STUDY OF THE APPLICABILTY OF CONTENT UNIFORMITY AND DISSOLUTION VARIATION TEST ON ROPINIROLE HYDROCHLORIDE TABLETS

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Abstract

When considering single-dose preparations, it is fundamental that the patient receives in his individual dose an amount of drug close to that claimed on the label. Since drug content and content uniformity of single-dose preparations depend on a number of processes associated with their manufacture, it is obviously unrealistic to expect every unit of product to possess exactly the same amount of the active ingredient. For that reason, pharmacopeial standards and specifications have been established to provide limits for permissible variations in the amount of active ingredient of individual single-dose units. The aim of our study was to determine the applicability of content uniformity and dissolution variation test on ropinirole hydrochloride tablets.

According to the results obtained, we may conclude that analyzed ropinirole hydrochloride tablets satisfied pharmacopeial requirements concerning content uniformity and dissolution testing. In this case RSD tended to increase with the decrease of the labeled strength. It is obvious from the R^2 value, as well. On the other side, if consider larger number of lots, analyzed by different assay methods and various sample preparation procedures this correlation is less pronounced. This may be a consequence of different assay techniques applied, HPLC, UV-D1 or UV.

KEY WORDS: ropinirole hydrohloride, dissolution test, content uniformity

Introduction

When considering single-dose preparations, it is fundamental that the patient receives in his individual dose an amount of drug close to that claimed on the label. Since drug content and content uniformity of single-dose preparations depend on a number of processes associated with their manufacture, it is obviously unrealistic to expect every unit of product to possess exactly the same amount of the active ingredient. For that reason, pharmacopeial standards and specifications have been established to provide limits for permissible variations in the amount of active ingredient of individual single-dose units (1). Content uniformity is one in a series of tests in a therapeutic product specification that assesses the quality of a batch. Testing for content uniformity helps ensure that the strength of a therapeutic product remains within specified acceptance limits. Recent national and international regulatory and compendial efforts have focused on harmonizing content uniformity testing, with several different approaches under consideration. The differing approaches arise from differing motivations (batch release vs. marketplace testing of a single unit), testing (uniformity of content vs. uniformity of mass), products covered (oral, oral inhalation and nasal drug products), and statistical strategies (2). The subject of content uniformity of single-dose units has been considered a lot. However, different methodologies and specifications are still prescribed in different official pharmacopeias like of European Pharmacopeia 6th (Eur. Pharm. 6th) (3) and United States Pharmacopeia 31st (USP 31) (4). Characterization studies conducted during product development assess safety, efficacy, and quality measures for a therapeutic product. For therapeutic products approved through a regulatory process, safety and efficacy characterization studies are reflected in the approved product label. Quality characterization studies are performed in relation to safety and efficacy studies and are at times associated with specified acceptance criteria. For example, product bioavailability and bioequivalence quality studies are one-time product performance characterization studies that, in the case of bioequivalence, may be assessed using specified criteria and pre-determined pass/fail bioequivalence limits (5,6). Quality characterization studies provide specifications, defined as a list of tests, references to analytical procedures to evaluate those tests, and appropriate acceptance criteria (7).

The aim of our study was to:

- compare content uniformity and dissolution variation test of different tablets, labeled strength 0,25; 0,5; 1; 2 and 5 mg, respectively (different assay techniques applied, HPLC, UV-D1 or UV).
- study the applicability of content uniformity and dissolution variation test of ropinirole hydrochloride tablets, labeled strength 0,25; 0,5; 1; 2 and 5 mg, respectively (HPLC assay techniques applied).

Current approaches to content uniformity data analysis

Current approaches to content uniformity testing are based on either parametric tolerance intervals or a nonparametric procedure that can be recognized as a nonparametric tolerance interval. Three decisions are needed to assess content uniformity using a tolerance interval approach (8). These are:

- acceptable tolerance limits (e.g., 85–115% of label claim);
- minimum proportion, p, of the batch that should fall within the limits (e.g., 90% of units in a batch); and
- degree of confidence needed to make an accept/reject decision (e.g., 95%).

