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Evaluation of the Compliance of Ultra-Low Dose Drugs Available in Local Iraqi Markets with Regulatory Weight Variation Test

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ORIGINAL STUDY

Evaluation of the Compliance of Ultra-Low Dose Drugs Available in Local Iraqi Markets with Regulatory Weight Variation Test

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ABSTRACT

Mixing and formulation of drugs with very low dose is a brutal challenge to formulators sometimes due to all kinds of difficulties like segregation, content uniformity and physicochemical stability issues. A careful consideration of all related factors is essential during manufacturing of very low dose drug products.

The aim of this study is to evaluate the quality control of ultra-low dose drugs of different companies available in local Iraqi and their compliance with regulatory weight variation test.

Quantitative analysis conducted to five drugs using weight variation technique with 20 randomly selected tablets for each drug. All of these drugs passed the test.

The variations amongst the tablet weights can be attributed to factors like the powder flowing properties, tableting machine speed, compression force and pressure and the type of machinery used for tableting process. These factors can affect tablet weight. However, the most important two causes of weight variation are differences in bulk densities of powder mixture ingredients and particle size distribution in tablet compression.

Further investigation is required to assess the content of these drugs using content uniformity technique with UV spectrophotometer.

Keywords: Weight variation test, Ultra-low dose drugs, Quality control

1. Introduction

Pharmaceutical research was able among many achievements has produced very potent drugs, since they require extra effort during formulation and production if used to produce solid oral dosage forms complying with the required homogeneity and physical stability standards. Since such drugs with narrow T.I. (therapeutic window) if allowed to have small change in drug content (in μg or mg) will alter the therapeutic range of drugs resulting in either underdose or overdose, both of which are harmful for patients. For example; a patient with congestive heart failure (CHF) on digoxin; underdose causes therapeutic failure of drug and death from cardiac failure while overdose causes toxicity and death due to arrhythmia [1].

The general public is not expected to be able to safely measure an accurate dose of a drug from a bulk material due to the high potency and low dose of most drug currently in use nowadays.

Since many drugs are used in milligram quantities or even less, since these quantities are way too low to be weighed by a sensitive prescription or electronic analytical balances only. An easy example is that if a 325 mg of aspirin can't be obtained from a bulk container of pure drug powder accurately by a patient, and if that was not possible, how could the dose of drugs that compared to the dose of aspirin, the dose of aspirin looks ginormous [2]. For example,

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- The dose of **ethinyl estradiol/gestodene** are 0.03 mg and 0.075 mg respectively, more than ten thousand ethinyl estradiol tablets, each containing 0.03 mg of drug, could be made from the amount of aspirin in just one tablet.
- For 0.25 mg **Digoxin**, more than one thousand digoxin tablets could be made from the amount of aspirin in just one tablet.
- For 0.5 mg **Dexamethasone**, six hundred dexamethasone tablets could be made from the amount of aspirin in just one tablet.
- For 0.05 mg **Levothyroxine**, six thousand and five hundred Levothyroxine tablets could be made from the amount of aspirin in just one tablet.
- For 0.4 mg **Folic acid**, seven hundred and fifty folic acid tablets could be made from the amount of aspirin in just one tablet.

When the dose of the drug is that low as with the few drugs mentioned before, tablets and capsules must be formulated with fillers or diluents so that the tablet or capsule weight is high enough to be picked up with fingertips [3]. Assuring the dose accuracy of such powder blend is a very important quality assurance hurdle.

1.1. Consequences of inaccurate dose

Inaccurate dose leads a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient, either by not achieving minimum effective concentration (MEC) or going over the minimum toxic concentration (MTC). In both situations the desired patient's outcomes will be altered.

The dose of active ingredient should be adjusted to right dose precisely especially low dose drugs because some specific drugs could have few effects rather than just one exquisite effect, depending on what was the used dose. A glaring example can be found in barbiturates where a low dose does cause sedation, but higher doses cause hypnotic effects. The usual dosage range is the range of amounts of a drug that can be prescribed safely within medical practice. Outside of this dosage range can produce either underdosage or overdosage. Such an issue can be even more complicated in the case of ultra-low dose drug [4].

