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DESIGN AND DEVELOPMENT OF EXTENDED RELEASE TABLET OF DILTAZEM

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ABSTRACT

The main objective of this project is to develop extended release tablets of Anti hypertensive drug to reduce Hypertension. Following administration of diltiazem, a reduction in blood pressure generally occurs within 2 to 5 hours. During chronic administration, substantial blood pressure control lasts for 24 hours, with trough reductions in diastolic blood pressure approximately 40-50% of peak reductions. The antihypertensive effect is dose dependent and correlates with the plasma concentration of diltiazem Wet granulation approaches were used for the prototype development of extended release tablet to produce the quality product consistency. Film coating are applied for tablets. The aim of the film coating is to improve the appearance of the tablet and improve the mechanical strength of the tablet.

Keywords: Diltiazem, Hypertension, Extended release, Wet granulation method, Cremophor RH 40, HPC (Klucel- LF). Film coating.

1.Introduction

1.1 In process Quality Control Parameters during Compression[13]

Compressed tablets may be characterized by a number of specifications. These include size, shape, thickness, and Weight, hardness, and disintegration time and dissolution characteristics.

Hardness:

The resistance to the tablet to chipping, abrasion or breakage under condition of storage, transportation and handling before usage depends upon its hardness. The most widely used apparatus to measure tablet hardness or crushing strength is the Schleuniger digital tester[1-3]. This and other newer electrically operated test equipment eliminates the operator variability inherent in the measurement i.e. it measure the force required to break the tablet when the force is applied diametrically to the tablet. The force is measured in kilograms when used in production, hardness of 4 kg is considered to be minimum for a satisfactory tablet. Hardness determinations are made

throughout the tablet runs to determine the need for pressure adjustments on the tablet compression machine[4].

Friability:

Tablet friability measurement is made by use of the Roche friabilator. Rather than a measurement of the force required to crush a tablet, the instrument is design to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping[5-9]. A number of tablets are weighed and place in apparatus where they are exposed to rolling and repeated shocks resulting from freefalls with the apparatus. After a given number of rotations the tablets are weighed and the loss in weight indicates the ability of the tablet to withstand the type of wear.

Thickness:

The thickness of the tablet from production run to production is carefully controlled. Thickness can vary with no change in weight due to difference in the dosing of the granulation and the pressure applied to the tablets as well as the speed of the tablet compression. Tablet thickness also becomes an important characteristics packaging.[10] If thickness varies throughout the lot, the result will vary in the count. Thickness is determined with Vanier calipers in millimeters. ± 5% may be allowed, depending upon the size of the tablet.

Weight variation:

The volumetric fill of the die cavity determines the weight of the compressed tablet. In setting up the tablet machine the fill adjusted to give the desired tablet weight. After the tablet machine is in operation the weights of the tablets were checked routinely to ensure that proper weight of tablet are being made.

Disintegration:

To release the drug component from the tablet, it must disintegrate. So disintegration time is noted after added six tablets in each cylinder of DT apparatus containing water at 37±0.5 ^{0}C.

In vitro dissolution study[16]

Dissolution Parameter

Medium	**:** 500 mL; pH 6.5, Phosphate buffer with 1 % Sodium lauryl sulphate
Apparatus	**:** USP-2 (Paddle)
Rpm	**:** 50
Time	**:** 2, 6, 10 hours
Temperature	**:** 37°C ± 0.5°C

Preparation of medium *(pH 6.5, Phosphate buffer with 1 %SLS)***: -** Dissolve 28.4 g of sodium dihydrogen orthophosphate monohydrate ($NaH_2PO_4.H_2O$), 13.9 g of disodium hydrogen orthophosphate (Na_2HPO_4) and 50 g of sodium lauryl sulfate in 5 liters of purified water. Adjust the pH to 6.5 with 10 % sodium hydroxide solution.

Standard preparation: Transfer an accurately weighed quantity of about 25 mg of Diltiazem USPRS/working standard to a 100 mL volumetric flask. Add about 50 mL of alcohol and syndicate to dissolve. Make volume up to the mark with alcohol and mix. Dilute 2.0 mL of this solution to 25.0 mL with dissolution medium and mix.

