INFLUENCE OF SPLITTING ON DISSOLUTION PROPERTIES OF METOPROLOL TABLETS

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Abstract

The objective of this work was to compare several profiles of dissolution data for metoprolol controlled release tablet formulations in order to identify possible changes in dissolution profiles of whole and scored tablets. Adequate design of score lines (on one or both sides) as well as the technology of preparation of tablet mixtures ensure forming a score line of adequate thickness, shape, size, curvature. According to the obtained results, this type of extended release formulation is eligible for splitting and use in therapy either as a whole or scored tablets.

KEY WORDS: metoprolol, extended release, tablet splitting, dissolution profile

Introduction

Metoprolol is a cardioselective β-blocker that is classified as a class I substance according to the Biopharmaceutics Classification Scheme BCS (1), meaning that it is highly soluble and highly permeable. The drug is readily and completely absorbed throughout the whole intestinal tract (2-4) but is subject to extensive first-pass metabolism resulting in incomplete bioavailability (about 50%). When administered as single oral dose, peak plasma concentrations occur after 1-2 hours. The drug is eliminated within 3 to 4 hours, which, depending on therapeutic intentions, makes it necessary to administer simple formulations of metoprolol up to 4 times daily (5). Based on these properties and the well-defined relationship between the β-blocking effect and plasma drug concentration (6), metoprolol is accommodated into extended-release (ER) formulation (7,8,9). Metoprolol ER formulations smooth out peaks and valleys in the plasma levels and enable less frequent administration. Dosing intervals are typically reduced to once or twice per day (10).

On the other hand, the ability to adjust doses to individual patients depends on the availability of multiple dose sizes and adequate dose response information. These are not always provided, so splitting of the tablets is sometimes necessary (11). Tablet splitting is an accepted practice in dispensing medications. It is used when a dosage form of the required strength is not available commercially (12).

The aim of this study was to establish possible influence of tablet splitting on dissolution profile of metoprolol extended release tablets.

Materials and Methods

Reagents

The used reagents were of analytical grade, unless otherwise stated. Metoprolol tartarate working standard was provided by Merck (Darmstadt, Germany). Sodium dihydrogen phosphate, disodium hydrogen phosphate were provided by Carl Roth GmbH & Co (Karlsruhe, Germany).

Drug dosage form (extended release tablets) tested

The tablets applied for this study were in the form of snap-tab-tablets. Each tablet consisted of 200 mg of metoprolol tartarate as an active ingredient. The tablet core consisted of eudragit RL PO/ RS PO; lactose monohydrate; magnesium stearate; maize starch; anhydrous colloidal silica. Film-coating suspension consisted of methylhydroxypropyl cellulose, polyethylene glycol 4000, talc and titanium –dioxide (E171).

Breakability test method-manual method

The tablet was held between the thumb and the index finger of each hand on either side of the score line (score line was on both sides of tablet) and without using the nail. Separation into two halves was done by breaking open the tablet at the deeper score line side (Figure 1.).

FIGURE 1. Metoprolol tablets

Preparation of standard solutions

A standard curve of absorbance versus concentration was constructed using previously degassed solutions of metaprolol tartarate in the dissolution medium (phosphate buffer, pH= 6,8), ranging in concentration from 0,044 to 0,219 mg/ml.

Absorbance versus concentration plot was linear over this concentration range and was used to determine percent of drug dissolved in the dissolution experiments. UV absorbance of each standard solution was measured spectrophotometrically at 274 nm.

Dissolution test conditions and analysis procedure

The dissolution test of metoprolol extended release tablets (n=12), was performed using USP apparatus 2, Van Kel VK 7010 dissolution tester, at a stirring speed of 100 rpm (Van Kel, Cary, NC, USA). The dissolution apparatus was maintained at 37°C throughout the experiment. The test was carried in phosphate buffer solution, pH=6,8. Prior to use, the dissolution medium was deareated in the ultrasonic bath and warmed up to 41°C, filtered using a 0,45 μm membrane filter (Sartorious GmbH, Goettingen, Germany) and transferred to dissolution vessel. The analysis was initiated once the medium cooled to 37°C.

