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Research Article

**FORMULATION CHARACTERIZATION AND *IN VITRO*
EVALUATION OF PULSATILE DRUG DELIVERY OF
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Abstract:

The Montelukast pulsatile delivery system was created with the goal of delivering the drug to the colon for successful treatment of nocturnal asthma. The microspheres were sealed within the insoluble hard gelatin capsule body with an erodible hydrogel plug to create a time delayed capsule. Emulsion solvent evaporation was used to make the microspheres. Based on dissolving tests, optimised microsphere formulations were designed. The entire device was enteric coated in order to overcome the variability in gastric emptying time and achieve colon-specific delivery. The hydrogel plug (HPMC K100 and lactose in a 1:1 ratio) with a hardness of 4.5kg/cm² and a weight of 100 mg was placed in the capsule opening and found to be effective in delaying release of the drug in small intestinal fluid, ejecting the plug into colonic fluid, and releasing the microspheres into colonic fluid after a 5-hour lag time. Three dissolving medium with pH 1.2, 7.4, and 6.8 were employed consecutively to imitate pH fluctuations along the GI tract. The medication and polymer had no interaction, according to the FTIR analysis. Montelukast microspheres 1:4 ratio had the longest release time of all the formulations, lasting 12 hours. The results showed that the device is capable of delaying drug release for a programmable period of time and treating asthma.

Keywords: Montelukast, hydrogel plugs, pulsatile delivery, nocturnal asthma, microspheres.

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INTRODUCTION:

Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. These systems are useful for pharmaceuticals with a high first-pass effect, drugs for diseases with chronopharmacological behaviour, drugs with a specific absorption location in the GIT, drugs that are targeted to the colon, and circumstances where night-time dosing is essential. A pulsatile release profile is distinguished by a delay in medication release followed by rapid and full drug release. Nocturnal Asthma is recognized as a fluctuating overnight aggravation of the underlying asthma illness with increased symptoms and drug needs, increased airway reactivity, and impaired lung function, which affects two-thirds of asthmatics. Symptoms usually appear between the hours of midnight and 8 a.m., especially around 4 a.m. A medication delivery system that may release the medicine at a predefined period to ensure therapeutic efficacy is required in this situation. This can be accomplished by creating a pulsed release system after a well-defined lag time, a system capable of administering the medicine at the needed time.^[1]

The development of a pulse release formulation of Montelukast could be beneficial, as it would give a specified lag time and boost patient compliance with the dosage form. Pulsatile medication administration should restrict release of drug in the stomach and small intestine while allowing for a progressive commencement of drug release once the drug reaches the colon. In the current work, a pulsatile Montelukast drug delivery system was developed with the goal of delivering the medicine to the colon for successful treatment of asthma.^[2,3]

MATERIALS AND METHODS:

Aurobindo Pharma Limited, Hyderabad, provided a free sample of Montelukast sodium. Himedia in Mumbai provided Eudragit S-100 and Eudragit L-100. SD Fine Chemicals in Mumbai provided HPMC K100M, Methyl Cellulose. All of the reagents used were analytical grade.

Cross-Linked Gelatin Capsule Preparation

A total of 100 hard gelatine capsules, size 0 were taken. To make formalin vapours, the bodies were detached from the cap, and 25 ml of 15% (v/v) formaldehyde was placed in desiccators with a pinch of potassium permanganate. After that, the wire mesh containing the empty capsule bodies was subjected to

formaldehyde vapours. Because the caps were not exposed, they became water soluble. The desiccators were securely shut. After 12 hours, the bodies were removed and dried at 500°C for 30 minutes to guarantee that the reaction between gelatine and formaldehyde vapours was complete. After that, the remains were dried at ambient temperature to remove any remaining formaldehyde. These capsule bodies had untreated caps on them.^[4]

Preparation of Hydrogel Plug

Plug for sealing the capsule body was prepared by compressing equal amount of equal amount of HPMC K100M: lactose, and Methyl Cellulose: lactose using 7 mm punches and dies on rotary tablet press.

