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Enteric Film Coating Using Completely Aqueous Dissolved Hydroxypropyl Methyl Cellulose Phthalate Spray Solutions

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SUMMARY

A completely aqueous film coating spray system has been developed for the enteric film coating of tablets. The method uses conventional aqueous film coating equipment and techniques. The coatings produced compare in enteric quality with the best that can be achieved with enteric film coatings applied from organic solutions. Dissolution rate data were mainly used to judge the enteric quality, and such data for a number of enteric film coating trials are presented.

INTRODUCTION

Exhaust air from enteric film coating plants is generally eventually released to the atmosphere, so the use of completely aqueous spray systems has obvious ecological advantages. In addition, many of the organic

solvent systems which could be used for enteric film coating constitute a fire, explosion and/or health hazard. Aqueous systems eliminate these hazards or the cost of making the working area safe for the use of such solvents. Water, even when highly purified, is so cheap that recovery from exhaust air can be ignored. Also, the very high sensitivity of present day analytical techniques makes water a very desirable solvent with respect to residues in the product since water presents no toxicity problems.

Mixed organic-aqueous solvent systems have been proposed for enteric coatings[1)], but these do not have all the advantages listed above. Completely aqueous enteric coating dispersions based on methacrylic acid copolymers[2)] have been commercially available for years, but have only very recently achieved world wide acceptance by registration authorities. Still more recently, a powder dispersion system in water based on hydroxypropyl methyl cellulose phthalate, HPMCP, has been offered for sale[3)].

Some technical difficulties may be encountered in using dispersions for spray coatings. These mainly concern pistol blockage during spraying. Additionally, some stability problems concerning post-hardening of the coatings, or discolouration and sticking together may be encountered.

The present process described here has been the basis of a patent application[4)] and uses a completely dissolved enteric film former, so the pistol blockage problems typical of dispersions are not encountered.

The process uses neutralised, completely water soluble HPMCP to provide the enteric properties.

The Shinetsu Chemical Company discloses a patent[5] whereby HPMCP is dissolved in water by neutralising with a base and applied to tablets by a spray coating technique, but the coatings are not enteric until they undergo a subsequent acid treatment step.

MATERIALS AND METHODS

Film coatings were carried out in a 24 inch Accela Cota, Manesty Machines, Ltd. The spray pistol used was a Binks Model 2610 from Binks (International), Waterloo, Belgium.

The hydroxypropyl methyl cellulose phthalate was HP 50 from Shinetsu Chemical Company, Tokyo, Japan. Pro analysi sodium hydroxide pellets, Merck; pro analysi 25 % ammonia solution (density 0.91 g/cm^3), Merck; and triethanolamine, pure, Ph. Helv. VI, Siegfried, Switzerland, were used to neutralise the HPMCP.

Other excipients used in the coatings were Talc Pharm. from Prechel Herbert, Mannheim, Germany, titanium dioxide USP XIX from ICI, Great Britain and water soluble erythrosine from D.F. Anstead, Great Britain.

The tests included the USP XIX disintegration time apparatus, the USP XX rotating basket dissolution rate apparatus and the flow through cell dissolution rate apparatus[6]. The USP XIX disintegration time apparatus was used but the enteric requirements of Eur. Ph. I

TABLE 1

Spraying Conditions

Cores: Propyphenazone containing cores, weight 240 mg, diameter 10 mm, curved faces (18 mm radius of curvature) and bevelled edges.

Charge: 10 kg in the 24 inch Accela Cota

Drum rotation speed	16 rpm
Inlet air: quantity	3000 m^3/hour
temperature	57°C
Exhaust air: quantity	3200 m^3/hour
temperature	34.5°C
Spray pistol	Binks Model 2610
Nozzle	No. 63
Needle	No. 636
Spray cap	No. 63 PB
Distance, spray nozzle to rolling core bed	20 cm
Compressed air	3 atmospheres
Spray programme: Spray	60 seconds
Spray interval	2 seconds
Spray speed, finger pump*	45 UpM
Total coating time	4 hours 25 minutes

* Finger pump arm diameter ca. 5 cm, finger pump tubing internal diameter 5 mm.

were also followed, that is residence for two hours in simulated gastric juice at 37°C before changing to pH 6.8.

About 12.5 % by weight of HPMCP is dispersed in water and neutralised with base to make the spray solution. The amount of base required per 100 g HPMCP was found to be 11.8 g of 25 % aqueous ammonia, 6.74 g of NaOH (added dissolved in a little water for rapid dispersion) or 25.3 g triethanolamine. The HPMCP is usually fully dissolved after a few hours.

