RESEARCH PAPER

Accepted 25 October 2005
Revised 11 April 2005
Received 17 January 2005
Indian J. Pharm. Sci., 2005, 67(5): 598-602

Development and Evaluation of Theophylline and Salbutamol Sulphate Sustained Release Matrix Tablets

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The objective of the present study was to develop theophylline and salbutamol sulphate matrix tablet for sustained release combined dosage form, for treatment of chronic obstructive pulmonary disease. Simultaneous equations were formed to calculate the concentration values of theophylline and salbutamol sulphate and drug compatibility studies were established through Infrared and Differential Scanning Calorimetry studies. The matrix tablets were prepared by wet granulation method using hydroxypropyl methylcellulose K4M and K15M in various percentages. The granules showed satisfactory flow properties and compressibility. All the five tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for tested parameters. The results of formulation FH-3 (20% hydroxypropylmethylcellulose of grade K15M and K4M in 1:2 ratio) could extend the release of theophylline and salbutamol sulphate up to 12 h and was found comparable to marketed sustained release tablet. Model fitting analysis for formulation FH-3, theophylline fitted in the Zero order and Korsmeyer-Peppas model, while salbutamol sulphate fitted in the Zero order model. Scanning Electron Microscopy studies of FH-3 indicates good swelling and gel formation property of hydroxy propyl methyl cellulose, supporting the drugs release followed both diffusion and erosion mechanism. Successful formulation was found stable after evaluation for physicochemical parameters, kept for 30 d at 25° /60% RH and 40° /75% RH.

Chronic obstructive pulmonary disease (COPD) includes bronchial asthma, chronic bronchitis and emphysema. These three disorders differ in their etiology but have one common characteristics i.e. airway obstruction which blocks effective pulmonary ventilation[1]. The disease is associated with intermittent exacerbations characterized by acute deterioration in symptoms, lung function and quality of life[2]. Prevention and relief of symptoms by regular use of bronchodilators remains central to the management of COPD. Combining bronchodilators may improve efficacy and decrease side effects compared with increasing the dose of a single bronchodilator[3].

Theophylline and its derivatives have long been used for their bronchodilator properties in the management of asthma and chronic obstructive pulmonary disease, but the narrow therapeutic range and the propensity for interactions with other drugs make theophylline a difficult drug to use, and it tends to be reserved for combination therapy in patients who cannot be managed with other bronchodilators (such as the β_2 agonists) alone[4]. Salbutamol and theophylline both cause bronchodilation by increasing cellular cyclic AMP using different mechanisms. The combination appeared to be superior due to synergistic effect with no added side effect[5]. The combined effect of salbutamol and theophylline was always greater than the sum of their individual effects[6].

Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action[7]. Sustained release preparations are helpful to reduce the dosage frequency and side effects of drugs and

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improve patient's convenience[8]. Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules in slowly disintegrating or inert porous materials. Marketed sustained release bilayer tablet is available for the above combination, but the formulation of bilayer tablet is time consuming and uneconomical.

Present study is undertaken to combine the additive effective of theophylline and salbutamol sulphate as a matrix tablet for sustained release combined dosage form, which will prolong the drug release leading to minimize the incidences of nocturnal and early morning asthmatic attacks, exhibit patient convenience and provide a cost effective product, thus ensuring an effective treatment for prevention of COPD.

MATERIALS AND METHODS

Theophylline anhydrous was a gift sample from Modi Mundipharma Ltd., New Delhi. Salbutamol sulphate was obtained as a gift sample from Cipla Ltd., Mumbai. Hydroxypropyl methylcellulose K4M and K15M premium USP/EP were gift samples received from Colorcon Asia Pvt. Ltd., Verna, Goa. Microcrystalline cellulose NF (Avicel PH 102) was a gift sample from Signet Chemical Corporation, Mumbai. All other chemicals and reagents used were obtained from commercial sources and were of analytical grade. All materials were used as received.

Compatibility studies:

IR spectra of mixture of drugs, drugs and polymers and the formulations were obtained using Thermo Nicolet FT (IR-200). Thermal analysis was performed on the mixture of drugs and the selected formulation using a Mettler TCII TA Processor-differential scanning calorimeter to establish the compatibility of ingredients.

