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Formulation & Characterization Study of Immediate Release Progestrin Tablet and its Comparative Study with Innovator Drug

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ABSTRACT

The present study was an attempt to develop a stable immediate release tablet formulation of Levonorgestrel and involves the scientific approach used begins with identification of the desired dosage form and performance attributes through the target product profile. The prepared formulations were evaluated for hardness, weight variation, friability, disintegration and flow property. The values of pre-compression parameters were within prescribed U.S.P. limits and indicate good free flowing properties. In all the formulations friability was less than 1% indicates tablets had a good mechanical resistance. Hardness of the tablets was found to be in the range. The physical and chemical evaluation of Levonorgestrel was done. Further the identification test confirmed the Levonorgestrel as an authentic batch. The Pre-formulation studies confirmed that there was no interaction between the drug and the proposed excipients. The objective was to develop a tablet, which has a similar dissolution pattern in official media as that of innovator (for which an NDA has already been approved). This is with accordance with the USFDA rules and regulation for the approval of ANDA**.**

KEYWORDS: Immediate Release, Levonorgestrel, Lactose monohydrate, oral contraception, tablet hardness tester, etc.

INTRODUCTION

Oral route of drug administration is the most important method of administering drugs for systemic effects. Nevertheless, it is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route. When a new drug is discovered, one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by the oral route. If patient

self administration cannot be achieved, the sale of the drug constitute only small fraction of what the market would be otherwise. Drug may be administered by variety of routes, but oral administration is adopted wherever possible. It is safest, easiest and most economical route of drug administration. Amongst drugs that are administered orally, solid oral dosage forms i.e. tablets and capsules, represent the preferred class of products. Out of the two oral solid dosage forms, the tablets have number of advantages like low cost, speed of manufacturing, ease of administration, patient compliance and flexibility in formulation.

From many decades, conventional dosage forms, which are of prompt releasing nature, are used for treatment of acute and chronic diseases. The conventional dosage forms provide no control over release of drug. To maintain the drug concentration within the therapeutically effective range, it is often necessary to take these types of conventional dosage forms several times a day. This results in several potential problems like saw tooth kinetics characterized by large peaks and troughs in the drug concentration time curve, frequent dosing for drugs with short biological half life and patient noncompliance. Recently, several technical advancements have been made. These have resulted in the development of new techniques in drug delivery. These techniques are capable of controlling the rate of drug delivery to targeted tissue (temporal delivery), sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue (spatial delivery). An ideal drug delivery system (DDS) should aid in the optimization of drug therapy by delivering an appropriate amount to the intended site and at a desired rate. The scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects:

1) The anatomic and physiologic characteristics of the gastrointestinaltract.
2) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.
3) Physicomechanical characteristics and the drug delivery mode of the dosage form to be designed.

Levonorgestrel is a progestin or a synthetic form of the naturally occurring female sex hormone, progesterone. In a woman's normal menstrual cycle, an egg matures and is released from the ovaries (ovulation). The ovary then produces progesterone, preventing the release of further eggs and priming the lining of the womb for a possible pregnancy. If pregnancy occurs, progesterone levels in the body remain high, maintaining the womb lining. If pregnancy does not occur, progesterone levels in the body fall, resulting in a menstrual period. Levonorgestrel tricks the body processes into thinking that ovulation has already occurred, by maintaining high levels of the synthetic progesterone. This prevents the release of eggs from the ovaries. It binds to the progesterone and estrogens receptors. Target cells include the female reproductive tract, the mammary gland, the hypothalamus, and the pituitary. Once bound to the receptor, progestin’s like Levonorgestrel will slow the frequency of release of gonadotropin releasing hormone (GnRH) from the hypothalamus and blunt the pre-ovulatory LH (luteinizing hormone) surge. Levonorgestrel is not subjected to a "first-pass" effect and is virtually 100%

bioavailable. About 45% of Levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in faeces, mostly as glucuronide conjugates.

The present aim is to develop and optimize stable and efficacious immediate release tablet of contraceptive tablets that is comparable to the innovator or reference (marketed) product and to carry out the stability studies of the selected formulations as per ICH guidelines.

MATERIALS AND METHODS

The following drugs, excipients were used for the formulation and evaluation of immediate release tablets listed in **Table 1.**

Table 1: List of Drug and Excipients

Sr. No.	List of API/ Excipients	Specification	Supplier	Functional Category
1.	Levonorgestrel	BP	Indo Phyto Chemicals Pv**t.** Ltd., India	API
2.	Lactose Monohydrate (Lactochem Fine Powder	Ph.Eur	DMV- Fonterra Excipients GmbH, Germany	Diluent
3.	Maize Starch (Maize starch B)	Ph.Eur	Roquette, France	Disintegrant &additional Diluent
4.	Potato Starch	Ph.Eur	Roquette, France	Binder
5.	Talc (Talc Luzenac Pharma)	Ph.Eur	Luzenac Val Chisone Spa, Italy	Antiadherent
6.	Silica, Colloidal Anhydrous (Aerosil® 200 Pharma)	Ph.Eur	Evonik Degussa GmbH, Germany	Glidant
7.	Magnesium Stearate (Magnesium Stearate VG EP)	Ph.Eur	Ferro Corporation, USA	Lubricant

PREFORMULATION STUDIES

Characterization of Drug

Visual Examination

A small quantity of Levonorgestrel powder was taken in butter paper and viewed in well-illuminated place.

Solubility

The equilibrium solubility at a given pH and temperature was determined by the shake flask method. In this method the compound was added in surplus to a certain medium which shaken at about 24h. The saturation was confirmed by observation of the presence of un-dissolved material. The amount of solute contained in the sample was determined by chromatographic technique, affected by the nature of the solute /solvent and by the concentration.

UV Spectrum

The UV spectrum of Levonorgestrel solution in Ethanol was scanned at 400nm to 200nm. The Loss on Drying Test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. It is determined on 0.5 to 1.0 g by drying in an oven at 100°C to 105°C for 5 minutes. The substance to be tested was mixed.

Analysis of Particle Size and Micronization

Particle size distribution was carried out in "Malvern Particle Size Analyzer" model-Mastersizer-2000. The Dry method was preferred for determination of particle size. A uniform Particle size distribution curve was obtained and geometric mean diameter (d) was calculated from graph. Levonorgestrel drug was micronized using a Air Jet Mill (Promas India, 2" model).

Compatibility studies

Drug - excipient compatibility studies are required to identify any unwanted interaction between the active pharmaceutical ingredient and the excipients used and Bromobutyl rubber closures were used. A blend of the drug with the excipients in a ratio as given in the **Table 2** was filled in USP Type I Glass vials having 5 ml capacities and charged at 40°C±2°C/75%±5%RH and 60°C±2°C / Ambient RH for 2 weeks. Blend of the API (Levonorgestrel) and Excipients were taken in different ratio. The drug-excipient was mixed uniformly

Table 2: Drug-Excipient Compatibility Studies

Sample No.	Sample Details	Drug : Excipient Ratio
1.	Levonorgestrel	Drug alone
2.	Lactose monohydrate	Excipient alone
3.	Maize Starch	Excipient alone
4.	Potato Starch	Excipient alone
5.	Talc	Excipient alone
6.	Silica, Colloidal Anhydrous	Excipient alone
7.	Magnesium Stearate	Excipient alone
8.	Levonorgestrel + Lactose monohydrate	1:150
9.	Levonorgestrel + Maize Starch	1:40
10.	Levonorgestrel + Potato Starch	1:10
11.	Levonorgestrel + Talc	1:5
12.	Levonorgestrel Anhydrous+ Silica coloids	1:5
13.	Levonorgestrel + Magnesium Stearate	1:5
14.	Levonorgestrel + All excipients [Lactose monohydrate + Maize starch + Potato Starch + Talc + Silica, Colloidal Anhydrous + Magnesium Stearate]	1:150:40:10:5:5:5
15.	All excipients [Lactose monohydrate + Maize starch + Potato Starch + Talc + Silica, Colloidal Anhydrous + Magnesium Stearate]	150:40:10:5:5:5

Compatibility study by HPLC method

The Mobile phase A (Mixed HPLC grade water and methanol) in the ratio of 950:50 v/v respectively) Filtered through 0.45 µm membrane filter and degassed it and Mobile phase B is HPLC Grade Acetonitrile. Injected 50µ L of diluent as Blank, Diluted Standard preparation (two injections) and Test preparation (one injection) into the chromatograph recorded the chromatograms and measured the peak responses. Retention time of Levonorgestrel peak was found to be 13.5min. The Chromatographic system parameters are:

Column : Waters Symmetry C18, 150 x4.6mm, 5µm
Column temperature : 30°C
Flowrate : 1.0 mL/ minute
Injectionvolume : 50□l.
Detector Wave length : 244 nm
RunTime : 60minutes

Preparation of Immediate Releases Levonorgestrel Tablets:

Preparation by Direct compression method- Direct compression was selected for

initial development due to ease of processibility, convenience and being not a tedious process but further it was dropped as the amount of drug was very low i.e. 1.5 mg which may result in Content Uniformity problem during the course of development. This supports the selection of the wet granulation for development of product.

