

## Formulation Development of Chlorpheniramine Maleate Tablet by Direct Compression

Huma Ali<sup>1</sup>, Muhammad Harris Shoaib<sup>2</sup>, Rabia Bushra<sup>1</sup>✉

<sup>1</sup> Ziauddin College of Pharmacy, Ziauddin University.

<sup>2</sup> Department of Pharmaceutics, Faculty of Pharmacy, Karachi University.

### ABSTRACT

Direct compression has continued to grow in pharmaceutical industries, since it cuts down the laborious events, faced in wet or dry granulation. The study aims at developing a new tablet formulation of chlorpheniramine maleate (4mg), using microcrystalline cellulose (Avicel PH 102), lactose DC, starch, talc, and magnesium stearate by direct compression. Different pharmacopoeial and non-pharmacopoeial tests were conducted to evaluate the characteristics of tablets. The new directly compressible tablets met the official standards and showed a percent drug release of 94.95 within 45 minutes and the assay was 100.66%. Results were compared with three commercially marketed tablet brands of chlorpheniramine maleate. Tablets were blister packed, and stability studies were carried out at room temperature and accelerated stability conditions. The analysis of stability was in accordance with the official limits, showing no substantial change during storage period. The physico-chemical data reveal that low dose drugs could be developed by a direct compression technique using suitable directly compressible excipients since it is a simplest, time saving and cost effective method of manufacturing.

**Keywords:** Chlorpheniramine Maleate, Tablets, Direct Compression, Stability Testing, Formulation Development.

### INTRODUCTION

Tablet manufacturing by direct compression has increased over the years. It offers benefits to other manufacturing processes for tablets, such as low cost, use of conventional processes and equipment, and ease of manufacturability.<sup>1,2</sup> Extensive literature has been documented on tablet manufacturing through direct compression.<sup>3-7</sup> The other methods of tableting (wet granulation and slugging) not only increase the cycle time, but also not suitable for thermolabile and moisture sensitive ingredients, hence pharmaceutical industries are now focusing increasingly on direct compression.<sup>8,9</sup>

The tablets prepared by direct compression

disintegrate into Active Pharmaceutical Ingredients API particles instead of granules that directly come into contact with the dissolution fluid and exhibit a comparatively faster dissolution than wet-granulation.<sup>10</sup> Selection of appropriate excipients and their levels in formulation is crucial for a successful tablet formulation. The compressibility, flowability, and carrying capacity of excipients must be considered when developing the tablet formulation.<sup>11</sup> A wide range of material from various sources have been developed and marketed as directly compressible vehicles.<sup>12</sup> But, currently, only a few materials meet the criteria to allow their classification as DC binders. It is now possible to commercially obtain co-processed excipients which are a preblend of two or more excipients and exhibited improved tablet strength, compressibility and superior flow properties as compared an excipient used on its own.<sup>13</sup>

---

Received on 21/1/2010 and Accepted for Publication on 14/4/2010.

✉ E-mail: rabia\_pharmacist@hotmail.com

It is now well accepted that stability is an essential property of drug products. Stability testing is the primary tool used to assess expiration dating and storage conditions for pharmaceutical products. Key steps on the path of product development include pharmaceutical analysis and stability studies that are required to determine and assure the identity, potency and purity of ingredients and as well as the formulated products.<sup>14, 15</sup>

The model drug is chlorpheniramine, commonly marketed as its salt chlorpheniramine maleate, is a first-generation propylamine (alkylamine) antihistaminic agent.<sup>16</sup> Its usual dose is 4 mg every 4-6 hours. It is widely used in the prevention of the symptoms of allergic conditions such as rhinitis and urticaria, relieves red, itchy, watery eyes, sneezing, itchy nose or throat, and runny nose caused by allergies, hay fever, and the common cold.<sup>17</sup> Chlorpheniramine binds to the histamine H1 receptor and so blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine. Its sedative effects are relatively weak compared to other first-generation antihistamines.<sup>18, 19</sup> The drug is well absorbed after oral administration, but because of a relatively high degree of metabolism in the GI mucosa and the liver, only about 25-60% of the drug is available to the systemic circulation. Most commonly seen adverse effects are CNS depression (lethargy, somnolence) and GI effects (diarrhea, vomiting, and anorexia). The sedative effects of antihistamines may diminish with time. Anticholinergic effects (dry mouth, urinary retention) are a possible to occur.<sup>20, 21</sup>

