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Formulation and Evaluation of Delayed Release Fenofibric Acid Capsule

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Abstract

The active pharmaceutical ingredient Choline fenofibate was subjected to preformulation study, which encompasses the "Accelerated, intermediate, long term Drug – excipient compatibility study" , and the result obtained with selected excipients showed good compatibility with Choline fenofibrate.Choline fenofibrate pellets were formulated by utilization of FBP, and Choline fenofibrate coated pellets were filled by capsule filling machine.

The stability study of the capsule and pellets were detected by conducting "accelerated 40°C±5%/75%RH" for 6 months. Finally, after the duration, the product was analyzed for content and dissolution study. By the stability studies, the formulated Fenofibric acid Delayed release capsules and pellets proved to be throughout the period of storage.TheFenofibric acid delayed release pellets were loaded in size '0' capsules. It showed good results in formulation of stable dosage.

1. Introduction

Dosage forms are designed for modify the drug release over a allowed time or after the dosage form reaches the appropriate location.

(a) FIBRIC ACID DERIVATIVES (FIBRATES)[1-3]

Fibrates are cholesterol-bringing down drugs that are primarily effective in lowering triglycerides and to a lesser extent in increasing HDL-cholesterol levels [29].

(b) BILE ACID SEQUESTRANTS[4-6]

The bile acid ensuing are a group of medications used to bind certain bile components in the GI tract.

(c) NICOTINIC ACID FOR HIGH CHOLESTEROL

Mode of action

Nicotinic corrosive diminishes the generation of triglycerides and VLDL (low-thickness lipoprotein, which is changed over to LDL in the blood) [7]. This prompts diminished LDL ("terrible") cholesterol, expanded HDL ("great") cholesterol, and brought down triglycerides.

Delayed release

DR dosage forms also can be known as processes which are formulated to release the active substances quickly or at a time after administration.

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From oral dosage forms, delayed release can control at the point when the dose structure achieves the small digestive tract or the colon.

This framework can be utilized to shield the stomach from aggravation by the medication or to shield the medication from debasement in the low pH condition of the stomach. In these cases arrival of medication ought to be delayed until the drug release has achieved the small digestive tract.

The dosage form (for example, the granules or any tablet before tableting) can be coated with a suitable polymer. The polymer dissolves as a reason of pH, so when the dosage forms move from the low-pH environment of the stomach to the higher-pH environment of the small intestine, the drug can be released and the polymer coat dissolves. Once this occurs, the release is again immediate and the resulting time versus plasma concentration curve is similar to the one for immediate release dosage forms.

2. Pellets and Pelletization

PELLETS

- It can be defined as small spherical, free - flowing, spherical particulates manufactured by the accumulation of granules and fine powders of drug substances and excipients using suitable processing equipment.

PELLETIZATION TECHNIQUES

The preparation of spherical mass can be reached by different techniques which can be sub divided into the basic types of systems shown in below

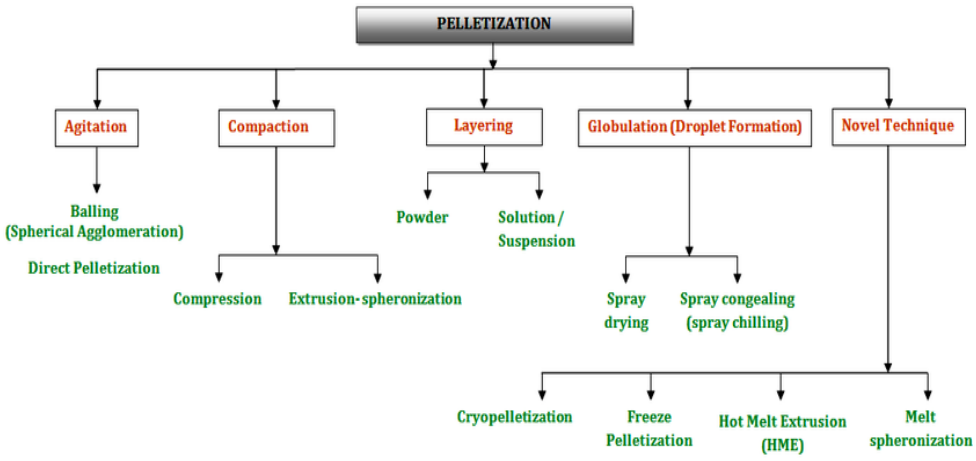

Figure 1 Pelletization technique

In pharmaceutical industry, drug layering and compaction are the mostly used pelletization techniques. Extrusion and spheronization is the most suitable method of the compaction techniques. There are various methods of pelletization such as balling, globulation, cryopelletization, and compression are also used in development of pharmaceutical pellets but in a medium scale.

Hot Melt Extrusion

This is a newly modified variation of extrusion - spheronization method. To provide pellets or solid spheres, a drug substance and excipients are converted into a semi-molten or molten state and eventually shaped using suitable equipment. This is a simple and continuous process.

Pelletization by Layering

Pelletization by layering can be defined s pellet build-up , layer by layer around a specific starting core diameter should be between 0.6mm and 2.5mm.

There are 2 types

A. Suspension or solution layering

B. Powder layering

A. Suspension or solution layering

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The more popular process for manufacturing pellets is coating a core with a suspension or solution. By spraying process required amount of active ingredient can be reached. By solution layering , forms round pellets with a thick structure and even surface.

B. Powder layering

Dry powder layering is a procedure for developing active substance pellets by coating a starter core with an excipient in powder form. This is finish with the help of a binding solution fixed to the starter core. The advantage of this layering compared to layering with liquid active compounds is that the processing time is significantly decrease which leads to a higher efficiency.

3. Experimental Work

FORMULATION DEVELOPMENT

Fenofebric acid Delayed release capsules were prepared. The process was displayed in the below flow chart

MANUFACTURING PROCESS:

DRUG COAT

PREPARATION OF DRUG LOADING SOLUTION

Take the dispensed quantity of purified water in SS container.

Add polyethylene glycol 6000 and plasdone K29/32 in purified water under continuous stirring to get the clear solution . Then add Choline fenofibrate to above solution and continue the stirring to get a clear solution.

