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Preparation and Evaluation of Mucoadhesive Microcapsules of Indomethacin

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Indomethacin microcapsules with a coat consisting of alginate and a mucoadhesive polymer such as sodium carboxymethylcellulose, methyl cellulose, carbopol and hydroxypropylmethylcellulose were prepared by an emulsification-ionic gelation process and were investigated with a view to develop mucoadhesive microcapsules. The resulting microcapsules were discrete, large, spherical and free flowing. Microencapsulation efficiency was 41-70% and relatively high with alginate-sodium carboxymethylcellulose. The microcapsules exhibited good mucoadhesive property in the *in vitro* wash-off test. Indomethacin release from these mucoadhesive microcapsules was slow and extended over longer periods of time and depended on the composition of coat and size of the microcapsules. Drug release was diffusion controlled and followed first order kinetics. Alginate-methyl cellulose and alginate-sodium carboxymethylcellulose microcapsules were found suitable for oral controlled release. Release from some microcapsules fulfilled the official (USP 23) drug release test-2 requirement of indomethacin extended release capsules.

Microencapsulation by various polymers and their applications are described in standard text books[1,2]. Microencapsulation and the resulting microcapsules have gained good acceptance as a process to achieve controlled release and drug targeting. Mucoadhesion is a topic of current interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs[3-5]. Several studies[6] reported mucoadhesive drug delivery systems in the form of tablets, films, patches and gels for oral, buccal, nasal, occular and topical routes. There were no reports on mucoadhesive microcapsules. This study describes the development and evaluation of mucoadhesive indomethacin containing microcapsules employing various mucoadhesive polymers designed for oral controlled release. Indomethacin, which requires controlled release owing to its short biological half-life[7] of 2.4±0.4 h and gastrointestinal side effects such as peptic ulceration with bleeding, was used as a core in microencapsulation.

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MATERIALS AND METHODS

Indomethacin was a gift sample from M/s Micro Labs, Pondicherry. Sodium carboxymethylcellulose (sodium CMC, with a viscosity of 1500-3000 cps of 1% w/v aqueous solution at 25°), methyl cellulose (with a methoxyl content of 28.32 % by weight and viscosity of 65 cps in 0.5% w/v aqueous solution at 25°) and hydroxypropyl- methylcellulose (which gives a viscosity of 50 cps in a 2 % by weight aqueous solution at 20°) were gift samples from M/s Natco Pharma Ltd., Hyderabad. Carbopol 934 P was a gift sample from M/s SmithKline Beecham Pharmaceuticals, Bangalore. Sodium alginate (SD Fine Chem, Mumbai), calcium chloride (Qualigens, Mumbai) was procured from commercial sources. All other reagents used were of analytical grade.

Preparation of microcapsules:

Microcapsules containing indomethacin were prepared

employing sodium alginate in combination with sodium CMC, methyl cellulose, carbopol and HPMC as coat materials. No methods are reported for microencapsulation by these polymers. The ionic gelation processes[8,9] which has been extensively used to prepare large sized alginate beads, was used to prepare the microcapsules.

Sodium alginate (1.0 g) and the mucoadhesive polymer (1.0 g) were dissolved in purified water (32 ml) to form a homogeneous polymer solution. Core material, indomethacin (2.0 g) was added to the polymer solution and mixed thoroughly to form a smooth viscous dispersion. The resulting dispersion was then added in a thin stream to about 300 ml of groundnut oil contained in a 600 ml beaker while stirring at 400 rpm. A Remi medium duty stirrer with speed meter (Model RQT 124) was used for stirring. The stirring was continuous for 5 min to emulsify the add dispersion as fine droplets. Calcium chloride (10% w/v) solution (40 ml) was then added slowly while stirring for ionic gelation (or curing) reaction. Stirring was continued for 15 min to complete the curing reaction and to produce spherical microcapsules .The mixture was then centrifuged and the product thus separated was washed repeatedly with water and dried at 45° for 12 h. The microcapsules prepared along with their coat composition are listed in Table 1.

Estimation of indomethacin:

Indomethacin content in the microcapsules was estimated by using UV spectrophotometric method[10] based on the measurement of absorbance at 318 nm in phosphate buffer of pH 6.2. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in concentration range 1-40 μg/ml. When a standard drug solution was assayed repeatedly (n=6), the mean error (accuracy) and relative standard deviation (precision) were found to be 1.2% and 2%, respectively.

Evaluation of microcapsules:

For size distribution analysis, different sizes in a batch were separated by sieving using a range of standard sieves. The amounts retained on different sieves were weighed. Microencapsulation efficiency was calculated using the formula, microencapsulation efficiency=(estimated percent drug content/theoretical percent drug content)×100.