Preparation by Wet granulation method- A wet granulation process was chosen based on prior scientific knowledge of products with similar physical and chemical properties, and available technologies and equipments. The manufacturing process for batch is as follows:

Dispensing Technique: All the ingredients were weighed accurately and followed by Sifting & Geometrical Mixing-

1. Lactose Monohydrate (Lactochem Fine Powder), Maize Starch and Talc were sifted individually through #40 mesh sieves, Silica Colloidal Anhydrous was sifted through #20 mesh sieve, Magnesium Stearate was sifted through #80 mesh sieve and Levonorgestrel was co sifted geometrically with Lactose Monohydrate through #40 mesh sieve.
2. The above blend was geometrically mixed with Maize starch and sifted through #40 mesh sieve during each step of geometric mixing.
3. All the sifted ingredients were mixed geometrically, except extra granular materials i.e. Maize starch, Silica Colloidal Anhydrous, Talc and Magnesium Stearate.
4. The above blend was mixed in Rapid Mixer Granulator for 10 minutes for granulation and Granules were dried in Fluidized Bed Dryer at 60ºC till the LOD was below 2.0%w/w (checked at 105ºC, for 5min.).
5. Granules were passed through #20 mesh sieve. Milled the retention using 1.5 mm sieve in Multimill and passed the granules through #20 mesh sieves.
6. The above blend was mixed with sifted Maize starch, Silica Colloidal Anhydrous & Talc in an Octagonal Blender for 15 min at 15 rpm.
7. The above blend was mixed with sifted Magnesium Stearate in an Octagonal Blender for 5 min at 15 rpm.
8. The lubricated blend was compressed using a punch of 8 mm diameter, the compression and physical parameters of lubricated blend were recorded.

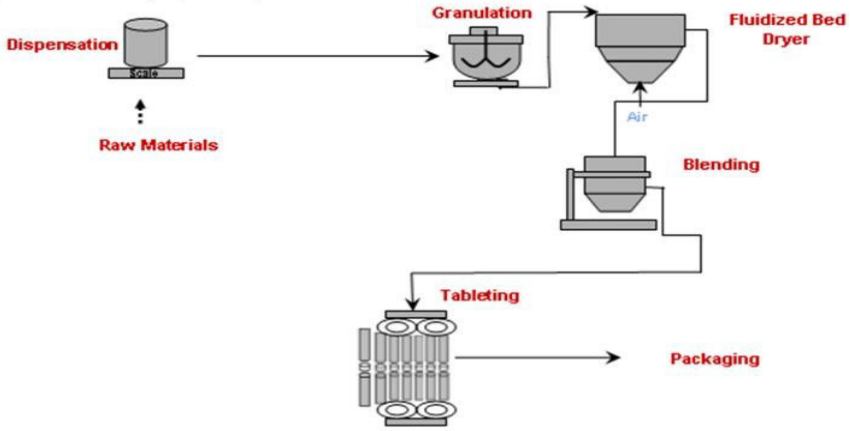


Figure 1: Unit operations of the proposed Manufacturing Process

9. The following Formulae for preparation of immediate release Levonorgestrel Tablets

Table 3: Formulation Design of Levonorgestrel tablet.

S. No.	Ingredients	L-1 (Non-micronized) Qty./Unit (mg)	L-2 (Non-micronized) Qty./Unit (mg)	L-3 (Micronized) Qty./Unit (mg)	L-4 Qty./Unit(mg)	L-5 Qty./Unit(mg)	L-6 Qty./Unit(mg)	L-7 Qty./Unit(mg)	L-8 Qty./Unit (mg)
1	Levonorgestrel	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
2	Lactose monohydrate	118.00	118.00	118.00	122.00	120.00	160.00	156.50	156.50
3	Maize Starch	64.00	64.00	64.00	67.00	67.00	27.00	25.00	25.00
4	Potato Starch	1.50	1.50	1.50	1.50	1.50	1.50	1.00	1.00
5	Purified Water	Q.S.	Q.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
6.	Maize Starch	10.00	10.00	10.00	3.00	5.00	12.50	10.00	10.00
7	Silica,Colloidal Anhydrous	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
8.	Talc	1.00	1.00	1.00	1.00	1.00	1.00	2.00	2.00
9	Magnesium Stearate	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00

Evaluation of tablets:

Pre-compression parameters-

2.3.1.1 Bulk density- Bulk Density (BD) was determined. Accurately weighed amount of sample was transferred into a 100 ml measuring cylinder. The volume of packing was recorded. The measuring cylinder was then tapped 750 times on a bulk density apparatus and the tapped volume of packing was recorded. BD and Tapped Density (TD) were calculated by the following formula:

Bulk Density (BD) = Weight of Granules/Untapped Volume

Tapped Density-

TD= Weight of Granules/Tapped Volume

Compressibility Index (Carr's index)- Percent compressibility of granules as determined by the following formula:

Carr's index= (TD-BD/TD)*100

Table 4: Flow properties as indicated by Carr's index

Percent Compressibility	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-25	Poor
33-38	Very poor
<40	Extremely poor

Hausner's Ratio (HR) - It is the ratio of tapped density to the bulk density. It is given by-

HR = TD / BD

Where, TD- Tapped density and

BD- Bulk density

Table 5: Flow properties as indicated by Hausner's ratio

Hausner's ratio	Flow of Powder
1-1.2	Free flow
1.2-1.6	Cohesive flow

Post-compression parameters-

Thickness- The tablet dimensions were measured using a calibrated vernier calliper. 5 tablets of each batch were picked randomly and its thickness was measured individually.

Friability- A sample of 6.5 gm of tablets was taken and was carefully dedusted prior to testing. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre- weighed 6.5 gm tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed and friability was calculated by the following formula. Loss in weight indicates the friability. The tablets are considered to be of good quality if the loss in weight is less than 0.8% as per IP.

Hardness test- For each formulation, the hardness of 6 tablets was determined using the Digital hardness tester and the average was calculated. Tablet hardness can be defined as the force required breaking a tablet in a diametric compression. In this test the tablet is placed between two anvils, force is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded.

Weight Variation- To study weight variation, 20 tablets of each formulation were weighed using an electronic balance. Not more than 2 of the individual weights may deviate from the average weight by more than the percentage deviation given in the table.

Table 6: Weight variation allowed according to IP

S. No.	Average weight of a tablet deviation	Percentage deviation allowed
1.	80 mg or less	10
2.	More than 80 mg and less than 250 mg	7.5
3.	250 or more	5

Disintegration test-

Disintegration is defined as that state in which no residue of the tablet remains on the screen of the apparatus or, if a residue remains, it consists of fragments of insoluble coating of the tablets. One tablet is placed in each of the 6 tubes of the basket. Added a disc to each tube and operated the apparatus, using water maintained at 37±2ºC as the immersion liquid.

In vitro dissolution studies-

The test is done for measuring the amount of time required for a given percentage of the drug substance in a tablet to go into solution under specified condition in-vitro. Introduce the 1000 ml of the dissolution medium and warmed the dissolution medium between 36.5ºC and 37.5ºC.Operated the apparatus immediately at the 75 rpm. Within the time interval specified, withdrawn a specimen from a zone midway between the surface of the dissolution medium and the top of the rotating blade or basket, not less than 10mm from the wall of the vessel. Determine each test by the amount of active ingredient in solution per tablet and calculated as a percentage of the stated amount

Table 7: Acceptance Table for Dissolution

Stage	Number Tested	Acceptance criteria
S1	6	Each unit is not less than D* + 5%
S2	6	Average of 12 units (S1 +S2) is equal to or greater than D, and no unit is less than D -15%.
S3	12	Average of 24 units (S1+S2+S3)is equal to or greater than D, not, More than 2 units are less than D - 15% and no unit is less than D - 25%

***D is the amount of dissolved active ingredient specified in the individual**

Monograph, expressed as a percentage of the stated amount.

Acceptance criteria for Dissolution: If the results do not conform to the requirements at stage S1 given in the accompanying acceptance table (Table 21), continue testing with additional tablets or capsules through stages S2 and S3 unless the result conform at stage S2.