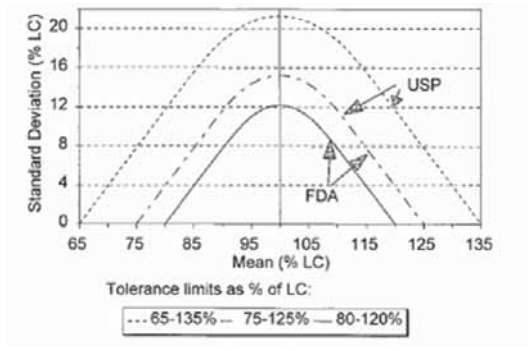

FIGURE 1. Combination of means and standard deviations corresponding to 90% coverage (*p*) (8)

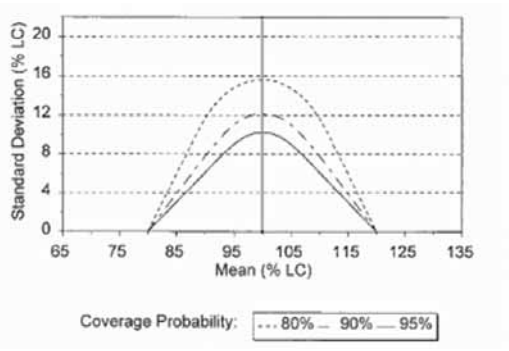

FIGURE 2. Means and standard deviations in the batch corresponding to 80–120% tolerance limits (8)

For *nonparametric* approaches, conformance is determined based on the number of assay values that fall within a specified accept/reject limit, irrespective of the actual values. With parametric tolerance intervals, an accept decision is reached if the test data expressed in terms of the criterion yield an observed tolerance interval that falls entirely within the tolerance limits. Parametric tolerance intervals provide simultaneous direct control on the mean and standard deviation of the batch (Figures 1 and 2). For all combinations of means and standard deviations on or below each curve, at least 90% of the distribution falls within the tolerance limits (Figure 1). The upper curve is for wide tolerance limits, 65–135% of label claim, and thus allows more combinations of means and variances. The lowest curve, with narrow specified tolerance limits of 80–120%, is more restrictive. For all combinations of means and standard deviations on or below each curve, at least a specified portion of the distribution falls within the tolerance limits of 80–120% (Figure 2). The lowest curve is a high coverage probability of 95% and thus allows fewer combinations of means and variances. The upper curve, with lower coverage probability is less restrictive. For *parametric* tolerance interval testing, the general form of the criterion is $\overline{Y} \pm kS$, where S is the observed standard deviation, and k is a tolerance interval constant that accounts for sample size as well as the population fraction p (9). For this application, $\overline{Y}$ is the difference between a test mean, $\overline{X}$, and a reference mean. The reference mean in content uniformity may be fixed as either the label claim or rubric mean, M, expressed as a percent. The rubric mean can sometimes be greater or less than 100% of label claim, with corresponding changes in tolerance limits. After subtracting the reference mean the tolerance limits are similarly adjusted, e.g., 85%–115% of label claim becomes ±15%. When the tolerance limits are symmetric about zero, as ±15%, the decision to accept the batch can be made using the largest absolute value from the interval; that is, reducing the tolerance interval to a single value, $|\overline{Y}|$+ kS. Usually, parametric tolerance interval approaches assume normal distribution of the data, possibly following a transformation, such as to log scale. Nonparametric approaches do not assume normal distribution of test data. If the normality assumption is correct (and normality seems reasonable for content uniformity testing), the parametric tolerance interval approach ought to make better use of the data than approaches based on counts of values falling within specified intervals (10). All current content uniformity tests, whether non-parametric or parametric, use a two tier approach with fixed numbers of units allowed for testing in each tier. If results are sufficiently positive in the first stage (tier) of testing, then the study stops. If insufficiently positive, the study may continue to the second stage. In the language of clinical trials, the initial tiers of multiple-tier testing are interim analyses. When two tiers are used, the calculation of the actual type I (false positive) error rate for the full two-tier design needs to take into account both tiers. For example, a 5% test at each tier will have a combined type I error rate exceeding 5% (11). For nonparametric tolerance intervals, the method of Simon (12) can be adopted for two-tier designs. Hauck and Shaikh (13) developed a method for parametric tolerance intervals and designs of one or more tiers.

