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Formulation Development and Stabilization of Quinapril in Low dose Pill

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Abstract : Hypertension is the most common risk factor for cardiovascular diseases, stroke and renal failure. A recent guideline by the Joint National Commission (JNC8 guidelines) recommended both angiotensin-converting enzyme (ACE) inhibitors & calcium channel blockers (CCB) as first-line drugs, in addition to diuretics. The increasing prevalence of hypertension leads to boom in the medicinal sector for the effective medications, fixed dose & multiple dose combinations are studied & provided to patient's leads to the several adverse effects to patients therefore Low Dose Single Pill Therapy got recognition. Quinapril is efficacious drug of BCS Class I (high soluble, high permeable), but it prone to degradation reactions like hydrolysis, oxidation & cyclization easily to diketopiperazine impurity. Formation of diketopiperazine is a major stability issue to the potent ACE inhibitors. Therefore a stable formulation designing is a basic challenge in the formulation of the quinapril tablets. Degradation can be observed in the tablets at processing, storage & packing stage on elevated temperature or moisture to the active moiety & formulation. Therefore formulating & is quite challenging. Formulation designed contains a magnesium carbonate as stabilizer in different process optimization which prevent API to form impurity. The optimized formulation results found are satisfactory with accelerated stability study.
Keywords: Quinapril, Low dose pill, Formulation, stabilization.

Introduction

Oral Dosage Form

Oral Drug Delivery is the most desirable and preferred method of administrating therapeutic agents. For many drug substances, conventional immediate release formulations provide effective therapy while maintaining pharmacokinetic and pharmacodynamics profiles with an acceptable level of safety to patient.

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and lower medicine production costs (Yadav, 2009).

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Immediate Release Tablet

The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations (Gabrielsson J *et. al*, 2002).

Immediate release formulations are intended for immediate action i.e. to disintegrate quickly when come in contact with body fluid based on type of Disintegrant used.

Tablets for immediate release often consist of filler, a binder, lubricants and disintegrants. In many cases, the disintegration time of solid dosage forms is too long to provide appropriate therapeutic effect. To improve the disintegration time, so-called super-disintegrants are used.

An immediate release pharmaceutical preparation offers

- Improved compliance/added convenience and stability.
- Suitable for controlled/sustained release actives.
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery.
- Economical and cost effective.
- Quick onset of action.
- Suitable for industrial production.
- Improved stability and bioavailability.
- Unique product differentiation.

Hypertension or high blood pressure is the condition when blood pressure increases to an unhealthy level. It is very harmful and can lead to stroke, heart failure, heart attack, kidney diseases & several other heart dysfunctions. The main purpose of anti-hypertension drug is to lower and control high blood pressure to protect organs like brain, heart, kidneys. Change in lifestyle and elevated stress levels have increased the prevalence of hypertension globally, thereby increasing the demand for hypertension drugs.

Anti-Hypertensive Drugs are used for treat hypertension &prevent the complications of high blood pressure to treat conditions like cardiovascular disease, strokes, myocardial infarction, ischemic heart disease & other complications.

ACE Inhibitors ACE inhibitors are category of anti- hypertensive drugs which inhibits the angiotensin-converting enzyme (ACE) activity. ACE enzyme is engaged in conversion of angiotensin I into angiotensin II. Angiotensin II is a potent vasoconstrictor. Examples: captopril, enalapril, fosinopril, quinapril, ramipril etc.

Quinapril is anti- hypertensive drugs of category of ACE inhibitor used to treat hypertension by decreasing reninangiotensin-aldosterone system activity effectively. Quinapril is used in adjunctive therapy in the management of heart failure & ischemic heart disease with combination with diuretics, calcium channel blockers & other hypertensive drugs.

Mechanism of Action

Quinapril inhibits angiotensin converting enzyme (ACE), an enzyme which catalyses the formation of angiotensin II from angiotensin I. Angiotensin II increases blood pressure by vasoconstriction.

Quinapril HCl is a non-peptide, non-sulfhydryl pro-drug that is de-esterified to quinaprilat (quinapril diacid) which is an active metabolite. Quinaprilat lowers blood pressure by antagonizing the effect of the Renin-Angiotensin-Aldosterone System (RAAS).

The RAAS is a body homeostatic mechanism for regulating water and electrolyte balance. During sympathetic stimulation or when blood pressure is reduced, renin is released from kidneys. In the blood stream, renin cleaves angiotensinogen to AT I, which is converted to AT II by Angiotensin-Converting Enzyme (ACE).

ATII increases blood pressure by stimulating the aldosterone secretion. Aldosterone increases sodium and water reabsorption. ATII also stimulates the vasopressin secretion (Anti-Diuretic Hormone or ADH) which enhances water reabsorption from the kidneys. ACE inhibitors inhibit the rapid conversion of ATI to ATII and antagonize the RAAS system. Angiotensin-Converting Enzyme is also involved in the bradykinin deactivation which is a vasodilator. ACE Inhibitors increases bradykinin levels in blood causing increased vasodilation and decreased blood pressure.

Materials And Methods

(Aarti Industries) Ltd., Basic magnesium carbonate Heavy P Grade (AICL), Lactose Monohydrate (Pharmatose 200M) (DFE), Crospovidone (Kollidon CL F) (BASF), Povidone K 30 (Kollidon 30) (BASF), Magnesium stearate (Ligamed MF-2-V) (Peter Greve

Table 1: Comparative composition of Reference product& Test products:

Component	**Function**	**Manufacturer / Supplier**
Quinapril Hydrochloride	Active pharmaceutical ingredient	Aarti Industries Ltd.
Crospovidone	Disintegrant	BASF
Povidone	Binder	BASF
Lactose	Filler/ Diluent	DFE
Magnesium carbonate	Stabilizer	AICL
Magnesium stearate	Lubricant	Peter Greven

Formulation Trials (Prototype to final formulations)

