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PHENYLPROPANOLAMINE HCL MICROCAPSULES: PREPARATION AND RELEASE STUDIES

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ABSTRACT

Microcapsules of phenylpropanolamine HCl were prepared by three techniques, viz. coacervation-phase separation, air suspension, and pan coating, using different polymers and/or waxes as wall-forming materials.

Formulations showed reasonable dissolution behaviour, viz. microcapsules prepared by air suspension with polymer level of 20% polyvinyl acetate copolymer (PVAC) associated with 40% carnauba wax (II) and microcapsules prepared by pan coating with polymer level of 25% Rodopace^{R} (III), were evaluated for their absorption rates by demonstrating their toxicities compared to pure grug (I) by the LD_{50} method. Toxicity assessment showed close agreement between the increase in lethal dose and the decrease in dissolution rate and revealed

1 Correspondence

that Formula III has more prolonged action than Formulae II and I.

INTRODUCTION

Phenylpropanolamine, a sympathomimetic agent, used to relieve congestion in the treatment of colds is also used to control urinary incontinence and as an appetite suppressant. Nervousness, restlessness, insomnia, headache, nausea, excessive rise in blood pressure and cardiac arrhythmias are some of its adverse effects (1,2).

Rhodes et al. (3) prepared controlled-release phenylpropanolamine by the facilitated molecular scale drug-entrapment method. Caldwell et al. (4) prepared five enamine derivatives of phenylpropanolamine in a search for prodrug derivatives that would hydrolyze at significantly different rates. Raghunathan et al. (5) in an attempt to formulate sustained-release dosage forms of phenylpropanolamine using the sulfonic-acid cationic resin system, applied a diffusion barrier coating on the resin-drug complex using an air suspension technique.

A long-acting appetite suppressant oral products were recently developed from the controlled-release osmotic pump technology (6) and the sustained-release Spansule^{R} technology (7) to deliver phenylpropanolamine at controlled rate for 16 and 18 hours, respectively.

The following study is a trial to prepare prolonged-release phenylpropanolamine HCl microcapsules using different techniques and different wall-forming materials so as to help esteblish product specifications for the finished dosage forms.

MATERIALS

All drug, chemicals and solvents were analytical grade.

PROCEDURES

Microencapsulation by Coacervation-Phase Separation

Coacervation-phase separation was achieved by adding dropwisely a suspension of phenylpropanolamine Hcl in a solution of polyvinyl acetate (Rodopace^{R}) or PVAC in acetone to petroleum ether (the non-solvent).

Microencapsulation by Air Suspension Technique

The drug was fluidized and granulated with the specified polymer or wax solution using the fluidized-bed apparatus (Uni-Glatt "Wurster" System, CH-4133, Binzen-Haltingen, W. Germany). The fluidized dry granules were then microencapsulated by coating with the specified polymer and/or wax solution at different coat levels (Table 2).

N.B.: Acetone was used as a solvent for Rodopace^{R} and PVAC, chloroform for polystyrene and carnauba wax, and chloroform/acetone mixture (1:1) for hydrogenated castor oil.

Microencapsulation by Pan Coating

The drug was granulated with a mixture of acetone and 70% ethyl alcohol (1:1). The dried granules were then rounded in a coating pan (Brookmotor, Gryphon, Huddersfield, England), sieved, and coated with the specified polymer or wax solution at different coat levels (Table 3) using spray gun atomizer.

Non-Disintegrating Tabletted Microcapsules Preparation

The microcapsules prepared by air suspension and pan coating were compressed by Manesty Tablet Machine (Type E_2, Speke, Liverpool, England) into non-disintegrating tablets, each weighing about 200 mg using 3/8 inch punches and dies. The hardness of the prepared tablets was adjusted to 4-5 kg.

Determination of Free and Microencapsulated Drug

A sample of the microcapsules was placed in a Buchner funnel, washed with 0.1 N HCl and the adhering

TABLE 1

Dissolution Rate of Phenylpropanolamine HCl Microcapsules (8/12 -Mesh Screen, B.P.) Prepared by the Drop Method of Coacervation-Phase Separation.

Polymer	Initial Polymer Concen. % w/v	Percent Dissolved (Min.)							
		15	30	45	60	75	90	105	120
Rodopace^{R}	15	14.9	32.3	51.0	79.8	100			
	25	11.2	24.3	40.8	65.3	78.0	88.9	100	
Polyvinyl Acetate Copolymer	15	15.0	26.0	41.0	56.3	75.0	84.3	100	
	25	10.3	21.5	36.9	50.0	69.3	78.6	89.3	100

(free) drug in the filtrate was then spectrophotometrically determined at 257 nm (8) using Beckman Spectrophotometer (Type DU_7, U.S.A.). The washed microcapsules were then pulverised and its drug content was determined. Having estimating the free and microencapsulated drug in each batch, the coat level percentage could be calculated.