This work aims at developing chlorpheniramine maleate tablets (4 mg) by direct compression. The tablets' properties of new directly compressible formulation were evaluated by performing different official and unofficial tests, and results were compared against the available marketed brands of the same formulation.

### Materials and Methods:

#### Chemicals:

Chlorpheniramine maleate was gifted by Tabrose

Pharma (Karachi, Pakistan), microcrystalline cellulose (Avicel, PH 102) (FMC Corporation, USA), lactose DC (Dow chemicals), starch (FMC Corporation, USA) and talc (FMC Corporation, USA), ether (Merck, Kga A, and Darmstadt, Germany) and sulphuric acid (0.05M, 0.25M), Kga A, and Darmstadt, Germany) all procured from the commercial market.

#### Packaging Materials:

Packaging material was comprised of polyvinyl chloride (PVC), 218 mm and aluminum foil 206 mm (Zibo Omy Economic and Trading Co. Ltd., China).

#### Preparation of Tablets:

All the listed ingredients (table 1) were properly weighed and sieved through 20 mesh screen. Microcrystalline cellulose, starch, lactose and chlorpheniramine maleate were mixed homogeneously by tumbling in a big poly bag (batch size was 1Kg) for 5 minutes. Magnesium stearate and talc were then added and additionally blended for 5 minutes. The powder mix was compressed using rotary press (Auto-Memota B4ADS Manesty, England).

**Table 1: Composition and percentage of Chlorpheniramine maleate tablets**

Ingredients	Quantity (mg)	Percentage
Chlorpheniramine maleate	4	1.904
Microcrystalline Cellulose (Avicel PH102)	90	42.857
Lactose DC	90	42.857
Starch	15	7.142
Magnesium stearate	6	2.857
Talc	5	2.387
Total Weight	210	100.002

#### Evaluation of Tablet Properties:

Different physico-chemical variables of compressed tablets (tablet weight, hardness, thickness, friability,

disintegration, dissolution and assay) were assessed. The tablet weight were evaluated using electronic balance (Mettler Toledo B204-S, Switzerland), thickness and diameter was measured using digital vernier caliper, hardness was assessed by digital hardness tester (Fujiwara, Ogawa Seiki Co. Tokyo, Japan) and friability was determined with Roche friabilator (H.Jurgens GmbH & Co. Bremen, Germany).

Disintegration time was measured for six tablets using 900 ml of purified water in disintegration apparatus (Erweka ZT-2, Heuesnstanm, Germany). Dissolution was conducted according to USP monograph, in a dissolution apparatus II (Erweka DT 700, Heuesnstanm, Germany) operated at 50 rpm for 45 minutes using 0.01N HCl as a dissolution medium. The percent amount dissolved was determined by UV-Visible spectrophotometer (Heliosa UV-Visible spectrophotometer 150, England), at 262 nm from the filtered portion of the solution under test, by comparing with a standard solution having known concentration of chlorpheniramine maleate RS in the same medium.<sup>22</sup> Assay was performed according to the same BP monograph, through extraction technique using ether as a solvent. Absorption was determined by UV-Visible spectrophotometer at 265 nm<sup>23</sup>

**Testing of Commercial Brands of Chlorpheniramine Maleate (4 mg) Tablets**

Three common commercially available brands of chlorpheniramine maleate tablets (4mg) were purchased from the local market, namely Piriton tablets, *Glaxo Smith Kleine, Karachi (Manufacturing year: 2008; Expiry; 2011)* is blister pack, Pheneramin, *Semos Pharmaceuticals, PVT, LTD. Karachi (Manufacturing year: 2008; Expiry; 2010)*, is available in PVC bottle, Chlorpheniramine maleate B.P, *Medicure Laboratories, Karachi, Pakistan (Manufacturing year: 2008; Expiry; 2011)*, is packed in PVC bottle.

