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FORMULATION AND EVALUATION OF THEOPHYLLINE SUSTAINED RELEASE MATRIX TABLETS USING SYNTHETIC POLYMERS

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ABSTRACT
The aim of present work was to develop theophylline sustained release tablets which could improve patient compliance towards the effective management of asthma The polymers, HPMC (Hydroxy propyl methyl cellulose) K4M, HPMC K100M, Eudragit, Chitosan in blending and granulation stage of processing and evaluate their physico-chemical properties. The precompression limits of the powder blends used for the preparation of sustained-release tablets were in an acceptable range of pharmacopeial specification with excellent flow and good compressibility. Wet granulation method prepared tablets using different grades of polymers HPMC K100, HPMC K4M, Eudragit, Chitosan. The active ingredient, release retardants, diluents, fraction of polymer are mixed to make wet mass for granulation. The in- vitro release was prolonged to 12 hours using HPMC K4M, HPMC K100M, Chitosan, Eudragit. F9 formulation prolonged the theophylline release in 12 hours. The effect of polymer on drug release was studied. Thus, sustained release matrix tablets can promise better patient compliance through reduction in over-all dose and dosage regimen, which can be of excessive support to treat chronic disease.

INTRODUCTION

Asthma is a permanent inflammatory ailment of the airways that distresses approximately 15 million individuals in the United States, with an increase in prevalence of over 75% from 1982 to 1995 [1]. This inflammatory disease results in a hyper responsiveness of the airways that can be started by revelation to various stimuli, including allergens, exercise, cold temperatures, aspirin and viral infections. In addition, many asthmatic patients have nocturnal asthma, with symptoms that awaken them during the night or affect them upon emergent in the morning. Drug therapy plays an important role in the suitable management of asthma [2,3]. Theophylline has been used to treat airway sicknesses for more than 80 years. It was earlier used as a bronchodilator, but high doses required are related with frequent side effects, so its use decayed as inhaled β2-agonists became more widely used [4]. More recently it has been exposed to have anti-inflammatory effects in asthma and chronic obstructive pulmonary disease at minor concentrations. The molecular mechanism of bronchodilatation is inhibition of

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phosphodiesterase, but the anti-inflammatory effect may be due to inhibition of PDE4 and histone deacetylase-2 initiation, ensuing in substituting off of initiated inflammatory genes [5-7]. Through this mechanism, theophylline also contraries corticosteroid resistance, and this may be of particular value in severe asthma and chronic obstructive syndrome, where in histone deacetylase-2 activity is reduced [8].

MATERIALS & METHODS:

Theophylline anhydrous (Arco pharma Pvt. Ltd., Mumbai), Chitosan (Swakit Biotech Pvt. Ltd.), HPMC (Hydroxy propyl methyl cellulose) K4M (Otto Kemi, Mumbai), HPMC K100M (Otto Kemi, Mumbai), Eudragit (Otto Kemi, Mumbai), PVP (Poly vinyl pyrrolidone) K30 (Parkash Chemicals Pvt. Ltd.), Lactose Anhydrous (ISCO Research Laboratories Pvt. Ltd. Mumbai), Isopropyl Alcohol (JK Chemicals.), Magnesium Stearate (Arora &Co. Delhi) and Talc (Central Drug House (p) Ltd., Mumbai).

Preparation of sustained release layer of theophylline [9-15]

Sustained release tablet layer was organized by wet granulation method according to the formula. All the ingredients including drug were weighed exactly and passed through 60 mesh sieve separately. A mixture of all ingredients except the lubricant and glidant were mixed in a porcelain mortar using Isopropyl alcohol as the granulating fluid until a dump mass which easily destitute into lumps when pressure was applied to it using the thumb was formed.

