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Formulation and evaluation of modified drug release tablet in tablet dosage with novel coating of β_2-adrenergic receptor agonists

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ABSTRACT

Controlled drug dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. Hence an attempt has been made to develop modified drug release by using tablet in tablet technique with barrier coating by using natural and synthetic polymers with Salbutamol as model drug. The inner core tablets were prepared by using direct compression method. The formulation F7 was selected for press coat by using different polymers like HPMC, Ethyl cellulose, Xanthum gum and Guar gum in different ratios among which 1part of Xanthum gum and 1part of Guar gum was optimized based on the lag time (20.75% in 4 hours) and percent of drug release and also further evaluated.

Keywords: Tablet in tablet, Polymer coating, Salbumtamol and controlled drug dosage form.

INTRODUCTION

Traditionally, drug delivery has meant getting a simple chemical absorbed predictably from the gut or from site of injection. A second-generation drug delivery goal has been the perfection of continuous, constant rate (zero order) delivery of bioactive agents. However, living organisms are not zero order in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle in order to maximize desired and minimize undesired drug effects. Due to advances in chronobiology, chronopharmacology and globalmarket constraints, the traditional goal of pharmaceutics (e.g. design drug delivery system with a constant drug release rate) is becoming obsolete. However, the major bottleneck in the development of drug delivery systems that match circadian rhythms (chronopharmaceutical drug delivery system: ChrDDS) may be the availability of appropriate technology. The diseases currently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify ChrDDS compared to the

conventional drug administration approach. These include asthma, arthritis, duodenal ulcer, cancer, diabetes, cardiovascular diseases, hypercholesterolemia, ulcer and neurological diseases [2].

If the organization in time of living system including man is borne in mind, it is easy to conceive that not only must the right amount of the right substance be at right place but also this must occur at the right time. In the last decade numerous studies in animals as well as clinical studies have provided convicing evidence, that the pharmacokinetics &/or the drugs effects -side effects can be modified by the circadian time &/or the timing of drug application within 24 hrs of a day [3].

Circadian variation in pain, stiffness and manual and manual deyterity in patients with osteo and rheumatoid arthritis have been studied and has implication for timing antirheumatide drug treatment [4]. Morning stiffness associated with pain at the time of awakening is a diagnostic criterion of the rheumatoid arthritis and these clinical circadian symptoms are supposed to be outcome of altered functioning of hypothalamic pitutary adrenocortical axis.

Chronopharmacotherapy for rheumatoid arthritis has been recommended to ensure that the highest blood levels of the drug coincide with peak pain and stiffness.[5]A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutic system [5,6].

Drug targeting to colon would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of disease that have peak symptoms inthe early morning such as nocturnal asthma, angina, arthritis [1,4,7,8].

Some orally administered drugs (E.g. Diclofenac, Theophyllin, IbuprofenIsosorbide) may exhibit poor uptake in the upper regions of GIT or degrade in the presence of GIT enzymes. Better bioavailability can be achieved through colon-specific drug delivery. Colonic targeting is also advantageous where delay in systemic absorption is therapeutically desirable [4, 7].

Circadian rhythms and their implications

Circadian rhythms are self-sustaining, endogenous oscillation, exhibiting periodicities of about one day or 24 hours. Normally, circadian rhythms are synchronized according to the bodys pacemaker clock, located in the suprachiasmic nucleus of the hypothalamus.

The physiology and biochemistry of human being is not constant during the 24 hours, but variable in a predictable manner as defined by the timing of the peak and through of each of the bodys circadian processes and functions. The peak in the rhythms of basal gastric and secretion, white blood cells (WBC), lymphocytes, prolactin, melatonin, eosinophils, adrenal corticotrophic hormone (ACTH), follicle stimulating hormone (FSH), and leuteinizing hormone (LH), is manifested at specific times during the nocturnal sleep span. The peak in serum cortisol, aldosterone, testosterone plus platelet adhesiveness and blood viscosity follows later during the initial hours of diurnal activity. Hematocrit is the greatest and airway caliber the best around the middle and afternoon hours, platelet numbers and uric acid peak later during the day and evening. Hence, several physiological processes in humans vary in a rhythmic manner, in synchrony with the internal biological clockThrough a number of clinical trials and epidemiological studies, it has become evident that the levels of disease activity of number of clinical disorders have a pattern associated with the bodys inherent clock set according to circadian rhythms. Infect just as the time of day influences normal biologic processes, so it affects the pathophysiology of disease and its treatment

MATERIALS AND METHODS FORMULATION DEVELOPMENT

Formulation of core tablets by direct compression

The inner core tablets were prepared by using direct compression method. As shown in Table powder mixtures of Salbutamolsulphate, microcrystalline cellulose (MCC, Avicel PH-102), cross-carmellose sodium (Ac-Di-Sol), SSG, crospovidone, starchingredients were dry blended for 20 min, followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 180mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with a 8mm punch and die to obtain the core tablet.

