

FORMULATION AND DEVELOPMENT OF LENALIDOMIDE LOADED DELAYED RELEASE MINI TABLETS IN CAPSULES

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ABSTRACT

Objective: Formulation and development of delayed release mini tablets in the capsule of drug lenalidomide in terms of dissolution and stability was the objective of the present work.

Methods: Tablets of less than or equal to 3 millimetres diameter are Mini-tablets, which were filled into a capsule. Direct compression method using multi-punch was used for compression and coated with eudragit L100 as a seal coating material and with eudragit L30D55 as an enteric coating material was done. Different formulations were prepared and subjected for evaluation like weight variation, hardness, friability, disintegration, and dissolution studies. The optimized formulation was compared to marketed product based on drug released profile and also subjected for stability studies.

Results: The results revealed that the *in vitro* drug release of prepared formulations, F1, F2, F3, and F4 was subjected for acid resistance test for 2 h in 0.1N HCl and has a comparable dissolution profile in phosphate buffer of 6.8 pH. Formulation F4 was subjected for stability studies and no significant difference was observed in 3 mo 40 °C/75% RH accelerated stability condition.

Conclusion: The dissolution profile of formulation F4 was found better than that of market product. Based on evaluation results, the study concluded that F4 formulation was considered as an optimized formulation.

Keywords: Immuno-modulator, Mini-tablets, Delayed-release, Tablets in capsule, Lenalidomine

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INTRODUCTION

The aim of any dosage form was to release the effective and precise amount of drug at the target site to give a desired pharmacological response. Delayed release systems are systems used for repetitive and intermittent dosing of a drug from multiple immediate release units that is merged into a single dosage form [1]. Mini tablets are slightly curved or flat tablets which have diameter ranged between 1.0-3.0 millimeters; they can thus be filled into capsules. Mini tablets can be compressed into larger tablets, and occasionally it can be filled in sachets for easy administration [2]. The drug release can be achieved due to increase surface in relationship with volume of drug.

The rationale of mini tablets formulation is to accomplish several releases in one formulation by combining altered dose. Passage of mini tablets through the stomach is better than normal tablets due to their small dimension. Due to this, mini tablets are formulated in the study to achieve the desired drug concentration in plasma is achieved [3].

Formulation of one capsule containing different mini tablets, each developed independently and designed to release at the different site of the gastrointestinal tract can be achieved. Mini tablets have the merit of achieving multi-particulate dosage forms with the conventional manufacturing systems of tableting [4]. A further advantage of mini tablets includes their uniformity in size, shape, and surface, thereby offering an exceptional well substrate for coating with modified release polymeric systems [5].

When the capsule disintegrates, mini-tablets inside the capsule release and distribute throughout the gastrointestinal tract. The subunits act as self-contained depots, which makes it possible for the division of multiple unit tablets with no loss in depot effect. Mini tablets represent total subunits present in the capsules. The therapeutic effect of the capsule is directly related to the functionality of each mini tablet in the capsule [6].

Thalidomide on chemical modification yields lenalidomide. This potent analogue has decreased neurological effects such as sedation and neuropathy as compared to parent molecule. It shows an effect against haematological and solid malignancies. Lenalidomine being immunomodulatory shows the effect on the immune system at both cellular and humoral limbs. It also exhibits anti-angiogenic action. The novelty of the study lies in formulation and development of delayed release mini tablets in the capsule of drug lenalidomide. The drug was chosen with the aim to reduce the side effects of thalidomide and improve the increases the efficacy [7].

MATERIALS AND METHODS

Materials

Lenalidomide was obtained as a sample from Sigma Alrich Pvt. Ltd, Mumbai, India, along with triethyl citrate. Microcrystalline cellulose, silicified microcrystalline cellulose, magnesium stearate, and talc was procured from Loba Chemie Pvt. Ltd. croscarmellose sodium, silica colloidal silicon dioxide and type a methacrylic acid copolymer dispersion was procured from Merck Pvt. Ltd.