To the above solution ad talc and continue stirring to get uniform dispersion, filter the final dispersion through nylon mesh.

DRUG LOADING

Sift dispensed quantity of sugar pellets(#25-#30) through ASTM #25 and ASTM #30 and collect retains and passing separately. Collect the specified quantity of sifted sugar pellets (#25-#30) for drug loading and the excess remained should be discarded.

Load sugar spheres(#25-#30) into FBC bowl.

Set the inlet temperature 60°c±5°c to reach the core bed temperature of about 45°c±5°c.

Coat the sugar spheres by bttom spray wurster at peristaltic pump rpm of 10-60 with atomizing air pressure of 2.0-5.0 Kg/cm^2 and blower 2000-5000cfm till the target weight build up 186.80 (177.46%-196.14%) has achieved while excess dispersion remained should be discarded.

After completion of drug loading, dry the pellets in FBC for about 15 minutes at be temperature 40°c-±5°c and unload the pellets into pre-labeled HDPE containers lined with double polyethylene bags.

Record the inlet air temperature, bowl temperature, sprays rate and atomization pressure every 30 minutes in BMR.

SIFTING:

Sift the dried pellets through #16 and collect #16 retains and passing separately.

Now pass #16 passing pellets through #25 and collect retains and passing separately.

The sifted pellets (#16-#25) are collected into HDPE container lined with double polyethylene bags.

Collect the sample as per protocol.

EXTENDED RELEASE COAT

PREPARATION OF EXTENDED RELEASE COATING SOLUTION

Take the dispersion quantity of purified water and isopropyl alcohol into two separate SS containers.

Add Hypromellose to the purified water under continuous stirring and continue stirring till clear solution has obtained.

Add Polyethylene glycol 6000 to the Hypromellose solution under continuous stirring and continuous stirring till clear solution has obtained.

Add ethyl cellulose to the IPA under continuous stirring and continue stirring till clear solution has obtained.

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Add step no. 7.1.4.1.3 to ethyl cellulose dispersion of step 7.1.4.1.4 and continue stirring till clear solution has obtained.

Add Magnesium stearate and continue stirring till uniform dispersion has obtained. Filter the above dispersion through nylon mesh.

EXTENDED RELEASE COATING

Load the drug loaded pellets into FBC bowl.

Set the inlet temperature 50°c±5°c to reach the core bed temperature of about 40°c±5°c.

Coat the pellets by bottom spray wurster at peristaltic pump rpm of 10-60 with atomizing air pressure 2.0-5.0 Kg/cm^2 and blower 3000-5000 cfm till the target weight build up 4.38% (4.16-4.59%)

After completion of the coating , dry the pellets in FBC for about 15 minutes at bed temperature 40°c-±5°c and unload the pellets into pre-labeled HDPE containers lined with double polyethylene bags.

Record the inlet air temperature, bowl temperature, spray rate and atomization pressure every 30 minutes in BMR.

SIFTING:

Sift the extended release coated pellets through #16 and collect #16 retains and passing separately.

Now pass #16 passing pellets through #25 and collect retains and passing separately.

The sifted pellets (#16-#25) are collected into HDPE containers lined with double polyethylene bags.

ENTERIC COAT

PREPARATION OF ENERIC COATING SOLUTION

Take the dispensed quantity of purified water in SS container.

Add Triethylcitrate in purified water and continue stirring until a clear solution was observed. Then ad Talc under continuous stirring till uniform dispersion has obtained.

Add Eudragit L30 D 55 to the above dispersion (8.1.5.1.2) and continue stirring till uniform dispersion has obtained. Filter the dispersion through nylon mesh.

ENTERIC COATING

Load extended release coated pellets into FBC bowl.

Set the inlet temperature 50°c±5°c to reach the core bed temperature of about 40°c ±5°c 8.1.5.2.3 coat the pellets by bottom spray wurster at peristaltic pump rpm of 10-60 with atomizing air pressure of 2.0-5.0Kg/cm^2 and blower 2000-5000 cfm till the target weight build 44.61% (42.38%-46.84%) has achieved while rest of the remained dispersion should be discarded.

After completion of the coating, dry the pellets in FBC for about 120 minutes at bed temperature of 30°c±5°c and unload the pellets into pre-labeled HDPE containers lined with double polyethylene bags.

Record the inlet air temperature, bowl temperature, spray rate and atomization pressure every 30 minutes in BMR.

SIFTING:

Sift the enteric coated pellets through #14 and collect #14 retains and pssing separately.

Now pass #14 passing pellets through #18 and collect retains and passing separately.

PACKAGING

Transfer the sifted Fenofebric acid DR pellets (#14-#18) to HDPE containers lined with virgin double polyethylene bags

STORAGE

Transfer the HDPE container into finished good store and store below 25°c.

FILLING

Filling of pellets into capsules.

EVALUATION OF CAPSULES

Description

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Randomly selected capsules from each formulation were examined for the description.

Capsule size:-'0'

Red colour cap with blue colour body, with white colo pellets.

Weight variation [9-10]

Twenty capsules are randomly selected from each formulation and weigh individually to check for weight variation. The following percentage deviation in weight variation according to USP is allowed.

Note: Capsule Size: '0'

Target Fill weight of pellets: 465.50 ±5%

Empty capsule shell Weight: 96 ±3 mg

Average weight of filled capsule: 561.50 mg± 5% %

Table No.20: Standard value of weight variation of capsule

Average weight of capsules	**Percentage weight variation (%)**
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

As our target weight of pellets to be filled in a capsule is about to 465.50 mg, hence a maximum deviation of ±5 % from the average capsule weight was allowed.

Moisture content

About 5g of pellets are taken and tested for moisture content on a Krlfisher titration. The drying is completed, if measured moisture content is NMT 5%.

Lock strength

It was tested by using Vernier calipers. Specification is 21.4±0.4mm

Uniformity of drug content and Assay

To assure the consistency of the dosage units, each unit in a batch should have a drug substance content within a narrow range about the label claim. Dosage units are known as dosage forms containing a single dose of drug substance in each unit. The term "uniformity of dosage unit" is also known as the degree of uniformity in the amount of the drug substance among dosage units [38].