Microsphere preparation

Table 1 shows the composition of all microsphere formulations made using the emulsion solvent evaporation technique. By varying the polymer: drug ratio, the influence of various formulation and processing parameters on microsphere properties was examined. MLS and polymer were weighed and dissolved in 10ml acetone in a 1:1 ratio. With continual stirring for 1 hour, the homogenous drug and polymer organic solution was gently added in a thin stream to 75ml of liquid paraffin containing 0.1% surfactant. Filtration separated the microspheres, which were then washed with petroleum ether. The microspheres were then air dried for 12 hours and stored in a desiccator.^[5]

Pulsatile capsule preparation

The Pulsincap was created by manually putting microspheres with 10 mg of drug into formaldehyde-treated bodies. The microsphere-filled capsules were subsequently plugged using an optimized hydrogel plug. A tiny amount of the 5 percent ethyl cellulose ethanolic solution was used to seal the junction between the capsule body and cap. To prevent variable stomach emptying, the sealed capsules were thoroughly coated with 5 percent cellulose acetate phthalate in a 5:5 (v/v) mixture of acetone: ethanol plasticized with n-dibutylphthalate (0.75 percent).^[6]

Physicochemical Characterization of Hydrogel Plug

Hydrogel Plugs were studied for hardness, friability, weight variation and lag time.

Pulsincap conception

The Pulsincap was created by manually putting 10mg MKS microspheres into formaldehyde-treated bodies. The microsphere-filled capsules were then plugged using a specially designed hydrogel plug. A tiny amount of 5 percent ethyl cellulose ethanolic solution was used to seal the junction between the capsule body and cap. To eliminate variable stomach emptying, the sealed capsules were thoroughly wrapped with 5% cellulose acetate phthalate in a 5:5 (v/v) mixture of acetone: ethanol plasticized with 0.75 percent n-dibutylphthalate.^[7]

In-vitro study

Because the usual gastric emptying time is roughly 2 hours, drug release experiments of pulsincaps were conducted using a USP XXIII dissolving rate test apparatus (Apparatus 2, 100 rpm, 37 °C) for 2 hours in 0.1 M HCl (900 ml). The dissolving liquid was then replaced for 3 hours with pH-7.4 phosphate buffer (900 ml), as the usual small intestine transit duration is about 3 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) after 5 hours and the results were examined for the next 24 hours. The rotational speed was set to 100 rpm, and the temperature was kept at 37°C. At regular intervals, five millilitres of extraction solvent were scrapped and replaced with additional dissolution media. UV absorption spectroscopy was used to evaluate the withdrew specimens at 370 nm, and the cumulative percentage release was computed over the sampling periods.^[8]

IR spectral research

On a JASCO FT-Infrared, the IR Spectra for the formulation, pure medicines, and excipients were recorded.^[9]

RESULTS & DISCUSSION:

The pulsatile capsule was prepared. The water-soluble cap dissolves in the stomach juice when the pulsating cap is eaten, causing the exposed hydrogel plug to swell. After a certain period of time, the enlarged plug was expelled, and The medication formulation was then encapsulated. It is dissolved and discharged into the colon. After that, it's absorbed into the bloodstream. The emulsion solvent evaporation process was used to make the microspheres. Discrete, spherical, non-sticky, and free-flowing microspheres were produced using the approach. The optimal concentration of surfactant was found to be 0.1%. Because of completely inadequate decline of interfacial tension, dispersed globules/droplets tend to merge and produce larger globules below optimal concentration, whereas no huge reduction in particle size is noticed above optimal concentration because a massive concentration of emulsifying agent increases the viscosity of the dispersion medium. The ideal surfactant concentration was discovered to be 0.1 percent. All the formulations offered good flow properties. The particle size of the microspheres ranged between 140.55 and 162.49 μm . The effect of coating material concentration on the release rate of MLS was investigated using microspheres with core: coat ratios of 1:3, 1:4, and 1:6. (Table 1)

Table 1: Formulation ratios of Polymers used

Polymers Used			
ES:100(core:coat ratio)		EL:100(core:coat ratio)	
F-1	1:3	F-4	1:3
F-2	1:4	F-5	1:4
F-3	1:6	F-6	1:6

The drug content and percent encapsulation efficiency of these microspheres were measured. Table 2 summarises the findings. Entrapment efficiency was similarly high with this strategy.

