DESIGN AND EVALUATION OF HPMC AND XANTHAN GUM-BASED SUSTAINED RELEASE MATRIX TABLETS OF THEOPHYLLINE

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Summary

In the present investigation, an attempt has been made to increase therapeutic efficacy, reduce frequency of administration, and improve patient compliance, by developing sustained release matrix tablets of theophylline. Hence, in the present work, an attempt has been made to develop sustained release matrix tablets using polymer such as hydroxyl propyl methyl cellulose (HPMC) and xanthan gum. The tablets were prepared by direct compression method. Tablets blends were evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The compressed tablets were then evaluated for various physical tests like diameter, thickness, uniformity of weight, hardness, friability, and drug content. The results of all these tests were found to be satisfactory. The in vitro dissolution study was carried out for 12 hours using paddle method in phosphate buffer (pH 6.8) as dissolution media. Formulation F1 and F2 failed to sustain release beyond 8 hours. Among all the formulation, F3 shows 98.12% of drug release at the end of 12 hours. This finding reveals that above a particular concentration of HPMC K-100 and xanthan gum are capable of providing sustained drug release.

Key words HPMC K-100, Xanthan gum, Theophylline, matrix tablets

Introduction

In recent years oral controlled delivery systems have gained increased importance and interest since it is necessary to improve the systemic absorption of the drugs and patient compliance. In addition, controlled delivery systems maintain uniform drug levels, reduce dose, side effects, and increase the safety margin. Matrix controlled release tablet formulations are the most fashionable and straightforward to formulate on a commercial scale. A wide variety of polymer matrix systems have been used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance[1,2].

Theophylline, also known as dimethylxanthine, usually administered orally, is an effective bronchodilator which may be used in the management of both asthma and chronic obstructive pulmonary disease (COPD)[3,4]. It is widely available, and less expensive than many other bronchodilators.

In industrialized countries, it has been used as a third line treatment of asthma in uncontrolled asthmatic as add on therapy by acting as a bronchodilator in asthma. The half-life of Theophylline is also short (5-6 hrs) which makes it suitable candidate for sustained release formulation, moreover it reducing side effects, decreasing frequency and improve patient compliance[5-7]. Keeping these factors in view it was aimed to formulate and evaluate sustained release matrix tablets, to provide a controlled and predictable release of Theophylline, which is an oral antiasthmatic drug used in the management of asthma.

Materials and methods

Materials: Theophylline, HPMC K-100, xanthan gum, were received as gift samples from Alkem Laboratories, Himachal Pradesh. Colloidal silicon dioxide, aerosil, magnesium stearate, was of AR Grade.

Methods

Preparation of matrix tablets: All ingredients was collected and weighed accurately. Sifted Theophylline and polymers through sieve no. 60# and then rinsed with remaining excipients. Sifted colloidal silicon dioxide (Aerosil-200) and magnesium stearate separately, through sieve no. 60#. Preblending of all ingredients (except lubricant magnesium stearate) in blended for 15 minutes. Blend then again blended for 5-6 min then added magnesium stearate blended 5 min. Lubricated powder was compressed by rotary machine having circular concave shaped and one side break line on upper punch, with pressure of 7-8 tons. Compressed tablets were examined as per official standards and unofficial tests. Prior to the compression the drug and polymers were evaluated for several tests.

Evaluation of tablet blends

Angle of repose: The angle of repose of tablet blends was determined by the funnel method. The blends were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where ‘h’ and ‘r’ are the height and radius of the powder cone, respectively.

Bulk density: Apparent bulk density was determined by pouring a weighed quantity of tablet blends into graduated cylinder and measuring the volume and weight.

Bulk Density = Mass of powder / Bulk Volume of the powder

Tapped bulk density: It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals.
The tapping was continued until no further change in volume was noted.

