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Design, Formulation and Evaluation of Extended Release Tablet Containing Nisoldipine

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Abstract

The aim of the present work is to formulate evaluate and develop a dissolution profile for an orally administrable extended tablet of nisoldipine, a calcium channel blocker drug by using various controlled release polymers including Methocel K100LVCR, Hydroxypropyl Cellulose (HPC-L), Hydroxypropyl cellulose (HPC-M), Lactose Monohydrate NF, Sodium Lauryl Sulphate (SLS), Eudragit L30D-55, Glyceryl behenteNF, Collodial silicon dioxide NF (Aerosil200), Magnesium Sterate NF, Methocel E_{50}, Methocel K100M CR in various ratios with active pharmaceutical ingredient (API) which show comparable dissolution profile with the reference product. The tablets were evaluated for drug content, weight variation, hardness, thickness, friability, film coating, high performance liquid chromatography, stability profile, and zero order kinetics *in-vitro* drug release study. The drug excipients compatibility studies indicated that the studied excipients have no interaction with drug .the excipients were compatible with API. The stability testing of finalized batch at 40°C / 75 % RH revealed no significant change with respect to assay and drug release pattern hence concluding that the finished product is highly stable.

Keywords: Nisoldipine; Extended release tablets; Zero order kinetics; Stability testing

Introduction

Oral drug delivery is the most convenient and preferable route of drug administration considering patient compliance, low cost, flexibility in drug design and ease of production[1]. Extended release matrix tablets are relatively simple systems that are more flexible in terms of variations in ingredients, production methods, and end-use conditions than film coated ER tablets and other systems. This results in more uniform release profiles with a high resistance to dose dumping[11]. The most common approach of extending and controlling rate of release of drug is to incorporate a drug in hydrophilic colloid matrix such as hydroxyl propyl methyl cellulose[13]. Currently available therapies for hypertension include drugs which block the activity of peripheral sympathetic nervous system, diuretics, centrally acting drugs, selective and non-selective α and β receptor blockers, calcium channel blockers, vasodilators, ACE inhibitors, angiotensin receptor blockers, used individually or in combination[14-20]. Most of these drugs have different kinds of disadvantages associated with them such as short half-life, low bioavailability, poor permeability and adverse effects associated with them. Various attempts have been made to design drug delivery systems for calcium channel blockers to:

- reduce the dosing frequency,
- increase the bioavailability and decrease the degradation/metabolism in the gastrointestinal tract,
- improve the central nervous system (CNS) penetration and inhibit the CNS efflux, and
- Deliver them to the target cells selectively with minimal side.

Nislodipine is an extended release tablet dosage form of the dihydropyridine calcium channel blocker. Nisoldipine is 3, 5-pyridinedicarboxylic acid, 1, 4-dihydro-2, and 6-dimethyl-4-(2-nitrophenyl)-, methyl-2-methylpropyl ester, $C_{20}H_{24}N_2O_6$, and has the structural formula:

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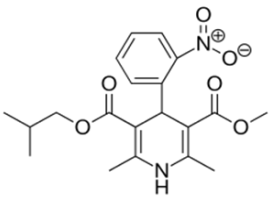

Nisoldipine belongs to the class of dihydropyridine class of calcium channel blockers (calcium channel inhibitors or slow channel blockers) that prevents the transmembrane influx of calcium into vascular smooth muscle and cardiac muscle. It reversibly competes with other dihydropyridines for binding to the calcium channel. The heart contracts as a result of movement of calcium ions through specific ion channels. Blockage of such ion channels causes dilation of arterioles. *In vitro* study profile of nisoldipine indicates that contractile processes are selective, with greater potency on vascular smooth muscle than on cardiac muscle. Although, like other dihydropyridine calcium channel blockers, nisoldipine has negative inotropic affects as justified *in vitro*, studies. The effect of nisoldipine on blood pressure is principally a consequence of a dose-related decrease of peripheral vascular resistance. Nisoldipine exhibits a mild diuretic effect[21].

