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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLET OF IMMUNOSUPPRESIVE DRUG

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Abstract

Immunosuppresive drug is used for the immunity suppression in organ transplant so it is required to prepare an immediate release formulation to produce rapid effect during organ transplant. The main objective of the present study is to formulate and evaluate an immediate release tablet of Immunosuppresive drug by wet granulation method. Preformulation studies were performed prior to compression. The tablets were compressed using microcrystalline cellulose, hydroxy propyl cellulose, pregelatinized starch, croscarmellose sodium, talc, magnesium stearate. The fabricated tablets were evaluated for various micromeritic properties like bulk density, tapped density, compressibility index, hausner's ratio, angle of repose and post compression characteristics like thickness, hardness, friability, disintegration time and drug release. The final selection of the formulation (F9) was done on the basis of comparison of disintegration time and in vitro drug release to that of the innovator product. The results of the present study indicate that, the prepared tablets of Immunosuppresive drug could perform therapeutically, with improved efficacy and better patient compliance like that of the Innovator product.

INTRODUCTION

Tablets remain popular as a dosage from because of the advantages, affordability by both, manufacturer (e.g. simplicity and economy of preparation, stability and convenience in packing, shipping and dispatching) and the patients (e.g. accuracy of dosage, compactness, portability, blandness of taste and ease of adminsistration).[1] In tablets dose of drug has been accurately placed, but liquid forms such as suspensions and solutions are usually designated to contain one medication in 5-30 ml. The error in measuring such dosage form could be 20-50%. Liquid oral dosage forms have other disadvantages and limitations. They are more expensive to ship, breakage or leakage is more serious problems with liquids dosage form. Liquids are less portable and require more space in pharmacist's shelf. Drugs are generally less stable in liquid form when compared to solid dosage forms. To provide the patients with the most convenient mode of administration, there was a need to develop Tablet dosage form.[2,3]

The immune system helps the body fights infections or reject an organ such as a kidney, liver or heart transplant. Immunosuppressant's are drugs to prevent transplant rejection after organ transplantation by inhibiting the reaction of the immune system and suppression of body's ability to recognize and destroy foreign substances. This means that they reduce the strength of your immune system. Immunosuppressive medicines are sometimes necessary to help your body accept an organ transplant, or to treat some diseases where your immune system is reacting against your own body (autoimmune diseases). It is required to prepare an immediate release formulation to produce rapid effect during organ transplant. To provide the patients with the most convenient mode of administration, there was a need to develop immediate release formulation, particularly one that disintegrates rapidly and disperses and helps in producing rapid effect during organ transplant.[4]

Different formulations were prepared with varying concentrations of binders, super disintegrating agents and lubricants and the optimized formulation was to be found in

this present study. To Prepare Immediate release tablets of Immunosuppresive drug for rapid action and patient compliance.

MATERIALS AND METHODS

Materials

The raw drug was gifted by Biocon India limited. Bangalore and the tablet excipients like Hydroxypropylcellulose, Pregelatinized starch, Croscarmellose sodium, Sodium starch glycolate, Crospovidone, Microcrystalline cellulose, Magnesium stearate, talc and all the reagents used were of analytical grade.

FORMULATION OF TABLETS

The method used in the formulation of Immediate Release tablets was wet granulation method. All the batch formulations are formulated by wet granulation method. Immunosuppresive drug (Active pharmaceutical agent), Microcrystalline cellulose, Hydroxy propyl cellulose sifted through sieve No. 40 and thoroughly mixed in a Rapid Mixer Granulator (RMG) for 10 min. Pregelatinized starch dissolved in sufficient quantity of water, and used as a binder solution. Granulation was done in Rapid Mixer Granulator using Preglatinized starch as binder solution. Wet granules were dried in fluid bed dryer (FBD) at 60-65^{0}C till a LOD (Loss of drying) of dried granules obtained not more than 2% w/w. Dried granules were passed through sieve No.24. The dried granules were blended in a blender with Croscarmellose sodium, Microcrystalline cellulose and talc for 5 min which was already passed through sieve No. 40. Above mixer was lubricated for 2 min with Magnesium Stearate which was already passed through sieve No. 60. The lubricated granules were then compressed in to tablets on a 16 station rotary tablet machine. The formulation composition is as shown in Table 1.

