent to 15 mg of drug (mg)
1	MH1	100	50	34.79	69.58	21.5
2	MH2	100	33.3	26.57	79.78	18.79
3	MS1	100	50	33.02	66.04	22.71
4	MS2	100	33.3	21.86	65.64	22.84
5	MC1	100	50	38.49	76.98	19.48
6	MC2	100	33.3	24.93	74.86	20.03
7	MM1	100	50	37.43	74.86	20.03
8	MM2	100	33.3	25.01	75.10	19.97

alginate in combination with different polymers like sodium CMC, Methylcellulose, Carbopol and HPMC as coat materials. Sodium alginate and the mucoadhesive polymer are dissolved in purified water to form a homogenous polymer solution. Core material (drug) is added to the polymer solution and mixed thoroughly to form a smooth viscous dispersion. The resulting dispersion is then added drop wise into sufficient quantity of calcium chloride (10% w/v) solution through a syringe with a needle of size No. 18. The added droplets are retained in the calcium chloride solution for 15 to 20 min. to complete the curing reaction and to produce spherical rigid microcapsules. The microcapsules are collected by decantation and the product thus separated is washed repeatedly with water and dried at 45^{o}C for 12 hrs.Mucoadhesive Microcapsules of Nimodipine were prepared employing Sodium Alginate in combination with Sodium Carboxy Methyl Cellulose (sodium CMC), Methyl Cellulose, Carbopol and Hydroxy Propyl Methyl Cellulose (HPMC) as coat materials as per the formulae given in Table 1.

Table 5: Comparative Drug release study of Micro capsules

Time (hrs.)	Cumulative % Drug remained							
	MH1	MH2	MS1	MS2	MC1	MC2	MM1	MM2
0.3	76.97	80.97	76.54	74.92	72.61	79.42	81.01	82.78
1	70.19	76.8	70.45	67.96	65.53	74.29	77.47	79.77
2	64.31	69.57	65.89	61.8	58.44	67.21	73.89	76.54
3	58.56	62.37	54.99	54	51.34	61.08	67.12	69.93
4	52.59	57.19	52.18	46.84	44.26	54.79	60.49	63.3
5	46.71	50.59	46.03	42	39.21	47.26	53.76	58.93
6	42.8	44.71	38.17	38.94	35.86	44.2	47.08	53.23
7	34.91	38.59	33.91	34.83	31.81	36.51	44.38	49.39
8	29.5	34.36	27.82	31.87	27.82	31.33	41.8	44.29
9	23.15	27.16	25.89	28.81	25.83	28.98	35.94	39
10	18.27	22.17	20.89	23.95	21.25	24.4	30.84	34.9

Estimation of Nimodipine content of the microcapsules

Nimodipine content in the microcapsules (Chowdary K.P.R.et al., 2003) was estimated by UV spectrophotometric method based on the measurement of absorbance at 317 nm in methanol. The results of drug content are presented in Table 2.

Evaluation of microcapsules

Size Distribution Analysis: Different sizes (Chowdary K.P.R et al., 2003) in a batch were separated by sieving using a range of standard sieves. The amounts retained on different sieves were weighed and results are depicted in Table 3.

Micro Encapsulation Efficiency: It was calculated using the formula, (Manvi F.V. et al., 2004) micro encapsulation efficiency = (estimated percent drug content/theoretical percent drug content) x 100. The results are presented in Table 4.

Drug release study: Release of Nimodipine (Potal R.K. et al., 2004, Syed A. Mortazavi et al., 2003) form microcapsules of size 16/25, and 25/36 was studied in Acetate buffer of pH 4.5 (900 ml) using USP XXIV six-station Dissolution Rate Test Apparatus with a basket stirrer at 100 rpm. A sample of microcapsules equivalent to 60 mg of Nimodipine was used in each test. Samples were withdrawn through a filter at different intervals and were assayed at 317 nm for Nimodipine using a Shimadzu UV-150 double-beam spectrophotometer. The drug release experiments were conducted in triplicate. The comparative studies of results are presented in Table 5.