- Digoxin
  Overdose of digoxin causes GIT side effects initially and neurological symptoms. Eventually It will cause life-threatening arrhythmias.
- Dexamethasone
  Overdoses of dexamethasone or corticosteroids in general may not be life-threatening but their use on the long-term may result in skin thinning with easy bruising, body fat redistribution, flaring up of acne or unexpected growth of facial hair, irregularities in menstruation, erectile dysfunction, or libido loss.
- Folic acid
  Overdosing of folic acid is quite hard since it's a highly water-soluble compound with very high elimination rate that prevent any significant toxicity by it.
- Levothyroxine
  Overdose cause elevated thyroid hormone and then lead to sympathetic overstimulation. Common presenting symptoms include tachycardia, hypertension, fever, hyperglycemia, irritability, and finally seizures.
- Ethinyl estradiol/Gestodene
  Possible symptoms of COC overdose include breast tenderness, change in the color of urine, sedation, emotional changes, nausea, vomiting and headaches.

1.2. Quality control

The concept of total energy quality control refers to denotes a comprehensive, company-wide quality management paradigm aimed at the consistent manufacture of defect-free pharmaceutical products. This methodology employs a preventive, process-integrated approach wherein every stage of production is scrutinized and optimized to minimize variability and eliminate deviations. Although the Quality Assurance unit holds primary accountability for product conformity, effective quality control mandates cross-functional collaboration across production, engineering, regulatory compliance, and analytical services. Its efficacy hinges on a synchronized, systems-based implementation strategy. the standard quality controls tests that can be used for solid dosage direct compression tablets are:

- In-Process Weight Uniformity Checks: Periodic sampling and gravimetric analysis to ensure compliance with pharmacopeial tablet weight variation criteria.
- Mechanical Integrity Testing: Evaluation of tablet hardness (crushing strength), friability, and mechanical resilience at defined intervals (e.g., start-up, steady-state, and termination phases of batch production).
- Disintegration and Dissolution Profiling: Determination of disintegration times and dissolution rates per USP/EP specifications to verify bioavailability parameters.
- Solubility Assessment for Effervescent/Soluble Tablets: Testing to confirm compliance with dissolution time thresholds specific to soluble formulations.

- Automated and Manual Visual Inspection: Implementation of line inspection protocols or validated automated systems to identify and reject nonconforming units prior to secondary packaging operations [5].

1.3. Weight variation test

With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measured to help ensure that a tablet contains the proper amount of drug.

Per the United States Pharmacopeia and National Formulary, the acceptable weight variation for uncoated tablets is defined as a percentage deviation from the mean tablet weight. The test involves individually weighing 20 dosage units, computing the average, and determining each tablet's deviation from this mean. A batch complies with the USP criteria if not more than two tablets deviate beyond the specified percentage limit, and none exceed twice that limit.

The weight variation test alone is clearly not sufficient to assure uniform potency of tablets of moderate- or low-dose drugs, in which, excipients make up the bulk of the tablet weight, but it will give us a clue if there were defects in manufacturing process, which eventually leads to nonuniformity [6].

1.4. Content uniformity test

In tablets with smaller dosages, a good weight variation does not ensure good content uniformity, but a large weight variation precludes good content uniformity. To ensure dose uniformity in low-strength active pharmaceutical ingredient formulations, this test is employed.

Since content uniformity tests were beyond the current research's objective as shown in the title, it's worth mentioning that the next natural step in further proofing that these tablets do indeed has the right amounts of active ingredients in them. Tablets which passed the weight variation test will be forwarded to content uniformity tests at different research planned in the not-too-distant future hopefully.

In evaluating a particular lot of tablets, several samples of tablets should be taken from various parts of the production run to satisfy statistical procedures [7].