Table 1: List of equipment and instruments

S. No.	Name	Manufacturer
1.	Blender	Ganson Engineers Private Limited
2.	Tablet Compression machine	Cadmach machine Co. PVT LTD
3.	Tablet Coating machine	Gansons Limited
4.	Digital weighing balance	Shimadzu
5.	Hardness tester	Monsanto
6.	Disintegration test apparatus	Electro lab

Pre-formulation studies

Fourier transform infra-red (FT-IR) spectrum

A Fourier Transform Infrared (FTIR) spectrum was carried out to check the chemical compatibility of Drug and Excipient by Shimadzu 8400S FTIR (Tokyo, Japan) by KBr pellet press method. The Spectrum was recorded over the range 40-4 m^{-1} [8].

Preparation procedure

The preparation was carried out after obtaining all the ingredients. Sifting was done by co-sifting API, Microcrystalline cellulose, Silica colloidal silicon dioxide, and Acdisol, Aerosil, through sieve #40. The sifted granules were mixed in a blender for 20 min at 15 rotations per min to achieve uniform blending. The lubrication was done by using Magnesium stearate. Compression of the tablet was done using a double rotatory compression machine using 2 millimeters diameter standard concave plain punch [9]. Seal coating was done by using eudragit L 100 solution.

Preparation of eudragit L100 solution

Was done by weighing required quantity of eudragit L 100, isopropyl alcohol and triethylcitrate (TEC). In lenalidomide, steadily add triethyl citrate and mixing for 10 min was done. Then eudragit L 100 was added to the above solution. Stirred for one and a half hours until a clear solution was formed [10, 11]. Then seal coating was

carried out on compressed core mini tablets. The enteric coating was done by eudragit L30D55 solution.

Preparation of eudragit L30D55 solution

Was done by, weighing required quantity of Purified Water, talc, TEC, eudragit L30 D55, in water, TEC was gradually added. Talc was diversified for 15 min followed by addition of dimethicon. In the above solution Eudragit L30D55 was slowly added, with continuous stirring for thirty minutes. Then enteric coating was performed on seal coated mini tablets [12, 13]. Capsule filling and Packing was done in the next step; the drug product was intended to be labelled for storage at 15 °-30 °C [14, 15].

All the other ingredients were kept constant and the concentration of eudragit L30D55 as enteric coating and eudragit L100 as seal coating were changed for different formulations from F1 to F4 (table 2).

Post-compression and coating parameters

Evaluation of mini tablets was done for parameters like weight variation, hardness, thickness, and disintegration and tableting issues such as capping, sticking. The mini-tablets were inspected for shape, colour and other tablet defects by keeping the tablets in light. Uniformity of weight and drug content, as per I. P was also determined. Friability was measured using electrolabfriabilator. Hardness tester was used to determine the hardness.

Table 2: Formulation chart for mini tablets compression and coating

S. No.	Ingredients	Qty/Tab (mg)			
		Core Tablet			
		F1	F2	F3	F4
1	Lenalidomide	3.038	3.038	3.038	3.038
2	Avicel 200	0.700	0.700	0.700	0.700
3	Prosol SMCC 90	1.722	1.722	1.722	1.722
4	Crosscarmellose sodium	0.360	0.360	0.360	0.360
5	Aerosil 200	0.060	0.060	0.060	0.060
6	Magnesium Stearate	0.120	0.120	0.120	0.120
Total weight of core tablets (mg)		6.000	6.000	6.000	6.000
Seal Coating		5.00%	5.00%	3.50%	3.50%
1	Eudragit L 100	0.180	0.180	0.126	0.126
2	Triethyl citrate	0.120	0.120	0.084	0.086
3	IPA	q. s.	q. s.	q. s.	q. s.
Total weight of seal coated tablets (mg)		6.300	6.300	6.210	6.210
Enteric Coating		25%	20%	20%	25%
1	Eudragit L 30D55(Solid)	0.742	0.594	0.585	0.731
2	Triethyl citrate	0.742	0.594	0.585	0.731
3	Talc	0.082	0.066	0.065	0.081
4	Dimethicon	0.009	0.007	0.007	0.009
5	Purified Water	q. s.	q. s.	q. s.	q. s.
Total weight of Enteric coated tablets (mg)		7.875	7.560	7.450	7.760

Weight variation

Initially, 20 units of pellets were randomly selected which was weighed individually and the average was calculated. Weight variation was carried out by using digital balance [16]. The digital weighing balance model used to calculate weight variation is shimadzu (model no. BL 220H). The percentage deviation in weight was calculated by:

$$\% \text{ Deviation} = \frac{\text{Average weight} - \text{weight of tablet}}{\text{Average weight}} \times 100$$

Tablet thickness

In this, 10 tablets were assessed for thickness by using an electronic vernier caliper, Mitutoyo, Japan.