Table 2: Micromeritics of Microspheres

Formulation Code	Angle of Repose	Bulk Density (g/cm ³)	Carr's Index	Hausner's Ratio	Average Particle Size (µm)	% Drug Content	%EE
F-1	26.67	0.866	15.12±0.06	1.17±0.04	140.55	40.96	88.29
F-2	25.43	0.872	15.13±0.03	1.17±0.03	152.35	43.32	87.69
F-3	22.42	0.813	14.34±0.02	1.16±0.02	155.66	46.62	86.63
F-4	26.66	0.610	13.34±0.06	1.09±0.02	160.49	45.23	92.23
F-5	27.00	0.623	13.00±0.05	1.09±0.06	161.19	37.72	89.0
F-6	23.36	0.609	12.21±0.02	1.08±0.05	162.49	31.11	87.79

Table 3 shows the results of testing Hydrogel Plugs for hardness, friability, weight fluctuation, and lag time.

Table 3: Evaluation characteristics of hydrogel plugs prepared with various natural polymers

Hydrogel Plug	Composition (1:1)	Weight	Thickness(m m)	Hardness(kg/cm ²)	Lag time (hours)
HGP1	HPMC K100M: Lactose	100±1.21	3.46±0.12	4.5±0.01	5.01±0.01
HGP2	Methylcellulose: Lactose	100±1.21	3.43±0.12	4.3±0.03	3.50±0.02

The hardness of a 100 mg hydrogel plug (HPMC K100M: lactose in a 1:1 ratio) with a hardness of 4.5kg/cm² was shown to be sufficient for delaying drug delivery in small intestine fluid, ejecting the plug into colonic fluid, and releasing the microspheres into colonic fluid. This demonstrated that the plug content could potentially affect and change the lag duration. *In-vitro* release experiments of the device revealed that there had been no medication release in simulated gastric fluid (acidic pH 1.2) for 2 hours and simulated intestinal fluid (pH 7.4 phosphate buffer) with any formulation. The burst effect was discovered in the colonic media (pH 6.8 phosphate buffer). The efficacy of *in-vitro* release

profiles in colonic media was shown to be extremely good.

Pulsincaps loaded with Montelukast sodium microspheres prepared with Eudragit L100 in 1:3,1:4 and 1:6 ratios shown sustained drug release for a period of 9.5 hours (5th hour to 14.5 th hour), 11 hours (5th hour to 16th hour) and 12 hours (5th hour to 17thhour) respectively. and are shown in Figure 1(a). Pulsin caps loaded with Montelukast sodium microspheres prepared with Eudragit S 100 in 1:3,1:4 and 1:6 ratios shown sustained drug release for a period of 8 hours (5th hour to 13h hour), 9 hours (5th hour to 14th hour), and 10.5 hours (5th hour to 15.5 hour) respectively and are shown in Figure 1(b).

