A study of physicochemical and biopharmaceutical properties of Amoxicillin formulations developed by direct compression using full factorial design with multiple responses

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Direct compression technique presents an economic advantage in time, costs and energy, when compared to the traditional granulation methods.[1] The variables that influence the tablets obtained by direct compression method deserve to be studied to minimize formulations costs and to improve the physicochemical and biopharmaceutical properties of the resulting compacts. Amoxicillin 500 mg formulations were previously developed by direct compression,[2] and the adjuvants investigated were microcrystalline cellulose, spray-dried lactose, and croscarmellose sodium, which is a superdisintegrant agent. In this study, the purpose was to explore the adjuvants (independent variables) effects on the resulting amoxicillin tablet formulations considering multiple responses (physicochemical and biopharmaceutical properties – dependent variables), as well as to indicate the most suitable formulation composition.

A 2^3 full factorial design[3] was built to eight different amoxicillin formulations, each one containing three replicate batches, and eight responses were obtained. Each independent variable was investigated at two levels: the microcrystalline cellulose (MCC) type Avicel® PH-102 (low) or PH-200 (high), the absence (low) or presence (high) of spray-dried lactose (LAC), and the absence (low) or presence (high) of disintegrant (DIS). The evaluation of the resulting compacts was based on their physicochemical properties as average weight, thickness and diameter, hardness, friability, amoxicillin concentration (iodometric assay), disintegration time, and dissolution profile.[2] The responses more relevant to the distinct formulations from the experimental design were hardness, friability, and the amount of amoxicillin dissolved during the first hour. Three models were built for each response, using multiple linear regression (MLR). The coefficients were considered as independent variables, and the response obtained to this new set was the optimum response for each original variable. A new model was constructed, and its respective coefficients indicate the level of each variable should be fixed to obtain better responses. A criterious statistical evaluation considering each response, individually, was also performed. The comparison between the best levels from simultaneous and individual response evaluation was carried out.

Regarding each response individually, the MCC and DIS levels were significant and negative for hardness (see the side table). The variables LAC and DIS presented an interaction for the friability response. The presence of LAC and the absence of DIS increased the friability. The MCC type Avicel® PH-200 also contributed to increase that physicochemical property. Tablet formulations presenting high friability values are not recommended. The amount of drug dissolved presented two interactions, one between the MCC and DIS levels, and another between the LAC and DIS levels. The combination of MCC low level (Avicel® PH-102), LAC low level (absence), and DIS high level (presence) simultaneously increases the amount of drug dissolved, considering the plot of marginal means analysis. The individual response evaluation indicated that the most suitable amoxicillin tablet formulation should present the microcrystalline cellulose Avicel® PH-102 and the superdisintegrant agent, croscarmellose sodium, in its composition. The simultaneous and individual response analysis generated similar results (table above), except to the MCC level. The multiple response analysis did not allow taking any information related to the type of MCC (level 0) in the most suitable amoxicillin tablet formulation.

	Hardness		Friability		Amount Amox. Dissolv.	
	Coeff.	p	Coeff.	p	Coeff.	p
Mean	*107.13*	*0.000*	*0.20*	*0.000*	*3.62*	*0.000*
MCC	*-6.46*	*0.021*	*0.03*	*0.004*	*-0.20*	*0.032*
LAC	-2.92	0.263	*0.05*	*0.000*	*-0.31*	*0.002*
DIS	*-6.13*	*0.027*	0.00	0.895	0.07	0.394
MCCxLAC	0.00	1.000	0.02	0.058	0.00	0.973
MCCxDIS	-1.63	0.527	0.02	0.081	*-0.22*	*0.020*
LACxDIS	-3.92	0.139	*0.03*	*0.006*	*-0.23*	*0.014*

Multiple response	
Variables	Levels
MCC	**0**
LAC	**-1.33**
DIS	**6.03**

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