Table 2: Prototype Formulation Plan

FORMULATIONS									
FORMULATION	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
AIM/OBJECTIVE	Wet Granulation	Organic Solvent in wet granulation to reduce related substances	API addition (Quinapril HCl) in lubrication	Organic slurry method with Stabilizer (MgCO3) & API (Quinapril HCl) to reduce related substances	Binder change from gelatin to Povidone 30 (Slurry method) in wet granulation	Use of Light magnesium oxide instead of magnesium carbonate as stabilizer	Batch with MCC & SSF	Direct compression with Compactol, Tablettose & SSF	Dissolution profile matching with povidone binder
Material Name	**Quantity (mg/tablet)**								
DRY MIX									
Quinapril Hydrochloride eq. to Quinapril	43.320	43.320	-	43.320	-	43.638	43.638	43.638	43.320
Lactose Monohydrate	256.680	95.180	220.680	-	145.000	200.000	144.362	-	144.680
Crospovidone	15.000	8.500	10.000	-	16.000	10.000	12.000	18.000	12.000
Basic Magnesium Carbonate (Heavy)	-	240.000	110.000	110.00	-	-	-	-	180.000
Povidone K 30	-	-	-	-	20.000	30.000	-	-	-
Light Magnesium Oxide	-	-	-	-	-	113.317	-	-	-
Microcrystalline cellulose	-	-	-	-	-	-	180.000	-	-
Compactrol (Calcium sulfate dehydrate)	-	-	-	-	-	-	-	180.000	-
Tablettose 100 (Lactose)	-	-	-	-	-	-	-	154.362	-
BINDER	**11.11%**	**5.56%**	**7.06%**	**17.34%**	**1.08%**	**7.70%**	**7.70%**	**-**	**7.70%**
Gelatin	10.000	10.000	12.000	12.000	-	-	-	-	-
Povidone K 30	-	-	-	-	-	-	10.000	-	10.000
Quinapril Hydrochloride eq. to Quinapril	-	-	-	-	43.320	-	-	-	-
Basic Magnesium Carbonate (Heavy)	-	-	-	-	171.680	-	-	-	-
Ethanol	-	q.s	-	q.s	-	-	-	-	-
Purified water	q.s.	-	q.s.	-	q.s.	q.s.	q.s.	-	q.s.
PRE-LUBRICATION									
Crospovidone	15.000	2.000	-	10.000	-	-	6.000	-	6.000
Basic Magnesium Carbonate	65.000	-	-	-	-	-	-	-	-
Quinapril Hydrochloride eq.	-	-	43.320	-	-	-	-	-	-

to Quinapril									
Lactose Monohydrate	-	-	-	220.680	-	-	-	-	-
Magnesium stearate	-	-	-	-	-	3.000	-	-	-
LUBRICATION									
Magnesium stearate	5..000	1.000	4.000	4.000	4.000	-	-	-	4.000
Sodium steryl fumarate	-	-	-	-	-	-	4.000	4.000	-
Core tablets weight	**410.000**	**400.000**	**400.000**	**400.000**	**400.000**	**410.000**	**400.000**	**382.000**	**400.00**

Tablet 10 : Prototype Formulation Process

FORMULATIONS									
FORMULATION	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
AIM/ OBJECTIVE	Wet Granulation	Organic Solvent in wet granulation to reduce related substances	API addition (Quinapril HCl) in lubrication	Organic slurry method with Stabilizer (MgCO3) & API (Quinapril HCl) to reduce related substances	Binder change from gelatin to Povidone 30 (Slurry method) in wet granulation	Use of Light magnesium oxide instead of magnesium carbonate as stabilizer	Batch with MCC & SSF	Direct compression with Compactol, Tablettose & SSF	Dissolution profile matching with povidone binder
SIFTING	Sieving of all the ingredients through sieve # 40								
DRY MIX	Quinapril HCl, Lactose Monohydrate & Crospovidone were mixed in RMG for 10 mins.	Quinapril HCl, Lactose Monohydrate, Crospovidone & heavy Magnesium Carbonate were mixed in RMG for 10 mins.	Lactose Monohydrate, Crospovidone & Basic Magnesium Carbonate, were mixed in RMG for 10 mins.	Quinapril HCl & Basic Magnesium Carbonate was mixed in RMG for 10 mins.	Lactose Monohydrate, Povidone K 30 & Crospovidone were mixed in RMG at for 10 mins.	Quinapril HCl, Lactose Monohydrate, Crospovidone, Povidone K 30 &Light Magnesium oxide were mixed in a RMG mix for 10 mins	Quinapril HCl, Lactose Monohydrate, Crospovidone , microcrystalline cellulose were mixed in a RMG mix for 10 mins	Quinapril HCl, Crospovidone , compactrol & tablettose were mixed in a RMG mix for 10 mins	Quinapril HCl, Lactose Monohydrate & Crospovidone, heavy Magnesium Carbonate were mixed in RMG for 10 mins.
BINDER	11.11% gelatin binder	5.56% gelatin binder	7.06% gelatin binder	17.34% gelatin binder	1.08%	7.70% Povidone K 30	7.70% Povidone K 30	-	7.70% Povidone K 30
WET MIX	Binder was added to dry mix slowly & properly to get desired	Binder was added to dry mix slowly & properly to get desired	Binder was added to dry mix slowly & properly to get desired	Binder was added to dry mix slowly & properly to get desired granules.	Slurry was added slowly in dry mix in 5 mins at slow speed. After	Binder was added to dry mix slowly in6 mins at 50	Binder was added to dry mix slowly in 6 mins at 50	-	Binder was added to dry mix slowly in 6 mins at 50 RPM. Kneading

	granules.	granules.	granules.		mixing chopper & Impeller were run for 1 min.	RPM. Kneading was provided for 1 min at 100 RPM. Wet granules were passed through sieve #8.	RPM. Kneading was provided for 1 min at 100 RPM. Wet granules were passed through sieve #8		was provided for 1 min at 100 RPM. Wet granules were passed through sieve #8
DRYING	Heat dried at 60°C until LOD is not more than 2.0% then sifts through #20.	Heat dried at 60°C until LOD is not more than 2.0% then sifts through #20.	Heat dried at 60°C until LOD is not more than 2.0% then sifts through #24.	Heat dried at 60°C until LOD is not more than 2.0% then sifts through #30.	Heat dried at 60°C until LOD is not more than 2.0% then sifts through #24.	Heat dried at 60°C until LOD is not more than 2.0% then sifts through #20.	Heat dried at 60°C until LOD is not more than 2.0% then sifts through #30.	LOD checked at 105°C - 1.80%)	Heat dried at 60°C until LOD is not more than 2.0% then sifts through #30.
PRE-LUBRICATION	Add Crospovidone & Basic Magnesium Carbonate with dried blend and mixed properly for 10 mins.	Add Crospovidone with dried blend and mixed properly for 10 mins.	Add Quinapril Hydrochloride with dried blend and mixed properly for 10 mins.	Add Lactose Monohydrate and Crospovidone with dried blend and mixed properly for 10 mins.	-	Add magnesium stearate with dried blend in an octagonal blender at 110 RPM for 10 mins.	Add Crospovidone with dried blend in an octagonal blender at 110 RPM for 10 mins.	-	Add Crospovidone with dried blend in an octagonal blender at 110 RPM for 10 mins.
LUBRICATION	Add Magnesium stearate with prelubricated blend and mix properly for 3 mins.	Add Magnesium stearate with prelubricated blend and mix properly for 3 mins.	Add Magnesium stearate with prelubricated blend and mix properly for 3 mins.	Add Magnesium stearate with prelubricated blend and mix properly for 3 mins.	Add Magnesium stearate with blend in sandwich manner and blend for 3 mins at 10 RPM.	-	Add sodium steryl fumarate with blend in an octagonal blender at 110 RPM for 3 mins.	Add sodium steryl fumarate with blend in an octagonal blender at 110 RPM for 3 mins.	Add Magnesium stearate with pre-lubricated blend in an octagonal blender at 110 RPM for 3 mins.
COMPRESSION	Compress the lubricated blend in double rotary) compression machine using Upper punch: 15.00 x 6.85 mm capsule shape, concave, embossed with QU40 Lower punch: 15.00 x 6.85 mm capsule shape, concave Dies: 15.00 x 6.85 mm capsule shape								

Optimization Trials:

Optimization of Stabilizer (Basic magnesium carbonate Heavy P Grade):

Objective : Trials were performed with ± 22.22% of target concentration of stabilizer Qty. (Basic magnesium carbonate Heavy P Grade).