Current approaches for dissolution testing data analysis

Acceptance criteria for the dissolution procedure can either be a limit (the Q value) or a range (upper and lower percent dissolved at a specified time). Although acceptance criteria may be based on an *in vitro–in vivo* correlation (14), setting acceptance criteria frequently lacks a formal approach for most dosage forms (15). USP and other pharmacopeas currently mostly use nonparametric approach for both content uniformity and dissolution testing. For content uniformity testing, Katori et al. (1) proposed replacing the current USP approach (test by attributes) with a parametric approach (test by variables), using a tolerance interval (16). Moving from a nonparametric to a parametric approach depends in part on whether a specific distribution, such as the normal, can be assumed. The normal distribution can be a reasonable assumption for content uniformity testing but not necessarily for dissolution testing. Normal distribution of dissolution data may be unlikely due to the boundary of 100% dissolved—with values sometimes greater than 100% given variability in assay and content. The 100% boundary forces non-symmetry and hence non-normality of distribution. Although data transformation may help, one solution to this issue would be to choose the time at which dissolution is measured to achieve values that are acceptably below 100%. In contrast to use of a parametric tolerance interval approach for content uniformity testing, Katori *et al.* (17) proposed a parametric confidence interval approach for dissolution testing (Table I). Both confidence and tolerance intervals estimate the characteristics of a distribution. Confidence intervals assess the precision of

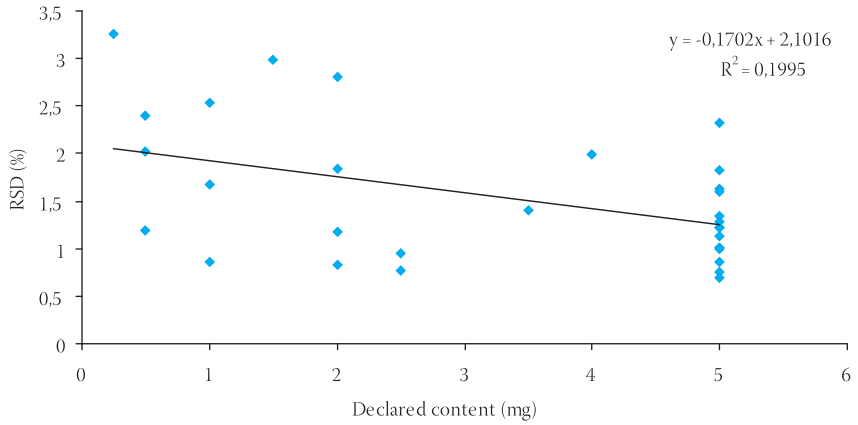

FIGURE 3. Relation between declared content of different tablets (mg) and RSD of content uniformity (30 lots)

estimates of single quantity (e.g., mean, variance). For example, a 95% confidence interval for a mean consists of all values within ±2 standard errors of the estimated mean; the more precise the estimate, the narrower the confidence interval. In contrast, tolerance intervals describe ranges of specified coverage for a distribution of values (16); for example, at least 80% of dissolution values for a product fall within a specified range with some specified level of confidence. A choice between the two approaches is based on what quantity (or quantities) best characterizes the distribution for the problem of interest. Characterizing the distribution solely by the mean and its confidence interval is insufficient—they are essentially uninformative as to the width of the distribution. In order to consider variability as well, standard deviation controls could be established.

Materials and Methods

Materials

For this study, ropinirole hydrochloride tablets were used; labels claim 0,25; 0,5; 1; 2 and 5 mg, respectively.

Methods

Content uniformity analysis

For each individual lot, 10 units were sampled. Measurements were done by the individual manufacturer. The assay methods used were HPLC and UV absorption. The mean and SD of drug content, formulation weight and concentration of active ingredient (w/w%) were calculated for each group of 10 units in a single lot.

Units were weighed and assayed in succession. The concentration of the active ingredient was calculated by dividing drug content by formulation weight that included the weight of coating.

