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Development of Pulsincap Drug Delivery of Salbutamol Sulphate for Drug Targeting

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A special dosage form called 'pulsincap' of salbutamol sulphate was developed to target the drug release in the colon. An empty gelatin capsule was coated with ethyl cellulose keeping the cap portion as such. A hydrogel plug made of gelatin was suitably coated with cellulose acetate phthalate in such a way that it was fixed to the body under the cap. Eudragit microcapsules containing salbutamol sulphate were prepared by emulsion solvent evaporation method and were incorporated into this specialized capsule shell. This pulsincap system was evaluated for its physical nature, which showed a minimum change of 3.79% in the body weight and maximum swelling ratio (3.52) of hydrogel plug at intestinal pH. The *in vitro* dissolution results indicated that the onset of drug release was after 7 to 8 h of the experiment started and revealed its better sustaining efficacy over a period of 24 h. Thus, this pulsincap dosage form of salbutamol sulphate may be used for colon specific drug release. When administered in the evening, it may prevent nocturnal attacks of asthma and thereby may reduce the unexpected mortality rate.

Salbutamol sulphate is widely used for the treatment of asthma[1]. Due to irregular drug regimen for asthma whose onset is in late night or early morning fatal responses are often observed which may even lead to death and this can mainly be attributed to insufficient dosage schedule of this drug. Recently, a great amount of interest has been generated in the use of the colonic route, to provide nocturnal release of drugs for such disease conditions like asthma[2]. Colonic drug delivery following administration via the oral route is generally based on a technology allowing a targeted release to the terminal ileum and proximal colon[3,4].

The approach to prepare such formulation has traditionally been based on polymers that resist degradation through the stomach and small intestine but release the drug in the lumen of large bowel. Radio-telemetry has been used to measure the gastrointestinal pH in healthy human subjects. On entry into the colon, the pH is 6.4±0.6. The pH in the mid colon is 6.6±0.8, in left colon is 7.0±0.7 and in rectum 7.2 - 7.5. The fall in pH on entry into the colon is due to the presence of short chain fatty acids arising from the bacterial fermentation of polysaccharides[5]. Co-polymers with pH dependent solubility properties are frequently employed to delay drug release until the formulation has arrived in the colon. The eudragit series of co-polymers are widely used for this purpose[6]. The *in vitro in vivo* performances of model tablets coated with eudragit S-100 were investigated by some authors and were well appreciated[7,8]. In man, studies have shown that, after leaving the stomach, a formulation arrives at the ileococal junction in about 6 h after administration. Thus, once gastric emptying has occurred, a time-based system can be employed for the targeted release[9]. Based on this basic concept the pulsincap dosage form has been developed. This pulsincap is similar in appearance to a hard gelatin capsule, but the main body is water insoluble. The drug is remained within the body packed with hydrogel plug. the hydrogel plug begins to swell in a suitable condition and when swelling reaches to a critical point, the plug pops out of the capsule body and the contents are released[10]. Depending upon the properties of the plug used, the time at which this occurs can be

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controlled. This hydrogel plug is concealed inside the gelatin cap of the shell. The main focus is the generation of excipients which degrade essentially in colonic environment and therefore, can be employed as a coating material for matrices[11].

The rationale of this study is to design eudragit microcapsules-loaded pulsincap dosage form containing salbutamol sulphate which can be targeted to colon in a pH and time-dependent manner. Once administered in the evening, can prevent attack of asthma during late night or early morning.

EXPERIMENTAL

Salbutamol sulphate was obtained from Cipla India Limited, Bangalore and also from Nicholas Piramal India Ltd., Mumbai as gift samples. Eudragit L-100 and S-100 were purchased from Rohm, GMBM, Germany. Other chemicals such as gelatin, heavy liquid paraffin, cellulose acetate phthalate, ethyl cellulose, petroleum ether and acetone were of laboratory grade and purchased locally. All these chemicals were used as received without further purification.

Pre-formulation studies:

A physical combination of eudragit L-100 and S-100 was designed for maintaining the same pH (6.8) as that of the proximal colon. Accordingly, eudragit L-100 (soluble in pH 6 and above) and S-100 (soluble in pH 7 and above) were mixed physically in different ratios (1:1, 1:1.5, 1:2 and 1:3) and the final mixtures were undergone the solubility studies. The solubility parameters indicated that 1:1.5 ratio of L-100 and S-100 was highly soluble in 6.8 pH. Hence, this combination was selected for further studies.

