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Development and Testing of an Immediate Release Tablet of Levonorgestrel

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Abstract

The study's goal was to create and optimise an oral medication delivery formulation of the hormonal contraceptive levonorgestrel. Pre-formulation tests were carried out to determine the medication excipient compatibilities. Crospovidone and sodium starch glycolate superdisintegrants were utilised to provide quick medication release from tablets. All pre-compression and post-compression characteristics were examined for the manufactured tablets. FTIR was used to evaluate the drug-excipient interaction. The pharmacopoeial standard was met by all formulations. The study found that formulations created by direct compression F9 have the greatest dissolution employing both crospovidone and SSG, resulting in 93.13% quicker drug release over a 60-minute period, with a 45-second disintegration time when compared to other Levonorgestrel formulations. The current project's goal was accomplished by generating a product with the same release profile as the innovator's product. We may infer from this study that an instant release tablet of Levonorgestrel can be developed and has a better drug release response.

Keywords: *Immediate Release, Levonorgestrel, Superdisintegrants, Direct Compression*

INTRODUCTION

Tablets are the most common dosage form available today due to their ease of self-administration, compactness, and ease of production, as well as their often instantaneous beginning of action and,

most importantly, their ability to retain their stability parameter throughout the shelf life.

Contraceptives include IUDs, tablets, pills, and implants. There are significant drawbacks to utilising tablets, including a longer period to medication release and a slower start of effect. As a result, the rapid release tablet works without producing any complications. An instant release dosage form allows a firm to maintain market exclusivity while providing a convenient dose form or dosing regimen to the patient. Instant release tablets are ones that are designed to dissolve and release their medication without the use of a particular rate regulating element, such as a special coating or other procedures. An immediate release drug delivery system may provide a solution to these issues. Recently, rapid release tablets have gained appeal and acceptability as a medication delivery strategy, owing to its convenience of administration, early beginning of action, low cost, and improved patient compliance.

They may also be used to grow markets, prolong product life cycles, and generate possibilities. Immediate release pills breakdown quickly and dissolve to release the medication. Immediate release can be achieved by using an adequate pharmaceutically acceptable diluent or carrier that does not significantly slow down the rate of drug release and/or absorption.

Emergency contraception (EC) is a type of contraception intended to prevent pregnancy following unprotected sexual contact. Emergency contraception is only effective in the first few days after a sexual encounter, before the ovum is released from the ovary and the sperm fertilises the ovum. Emergency contraception tablets cannot disrupt an ongoing pregnancy or injure a growing embryo, and so cannot result in abortion. Emergency contraception prevents around 85 percent of births but does not substitute for regular contraception. Levonorgestrel EC does not interfere with a previously established pregnancy. Levonorgestrel belongs to the progestin drug class. It prevents fertilisation of the egg by inhibiting the release of an egg from the ovary. It may also function by altering the uterine lining to inhibit pregnancy development. Although levonorgestrel can prevent pregnancy, it cannot prevent the transmission of HIV and other sexually transmitted infections.

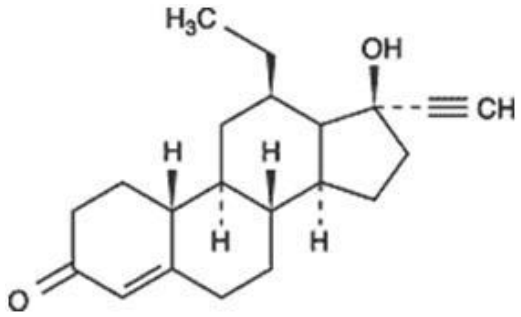

Figure 1: Structure of Levonorgestrel.

The present study subject aims to develop and test an instant release drug delivery system for levonorgestrel via a direct compression approach, which eventually improves drug bioavailability and provides an immediate release effect that improves birth control. The primary goal of the present study issue is to provide quicker drug release from the tablet, resulting in immediate action and aiding in birth control by acting as an emergency contraceptive.

MATERIALS AND METHODS

Materials

Levonorgestrel was received as a gift sample from Famy care Pvt. Ltd. Ahmadabad. Sodium starch glycolate was purchased from Yarrow Chem Pvt. Ltd. Mumbai. Crospovidone, Mannitol, Magnesium stearate and Talc were procured from Loba Chem Pvt. Ltd. Mumbai. All other chemicals and reagents used for these studies were of analytical grade.