CHARACTERIZATION OF BLEND [5, 6, 7, 8, 9]

Prior to compression, the blend was evaluated for their micromeritic properties such as bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose.

Bulk density [5, 6, 9]

Weigh accurately 25 g of drug (M), which was previously passed through 20 # sieve and transferred in 100 ml graduated

cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula. The results obtained are as shown in Table 4.

Bulk density = Weight of powder / Bulk volume

Tapped bulk density [5,6,9]

Weigh accurately 25 g of drug, which was previously passed through 20 # sieve and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V2).Calculate the tapped bulk density in gm/ml by the following formula. The results obtained are as shown in Table 4.

Tapped density = Weight of powder / Tapped volume

Carr's index [5,6,9]

The compressibility index of the powder blend was determined by carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below.

$$Carr's\ Index \quad (\%) = \frac{(TBD - LBD)\times 100}{TBD}$$

Fixed quantity of powder was taken in measuring cylinder. Then switch to USP density apparatus. Set the mode USP-1/USP-2. Set the weight, volume and no. of tap. Set the 3 sets of tap 500, 750, 1200. Then press run after setting cylinder in holder for first 500 taps. Note the volume. Then press run to continue the test for 750 taps. If the difference in density of 500 & 750 taps is NMT 2% then no need to go for 1200 taps. Calculate Bulk density, tapped density & carr's index & housner's ratio. If hausnor's ratio is <1.25 than flow property good, but if > 1.25 than flow property is poor. The results obtained are as shown in

Table 4.

Hausner's ratio [5,6,9]

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. Relation of carr's index and hausner's ratio with flow characteristic of material mentioned in Table 2 and results obtained are as shown in Table 4.

Hausner's ratio = Tapped density / Bulk density

Angle of repose [5,6,9]

The angle of repose of mycophenolate mofetil powder was determined by the funnel method. The accurately weight powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. Effect of angle of repose on flow property of blend showed in Table 3 and results obtained are as shown in Table 4.

$\tan \theta = h/r$

Evaluation of Tablets [5, 6, 9, 10]

The formulated tablets were evaluated for the following physicochemical parameters.

Weight variation [5, 6, 9, 10]

Twenty tablets were weighed individually and average weight was determined. The individual tablet weight was compared with average tablet weight. The tablet weight for immediate release tablet is 885.00 mg and the maximum percent difference allowed is 7.5% i.e. ± 7.5 mg. The results obtained are as shown in Table 5.

Thickness [5, 6, 9, 10]

Tablet was selected at random from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement. Tablet thickness should be controlled within a ± 0.5% variation of standard value. The results obtained are as shown in Table 5.

Friability Test [5, 6, 9, 10]

Friability test is performed to assess the effect of friction and shocks, which may

often cause tablet to chip, cap or break. Roche friabilator was used for this purpose. This device revolves at 25 rpm, dropping the tablets at distance of 6 inches with each 100 times revolution. Friability of immediate release tablets was determined for both 100 revolutions. Friability of the tablets should be less than 1%. The results obtained are as shown in Table 5.

The percentage friability was measured using the formula,

% F = {1-(Wo/W)} ×100

Where, Wo = Initial weight of tablet

W = wt. of tablets after revolution

Hardness[5,6,9,10]

Tablet was selected at random from individual formulations and hardness was measured using Scheluniger hardness tester.

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The force is measured in Newton. The hardness was tested using Dr Scheuilnger hardness tester. "Hardness factor", the average of the six determinations, was determined and reported. The results obtained are as shown in Table 5.

Disintegration Test [11]

The disintegration time of immediate release tablet was carried out using disintegration apparatus by using water as disintegration media maintained at 37˚ C. Keep six tablets in disintegrator and carried out the test until no residual of tablets remains in basket. When all the six tablets are completely disintegrated, the time was noted. The results obtained are as shown in Table 5.

