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Quality by design approach for optimizing the formulation and physical properties of extemporaneously prepared orodispersible films

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ABSTRACT

The quality by design (QbD) approach was applied for optimizing the formulation of extemporaneously prepared orodispersible films (ODFs) using Design-Expert® Software. The starting formulation was based on earlier experiments and contained the film forming agents hypromellose and carbomer 974P and the plasticizer glycerol (Visser et al., 2015). Trometamol and disodium EDTA were added to stabilize the solution. To optimize this formulation a quality target product profile was established in which critical quality attributes (CQAs) such as mechanical properties and disintegration time were defined and quantified. As critical process parameters (CPP) that were evaluated for their effect on the CQAs the percentage of hypromellose and the percentage of glycerol as well as the drying time were chosen. Response surface methodology (RMS) was used to evaluate the effects of the CPPs on the CQAs of the final product. The main factor affecting tensile strength and Young's modulus was the percentage of glycerol. Elongation at break was mainly influenced by the drying temperature. Disintegration time was found to be sensitive to the percentage of hypromellose. From the results a design space could be created. As long as the formulation and process variables remain within this design space, a product is obtained with desired characteristics and that meets all set quality requirements.

1. Introduction

Pharmaceutical quality, patient safety and efficacy are best controlled by a fundamental understanding of the formulation and manufacturing of pharmaceutical preparations (Yu, 2008). Quality by design (QbD) is a systematic approach to optimize pharmaceutical preparations and to improve the control over and the quality of the production process. The quality by design approach consistently yields a product with desired characteristics and built in quality (ICH Q8, 2008).

Extemporaneously prepared orodispersible films (ODFs) are a promising new development, which - as small scale pharmacy preparations – can be applied in personalized medicine approach (Visser et al., 2015). ODFs have various advantages over other oral dosage forms such as tablets or syrups that are directly swallowed: they stick to the tongue or palatal immediately which prevents spitting out or choking, they disintegrate within a few seconds, there is no need of fluid intake, they may enhance the onset of action by bypassing first-pass metabolism (when absorption occurs via the oromucosal route) and can be used for systemic as well as local drug delivery (El-Malah and Nazzal, 2013; ElMeshad and El Hagrasy, 2011; Hoffmann et al., 2011). Extemporaneously prepared ODFs can be made from a standard casting solution in which different active pharmaceutical ingredients (APIs) are dissolved or suspended. The desired composition and characteristics of a standard casting solution should be defined in relation to the properties of the final product.

The preferred tool for strategic drug development using the QbD approach is the establishment of a quality target product profile (QTPP) (Delasko et al., 2005; Rathore and Winkle, 2009). A QTPP starts with defining the critical quality attributes (CQAs) for the final product. A CQA can be defined as: 'a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality' and thereby adequate performance and safety of the drug product when used (Rathore and Winkle, 2009). If we consider an ideal ODF to be flexible, easy to administer, easy to handle and physically stable (Hoffmann et al., 2011) these characteristics can be translated into a high tensile strength, high elongation at break and low Young's modulus (Preis et al., 2013,

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Table 1
Ranges of CPPs (percentage HPMC, percentage glycerol and drying temperature).

Run	Standard order (Std)	Percentage HPMC (%) X_1	Percentage glycerol (%) X_2	Drying temp. (°C) X_3
1	16	10.0	20.0	30.0
2	7	7.5	30.0	40.0
3	8	12.5	30.0	40.0
4	19	10.0	20.0	30.0
5	3	7.5	30.0	20.0
6	18	10.0	20.0	30.0
7	15	10.0	20.0	30.0
8	11	10.0	3.18	30.0
9	13	10.0	20.0	13.18
10	9	5.8	20.0	30.0
11	20	10.0	20.0	30.0
12	17	10.0	20.0	30.0
13	2	12.5	10.0	20.0
14	14	10.0	20.0	46.82
15	1	7.5	10.0	20.0
16	4	12.5	30.0	20.0
17	6	12.5	10.0	40.0
18	5	7.5	10.0	40.0
19	12	10.0	10.0	30.0
20	10	14.2	36.82	30.0

2014). Furthermore, a short disintegration time is favourable. A subsequent step of the QTTP is the identification of the critical process parameters (CPP). CPP include the process variables, e.g. concentration film forming agents and amount of plasticizer that influence the CQA. By combining the CQA and CPP a design space can be created. As long as the formulation and process variables remain within the design space, a product will be obtained that meets the quality requirements (ICH Q8, 2008; Yu, 2008).

The aim of the present study was to apply QbD for the optimization of a standard formulation of orodispersible films (ODFs) using the scientific expert system software Design-Expert®. The CQA in the present study were mechanical properties (tensile strength, elongation at break and Young's modulus) as well as disintegration time. For every CQA Design-Expert® gives a unique matrix of probabilities that helps to determine the best crossed model. The varied CPP in this study were the percentage of film forming agent hypromellose, the percentage of the plasticizer glycerol and the drying temperature. The other excipients and conditions (such as manufacture of the casting solution, used casting speed) were kept constant.

2. Materials and methods

2.1. Materials

Hypromellose (HPMC, Methocel E3 premium LV) was a gift from Colorcon, Kent, UK. Carbomer 974P, glycerol 85% (w/w) and disodium EDTA were obtained from Bufa, IJsselstein, The Netherlands. Trometamol was obtained from Genfarma, Maarssen, The Netherlands. All other excipients were of analytical grade.

