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FORMULATION AND EVALUATION OF DELAYED-RELEASE TABLETS OF PALIPERIDONE

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ABSTRACT: Paliperidone is a well-known dopamine antagonist of the atypical antipsychotic class. The present research work was an attempt to formulate and evaluate paliperidone delayed-release tablets. A combination of hydroxypropyl methylcellulose (HPMC K100M) and polyvinyl acetate phthalate, cellulose acetate phthalate were used as polymers. The tablets were prepared by direct compression method. 12 formulations were prepared by changing the ratios of the drug and polymer to study the effect of variable concentrations of polymers and characteristics of the tablets. The prepared tablets were evaluated by different parameters such as Thickness, weight variation, hardness, content uniformity. The tablets were also evaluated for in vitro drug release in 0.1N HCl for 12 h in USP Type II dissolution apparatus. Among all the formulations (F-I to F-XII) prepared, batch F-12 gave good results of Paliperidone when compared to other formulations. Hence, formulation F12 was found to be equivalent to a marketed product with good bioavailability properties. It also showed no significant change in physical appearance and drug content.

Keywords: Dopamine antagonist, Atypical antipsychotic class, HPMC K100M, Cellulose, Acetate phthalate, Polyvinyl acetate phthalate, FTIR studies

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INTRODUCTION: The oral administration of drugs represents the most common way of drug application due to its high patient acceptance. The immediate release of drug delivery systems is particularly used to produce fast therapeutic drug plasma levels. This results in reduction or loss in drug effectiveness or also increased the incidence of side effects. Modified release drug delivery systems include the systems with pH dependent, extended, delayed, or pulsed drug release [1-5].

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Sustained, extended or prolonged release drug delivery devices, by contrast, are delayed release dosage forms have to be distinguished from the ones mentioned as they exhibit a more or less pronounced lag time before drug release [6].

A delayed-release dosage form is designed to release the drug at a time other than promptly after administration. Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location. To overcome the disadvantages of conventional release dosage forms, the formulations can be modified to provide either delayed release or extended release of drugs. A delayed-release dosage form is designed to release the drug at a time other than promptly after administration. Dosage forms can be designed to modify the

release of the drug over a given time or after the dosage form reaches the required location. Delayed Release oral dosage forms can control where the drug is released, *e.g.*, when the dosage form reaches the small intestine (enteric-coated dosage forms) or the colon (colon-specific dosage forms). Delayed Release systems release a bolus of the drug after a predetermined time in a predetermined location, *i.e.*, they do not release the drug immediately after ingestion, for example, enteric-coated tablets, pulsatile-release capsules.

Paliperidone is the primary active metabolite of the older antipsychotic risperidone. While its specific mechanism of action is unknown, it is believed paliperidone and risperidone act *via* similar, if not identical, pathways. Paliperidone has antagonist effect at α_1 and α_2 adrenergic receptors and H_1 histamine receptors. It does not bind to muscarinic acetylcholine receptors. Also, it binds with dopamine and serotonin receptors. Paliperidone has more affinity D4 receptors than risperidone [7-14].

MATERIALS AND METHODS:

TABLE 1: LIST OF MATERIALS

S. no.	Material Name	Monograph Ref.	Functional Category
1	Paliperidone	IH	Active
2	Microcrystalline cellulose	USP	Diluent
3	Sodium starch glycolate	NF	Disintegrant
4	Sodium carbonate anhydrous	USP	Stabilizer
	Lubrication		
5	Sodium stearyl fumarate	NF	Lubricant
	Seal coating		
6	Ethyl cellulose	NF	Seal coat former
7	Water insoluble polymer (Compound A)	NF	Channeling agent
8	Water soluble polymer (Compound B)	NF	Channeling agent
9	Dehydrated alcohol#	USP	Solvent
	Enteric coating		
10	HPMC K 100M	NF	Enteric polymer
11	Diacetylated monoglycerides	USP	Plasticizer
12	Pigment blend –Yellow powder	IH	Colorant
13	Dehydrated alcohol#	USP	Solvent
14	Purified Water #	USP	Solvent

TABLE 2: LIST OF TYPES OF EQUIPMENT

S. no.	Equipment	Manufacturer	Model No.
1	Electronic Balance	Shimadzu	AUX220
2	Sieves	United Engineering Ltd.	ASL00
3	Tab density Tester	Electrolab	ETD-020
4	Electromagnetic Sieve Shaker	Electropharma	EMS- 8
5	Double Cone bin	United Eng.	Double Cone
6	Laboratory Stirrer	Remi	RQT-124A
7	Automatic Coating System	Nano machines	Neocota 5T
8	Rapid dryer	Retsch	TG-200
9	pH Meter	Thermo	Orion 2 Star
10	Dissolution test apparatus	Electro lab USP XXII	TDT-08L
11	Stability chambers	Thermo lab	Standard
12	Disintegration Tester	Electrolab	ED-2L
13	Hardness tester	Pharmatest	PTB-311E
14	Friabilator	Electrolab	EF-1W
15	Tablet Compression machine-16 Station	Cadmech Machinery co. Pvt.Ltd	CM D3-16
16	Induction Cap Sealer	Electronic Devices	Sigma Jr.(CSP 300)
17	Peristaltic pump	Electrolab	PP-50V
18	Homogenizer	Chamunda pharma machinery pvt. Ltd.	CPM-HO
19	Dehumidifier	Bry air Asia Pvt. Ltd.	FFB-300

Preformulation Study: Preformulation testing was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It was the first step in the rational development of dosage forms [15].