**Table: 2 Physico-chemical parameters for compressible and sample tablets**

Formulatons	Thickness (mm)	Diameter (mm)	friability	Disintegratio n time	Percent dissolution	Percent assay
<i>Formulation DC</i>	3.66 ± 0.093	9.51 ± 0.179	0.186	3	93.83 ± 0.75	100.66
<i>Piriton</i>	2.72 ± 0.002	7.25 ± 0.006	0.230	6-7	90.83 ± 1.17	99.33
<i>Phenermin</i>	3.01 ± 0.048	7.20 ± 0.003	0.486	7-8	88.0 ± 1.09	98.00
<i>CPM (B.P)</i>	3.07 ± 0.005	7.18 ± 0.004	0.376	7-8	87.5 ± 1.87	96.66

Similar pharmacopoeial and non-pharmacopoeial tests were performed on these samples (as above). Descriptive statistics included mean (± standard deviation) for variables were computed.

**Stability Studies:**

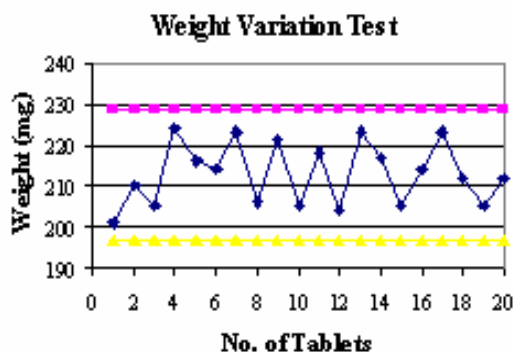
Chlorpheniramine maleate tablets (4mg) were blister packed using PVC 60 mm (Zibo Omy Economic & Trading Co. Ltd., China) and aluminium foil (Zibo Omy Economic & Trading Co. Ltd., China) using a packing machine (Uhlmann-200, Germany). Stability studies were carried out according to ICH guidelines<sup>24</sup>, at Room Temperature (RT) and accelerated conditions both, in a humidity chamber (Pajam Climatic Chamber, KBF-720, Technoman, Pvt. Ltd.). The samples designed for RT storage were kept at 30± 2 °C and 65% Relative Humidity (RH). The samples in the accelerated study were held in reserve at 40±2 °C and 75 % RH. Analytical testing was done from the date of packaging. For RT, samples were analyzed for percent dissolution and percent assay at 0, 3, 6, 9, and 12 months while for accelerated conditions samples were pulled for the same testing at 0, 1, 2, 3 and 6 months.

**Results:**

Chlorpheniramine maleate tablets were successfully prepared by direct compression. All tablets were free from any physical defects like capping, chipping, sticking and lamination etc. The flow of powder mix from hopper to die was even and without ant adhesion to wall. The ejection of tablets from the die wall was also very smooth and this reflects that talc and magnesium stearate was suitably added. The results of physical parameters including thickness, diameter, weight variation, hardness and friability were found within the acceptable limits conforming to those given in official compendia (Table 2).

The weight variation among the tablets was least and shows a good selection and proper ratio of excipients (Figure 1). Tablets were disintegrated within the specified time mentioned for the uncoated tablets. The release of drug from the tablets and the assay were excellent and fulfilling the official limits.

**Figure 1: Weight Variation of directly compressible Chlorpheniramine maleate Tablets with upper and lower control limits ( $\pm 7.5\%$ )**



Results of stability testing were satisfactory showing no change in physical properties like color and appearance. The percent dissolution and assay of tablets were within the acceptable limits (Table 3).