Dissolution Method (HPLC method) for Levonorgestrel Tablets BP

The Mobile Phase (Mixed Water and Acetonitrile) in the ratio of 600:400v/v respectively. Filtered through 0.45 µm membrane filter and degassed it. Dissolved 85ml of Concentrated Hydrochloric acid in 10 liters of Purified Water and added 10gm of Sodium Lauryl Sulfate (SLS) and mixed well for dissolution medium. Injected 100µL portion of dissolution media as Blank (One injection), Standard preparation (Six injections) and Test preparation (One injection) into the chromatograph, recorded the chromatogram and measured the Levonorgestrel peak response. Retention time of Levonorgestrel peak was found to be 4.5 min.

Chromatographic Condition:

Column: Waters symmetry C18, 4.6mm x 150mm,5µm.
Column temperature :25°C
Flowrate : 1.0 mL/minute
Injection volume : 100□l.
Detector Wave length : 247 nm
Run time : 8Minute

Table 8: Dissolution Parameter for Levonorgestrel Tablets BP

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (ml)	Sampling Times (min.)
Levonorgestrel	Tablet	II (Paddle)	75 at 37.0 ±0.5°C	0.1N Hydrochloric acid with 0.1% SLS	1000	10, 20, 30, 45, 60 and 90

Stability Studies-

Stability studies ensuring the maintenance of product quality, safety and efficacy throughout the shelf life are considered as pre-requisite for the acceptance and approval of any pharmaceutical product. These studies are required to be conducted in a planned way following the guidelines issued by ICH.

Table 9: **Protocol for stability studies**

CONDITIONS	PERIOD		
25°C/ 60% RH	-	-	3M √
30°C/ 65% RH	-	-	3M √
40°C/75% RH	1M* √	2M √	3M √

M- Month*

Assay procedure of drug (By HPLC Method):

The Mobile phase was (Acetonitrile and water) in the ratio of 500:400v/v respectively. It was filtered through 0.45 µm membrane filter and degassed it.

The Mixed Acetonitrile and water is used as diluents, in the ratio of 500:500v/v respectively. Injected 25µ L of diluent as Blank, Standard preparation (six injections) and Test preparation (one injection each) into the chromatograph, recorded the chromatogram and measured the Levonorgestrel peak response. Retention time of Levonorgestrel peak was found to be 4 min.

Its Chromatographic System Parameters are:

Column : Thermo Hypersil ODS, 125 x 4.6mm, 5µmorequivalent
Column temperature : 25°C
Flowrate : 1.3 mL/ minute
Injectionvolume : 25□l.
Detector Wavelength : 244 nm
Run time : 8 min

RESULT & DISSCUSSION

Characteristization of Drug:

All Preformulation parameters complies with BP specifications (Shown in Table No.10)

Visual Characterization: The following *Table shows Characteristic property of drug Levonorgestrel.*

Table 10: Characterization result of levonorgestrel

Test	Specifications	Results
Batch No.	-	LNG-10-01
Mfg. date	-	16-03-2010
Exp. Date	-	02-2014
Appearance	A white or almost white, crystalline powder	White crystalline powder

Solubility	Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in	Complies
Identification	IR spectrum should match with that of standard	Complies
Specific optical rotation	Between -30.0° and -35.0°	-32.5°
Loss on drying	NMT 0.50% w/w	0.15%
Sulphated ash	NMT 0.10%	0.03%
Related substances by TLC	For single spot: NMT 0.5% If two spot: NMT 0.2%	< 0.5% ND
Assay (on dried basis)	NLT 9 w/w and NMT 102.00%w\w	99.50%
Residual solvents by GCHS (ppm): Acetone Methylene	NMT 5000 ppm NMT 600 ppm	1575 410 M

Solubility of Levonorgestrel

The aqueous solubility of Levonorgestrel was approximately 9.9µg/ml at 25ºC. Sparingly soluble in methylene chloride, slightly soluble in alcohol.

Particle size analysis

Table 11: Particle Size Distribution for Levonorgestrel, BP after micronization by Malvern Method

Batch No.	Particle Size	Specifications	Results
LNG-10-03	d (0.9)	NMT 10	5.497 µ

Table 12: Particle Size Distribution for Levonorgestrel, BP

Batch No.	Specifications	Results
LNG-10-01	90% of the Particle must be less than 10µ	95% of the Particles less than 10µ

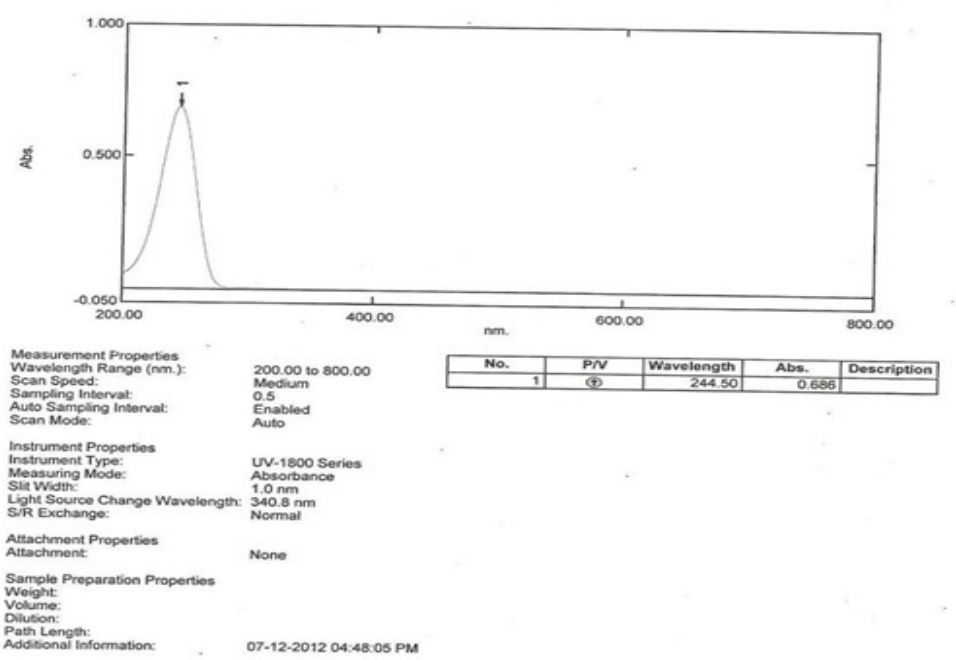


Figure 2: UV Spectrum analysis of Levonorgestrel

UV Spectrum analysis of Levonorgestrel

The UV spectrum of Levonorgestrel was found to be on 244 nm (Shown in Figure No.2).

Compatibility studies

The samples stored at 40°C±2°C/75%±5%RH did not show significant changes in physical parameters. No discoloration or odour formation was observed (Table No.12). The samples stored at 60°C±2°C / Ambient RH did not show significant changes in physical parameters. All the samples were observed for any physical change against the initial samples. No discoloration or odour formation was observed (Table No.14).The physical observation (Table 12) and related substance results (Table 13) obtained from the vials incubated with samples subjected to storage condition of 40^{O}C ±2^{O}C/75% ±5% RH are provided below:

Table 13: Physical Observation of Compatibility Samples Stored 40°C±2°C/75%±5%RH

S. No.	Samples	Drug : Excipient Ratio	Observation (Initial)	Week 2	Week 4
1	Levonorgestrel	Drug alone	A white or almost white, crystalline powder.NFF	NC	NC
2	Lactose monohydrate	Excipient alone	White to off - white, NFF powder	NC	NC
3	Maize Starch	Excipient alone	White to off - white, NFF powder	NC	NC

4	Potato Starch	Excipient alone	White to off - white, NFF powder	NC	NC
5	Talc	Excipient alone	White to off - white, NFF powder	NC	NC
6	Silica, Colloidal Anhydrous	Excipient alone	White to off - white, NFF powder	NC	NC
7	Magnesium Stearate	Excipient alone	White to off - white, NFF powder	NC	NC
8	Levonorgestrel + Lactose monohydrate	1:150	White to off - white, NFF powder	NC	NC
9	Levonorgestrel + Maize Starch	1:40	White to off - white, NFF powder	NC	NC
10	Levonorgestrel + Potato Starch	1:10	White to off - white, NFF powder	NC	NC
11	Levonorgestrel + Talc	1:5	White to off - white, NFF powder	NC	NC
12	Levonorgestrel + Silica, Colloidal	1:5	White to off - white, NFF powder	NC	NC
13	Levonorgestrel + Magnesium Stearate	1:5	White to off - white, NFF powder	NC	NC
14	Levonorgestrel+All excipients [Lactose monohydrate+ Maize starch+ Potato Starch +Talc+Silica, Colloidal	1:150:40:10:5:5:5	White to off - white, NFF powder	NC	NC
15	All excipients monohydrate+Maize starch + Potato Starch Talc + Silica, Anhydrous+ Magnesium Stearate]	150:40:10:5:5:5	White to off - white, NFF powder	NC	NC

Where, NC = No Change; NFF = Non Free Flowing

Table 14: Related Substances Results of Compatibility Samples Stored at 40ºC±2°C / 75%±5%RH in open vials.