Objective / Purpose of Preformulation Study: [16-19] Pre-formulation studies on active pharmaceutical ingredients (API), inactive ingredients (Excipients), and their combinations were carried out to serve the following purposes:

- ✓ To finalize specifications of active pharmaceutical ingredients (API)
- ✓ To study the compatibility between active and inactive ingredient
- ✓ Characterization of the reference product.

Scope: The use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious, and stable product.

Class: The preformulation study can be divided into two subclasses:

1. API characterization,
2. Compatibility study

Active Pharmaceutical Ingredient (API) Characterization:

Organoleptic Evaluation: These are preliminary characteristics of any substance which is useful in the identification of specific material. Following physical properties of API were studied.

- Color
- Odour
- Taste

Parameter	Paliperidone
Organoleptic Evaluation	White to slightly yellowish-white solid
Solubility Analysis	Very soluble in water, Very soluble in methanol, Freely soluble in ethanol, chloroform, and ethyl acetate, insoluble in ether and n-hexane.

Loss on Drying: 0.5g of a sample of Paliperidone was accurately weighed, and the powder was kept in a moisture balance apparatus for 5min. at 106ºCand the moisture content was calculated.

Bulk Density: Bulk density was determined by pouring 15.3 gm of the sample (paliperidone) through a glass funnel into 50ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density = Weight of sample in gm / Volume occupied by the sample

Tapped Density: Tapped density was determined by using Electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%. A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted, and taped density is calculated using the following formula.

Compressibility Index and Hausner ratio: In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.

Carr's index = Tapped density – Bulk density / Tapped density × 100

Hauser's ratio = Tapped density / Bulk density

TABLE 3: RELATION OF FLOW PROPERTY WITH HR & CI

Compressibility Index (%)	Flow Character	Hauser's Ratio
<10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Calculation of BD, TD, CI, & HR of API:

For Paliperidone:

The initial weight of API taken = 14.6 gm
The initial volume of API taken = 28 ml
Volume after 500 tap = 20 ml
Volume after 750 tap = 19 ml

TABLE 4: CALCULATION OF BD, TD, CI, & HR OF API

Parameter	Value	Unit
LOD	1.0	% w/w
BD	0.5214	gm/ml
TD	0.7684	gm/ml
CI	32.140	%
HR	01.473	----

The Angle of Repose: (USP29-NF-24): The angle of repose has been used to characterize the flow properties of solids. The angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between the surface of the pile of powder or granules and the horizontal plane.

$$\text{Tan } \theta = h / r \text{ or } \theta = \text{Tan}^{-1} h / r$$

Where, θ = angle of repose, h = height, r = radius.

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed. Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder.

TABLE 5: FLOW PROPERTIES AND CORRESPONDING ANGLES OF REPOSE

Flow Property	The angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair - aid not needed	36–40
Passable - may hang up	41–45
Poor - must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Sieve Analysis: The procedure involves the Electromagnetic Sieve shaking of the sample through the series of successively arranged sieves (sieve no. - 20, 30, 40, 60, 80, and receiver), and weighing of the portion of the sample retained on each sieve and calculate percentage retained on each sieve.

Compatibility Studies: [20-24]

Drug-Excipient Compatibility Studies: The compatibility of drug and formulation components is important prerequisite before formulation. It is, therefore, necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of the product or any other unwanted effects on the formulation.

Procedure: The drug is mixed with excipients in a different ratio. These mixtures were kept in a 5 ml glass white colored vials and packed properly. These vials are exposed to 1) room temperature 2) 2-8 °C and 3) 40 °C / 75% RH. 15 gm of the blend is prepared, which is filled in 3 vials. Observations for physical appearance are made at zero weeks, 2 weeks, and 4week, the samples were withdrawn for analysis of the following parameter:

1. Moisture content
2. Assay
3. Related substance
4. Appearance.

Formulation Development: [25-31]

Formulation Development of Paliperidone Enteric Coated Tablets: Based on Preformulation data, various excipients were selected, and their compilation was shown in the below table.

TABLE 6A: COMPILATION OF PALIPERIDONE ENTERIC COATED TABLETS

S. no.	Ingredients	mg/tab					
		F 1	F 2	F 3	F 4	F 5	F 6
1	Paliperidone sodium (API)	20	20	20	20	20	20
2	Microcrystalline cellulose (Diluent)	52.20	52.20	66.30	66.30	40.30	40.30
3	Sodium carbonate anhydrous (Stabilizer)	10	10	10	10	10	10
4	Sodium starch glycolate (Disintigrent)	33.80	33.80	23	23	44	44
5	Hydroxy propyl cellulose (Binder)	2.50	2.50	-	-	5.00	5.00
6	Sodium steryl fumarate (Lubricant)	2.70	2.70	2.70	2.70	2.70	2.70
	Seal Coating Stage						
7	Ethyl cellulose	1.62	2.16	2.7	4.05	2.7	4.05
8	Water insoluble polymer (compound A)	-	-	2.7	4.05	2.7	4.05
9	Water soluble polymer (compound B)	6.48	8.64	-	-	-	-
10	Ethanol	q.s	q.s	q.s	q.s	q.s	q.s
	Enteric coating stage						
11	HPMC K 100 M	17.17	17.50	16.85	17.17	16.85	17.17
12	Myvacet	1.72	1.75	1.69	1.72	1.69	1.72
13	Pigment blend Yellow	2.58	2.62	2.52	2.58	2.52	2.58

