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Research paper

FORMULATION, PROCESS PARAMETER OPTIMIZATION AND EVALUATION OF DELAYED RELEASE TABLETS OF RABEPRAZOL SODIUM

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A recent advance in novel drug delivery systems aims to enhance safety and efficacy of drug molecules by formulating a convenient dosage form with ease of administration and better patient compliance. They rarely possess pharmacological activity and are accordingly loosely categorized as 'inert'. However excipients can initiate, propagate or participate in chemical or physical interaction with an active, possibly leading to compromised quality or performance of the medication. We have study at designing an extended-release solid oral matrix formulation of Drug A through application/incorporation of swellable and/or soluble cum erodible hydrophilic polymers and immediate release formulation of Drug B using various diluents and disintegrants. The stable crystalline forms of lactose are a-lactose monohydrate, b-lactose anhydrous, and stable a-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; a-lactose is approximately 20% as sweet as sucrose, while b-lactose is 40% as sweet. Formulation trial no. 8 shows good delayed action and satisfactory all parameters of delayed release formulation. was stable under accelerated conditions of temperature for 3 months since there were no significant changes in drug content and physical parameters. A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. The Maillard interaction has also been shown to occur between lactose and secondary amine. Sodium starch glycolate is incompatible with ascorbic acid. Stearic acid is incompatible with most metal hydroxides and may be incompatible with bases, reducing agents, and oxidizing agents. Our goal in designing delayed or enteric coated delivery systems is to improve the acid sensitive drugs and reduce the gastric irritation.

Keywords: Eudragit L100, CAP, PVAP, RMG, HMPC

INTRODUCTION

The dosage forms available for oral administration are solution, emulation, syrup, tablet, capsule, lozenges, powders etc. Oral route for drug administration is very preferable for patient. with the patient compliance oral dosage forms are easy to administered.[1] Orally administered drug must be absorbed through the gut which depends on various factors such as gastric emptying, intestinal motility, mucosal surface area, degradation of drug in the stomach and first pass effect. These enteric coated dosage forms resist the acidic environment of the stomach and allow disintegration in the higher pH environment of the intestinal fluid.[2] Sodium stearyl fumarate is reported to be incompatible with chlorhexidine acetate. Sodium lauryl sulfate reacts with cationic surfactants, causing loss of activity even in concentrations too low to cause precipitation. Bulk density is defined as a mass of a powder divided by the bulk volume. Some drugs possessing pH dependent stability which is not stable in acidic environment (in the stomach). The Drug A tablet formulated by wet granulation technique with different excipients concentrations like Hypromellose phthalate, HPMC 3cps, SSG, Sodium stearate, Lactose monohydrate, Red ferric oxide. Hypromellose is incompatible with some oxidizing agents.[3] Since it

is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates. Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. Delayed release drug administration means not only prolongation of duration of drug delivery, similarly to the action in the sustained and prolonged release, but the term also implies the predictability and reproducibility of drug release kinetics.[4] The controlled release of drug substances and their effective transport to sites of action can be exploited to maximize the beneficial clinical response and to minimize the incidence of unbeneficial adverse reaction and side effects.[5] Enteric coatings have been applied to solid oral dosage forms to improve the chemical stability of acid-sensitive drugs, to decrease gastric irritation and to target drug release to the intestine. Reduced potential for dose adjustment of drugs normally administered in varying strengths.[6,7]

MATERIAL AND METHODS

Standard solution:- Transfer 50 mg of Drug A RS to a 250 ml volumetric flask, dissolve in 50 ml of alcohol, and dilute with 0.01 M sodum borate solution to volume.Transfer 10.0 ml of this solution into 100 ml volumetirc flask, add 20 ml of alcohol, dilute with 0.01 M sodium borate solution to volume, and mix. Sample solution:- After 2 hr , filter the medium containing the Drug A tablet through a sieve with an aperture of NMT 0.2 mm. Collect the tablet on the sieve, and rinse them with water. Using approximately 60 ml of 0.01 M sodium borate solution , carefully transfer to a 100 ml volumetric flask, dilute with 0.01 M sodium borate solution to volume, and mix. Dilute an appropiate amount of this solution with 0.01 M sodium borate solution to obtain a solution conatianing 0.02 mg/mL. Methanol & ethanol (Chaudhary chemicals UP), Ether (Vats International, Delhi), Chloroform (Kay Cee Chemicals, Delhi), Sodium stearyl fumarate (Signet chemicals Delhi), Acetone (Trivalent Chemical, Vapi), lactose monohydrate (Vats International, Delhi), Sodium lauryl sulfate (Sigma chemical company, St. Louis Mo, USA), Isopropyl alcohol(Changshu yangyuan chemical, china), Benzene (Motion Aerosols, Delhi), Sodium hydroxide, Sodium Chloride & Sucrose (Vats International, Delhi), were provided by Rajasthan college Pharmacy, Udaipur. Spectral Analysis (IR, NMR & Mass) was done at NIPER Mohali.

Experimental work

❖ **Formulation of Delayed release tablets by using different excipients:**

The delayed release tablets are formulated by using different excipients to achieve product specification of innovator. The trials were initiated with wet granulation method. The entire processing for all batches was carried out in controlled condition: At relative humidity: NMT 65% RH and temperature: 22 ± 5°C.

The blend and tablets were evaluated for

1. Physical Parameters such as loss on drying,
2. average weight, disintegration time, hardness etc.
3. Assay

4. Dissolution

Physicochemical analysis

Physical evaluation of lubricated blend.

The lubricated blend of both drug for all batches were subjected to the following physical parameter.

❖ **Bulk density:** Bulk density is defined as a mass of a powder divided by the bulk volume. A blend (20 gm) was introduced in 100 ml graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated by the formula given below;

Bulk density (ρ_0) = M/Vo

Where, M = mass of the powder, Vo = volume of the powder

❖ **Tapped Density:** The mechanical tapping of the cylinder was carried out at a rate of 300 drops per minute for 500 times from 3" height and the tapped volume Vf was noted. The tapped density was calculated in gm/ cm^3 by the formula,

Tapped density (ρ_t) = M/Vf

Where, M = weight of sample powder taken, Vf = tapped volume

❖ **Compressibility Index:** The bulk density and tapped density was measured and compressibility index was calculated using the formula.

C.I. = {(ρt – ρo) / ρt} ×100

Where, ρt = tapped density, ρo = bulk density

Hausner ratio: Tapped density and bulk density were measured and the Hausner ratio was calculated using the formula.

Hausner ratio = ρt/ρo

Where, ρt = tapped density, ρo = bulk density

❖ **Loss on drying:** The moisture in solid can be expressed on a wet-weight or dry-weight basis. On wet-weight basis, the water content of a material is calculated, as a percentage of the weight of the wet solid. The term loss on drying commonly referred to as LOD, is an expression of moisture content on a wet-weight basis sswhich is calculated as

% LOD = Wt. of water in sample / Total wt. of wet sample × 100

The LOD of wet sample is often determined by the use of moisture balance, which has a heat source for rapid heating and a scale calibrated in % LOD. A weighted sample is placed on the balance and allowed to dry until it is constant weight. The water lost by evaporation is read directly from percent LOD scale.