METHODS

Formulation of Levonorgestrel Immediate Release Tablets [8,9]

Levonorgestrel tablets were prepared by direct compression techniques as per the formula given in the table1. The superdisintegrants such as crospovidone and SSG were used in different proportions.

All the ingredients were passed through sieve no. #40 and were subjected for drying to remove moisture content at 40-45ºC. Weighed amount drug and excipients except magnesium stearate and talc were mixed properly by geometric addition method for 20 min. manually. Talc and magnesium stearate were then passed through sieve no. #80 then mixed and blended well with the initial mixture. The mixed blend of drug and the excipients were compressed on Karnavati rotary punching machine.

Table 1: Composition of Levonorgestrel Immediate release tablets

Sr. no.	Ingredients (mg/tablets)	Batch number								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Levonorgestrel	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
2	Crospovidone	10	20	30	-	-	-	5	10	15
3	SSG	-	-	-	10	20	30	5	10	15
4	Mannitol	104.5	94.5	84.5	105.5	94.5	84.5	104.5	94.5	84.5
5	MCC	80	80	80	80	80	80	80	80	80
6	Magnesium stearate	2	2	2	2	2	2	2	2	2
7	Talc	2	2	2	2	2	2	2	2	2
	Total weight	200	200	200	200	200	200	200	200	200

Evaluation Parameters [10-18]

Drug excipient compatibility study

Infrared (IR) spectroscopy

Fourier Transform Infra-Red Spectroscopy of drug and polymer were recorded on JASCO FT-IR-4600 spectrophotometer using KBr powder. The instrument was operated under dry air purge and the scans were collected at scanning speed 2mm/sec with resolution of 4 cm^{-1} over region 4500-400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry was performed for drug on Hitachi 2070 instrument. Thermographs were obtained by heating 1mg samples in aluminum pans at heating rate 100°/min, from 30°C to 350°C, in a nitrogen atmosphere (flow rate 20ml/min).

Pre-compression parameters Angle of repose

The fixed funnel method was used to calculate the angle of repose. The precisely weighed powder enters the funnel. The height of the funnel is adjusted such that the tip of the funnel just reaches the peak of the pile's head. The powder is allowed to pour through the funnel and onto the surface. The following formula is used to calculate the angle of repose:

$$\mathbf{Tan\theta = h/r}$$

Where,

h - Height of pile. r - Radius of pile.

Loose bulk density (LBD)

Apparent LBD was determined by pouring blend into a cylinder. The bulk volume and weight of the powder were determined.

LBD = Weight of the powder (M)/volume of the packing (Vo)

Tapped bulk density (TBD)

The measuring cylinder containing mass of blend was tapped for a fixed time. The minimum volume occupied on the cylinder and weight of the powder blend as measured.

TBD = Weight of the powder (M)/tapped volume of packing (Vt)

Carr's compressibility index

The compressibility index is measure of the propency of the powder to be compressed. As such they are measures of relative importance of inter-particulate interactions. Compressibility is the ability of powder to decrease in volume under pressure using bulk density and the tapped density the percentage compressibility of powder were determined, which is given as Carr's compressibility index. It is indirectly related to the relative flow rate.

Carr's compressibility index = [(TBD-LBD) ×100] / TBD

Hausner's ratio

Hausner's ratio indirectly the flow property of the powder and measured by the ratio of tapped density to bulk density.

Hausner's ratio = Tapped density / bulk density

Post compression parameters

All 9 batches of tablet were evaluated for various parameter such as weight variation, friability, hardness, drug content, dissolution, disintegration and result are reported in table no 3 and 4.

Weight variation test

The weight variation test is carried out to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average weight is calculated. The individual weight of each tablet is also determined to find out the weight variation.

Percentage weight variation = (average wt. of tablet - wt. of each tablet) / average wt. tablet

Hardness

Hardness of the tablet was determined by Monsanto hardness tester. It is expressed in kg/cm^2.

Thickness

The thickness and diameter of the tablet were determined using electronic Vernier's caliper. Totally 3 tablets of each type of formulation were used and average values were calculated. It is expressed in millimeter (mm).

