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ORIGINAL ARTICLE

Formulation and Assessment of Clomifene Citrate Tablet by Direct Compression Method

Fatima Qamar[1,*], Safila Naveed[1], Samina Alam[1], Fouzia Hamid[1], Ghulam Sarwar[1], M. Tanweer Alam[3], Khan Usmanghani[1], Syeda Zainab[2], Muhammad Ibrar Shinwari[3]

[1]*Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan*

[2]*Faculty of Pharmacy, University of Karachi, Karachi, Pakistan*

[3]*Department of Environmental Sciences, Faculty of Basic & Applied Sciences, International Islamic University, Islamabad, Pakistan*

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Address of Correspondence Author:
fatimamudassar2009@hotmail.com

ABSTRACT

The problem of Infertility is developing in western societies and also in eastern societies, some researches have examined the utilization of drug for widespread treatments of infertility. Clomifene citrate is the first-line management intended for norm gonadotropic females with absent or asymmetrical ovulation. The objective of this study was to manufacture and analyze the clomifene citrate 50mg tablet by direct compression method. The manufacturing formula contain the material Clomifene citrate, lactose anhydrous, Silicon dioxide, MCC ph 102, Cross Carmellose Sodium, Primogel, Talcum, PVK-30 and Magnesium Stearate. After mixing these active and inactive ingredients, tablets were manufactured by direct compression method. We evaluated the formulation by pharmacopeial and non pharmacopeial methods such as hardness, thickness, friability, disintegration test, weight variation test, content uniformity and assay. The results were found satisfactory. The individual weights, average weights, thickness, disintegration tablets met the limits specified in BP and USP. Hardness, friability, assay and content uniformity also met the specified limits.

INTRODUCTION

Clomifene citrate is a combination of the (*E*)-and (*Z*)-isomers of 2-[4-(2-chloro-1,2-diphenylethenyl) phenoxy]-*N*, *N*-di ethyl ethanamine dihydrogen citrate (Figure **1**) and is used for sub fertility associated with oligo ovulation by rising the production and discharge of FSH within the women [1-3]. It is also indicated in Oligo amenorrhea [4] and sub fertility in man [5]. As described under the UK guiding principle, National Institute of Clinical Excellence NICE in 2004 in addition to course of action of Dutch Society of Obstetrics and Gynecology NVOG, clomifene citrate is given to females with missing or lopsided ovulation WHO class II of an ovulation, it is an anti-estrogenic amalgamated that links with the estrogen receptors contained by the hypothalamus besides the pituitary gland. As upshot, FSH formation inside the pituitary gland is encouraged; this elevates FSH inside the blood which stimulates the intensification of follicles as well as ovulation. Normally clomifene citrate is prescribed as a 50mg tablet by the oral route of administration for 5 days in the earlier stage, the treatment extent is equal to 12 months of Clomifene citrate and recommended on a daily basis as 50-100mg and 250mg on a daily

basis in North America. In women, it is commonly use to improve fertility, even though in these females the standard dosage amount barely exceeds 100mg. Oral route of administration of clomifene citrate is much cheaper compared through injected alternatives (i.e. gonadotrophins) [16]. Literature assessment reveals many of its analysis by HPLC [7, 8, 9], MS [10,11], IR [12]. Clomifene citrate as tablet dosage form have been manufactured by three methods including dry granulation, wet granulation and direct compression and they are applied as per their requirement [13,14]. The direct compression being economical, flow ability and a low tendency to stick to the punches [15]. Direct compression is a method by which tablets are compacted directly in amalgamation of the active drug and non-active parts of formulation, without any preliminary treatment. A simple formula is considered to be composed of an active ingredient, diluents and lubricants. The molecular weight and chemical structure is $C_{26}H_{28}ClNO$, $C_6H_8O_7$, 598.1 in BP, 2013.