❖ **% fines through 60 #:** The particle size distribution was carried by sieve analysis and % fines were determined by calculating weight of granules passed through 60 #.

Angle of repose: Angle of repose is characteristic related to interparticulate friction or resistance to movement between particles.20 gm of blend was passed through resperograph. Angle of repose was determined by measuring the height of the cone of the powder and calculating the angle of repose from following formula-

$\theta = \tan^{-1}$ (h/r)

Where, h = height of pile, r = radius of pile [8]

Physical evaluation of Tablets

❖ **Description:** Color and shape of the tablets were observed by visual observation.

Acceptance criteria**:** Circular shape, biconvex, uncoated bilayer tablet plain on both sides. Upper

layer White in colored and lower layer blue in colored.

Table 1: Scale for flow properties

Angle of repose	Hausner ratio	%Compressibility index	Flow description
25 – 30	1.2 – 1.3	5 – 15	Excellent
31 – 35	1.3 – 1.4	12 – 16	Good
36 – 40	1.4 – 1.5	18 – 21	Fair
41 – 45	1.5 – 1.6	23 – 28	Poor
46 – 50	> 1.6	35 – 38	Very poor

❖ **Average weight of tablets:** Twenty tablets were dedusted and weighed accurately.

Acceptance criteria: Average weight of the tablet was fixed at 250.0± 2 %(mg).

❖ **Thickness:** Five tablets were randomly selected and thickness of the tablets was measured by previously calibrated vernier caliper.

Acceptance criteria: 3.7 ± 0.3 mm. Thickness was decided as per the hardness of the tablet.

❖ **Hardness test:**

Apparatus: Hardness tester

Procedure: Five tablets were randomly selected. One tablet at a time was placed in the hardness tester which was already set to zero. Pressure was applied by pressing start button of the apparatus, till the tablet breaks. Reading on the tester i.e. the hardness of tablets was noted down in Newtons.

Acceptance criteria: The tablets pass the test if they fall in the range of 70-90 N. The lowest hardness at which the tablets pass the friability test was used to decide the hardness range.

❖ **Friability test:**

Apparatus: Friability test apparatus

Procedure: Average weight of tablet was less than 0.65 g, hence a sample of whole tablets corresponding to about 6.5 g (X) was taken. These tablets were added to the friability test apparatus which was already set to 25 rpm. After completion of 4 minutes, tablets were removed and dedusted. Weight of the tablets was noted down (Y).

% Friability calculated by following formula:

% Friability = X-Y/X * 100

Acceptance criteria: Friability of tablets should be less than 1% as per USP

❖ **Disintegration test: (Drug A)**

Apparatus: Disintegration test apparatus, Reagent: Distilled water

Procedure: The assembly was suspended in the specified liquid medium in a 1000 ml beaker. The volume of liquid was taken such that when the assembly was in highest position the wire mesh was at least 25 mm below the surface of the liquid and when the assembly was in lowest position the wire mesh was at least 25 mm above the bottom of the beaker. One tablet was placed into each of the tube of the assembly and disk was added to each tube. The apparatus was operated for specified time and temperature at 37 ± 2^0 C. Time for complete disintegration of tablet was noted down.

Acceptance criteria: The tablets pass the test if all of them have disintegrated in less than 15 mins.

Uniformity of weight: Apparatus: Analytical balance

Procedure: 20 tablets were randomly selected, dedusted and weighed individually.

% Weight variation from actual average weight of tablet = 100 × (Individual tablet weight- Avg. weight) / Avg. weight of tablet

Acceptance criteria: The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit. The following percentage deviation in weight variation is allowed according to IP:

Table 2: % Weight variation limit as per average weight of tablet

Average weight of tablet	Percentage deviation
80 mg or less	10 %
More than 80 mg and less than 250 mg	7.5 %
250 or more	5%

Chemical evaluation of Tablets

❖ **Assay of tablets:**

10 tablets were weighed and assayed as per USP specification. The assay of tablets was carried out using HPLC method.

Acceptance criteria: The average drug content of Drug A and Drug B should be within the range of 90 – 110% as per USP.

❖ **Acid resistivty test:**

Medium: 0.1 N Hydrochloric acid; 500 ml, Apparatus 2: 100 rpm, Time: 2 hr

Standard solution: Transfer 50 mg of Drug A RS to a 250 ml volumetric flask, dissolve in 50 m l of alcohol, and dilute with 0.01 M sodum borate solution to volume.Transfer 10.0 ml of this solution into 100 ml volumetirc flask, add 20 ml of alcohol, dilute with 0.01 M sodium borate solution to volume, and mix. Sample solution: After 2 hr , filter the medium containing the Drug A tablet through a sieve with an aperture of NMT 0.2 mm. Collect the tablet on the sieve, and rinse them with water. Using approximately 60 ml of 0.01 M sodium borate solution , carefully transfer to a 100 ml volumetric flask, dilute with 0.01 M sodium borate solution to volume, and mix. Dilute an appropiate amount of this solution with 0.01 M sodium borate solution to obtain a solution conatianing 0.02 mg/mL. Calculate the quantity of the labeled amount of Drug A dissolved in medium in mg:

Result= $T\text{-}C_S \times D \times (r_u/r_s)$,

T = labeled quantity of Drug A in the Tablet (mg), C_s = concentration of USP Drug A RS in the Standard solution (mg), D = dilution factor used in preparing the sample solution, r_u= peak response from the sample solution, r_s = peak response from the standard solution.

❖ **Dissolution:**

Dissolution testing for the amount of Drug A released with different concentration of polymers was studied using the following dissolution parameters.

One tablet was transferred into each vessel containing 900 ml of dissolution medium. % Drug A released was calculated by estimating drug in dissolution medium using HPLC system.

Table 3: Dissolution parameters for drug A

Parameters	Specification
Apparatus	paddle , USP type II
Speed	100 rpm
Dissolution media	6.8 phosphate buffer
Volume of dissolution medium	900ml
Sampling time	15,30,45 (min)
Temperature	37 ± 1^0C

Acceptance criteria: The tablets pass the test if the drug release for Drug A meets the following specifications as per USP[10]

Table 4: Specified limits for drug A

Time (min)	Specified limits for amount of drug released
15	55±5
30	78±5
45	92±5

Competitor product details

Marketed name : XXX

Dosage form : Delayed release tablet

Table 5: Complete physical and chemical characterization of Competitor product

Test	Specification	Observation
Description	A brown colored, caplet shaped enteric coated tablet	Complies
Average weight	299 mg ± 3.0%	299.3 mg
Thickness	3.74 ± 0.3 mm	3.76 mm
Friability	Not more than 1.0%	0.74 %
Hardness	Not less than 110 N	Complies
Disintegration time	Not more than 15 min in phosphate buffer 6.8	6.5- 8.5 min
Dissolution time 15 min 30 min 45 min	Not more than 75 % Q release at 45 min	Complies
Assay of Drug A	Not less than 90.0% and not more than 110%	99.5% (on dry basis)

Formulation approaches of Drug A containing delayed release tablet

- **Batch no.: 1 (Table 7.8)**

Batch size: 3000 tablets

Aim: To take trial batch using wet granulation method with tabletting excipients for Drug A

The quantity of materials (active & excipients) is weighed according to formula for the batch no. 01 & then compression is carried out according to procedure..