Table 1: Composition of Theophylline sustained release layer

Ingredients	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**
Theophylline	200	200	200	200	200	200	200	200
H.P.M.C K4M	25	50	75	100	-	-	-	-
H.P.M.C K100 M	-	-	-	-	25	50	75	100
PVP K30	50	50	50	50	50	50	50	50
Lactose anhydrous	205	180	155	130	205	180	155	130
Iso Propyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
Total	500	500	500	500	500	500	500	500
Ingredients	**F-9**	**F-10**	**F-11**	**F-12**	**F-13**	**F-14**	**F-15**	**F-16**
Theophylline	200	200	200	200	200	200	200	200
Chitosan	25	50	75	100	-	-	-	-
Eudragit	-	-	-	-	25	50	75	100
PVP K30	50	50	50	50	50	50	50	50
Lactose anhydrous	205	180	155	130	205	180	155	130
Iso Propyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
Total	500	500	500	500	500	500	500	500

All the quantities expressed as mg per Tablet.

Evaluation of blend

There are many formulations and progression variables involved in socializing step and all these can affect the characteristics of blend designed. The characterization of mixed blend done for the undertaking property of powder such as bulk density, tapped density, Hausner's ratio, Compressibility index and angle of repose. The numerous characteristics of blends were tested.

Bulk Density

Bulk density is well-defined as the mass of powder divided by the bulk volume and is expressed as g/cm^3. The bulk density of a powder largely depends on particle size distribution, particle shape and propensity of particles to observe together. A standard procedure was tracked to determine the bulk density of blends. The bulk volume and weight of powder was determined [16]. The cylinder was released into a hard wooden surface three times

from a height of 1 inch at an interval of 2 sec. The bulk density was calculated via the formula

$$Pb = M/V_b$$

Where, Pb = Bulk density; M = Mass of sample in g;
Vb = Bulk volume of blend in cm^3

Tapped Density

Tapped density can be well-defined as mass of blend in the measuring cylinder alienated by its upped volume. The measuring cylinder containing a predictable mass of blend was tapped 100 times on a hard wooden surface. The tapped volume occupied in the cylinder and the weight of the blend was measured [16]. The tapped density was calculated by the formula

$$Pt= M/Vt$$

Where, Pt = Tapped density; M=Mass of blend in g
Vt = Tapped volume of blend in cm^3

Compressibility Index

The simplest way for measurement of movement of powder is its compressibility, an sign of the event with which a material can be induced to movement is given by compressibility index [17], which is calculated as follows

$$I= Pt-Pb/ Pt (100)$$

Where, Pt= Tapped density; Pb= Bulk density

Hausner Ratio

Hausner ratio (HR) is an indirect index of case of powder movement. It was calculated by the following formula

$$HR= pt/pb$$

Where, pt is tapped density and pb is bulk density. Lower Hausner ratio (<1.25) designates better movement properties than higher ones (>1.25)

Angle of Repose

Angle of repose postulates the frictional forces in a slack powder. It can be distinct as the determined angle between the slope of pile of powder and its base. The Angle of Repose was determined using funnel method, intended by Newman [18]. The blend was emptied through a funnel that could be elevated vertically until a specified cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (0) was calculated via the formula

$\tan \theta = h/r$; Therefore, $\theta = \tan^{-1}(h/r)$, Where

θ = angle of repose; H = height of cone; R = radius of cone

Evaluation of sustained release tablets

After compression of powder, the tablets were evaluated for organoleptic characteristics like color, odor, diameter, thickness and physical characteristics like hardness, friability, weight uniformity and dissolution studies.

General Appearance

The general appearance of a tablet, its visual documentation and over all elegance is essential for consumer acceptance. These comprise tablet's size, shape, colour, presence or absence of an odour, taste, surface texture and physical flaws.

Thickness

Micrometer was used to measure the thickness of the tablet as done in case of conventional tablets 10 tablets were aimlessly selected to perform the process [19].

Diameter

Micrometer was used to ration the diameter of the tablet is done in case of conventional tablets. Ten tablets were aimlessly selected to perform the process.

Weight uniformity

The standard pharmacopoeial dealings were followed for this purpose. According to IP, 20 tablets were aimlessly selected and individually as well as mutually weighed on a digital balance. The average weight was calculated. The weight variation test would be reasonable method of determining the drug content uniformity [19].