**Table 3: Stability studies at RT ( $30 \pm 2^\circ\text{C}$ ; RH  $65 \pm 5\%$ ) and Accelerated Condition ( $40 \pm 2^\circ\text{C}$ ; RH  $75 \pm 5\%$ )**

Stability Test Condition	Period (Months)	Physical Characteristics	Assay (4mg/Tab) (95-105%)	Dissolution (4 mg/Tab) (NLT 80%)
RT	0	Complies	100.66	94.95
	3		100.02	94.65
	6		99.87	94.36
	9		99.76	94.02
	12		99.15	93.88
Accelerated	0		100.66	94.95
	1		100.31	94.55
	2		99.89	94.34
	3		99.56	94.05
	6		99.17	93.84

**Discussion:**

The compressed tablet is by far the most widely used dosage form having advantages for both producer and user. The formulation of solid oral dosage forms and tablets in particular, has undergone rapid change and development over the last several decades. The correct selection and balance of excipients for active ingredient or excipients in a tablet formulation to produce the desired response (i.e. production of a safe, effective, and highly reliable product) is not a simple goal to achieve. Add to this fact, the need of today, is to develop tablet formulations and processing methods which may be validated, and competition among manufacturers (brand versus generic, generic versus generic, and brand versus brand) has necessitated that product and processes are cost efficient.

In this study, a new formulation of chlorpheniramine (4mg) was developed through direct compression technique. Direct compression formulation is simple but critical in a sense that any wrong selection of excipients may lead to segregation and results in excessive friability with poor content uniformity. Thus, the choice of excipients is extremely critical in formulating direct-compression tablets, especially filler-binder. The formulation consists of avicel PH102, lactose, starch, and magnesium stearate. Avicel PH102 is selected as filler/binder which offers good compressibility, flowability and having low bulk density. It also provides strength to the tablets. To further enhance the flow property, a portion of lactose was mixed with avicel PH 102. Starch was added as disintegrant and magnesium stearate and talc were utilized as lubricant and anti-adherent. There is a significant influence of the duration of mixing of lubricant and excipients, on the processing characteristics of powders, and on properties of compacts, so proper blending time should be decided. Here magnesium stearate and talc was added in the last, and blended just for 5 minutes, for even coating of particles with lubricant.

Various physico-chemical parameters were evaluated and shown in table 2. All results were in accordance with the official limits. Tablets must be sufficiently strong and

resistant to bear the shocks; this can be measured by hardness and friability. The great paradox in pharmaceutical tableting is to produce compact having sufficient mechanical strength. One of the major problems which the manufacturers have faced during direct compression is the weight variation among the units of the same batch. The resultant tablets could be softened because of lubricant and the anti-adherent. In this study, hardness of tablets was optimum and the weight variation among tablets was marginal. The target weight was 210 mg and the mean of 20 tablets were 212.9 mg with 7.5% of upper and lower limits (Figure 1) according to the monograph given in USP. The mean hardness of 20 tablets was  $8.10 \pm 0.456$  Kg (figure 2).

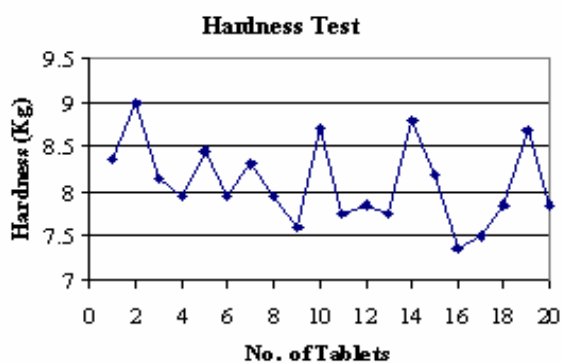


Figure 2: Hardness of directly compressible Chlorpheniramine Tablets

Dissolution is a key property since *in vitro* dissolution test can be used as a predictor of *in vivo* behavior and that is why dissolution has been widely recognized by official compendia and drug regulation authorities.<sup>25</sup> The new developed formulation was quickly disintegrated in aqueous medium (3 min) and showed an excellent dissolution (93.83%). Assay was determined through extraction technique using ether and sulphuric acid as solvents.<sup>23</sup> Extraction from a physical mixture using two immiscible solvent is relatively simple. The solvent is chosen to provide good solubility of the substance of interest and minimal solubility of other components of the mixture (including binder, filler, lubricant and disintegrant).