Preparation of Eudragit microcapsules containing Salbutamol Sulphate:

The preparation of microcapsules with eudragit L/S-100 containing salbutamol sulphate was done by emulsion-solvent evaporation method[12]. Accurately weighed eudragit L-100 and S-100 (1:1.5 ratio) were dissolved in 10 ml of acetone to form a homogenous polymer solution. Salbutamol sulphate was added to the polymer solution and the resulting mixture was then added in a thin stream to the heavy liquid paraffin (60 ml) contained in a 100 ml beaker. Different stirring rates (600, 800, 1000 and 1400 rpm) were maintained for different batches (D: P = 1:0.5. 1:1, 1:2 and 1:3). Stirring was continued for 15 min to disperse the added mixture as fine droplets. The solvent was then removed by evaporation at room temperature (20°) to produce spherical microcapsules. The microcapsules were collected by decantation and washed with petroleum ether to remove the adhering liquid paraffin.

Development of Plusincap Dosage form:

The development of pulsincap dosage form was carried out by the coating of the body of the capsule shell, preparing the hydrogel plug and finally incorporating the formulated microcapsules. The body of hard gelatin capsule shell (size - 3) was taken and coated with different concentrations of ethyl cellulose solution (2.5 to 5%) by simple dipping method. Successive three coatings were given immediately after drying of each coating.

Gelatin powder was made into plug form with help of a suitable size mould by the process of melting. The gelatin hydrogel plug was coated with different concentrations (2.5, 5, 7.5 and 10%) of cellulose acetate phthalate (CAP) in order to get dissolve only in intestinal fluid (pH 6.4). The half-coated hydrogel plug was used in the pulsincap dosage form.

The microcapsules equivalent to 20 mg of drug of ideal formulations was incorporated into ethyl cellulose coated body of empty capsule shell. Then it was set with formulated hydrogel plug and thereafter fixed the normal gelatin capsule cap. The whole system, thus produced, is pulsincap dosage form.

Determination of particle size and flow properties:

Particle size of the prepared microcapsules was determined by optical microscopy in which stage micrometer was employed. A minute quantity of microcapsules was spread on a clean glass slide and average size of 50 microcapsules were determined. The flow properties of the microcapsules were studied by measuring the angle of repose of the formulation by employing fixed funnel method.

In vitro dissolution study:

The *in vitro* release study was carried out according to USP XXIII, type II (Paddle) method. Twenty five milligram of accurately weighed microcapsules were dispersed in a dissolution media (500 ml) of phosphate buffer (pH 6.8) maintained at 37° (±1°). The dissolution media was rotated at 50 rpm. Five millilitres of samples were withdrawn at specific time intervals and equal volume of

TABLE 1 : NATURE OF DISSOLUTION MEDIA

Time (h)	0-2	2-3	3-4	4-5	5-6	6-7
Half of dissolution media replaced with buffer	-	6.0	6.0	7.6	7.6	6.0
pH of the dissolution media obtained	1.2	3.0	5.4	6.4	7.2	6.8

pH of the dissolution media was changed by half-dilution method at different time intrevals during dissolution operation. The table indicates the resultant pH obtained during the specific time simulating the GIT condition.

TABLE 2 : REPRODUCIBILITY OF MICROCAPSULES

Batch code	Rotating speed (RPM)	D:P ratio	% Recovery	Drug loading efficiency, %	Average particle size in microns	Angle of repose (degree, min)	CPR during 24h, %	t1/2 (h)
F_1	600	1:0.5	66.66	69.94	169.89	35°52'	87.80	2.58
F_2	600	1:1	76.00	76.10	165.37	31°18'	96.53	2.78
F_3	600	1:2	80.66	85.03	162.14	32°24'	90.39	3.06
F_4	600	1:3	84.51	85.73	168.96	37°19'	90.96	4.38
F_5	800	1:0.5	70.66	74.61	140.89	34°46'	90.05	3.34
F_6	800	1:1	77.51	73.67	145.68	36°33'	95.58	2.05
F_7	800	1:2	82.33	85.13	141.47	34°57	90.33	3.76
F_8	800	1:3	86.75	88.98	150.16	36°27'	93.47	3.76
F_9	1000	1:0.5	76.00	76.03	103.36	30°16'	92.14	2.76
F_{10}	1000	1:1	78.50	77.47	91.08	26°24'	93.85	4.30
F_{11}	1000	1:2	85.33	86.72	96.90	28°07'	92.60	3.73
F_{12}	1000	1:3	89.50	82.69	102.60	29°54'	97.98	3.48
F_{13}	1200	1:0.5	79.33	72.96	79.45	27°31'	97.59	1.40
F_{14}	1200	1:1	83.50	73.82	87.04	26°04'	94.36	2.15
F_{15}	1200	1:2	89.33	85.47	76.87	26°28'	98.02	3.00
F_{16}	1200	1:3	89.75	79.68	81.39	27°17'	92.05	4.12
F_{17}	1400	1:0.5	76.66	80.75	71.70	26°29'	98.15	1.84
F_{18}	1400	1:1	81.50	76.56	78.76	27°19'	94.97	2.20
F_{19}	1400	1:2	84.66	81.60	74.93	28°47'	94.22	2.00
F_{20}	1400	1:3	87.25	77.80	71.06	25°53'	94.27	3.01