Material and Methods

Physical properties of nislodipine such as bulk density tap density and powder compressibility were evaluated. The results are as given in Table 1.

Table 1: Physical properties of Nislodipine.

Ingredient	Bulk Density	Tapped Density	Hausner ratio	Compressibility Index	Angle of Repose
API	0.42	0.59	1.40	40.47	490

Particle size determine by Malvern method: Particle size is one of the most important properties influencing the dissolution rate of a drug and thus potentially its bioavailability. Particle size reduction (e.g. micronization) is often utilized to enhance dissolution rate. Small particles present a larger surface area per unit length to the dissolution media and hence dissolve more rapidly than large particles. Particle size may also affect the stability of drug substances, in that it governs the surface area available for oxidation and hydrolysis. Surface area is critical for interaction with excipients in tablet dosage forms and can greatly affect stability[22].

Conclusion

Active Pharmaceutical Ingredients (API) complies as per the specification 90% having particle size 15.14 micron as seen in Figure 1

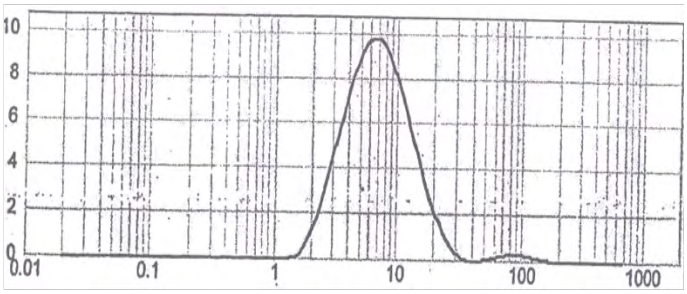

Figure 2: Particle Size Distribution.

X-Ray Diffraction Studies: The X-Ray diffraction pattern of candidate drug exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug.

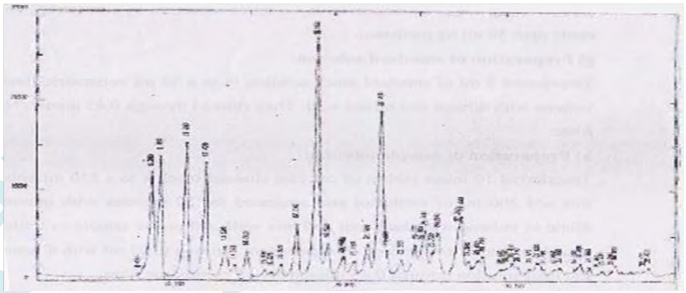

Figure 3: XRD analysis of candidate drug.

Analytical method

Instrumentation: Water Alliance HPLC system or equivalent

Preparation of buffer: Add 1.36 gm of potassium dihydrogen orthophosphate and dissolve in 1000 ml of water, mix well and filter through 0.45 micron size membrane filter.

Preparation of mobile phase: Mixture of buffer and methanol is taken in the ratio of 32:68 and degased.

Preparation of diluents: Mixture of water and methanol is taken in the ratio of 50:50 and degased.

Chromatographic conditions: Column: Graces Kromasil C 18 (150 x 4.6 mm), 5 micron is selected

Flow: 1.7 ml / min

Wavelength: 237 nm

Injection volume: 10 micron

Preparation of standard stock solution: Precisely 41 mg of drugs were dissolved in 40 ml of methanol by sonication. Then volume was made up to 50 ml by methanol.

Preparation of standard solution: Transfer 5 ml of standard stock solution in to a 50 ml volumetric flask and make up the volume with diluents and mix well. Then filter through 0.45 micron nylon membrane filter.

Preparation of sample solution: Transfer 10 intact tablets of calcium channel blocker in a 250 ml volumetric flask, to this add 200 ml of methanol and sonicate for 30 min with intermittent shaking. Make up the volume with methanol and mix well. Allow the sample to settle down for more than 15 minutes. Dilute 3 ml of supernatant solution to 25 ml with diluents and mix. Filter the solution through 0.45 micron nylon membrane filter.