S. No.	Samples	Drug : Excipient Ratio	Related Substances	Initial (%)	Week 2 (%)	Wee k 4 (%)
1	Levonorgestrel	Drug alone	Single Max Unknown Impurity	0.20	0.22	0.25
			Total impurities (NMT 2.00%)	0.86	0.92	1.12

2	Levonorgestrel + Lactose monohydrate	1:150	Single Max Unknown Impurity	0.12	0.14	0.20
			Total impurities (NMT 2.00%)	0.33	0.50	0.59
3	Levonorgestrel + MaizeStarch	1:40	Single Max Unknown Impurity (NMT	0.27	0.45	0.51
			Total impurities (NMT 2.00%)	0.73	1.44	1.49
4	Levonorgestrel + Potato Starch	1:10	Single Max Unknown (NMT Impurity 1.00%)	0.03	0.06	0.12
			Total impurities (NMT 2.00%)	0.03	0.13	0.35
5	Levonorgestrel + Talc	1:5	Single Max Unknown (NMT Impurity 1.00%)	0.02	0.07	0.08
			Total impurities (NMT 2.00%)	0.10	0.24	0.29
6	Levonorgestrel+ Silica,Colloidal Anhydrous	1:5	Single Max Unknown (NMT Impurity 1.00%)	0.10	0.25	0.32
			Total impurities (NMT 2.00%)	0.27	0.84	0.88
7	Levonorgestrel + Magnesium Stearate	1:5	Single Max Unknown (NMT Impurity 1.00%)	0.02	0.09	0.12
			Total impurities (NMT 2.00%)	0.23	0.29	0.49
8	Levonorgestrel + All excipients [Lactose monohydrate + Maize starch + Potato Starch + Talc + Silica, Colloidal Anhydrous + Magnesium Stearate]	1:150:40: 10:5:5:5	Single Max Unknown (NMT Impurity 1.00%)	0.05	0.07	0.09
			Total impurities (NMT 2.00%)	0.16	0.26	0.42

60°C±2°C / Ambient RH

The vials were incubated for 2 weeks at 60°C±2°C / Ambient RH. They were observed for any physical change against the initial samples and the results of the studies performed were given in Table 14.

Table 15: Compatibility Study Observation of Samples Stored at 60°C±2°C/ Ambient RH

S. No.	Samples	Drug : Excipient Ratio	Observation (Initial)	Week 1	Week 2
1	Levonorgestrel	Drug alone	White to off - white, NFF powder	NC	NC
2	Lactose monohydrate	Excipient alone	White to off - white, NFF powder	NC	NC
3	Maize Starch	Excipient alone	White to off - white, NFF powder	NC	NC
4	Potato Starch	Excipient alone	White to off - white, NFF powder	NC	NC
5	Talc	Excipient alone	White to off - white, NFF powder	NC	NC
6	Silica, Colloidal Anhydrous	Excipient alone	White to off - white, NFF powder	NC	NC
7	Magnesium Stearate	Excipient alone	White to off - white, NFF powder	NC	NC
8	Levonorgestrel + Lactose monohydrate	1:150	White to off - white, NFF powder	NC	NC
9	Levonorgestrel + Maize Starch	1:40	White to off - white, NFF powder	NC	NC
10	Levonorgestrel + Potato Starch	1:10	White to off - white, NFF powder	NC	NC
11	Levonorgestrel + Talc	1:5	White to off - white, NFF powder	NC	NC
12	Levonorgestrel + Silica, ColloidalAnhydrous	1:5	White to off - white, NFF powder	NC	NC

13	Levonorgestrel + MagnesiumStearate	1:5	White to off - white, NFF powder	NC	NC
14	Levonorgestrel + All excipients [Lactose monohydrate + Maize starch + Potato Starch + Talc + Silica, Colloidal Anhydrous + Magnesium Stearate]	1:150:40:10:5:5:5	White to off - white, NFF powder	NC	NC
15	All excipients [Lactose monohydrate + Maize starch + Potato Starch + Talc + Silica, Colloidal Anhydrous + Magnesium Stearate]	150:40:10:5:5:5	White to off - white, NFF powder	NC	NC

Where NC = No Change; NFF = Non Free Flowing

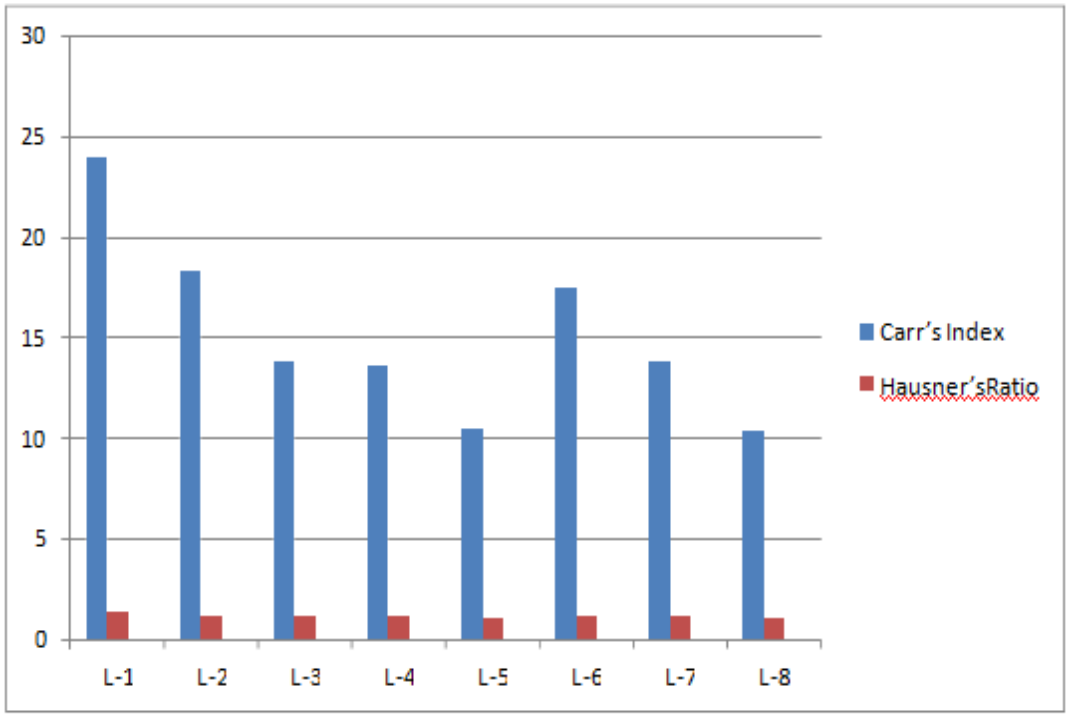
Evaluation of Pre-compression parameters

The formulation was undertaken with the aim to formulate and evaluate Levonorgestrel Immediate Release Tablet. Formulation of tablet was done by wet granulation technique because the flow properties of the powder blend (Table No.16-17) was excellent and to minimize the weight variation, improper dye filling problems. That's why the selection of excipient like Lactose monohydrate was based on wet granulation.

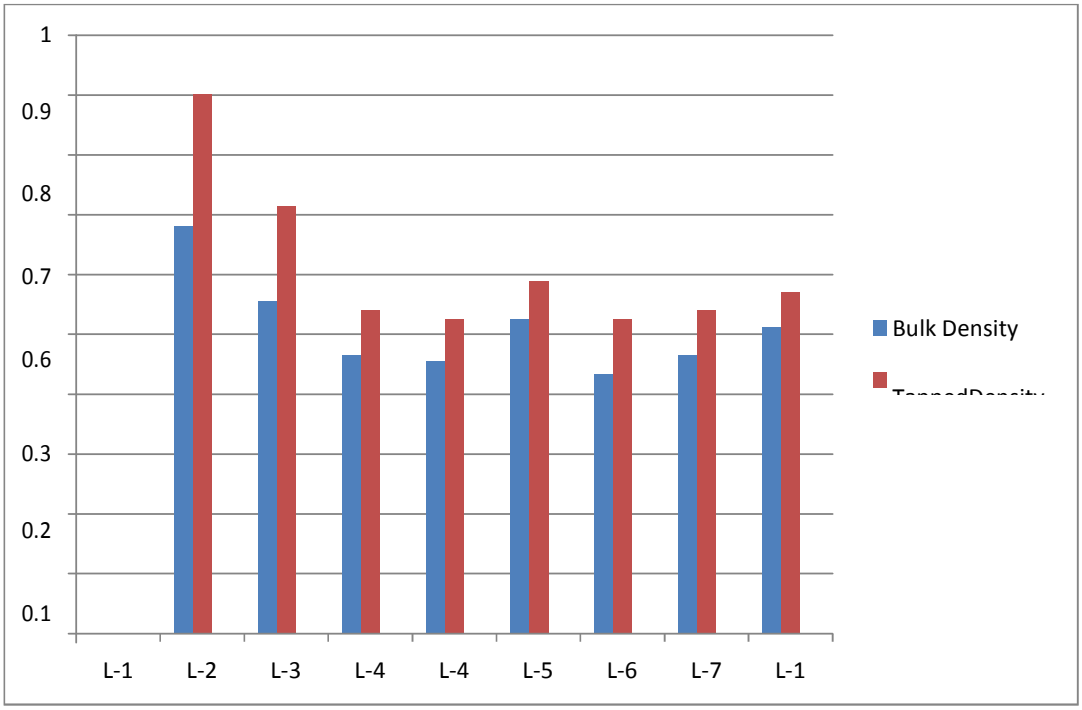
Carr's index and Hausner's ratio were in the range of 5-15 and 1.00-1.20 respectively (Table No.16-17). Hence the prepared granules have good flow property and can be used for tablet manufacturer.

