

USE OF AVICEL AND SPRAY DRIED LACTOSE IN THE DEVELOPMENT OF LEVOFLOXACIN 250mg TABLETS BY DIRECT COMPRESSION METHOD

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ABSTRACT

In present study a formulation of Levofloxacin tablet 250mg was prepared by direct compression method, using two directly compressible excipients, i.e Avicel PH101 (62.5mg) and spray dried lactose (62.5mg) with magnesium stearate(5mg) as lubricant glidant on Erweka single punch machine. These tablets are round in shape having mean weight of 373.55 ± 8.463 mg with mean diameter and thickness of 12.3 ± 0.03 mm and 2.4 ± 0.11 mm. The hardness of the tablets was 12 ± 0.39 kg. Friability of tablets were 0.67% using Roche friabilator and disintegration time was 10 min in Erweka basket rack assembly. Dissolution test was performed on USP apparatus-I and %Q was found to be 94.59. Assay results was 100.54% when performed by HPLC technique using C18 column. This formulation gives excellent results using minimal excipient and simple manufacturing procedure. This type of work gives direction to try to make formulation simple and cost effective. As direct compression method is not cheap in terms of raw materials but also produces batch in short period of time. Moreover considering biopharmaceutical aspects, tablet manufactured by direct compression dissolved rapidly in gastrointestinal tract due to prime particle dissociation as compared to that of wet granulation method.

INTRODUCTION

Tablets are now the most popular dosage form, accounting for some 70% of all ethical pharmaceutical preparations produced (Rubinstein, 2000). According to a survey conducted by Shangraw and Demarest in 1993, direct compression is the preferred manufacturing process for pharmaceutical tablets. (Shangraw and Demarest., 1993) Tablet manufacturing by direct compression method has increased steadily over the years. It offers advantages over other manufacturing processes, such as wet granulation method and provides high efficiency (Zhang *et al.*, 2003).

The most obvious advantage of direct compression method is economy. Saving can occur in a number of areas including reduced

processing and thus reduced labor cost, fewer manufacturing steps and pieces of equipments, less process validation, and lower consumption of power. The process does not require moisture and heat, which is inherent in wet granulation procedure which can affect the drug stability, and length of mixing, the method and rate of wetting and dry screening can change the size and density of granules which can have major effect on fill weight and compaction qualities. Probably one of the least recognized advantages of direct compression is the optimization of tablet disintegration, in which each primary particle is liberated from the tablet, mass and is available for dissolution. In granulation process, where in small drug particles with a large surface area "glued" into larger agglomerates, is in direct opposition to the principle of increased surface

area for rapid dissolution. The choice of excipients is extremely critical in formulating direct compression tablets. This is moisture of the filler-binder, which often serves as a matrix around which revolves the success or failure of the formulation, direct compression filler-binder posses both fluidity and compressibility. There is also need to set functionality specifications on properties such as compressibility and fluidity, as well as physical and chemical properties. Many factors influence the choice of the optimum direct compression filler to be used in tablet formulation. These factors vary from primary properties of powder i.e. particle size, shape, bulk density, solubility, to characteristics need to make compacts (Lieberman *et al.*, 1989). In present work microcrystalline cellulose (Avicel PH101) and spray dried lactose was used for the preparation of tablet by direct compression method. Microcrystalline cellulose (Avicel), was introduced as a direct-compression tableting agent in the early 1960s and stands today as the single most important tablet excipient developed in modern times (Fox 1963). Similarly spray-dried lactose is the earliest and still one of the most widely used direct compression fillers (Milosovitch 1962).

