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Research Article

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Divisibility control of Ramipril tablets

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ABSTRACT

The objective of this work was to study the control the divisibility of Ramipril tablets 10 milligrams of two pharmaceutical products marketed in morocco, the reference drug and generic, using two quality control tests. This study shows that the test uniformity of content is more reliable to check the divisibility of tablets compared to the test uniformity of masse.

Keywords: Divisibility, ramipril, tablet

INTRODUCTION

Ramipril, chemically described as [(2*S*, 3a*S*, 6a*S*)-1-[(*S*)-2-[[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl] amino] propanoyl] octahydrocyclopenta [*b*] pyrrole-2-carboxylic acid (**Fig. 1**) is potent and specific angiotensin-converting enzyme (ACE) inhibitor that lower peripheral vascular resistance without affecting heart rate. It is used in treatment of hypertension and congestive heart failure. The role of this kind of drugs is to inhibit the last step of the biosynthesis of angiotensin II, a potent vasoconstrictor, and therefore, it causes a general vasodilatation and lowers blood pressure[1–3].

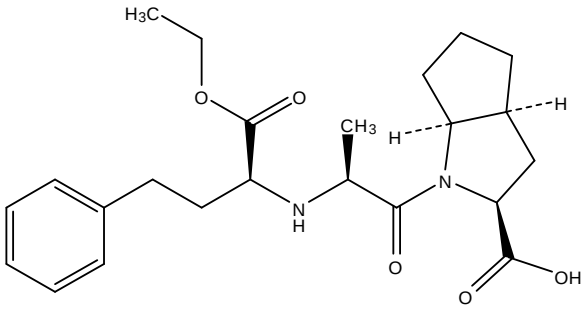

Figure 1: Chemical Structure of Ramipril

A tablet may be described as divisible only if the requirements of the European Pharmacopoeia are met: such, the effectiveness of the score line to be evaluated through the uniformity of mass fractions of tablets [11].

It is generally accepted that the division of a tablet provides two equal moieties. This assumption is not always correct because a groove does not guarantee the tablet. The presence of the latter as a decorative or lack of

uniformity of mass of the fragments of a compressed test prohibit division to divide the dose. Some business information contain phrases prohibiting the break. To facilitate decision, this division is mentioned most often in professional information. It is based on the dosage-form which guarantees the same bioavailability after fragmentation, but not necessarily an exact dose. This is why the "divisible" indication is insufficient.

Difficulties for breaking scored tablets are frequently reported. Breaking scored tablets is particularly difficult for the elderly and especially tablets small size [4,5].Scored tablets broken cause many problems of unequal rupture may cause variability in dose [6,7]. Another problem reported for divisible tablets is the mass loss due to fragmentation and coating line marking where a tablet is broken. Mass loss leads to risk of loss assay, contamination and the health of persons other than the patient [7-10].

The main objective of this study is to control the divisibility of Ramipril tablets 10 milligrams of two pharmaceutical products marketed in Morocco, the innovator and generic, using two quality control tests.

The choice of drug is based on its indication in cardiology particularly for older people with a dosage ranging from 1.25 mg / day and 10 mg / day [11], sometimes it is administered in half a tablet where the risk underdosing.

EXPERIMENTAL SECTION

Asked single blind three different people, the head nurse of Cardiology B of the Ibn Sina Hospital in Rabat and two cardiopathic inpatients said service, a 60 year old man (M2) and a woman 70 years old (M1) to manually split the tablets Ramipril tablets containing 10 milligrams. In total, we obtained six different samples: Inovator divided by the nurse (**PIN**), Inovator divided by the patient M1(**PM1**), Inovator divided by the patient M2(**PM2**), Generic divided by the nurse (**GIN**), Generic divided by the patient M1(**GM1**), Generic divided by the patient M2(**GM2**).

2.1 Apparatus

Chromatographic separation was achieved by using a PERKINELMER SERIE 200 photodiode-array detector (PDA). Data acquisition was performed by the Totalchrom Software data registration (USA), the Mettler Toledo scale made in Switzerland and pH meter used was from Schott (Germany).

2.2 Reagents and Materials

All chemical products were of analytical grade and were supplied by the National Laboratory of Drugs Control (LNCM) Rabat, Morocco.