Table 11: Optimization of Stabilizer (Basic magnesium carbonate Heavy P Grade):

Formulation		S1	S2	S3
S. No.	**Ingredient**	**Qty/Tablet (mg)**		
DRY MIX				
1	Quinapril Hydrochloride	43.320	43.320	43.320
2	Basic magnesium carbonate Heavy P Grade	140.000	180.000	220.000
3	Crospovidone (Kollidon CL F)	12.000	12.000	12.000
4	Lactose Monohydrate (Pharmatose 200M)	184.680	144.680	104.680
BINDER				
5	Gelatin	-	-	-
6	Povidone K 30 (Kollidon 30)	10.000	10.000	10.000
7	Purified water	q.s.	q.s.	q.s.
PRE-LUBRICATION				
8	Crospovidone (Kollidon CL F)	6.000	6.000	6.000
LUBRICATION				
9	Magnesium stearate (Ligamed MF-2-VF)	4.000	4.000	4.000
Core tablet weight		400.000	400.000	400.000

Optimization of Disintegrant (Crospovidone (Kollidon CL F)) Concentration:

Objective: Trials were performed with ± 20.00% of target concentration of Disintegrant (Crospovidone (Kollidon CL F) **:**

Table 12: Optimization of Disintegrant (Crospovidone (Kollidon CL F)) Concentration:

Formulation		D1	D2	D3
S. No.	**Ingredient**	**Qty/Tablet (mg)**		
DRY MIX				
1	Quinapril Hydrochloride**	43.320	43.320	43.320
2	Basic magnesium carbonate Heavy P Grade	180.000	180.000	180.000
3	**Crospovidone (Kollidon CL F)**	**9.600**	**12.000**	**14.400**
4	Lactose Monohydrate (Pharmatose 200M)	148.280	144.680	141.080
BINDER (7.7% binder paste)				
5	Povidone K 30 (Kollidon 30)	10.000	10.000	10.000
6	Purified Water	q.s.	q.s.	q.s.
PRELUBRICATION				
7	**Crospovidone (Kollidon CL F)**	**4.800**	**6.000**	**7.200**
LUBRICATION				
8	Magnesium stearate (Ligamed MF-2V)	4.000	4.000	4.000

Optimization of Binder (Povidone K 30) Concentration:

Objective: Trials were performed with ±20.0% of target concentration of binder Povidone K 30:

Table 13: Optimization of Binder (Povidone K 30) Concentration:

Formulation		B1	B2	B3
S. No.	**Ingredient**	**Qty/Tablet (mg)**		
DRY MIX				
1	Quinapril Hydrochloride	43.320	43.320	43.320
2	Basic magnesium carbonate Heavy P Grade	180.000	180.000	180.000
3	Crospovidone (Kollidon CL F)	12.000	12.000	12.000
4	Lactose Monohydrate (Pharmatose 200M)	146.680	144.680	142.680
BINDER (7.7% binder paste)				
5	**Povidone K 30 (Kollidon 30)**	**8.000**	**10.000**	**12.000**
6	Purified Water	q.s.	q.s.	q.s.
PRELUBRICATION				
7	Crospovidone (Kollidon CL F)	6.000	6.000	6.000
LUBRICATION				
8	Magnesium stearate (Ligamed MF-2V)	4.000	4.000	4.000

Optimization of Lubricant (Magnesium Stearate) Concentration:

Objective: Trials were performed with ± 25.0% of target concentration of Magnesium stearate as lubricant.

Table 14: Optimization of Lubricant (Magnesium Stearate) Concentration:

Formulation		L1	L2	L3
S. No.	**Ingredient**	**Qty/Tablet (mg)**		
DRY MIX				
1	Quinapril Hydrochloride	43.320	43.320	43.320
2	Basic magnesium carbonate Heavy P Grade	180.000	180.000	180.000
3	Crospovidone (Kollidon CL F)	12.000	12.000	12.000
4	Lactose Monohydrate (Pharmatose 200M)	146.680	145.680	144.680
BINDER (7.7% binder paste)				
5	Povidone K 30 (Kollidon 30)	10.000	10.000	10.000
6	Purified Water	q.s.	q.s.	q.s.
PRELUBRICATION				
7	Crospovidone(Kollidon CL F)	6.000	6.000	6.000
LUBRICATION				
8	**Magnesium stearate(Ligamed MF-2V)**	**2.000**	**3.000**	**4.000**

Compression: Compress the lubricated blend in 35-station (double rotary) compression machine using
Upper punch: 15.00 x 6.85 mm capsule shape, concave, embossed with QU40
Lower punch: 15.00 x 6.85 mm capsule shape, concave
Dies: 15.00 x 6.85 mm capsule shape

Table 15: Physical parameter of tablet and their limits

S. No.	Physical Parameter	Limits
1	Appearance	White to off white elliptical tablets, debossed with 'QU 40"on one side and plain on another side.
2	Average weight	400.00 mg ± 3.0 % w/w (388.00 mg to 412.00 mg)
3	Weight variation	400.00mg ± 5.0 % (380.00 mg to 420.00 mg)
4	Thickness	4.6 mm ± 0.3 mm (4.3 mm to 4.9 mm)
5	Dimensions	15.00 x 6.85mm ± 0.1mm (14.90x6.75mm to 15.10x6.95mm)
6	Hardness	120 N± 40 N (80 N to 160 N)
8	Friability	NMT 1% w/w
9	Disintegration Time	NMT 15 Mins

Results & Discussion

Protoype Formualtion

Table 21: Physical Properties of Prototype Formulation

Formulation	Physical Properties			
	Bulk Density	Tapped Density	Hausner Ratio	Carr's Index
F1	0.647 g/mL	0.852 g/mL	1.317	24.10%
F2	0.590 g/mL	0.760 g/mL	1.281	22.37%
F3	0.613 g/mL	0.798 g/mL	1.302	23.18%
F4	0.598 g/mL	0.802 g/mL	1.341	25.44%
F5	0.490 g/mL	0.627 g/mL	1.278	21.74%
F9	0.545 g/mL	0.690 g/mL	1.266	21.01%

Compression Parameters				
Formulation	**Average Weight**	**Thickness**	**Hardness**	**Disintegration Time**
F1	409.852 mg to 411.710 mg	4.84mm to 4.89mm	94.5 N to 104.5 N	53 secs to 1 min
F2	400.10 mg to 403.71 mg	4.80mm to 4.84mm	90.2 N to 83.2 N	2 min 30 secs to 3 mins
F3	400.14 mg to 402.62 mg	4.78mm to 4.84mm	78.3 N to 87.5 N	1 min 36 secs to 2 mins
F4	401.10 mg to 403.58 mg	4.77mm to 4.84mm	78.8 N to 87.5 N	2 min 36 secs to 3 min 05 secs
F5	401.80 mg to 402.91 mg	4.96mm to 4.99mm	63 N to 79N	4 min 52 secs to 5 min 10 secs
F9	400.30 mg to 401.300 mg	4.50mm to 4.57mm	126N to 142 N	3 min.10 sec to 3 min. 42 sec.