- **Batch no.: 2 (Table 7.10)**

Batch size: 3000 tablets

Aim: To take trial batch to get proper flow of granules and overcome the problem of capping. For that SSG quantity is divided into two equal parts, one of that two part adding in lubrication. Granulation was taken with purified water using as binder solution.[11]

- **Batch no.: 3 (Table 7.13)**

Batch size: 3000 tablets

Aim: To take trial batch with same formula as batch no. 2 to overcome the problem of low hardness. For that granulation was taken in FBP with spraying purified water as binder solution.

- **Batch no.: 4 (Table 7.14)**

Batch size: 3000 tablets

Aim: To take trial batch using HPMC as binding agent for overcome the problem of hardness. For granulation HPMC (3 cps) dissolved in purified water using as binder solution.[12]

- **Batch no.: 5, 6, 7 (Table 7.17)**

Batch size: 3000 tablets

Aim: To take trial batches using different conc. of HPMC as binding agent with same conc. of disintegrent (SSG) to optimize the conc. of binding agent.

Batch no.: 8, 9.(Table 7.20)

Batch size: 3000 tablets

Aim: To take trial batches using different conc. of SSG as disintegrating agent with same conc. of binder (HPMC) to optimize the conc. of disintegrating agent. [13]

➢ **The formula for Batch no. 01 is as follows:**

Table 6:Core formula of formulation using wet granulation for Trial 1

Item No.	Ingredients	Trial 1 (mg/tab)	Batch quantity (gm)
Pre-Mix:			
1.	Drug A	20.0	60.0
2.	Lactose Monohydrate	205.0	615.0
3.	Sodium Starch Glycolate	12.0	36.0
4.	Sodium Stearate	10.0	30.0
5.	Purified Water	QS	QS
Lubrication:			
6.	Sodium Steryl Fumarate	3.0	9.0
	Total Weight	250	750.0

- **Table 7: Manufacturing process of Trial 1 by wet granulation**

Step No.	Unit operation	Conditions
1.	Pre-mixing: Items no. 1, 2, 3, 4 are accurately weighed and shifted through 30 # sieve and transferred into RMG.	Pre-mixing done for 5 minutes at slow speed (50 rpm) of impeller.
2.	Wet granulation: Items No. 5 Purified Water, USP was weighed to 200 mL and added to the Pre-mix blend while mixing.	Mixed until uniform wet granulation was formed. (added 100 mL of Purified water for additional to achieve granulation)
3.	Drying: Wet granules were dried in a FBD.	Dried at 60°c upto get LOD less than 3%.
4.	Size-reduction: Dried granulation was sifted through 20#.	Sizing will give optimum particle size distribution.
5.	Final-mixing/Lubrication: Item No. 6 was added to the above blend.	Mixed for 5 minutes.
6.	Compression: The final-mix was compressed into tablets using compression machine with 12.0 x 6.00 mm, Caplet shaped Embossed Tooling (Upper punches: Embossed with "N", Lower punches: plain). Tablets were compressed at 4.0 ton pressure.	Average Tablet Weight: 250.00 mg Tablet Thickness: 3.75 to 3.80 mm Tablet Hardness: 2.5 - 3.0 kg DT: 1 min 40 sec to 1 min 50 sec

The formula for batch no. 2 as follows

Table 8: Core formula of formulations using wet granulation for Trial 2

Item No.	Ingredients	Trial 2 (mg/tab)	Batch quantity (gm)
Pre-Mix:			
1.	Drug A	20.0	60.0
2.	Lactose Monohydrate	205.0	615.0
3.	Sodium Starch Glycolate	6.0	18.0
4.	Sodium Stearate	10.0	30.0
5.	Purified Water	QS	QS
Lubrication:			
6.	Sodium Starch Glycolate	6.0	18.0
7.	Sodium Steryl Fumarate	3.0	9.0
	Total Weight	250	750.0

- **Table 9: Manufacturing process of Trial 2 by wet granulation**

Step No.	Unit operation	Conditions
1.	Pre-mixing: Items no. 1, 2, 3, 4 are accurately weighed and shifted through 30 # sieve and transferred into RMG.	Pre-mixing done for 5 minutes at slow speed (50 rpm) of impeller.
2.	Wet granulation: Items No. 5 Purified Water, USP was weighed to 200 mL and added to the Pre-mix blend while mixing. (While adding binder impeller speed was 50 rpm after that for proper mixing impeller speed was 100 rpm and chopper speed was 1400 rpm for 1 min, chopper is imp for breaking lumps.)	Mixed until uniform wet granulation was formed. (added 100 mL of Purified water for additional to achieve granulation)
3.	Drying: Wet granules were dried in a FBD.	Dried at 60°c upto get LOD less than 3%.
4.	Size-reduction: Dried granulation was sifted through 20#.	Sizing will give optimum particle size distribution.
5.	Pre-lubrication: Item no. 6 was added to the dried granules.	Mixed for 10 minutes.
6.	Final-mixing/Lubrication: Item No. 7 was added to the above blend.	Mixed for 5 minutes.
7.	Compression: The final-mix was compressed into tablets using compression machine with 12.0 x 6.00 mm, Caplet shaped Embossed Tooling (Upper punches: Embossed with "N", Lower punches: plain). Tablets were compressed at 4.0-ton pressure.	Average Tablet Weight: 250.00 mg Tablet Thickness: 3.72 to 3.78 mm Tablet Hardness: 2.5 - 3.5 kg DT: 1 min 05 sec to 1 min 15 sec

The formula for batch no. 3 as follows:

Table 10: Core formula of formulations using wet granulation for Trial 3

Item No.	Ingredients	Trial 3 (mg/tab)	Batch quantity (gm)
Pre-Mix:			
1.	Drug A	20.0	60.0
2.	Lactose Monohydrate	205.0	615.0
3.	Sodium Starch Glycolate	6.0	18.0
4.	Sodium Stearate	10.0	30.0
5.	Purified Water	QS	QS
Lubrication:			
6.	Sodium Starch Glycolate	6.0	18.0
7.	Sodium Steryl Fumarate	3.0	9.0
	Total Weight	250	750.0

- **Table 11: Manufacturing process of Trial 3 by wet granulation**

Step No.	Unit operation	Conditions
1.	Pre-mixing: Items no. 1, 2, 3, 4 are accurately weighed and shifted through 30 # sieve and transferred into FBP.	Pre-mixing done for 5 minutes by air flow at 25% damper.
2.	Wet granulation: Items No. 5 Purified Water, USP was weighed to 200 mL and sprayed to the Pre-mix blend in FBP.	Mixed until uniform wet granulation was formed. (Sprayed Purified water at 30mL/min spray rate to achieve granulation)
3.	Drying: Wet granules were dried in a FBP.	Dried at 60°c upto get LOD less than 3%.
4.	Size-reduction: Dried granulation was sifted through 20#.	Sizing will give optimum particle size distribution.
5.	Pre-lubrication: Item no. 6 was added to the dried granules.	Mixed for 10 minutes.
6.	Final-mixing/Lubrication: Item No. 7 was added to the above blend.	Mixed for 5 minutes.
7.	Compression: The final-mix was compressed into tablets using compression machine with 12.0 x 6.00 mm, Caplet shaped Embossed Tooling (Upper punches: Embossed with “N”, Lower punches: plain). Tablets were compressed at 4.0 ton pressure.	Average Tablet Weight: 250.0 mg Tablet Thickness: 3.70 to 3.80 mm Tablet Hardness: 3-4 kg DT: 30-40 sec