The Ramipril standard (99,9 %) was provided by the National Laboratory of Drug Control of Morocco. Methanol was of HPLC grade from Sigma- Aldrich (Germany).

Ramipril tablet 10 mg, innovator and generic made by pharmaceutical industries in Morocco, were purchased from reputable pharmacies in Rabat for the purpose of the study. The study was performed within the expiration dates of the products.

2.3 Uniformity of weight half- units

Weighed on an analytical balance individually 20 half-tablets selected from each brand and the average weight calculated. In accordance with EP and USP, not more than two of the individual weights should deviate from the average weight by more than the percentage given in the pharmacopoeia and none deviates by more than twice that percentage[12,13].

2.4 Uniformity of dosage half- units

Estimation of Ramipril in half of tablet by HPLC method. The assay was carried out using official monograph of Ramipril tablet as reported USP HPLC method, revision bulletin 2011[13].

- Chromatographic Conditions

The chromatographic column utilized in these studies was an Waters Symmetry C18 column (150 mm×4.6 mm, 5 µm). The column temperature was maintained at 30 ºC.

The mobile phase A consisted of Acetonitrile and Phosphoric acid (30ml/l of phosphoric acid in water) : (2:3, v/v) . The flow rate was 1.0 mL/min, the detection wavelength was set at 250 nm and the injection volume was 25µL.

- Standards solutions

The Standard solution was prepared with mobile phase and contained 0,03mg/ml.

- Samples solutions
Transfer each half- tablet into flask 200ml. add mobile phase (about 50% of total volume), and sonicate for 25 min. Mechanically shake for 10 min, and dilute with mobile phase to 200 ml.

- Specificity of the chromatographic method
The selectivity of the method was confirmed by observing potential interferences caused by excipients of tablet formulations.

The chromatogram of the tablet excipients (Fig. 2) shows that there were no interference of peaks to the determination of Ramipril.

The peak purity indices for Ramipril were found to be better (purity angle < purity threshold) indicating that no additional peaks were co-eluting with the analytes and also evidencing the ability of the method to assess unequivocally the analytes of interest in the presence of potential interference.

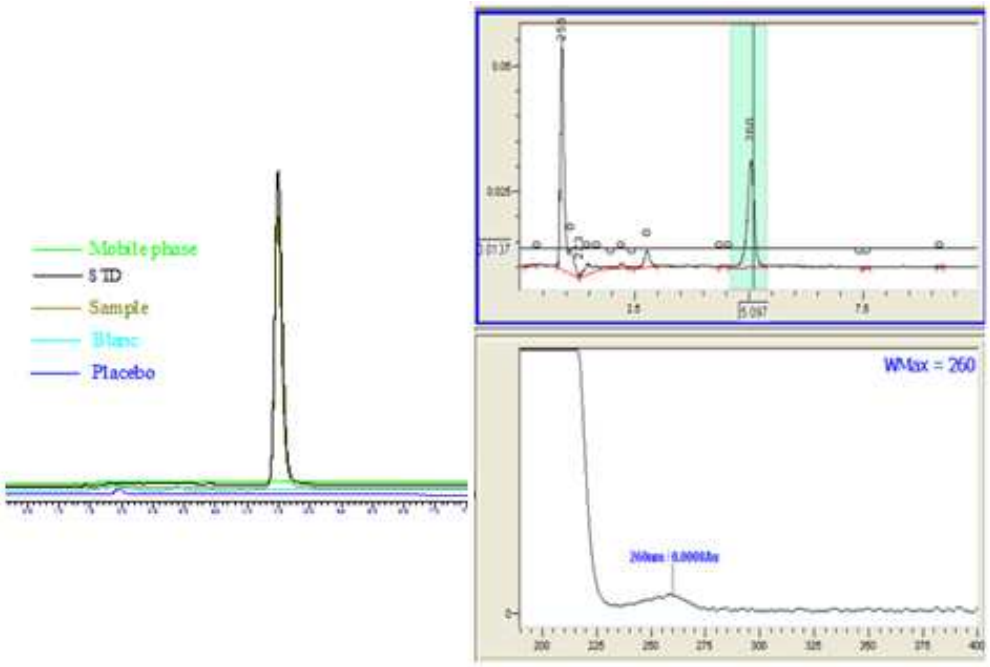

Fig.2: Specificity of the chromatographic method

RESULTS AND DISCUSSION

3.1 Uniformity of weight of half-tablets

The control of the divisibility by testing the uniformity of the mass of the half - tablets revealed the results shown in (Table I) and (Fig 3).

