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Original Research Article

Effect of Curing Time on pH and Time Dependant Coated Pellets

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Abstract

PURPOSE: The drug release from coated pellets depends on many process and formulation variables, including plasticization, curing treatment, and properties of the core. In this study, effect of currying on eudragit coated pellets was investigated.
METHODS: Theophylline loaded pellets were coated with a non aqueous time and pH dependant eudragit solution. The coated pellets were cured at constant process parameters (45℃) for different time periods (05, 10, or 20 min) and the drug release profile and other characteristics of formulation were evaluated.
RESULTS: In *vitro* release studies shows retardation of drug release from the coated pellets. The DSC thermogram revealed no interaction between the polymer and drug in the formulation. The SEM data shows no change in the surface topography after 20 min curing.
CONCLUSION: In general, curing reduced the drug release and resulted in stable drug release profiles.

Keywords: Time and pH dependant polymers, curing of pellets.

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Introduction

The drug release from coated pellets depends on many process and formulation variables, including plasticization, curing treatment, and properties of the core.[1] In this respect, a decrease in dextromethorphan hydrobromide release from aquacoat-coated pellets upon storage for 4 months at room temperature was reported.[2] In contrast, theophylline pellets coated with aqueous ethylcellulose dispersion showed an increase in release from uncured pellets.[3] A curing step subsequent to the coating process is often recommended to reduce stability problems due to enhanced film formation by further coalescence.[4,5] Besides the water solubility of the drug,[6,7] the solubility of the other core ingredients can also have a major impact on the drug release by creating an osmotic pressure gradient across the polymeric coating upon contact with dissolution medium.[8,9]

Marked difference between the curred and uncured dissolution profile was revealed in Kollicoat SR 30D coated non-pareil-based system.[11] Curing the pellets resulted in release profiles, which did not change during storage for 3 years and also had a smooth, continuous surface and a dense film structure after curing.[12]

The objective of this study was to evaluate the influence of curing conditions on the drug release from pellets coated with time dependant polymer (eudragit RL 100) and pH dependant enteric coated polymer (eudragit S 100). The polymers were applied for coating to achieve the pulsatile drug release.

Materials and Methods

Materials

Theophylline (particle size: 100-130 µm) was obtained from Aarti Chemicals (Mumbai, India). Hydroxy propyl cellulose and celphere CP 203 (microcrystalline cellulose spheres) were obtained from Signet Chemical Corporation Pvt Ltd (Mumbai, India). Signet Chemical Corporation Pvt. Ltd (Mumbai, India). Eudragit RL100 and Eudragit S100 were obtained from Rohm Pharma, Gmbh (Germany). Triethylcitrate (TEC) and dichloromethane (DCM) were obtained from Merck (Germany) while isopropyl alcohol (IPA) was obtained from Loba Chemicals (Mumbai, India). Other ingredients such as lubricants and glidants used to prepare the tablet were of standard pharmacological grade.

Methods

Preparation of Drug-Containing Pellets

Theophylline (TH) loaded pellets were prepared by layering a drug-binder solution (7.5% w/w) on to celphere CP 203 beads using a fluidized bed coater (Miniglatt, Wurster insert, Glatt GmbH, Binzen, Germany). Aqueous dispersion of TP and hydroxy propyl cellulose (HPC) was sprayed using the bottom spray mode. Layered beads were dried in miniglatt at 40 ^{o}C for 5 min. The detailed composition of drug layering and polymer coating is given in Table 1 and the process parameter of the drug layering processes and coating are given in Table 2.

Coating of the drug layered Pellets

The drug layered pellets were coated in a fluidized bed coater using the bottom spray mode (Miniglatt, Wurster insert, Glatt GmbH, Binzen, Germany) with a plasticized non aqueous solution of time dependant polymer (eudragit RL 100) and pH dependant polymer (eudragit S 100) ratio 8:2. The solution was plasticized with TEC (10 wt%, based on the mass of the polymer). The non aqueous solvents contain the IPA and DCM in 8:2 ratios. The polymer content of the plasticized dispersion was then adjusted to 10 wt%. The final coating solution was sprayed onto a drug-loaded celphere beads to achieve weight gain of 7.5%. The process parameters for the coating step are

Table 1: Composition of core and coating layer

Excipients	Mg/capsule
Drug Layering	
Celphere CP 203	45
Theophylline	200
HPC	100
Water	3.7
Total weight of drug layered pellets	348.7
Polymer Coating	
Drug layered pellets	345
Eudragit RL100	20.7
Eudragit S 100	5.175
TEC (10%)	2.587
IPA	186.30
DCM	46.57
Total weight of enteric coated pellets	370.87
Lubrication	
Talc (2.5%)	9.27
Total weight of lubricated pellets	380.14

DCM, dichloromethane; HPC, hydroxy propyl cellulose; IPA, isopropyl alcohol; TEC, Triethylcitrate