Table 16: Evaluation of Pre-compression parameters

Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
L-1	0.681±0.01	0.901±0.02	24.00±0.57	1.37±0.06
L-2	0.555±0.02	0.714±0.03	18.31±1.09	1.22±0.12
L-3	0.465±0.03	0.540±0.03	13.88±0.98	1.16±0.09
L-4	0.454±0.02	0.526±0.03	13.68±1.11	1.15±0.16
L-5	0.526±0.01	0.588±0.02	10.54±0.71	1.11±0.08
L-6	0.434±0.02	0.526±0.03	17.50±1.07	1.22±0.12
L-7	0.465±0.02	0.540±0.01	13.88±1.01	1.16±0.11
L-8	0.512±0.01	0.571±0.02	10.40±0.69	1.12±0.07



Graph-1: Graph showing Bulk Density and Tapped Density of various formulations



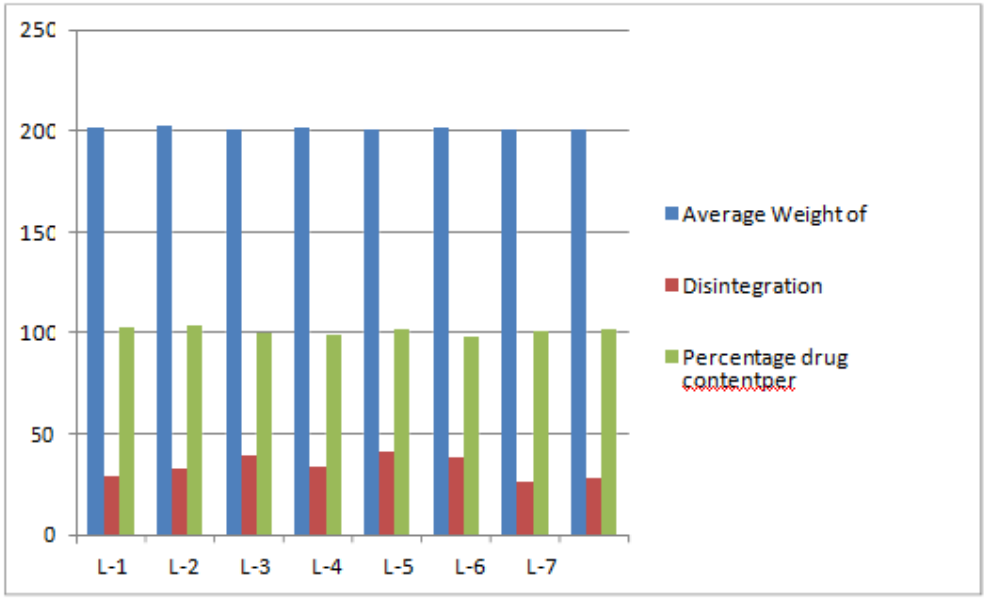
Graph-2: Graph showing Carr's Index and Hausner's Ratio of various formulations

Evaluation of Post-Compression Parameters:

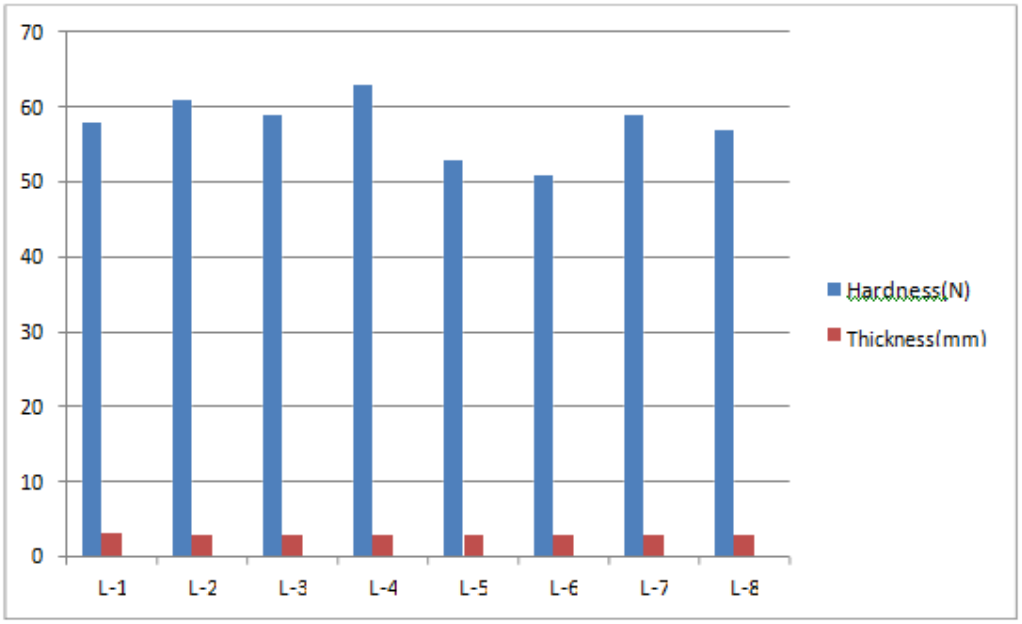
The Active pharmaceutical ingredient (Levonorgestrel) was micronized in an Air Jet Mill and the particle size of micronized API was found to be 5.49 µ which finally helped in enhancing Dissolution rate (Table No.11-12). The optimized batch was selected on the basis of better dissolution. In formulation L-1, L-2 unmicronized Levonorgestrel API was employed which shows lower in-vitro dissolution rate while all other formulations (L-3, L-4, L-5, L-6, L-7 and L-8), developed with micronized Levonorgestrel API showed good dissolution profile. Out of all the formulations L-7, L-8 showed best in-vitro release.

Table 17: Evaluation of Post-Compression Parameters

Formulation Code	Average Weight of 20 Tablets (mg)	Hardness(N)	Thickness (mm)	Disintegration time (Sec.)	Friability (%) at 100 rpm	Percentage drug content per Tablet
L-1	201.8±1.04	58±3.04	3.03±0.02	29±2.08	0.08±0.006	102.7±0.20
L-2	202.3±1.01	61±2.97	2.96±0.02	33±3.11	0.09±0.005	103.4±0.25
L-3	200.3±0.99	59±2.01	3.01±0.01	39±2.89	0.14±0.005	100.3±0.24
L-4	201.3±1.00	63±3.11	2.96±0.03	34±2.43	0.20±0.006	99.4±0.19
L-5	200.9±0.72	53±2.76	2.97±0.02	41±1.98	0.12±0.006	101.9±0.25
L-6	202.1±0.89	51±2.87	2.95±0.01	38±2.23	0.18±0.005	98.6±0.57
L-7	200.5±1.01	59±2.43	2.99±0.02	26±2.01	0.13±0.004	100.5±0.18
L-8	200.6±0.73	57±2.54	2.96±0.01	28±1.98	0.11±0.005	101.6±0.22