Hardness

Monsanto hardness tester was employed to evaluate the hardness of randomly selected mini tablets [16].

Disintegration

The disintegration of the capsule was examined by electro lab disintegration tester (USP) ED-2AL for 15 min.

Dissolution

The apparatus used for dissolution is electro lab TDT USL. Lenalidomide has high solubility across the physiological pH range. For carrying out dissolution profiles studies of lenalidomide delayed-release capsule, USP apparatus II was employed at 100 rotations per min with 0.1 N HCl for first two hours and later at pH 6.8 phosphate buffer [17].

Stability studies

Stability studies were carried out by storage of tablets in containers inside thermolab S. S. 304 and analysed at regular intervals for different parameters like appearance, assay of API, determination of degradation products, dissolution time etc.; Stability studies were conducted at following conditions. Storage conditions: 40 °C±2 °C/75% RH±5% RH, 25 °C±2 °C/60% RH±5% RH for the period of 1 and 3 mo [18].

RESULTS AND DISCUSSION

Preformulation studies

Drug-excipient compatibility studies were examined using FTIR. The following graph was obtained (fig. 1). The drug and excipient were found to be compatible.

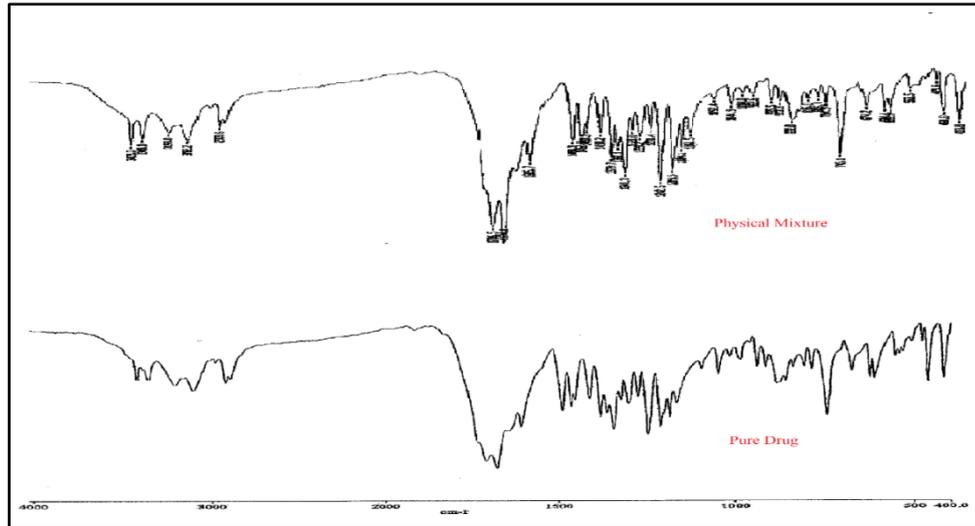


Fig. 1: FTIR of pure drug and physical mixture

Post-compression and coating parameters

Prepared tablets were evaluated during the process for weight variation, hardness, thickness, disintegration and tab letting issues such as capping, sticking, coating and results are tabulated in table 4.

Dissolution studies

Dissolution studies were carried out by using 0.1N HCl buffer followed by 6.8 pH buffer, and the results are depicted in table 5.

The dissolution varied for all the formulation, the desired dissolution profile on comparison was achieved by formulation F4. The results obtained indicate that F4 meets all the in process parameters and hence, increased concentration of eudragit L30D55 of 25% has shown an increase in the drug release.