Tablet Hardness

Hardness of tablet is distinct as the force applied across the diameter of the tablet in order to disruption the tablet, the resistance of the tablet to chipping, breakage under state of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of individually formulation was determined by using Monsanto Hardness Tester [20].

Friability

Friability of the tablets was determined by using Roche friabilator. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions [21]. Tablets were the dosed using a lenient muslin cloth and reweighed. The friability (F%) is given by the formula $F\%= \{Wo/ W\} \times 100$
Where, W, is weight of the tablets before t the tablets after test.

In-vitro dissolution studies

The in vitro release of drug from theophylline tablet was carried out for 12 hours using paddle type tablet dissolution apparatus containing 900 ml of dissolution medium maintained at 37±5°C and speed of agitation at 50 rpm. For the first 2 hours, 0.1N HCI buffer solution was used as dissolution medium and then the dissolution medium was changed by replacing with pH 6.8 phosphate buffer solution for extra 10 hours. At started time interval, 5 ml of solution was analyzed spectrophotometrically at 272 nm after appropriate dilution. The volume of the dissolution medium was adjusted to 900 ml at every sampling time by replacing 5 ml with same dissolution medium [22-25].

Table 2: Characterization of blends (F1-F16) Formulation n=3

Formulation	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's index (%)	Hausner's Ratio	Angle of Repose
F-1	0.520±0.14	0.608±0.15	13.65±0.02	1.169±0.02	26.5±0.2
F-2	0.474±0.12	0.555±0.12	14.59±0.04	1.170±0.08	26.0±0.8
F-3	0.520±0.10	0.658±0.04	20.97±0.02	1.265±0.02	26.7±0.4
F-4	0.472±0.05	0.565±0.14	15.12±0.01	1.197±0.05	25.1±0.1
F-5	0.507±0.02	0.631±0.17	19.65±0.02	1.244±0.03	26.0±0.6
F-6	0.489±0.02	0.559±0.16	14.31±0.03	1.143±0.04	25.6±0.3
F-7	0.496±0.02	0.569±0.06	12.82±0.05	1.147±0.05	25.9±0.9
F-8	0.498±0.02	0.601±0.08	17.13±0.06	1.206±0.03	25.2±0.1
F-9	0.489±0.01	0.569±0.04	16.35±0.04	1.163±0.04	24.2±0.1
F-10	0.528±0.05	0.663±0.21	20.36±0.03	1.255±0.03	24.3±0.2
F-11	0.453±0.15	0.512±0.02	11.52±0.03	1.130±0.05	24.8±0.4
F-12	0.433±0.15	0.561±0.13	22.81±0.01	1.298±0.02	25.6±0.3
F-13	0.459±0.07	0.545±0.08	15.77±0.07	1.187±0.04	26.9±0.4
F-14	0.490±0.06	0.578±0.08	15.22±0.06	1.179±0.08	26.4±0.4
F-15	0.442±0.06	0.523±0.11	15.48±0.05	1.194±0.05	26.4±0.5
F-16	0.468±0.06	0.528±0.10	11.36±0.10	1.128±0.04	25.7±0.4

Table 3: Characterization of Tablet formulation

Formulation	Hardness (kg/cm^2)	Thickness (mm)	Weight Variation (mg)	Friability (%)
F-1	9.42± 0.08	3.83±0.06	501.4±1.02	0.24±0.03
F-2	9.39±0.03	3.76±0.02	503.0±1.12	0.12±0.02
F-3	9.21±0.01	3.71±0.02	501.0±1.02	0.19±0.03
F-4	8.95±0.06	3.73±0.05	501.1±1.15	0.09±0.01
F-5	7.99±0.08	3.83±0.05	499.3±1.03	0.04±0.01
F-6	9.02±0.01	4.02±0.04	498.6±1.09	0.21±0.02
F-7	8.95±0.01	3.70±0.05	501.1±1.13	0.16±0.03
F-8	7.39±0.09	3.89±0.04	500.9±1.14	0.13±0.04
F-9	9.59±0.01	3.82±0.02	500.0±1.15	0.07±0.04
F-10	9.89±0.04	4.03±0.02	498.5±1.15	0.10±0.02
F-11	7.38±0.05	3.73±0.03	497.9±1.12	0.09±0.02
F-12	8.59±0.01	3.69±0.04	500.2±1.02	0.07±0.01
F-13	9.79±0.02	4.07±0.05	501.0±1.06	0.22±0.01
F-14	9.56±0.01	3.84±0.06	502.1±1.11	0.13±0.03
F-15	9.99±0.02	3.80±0.05	499.1±1.12	0.09±0.02
F-16	9.79±0.01	3.73±0.05	498.5±1.03	0.15±0.03