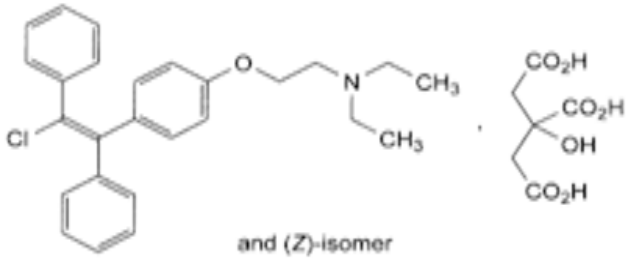

Figure 1. Chemical structure of clomifene citrate.

METHODOLOGY

The methodology involved manufacturing and analysis of new formulation.

Direct compression

The manufacturing of clomifene citrate involves the direct compression method. The expression “direct compression” is definite as the course of action in which tablets are compacted from blend of powder of active pharmaceutical ingredients and appropriate non-active material. Pretreatment of the powder blend is not required as needed for wet and dry granulation procedure in the process of tableting [17].

Weight variation test

Weight variation test is performed to check the uniformity of weight of all the tablets and all the tablets should be within their limits of BP/USP requirements which specify that not more than two tablets from the 20 tablets should be deviate ±7.5 %.

Thickness test

Thickness test includes average, standard deviation, upper and lower limits of tablet thickness are in conformity through BP/USP.

Hardness test

Hardness test tablets include the cracking of tablets by applying the force as per guidelines specified in BP/USP the authorized range of hardness declared in BP/USP is not less than 4.00 Kg of pressure is obligatory to crack a tablet.

Friability test

It is proposed to establish, under defined circumstance the friability of uncoated tablets, the incident where by tablet surfaces are scratched and/or show proof of lamination or else breakage while subjected to motorized shock or attrition. (British Pharmacopoeia 2000). According to the BP/USP standards Friability of all tablets should be less than 1%.

Disintegration test

The following factors can influence disintegration time of a tablet, the type of granulating agent, diluents, use of water repulsive lubricant, kind as well as quantity of disintegrating agent, the strength used to compress or compact the tablet. The official limits in BP/USP for uncoated tablets be not more than 15 minutes.

Pharmaceutical assay

By using spectrophotometer along with particular wavelength, we performed and record the absorbance of sample and standard.

Materials

Clomifene citrate, lactose anhydrous, Silicon dioxide, MCC ph 102, Cross Carmellose Sodium, Primogel, Talcum, PVK-30 and Magnesium Stearate were used.

Methods

Manufacturing Method of Clomifene Citrate Tablets

The formulation of clomifene citrate tablet was prepared through direct compression process. It involves the procedure in which the mixture of Clomefene citrate, lactose anhydrous, Silicon dioxide, MCC ph 102, Cross Carmellose Sodium, Primogel, Talcum, PVK-30 and Magnesium Stearate were thoroughly mixed for 10 minutes and then this mixture was passed through sieve #16 into blender and again mixed for 30 minutes then the granules were analyzed by pharmacopeal and non pharmacopeal method and then tablets were compressed by single punch tablet machine.

Analysis of Clomifene Citrate Tablets

White round biconvex shaped tablets were evaluated by various physical testing which include the hardness test in which 20 tablets were used to evaluate the hardness or the crushing of tablet by hardness tester, the thickness test was performed by vernier caliper by taking 20 tablets thickness and diameter. Weight variation test was performed by obtaining the individual weight of the 20 tablets and calculate the average weight of the batch size, friability test was performed for checking abrasion, for this purpose 20 tablets were placed in friability apparatus and calculation of weights before and after placing in friability apparatus was done. Disintegration test was performed in a disintegration apparatus by following the procedure as describe in BP and USP, assay and content uniformity test was performed by using UV spectrophotometer.