Uniformity of drug content is established by analytical development department of Ra chem. Parma Ltd.

Uniformity of drug content is determined using UV-VIS Spectrophotometer. The procedure for preparation of standard and sample is as per USP monograph.

Calculations

$$\text{Mg/capsule} = \frac{\text{Sample abs.} \times \text{Std. weight (mg)} \times 1\times 100 \times 100 \times \text{Avg. wt. (gm)} \times \text{std potency}}{\text{Standard abs} \times 100 \times 100 \times \text{Sample weight (gm)} \times 1\times 100}$$

$$\text{Assay (\%)} = \frac{\text{Mg/capsule}}{\text{Label claim}} \times 100$$

Specification for Assay

Fenofibric acid DR capsule contains Not less than 95.0% and not more than 105.0%.

Dissolution

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Following procedure was employed throughout the study to determine the *in vitro* dissolution rate for all formulations.

STABILITY STUDY [11-13]

Stability study of a drug product has been defined as the ability of a particular formulation, in a particular container, to remain within its physical, chemical, therapeutic and toxicological expected specifications.

The aim of stability testing is to provide data on how the quality of a drug substance or drug product differs with time under the influence of a change of environmental factors such as humidity, temperature, and light, and enables recommended conditions of storage, retest periods and shelf lifes to be published.

ICH specifies the length of study and storage conditions as follows -

Long term testing- 25°c ± 2 °C / 60 % RH ±5 % for 12 months

Accelerated testing -40°C ± 2 °C / 75 % RH ± 5 % for 6 months

In the present study, stability studies were done at 40 ±2 °C/ 75 ± 5 % RH, 30 ± 2 °C/ 75 ± 5 % RH and 25 ± 2 °C/ 60 ± 5 % RH for a specific time period up to 90 days for developed formulation.

4. Result and Discussion

The present study was undertaken to formulate Fenofibric acid DR pellets pellets present in the capsule. The study involves preformulation studies of drug and excipients, formulation and processing development along with evaluation of capsules and pellets made with the optimized formulation. Finally delayed release capsules were evaluated by invitro method.

Results and discussion of the above studies are presented below;

Results of preformulation studies

Physical Evaluation Choline fenofibrate

Table No. 1: *Characteristics of Choline Fenofibrate*

Characteristics	**Result**
Physical appearance	white to off white crystalline powder
Solubility	Soluble in water and slightly soluble in Methanol
Bulk density	0.23 gm/ml
Tap density	0.26 gm/ml
Compressibility index	13%
Hausner' ratio	1.13
Melting point	79 -83°C
Angle of repose	44°

The characteristics of choline fenofibrate and other derived properties evaluated for all the formulations are proved to be within the limits .

Compatibility studies

40°C, 30°cAnd 25ºCtemperatures for initial, 7days, 15days,30days respectively there is no change in drug were observed.

Formulation studies

Formulation studies Fenofibric acid DR pellets

Formulation studies Fenofibric acid delayed release capsules is based on preformulation data of various excipients selected and their compilation was shown in the following Table.

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Table no.2:- *Formulas and their quantities as per percentage w/w*

S.No.	INGRADIENTS	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
	CORE							
1	Sugar Spheres (#25-#30)	35.36	28.08	26.46	26.65	24.64	26.54	26.54
	DRUG MIXTURE							
2	Choline fenofebrate	38.35	38.35	38.35	38.35	38.35	38.35	38.35
3	Plasdone k29/32	3	3	3	3	5	3	3
4	PEG 6000	0.3	0.3	0.3	0.3	0.3	0.3	0.3
5	Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5
6	Purified Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	ER COATING							
7	Ethocel N45	2.1	1.9	1.4	1.5	1.5	1.6	1.6
8	Pharma coat 606	0.16	0.4	0.5	0.2	0.2	0.2	0.2
9	PEG 6000	0.21	0.14	0.14	0.15	0.16	0.16	0.16
10	Magnesium stearate	0.64	0.64	0.64	0.64	0.64	0.64	0.64
11	IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
12	P. Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	ENTERIC COATING							
13	Eudragit L30 D55	18	24	26	26	26	26	26
14	Triethyl citrate	0.20	0.24	0.26	0.26	0.26	0.26	0.26
15	Talc	0.18	1.45	1.45	1.45	1.45	1.45	1.45
16	P. Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	TOTAL	100	100	100	100	100	100	100

Formulation Development : Trial-1(F1)

The following experiment were taken to prepare and evaluate Fenofibric acid DR capsules.

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Table No.3: Formulation (Trial 1)

S.No.	INGRADIENTS	F1
	CORE	
1	Sugar Spheres (#25-#30)	35.36
	DRUG MIXTURE	
2	Choline fenofibrate	38.35
3	Plasdone k29/32	3
4	PEG 6000	0.3
5	Talc	1.5
6	Purified Water	Q.S
	ER COATING	
7	Ethocel N45	2.1
8	Pharma coat 606	0.16
9	PEG 6000	0.21
10	Magnesium stearate	0.64
11	IPA	Q.S
12	P. Water	Q.S
	ENTERIC COATING	
13	Eudragit L30 D55	18
14	Triethyl citrate	0.20
15	Talc	0.18
16	P. Water	Q.S

Chemical parameters:

Dissolution profile

(Condition: 0.05M Sodium phosphate buffer pH3.5, 500ml, 50rpm

Table No. 4:- Dissolution result in acidic stage

Time	Specification	%Drug release
2hrs	NMT 10%	14

(Conditions: pH 6.8 Phosphate buffer, 900ml., 50rpm and Apparatus USP-1)

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Table No.5: Dissolution result in buffer stage

Time	Specification	%Drug release
30 min.	15-40%	10.3
2hrs	NMT 50%	37
4hrs	NMT 75%	75.5

