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RESEARCH ARTICLE

Formulation and Evaluation of Sustained Release Pellets of Theophylline by Spray Drying Technique

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ABSTRACT

The present study was aimed to Theophylline sustained release pellets for the treatment of Asthma. The biological half life of Theophylline is 3 hour. Hence it requires twice or three times a day dosing. Theophylline sustained release pellets sustained the half life to 8 hour i.e. shows increase in half life means reduce dosing frequency. A total of 6 formulation containing drug: polymer complexes prepared by Spray drying method have show better physicochemical properties. HPMC K4M and Ethyl cellulose as binding solution was optimized as sustained release polymer for pellet of Theophylline. The pellets were evaluated for parameters such as bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. Evaluation tests of pellets such as general appearance, Scanning electron microscopy and *in vitro* release studies were performed. Out of 6 formulations, the formulation batch F4 shows more drug release i.e. upto 96.426±0.32%. Hence it can be concluded that formulation F4 containing HPMC K4M and Ethyl cellulose are suitable for development of Sustained release pellets of Theophylline.

KEYWORDS

Hydroxy Propyl Methyl Cellulose, Theophylline

INTRODUCTION

The expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of Sustained drug delivery; greater attention is being paid on development of oral sustained release drug delivery systems. The goal in designing sustained release drug delivery system is to reduce the frequency of the dosing, reducing the dose & providing uniform drug delivery. So, Sustained release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ [1-3]. Sustained release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery[4,5]. Multiparticulate system along with the modified release drug delivery is the most versatile technique for the treatment of Asthma. Theophylline is an oral bronchodilator with modest anti-inflammatory effects. Given its narrow therapeutic window and frequent adverse events (e.g., gastrointestinal symptoms, loose stools, seizures, cardiac arrhythmias, nausea and vomiting), its use is generally reserved for patients whose asthma is uncontrolled despite an adequate trial of ICS,

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LABAs and/or LTRA[6,7]. The biological half life of Theophylline is 3 hour. Hence it requires twice or three times a day dosing[8]. Therefore Theophylline is suitable candidate for development of Sustained release dosage form. A total of 6 formulation containing drug: polymer complexes prepared by Spray drying method have show better physicochemical properties. HPMC K4M and Ethyl cellulose as binding solution was optimized as sustained release polymer for pellet of Theophylline.

MATERIALS AND METHOD

Materials

Theophylline was obtained from Balaji Drugs, Ahmednagar. HPMC K4M and Ethyl cellulose were produced from Ozone International, Mumbai.

Methods

Formulation of Theophylline Sustained Release Pellets

Theophylline Sustained release pellets were prepared by Spray Drying method. The polymer was first dissolve in sufficient quantity of water at room temperature by using sonicator and Theophylline drug in different weight ratios of drug to polymer (Table shows the details of composition of drug and polymer). By using sonicator drug and polymer are uniformly dispersed in solvent i.e. in water. By setting all the parameters of Spray dryer as per given in (Table 1). Sprayed the powder from prepared feed solution of drug and polymer.

Pour the spray dried powder into the pan of the pelletizer and then it rolls down in an even stream to the lower half of the pan. Then add ethyl cellulose liquid to form pellets in certain places. The rolling movement and the additional of moisture cause pellets form.

Due to the tilted pan and the movement of the material, the larger pellets are carried to the top surface. The size of pellets can be influenced by tilting angle of the pan, by the amount of liquid added and the method with which it introduced. As soon as the pan fills the pellets will continuously roll over the edge of the pan.

The Formulation of Theophylline Sustained release pellets are listed in (Table 2).