Procedure: Inject diluents as blank, standard solution and sample solution into chromatographic system. Measure the peaks area count for candidate drug.

Formula: % Assay of candidate drug for 17 mg strength

$$\frac{\frac{AT}{AS \times W}}{\frac{50 \times 5}{50 \times 250}} \times \frac{N \times 20}{\frac{5P}{L}}$$

Where
AT: average peak area counts of drug in sample solution
AS: average area counts of drug in standard solution
W: Weight of drug working standard in mg
N: Number of tablet taken for analysis
P: Percent potency of drug
L: Label claim of drug candidate in mg per tablets

Discussion

Assay of API on the dried basis = 99.7 %

Table. 2: Determination of solubility.

pH range	Solubility (mcg/ml)
Distilled water	1.1394
Phosphate buffer p^H 2	1.2500
Phosphate buffer p^H 4	1.2175
Phosphate buffer p^H 6	1.2983
Phosphate buffer p^H 6.8	1.0400
Phosphate buffer p^H 8	0.7463
SLS 0.25%	24.3
SLS 0.50%	48.4

API (CCB) showed more solubility in SLS containing media, its solubility increases as the concentration of SLS increased
API showed minimum solubility in water as well as in phosphate buffer without SLS at different ranges of p^H

Calibration curve of API: The following concentrations were taken and the absorbance for respective concentrations was obtained. A calibration plot was obtained and the equation obtained. The equation was as follows Y = 0.113x + 0.022. The value of R_2 was found to be 0.998. On the basis of results obtained it was concluded that Active Pharmaceutical Ingredient (API), obeyed Beer – Lambert's law in the range of 2- µg / ml

Table. 3: Concentration of standard solutions and their absorbance.

Sr. No.	Conc (µg/ml)	Absorbance
1	0	0
2	2	0.25
3	4	0.50
4	6	0.72
5	8	0.92
6	10	0.139

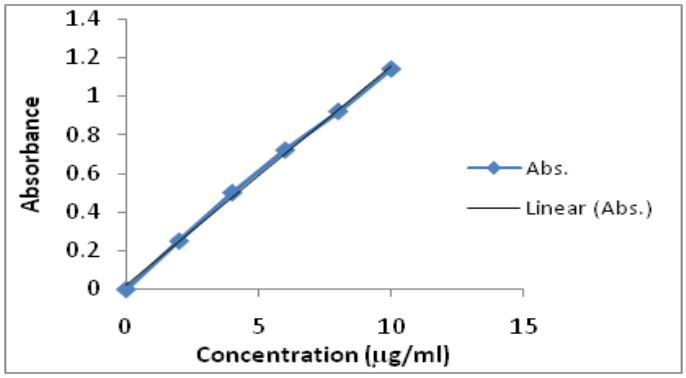

Figure 4: Calibration curve of active pharmaceutical ingredient.

Drug-Polymer Interactions: Physical observation of drug excipients compatibility study at accelerated condition (40°C / 75 % RH)

Table 4: Physical observation of drug excipients compatibility study at accelerated condition (40°C/75%RH).

S r No	Physical admixture	Drug excipient ratio	Initial description	Observation
1	API	.....	Yellow powder	NC
2	API+ MethocelK100LVCR	1:17	Light yellow powder	NC
3	API+MethocelK4MCR	1:5	Light yellow powder	NC
4	API +Hydroxypropyl Cellulose (HPC-L)	1:5	Yellow powder	NC
5	API+Hydroxypropyl cellulose (HPC-M)	1:5	Yellow powder	NC
6	API +Lactose Monohydrate NF	1:7	Light yellow powder	NC
7	API +Sodium lauryl sulphate	1:3:5	Light yellow powder	NC
8	API+Eudragit L30D-55	1:2	Light yellow powder	NC
9	API +Glyceryl behenteNF (Compritol888AT)	1:1	yellow powder	NC
10	API+Collodial silicon dioxide NF (Aerosil200)	1:1	yellow powder	NC
11	API +Magnesium Sterate NF	1:0:5	yellow powder	NC
12	API+Methocel E50	1:17	Light yellow powder	NC
13	Opadry 03f52057	1:5	Light yellow powder	NC
14	API+Methocel K100M CR	1:1:7	Light brown powder	NC

NC-No chang

Table 5: Formulation of tablets.