Preparation of matrix tablets:

Different tablet formulations were prepared by wet granulation technique (formulations FH-1 to FH-5). Table 1 shows composition of each tablet formulation. The formulations are composed of polymers HPMC K15M and HPMC K4M in the ratio 1:2 in various percentages. All the powders were passed through 100 mesh sieve. Required quantity of drugs, polymers and diluents were mixed thoroughly and a sufficient quantity of granulating agent (isopropanol and water in the ratio 3:1) was added slowly to get a dough mass. The mass was sieved through 22/40 mesh and dried at 50° for 2 h. The dried granules retained on 40 mesh were mixed with 10 % fines, 2 % talc and 1 % magnesium stearate. Tablets were compressed using 10 mm round flat faced punches to get tablets with target weight 600 mg on a manual hydraulic press, at a compression force of 1.5 ton with hardness of all tablets maintained between 3.5 to 6 kg/cm^2.

TABLE 1: COMPOSITION OF TABLET FORMULATIONS.

Ingredients (mg/tablet)	FH-1	FH-2	FH-3	FH-4	FH-5
Theophylline	300	300	300	300	300
Salbutamol Sulphate	4	4	4	4	4
HPMC K15M	10	20	40	60	70
HPMC K4M	20	40	80	120	140
Avicel PH 102	248	218	158	98	68
Talc	12	12	12	12	12
Magnesium Stearate	6	6	6	6	6
Total	600	600	600	600	600

Quantities in milligrams per tablet.

Evaluation of granules:

The angle of repose was measured by a reposograph, whereby the cone formed on the base of reposograph was examined to observe the zone, which indicates the flowabiltiy of the granules. Loose bulk density (LBD) and tapped bulk density (TBD)[9] were measured using the formulae: LBD=weight of the powder/volume of the packing, TBD=weight of the powder/tapped volume of the packing. Compressibility index[9] of the granules was determined by using the formula CI (%)=[(TBD-LBD)/TBD] x100.

Physical characteristics of fabricated tablets[10]:

The thickness and diameter were measured using a dial caliper. Weight variation test was conducted as per specifications. Hardness test was performed using a Monsanto hardness tester. Friability test was performed using a Roche friability testing machine and drug content uniformity test[10,14] was performed accordingly.

Swelling characteristics and gel strength[11]:

To evaluate the water penetration characteristics, tablets were exposed to purified water and the evolution of tablet surface area were determined by recording the change in surface area (SA) of the tablets as calculated with formula: $SA=2\pi rh$, where r is the radius of the tablet and h is the thickness. Gel strength of hydrated matrix tablets was determined by using method reported by Van Aerde[11].

TABLE 2: EVALUATION DATA OF GRANULES

Formulation Code	Loose Bulk Density (LBD) (g/ml)	Tapped Bulk Density (TBD) (g/ml)	Compressibility Index (%)
FH-1	0.465±0.03	0.533±0.04	12.75±0.02
FH-2	0.476±0.04	0.540±0.03	11.85±0.04
FH-3	0.481±0.03	0.552±0.02	12.86±0.03
FH-4	0.512±0.02	0.579±0.03	11.57±0.04
FH-5	0.519±0.03	0.583±0.02	10.97±0.03

All the values are Mean±S.D. of n=5.

Mass degree of swelling[12]:

Each tablet from all formulations pre-weighed and allowed to equilibrate with 100 ml of water for 5 h, was then removed, blotted using tissue paper and weighed. The mass degree of swelling then was calculated using the formula: Q=mass of the swollen gel/mass of the dry powder.

***In vitro* dissolution studies[13,14]:**

In vitro drug release studies were carried out using tablet dissolution test apparatus USP XXIII at 100 rpm. The dissolution medium consisted of 900 ml of standard buffer pH 1.2 for the first 2 h, followed by pH 4.5 for the next 2 h and pH 7.2 for the remaining period of 12 h, maintained at 37±1°. Aliquots of 1 ml were withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots withdrawn were diluted up to 100 ml with 0.05 M sodium hydroxide solution, filtered and analyzed by measuring the absorbance at 275.5 nm and 245 nm for theophylline and salbutamol sulphate and solved by the simultaneous equations method[14]. *In vitro* dissolution study was also carried out with the marketed sustained release product (MSR) for a comparative analysis.

The selected formulation FH-3 was subjected to model fitting analysis to know the mechanism of drug's (theophylline and salbutamol sulphate) release, by treating the data according to Zero Order (cumulative amount of drug released versus time) and Korsmeyer–Peppas (log cumulative amount of drug released versus log time) equations[15].