Tapped density = Weight of powder / Tapped volume of the powder

Carr's index: Carr's compressibility index CI (Carr, 1965) is defined as follows:

$CI = \rho t - \rho a / \rho t = Va - Vt / Vt$

Where ρt and ρa – tapped and poured bulk density; And Vt and Va – tapped and poured bulk volume respectively.

Hausner's ratio: A similar index has been defined by Hausner[8-11].

Hausner's ratio = Tapped density / Poured Density

Evaluation of Tablets

Thickness: The thicknesses of the tablets were determined using a Vernier caliper, 20 tablets from each batch were used and average values were calculated.

Uniformity of weight: Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. The weights were determined to within ±1mg by using digital balance. Weight control is based on a sample of 20 tablets

Drug content: The estimation of drug content of theophylline was done by HPLC analysis. Place 10 Tablets in a 500 mL volumetric flask, add 50 mL of water, and when the tablets have disintegrated add 50 mL of 6 N Ammonium hydroxide. Shake until no more dissolves, dilute with water to volume, mix, and filter through a dry filter with the aid of suction, if necessary, into a dry flask, discarding the first 20 mL of the filtrate. Transfer an accurately measured aliquot portion of this concentrate, equivalent to about 10 mg of theophylline, to a 100 mL volumetric flask. Add 20.0 mL of internal standard solution, dilute with mobile phase to volume, and mix. Separately inject equal volumes (between 10 µL and 25 µL) of the standard preparation and the assay preparation into the chromatograph, and measure the peak responses for the major peaks. The retention time of theophylline relative to that of theobromine is about 1.6. Calculate the quantity, in mg, of $C_7H_8N_4O_2$.

Hardness and friability: For each formulation, the hardness and friability of 20 tablets each were determined using the Pfizer hardness tester and Electro lab friabilator test apparatus, respectively.

***In vitro* release studies:** The *in vitro* dissolution studies were performed using USP -22 type I dissolution apparatus 37±5°C, at 50 rpm. Placed the 900 ml of pH 6.8 phosphate buffer in the vessel of apparatus and assembled, equilibrate the dissolution medium to 37 ±0.5 °C. Placed 1 tablet in basket and immediately operated the apparatus at 100 rpm. Withdrawn the 5 ml samples at 1 hour, 2 hours, 4 hours, 8 hours and 12 hours, from midway between the surface of dissolution medium and the top of the rotating basket, not less than 1 cm from the vessel wall and replaced with fresh buffer solution. After appropriate dilution the samples were analyzed [12-18].

Results and Discussions

The present investigation was undertaken to design, formulate and evaluate theophylline matrix tablets for sustained release dosage form. The blends of different formulations were evaluated for angle of repose, bulk density, tapped bulk density, compressibility index and hausner's ratio. The results of bulk density, tapped bulk density, compressibility index and hausner's ratio are mentioned in table 2. The bulk density of the tablet blend was in the range of 0.571± 0.02 to 0.652± 0.04 g/ml; the tapped density was in the range of 0.592± 0.02 to 0.712± 0.05 g/ml, which indicates that the powder was not bulky. The blend indicated good flow properties for all the formulation with the angle of repose values 34-37° according to fixed funnel and free standing cone method. The results of compressibility index lies between range from 15.34±0.11 to 19.52±0.06, while hausner's ratio lies between 1.14±0.02 and 1.20±0.04 indicating good to excellent flow properties. The tablets of different batches formulated were evaluated for test such as hardness, friability, thickness, uniformity of weight and drug content. The results obtained from all formulations were within the range. The weight variation test indicates that all the tablets were uniform with low standard deviation values and hence all formulation passed the test for uniformity of weight. The tablets mean thickness and mean diameter values ranged from 4.8±0.25 mm to 4.8±0.67 mm and 9.3±0.02 to 9.3±0.04, respectively. The hardness of all the tablets was within the range of 9±0.05 to 10±0.07kg/cm^2. The loss in friability test was in a range of 0.18 to 0.41%. The percentage drug content for different tablet formulations were discrete from 97.25% to 98.79%, were found to be within range (table 3).