Data represents for different batch formulations and their physico-mechanical evaluation. CPR indicates cumulative % release, D:P means drug-polymer ratio and t 1/2 i.e. Half-life was determined based on dissolution data.

TABLE 3 : CHANGE OF WEIGHT OF CAPSULE BODY COATED WITH ETHYLCELLULOSE

Sl. No	Conc. of ethyl cellulose (%)	Wt. of empty gelatin body (mg)	Wt. of completely coated gelatin body(mg)	Soaked in pH	Wt. of the body shell at various time interval in h (mg)						% change of weight at 24 h
					1	3	6	9	12	24	
1	2.5	67	74	1.2	74	75	76	77	79	81	9.45
2	2.5	63	71	6.4	71	72	74	75	76	77	8.45
3	2.5	66	74	6.8	74	75	76	77	79	80	8.10
4	2.5	65	73	7.2	73	74	76	77	79	79	8.21
5	3	63	72	1.2	72	73	73	75	77	78	8.33
6	3	61	70	6.4	70	71	73	74	75	75	7.14
7	3	62	72	6.8	72	73	74	75	77	79	9.72
8	3	62	73	7.2	7.3	74	76	77	78	79	8.21
9	4	64	74	1.2	74	74	75	77	78	79	6.75
10	4	65	76	6.4	76	76	77	78	79	80	5.26
11	4	60	72	6.8	72	73	74	76	77	77	6.94
12	4	62	73	7.2	73	73	74	75	77	78	6.84
13	5	65	78	1.2	78	78	79	79	80	81	3.84
14	5	66	80	6.4	80	80	81	81	82	82	2.50
15	5	63	79	6.8	80	80	80	81	82	82	3.79
16	5	61	77	7.2	77	78	78	78	80	80	3.89

The table is showing the percentage changes of weight of coated shell during time intervals when soaked in different pH A 5% Coating was minimum change in weight indicates perfect coating.

media was replaced immediately. Withdrawn samples were then filtered and suitably diluted. The absorbance of the samples was determined at its wavelength of 276 nm and from the absorbance the cumulative amount of drug released was calculated.

Evaluation of pulsincap dosage form:

A coating is said to be ideal when the change of weight after soaking in different pH solutions would be minimum. Accordingly, it was immersed in different pH solutions (1.2, 6.4, 6.8 and 7.2) and % change of weight during 24 h was observed. The hydrogel plug in the plusincap dosage form should have the property to swell maximum and eject from the body in intestinal fluid. Accordingly, the swelling characteristics were determined by observing the swelling ratio in different pH solutions (1.2, 6.0 and 7.2) and in water.

Half change method was employed to maintain the different pH conditions in the dissolution studies. The dissolution tests were carried out by the paddle method. Half of the amount of dissolution media was withdrawn at specific time intervals and replaced with appropriate pH solutions as shown in the following table 1. This pulsincap was taken in a 500 ml of 0.1N HCl (pH 1.2) buffer maintained at 37° (±1°). A similar study was made by taking microcapsules formulations without incorpo-

TABLE 4 : SWELLING CHARACTERISTICS OF GELATIN HYDROGEL PLUG

Sl. No	Type of coating	Conc. of C.A.P (%)	Wt. of dry hydrogel plug(mg)	Wt. of dry coated hydrogel plug(Wd)(mg)	pH/ solvent	Wt. of swollen hydrogel plug at time "t" in hours(Ws)(mg)					Swelling ratio, R=Ws/Wd at 12 h
						2	4	8	10	12	
1	Uncoated	-	188	188	water	264	352	415	469	543	2.88
2	Uncoated	-	192	192	1.2	231	309	443	561	689	3.58
3	Uncoated	-	187	187	7.2	214	268	356	447	506	2.70
4	Full coated	2.5	175	181	water	221	277	357	406	498	2.75
5	Full coated	5	184	192	water	278	313	343	398	424	2.20
6	Full coated	7.5	187	199	water	234	281	324	373	407	2.04
7	Full coated	10	181	197	water	227	287	316	349	373	1.89
8	Full coated	10	185	196	1.2	199	207	209	211	214	1.09
9	Full coated	10	196	209	7.2	325	349	363	377	383	1.85
10	Full coated	10	179	194	6.0	227	294	387	531	658	3.39
11	Half coated	2.5	203	208	water	296	336	415	597	581	2.79
12	Half coated	5	216	224	water	315	387	467	507	593	2.64
13	Half coated	7.5	197	203	water	256	317	376	423	489	2.40
14	Half coated	10	178	187	water	225	294	319	343	377	2.01
15	Half coated	10	183	196	1.2	241	301	387	453	486	2.48
16	Half coated	10	187	199	7.2	236	285	347	412	439	2.21
17	Half coated	10	184	195	6.0	287	368	497	563	686	3.52