Table 4: Cumulative % drug release of Theophylline from sustained release tablet

Time (hours)	0	0.5	2	4	6	8	10	12
F1	0.00	6.93	26.93	42.39	65.59	73.40	79.97	93.31
F2	0.00	5.99	25.90	40.93	63.29	70.12	76.39	92.31
F3	0.00	5.32	26.31	40.63	62.32	69.91	75.21	90.35
F4	0.00	5.06	25.21	39.91	61.08	68.34	74.29	89.56
F5	0.00	5.97	26.45	45.20	65.34	71.42	84.99	96.07
F6	0.00	5.61	26.03	43.98	64.36	69.63	78.21	93.55
F7	0.00	5.31	25.49	42.69	61.56	68.64	77.10	87.44
F8	0.00	5.04	23.91	41.38	61.23	68.31	72.14	86.50
F9	0.00	5.46	26.42	46.34	67.51	74.86	79.44	95.97
F10	0.00	5.39	25.86	44.86	65.49	71.34	78.59	93.39
F11	0.00	5.13	25.31	41.34	61.38	70.46	77.55	89.80
F12	0.00	4.86	22.32	39.99	59.25	69.59	75.46	85.19
F13	0.00	6.39	26.54	45.41	66.49	78.69	89.39	96.44
F14	0.00	5.86	25.34	43.34	65.79	74.49	84.79	90.36
F15	0.00	5.72	24.79	42.99	60.86	73.31	80.56	89.74
F16	0.00	5.56	23.59	40.34	59.93	68.34	75.44	88.32

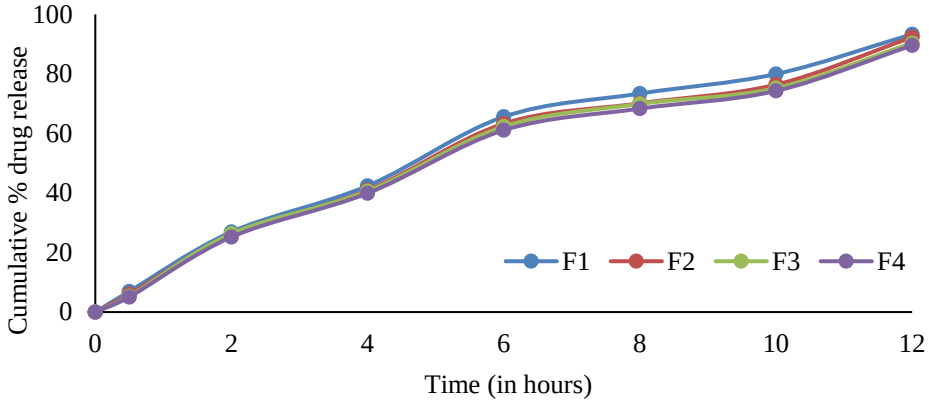

Figure 1: Cumulative % drug release of theophylline from sustained release tablet F1-F4