According to *Umesh N Et al.* Mini particulate formulation coated with eudragit were targeted to release the drug in the intestine. A similar observation was made in the dissolution profile of the present study,

wherein the drug showed no release in the acidic medium but exhibited 89.12-95.91 % release in the intestinal pH [19].

The comparative dissolution profile of the marketed product and lenalidomide DR capsule:

The Prepared lenalidomide DR capsules have shown more percentage of drug release than the available marketed formulation and the values are as shown in table 6.

Stability studies

The stability studies for lenalidomidedelayed release mini tablets in capsules was carried out for optimized formulation. In accordance to ICH guidelines, stability studies were carried out by storing at 25 °C/ 60% RH and 40 °C/75% RH for 1 and 3 mo was carried out for the optimized formulation. The samples were analysed and checked for changes in physical appearance and release profile at 1st and 3rd month, and the results are tabulated in table 7.

Table 4: Post-compression and coating parameters

Formulations	F1		F2		F3		F4	
	CT	ECT	CT	ECT	CT	ECT	CT	ECT
Average weight (mg)	6.03±0.17	7.88±0.11	6.05±0.23	7.5±0.12	6.15±0.34	7.42±0.15	6.09±0.23	7.74±0.11
Hardness (N)	18.5±0.25	24.61±0.23	17.18±0.42	24.11±0.15	19.53±0.38	23.43±0.24	19.33±0.21	24.53±0.17
Thickness (mm)	1.85±0.09	2.05±0.13	1.83±0.21	2.12±0.53	1.79±0.28	1.97±0.13	1.85±0.17	1.95±0.11
Disintegration (min) at pH 6.8 buffer	-	15	-	15	-	<15	-	<10
Capping	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Lamination and Sticking								

mean±SD, n = 3, CT= Core tablet; ECT= Enteric Coated Tablet

Table 5: Dissolution profile of the drug

Time (min)	% Drug release			
0.1N Hcl buffer	Formulations			
120	F1	F2	F3	F4
6.8 pH Phosphate buffer	2.09±0.27	1.25±0.44	2.31±0.45	1.02±0.37
5	44.32±0.37	53.81±0.54	54.32±0.48	37.51±0.21
10	73.3±0.51	83.7±0.24	84.4±0.24	93.21±0.24
15	89.12±0.24	91.2±0.57	93.4±0.28	95.91±0.15

mean±SD, n = 3

Table 6: Comparative dissolution profile of the marketed product and lenalidomide DR capsule

Time (min)	% Drug released of a marketed product	% Drug released of lenalidomide capsule
0	0	0
10	94.06±0.33	93.21±0.24
15	95.21±0.18	95.91±0.15
30	96.72±0.15	97.2±0.31
45	97.5±0.52	98.14±0.29

mean±SD, n = 3

Table 7: Stability studies

Condition and month	Initial	25 °C/60% RH (1-M)	40 °C/75% RH (1-M)	25 °C/60% RH (3-M)	30 °C/65% RH (3-M)	40 °C/75% RH (3-M)
Dissolution ^a						
Time preformed	% Drug release					
120 min (0.1 N HCl)	1±0.00	1±0.00	1±0.00	1±0.00	1±0.00	1±0.00
pH 6.8 Phosphate buffer						
10 min	93.54±0.31	95.13±0.47	93.63±0.37	94.32±0.19	89.43±0.29	89.12±0.21
15 min	94.42±0.53	95.43±0.42	95.65±0.54	94.22±0.47	94.29±0.39	93.13±0.91
30 min	95.91±0.54	95.57±0.45	95.31±0.29	95.12±0.37	94.42±0.37	93.91±0.37
45 min	97.42±0.42	97.54±0.24	97.82±0.65	98.43±0.18	95.21±0.82	94.32±0.44

mean±SD, n = 3, There was no significant difference observed under 25 °C and 60% RH and 40 °C and 75% RH accelerated stability condition at the end of 1st and 3rd month.

CONCLUSION

The delayed release of mini tablets in the capsule of lenalidomide was developed. The drug lenalidomide is found to have better *in vitro* drug release in mini-tablets form than the conventional dosage form. However, further clinical trials are necessary to ensure the improved efficacy and safety of lenalidomide mini tablets.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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