Table 23: Impurity Profiling of Prototype Formulations

Formulation	Related Substances				Assay
	Quinapril Related Compound A (NMT 1.0%)	Quinapril Related Compound B (NMT 3.0%)	Single Unknown Impurity (NMT 0.2%)	Total Impurity (NMT 3.6%)	
F1	9.04%	0.35%	0.06%	9.51%	94.90%
F2	3.68%	0.65%	0.08%	4.62%	100.80%
F3	0.74%	0.27%	0.34%	1.50%	96.80%
F4	2.17%	7.33%	0.66%	10.47%	96.80%
F5	0.27%	0.14%	0.01%	0.42%	99.10%
F7	0.22%	0.10%	BQL	0.32%	100.70%

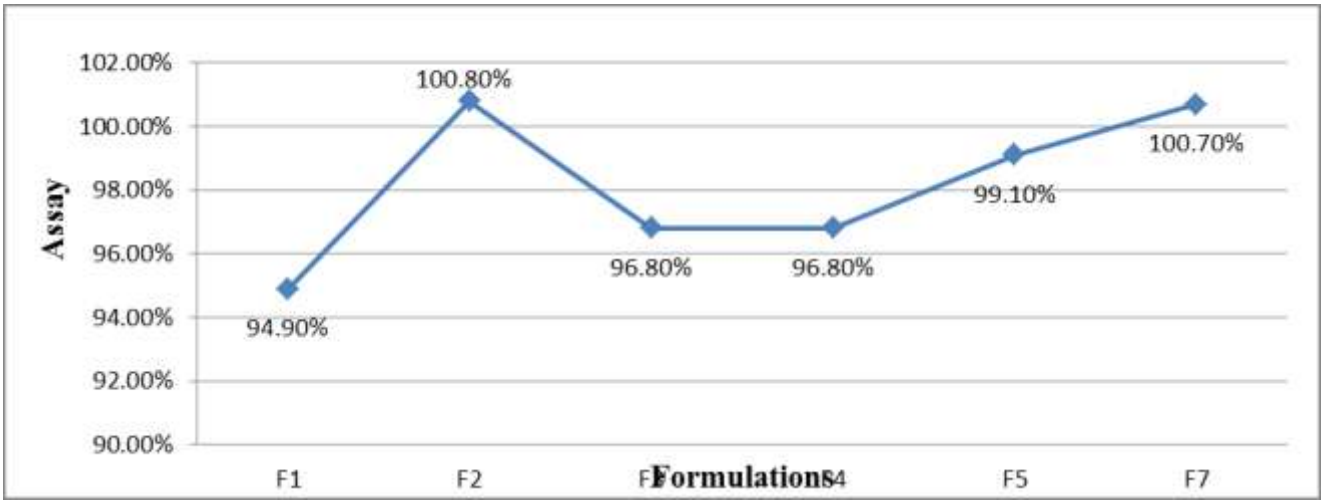

Figure 9: Graphical representation of assay of prototype formulation

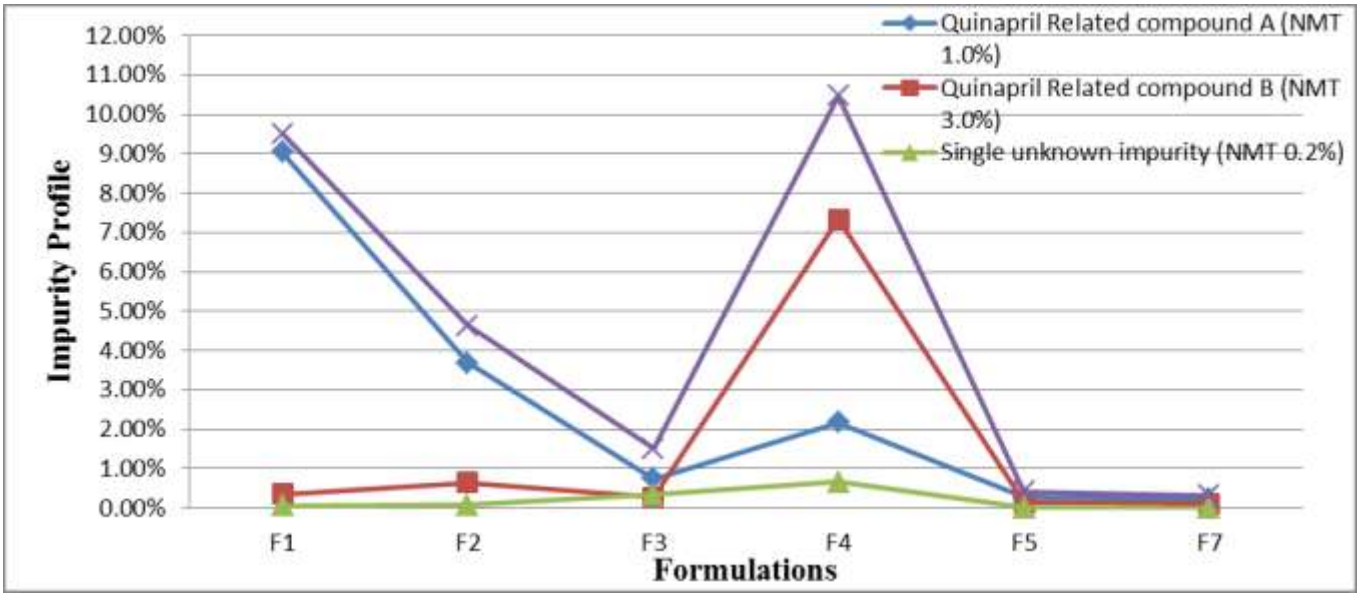

Figure 8: Graphical representation of impurity profiling of prototype formulations

Table 24: Dissolution Profile of Prototype Formulations

Formulation	Dissolution Apparatus : USP Type I (Basket) Medium : Water (900mL) Agitation speed :100 RPM				
	10 min	**15 min**	**20 min**	**30 min**	**45 min**
F1	89 %	89 %	89 %	89 %	89 %
F5	48 %	78 %	91 %	94 %	94 %
F9	93 %	99 %	99 %	99 %	99 %