1.5. Criteria for selection of drugs in the study

Five drugs have been selected to be included in the study that all

- Have a dose of less than 1 mg.
- Available and commonly used in Iraqi pharmacies.
- Available as conventional tablets (non-coated)

2. Materials and methods

2.1. Materials

- Twenty random tablets of each of the drugs in Table 2.
- NewClassic ML laboratory balance from the analytical laboratory instrument manufacturing company, Mettler Toledo (Fig. 1).

Fig. 1. NewClassic ML laboratory balance.

2.2. Methods

- Weight variation test

Twenty tablets were taken from their aluminum foil sheets of each drug and the weight of each tablet was measured separately by NewClassic ML balance. The

mean weight then was measured and the weight variation tolerances of USP (Table 1) was used to measure the accepted percentage of variation. The weights of each tablet were compared with the error percentage to determine the compliance of the companies with the quality standards.

Table 1. Weight variation tolerances for uncoated tablets.

Average Weight of Tablets (mg)	Maximum Percentage Difference Allowed
130 or less	10
130–324	7.5
More than 324	5

3. Results

3.1. Digoxin

Digoxin			
#	Weight	#	Weight
1	147 mg	11	148 mg
2	144 mg	12	146 mg
3	141 mg	13	148 mg
4	144 mg	14	144 mg
5	147 mg	15	148 mg
6	148 mg	16	145 mg
7	141 mg	17	145 mg
8	145 mg	18	148 mg
9	145 mg	19	149 mg
10	150 mg	20	149 mg
		Total	2922 mg

Average weight $= 2922/20 = 146.1$ mg

$$\text{Upper limit} = \text{Average wt.} + (\text{Average} * \text{Error\%}) = 146 + (146 * 7.5\%) = \mathbf{157\ mg}$$

$$\text{Lower limit} = \text{Average wt.} - (\text{Average} * \text{Error\%}) = 146 - (146 * 7.5\%) = \mathbf{135\ mg}$$

All tablets were within the accepted range and no tablet was outside the range. The test batch passes the test criteria.

3.2. Dexamethasone

Dexamethasone			
#	Weight	#	Weight
1	104	11	104
2	104	12	105
3	102	13	104
4	107	14	104
5	105	15	101
6	110	16	103
7	107	17	106
8	106	18	109
9	111	19	106
10	106	20	103
		Total	2107 mg

Average weight $= 2107/20 = 105.4$ mg

$$\text{Upper limit} = \text{Average wt.} + (\text{Average} * \text{Error\%}) = 105 + (105 * 10\%) = \mathbf{116\ mg}$$

$$\text{Lower limit} = \text{Average wt.} - (\text{Average} * \text{Error\%}) = 105 - (105 * 10\%) = \mathbf{94\ mg}$$

All tablets were within the accepted range and no tablet was outside the range. The test batch passes the test criteria.

3.3. Folic acid

Folic Acid			
#	Weight	#	Weight
1	76	11	78
2	75	12	77
3	78	13	76
4	79	14	76
5	78	15	75
6	73	16	79
7	78	17	80
8	79	18	79
9	77	19	79
10	71	20	77
		Total	1540 mg

Table 2. Drugs used in this study.

#	Drugs		Manufacturing Company	Dose	Batch No.
	Scientific	Trade			
1	Digoxin	Digoxin	Accord	250 mcg	DG408
2	Dexamethasone	Dexon	SDI	500 mcg	B.XTOK019
3	Folic acid	Folic acid	Flamingo	500 mcg	18183
4	Levothyroxine	Euthyrox	Merck Sharp & Dohme (MSD)	25 mcg	G01688X
5	Ethinyl estradiol/Gestodene	Katya 30/75	Stragen UK	30 mcg, 75 mcg	A7823

Average weight = 1540/20 = 77 mg

Upper limit = Average wt. + (Average * Error%)

= 77 + (77 * 10) = **85 mg**

Lower limit = Average wt. − (Average * Error%)

= 77 − (77 * 10) = **65 mg**

All tablets were within the accepted range and no tablet was outside the range. The test batch passes the test criteria.