Friability test

About 10 previously weighed tablets were placed in the friability apparatus chamber, which was given 100 revolutions in 4 minutes and the tablets reweighed. The percentage friability was calculated using following formula:

Percentage friability = (initial wt.-final wt. / initial wt.)×100

Disintegration test

The disintegration test was done on six tablets using Indian pharmacopoeia method. At the end of the specific time lift the basket and observe that the tablets pass the test that is all six units disintegrated.

Drug content

An accurately weighed tablet containing about 1.5mg of Levonorgestrel is dissolved in methanol and taken into 100 ml of volumetric flask. Then pipette out 10 ml of above solution then diluted up to 50 ml. From this standard solution again 5ml pipette out and diluted upto 50 ml with 0.1 N HCl, resulting solution was measured at 242 nm and drug content was calculated against 0.1 N HCl as blank.

In vitro dissolution study

In vitro dissolution study was performed using USP type 2 apparatus (Paddle) at 50 rpm, 900 ml 0.1 N HCl was used as dissolution medium which maintained at 37± 0.5ºC. At definite time interval 2ml of the sample fluid was withdrawn, filtered through 0.45µm membrane filter and again 2ml fluid sample was replaced. Suitable dilutions were done with dissolution sample, and the sample was analyzed spectrophotometrically at 242 nm.

Stability study

The 45 days accelerated stability studied ware carried out for optimized formulation according to international conference on harmonization (ICH) guidelines. Selected sterile formulations were subjected to stability testing. The Immediate release tablet formulation were filled in glass vials, closed with gray rubber closure and sealed with aluminium caps. The formulation vials kept in stability chamber maintained at 40±2ºC temperature and relative humidity 75±5% for 45 days.

RESULT AND DISCUSSION

Analytical method

The calibration curve in 0.1 N HCl was linear in concentration range between 1-10 µg/ml at 242 nm. Results were plotted in figure 1.

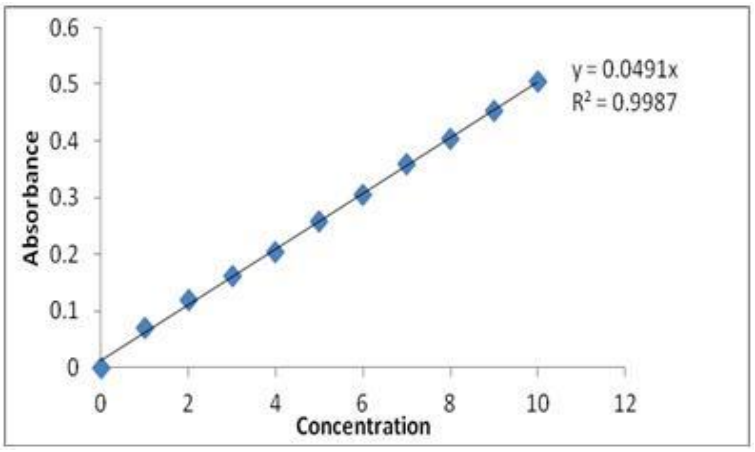

Figure 2: Standard calibration curve for Levonorgestrel in 0.1 N HCl.

Melting point determination

The melting point of Levonorgestrel was found to be 239ºC to 241ºC, thus indicating purity of the obtained drug sample. The observed melting point was in accordance with the literature.

Drug excipient compatibility studies

Drug excipient compatibility study of Levonorgestrel with different categories of excipients was carried out. The FTIR spectra Levonorgestrel showed the characteristic absorption peak at 1653.66 cm-1 assigned to C=O stretching, peak at 3347.82 cm^{-1} assigned to O-H stretching, peak at 656.64 cm^{-1} assigned to =C-H

Bending, peak at 1066.44 cm^{-1} assigned to C-O stretching and peak at 2932.23 cm^{-1} assigned to =CH stretching which correspondence with standards stated as per official pharmacopoeia. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipient used. From the IR spectrum figure 3 and 4, it was observed that there were no changes in these main peaks in IR spectra of drug and excipients, which shows that there were no physical interaction because of some bond formation between drug and polymer. This indicates that drug was compatible with the formulation component.

