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Formulation and in-vitro evaluation of theophylline sustained release tablet

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ABSTRACT

The aim of present study was to prepare sustained release tablet of Theophylline so as to prolong its elimination time and at the same time to keep cost of the formulation minimum. In this study ethyl cellulose and Eudragit are used in the formulation to sustain the release of Theophylline. Ethyl cellulose and Eudragit are added at the granulation step to form a sustained release coating around each granule. Different batches were designed one after another on trial and error basis to get the optimum drug release upto 12 hours.

Keywords: Theophylline, ethyl cellulose, Eudragit, sustained release, coating, tablet.

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INTRODUCTION

For decades acute disease and chronic illness is being clinically treated through delivery of drugs to patients in the form of tablets, capsules, pills, creams, liquids, ointments, aerosols, injectables and suppositories. To maintain the concentration of an administered drug within therapeutically effective range, it is required to take drug dosage several times and this result in fluctuations in plasma drug concentration[1]. This can be overcome by formulation of sustained release dosage form which gives drug release in an amount sufficient to maintain therapeutic drug level over extended period of time. As a result sustained release formulations are preferred for drugs which are administered orally and have high dosing frequency[2, 3].

Theophylline has long being used as a treatment for diseases, including bronchial asthma. However, as its therapeutic concentration range is narrow, and its absorption is prone to the effects of meals, the dosing management of the drug has been difficult. The drug release rate is difficult to control in a sustained release tablets. Moreover, as they are manufactured by a complicated process, the drug release rate is likely to vary among lots, and advanced processing is needed to ensure consistent quality. Drug absorption from a conventional matrix tablet is influenced heavily by its transition rate in the GI tract, and accordingly, the bioavailability of conventional matrix tablet varies widely. It is the purpose of this study to develop a new dosage form that overcomes these biological and technological problems[4, 5, 6].

In this study sustained release granules of theophylline were prepared, using granulation method. Unlike film coating, no expensive instrument was used.

MATERIALS & METHODS

Materials: Theophylline anhydrous, Ethyl Cellulose, Eudragit L100, Polyvinyl Pyrrolidione(K-30), Magnesium Stearate, Talc, Isopropyl Alcohol, Dichloromethane, Acetone.

Preparation of sustained release tablet of Theophylline anhydrous:

Sustained release tablets of Theophylline were prepared by wet granulation method. Different quantities of different polymers (Table 1) were dissolved in respective solvents and the resulting solution was added slowly to 20# passed Theophylline blend in Kenwood granulator. In present study ethyl cellulose was added at the granulation step in solubilized form. This results in application of ethyl cellulose at molecular level to form water insoluble coat around granule. The resulting granules were dried in Rapidrier at 30-40^{0}C till LOD becomes below 2.5%. Dried granules were passed through 20# and mixed with magnesium Stearate and talc. Tablets were prepared from these granules using 16 station rotary tablets compression machine.

Table 1: Formulation and composition of SR tablet of Theophylline anhydrous

Ingredients	Batch No						
	F1	F2	F3	F4	F5	F6	F7
TP	250	250	250	250	250	250	250
EC(20cps for F1, F2 & 7cps for F3- F7)	1	2	1	3	2	1.6	1.8
PVP K-30	5	8	-	-	-	-	-
IPA	qs	qs	qs	qs	qs	qs	qs
MDC	qs	qs	qs	qs	qs	qs	qs
Talc	2	2	2	2	2	2	2
Mag. Stearate	2	2	2	2	2	2	2
Eudragit L-100	-	-	15	10	13	14	13

TP- Theophylline anhydrous, EC - ethyl cellulose, PVP K-30 – Polyvinylpyrolidone, IPA - isopropyl alcohol, MDC - methylene dichloride, qs- quantity sufficient.

Evaluation of granule and powder properties [7, 8, 9]:

To determine physicochemical properties and release characteristics of the granules, all formulations are subjected to pre-formulation studied like Angle of repose, void volume, porosity.

Evaluation of compressed tablets [7, 8, 9, 10]:

Prepared tablets were evaluated for Thickness, hardness, friability, weight variation, disintegration and dissolution.

Weight variation:

Weight variation was performed by weighing 20 tablets individually, taking average weight and comparing individual weight with the average weight.

Hardness:

Hardness of randomly selected tablets was determined by Erweka hardness tester. Hardness was measured in Newtons.

Friability:

Friability was determined by first weighing 10 tablets before placing in Roche friabilator, which was then rotated for 4 minutes at 25 rpm. After dusting tablets were reweighed.

Disintegration:

Disintegration test was performed by introducing one tablet in each tube and then suspending the basket assembly in a beaker containing purified water and operating the apparatus until tablet disintegrates completely.

In-Vitro Dissolution test:

In-vitro dissolution studies were carried out using USP XXI Dissolution Test Apparatus Type II at 50 rpm. Dissolution test was carried out for the period of 12 hours using 0.1N HCl (pH 1.2) solution as a dissolution medium at 37 ± 0.5^0 C for one hour and Phosphate Buffer (pH-6.8) for rest of the time. 5ml sample was withdrawn at predetermined time interval up to 12 hours and replaced with same volume of fresh dissolution medium. The withdrawn samples were analyzed by SHIMADZU UV spectrophotometer at 274 nm using Phosphate Buffer as a blank. Percentage cumulative drug release was calculated.

RESULTS AND DISCUSSION

Pre compression parameters: As shown in table 2, the angle of repose for all formulations fell within the range of 27–35^0 indicating good flow properties. Bulk density values of all theophylline formulations fell in the range of 0.35-0.5 g/cm^3 indicating good packing capacity.