Drug release study:

Release of indomethacin from the microcapsules of size 16/20, and 20/35 was studied in phosphate buffer of pH 6.2 (900 ml) using an USP XXIII three-station Dissolution Rate Test Apparatus (Model DR-3, M/s Campbell Electronics) with a basket stirrer at 75 rpm as per USP XXIII drug release

TABLE 1: COAT COMPOSITION, DRUG CONTENT AND MICROENCAPSULATION EFFICIENCY OF THE MICROCAPSULES PREPARED.

Microcapsules	Coat composition	Drug content (%) of microcapsules		Microencapsulation efficiency
		Theoretical	Practical	(%)
Size-16/20				
MC1	Alginate-sodium CMC (1:1)	50	35.31 (1.2)*	70.63
MC2	Alginate-methyl cellulose (1:1)	50	25.35 (1.8)*	50.70
MC3	Alginate-Carbopol (1:1)	50	24.74 (1.5)*	49.48
MC4	Alginate-HPMC (1:1)	50	27.42 (1..0)*	54.84
Size-20/35				
MC1	Alginate-sod CMC (1:1)	50	30.46 (0.13)*	60.92
MC2	Alginate-methyl cellulose (1:1)	50	21.41 (0.14)*	42.82
MC3	Alginate-Carbopol (1:1)	50	20.53 (3.3)*	41.06
MC4	Alginate-HPMC (1:1)	50	25.60 (1.71)*	51.20

* Figures in parenthesis are coefficient of variation (CV) values.

test prescribed for indomethacin extended release capsules[10]. A sample of microcapsules equivalent to 75 mg of indomethacin was used in each test. Samples were withdrawn through a filter (0.4 μm) at different time intervals and were assayed at 318 nm for indomethacin using a Shimadzu UV-150 double-beam spectrophotometer. The drug release experiments were conducted in triplicate.

***In vitro* wash-off test for mucoadhesion:**

The mucoadhesive property of the microcapsules was evaluated by an *in vitro* adhesion testing method known as wash-off method. The mucoadhesiveness of these microcapsules was compared with that of a non-bioadhesive material, ethylene vinyl acetate microcapsules. Pieces of intestinal mucosa (2×2 cm) were mounted on to glass slides (3×1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread on to each wet rinsed tissue specimen and immediately there after the support was hung on to the arm of a USP tablet disintegrating test machine. By operating the disintegrating test machine the tissue specimen was given a slow regular up and down moment in a test fluid at 37° taken in a 1 l vessel of the machine. At the end of 30 min, 1 h and later at hourly intervals up to 12 h, the machine was stopped and the number of microcapsules still adhering on to the tissue was counted. The test was performed in 0.1 N HCl and in phosphate buffer of pH 6.2.

RESULTS AND DISCUSSION

Microcapsules of indomethacin with a coat consisting of alginate and a mucoadhesive polymer (1:1) namely sodium CMC, or methylcellulose, or carbopol or HPMC could be prepared by an emulsification and ionic gelation process. Microcapsules with a coat of mucoadhesive polymer alone could not be prepared by this process due to their water-soluble nature. The microcapsules were found to be discrete, large, spherical and free flowing. The sizes could be separated and more uniform size range of microcapsules could readily be obtained. The size analysis of different microcapsules showed that about 58.6±11 and 29.8±6.8 percent were in the size range of –16+20 (1015 μm) and –20+35 (670 μm) mesh size respectively. A lognormal size distribution of the microcapsules was observed in all the batches prepared.

Low C.V. (< 2.0 %) in percent drug content indicated uniformity of drug content in each batch of microcapsules (Table 1). Drug content of the microcapsules was same in different sieve fractions. The microencapsulation efficiency was in the range of 41-70%. The microencapsulation efficiency was relatively high with alginate-sodium CMC combination.

Microcapsules with a coat consisting of alginate and a mucoadhesive polymer exhibited good mucoadhesive property in the *in vitro* wash-off test when compared to a non-mucoadhesive material, ethylene vinyl acetate microcapsules. The wash-off was slow in the case of microcapsules containing alginate-mucoadhesive polymer as coat when compared to that of EVA microcapsules (Table 2). The wash off was relatively rapid in phosphate buffer than in acid fluid. The results of wash-off test indicated fairly good mucoadhesive property of the microcapsules.