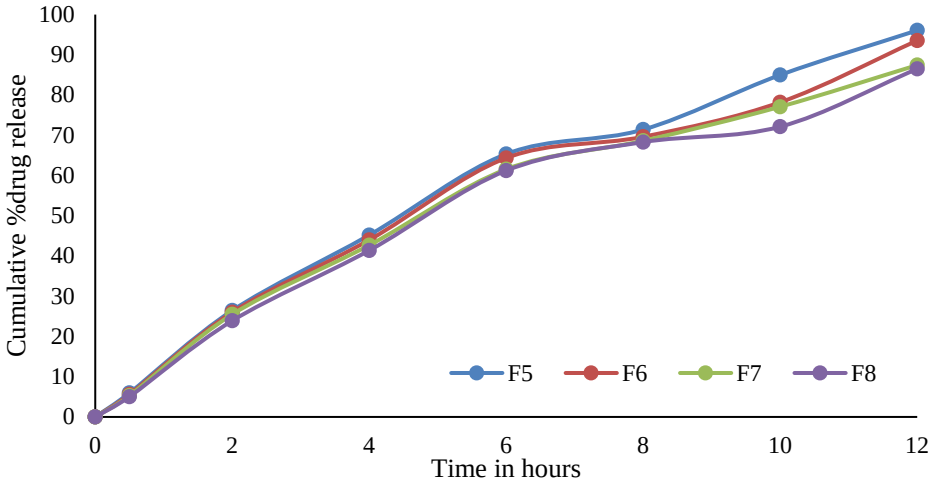

Figure 2: Cumulative % drug release of theophylline from sustained release tablet F5-F8

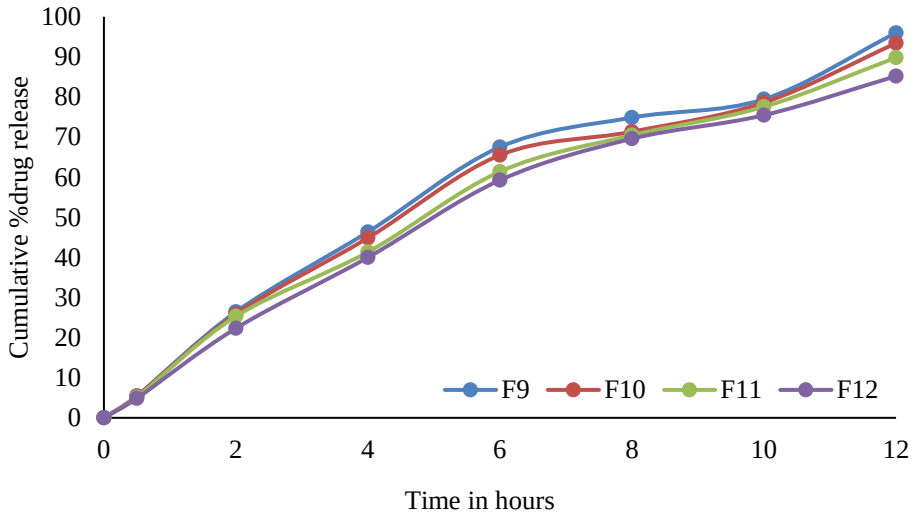

Figure 3: Cumulative % drug release of theophylline from sustained release tablet F9-F12

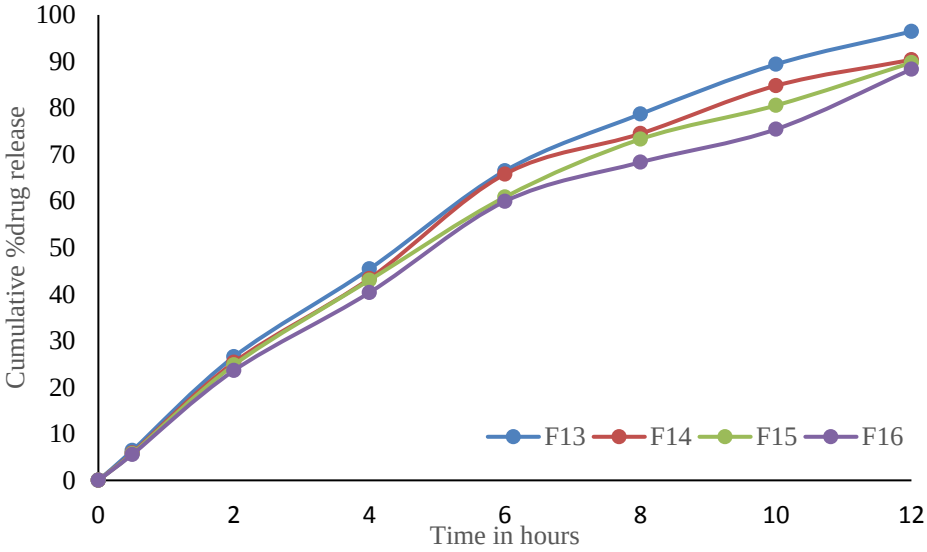

Figure 4: Cumulative % drug release of theophylline from sustained release tablet F13-F16