TABLE 6B: COMPILATION OF PALIPERIDONE ENTERIC COATED TABLETS

S. no.	Ingredients	mg/tab					
		F 1	F 2	F 3	F 4	F 5	F 6
1	Paliperidone	20	20	20	20	20	20
2	Microcrstalline cellulose	60.30	60.30	52.80	52.80	45.30	45.30
3	Sodium Carbonate Anhydrous	10	10	10	10	10	10
4	Sodium starch glycolate	24	24	34	34	44	44
5	Hydroxy propyl cellulose	5.00	5.00	2.50	2.50	-	-
6	Sodium starch Fumarate	2.70	2.70	2.70	2.70	2.70	2.70
	Seal Coating Stage						
7	Ethyl Cellulose	2.7	4.05	2.7	4.05	2.7	4.05
8	Water Insoluble Polymer (Compound A)	2.7	4.05	2.7	4.05	2.7	4.05
9	Water soluble polymer (compound B)	-	-	-	-	-	-
10	Ethanol	q.s	q.s	q.s	q.s	q.s	q.s
	Enteric coating stage						
11	HPMC K 100M	16.85	17.17	16.85	17.17	16.85	17.17
12	Myvacet (emulsifier lubricant anti foaming agent)	1.69	1.72	1.69	1.72	1.69	1.72
13	Pigment blend Yellow (colouring agent refinishing coating)	2.52	2.58	2.52	2.58	2.52	2.58
14	Ethanol	q.s	q.s	q.s	q.s	q.s	q.s

In the preparation of enteric coating dispersion the ratio of ethanol: purified water used is 80:20.The strength of both seal coating and enteric coatings is 10% w/w.

Formulation Batches:

F1: In the first trial F1, 20 mg of API, 10 mg of stabilizer, 52.20 mg of diluent, 33.80 mg of disintegrant, 2.50 mg of HPC, 2.7 mg of lubricant was used, and the blend was compressed into tablets. On that seal coating was given by using 20:80 of ethyl cellulose: water-soluble compound (compound C) up to a weight build-up of 6%w/w and on that 15% w/w of the enteric coating was given.

F2: In formulation F2, the core is same as that of F1, and the seal coating material is also same but the seal coat is given up to weight build-up of 8%w/w and on that 15% w/w of the enteric coating was given.

F3: In formulation F3, then amounts of API, stabilizer, lubricant are same but the amount of disintegrant was decreased from 30+ to 20+, and HPC was removed from the formula and those are compensated by increasing the amount of diluent. The seal coat was given up to a weight build-up of 4% w/w using 50:50 of ethyl cellulose: water insoluble polymer and on that 15%w/w of the enteric coating was given.

F4: In formulation F4 the core is same as that of F3 and the composition of seal coating is also same but the seal coating is given up to a weight build-up of 6%w/w and on that 15%w/w of the enteric coating was given.

F5: In formulation F5, the the amounts of API, stabilizer, lubricant are the same but the amount of disintegrant was increased to 40+ and also 5.0 mg/unit of HPC was added, and these amounts were compensated by taking less amount of diluent the seal coat was given up to a weight build-up of 4% w/w using 50:50 of ethyl cellulose: water insoluble polymer and on that 15%w/w of enteric coating was given.

F6: In formulation F6 the core is same as that of F5 and the composition of seal coating is also same but the seal coating is given up to a weight build-up of 6% w/w and on that 15% w/w of the enteric coating was given.

F7: In formulation F7, the amounts of API, stabilizer, lubricant are same but the amount of disintegrant was decreased from 40+ to 20+ and 5.0 mg/unit of HPC was used, and the decrease in weight was compensated by an increasing amount of diluent. The seal coat was given up to a weight build-up of 4%w/w using 50:50 of Ethylcellulose: Water insoluble polymer and on that 15%w/w of the enteric coating was given

F8: In formulation F8 the core is same as that of F7 and the composition of seal coating is also same but the seal coating is given up to a weight build-up of 6% w/w and on that 15% w/w of the enteric coating was given.

F9: In formulation F9, then amounts of API, stabilizer, lubricant are same, but the amount of disintegrant used is 30+ mg/unit, and the amount of HPC was decreased to 2.5 mg/unit, and the weight was compensated by increasing amount of diluent.

The seal coat was given up to a weight build-up of 4% w/w using 50:50 of ethyl cellulose: water insoluble polymer and on that seal coating 15% w/w of the enteric coating was given.

F10: In formulation F10 the core is same as that of F9 and the composition of seal coating is also same but the seal coating is given up to a weight build-up of 6%w/w, and on that seal coating 15%w/w of the enteric coating was given.

F11: In formulation F11, the amounts of API, stabilizer, lubricant are same, but the number of disintegrants used is 40+ mg/unit, and the HPC was removed from the formula, and the weight was compensated by diluent. The seal coat was given up to a weight build-up of 4% w/w using 50:50 of ethyl cellulose: water insoluble polymer and on that seal coating, 15% w/w of the enteric coating was given.

F12: In formulation F12 the core is same as that of F11 and the composition of seal coating is also same but the seal coating is given up to a weight build-up of 6%w/w, and on that seal coating, 15%w/w of the enteric coating was given.

Paliperidone Delayed - Release Tablets: Paliperidone delayed-release tablets were prepared by direct compression technique using different excipients as well as with varying concentrations of polymer proportions using HPMC Phthalate 55S as an enteric coating material.