Sr.no	Ingredient	T_1 (Mg)	T_2 (Mg)	T_3 (Mg)	T_4 (Mg)	T_5 (Mg)	T_6 (Mg)	T_7 (Mg)	T_8 (Mg)	T_9 (Mg)
1	CCB	17	17	17	17	17	17	17	17	17
2	Hypromellose	362	362	222	242	272	272	172	232	232
3	Methocel	100	100	50	30	----	---	---	---	
4	K100MCR Lactose monohydrate	205	205	105	102	95	105	105	105	---
5	Povidone	10	10	16	6	6	6	6	6	6
6	SLS	50	50	40	40	40	40	40	40	40
7	IPA:DCM(60:40)	--	---	---	---	---	---	---	---	---
8	Hypromellose	12	12	---	---	---	---	---	---	---
9	Eudragit	12	12	---	---	---	---	---	---	---
10	Glyceryl behenate	20	20	10	10	10	10	10	10	10
11	Colloidal silicone dioxide	8	8	6	6	6	7	7	7	7
12	Magnesium sterate	4	4	4	4	4	3	3	3	3
13	Opadry	---	24	---	14	14	11	12.9	12.9	12.9
14	Purified water	---	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total weight	800	824	870	954	954	751	751	812	812

Table 6: Evaluation of tablets.

Formulations	Hardness (kg/cm^2 ± S.D)	Friability (%w/w) ± S.D	Thickness (mm ± S.D)	Average wt. (mg)	Film coating
T_1	110	Nil	6.08	795	-
T_2	106	Nil	6.02	800	3.21
T_3	70	Nil	5.29	475	3.12
T_4	76	Nil	4.80	473	3.15
T_5	65	Nil	4.84	470	3.04
T_6	62	Nil	4.35	472	3.00
T_7	66	Nil	4.81	372	3.04
T_8	69	Nil	4.59	430	3.00
T_9	68	Nil	4.42	432	3.01

Table.7: % Drug concentration of innovator and trial batch-1.

Time in hors	Innovator	Trial 1
0	0	0
1	2	1
2	5	3
4	16	4
6	30	7
8	38	10
10	54	17
12	68	22
15	84	27
18	89	35
21	91	43
24	92	52
F2	17.15	

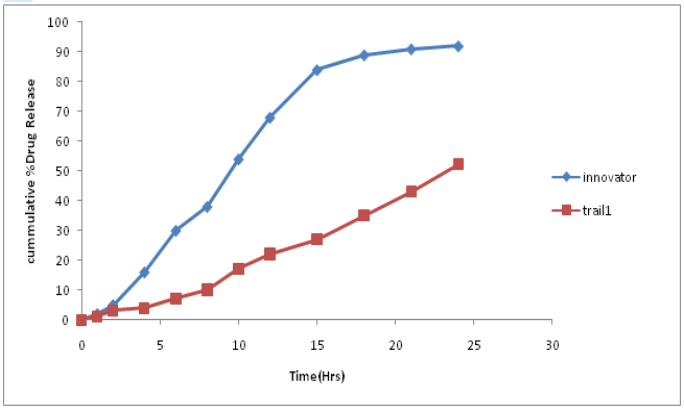

Figure 5: Dissolution curve of Trial-1 batch.

Discussion of Trial number 1

- Current batch showed formation of fine (>70%) and poor flow property, which is unacceptable for compression process. Hence change in granulation process is required to increases the amount of granules.
- Dissolution profile was very slow as compare to innovator dissolution profile.
- Change in granulation process was decided to minimize fine formation.

Table 8: % Drug concentration of innovator and trial batch-2.