EXPERIMENTAL

Formulation Design:

Levofloxacin.....	250mg
Avicel (PH 101)	62.5mg
Lactose spray dried.....	62.5mg
Magnesium stearate.....	5mg
Total wt.	380mg

MATERIAL AND METHOD

Equipment and Chemicals:

Microcrystalline cellulose (Avicel PH 101, FMC Corp., USA), Lactose D.C. (FMC Corp, USA), Magnesium stearate (FMC Corp, USA), Levofloxacin (Gifted by Aventis Pharma, Single punch machine (Erweka, Germany), Sieves, Electronic Balance (Mettler Toledo), Beaker (Pyrex, England), Computer with Pentium III Processor, Vernier Calliper,

Hardness tester (Fujiwara, Seisukusho Corporation, Japan).

Procedure:

250mg levofloxacin was mixed by tumbling method with 62.5mg of Avicel and 62.5mg of Lactose DC and 5mg Magnesium stearate in a 1000ml beaker, after passing through 20-mesh sieve. These mixed materials were then compressed on a single punch tablet machine.

Physical Tests:

Weight variation, Thickness, Diameter and Hardness Evaluation:

20 tablets were taken at random and then these tablets were evaluated for weight variation, thickness, diameter and hardness. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown and none deviates by more than that percentage (B.P 2002). Thickness will be in $\pm 5\%$ S.D and out of 20 tablets only 2 are allowed to exceed the limit. Diameter will be in $\pm 5\%$ S.D limit up to 12.5mm and by $\pm 3\%$ above (James 1996). Out of 20 tablets only 2 are allowed to exceed the limit. Hardness should be more than 5 kg. And out of 20 tablets only 2 are allowed to exceed the limit. Results were analysed using three sigma charts (Bolton, 1997) (Table 2 and fig. 1).

Friability Test:

Friability of these tablets was determined by using Roche Friabilator (Erweka, Germany) with a plastic chamber which revolves at 25 r.p.m., dropping the tablets at the distance of 6 inches with each revolution. Normally preweighed tablets sample is placed in chamber which is then rotated for 100 revolutions. Tablets were removed dusted and reweighed. Tablets weight loss less than 1% is acceptable.

Disintegration Test:

Disintegration test was determined by using Basket rack assembly (Erweka, Germany) by placing tablet in each tube and then add a perforated disc to each tube (USP,

1985). Suspend the assembly in the beaker containing specified liquid and operate the apparatus for the specified time. All the six tablets in six tubes should be disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on additional 12 tablets, not less than 16 tablets of the total 18 tablets disintegrate completely (Gibaldi 1991).

Dissolution Test:

Same method was used which was there in US Pharmacopeia for ofloxacin, as Levofloxacin is an optical isomer for ofloxacin. Dissolution test was determined by using USP Dissolution apparatus I (Erweka, Driech, Germany). The basket was rotated at 100 rpm containing 900 ml of 0.1NHCl (Merck, Darmstadt Germany) as a dissolution medium (USP, 1995). Drawn and filtered 2 ml of the sample after 45 min and dilute with dissolution medium in a 50 ml volumetric flask. Reference standard was prepared by dissolving 100mg of Levofloxacin RS in 0.1N HCl to make the volume 100ml. Absorbance of both the reference and sample solution was taken in UV-VIS Spectrophotometer (Heliox UV VIS spectrophotometer 150 England).

Content Uniformity test:

Same method was used which was there in US Pharmacopeia for ofloxacin, as Levofloxacin is an optical isomer for ofloxacin (USP, 1995).

Equipment:

HPLC Pump (LC-10A, Shimadzu Corp. Tokyo, Japan), Spectrophotometric detector (SPD 10A, Shimadzu Corp. Tokyo, Japan), Column (Shimpack CLC ODS, 15 cm × 6 mm), Communication Bus Module (CBM 102, Shimadzu, Corp, Tokyo, Japan), Software for data handling (LC-10A, Shimadzu, Corp, Tokyo, Japan), Ultrasonic water bath (Clifton, Nickel Electro Ltd., Somerset, England), Filtration assembly (Sartorius, Gottingen, Germany), Swinney Filtration assembly (Millipore, England), Microliter syringe (SGE Corp. Australia), Membrane filter, 0.45µ pore size-47 diameter (Scheier & Schuell, Dassel, Germany).