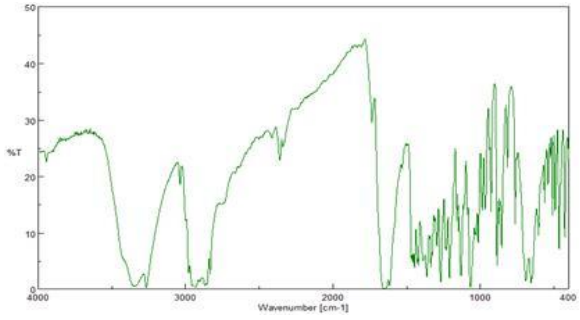

Figure 3: FTIR spectrum study of Levonorgestrel

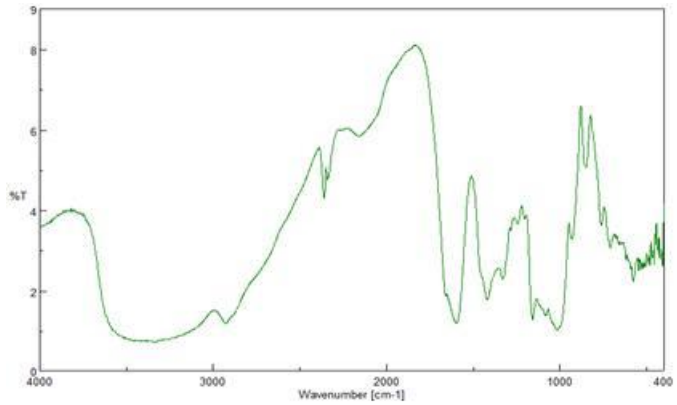

Figure 4: FTIR spectrum study of Levonorgestrel with Crospovidone and SSG

Pre-compression parameters Powder flow characteristics

Table 2: Pre-compression parameters of Levonorgestrel Immediate release tablets.

Formulation code	Bulk density(gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose(θ)	Carr's index(%)	Hausner's ratio
F1	0.40±0.025	0.45± 0.037	25.3 ±0.72	11.11±0.8	1.12 ±0.06
F2	0.42±0.010	0.50± 0.019	28.3 ±0.35	16.60±0.7	1.19±0.02
F3	0.46±0.022	0.55± 0.022	25.6 ±0.41	16.36±0.5	1.19±0.05
F4	0.44±0.015	0.49± 0.021	26.8 ±0.45	17.03±0.4	1.06±0.06
F5	0.49±0.030	0.53± 0.030	27.4 ±0.45	14.44±0.7	1.18±0.05
F6	0.41±0.034	0.49± 0.010	26.7 ±0.30	13.62±0.6	1.09±0.02
F7	0.47±0.017	0.56± 0.023	26.8 ±0.41	12.88±0.5	1.10±0.01
F8	0.42±0.040	0.54± 0.012	25.4 ±0.32	15.97±0.5	1.17±0.07
F9	0.46±0.020	0.51± 0.027	27.7 ±0.51	11.56±0.7	1.13±0.03

Mean±SD (n=3)

The powder prepared for compression of immediate release tablets were evaluated for their flow properties; the results are shown in table 2. The angle of repose was in the range of 25.3º±0.72 to 28.3º±0.35 which indicate excellent flow of the powder for all formulations. The

LBD of the powder formulations were in the range of 0.40±0.025 to 0.49±0.030 gm/ml; the TBD was in the range of 0.45±0.037 to 0.56±0.023 gm/ml, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 11.11±0.8% to 17.03±0.4%, and the Hausner's ratio was found to be in the range of 1.06±0.06 to 1.19±0.05, indicating compressibility of tablet blend was good. Hausner ratio was <1.25 for all bathes indicating good flow properties. These values indicate that the prepared powder exhibited good flow properties.

Post compression parameters Thickness test

The values are almost uniform in all formulations. Thickness was found to be in the range of 3.41±0.01 mm to 3.42±0.06 mm respectively. Results are discussed in table 3.

Hardness and Friability

Tablet required specific amount of strength or hardness and resistance of friability. It is necessary or important to withstand mechanical shocks of handling in manufacture and packaging. The measured hardness of tablets of all formulations, ranged in between 3.41±0.16 to 4.17±0.24 kg/cm^2. This insures good handling characteristics of all formulations. Friability was found in the range of 0.65±0.02 to 0.86±0.06%. it shows that the tablets possess good mechanical strength. Results are discussed in table 3.

Weight variation test

All the tablets passed weight variation test as the % variation was within the pharmacopoeia limit of ±7.5%. It was found to be from 197±1.1 to 201±0.7 mg. the weight of the all tablets found to be uniform range. This is due to good flow characteristics and compressibility.

