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RESEARCH ARTICLE

Kinetics and Mechanism of Drug Release from Loratadine Orodispersible Tablets Developed without Lactose

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Objective: The aim of this study is to develop lactose-free orodispersible tablets with loratadine for patients with lactose intolerance. **Materials and methods:** Seven compositions (F1-F7) of 10 mg loratadine were prepared in form of orally disintegrating tablets, by direct compression, using croscarmellose sodium and pre-gelatinized starch in various concentrations as superdisintegrants, diluted with microcrystalline cellulose and combined with mannitol and maltodextrin as binder agents. The tablets had been studied in terms of their pharmacotechnical characteristics, by determining: the weight uniformity of the tablets, their friability, breaking strength and disintegration time, drug content and the dissolution profile of loratadine. The statistical analyses were performed with GraphPad Prism Software Inc. As dependent variables, both the hardness of the tablets and their disintegration ability differ between batches due to their compositional differences (as independent variables). DDSolver were used for modeling the kinetic of the dissolution processes by fitting the dissolution profiles with time-dependent equations (Zero-order, First-order, Higuchi, Korsmeyer-Peppas, Peppas-Sahlin). **Results:** All proposed formulas shows rapid disintegration, in less than 15 seconds, and the dissolution loratadine spans a period of about 10 minutes. Akaike index as well as R2 adjusted parameter have demonstrated that the studied dissolution profiles are the best fitted by Zero-order kinetic. **Conclusion:** In conclusion, association of croscarmellose sodium (7.5%) with pre-gelatinized starch (6%) as superdisintegrants and mannitol as the binder agent (35%), positively influences the dissolution properties of loratadine from orally fast dispersible tablets.

Keywords: loratadine, orodispersible, dissolution kinetic, lactose-free, superdisintegrant

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Introduction

Orodispersible tablets are characterized by enhanced dissolution and release of the active substance compared to conventional pharmaceutical forms. Considering their easy administration, this pharmaceutical form is preferred for children *[1,2,3]*, elder *[4]* and psychiatry ill *[5]*. The orally disintegration is attributed to the rapid water penetration into the tablets matrix, which creates a porous structure, and results in a fast disintegration. Considering this, the formulation and development of orodispersible tablets includes the maximization of porous structure of the matrix by incorporating a proper disintegrant and by using highly water soluble excipients *[6]*.

In order to formulate antihistaminic (loratadine) containing tablets for patients with lactose intolerance the following excipients were proposed: Manitol SD200, maltodextrin and microcrystalline cellulose as diluents, pre-gelatinized starch and croscarmellose sodium as superdisintegrants. In this study, the influence of formulation factors on the pharmacotechnical properties of tablets and the kinetic of the dissolution process were evaluated.

Methods

Materials

Loratadine, Mannitol SD 200, Maltodextrin (*kindly* supplied by Arena Group SA, Romania); Microcrystalline Cellulose NF 101 – Unitab®, Pre-gelatinized Starch – Lycatab®, Croscarmellose Sodium – Vivasol® (JRS Pharma GmbH & Co. KG, Germany); Silicon Dioxide – Aerosil® 200 (Evonik-*Degussa* GmbH, Germany); Magnesium Stearate, Aspartame, Cloves Aroma (*kindly* supplied by Gedeon Richter Romania SA); Reagents (analysis grade purity).

Apparatus and equipment

Eccentric Tablet Machine, punches of 7 mm diameters (Æ); Electronic Balance, precision of 0.01/0.1 mg (Kern&Sohn GmbH , Germany); Friability tester (Erweka, Germany); Tablet Hardness Tester (Erweka, Germany); Spectrometer Spektromom 195 D (MOM, Hungary); Dissolution tester type 1 (Erweka, Germany), rotating basket (#60 *mesh*).

-Preparation of Loratadine- orodispersible tablets: The ingredients were weighed, mixed for 10 minutes, sifted and mixed again in mortar with the help of pastel, without rubbing. The tablet machine was adjusted to achieve tablets of 200 mg weight. The homogenously mix of the ingredient was then directly compressed using a pair of punches of 7 mm diameters. The prepared tablets were kept in tightly closed containers, protected from light and sudden movements, at room temperature (15-25 °C).

