Fabrication and Evaluation of Modified Release Salbutamol Tablet in Tablet Dosage Comprising Novel Polymeric Coating

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ABSTRACT

In recent times, modified drug dosage forms offers manifold merits, such as maintain or sustaining constant drug level at the site of action, prevention of peak concentration fluctuation, reduction in dose of drug, reduced dosage frequency, averting the side effects and which in turn availing improved patient compliance. Hence in this current study, an effort has been made to develop a modified drug release by using tablet in tablet technique encompassing novel polymeric coating by using natural and synthetic polymers with Salbutamol sulphate. The inner core tablets were prepared by using direct compression method. It has been observed that 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: Modified release tablets; Novel polymer coating; Salbutamol sulphate; Tablet in tablet; Controlled drug delivery

INTRODUCTION

The 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 global market 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 [1, 9].

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 convincing evidence, that the pharmacokinetics &/or the drug's 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 dexterity 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 [10-15].

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 [16-24].

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 [25-31].

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 [32-41]. The peak in serum cortisol, aldosterone, testosterone plus platelet adhesiveness and blood viscosity follows later during the initial hours of diurnal activity.

MATERIAL AND METHODS

Formulation of core tablets by direct compression

The inner core tablets were prepared by using direct compression method. The powder mixtures of Salbutamol sulphate, microcrystalline cellulose (MCC, Avicel PH-102), cross-carmellose sodium (Ac-Di-Sol) ,SSG, crospovidone, starch ingredients were dry blended for 20 min, followed by addition of Magnesium Stearate [42-48]. 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 1).

Table 1: Composition of Press coat tablets

Press coat	Pr1(mg)	Pr2(mg)	Pr3(mg)	Pr4(mg)	Pr5(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 $40 \pm 2°$ 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.

RESULTS AND DISCUSSION

Pre formulation parameters (Tables 2-6) (Figure 1,2)

Table 2: Pre-compression parameters for formulation batches

Formulation code	Bulk density (gm/mL)	Tapped density (gm/mL)	Compressibility index (%)	Hausner's ratio	Flow property
Fr1	0.46±0.045	0.49 ± 0.07	12.19±0.6	1.12±0.04	Very good

Fr2	0.45±0.044	0.51 ± 0.09	12.01±0.8	1.17±0.08	Very good
Fr3	0.44±0.045	0.50 ± 0.04	15.02±0.1	1.16±0.06	Very good
Fr4	0.45±0.044	0.50± 0.01	16.01±0.6	1.17±0.08	Very good
Fr5	0.46±0.045	0.50 ± 0.04	13.43±0.8	1.14±0.09	Very good
Fr6	0.50±0.045	0.60 ± 0.04	14.38±0.8	1.16±0.09	Very good
Fr7	0.52±0.02	0.63±0.05	17.95±0.05	1.19±0.05	Very good
Fr8	0.53±0.03	0.64±0.05	17.24±0.07	1.18±0.06	Very good

Table 3: Physical evaluation parameters of core tablets

S. No	Physical parameter	Fr 1	Fr 2	Fr 3	Fr 4	Fr 5	Fr 6	Fr7	Fr 8
1	**Weight (mg)**	147	148	148	152	151	150	152	150
2	**Hardness (Kg/cm²)**	4.3	4.1	4.2	4.2	4.1	4.1	4.1	4.2
3	**Thickness (mm)**	3.05	3.02	3.22	3.5	3.26	3.51	3.4	3.2
4	**Friability %**	0.5	0.51	0.6	0.51	0.63	0.57	0.6	0.5
5	**Disintegration time**	3 min 50sec	3min 32 sec	2min	2min20sec	2min 15sec sec	2min	1min 15 sec	1min 20 sec