In vitro dissolution studies of all the formulations of sustained release tablets of theophylline were carried out in pH 6.8 phosphate buffers for 12 hours. All the tablet formulations showed acceptable properties as shown in table 4. The result of the dissolution study indicating that F1 and F2 released 99.12 and 96.38 at the end of 8 hrs, respectively, from the released pattern of first two formulation the 100% released was found before 12 hrs, this may be due to the high concentration of HPMC K-100 incorporated in the tablet. Formulation F4, F5 and F6 released 92.34, 90.91 and 82.73 at the end of 12 hrs, while F3 release 98.12 at the end of 12 hrs. Here we observed that on increasing the quantity of xanthan gum and decreasing the proportion of HPMC K-100, it retards the drug release from matrix. This might be due to slow hydration of matrix and its property to form a thick gel layer, which retard the drug release from the tablet. It is expected that the developed formulation should have the following theoretical drug release profile, i.e., 98% for 12 hrs. Formulations F1 to F2 and F4 to F6 failed to meet the needed theoretical drug release profile. Formulation F3 met the needed theoretical drug release profile and has the sustain action i.e., retarding the drug release so the release is for a long time and thus more bioavailability; for these reasons, it was considered the best formulation among all the six formulations of this series.

Table 1: Composition of theophylline SR matrix tablet

S. No.	Ingredient	F1	F2	F3	F4	F5	F6
1.	Theophylline	300	300	300	300	300	300
2.	HPMC K-100	230	210	190	170	150	130
3.	Xanthan Gum	20	40	60	80	100	120
4.	Aerosil	4	4	4	4	4	4
5.	Magnesium Stearate	2	2	2	2	2	2
6.	Theoretical Weight	556	556	556	556	556	556

Table 2: Physical characteristics of prepared blend of Theophylline

Parameters	F-1	F-2	F-3	F-4	F-5	F-6
Angle of repose	34° 21’ ± 0.21	31° 81’ ± 0.36	32° 48’ ± 0.71	33° 65’ ±0.47	34° 57’ ± 0.52	37° 72’ ± 077
Bulk density	0.571 ± 0.02	0.624 ± 0.03	0.592 ± 0.02	0.631 ± 0.06	0.652 ± 0.04	0.586 ±0.06
Tapped bulk density	0.657 ± 0.03	0.703 ± 0.05	0.641 ± 0.02	0.712 ± 0.05	0.674 ± 0.08	0.592 ± 0.02
Compresibility Index	17.68 ± 0.07	18.38 ± 0.04	18.23 ± 0.09	19.16 ± 0.05	15.34 ± 0.11	19.52 ± 0.06
Hausner’s Ratio	1.14 ± 0.02	1.19 ± 0.05	1.18 ± 0.01	1.16 ± 0.08	1.20 ± 0.04	1.17 ± 0.05

Table 3: Evaluation of Theophylline sustained release matrix tablet

Parameters	F-1	F-2	F-3	F-4	F-5	F-6
Uniformity of weight (mg)	506±7	506±8	506±7	506±5	506±4	506±5
Thickness (mm)	4.8±0.31	4.8±0.25	4.8±0.67	4.8±0.55	4.8±0.30	4.8±0.28
Diameter (mm)	9.3±0.03	9.3±0.02	9.3±0.03	9.3±0.04	9.3±0.04	9.3±0.02
Friability (%)	0.21	0.34	0.41	0.30	0.27	0.18
Tablet Hardness (Kp)	9±0.07	9±0.05	9±0.07	9±0.08	9±0.06	10±0.07
Assay (%)	98.63	97.25	98.79	96.19	97.83	97.64

Table 4: *In vitro* drug release data

Time in	Cumulative Percent Drug Release					
Hours	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
1	22.03	21.64	15.26	13.65	14.59	12.84
2	51.21	48.81	42.47	46.52	41.65	39.39
4	72.43	72.45	67.58	64.28	62.34	57.18
8	99.12	96.38	85.29	81.16	77.27	72.56
12	-	-	98.12	92.34	90.91	82.73