The formula for batch no. 4 as follows:

Table 12: Core formula of formulations using wet granulation for Trial 4

Item No.	Ingredients	Trial 4 (mg/tab)	Batch quantity (gm)
Pre-Mix:			
1.	Drug A	20.0	60.0
2.	Lactose Monohydrate	200.0	600.0
3.	Sodium Starch Glycolate	6.0	18.0
4.	Sodium Stearate	10.0	30.0
5.	HPMC (3 cps)	5.0	15.0
6.	Purified Water	QS	QS
Lubrication:			
7.	Sodium Starch Glycolate	6.0	18.0
8.	Sodium Steryl Fumarate	3.0	9.0
Total Weight		250	750.0

*** 9 % w/v solution was prepared.**

- **Table 13: Coating formula composition for Trial 4**

Item No.	Ingredients	mg per tablet	Batch quantity (gm)	Batch quantity*(10% extra)gm
Seal coating: 4% (260 mg)				
8.	Red ferric oxide	5.80	17.40	19.14
9.	Talc	4.00	12.00	13.20
10.	Triethyl citrate	0.20	0.60	0.66
11.	Purified Water**	QS	QS	QS
	Total weight :	10.00	30.00	33.00
Enteric coating : 15% (299 mg)				
12.	Hypromellose pthalate	25.00	75.00	82.50
13.	Triethyl citrate	6.25	18.75	20.63
14.	Talc	6.75	2.25	22.28
15.	Sodium Lauryl Sulphate	1.00	3.00	3.30
16.	Purified Water**	QS	QS	QS
	Total weight:	39.00	117.00	128.70

*** Taking 10% overages for overcome the process loss during coating.**

**** 12% w/v solution prepared**

- **Table 14: Manufacturing process of Trial 4 by wet granulation**

Step No.	Unit operation	Conditions
1.	Pre-mixing: Items no. 1, 2, 3, 4 are accurately weighed and shifted through 30 # sieve and transferred into FBP.	Pre-mixing done for 5 minutes by air flow at 25% damper.
2.	Wet granulation: Items No. 5is accurately weighed and dissolve in weighed quantity of Purified Water, USP. This binder solution sprayed to the Pre-mix blend in FBP.	Mixed until uniform wet granulation was formed. (Sprayed HPMC solution as binder solution at 30mL/min spray rate to achieve granulation)
3.	Drying: Wet granules were dried in a FBP.	Dried at 60°c upto get LOD less than 3%.
4.	Size-reduction: Dried granulation was sifted through 20#.	Sizing will give optimum particle size distribution.
5.	Pre-lubrication: Item no. 6 was added to the dried granules.	Mixed for 10 minutes.
6.	Final-mixing/Lubrication: Item No. 7 was added to the above blend.	Mixed for 5 minutes.
7.	Compression: The final-mix was compressed into tablets using compression machine with 12.0 x 6.00 mm, Caplet shaped Embossed Tooling (Upper punches: Embossed with "N", Lower punches: plain). Tablets were compressed at 4.0 ton pressure.	Average Tablet Weight: 250.0 mg Tablet Thickness: 3.74 to 3.82 mm Tablet Hardness: 4.5-5.0 kg DT: 5-6 min
8.	Coating: 1. Seal coating: Item no. 8, 9, 10 accurately weighed and prepare seal coating solution and during coating solution was stirred in solution tank. 2. Enteric coating: Item no. 12, 13, 14, 15 accurately weighed and prepare enteric coating solution which is continuously stirred during spraying the solution.	1. Seal coating: coating was done upto 4% seal coating achieved. 2. Enteric coating: coating was done upto 15% coating achieved.

The formula for batch no. 5, 6, and 7 as follows:

Table 15: Core formula of formulations using wet granulation for Trial 5, 6, 7

Item No.	Ingredients	Trial 5 (mg/tab)	Trial 6 (mg/tab)	Trial 7 (mg/tab)
Pre-Mix:				
1.	Drug A	20.0	20.0	20.0
2.	Lactose Monohydrate	197.5	195.0	192.5
3.	Sodium Starch Glycolate	6.0	6.0	6.0
4.	Sodium Stearate	10.0	10.0	10.0
5.	HPMC (3 cps)	7.5	10.0	12.5
6.	Purified Water	QS	QS	QS

Lubrication:				
7.	Sodium Starch Glycolate	6.0	6.0	6.0
8.	Sodium Steryl Fumarate	3.0	3.0	3.0
	Total Weight	250.0	250.0	250.0

* 9 % w/v solution was prepared.

- **Table 16: Coating formula composition for Trial 5, 6, 7**

Item No.	Ingredients	mg per tablet	Batch quantity (gm)	Batch quantity * gm
Seal coating: 4% (260 mg)				
8.	Red ferric oxide	5.80	17.40	19.14
9.	Talc	4.00	12.00	13.20
10.	Triethyl citrate	0.20	0.60	0.66
11.	Purified Water**	QS	QS	QS
	Total weight :	10.00	30.00	33.00
Enteric coating : 15% (299 mg)				
12.	Hypromellose phthalate	25.00	75.00	82.50
13.	Triethyl citrate	6.25	18.75	20.63
14.	Talc	6.75	2.25	22.28
15.	Sodium Lauryl Sulphate	1.00	3.00	3.30
16.	Purified Water**	QS	QS	QS
	Total weight:	39.00	117.00	128.70

* Taking 10% overages for overcome the process loss during coating.

** 12% w/v solution prepared

Table 17: Manufacturing process of Trial 5, 6 and 7

Step No.	Unit operation	Conditions
1.	Pre-mixing: Items no. 1, 2, 3, 4 are accurately weighed and shifted through 30 # sieve and transferred into RMG.	Pre-mixing done for 5 minutes at slow speed (50 rpm) of impeller.
2.	Wet granulation: Items No. 5 HPMC (3 cps) was weighed and dissolved in proper quantity of purified water and that solution added to the Pre-mix blend while mixing. (While adding binder impeller speed was 50 rpm after that for proper mixing impeller speed was 100 rpm and chopper speed was 1400 rpm for 1 min, chopper is imp for breaking lumps.)	Mixed until uniform wet granulation was formed. (added 100 mL of Purified water for additional to achieve granulation)
3.	Drying: Wet granules were dried in a FBP.	Dried at 60°c upto get LOD less than 3%.
4.	Size-reduction: Dried granulation was sifted through 20#.	Sizing will give optimum particle size distribution.
5.	Pre-lubrication:	

	Item no. 6 was added to the dried granules.	Mixed for 10 minutes.
6.	Final-mixing/Lubrication: Item No. 7 was added to the above blend.	Mixed for 5 minutes.
7.	Compression: The final-mix was compressed into tablets using compression machine with 12.0 x 6.00 mm, Caplet shaped Embossed Tooling (Upper punches: Embossed with "N", Lower punches: plain). Tablets were compressed at 4.0 ton pressure.	Average Tablet Weight: 250.0 mg Tablet
8.	Coating: 1. Seal coating: Item no. 8, 9, 10 accurately weighed and prepare seal coating solution and during coating solution was stirred in solution tank. 2. Enteric coating: Item no. 12, 13, 14, 15 accurately weighed and prepare enteric coating solution which is continuously stirred during spraying the solution.	1. Seal coating: coating was done upto 4% seal coating achieved. 2. Enteric coating: coating was done upto 15% coating achieved.