Table 1: Set Parameters of Spray Dryer for F1-F6

Parameters	Batches					
	F1	F2	F3	F4	F5	F6
Inlet Temperature	220	220	200	260	250	270
Outlet Temperature	210	210	190	250	240	260
Cool Temperature	100	100	80	100	110	120
Inlet High	230	230	210	270	260	280
Outlet High	210	210	190	260	250	270
Aspirator Flow Rate (Hm^3/hr)	40	40	40	40	40	40
Feed Pump Flow Rate (ml/min)	1	1	1	1	1	1
D-Block on (Sec)	1	1	1	1	1	1
D-Block off (Sec)	90	90	90	90	90	90
Cycle Temperature (Min)	200	200	200	225	230	240

Table 2: Formulation of Sustained Release Theophylline Pellets

Ingredients	Batches					
	F1	F2	F3	F4	F5	F6
Theophylline	5	5	5	5	5	5

HPMC K4M	10	10	15	15	20	20
Ethyl Cellulose in Ethanol	q.s	q.s	q.s	q.s	q.s	q.s

Preformulation Study of Drug and Excipients

Identification and Characterization of Theophylline[9]

i) Organoleptic Properties: This includes recording of colour, odour and taste of new drug using descriptive terminology. Record of colour of early batches is very useful in establishing appropriate specification for later production. Drugs generally have a characteristic odour and taste. Unpleasant ones are masked later during formulation.

ii) Melting Point Determination: Melting point determination done by open capillary method which containing liquid paraffin inside melting point apparatus. Take the capillary tube and sealed one end of capillary tube. Pour the drug inside tube and place that capillary tube in melting point apparatus.

Note the melting point of drug. Melting point was first indication of purity of the sample since the presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range.

iii) Assay of Theophylline: Weigh accurately about 0.25gm, add 50ml water and gently warm the mixture on water bath until complete solution is affected. Cool, add 20ml of 0.1N silver nitrate and 1ml of bromothymol blue solution and titrate with 0.1N sodium hydroxide to a blue end point. Each ml of 0.1N sodium hydroxide is equivalent to 0.01802gm of $C_7H_8N_4O_2$.

iv) Solubility of Theophylline: Solubility is an important consideration in formulations. The solubility of Theophylline was tested in various solvents such as distilled water, ethanol, 2-propanol and acetone, 0.1N sodium hydroxide and P^H of drug and polymers ranging from 4 to 9.

Evaluation of Pellets

Flow Property of Pellet

The pellets were prepared by spry drying technique. The prepared pellets were evaluated for parameters like Bulk density, Tapped density, Compressibility index, Angle of repose and Hausner's ratio.[10]

i) Angle of Repose: Angle of repose can be done by Funnel method. Take the funnel which is attached to stand.[11]

$$\theta = \tan^{-1}\frac{h}{r}$$

ii) Bulk Density: Apperant bulk density (ρb) was determined by pouring the pellets into a graduated cylinder. The bulk volume (vb) and weight of powder (M) was determined.[12]

$$\rho b = \frac{M}{vb}$$

iii) Tapped Density: The measuring cylinder containing a known mass of pellet (M) was tapped for a fixed time. The minimum volume (vt) occupied in cylinder and weight of pellet was measured. The tapped density (ρt) was calculated by,

$$Pt = \frac{M}{vt}$$

iv) Compressibility Index[13]: The simplest method of measurement of free flow of pellet is compressibility; an indication of ease with which material can be induced to flow is given by compressibility index which was calculated by,

$$I = \frac{\rho t - \rho b}{\rho t}$$

v) Hausner's Ratio: This is an indirect index of ease of pellets flow. It was calculated by,

$$H = \frac{\rho t}{\rho b}$$

Lower values (< 1.25) indicate better flow property than higher ones (> 1.25).[13]

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) is the technique of choice for measuring the shape and surface morphology of pellet to support visually the other qualitative and quantitative results.

In Vitro Drug Release Studies

Fill the 900ml of buffer solution in basket. Switch on n the dissolution apparatus and maintain the temperature of apparatus upto 37±5^{o}c. Place the sample inside the basket and after that start the paddle to rotating at 50rpm speed. Withdrawal 5ml of sample, from it withdrawal 1ml sample and transfer it into 10ml volumetric flask and make up the volume upto mark with buffer solution. Scanned this sample in entire UV range 200-400nm.[14]

Kinetics of Drug Release

To describe the kinetic of the drug release from the sustained release pellet mathematical model such as zero-order, first order, Higuchi-matrix model, Korsemeyers Pappas model, Hixson-Crowell model were used. The drug release data used was evaluated by model- dependant (curve fitting) using PCP- Dissolution-vz software model with the higher correlation coefficient was considered to be best model.[15,16]