***In vitro* release studies** [12]

The tablets were evaluated for *in vitro* active molecule release was carried out using USP dissolution apparatus. The following conditions were applied.

For gastric fluid (pH 1.2)

USP Dissolution apparatus: Type II (paddle)

Media**:** 0.1 N HCl

Volume of dissolution medium: 900ml

Speed of paddle rotation: 50 rpm

Temperature: $37^{o} \pm 0.5^{o}C$

Sampling point: 0, 5,10,15,20,30,45,60 mins

The gastric fluid, aqueous 0.1 N HCl solution (pH 1.2), was used as dissolution media. One tablet was put in type 2 USP apparatus, set in 900 ml of the dissolution medium pre-warmed at $37^{o} \pm 0.5^{o}C$, and rotated at 50 rpm. At appropriate time points, 5 ml of the tested medium was taken and filtered with a whatmann filter paper. Immediately after each sampling, 5 ml of fresh medium was added. The filtered sample analyzed spectrophotometrically at 250 nm to determine the amount of released drug.

The dissolution profiles of test batches were compared with innovator product which is an important aspect in predicting *in vivo* behaviour of drug release from formulation under investigation. The results obtained are as shown in Table 6 and Figure 1 -5.

Similarity & Dissimilarity Factors[13,14,15]

Comparison of therapeutic performances of two products containing the same active substance is a critical means of assessing the possibility of alternative using between the innovator and any essentially similar product. The dissolution profile comparison may be carried out using model independent or model dependent method. A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles.

$$f_2 = 50 \mathrm{X} \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} \mathrm{X}100\right\}$$

Where, R_t and T_t represent the average percent dissolved at time t for reference and test, respectively, and n is the number of time points tested. Dissolution profile was considered satisfactory if f_1 values lies below 15 (nearing zero) and f_2 value lies more than 50 (nearing 100).

The model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. The F2 value of optimized formulation is as shown in Table 7.

Stability studies [16,17,18,19]

In order to determine the change on storage, stability study was carried out a

25°C / 60% RH and 40°C / 75% RH in a stability chamber. Samples were withdrawn at regular intervals. Formulation was evaluated for changes in Hardness, Thickness, Disintegration time and *in vitro* release studies. Stability study of optimized formulation is as shown in Table 7.

RESULTS AND DISCUSSION

Precompression parameters

The granules thus prepared were evaluated and the results thus obtained are given in table 2. From the results of Carr's index and Hausner's ratio it was found that the flow property found to be poor in F1 and F10, passable in F2, F3, F4, F5, F6, F8 and F11, Fair flow property in F7 and F9. In particular, F9 formulation showed good flow property compared toF7. The Hausner's ratio and Carr's index were found to be good in F9.

Post-compression parameters

All the tablets were evaluated for the post compression parameters and the results are shown in table 3. It was clear that the weight variation holds good for all the formulation.

In the Formulation of immunosuppressive drug immediate release tablets, As generally used ratio of Microcrystalline cellulose & Hydroxy propyl cellulose 5.5:1. Based on material property we had taken F1-F3 trial for deciding this ratio. The thickness was found to be uniform in all formulations & ranged from 6.7-7.2 mm. The average weight was found to be 875 mg. Hardness in all batches ranged from 170-178 N. Disintegration time has been found less in formulation F3 due to increased amount of extragranular MCC and decreased amount of intragranular MCC and HPC.

In Formulation F3-F5 had prepared using 3 different disintegrants Croscarmellose sodium, Sodium Starch Glycolate, & Crospovidone. Hardness value was found to be in range of 175-180 N. Friability was also found to be less than 1%. Disintegration time of Croscarmellose sodium prepared tablets was lesser compared to Sodium Starch Glycolate and Crospovidone.

For optimization of disintegrant concentration we had used slight higher concentration than F3 batch. F6 and F7 batches were prepared by slight increasing

concentration of CCS for better results same as innovator. F3, F6 and F7 batches were prepared using 1.1-1.7% concentration of CCS as a disintegrant. Hardness was found to be in the range of 174-180 N. Friability was found to be < than 1%. Disintegration time was found to be less in F7 than F3 and F6.