Dissolution Studies

Dissolution studies were carried out as described by Raghunathan et al. (5). The dissolution assembly was essentially the same as described in U.S.P. XIX(9). 400 ml of deaerated 0.1 N HCl equilibrated at 37±0.5° was used as a dissolution medium for an amount of the microcapsules containing 500 mg of the drug. A three-bladed stainless steel propeller stirrer (2.5-cm blade size) was positioned just below the surface of the dissolution medium and rotated at 50 rpm. The dissoluted drug was spectrophotometrically determined at 257 nm.

TABLE 2

Dissolution Rate of Phenylpropanolamine HCl Microcapsules (420-840 μ) and Non-Disintegrating Tabletted Microcapsules Prepared by Air Suspension Technique.

Polymer and/or Wax	Total Percentage of Polym.&/ or Wax to Drug Weight w/w	Polymer or Wax Used in Granulation Percent w/w	Polymer &/or Wax in the Coating Solutions %, w/w Coats 1st	2nd	3rd	Type of Prepa-ration	Percent Dissolved (Hours) 0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00
PVAC	7.5	2	5.5			Mic.		100								
						T.Mic.		100								
	17.5	2	5.5	10		Mic.		100								
						T.Mic.		85.0	100							
	27.5	2	5.5	10	10	Mic.		92.0	96.2	98.5	100					
						T.Mic.	48.1	63.3	75.0	83.0	93.9	97.0	100			
Polystyrene	7.5	2	5.5			Mic.		100								
						T.Mic.		86.6	100							
	17.5	2	5.5	10		Mic.		100								
						T.Mic.		68.6	89.0	100						
	27.5	2	5.5	10	10	Mic.		100								
						T.Mic.	41.9	62.3	77.0	88.7	100					
Rodopace[R]	5.0	2	3.0			Mic.		100								
						T.Mic.		86.3	100							
	15.0	2	3.0	5	5	Mic.		100								
						T.Mic.	71.3	86.5	94.1	100						
	30.0	2	8.0	10	10	Mic.		90.3	100							
						T.Mic.	44.4	68.9	87.3	92.7	100					
Carnauba Wax	3.0	2	1.0			Mic.		100								
						T.Mic.		100								
	7.0	2	5.0			Mic.		100								
						T.Mic.		100								
	15.0	2	5.0	8		Mic.		92.2	94.2	100						
						T.Mic.	55.0	74.7	86.3	93.7	100					
	40.0	2	8.0	15	15	Mic.		88.7	93.3	100						
						T.Mic.	47.1	61.4	74.4	81.8	100					
Hydrogenated Castor Oil	3.0	2	1.0			Mic.		95.0	100							
						T.Mic.		64.7	96.1	100						
	15.0	2	3.0	10		Mic.		90.0	100							
						T.Mic.	46.4	72.0	81.7	88.2	94.5	100				
	40.0	2	8.0	15	15	Mic.		73.6	81.6	92.2	95.6	100				
						T.Mic.	36.5	50.4	57.6	68.4	81.8	92.0	100			
PVAC (P) + Car.Wax(CW)	20+ 40 (P)(CW)	5 (P)	15 (P)	20 (CW)	20 (CW)	Mic.	40.7	45.8	50.9	58.3	69.8	77.6	95.6	100		
						T.Mic.	19.4	25.2	32.3	37.5	50.6	55.8	70.2	88.0	95.2	100

N.B.: Uncoated drug granules and tablets prepared from uncoated granules released the drug in less than 5 and 7 minutes, respectively.

TABLE 3

Dissolution Rate of Phenylpropanolamine HCl Microcapsules (850-1250 μ) and Non-Disintegrating Tabletted Microcapsules Prepared by Pan Coating.

Coating Material	Coating Level, %	Type of Preparation	Percent Dissolved (Hours)																								
			0.25	.5	0.75	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10
PVAC	15	Mic.	29	44	49	60	76	85	100															
		T.Mic.	35	55	71	86	100																	
	30	Mic.	27	28	30	38	39	43	50	70	84	94	100											
		T.Mic.	15	22	32	41	51	69	81	100														
	45	Mic.	13	16	18	23	45	57	70	74	78	82	91	100										
		T.Mic.	12	23	30	46	56	72	100															
Polystyrene	15	Mic.	58	66	85	94	100																	
		T.Mic.	32	43	70	96	100																	
	20	Mic.	20	28	39	53	67	82	95	100														
		T.Mic.	53	61	86	92	100																	
	25	Mic.	8	20	33	38	49	57	72	83	100													
		T.Mic.	19	27	38	49	64	89	95	100														
	30	Mic.	15	21	26	35	44	59	73	77	86	100												
		T.Mic.	14	20	22	33	50	57	75	94	100													
Rodopace[R]	10	Mic.	43	53	66	74	82	94	100															
		T.Mic.	13	16	27	39	50	58	63	72	82	94	100											
	15	Mic.	21	40	47	52	69	78	83	91	96	100												
		T.Mic.	23	39	46	52	58	66	69	74	78	84	92	95	100									
	25	Mic.	10	16	25	31	41	53	72	79	85	95	100											
		T.Mic.	23	32	41	43	46	47	49	51	53	57	61	62	65	67	70	73	78	82	85	91	96	100
Carnauba Wax	15	Mic.	29	49	67	80	93	100																
		T.Mic.	28	49	68	85	100																	
	20	Mic.	7	17	32	42	57	77	87	100														
		T.Mic.	19	33	58	69	83	96	100															
	30	Mic.	0.5	1.4	3.5	5	9	13	18	22	28	35	41	42	51	57	62	70	77	81	87	92	100	
		T.Mic.	17	30	35	44	51	60	67	72	77	84	87	90	95	100								
Hydrogenated Castor Oil	40	Mic.	16	29	38	46	50	61	67	79	86	91	96	100										
		T.Mic.	20	30	37	45	59	78	85	94	100													
	45	Mic.	8	9	14	24	34	39	45	49	62	73	80	88	95	100								
		T.Mic.	24	40	51	61	70	80	90	100														
	50	Mic.	5	10	13	16	22	25	28	34	41	47	59	71	78	86	100							
		T.Mic.	5	14	19	25	30	36	42	48	55	61	68	75	86	100								