Insoluble excipients such as talc and titanium dioxide were ball milled as aqueous dispersions with a Dynomill (W.A. Bachofen, Switzerland) before adding to the spray solution.

The spray conditions for film coating propyphenazone tablets (see table 5) are given in table 1.

DEVELOPMENT

Provided that the spray coating process is strictly controlled, it was found that coatings of excellent enteric quality could be reproducibly achieved in a single stage film coating process.

Initial trials with film coating neutralised HPMCP showed that the enteric quality of the spray coating improved when the spray coating process was more strictly controlled to avoid defects that lower the quality of the enteric coatings produced.

Two main classes of defects can be distinguished:

(i) Frictional wear at tablet edges during film coating due to running the process too dry. This can reduce the thickness of the enteric coat without actually exposing the edge, and the remaining edge cover is not sufficient to afford the required enteric properties.

(ii) Incipient sticking, where tablets sticking to the apparatus or together, part without any visible mechanical damage or core-exposing holes in the applied film coat, but sufficient rupture or micro-blistering occurs to lower the resistance of the film coat to penetration by simulated gastric fluid. This occurs when the process is run too wet.

The effects caused by these two kinds of defects may be observed by careful examination with a magnifying glass or observation of the pattern of failure in the enteric disintegration test in simulated gastric fluid.

It should be noted that these two kinds of defects are of no consequence in conventional aqueous film coating with gastric-soluble polymers, since they are not readily apparent to even a close inspection of the coated tablets with the naked eye and the effect of the defects on disintegration, if noticeable, would be considered advantageous. Consequently, it is no surprise that satisfactory one-stage, completely aqueous enteric film coating with neutralised HPMCP requires a stricter control of the film coating process than is

the case with conventional completely aqueous gastric soluble film coating.

This stricter control consists of running the film coating process in a narrower region of conditions defined by being further from the dry side limit where edge frictional wear is visibly observable, and also far from the limit on the wet side where obvious sticking occurs.

With a little practice, running the film coating process with these two constraints presents little difficulty, and enteric coatings of excellent quality can be reproducibly achieved.

RESULTS

Two batches of cores containing pindolol in a sustained release formulation[7] coming from the same production charge were coated with 15 mg of aqueous neutralised HPMCP and HPMCP dissolved in an organic solvent (1:1 methanol/acetone), respectively. The film coated tablets from both trials completely satisfied the disintegration time enteric coating test (two hours residence in simulated gastric fluid at 37 ± 1°C with agitation) in terms of gastric juice resistance. A dissolution rate test according to the USP XIX rotating basket method, with pH jump from 1.2 to 6.8 after 60 minutes was carried out. The results, shown in table 2, indicate similar release profiles.

To check the reproducibility of the aqueous enteric film coating process, two further batches of pin-

TABLE 2

Dissolution Rate of Aqueous Enteric Coated Pindolol Cores Film Coat: 15 mg: Method: Rotating Basket with Rotation Speed of 100 rpm and 400 ml of Simulated Gastric Fluid. pH Jump from 1.2 to 6.8 after 60 minutes. The Mean of Six Determinations and the Standard Deviations are Given.

		HPMCP from aqueous solution		HPMCP from organic solution	
Time min	pH	Mean	standard deviation	Mean	Standard deviation
		%	%	%	%
60	1.2	3.2	3.7	2.6	2.0
120	6.8	33.0	3.8	25.2	1.9
180	6.8	44.4	4.2	43.4	9.7
240	6.8	53.4	5.4	64.2	10.8
300	6.8	66.2	7.1	76.8	9.0
360	6.8	70.2	9.0	86.6	7.1

dolol cores from a different production charge were then coated. In this case the dissolution rate test was carried out with the time of the pH jump from 1.2 to 6.8 occurring after 120 minutes. The dissolution rate results are shown in table 3. There is no significant difference between the results for these two batches. It is also evident that stomach juice protection is also assured over two hours.

Cores taken from a third production charge were coated with varying amounts of aqueous dissolved HPMCP

TABLE 3

Reproducibility of the Rotating Basket Dissolution Rate for Two Different Batches of Enterically Coated Pindolol Cores.