Equations to Study Drug Release Kinetics from Dosage Forms

i) Zero Order

$$\%R = kt$$

This model represents an ideal release in order to achieve prolonged pharmacological action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets containing low soluble drugs.

ii) First Order

$$\text{Log (fraction unreleased)} = kt/2.303$$

This model is applicable to hydrolysis kinetics and to study the release profile of pharmaceutical dosage forms such as those containing water soluble drug in porous matrices.

iii) Matrix (Higuchi Matrix)

$$\%R = kt\ 0.5$$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drugs.

iv) Peppas – Korsmeyer Equation

$$\%R = kt\ n \log \%R = \log k + n \log t$$

This model is widely used when release mechanism is well known or when more than one release phenomenon could be involved.

v) Hixon – Crowell Equation

$$\text{(Fraction unreleased) } 1/3 = 1 - kt$$

This equation is applies to pharmaceutical dosage forms like tablets where dissolution occurs in planes that are parallel to drug surface if the tablet dimension diminishes proportionally, in such manner that the initial geometric form keeps constant all the time. When this model is used, it is assumed that the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through polymer matrix.

RESULTS AND DISCUSSION

Identification of drug was carried out by organoleptic property, Assay of Theophylline and Melting Point determination. Theophylline is a white, odorless, crystalline powder with a bitter taste. Melting point of Theophylline was found to be 268^{o}c. Percent purity of Theophylline was found to be 99.4%. Solubility of drug and polymers in various solvents were studied. The various physical parameters of Theophylline and various polymers were given into (Table 3).

Flow properties of pellets are most important parameter for filling of pellets into empty capsule shell. The angle of repose ranges from 29.17^{0} to 32.20^{0}. The value of bulk density ranges from 0.15 to 0.21 gm/cm^{3}.The value of Carr's index below 10% (Table 4).

Table 3: The Various Physical Parameters of Theophylline and Various Polymers

Observed Parameters	Theophylline	HPMC K4M	Ethyl Cellulose
Description	White, odorless, crystalline powder with a bitter taste.	Odourless,tasteless, white or creamy white fibrous powder.	White or yellowish-white powder or granular powder, odourless.
pH	pH of (1%) aq.solution was 6.5	pH of (1%) aq.solution was 6.8	pH of (1%) aq.solution was 4 – 7.
Melting point	273^{o}c	70^{0}c	240-255^{o}c
Solubility	Soluble in water, 0.1 M NaOH, 0.1 M HCl, ethanol (moderately), alkali hydroxides, ammonia, dilute hydrochloric acid, nitric acid,dilute aqueous acid, and dilute aqueous base.	Soluble in the cold water, insoluble in alcohol, ether.	soluble in methylene chloride, slightly soluble in ethyl acetate and in methanol, insoluble in water.

Table 4: Flow Property of Pellets

Flow Property	Angle of Repose(θ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Compressibility index (%)	Hausner's ratio
F1	32.20^0±0.05	0.21±0.011	0.22±0.015	4.54±0.01	1.047±0.0015
F2	31.54^0±0.04	0.18±0.015	0.19±0.011	5.26±0.015	1.055±0.0015
F3	31.52^0±0.02	0.16±0.01	0.17±0.011	5.24±0.015	1.049±0.0013
F4	31.19^0±0.02	0.17±0.011	0.18±0.014	5.55±0.014	1.058±0.0016
F5	29.17^0±0.05	0.15±0.015	0.17±0.011	5.67±0.013	1.060±0.0014
F6	29.17^0±0.08	0.15±0.015	0.17±0.013	5.67±0.017	1.060±0.0013

*All values are expressed as mean± SD, n=3

The scanning electron microscopic evaluation is important for determining the surface morphology, shape and size and shape. Surface of pellet as shown in SEM photograph was spherical and size of pellets was found to be 963µm to 1003µm and ratio of length to width (Aspect Ratio) is 1.041 which indicates pellets are spherical in shape (Fig 1).

In-vitro drug release study of all formulation batches (F1-F6) were performed using USP apparatus Type-I (Basket). The batch F1 shows87.656 % release, batch F2 shows 84.748% drug release, batch F3 shows 94.690 % drug release, batch F4 shows 96.426 % drug release, batch F5 shows 93.453% and batch F6 shows 95.564% drug release in 8 hours. These

drug release sustained due to Ethyl cellulose as it is hydrophobic (Table 5).