The formula for batch no. 8, 9 as follows

Table 18: Core formula of formulations using wet granulation for Trial 8, 9

Item No.	Ingredients	Trial 8 (mg/tab)	Trial 9 (mg/tab)
Pre-mix:			
1.	Drug A	20.0	20.0
2.	Lactose Monohydrate	192.0	189.0
3.	Sodium Starch Glycolate	9.0	12.0
4.	Sodium Stearate	10.0	10.0
5.	HPMC (3 cps)	10.0	10.0
6.	Purified Water*	QS	QS
Lubrication:			
7.	Sodium Starch Glycolate	6.0	6.0
8.	Sodium Steryl Fumarate	3.0	3.0
	Total Weight	250.0	250.0

* 9 % w/v solution was prepared.

Table 19: Coating formula composition for Trial 8, 9

Item No.	Ingredients	mg per tablet	Batch quantity (gm)	Batch quantity *gm
Seal coating: 4% (260 mg)				
8.	Red ferric oxide	5.80	17.40	19.14
9.	Talc	4.00	12.00	13.20
10.	Triethyl citrate	0.20	0.60	0.66
11.	Purified Water**	QS	QS	QS

	Total weight :	10.00	30.00	33.00
Enteric coating : 15% (299 mg)				
12.	Hypromellose pthalate	25.00	75.00	82.50
13.	Triethyl citrate	6.25	18.75	20.63
14.	Talc	6.75	2.25	22.28
15.	Sodium Lauryl Sulphate	1.00	3.00	3.30
16.	Purified Water**	QS	QS	QS
	Total weight:	39.00	117.00	128.70

* Taking 10% overages for overcome the process loss during coating.
** 12% w/v solution prepared

Table 20: Manufacturing process of Trial 8 and 9

Step No.	Unit operation	Conditions
1.	Pre-mixing: Items no. 1, 2, 3, 4 are accurately weighed and shifted through 30 # sieve and transferred into RMG.	Pre-mixing done for 5 minutes at slow speed (50 rpm) of impeller.
2.	Wet granulation: Items No. 5 HPMC (3 cps) was weighed and dissolved in proper quantity of purified water and that solution added to the Pre-mix blend while mixing. (While adding binder impeller speed was 50 rpm after that for proper mixing impeller speed was 100 rpm and chopper speed was 1400 rpm for 1 min, chopper is imp for breaking lumps.)	Mixed until uniform wet granulation was formed. (added 100 mL of Purified water for additional to achieve granulation)
3.	Drying: Wet granules were dried in a FBP.	Dried at 60°c upto get LOD less than 3%.
4.	Size-reduction: Dried granulation was sifted through 20#.	Sizing will give optimum particle size distribution.
5.	Pre-lubrication: Item no. 6 was added to the dried granules.	Mixed for 10 minutes.
6.	Final-mixing/Lubrication: Item No. 7 was added to the above blend.	Mixed for 5 minutes.
7.	Compression: The final-mix was compressed into tablets using compression machine with 12.0 x 6.00 mm, Caplet shaped Embossed Tooling (Upper punches: Embossed with "N", Lower punches: plain). Tablets were compressed at 4.0 ton pressure.	Average Tablet Weight: 250.0 mg Tablet
8.	Coating: 1. Seal coating: Item no. 8, 9, 10 accurately weighed and prepare seal coating solution and during coating solution was stirred in solution tank. 2. Enteric coating: Item no. 12, 13, 14, 15 accurately weighed and prepare enteric coating solution which is continuously stirred during spraying the solution.	1. Seal coating: coating was done upto 4% seal coating achieved. 2. Enteric coating: coating was done upto 15% coating achieved.

- **Batch no.: 10**

Batch size: 3000 tablets

Aim: To take reproducible trial batch of trial 8 for proto type stability. [14]

The formula for batch no. 10 as follows

Table. 21: Core formula of formulations using wet granulation for Trial 10

Item No.	Ingredients	Trial 8 (mg/tab)	Qty/batch (gm)
Pre mix:			
1.	Drug A	20.0	60
2.	Lactose Monohydrate	192.0	576
3.	Sodium Starch Glycolate	9.0	27
4.	Sodium Stearate	10.0	30
5.	HPMC (3 cps)	10.0	30
6.	Purified Water*	QS	QS
Lubrication:			
7.	Sodium Starch Glycolate	6.0	18
8.	Sodium Steryl Fumarate	3.0	9
	Total Weight	250.0	750

* 9 % w/v solution was prepared.

Table 22 :Coating formula composition for Trial 10

Item No.	Ingredients	mg per tablet	Batch quantity (gm)	Batch quantity *gm
Seal coating: 4% (260 mg)				
8.	Red ferric oxide	5.80	17.40	19.14
9.	Talc	4.00	12.00	13.20
10.	Triethyl citrate	0.20	0.60	0.66
11.	Purified Water**	QS	QS	QS
	Total weight :	10.00	30.00	33.00
Enteric coating : 15% (299 mg)				
12.	Hypromellose pthalate	25.00	75.00	82.50
13.	Triethyl citrate	6.25	18.75	20.63
14.	Talc	6.75	2.25	22.28
15.	Sodium Lauryl Sulphate	1.00	3.00	3.30
16.	Purified Water**	QS	QS	QS
	Total weight:	39.00	117.00	128.70

* Taking 10% overages for overcome the process loss during coating.