Since tablets are the most suitable way of administering the drug, attention must be paid to their design, development and manufacturing technique in order to get the correct medicinal benefits. This directly compressible formulation was compared with three leading marketed brands for efficiency and competence. These marketed brands are manufactured through wet granulation technique. The majority of pharmaceutical industries have been using wet granulation especially for low dose drugs in order to prevent segregation, capping and other common defects of direct compression. These comparative results showed that chlorpheniramine (DC) had better or nearly equal dissolution and assay. This seems that the direct compression method can be used for manufacturing of low dose drugs like chlorpheniramine maleate tablets. In contrast to wet granulation, direct compression methods are rather simple, save labor time, equipment and space. It is an ideal method, since it requires neither heat nor moisture treatment. Force feeders and better compressible excipients have made this process very popular in recent years.

Quantifying the drug stability for the quality attributes of a product that change with time is essential.<sup>26</sup> The purpose of stability testing is to provide evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light.<sup>27</sup> Stability studies were performed according to ICH guidelines. Stability data showed that the directly compressible tablets were stable at RT and accelerated conditions. Dissolution and assay were performed using the same method before stability. Both, the dissolution and assay were within the specified limits given in USP and BP. Physical appearances of the samples were satisfactory throughout the storage period.

#### Conclusion:

The possibility of compressing mixed powders into tablets without an intermediate granulation step is an attractive one. DC formulations are likely to be more stable, easy, economic, less time consuming and show fewer aging effects. Chlorpheniramine maleate was successfully

formulated by direct compression; results were in accordance with the specifications. Stability studies data were satisfactory (both RT and accelerated conditions) and showed that tablets were stable during storage period. Thus,

direct compression method of manufacturing could be utilized as an alternative method for the production of low dose chlorpheniramine maleate (4 mg).