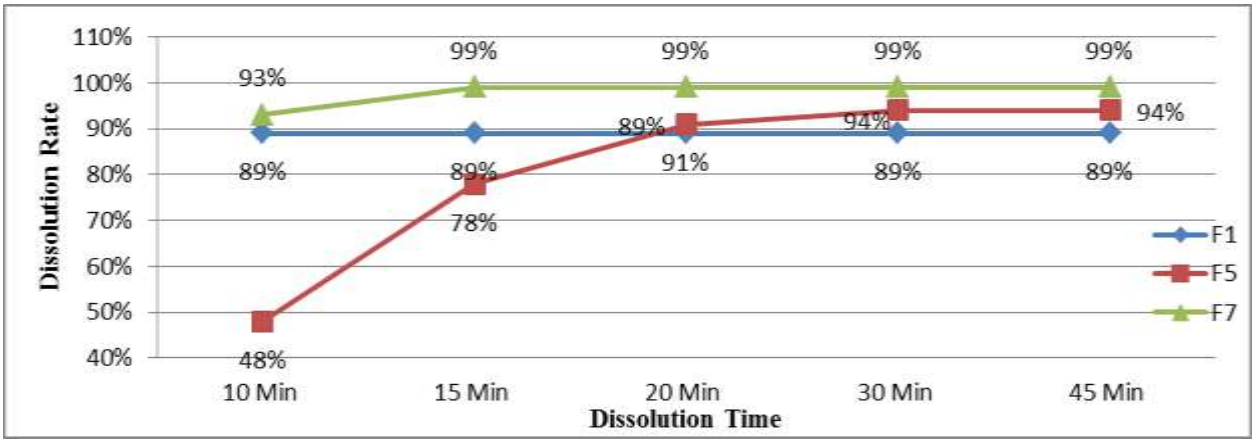

Figure 10: Graphical representation of Dissolution Profile of prototype formulation

Result

F1, F2& F4 formulation have higher impurity profile while formulation F3have lowest assay profile , F5 formulation have found to be variable drug release profile. F7 Formulation is found to have the lowest impurity profile,stable drug release profile as per IVIV Correlation therefore it is optimized final formulation.

5.3Optimization of stabilizer (Basic magnesium carbonate Heavy P Grade)

Table 25: Physical Properties of Prototype Formulation

Formulation	Physical Properties			
	Bulk Density	**Tapped Density**	**Hausner Ratio**	**Carr's Index**
S1	0.518	0.667	1.288	22.368
S2	0.545	0.690	1.266	21.014
S3	0.493	0.691	1.400	28.571

Compress Parameters				
Formulation	**Average Weight**	**Thickness**	**Hardness**	**Disintegration Time**
S1	412.01mg to 416.10mg	4.70mm to 4.80mm	94N to 118N	3 min.48 sec to 4 min.05 sec.
S2	414.40 mg to 414.90mg	4.62mm to 4.73mm	126N to 142N	3 min 55 secs to 4 min
S3	412.10 mg to 415.20mg	4.84 mm to 4.88 mm	110N to 130N	3 min 02 sec. to 3 min 30 sec.

Table 27: Analytical Results of Prototype Formulation

Formulation	Related Substances				Dissolution				
	Quinapril Related Compound A (NMT 1.0%)	Quinapril Related Compound B (NMT 3.0%)	Single Unknown Impurity (NMT 0.2%)	Total Impurity (NMT 3.6%)	10 min	15 min	20 min	30 min	45 min
S1	0.24%	0.16%	BQL	0.40%	97%	99%	99 %	99 %	99 %
S2	0.22%	0.10%	BQL	0.32%	93%	99%	99 %	99 %	99 %
S3	0.29%	0.15%	BQL	0.44%	97%	98 %	98 %	98 %	98 %

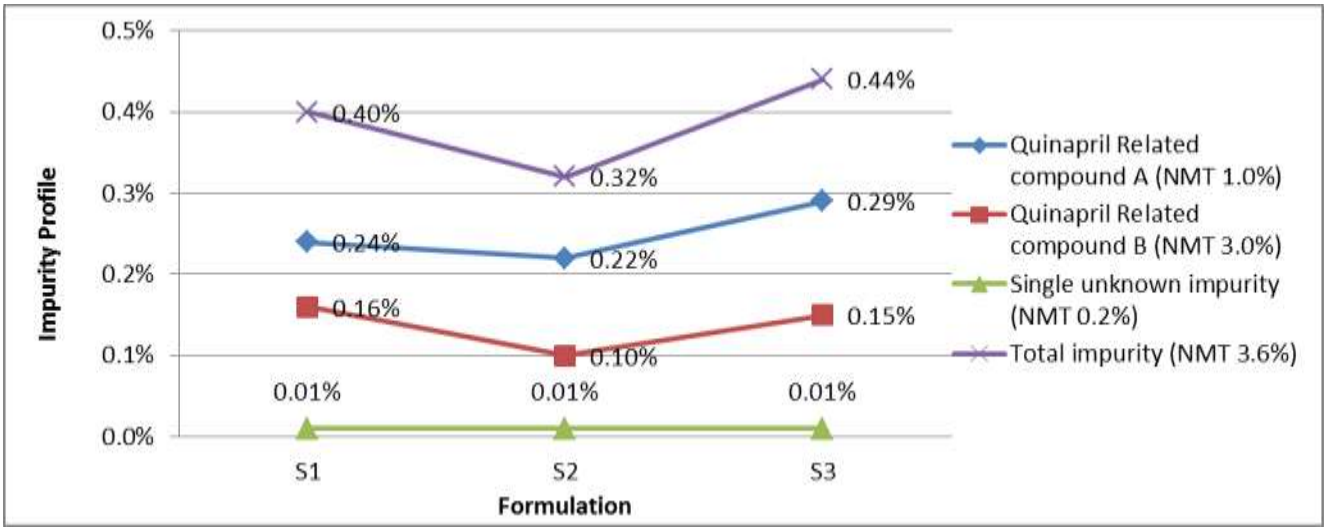

Figure 13: Graphical representation of Related Substances of prototypeformulation