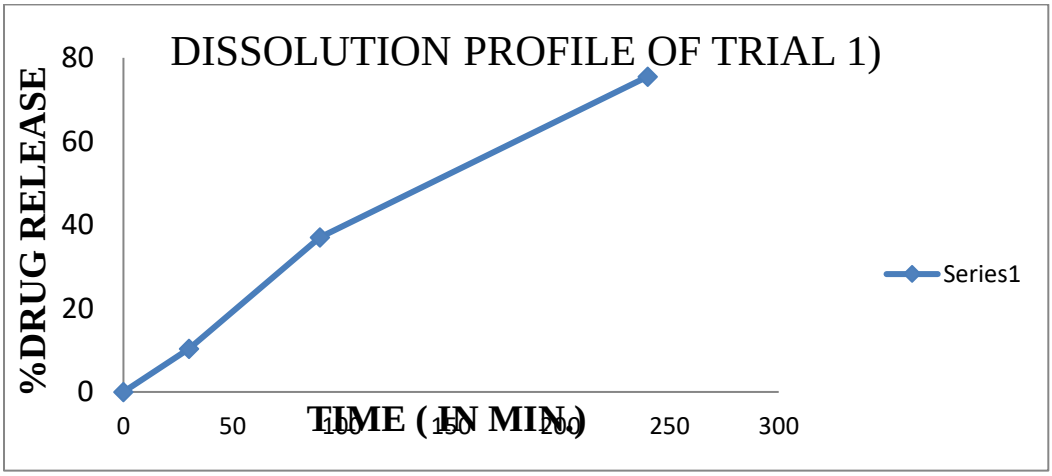

Figure no. 5 Dissolution profile of Trial 1

Conclusion:

Drug release at 2hr, in acidic media found to be faster and 30 min., 90min., 240min. in buffer stage found to be retarding . over all dissolution profile not found to be match the specification.

Formulation Development: Trial-2(F2)

Table No.6 :- Formulation (Trial 2)

S.No.	INGRADIENTS	F2
	CORE	
1	Sugar Spheres (#25-#30)	28.08
	DRUG MIXTURE	
2	Choline fenofibrate	38.35
3	Plasdone k29/32	3
4	PEG 6000	0.3
5	Talc	1.5
6	Purified Water	Q.S

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	ER COATING	
7	Ethocel N45	1.9
8	Pharma coat 606	0.16
z9	PEG 6000	0.21
10	Magnesium stearate	0.64
11	IPA	Q.S
12	P. Water	Q.S
	ENTERIC COATING	
13	Eudragit L30 D55	24
14	Triethyl citrate	0.24
15	Talc	1.45
16	P. Water	Q.S

Chemical parameters:

Dissolution profile

(Condition: 0.05M Sodium phosphate buffer pH3.5, 500ml, 50rpm)

Table No.7:- Dissolution result in acidic stage

Time	**Specification**	**%Drug release**
2hrs	NMT 10%	0.6

(Conditions: pH 6.8 Phosphate buffer, 900ml., 50rpm and Apparatus USP-1)

Table No. 8:- *Dissolution result in buffer stage*

Time	**Specification**	**%Drug release**
30 min.	15-40%	15
2hrs	NMT 50%	53.6
4hrs	NMT 75%	91.7

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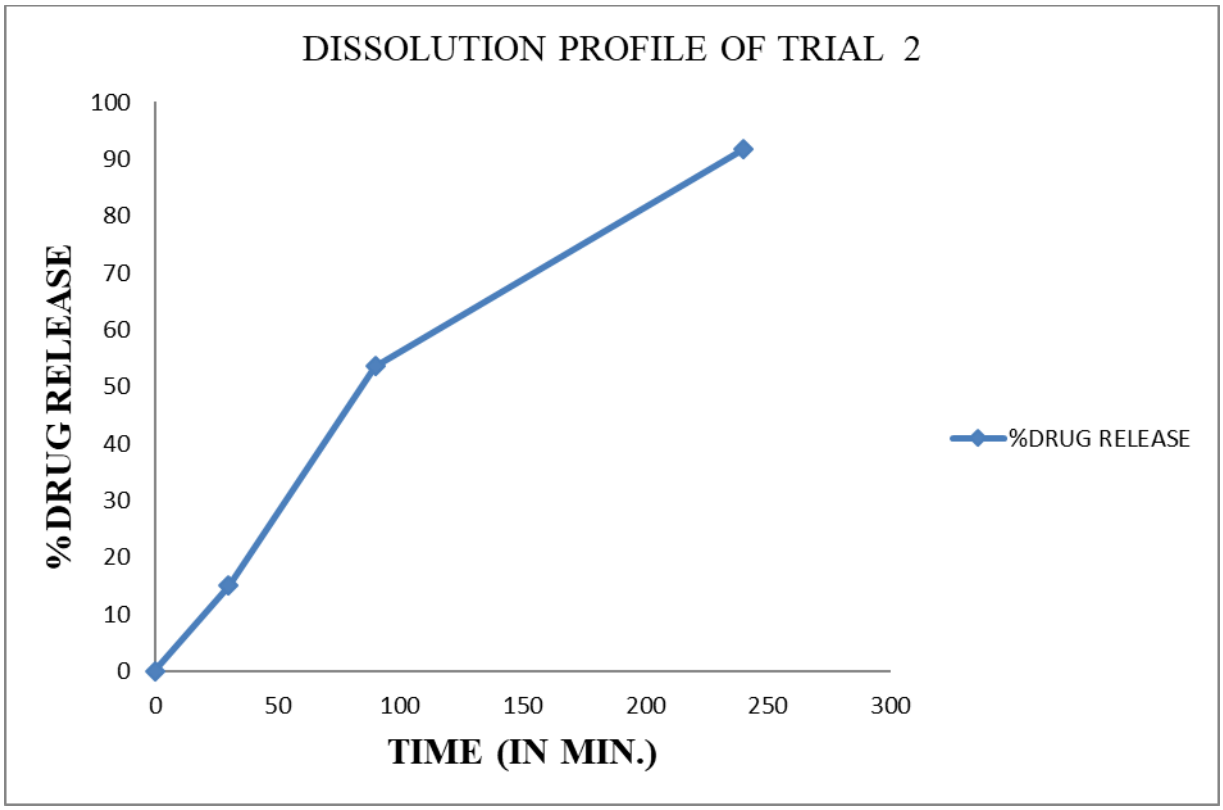
Figure No. 6: Dissolution profile of Trial 2



Conclusion:

Dissolution profile at 2hr. in acid stage found to be match the specification, where as in buffer stage the drug release increased than comparison of Trial 1. Over all dissolution drug profile match the specification. However release found to be lowered of specification.