F7 to F9 batches were prepared using 2.0-2.7% concentration of Preglatinized starch as a Binder. Formulation F9 confirmed to the required Hardness, Friability, Thickness and Disintegration time were within acceptable limits.

F9 to F11 batches were prepared using 0.5-1.5% concentration of Lubricant. In F11 During compression blacking and capping of tablet observed and hardness not achieved. Formulation F9 confirmed to the required Hardness, Friability, Thickness and Disintegration time were within acceptable limits than F10. F9 batch has been selected as optimized batch & Lubricant concentration 1% was taken as a optimized concentration.

In-vitro dissolution studies:

Release profile of Batch F1 to F3 was compared with reference product. As F3 batch has results near to innovator. From above data it has been seen that as concentration of intragranular MCC & HPC decreased and increased concentration of extragranular MCC % drug release was increased.

After 30 min % released from SSG & CP prepared tablets was found to be low compared to CCS prepared tablets. so, superdisintegrant CCS was finalized.

Release profile of F3, F6 and F7 were comparable, After 30 min % released from F3 and F6 prepared tablets was found to be low compared to F7. F7 has been selected as a optimized concentration of superdisintegrant.

Release profile of F7-F9 were comparable, After 30 min % released from F7 and F8 prepared tablets was found to be low compared to F9. F9 has been selected as a optimized concentration of Binder.

it was found that there was no major effect found by slightly increasing or decreasing the concentration of lubricant of optimized batch. F9 batch has been selected as optimized batch & Lubricant concentration 1% was taken as a optimized concentration.

Stability studies

Formulation F9 was charged for stability studies at 25°C / 60% RH and 40°C / 75% RH and the results are presented in table 5. There were no significant changes in stability results of F9 formulation. In case of Hardness and friability there were no changes in both the conditions. No significant changes were seen in case of disintegration time and the release profile was similar as that of the initial data.

CONCLUSION

The present research work was carried out to formulate immediate release tablet of immunosuppressive drug by wet granulation method. The prepared tablets were evaluated for various physicochemical evaluation tests like hardness, thickness, weight variation and *in vitro* dissolution study.

Among all the formulations, F9 formulation was better in all the terms of pre-compression and post-compression parameters, prepared by wet granulation method which has given good flow properties and post compression studies of all parameters like hardness, friability, thickness were good. No significant change was observed in physical properties, Hardness, Thickness, Disintegration time and dissolution rate of these tablets after the storage period of 1 month at 25°C / 60% RH and 40°C / 75% RH.

Hence, the study resulted Immediate release Formulation F9 prepared tablets of Immunosuppresive drug could perform therapeutically, with improved efficacy and better patient compliance like that of the Innovator product.