Time in hors	Innovator	Trial 2
0	0	0
1	2	1
2	5	3
4	16	5
6	30	7
8	38	12
10	54	18
12	68	23
15	84	28
18	89	36
21	91	43
24	92	53
F_2	17.51	

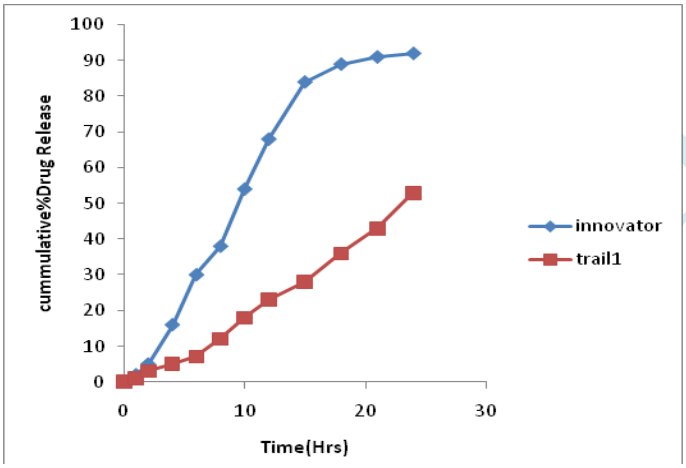

Figure 6: Dissolution curve of Trial-2 batch.

Discussion of Trial no-2: Quantity of fine flowing powder when decreased causes slowing of the drug release profile is as compared to innovator profile so the next batch plan begins with the increase in amount of sodium lauryl sulphate to increases the rate and extend of drug from tablet.

Table 9: % Drug concentration of innovator and trial batch-3.

Time in hours	Innovator	Trial 3
0	0	0
1	2	2
2	5	5
4	16	9
6	30	14
8	38	23
10	54	31
12	68	39
15	84	47
18	89	60
21	91	72
24	92	78
F_2	27.01	

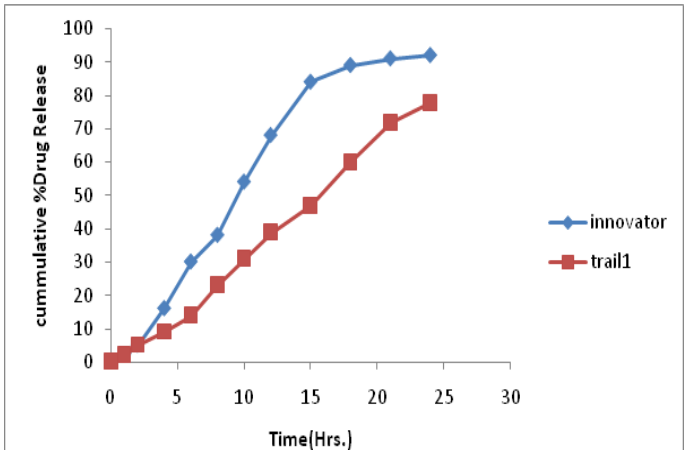

Figure 7: Dissolution curve of Trial-3 batch.

Granulation and compression parameters were satisfactory.

Drug release was slower compare to innovator profile. Hence composition should be changed Next batch was planned with decreased quantity of methocel K100MCR. Because it is a high viscosity grade polymer which slows down the dissolution rate as it is controlled release polymer. Therefore by decreasing quantity of his polymer there may be chances of increases in drug release profile.

Table 10: % Drug concentration of innovator and trial batch-4.

Time in hours	Innovator	Trial 3
0	0	0
1	2	1
2	5	4
4	16	11
6	30	19
8	38	28
10	54	39
12	68	48
15	84	61
18	89	73
21	91	82
24	92	85
F_2	33.97	

