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Short communication

Assessment of mucoadhesive buccal tablets with propranolol hydrochloride using principal component analysis

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Introduction

Multivariate analysis methods are a set of statistical techniques that allow multiple variables to be tested simultaneously. This makes them ideal for studying relationships in large complex datasets. Pharmaceutical products and drug manufacturing processes are complex systems by nature and can therefore, be described using multifactorial relationships. One of the commonly used methods of multivariate analysis is principal components analysis (PCA), which in short, transforms a large set of variables into a smaller set of new variables, which are designated as principal components (PCs). Principal component represents a linear combination of the original variables (Ferreira et Tobyn, 2015; Esbensen et Geladi, 2009). This study aimed to investigate the variability and the possibility of differentiation of the formulated buccal tablet formulations using PCA.

Materials and methods

The following excipients were used for the preparation of bilayer mucoadhesive tablets: polyethylene oxide, carbomer, polyvinyl alcohol and ethyl cellulose. Propranolol hydrochloride (PROP) was used as the model drug. Mucin from porcine stomach, type II, was used to prepare mucin discs for the tablets mucoadhesivity testing.

Preparation of buccal tablets

Tableting was performed by a two-step direct compression method on a single-station laboratory tablet press using a die of 10 mm. The first mucoadhesive layer consisted of a mixture of selected polymers and PROP, while the second barrier layer was composed of ethylcellulose. Fourteen formulations were prepared in total.

In vitro mucoadhesive study

The mucoadhesiveness of buccal tablets was tested on a TA.XTplus texture analyzer equipped with a mucoadhesive rig. The mucin disc prepared by raw mucin compression was used as a mucosal surrogate. The maximum force required to separate the tablet from the mucin disc was recoreded as an indicator of adhesive properties.

Dissolution study

To test the PROP dissolution rate, the reciprocating cylinder apparatus (Bio-Dis Extended Release Tester, VanKel Technology Group, USA), with a 5 dpm was used. Artificial saliva (200 ml) heated up to 37 ± 0.5 ºC was used as the dissolution medium, and the PROP concentration was determined by UV spectrophotometry.

In silico absorption modeling

Absorption modeling was performed with the GastroPlus™ software program using the Advanced Compartmental Absorption and Transit (ACAT) model linked with the Oral Cavity Compartmental Absorption and Transit (OCCAT) model to simulate the drug absorption through the oral mucosa. The obtained dissolution profiles were used as input parameters to

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predict the PROP absorption profiles after buccal administration.

Multivariate data analysis

Principal component analysis was applied to analyze the data obtained by *in vitro* and *in silico* testing of buccal tablets to evaluate the possibility of differentiation of tablet formulations, based on the variables that had the greatest contribution to separation. The following variables were selected for this analysis: the proportion of dissolved and permeated PROP after 30, 60, 180, 360 min; concentration of PEO, PVA and CB polymers, mucoadhesive strength and predicted pharmacokinetic parameters: C_{max} and t_{max}.

Results and discussion

PCA allowed us to summarize the information contained in the initial data set using only 3 variables, designated as principal components. The first two principal components explain 80% of the variance, while the first three principal components explain even 91% of the variance. The major contributors to the formation of the first component (PC1) were: the proportion of dissolved and permeated PROP, concentration of CB polymer, C_{max}, and t_{max}. Concentration of PEO polymer contributed most to the formation of the second component (PC2), and the formation of the third component (PC3) was mucoadhesion. The projection of the observations and variables in the new system (Fig. 1) showed that C_{max}, concentration of PVA and PEO polymers, proportion of dissolved and permeated PROP and mucoadhesive strength were clustered, indicating a positive correlation between them, and a negative correlation with t_{max} and the concentration of CB. The concentration of CB and t_{max} are also clustered indicating their positive correlation. Concerning the first component (PC1), the formulations F1, F3, and F6 clearly singled out, as well as F12 and F13 as an outliers. These are the formulations from which the highest PROP dissolution rate was achieved, while formulations F4, F8, and F14 with the highest mucoadhesion strength and slowest drug dissolution were distinguished from the third component (PC3).

Conclusion

It can be concluded that PCA as a multivariate analysis technique was successful because the first two principal components explain 80%, and the first three components 91% of the variance. PCA allowed the initial dataset of 14 variables to be transformed into a smaller set of 3 principal components. The results obtained suggest the separation of four groups, in the context of the selected variables. The use of this analysis revealed the existence of 4 groups of tablet formulations.

More specifically, the group of tablet formulations with the highest dissolution rate of PROP and the lowest t_{max} (group 1); the group with the highest mucoadhesion strength, the lowest PROP dissolution and permeation rate and the highest t_{max} (group 2); than the group whose drug dissolution rate was between the first two mentioned groups (group 3) and the outlier group (group 4) were separated.

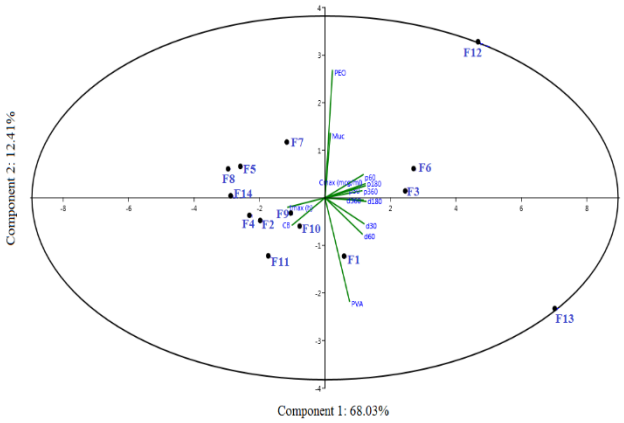

Figure 1. Projection of observations (F1-14) and variables in the new system of principal components

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