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Research paper

Development of PVP/PEG mixtures as appropriate carriers for the preparation of drug solid dispersions by melt mixing technique and optimization of dissolution using artificial neural networks

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ABSTRACT

The effect of plasticizer's (PEG) molecular weight (MW) on PVP based solid dispersions (SDs), prepared by melt mixing, was evaluated in the present study using Tibolone as a poorly water soluble model drug. PEGs with MW of 400, 600, and 2000 g/mol were tested, and the effect of drug content, time and temperature of melt mixing on the physical state of Tibolone, and the dissolution characteristics from SDs was investigated. PVP blends with PEG400 and PEG600 were completely miscible, while blends were heterogeneous. Furthermore, a single T_g recorded in all samples, indicating that Tibolone was dispersed in a molecular lever (or in the form of nanodispersions), varied with varying PEG's molecular weight, melt mixing temperature, and drug content, while FTIR analysis indicated significant interactions between Tibolone and PVP/PEG matrices. All prepared solid dispersion showed long-term physical stability (18 months in room temperature). The extent of interaction between mixture components was verified using Fox and Gordon–Taylor equations. Artificial neural networks, used to correlate the studied factors with selected dissolution characteristics, showed good prediction ability.

1. Introduction

In recent years, the number of active pharmaceutical ingredients (APIs) with low water solubility is estimated up to 40% of whole drugs. This poor solubility lowers their gastrointestinal track absorption, ultimately leading to a restriction in clinical utility. To confront this, several technological methods have been reported for the improvement of API solubility and dissolution rate [1–3]. Such an approach, with significant advantages, is the formulation of hydrophobic drugs in high-energy amorphous forms [3–5], such as solid dispersions (SDs). A lot of progress has been made concerning the methods used for the preparation of SDs, and new techniques have been applied [3,4,6]. Among them, hot-melt extrusion (HME), a well-known technique in the field of food and plastics industry for more than a century, only recently gained increased acceptance for preparing pharmaceutical SDs. HME is a technique with several advantages such as lower environmental impact (absence of solvents) and reduced cost (few processing steps in a continuous flow operation). Nowadays, HME is considered to be an efficient technique in developing SDs and has been proved to provide immediate, sustained, modified, and targeted drug delivery systems, resulting in improved bioavailability of the drug [7–10].

Formulation of an API in a high-energy amorphous forms is also desired in SDs prepared by HME in order to enhance API's solubility, dissolution rate and, consequently, oral bioavailability [11]. However, several limitations including API recrystallization due to the crystalline nature of the polymeric carrier [12] and polymorphism may also take place during melt mixing as verified from previous studies [13,14].

Melt mixing, a similar procedure to HME, has been used also as an alternative technique to prepare SDs with low environmental impact [11]. As HME, melt mixing has significant limitations. During processing, drug substances are exposed to elevated temperatures for prolonged periods of time (2–10 min), leading to decomposition of thermally unstable APIs. Furthermore, there is a possibility that the API, the polymer or both decompose if an extremely high temperature is used during melt mixing. One way to avoid this is first to convert the API into an amorphous form using an alternative technique such as solvent evaporation and then

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melt-mix the amorphous API with a suitable polymeric carrier [15]. In this case, since the glass transition temperature of the amorphous drug is lower than that of the polymer used, the drug substance itself acts as a plasticizer for the polymer. However, in this case, the use of organic solvents is not avoided.

An extensive literature review revealed that PVP and PEGs are the most frequently used polymers for the preparation of SDs [3–5]. Regarding the preparation of SDs without the use of solvents (such as melt methods including HME and melt mixing), PEGs are widely used because of their low melting point (approximately 55–60 °C), rapid solidification rate, capability of forming solid drug solutions, low toxicity, and low cost. However, at higher drug concentrations, the API is often present within the PEG dispersion in crystalline form, or it recrystallizes over time [3,4,14]. On the other hand, PVP based SDs face less stability issues than PEG SDs; however, its relatively high glass transition temperature (150 and 180 °C) limits its applicability for preparing SDs by melting methods. In order to be able to use PVP as carrier in melt mixing, plasticizers (such as PEGs) should be used to lower its T_g. Similar polymer blends were also studied in order to prepare SDs by melt mixing for carbamazepine and nifedipine (both water insoluble APIs) using pure polyethylene glycol 1500 (PEG1500) or a 1:1 mixtures of PEG1500 with polyvinylpyrrolidone (PVP 30, PVP 12), polyvinylpyrrolidone-co-vinylacetate (PVPVA), and Eudragit EPO (Eudragit) [22]. Hence, a combination of both materials as polymer carriers in SD preparations may be beneficial, as in the case of valdecoxib [16].