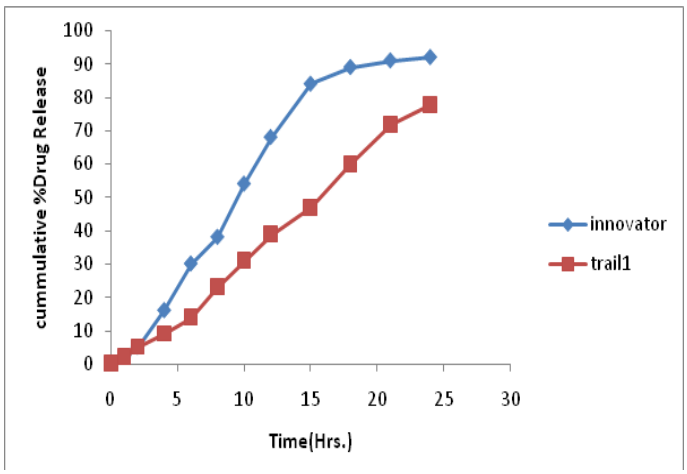

Figure 8: Dissolution curve of Trial-4 batch.

Discussion of Trial no 4

- Compression parameter was satisfactory and was similar to trial number 3.
- It was found that drug release profile is still slow and not matching with innovator profile.
- So in the next batch it is planned that Eudragit L_{30} D-55 would be added for granulation and methocel $K_{100}L$ VCR as matrix former.

Table 11: % Drug concentration of innovator and trial batch-5.

Time in hours	Innovator	Trial 5
0	0	0
1	2	1
2	5	6
4	16	15
6	30	25
8	38	35
10	54	45
12	68	55
15	84	68
18	89	79
21	91	85
24	92	89
F_2	39.90	

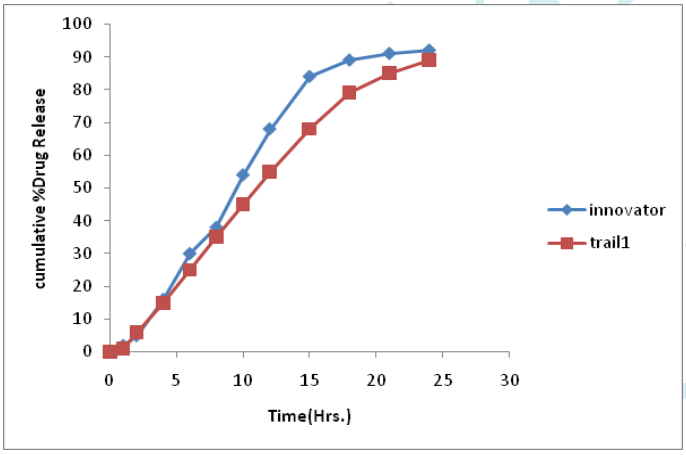

Figure 9: Dissolution curve of Trial-5 batch.

Discussion of Trial number 5

- Drug release profile was somewhat similar to innovator at starting phase but later it slowed down.
- Hence it was thought decided that active pharmaceutical ingredients (API) of size less than 10 microns can be used to enhance the drug release profile.

Table 12: % Drug concentration of innovator and trial batch-6.

Time in hours	Innovator	Trial 5
0	0	0
1	2	6
2	5	13
4	16	28
6	30	43
8	38	58
10	54	72
12	68	84
15	84	95
18	89	96
21	91	97
24	92	97
F_2	46.76	

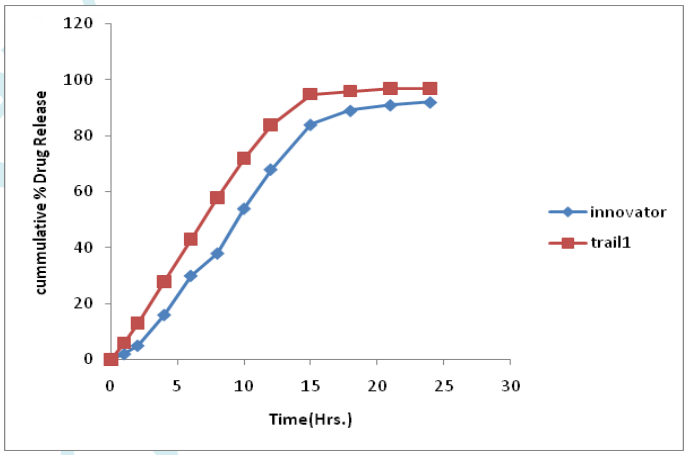

Figure 10: Dissolution curve of Trial-6 batch.