RESULT AND DISCUSSION

Theophylline was formulated as sustained release tablet using matrix forming polymer like HPMC K 4M, HPMC K100M, Chitosan and Eudragit alone and by wet granulation method (as in Table-1). The sustained release tablet was formulated using different drug to polymer ratios and finally optimized in the different ratios of drug to polymer. In all the formulated sustained release tablet, the ratio of theophylline was fixed. All the batches of formulated tablets were found produced under similar condition to avoid processing variables. The hardness of prepared theophylline tablets were found in the range of 7.38 to 9.99 kg/cm² which was acceptable range of sustained release formulation. The thickness of all the formulated sustained release tablet was in range of 3.69 to 4.07mm due to the constant tablet press setting across all the batches irrespective of weight variation. The average weight of formulated tablet was found to be uniform in the range of 497.9 to 503.4mg and the percent deviation in weight variation for all the formulated tablet was within the acceptable range of pharmacopeial specification. The percent friability value for all formulated tablets were found in range 0.07 to 0.24% indicated good handling properties of formulated tablets. The in vitro release studies of theophylline from sustained release tablet were conducted for first two hours in 0.IN HCI and then the dissolution study was continued replacing with pH 6.8 phosphate buffer for next 10 hour. The in-vitro release data of theophylline from sustained tablet is tabulated in Table 4. and illustrated in fig-1, 2, 3 and 4. The in vitro release of theophylline was slow in 0.IN HC1 due to the

slow swelling of polymer matrix used in the preparation of sustained release tablet. After two hours 26.93% from HPMC K4M, 26.45% from HPMC K100M, 26.42% from Chitosan, 26.54% from Eudragit polymer matrix of sustained release tablet was released. The in- vitro release was rapid in pH 6.8 phosphate buffer due to the more swelling of polymer matrix in alkaline medium A maximum of 93.31% from HPMC K4M, 96.07% from HPMC K100M, 95.97% from Chitosan, 96.44% from Eudragit polymer matrix of sustained release tablet was released within 12h. The in vitro release as depending upon nature of drug, nature of polymer, drug to polymer ratio and the medium used. In the present work HPMC, Chitosan and Eudragit were used as hydrophilic polymer as a matrix in the preparation of sustained release tablet. The highest release was observed with Eudragit which is commonly used hydrophilic matrix, gets swelled and dissolved in aqueous media forming viscous gel thereby rapidly releasing. The F-9 was selected as best formulation.

CONCLUSION

The tablets were prepared by wet granulation of theophylline as sustained release tablet. The IR study conducted using drugs and excipients concluded that the drug and polymers where compatible. The precompression parameters of the powder blends used for preparation of sustained release tablet were in acceptable range of pharmacopeial specification with excellent flow and good compressibility. Theophylline was prepared as sustained release tablet using HPMC K4M, HPMC K100M, Chitosan and Eudragit by wet granulation method. The physical parameters of tablet were within the acceptable limit with good mechanical and handling properties. The In vitro release was prolonged upto 12 hours using HPMC K4M, HPMC K100M, Chitosan and Eudragit. The in- vitro release followed zero order kinetics with mechanism of release was super case II transport due to diffusion of drugs from swellable matrix. Hence, F-9 formulation which prolonged the theophylline release in 12 hours. Hence, theophylline as sustained release tablet could be used to improve patient compliance towards the effective management asthma.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Navdeep Kaur conducted the practical work and wrote the manuscript draft; Mohit Kumar wrote the abstract revised and edited draft

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