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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLET OF LEVONORGESTREL

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ABSTRACT

The study was undertaken with an aim to develop and optimized formulation of Hormonal contraceptive, Levonorgestrel by oral drug delivery. Pre-formulation studies were conducted to know the drug excipient compatibilities. The superdisintegrants crospovidone and sodium starch glycolate were used for immediate release of drug from tablet. The prepared tablets were evaluated for all pre-compression parameters and post-compression parameters. The drug excipient interaction was investigated by FTIR. All formulation showed compliances with the pharmacopoeial standard. The study reveals that formulations prepared by direct compression F9 exhibits highest dissolution using both crospovidone and SSG showed faster drug release 93.13 % over the period of 60 min while disintegration time of the tablet was showed 45 sec comparison to other formulations of Levonorgestrel. The objective of the present project was successfully achieved by developing the product, giving the same release profile to that of innovators product. From this study we are conclude that the immediate release tablet of Levonorgestrel can be formulate and it shows better drug release response.

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INTRODUCTION [1-7]

Among all dosage forms tablet is the most popular dosage form existing today because of its easy of self-administration, compactness and easy manufacturing and sometimes immediate onset of action and above all it is easy to maintain its stability parameter throughout the shelf life.

A contraceptive are like IUD, Tablets, pills and other Implants. There are major problems occur by using pills that is there are requires longer time to drug release and slow onset of action. So the immediate release tablet shows action without causing such problems. An immediate release dosage form allows to manufacturer to extend market exclusivity, while offering patient a convenient dosage form or dosage regimen. Immediate release tablet are those tablets which are designed to disintegrate and release their medication with no special rate controlling feature, such as special coating and other techniques, immediate release drug delivery system may offer a solution to these problems. Recently immediate release tablet have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action and economical and lead to better patient compliance.

They are also a tool for expanding markets, extending product life cycles and generating opportunities. Immediate release tablets are those which are disintegrate rapidly and get dissolves to release medicament. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption.

Emergency contraception (EC) is a method of contraception that is used to prevent pregnancy after an act of unprotected sexual intercourse. Emergency contraception is effective only in the first few days following intercourse before the ovum is released from the ovary and before the sperm fertilizes the ovum. Emergency contraceptive pills cannot interrupt an established pregnancy or harm a developing embryo, thus cannot cause abortion. Emergency contraception prevents about 85 percent of pregnancies and does not replace regular contraception. Levonorgestrel EC does not disrupt an already established pregnancy. Levonorgestrel is in the class of medication called progestin. It works by preventing the release of an egg from the ovary to preventing fertilization of the egg by sperm. It also may works by changing the lining of the uterus to prevent development of the pregnancy. Levonorgestrel may prevent pregnancy, but it will not prevent the spread of human immunodeficiency virus (HIV) and other sexually transmitted diseases.

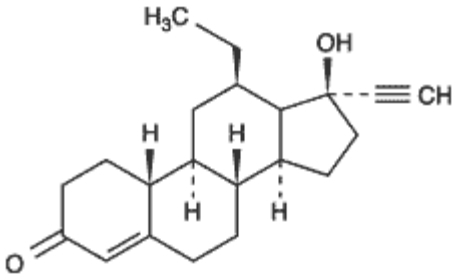

Figure 1: Structure of Levonorgestrel.

The current research topic undertaken to formulate and evaluate the immediate release drug delivery system of Levonorgestrel by direct compression method, which ultimately helps to improve the bioavailability of drug, and gives the immediate release effect which improve the birth control. The main purpose of current research topic is give faster release of drug from the tablet and shows immediate action and help for birth control by act 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

Angle of repose was determined using fixed funnel method. The accurately weighed powder takes in funnel. The height of funnel is adjusted in such a way the tip of funnel just touches apex of the head of the pile. The powder is allows to flow through funnel freely onto surface. Angle of repose is calculated using following formula:

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

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. The R^2 and the average slope were found to be 0.9987 and 0.0491 respectively.

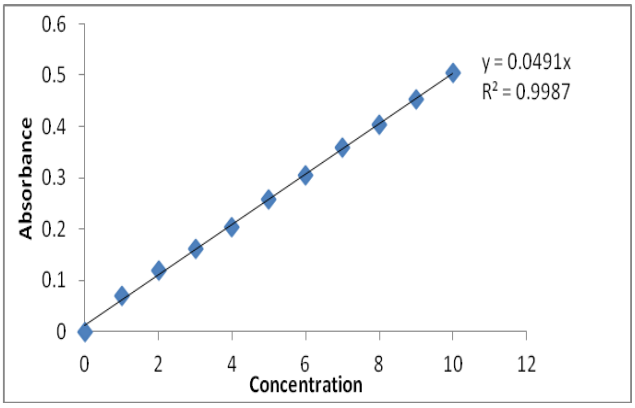

Figure 2: Standard calibration curve for Levonorgestrel in 0.1 N HCl.

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.