Scanning electron microscopy (SEM)[16]:

The SEM. analysis was conducted using a JEOL JSM-T330A scanning microscope for the optimized formulation on dry tablet surface, after 3 h and 8 h swelling. The samples were dehydrated and finely coated with gold. These samples were mounted in an electron microscope column and scanned to produce three dimensional images at various magnifications which were printed on a photographic film.

Stability studies:

The fabricated sustained release tablet formulation FH-3 was subjected to stability studies at 25°/60 % RH and 40°/ 75% RH for 30 d. The product was evaluated for appearance and hardness every 10 d. Drug polymer compatibility, drug content and drug release studies were conducted at the end of the storage period.

RESULTS AND DISCUSSIONS

The present investigation was undertaken to design, formulate and evaluate theophylline and salbutamol sulphate matrix tablet for sustained release combined dosage form and compare with marketed product. Simultaneous equations for calculating the concentration values of theo-

TABLE 3: RESULTS OF DRUG CONTENT UNIFORMITY TEST AND *IN VITRO* CUMULATIVE PERCENTAGE DRUG RELEASE AFTER 12 H

Formulation Code	Drug Content Uniformity (%)*		*In vitro* percentage drug release#	
	Theophylline	Salbutamol sulphate	Theophylline	Salbutamol sulphate
FH-1	100.79	098.86	96.97	98.87
FH-2	100.98	098.67	95.31	95.96
FH-3	100.91	101.25	92.58	97.20
FH-4	100.72	101.43	74.32	90.15
FH-5	099.41	102.70	66.58	84.68
MSR	101.27	099.76	94.05	96.23

* Values expressed as mean of n=5. # Values expressed as mean of triplicates.

TABLE 4: SWELLING PROPERTIES OF MATRIX TABLET FORMULATIONS

Formulation Code	Surface Area (cm^2)	Mass Degree of Swelling (Q)	Gel Strength (ml)
FH-1	2.0724	1.4653	10.39
FH-2	2.8574	1.7086	17.47
FH-3	3.0772	2.0480	31.94
FH-4	3.2970	2.3478	48.44
FH-5	4.0192	2.4310	52.69

phylline and salbutamol sulphate were established[14]. IR and DSC studies indicate good compatibility between drugs, polymers and excipients.

The granules of different formulations were evaluated for angle of repose, LBD, TBD and compressibility index. The granules indicated fair to good flowability with the angle of repose values ranging from 30-37°, according to reposograph readings. The results of LBD, TBD and compressibility index are mentioned in Table 2. The result of compressibility index lies between 10.97±.0.03 and 12.86±0.3 %, which is below 15 % indicating good to excellent flow properties. All tablet formulations were subjected to various evaluation parameters and the results obtained were within the range. The weight variation test indicates that all the tablets were uniform with low standard deviation values. The tablet mean thickness and mean diameter values ranged from 3.53±0.039 to 3.67±0.056 mm and 10.31±0.0019 to 10.31±0.0007 mm, respectively. The hardness of all the tablets were within a range of 4.88±0.49 to 5.43±0.31 kg/cm^2. The loss in total weight in friability test was in a range of 0.023 to 0.069 %. The percentage drug content for different tablet formulations (Table 3) varied from 99.41 to 100.98 % for theophylline and 98.67 to 102.70 % for salbutamol sulphate, were found to be within range.

The initial surface area of all the formulations were varying from 1.1209 to 1.1530 cm^2, which increases from 2.0724 to 4.0192 cm^2 for formulations FH-1 to FH-5 on subjecting them to swelling, indicating that with an increase in HPMC concentration from 5 to 35 %, the swollen elastic gel formation also increases. The swelling degree and gel strength were found to be maximum for FH-5, due to highest polymer content (35%), indicating high swelling and gelling capacity of the HPMC polymer. This property of the