Drug content

Drug content of all the formulations was in the range of 96.55±0.5 to 100.76±0.4 % of Levonorgestrel. It complies with official specifications in pharmacopoeia. Results are discussed in table 4.

Table 3: Post-compression parameters of Levonorgestrel Immediate release tablets

Formulationcode	Thickness(mm)	Hardness(kg/cm^2)	Friability(%)	Weight variation (mg)
F1	3.41±0.06	3.73±0.24	0.69±0.05	198±0.4
F2	3.42±0.05	3.53±0.13	0.73±0.04	200±0.5

F3	3.42±0.06	4.03±0.32	0.68±0.03	199±0.5
F4	3.41±0.03	3.96±0.41	0.78±0.01	197±1.1
F5	3.41±0.01	3.83±0.18	0.65±0.02	200±0.9
F6	3.42±0.04	3.85±0.08	0.77±0.04	201±0.7
F7	3.41±0.02	4.15±0.10	0.86±0.06	201±0.7
F8	3.41±0.05	4.17±0.24	0.82±0.01	200±0.8
F9	3.42±0.03	3.41±0.16	0.72±0.02	200±0.4

Mean±SD (n=3)

Table 4: Post-compression parameters of Levonorgestrel Immediate release tablets

Formulationcode	Drug Contents(%)	Water Absorption Ratio	Wetting Time (Sec.)	Disintegration time (Sec.)
F1	98.66±0.1	21.28±0.39	26±0.57	55±0.57
F2	96.55±0.5	26.76±0.38	24±0.5	59±1.52
F3	99.66±0.5	25.61±0.28	21±0.57	61±2.30
F4	97.33±0.3	31.00±0.49	35±1.15	98±1.15
F5	98.89±0.8	33.13±0.43	31±1.52	92±1.52
F6	97.09±0.2	37.18±0.49	33±1.15	87±2.64
F7	99.00±0.6	20.98±0.39	16±1.0	58±2.51
F8	98.65±0.3	21.17±0.39	17±1.15	52±1.15
F9	100.76±0.4	22.88±0.49	15±0.57	45±0.57

Mean±SD (n=3)

Water absorption ratio

The ratio values of formulations found in the range of 20.98±0.39 to 37.18±0.49, the water absorption ratio result shown in table 4.

Wetting time

Wetting is closely related to inner structure of tablet and the hydrophilicity of the polymers. The wetting time of all the formulations was very fast. This may be due to swelling and also capacity of the absorption of water. Crospovidone, SSG and MCC absorb water in all formulations and shows fast wetting time. The results are shown in table 4.

Disintegration test

Disintegration was carried out according to Indian pharmacopoeia. For all the formulations disintegration time was found to be in the range between 45±0.57 to 98±1.15 sec. The results are discussed in table 4.

In-vitro dissolution study

Dissolution rate studies showed that about 67.36 to 93.13 % drug release within 1 hour for all formulations using superdisintegrants such as crospovidone and SSG. The results are shown in table 5. The results indicate that the formulation F9 which was prepared using both crospovidone and SSG as superdisintegrants, showed the drug released within 45 min. The in-vitro drug release of all developed formulations were within acceptable ranges of values as given in official pharmacopoeia but it was observed that the physical properties of F9 was best comparable with marketed formulation. The results indicate that the drug release increases with increase in concentration of superdisintegrants. The results are discussed in figure 5 & 6.

Table 5: Dissolution Study for the prepared IR formulations and innovator

Time	Cumulative % Drug release from immediate release tablets and innovator									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	Innovator
0	0	0	0	0	0	0	0	0	0	0
5	10.99	13.44	12.21	7.331	7.33	10.99	17.10	17.10	12.21	18.32
10	17.12	20.78	20.78	14.67	20.78	20.78	26.90	29.34	29.34	26.90
15	31.80	31.80	31.80	26.90	29.35	29.36	41.59	41.59	39.15	45.26
30	53.83	58.72	53.83	37.93	39.16	39.17	64.86	64.86	70.96	67.31
45	73.44	66.12	66.11	48.97	51.43	59.98	75.93	77.15	85.70	77.16
60	75.97	77.19	84.52	67.36	69.81	72.27	88.23	89.46	93.13	89.41

Stability studies

The formulations F9 was selected for stability studies on the basis of their high cumulative % drug release and also result of in-vitro disintegration time. The stability studies were carried out 40ºC±2ºC temp. & 75±2% RH for the selected formulation upto 45 days. The results obtained are discussed in table 6, from these results it was concluded that, formulation F9 was stable and retained their original properties.