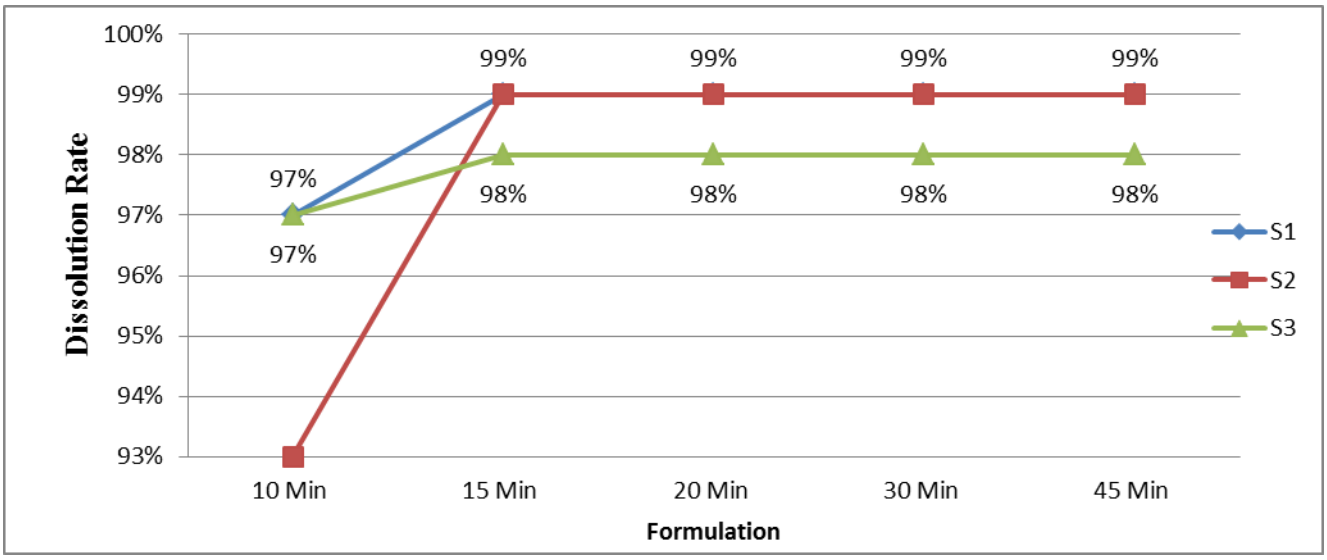

Figure 14: Graphical representation of dissolution profiling of prototype formulation

Inference:

All the physical parameters were found satisfactory. There is also no significant difference found within related substance & dissolution data obtained from tablets with different concentration of Basic magnesium carbonate Heavy P Grade as stabilizer within the studied range.

5.4 Optimization of Disintegrant (Crospovidone (Kollidon CL F) Concentration:

Table 28: Physical Properties of Prototype Formulation

Physical Properties				
Formulation	**Bulk Density**	**Tapped Density**	**Hausner Ratio**	**Carr's Index**
D1	0.501	0.679	1.356	26.25
D2	0.545	0.69	1.266	21.014
D3	0.505	0.638	1.264	20.879

Compress Parameters				
Formulation	**Bulk Density**	**Tapped Density**	**Hausner Ratio**	**Carr's Index**
D1	411.20mg to 412.80mg	4.65mm to 4.70mm	115N to 123N	2 min.48 sec to 3 min.15 sec.
D2	414.40 mg to 414.90mg	4.62mm to 4.73mm	126N to 142N	3 min 55 secs to 4 mins
D3	411.50mg to 413.20mm	4.65mm to 4.71mm	112N to 127N	2 min 32 sec. to 3 min 05 sec.

Table 30: Dissolution Profiling of Prototype Formulation

Formulation	**Analytical Results**				
	Dissolution Apparatus : USP Type I (Basket) Medium : Water (900mL) Agitation speed :100 RPM				
	10 min	15 min	20 min	30 min	45 min
D1	96%	98%	98%	98%	98%
D2	93%	99%	99%	99%	99%
D3	98%	100%	100%	100%	100%

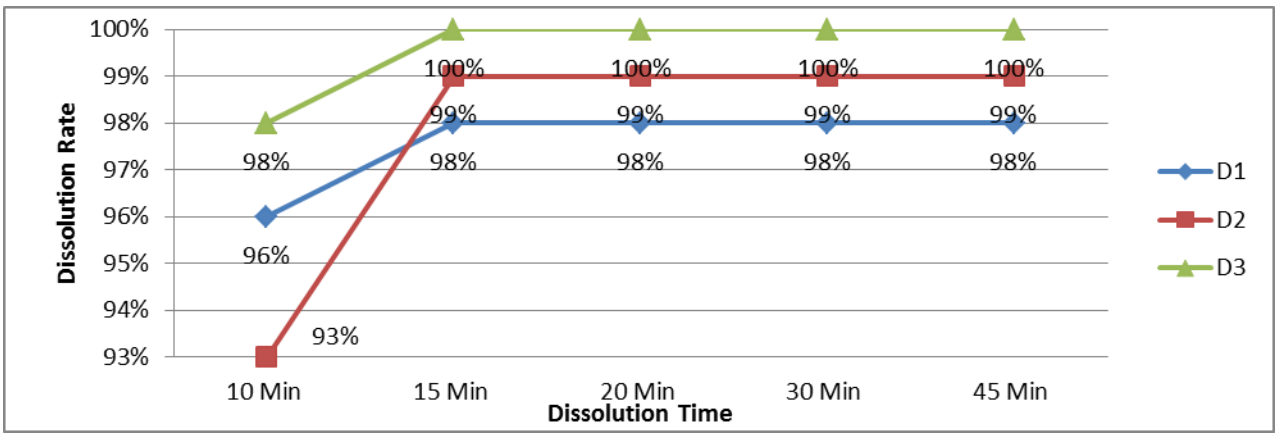

Figure 17: Graphical representation of dissolution profilingof prototype formulation

Inference:

All the physical parameters were found satisfactory. There is no significant difference found within dissolution data obtained from tablets with different concentration of Crospovidone (Kollidon CL F) as Disintegrant within the studied range

5.5 Optimization of Binder (Povidone K 30) Concentration:

Table 31: Physical Properties of Prototype Formulation

Compress Parameters				
Formulation	**Bulk Density**	**Tapped Density**	**Hausner Ratio**	**Carr's Index**
B1	0.51	0.641	1.258	20.482
B2	0.545	0.69	1.266	21.014
B3	0.499	0.641	1.286	22.222

Compression Parameters				
Formulation	**Average Weight**	**Thickness**	**Hardness**	**Disintegration Time**
B1	411.50mg to 412.80mg	4.65mm to 4.70mm	128N to 138N	2 min.50 sec to 3 min.10 sec.
B2	414.40 mg to 414.90mg	4.62mm to 4.73mm	126N to 142N	3 mins 55 secs to 4 mins
B3	412.00mg to 413.20mm	4.60mm to 4.65mm	125N to 136N	4 min to 4 min 20 sec.

