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Design, Development, Evaluation and Optimization of an Extended Release Tablet for Theophylline

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ABSTRACT:

Developing oral controlled release tablets for water soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these water soluble drugs if not formulated properly, may readily release the drug at a faster rate and produce a toxic concentration of drug on oral administration. Hence it is a challenging task to formulate a suitable tablet dosage form for prolonged delivery of water soluble drugs. Theophylline is a bronchodilator agent and commercially available as Elixir, Liquid and Solution which require two or three times a day dosing. Fast acting dosage forms leads to patient noncompliance and fluctuation in plasma concentration. To overcome this extended release dosage form is better choice. It is desirable in the therapeutic and prophylactic treatment of diseases to provide the Theophylline in extended release form. Extended release dosage forms can increase patient compliance due to reduction in frequency of dosing. They may also reduce the severity and frequency of side effects as they typically maintain substantially constant plasma levels. Hence the current research work is carried out to develop pharmaceutical equivalent extended release dosage form in comparison with innovator product. The most commonly used method of modulating the drug release is to include it in a matrix system. Diffusion controlled polymeric matrix devices have been widely used as drug delivery systems owing to their flexibility to obtain a desirable drug release profile, less chance of dose dumping, cost effectiveness and broad regulatory acceptance. The controlled drug-delivery systems are useful to increase the retention time of the drug-delivery systems for more than conventional dosage forms.

KEYWORDS: Theophylline, Bronchodilatation**,** Extended release, Glyceryl Behenate, HPMC

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INTRODUCTION:

The route of administration has a significant influence on the therapeutic effect of a drug. Oral route of drug administration is oldest and safest mode of drug administration. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed. On oral administration, during passage of the gastrointestinal tract the dosage form will encounter different anatomical and physiological factors like pH, gastric emptying, intestinal transit time, mucosal surface area, specific absorption sites and degradation and metabolism in the gastrointestinal tract, which able to influence drug release from the dosage form and subsequent absorption.[1, 2, 3, 4] In recent years, sophisticated drug delivery systems have been devised and developed to release the drug substance into the body at a controlled and predetermined rate. Through these controlled release devices, the drug is administered at a specific rate that maintains its concentration within optimum limit and directs the active ingredient to the target area.

There are several terms used interchangeably viz. controlled release, programmed release, sustained release, prolong release, timed release, slow release, extended release and other such dosage forms. However, controlled release systems differ

from the sustained release systems. Sustained release systems simply prolong the drug release and hence plasma drug level for an extended period of time (i.e. not necessarily at a predetermined rate).[5]

Modified release tablets are coated or uncoated tablets containing auxiliary substances or prepared by procedures that separately or together, are designed to modify the rate or the place at which the active ingredient is released. Modified release tablets may be divided into following categories,

1) Enteric coated tablet

2) Prolonged release tablet

- Sustained release tablet
- Extended release tablet

3) Delayed release tablet

Enteric coated tablets (gastro resistant tablets) are delayed release tablets that are intended to resist the gastric fluid but to release their active ingredients in the intestinal fluid. For these purpose substances such as cellulose acetate phthalate and anionic copolymers of methacrylic acid and its ethers are used for providing tablets with a gastric resistant coating or for covering either granules or particles with gastric resistant coating. Prolonged release tablets are also known as sustained release tablets or extended release tablets which are formulated in such a manner as to make the contained active ingredient available over an extended period of time after ingestion.[6]

MATERIALS AND METHODS

1. Materials Used:

Table: 1 Material used

Sr. No.	Name of Chemical	Function
1	Theophylline	API
2	Lactose monohydrate	Pore former agent
3	Hydroxypropyl methylcellulose	Rate controlling polymer
4	Glyceryl Behenate	Rate controlling polymer
5	Povidone K-30	Binder
6	Purified water	Solvent
7	Talc	Anti adherent
8	Magnesium state	Lubricant