Table 2: Glatt parameters applied for the drug-layering and coating

Process Parameter Coating	Drug Layering	Polymer
Inlet temperature	45-50 ^{o}C	45–50 ^{o}C
Air volume	40-60 m^3h^{-1}	40-60 m^3h^{-1}
Product temperature	38–40 ^{o}C	35-36 ^{o}C
Spray rate	0.5–3 g/min	0.5-3 g/min
Atomization pressure	40-60 m^3h^{-1}	40-60 m^3h^{-1}
Nozzle diameter	0.5 mm	0.5 mm

given in Table 2. Initially, the pellets were coated at a slow spray rate (0.5–1 g/min for the first 20 min) in order to avoid over wetting of the pellets and drug migration into the film.[1]

After the coating process, the pellets were further fluidized the preparation for 5 min (constant process parameters) in order to evaporate residual solvents in the coating prior to the curing step. The coated pellets were cured at constant process parameters (45 ^{o}C) for different time periods (5, 10, or 20 min). For in vitro release studies, tests were carried out in a USP dissolution basket assembly at 37±5 ℃, at 100 r/min using 0.1 N HCl (first fluid, simulated gastric fluid) for 2 h. The pellets were then transferred to pH 7.4 phosphate buffer (second fluid, simulated intestinal fluid) for 3h and finally the pellets were transferred to the pH 6.8 phosphate buffer (third fluid, simulated colonic fluid) for remaining 7 h.[10]

The aliquot of the dissolution fluid was removed at specified time intervals and assayed for the amount of TP released by spectrophotometer (Model Shimadzu UV 1700, Japan) at 271 nm.

Scanning Electron Microscopy (SEM)

SEM (Model JEOL JSM-6360A scanning microscope, Japan) was used to examine the surface morphology and texture of formulation cured for 5 min and 20 min.

Analysis was conducted using. Cured pellets were sputter coated with platinum to a thickness of about 30 nm for 6-7 min in a coating machine. [13, 14]

Differential Scanning Colorimetry (DSC)

The effect of curing on the interaction between TP, polymers and other excipients used in the formulation was assessed by analysis of TP and 20 min cured formulation using differential scanning colorimeter (Model Mettler Toledo Star^e DSC 822c, Germany). The thermograms of the sample were obtained at a scanning rate of 10 ^oC/min conducted over a range of 0 to 350 ^oC under an inert atmosphere flushed with nitrogen at a rate of 20 ml/min.

Results

Scanning Electron Microscope (SEM)

Using SEM, the surface topography and morphology of the 5 and 20 min pellets (D1 and D4) exhibited smooth and uniform coating of the polymeric layer as indicated in Figure 1.

Differential Scanning Colorimeter (DSC)

The DSC thermogram shows a sharp endothermic peak at 269.95 ℃ for TP (Figure 2 (A)). While in formulation D4, the endothermic peak was observed at 267.25 ℃ and 97.86 ℃ (Figure 2(B)).

Dissolution of coated pellets

Enteric coated pellets were subjected to preliminary *in vitro* release studies for a period of 12 h. Dissolution was performed in different medias, such as simulated gastric fluid (pH 1.2 acidic buffer) for first 2 h, simulated intestinal fluid (pH 7.4 phosphate buffer) for 3 h and simulated colonic fluid (pH 6.8 phosphate buffer) for subsequent 7h. The buffer system having pH 7.4 and pH 6.8 was selected to simulate the conditions in the small intestine and colon.[15] There was no drug release in simulated gastric fluid, thus indicating the efficiency of enteric coating polymer

The drug release from uncured pellets, 5 min and 20 min cured pellets were studied. The drug release in uncured pellets shows initial 6 h lag phase followed by 98 % drug release in 7 h. In 5 min cured pellets, the pellets shows 7 % lag phase and achieve 98 % drug release in 8 h. Whereas the pellets cured for 20 min shows 8 h lag phase and achieve 97 % drug release in 10 h. The dissolution profile data is given in Table 3. Compared dissolution data is given in Figure 3.

Discussion

SEM is a qualitative tool for the assessment of size, shape, morphology, porosity, size distribution, crystal form, and consistency of