Time, min	pH	Batch No. 1 Mean release %	Batch No. 2 Mean release %
15	1.2	1.2	0.9
30	1.2	1.3	1.1
60	1.2	2.0	1.9
120	1.2	2.8	2.2
135	6.8	12.6	7.1
150	6.8	19.2	14.7
180	6.8	26.1	22.1
240	6.8	36.8	33.4
300	6.8	47.9	46.4
360	6.8	59.8	62.4
420	6.8	74.8	71.8
24 hours	6.8	100	100

film. Again, all coated tablets satisfied the gastric resistance requirement of the disintegration time test (two hours residence with agitation in simulated gastric juice with pH jump after two hours from 1.2 to 6.8). Again, the coated tablets were also tested by the rotating basket dissolution rate method. The results are shown in Table 4.

The dissolution rate data shows that there is a steady improvement in enteric properties with increas-

TABLE 4

Variation of Enteric Performance of Pindolol Cores Coated with Various Amounts of Neutralised HPMCP. Film Weight is Given in Terms of Amount of HPMCP before Neutralisation.

		Amount of HPMCP applied		
		Mean release		
Time, min	pH	5.5 mg	8.25 mg	11 mg
		%	%	%
5	1.2	0,18	0.19	0.90
15	1.2	0.28	0.28	0.99
30	1.2	0.74	0.37	1.08
60	1.2	4.52	0.93	1.17
90	1.2	8.12	1.85	1.17
120	1.2	10.52	4.26	1.26

ing film thickness, as seen in the lowered release during the first two hours at pH 1.2.

A fast releasing, fast disintegrating tablet formulation was also coated with the completely aqueous neutralised HPMCP film coating solution according to the conditions shown in table 1. The tablet core characteristics are given in table 5.

The propyphenazone enteric coated tablets fully met the enteric coated tablet test (withstanding two hours residence with agitation in simulated gastric fluid at 37 $\pm$ 1°C and disintegrating in 5.5 min when the pH was jumped to 6.8). The dissolution rate data

TABLE 5

Characteristics of the Fast Releasing, Fast Dissolving Propyphenazone Tablets.

Formulation	mg
Propyphenazone	24.0
Lactose	162.23
Corn starch	40.07
Polyvinyl pyrrolidone	4.47
Magnesium stearate	1.79
Talc	2.44
	240.0

Schleuniger hardness	42 N
Friability, Roche Friabilator	0.7 %
Disintegration time, USP	1.7 min
Tablet diameter	9 mm
Tablet shape	Low curvature (radius 18 mm) Bevelled edge

measured in the flow-through cell is shown in table 6 for a pH maintained at 1.2 for two hours. For comparison, the dissolution rate of uncoated tablets measured under the same conditions are also given. The data for the coated tablets apply to samples stored for 12 months at room temperature in closed brown glass bottles.

The dissolution rate test shows no loss in stomach juice resistance, even after 12 months storage.

TABLE 6

Dissolution Rate Data for Propyphenazone Tablets, Uncoated and Coated with HPMCP Neutralised with Ammonia or NaOH. The Flow Through Cell Data Apply to Film Tablets Stored 12 Months at Room Temperature in Closed, Brown Glass Bottles.

Time min	pH	Uncoated tablets, release %	Coated with HPMCP neutlised with ammonia, release %	Coated with HPMCP neutralised with NaOH, release %
5	1.2	49.1	--	--
10	1.2	81.1	--	--
15	1.2	94.9	2.63	1.75
30	1.2	100	3.47	1.95
60	1.2	--	4.62	2.26
120	1.2	--	6.00	3.29

The Gillazym® cores described by Ehrhardt, et. al.[8] were also coated by a completely aqueous neutralised HPMCP spray coating solution. The 750 mg oblong tablets with curvature contain acid-sensitive enzymes. The experimental details for the film coating are given in table 7.

The enteric coating disintegration test used here was residence with agitation for 60 minutes in simulated gastric juice at 37 ± 1°C. The aqueous film coated tablets remained fully intact and firm during this

TABLE 7

Film Coating Details for Coating a 10 kg Charge of Gillazym® Cores in the 24" Accela Cota with Neutralised Aqueous HPMCP.

Base coat	HPMCP	134.6 g
	25 % aqueous ammonia	15.1 g
	Erythrosine, water soluble	0.67 g
	Demineralised water	925.63 g
Second coat	HPMCP	269.2 g
	25 % aqueous ammonia	30.15 g
	Erythrosine, water soluble	1.35 g
	Talc	50.0 g
	Titanium dioxide	47.5 g
	Demineralised water	1753.8 g
Final coat	HPMCP	403.8 g
	25 % aqueous ammonia	45.2 g
	Erythrosine, water soluble	2.0 g
	Demineralised water	2777.0 g
Spray rate	46.11 g/min, otherwise conditions as in table 1.	

test and should disintegrate fully within about 15 minutes when the pH is jumped to pH 5.5. The actual results were

Disintegration time, cores, pH 5.5: 6.4 - 9.3 min
Disintegration time, aqueous enteric coated tab-

lets, modified USP (60 min, pH 1.2, pH jump to 5.5): 14.7 - 17.1 min.