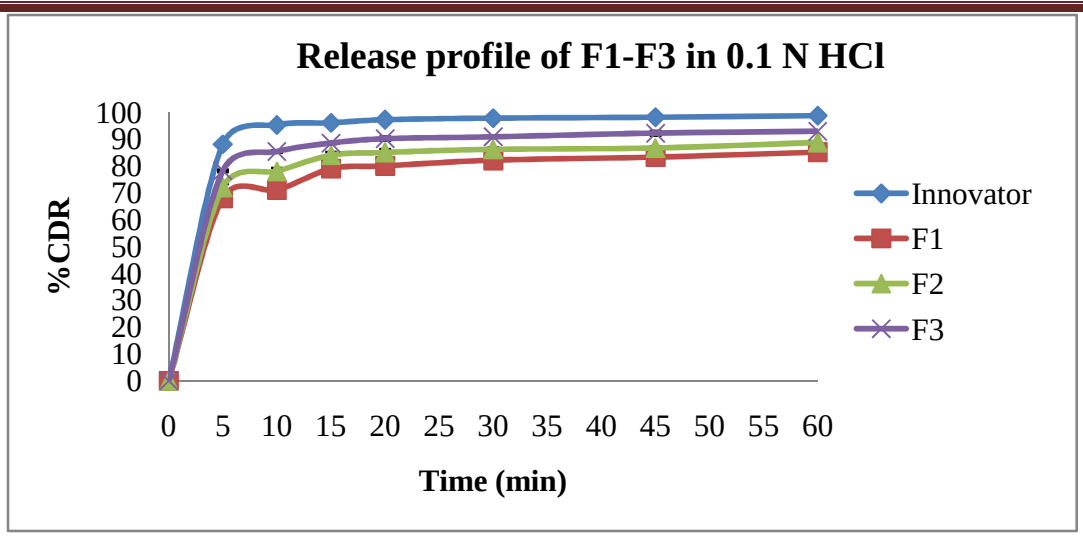

Figure 1: Comparative In-vitro drug release profiles of Preliminary Batches with Innovator

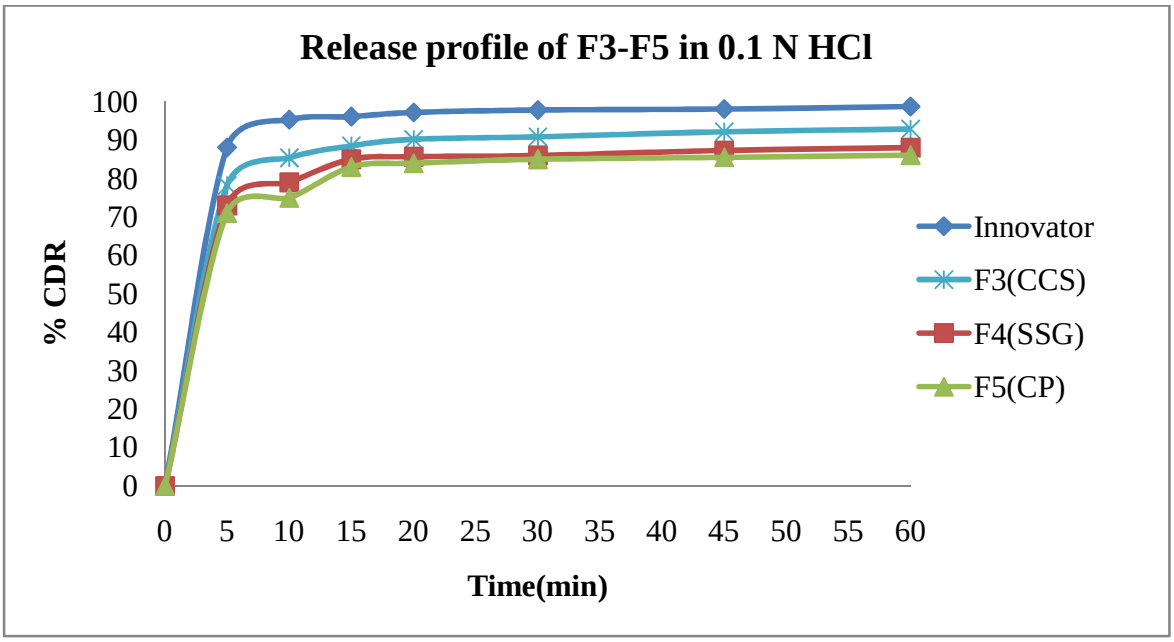

Figure 2: Comparative In-vitro drug release profiles of different superdisintegrant with Innovator