## REFERENCES

- (1) Terashita K. and Imamura K. Preparation of antipyretic analgesic by direct compression and its evaluation. *Chem. Pharm. Bull. (Tokyo)*. 2005; 50(12): 1542-1549.
- (2) Zhang Y., Law Y., and Chakrabarti S. Physical Properties and Compact Analysis of Commonly Used Direct Compression Binders. *AAPS Pharm. Sci. Tech.* 2004; 4(4): 1-11.
- (3) Viçosa AL., Chatah EN., Santos TC., Jones Jnr LF., Dantas CB., Dornelas CB., Rodrigues CR., Castro HC., Sousa VP., Dias LR. and Cabral LM. Bioequivalence studies and sugar-based excipients effects on the properties of new generic ketoconazole tablets formulations and stability evaluation by using direct compression method. *Pharm Dev Technol.* 2009.
- (4) Kulkarni AS. and Bhatia MS. Design of floating bilayer tablets of diltiazem hydrochloride and lovastatin. *PDA J Pharm Sci Technol.* 2008; 62(5):344-52.
- (5) Genç L. and Jalvand E. Preparation and *in vitro* evaluation of controlled release hydrophilic matrix tablets of ketorolac tromethamine using factorial design. *Drug Dev Ind Pharm.* 2008; 34(8):903-10.
- (6) Lopes CM., Lobo JM., Pinto JF. and Costa PC. Compressed matrix core tablet as a quick/slow dual-component delivery system containing ibuprofen. *AAPS PharmSciTech.* 2007; 21;8(3):E76.
- (7) Bushra R., Shoaib HR., Aslam N., Hashmat D. and Rehman M. Formulation development and optimization of ibuprofen tablets by direct compression method. *Pak. J. Pharm. Sci.* 2008; 21 (2): 113-120.
- (8) Yasmeen R., Shoaib MH. and Khalid H. Comparative Study of Different Formulations of Atenolol. *Pak. J. Pharm Sci.* 2005; 18(1): 49.
- (9) Beyer T., Day GM. and Price S.L. The prediction, morphology and mechanical properties of the polymorphs of Paracetamol. *J. Am. Chem. Soc.* 2001; 123: 5086-5094.
- (10) Gohel MC. A review of Co-processed Directly compressible excipients. *J. Pharm. Sci.* 2005; 8(1): 76-93.
- (11) Jivraj M., Martini LG. and Thomson CM. An overview of different excipients useful for the direct compression of tablets. *Pharm. Sci. Technol.* 2000; 3(2):58-63.
- (12) Limvong V., Suthathvial N. and Kulvanich P. Spherical composite particles of rice, starch and microcrystalline cellulose: a new co processed excipient for direct compression. *AAPS Pharm. Sci. Tech.* 2004; 5(2), Article 30.
- (13) Kottke MK. and Rudnic EM. In: *Modern Pharmaceutics*. Banker GS. and Rhodes CT. (Ed.); Marcel and Dekker, New york, 2002; 4<sup>th</sup> edition, pp. 306-309.
- (14) Singh S. In: *Pharmaceutical product development*. Jain NK. (Ed.); CBS Publishers and distributors, New Delhi, 2006, pp 272-277.
- (15) Rhodes CT. In: *Drug stability, Principle and practices*, Carstensen JT and Rhodes CT. (Ed.); Marcel dekker, Inc. New York, 2000, 3<sup>rd</sup> edition, pp. 2-3.
- (16) Dollery C. In: *Therapeutic drugs*. Churchill Living Stones, New York, 1991, 2<sup>nd</sup> edition, pp. 198-200.
- (17) Corelli RL. In: *Basic and clinical pharmacology*. Katzung BG. (Ed); McGraw Hill, Boston, 2007, 10<sup>th</sup> edition, pp.1043.
- (18) Simons F.E. and Simons KJ. The pharmacology and use of H1 receptor antagonist drugs. *New Engl.J.Med.* 1994, 330:1663-1670.
- (19) Martindale: The complete drug reference. Pharmaceutical Press, London, 2005, 34<sup>th</sup> edition, pp. 427-428.
- (20) Hellbom, E. Chlorpheniramine, selective serotonin-reuptake inhibitors (SSRIs) and over-the-counter (OTC) treatment. *Medical Hypotheses*, 2006; 66(4), 689 - 690.
- (21) Bhattacharya SK., Sen P. and Ray A. 2003. In: *Pharmacology*. Das PK (Ed); Elsevier, New Delhi,

- 2003, 2<sup>nd</sup> edition, pp 104-109.
- (22) United State Pharmacopoeia. United State Pharmaceutical convention, Inc. Rockville, 2004, 23<sup>rd</sup> edition, pp 429.
- (23) British Pharmacopoeia. Stationary office, London, 2004, pp: 2273-2274.
- (24) ICH Guidelines, Stability testing of new drug substances and products, Q1A(R2) Step 4 version, dated 6 February 2003. Available at: <http://www.ich.org/cache/compo/363-272-1.html#Q1C>.
- (25) York P. In: The Science of Dosage Form. Aulton ME. (Ed); 1<sup>st</sup> chapter, Churchill Livingstone, Elsevier, 2005, 3<sup>rd</sup> edition pp.11.
- (26) Rhodes CT. In: Drug stability principles and practices. Carstensen JT and Rhodes CT (Ed); Marcel and Dekker, New York, 2008, 3<sup>rd</sup> edition, pp. 1-3.
- (27) WHO guidelines for Eastern Mediterranean region stability testing of active substances and pharmaceutical products, 2006.