2.2. Methods

2.2.1. Preparation of the casting solution and ODFs

The formulation used as starting point for this research was described earlier (Visser et al., 2015). The casting solution contained 9 g HPMC and 1.99 g glycerol 85% (22.1% of the weight of HPMC). Other excipients were 0.45 g carbomer 974P, 0.045 g disodium EDTA, 0.45 g trometamol and water up to 100 g.

The film forming agents HPMC and carbomer 974P together with glycerol 85%, disodium EDTA and trometamol were dissolved in water under constant stirring at 1100 rpm at room temperature with a magnetic stirring bar until a clear solution had been obtained. Subsequently, it was stirred at room temperature overnight at 100 rpm to allow entrapped air bubbles to disappear. The solution was then casted onto a release-liner (Primeliner® 410/36, Loparex. Apeldoorn, the Netherlands) with a quadruple film applicator using a casting height of 1000 μm. The release liner was fixed to a film applicator (Erichsen, Hemer, Germany) by vacuum suction. The casting speed was 10 mm/s. The amount of HPMC and glycerol 85% as well as the drying temperature were varied as shown in Table 1. The film layer was dried at a set temperature and ambient relative humidity (40–50% RH). After the films had dried they were carefully removed from the release liner and punched in squares of 1.8 × 1.8 cm using an Artemio perforator (Artemio, Wavre, Belgium), yielding stamp-shaped ODFs.

Table 2
Thickness and weight (mean ± SD, $n = 20$), mechanical tests (mean ± SD, $n = 6$), disintegration time (mean ± SD, $n = 5$).

Run	Std	Thickness (μm)	Weight (mg)	Tensile strength (N/mm²)	Elongation at break (%)	Young's modulus (N/mm²)	Disintegration time (s)
1	16	66.4 (±3.3)	25.55 (±0.66)	2.26 (±0.12)	10.07 (±1.57)	363.40 (±32.95)	24.6 (±1.04)
2	7	56.5 (±3.7)	21.30 (±0.45)	1.39 (±0.14)	8.69 (±0.85)	275.71 (±29.87)	19.6 (±1.15)
3	8	79.7 (±3.5)	30.91 (±1.01)	1.28 (±0.07)	7.99 (±2.05)	277.85 (±27.44)	37.6 (±3.01)
4	19	64.7 (±4.1)	25.92 (±0.87)	1.77 (±0.34)	9.71 (±1.08)	313.40 (±54.41)	27.3 (±1.14)
5	3	52.9 (±3.7)	21.72 (±0.85)	1.49 (±0.27)	10.38 (±0.01)	280.15 (±32.48)	17.3 (±1.98)
6	18	68.8 (±5.1)	25.42 (±0.51)	1.83 (±0.08)	9.01 (±1.68)	330.37 (±47.31)	25.5 (±2.63)
7	15	64.9 (±4.7)	25.04 (±0.64)	1.90 (±0.23)	8.67 (±1.55)	375.30 (±29.14)	25.1 (±2.11)
8	11	52.5 (±3.4)	21.68 (±0.39)	4.35 (±0.34)	12.14 (±1.58)	576.77 (±50.87)	21.2 (±1.42)
9	13	60.5 (±2.6)	25.01 (±1.04)	2.56 (±0.18)	11.80 (±2.85)	401.36 (±45.32)	21.4 (±0.95)
10	9	44.4 (±4.0)	16.78 (±0.33)	1.34 (±0.24)	7.64 (±1.07)	311.02 (±57.99)	9.0 (±1.00)
11	20	75.1 (±5.2)	25.34 (±2.85)	1.90 (±0.12)	10.42 (±1.86)	330.81 (±37.25)	29.7 (±3.03)
12	17	71.5 (±5.0)	25.01 (±0.74)	1.90 (±0.17)	10.07 (±2.05)	329.82 (±17.21)	23.1 (±1.20)
13	2	68.0 (±2.0)	28.36 (±0.48)	3.33 (±0.25)	12.16 (±2.06)	446.15 (±45.56)	30.7 (±2.30)
14	14	62.3 (±3.3)	24.29 (±0.65)	1.76 (±0.12)	9.37 (±2.19)	305.07 (±67.82)	29.9 (±2.51)
15	1	46.3 (±1.9)	19.36 (±0.92)	2.73 (±0.53)	9.71 (±1.70)	512.48 (±81.14)	17.2 (±1.82)
16	4	80.3 (±4.6)	32.75 (±0.88)	1.48 (±0.15)	11.46 (±2.20)	238.92 (±18.65)	30.0 (±2.02)
17	6	72.7 (±3.8)	26.92 (±0.66)	2.46 (±0.16)	9.72 (±1.69)	382.60 (±31.10)	34.3 (±0.78)
18	5	49.3 (±5.1)	18.03 (±0.48)	2.42 (±0.30)	8.68 (±1.58)	428.00 (±43.59)	18.0 (±1.06)
19	12	64.4 (±3.1)	26.58 (±0.62)	1.48 (±0.11)	9.71 (±1.69)	254.11 (±12.95)	24.3 (±3.05)
20	10	77.6 (±3.0)	31.66 (±0.78)	2.39 (±0.16)	11.80 (±1.08)	341.07 (±25.40)	43.7 (±3.86)