RESULTS

Direct compression is a procedure in which tablets are compacted from powder of API in addition to suitable excipients. There is no need for the pretreatment of the powder blend as required for wet or dry granulation procedure [17]. Tablet manufacturing involves variety of processing stages including procedures where particles are processed with the objective of optimizing their properties. This needs certain features related to the powder such as little tendency of segregation, excellent flowability and compatibility. A quite inexpensive technique in manufacturing of tablets described in various literatures is a direct compression method [18]. Intend of this study was to produce and develop the manufacturing procedure of the clomifene citrate 50mg tablet by direct compression method using different non active materials like anhydrous lactose, Silicon in dioxide, MCC with pH 102, Cross Carmel lose Sodium, Primogel, Talcum, PVK-30 and Magnesium Stearate by calculating their percentage composition, quantity and parameters as described in Table **2** and **3**. The formulation of clomifene citrate tablet was prepared by direct compression process in which the mixture of Clomifene citrate, lactose anhydrous, Silicon dioxide, MCC ph 102, Cross Carmellose Sodium, Primogel, Talcum, PVK-30 and Magnesium Stearate were thoroughly mixed for 10 minutes and then this mixture was passed through sieve#16 into blender and again mixed for 30 minutes. For the analysis of granules, test called percent potency test was performed. Standard of Clomifene citrate BP was purchased and its Potency was 99.34%. Standard solution was prepared by dissolving weigh quantity of 25mg of clomifene citrate in methanol in the 50ml volumetric flask. For sample preparation we added the average tablet weight of clomifene citrate 50mg tablet in the 50ml volumetric flask (average weight of tablet in mg 180) dissolved in

methanol and make up the volume with methanol now 1ml taken from this solution in 50ml volumetric flask along with make up the volume through methanol again and by mixing it with properly the absorbance was noted at 233 nm according to this method we obtain the two samples results which was 105.54% and 107.47% (Table **1**). After compression of all tablets the average weight of 20 tablets were found by weighing balance. For this purpose, we collected the random sample tablets and weighed and the average weight of tablet calculated was 180.97mg / tablet (+7.5% = 194.54, -7.5% = 167.39) and hardness test was performed by hardness tester. The tablets comply BP and USP limit which is NLT 4Kg the average hardness of 20 tablets was (8.05 kg). The disintegration test was performed by disintegration tester and it complies the limit as prescribed in BP and USP, that is not more than 15 minutes the average disintegration time of tablet was (7 minutes). The thickness of the tablet was performed on vernier caliper in millimeters, average thickness of the tablet was (4.06 mm). The friability test complies the limit as prescribed in BP and USP, that is not more than 1%. Friability according to the formula was calculated 0.179% The content uniformity test was performed by weighing the standard 26.8mg of clomifene citrate in 50ml volumetric flask. 2ml was taken from the standard solution and transfer it to the 50ml volumetric flask and make up the volume with methanol. The absorbance was noted at 233 nm and for the sample preparation we taken 1 tablet in a 50ml volumetric flask and dissolve it with methanol now 2ml was taken from this solution in 50ml volumetric flask along with composition the volume by methanol by this procedure we prepared 10 individual dilution for 10 individual tablets and absorbance was noted by comparing both standard and samples, the results were satisfactory and within the limits as described in BP and USP.

DISCUSSION

The purpose of the study was to develop and evaluate the clomifene citrate 50mg tablet by direct compression method. The results were found to be satisfactory. The individual weights, weight variation test, thickness, disintegration, hardness, friability of tablets met the limits specified in BP and USP, assay as well as the content uniformity also met the specified limits (85%-115%). The results of the present study shows that direct compression is a conventional competent method used. This method can be frequently used (Table **4**).

Tabular and Graphical Representation of Data

Table 1. Percentage assay of granules of Clomifene citrate 50 mg tablet.

S. No.	Percent Assay
Sample 1 (Granules)	105.54
Sample 2 (Granules)	107.47

Table 2. Percentages in content uniformity test of Clomifene citrate 50 mg tablet.