-Mass uniformity test: 20 tablets had been accurately weighted and the average mass of a tablet was calculated (M). Same tablets were then individually accurately weighted (M_i). The M_i-M difference was expressed as percentage of M [7].

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-*Tablet friability:* 20 tablets of knowing mass (M_{in}) were stirred in the friabilator drum for 4 min (corresponding to 100 rpm), de-dusted and then accurately weighted again (M_{fn}). The difference M_{in}-M_{fn} was expressed as *percentage of M_{in} [7]*.

-*Tablet hardness:* 20 tablets were individually crashed in the harness tester, determining for each of them the diametrically pressing force, in newton (N), which crushed the tablet. The tablets hardness was then expressed as the calculated mean force *[7]*.

-*In vitro disintegration test:* 20 tablets were individually kept (not more than 3 min) in 50 mL distilled water, unstirred and maintained at 37 °C, without stirring. There has been recorded the time (in seconds/ minutes) passed till the tablet was turned into soft mater. The disintegration time was then expressed as the calculated mean time *[7]*.

-*Uniformity of loratadine content test*: 20 tablets were weighed and powdered in mortar rubbing vigorously with the pestle. The powder equivalent to 10 mg of loratadine (»200 mg) was weighed, then extracted by vigorously stirring for 10 minutes in 50 mL of hydrochloric acid 1N and diluted to 100 mL with the same solvent, in volumetric flask. After discarding the first filtered portion, 10.0 mL of filtrate was diluted with hydrochloric acid 0.1N to 25 mL, in a volumetric flask (sample). The absorbance of sample was then determined by spectrophotometry at 280 nm, using the hydrochloric acid 1N as blank. *The calibration curve* was prepared in same conditions, using 10 mg of loratadine (reference substance) dissolved in 1-2 mL of ethanol and diluted to 100 of hydrochloric acid 1N, in volumetric flask (stock solution: 0.1mg loratadine/1mL). The series of etalon solutions was prepared by diluting the stock solution as it follows: 5 mL, 7.5 mL, 10 mL, 15 mL, 20 mL and 25 mL of stock solution were diluted to 25 mL, by adding hydrochloric acid 0.1N, in volumetric flasks. The absorbance of each etalon solution was determined at 280 nm, using the 1N hydrochloric acid as blank *[7,8]*.

-*In vitro dissolution study:* The release rate of loratadine from tablets formulated for orally fast disintegration was determined by the United States Pharmacopeia (USP) method, using a tester similar to apparatus 1 (the rotating basket method) *[8]*. The test was performed on 6 tablets collected from each batches. Each tablet was individually introduced in a rotating basket (#60 *mesh*) and then immersed for 10 minutes in 900 ml hydrochloric acid 1N (media), at 37±0.5 °C and 50 rpm. The sample (5 ml) was withdrawn from the dissolution apparatus at every minute, each time replacing the subtracted solution with fresh dissolution media. The collected samples were filtered through filter paper and then the absorbance of the clear solution was measured by spectrophotometry (at 280 nm), using the hydrochloric acid 1N as blank. *The calibration curve* was prepared in same conditions as it is described above. Loratadine determined as released in media was expressed as percentage of 10 mg (the initial dose of Loratadine in tablet) and then plotted against time to determine the dissolution (release) profile.

Statistical analysis

GraphPad Prism software (GraphPad Software, Inc., v.5 trial demo version [9]) were used for performing: Anova test, Bonferroni multiple comparison, linearization of the curves by regression, calculation of and the descriptive statistical indicators. DDSolver -an Excel Ad in Program [10]- were used for modeling the kinetic of the dissolution processes by fitting the dissolution profiles with time-dependent equations (Zero-order, First-order, Higuchi, Korsmeyer-Peppas, Peppas-Sahlin) and for calculating the goodness of fit parameters (R^2 adjusted coefficient, Akaike index).