Dissolution profile analysis

For each individual lot, 6 units were sampled. Dissolution samples were collected for analysis and re-

Labeled strength (mg)	RSD	$\overline{X}$ (% of declared content) (n=10)	Assay method	Lot
0,25	3,26	100,4	HPLC	1
0,5	2,40	98,25	HPLC	2
0,5	2,02	98,36	HPLC	3
0,5	1,19	99,65	HPLC	4
1	0,86	99,07	HPLC	5
1	2,54	94,42	HPLC	6
1	1,68	102,8	HPLC	7
1,5	2,98	98,38	UV-242	8
2	1,18	98,87	HPLC	9
2	2,80	99,95	HPLC	10
2	0,83	104,5	UV-368	11
2	1,84	96,70	UV-284	12
2,5	0,77	100,73	HPLC	13
2,5	0,95	100,22	HPLC	14
3,5	1,41	101,44	UV-300	15
4	1,99	100,4	HPLC	16
5	0,75	98,30	HPLC	17
5	1,63	99,71	UV-300	18
5	1,01	100,52	D1-250	19
5	2,32	100,84	HPLC	20
5	1,22	102,29	HPLC	21
5	1,13	99,92	UV-276	22
5	1,28	101,07	HPLC	23
5	1,60	98,64	D1-281	24
5	1,00	99,60	HPLC	25
5	0,86	105,12	UV-300	26
5	1,34	102,12	UV-300	27
5	0,69	103,02	UV-300	28
5	1,22	100,61	HPLC	29
5	1,83	102,64	UV-284	30

TABLE 1. Content uniformity of different tablets (30 lots), labeled strength 0,25; 0,5; 1; 2 and 5 mg, (different assay techniques applied, HPLC, UV-D1 or UV) expressed as % of the declared content

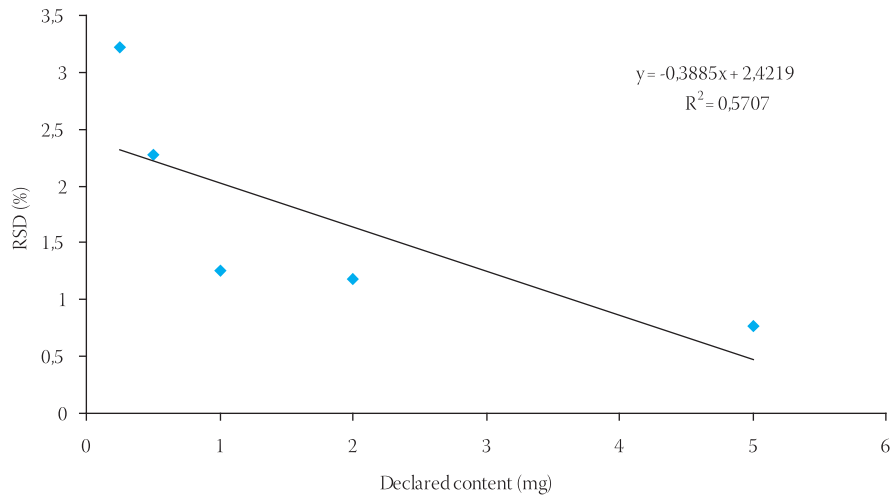

FIGURE 4. Relation between declared content of ropinirole hydrochloride (mg) for five different label strengths and RSD of content uniformity

placed with an equal volume of fresh dissolution fluid to maintain a constant total volume. The assay methods used were HPLC and UV absorption.

Results and Discussion

The content and dissolution testing values are accessible only through chemical analysis subject to measurement errors. As the purpose is to calculate tolerance interval for the true active content, the standard deviation and relative standard deviation should stand for the variability of the dosage units. In the measurements, however, there are two sources of variation: variability of the dosage units (non-homogeneity) and the measurement (analytical) error.

Relationship between labeled strength and content uniformity

The results of our content uniformity analysis of different tablets (30 lots), labeled strength 0,25; 0,5; 1; 2 and 5 mg are summarized in Table 1 and Figure 3. The results of content uniformity analysis of ropinirole hydrochloride tablets (1 lot, 5 different label strengths, HPLC assay method) are summarized in Table 2 and Figure 2.