TABLE 4

Acute Toxicity of Phenylpropanolamine HCl in Mice

Formulation	Dose mg/kg	Number Dead/ Number Dosed	LD_{50} (mg/kg) Mean (95% Con. Lim.)
I	2000	6/6	750 (551 - 1020)
	1500	5/6	
	1200	4/6	
	1000	4/6	
	800	3/6	
	600	2/6	
	400	1/6	
	200	0/6	
	100	0/6	
II	2300	6/6	1200 (902 - 1596)
	2000	5/6	
	1800	4/6	
	1500	4/6	
	1200	3/6	
	1000	2/6	
	800	2/6	
	600	1/6	
	400	0/6	
III	2400	6/6	1500 (1099- 2048)
	2000	5/6	
	1800	4/6	
	1500	3/6	
	1200	2/6	
	1000	2/6	
	800	1/6	
	600	0/6	
	400	0/6	

LD_{50} Studies

Formulations showed reasonable dissolution behaviour, viz. microcapsules prepared by air suspension with polymer level of 20% PVAC associated with 40% carnauba wax (II) and microcapsules prepared by pan coating with polymer level of 25% Rodopace^{R} (III), were selected along with pure drug (I) to assess the relative rate of drug absorption. Formulae II and III were suspended in 2% gum acacia solution so as to contain 50

TABLE 5

Acute Toxicity of Excipients Used in Phenylpropanolamine HCl Formulations.

Formulation	Excipients	Dose (mg/kg)		Number Dead/Number Dosed	
		Drug	Excip.	Excipients and Drug	Excipients Alone
II	PVAC + Carn. Wax	2300	1150 +2300	6/6	0/6
III	Rodopace^{R}	2400	800	6/6	0/6

and 25% drug, respectively, while in case of Formula I a 20% aqueous solution of the drug was used. Mice, each weighing 18-22 g were used. The doses were administered orally by intubation to 6 mice per dose level. The LD_{50} values were calculated adopting the method of Litchfield and Wilcoxon (10).

Oral Toxicity of Excipients

The excipients added to the formulation were evaluated in the same manner as the drug and were found to have no effect on the LD_{50} values in the maximum amount used in the formulation (Table 5).

RESULTS AND DISCUSSION

Dissolution Studies

The microcapsules prepared by coacervation-phase separation did not show promising prolongation of the drug, as the maximum prolongation achieved was 2 hours (Table 1). This may be due to the formation of microcapsules having porous coat which might have led to rapid leaching of the drug by the dissolution medium.

From Table 2, it can be shown that, the maximum prolongation achieved was 3 and 4 hours in case of

microcapsules and non-disintegrating tabletted microcapsules containing 20% PVAC associated with 40% carnauba wax, respectively. The prolongation achieved upon compressing the drug microcapsules, can be explained as a network of polymer and/or wax is produced forming a honey comb structure around the drug particles so that the drug is contained in a small cellular compartments (11). The type and level of the polymer and/or wax forming the network, thus, play an important role in permitting penetration of the fluids into the cellular compartments, whereby, the enclosed drug dialyses out into the surrounding fluids.

From Table 3, one can observe the successful prolongation achieved on using the pan coating technique. Thus, 100% drug release was achieved after 1.5-9.5 and 1.5-10 hours, from the microcapsules and tabletted microcapsules, respectively. This marked prolongation achieved may be due to the coating technique itself, where numerous thin coats are applied, and to the large microcapsule size, whereby, a marked decrease in drug surface area exposed to dissolution resulted.

LD_{50} Studies

Table 4 shows that Formulae II & III, containing microencapsulated drug, have significantly high lethal doses than Formula I containing plain drug. The increase in lethal dose was attributed to slower absorption of the drug from the microencapsulated forms. Thus,one may conclude that Formula III has more prolonged action than II & I. Comparing the results of this in-vivo technique with that of the in-vitro dissolution reveals close agreement between the increase in lethal dose and the decrease in dissolution rate.

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