2. Flow chart of detailed manufacturing process:

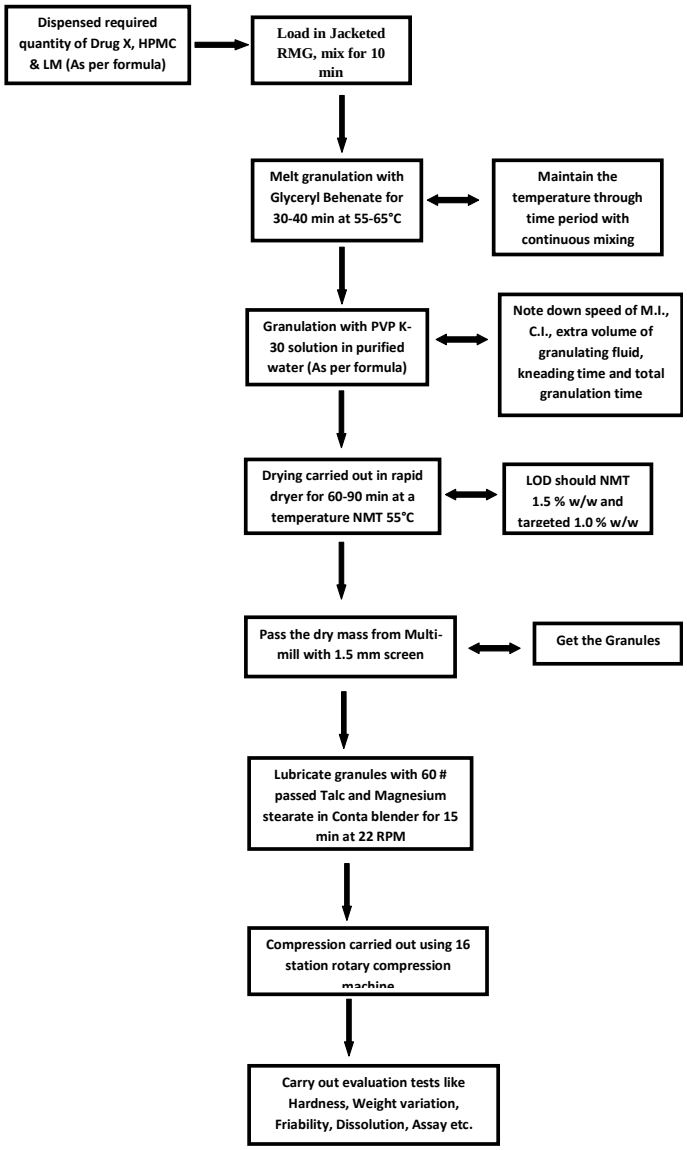

Figure: 2. Flow chart of manufacturing process

3. Manufacturing of Theophylline extended release tablet:

Table: 2 Composition of extended release tablet:

FORMULA	A-001	A-002	A-003	A-004	A-005	A-006	A-007
API	600	600	600	600	600	600	600
Lactose Monohydrate	-	-	-	-	-	-	-
Glyceryl Behenate	-	82	67	62	47	47	47
HPMC K-100	82	-	15	-	15	15	15
PVP K-30	-	-	-	20	20	10	4
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
PVP K-30	-	-	-	-	-	10	16
Talc	15	15	15	15	15	15	15
Mg. Stearate	8	8	8	8	8	8	8
TOTAL	705	705	705	705	705	705	705

4. Methods Used:

4.1 Preformulation Study: [7, 8, 9, 10]

Pre-formulation is a branch of pharmaceutical sciences that utilizes biopharmaceutical principles in the determination of physicochemical properties of a drug substance. The goal of pre-formulation studies is to choose the correct form of the drug pre-requisite for formulation. Therefore, in pre-formulation substance, evaluate its physical properties and generate a thorough understanding of the material's stability under various conditions, leading to the optimal drug delivery system. The pre-formulation study focuses on the physicochemical parameters that could affect the development of efficacious dosage form. A thorough understanding of these properties may ultimately provide a rationale for formulation design. Also it will help in minimizing problems in later stages of drug development, reducing drug development costs and decreasing product's time to market.

Scope:

The use of pre-formulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Followings are the tests carried out for the preformulation study.