Table 33: Dissolution profiling of Prototype Formulation

Formulation	**Analytical Results (Dissolution)** Apparatus : USP Type I (Basket) , Medium : Water (900mL), Agitation speed :100 RPM				
	10 min	15 min	20 min	30 min	45 min
B1	91%	98%	100%	100%	100%
B2	93%	99%	99%	99%	99%
B3	98%	102%	102%	102%	102%

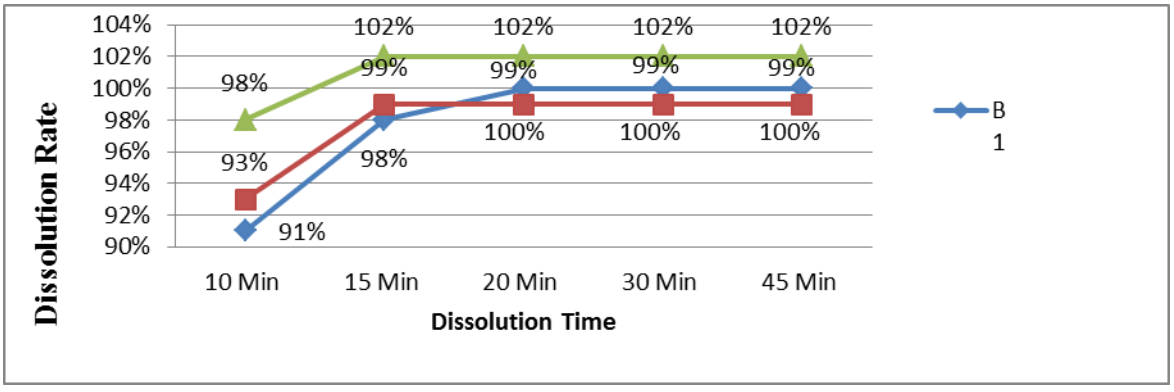

Figure 20: Graphical representation of dissolution profilingof prototype formulation

Inference:

All the physical parameters were found satisfactory. There is also no significant difference found within dissolution data obtained from tablets with different concentration of binder Povidone K 30 (Kollidon 30) within the studied range.

5.6 Optimization of Lubricant (Magnesium Stearate) Concentration:

Table 34: Physical Properties of Prototype Formulation

Physical Properties				
Formulation	**Bulk Density**	**Tapped Density**	**Hausner Ratio**	**Carr's Index**
L1	0.529	0.799	1.51	33.76
L2	0.545	0.69	1.266	21.014
L3	0.534	0.685	1.28	22.078

Compression Parameters				
Formulation	**Average Weight**	**Thickness**	**Hardness**	**Disintegration Time**
L1	399.60mg to 401.10mg	4.63mm to 4.69mm	120N to 130N	2 min.35 sec to 3 min.05 sec.
L2	400.30 mg to 401.300 mg	4.50 mm to 4.57 mm	126N to 142 N	3 min.10 sec to 3 min. 42 sec
L3	399.20 mg to 401.40mm	4.63mm to 4.68mm	110N to 125N	3 min to 3 min 20 sec.

Table 36: Analytical Results of Prototype Formulation

Formulation	**Analytical Results**								
	Related Substance				**Dissolution**				
	Quinapril Related Compound A (NMT 1.0%)	**Quinapril Related Compound B (NMT 3.0%)**	**Single Unknown Impurity (NMT 0.2%)**	**Total Impurity (NMT 3.6%)**	Apparatus : USP Type I (Basket) Medium : Water (900mL) Agitation speed :100 RPM				
					10 min	15 min	20 min	30 min	45 min
L1	0.23	0.11	BQL	0.34	90%	96%	97%	97%	97%
L2	0.22	0.1	BQL	0.32	93%	99%	99%	99%	99%
L3	0.14	0.11	BQL	0.25	90%	99%	100%	100%	100%

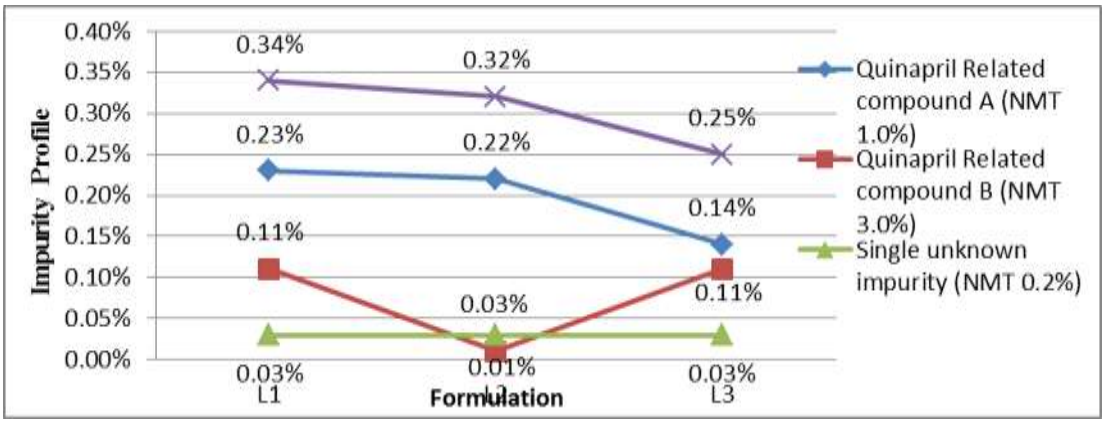

Figure 23: Graphical representation of impurity profile of prototype formulation

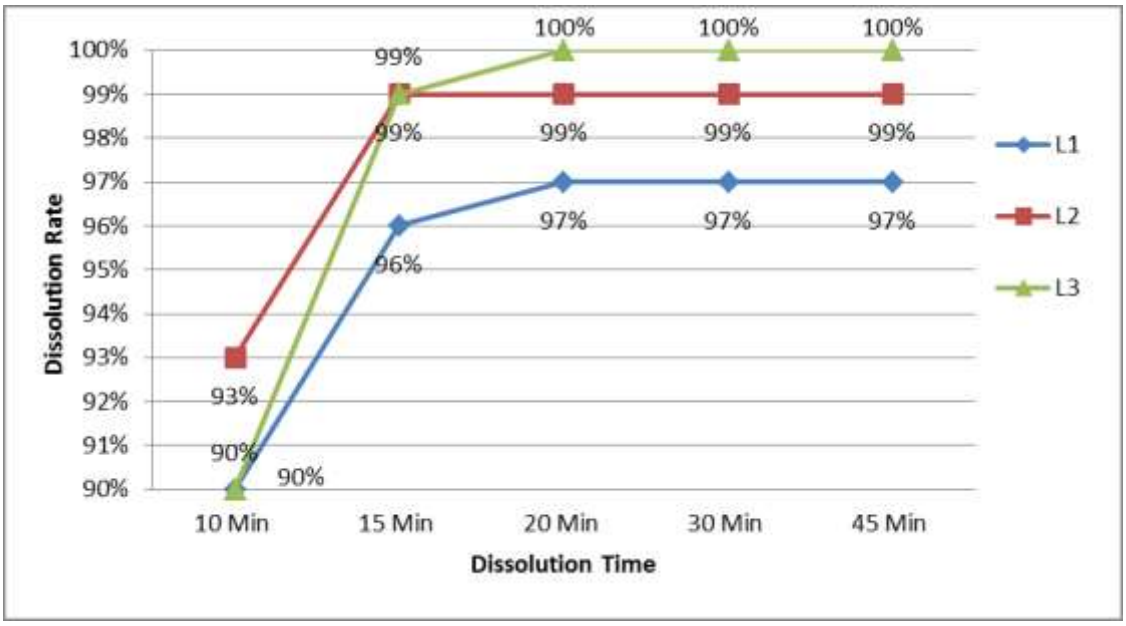

Figure 24: Graphical representation of Dissolution profile of prototype formulation

Inference:

All the physical parameters were found satisfactory. There is also no significant difference found within dissolution data obtained from tablets with different concentration of Magnesium stearate as lubricant within the studied range.