Discussion of Trial number 6

- Drug release profile was faster at initial phase but latter it's showed similar drug release as compared to innovator profile.
- It was further thought to increase the quantity of methocel E-50 to match drug release profile with innovator profile.

Table 13: % Drug concentration of innovator and trial batch-7.

Time in hours	Innovator	Trial 7
0	0	0
1	2	4
2	5	9
4	16	22
6	30	34
8	38	46
10	54	60
12	68	73
15	84	88
18	89	89
21	91	91
24	92	93
F_2	67.23	

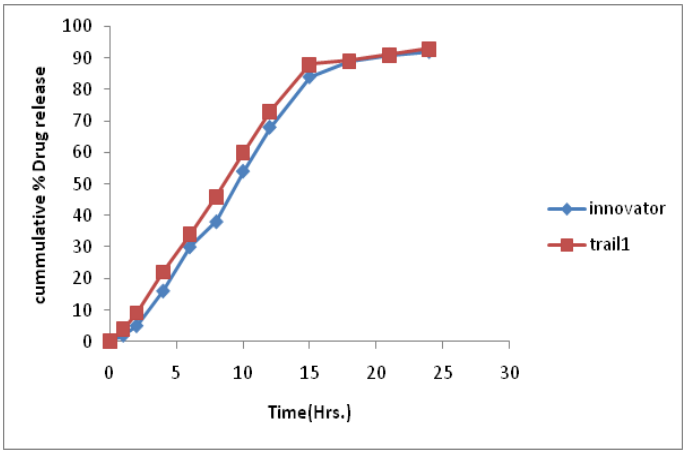

Figure 11: Dissolution curve of Trial-7 batch.

Discussion of Trial number 7

- Drug release profile was faster at initial phase but latter it's showed similar drug release as compared to innovator profile.
- Hence it was planned to increase the quantity of methocel E-50 to match drug release profile with innovator profile.

Table 14: % Drug concentration of innovator and trial batch-8.

Time in hours	Innovator	Trial 7
0	0	0
1	2	2
2	5	7
4	16	18
6	30	30
8	38	42
10	54	53
12	68	64
15	84	81
18	89	89
21	91	94
24	92	94
F2	80	

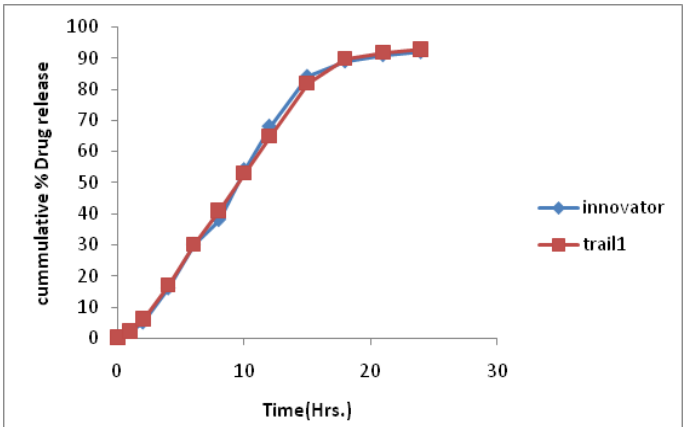

Figure 12: Dissolution curve of Trial-8 batch.

Discussion of Trial number 8

- Drug release profile of test batch was close to drug release profile of innovator in official media; F_2 value was 79.30.
- Compression parameter was satisfactory found in this batch.

Table 15: % Drug concentration of innovator and trial batch-9.