S. No.	Percent in Content Uniformity Test
Sample1 (Tablet)	99.24
Sample 2 (Tablet)	99.56
Sample 3 (Tablet)	100.83
Sample 4 (Tablet)	99.56
Sample 5 (Tablet)	100.68
Sample 6 (Tablet)	97.71
Sample 7 (Tablet)	100.83
Sample 8 (Tablet)	100.68
Sample 9 (Tablet)	99.24
Sample 10 (Tablet)	99.56

Table 3. Composition of Clomifene citrate 50 mg tablet.

S. No.	Material
1	Clomifene citrate
2	Lactose Anhydrous
3	Silicon dioxide
4	Microcrystalline cellulose PH102
5	Cross, Carmellose Sodium
6	Primogel
7	Talcum
8	Magnesium stearate
	Total

Table 4. Evaluation of Clomifene citrate 50 mg tablet by different parameters.

Parameters	Evaluation of New Formulation
Thickness (mm) (n=20)	4.06 mm
Hardness (kg) (n=20)	8.05kg
Weight (mg) (n=20)	180.97mg
Friability (%) (n=20)	0.71 %
Disintegration (minutes) (n=6)	7 minutes
% Assay (n=2)	98.24 %
Content Uniformity in % (n=10)	96.75%

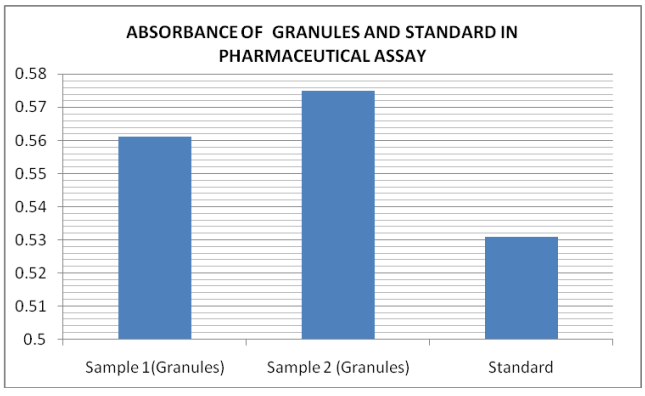

Figure 2. Absorbance of granules and standard.

Absorbance of granules and standard in pharmaceutical assay by collecting the granules after blending we performed the pharmaceutical assay for analysis of different samples of the batch hence absorbance of samples was recorded. For calculation of percent potency in particular pharmaceutical product, the absorbance of samples in pharmaceutical assay were obtained, presented in Figure **2**.

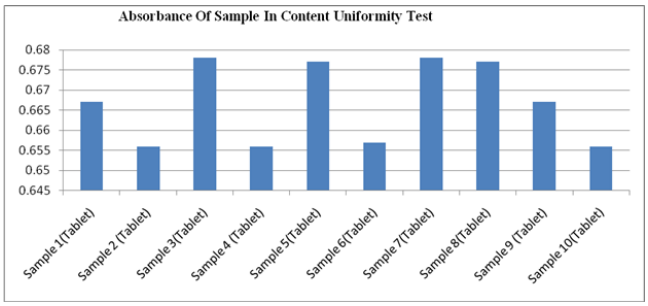

Figure 3. Absorbance of sample in content uniformity test.

Absorbance of sample in content uniformity test by compressing the tablets we performed the content uniformity test for analysis of variation in the batch hence absorbance of samples was recorded for calculation of uniformity in the whole batch of pharmaceutical product, the absorbance of samples in content uniformity test presented in Figure **3**.

CONCLUSION

The purpose of the study was to develop and evaluate the clomifene citrate 50mg tablet by direct compression method, the results were found to be satisfactory. The individual weights, weight variation test, thickness, disintegration, hardness, friability of tablets met the limits specified in BP and USP, assay as well as the content uniformity also met the specified limits (85%-115%).

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