Sample preparation: Set the dissolution parameters of the instrument as mentioned above. Place one tablet each in a specially made quadrangular basket (refer annexure I and II). Place the tablet cover in the horizontal diagonal of the basket. Put the rod assembly up through the cover of the dissolution vessel, and fix it by means of two Teflon nuts, 3.2 cm from the center of the vessel. Adjust the lower edge of the bottom of the basket to approximately 1 cm above the top of the paddle blade. Orient the large side of the basket tangentially to the flow stream with the tablet standing on its edge. Program for withdrawal of sample after 2 hours, 6 hours and 10 hours the buffer stage. At each withdrawal point, withdraw about 10 mL of solution from zone midway between the surface of the dissolution medium and top of the rotating paddle is not less than 1 cm from the vessel wall. Compensate the volume withdrawn with dissolution medium into each vessel at each time point. Filter the solution through 0.45 µm Millipore PVDF filter; collect the filtrate by discarding first few mL of the filtrate

Assay

Note: -Prepare standard and sample preparations fresh prior to analysis.

Buffer solution*:* Dissolve 6.9 g of monobasic sodium phosphate in 400 mL of water in a 1000-mL volumetric flask. Add 8.0 mL of 1 M phosphoric acid, dilute with Milli Q water to volume, and mix.

Mobile phase: Prepare a filtered and degassed mixture of buffer solution, acetonitrile and methanol in the ratio of (40: 40: 20). Make adjustment if necessary.

Diluent: Use mobile phase as diluent**.**

Resolution solution: Dissolve 150 mg of sample in a mixture of 25 mL of tertiary butyl alcohol and 25 mL of 1 N perchloric acid, add 10 mL of 0.1 M ceric sulfate, mix, and allow standing for 15 minutes. Add 3.5 mL of 10 N sodium hydroxide, and neutralize with 2 N sodium hydroxide. Shake the mixture with 25 mL of methylene chloride in a separator. Draw off the lower layer, and evaporate it to dryness under a stream of nitrogen on a water bath. Dissolve 10 mg of residue (diltiazem oxidation product) and 5 mg of diltiazem USPRS/working standard in mobile phase, dilute with mobile phase to 100.0 mL, and mix. Dilute 1.0 mL of the resulting solution to a 100.0 mL with diluent and mix.

Standard preparation*:* Transfer an accurately weighed quantity of about 15 mg of diltiazem USPRS/working standard to a 50-mL volumetric flask. Add about 25 mL of diluent and sonicate to dissolve. Make volume up to the mark with diluent and mix.

Sample preparation*:* Transfer an accurately weighed quantity of about 30 mg of sample to a 100-mL volumetric flask. Add about 50 mL of diluent and sonicate to dissolve. Make volume up to the mark with diluent and mix.

Chromatographic system

Column : Kromasil C18, (15 cm x 4.6 mm), 5 µm
Detector : 254 nm

Flow rate : 1.0 mL/minute
Injection volume : 40 µL for standard preparation and sample preparation and 20 µL for resolution solution

Developmental trial by Wet granulation approach:

Objective to design formulation by wet granulation was to improve the flow of powder by increasing particle size and sphericity. Wet granulation forms the granules by binding the

powders together with an adhesive[22]. It improves and increases the uniformity of powder density and improves cohesion during and after compression.

The wet granulation technique employs a solution, suspension or slurry containing a binder which is usually added to powder mixture however the binder may be incorporated dry into the powder mixture and the liquid may be added by itself. The liquid plays a key role in the granulation process. Liquid bridges are developed between particles and the tensile strength of these bonds increases as the amount of liquid added is increased. So we can improve the hardness of tablets using wet granulation strategies[21].