Manufacturing Process: [31-34]

- Co-shift Paliperidone, sodium carbonate anhydrous, and Crospovidone through sieve # 30.
- Shift microcrystalline cellulose through sieve # 30.
- Shift the Step 1 and Step 2 materials through # 30 meshes.
- Load the step 3 materials into a blender and mix for 30 min.
- Shift sodium stearyl fumarate through sieve # 40 along with a portion of prelubricated blend.
- Load the step 5 material to the blender and mix for 5 min.
- Compress the lubricated blend of step no. 6 into tablets.
- Disperse ethyl cellulose in dehydrated ethanol under stirring to prepare a clear solution to add Water insoluble polymer and stir well.
- Divide the core tablets of step no. 7 into 2 equal lots and coat tablets in a coating machine with step no. 8 dispersion to achieve a target weight gain of 4.0 ± 0.5% w/w and 6.0 ± 0.5% w/w each.
- Warm the Seal-coated tablets in coating pan at 50°C ± 5°C for 20 -30 min.
- Disperse hydroxypropyl methylcellulose (HPMC K 100M) in a mixture of dehydrated ethanol and purified water (80:20) under stirring to prepare a clear solution.
- Add diacetylated monoglycerides to the step no. 11 solution.
- Prepare dispersion of pigment blend yellow with purified water using homogenizer and add to the step no. 12 solution and stir well.
- Coat the seal coated tablets of step no. 10 (4% w/w and 6% w/w) in a coating machine with step no. 13 dispersion to achieve a target weight gain of 10.0 ± 0.5% w/w.
- Warm the enteric-coated tablets in coating pan at 50°C ± 5°C for 20 -30 min.

Tooling: 7.50 mm round shaped, deep concave plain tooling with corresponding dies.

Tablet Compression Parameters: [34-35]

Weight of the tablet	150 mg
Hardness range	6-10 kP
Thickness range	4.4 ± 0.3 mm

There are various in process control parameters should be performed. They are

A) During Tablet Compression:

- ✓ Appearance
- ✓ Average weight
- ✓ Weight uniformity
- ✓ Hardness
- ✓ Thickness
- ✓ Disintegration time

B) During Film Coating:

- Appearance
- The average weight of film coated tablets
- Disintegration time

C) During Enteric Coating:

- Appearance
- The average weight of enteric coated tablets
- Acid resistance

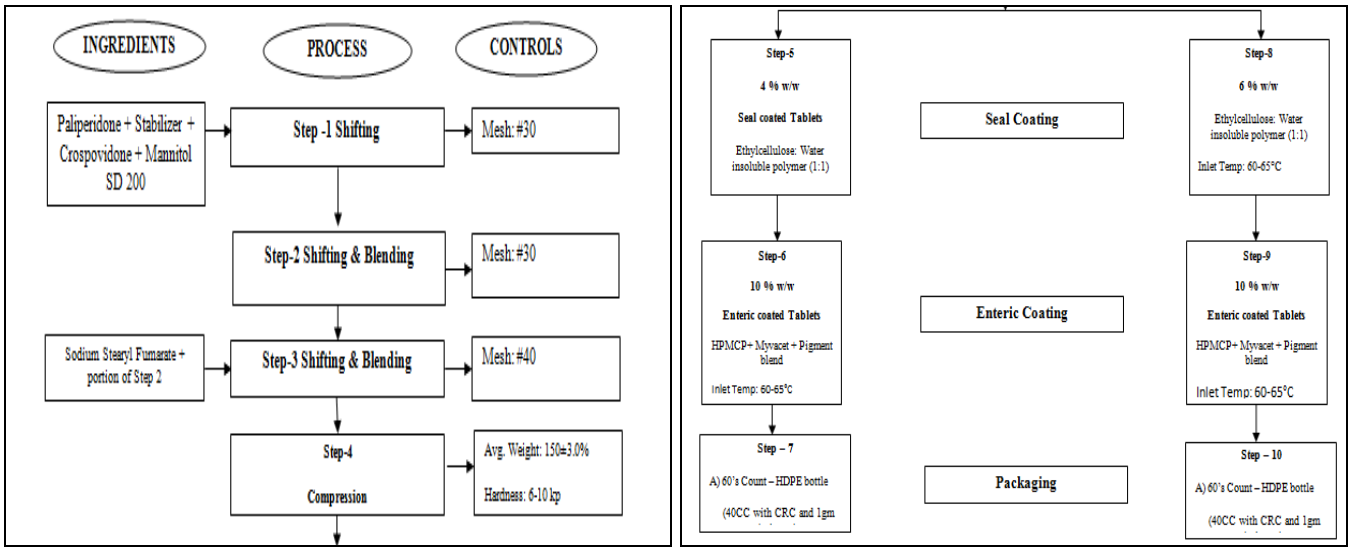

FIG. 1: MANUFACTURING FLOW CHART FOR DELAYED-RELEASE TABLETS

Paliperidone delayed-release tablets were prepared by dry granulation method. The process was displayed in the flow chart.