1) Organoleptic characteristics
2) Solubility of drug
3) Particle size and size distribution
4) Bulk density
5) Tapped density
6) Carr's index
7) Hausner's ratio
8) Compatibility study

4.2 Methods adopted for evaluation of Theophylline extended release tablet: [7, 8]

Weight variation:

Every individual tablet in a batch should be in uniform weight and weight variation within permissible limits. Twenty (20) tablets from each batch were randomly selected and individually weighed in milligrams (mg) on an analytical balance. The average weight, standard deviation and relative standard variation were reported in table.

Tablet thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using Vernier Calipers. The average thickness, standard deviation and relative standard variation were reported in table.

Tablet hardness: Tablet hardness was measured using a Dr. Schleuniger hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kilopond (kp) and the average hardness, standard deviations and relative standard variation were reported in table.

Friability:

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Electrolab tablet friabilitor. The tablets were then dedust and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets and reported in table.

Uniformity of dosage units:

This was assessed according to the USP requirements for content uniformity. The batch meets the USP requirements if the amount of the active ingredient in each of the 10 tested

tablets lies within the range of85% to 115% of the label claim and the RSD is less than or equal to 6%. According to the USP criteria, if one of these conditions is not met, an additional 20 tablets need to be tested. Not more that 1 unit of the 30 tested should be outside the range of 85% and 115% of the label claim and no unit outside the range of 75% to 125% of label claim. For all RSD should not exceed 7.8%.

In vitro drug release:

In vitro drug release was performed for the manufactured tablets according to the USP 26 "Dissolution procedure", over a 24-hour period, using an automated Vankel dissolution system. A minimum of 6 tablets per batch were tested. The dissolution of Drug X from the extended release tablets was monitored using an automated VK 7010 dissolution tester coupled to an automated VK 8000 sample collector. The USP 24 (apparatus II) method was used at 50 rpm. The media used was 900 ml of 0.1N HCl at a pH 2.0 for the first 1 hr after which 900 ml of pH of 6.8 buffer up to 24 hr and maintained at 37± 0.5°C. Sample should be collected at 1, 2, 4, 6, 8, 12, 16, 18, 20, 24 hr.

Similarity value calculation:

Different dissolution profiles were compared to establish the effect of formulation or process variables on the drug release as well as comparison of the test formulations to the marketed product. The dissolution similarity was assessed using the FDA recommended approach (f2 similarity factor) (Food and Drug Administration 1997b). The similarity factor is a logarithmic, reciprocal square root transformation of the sum of squared errors, and it serves as a measure of the similarity of two respective dissolution profiles:

$$f2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} x100\right\}$$

where: f_2= Similarity factor

n = number of time points

R_t = percent of marketed product release profile/ Dissolution value of the reference at't' time

T_t = percent of test formulations release observed/ Dissolution value of test formulation at't' time

RESULTS

Table 3: Result of preformulation parameters

Parameter	API
Bulk Density (gm/cm^3)	**0.368 gm/cc**
Tapped Density (gm/cm^3)	**0.423 gm/cc**
Compressibility Index (%)	**10.36%**
Hausner's Ratio	**1.12**

Table 4: Results of blend uniformity of lubricated blend RPM: 22, blending time: 15 Minutes.

Sample location	Acceptance Criteria	Location 1	2	3	4	5	Mean	STD
Top	NLT 90.00 % and NMT 110.00 % of label claim, RSD : NMT 5.00 %	101.4	99.1	101.4	100.3	100.8	100.3	0.92
Bottom		99.6	100.8	99.2	100.9	99.3		

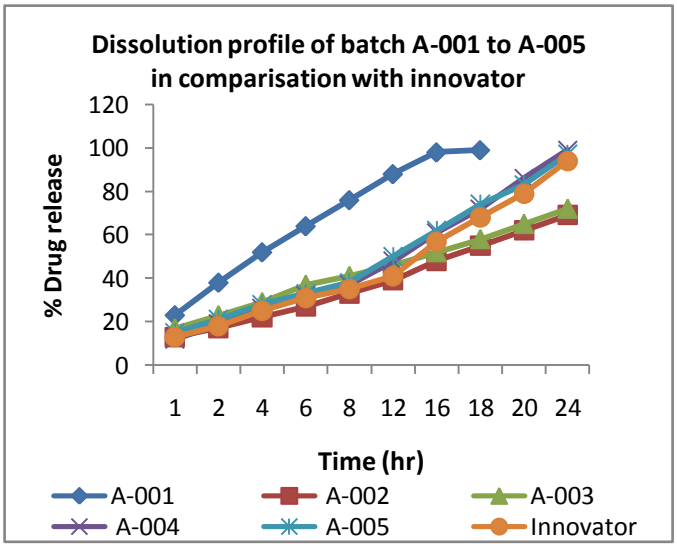

Figure 2: In-vitro release profile of batch A-001 to A-005 in comparison with innovator according to Table 5.