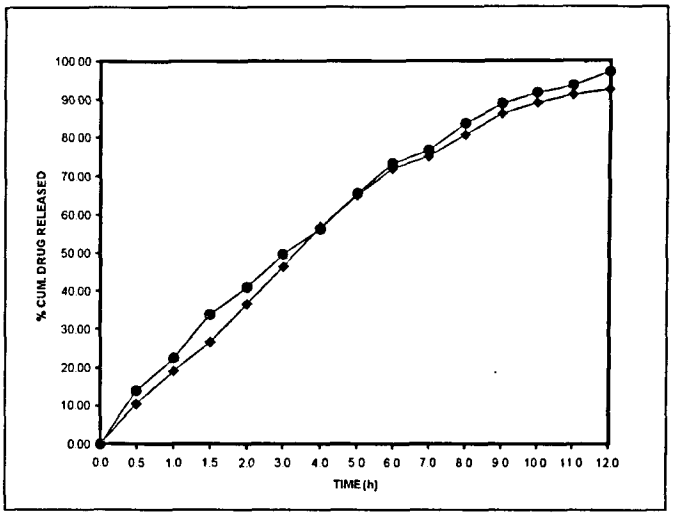

Fig.1: *In vitro* cumulative percent drug release Vs time (h) profiles for selected formulation FH-3.

Release profile of Theophylline [□] and Salbutamol sulphate [●] matrix tablet formulation FH-3 (containing 20% HPMC K15M and K4M in ratio 1:2).

HPMC polymer helps in retarding the drug release from the matrix (Table 4).

FH-3 was selected as the optimum formulation on the basis of results of *in vitro* dissolution studies, which indicates maximum sustained release till 12 h, for both the drugs from a single sustained release matrix tablet, simultaneously. FH-3 (20% HPMC K15M and K4M grades in 1:2 ratio) showed 92.58 % theophylline and 97.20 % salbutamol sulphate release at the end of 12 h (Table 4). The marketed sustained release product (MSR) showed 94.05 % theophylline and 96.23 % salbutamol sulphate release at the end of 12 h, which is comparable to fabricated formulation FH-3. Upon model fitting analysis for FH-3, theophylline fitted in the Zero order and Korsmeyer-Peppas model with R values as 0.9468 and 0.9369, while salbutamol sulphate fitted only in the Zero order model with R value 0.9519. This indicates that both the drugs follow zero order kinetics or concentration independent release of drugs from the matrix.

The examination of Scanning Electron Microscopy (SEM) photographic results of formulation FH-3 indicated that tablet in dry state have smooth, plain, porous, less sectioned surface, while after 3 h swelling indicates gel formation, whereas swelling after 8 h indicated fully swelled uniform matrix formation. This proves good swelling and gel formation property of HPMC and uniformity in mixing of all

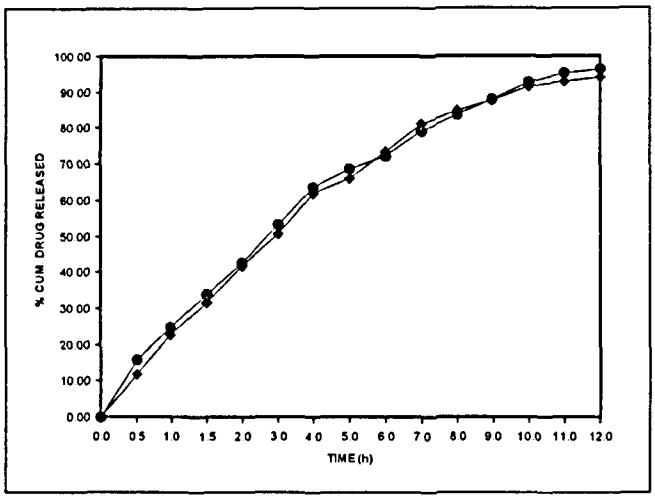

Fig.2: *In vitro* cumulative percent drug release Vs time [h profiles for marketed product (MSR).

Release profile of Theophylline [□] and Salbutamol sulphate [●] for marketed sustained release tablet (MSR).

ingredients. The results of stability studies conducted on FH-3 revealed no change in physical appearance, hardness, drug content and *in vitro* dissolution profiles whereas IR spectrums obtained exhibits no incompatibility. Hence these formulations were found to be stable at tested temperatures.

From the above results it can be concluded that formulation FH-3 has achieved the objectives of prolonged drug release, patient convenience and cost effectiveness as a combined dosage form and appears to be assessed further by conducting bioavailability studies in human volunteers and long term stability testing.

ACKNOWLEDGEMENTS

Authors are thankful to Cipla Ltd., Mumbai, Modi Mundipharma Ltd., New Delhi, Colorcon Asia Pvt. Ltd., Verna, Goa for providing generous quantities of required material and KLES's College of Pharmacy, Belgaum, for providing necessary facilities to conduct the work.

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