Saudi Pharmaceutical Journal (2012) **20**, 229–238

King Saud University

Saudi Pharmaceutical Journal

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ORIGINAL ARTICLE

Formulation and in vitro evaluation of theophylline matrix tablets prepared by direct compression: Effect of polymer blends

Ibrahim El-Bagory [a,*], Nahla Barakat [b], Mohamed A. Ibrahim [a,c,1], Fouza El-Enazi [b]

[a] *Kayyali Chair for Pharmaceutical Industries, Department of Pharmaceutics, Faculty of Pharmacy, King Saud University, Riyadh, Saudi Arabia*
[b] *Department of Pharmaceutics, Faculty of Pharmacy (Girls), King Saud University, Riyadh, Saudi Arabia*
[c] *Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University, Assiut, Egypt*

Received 13 October 2011; accepted 27 November 2011
Available online 3 December 2011

KEYWORDS

Theophylline;
Matrix tablets;
Deformation mechanism;
In vitro release

Abstract The deformation mechanism of pharmaceutical powders, used in formulating directly compressed matrix tablets, affects the characteristics of the formed tablets. Three polymers of different deformation mechanisms were tested for their impact on theophylline directly compressed tablets namely Kollidon SR (KL SR, plastic deformation), Ethylcellulose (EC, elastic deformation) and Carnauba wax (CW, brittle deformation) at different compression forces. However, tablets based mainly on KL SR, the plastically deformed polymer (TN1) exhibited the highest hardness values compared to the other formulae which are based on either blends of KL SR with CW, the very brittle deformed polymer. The upper detected force for TN formulae and the lower punch force were found to dependent mainly on the powder deformation. This difference is attributed to the work done during the compression phase as well as the work lost during the decompression phase. Furthermore, the release profiles of TN from formulae TN2 and TN4 that are based on the composition (2KL SR:1EC) and (1KL SR:2EC), respectively, were consistent with different deformation mechanisms of KL SR

* Corresponding author.
E-mail address: ielbagory@gmail.com (I. El-Bagory).
[1] Current address: Kayyali Chair for Pharmaceutical Industries, Department of Pharmaceutics, Faculty of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

Peer review under responsibility of King Saud University.
doi:10.1016/j.jsps.2011.11.007

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and EC and on the physicochemical properties like the water absorptive capacity of EC. Upon increasing the weight ratio of KL SR (TN2), the release rate was greatly retarded (39.4%, 37.1%, 35.0% and 33.6% released after 8 h at 5, 10, 15 and 20 kN.

1. Introduction

The mechanism of powder compaction not only depends on the powder properties (Jones, 1977) but also affected by particle size, shape (Wong and Pilpel, 1990), moister content (Sebhatu et al., 1997; Bell and Labuza, 2000) and experimental conditions, e.g. applied pressure (Holman and Leuenberger, 1988) and velocity of compaction (Roberts and Rowe, 1985). In addition, the properties of the resulting compact can be influenced by the presence of a lubricant and binder (Nystrom et al., 1982), since pharmaceutical materials normally consolidate by more than one of the mechanisms (Duberg and Nystrom, 1986), adequate characterization techniques are needed. Various techniques have been utilized to determine the extent of consolidation and bonding mechanisms in pharmaceutical powders (Luangtana-Anan and Fell, 1990; Karehill et al., 1990), such as stress relief under pressure (Rees and Rue, 1978), X-ray diffraction (Munoz-Ruiz et al., 1996) and multi-compression cycle (Khossravi and Morehead, 1997).

There exists no pharmaceutical powder that exhibits only one of the above mentioned deformation mechanisms, although there is a spectrum of ranges from highly elastically deforming to highly plastically deforming or highly brittle materials. Even for materials that are known to be brittle, smaller particles may deform plastically (Amidon, 1989). A prerequisite for the formation of a coherent compact is that the surfaces deform to such an extent that the combined effects of bonding with intermolecular forces and solid bridges are greater than the elastic component of the material. This can be expressed as the critical compaction pressure needed to form a compact (Karehill et al., 1990).

The frequency of defects in crystalline solids can be related to deformation during compression (Huttenrauch, 1977). The change can take place in crystal structure and shape. Such structural changes are opposed by intermolecular forces which restore the crystal to its original form, as in the case of elastic materials. If the intermolecular forces are exceeded, plastic or permanent deformation will result and, if the stress is continued, plastic flow will continue (Hess, 1978).

Polymer blending is an alternative approach to obtain new materials with desirable properties based on commercially available polymers rather than to design and synthesize completely new polymers. Polymer blending is designed to generate materials with optimized chemical, structural, mechanical, morphological and biological properties (Calvert et al., 2000; Meredith et al., 2003; Lua et al., 2007). The use of polymers as release rate modifiers has become an important area of drug development work. Over the years, the use of polymers and other materials to prolong the drug release rate has become more popular. The use of polymer combinations is an approach that may allow formulators to develop sustained release drug dosage forms that may show performance improvements over the individual polymer components. Polymer blending provides a neat and smooth means of combining desirable properties of different polymers. Biodegradable matrices with new combinations of polymer properties and modification of drug release profiles can thus be obtained (Domb, 1990; Illum, 1998).

Theophylline (TN) structurally classified as methyl xanthine is widely used as a bronchodilator in patients with airflow limitation diseases such as bronchial asthma and chronic obstructive pulmonary disease (COPD) Yoon et al., 2008. Theophylline is rapidly and completely absorbed from liquid preparation, capsules and uncoated tablets. The rate, but not the extent, of absorption is decreased by food. Theophylline is approximately 40% bound to plasma proteins, but in neonates, or adults with liver disease, binding is reduced (Reynolds, 1993). There are marked variations in TN pharmacokinetics with plasma half-lives ranging from 3 to 9 h.

The objective of this study was to formulate sustained release of TN tablets by direct compression of the tablets with four different compression forces using different polymer blends. Tablets were evaluated for their strength, uniformity of thickness, friability, in addition to their mechanical behavior as hardness, upper and lower compression force, ejection force and tensile strength. Moreover, the in vitro release patterns of TN from the formulated tablets were studied over the sustained release period.

2. Methodology

2.1. Materials

Anhydrous theophylline (TN) and Carnauba wax (CW) were kindly supplied from Tabuk Pharmaceutical Manufacturing CO, KSA. Ethylcellulose, EC (having a dynamic viscosity of 14 cp for 5% solution in toluene 80 : ethanol 20), was purchased from BDH Laboratory Supplies Poole, England. Kollidon SR (KL SR) was obtained from BASF Aktiengesellschaft, Germany. Magnesium stearate and hydrochloric acid were obtained from Riedel-de-Haen, AG, Germany, tribasicphosphate octahydrate (Scharlau Chemies.A, European). All other materials and solvents used are of reagent or analytical grade and they were used without further purification.

2.2. Formulation of directly compressed tablets

The compositions of the prepared direct compressed tablets containing TN are shown in Table 1. Each tablet contains 50 mg drug and uses one polymer or blend of the polymer KL SR, EC and CW in different ratios. The powders of all ingredients were passed separately through a sieve of 250 μm opening size and the powders were then thoroughly mixed using turbula mixer for 15 min. The powder then compresses into tablets by using Flexitap single punch machine (IWKA