** 12% w/v solution prepared

Table 23 :Manufacturing process of Trial 10

Step No.	Unit operation	Conditions
1.	Pre-mixing: Items no. 1, 2, 3, 4 are accurately weighed and shifted through 30 # sieve and transferred into RMG.	Pre-mixing done for 5 minutes at slow speed (50 rpm) of impeller.
2.	Wet granulation: Items No. 5 HPMC (3 cps) was weighed and dissolved in proper quantity of purified water and that solution added to the Pre-mix blend while mixing. (While adding binder impeller speed was 50 rpm after that for proper mixing impeller speed was 100 rpm and chopper speed was 1400 rpm for 1 min, chopper is imp for breaking lumps.)	Mixed until uniform wet granulation was formed. (added 100 mL of Purified water for additional to achieve granulation)
3.	Drying: Wet granules were dried in a FBP.	Dried at 60°c upto get LOD less than 3%.
4.	Size-reduction: Dried granulation was sifted through 20#.	Sizing will give optimum particle size distribution.
5.	Pre-lubrication: Item no. 6 was added to the dried granules.	Mixed for 10 minutes.
6.	Final-mixing/Lubrication: Item No. 7 was added to the above blend.	Mixed for 5 minutes.
7.	Compression: The final-mix was compressed into tablets using compression machine with 12.0 x 6.00 mm, Caplet shaped Embossed Tooling (Upper punches: Embossed with "N", Lower punches: plain). Tablets were compressed at 4.0 ton pressure.	Average Tablet Weight: 250.0 mg Tablet
8.	Coating: 1. Seal coating: Item no. 8, 9, 10 accurately weighed and prepare seal coating solution and during coating solution was stirred in solution tank. 2. Enteric coating: Item no. 12, 13, 14, 15 accurately weighed and prepare enteric coating solution which is continuously stirred during spraying the solution.	1. Seal coating: coating was done upto 4% seal coating achieved. 2. Enteric coating: coating was done upto 15% coating achieved.

7.5 Stability studies

Stability study was performed by exposing the formulation to different conditions including stress conditions of temperature and pressure. The formulations were analyzed at 1, 2, 3, 6, 9, 12 and 24 months.

Table 24: Protocol for stability studies

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	3, 6, 9,12 & 24 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	3, 6, 9 & 12 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	1, 2, 3 & 6 months

* It is up to the applicant to decide whether long term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH

** If 30°C ± 2°C/65% RH ± 5% RH is long term condition, then there is no intermediate condition.

RESULTS

Preliminary study: Drug A

- The results of the tests of Drug A substance (Active) are given in the Table 8.1

Table 25: Test and results for Drug A

Sr. no.	Tests	Results
1.	Description	White to off-White powder
2.	Solubility	Freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water.
3.	Clarity and color of solution	0.003
4.	Identification By IR	The IR spectrum of sample should be concordant with the spectrum obtained from working standard
5.	pH	7.36
6.	Loss on Drying	NMT 0.06 % w/w
7.	Residue on ignition	NMT 0.04 % w/w
8.	Heavy metals	NMT 0.001% W/W
9.	Related substances (By TLC)	Less than 0.2%
9 A.	Related substances (By HPLC)	Any single impurity : NMT 0.04% Total impurities : NMT 0.04 %
10.	Assay (By HPLC)	99.7% (on dried basis)

Evaluation of physicochemical properties of Drug A DR tablet batches
Physical evaluation of Batch no. 1, 2 & 3:

Table 26: In-process and finished product evaluation of batch no. 1, 2 & 3

Sr. No.	Parameter	Trial 1	Trial 2	Trial 3
In process evaluation				
1	Unlubricated LOD % w/w	2.15	2.13	2.18
2	Lubricated LOD % w/w	2.50	2.47	2.61
3	Tapped density	0.683	0.648	0.678
4	Bulk density	0.532	0.537	0.535
5	Compressibility index	22.11	17.13	21.09
6	Hausner's ratio	1.28	1.20	1.26
7	% Fines through 60#	70.0 %	67.3 %	68.0 %
Finished product evaluation				
1	Tablet dimension (12x6 mm caplet)	Complies	Complies	Complies
2	Average weight	250 mg	250 mg	250 mg
3	Thickness	3.75-3.80 mm	3.72-3.78 mm	3.70-3.80 mm
4	Hardness	2.5-3.0 kg	2.5-3.5 kg	3.0-4.0 kg
5	Friability	Capping	1.10 %	0.85 %
6	Disintegration time (For immediate release part only)	1: 39 to 1:54 min	1:05 to 1:15 min	30-40 sec

Batch no: 4 Evaluation of physicochemical properties of Drug A delayed release tablet.

Physical evaluation of Batch no. 4:

Table 27: In-process and finished product evaluation of trial 4 (Chemical evaluation of batch no. 4)

Sr. No.	Parameter	Trial 4
In process evaluation		
1	Unlubricated LOD % w/w	2.20
2	Lubricated LOD % w/w	2.60
3	Tapped density	0.576
4	Bulk density	0.720
5	Compressibility index	20.00
6	Hausner's ratio	1.25
7	% Fines through 60#	70.0 %
Core tablet evaluation		
1	Tablet dimension (12x6 mm caplet)	Complies
2	Average weight	250 mg

3	Thickness	3.74 to 3.82 mm
4	Hardness	4.5-5.0 kg
5	Friability	0.35%
6	Disintegration time (For immediate release part only)	5-6 min
Finished product evaluation		
1	Average weight	300 mg
2	Thickness	4.10-4.21 mm
3	Disintegration time	8-9 min
4	Hardness	10-11 kg

Table 28 :% Drug release of Drug A of Batch no. 4 with competitor

Drug A		
Assay (%)	**96.5**	
Dissolution profile (% Drug release)		
Time (min)	**Competitor**	**Batch no : 4**
15	55	78
30	80	85
45	*94*	*92*

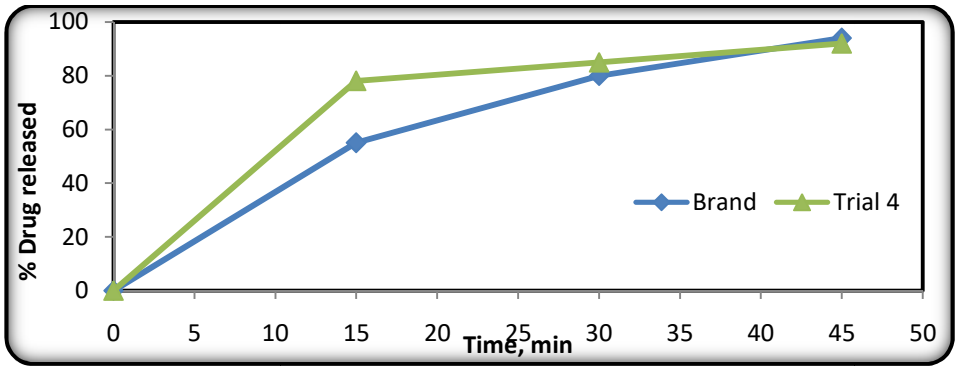

Fig. 1: Dissolution profile for Drug A of Batch no. 4 with competitor

<u>Batch no: 5, 6 & 7</u> Evaluation of physicochemical properties of Drug A delayed release tablet.