Chemicals and Glasswares:

Volumetric flasks, conical flasks and pipettes (Pyrex, England), Methanol (HPLC grade, Lab Scan, Dublin Ireland), Acetonitrile (Merk, Darmstadt, Germany), Ammonium acetate (Merk, Darmstadt, Germany), Sodium Perchlorate (Reidl De Hein, AG Seelze), Phosphoric acid (Merk, Darmstadt, Germany).

Preparation of Reference Solution:

Solvent system was prepared by taking 1200ml H₂O and Acetonitrile. 20 mg of Levofloxacin (pure) was dissolved in the above solvent system and final volume was made in 50ml volumetric flask, and 25ml from this was taken and its final volume of 50ml was made with the same solvent system in another 50ml flask. After filtration 100µl of that soln. was then injected through injector, its peak area was then observed on HPLC.

Table 1
Different Physical Test of Tablets

Test	Results	Limits
Friability	0.67%	<1%
Disintegration	10 min	<15min
Dissolution	94.49%	At least 75%
Content uniformity (Assay)	100.54%	90-110%

Preparation of Test Solution:

10 tablets of this new formulation were crushed and their average weight was determined that was 392mg. 20mg of pure Levofloxacin was taken as a reference standard. Its solution was prepared, and 250mg Levofloxacin is found in tablet of 380mg, when the average weight of 10 tablets were 392mg, then 31.36mg is the calculated amount from its crushed powder that was taken and its solution was made in 50ml flask with the same solvent. Then 25ml from that solution was pipetted out and its final volume was made in another 50ml volumetric flask with the same solvent.

Table 2

No. of Tablets	Weight	Hardness	Diameter	Thickness
	(mg)	(kg)	(mm)	(mm)
1	369	12.6	12.3	2.4
2	385	12.2	12.3	2.35
3	369	12.02	12.3	2.7
4	370	12.55	12.3	2.4
5	382	12.4	12.35	2.3
6	375	12.2	12.3	2.7
7	363	12	12.3	2.35
8	398	12.15	12.3	2.4
9	376	11.75	12.3	2.35
10	376	11.75	12.35	2.3
11	373	11.25	12.3	2.4
12	368	12.25	12.35	2.3
13	372	12.2	12.3	2.35
14	365	11.45	12.3	2.35
15	384	11.63	12.3	2.4
16	368	12.22	12.4	2.45
17	365	12.4	12.35	2.3
18	366	11.75	12.3	2.35
19	372	11.4	12.3	2.45
20	375	12.2	12.35	2.45
Mean	373.55 ± 8.463	12 ± 0.39	12.3 ± 0.03	2.4 ± 0.11
Upper 5%	392.55	12.6	12.9	2.52
Lower 5%	354.87	11.4	11.7	2.28
*UCL1	382.1	12.4	12.35	2.52
UCL2	390.7	12.8	12.39	2.62
UCL3	399.3	13.2	12.42	2.74
**LCL1	365	11.6	12.29	2.29
LCL2	356.4	11.2	12.25	2.18
LCL3	347.8	10.9	12.22	2.06

*UCL1 = $\bar{X} + 1S$, UCL2 = $\bar{X} + 2S$, UCL3 = $\bar{X} + 3S$

**LCL1 = $\bar{X} - 1S$, LCL2 = $\bar{X} - 2S$, LCL3 = $\bar{X} - 3S$ (Bolton., 1997)

(Where UCL = Upper Control Limit, LCL = Lower Control Limit, S = Standard Deviation)

Preparation of Mobile Phase:

Mobile phase mixture prepared as follows: dissolve 4.0g of Ammonium acetate R and 7.0g of Sodium perchlorate R in 1300ml of water R. Adjust to pH 2.2 with phosphoric acid R. Add 240ml of Acetonitrile R (USP, 1995).

