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SUSTAINED RELEASE TABLETS OF THEOPHYLLINE

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ABSTRACT

Sustained release tablets of theophylline (anhydrous) were prepared using hydrophilic polymers (Methyl Cellulose, Methocel K_4M and $K_{15}M$) and hydrophobic polymers (ethyl cellulose, cellulose acetate). In addition water soluble adjuvants were used to modify release rate. With methocel, rapid gelling was observed and release was near zero-order, whereas with hydrophobic polymers release followed Fickian law of diffusion.

INTRODUCTION

Theophylline has been used as a bronchodilator in the treatment of asthma. The relatively narrow safety margin of the drug 5-20 mcg/ml (1) formerly created many problems and its use remained limited. The most significant factor in increasing medical awareness of theophylline is the development of sustained release preparations of the drug. This improves the likelihood of therapeutic effect while reducing the risk of serious toxicity.

EXPERIMENTAL

Materials

Theophylline (anhydrous) I.P./B.P. obtained as a gift sample from FDC (Pvt.) Ltd. and CIPLA LABS.

HPMC (Methocel K_4M, $K_{15}M$) COLORCON LTD., Methyl Cellulose (BDH) 50 cps, Ethyl Cellulose (BDH) 50 cps, Cellulose acetate (LOBA) PVA, PVP, PEG 4000,

lactose, dicalcium phosphate, microcrystalline cellulose, were all obtained from commercial sources and were used as supplied.

Methods

Granules were prepared by mixing theophylline (anhydrous) 300 mg per tablet with the cellulose derivatives and using ethanol (U.S.P.) as granulating agent. Granules were dried and 20/40 fraction was collected. Compression was done using a 8/16 inches flat faced punch and die on a cadmach single stroke tabletting machine. All the tablets were subjected to quality control tests such as weight variation, drug content uniformity, hardness, friability and in vitro dissolution (U.S.P. XIX).

In vitro dissolution studies : U.S.P. rotating basket method was used to investigate in vitro drug release. Dissolution medium (900 ml) (pH 1.2 for 2 hours and pH 7.2 for 10 hours) maintained at 37°C±0.5°C was used. Amount of theophylline released was determined only aft er suitable dilution, on a Beckmann DB spectrophotometer at λ = 271 nm.

RESULTS AND DISCUSSIONS

All the compressed tablets complied with the quality control tests. Weight Variation ±5% w/w, Content Uniformity ±3% w/w, Friability < 1% w/w. Moisture content of all the granulations were less than 2% w/w. Matrix formulations were designed which could be theoretically divided into 'hydrophilic' and 'inert' matrices depending on mechanism of release. Drug release occurred by combination of two mechanisms, diffusion of drug through a gel and erosion of tablet surface.

With methocel, rapid gel formation was observed. This gel impeded further liquid penetration into tablet core and thus provided a rate controlling barrier. Release rate was determined by viscosity of the gel. Methyl cellulose gel did not resist attrition and therefore did not remain intact. Drug release was not retarded significantly. Inert matrices did not gel and the tablet surface was eroded slowly exposing particles of the drug which then dissolved.

Kinetics of Drug Release

The dissolution data obtained was analysed by using the equation (2) :

$$\frac{Mt}{M\infty} = Kt^n$$

Matrix tablets prepared using only Methocel K_4M exhibited non-Fickian diffusion whereas those prepared using $K_{15}M$ followed zero-order kinetics (Table 1).