Graph-3: Graph showing avg wt, DT and % Drug content of various formulations



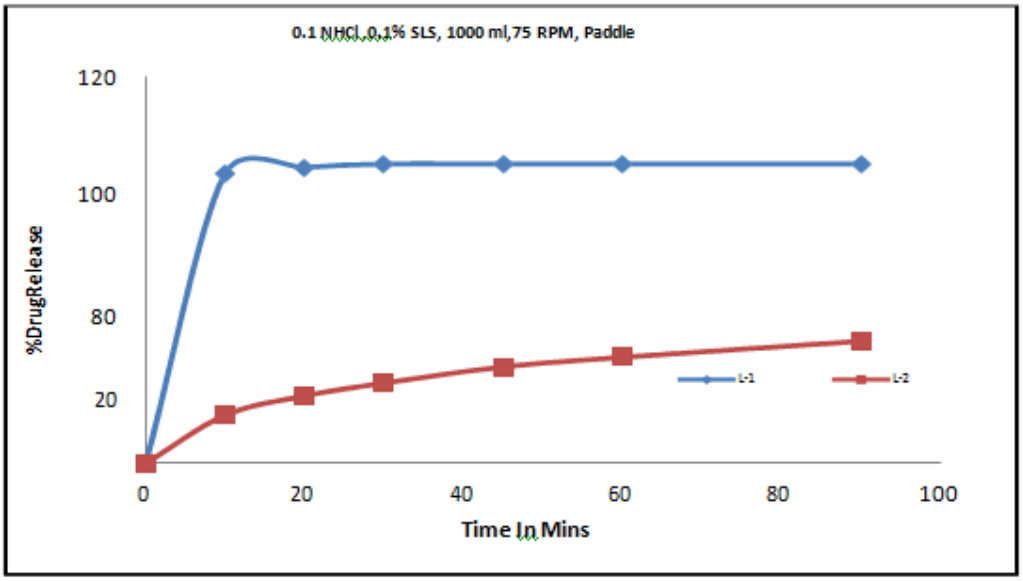
Graph-4: Graph showing Hardness, Thickness and Friability of various formulations

In-Vitro Drug Release Study of Various Formulations

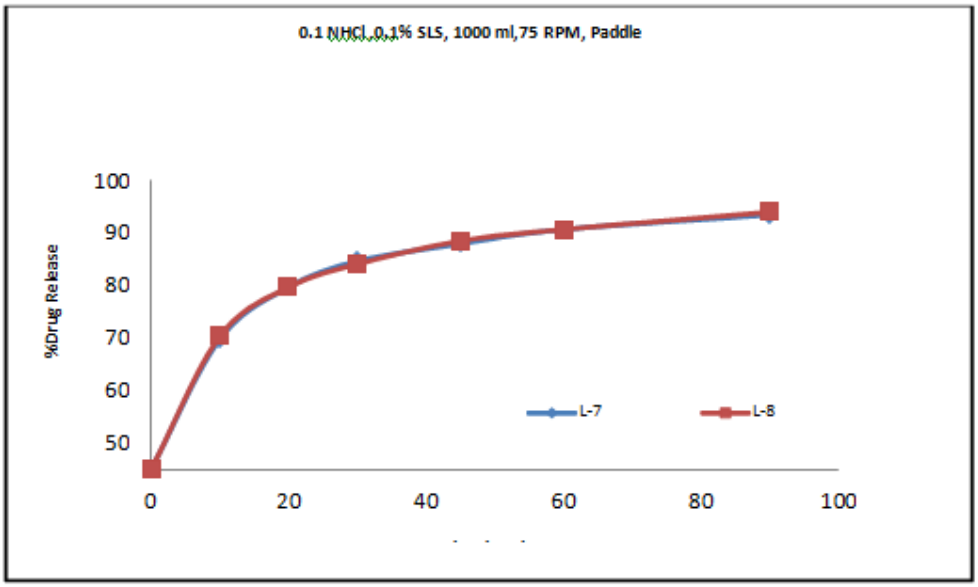
The use of disintegrates accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. Disintegration time will assists swallowing and also plays a role in increasing drug absorption, thus promoting bioavailability. Disintegration time of prepared tablets was within the range (Table No.17). In-vitro drug release study on the prepared tablets were done using 0.1N HCl, at 37± 0.5^0C. Assay of the optimized batch (L-8) was carried out by the HPLC method and was found to be 101.6±0.22%.

Table 18: In-Vitro Drug Release Study of Various Formulations

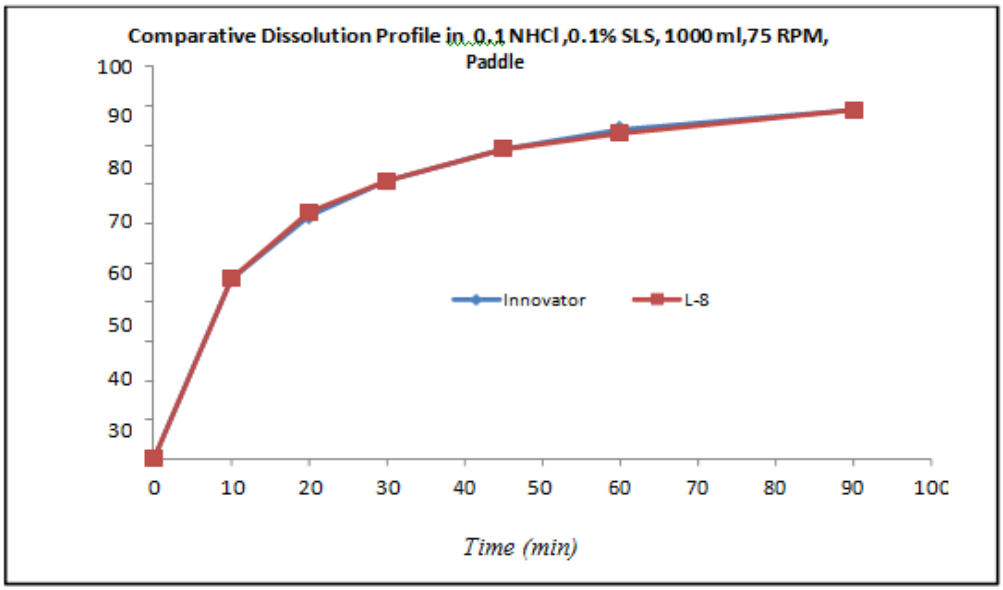
Formulation Code	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
L-1	91±0.57	92±0.50	93±0.00	93±0.51	93±0.57	93±0.50
L-2	15±1.21	21±0.98	25±0.50	30±0.59	33±0.57	38±0.81
L-3	34±0.89	47±0.57	59±1.27	68±1.51	74±0.50	77±0.68
L-4	39±1.64	50±1.23	61±0.61	68±0.58	76±1.16	79±0.45
L-5	41±1.09	50±1.32	62±0.71	67±0.57	77±0.69	80±0.50
L-6	49±0.87	61±1.19	69±0.97	76±0.59	81±0.72	88±1.21
L-7	45±0.79	63±0.52	72±0.59	78±0.87	83±0.75	88±0.00
L-8	46±0.50	63±0.57	71±0.00	79±0.50	83±0.51	89±0.46



Graph-5: Dissolution profile of L-1 and L-2 Formulations in 0.1N HCl at 75 rpm



Graph-6: Dissolution profile of L-7 and L-8 Formulations in 0.1N HCl at 75 rpm



Graph-7: Comparative Dissolution Profile of Innovator and Optimized formulation L-8 in 0.1 N HCl, 0.1% SLS, 1000 ml, 75 RPM, Paddle

Stability Studies of Selected Formulations

Based on available stability data of two batches L-7 & L-8 shows that the formulation was stable as shown in table. Stability studies revealed that there was no significant change in appearance, assay, and drug release profile at 25°C/ 60% RH, 30°C/ 65% RH, 40°C/ 75% RH After 3 Month (Table No.19,20,21).

Table 19: Stability report of L-7, L-8 at 40^0C/75% RH after 3 Month

Parameters	Formulation L-7		Formulation L-8	
	Before Stability	After Stability	Before Stability	After Stability
Average Wt.(mg)	200.5±1.01	200.6±0.32	200.6±0.73	200.4±1.21
Thickness (mm)	2.99±0.02	2.98±0.03	2.96±0.01	2.99±0.03
Hardness (N)	59±2.43	60±3.21	57±2.54	55±3.69
Disintegration Time (Sec.)	26±2.01	25±2.26	28±1.98	30±2.09
Assay (%)	100.5±0.18	100.7±0.21	101.6±0.22	100.7±0.39
Dissolution (%)	88±0.00	88±0.51	89±0.46	89%±0.67

Table 20: Stability report of L-7, L-8 at 30^0C/65% RH after 3 Month

Parameters	Formulation L-7		Formulation L-8	
	Before Stability	After Stability	Before Stability	After Stability

Average Wt.(mg)	200.5±1.01	201.1±0.76	200.6±0.73	200.4±2.11
Thickness (mm)	2.99±0.02	3.02±0.03	2.96±0.01	2.97±0.04
Hardness (N)	59±2.43	57±3.83	57±2.54	59±2.71
Disintegration Time (Sec.)	26±2.01	26±3.06	28±1.98	27±2.82
Assay (%)	100.5±0.18	101.3±0.39	101.6±0.22	100.9±0.52
Dissolution (%)	88±0.00	88±0.44	89±0.46	89%±0.0.39

Table 21: Stability report of L-7, L-8 at 25^0C/60% RH after 3 Month

Parameters	**Formulation L-7**		**Formulation L-8**	
	Before Stability	**After Stability**	**Before Stability**	**After Stability**
Average Wt.(mg)	200.5±1.01	201.4±0.98	200.6±0.73	200.1±2.01
Thickness (mm)	2.99±0.02	2.99±0.04	2.96±0.01	2.98±0.03
Hardness (N)	59±2.43	57±2.26	57±2.54	59±2.47
Disintegration Time (Sec.)	26±2.01	29±3.18	28±1.98	31±2.11
Assay (%)	100.5±0.18	100.7±0.41	101.6±0.22	101.9±0.37
Dissolution (%)	88±0.00	88±0.66	89±0.46	89%±0.72

CONCLUSION

The present study was an attempt to develop a stable immediate release tablet formulation of Levonorgestrel. The Pre- formulation studies (Physical) confirmed that there was no interaction between the drug and the proposed excipients. By using same ingredients as used by innovator we have better chance of clearing the bioavailability and bioequivalence test, therefore we were using the same ingredients as used by the innovator. After optimizing the grade of ingredients, which gave similar dissolution (75 rpm in media i.e. 0.1N Hydrochloric Acid) and disintegration time as that of innovator tablet.