Table: 1 Manufacturing Procedure for extended release tablet of Diltiazem

Sr.No.	Ingredients	F1	F2	F3	F4
Drug solution preparation					
1	Diltiazem	10	10	10	10
2	Cremophor RH 40	20	20	20	20
3	IPA	qs	qs	qs	qs
Binder solution preparation					
4	HPC(Klucel- LF)	--	--	22.5	22.5
5	Povidone K 90	--	18	--	--
6	IPA	--	qs	qs	qs
Dry mixing					
7	HPC(Klucel- LF)	90	90	--	--
8	Lactose Anhydrous	45	45	45	45
9	HPMC E4M	--	--	45	45
10	HPMC K 100	--	--	--	--
11	HPMC E6	135	135	--	160
12	Avicel PH 101	141	123	231	138.5
Lubrication					
13	Avicel pH 102	--	--	67.5	--
14	Sodium stearyl fumrate	4.5	4.5	4.5	4.5
15	Colloidal Silicon Dioxide (Aerosil-200)	4.5	4.5	4.5	4.5

Dispensing: Dispensed raw materials quantities as per mentioned in the formula.

Preparation of Drug Solution*:* Dissolve the Cremophor RH 40 in Isopropyl Alcohol with stirring till clear solution obtain. Add Diltiazem to this solution with stirring till clear solution obtained.

Preparation of Binder solution: - Add hydroxy propyl cellulose to the Isopropyl Alcohol with continuous stirring to get homogeneous dispersion.

Dry mixing: - Mix Lactose Anhydrous, Hypromellose 50 cps, Hypromellose 15 cps and Sodium aluminium silicate in High speed rapid mixture granulator for 10 min.

Adsorption of Diltiazem solution: - Add Diltiazem solution to the dry mixed blend with slow impeller speed. Finally it with impeller slow and chopper fast for 2 min to get uniform distribution of drug.

Wet granulation: - Add the binder solution to the blend with slow impeller speed. Finally mix it with fast impeller and chopper for 2 to 5 minutes.

Drying: - Dry the granules in Tray dryer with inlet temperature is 55° C to 60° C for around 2 hr to achieve LOD between 0.5 to 1.5 % w/w.

Milling: - Sift the dried granules with Colloidal silicon dioxide through oscillating granulator equipped with 20 mm screen to get uniform size granules

Compression:- Compress the blend into tablets using B-Tooling 16- station compression machine.

Table: 2 Flow properties of the lubricated blend for extended release tablet of Diltiazem

Flow properties of the lubricated blend				
Observation	**F_1**	**F2**	**F_3**	**F_4**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Tapped density(g/ml)	00.76± 0.004	00.71± 0.066	00.74 ± 0.009	00.77± 0.013
Bulk density (g/ml)	00.65± 0.004	00.51± 0.001	00.56 ± 0.010	00.65± 0.001
Compressibility Index (%)	13.94± 0.081	28.00± 0.811	24.54 ± 0.802	15.74± 0.416
Hausner's Ratio	01.16± 0.001	01.38± 0.015	01.31 ± 0.034	01.18± 0.005
Moisture content(%)	01.14± 0.010	01.16± 0.020	01.21 ± 0.101	01.23± 0.110
Physical parameters of ER tablets				
Tablet thickness(mm)	5.28 ± 0.184	5.35 ± 0.143	5.37± 0.126	5.38± 0.140
Weight (mg)	450 ± 0.378	450 ± 0.305	450 ± 0.152	450 ± 0.200
Hardness (Kp)	4.6 ± 0.305	4.70 ± 0.200	7.66 ± 0.157	8.93 ± 0.152
Friability (%)	00.21± 0.014	00.61 ± 0.055	00.63± 0.015	00.59± 0.020

Discussion:

- B.No.F_1 taken with HPMC and HPC hardness found at lower side.
- For improve the hardness purpose in B.No F2 taken with PVP K 90 but hard ness was not satisfied.
- In B.No F3 was taken with 10% HPMC E 4M and microcrystalline cellulose to achieved good hardness. But in this trail dissolution is completed with in one hour.

- In B.No F4 10% HPMC E 4M, microcrystalline cellulose and HPMC 6 cps 35% are taken In this trial hard ness will come satisfactory but the dissolution results are faster than target.