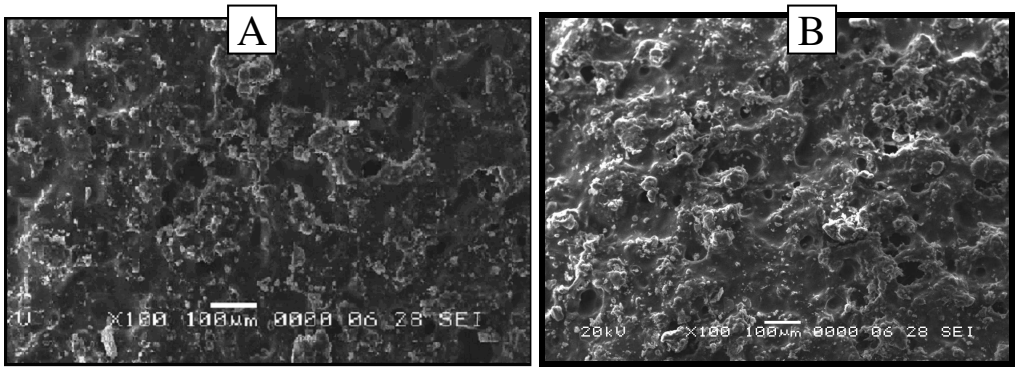

Figure 1: Surface morphology of 5 min (A) and 20 min cured pellets

powders or compressed dosage forms. The information obtained from SEM can be correlated to assess dissolution behavior, bioavailability, and crystalline structure. The images also help analysts determine whether particles are maintaining desired physical characteristics during processing, including after compaction or direct compression.[16] The observed maintenance of the surface morphology and topography of the tablet coating is an indication of the stability of the coated layer. Visually, both the figure shows similar appearance and indicates no change in physical parameters.

The data for the DSC indicate the stability of the drug with other ingredients even after the curing of pellets as there was no interaction between the polymer and drug in the formulation.

The drug release was fast from the uncured pellets and decreased with increasing curing temperature and increasing curing time.[18] Drug release from the formulation is depends on the nature and type of polymers used in it. The coating polymers which were used in the study was Eudragit RL-100 (ERL) and S100 (ERS). ERL is copolymer of acrylic and

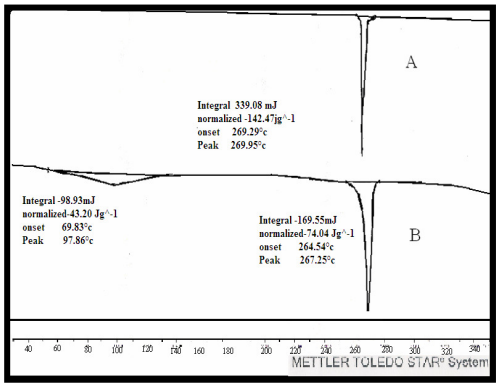

Figure 2: DSC thermogram of TP (A) and 20 min cured pellets (B)

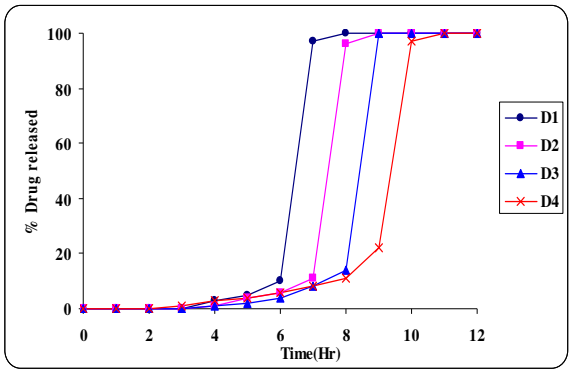

Figure 3: Dissolution profile of enteric coated pellets

Table 3: Dissolution profile of enteric coated pellets

Time (min)	D1 (Uncured pellets)	D2 (5 min cured pellets)	D3 (10 min cured pellets)	D4 (20 min cured pellets)
0	0	0	0	0
1	0	0	0	0
2	0	0	0	0
3	0	0	0	1
4	3	1	1	3
5	5	4	2	4
6	10	6	4	6
7	97	11	8	8
8	100	96	14	11
9	100	100	100	22
10	100	100	100	97
11	100	100	100	100
12	100	100	100	100

methacrylic acid esters with a low content of quaternary ammonium groups which is insoluble in water. ERL and S100 coated pellets shows decrease in drug release of cured pellets possibly due to the evaporation of water and solvent phase from the surface. The 20 min curing also shows the change in flow properties.

The findings of the study presented here imply that combination of ES100 and ERL 100, could be used to deliver drug molecules to the colon and releases the drug in predetermined rates accompanied by molecules of different physico-chemical nature. The immediate association is antiasthmatic drugs. Successful oral administration of antiasthmatic drugs can be possible for nocturnal asthma. This prerequisite is difficult to meet and in many cases all formulation components are packed in a dosage forms such as a conventional tablet which dissolves rapidly and exposes its contents to the large dilution effect in the GI tract. Because of different water solubilities this could lead to a situation in which the proteinaceous drug is left with no protection or absorption aids. A significant solution would be the use of pulsatile technology which releases the drug after a predetermined lag phase.

Conclusion

From the results of this study, eudragit S 100 and eudragit RL 100 coated pellets has curing effect. The pellets demonstrated stability of the drug with other excipients.

We can achieve required lag phase by playing with curing time and could release the drug with predetermined release profile hence it is advisable that curing time should be fixed for better and reproducible results.

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