RESULTS: The present study was undertaken to formulate Paliperidone enteric coated tablets. The study involves preformulation studies of drug and excipients, formulation and processing development along with an evaluation of tablets made with the optimized formulation. Finally, delayed-release tablets were evaluated by *in vitro* methods. Results and discussion of the above studies are presented below:

TABLE 7: PREFORMULATION STUDIES

S. no.	Characteristics	Results
1	Organoleptic Evaluation	White to slightly yellowish-white solid
2	Solubility Analysis	Very soluble in water, Very soluble in methanol, Freely soluble in ethanol, chloroform, and ethyl acetate, insoluble in ether and n-hexane.
3	Bulk density	0.5214 gm/ml
4	Tap density	0.7684 gm/ml
5	Compressibility index	32.14 %
6	Hausner's ratio	01.473
7	Melting point	Because of the gradual degradation of Paliperidone during heating, the melting point cannot be determined.
8	Molecular weight	381.43

TABLE: 8 SIEVE ANALYSIS

Sieve no	Empty sieve (gm)	Sample sieve(gm)	Difference (gm)	% Retained	%Cumulative Retained
#20	321.4	321.4	0	0	0
#30	328.6	328.8	0.2	0.2	0.2
#40	299.0	300.0	1.0	1.0	1.2
#60	287.2	297.4	10.2	10.2	11.4
#100	255.0	275.0	20.0	20.0	31.4
#120	274.0	299.0	25.0	25.0	56.4
#200	270.0	303.2	33.2	33.2	89.6
Receiver	348.8	359.0	10.2	10.2	99.8

Weight of sample=100gm

TABLE 9: BLEND PROPERTIES OF DIFFERENT FORMULATIONS

Formulation	Blend Property				
	B.D (gm/ml)	T.D (gm/ml)	C.I (%)	H.R	Property
F1	0.710	0.873	19.714	1.251	fair
F2	0.710	0.873	19.714	1.251	fair
F3	0.483	0.681	29.03	1.409	passable
F4	0.483	0.681	29.03	1.409	passable
F5	0.461	0.714	35.385	1.548	fair
F6	0.461	0.714	35.385	1.548	fair
F7	0.500	0.600	23.22	1.295	passable
F8	0.500	0.600	23.22	1.295	passable
F9	0.541	0.691	21.62	1.276	passable
F10	0.541	0.691	21.62	1.276	passable
F11	0.501	0.605	17.19	1.207	fair
F12	0.501	0.605	17.19	1.207	fair

Through this sieve analysis, we came to know that as large quantity of powder was retained on sieve no. 200, which indicates the poor flow of the drug. Flow property and particle size are inversely proportional to each other as Paliperidone has fine grade of particles; it has poor flow.

Compatability Studies:

Drug-Excipient Compatibility Studies: The compatibility of drug and formulation components is important prerequisite before formulation. It is, therefore, necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of the product or any other unwanted effects on the formulation.

Procedure: The drug is mixed with excipients in a different ratio. These mixtures were kept in a 5 ml glass white colored vials and packed properly. These vials are exposed to 1) room temperature 2) 2-8 °C and 3) 40 °C / 75% RH. 15gm of the blend is prepared, which is filled in 3vials. Observations for physical appearance are made at zero weeks, 2 week, and 4 week, the samples were withdrawn for analysis of the following parameter:

1. Moisture content
2. Assay
3. Related substance
4. Appearance.

TABLE 10: RESULTS OF COMPATIBILITY STUDY

S. no.	Name of the Excipient	Ratio API: Expt	Initial Observation	Final observation 40 °C/75% RH		Conclusion
				2nd week	4th week	
1	API	---	White to yellowish white	White to yellowish white	White to yellowish white	Compatible
2	API+Stabilizer (Compound A)	1: 0.5	White fine powder	White fine powder	White fine powder	Compatible
3	API + HPC	1 : 1	off-white	off-white	off-white	Compatible
4	API+Water insoluble polymer	1: 1	white	White	White	Compatible
5	API+Mannitol SD-200	1 : 1	Off white	Off white	Off white	Compatible
6	API+Sodium stearyl fumarate	1 : 0.05	White	White	White	Compatible
7	API+Mg. Stearate	1 : 0.05	White	Colour change	Colour change	incompatible
8	API+Ethylcellulose	1: 2	White	White	White	Compatible
9	API+Crospovidone	1: 1	White	White	White	Compatible
1	API+HPMCP-55S	1:1	White	White	White	Compatible
11	API+Pigment blend (yellow)	1: 0.5	yellow	yellow	yellow	Compatible
12	API+Myvacet	1:0.5	White	White	White	Compatible

FTIR STUDY: The FT- IR Spectrum of pure Paliperidone drug was compared with that of the physical mixture of Paliperidone and HPMCK 100M. There was no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug and the polymers used in the tablets. The presence of peaks at the expected range confirms that the materials taken for the study are genuine.