Table No. 1. Composition of core tablets

Ingredients (mg)	F 1	F2	F 3	F 4	F5	F6	F7	F8
Salbutamolsulphate	4	4	4	4	4	4	4	4
CCS	7.5	--	--	15	--	--	18.75	22.5
Crospovidone	--	7.5	--	--	15	--	--	--
SSG	--	--	7.5	--	--	15	--	--
Magnesium stearate	3.75	3.5	3.75	3.75	3.75	3.75	3.75	3.75
Starch	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
MCC	131	131	131	123.5	123.5	123.5	119.75	116
Total wt	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg

MCC: Micro crystalline cellulose, CCS: Cross caramellose sodium, SSG: Sodium starch glycolate.

Table No. 2. Composition of Press coat tablets

Press coat	P1(mg)	P2(mg)	P3(mg)	P4(mg)	P5(mg)
HPMC	200	300	--	400	--
Ethyl cellulose	200	100	--	--	--
Xanthum gum	--	--	300	--	200
Guar gum	--	--	100	--	200
Total wt(mg)	400	400	400	400	400

Formulation of mixed blend for barrier layer

The various formulation compositions containing HPMC, Ethyl cellulose, Xanthum gum and Guar gum. Different compositions were weighed dry blended at about 10 min. and used as press-coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Stability Studies

The stability study of the formulations was carried out according to ICH guidelines at 40 ± 2° C/75 ± 5 % RH for three months by storing the samples in stability chamber (Lab-care, Mumbai).

The purpose of stability testing is to provide evidence of the quality of the drug substance or drug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air etc). The final formulation was packed in suitable packing like blister and strip packs and then they will be kept at different temperature, humidity conditions and the samples will be analyzed for their physical and chemical properties.

RESULT AND DISCUSSION

Pre formulation parameters

Table No. s3. Pre-compression parameters for formulation batches

Formulation code	Bulk density (gm/mL)	Tapped density (gm/mL)	Compressibility index (%)	Hausner's ratio	Flow property
F1	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04	Very good
F2	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08	Very good
F3	0.45±0.045	0.52 ± 0.04	15.19±0.1	1.15±0.06	Very good
F4	0.44±0.044	0.52± 0.01	15.48±0.6	1.18±0.08	Very good

F5	0.45±0.045	0.51 ± 0.04	13.48±0.8	1.13±0.09	Very good
F6	0.51±0.045	0.59 ± 0.04	14.48±0.8	1.15±0.09	Very good
F7	0.521±0.02	0.629±0.05	17.17±0.05	1.20±0.05	Very good
F8	0.518±0.03	0.627±0.05	17.38±0.07	1.21±0.06	Very good

Table No. 4. Physical Evaluation Parameters ForCore Tablets

S.No	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
1	**Weight (mg)**	148	149	149	151	150	150	151	148
2	**Hardness (Kg/cm^2)**	4	4.2	4.3	4.1	4.3	4.4	4.2	4.3
3	**Thickness (mm)**	3.25	3.22	3.24	3.24	3.4	3.50	3.20	3.18
4	**Friability %**	0.4	0.55	0.62	0.54	0.62	0.57	0.65	0.52
5	**Disintegrationtime**	3 min 55sec	3min 30 sec	2min	2min 30sec	2min 12sec	2min	1min 30 sec	1min

Table No.5. Dissolution for core tablet

Time in mins	F1	F2	F3	F4	F5	F6	F7	F8
5	22.5	19.8	17.9	25	21.62	20.8	32	35.1
10	30.82	31.8	28.6	34	37.4	32.83	47.43	46.14
15	38.7	45.5	40.1	48	45.6	49.25	58.98	52.22
20	55.5	53.4	52.5	60	50.3	55.33	78.6	71.74
30	69.2	56.6	59.7	82	74.45	62.8	96.1	80.5
45	86.4	76.8	68.6	96.4	89.36	79.5	--	95.5
60	95.5	88.8	79.6	--	--	--	--	--

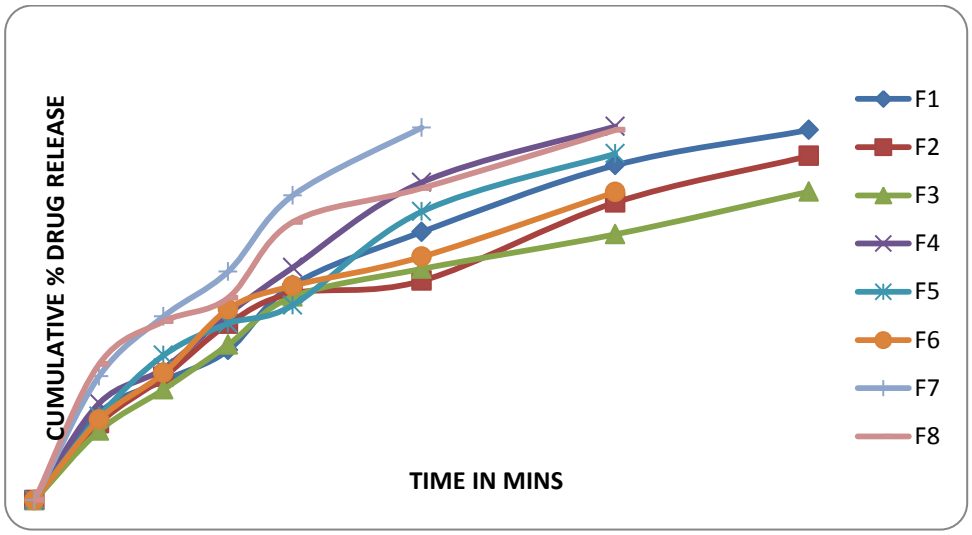

Fig No- Dissolution graph for core formulations F1-F8

Based on the drug release within the required time period F7was optimizedand further formulated for press coating.