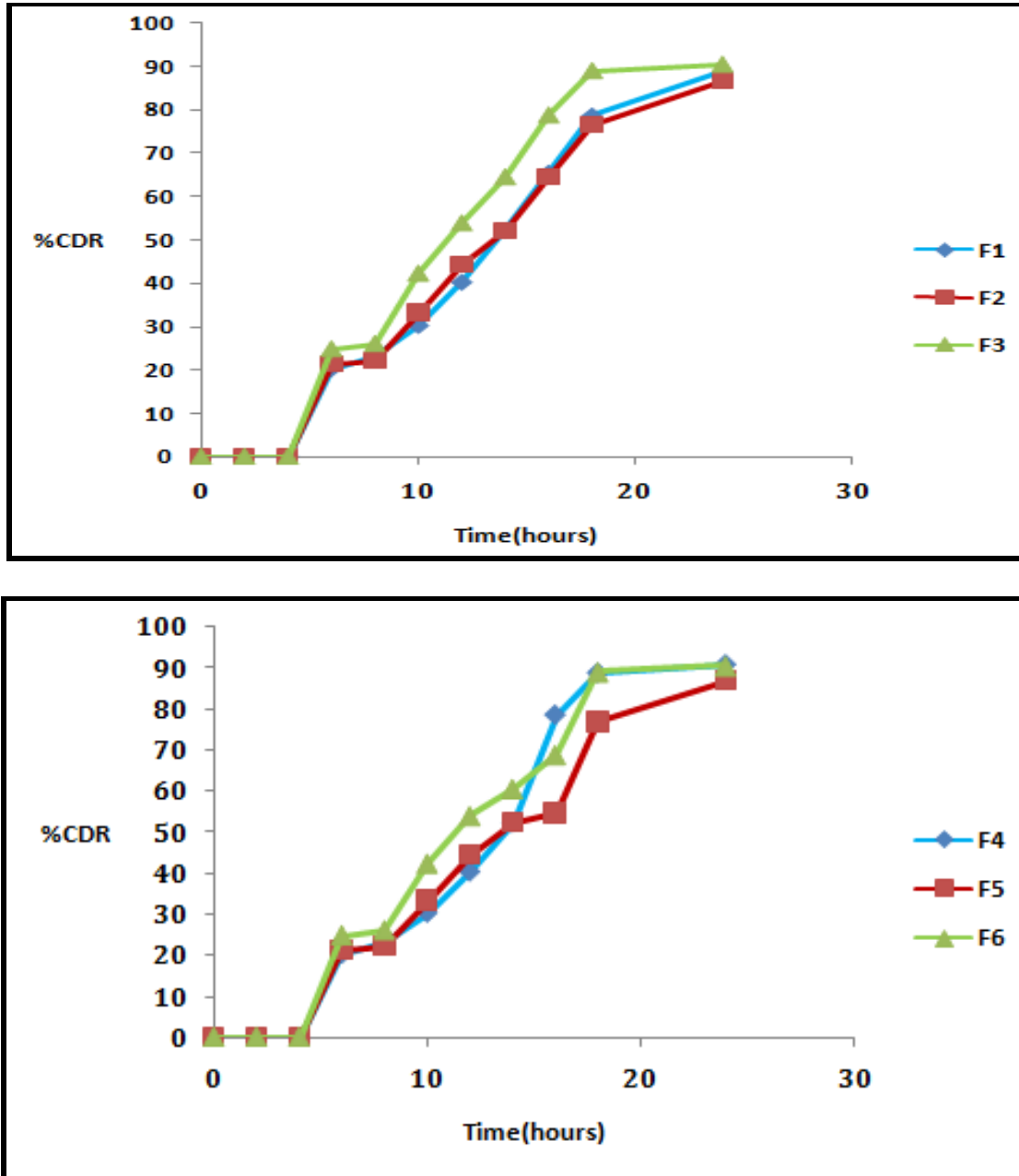


Figure 1: Comparative release profile of formulation containing a) ES: 100(F1-F3)b) EL: 100(F4-F6)

FTIR typical peaks in the graph did not change or shift. The presence of drug-loaded microspheres showed that there was no evidence of a strong drug-polymer interaction. This demonstrates the drug's long-term stability improved formulation.