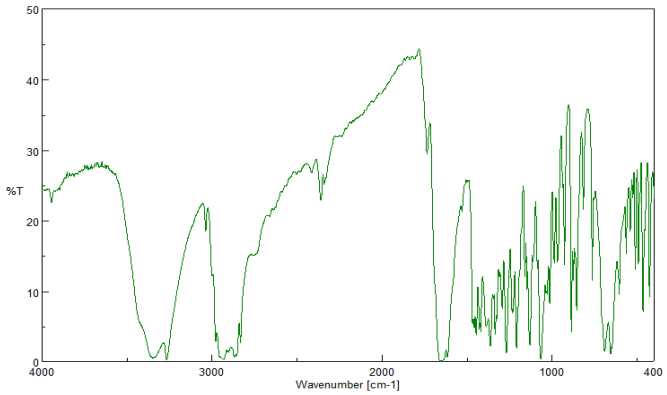

Figure 3: FTIR spectrum study of Levonorgestrel.

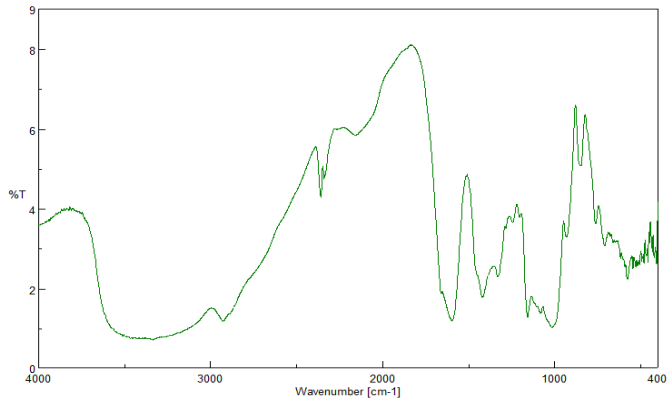

Figure 4: FTIR spectrum study of Levonorgestrel with Crospovidone and SSG.

Pre-compression parameters

Powder flow characteristics

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.

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)

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.

Formulation code	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.

Formulation code	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

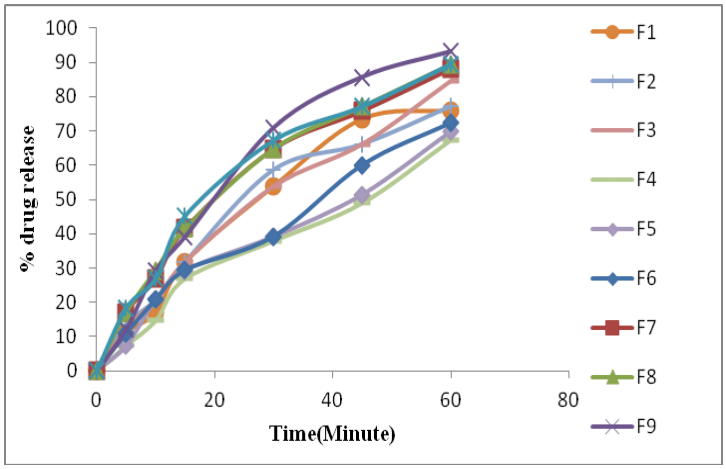

Figure 5: % Drug release of formulated IR tablets and marketed innovator.

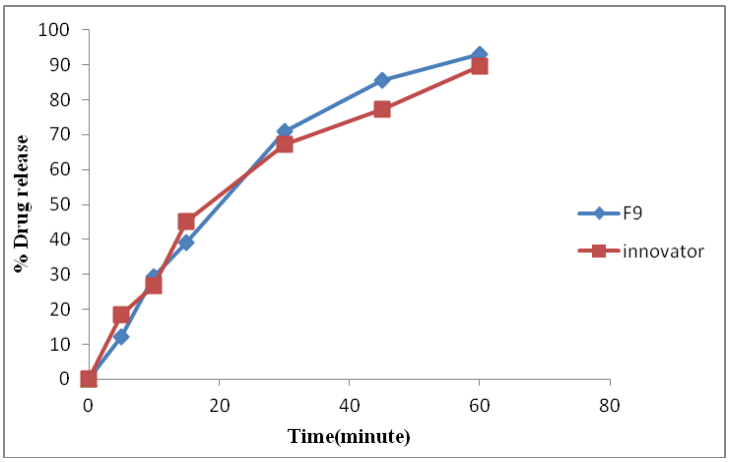

Figure 6: Comparative Dissolution profile of innovator and optimized formulation (F9).

CONCLUSION

Levonorgestrel immediate release tablets were formulated by direct compression method using the selected excipient quantities. The formulated tablets tested for both pre compression parameters, post-compression parameters as per requirement of standards performed and found to be within the limit. During the optimization of formulation it was observed in dissolution study that by decreasing the concentration of diluents and by increasing the concentration of superdisintegrants an increase release profile was achieved. As a result of this study, it was concluded that the addition of superdisintegrants and subsequently its formulation in to the immediate release tablet was successfully improved the disintegration time, dissolution rate and subsequently bioavailability and onset of action of poorly water soluble drug Levonorgestrel. From this study, it was concluded that optimized Levonorgestrel tablet (F9) containing crospovidone and SSG could be successfully manufactured in developing Levonorgestrel immediate release tablets for the effective treatment against pregnancy and act as a better emergency contraceptives. From the present studies, it can be concluded that Levonorgestrel 1.5mg immediate release tablet can be prepared successfully.

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Conflict of interest statement

We declare that we have no conflict of interest. The authors alone are responsible for the content and writing of the content.

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