Time in hours	Innovator	Trial 9
0	0	0
1	2	2
2	5	6
4	16	17
6	30	30
8	38	41
10	54	53
12	68	65
15	84	82
18	89	90
21	91	92
24	92	93
F_2	86.92	

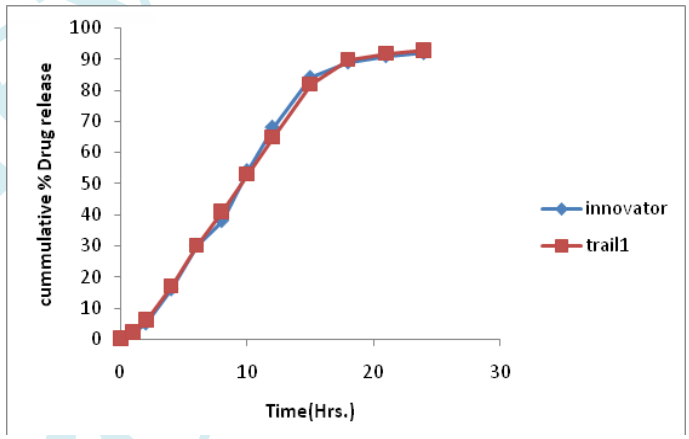

Figure 13: Dissolution curve of Trial-9 batch.

Discussion of Trial number-9

- Drug release profile of test batch was close to drug release profile of innovator in official media; F2 value was 86.92.
- Compression parameter was satisfactory found in this batch.

Table 16: Zero order release kinetics result.

Time points	Initial (%)	1month (%)	2 month (%)
0	0	0	0
1	2	2	2
2	7	6	6
4	18	18	17
6	30	29	28
8	42	40	40
10	53	52	50
12	64	62	62
15	81	79	79
18	89	89	87
21	94	92	93
24	94	93	93

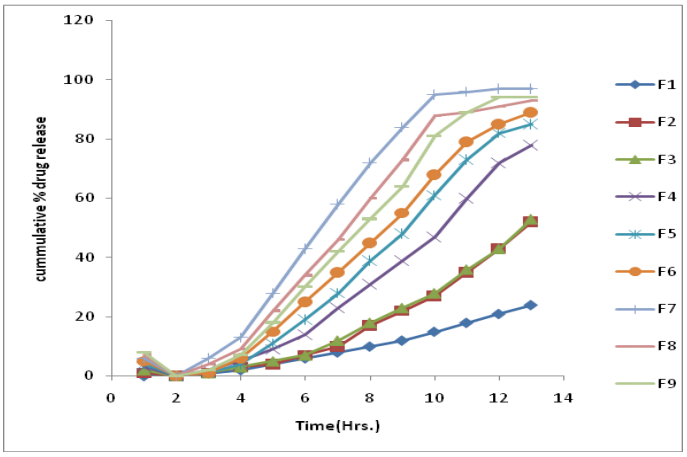

Figure 13: Zero order release of all trial batches.

Conclusion

In the given Trial batches dissolution release (Trial number 8) is release by zero order kinetics i.e. the constant amount of release dose does not depend of drug concentration[23].

Table 17: Assay result

Sr.no	Trial1	Trial2	Trial3	Trial4	Trial5	Trial6	Trial7	Trial8	Trial9
Assay % w/w	98.60	98.23	97.86	99.23	98.66	100.86	97.23	100.6	99.56

Table 18: Stability data

Parameter	Initial	Months & condition 40°C/75 % RH	
		1M	2M
Assay (%w/w)(By HPLC)	100.6	98.9	99.5

Conclusion

- The drug excipients compatibility studies showed that the studied excipients have no interaction with drug .the excipients were compatible with API.
- Evaluation of physiochemical parameter like hardness, friability, dissolution and assay indicated that the tablet were mechanically stable and complied with necessary pharmacopoeia specification and comparable to innovator product.
- The stability testing of finalized batch at 40^0C / 75% RH revealed no significant change with respect to assay and drug release pattern that indicate the stability of the finished product.
- Finally, it is concluded that the process adopted for the manufacturing provides a product meeting all the predetermined specification and quality characteristics. The process would imbibe reproducibility and robustness in the formulation.

Future Scope

- The research project has a wide future scope to modify the delivery system of drug for the treatment of angina.
- Following are the certain future scope;
- Bioequivalent study.
- Development of other strength using scale up /scale down technique.
- ANDA filing

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