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ORIGINAL ARTICLE

Galenic approaches in troubleshooting of glibenclamide tablet adhesion in compression machine punches

Janine Boniatti [a], Ana Lúcia Pereira Cerqueira [a], Alexandre Carnevale de Souza [a], Cristiane Rodrigues Drago Hoffmeister [a], Maira Assis da Costa [a], Livia Deris Prado [a,*], Leandro Tasso [b], Helvécio Vinícius Antunes Rocha [a]

[a] *Farmanguinhos (FIOCRUZ), Av. Comandante Guaranys 447, 22775-903 Rio de Janeiro, RJ, Brazil*
[b] *University of Caxias do Sul, R. Francisco Getúlio Vargas 1130, 95070-560 Caxias do Sul, RS, Brazil*

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Abstract This study aimed to examine the adhesion of glibenclamide 5 mg tablets to the tools of compression machines. This problem is not commonly reported in the literature, since it is considered as tacit knowledge. The starting point was the implementation of three technical alternatives: changing the parameters of compression, evaluating the humidity of the powder blend and the manufacturer of the lubricant magnesium stearate. The adhesion was directly related to the characteristics of magnesium stearate from different manufacturers, and the feasibility of evaluating powder flow characteristics by different techniques that are not routinely followed in various pharmaceutical companies. In vitro dissolution tests showed that the magnesium stearate manufacturer can influence on the dissolution profile of glibenclamide tablets. This study presented various aspects of tablet adhesion to compression machine punches. Troubleshooting approaches can be, most of times, conducted based on previous experience, or an experimental research needs to be implemented in order to have confident results.
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1. Introduction

Solid dosage forms, in particular tablets, dominate the global pharmaceutical landscape. Different dosage forms have changed over time, mainly by the use of excipients, which have distinct functions in formulations (Sastry et al., 2000). Many difficulties in the manufacture of tablets, however, are still quite common in factories around the world. Among these difficulties is the adhesion of tablets to the tools of compression machines. Adhesion may have different causes

* Corresponding author. Tel.: +55 213 348 5319; fax: +55 213 348 5050.
E-mail addresses: liviaderis@yahoo.com.br, liviaderis@gmail.com (L.D. Prado).
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and consequences of varying degrees, and can lead to failure in entire production batches. There are few research studies on this subject in the literature. This problem is typically resolved by trial and error, although has been reported that the use of more advanced techniques, such as determining the force exerted by the punch and dies, can predict this phenomenon (Führer, 1996; Picker-Freyer, 2008). Evaluation of force exerted is of great value, since a commonly accepted hypothesis for adhesion is the interaction between the powder particles and the metal surface of punches.

Several factors may be related to the origin of adhesion, including: manufacturing process (adjustment of the compressive force and of the contact area between tools and formulation powder), formulation (use of lubricants and other excipients), conditions of blends (humidity) and equipment (integrity and cleanliness of the punches) (Führer, 1996; Picker-Freyer, 2008). In a manufacturing process, adhesion can be seen as a serious or critical deviation, depending on the amount of mass lost (Alderborn, 2005). In an attempt to explain this deviation, three possibilities were evaluated: (a) change in the compression process, (b) drying the blend to reduce its humidity and (c) the influence of lubricant on the compression process.

Magnesium stearate is the most widely used lubricant in the pharmaceutical industry in manufacturing of tablets and capsules, due to its capacity to reduce friction. However, it should be noted that the lubricant amount can significantly affect the product performance and quality, causing problems such as: decrease in content uniformity, decrease in tablet hardness, increase in tablet disintegration time, decrease in dissolution rate and decrease in bioavailability. Thus, it is recommended to use the minimum quantity of lubricant required (Andrès et al., 2001; Wada and Matsubara, 1994). A large number of studies have reported that variations in physical and chemical properties of magnesium stearate have great influence on its lubricating action. Currently, it is known that variables such as molecular structure, crystallinity, water content, thermal stability and granular properties are able to influence the functional properties of the material in question (Bracconi et al., 2005; Wang et al., 2010). Particle size and specific surface area of magnesium stearate may be key factors influencing its lubrication efficiency (Wang et al., 2010).

It is important to note that materials supplied by different manufacturers are unlikely to be of exactly the same physical properties, but lot to lot variability of materials obtained from the same manufacturer is less likely to present a problem (Wang et al., 2010). Another parameter that can influence compression is the moisture of the powder blend and also the relative humidity of the manufacturing environment. It is necessary to identify the moisture range in which the particulate material shows good performance to carry out the compression process. If the relative humidity can increase the rate and extent of water absorption by the formulation, it is very likely that adhesion will be evident in the final product. Furthermore, the humidity has a direct influence on the lubricant added to the formulation (Alderborn, 2005).

With regard to magnesium stearate, it is known that its functionality is based on the fact that water and air penetrate into spaces between crystalline particles, increasing the movement of these particles. This mechanism reduces the forces necessary to break the crystalline structure of magnesium stearate, which facilitates their spread on the surface to be lubricated. However, the crystalline form found in commercial batches of magnesium stearate depends on the process for preparing the excipient and on the humidity to which the material was exposed after the manufacturing process (Rajala and Laine, 1995; Wang et al., 2010).

The adhesion of tablets to the tools of compression machines was observed by Farmanguinhos, a pharmaceutical laboratory linked to the Brazilian Ministry of Health, during the manufacture of glibenclamide 5 mg tablets. Therefore, the technical group developed a research in attempt to solve the case and to continue to manufacture the product without problems.

2. Materials and methods

2.1. Materials

Glibenclamide (Cadila Pharmaceuticals LTDA), mannitol powder (Launcher International), sodium lauryl sulfate (Cognis Brasil LTDA), microcrystalline cellullose 102 (Blanver Farmoquímica LTDA), silicon dioxide colloidal (Cabot Corporation) e sodium croscarmellose (Blanver Farmoquímica LTDA). Magnesium stearate was supplied by different manufacturers whose names are not mentioned here.

2.2. Methods

2.2.1. Preparation of formulations

Table 1 shows all the components used for manufacturing glibenclamide 5 mg tablets. Glibenclamide and magnesium stearate concentrations were 4.17% and 1%, respectively. The concentrations of other components were in accordance with the recommendations of official compendium of the area.

The manufacturing process was carried out by direct compression, i.e., the active ingredient and the excipients were mixed and then, directly compressed into tablets. The powder blend was added to a "V" blender (Lawes®) and compression occurred in a 35 punch rotary tablet machine (Manesty® BB4). All tests were performed under the same environmental conditions in the manufacturing rooms, with temperature about 20 °C and relative humidity about 33%. Thus, these parameters were disregarded.

2.2.2. Tests of changing the compression parameters

All tests were conducted with a low rate of compression and with an increased pressure, i.e., higher compression force resulting in tablets with higher tensile strength. The same blend of the industrial batch with the problem of adhesion was used. The tablet hardness range was fixed from 14.0 to 19.0 Kp.

Table 1 Components of Glibenclamide 5 mg formulation.

Formulation	Function
Glibenclamide	Active principle (hypoglycemic)
Mannitol powder	Diluent
Sodium lauryl sulfate	Surfactant
Microcrystalline cellulose 102	Diluent/agent compression
Colloidal silicon dioxide	Flow enhancer/absorbent
Magnesium stearate	Lubricant/nonstick/sliding
Sodium croscarmellose	Disintegrant

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