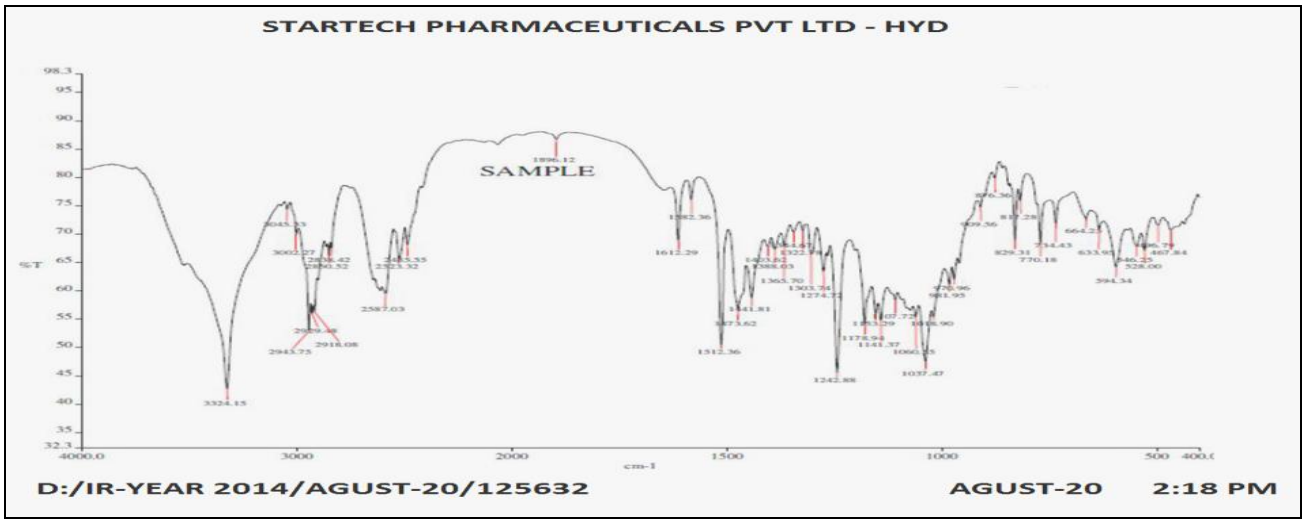

FIG. 2: IR SPECTRUM OF PALIPERIDONE WITH HPMC K100M AND MCC

Standard Calibration Curve of Paliperidone: Standard curve of Paliperidone was determined by plotting absorbance (nm) versus concentration (µg/ml) at 276nm. The results obtained are as follows: -

TABLE 11: STANDARD CURVE OF PALIPERIDONE

Conc. in µg	Absorbance at 276nm
0	0
2	0.119
4	0.245
6	0.367
8	0.488
10	0.603

The linear regression analysis was done on absorbance data points. A straight-line equation was generated to facilitate the calculation of the amount of drug. The equation is as follows.

$$(Y = mx+c)$$

Where, Y= Absorbance, m = slope, x = Concentration, c = Intercept.

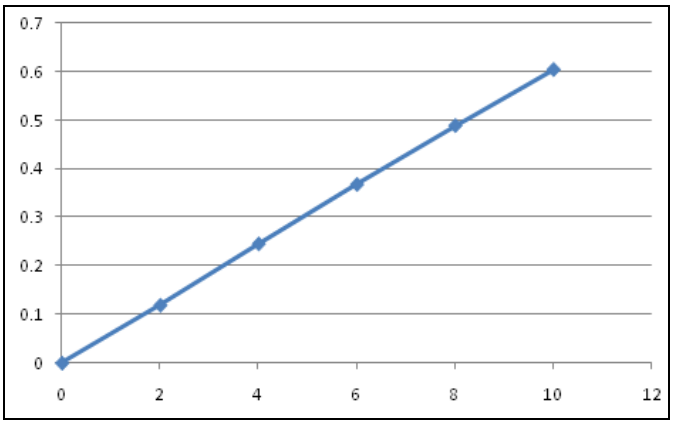

FIG. 3: STANDARD CURVE OF PALIPERIDONE

Evaluation Studies:

TABLE12: PHYSICAL EVALUATION (CORE TABLET)

S. no.	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
1	Weight variation	1.65	1.57	1.42	1.54	1.18	1.35	1.44	1.23	1.48	1.54	1.63	1.38
2	Hardness (kP)	7.8	7.4	7.2	7.4	7.1	6.8	7.4	7.8	7.5	7.8	8.0	7.6
3	Thickness (mm)	3.97	3.99	3.97	3.99	3.97	3.95	3.99	3.94	4.00	3.98	3.92	3.94
4	Friability %	0.45	0.52	0.21	0.18	0.38	0.57	0.46	0.48	0.55	0.49	0.42	0.48
5	Disintegration time	2min 44sec	2min 50sec	1min 50sec	1min 44sec	3min 10sec	3min 18sec	2min 50sec	2min 44sec	2min 15sec	2min 22sec	2min	2min 10sec

TABLE 13: PHYSICAL EVALUATION (AFTER SUB COATING AND ENTERIC COATING)

S. no.	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
1	Hardness (kP)	8.2	8.0	8.2	8.4	8.3	8.1	8.5	8.8	8.6	9.0	9.2	8.8
2	Thickness (mm)	4.01	4.03	4.00	4.04	4.01	4.00	4.06	4.00	4.02	4.04	3.99	4.00
3	Hardness (kP)	8.6	8.4	8.6	8.8	8.7	8.5	9.0	9.4	9.2	9.6	9.6	9.4
4	Thickness (mm)	4.05	4.07	4.04	4.08	4.05	4.04	4.10	4.04	4.06	4.08	4.04	4.05

TABLE 14: CHEMICAL EVALUATION

S. no.	Parameters	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
1	Acid resistant analysis (NMT 10% in 2 h)	1.38	1.36	1.48	1.78	1.82	1.69	1.80	1.86	1.84	1.90	1.90	1.28
2	Assay (90-110%)	91.8	91.5	93.4	96	95.1	98.5	99	97.3	98.1	96.1	99.3	99.72
3	Dissolution study (NLT 75% in 30 min in buffer stage)	97	98	98	96	83	87	94	91	97	97	84	97