Indomethacin release from the microcapsules was studied in phosphate buffer (pH: 6.2) for a period of 12 h as prescribed in the drug release test-2 of indomethacin ex-

TABLE 2: RESULTS OF *IN VITRO* WASH-OFF TEST TO ASSESS MUCOADHESIVE PROPERTY OF THE MICROCAPSULES.

Microcapsules	Percent of microcapsules adhering to tissue at 5 times (h)									
	0.1 N HCl, pH 1.2					Phosphate buffer, pH 6.2				
	1	2	4	6	8	1	2	4	6	8
MC 1	88 (1.2)*	76 (2.0)	58 (1.7)	38 (1.9)	21 (2.3)	72 (1.9)	56 (2.3)	24 (2.0)	07 (1.8)	-
MC 2	85 (2.1)*	77 (2.2)	62 (1.5)	32 (2.2)	24 (1.9)	73 (2.0)	55 (1.8)	26 (2.2)	04 (2.1)	-
MC 3	75 (2.0)*	68 (2.5)	60 (2.1)	48 (2.3)	30 (2.0)	69 (2.2)	65 (1.7)	35 (1.9)	20 (1.5)	17 (1.8)
MC 4	82 (1.8)*	71 (1.8)	61 (2.0)	35 (2.5)	20 (1.8)	71 (2.1)	57 (1.9)	30 (2.1)	12 (1.9)	06 (2.2)
EVA	55 (1.5)*	41 (1.4)	11 (1.8)	-	-	52 (2.3)	40 (2.5)	08 (2.7)	-	-

* Figures in parenthesis are coefficient of variation (CV) values.

TABLE 3: RELEASE CHARACTERISTICS OF MUCOADHESIVE MICROCAPSULES PREPARED

Microcapsule	Percent Indomethacin Released at 5 time points (h) ($\bar{x}$ ±s.d)					T_{50} (h)	$K_1 \times 10^2$ (h^{-1})
	1.0	2.0	4.0	8.0	12.0		
Size-16+20							
MC1	33.6±4.20	48.6±4.90	63.1±5.40	79.8±10.00	87.7±7.03	3.3	17.4
MC2	8.8±0.08	22.5±5.10	44.5±8.80	66.6±1.21	75.7±1.43	5.0	12.5
MC3	16.6±0.90	34.9±0.19	63.1±0.11	90.8±0.87	97.1±0.21	2.4	29.1
MC4	25.2±0.21	45.5±1.25	74.2±0.97	89.5±2.50	98.2±0.11	2.9	36.9
Size-20+35							
MC1	47.6±5.90	65.5±5.00	77.1±3.90	93.1±3.71	100.0±0.27	1.1	30.0
MC2	27.6±0.93	45.1±1.79	60.8±0.67	76.4±0.94	92.2±0.45	2.5	17.6
MC3	48.8±0.39	65.0±1.26	79.9±0.64	94.7±0.64	99.9±2.84	1.6	30.5
MC4	30.9±1.00	51.8±1.76	78.2±1.33	96.3±2.31	99.9±0.16	1.2	43.1

T_{50} is time for 50% release and K_1 is first order release rate constant.

tended release capsules in USP XXIII. Indomethacin release from the microcapsules was slow and spread over extended periods of time (Table 3). Release followed first order kinetics (r>0.98) and depended on the composition of the coat and size of the microcapsules. The release increased as the size of the microcapsules decreased. Microcapsules of alginate-carbopol and alginate-HPMC gave relatively fast release when compared to alginate-sodium CMC and alginate-methylcellulose. The order of increasing release rate observed with various microcapsules was alginate-methyl cellulose<alginate-sodium CMC<alginate-carbopol<alginate -HPMC in both the sizes studied. The drug release from the microcapsules was diffusion controlled as plots of amount released vs t was found to be linear (r>0.97). Indomethacin release from alginate-methyl cellulose (MC2) and alginate-sodium CMC (MC1) was slow and extended over a period of 12 h and these microcapsules were found suitable for oral controlled release formulations. Indomethacin release from microcapsules MC2 (size 20/35) also fulfilled the official (USP XXIII) drug release test-2 requirement of indomethacin extended release capsules.

Thus, large sized spherical microcapsules with a coat consisting of alginate and a mucoadhesive polymer (sodium CMC or methyl cellulose or carbopol or HPMC) could be prepared by emulsification-ionic gelation process. The microcapsules exhibited good mucoadhesive property *in vitro* tests. Indomethacin release from these mucoadhesive microcapsules was slow and extended over longer periods of time. Drug release was diffusion controlled and followed first order kinetics. Alginate-methylcellulose and alginate-sodium CMC microcapsules were found suitable for oral controlled release.

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