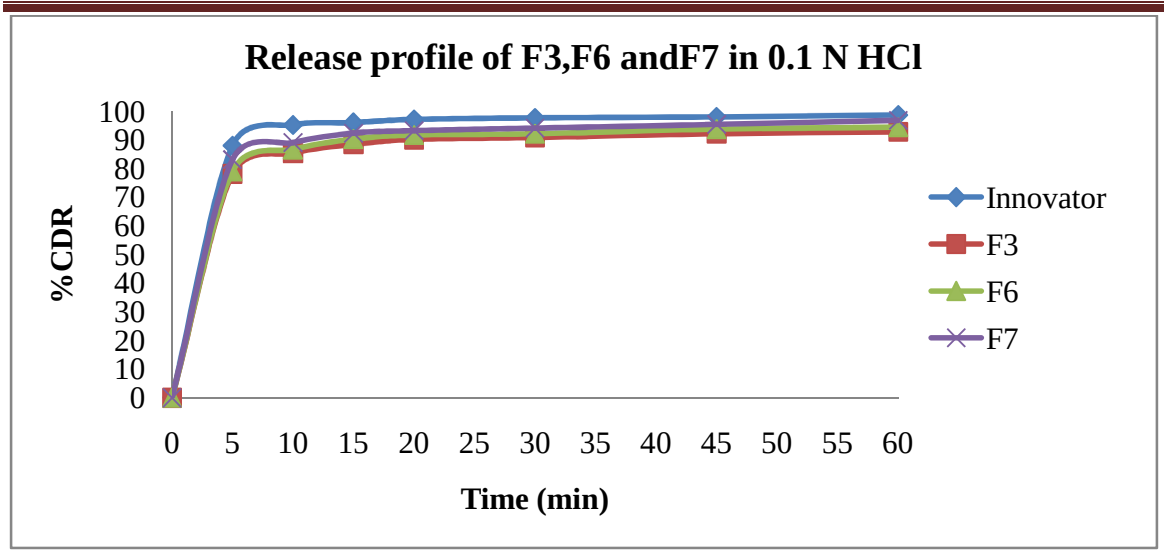

Figure 3: Comparative In-vitro drug release profiles of optimization of disintegrant concentration with Innovator

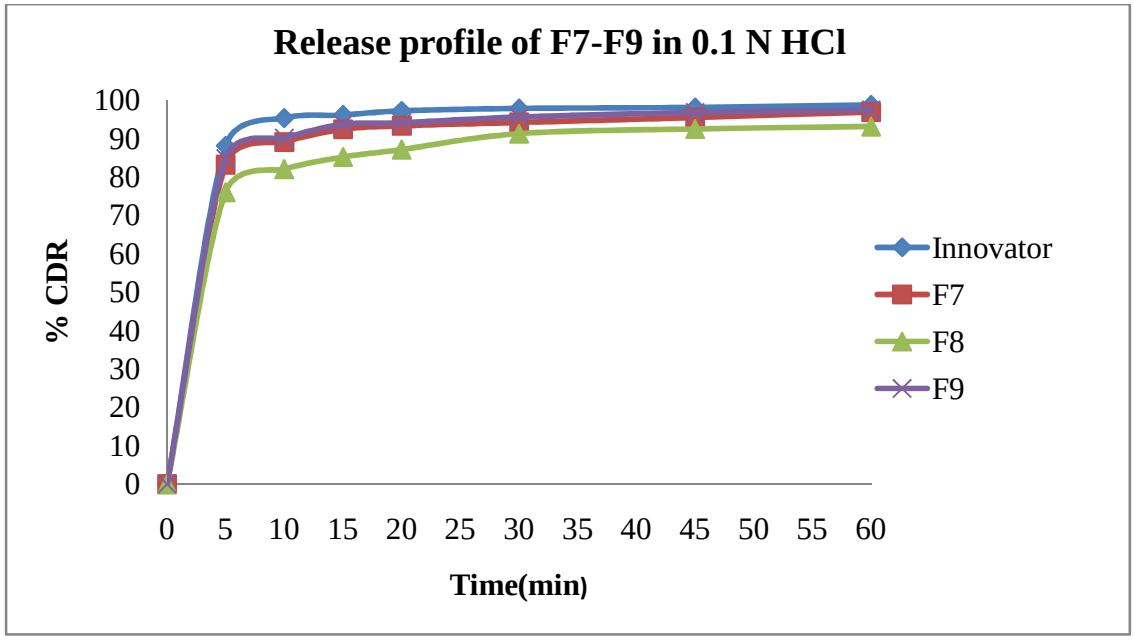

Figure 4: Comparative In-vitro drug release profiles of optimization of Binder concentration with Innovator