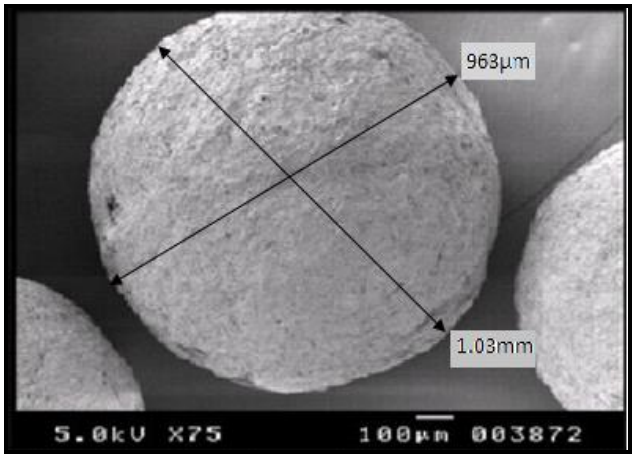

Figure 1: SEM Analysis of Optimized F4 Batch

The drug release pattern of formulation F4 shown in (Fig 2). By using PCP Disso V3 software we concluded that the best fit model for F4 formulation is Hixon-Crowell model. As it showed regression coefficient value near to one.

To describe the kinetics of drug release from the matrix pellets, release data was evaluated by model dependent (curve fitting) method using USP Disso v3 software and model with higher correlation coefficient was considered to be the best model. The result showed that the most batches F1, F2, F3, F4, F5 and F6 followed Hix.Crowell order kinetics. The observation was summarized in (Table 6).

Table 5: In Vitro % Drug Release of F1 to F6

Time (Min)	F1	F2	F3	F4	F5	F6
15	5.632±0.60	6.364±0.64	7.453±0.44	6.318±0.32	8.543±0.54	7.453±0.33
30	9.524±0.002	10.425±0.46	9.647±0.23	11.755±0.43	10.654±0.33	9.564±0.45
45	15.435±1.21	16.532±1.02	17.536±0.86	19.486±0.44	17.685±0.23	16.432±0.65
60	22.245±0.47	21.674±0.43	22.532±0.45	25.172±0.65	23.564±0.56	24.664±0.42
90	32.724±0.52	34.893±0.32	31.428±0.57	35.393±0.88	38.786±0.45	39.656±0.34
120	38.672±0.62	39.673±0.45	40.726±0.75	41.486±0.22	45.383±0.56	47.675±0.45
150	44.856±0.43	45.783±0.64	46.734±0.46	48.418±0.32	46.544±0.34	49.675±0.56
180	49.345±0.22	51.453±0.22	52.715±0.65	54.932±0.61	56.673±0.24	55.767±0.12
210	50.564±0.43	54.754±0.79	55.825±0.34	56.546±0.24	58.391±0.11	58.433±1.05
240	56.843±0.64	60.478±0.46	62.619±0.67	64.186±0.45	66.528±0.55	68.535±0.34
270	62.465±0.35	66.329±0.67	64.782±0.86	67.543±0.56	68.423±0.45	71.721±0.75
300	69.564±0.22	71.532±0.55	72.796±0.33	75.087±0.64	76.838±0.64	75.352±0.45
360	74.293±0.54	75.640±1.05	78.643±0.23	81.140±0.55	83.443±0.45	82.432±.67
420	76.634±0.85	79.564±0.13	87.001±0.34	88.176±1.43	86.355±0.86	88.138±0.43
480	87.656±0.32	84.748±0.54	94.690±0.55	96.426±0.32	93.453±0.24	95.564±0.34

*All values are expressed as mean ± SD, n=3

Table 6: Drug Release Kinetics of All Batches.