Labeled strength (mg)	RSD	$\overline{X}$ (% of declared content) (n=10)	Assay method
0,25	3,22	100,36	HPLC
0,5	2,28	99,28	HPLC
1	1,26	99,17	HPLC
2	1,18	98,71	HPLC
5	0,77	98,2	HPLC

TABLE 2. Content uniformity of ropinirole hydrochloride for five different label claims expressed as % of declared content

Relationship between labeled strength and percent of drug dissolved

The results of our dissolution test analysis of ropinirole hydrochloride tablets (60 lots) are summarized in Table 3 and Figure 5.

Labeled strength (mg)	RSD	$\overline{X}$ (% of declared content) (n=10)	Assay method	Lot
0,5	1,56	86,89	HPLC	1
0,5	4,69	92,27	HPLC	2
1	5,33	95,54	HPLC	3
1	1,42	99,26	HPLC	4
1,25	2,74	101,9	HPLC	5
1,5	3,98	95,11	UV-585	6
1,5	3,43	95,15	D2-239	7
2	2,19	92,4	HPLC	8
2	2,72	105,06	UV-242	9
2,5	2,56	93,23	HPLC	10
2,5	4,05	96,77	UV-580	11
2,5	2,58	91,97	HPLC	12
2,5	3,07	86,39	HPLC	13
2,5	0,58	98,76	HPLC	14
2,5	2,16	99,94	UV-580	15
2,5	2,82	97,57	HPLC	16
2,5	3,35	98,94	HPLC	17
2,5	1,99	86,86	HPLC	18
3	1,33	88,72	D2-241	19
3	3,87	102,11	UV-270	20
3	1,38	95,84	HPLC	21
3	3,92	95,42	D2-239	22
3,125	2,15	98,27	UV-285	23
3,125	2,92	93,63	UV-285	24
3,5	0,74	97,59	HPLC	25
3,5	1	94,4	HPLC	26
4	2,72	93,51	UV-284	27
4	3,19	97,84	HPLC	28
4	2,45	97,87	UV-310	29

4	1,16	100,33	UV-284	30
5	1,26	95,71	D1-250	31
5	1,42	101,82	HPLC	32
5	0,88	96,02	HPLC	33
5	1,5	92,62	D1-250	34
5	1,63	98,97	UV-286	35
5	0,52	91,99	UV-280	36
5	2,76	94,04	UV-360	37
5	0,86	98,27	UV-255	38
5	3,2	93,97	HPLC	39
5	0,69	82,05	UV-227	40
5	0,68	103,72	UV-363	41
5	0,29	99,24	UV-363	42
5	2,63	91,13	HPLC	43
5	1,27	100,9	HPLC	44
5	1,82	102,48	UV-280	45
5	3,2	97,36	D1-250	46
5	3,22	96,29	HPLC	47
5	2,81	90,97	HPLC	48
5	1,48	100,28	UV-307	49
5	2,72	98,8	HPLC	50
5	0,97	101,54	HPLC	51
5	2,1	100,28	HPLC	52
5	2,77	100,29	UV-242	53
5	3,93	92,47	UV-280	54
5	4,03	101,35	UV-237	55
5	2,27	97,67	UV-280	56
5	3,18	101,65	HPLC	57
5	3,48	93,39	UV-237	58
5	1,93	100,07	UV-295	59
5	1,44	96,05	UV-366	60

TABLE 3. Dissolution test analysis of different tablets (60 lots), labeled strength 0,25; 0,5; 1; 2 and 5 mg, (different assay techniques applied, HPLC, UV-D1 or UV) expressed as % of drug dissolved

The results for dissolution testing of ropinirole hydrochloride tablets (1 lot, 5 different label strengths, HPLC assay method) are summarized in Table 4 and Figure 6.