RESULTS AND DISCUSSION

In present study Levofloxacin tablets were prepared by Direct Compression method using microcrystalline cellulose. This excipient have excellent compressibility and flow property (Milosovitch 1962). Tablets were compressed

Three sigma quality control charts

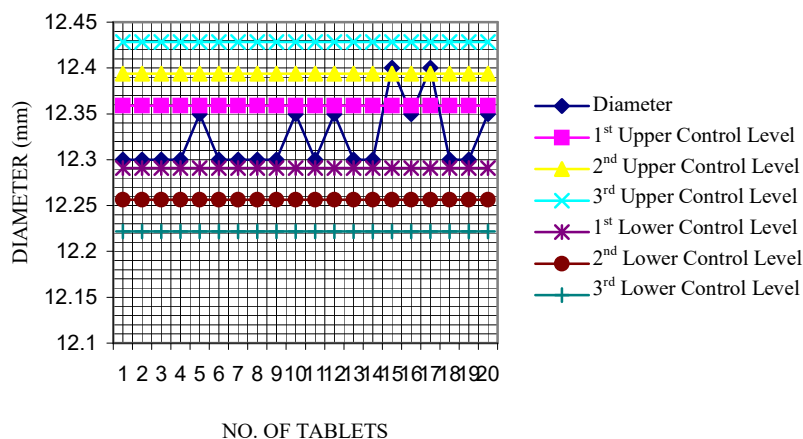


Fig. 1a: Number of tablets vs diameter.

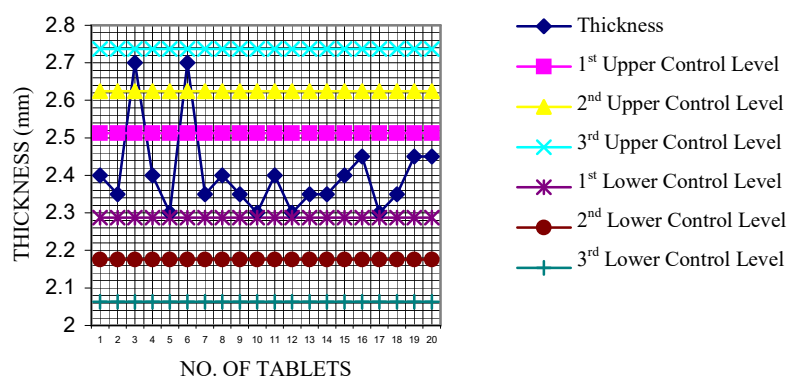


Fig. 1b: Number of tablets vs thickness.

at an average weight of 373.55 ± 8.463 mg with mean diameter and thickness of 12.3 ± 0.03 mm and 2.4 ± 0.11 mm. The hardness of the tablets was 12 ± 0.39 kg (Table 1). Zhang *et al* in 2003 also demonstrated that the microcrystalline cellulose had moderate flow ability, excellent compressibility and hardness. Microcrystalline cellulose performed as binder because of its plastic deformation under pressure; fragmentation was the predominant

mechanism in the case of lactose and DCP; starch and sugar perform by both mechanisms. Bolhuis in 1996, Lee *et al* 2000 and Tsai *et al* in 1998 studied that microcrystalline cellulose showed excellent compact hardness and hydrogen bonding played a big role in compact hardness. Hydrogen bonding is important because MCC undergoes significant plastic deformation during compression bringing an extremely large surface area into