3.4. Levothyroxin

Euthyrox			
#	Weight	#	Weight
1	100	11	100
2	100	12	103
3	99	13	100
4	101	14	101
5	102	1533	101
6	101	16	100
7	100	17	99
8	99	18	101
9	99	19	101
10	103	20	101
		Total	2011 mg

Average weight = 2011/20 = 100.6 mg

Upper limit = Average wt. + (Average * Error%)

= 100.6 + (100.6 * 10%) = **111 mg**

Lower limit = Average wt. − (Average * Error%)

= 100.6 − (100.6 * 10%) = **90 mg**

All tablets were within the accepted range and no tablet was outside the range. The test batch passes the test criteria.

3.5. Ethinyl estradiol/gestodene

Ethinyl estradiol/Gestodene			
#	Weight	#	Weight
1	89	11	89
2	91	12	93
3	86	13	95
4	85	14	83
5	85	15	81
6	96	16	96
7	83	17	88
8	**98**	18	81
9	84	19	85
10	83	20	91
		Total	1762 mg

Average weight = 1762/20 = 88.1 mg

Upper limit = Average wt. + (Average * Error%)

= 88.1 + (88.1 * 10%) = **97 mg**

Lower limit = Average wt. − (Average * Error%)

= 88.1 − (88.1 * 10%) = **79 mg**

Nineteen tablets were within the accepted range and one tablet was outside the range. The test batch passes the test criteria.

4. Discussion

The result of the weight variation tests done to the tablets show that, with the consideration of the acceptable limits of error, not all tablets under study were compliant with the test limit. All five batches of the remaining drugs were within the accepted range except Ethinyl estradiol tablets that had one tablet outside of the accepted range (but still within the double accepted range limit); So, they all passed the weight variation test requirements.

5. Conclusion

Weight uniformity test with all of its simplicity and low time and cost requirement, can be utilized to avoid using the more intensive content uniformity test. All of the tested ultra-low dose tablets passed the test with results that can successfully run through even stricter regimes (lower margin of acceptable error). These are considered satisfactorily and comforting the concerned health practitioner to a certain extent. Frequent inspection of the tablet batches for these kinds of drugs is always recommended and currently assuming that all tablets being marketed in the local Iraqi market can definitely pass weight variation test is not justified as more and more examples need to be selected and studied and the successful ones should head to content uniformity test as the ultimate proof of dose uniformity.

References

1. V. Kukkar, V. Anand, M. Kataria, M. Gera, and P. K Choudhury, “Mixing and formulation of low dose drugs: underlying problems and solutions,” *Thai J Pharm Sci*, vol. 32, no. 3-4, pp. 43–58, Dec 31 2008.
2. M. Hacker, W. S Messer, and K. A Bachmann, *Pharmacology: Principles and Practice*. Academic Press, Jun 19 2009.
3. A. J Winfield, “Oral unit dosage forms,” *Pharmacy Practice: Pharmacy Practice E-Book*, vol. 127, Jul 24 2019.
4. P. N Patsalos, D. J Berry, B. F Bourgeois, J. C Cloyd, T. A Glauser, S. I Johannessen, I. E Leppik, T. Tomson, and E. Perucca, “Antiepileptic drugs—best practice guidelines for

therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE commission on therapeutic strategies," *Epilepsia*, vol. 49, no. 7, pp. 1239–76, Jul 2008.

5. A. Mitra, *Fundamentals of quality control and improvement*. John Wiley & Sons; May 2 2016.
6. T. A Basher and E. J Al-Akkam, "Formulation and in-vitro evaluation of itraconazole floating microparticles," *Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512)*, vol. 29, no. 1, pp. 236–46, Jun 25 2020.
7. M. M Abdel Hamid, M. A Elnabrawi, F. K Alanazi, M. I Mohamed, and A. A Sakr, "Content uniformity testing: suitability of different approaches for marketed low dose tablets," *Pharmaceutical Development and Technology*, vol. 18, no. 6, pp. 1277–87, Dec 1 2013.