The stability studies done for final optimized batch No. L-7 & L-8 according to the ICH guidelines. Evaluation of stability data indicates that there is no significant change at the end 3 Months at 40°C/75% RH, 30°C/65% RH, 25°C/60% RH with respect to all parameters as compared to the initial data. Hence the product was assumed to be stable, though the results of 6-months data will confirm its overall stability.

REFERENCES

1. Gilbert S. Banker and Neil R. Anderson Pharmaceutical dosage form Tablet. In Lachman L, Liberman HA, Kanig, JL eds. The Theory and Practice of Industrial Pharmacy. 3rd edn. Philadelphia, USA: Varghese Publishing House 1987:293

2. Chien YW. Novel drug delivery systems: fundamentals, developmental concepts, biomedical assessments. 1st edn. New York: Marcel Dekker, INC2001:1
3. Aulton ME. Pharmaceutics: the science of dosage form design. 2nd edn. Livingstone: Elsevier science Ltd2002:289-305,315-320.
4. Jain KK. Drug Delivery system-an overview. In Jain KK, Walker J, eds. Drug Delivery Systems. 8th edn. Humanapresss.2006:1
5. Swarbrick J, Boylan JC, 2002. Superdisintegrants: Characterization and function. 2nd ed. Encyclopedia of pharmaceutical technology. Marcel Dekker New York, ; 265
6. Lee TW, Robinson JR. Controlled release drug delivery system. In Gennaro A, eds. Remington: The science and practice of pharmacy. 20th edn. Pennsylvania: Mack publishing company.2001:903-905
7. Rishikesh, Mohiuddin Ahmed Bhuyian, Irin Dewan, Drishti Rani Ghosh & Md. Asraful Islam. Immediate release drug delivery system (Tablets). International journal of pharmaceutical science and research. 2012 Dec.; Vol. 4(1):124-131.
8. Richa Sood, Rathore MS, Sharma Anil, Richa Thakur, Chaudhari Jayesh, Soni Vijay. Immediate Release Antihypertensive Valsartan oral tablet: A Review. Journal of Scientific Research in Pharmacy. 2012 May; 1(2):20-26.
9. Azeem Syed, Shaweta Sharma. Immediate release drug delivery system: A Review. International Journal of Biopharmaceutical & Toxicological Research. May 2011; 1(1):24-46.
10. Chaudhary Amit, Nagaich Upendra, Neha Gulati, Sharma V. K., Khosa R. L.Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. Journal of Advanced Pharmacy Education & Research. 2012; 2(1): 32-67.
11. Mende S. Micronization of Active Pharmaceutical Ingredients (API) – from R&D to the production scale. International Nanotechnology Exhibition & Conference. 2011.
12. Brahmankar DM, Jaiswal SB. Controlled release medications, Biopharmaceutics and pharmacokinetics: A treatise. 1st edition, New Delhi: Vallabh prakashan. 1995:336,337
13. Parikh D. M. Handbook of Pharmaceutical Granulation Technology. 2nd edition. Boca Raton, FL LLC: Taylor & Francis Group; 2005. P. 1-9,191-224,159-188.
14. De Beer Thomas, Burggraeve Anneleen, Monteyne Tinne, Vervaet Chris, Remon Jean Paul. Process analytical tools for monitoring, understanding, and control of pharmaceutical fluidized bed granulation: A review. European Journal of Pharmaceutics and Biopharmaceutics. 2012 Oct.; 83(2013):2-15.
15. York P., Faure A., Rowe R.C. Process control and scale-up of pharmaceutical wet granulation processes: a review. European Journal of Pharmaceutics and Biopharmaceutics. 2001 May; 52(2001):269-277.
16. TouseyMD.Thegranulationprocess101.Basic technologies for tablet making. Pharm Tech. 2002; p. 8-13.
17. Ayasa Rana, Khokra Sukhbir Lal, Chandel Abhishek, Anda Gauri Prasad, Sahu Ram Kumar. Overview on roll compaction/dry graulation process. Pharmacologyonline. 2011; p.286-298.

18. Kleinebudde Peter. Roll compaction/dry granulation: pharmaceutical applications. European Journal of Pharmaceutics and Biopharmaceutics. 2004 July; 58 (2004): 317–326.
19. Mira Jivraj, Luigi G. Martini and Carol M. Thomson. An overview of the different excipients useful for the direct compression of tablets. PSTT, February 2000; 3(2): 58-63.
20. Sunita Rani Patra, Giri Chandan Kumar, Mallick Subrata. Preparation and Physicomechanical characterisation of Naproxen tablets by direct compression method. International journal of Pharma. Research & Development- Online (IJPRD). 2011 April; 3(2):193-201.
21. Swarbrick James, Superdisintegrants: Characterization and function, In: Augsburger Larry L. Et al. Encyclopedia of pharmaceutical technology, 3rd ed., New York: Informa Healthcare; 2002, Vol. 1. P.3553-3566.
22. Sampath Kumar K. P., Bhowmik Debjit, B Chiranjib, Yadav Jitendra, ChandiraR.M. Emerging Trends of Disintegrants used in Formulation of Solid Dosage Form.Der Pharmacia Lettre. 2010; 2 (1): 495-504.
23. S. Chandrashekhara, Deshmkh Himanshu, C. Nagesh, Murade Amol, Usgaunkar Shridhar. Superdisintegrants: A Recent Investigation and Current Approach. Asian J. Pharm. Tech. 2012; 2(1):19-25.
24. http://www.pharmainfo.net/exclusive/reviews/current status of tablet disintegrants: areview.
25. Sunada HY, Yonezawa Y, Danjo K. Evaluation of rapidly disintegrating tablets prepared by a direct compression method. Drug development and industrial pharmacy, 1999; 25 (5),571-581
26. http://formulation.vinensia.com/2011/05/tablet-defects-cause-and-remedy.html
27. http://www.pharmainfo.net/rajapicta1023/blog/problems-associated-tabletmanufacturing.
28. Swarbrick James. Biopharmaceutics. In: Leon Shargel, Andrew B.C. Yu. Encyclopedia of pharmaceutical technology," 3rd ed., New York: Informa Healthcare USA, 2002, Vol.1. P.223.
29. Tripathi KD, "Essentials of Medical Pharmacology," 4th edition, New delhi: Jaypee Brothers medical publishers (p) ltd; 2004, P.285 -286.
30. Machin David, Day Simon, Green Sylvan, "Textbook of Clinical Trials," John Wiley & Sons Ltd, 2004, P. 315-336.
31. Laurence L. Brunton, **"**Estrogens and Progestins," Goodman and gillman's The Pharmacological basis of Therapeutics, 11th edition, Newyork:McGraw-Hill.
32. Westley E., Hertzen H. von, Faundes A. Expanding access to emergency contraception. International Journal of Gynecology and Obstetrics. 2007; vol. 97: 235–237.Hertzen Helena von, Piaggio Gilda. Levonorgestrel and mifepristone in emergency contraception. Elsevier Steroids. 2003; 68:1107–1113.
33. Abu Hasanat Md. Zulfiker, Km. Monirul Islam, Rubaya Islam, Kazi Rashidul Azam, Md. Selim Reza, "Formulation Development Using Maize Starch & Avicel Ph101 As

Disintegrating Agents And Their Effect on Physical Characteristics &In Vitro Release Profile," International journal of pharmaceutical science and research, 2011, Vol. 2(8),2136-2141.