Table 3: Manufacturing Procedure for extended release tablet of Diltiazem

Sr.No.	Ingredients	F5	F6	F7	F8
Drug Solution Preparation					
1	Diltiazem	10	10	10	10
2	Cremophor RH 40	20	20	20	20
3	IPA	qs	qs	qs	qs
Binder Solution Preparation					
4	HPC(Klucel- LF)	22.5	22.5	22.5	22.5
5	Povidone K 90	--	--	- -	--
6	IPA	qs	qs	qs	qs
Dry mixing					
7	HPC(Klucel- LF)	--	--	--	--
8	Lactose Anhydrous	45	45	45	45
9	HPMC E4M	56	67.5	--	--
10	HPMC K 100	--	--	157.5	135
11	HPMC E6	160	160	90	112.5
12	Avicel PH 101	127.5	116	96	96
Lubrication					
13	Avicel pH 102	--	--	--	--
14	Sodium stearyl fumerate	4.5	4.5	4.5	4.5
15	Colloidal Silicon Dioxide	4.5	4.5	4.5	4.5

Manufacturing Procedure[18-20]:

Dispensing: Dispensed raw materials quantities as per mentioned in the formula.

Preparation of Drug Solution: Dissolve the Cremophor RH 40 in Isopropyl Alcohol with stirring till clear solution obtain. Add DILTIAZEM to this solution with stirring till clear solution obtained.

Preparation of Binder solution: Add Hydroxy propyl cellulose to the Isopropyl Alcohol with continuous stirring to get homogeneous dispersion.

Dry mixing: Mix Lactose Anhydrous, and different grades of Hypromellose and microcrystalline cellulose in High speed rapid mixture granulator for 10 min.

Adsorption of diltiazem solution: Add diltiazem solution to the dry mixed blend with slow impeller speed. Finally it with impeller slow and chopper fast for 2 min to get uniform distribution of drug.

Wet granulation: Add the binder solution to the blend with slow impeller speed. Finally mix it with fast impeller and chopper for 2 to 5 minutes.

Drying: Dry the granules in Tray dryer with inlet temperature is 55° C to 60° C for around 2 hr to achieve LOD between 0.5 to 1.5 % w/w.

Milling: Sift the dried granules with Colloidal silicon dioxide through oscillating granulator equipped with 20 mm screen to get uniform size granules

Compression: Compress the blend into tablets using B-Tooling 16- station compression machine.

Table 4: Properties of the lubricated blend for extended release tablet of Diltiazem

Flow properties of the lubricated blend				
Observation	**F_5**	**F6**	**F7**	**F_8**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Tapped density(g/ml)	00.61 ±.006	00.71 ± .011	00.65 ±0.006	00.72 ± 0.006
Bulk density (g/ml)	00.47±0.005	00.55 ±0.013	0.48 ± 0.004	00.53 ± 0.014
CompressibilityIndex(%)	22.24 ± 1.654	22.34 ±0.719	25.97 ±0.973	26.17 ± 2.650
Hausner's Ratio	01.28 ± 0.026	01.28 ±0.030	01.31 ±0.017	10.32 ± 0.050
Moisture content (%)	01.04 ± 0.055	01.11± 0.043	00.09± 0.049	01.17 ± 0.055
Physical parameters of ER tablets				
Tablet thickness(mm)	5.30 ± 0.184	5.38 ± 0.243	5.29 ± 0.226	5.40 ± 0.240
Weight (mg)	450 ± 0.378	450 ± 0.305	450 ± 0.152	450 ± 0.200
Hardness (Kp)	8.6 ± 0.305	8.60 ± 0.200	8.66 ± 0.157	09.93± 0.152
Friability (%)	00.21± 0.014	00.61± 0.055	00.63± 0.015	00.59± 0.020

DISCUSSION

- In B.No F5 12% HPMC E 4M, microcrystalline cellulose and HPMC 6 cps 35% are taken. In this trial hard ness will come satisfactory but the dissolution results are slight faster than target.
- In B.No F6 15% HPMC E 4M are taken in this trail the dissolution results are matching with target.
- In B.No F7 trail HPMC E 4M replace with 35% HPMC K 100 in this trail the dissolution rate is slower than target.
- In F8 B.No trail taken with 25% HPMC E6and 30% HPMC K100 in this trail the dissolution rate is match with target.