References

1. Yadav AS, Kumar AP, Vinod R, Rao SB, Kulkarni SV. Design and evaluation of guar gum based controlled release matrix tablets of Zidovudine. Journal of Pharmaceutical Science and Technology. 2010; 2 (3): 156-162.
2. Shanmugam S, Chakrahari R, Sundaramoorthy K, Ayyappan T, Vetrichelvan T. Formulation and evaluation of sustained release matrix tablets of Losartan potassium. International Journal of PharmTech Research. 2011; 3(1): 526-534.

3. Reza MS, Quadir MA, Haider SS. Development of theophylline sustained release dosage form based on kollidon SR. Pakistan Journal of Pharmaceutical Sciences. 2002; 15(1): 63-70.
4. Rall TW. Drugs used in the treatment of asthma. In: The pharmacological basis of therapeutics. (Hardman, J.G., Gilman, A.G. and Limbird, L.E., Eds.). 9th edition. McGraw- Hill Companies Inc. USA. 1996; 672-677.
5. Filiz A, Bozkurt N. Addition of Salmeterol or Theophylline to an inhaled corticosteroid regimen in patients with severe asthma. Turkish Respiratory Journal. 2002; 3(3): 98-101.
6. Barnes PJ, Pauwels RA. Theophylline in the management of asthma. Time for reappraisal?. Eur. Respir. J. 1994; 7(3): 579-591.
7. Jones ACE, Higenbotram TW, Barnes ND, Godden DJ. Sustained release theophylline in nocturnal asthma. Archives of Disease in Childhood. 1984; 59: 1159-1161.
8. Meshali MM, El Sayed GM, Syed EL. Preparation and evaluation of theophylline sustained release tablets. Drug Develop Ind Pharm 1996; 22:373-376.
9. Nath BS, Venkatesh, Hiremath D. Formulation and evaluation of sustained release dosage form of theophylline using a combined hydrophobic and hydrophilic matrix. Indian J Pharm Sci 2000; 62: 33-36.
10. Hajare AA, More HN, Dsouza JI. Design and evaluation of sustained release tablets of diltiazem hydrochloride. Indian Drugs 2004; 41:175-176.
11. Talukdar MM, Rommbaut P, Kinget R. Comparative study on xanthan gum and hydroxypropyl methylcellulose as matrices for controlled-release drug delivery. Int J Pharm. 1996; 129: 233-241.
12. Reza MS, Abdul Quadir M, Haider SS. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. J Pharm Pharm Sci. 2003; 6: 282-291.
13. Pandey VP, Manavalan R, Rajan TS, Ganesh KS. Formulation and release characteristics of sustained release diltiazem hydrochloride tablet. Indian J Pharm Sci 2003; 65 (1): 44-48.
14. Sanghavi NM, Kamath PR, Amin DS. Sustained release tablets of theophylline. Drug Dev. Ind. Pharm. 1990; 16: 1843-1848.
15. Ceballos A, Cirri M, Maestrelli F, Corti G, Mura P. Influence of formulation and process variables on in vitro release of theophylline from directly-compressed Eudragit matrix tablets. IL Farmaco. 2005; 60: 913-918.
16. Brabander CD, Vervaet C and Remon JP. Development and Evaluation of sustained release matrix tablet. J. Controlled Release. 2002; 77(1): 245-254.
17. Raparla DV and Murthy TE. Formulation and evaluation of oral controlled release Glimepiride matrix tablets. Adv. Phamacol. Toxical. 2007; 8(2): 59-62.
18. Basak SC, Shrinivasa R, Manavalan R and Rao P. Controlled release HPMC matrix tablet of propranolol HCl. Indian J. Pharm. Sci**.** 2004; 66(6): 827-833