Table 1 : Results of uniformity of the mass of the half-tablets

Série / Demi-comprimé De&&&&&mi-comprimé	**PIN** (mg)	**PM1** (mg)	**PM2** (mg)	**GIN** (mg)	**GM1** (mg)	**GM2** (mg)
½ Tablet **1**	**55,30**	48,30	41,30	**53,60**	47,80	50,00
½ Tablet **2**	48,40	**56,50**	**62,40**	50,20	**56,00**	**53,50**
½ Tablet **3**	59,70	**55,00**	**57,90**	**52,60**	44,70	48,40
½ Tablet **4**	46,10	45,30	47,20	48,50	**57,50**	**54,60**
½ Tablet **5**	**58,20**	42,80	46,60	**54,20**	**57,00**	50,80
½ Tablet **6**	45,60	**59,40**	**57,10**	49,50	45,20	52,30
½ Tablet **7**	**54,90**	44,90	**55,40**	**54,80**	47,10	**56,50**
½ Tablet **8**	50,60	**58,20**	48,20	49,70	**57,10**	47,30
½ Tablet **9**	**54,50**	**53,80**	**54,40**	**55,00**	50,00	49,90
½ Tablet **10**	51,10	51,80	48,60	50,20	**52,90**	**54,10**
½ Tablet **11**	**54,90**	44,90	**54,40**	**54,20**	47,10	48,40
½ Tablet **12**	50,60	**58,20**	48,20	49,50	**57,10**	**54,60**
½ Tablet **13**	**55,30**	**55,00**	41,30	**55,00**	44,70	49,90
½ Tablet **14**	48,40	45,30	**62,40**	50,20	**57,50**	**54,10**
½ Tablet **15**	**58,70**	**53,80**	**54,40**	**52,60**	47,80	50,00
½ Tablet **16**	46,10	**51,80**	48,60	48,50	**56,00**	**53,50**
½ Tablet **17**	**58,20**	48,30	46,60	**53,60**	50,00	**56,50**
½ Tablet **18**	45,60	56,50	**57,10**	50,20	**52,90**	**51,60**
½ Tablet **19**	**54,50**	42,80	**57,90**	**54,80**	**57,00**	50,80
½ Tablet **20**	51,10	**59,40**	47,20	49,70	45,20	**52,30**
Average	**52,39**	**51,60**	**51,86**	**51,83**	**51,53**	**51,36**
RSD	8,89	11,21	12,13	4,62	9,87	5,14
Unit Not accepted / Pharmacopoeia	9	10	10	10	10	10