Formulation Development: Trial-3(F3)

Table No.8: *Formulation (Trial 3)*

S.No.	INGRADIENTS	F3
	CORE	
1	Sugar Spheres (#25-#30)	26.46
	DRUG MIXTURE	
2	Choline fenofibrate	38.35
3	Plasdone k29/32	3
4	PEG 6000	0.3
5	Talc	1.5
6	Purified Water	Q.S

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	ER COATING	
7	Ethocel N45	1.4
8	Pharma coat 606	0.5
9	PEG 6000	0.14
10	Magnesium stearate	0.64
11	IPA	Q.S
12	P. Water	Q.S
	ENTERIC COATING	
13	Eudragit L30 D55	26
14	Triethyl citrate	0.26
15	Talc	1.45
16	P. Water	Q.S

Chemical parameters:

Dissolution profile

(Condition: 0.05M Sodium phosphate buffer pH3.5, 500ml, 50rpm

Table No. 9: *Dissolution result in acidic stage*

Time	**Specification**	**%Drug release**
2hrs	NMT 10%	0.6

(Conditions: pH 6.8 Phosphate buffer, 900ml., 50rpm and Apparatus USP-1)

Table No. 10: *Dissolution result in buffer stage*

Time	**Specification**	**%Drug release**
30 min.	15-40%	55.7
2hrs	NMT 50%	88.3
4hrs	NMT 75%	99.5

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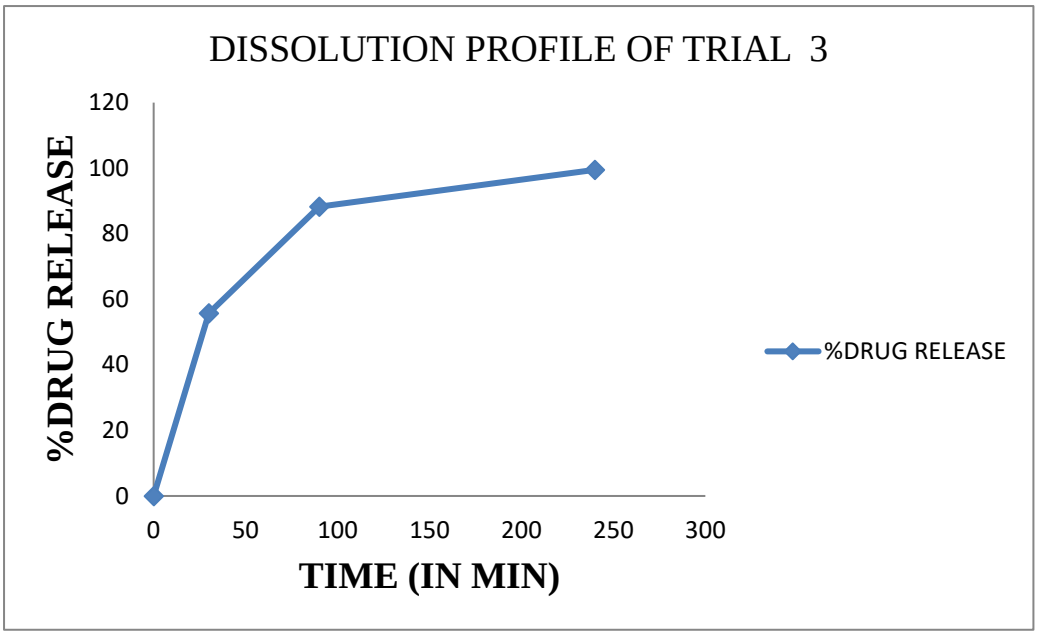

Figure no. 7: Dissolution profile of Trial 3

Conclusion:-

Dissolution profile at 2hrs, in acid stage found to be match the specification and drug release in buffer stage is faster than the Trial 2 but , drug release at 30 min. did not comply with the specification.

Formulation Development : Trial-4(F4)

Table No.11 : Formulation (Trial 4*)*

S.No.	**INGRADIENTS**	**F4**
	CORE	
1	Sugar Spheres (#25-#30)	26.65
	DRUG MIXTURE	
2	Choline fenofibrate	38.35
3	Plasdone k29/32	3
4	PEG 6000	0.3
5	Talc	1.5
6	Purified Water	Q.S
	ER COATING	
7	Ethocel N45	1.5
8	Pharma coat 606	0.2

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9	PEG 6000	0.15
10	Magnesium stearate	0.64
11	IPA	Q.S
12	P. Water	Q.S
	ENTERIC COATING	
13	Eudragit L30 D55	26
14	Triethyl citrate	0.26
15	Talc	1.45
16	P. Water	Q.S

Chemical parameters:

Dissolution profile

(Condition: 0.05M Sodium phosphate buffer pH3.5, 500ml, 50rpm

Table No. 12: Dissolution result in acidic stage

Time	**Specification**	**%Drug release**
2hrs	NMT 10%	1.5

(Conditions: pH 6.8 Phosphate buffer, 900ml., 50rpm and Apparatus USP-1)

Table No. 13: Dissolution result in buffer stage

Time	**Specification**	**%Drug release**
30 min.	15-40%	40.3
2hrs	NMT 50%	79.7
4hrs	NMT 75%	97