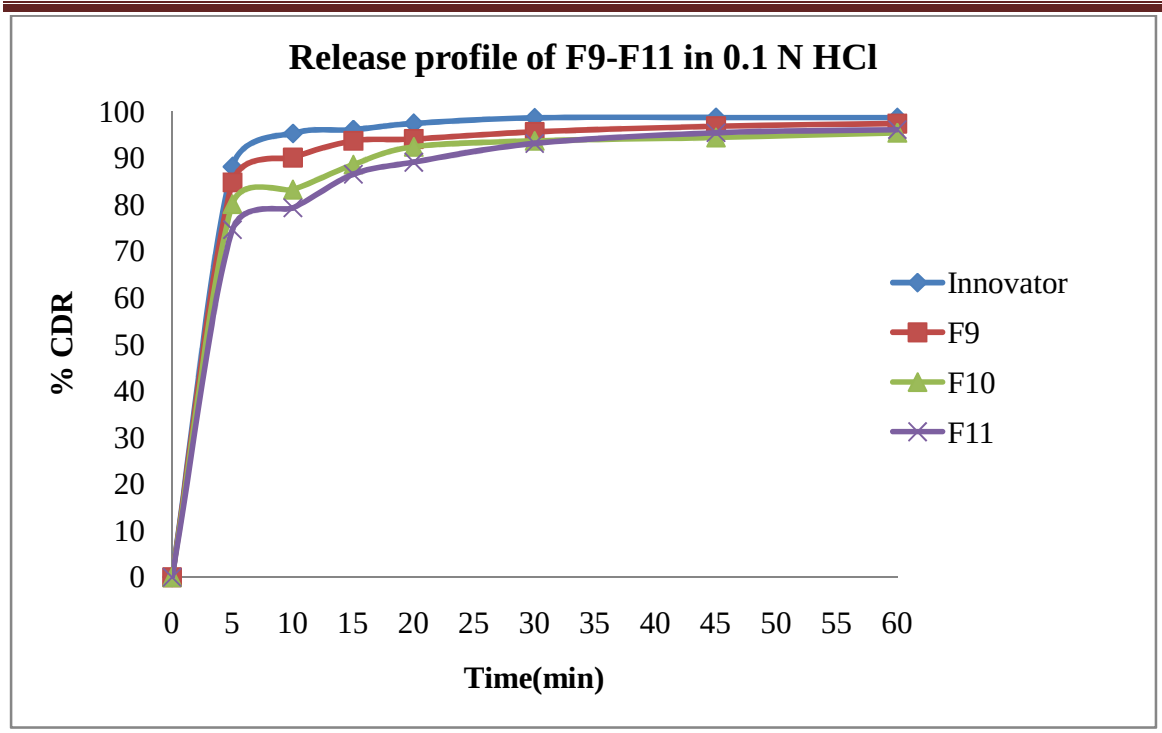

Figure 5: Comparative In-vitro drug release profiles of optimization of Lubricant concentration with Innovator

Table 1

Formulation Batches of Immediate Release Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Immuno-suppresive drug	500	500	500	500	500	500	500	500	500	500	500
Microcrystalline cellulose	190	90	75	75	75	75	75	75	75	75	75
Hydroxy Propyl Cellulose	30	20	15	15	15	15	15	15	15	15	15
Pregelatinized starch	21	21	21	21	21	21	21	18	24	24	24
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Croscarmellose Sodium	10	10	10	-	-	12.5	15	15	15	15	15
Sodium starch glycolate	-	-	-	10	-	-	-	-	-	-	-
Crospovidone	-	-	-	-	10	-	-	-	-	-	-
Microcrystalline cellulose	108	220	240	240	240	237.5	235	238	232	6	6
Talc	8	6	6	6	6	6	6	6	6	235.5	226.4
Magnesium stearate	8	8	8	8	8	8	8	8	8	4.5	13.6
Total weight	875	875	875	875	875	875	875	875	875	875	875

Table 2

Effect of Carr's Index and Hausner's Ratio on flow property

Carr's Index (%)	Flow Character	Hausner's Ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Table 3

Effect of Angle of repose on Flow property

Angle of Repose	Type of Flow
< 20	Excellent
20-30	Good
30-34	Passable
>35	Very poor