***In-Vitro* wash-off test for Mucoadhesive Microcapsules**

The mucoadhesive property of the microcapsules was evaluated (Edith M.et al., 1999, Guo JH et al., 1994) by an *in vitro* adhesion testing method known as wash-off method. A piece of intestinal mucous (2x2 cm) was mounted on to glass slides of (3x1 inch) with Cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread on to each wet tissue specimen and there after the support was hung on to the arm of a USP tablet disintegrating test machine. The disintegration machine containing tissue specimen was adjusted at slow, regular up and down moment in a test fluid at 37 ^{o}C taken in a beaker. AT the end of 30 min., 1 hr and later at hourly intervals up to 6 hrs, the machine was stopped and the number of microcapsules still adhering on to the tissue was counted. The test was performed in acetate buffer of pH 4.5. The results are given Table 6.

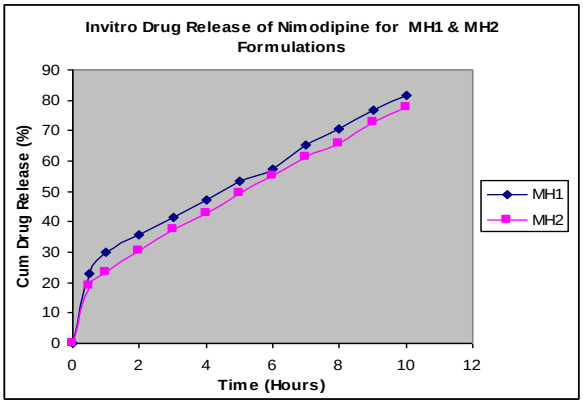

Figure 1: In-Vitro Drug Release of Nimodipine for MH1 & MH2 Formulations

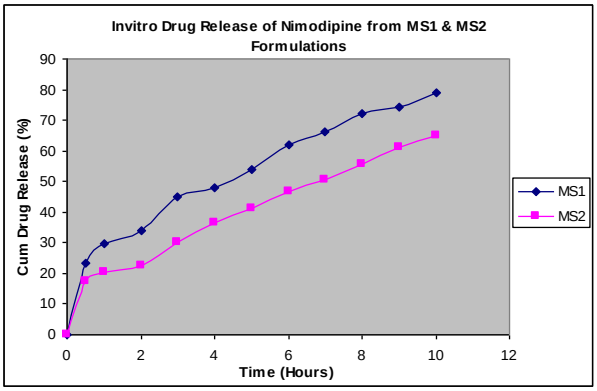

Figure 2: In-Vitro Drug Release of Nimodipine for MS1 & MS2 Formulations

RESULTS AND DISCUSSION

Mucoadhesive micro capsules of Nimodipine were prepared by the orifice-ionic gelatin process. The formulae of Mucoadhesive Microcapsules are given in Table: 1. Microcapsules of Nimodipine with a coat consisting of Sodium Alginate and Mucoadhesive polymers namely sodium CMC, methylcellulose, HPMC and Carbopol in 1:1 and 1:2 ratio. Good linearity was observed with the plot. It's 'r' value is 0.9953 and hence, obeyed Beer-Lambert's law in the concentration range of 5 – 30 μg/ml. The percentage of drug content in Microcapsules was found to be 21.86 (SCMC) – 38.49 % (Carbopol) and drug entrapment was found to be 51.18 (HPMC) – 76.44 % (Carbopol).The entrapment efficiency of drug was gradually decreased in the order of Carbopol <MC<SCMC<HPMC. The results of the drug content uniformity in each of Microcapsules are presented in Table: 2. The IR spectra of the pure drug and Mucoadhesive Microcapsules were shown in Charts. The characteristic peak (N-H=3298.28 cm^{-1}) Mucoadhesive Microcapsules in the spectra was found to be super imposable to that of pure drug and there are no extra