- Hence this formula was selected as a lead formula for coating trails.

TABLE: 5 Percentage of Drug Release for extended release tablet of Diltiazem

Time(hr)	Target	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0
2	17.2	80	34.6	30.8	19.7	12.1	18.1
4	39.6	89.8	52.7	48.2	40.4	38	41.2
6	60.2	95	72.2	65	54.2	45.1	59.1
8	77.5	98.6	89.5	77.8	71.6	56	78.6
10	93.6	99.5	104	98.8	88.4	70	98.8

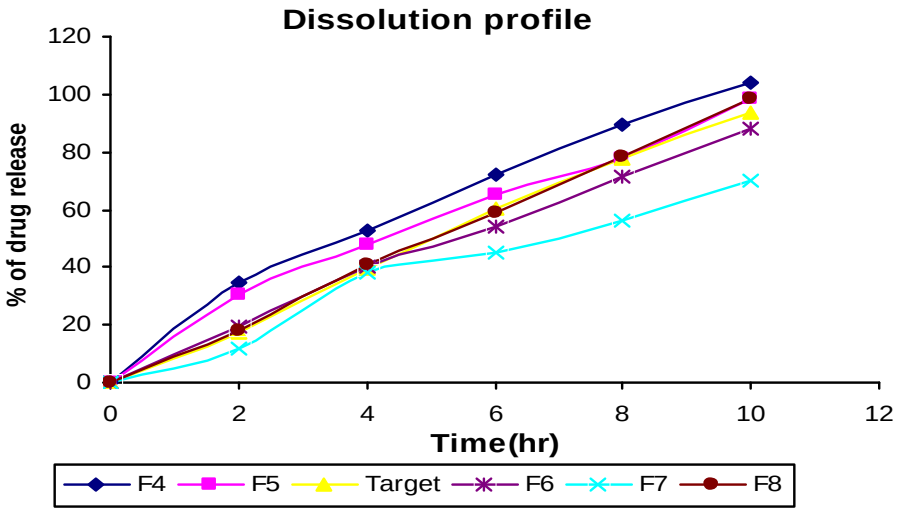

Figure: 1 Percentage of Drug Release Representation in Graph

DEVELOPMENT OF COATING FORMULA

Film coating is a high sophisticated process. The first film-coated tablet became commercially available in 1954. The technology advanced with the introduction of the semi synthetic cellulose derivatives and synthetic acrylic polymers.

Film coating applied for several reasons.

- Taste masking and moisture protection.
- Light protecting coating.
- Improved the product appearance.
- Improved the mechanical resistance of the coated product.
- Modified drug release.

The properties and performance of the final coat is strongly affected by the polymer properties and the formulation parameters. According to the interesting aspect for the specific use the polymer may be classified as

- Protective coating.
- Functional coating.

Protective coating: - Thin films of water soluble polymers are often applied for taste or odour masking, to improve the stability of the moisture sensitive products or better mechanical resistance of the product.E.g. HPMC, PVP, PVA

Functional coating: - Film coatings which are applied to achieve a certain desired release profile of the incorporated drug[26-28]. These are generally called as functional coating or modified release coating. Those intended to protect the drug from the acidic environment of the gastric medium(generally called as enteric coating) extended release coatings in contrast are requested to control the release of the drug over a prolonged period of time. During coating process parameters to be considered are –

- Pan rotation speed
- Inlet temperature
- Product temperature
- Spray rate
- Atomization

Preparation of aqueous coating solution:-

Weighed accurately opadry white (50gm) Added slowly into 450ml purified water Stirred for 45 minutes. The tablets were coated in NEOCOATA Coating machine under controlled conditions.