Results

Seven compositions (F1-F7) of 10 mg loratadine were prepared in form of orally disintegrating tablets, by direct compression, using croscarmellose sodium and pre-gelatinized starch in various concentrations as superdisintegrants diluted with microcrystalline cellulose and combined with mannitol and maltodextrin as binder agents, as it is shown in Table I. All tablets were in form of small white discs (Æ 7 mm), with flat faces and intact edges. After the organoleptic examination, the tablets had been studied in terms of their pharmacotechnical characteristics, by determining: the weight uniformity of the tablets, their friability, breaking strength and disintegration time, and the dissolution profile of loratadine previously assessed as tablet active dose, respectively.

Table I. Composition of the orodispersible tablets

Ingredient (agent type)	Formula / Composition (%)						
	F1	F2	F3	F4	F5	F6	F7
Loratadine (API)	5	5	5	5	5	5	5
Mannitol SD 200 (binder agent)	34.38	34.38	34.38	-	-	20.5	20.5
Maltodextrin (binder agent)	-	-	-	32.5	32.5	12	12
Microcrystalline Cellulose NF 101 (diluent)	46.87	44.37	41.87	48.45	52.45	48.45	52.45
Pre-gelatinized Starch – Lycatab® (superdisintegrant)	6	6	6	4	-	4	-
Croscarmellose Sodium - Vivasol® (superdisintegrant)	5	7.5	10	7	7	7	7
Aerosil® 200 (glidant)	1	1	1	1	1	1	1
Magnesium Stearate (lubricant)	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Aspartame (sweetener)	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Clove Aroma	-	-	-	0.3	0.3	0.3	0.3
Weight = 200 mg ± SD (n=20):	± 0.1%	± 1.0%	± 0.2%	± 0.1%	± 0.8%	± 0.2%	± 0.1%
Loratadine = 10 mg ± SD (n=20):	± 0.7%	± 1.4%	± 2.3%	± 1.0%	± 2.1%	± 0.5%	± 2.7%

Compared to the average mass (experimentally determined) and to the declared active content (established by formulation), the individual weight of tablets had the percentage deviations less than ±1% and the assessed active content less than ±3%, ±7.5% being the maximum allowed in both of the cases [7]. In terms of friability, two of the formulations (F4 and F6) do not meet the imposed requirements [7], their friability being greater than 1% (Figure 1).

As dependent variables, both the hardness of the tablets (expressed by the crushing force) and their disintegration ability (expressed by the period of time in which the tablet is transformed in very fine particles) differ between batches due to their compositional differences (as independent variables). The interactions of the two dependent variables can be considered extremely significant (P < 0.0001), so that the P values that follow for the row and column effects are difficult to interpret (excepting F4 for which the value of P is > 0.05, that means an insignificant effect of the interaction). In the same time, both of the dependent variables are directly affected by the ingredients of the tables, as these effects are also considered extremely significant (P < 0.0001). However, all tablets batches disintegrate without stirring in less than 3 minutes (the maximum admissible limit for this kind of tablets [7])

Although it is supported by a fast disintegration (in less than 15 seconds), the dissolution of loratadine lies on a period of about 10 minutes for all batches, but showing significantly different dissolution profiles that all are perfectly linearized by the simple regression (Figure 2).

In order to prove their linearity, the dissolution curves were supplementary fitted with usual time-dependent kinetic equations (Zero-order, First-order, Higuchi, Korsmeyer-Peppas, Peppas-Sahlin) and in all cases, the Akaike index as well as R^2adjusted parameter have demonstrated that the studied dissolution profiles are the best fitted by Zero-order kinetic. This means that in all seven cases, the dissolution of loratadine from tablet occurs at a constant rate which is numeric quantified by the value of k_0 - the constant of the implied dissolution process (Figure 3).