Batch code	R^2						
	Zero order	First order	Matrix	Korsmeyer Peppas	Hixon Crowell	n	K
F1	0.9376	0.9863	0.9839	0.9923	0.9899	0.7386	1.0020
F2	0.9673	0.9929	0.9680	0.9945	0.9959	0.7898	0.7154
F3	0.9587	0.9586	0.9742	0.9922	0.9908	0.8135	0.7037
F4	0.9396	0.9602	0.9813	0.9891	0.9913	0.7613	0.9807
F5	0.9303	0.9864	0.9816	0.9879	0.9953	0.7485	1.0593
F6	0.9290	0.9733	0.9802	0.9831	0.9941	0.7875	0.8689

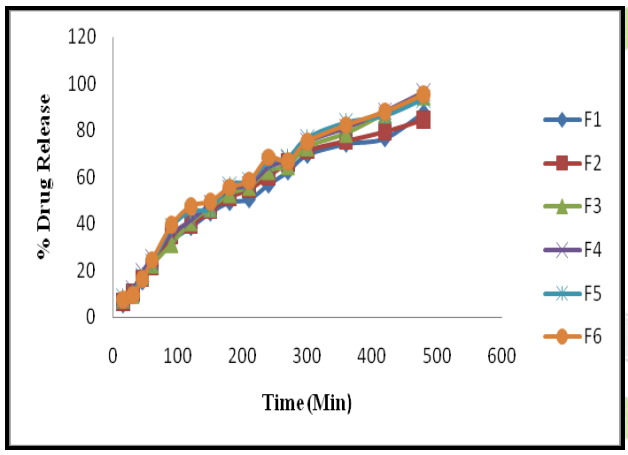

Figure 2: % Drug Release Vs Time of All Formulations (F1 to F6)

CONCLUSION

All formulation containing drug: polymer complexes prepared by Spray drying method have show better physicochemical properties. HPMC K4M and Ethyl cellulose as binding solution was optimized as sustained release polymer for pellet of Theophylline and release was sustained to 8 hours i.e. shows increase in half life means reduce dosing frequency.

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REFERENCES

1. John, C., Morten, C. (2002). The Science of Dosage Form Design, Aulton: Modified release peroral dosage forms. 2nd ed. Churchill Livingstone, 290-300.
2. Brahmankar, D. M., Jaiswal, S. B. (2009). Biopharmaceutics and Pharmacokinetics: Pharmacokinetics. 2nd ed. Vallabh Prakashan, Delhi, 399-401.
3. Lee, V. H. L. (1987). Controlled Drug Delivery Fundamentals and Applications: Influence of drug properties on design. 2nd ed. Marcel Dekker, Inc. New York, n16-25.
4. Wani, M. S. (2008). Controlled Release System-A Review. 6. Available on www.pharmainfo.net/review.URL:http://www.pharmainfo.net/reviews/controlled-released-system-review.
5. Global Initiative For Asthma (GINA): Global Strategy For Asthma Management And Prevention.2009.Available At: Http://Www.Ginasthma.Com Webcite Accessed on July 15, 2010.
6. Lemanske, R. F., Busse, W. W. (2010). Asthma: Clinical Expression and Molecular

Mechanisms. *J Allergy Clin Immunol*., 125, S 95-102.

7. Prescribing Information for Theophylline Available from: http://www.Drugs.com/mtm/theophylline.html
8. Prescribing Information for Theophylline Available from: http://www.thegoodscentscompany.com/data/rw/288881.html
9. Herbert, A. L., Lachman, L., Joseph, B. S. (1989). Pharmaceutical Dosage Forms, Tablets. New York Marcel Dekker Inc, 2nd Ed. Vol-I, 195-197, 285-286.
10. Cooper J, Gunn C. (1986). Powder flow and compaction. Carter SJ, eds. Tutorial Pharmacy. New Delhi, India: CBS Publishers and Distributors; 211-233.
11. Martin A. (2001). Micromeritics. Martin A, ed. Physical Pharmacy. Baltimore, MD: Lippincott Williams & Wilkins; 423-454.
12. Shayne Cox Gad Pharmaceutical Manufacturing Handbook: Production and Processes, John Wiley & Sons publications. 2nd edition.881-898.
13. The United State of Pharmacopoeia 24/NF26. The official compendia of United States of pharmacopoeial Convection Inc. Rockville, 1995; Asian Ed.:1015-1016.
14. Higuchi, T. (1963). Mechanism of sustained action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci.*, *52*, 1145–1148.
15. Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., Peppas, N. A. (1983). Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm. 15*, 25–35.