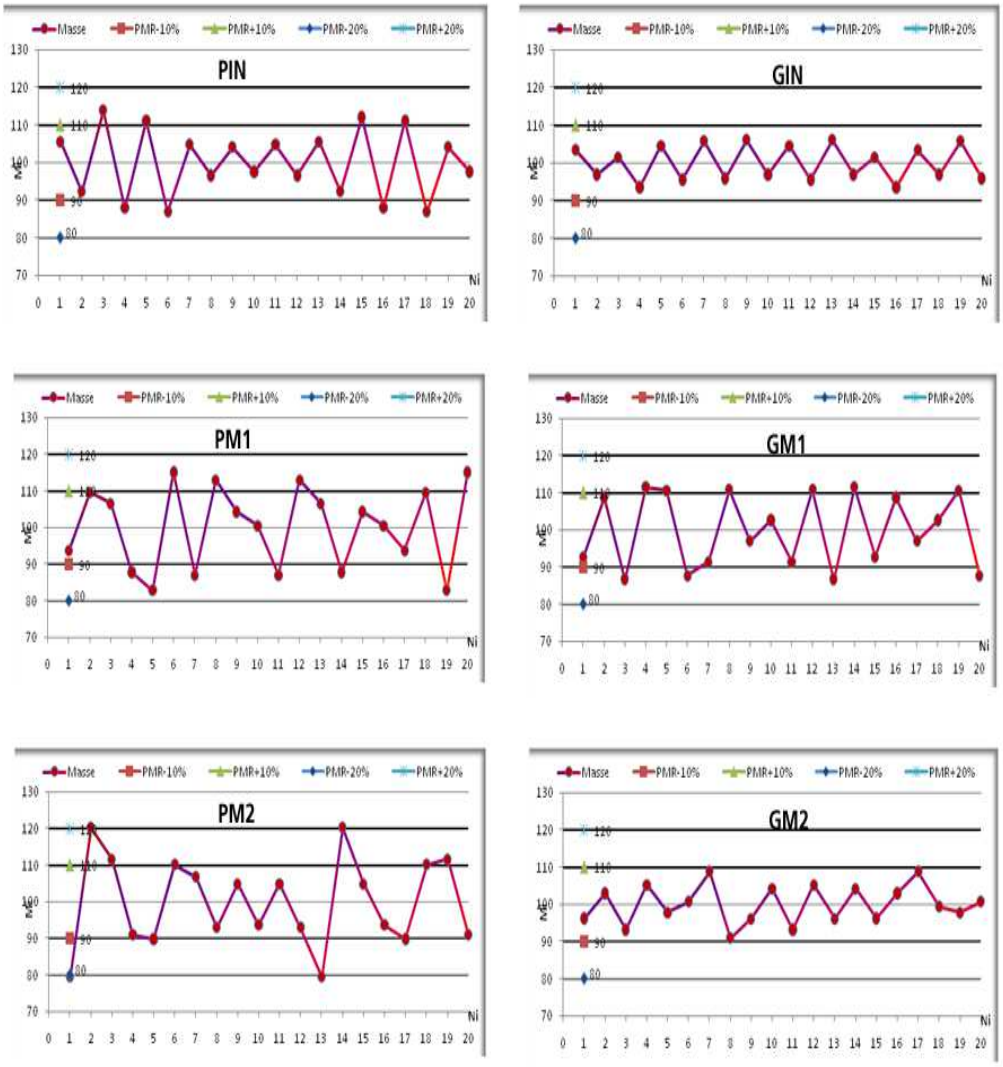

Fig. 3 : Variation curves of the mass of the half-tablets verified by the uniformity of the mass test

3.2 Uniformity of content t of half-tablets

The Control of divisibility by testing the consistency of the content of half tablets revealed the results shown in (Table 2) and (Fig.4).

Table 2: Results of uniformity of content of the half-tablets

Série / Half-tablet	Assay (%) PIN	Assay (%) PM1	Assay (%) PM2	Assay (%) GIN	Assay (%) GM1	Assay (%) GM2
½ Tablet 1	102,38	98,78	94,34	98,53	92,20	97,36
½ Tablet 2	106,81	94,90	84,55	98,65	92,44	96,85
½ Tablet 3	92,90	99,10	100,90	102,05	107,33	98,28
½ Tablet 4	97,93	107,06	107,85	98,13	90,99	99,21
½ Tablet 5	93,80	105,13	101,26	98,08	99,09	102,24
½ Tablet 6	96,02	86,48	96,06	98,62	92,92	96,97
½ Tablet 7	92,67	111,57	95,20	101,23	97,34	95,31
½ Tablet 8	103,05	91,99	97,88	106,58	90,78	103,94
½ Tablet 9	96,98	100,60	95,69	91,84	101,23	94,53
½ Tablet 10	101,45	98,74	105,78	96,24	93,50	95,75
Average	98,40	99,44	97,95	99,00	95,78	98,04
Unit Not accepted / Pharmacopoeia	0	1	0	0	0	0

