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Short communication

Application of the experimental design techniques for donepezil hydrochloride orodispersible tablet formulation

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Introduction

The greatest challenges for orodispersible tablet (ODT) formulation are to obtain adequate tablet disintegration time < 3 min and to cover the unpleasent or bitter taste of the active pharmaceutical ingridient (API). When the API is very bitter like donepezil hydrochloride, numerous modern techniques could be used: co-processing or multifunctional excipients, API complexation with cyclodextrins, ion-exchange resins, chemical modification of drug particles, addition of taste enhancers, crosslinking with polymers, film-coating of drug particles (droplets), microincapsulation, nanoparticles etc (Brniak et al., 2015). Application of the experimental design techniques provides prediction and better quality control in formulation of ODTs and evaluation of different formulation factors on the extremely bitter drug taste, with smaller number of experiments and less time and production cost (Draskovic et al., 2017). The purpose of these experiments was to observe how formulation factors influenced the drug taste masking, hardness, friability and disintegration time of ODTs.

Materials and methods

Following materials were used: Donepezil-hidrochlorid (ChemAgis,Israel), Sodium starch glicolate (Gujart Microvax, India), Lemon acid (Merck, KG, Germany), Lemon aroma (Givaudan, Switzerland), Magnesium stearate (Faci Spa, Italy), Sorbitol, (Roquette Feres SA), Mannitol (Roquette Feres SA), Crospovidon CL (BASF, Germany), Sodium-hydrogen carbonate (Merck, KG, Germany), Saccharin-sodium (Kaifeng Xinghua Fine Chem. Factory, China) and Povidon K25(BASF, Germany).

ODTs were produced by wet granulation method. Mannitol was used as a filling agent and a taste masking excipient, crospovidone CL as a disintegrant, saccharin sodium as a sweetening agent, while povidone was used as a binding agent. Sodium starch glycolate was used to improvet flowing properties and compressibility of the tabletting mass, friability and disintegration time as one of the most important parameters for ODTs. Lemon acid, lemon aroma and sorbitol were added as sweetening and taste masking agents. Tablets were compressed on the excenter tablet machine (Erweka EKO) with diameter 8 mm (200 mg). The experimental design- Fractional Factorial Design FFD 2^{5-2} (Stat Soft Statistica 12) was applied with following independent variables (Table 1): sorbitol (X_1), mannitol (X_2), lemon aroma (X_3), concentration of polymer-Povidone K-25 (X_4), concentration of disintegrant (X_5), while ODTs disintegration time (Y_1) and ODTs taste (Y_2) were used as dependent variables. Using FFD 2^{5-2} F1-F8, 8 formulations were designed (Table 2) and prepared with 5 mg API per tablet

Table 1. Coded and real values of independent variables

	Level	
Independent variables	-1	+1
X_1 (sorbitol)	5	10
X_2 (mannitol)	30	65
X_3 (lemon aroma)	9	17
X_4 (Povidone K-25)	1.5	3
X_5 (crospovidone CL)	3	6

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The disintegration test was carried out in Erweka disintegration apparatus with 900 mL of water at 37±0.5 °C. The taste of the ODTs were examined by human taste panel. A selected panel of 20 healthy human volunteers was requested to taste the taste-masked ODTs by keeping it in the mouth till they disintegrated and rank it on a scale of perception ranging from 0-5 (0=good, 1=tasteless, 2=slightly bitter, 3=bitter, 4=very bitter, 5=awful). For comparison, ODTs of pure donepezil were also subjected to taste evaluation by the same panel and the results were compared.

Table 2. Experimental design and responses for 2^{5-2} FFD

Exp	X_1 %	X_2 %	X_3 %	X_4 %	X_5 %	Y_1 D.time	Y_2 Taste
F1	-1	-1	-1	+1	+1	14s	84
F2	+1	-1	-1	-1	-1	21s	71
F3	-1	+1	-1	-1	+1	10s	63
F4	+1	+1	-1	+1	-1	52s	45
F5	-1	-1	+1	+1	-1	45s	32
F6	+1	-1	+1	-1	+1	16s	11
F7	-1	+1	+1	-1	-1	27s	15
F8	+1	+1	+1	+1	+1	19s	6

Results and discussion

Based on the results presented in Table 2 disintegration time and ODTs taste, responses (Y_1 and Y_2) were fitted into linear model: $Y = b_o + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_5X_5$, where b_1-b_5 represent factorial effects. The equation was as follows: $Y_1 = +25.5+1.5X_1+1.5X_2+1.25X_3+7.0X_4-10.75X_5$. Calculated values of factorial effects for both responses are presented in Fig. 1 and Fig. 2.

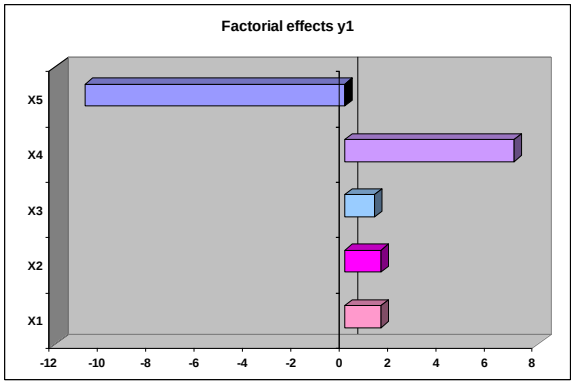

Fig. 1. Factorial effects value for disintegration time (Y_1)

From the results it can be seen that the concentration of crospovidone CL was the most important factor influencing the disintegration time, the higher the concentration, the shorter disintegration time. It was followed by the concentration of Povidone K-25 (Fig. 1). Other factors did not have significant influence on disintegration time. Lemon aroma efficiently masked the taste and no bitterness was sensed. It was followed by mannitol and sorbitol that were less effective in taste masking, accordingly (Fig. 2). Considering both examined responses the optimal formulation would be F8 where disintegration time was less than 20 s and efficient taste masking was achieved.

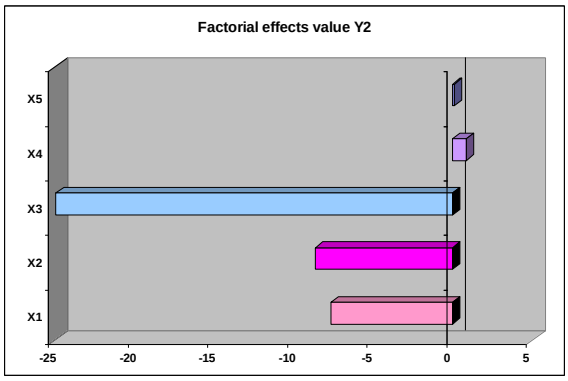

Fig. 2. Factorial effects value for ODTs taste (Y_2)

Conclusion

Donepezil orally disintegrating tablets were successfully prepared by application of experimental design study. The study demonstrated that concentration of the disintegrant and lemon aroma as independent variables are the most significant factors influencing disintegration time and taste masking.

References

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