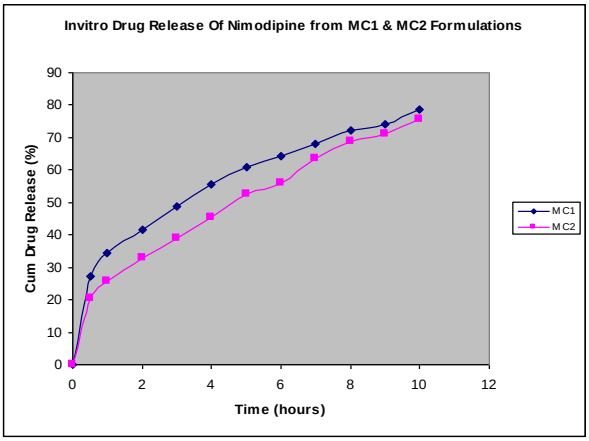

Figure 3: In-Vitro Drug Release of Nimodipine for MC1 & MC2 Formulations

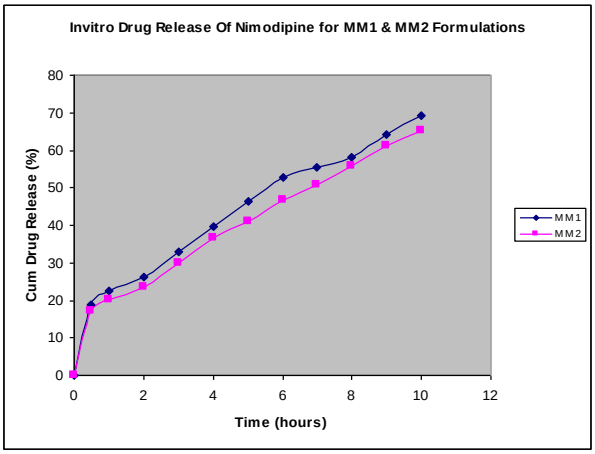

Figure 4: In-Vitro Drug Release of Nimodipine for MM1 & MM2 Formulations

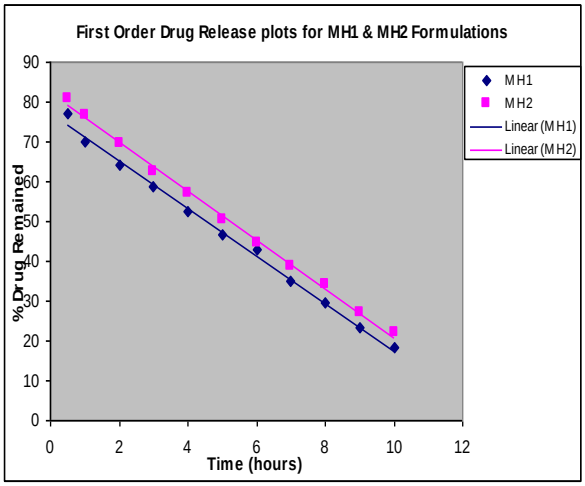

Figure 5: First Order Drug Release Plots for MH1 & MH2 Formulations

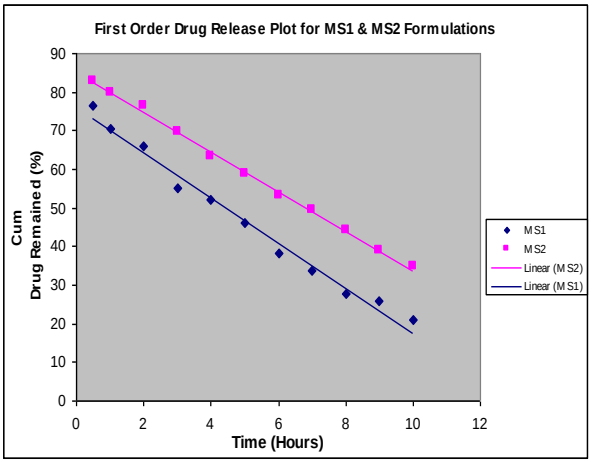

Figure 6: First Order Drug Release Plots for MS1 & MS2 Formulations

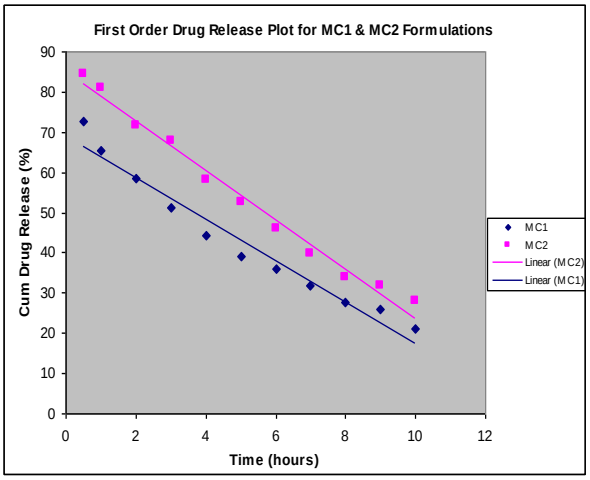

Figure 7: First Order Drug Release Plots for MC1 & MC2 Formulations

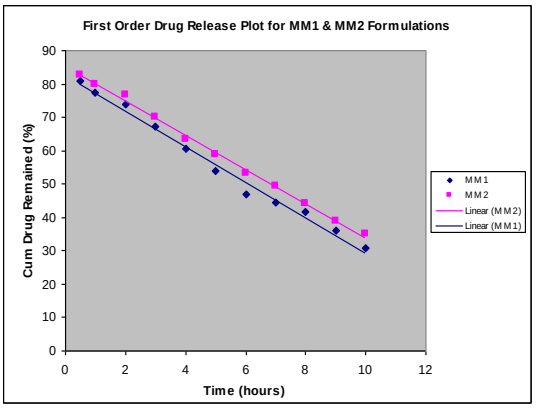

Figure 8: First Order Drug Release Plots for MM1 & MM2 Formulations

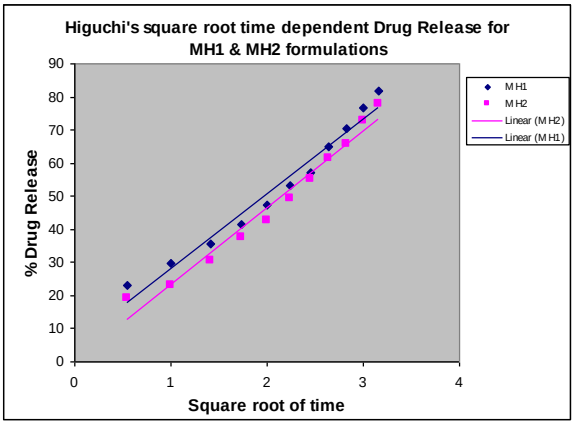

Figure 9: Higuchi's plots of MH1 & MH2 formulations

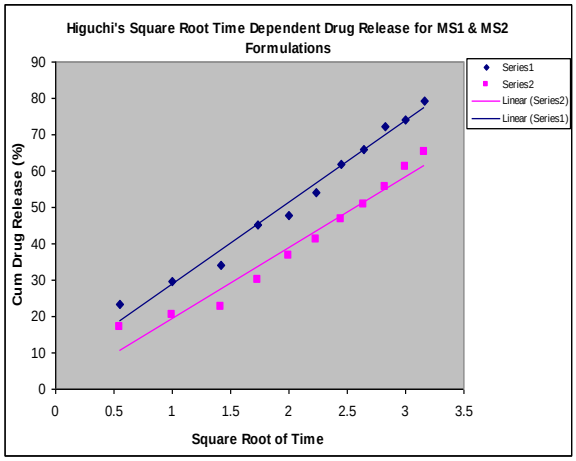

Figure 10: Higuchi's plots of MS1 & MS2 formulations

peaks, which gives an evidence that the drug is intact in Mucoadhesive polymers. The dissolution rate studies were performed by using USP-XXIV dissolution apparatus employing rotating paddle at a speed of 100 rpm in the dissolution medium of Acetate buffer of pH 4.5 and study was continued up to 10 hrs at suitable time intervals, samples of 5ml were withdrawn by means of pipette and it was immediately replaced with fresh dissolution medium. The withdrawn samples were analyzed for the drug content after appropriate dilutions by measuring the absorbance at 317 nm with UV spectrophotometer. The dissolution data were analyzed by computer and it was observed that the release profile of Microcapsules followed First Order release kinetics and Higuchi's Square root plot. Nimodipine release from these Microcapsules was sustained over a prolonged period of time. The drug release data and the drug release profiles were shown in Tables–5 and Figures 1-12 respectively. The prepared Microcapsules were found to be discrete, large, spherical and free flowing and having uniform size. The size analysis is shown in Table – 3. It was showed that about 48.47% and 63.53% were in the size range of 25/36. Micro encapsulation efficiency was calculated using the formula, micro encapsulation efficiency = (estimated % drug content / theoretical % drug content) X 100. The results of Micro encapsulation efficiency were found in the range of 65.64 – 79.78% with Sodium CMC having 65.64% and HPMC having 79.78%.The results of Mucoadhesive Microcapsules are presented in Table – 4and showed fairly good Mucoadhesive property of Microcapsules in all the cases.