Dissolution samples in the amount of 5 ml were withdrawn at the following intervals (after 60, 120, 180, 240, 360, 480 and 600 minutes). Correction for volume was calculated mathematically, considering that withdrawn samples were not supplemented with an equal volume of fresh dissolution fluid to maintain a constant total volume.

These samples were also filtered using a 0,45 μm membrane filter (Sartorious GmbH, Goettingen, Germany). The dissolution apparatus was connected with UV/VIS spectrophotometer Shimadzu 1601 (Shimadzu, Kyoto, Japan). Determination of dissolution rates for the active ingredient in film tablets was carried out according to the previously described spectrophotometric method. All the dissolution tests were performed in triplicate.

Applied method to compare dissolution profiles

In this study, as model-independent approaches (13, 14), two fit factors that compare the dissolution profiles of a pair of drug products were applied to the dissolution data. These fit factors directly compare the difference between percent of drug dissolved per unit of time for the tested product and the reference. The fit factors are denoted *f1* (difference factor), and *f2* (similarity factor) (15) and are defined by Eqs. (1) and (2):

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100 \qquad \text{(Eq. 1)}$$

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0,5} \times 100 \right\} \text{ (Eq. 2)}$$

where *n* is the number of dissolution sample time points, and R_t and T_t are individual or mean percent dissolved at each time point, *t*, for the reference and test dissolution profiles, respectively (13, 14).

The similarity factor fits the result between 0 and 100. When the test and reference profiles completely coincide the value is 100 and tends to 0 as the dissimilarity increases. This method is more adequate to dissolution profile comparisons when more than three or four dissolution time points are available. Eq. (1) can only be applied if the average difference between R and T is less than 100. If this difference is higher than 100 normalisation of the data is required (15). This similarity factor has been adopted by the Center for Drug Evaluation and Research (FDA) and by Human

Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products (EMEA), as a criterion for the assessment of the similarity between two in vitro dissolution profiles and is included in the "Guidance on Immediate Release Solid Oral Dosage Forms; Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation" (16), commonly called SUPAC IR, and in the "Note For Guidance on Quality of Modified Release Products: A. Oral Dosage Forms; B. Transdermal Dosage Forms; Section I (Quality)" (17). Similarity factor (*f2*) as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the tested product and the reference.

This equation differs from the one proposed by Moore and Flanner in the weight factor and in the fact that it uses percent dissolution values. In order to consider the similar dissolution profiles, the *f1* values should be close to 0 and values *f2* should be close to 100. In general, *f1* values lower than 15 (0–15) and *f2* values higher than 50 (50–100) indicate similarity of dissolution profiles. FDA and EMEA suggest that two dissolution profiles are declared similar if *f2* is between 50 and 100. In addition, it requests the sponsor uses the similarity factor to compare the dissolution treatment effect in the presence of at least 12 individual dosage units.

Results and Discussion

The results of dissolution analysis are summarized in Table 1, and Figure 2, which show the fraction of the dissolved drug as a function of time.

t (h)	% dissolved		
	Whole tablets (1 200 mg)	1/2 tablets (1 100 mg)	Halved tablets (2 100 mg)
1	36,03	42,79	39,92
2	48,81	52,82	53,59
3	59,10	65,87	64,26
4	66,15	71,59	71,70
6	75,49	80,10	81,32
8	82,58	84,31	85,53
10	85,82	87,91	87,24

TABLE 1. Fraction of the dissolved drug as a function of time from the whole tablets (1x200 mg), 1/2 tablets (1x100 mg) and halved tablets (2x100 mg)