(HPMCP film applied to these cores from organic solution requires about 6 - 13 minutes to dissolve from the cores at pH 5.5).

When acid penetration occurs through the enteric coating during residence with agitation in simulated gastric juice at 37 ± 1°C, the core is discoloured to the depth of penetration. The depth of acid penetration into the cores coated with aqueous neutralised HPMCP was of the same order as for Gillazym® cores coated with HPMCP from organic solution (namely, about 0.5 mm).

DISCUSSION

The neutralised HPMCP film former is completely water soluble. To provide enteric protection, the neutralised HPMCP film on the tablet is converted to the insoluble acid at the simulated gastric juice pH. This conversion to acid must occur very rapidly, otherwise the enteric coating of the fast disintegrating, fast releasing propyphenazone formulation, see tables 5 and 6, would not have been successful.

The fact that the neutralised HPMCP enteric film is not actually enteric until it comes in contact with acid media is not a problem since tests have shown that tablets coated with HPMCP from organic solvents disintegrate quickly in non-acidic media like demineralised water.

Gastric juice is generally said to vary in pH from 1 to 3. To test if fast disintegrating tablets coated with aqueous neutralised HPMCP are still enteric at higher pH, a disintegration time test was carried out in aqueous media at pH 4. The coated tablets remained intact after two hours residence with agitation at 37 $\pm$ 1°C in this medium. The conversion of the neutralised HPMCP at pH 4 is sufficiently fast and complete to provide an enteric coating.

There are four classic tests for any satisfactory aqueous enteric film coating process:

(i) coating fast disintegrating and releasing tablets
(ii) coating hydrophobic tablets
(iii) coating formulations such that little or no active ingredient should be released to the stomach (because it is irritating or injurious to the stomach, but not to the intestine)
(iv) coating tablets containing an acid sensitive active ingredient.

Test (i) is satisfactorily accomplished with the propyphenazone tablets (see table 6). Although the tablets are fast disintegrating and rapidly release the active ingredient, little drug substance is released until the pH is raised above the value encountered in the stomach.

Test (ii) can be regarded as accomplished with the pindolol cores, which contain a significant amount

of hydrophobic ethyl cellulose in the formulation. Other trials with a very high dosage of a very hydrophobic development drug also confirm this result.

Test (iii) can also be regarded as accomplished in view of the very low drug releases observed during contact with simulated gastric fluid when dissolution rates are performed on tablets coated with aqueous neutralised HPMCP.

Test (iv) is satisfactorily accomplished with the aqueous enteric coating of Gillazym® cores which compare well with the same cores coated with HPMCP from organic solution in the disintegration time test.

A recent survey of enteric coated tablets on the market[9] has shown that they all show greater or lesser penetration of simulated gastric fluid through the enteric coating during residence in artificial gastric juice in the disintegration time test. Consequently, some acid penetration has to be taken into account, and tests have shown that the penetration into Gillazym® cores coated with aqueous HPMCP is of the same order as that encountered with the same cores coated with HPMCP from organic solution.

The disintegration time test for enteric coatings can be a misleading test in terms of the enteric quality of the coating. Pindolol cores coated with insufficient HPMCP could satisfactorily pass the enteric disintegration time test, but still show in excess of 30 % drug release during the first two hours in contact with simulated gastric fluid in the rotating basket

dissolution rate test. Consequently, the dissolution rate with pH jump after 1 or 2 hours is a more severe test than the enteric disintegration time test.

In practice, enterically coated cores seldom, if ever, show zero drug release during the first two hours residence in gastric juice in the dissolution rate test[10]. The releases shown in tables 2 and 4 are in the range of the best that can be accomplished with enteric coatings produced from organic solution or from dispersions.

Some indication of the storage stability of completely aqueous neutralised HPMCP enterically coated film tablets is given in table 6. There is no loss in enteric properties over 12 months at room temperature for samples stored in closed brown glass bottles. A fuller report on the stabilities of enteric film coating will be given at a later date.

Finally, an aqueous spray coating system using completely dissolved HPMCP has been developed to produce enteric film coated tablets of excellent enteric properties using conventional film coating techniques and equipment.

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