Physical evaluation of Batch no. 5, 6 & 7:

Table 29:In-process and finished product evaluation of trial 4(Chemical evaluation of Batch no. 5, 6 & 7)

Sr. No.	Parameter	Trial 5	Trial 6	Trial 7
In process evaluation				
1	Unlubricated LOD % w/w	2.25	2.30	2.28
2	Lubricated LOD % w/w	2.56	2.61	2.75
3	Tapped density	0.720	0.731	0.719
4	Bulk density	0.600	0.575	0.612
5	Compressibility index	16.67	21.34	14.88
6	Hausner's ratio	1.20	1.27	1.17
7	% Fines through 60#	68%	71%	73.50%

Core tablet evaluation				
1	Tablet dimension (12x6 mm caplet)	Complies	Complies	Complies
2	Average weight	250 mg	250 mg	250 mg
3	Thickness	3.75 to 3.80 mm	3.77 to 3.82 mm	3.78 to 3.85 mm
4	Hardness	5-6 kg	5-6.5 kg	5-7 kg
5	Friability	0.39%	0.21%	0.17%
6	Disintegration time	6.5-7.5 min	8-8.5 min	8.5-9 min
Finished product evaluation				
1	Average weight	300 mg	300 mg	300 mg
2	Thickness	4.10 to 4.21 mm	4.15 to 4.22 mm	4.17 to 4.25 mm
3	Disintegration time	8.5-9.5 min	8.5-9 min	9.5-11.0 min
4	Hardness	11-12.5 kg	13-14 kg	13-14.5 kg

Chemical evaluation of Batch no. 5, 6 & 7

Table 30: % drug release of Drug A and Drug B of Batch no. 5, 6 & 7 with competitor

Drug A				
	Batch no. 5	Batch no. 6	Batch no. 7	
Assay (%)	96.7	96.4	95.9	
Dissolution profile (% Drug release)				
Time (min)	Competitor	Batch no. 5	Batch no. 6	Batch no. 7
15	55	68	57	48
30	80	76	74	70
45	94	93	90	85

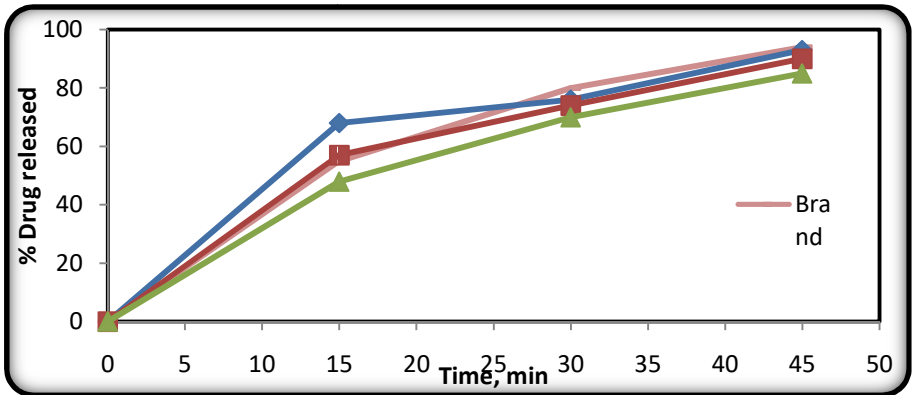

Fig. 2: Dissolution profile for Drug A of Batch no. 5, 6 & 7 with competitor

Batch no: 8 & 9 Evaluation of physicochemical properties of Drug A delayed release tablet.

Physical evaluation of Batch no. 8 & 9

Table 31: In-process and finished product evaluation of trial 8 & 9

Sr. No.	Parameter	Trial 8	Trial 9
In process evaluation			
1	Unlubricated LOD % w/w	2.28	2.33
2	Lubricated LOD % w/w	2.52	2.69
3	Tapped density	0.728	0.708
4	Bulk density	0.585	0.605
5	Compressibility index	19.65	14.55
6	Hausner's ratio	1.24	1.17
7	% Fines through 60#	65.4%	72.1%
Core tablet evaluation			
1	Tablet dimension (12x6 mm caplet)	Complies	Complies
2	Average weight	250 mg	250 mg
3	Thickness	3.72 to 3.78 mm	3.70 to 3.75 mm
4	Hardness	5-6.5 kg	4.5-5.5 kg
5	Friability	0.18%	0.49%
6	Disintegration time	6-7.5 min	5.5-6.5 min
Finished product evaluation			
1	Average weight	300 mg	300 mg
2	Thickness	4.25 to 4.28 mm	4.21 to 4.26 mm
3	Disintegration time	8.5-9.5 min	7.0-8.5 min
4	Hardness	12-14 kg	10-12 kg

Chemical evaluation of Batch no. 8 & 9

Table 32: % Drug release of Drug A and Drug B of Batch no. 8 & 9 with competitor

Drug A			
	Batch no. 8		Batch no. 9
Assay (%)	96.4		95.9
Dissolution profile (% Drug release)			
Time (min)	Competitor	Batch no. 8	Batch no. 9
15	55	55	59
30	80	80	82
45	94	92	93

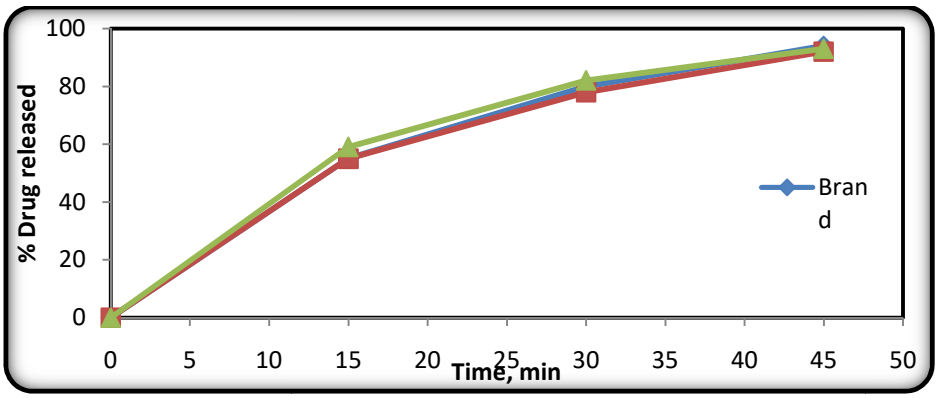

Fig. 3: Dissolution profile for Drug A of Batch no. 8 & 9 with competitor

8.3 Comparative *In-vitro* release profile of formulation with competitor formulation f_1 - f_2 study.[15]

Table 34: Comparative *In-vitro* release profile of Batch no. 8 with competitor formulation

% drug release in phosphate buffer pH 6.8 for Drug A				
Time (min)	Avg. Reference (R) Competitor	Avg. Test (T) B-8	(R-T)	$(R-T)^2$
15	55	55	0	0
30	80	78	2	4
45	94	92	2	4
sum	229	225	4	8

$f_2 = 50 + \log \{[1+ (1/n) \sum_{t=1} * n (R_t-T_t)^2]^{-0.5} *100\}$ f1= $\{[\Sigma_{t=1}^{n} |R_t-T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100$

0

Table 35 : Results of f_1 – f_2 study

f_2	86
f_1	2

Values of f_1 (<15) and f_2 (>50) indicate, that the curves can be considered similar.

Number of points consideration is based on the guidance of the FDA.

From the above results batch no 6 formula can be considered similar with competitor formula.

Results of stability studies

Development of formulation was completed with the final formula. Form that formula stability batches were taken to see the effect of temperature and humidity. Initial observations of stability formulations for physical characterization had shown that, all of them comply with the specifications as per the Indian pharmacopoeia.