Table 5: In-Vitro drug release profile

	Dissolution profile						
	Strength	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg
Dissolution medium	Batch No	**A-001**	**A-002**	**A-003**	**A-004**	**A-005**	**Innovator**
	Time (hr)	% CDR	% CDR	% CDR	% CDR	% CDR	% CDR
0.1 N HCl	1	23	13	17	12	15	13
	2	38	17	23	19	21	18
	4	52	22	29	26	28	25
	6	64	27	37	32	33	31
	8	76	33	41	37	38	35
pH 6.8 Buffer	12	88	39	46	48	50	41
	16	98	48	52	61	62	57
	18	99	55	58	72	74	68
	20		62	65	86	83	79
	24		69	72	99	97	94
Similarity factor (F2)		26	47	49	79	75	-

Post-formulation studies:

Table 6: Results of post formulation studies of formulated batches

Batch No.	**A-001**	**A-002**	**A-003**	**A-004**	**A-005**	**Innovator**
LOD	1.22%	0.30%	0.74%	0.94%	0.89%	0.30%
Average weight in mg	705 ± 3%	705 ± 2%	705 ± 4%	705 ± 3%	705 ± 3%	705 ± 2%
Tablet hardness in kp	10.9-11.2	11.4-12.2	10.5-11.8	10.4-12.1	5.8-7.2	11.4-12.2
Thickness in mm	5.42-5.48	4.98-5.01	4.98-5.01	5.27-5.30	5.05-5.12	4.98-5.01
Friability	0.64%	0.64%	0.59%	0.61%	0.78%	0.64%
Assay	95.68%	97.30%	96.73%	97.69%	97.41%	97.30%
Dissolution	99%	69%	72%	99%	97%	69%
F2 Value	26	47	49	79	75	47

SUMMARY AND CONCLUSION

An extended release tablets are also known as prolonged release or sustained release tablets, which are formulated in such a manner so as to make the contained active ingredient available over an extended period of time after ingestion. There are certain approaches which use to formulate an extended release dosage form like diffusion controlled, dissolution controlled, diffusion and dissolution controlled etc. In the present experiment matrix tablet of Drug X was prepared using several polymers like Glyceryl Behenate, HPMC, Povidone and Lactose monohydrate which follow diffusion controlled delivery principle. Here different polymers are used with different purpose like GB use as hydrophobic release retarding agent, HPMC as hydrophilic controlling agent, Povidone as a binder as well as pore former agent and Lactose monohydrate as pore former agent. Before the development of an extended release tablet various preformulation test is also carried out to determine Bulk density, Tapped density, Compressibility index, Hausner's ratio, solubility, particle size, drug-excipients compatibility [by physical observation, Impurity detection, Water content and DSC]. From all this results we can concluded that drug have higher water solubility, light in density [so melt granulation method is adopted for formulation], sufficient particle size and compatible with all other excipients.

Extended release tablet of Drug X was prepared with different polymers such as GB, HPMC, PVP and LM in various ratios, also with different addition pattern, different fusion time and different hardness. All the formulations were subjected to various evaluation parameters i.e. weight variation, hardness, friability, diameter, assay, in-vitro release for 24 hr. From all these results, it was concluded that A-018 was the best formulation and release mechanism was diffusion controlled from all prepared batches. The formulation was also subjected to accelerated stability studies for 2 months in HDPE bottle along with purified cotton and sealed with heat induction sealer by storing at various ICH storage conditions. At 40°C / 75% RH storage condition, it shows better stability than other two conditions at higher temperature.

Thus, it can be concluded that A-018 formulation shows better results, comparable with innovator product and so it can be concluded that antiasthmatic Drug X can be successfully formulated as an extended release tablets.

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