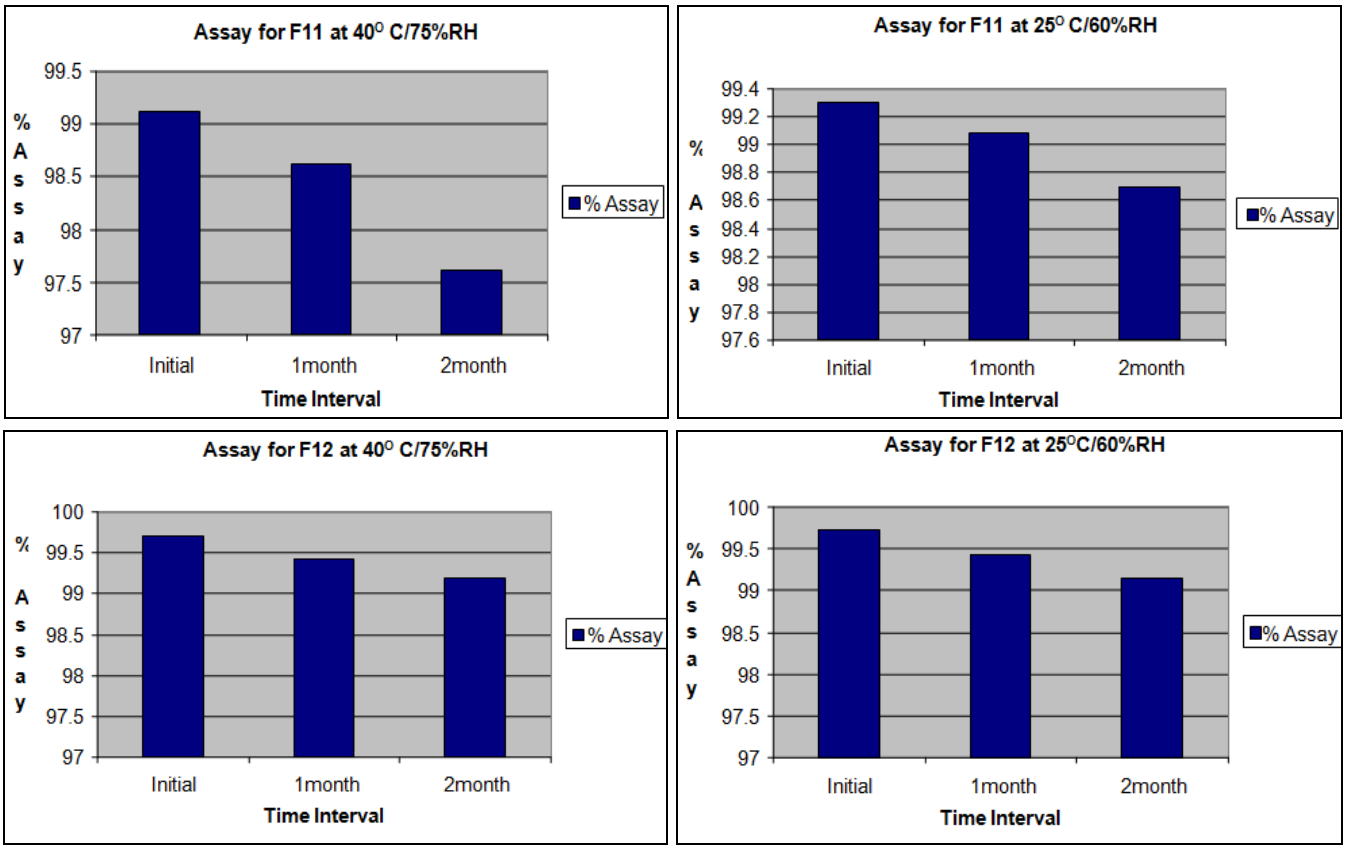

FIG. 4: ASSAY STUDY OF F11-F12

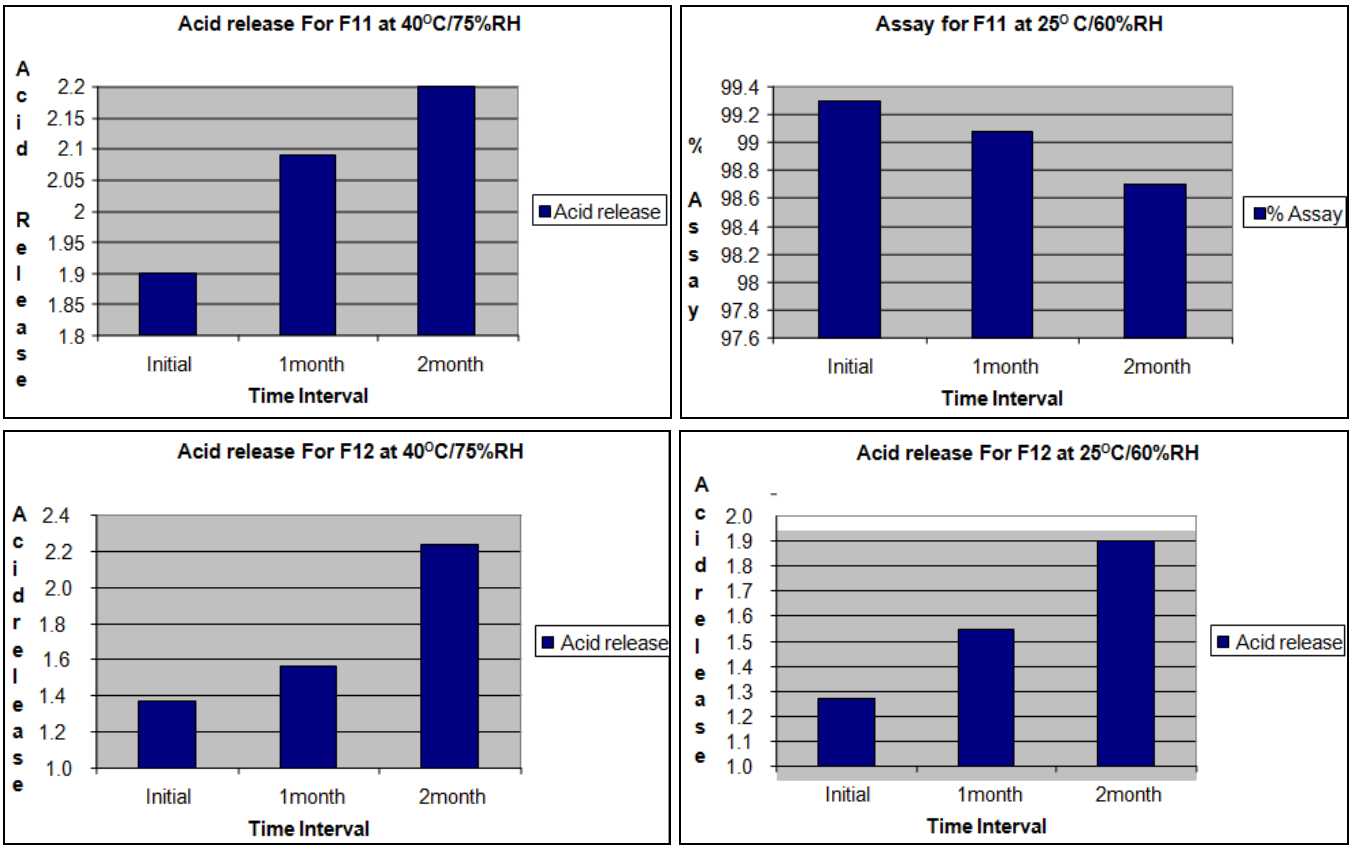

FIG. 5: ACID RELEASE STUDY OF F11-F12

Acid Release: This indicates that the dosage form is resistance to acid media after 2 h. In formulation 11 the acid release of the drug from tablets was found to be 1.90% initially, after 1 month it raises

to 2.09% and 2.04%, later it was found to be 2.20 and 2.12% after 2 months at 40 °C/75% RH and 25 °C/75% RH respectively. This indicates that there is little change in the acid resistance of Paliperidone delayed-release tablets for batch 11.

In formulation 12 the acid release of the drug from tablets was found to be 1.28 % initially, after 1 month it raises to 1.54% and 1.32%, later it was found to be 2.26% and 2.00% after 2 months at 40 °C/75%RH and 25 °C/75% RH respectively. This indicates that there is little change in the acid resistance of Paliperidone delayed-release tablets for batch 12.

Dissolution Studies: The dissolution was carried out for different experimental trials and also for the innovator. The various results that are obtained are tabulated below. Dissolution studies are carried out in the following Media.

Acidic Stage: (pH 1.2)

Medium : 0.1N HCl
Type of apparatus : USP - II (paddle type)