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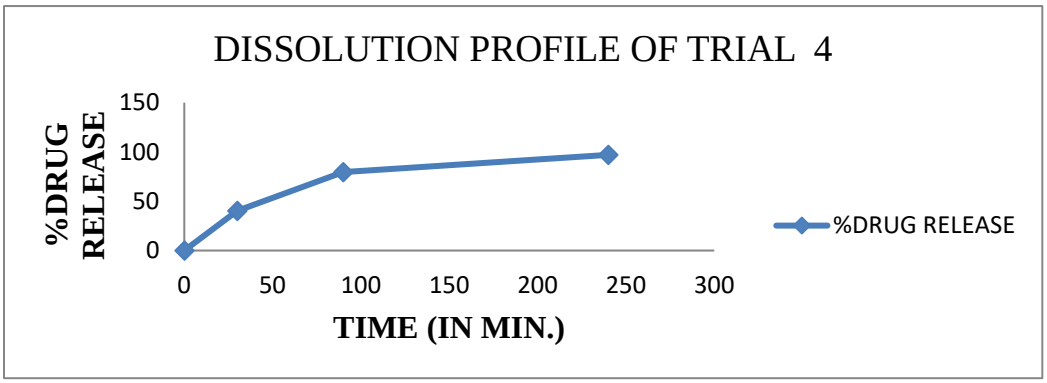

Figure No.8: Dissolution profile of Trial 4

Conclusion:-

Dissolution profile at 2hrs in acid stage found to be matching the specification. Drug release in buffer stage retarded compare to to the Trial 3. However the drug release at 30min. in buffer stage did not match the specification.

Formulation Development: Trial-5(F5)

Table No.14 : Formulation (Trial 5)

S.No.	INGRADIENTS	F5
	CORE	
1	Sugar Spheres (#25-#30)	24.65
	DRUG MIXTURE	
2	Choline fenofibrate	38.35
3	Plasdone k29/32	5
4	PEG 6000	0.3
5	Talc	1.5
6	Purified Water	Q.S
	ER COATING	
7	Ethocel N45	1.5
8	Pharma coat 606	0.2
9	PEG 6000	0.16
10	Magnesium stearate	0.64
11	IPA	Q.S

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12	P. Water	Q.S
	ENTERIC COATING	
13	Eudragit L30 D55	26
14	Triethyl citrate	0.26
15	Talc	1.45
16	P. Water	Q.S

Chemical parameters:

Dissolution profile

(Condition: 0.05M Sodium phosphate buffer pH3.5, 500ml, 50rpm)

Table No. 9: Dissolution result in acidic stage

Time	**Specification**	**%Drug release**
2hrs	NMT 10%	2

(Conditions: pH 6.8 Phosphate buffer, 900ml., 50rpm and Apparatus USP-1)

Table No. 16: Dissolution result in buffer stage

Time	**Specification**	**%Drug release**
30 min.	15-40%	37
2hrs	NMT 50%	75
4hrs	NMT 75%	92

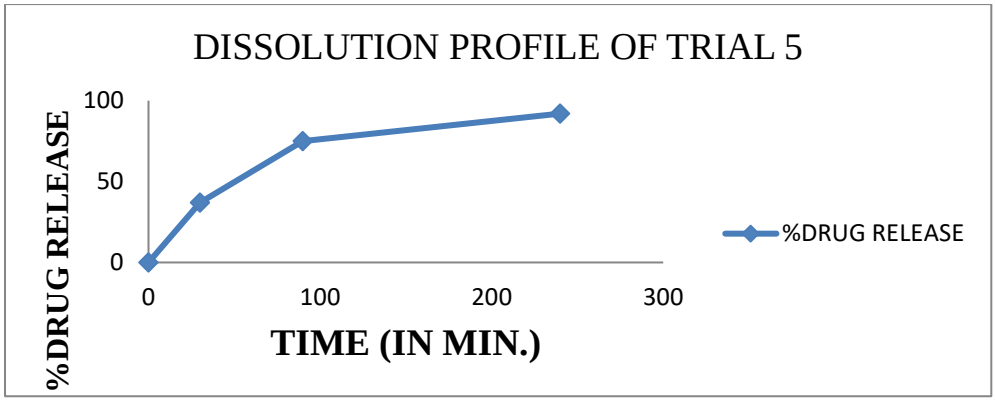

Figure No. 10: Dissolution profile of Trial 5

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Conclusion:

Acid stage was common as previous trial (Trial 4). Drug release in buffer stage retarded a little bit compare to Trial 4, and drug release was meted the specification. however need to retard the drug release at 30min. time part in buffer stage.

Formulation Development: Trial-6(F6)

Table No.17: Formulation (Trial 6)

S.No.	**INGRADIENTS**	**F6**
	CORE	
1	Sugar Spheres (#25-#30)	24.65
	DRUG MIXTURE	
2	Choline fenofibrate	38.35
3	Plasdone k29/32	3
4	PEG 6000	0.3
5	Talc	1.5
6	Purified Water	Q.S
	ER COATING	
7	Ethocel N45	1.6
8	Pharma coat 606	0.2
9	PEG 6000	0.16
10	Magnesium stearate	0.64
11	IPA	Q.S
12	P. Water	Q.S
	ENTERIC COATING	
13	Eudragit L30 D55	26
14	Triethyl citrate	0.26
15	Talc	1.45
16	P. Water	Q.S

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Chemical parameters:

Dissolution profile

(Condition: 0.05M Sodium phosphate buffer pH3.5, 500ml, 50rpm)

Table No. 11:- Dissolution result in acidic stage

Time	Specification	%Drug release
2hrs	NMT 10%	2.1

(Conditions: pH 6.8 Phosphate buffer, 900ml., 50rpm and Apparatus USP-1)

Table No. 19:- Dissolution result in buffer stage

Time	Specification	%Drug release
30 min.	15-40%	26.1
2hrs	NMT 50%	65.9
4hrs	NMT 75%	89.9