TABLE - 1

Formulation	'n'	Release Rate Constant (hr^{-1})	t_{50} Hours	t_{90} Hours
10% K_4M	0.48	K_1 = 0.1178	3.82	17.48
20% K_4M	0.61	K_o = 0.782	8.31	16.68
30% K_4M	0.61	K_o = 3.965	9.99	20.08
40% K_4M	0.60	K_o = 3.546	11.686	22.967
10% $K_{15}M$	1.0	K_o = 6.030	8.1229	14.756
20% $K_{15}M$	1.0	K_o = 4.723	10.321	18.789
30% $K_{15}M$	0.97	K_o = 3.497	13.851	25.287
40% $K_{15}M$	0.97	K_o = 2.902	16.914	30.698
10% M.C.	0.83	K_1 = 0.9436	1.605	3.311
20% M.C.	0.69	K_1 = 0.6167	2.207	4.880
30% M.C.	0.77	K_o = 9.5968	4.049	8.207
40% M.C.	0.79	K_o = 5.2316	8.517	16.163
10% E.C.	0.54	K_1 = 0.05219	10.615	41.539
20% E.C.	0.50	K_1 = 0.0375	14.914	57.794
30% E.C.	0.57	K_o = 2.5194	18.846	34.722
40% E.C.	0.48	K_o = 1.4904	30.205	57.043
10% C.A.	0.49	K_1 = 0.0687	7.855	31.33
20% C.A.	0.45	K_1 = 0.04939	10.993	43.594
30% C.A.	0.59	K_o = 3.5557	11.667	22.917
40% C.A.	0.48	K_o = 2.5671	15.674	31.255

TABLE - 2

Effect of channeling agents

Channeling Agent % w/w		'n'	Release Rate Constant (hr^{-1})	t_{50} Hours	t_{90} Hours
PEG 4000	2	0.47	K_1 = 0.2388	3.0617	9.8013
	4	0.56	K_1 = 0.5125	2.1477	5.2889
PVA	2	0.494	K_o = 6.988	5.839	11.563
	4	0.496	K_o = 9.7512	4.0119	8.1139
PVP	2	0.39	K_o = 7.3902	5.209	10.5499
	4	0.38	K_o = 9.795	3.281	7.365

Increasing the percentage of methyl cellulose from 10% w/w to 30% w/w did not retard release significantly. To increase release of theophylline from matrix tablets containing 20% K_4M water soluble additives such as PVA, PVP and PEG 4000 were incorporated as channeling agents. These had a significant effect on the release rate, because the dissolution medium diffusion into the tablet was facilitated. Channeling agents aided disintegration. This thus led to multiplicity of matrices which followed the same release kinetics (Table 2).

FACTORS INFLUENCING DRUG RELEASE

1. Effect of varying drug content : Release was not significantly affected. Diffusion was non-Fickian in nature (Table 3).

2. Effect of diluents : Effect of water soluble, lactose and water insoluble, dicalcium phosphate and microcrystalline cellulose, diluents at concentration of 5% and 10% w/w was evaluated. Increase in specific release rates were observed. Diluents decreased the tortuosity of the matrix. Lactose diffused outward forming channels whereas DCP and MCC were retained in the matrix which reduced

TABLE - 3

Theophylline dose (mg)	'n'	Release Rate Constant (hr^{-1})	t_{50} Hours	t_{90} Hours
75	0.594	K_o = 3.1288	13.893	26.67
150	0.567	K_o = 3.359	11.318	23.22
300	0.615	K_o = 4.7821	10.231	16.68

TABLE - 4

Effect of diluents on release of theophylline

Diluent	(% w/w)	'n'	Release Rate Constant (hr^{-1})	t_{50} Hours	t_{90} Hours
Lactose	5	0.7623	K_o = 7.8921	5.7902	10.8585
	10	0.7461	K_o = 8.8321	5.7902	8.9614
DCP	5	0.4244	K_1 = 0.1663	1.9847	11.665
	10	0.3889	K_1 = 0.1779	2.847	11.900
MCC	5	0.9145	K_1 = 0.3008	2.9805	8.3320
	10	0.7917	K_o = 10.317	2.5494	6.425

the gum concentration. Release was non-Fickian with lactose, Fickian with DCP and zero-order using MCC (Table 4).

3. Effect of various electrolytes : Release of ttheophylline was increased due to non-uniform gelling of HPMC. In 0.2 M solutions of Na_2SO_4 and $MgSO_4$, 100% release was obtained in just 3 hours. Shape of the tablet was also destroyed and it became elongated referred to as inverted gum drop (3).

SUMMARY

1. When using celluloses as matrices, an ideal choice would be one which gels rapidly and resists attrition on gelling. HPMC was found to fulfil these criteria.

2. Binder and tablet hardness had no significant effect on drug release.

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