Table 2: Powder properties of different formulations

Formulation	Angle of repose	Bulk density(g/cc)	Void volume(cc)	% porosity
F1	30.17	0.457	1.3	27
F2	30.31	0.442	1.7	32
F3	32.13	0.532	1.6	26
F4	29.12	0.567	1.3	27
F5	31.29	0.439	1.7	29
F6	34.32	0.547	1.4	26
F7	33.57	0.522	1.6	27

Post compression parameters:

All the theophylline formulations were evaluated for various parameters; observations are depicted in Table 3.

The % deviation in weights of tablets was ± 5% which is within the range according to IP. This shows uniform die fill during tablet compression. The tablets were analyzed for potency. The drug content was in range of 98-103% showing uniform distribution of drug in tablet.

As there was no much variation in thickness of tablets in each formulation, it shows that granules and powder blends were consistent in particle size and uniform behavior during compression process. The hardness of tablet was measured by Erweka hardness tester. The tablet hardness was in the range of 110 – 123 N. Friability was found to be 0.2 – 0.3 %. As friability was below 0.8 %, tablets in each formulation can withstand the mechanical shocks.

Table 3: Tablet properties of theophylline formulations

Formulation	Average weight(mg)	Thickness(mm)	% drug content	Hardness(N)	% Friability
F1	265	3.82	99.33	113	0.23
F2	263	3.81	98.63	110	0.25
F3	271	3.83	103.83	120	0.26
F4	267	3.82	101.13	121	0.34
F5	265	3.81	103.59	125	0.35
F6	270	3.83	102.7	107	0.26
F7	268	3.82	101.6	114	0.31

In-vitro dissolution studies:

Table 4: Cumulative % Drug Release (%CDR)

Time(hrs)	Cumulative % Drug Release (% CDR)						
	F1	F2	F3	F4	F5	F6	F7
1	22.9	23.3	18.5	17.6	17.7	17.0	17.4
2	35.7	34.0	56.1	25.2	25.7	33.8	28.1
4	49.7	46.5	101.3	33.9	47.6	60.7	47.8
8	68.9	64.8	103.5	49.0	70.7	93.6	77.3
12	82.7	77.9	105.2	62.8	87.4	99.6	96.9

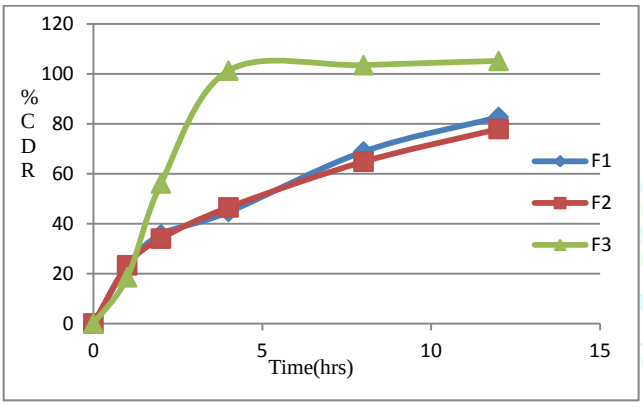

Figure 1: In-vitro dissolution profile F1-F3

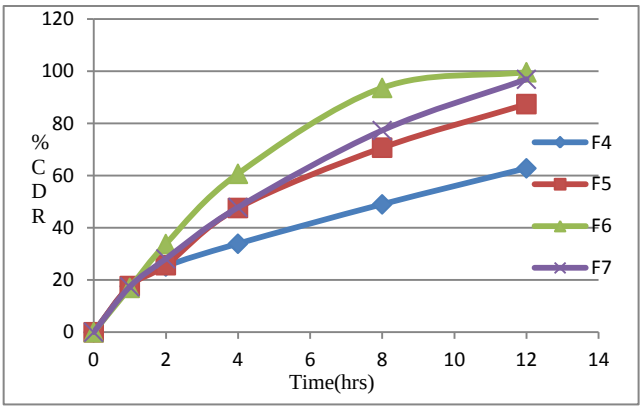

Figure 2: In-vitro dissolution profile F4-F7.

F1 & F2 showed very slow drug release (82% & 77% after 12 hours) due to use of EC (20cps) in wet granulation. Since EC is solubilized in granulating solvent it gets applied to granules at molecular level. Degree of formation of film around granules is more when EC is applied at molecular level[11].

According to Percolation theory, when matrix is composed of water soluble drug and a water insoluble polymer, drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network. The total number of EC molecules surrounding granules increases when EC is applied at molecular level. When more EC particles present the fewer clusters of soluble drug substance are formed. Due to this pore network becomes less extensive and more torturous resulting in slower drug release[12].

As the drug release rate was found to be slower with EC (20cps), EC of 7 cps was used in next formulation. In addition to EC it was found that PVP K-30 produces harder granules, which upon coating with EC resist the drug release for longer time. These harder granules do not allow the erosion of the tablet for the drug release. To control the drug release in first hour that is in acidic media, an enteric polymer (Eudragit L-100) was used in next formulations instead of PVP K-30.

F3 showed faster drug release (56% after 2 hours and 101% after 4 hours) since tablet eroded completely after 3 hours. Therefore to maintain the structural integrity of tablet, EC concentration was increased and thereafter it was optimized along with concentration of Eudragit in the next formulations until desired drug release pattern was obtained.

CONCLUSION

Conclusion can be drawn from the present investigation that, a combination of hydrophobic polymer and enteric polymer can be used successfully for sustained release tablets of theophylline. Optimized formulation containing ethyl cellulose and Eudragit had successfully sustained the drug release up to 12 hours. Thus the sustained release tablet of theophylline can be using biocompatible polymers can be formulated, evaluated and found to be suitable candidate for prolonging the release of theophylline.

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CONFLICT OF INTEREST

The author has no conflict of interest.

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