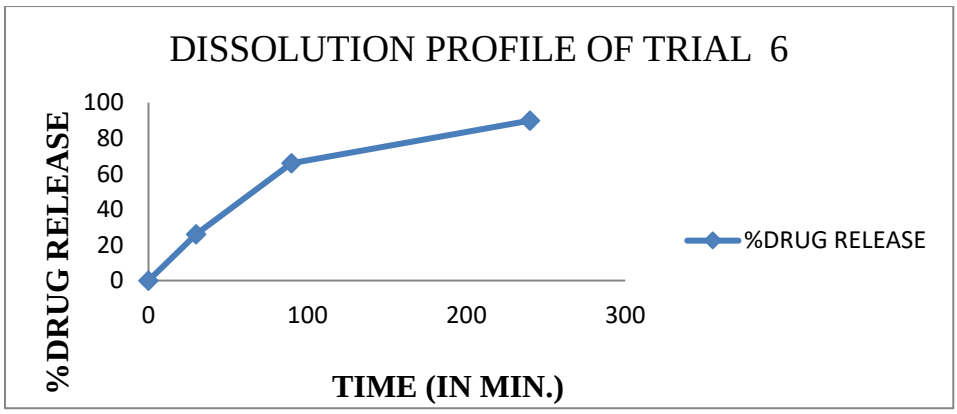

Figure no. 12: Dissolution profile of Trial 6

Conclusion:

Acid stage was common as previous trial (Trial 5). Drug release in buffer stage meeting the specification with F2>50. Hence proceeds for scale up batch (5Kg) with the prototype formula.

Formulation Development: Trial-7(F7)

Table No20: Formulation (Trial 7)

S.No.	INGRADIENTS	F7
	CORE	
1	Sugar Spheres	24.65

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	(#25-#30)	
	DRUG MIXTURE	
2	Choline fenofibrate	38.35
3	Plasdone k29/32	3
4	PEG 6000	0.3
5	Talc	1.5
6	Purified Water	Q.S
	ER COATING	
7	Ethocel N45	1.6
8	Pharma coat 606	0.2
9	PEG 6000	0.16
10	Magnesium stearate	0.64
11	IPA	Q.S
12	P. Water	Q.S
	ENTERIC COATING	
13	Eudragit L30 D55	26
14	Triethyl citrate	0.26
15	Talc	1.45
16	P. Water	Q.S

Chemical parameters:

Dissolution profile

(Condition: 0.05M Sodium phosphate buffer pH3.5, 500ml, 50rpm)

Table No 21: Dissolution result in acidic stage

Time	**Specification**	**%Drug release**
2hrs	NMT 10%	2.4

(Conditions: pH 6.8 Phosphate buffer, 900ml., 50rpm and Apparatus USP-1)

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Table No. 22: Dissolution result in buffer stage

Time	Specification	%Drug release
30 min.	15-40%	28
2hrs	NMT 50%	68
4hrs	NMT 75%	90

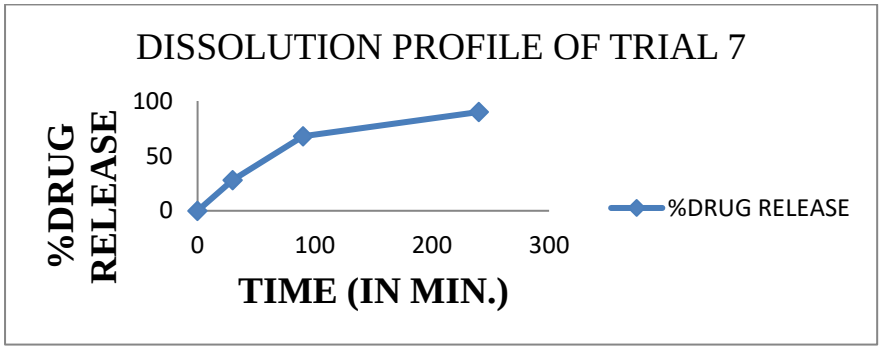

Figure No. 13: Dissolution profile of Trial 7

Conclusion:

Drug release profile found to be matched the drug release profile with F2>50. Hence proved the scalability with the manufacturing formula.

EVALUATION OF CAPSULE

Table No. 23: Evaluation of capsules of of all formulations

S. No.	Parameter	Innovator product	F1	F2	F3	F4	F5	F6	F7
1	Description	White to off white color pellets	As per required						
2	Weight variation in mg	464.00-466.00	466.20	464.80	466.78	465.39	466.20	465.40	465.80
3	Moisture content (NMT 5%)	3.4%	2%	2.1%	1.8%	2.5%	1.7%	2.29%	2.67%
4	Lock strength (in mm)	21.4±0.4mm	21.2	22.1	21.3	21.0	21.4	21.2	21.7
5	Assay in %	99.4%	100	99	100	101.2	98.5	101.4	100.4

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- *Description:* Randomly selected capsules from each formulation were examined.
- *Moisture content by KF*: The finished product was analyzed for moisture content estimation by KF test and found satisfactory results.
- *Weight Variation:* The variation in the weight of the capsules is within standard official limits.
- *Lock Length:* Lock Length of capsules was observed by Vernier Caliper. Lock Length of capsules does not show any measurable deviation
- *Drug Content Uniformity and Assay*: The Pelletization process ensures the uniform coating of drug over inert sugar spheres. It is also proved by individual capsule, which was within the specified limits of assay.

IN VITRO DISSOLUTION COMPARISON OF DEVELOPED BATCHES WITH INNOVATOR

Table 24: Dissolution Profile of innovator & different development batches

Time Points	Cumulative % Drug release							
	Innovator	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
30	22.5	10.3	15	55.7	40.3	37	26.1	28
90	61	37	53.6	88.3	79.7	75	65.9	68
240	99.7	75.5	91.7	99.5	97	92	89.9	90
Similarity factor (F_2)							61.29	58.48