Also, the results of *f1* and *f2* analysis are summarized in Table 2, 3 and 4 and indicate similarity of dissolution profiles
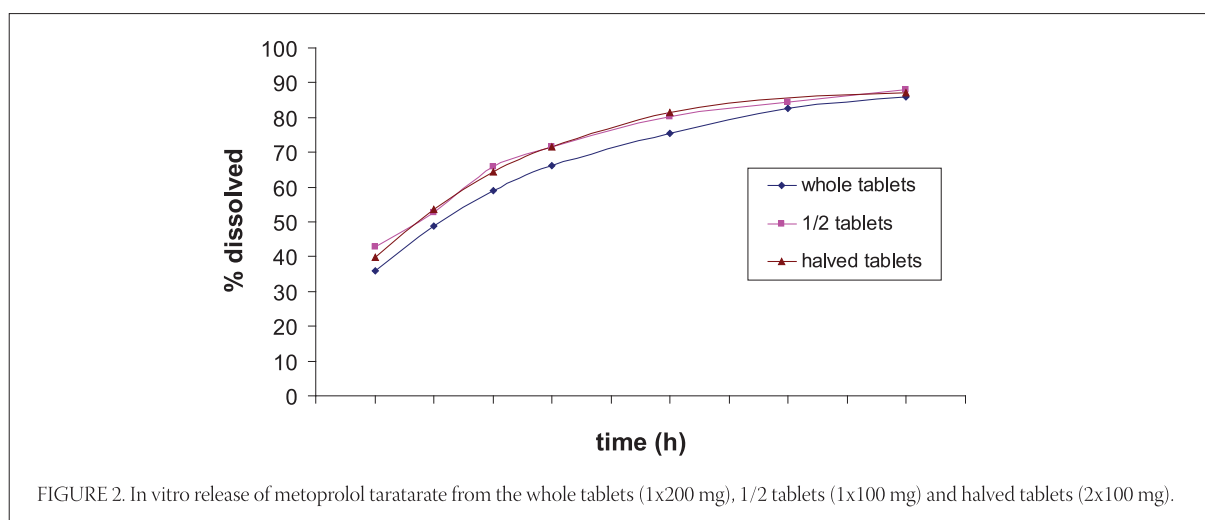
FIGURE 2. In vitro release of metoprolol taratarate from the whole tablets (1x200 mg), 1/2 tablets (1x100 mg) and halved tablets (2x100 mg).

Dissolution profiles (Table 1, Figure 2) of whole and scored tablets (each ½ of the tablet and both halves together) show mutual similarity using f_1 and f_2 test (f_1 test: results ≤ 15; f_2 test: results ≥ 50). Tablet splitting causes damaging of the integrity of the tablet, which leads to greater variability of dissolution profile of halved tablets (2 100 mg) compared to the profile of the whole tablets (1 200 mg): f_1 = 6,5; f_2 = 68,8 (Table 2). Dissolution profiles obtained for ½ tablets (1 100 mg) compared to the profile of the whole tablet (1 200 mg) which were used as control probes f_1 =6,9; f_2=66,2 (Table 3.), indicated that the variation in labelled strength has lower influence on the difference in the case of mutual comparison of ½ of the tablets versus scored tablets (2 100 mg): f_1 = 1,8; f_2 = 87,9 (Table 4).

f_1 and f_2 analysis		
Time (h)	T_t halved tablets	R_t whole tablets
1	39,92	36,03
2	53,59	48,81
3	64,26	59,10
4	71,70	66,15
6	81,32	75,49
8	85,53	82,58
10	87,24	85,82
	f_1:	6,5
	f_2:	68,8

TABLE 2. f_1 and f_2 values: halved tablets (2x100 mg) vs. whole tablets (1x200 mg)

f_1 and f_2 analysis		
Time (h)	T_t halved tablets	R_t whole tablets
1	42,79	36,03
2	52,82	48,81
3	65,87	59,10
4	71,59	66,15
6	80,10	75,49
8	84,31	82,58
10	87,91	85,82
	f_1:	6,9
	f_2:	66,2

TABLE 3. f_1 and f_2 values: 1/2 tablets (1x100 mg) vs. whole tablets (1x200 mg)

f_1 and f_2 analysis		
Time (h)	T_t halved tablets	R_t whole tablets
1	42,79	39,92
2	52,82	53,59
3	65,87	64,26
4	71,59	71,70
6	80,10	81,32
8	84,31	85,53
10	87,91	87,24
	f_1:	1,8
	f_2:	87,9

TABLE 3. f_1 and f_2 values: 1/2 tablets (1x100 mg) vs. halved tablets (2x100 mg)

Conclusion

Integrity changes of the analysed tablets during tablet splitting (halved vs. whole tablets) showed greater influence on the results obtained than the difference in declared content (100 mg vs. 200 mg). Adequate design of score lines (on one or both sides) as well as the technology of preparation of tablet mixture ensures forming a score line of adequate thickness, shape, size, curvature. This line would minimize the contact area at splitting position and represents an important criterion in the design of products with extended release which would be appropriate in the therapy as a whole or halved tablets (dosage forms). According to the results obtained, this formulation is eligible for splitting and may be used in therapy either as a whole or scored tablets.