Table No. 6. Evaluation Parameters For Tablet in Tablet

S. No	Physical parameter	P1F7	P2F7	P3F7	P4F7	P5F7
1	**Weight (mg)**	552	551	553	550	550
2	**Hardness**	7.5	7.7	7.8	7.2	7.6

	(Kg/cm^2)					
3	**Thickness (mm)**	2.5	2.6	2.4	2.4	2.5
4	**Friability %**	0.56	0.55	0.62	0.54	0.62

Table No. 7. Dissolution data for press coated tablet / Tablet in Tablet

Time in hrs	**Formulation code**				
	P1F7	**P2F7**	**P3F7**	**P4F7**	**P5F7**
1	8.89	9.62	5.65	8.95	2.74
2	15.45	18.74	10.20	25.65	9.77
3	40.32	45.98	25.65	42.98	13.85
4	51.21	56.12	41.35	60.45	20.75
5	74.85	78.66	65.32	82.80	44.35
6	82.66	89.90	76.32	95.64	69.41
7	90.74	95.55	85.64	--	80.60
8	94.22	--	94.65	--	96.4

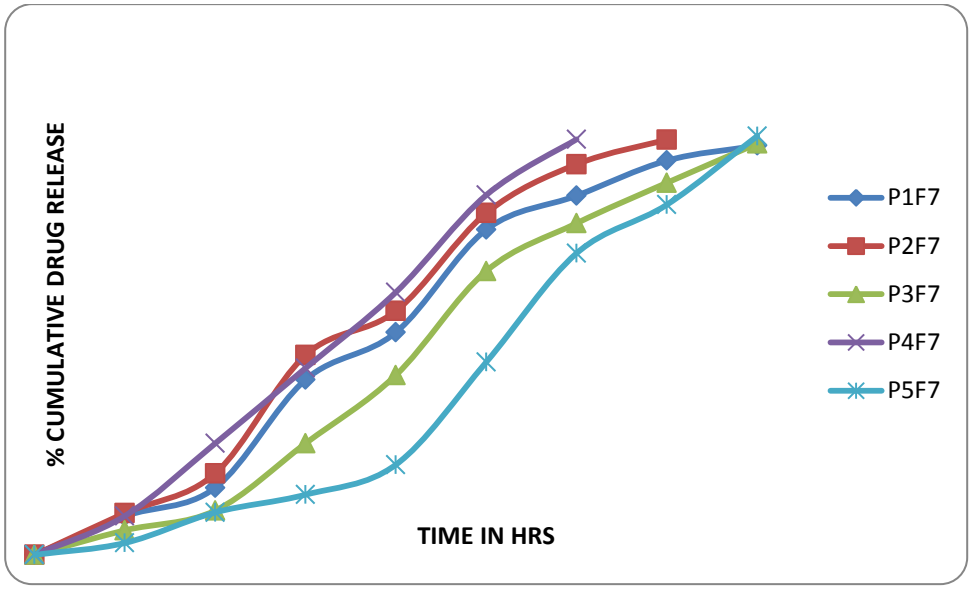

Fig No- Dissolution graph for Tablet in Tablet /press coated tablets of formulations (P1F7, P2F7, P3F7, P4F7, P5F7).

From the above core formulations F7 was selected for press coat by using different polymers like HPMC, Ethyl cellulose, Xanthum gum and Guar gum in different ratios among which 1part of Xanthum gum and 1part of Guar gumwas optimized based on the lag time(20.75% in 4 hours) and percent of drug release and also further evaluated.

Table No. 8. Stability Studies

Cumulative %drug release during 8h			
Sampling interval	25^{0}C/60%RH	30^{0}C/65%RH	40^{0}C/75%RH
0 Days	96.4	96.4	96.4
30Days	96.0	96.1	96.1
60 Days	95.2	95.5	94.8
90 Days	94.8	94.8	93.8

Stability studies of the formulation P5F7 of Salbutamol press coated were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25^{O}C/60%RH, 30 ^{o}C/65% RH and 40 ^{o}C/75% RH for 90 days. There was no significant change in the physical property and percent of drug release was within the limits±4 during 8hour during the stability period.

CONCLUSION

From the research results it can be concluded that, Formulated tablets gave satisfactory results for various physicochemical parameters like hardness, friability, thickness, weight variation and content uniformity. Xanthum gum and Guar gum (1:1) haspredominant effect on the lag time, while also shows significant effect on drug release. Hence it is conducive to prepare the formulation of novel tablet in tablet formulation with novel polymer coating containing β_2-adrenergic receptor agonists.

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