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Research Paper

Ethylcellulose film coating of guaifenesin-loaded pellets: A comprehensive evaluation of the manufacturing process to prevent drug migration

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ABSTRACT

The aim of the research was to investigate the complete process of pellet production in a Wurster fluidized bed coater in order to determine the main factors affecting the migration phenomenon of a soluble API through the ethycellulose film coating (Surelease®) and hence the long-term stability of the controlled release pellets. Guaifenesin (GFN), as BCS class I model drug, was layered on sugar spheres using a binder-polymer solution containing the dissolved GFN. The drug loaded pellets were then coated with Surelease®. The influence of drug loading (4.5–20.0% w/w), curing conditions (40–60 °C and dynamic-static equipment), coating level (12–20% theoretical weight gain) and composition of the binder-layering solution (hypromellose versus Na alginate) on process efficiency (RSD_W%), GFN content uniformity (RSD_C%), GFN solid state (DSC and XRD) and pellet release profiles was evaluated. The effectiveness of the Surelease film was strongly affected by the ability of GFN to cross the coating layer and to recrystallize on the pellet surface. Results indicated that this behaviour was dependent on the polymer used in the binder-layering solution. Using hypromellose as polymer, GFN recrystallized on the coated pellet surface at both drug loadings. The curing step was necessary to stabilize the film effectiveness at the higher drug loading. Increasing the coating level delayed but did not prevent the GFN diffusion. Replacing hypromellose with Na alginate, reduced the migration of GFN through the film to a negligible amount even after six months of storage and the curing step was not necessary to achieve stable controlled release profiles over storage.

1. Introduction

Ethylcellulose is an insoluble polymer used in film coating which offers a great potential to accurately control drug release from pharmaceutical oral solid dosage forms [1,2]. Water-insoluble polymeric film coatings can either be applied from organic polymer solutions or from aqueous polymer dispersions [2]. Functional aqueous polymer coatings are of steadily increasing importance while avoiding the well known concerns related to the use of organic solvents [2,3]; moreover higher solids content in aqueous coating formulations can be used, due to lower viscosities and decreased sticking tendencies, considerably reducing processing time [2]. However, a challenging task of aqueous polymer dispersions is to achieve an efficient polymer particle coalescence during the coating process, fundamental to obtaining stable drug release profiles. When coalescence is not complete at the beginning, polymer particle fusion can continue during storage, affecting film-coating structures and, thus, the stability of the release patterns [3–5]. This is the reason why a thermal post-coating treatment, known as a curing-step, is generally required to achieve complete film formation and prevent or stabilize physical ageing on diffusion based-drug release [3,6].

One of the major remaining challenges associated with a potential imperfect film formation during coating and curing is to provide the long-term stability of aqueous polymeric controlled release film coatings. Several excellent reviews have provided an overview on the current state of the art in this field, covering different types of polymer coatings and drugs, and exhaustively identify different strategies to effectively overcome the stability hurdle [2,6]. These include different coating levels, the use of appropriate

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plasticizers, the addition of immiscible hydrophilic excipients or high glass transition temperature of polymeric materials and finally the optimization of curing and storage conditions.

A further problem that negatively affects the stability of aqueous polymeric coatings is the phenomenon of migration of several APIs through the barrier membrane coating layer. It has been reported [7–10] that this phenomenon occurred regardless of the polymer used (Eudragit NE 30D, Eudragit L100-55 or Acryl-EZE®, ethylcellulose both as Aquacoat® and Surelease®). In particular, water soluble drugs are subjected to significant migration when coated with aqueous systems and in the case of diltiazem hydrochloride, the amorphous drug migrated and recrystallized in the film coating [7]. A highly soluble drug, such as isosorbide 5 mononitrate, migrated to the surface of the coating exhibiting crystallization followed by sublimation [8]. In addition to drug-polymer affinity, when drugs with low melting point such as ibuprofen or guaifenesin were used, the high temperature involved in the curing step accelerated the migration process [9]. Such behaviour is responsible of unstable drug release profiles from pellets or tablets upon storage. This phenomenon was controlled by applying either a double layer coating [8] or a seal-coating with a polymer having a low affinity for the drug thus avoiding the contact of the drug and ethylcellulose membrane [9] or by modifying the curing time and/or temperature according to the formulation variables [10].

The influence of several variables involved in the whole manufacturing process of pellets has not deeply investigated and the influence of the drug layer underneath the barrier membrane film coating has not yet been studied. The aim of this work was to investigate the formulation factors and the process parameters that influence drug migration through the ethylcellulose film and the strategies to hinder or inhibit this phenomenon. Guaifenesin (GFN), a highly water soluble drug (BCS Class I) was used as model drug. It also has a melting point very close to coating process conditions. Therefore, it has the potential to migrate through the barrier membrane and crystallize in or on the film surface. In particular, pellets were prepared by drug layering and then film coating in a Wurster fluidized bed coater, analysing both formulation variables (drug loading, coating level, polymer type in the binding solution) and process-related parameters (different curing conditions) that might influence process efficiency, GFN content uniformity, film properties, drug migration process and pellet stability upon storage.