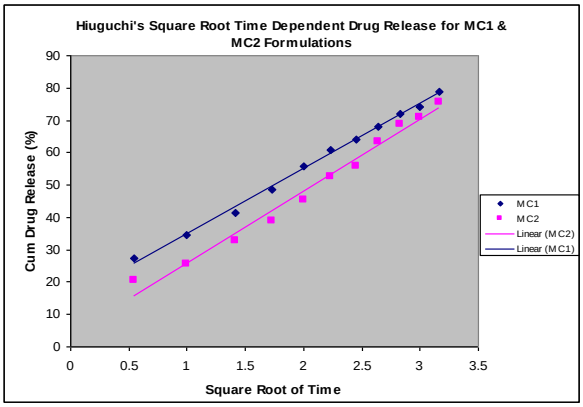

Figure 11: Higuchi's plots of MC1 & MC2 formulations

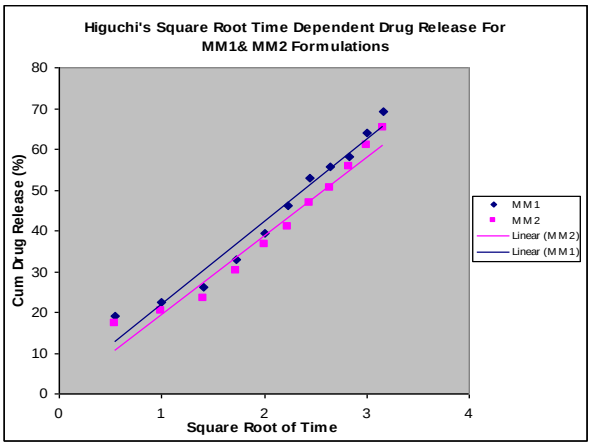

Figure 12: Higuchi's plots of MM1 & MM2 formulations

CONCLUSION

Microcapsules of Nimodipine with a coat consisting of Sodium Alginate and a mucoadhesive polymers namely

Table 6: Results of In-Vitro Wash – Off Test to Assess Mucoadhesive Property of the Microcapsules

S. No.	Microcapsules	Percent Microcapsules adhering to tissue at (h)				
		Acetate buffer, pH 4.5				
		1	2	4	6	8
1	MH1	66 ± 1.5	51 ± 2	20 ± 2	06 ± 2	-
2	MH2	71 ± 0.5	56 ± 1.5	27 ± 0.5	10 ± 1	04 ± 1.5
3	MS1	27 ± 2	15 ± 1	10 ± 2	01 ± 1	-
4	MS2	32 ± 0.5	19 ± 1	14 ± 0.5	05 ± 0.5	-
5	MC1	63 ± 0.5	60 ± 0.5	25 ± 1	14 ± 1	-
6	MC2	69 ± 1.5	65 ± 2	32 ± 2	19 ± 2	15 ± 0.5
7	MM1	57 ± 0.5	37 ± 1.5	12 ± 0.5	-	-
8	MM2	61 ± 0.5	43 ± 1	14 ± 0	-	-

Sodium CMC, Methyl Cellulose, Carbopol and HPMC in 1:1, and 1:2 ratios could be prepared by the orifice ionic gelation process. Micro encapsulation efficiency was found in the range of 65.64 – 79.78% with Sodium CMC having 65.64% and HPMC having 79.78%.Nimodipine release from the microcapsules was slow, spread over extended periods of time and depended on the composition of coat. The released was followed first order kinetics and Higuchi's Square root time plot. Microcapsules of sodium alginate – HPMC gave relatively fast released when compared to others. The order of increasing release rate observed with various microcapsules was sodium alginate – methyl cellulose < Sodium Alginate – Carbopol < Sodium Alginate – Sodium CMC < Sodium Alginate – HPMC. The Mucoadhesive Micro encapsulation technique could be adaptable in laboratory and in Industry as well since it is simple and reproducible. We therefore presume that the further controlled released products could be developed on these lines rather than other techniques. In conclusion, Alginate – Methyl Cellulose and Alginate – Carbopol Microcapsules could be used for sustained action for over long period of time. However, further In-vivo studies are needed to optimize for sustained action in human beings for better bioavailability, efficacy thus safety.

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