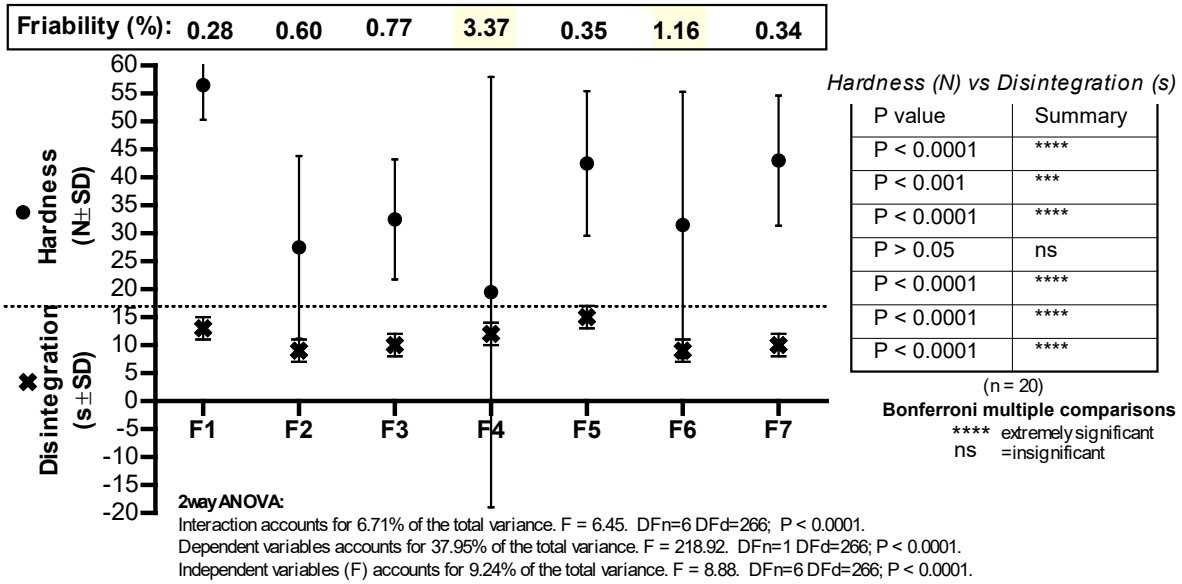

Fig. 1. The mechanical resistance vs. the disintegration ability of the orodispersible tablets

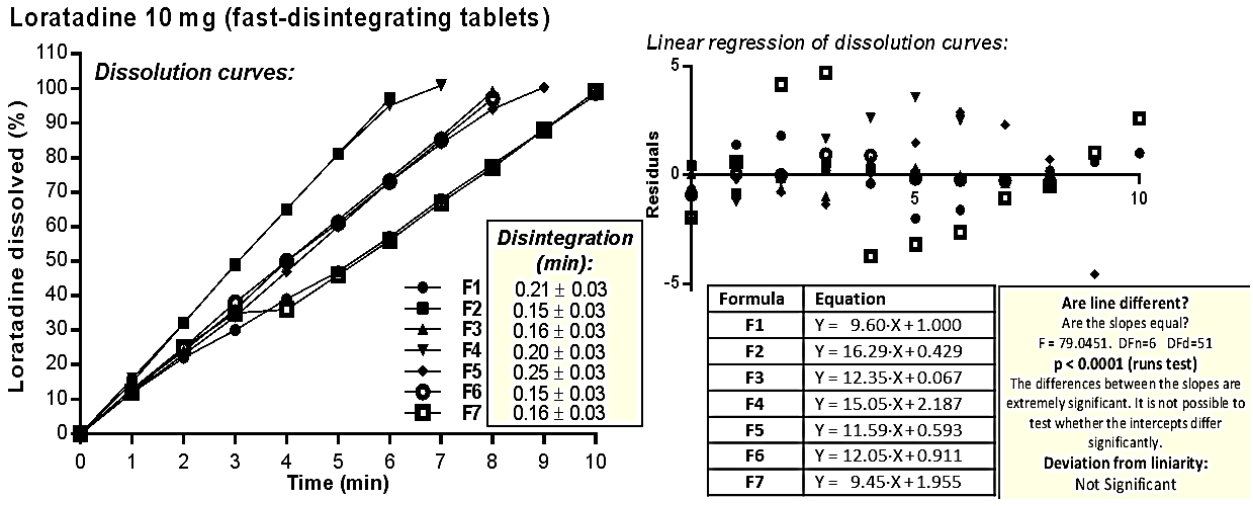

Fig. 2. The dissolution profiles of Loratadine vs. the disintegration time of tablets