2. Materials and methods

2.1. Materials

Guaifenesin (USP/Eur. Ph. Grade, Rhodia, France, batch no. FGG0529902), Sugar spheres (Suglets®25-30 mesh size, 600–710 μm diameter, composed of sucrose and starch), Hypromellose (Methocel E5, E10, E15 LV, Hydroxypropylmethylcellulose, HPMC, 2910 USP grade) and Surelease® Ethylcellulose Aqueous dispersion (type B NF, grade E-7-19040) were kindly supplied by Colorcon Ltd. (Dartford, Kent, UK). Sodium alginate from brown algae (medium viscosity), chitosan FG90 high purity (⩾93% w/w, 100 kDa) and methylcellulose (low viscosity) were purchased from Fluka (Sigma Aldrich, Milan, Italy). Phosphate buffer pH 6.8 was prepared as reported in Eur.Ph. 8.Ed; all components were from Sigma–Aldrich and Milli-RX20 water (Millipore, Molsheim, France) was used throughout.

2.2. Methods

2.2.1. Preparation of drug loaded pellets

Drug loaded multiparticulate pellets were prepared by solution layering, involving the deposition of the GFN onto starting non-Suglet seeds in a Mini-Glatt fluidized bed (Glatt GmbH, Binzen, Germany) equipped with a Wurster column (bottom spray assessment). Three different batches were prepared: batches L1 and L2 with HPMC (Methocel E5) and batch L3 with sodium alginate as drug layering binders.

For batches L1 and L2, GFN was loaded at two different theoretical concentrations (4.5% and 20% w/w, respectively) on batches of 200 g of Suglets®. The aqueous layering solution was prepared adding 10% or 20% w/w of GFN to a 5% w/w HPMC E5 solution. For batch L3, the 20% w/w of GFN was added to a 2% w/w sodium alginate aqueous solution. The liquid temperature was set at 50 °C during the preparation of all the layering solutions to ensure complete GFN solubilization.

Drug layering conditions within the fluid bed equipment were as follows: inlet air temperature 60.0 ± 0.5 °C; product temperature 40.0 ± 0.5 °C; fluidization air flow 21–38 Nm^3/h; atomizing air pressure 1.45 ± 0.05 bar and a spray rate 1.12 ± 0.03 g/min.

The yield, the theoretical drug loading and the process efficiency expressed as the Relative Standard Deviation of the weight applied (RSD_W) on a mean of three layering experiments [11,12] were calculated using the following equations:

$$\text{Yield } \% = \frac{W_{LP}}{W_S + W_{GFN} + W_p} \cdot 100 \quad (1)$$

$$\text{Theoretical drug loading} = \frac{W_{GFN}}{W_S + W_P + W_{GFN}} \cdot 100 \quad (2)$$

$$RSD_W\ \% = \frac{\sqrt{(SD\ W_{LP})^2 - (SD\ W_S)^2}}{W_{LP} - W_S} \cdot 100 \quad (3)$$

where W_{LP} = weight of loaded pellets; W_S = weight of Suglets; W_{GFN} = GFN weight; W_P = polymer weight and SD = standard deviation.

The composition of the different batches and the process related parameters are summarized in Table 1.

2.2.2. Viscosity measurements of the layering solutions

Several polymers with different viscosity and at various concentrations were examined in the layering solution: HPMC E5, E15, E50, sodium alginate, methylcellulose and chitosan.

The viscosity determination was performed on binder solutions, before and after the GFN solubilization at 50 °C. Briefly, 10 ml of each layering solution was placed in the small sample adapter of the rheometer (Visco Star R, Fungilab SA, Barcelona, Spain), which was previously heated to the temperature set for the layering

Table 1
Composition of the batches and results of drug layering and barrier membrane film coating processes.

Process related parameters	Drug LAYERING PROCESS		
	Batch L1	Batches L2	Batch L3
Binder solution	Methocel E5 LV (5% w/w)	Methocel E5 LV (5% w/w)	Sodium Alginate MV (2% w/w)
Yield %	98.5	96.0	96.4
RSD_W %	5.36	4.08	n.a.[a]
GFN ± SD %	4.65 ± 0.09	19.5 ± 0.22	19.20 ± 0.08
RSD_C %	1.94	1.14	0.42

Process related parameters	Barrier Membrane COATING PROCESS			
	Batch C1	Batch C2	Batch C3	Batch C4
Wg %	13.36	12.60	20.50	17.80
Yield %	98.4	95.0	94.0	93.3
RSD_W %	n.a[a]	4.12	3.51	n.a[a]
Coating loss %	1.04	4.50	3.12	4.85
GFN ± SD %	4.10 ± 0.25	17.3 ± 0.35	15.5 ± 0.23	16.3 ± 0.78
RSD_C %	6.1	2.02	1.48	4.85

[a] Single batch.