The aim of this work is to continue our previous effort [11] to study the effectiveness of PVP/PEG blends as appropriate carriers in order to prepare solid dispersions of poorly water soluble drugs by melt mixing. Tibolone (Tibo) was used as a poorly water soluble model drug. Tibo is practically insoluble in water, has a melting point of 171 °C, while there are two polymorphs identified (Form I and II). Attempts for enhancing Tibo dissolution rate in the past included solid dispersions with PVP/SiO_2 and microwave-induced enhancement with PEG [17,18]. Three different PEGs with MW of 400, 600, and 2000 g/mol were tested as plasticizers in combination with amorphous PVP in a standard PVP/PEG80/20 weight ratio. The impact of melting temperature, mixing time, and drug content on the physicochemical properties of SDs was tested using several techniques (HSM, DSC, WAXD, and FTIR) and evaluated for long-term physical stability (18 months in room temperature), while the effect of these factors on the% of API dissolved in 30 min (Y_{30min}) was studied with the aid of statistical experimental design and artificial neural networks (ANNs).

Systematic experimental techniques based on statistical experimental design in combination with non-linear model-fitting methods, such as artificial neural networks (ANNs), provide a highly efficient approach during formulation development including solid dispersions [11,19].

2. Materials and methods

2.1. Materials

Crystalline Tibolone (Tibo) with assay of 99.59% (90% of the drug passed through a 50-lm sieve) was supplied by Zhejiang Xianju Junye Pharmaceutical Co, Ltd. Poly(vinyl pyrrolidone) (PVP) type Kollidon K30 with a molecular weight MW of 50.000–55.000, T_g = 167 °C (DSC), moisture content 1.95% (TGA), and bulk density 0.410 g/cm^3 was obtained from BASF (Ludwigshafen, Germany). Poly(ethylene glycol) with molecular weights 400 (PEG400), 600 (PEG600), and 2000 g/mol (PEG2000) was supplied by Aldrich chemicals. All the other materials and reagents were of analytical grade and purity.

Table 1
Melt mixing independent factors and design levels examined.

Independent factors	Levels		
X_1 = Molecular weight of PEG	400	600	2000
X_2 = Temperature of mixing (°C)	130		150
X_3 = Amount of Tibo in solid dispersions (%)	5	10	20
X_4 = Total mixing time (min)	5	15	

2.2. Experimental design and analysis

2.2.1. Statistical experimental design

A general factorial design with four independent factors: the MW of PEG used as plasticizer in the polymeric matrix (X_1), barrel temperature (X_2), the amount of API in solid dispersions (X_3), and the total mixing time (X_4) was employed. Preliminary studies provided the settings for the levels of each factor. The tested design points are given in Table 1.

A single dissolution parameter, namely the% release at 30 min (Y_{30min}) of Tibo, was used as a response, and a linear multiple regression (MLR) model was used in order to estimate the magnitude of main effects and two-way interactions (Eq. (1)):

$$Y_{30\,min} = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{14}X_1X_4 + b_{23}X_2X_3 + b_{24}X_2X_4 + b_{34}X_3X_4 \quad (1)$$

where Y_{30min} is the measured response, b_0 is an intercept term, b_i to b_{ij} are regression coefficients for the main effects and two-way

Table 2
Experimental domain of the general factorial design employed and the values of the measured response Y_{30min}.

Run	Independent factors				Response
	X_1	X_2 (°C)	X_3 (%)	X_4 (min)	Y_{30min}[a] (%)
1	400	130	5	5	87.49
2	400	130	10	15	75.31
3	400	130	20	15	36.81
4	600	150	5	5	96.71
5	2000	150	20	5	46.47
6	2000	130	20	5	33.98
7	600	130	10	15	76.31
8	400	150	5	5	93.45
9	600	130	20	5	61.77
10	400	150	5	15	94.71
11	400	130	10	5	69.63
12	2000	130	10	15	67.79
13	400	150	20	15	45.22
14	2000	150	20	15	46.50
15	400	150	10	5	79.36
16	600	150	10	5	77.22
17	2000	150	10	15	76.19
18	400	130	20	5	33.64
19	2000	130	5	15	100.0
20	400	150	10	15	80.94
21	600	150	5	15	100.0
22	600	150	10	15	89.32
23	600	130	10	5	73.82
24	600	150	20	15	65.77
26	2000	150	5	5	93.43
27	2000	130	10	5	62.49
28	2000	130	5	5	87.89
29	600	130	5	15	95.20
30	400	130	5	15	92.52
31	2000	150	10	5	73.33
32	600	150	20	5	66.70
33	2000	130	20	15	43.79
34	600	130	5	5	92.07
35	400	150	20	5	41.51
36	600	130	20	15	64.85

[a] S.D. from 0.02 to 0.21.

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