Evaluation of physicochemical properties of Drug A

Physical evaluation of stability Batch no. 10

Table 36: In-process and finished product evaluation of Trial 10

Sr. No.	Parameter	Trial 10
In process evaluation		
1	Unlubricated LOD % w/w	2.26
2	Lubricated LOD % w/w	2.59
3	Tapped density	0.731
4	Bulk density	0.589
5	Compressibility index	19.42
6	Hausner's ratio	1.24
7	% Fines through 60#	67.1%
Core tablet evaluation		
1	Tablet dimension (12x6 mm caplet)	Complies
2	Average weight	250 mg
3	Thickness	3.70 to 3.76 mm
4	Hardness	5-6.5 kg
5	Friability	0.21%
6	Disintegration time	6-7.5 min
Finished product evaluation		
1	Average weight	300 mg
2	Thickness	4.25 to 4.28 mm
3	Disintegration time	8.5-9.5 min
4	Hardness	12-14 kg

Evaluation of physicochemical properties of Drug A DR Tablet subjected to stability batches no. 1

Table 37: Stability data of Trial 10 at accelerated (40±2ºC & 75±5% RH) conditions

Test	Specification		Initial	1 month	2 month
Appearance	A red-brown colored caplet shaped enteric coated tablet		Complies	Complies	Complies
Hardness	NLT 98 – 198 N		99-120 N	Complies	Complies
Friability	Not more than 1.0 %		0.21 %	Complies	Complies
Dissolution (% drug release)	Time (min)	Competitor	Trial 10		
Drug A	15	55	54	52	52
	30	80	78	76	75
	45	94	92	91	91
Assay	**Drug A**		96.7	96.5	96.1

DISCUSSION

For Batch no. 1 In trial 1 we achieve good compression parameters. But flow of granules was not proper and weight variation occurs during compression. In this trial capping also occur.

Hardness was not achieved so not going for coating in this batch. Tablet disintegration time was not comparable to brand. For improving flow property of granules taking trial 2 with SSG concentration was split into two equal parts for premixing and lubrication to improve hardness and flow of granules. **For batch no. 2** In trial 2 SSG concentration split into two equal parts (6 mg/tab) for premixing and lubrication. The above results suggested that flow properties of granules was not improve and weight variation occur but hardness was less and friability was not in limit.Tablet disintegration time was not good. But still hardness was not proper to go for coating. From above result improvisation needed in flow property and hardness

for coating of tablets. For that next trial was taken in FBP. **For Batch no. 3** In trial 3 Granulation was done by spraying purified water as binding solution and granules were dried in FBP with same formula of trial 2. Form above results, flow properties of granules was improved and reduce weight variation. In this trial hardness was also improved but DT time was very less and friability was near to the limit. From above results need to add binder in next trial for improving hardness to go for coating of tablet. **For Batch no. 4** The above results suggest that the drug content for Drug A was in specified limits of 90 – 110 %. Hence *in-vitro* drug release studies were carried out for this batch. In this trial all compression parameters are satisfactory and hardness and disintegration time in comparable to brand. For optimization of binder concentrations next trials will taken. **For batch no. 5, 6 & 7** The above results suggest that the drug content for Drug A was in specified limits of 90 – 110 %. Hence *in-vitro* drug release studies were carried out for these batches. In these trials try to optimize the concentration of HPMC (3cps) as binder. From above results all compression parameters are in range and comparable to brand. But in these three trials trial no. 6 shows good results as optimum binder concentrations. Flow of granules, hardness and friability were good in trial 6. So going on conclusion that optimum concentration of HPMC as binder is 10.00 mg in as binder solution. Form above trials next two trials taken for optimization the concentration of SSG as a disintegrant. **For batch no. 8 & 9** The above results suggest that the drug content for Drug A was in specified limits of 90 – 110 %. So in-vivo drug release studies for these batches were carried out. In these trials we try to optimize the concentration of SSG as disintegrant. From above results disso profile of trial 8 and brand were near to superimpossible. All the compression parameters were satisfactory and disintegration time was near to brand. Due to all results were in specified limit Trial 8 taken as optimized formula and taken trial 10 as reproducible batch of trial 8 for proto type stability. **For batch no.7 & 8- For Drug A** The above results suggest that the drug content for Drug A was in specified limits of 90 – 110 %. In the above trial the release in the 15th, 30th and 45th min within the specified limits. The Drug A release also found within specified limits after 2 month 40^{0} C/75 %RH condition. Stability study was conducted on tablets of Trial 8. Tablets were evaluated batch no. 10 for *in-vitro* dissolution measurement and *in-vitro* release profile, after two month. No significant changes were observed in any of the studied parameters during the study period, thus it could be concluded that formulation was stable. The stability study revealed that there was not significant change in dissolution profile.

CONCLUSION

All compression parameter found satisfactory. But flow of granules were not proper and capping occurs, so coating was not done in this batch and plan for next batch no. 2. In this trial 2, compression parameters are satisfactory but flow of granules is not proper and friability failed due to low hardness. So going for taking trial 3 in FBP. In this trial 3,

compression parameters are satisfactory and flow of granules is also improved but friability was failed. So going to take trial 4 in FBP using binding agent. In this trial get some good flow properties of granules and also found improvement in hardness. So take trials on the basis of hardness with different conc. of HPMC (3 cps). No drug release during acid resistance stage. For above trial's result is as follow: **Trial 5**- Hardness:5-6 kg, DT: 6-8 min, Trial 6- Hardness: 5-6.5, DT: 8-8.5 min, Trial 7- Hardness:5-7 kg, DT: 8.5-9.5 min, So form above results take trials to optimize the disintegrent conc. No drug release during acid resistance stage. from above trials hardness and DT were optimized. **Trial 8-** Hardness: 5-6.5 kg, DT: 6.5-7.5, **Trial 9**- Hardness: 4.5-5.5 kg, DT: 5.5-6.5

From above results trial 8 was shown good results, so trial 10 was reproducible for trial 8. 0.03% drug release during acid resistance stage. Results of trial 10 Hardness: 5-6.5 kg, DT: 6.5-7.5

0.02% drug release during acid resistance stage. From above result trial 10 was reproducible batch of trial 8. So, trial 10 batch put for proto type stability.

Stability study was conducted on tablets of batch no. 10, which tablets were evaluated for *in-vitro* dissolution measurement and *in-vitro* release profile, after two months. No significant changes were observed in any of the studied parameters during the study period, thus it could be concluded that formulation was stable. The stability study revealed that there was no significant change in dissolution profile. From results of all formulation, I had concluded that developed formulation of enteric coated tablet containing Drug A was similar to standard specification of competitor with all respect and stable to effect of temperature and humidity. We have at designing an extended-release solid oral matrix formulation of Drug A through application/incorporation of swellable and/or soluble cum erodible hydrophilic polymers and immediate release formulation of Drug B using various diluents and disintegrants.

In vitro dissolution studies demonstrated that the release of Drug A at all time points was within specified limits for batches prepared using aqueous granulation and enteric coating technique. Delayed release tablet was formulated successfully using aqueous granulation method. Various qualitative and quantitative combinations of HPMC and SSG were used to optimized formula for Delayed release of Drug A using aqueous granulation method. For in vitro f1 (2.0) and f2 (86) value were found satisfactory to innovator formulation. The formulation showed good storage stability as assessed by stability data for two months at all conditions as per ICH guidelines

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