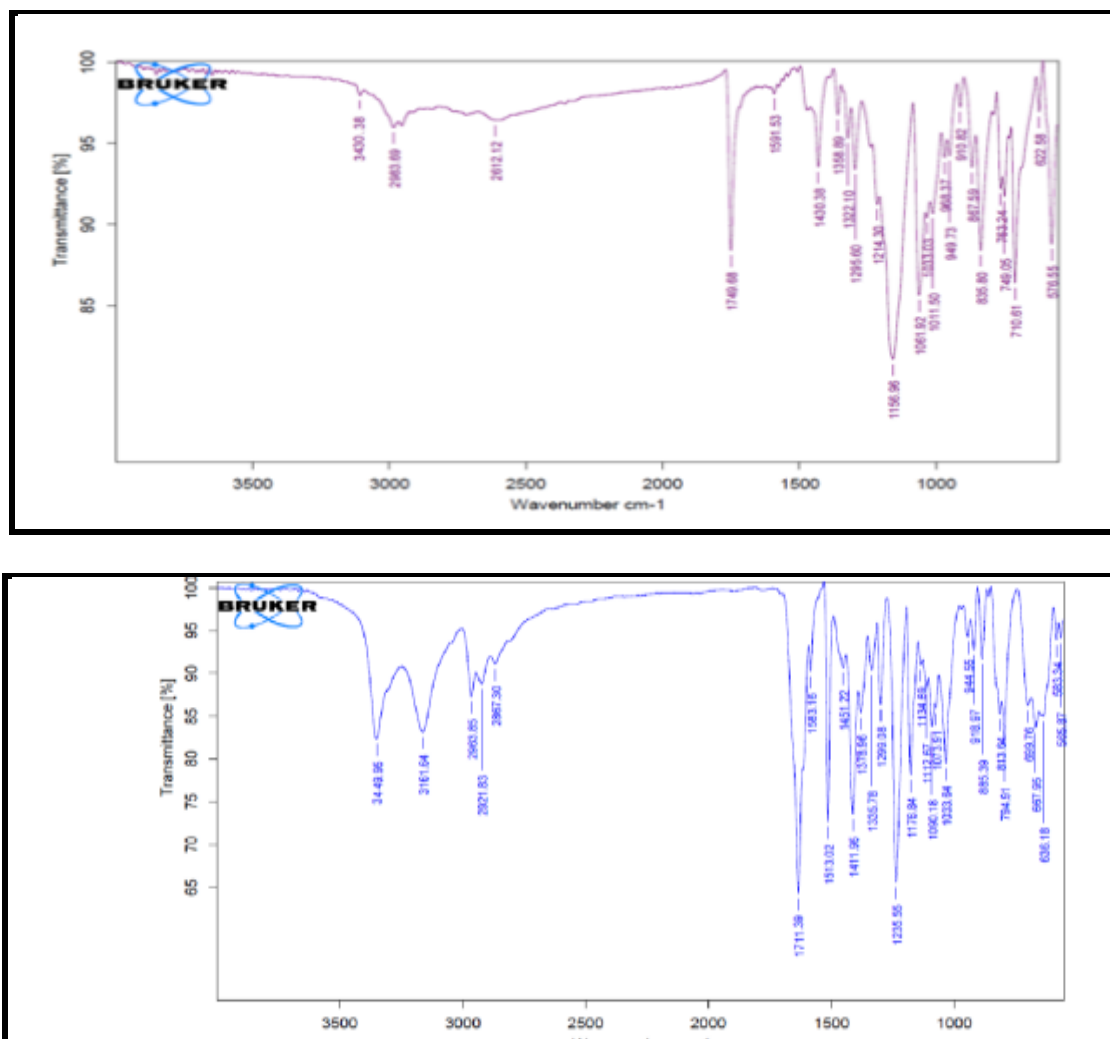


Figure: 2 FTIR Spectra of a) Montelukast b) Optimised formulation

CONCLUSION:

Among all the formulations Pulsin caps loaded with Montelukast microspheres prepared with Eudragit L-100 in 1:4 ratio shown prolonged release for a period of 12 hours. The obtained results showed the capability of the system in delaying drug release for a programmable period of time and the possibility of exploiting such delay to attain colon targeting for effective treatment of asthma.

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