34. Azeem Syed, Shaweta Sharma, "Immediate release drug delivery systems: A review, International Journal of Biopharmaceutical & Toxicological Research," Volume-1,issue-1,May2011,25-46.
35. Bansal Kailash, Pant Pankaj, Rao P. Rama Therdana, Padhee Kumud, Sathapathy Ajit, "Micronization And Dissolution Enhancement of Norethindrone," International Journal of Research In Pharmacy And Chemistry, 2011, 1(3),315- 319.
36. Bhardwaj Sudhir, Jain Vinay, Jat R.C., Mangal Ashish, Suman Jain, "Formulation and evaluation of fast dissolving tablet of aceclofenac," International Journal of Drug Delivery, 2 (2010),93-97.
37. Bresolin, Block, L.C., Schemling, L.O., Couto, A.G, Mourão, S.C., T.M.B., "Pharmaceutical equivalence of metformin tablets with various binders," Journal of Basic and Applied Pharmaceutical Sciences, 2008, v. 29, n.1, p.29-35.
38. Chandrashekhara S., Deshmkh Himanshu, Nagesh C., Murade Amol, Shridhar Usgaunkar. "Superdisintegrants: A Recent Investigation and Current Approach," Asian J. Pharm. Tech, 2012, Vol. 2: Issue 1, Pg19-25.
39. Consiglieri Vladi Olga, Mourao Samanta, Sampaio Mauricio, Patricia Granizo, Pedro Garcia, Valeska Martinello, Rodrigo Spricigo, Humberto Gomes Ferraz, "Improvement of fluconazole flowability and its effect on dissolution from tablets and capsules," Brazilian Journal of Pharmaceutical Sciences, vol. 46, n. 1, jan./mar.,2010,115-120.
40. Govedarica Biljana, Rade Injac, Rok Dreu, Stane Srcic," Formulation and evaluation of immediate release tablets with different types of paracetamol powders prepared by direct compression," African Journal of Pharmacy and Pharmacology,2011, Vol. 5(1), pp.31-41.
41. Gowtham M., Vasanti. S., Rohan R.D., Ashwath N., Paridhavi M., "Formulation and evaluation of immediate release folic acid tablets," Der Pharmacia Lettre, 2011, 3 (6):157-162.
42. Jayaprakash S., Halith S. Mohamed, Pillai K. Kulathuran, Priya Balasubramaniyam, P. U. Mohamed Firthouse, M .Boopathi, "Formulation and evaluation of bilayer tablets of amlodipine besilate and metprolol succinate," Der Pharmacia Lettre, 2011: 3 (4)143-154.
43. Lukkad Harish R., Bhoyar Pravin K., Baheti Jagdish R., Somnathe Nitin D., Nagulwar Dhanashri B., Kathade P.P., "Formulation And Evaluation of Aceclofenac Orodispersible Tablets Using Natural Disintegrant," World Journal of Pharmacy And Pharmaceutical Sciences, 2012, Volume 1, Issue 2,601-609.
44. Mowafaq M., Abdul Jaleel, Omar W, Abdulrasool, Alaa A, Ghareeb, "Preparation and Characterization of Orally Disintegrating Loratadine Tablets from PVP Solid Dispersions," International journal of pharmaceutical sciences, 2010;2(3):759- 770.
45. Mohammed B. B., Isah A. B., Ibrahim M. A., "Influence of Compaction Pressures On Modified Cassava Starch As A Binder In Paracetamol Tablet Formulations," Nig.

Journ. Pharm. Sci., March, 2009, Vol. 8 No. 1, P. 80 –88.

46. Nalini Shastri, Kiran T., Sistla Ramakrishna, Sadanandam M., "Surface Solid Dispersion of Glimepiride For Enhancement of Dissolution Rate," International Journal of PharmTech Research, Vol.1, No.3, pp822-831.
47. Othman A. A., David M. Tenero , Duane A. Boyle , Natalie D. Eddington , Michael J. Fossler, "Population Pharmacokinetics of S(–)-Carvedilol in Healthy Volunteers After Administration of the Immediate-Release (IR) and the Controlled-Release(CR) Dosage Forms of the Racemate, "The AAPS Journal,2007; 9(2), E208-E218.
48. Pathak Naveen, Kumar Anuj, Methkar Vishal, Pant Pankaj and Rao Rama Therdana, "Formulation and Optimization of Immediate Release Tablet of An Antialcohlic Drug By Dry Granulation Method," International Journal of Comprehensive Pharmacy, 2011, 3 (08),1-4.
49. Prasanth Sai R.V., I. Pujitha, Srinivas Thota and Nagu A., "Formulation and Development of Entecavir Tablets," International Journal of Research in Pharmaceutical and Biomedical Sciences, Jul – Sep 2011,Vol. 2 (3),1239-1247.
50. Rahman Md. Mofizur, Sumon Roy, Hasan Sayeed, Alam Md. Ashiqul, Mithilesh Kumar Jha, Ahsan Md. Qamrul, Ferdaus Md. Jannatul, "Effect of Mode of Addition of Disintegrates on Dissolution of Model Drug From Wet Granulation Tablets," International Journal of Pharma Sciences and Research (IJPSR), Vol.2(2), 2011,84-92.
51. Rajpoot A., Tiwari A.K., Shah H., Singhal Manmohan, "Formulation and In-vitro Evaluation of Immediate release tablets of Drotaverine HCl," Journal of Chemical and Pharmaceutical Research, 2011, 3(4),333-341.
52. Rao N. G. Raghavendra, Thube Ketan, Pentewar Ram and Suryakar V.B, "Comparison of Different Superdisintegrants In Designing of Fast Dissolving Tablets of Metoprolol Tartrate," International journal of pharmaceutical science and research, (2010), Vol. 1, Issue4,56-66.
53. Reddy Y. Dastagiri, Ravi Sankar V., Dachinamoorthy D., Rao A. Nageswar and Chandra Sekhar K. B., "Conseption and evaluation of Gemfibrozil as immediate drug delivery system," J. Chem. Pharm. Res., 2010, 2(2),590-597.
54. Wankhede Sachin V., Krishnaprasad M., Manjunath SY, Debnath Subal, "Formulation and stabilization of Atorvastatin tablets," J. Chem. Pharm. Res., 2010, 2(5):548-554.
55. Yadav Virendra, Parashar Bharat, Maurya Brajesh, Sharma Love, "Fast Dissolving Tablet," International Journal of Applied Pharmaceutics, Vol 4, Issue 2, 2012,17-22.
56. http://www.drugbank.ca/drugs/DB00367
57. Hand book of Pharmaceutical Excipients, 4th ed, Raymond C Rowe, PaulJ Sheskey, Pharmacuetical Press,297,186,508
58. USP/NF. Physical Tests: Disintegration (701). 22/17 ed. Rockville, MD: United States Pharmacopeial Convention Inc;1990
59. Raymond C Rowe, Pawl J Sheskey and Sian C Owen, Handbook of Pharmaceutical Excipients, 5th ed. London: Pharmaceutical Press, 188-191, 386- 395, 430-433, 725-

736,767-769.

60. Okoye Ebere I., Onyekweli Anthony O. and Kunle Olobayo O. Brittle fraction index (bfi) as a tool in the classification, grouping and ranking of binders in tablet formulation: Paracetamol Tablets. International Journal of Applied Biology and Pharmaceutical Technology. 2012, April-June; 3(2):261-271.
61. Burra Shashidher, Kudikala Sarala and Reddy Gopu Jayaparakash. Formulation and evaluation of Simvastatin liquisolid tablets. Scholars Research Library- Der Pharmacia Lettre. 2011; 3(2):419-426.
62. Shukla Vikesh, Manvi F.V. Effect of two different superdisintegrants on combinaion dispersible tablets of isoniazid and rifampicin for oral treatment of tuberculosis. International Journal of Drug Delivery 2 (2010);322-332.
63. Mohini K., Narmada G.Y. et al. Formulation, Evaluation and Optimization of fast dissolving tablets containing Amlodipine Besylate by sublimation method. Ars Pharm, 2009; 50 (3):129-144.
64. Bhawana Sati, Hemlata Sati, Bhatt Prakash Chandra. A study on evaluation and formulation of Amalakyadi tablets. Journal of Pharmacy Research. 2011; 4(12): 4453-4454.
65. Pharmaceutical Stability. USP 28 NF 23. Asian edition. The official compendia of standards. United States Pharmacopoeial Convention, Inc TwinbrookMD Mehta R.M. Pharmaceutics-I. 3rd edition. Delhi: Vallabh Prakashan; 2006. P.238.
66. ICH Topic Q 1 A (R2), Stability testing of new drug substances and products. August 2003CPMP/ICH/273699:2-5.
67. U.S. Food and Drug Administration. Draft Guidance for Industry, ANDAs: Impurities in Drug Substance. January2005.