Table 4: Dissolution of core tablet

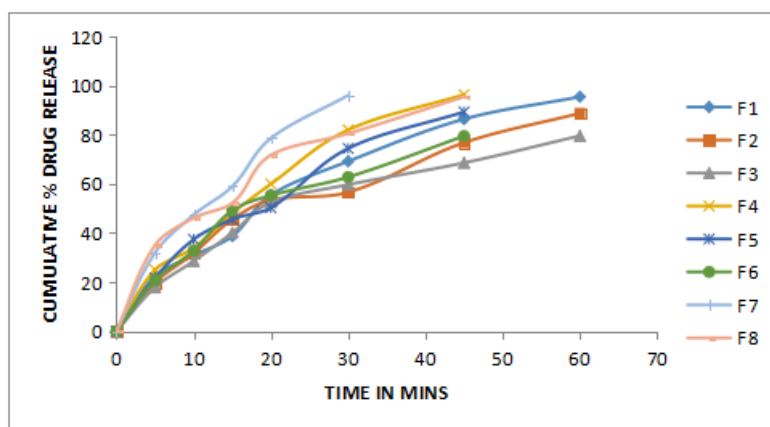| Time (min)	Fr1	Fr2	Fr3	Fr4	Fr5	Fr6	Fr7	Fr8
5	22.5	19.8	17.9	25	21.62	20.8	32	35.1
10	30.82	31.8	28.6	34	37.4	32.83	47.43	46.14
15	38.7	45.5	40.1	48	45.6	49.25	58.98	52.22
20	55.5	53.4	52.5	60	50.3	55.33	78.6	71.74
30	69.2	56.6	59.7	82	74.45	62.8	96.1	80.5
45	86.4	76.8	68.6	96.4	89.36	79.5	--	95.5
60	95.5	88.8	79.6	--	--	--	--	--

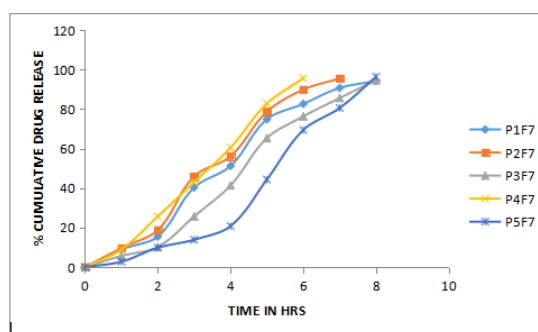**Figure 1**: Dissolution graph for core formulations F1-F8

Based on the drug release within the required time period F7 was optimized and further formulated for press coating.

Table 5: Press coated tablet evaluation parameters

S.No	Physical parameter	Pr1F7	Pr2F7	Pr3F7	Pr4F7	Pr5F7
1	Weight (mg)	552	551	553	550	550
2	Hardness (Kg/cm^2)	7.5	7.7	7.8	7.2	7.6
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 6: Dissolution data for press coated tablet / Tablet in Tablet

Time (hrs)	Formulation code				
	Pr1F7	Pr2F7	Pr3F7	Pr4F7	Pr5F7
1	9.01	9.62	6.02	9.15	2.73
2	15.45	18.72	10.2	25.65	9.77
3	40.12	46.08	26.05	42.98	14.81
4	50.21	55.92	41.35	60.45	21.33
5	72.85	79.06	64.32	83.8	45.35
6	81.66	90.1	76.32	95.64	70.41
7	91.74	95.53	85.62	--	80.6
8	93.22	--	94.65	--	96.4

Figure 2: Dissolution graph for Tablet in Tablet /press coated tablets of formulations (Pr1F7, Pr2F7, Pr3F7, Pr4F7, Pr5F7).

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 gum was optimized based on the lag time(20.75% in 4 hours) and percent of drug release and also further evaluated (Table 7).

Table 7: Stability Studies

Cumulative % drug release during 8 Hrs.			
Sampling interval	25°C/60% RH	30°C/65% RH	40°C/75% RH
0 Days	96.5	96.5	96.2
30Days	96.2	96.3	96.1
60 Days	95.3	95.6	95.82

| 90 Days | 95.1 | 95.2 | 94.3 |

Stability studies of the formulation Pr5F7 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 25ºC/60%RH, 30 ºC/65% RH and 40ºC/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

At this juncture, 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) has predominant 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 β2-adrenergic receptor agonists.

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