Table 6: Evaluation of various parameters of optimized F9 batch after stability study

Formulation code	Tested after time in days	Hardness (kg/cm^2)	Disintegration time (sec.)	Drug release(%)	Drug content(%)
F9	45	3.30±0.04	47±0.57	89.45	98.81

Table 6: Evaluation of various parameters of optimized F9 batch after stability study

Formulation code	Tested after time in days	Hardness (kg/cm^2)	Disintegration time (sec.)	Drug release(%)	Drug content(%)
F9	45	3.30±0.04	47±0.57	89.45	98.81

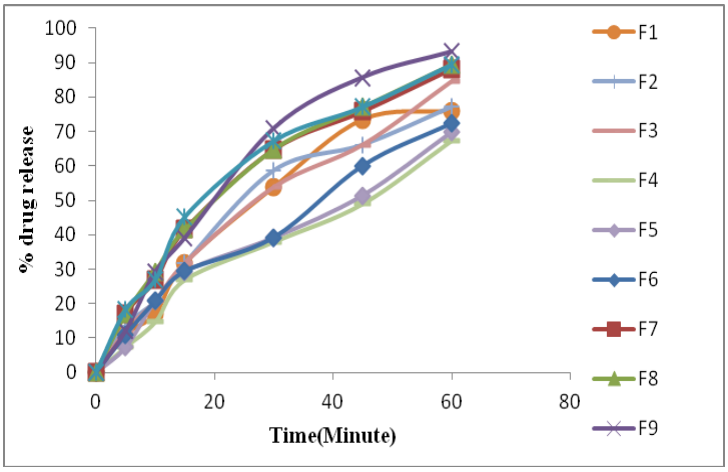

Figure 5: % Drug release of formulated IR tablets and marketed innovator

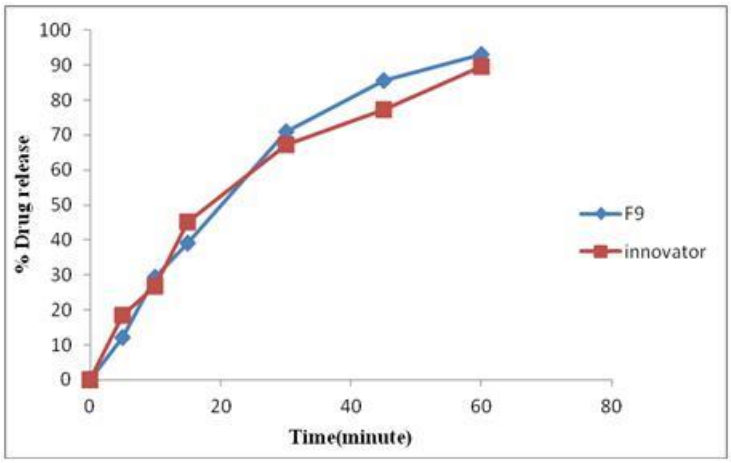

Figure 6: Comparative Dissolution profile of innovator and optimized formulation (F9).

CONCLUSION

The selected excipient amounts were used

to produce levonorgestrel instant release tablets using direct compression. The prepared tablets were tested for both pre-compression and post-compression characteristics as required by standards and confirmed to be within the limit. During formulation optimization, it was discovered in dissolving studies that reducing the proportion of diluents and increasing the concentration of superdisintegrants resulted in an improved release profile. This study concluded that the inclusion of superdisintegrants and subsequent formulation in to the quick release tablet significantly increased the disintegration time, dissolving rate, and consequently bioavailability and beginning of action of the weakly water soluble medication Levonorgestrel. Based on the findings of this study, it was concluded that an optimised Levonorgestrel tablet (F9) containing crospovidone and SSG could be successfully manufactured in the development of Levonorgestrel immediate release tablets for the effective treatment of pregnancy and as a better emergency contraceptive. Based on the current research, it can be concluded that Levonorgestrel 1.5mg instant release tablet may be successfully made.

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