The swelling ratios for hydrogel plug after different conditions of coating found that half coated with 10% CAP was suitable for pulsincap dosage form at pH 6

rating into the pulsincap dosage form into the dissolution media and percentage of drug released were calculated at specific time intervals.

RESULTS AND DISCUSSION

For the 20 prepared batches, of microcapsules, the drug loading efficiency was found quite reasonable and ranged from 69.9% to 89%. The average particle size of microcapsules of all batches was ranged from 71.1 to 167 microns. All formulations showed improved flow properties when compared with raw powdered drug having the angle of repose between 25° to 36°.

The dissolution was carried out for a maximum period of 24 h and the release profile for different batches at different rpm was varied between 87.8% to 98.2%. The results showed that the formulations F1, F5, F9, F13 and F17 with drug polymer ratio of 1:0.5 showed rapid release initially followed by zero order, where as all other formulations showed zero order followed by first order. But the half-life determined from dissolution profile of the formulated batches F4, F10 and F16 was found to have increased almost double and thereby these formulations were selected as the ideal batches for the development of pulsincap system (Table 2).

The coating of the shell body was done with ethyl cellulose polymer in different concentrations and it was

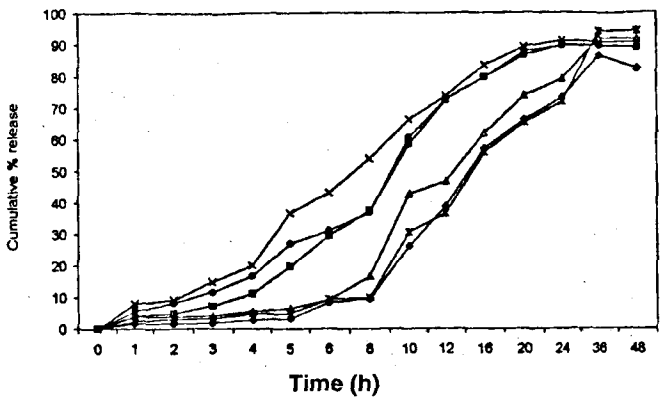

Fig. 1 : Dissolution Profiles of Formulations

A Characteristic difference in dissolution profile of Pulsincap dosage form (-◆-) for F_4, (-Δ-) for F_{10} and (-*-) for F_{16} release drugs approximately after 7-8 h compare to plain microcapsules (-□-) for F_4, (-●-) for F_{10} and (-X-) for F_{16} release within 1-2 h.

found that 5.0% coating was ideal for formulation, as the percentage change of weight in different pH solution was minimum (Table 3). From the results, it is indicated that half coated hydrogel plug was suitable in respect of its swelling characters (maximum swelling) needed for this pulsincap dosage form. This indicated that as soon as cap will get dissolved in stomach fluid the hydrogel plug could be swellable in upper intestinal pH (6.0) resulting in popping out of the hydrogel plug from the body of the capsule shell due to increase in volume by the time it reaches to proximal colon and thereby, releasing the microcapsules from the dosage form to this area.

The *in vitro* dissolution profiles of microcapsules-loaded pulsincap dosage form and for plain microcapsules during 48 h study were shown in figure 1. From, the graphical representation, it is revealed that the drug release from the pulsincap was started after roughly 7-8 h from the time of experiment started. Whereas, in plain microcapsules, the release was shown more or less immediately with in one hour of the experiment started. This implies the ideal behavioural characteristics of pulsincap dosage form which require the colon specific drug delivery system at a latter stage of time interval of roughly 7-8 h from the time of administration by oral route. About 93% drug was released during next 24 h with a sustaining efficacy.

Therefore, it can be concluded from the above observation that this pulsincap dosage form when to be administered in *in vivo* model may be a suitable alternative for drug administration for treatment of nocturnal attach of acute asthma.

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