Labeled strength (mg)	RSD	$\overline{X}$ (% of drug dissolved) (n=6)	Assay method
0,25	2,8	100,22	HPLC
0,5	2,71	98,14	HPLC
1	1,85	99,21	HPLC
2	1,23	99,04	HPLC
5	0,96	96,74	HPLC

TABLE 4. Percent of dissolved ropinirole hydrochloride from tablets for five different label strengths

The content uniformity and dissolution testing of a formulation is represented by intra-lot variation (RSD). In this case RSD tended to increase with the decrease of the labeled strength. It is obvious from the R^2 value, as well. On the other side, if we take into consideration larger number of lots, analyzed by different assay methods and different sample preparation procedures this correlation is less pronounced. This can be the consequence of different assay techniques applied, HPLC, UV-D1 or UV.

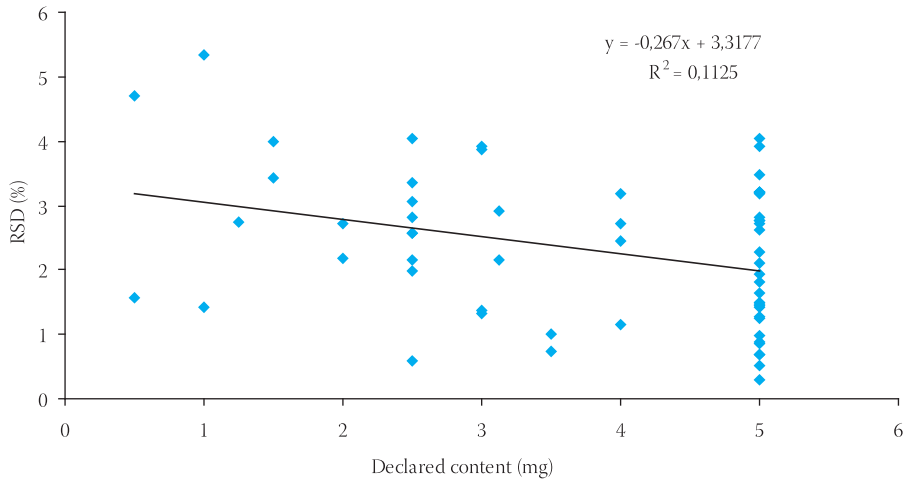

FIGURE 5. Relation between declared content of different tablets (mg) and RSD of drug dissolved (60 lots)

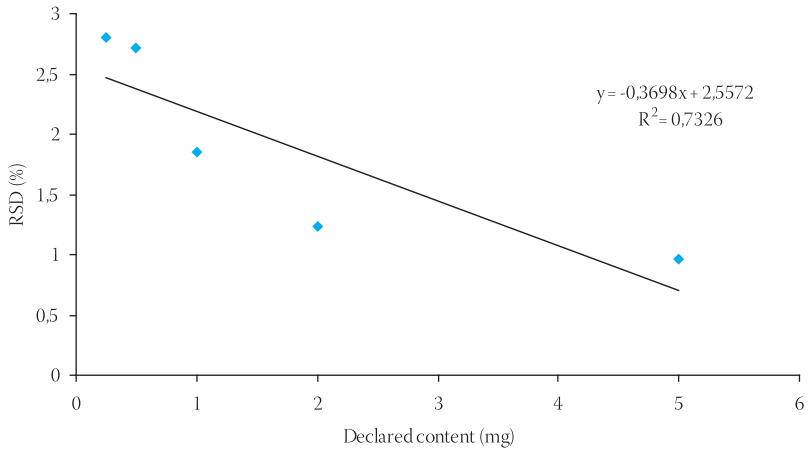

FIGURE 6. Relation between declared content of ropinirole hydrochloride (mg) for five different label strengths and RSD of drug dissolved

Conclusion

- According to the results obtained, we may conclude that the analyzed ropinirole hydrochloride tablets from satisfied pharmacopeial requirements concerning content uniformity and dissolution testing
- In this case, RSD tended to increase with the decrease of the labeled strength. It is obvious from the R^2 value, as well.
- On the other side, if we take into consideration larger number of lots, analyzed by different assay methods and different sample preparation procedures this correlation is less pronounced. This can be the consequence of different assay techniques applied, HPLC, UV-D1 or UV.

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