Pan speed : 5 RPM
Pan size : 3 KG
Spray rate : 2 RPM
Inlet temp : 47°c
Exhaust temp : 22°c

Dissolution parameter

Apparatus : USP Type II (Paddle method)
Rpm : 50 rpm
Media : 500 ml; pH 6.5, Phosphate buffer with 1 % SLS
Temperature : 37 ± 0.5 ^{0}C

Table 6: Percentage of drug release comparison with target after coating

Time in hours	% Drug release	
	Target	F8
0	0	0
2	17.2	17.9
4	39.6	42.0
6	60.2	59.5
8	77.5	79.0
10	93.6	99.0

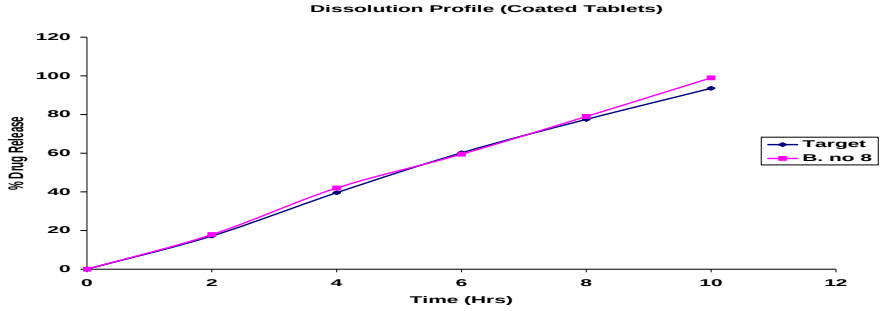

Figure: 2 Graphical Representation of Drug release

REPRODUCIBILITY BATCH:

Trial F_8 Diltiazem formula was selected as lead formula for the reproducibility batch.

Formula **Batch Size: 1000 Tablets**

Table 7: Trial F_8 Diltiazem Extended Release tablet formula for the reproducibility batch

Sr.No.	Ingredients	D F8	%	Category
Drug solution preparation				
1	Diltiazem	10	2.2	Active ingredient
2	Cremophor RH 40	20	4.4	Solubelizer
3	IPA	Qs	--	Solven
Binder solution preparation				
4	HPC(Klucel- LF)	22.5	5	Binder
5	IPA	--	--	Solvent
Dry Mixing				
6	Lactose Anhydrous	45	10	Filler
7	HPMC K 100	135	30	Polymer
8	HPMC E6	112.5	25	Polymer
9	Avicel PH 101	96	21.3	Filler
Lubrication				
10	Sodium stearyl fumrate	4.5	1	Lubricant
11	Colloidal Silicon Dioxide	4.5	1	Glidant
	Core tablet weight	450mg	100%	

Manufacturing Procedure:

Dispensing: - Dispensed raw materials quantities as per mentioned in the formula.

Preparation of Drug Solution: - Dissolve the Cremophor RH 40 in Isopropyl Alcohol with stirring till clear solution obtain. Add diltiazem to this solution with stirring till clear solution obtained.

Preparation of Binder solution: - Add Hydroxy propyl cellulose to the Isopropyl Alcohol with continuous stirring to get homogeneous dispersion.

Dry mixing:- Mix Lactose Anhydrous, and different grades of Hypromellose and microcrystalline cellulose in High speed rapid mixture granulator for 10 min.

Adsorption of diltiazem solution:- Add diltiazem solution to the dry mixed blend with slow impeller speed. Finally it with impeller slow and chopper fast for 2 min to get uniform distribution of drug.

Wet granulation: - Add the binder solution to the blend with slow impeller speed. Finally mix it with fast impeller and chopper for 2 to 5 minutes.

Drying: - Dry the granules in Tray dryer with inlet temperature is 55° C to 60° C for around 2 hr to achieve LOD between 0.5 to 1.5 % w/w.

Milling: - Sift the dried granules with Colloidal silicon dioxide through oscillating granulator equipped with 20 mm screen to get uniform size granules

Compression: - Compress the blend into tablets using B-Tooling 16- station compression machine.