5.7 Stbility Evaluation

Table 37: Final Formulation for Accelerated Stability Study

TEST		LIMITS	INITIAL	1 M	3 M	6 M
Average Weight		388.00 mg to 412.00 mg	409.852 mg to 411.710 mg	409.850 mg to 411.705 mg	409.850 mg to 411.709 mg	409.851 mg to 411.710 mg
Thickness		4.3 mm to 4.9 mm	4.84mm to 4.89mm	4.83mm to 4.89mm	4.84mm to 4.87mm	4.82mm to 4.87mm
Hardness		80 N to 160 N	94.5 N to 104.5 N	94.2 N to 104.2 N	94.0 N to 104.0 N	94.2N to 104.2 N
Disintegration Time		NMT 15 Mins	53 secs to 1 minute	45 secs to 1 min 10 secs	54 secs to 57 secs	58 secs to 1 min 05 secs
Dissolution		Not less than 80% (Q) of the labeled amount of Quinapril is dissolved in 30 minutes.	98.50%	98.30%	97.80%	97.20%
Assay		95% to 110%	99.60%	99.54%	99.52%	99.51%
Related Substances	Quinapril Related Compound A	(NMT 1.0%)	0.06%	0.07%	0.07%	0.10%
	Quinapril Related Compound B	(NMT 3.0%)	0.29%	0.29%	0.30%	0.31%
	Single Unknown Impurity	(NMT 0.2%)	0.05%	0.05%	0.06%	0.07%
	Total impurity	(NMT 3.6%)	0.40%	0.41%	0.43%	0.48%

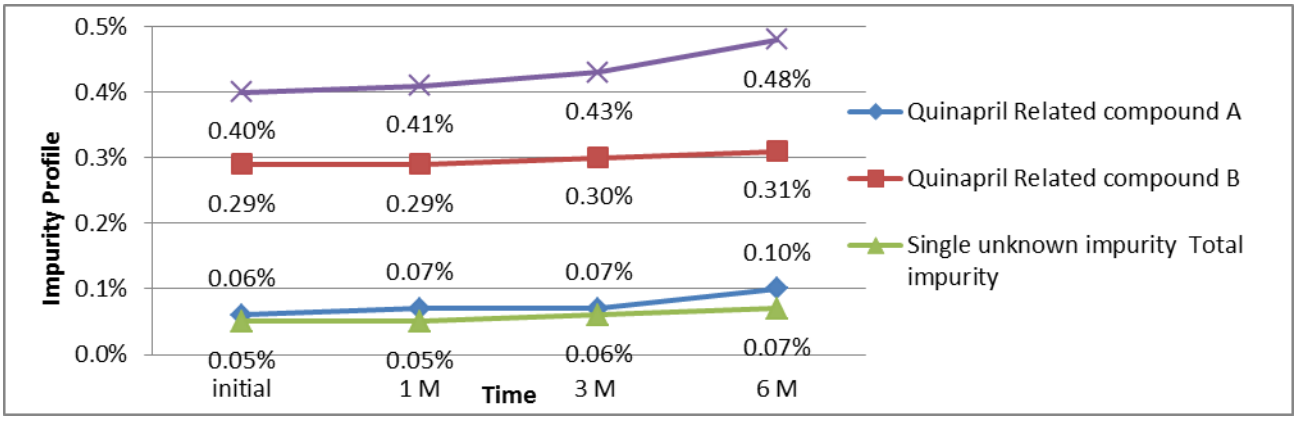

Figure 27: Graphical representation of impurity profile of accelerated stability study

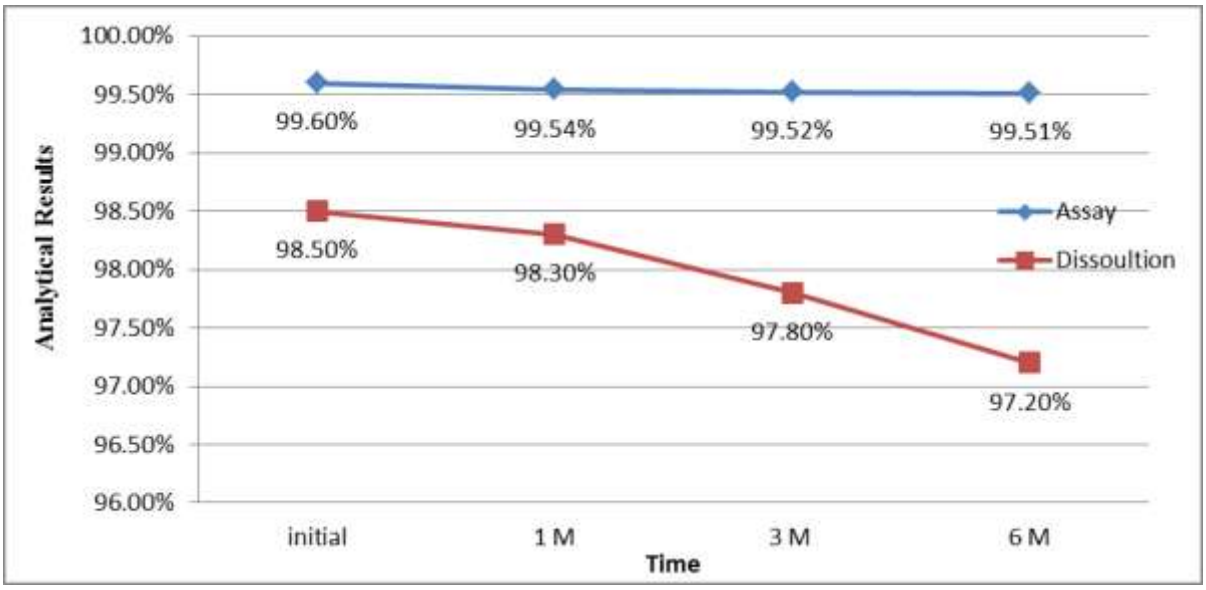

Figure 26: Graphical representation of assay & Dissolution profile of accelerated stability study

Inference:

All the physical parameters were found satisfactory during accelerated stability study. There is also no significant change found during the study period. Therefore shelf life of product can be suggested up to 24 months based on accelerated data.

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