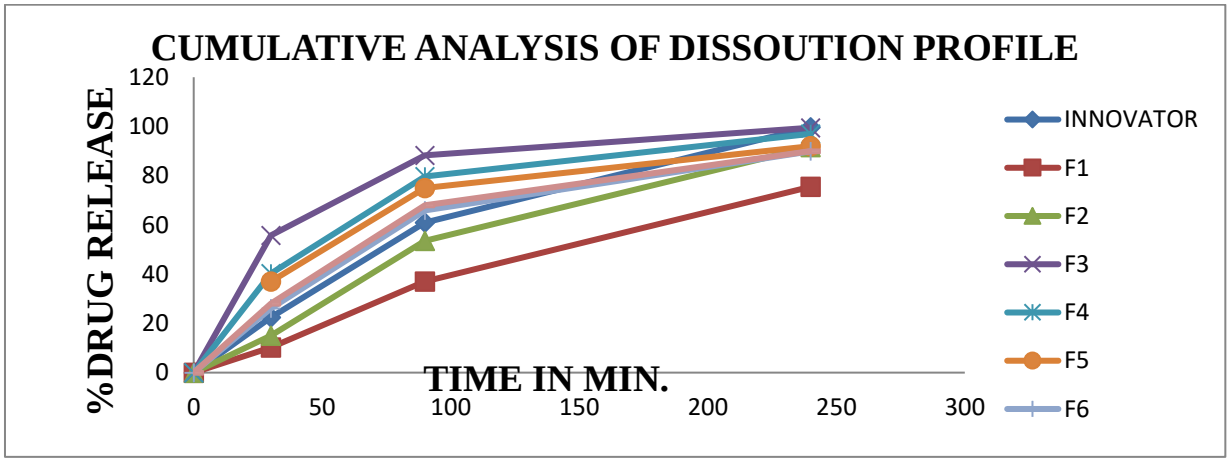

Figure No.14: Dissolution profile of all Trials

SELECTION OF OPTIMIZED FORMULATION IN COMPARISON WITH INNOVATOR

During product development, Trial 6 showed promising invitro dissolution profile similar in comparision to innovator. After getting dissolution profile matching with innovator product, an reproducible batch Trial 7 was planned.

This developed optimized batch was retained its similar behavior during development. The invitro dissolution profile was compared with innovator, which similar release profile with similarity factor value near to 60.

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As the optimized formulation was invitro equivalent with innovator, it was then further subjected to various stress studies and stability study.

TableNo.25: Dissolution Profile of innovator & finalized development batches

Time (min.)	Innovator	F6	F7
30	22.5	26.1	28
90	61	65.9	68
240	99.7	89.9	90

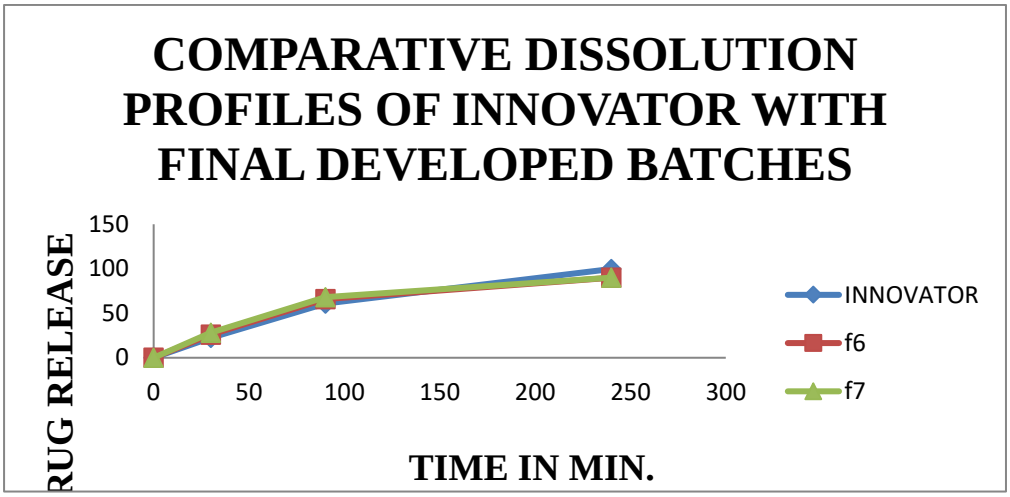

Figure no.15: Dissolution profile of Innovator with final developed batches

- *In vitro dissolution comparison of developed batches with innovator:*

The Fenofibric acid Delayed release Capsules were subjected to in vitro drug release studies in pH 6.8 Phosphate buffer media up to 240min.. The drug release studies carried out in dissolution test apparatus (USP-I I, peddle) using 900 ml of dissolution medium, maintained at 37°C ± 0.5°C. The dissolution profiles and graphs were represented in the *Table 46 and Figure 26* respectively.

STABILITY STUDY

Table No26: stability dissolution profile of optimized batch Trial 7(F7)

Time point	Innovator	Specification	Accelerated stability 40°C±5%/75%RH±5%				
			Initial	1M	2M	3M	6M
30min.	22.5	30min(15-40%)	28	26	24	29	27.5
90min.	61	90min.(NLT 50%)	68	67	67	69	69
240min.	99.7	240min.(NLT 75%)	90	90	89	89	86

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The stability studies of optimized formulation were done for 6 months by packing in HDPE container in stability chamber in accordance with ICH guidelines.

The result were given in *Table 47* for 6 months show in accelerated stability conditions. All parameters of formulation including physical parameters, impurity profile, assay and dissolution profile *(Table 47)* were within specification limit. So it indicates optimized formulation was stable.

5. Conclusion

The main emphasis of this research work is to develop a delayed release Fenofibric acid capsule which released the drug as a delayed manner up to four hours(240 min.). TriLipix, an innovator product of delayed release drug delivery of Fenofibric acid DR capsule was considered as reference standard for the formulation and process development of bioequivalent Fenofibric acid DR capsule. The bioequivalent product of Fenofibric acid DR capsule were developed by using novel pharmaceutical formulation design approach i.e. Pelletization by Wurster coating using release controlling polymers like ethyl cellulose. Optimized formulation (Batch number: F7) Fenofibric acid DR capsule was developed by employing Pelletization technique over inert sugar spheres by various layer coating which is composed of Choline fenofibrate, Plasdone K29/32, PEG 6000, Ethyl cellulose N45 cps, HPMC 6cps, Magnesium stearate, Eudragit L30d-55 , Tri ethyl citrate, Talc were found to be bioequivalent with the innovator product (TriLipix). For scale up and pharmaceutical commercialization of the optimized product various scientific approaches such as evaluation study and stability study were expounded.

The optimized formulation batch number F 7 of Fenofibric acid DR capsule developed successfully, not only satisfies the process variability and quality control test but also found to bioequivalent with the innovator product (TriLipix), which can be easily scaled up for pharmaceutical commercialization.

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