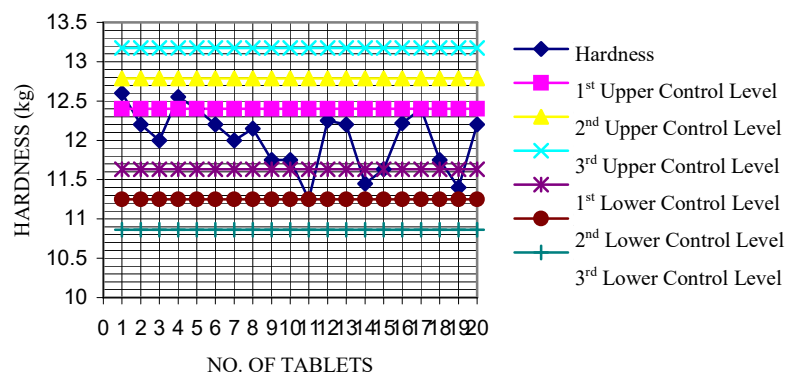


Fig. 1c: Number of tablets vs hardness.

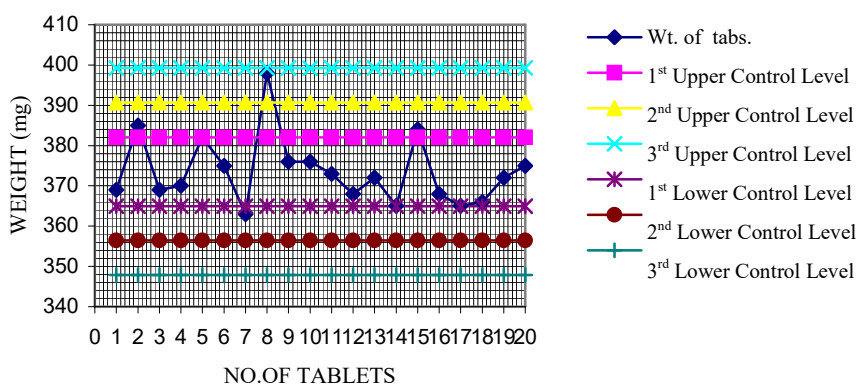


Fig. 1d: Number of tablets vs weight.

closed contact and facilitating hydrogen bond formation between the plastically deformed, adjacent cellulose particles. In addition, the existence of moisture within the porous structure of MCC acts as an internal lubricant. This facilitates slippage and flow within the individual microcrystals during plastic deformation, which enforces the formation of hydrogen bond bridges and gives MCC a very good hardness.

In present work using magnesium stearate as a lubricant and glidant, all tablets were within specified range when statistically compared by making three sigma quality control charts (Fig. 1). Capella in 2002 prepared a stable nitroglycerin tablet which is prepared by direct compression technology. The formulation closely replicates the properties of nitroglycerin molded sublingual tablets (e.g., adequate disintegration and

sublingual absorption), while reducing the problems experienced with compressed tablets (e.g., friability and weight variations). The stable tablets are characterized by a decreased migration of nitroglycerin, decreased potency loss, excellent content uniformity when stored. The preferred combination of components are: nitroglycerin/lactose dilution, hydrous lactose, glyceril monostearate, fumed silica, pregelatinized starch and calcium stearate. The preferred process employs direct compression technology to yield composition showing adequate disintegration, bioavailability and improved stability. Vromans *et al* in 1987 said that tablets containing spray-dried lactose disintegrated almost as fast as β -lactose monohydrate tablets.

In present work the friability of tablets were 0.67% and disintegration time was 10 min (Table 2). Wallace in 1983 evaluated that Avicel is not as effective disintegrant as starch in equivalent concentrations, it can be used as the only disintegrant at levels of 20% or higher and has an additive effect with starch at lower levels. Hard compacts of microcrystalline cellulose disintegrate rapidly due to the rapid passage of water into the compact and the instantaneous rupture of hydrogen bonds (Wallace 1983). In present work disintegration time was relatively higher but within limit, this may be due to the production of hard compact and the absence of suitable disintegrator. The assay using HPLC technique showed 100.54% of Levofloxacin in tablet and dissolution test using Apparatus I (USP 1995) showed 94.59% of the drug was dissolved (Table 2). Lieberman *et al* in 1989 said that spray dried lactose possesses excellent dissolution properties

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