TABLE 4

Precompression Parameters

Sr. No	Bulk density* (gm/ml)	Tapped density* (gm/ml)	Carr's index*(%)	Hausner's ratio*	Angle of repose*(θ)
F1	0.42±0.01	0.58±0.02	27.58±0.49	1.38±0.07	38.65±0.14
F2	0.49±0.01	0.65±0.02	24.61±0.17	1.32±0.02	34.27±0.24
F3	0.58±0.02	0.76±0.02	23.68±0.52	1.31±0.01	32.24±0.23
F4	0.41±0.02	0.52±0.02	21.15±0.45	1.26±0.13	34.25±0.54
F5	0.47±0.05	0.61±0.01	22.95±0.71	1.29±0.01	34.53±0.16
F6	0.60±0.02	0.76±0.02	21.05±0.12	1.26±0.02	31.31±0.23
F7	0.58±0.03	0.73±0.01	20.54±0.14	1.25±0.01	30.14±0.23
F8	0.39±0.02	0.50±0.02	22±0.45	1.28±0.13	33.25±0.54
F9	0.28±0.03	0.34±0.01	17.64±0.50	1.21±0.01	25.98±0.45
F10	0.43±0.01	0.59±0.02	27.11±1.05	1.37±0.09	38.12±0.23
F11	0.30±0.03	0.38±0.01	21.05±0.50	1.26±0.01	28.18±0.25

***Mean ±S.D. (n=3 determinations)**

TABLE 5

Postcompression Parameters

Sr. No	Hardness* (N)	Average Weight*(mg)	Thickness* (mm)	Friability* (%)	Disintegration Time*(sec)
F1	175±3.0	885.2±2.1	6.9±0.02	0.39±0.01	455± 5.0
F2	176±2.0	886.0±1.5	7.1±0.01	0.37±0.02	390±3.0
F3	173±2.0	886.0±1.5	7.0±0.02	0.32±0.02	328±4.0
F4	178±2.0	885.0±1.5	7.1±0.01	0.47±0.02	410±3.0
F5	179±1.0	884.0±1.5	7.0±0.02	0.27±0.02	440±4.0
F6	176±1.0	887.0±1.5	7.1±0.01	0.27±0.02	262±3.0
F7	178±2.0	885.0±1.5	7.0±0.02	0.14±0.02	196±4.0
F8	177±3.0	885.2±2.1	6.9±0.02	0.29±0.01	232±5.0
F9	176±2.0	885.0±1.2	7.0±0.02	0.08±0.02	150±4.0
F10	174±2.4	885.2± 2.2	7.1 ±0.02	0.02±0.01	194±2.0
F11	167±3.1	885.3± 2.4	7.1±0.03	1.23±0.02	110±4.0

***Mean ±S.D. (n=3 determinations)**

TABLE 6

Comparative % Release Profile of Formulation F1 To F11 With Innovator

Time (min)	% Drug Release											
	Innovator	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	88.1	63	72	78.2	73	71	79	83.2	76	84.8	80.1	74.6
10	95.3	71	78	85.4	79	75	86.7	89.1	82	90.1	83.2	79.3
15	96.1	79	84	88.5	85	83	90.3	92.4	85.2	93.7	88.6	86.5
20	97.2	80	85	90.2	85.7	84	91.8	93.3	87.1	94.1	92.4	89.1
30	97.8	82.1	86.15	90.9	86	85	92.2	94.2	91.3	95.6	93.7	93.1
45	98.1	83.3	86.7	92.2	87.31	85.51	93.8	95.5	92.5	96.8	94.4	95.4
60	98.7	85.1	88.7	92.9	88.02	86.12	94.5	96.9	93.1	97.4	95.4	96.1

Table 7

Stability Data for the formulation F9

Batch F9	Physical appearance	Hardness*	Friability*	*In vitro* disintegration time*	In-vitro drug release 30 min	F2 Value
Initial	White colour	176±2.0	0.08±0.02	150±4.0	97.4	83.10
After 1 month	No any change was found	175±1.46	0.13±0.12	156±2.13	97.1	81.93

*Mean ±S.D. (n=3 determinations)

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