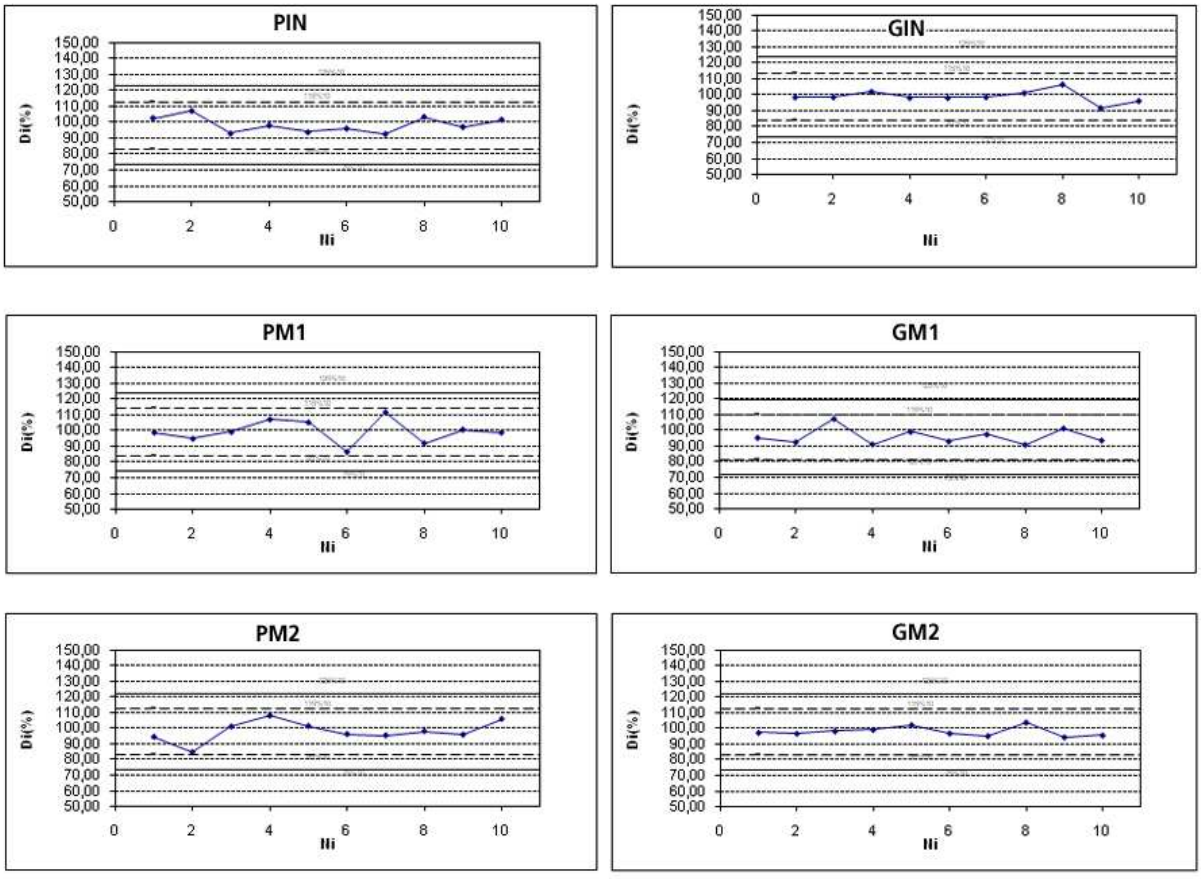

Fig. 4 : Variation curves contents of Ramipril in half- tablets by the uniformity of content test

Considering the standard of the European Pharmacopoeia for testing the consistency of the mass applied to the half-tablets which is roughly 10 % per theoretical weight average Half-compressed (50 milligrams), only two samples among the six are acceptable (GIN and GM2) while four samples in six does not meet the standard of pharmacopoeia (GM1, PIN, PM1 and PM2).

Considering the standard of the European Pharmacopoeia for testing the uniformity of the content of which is plus or minus 15 % relative to the average content of theoretical (half tablet (5 mg)). All results for this test are acceptable, whatever the type of drug tested (innovator or generic) or type of operator (nurse or patient) that is to say half tablets contain the content required by the pharmacopoeia.

CONCLUSION

The results of this study show that the test for uniformity of content used to check divisibility of half tablets Ramipril is more reliable than the uniformity of mass for all half-tablets of the two specialties tested contain recommended by the European Pharmacopoeia content of active ingredient which is roughly 15% compared to the theoretical content whatever the operator who carried fractionation. while testing the uniformity of the mass of the half-tablets showed unacceptable results compared to the standard of the European Pharmacopoeia.

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