Table: 8 Coating Formula Diltiazem Extended Release tablet

Formulation designation	Opadry white (mg)	% Coat relative to the core
F8	9	2%

After completion of the coating the tablet weight is 460mg

Table: 9 Physical Parameters of the Diltiazem Extended Release Tablets

Test	Observation
Tablet thickness (mm)	5.2-5.3
Weight (mg)	459
Hardness (kp)	8-9
Friability (%)	02

Dissolution Results of reproducibility data of trial F8 Diltiazem

Dissolution parameter

Apparatus : USP Type II (Paddle method)

Rpm : 50 rpm

Media : 500 ml; pH 6.5, Phosphate buffer with 1 % SLS

Temperature : 37 ± 0.5 0C

Table 10: Comparative study of Diltiazem Extended Release tablet

Time in hours	% Drug release	
	Target	F8
0	0	0

2	17.2	19.7
4	39.6	41
6	60.2	62.5
8	77.5	80.8
10	93.6	98.5

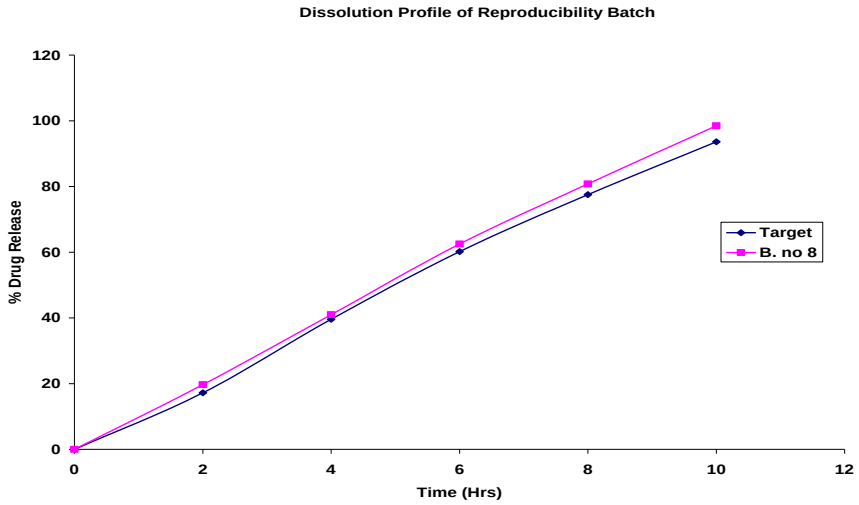

Figure: 3 Graphical Representation of Drug release

Discussion

- During compression Blend flow was found satisfactory, all physical parameters of the core tablets were found good.
- During coating, All Product and Process Parameters were found satisfactory.
- Dissolution profile of reproducibility data was same as previously prepared trial of F_8

CONCLUSION

Diltiazem is a calcium channel blocker widely used in the treatment of Hypertension. According to BCS diltiazem is class-II drug it's having low solubility and high permeability. The Preformulation studies are important step in the development of dosage form. There is no interaction of the drug with excipients. The overall objective of preformulation testing was found that diltiazem having good flow and poor compressible, melting point 140-145 ^{0}C, moisture content within controlled limit and diltiazem was non hygroscopic. pH 6.5+1% SLS phosphate buffer was used as dissolution medium. Wet granulation approaches were used for the prototype development of extended release tablet to produce the quality product consistency. From trials of F_1 and F2 it was concluded that low hardness was found.

To achieve required hardness HPMC E 4 M (10%) and microcrystalline cellulose is using in the F3 trial. In this trail hardness was improved but in this trail the dissolution is completed within

one hour. For controlling the dissolution time the trail F4 and F5 is taken with HPMC E6 in this trail the dissolution time is slightly faster than target. To achieve good dissolution results purpose in trial F6 taken with 15% HPMC E4 M in this trails the dissolution results were matching with target. The trail F7 is taken with 35% HPMC K 100 and 20% of the HPMC E6 in this trail the dissolution results are slower than the target. The trail F8 was taken with 30% HPMC K 100 and 25% of the HPMC E6 in this trail the dissolution results are matching with target. The trail F8 formula is taking for the coating trails.

Film coating is applied for tablets. The aim of the film coating is to improve the appearance of the tablet and improve the mechanical strength of the tablet. Opadry white is selected for coating of the tablets 2% coating will applied to tablets. To check the reproducibility of the formula one batch was planned there was no change in the dissolution profile of the tablets.

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