The lower value of R^2adj coefficients indicates that the dissolution process of loratadine from the tablets of F3, F6, F5 and especially F1 and F7 batches, is also accompanied by other kind of processes, possibly due to the associated ingredients which interact into the matrix of the tablet. F2 and F4 batches stand out by their faster dissolution rates, significantly higher than the others (k_0 constants showing the highest values). However, the very poor resistance of F4 tablets (both hardness and friability) determines its exclusion from the consideration. It follows that F2 batch shows the most suitable characteristics for orally administration of tablet and its dispersion: the loratadine dissolution is running steadily from the start (Figure 4) and over all period of at about 6 minutes (when at least 97% of active dose is dissolved), after few seconds of latency (Figure 5), but the kinetic process does not appear to be influenced by the interactions between its associated ingredients.

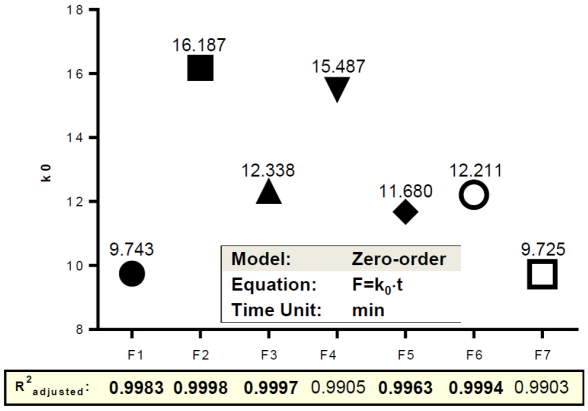

Fig. 3. The degree of curve fitting with Zero-order kinetic (R^2 adjusted) vs. the dissolution rate (k_0)

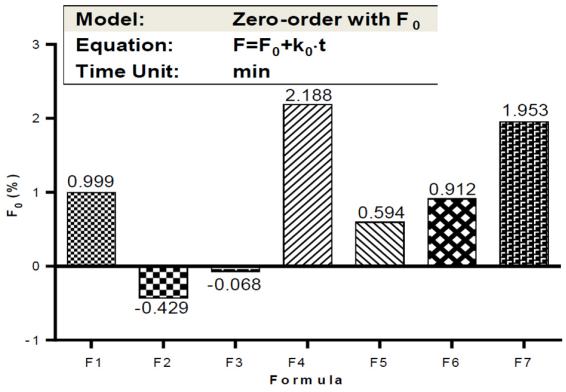

Fig. 4. The burst fraction (F_0) released previous to the dissolution process

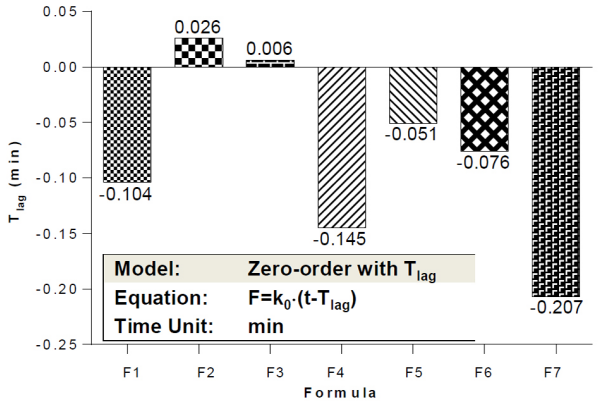

Fig. 5. The latency (T_{lag}) with which the dissolution process occurs

Conclusions

Association of croscarmellose sodium (7.5%) with pregelatinized starch (6%) as superdisintegrants, positively influences the dissolution properties of loratadine (5%) from orally fast dispersable tablets if mannitol is added as the binder agent (35%). The use of maltodextrin instead of mannitol determines a dramatic decrease, below the level of acceptability, in the hardness of tablets.

Pre-gelatinized starch (4%) associated to maltodextrin (12%) favors the dissolution processes, but only in the presence of mannitol (20%), otherwise the dissolution processes being slowed down. Approximately the same effect is determined if mannitol (35%) is associated to a combination of croscarmellose sodium (5%) and pre-gelatinized starch (6%).

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Conflict of interest

None to declare.

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