References

(1) Guidance for Industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, 2000.

(2) Jobin G., Cortot A., Godbillon J., Duval M., Schoeller J.P., Hirtz J., Bernier J.J. Investigation of drug absorption from the gastrointestinal tract of man. I. Metoprolol in the stomach, duodenum and jejunum. Br. J.Clin. Pharmacol. 1985;19 (Suppl. 2): 97S–105S.

(3) Vidon N., Evard D., Godbillon J., Rongier M., Duval M., Schoeller J.P., Bernier J.J., Hirtz J. Investigation of drug absorption from the gastrointestinal tract of man. II. Metoprolol in the jejunum and ileum. Br. J.Clin.Pharmacol. 1985;19 (Suppl. 2): 107S–112S.

(4) Godbillon J., Evard D., Vidon N., Duval M., Schoeller J.P., Bernier J.J., Hirtz J. Investigation of drug absorption from the gastrointestinal tract of man. III. Metoprolol in the colon. Br. J. Clin. Pharmacol. 1985; 19 (Suppl. 2): 113S–118S.

(5) Sweetman. S. C., Ed. Martindale: The Complete Drug Reference, 33rd ed.; Pharmaceutical Press: London, England, 2002.

(6) Kendall M.J., Maxwell S.R., Sandberg A., Westergren G. Controlled release metoprolol. Clinical pharmacokinetic and therapeutic implications. Clin. Pharmacokinet. 1991; 21 (5): 319–330.

(7) Siepmann F., Hoffmann A., Leclercq B., Carlin B., Siepmann J. How to adjust desired drug release patterns from ethylcellulose-coated dosage forms. J. Control. Release 2007; 119: 182–189.

(8) Siepmann F., Muschert S., Leclercq B., Carlin B., Siepmann J., How to improve the storage stability of aqueous polymeric film coatings, J. Control. Release 2008; 126: 26–33.

(9) Muschert S., Siepmann F., Leclercq B., Carlin B., Siepmann J. Drug release mechanisms from ethylcellulose: PVA-PEG graft copolymer-coated pellets. Eur. J. Pharm. Biopharm. 2009; 72: 130–137

(10) Plosker G.L., Clissold S.P. Controlled release metoprolol formulations. A review of their pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and ischaemic heart disease. Drugs. 1992;43(3):382-414.

(11) Cohen J.S. Tablet splitting: imperfect perhaps, but better than excessive dosing. J. Am. Pharm. Assoc. 2002; 42(2): 160-162

(12) Bachynsky J., Cheryl W., Krystal M. The practice of splitting tablets: Cost and therapeutic aspects. Pharmacoeconomics 2002; 20 (5): 339-346

(13) Yuksel N., Kanık A. E., Baykara T. Comparison of in vitro dissolution profiles by ANOVA-based, model-dependent and -independent methods. Int. J. Pharm. 2000; 209: 57–67

(14) Costa P., Sousa Lobo J. M. Modelling and comparison of dissolution profiles Eur. J. Pharm. Sci. 2001; 13: 123–133

(15) Moore J.W., Flanner H.H. Mathematical comparison of dissolution profiles. Pharm. Technol. 1996; 20; 64–74.

(16) Guidance on Immediate Release Solid Oral Dosage Forms; Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation, CMC, 1995

(17) Human Medicines Evaluation Unit. Note For Guidance on Quality of Modified Release Products: A. Oral Dosage Forms; B. Transdermal Dosage Forms; Section I (Quality). The European Agency for the Evaluation of Medicinal Products (EMEA), CPMP/ QWP/604/ 96. , 1999.