RPM : 100
Volume : 700 ml
Temperature : 37 ºC ± 0.5
Time : 2 h

Buffer Stage: (pH 8.0)

Medium : pH 8.0 Tris buffer
Type of apparatus : USP – I (paddle type)
RPM : 100
Volume : 1000ml
Temperature : 37ºC± 0.5
Time : 45 minutes

TABLE 15: DISSOLUTION PROFILE FOR PALIPERIDONE DR TABLETS: (INNOVATOR)

Reference Product- Pariet							
% Drug dissolved in time (min)							
Unit	**0**	**5**	**10**	**20**	**30**	**45**	**60**
1	0	3	26	96	99	92	90
2	0	3	29	95	97	91	90
3	0	3	17	76	99	93	91
4	0	3	41	97	95	92	87
5	0	3	23	97	95	93	90
6	0	3	38	96	97	93	91
Average	0.0	3.0	29.0	92.8	97.0	92.3	89.8
%RSD	0	0	31.4	8.9	1.8	1.9	1.6

TABLE 16: DISSOLUTION PROFILE OF FORMULATION 11

	% Drug dissolved in time (min) in Buffer Stage				
Unit	**0**	**10**	**20**	**30**	**45**
1	0	60	83	81	89
2	0	54	85	82	97
3	0	52	86	85	92
4	0	56	77	86	99
5	0	58	83	87	96
6	0	62	87	85	97
Average	0	57	84	84	96
%RSD	0	3.2	4.3	2.8	3.8

TABLE 17: DISSOLUTION PROFILE OF FORMULATION 12

		% Drug dissolved in time (min) in Buffer stage			
Unit	**0**	**10**	**20**	**30**	**45**
1	0	27	91	99	88
2	0	30	93	98	91
3	0	24	95	94	90
Average	0	27	93	97	90
%RSD	0	2.5	2.2	1.2	1.4
		Test product- 40^{O}C/75% RH, 1 Month			
1	0	28	89	94	83
2	0	22	94	93	89
3	0	22	87	95	85
Average	0	24	90	94	87
%RSD	0	3.4	2.6	1.1	2.8

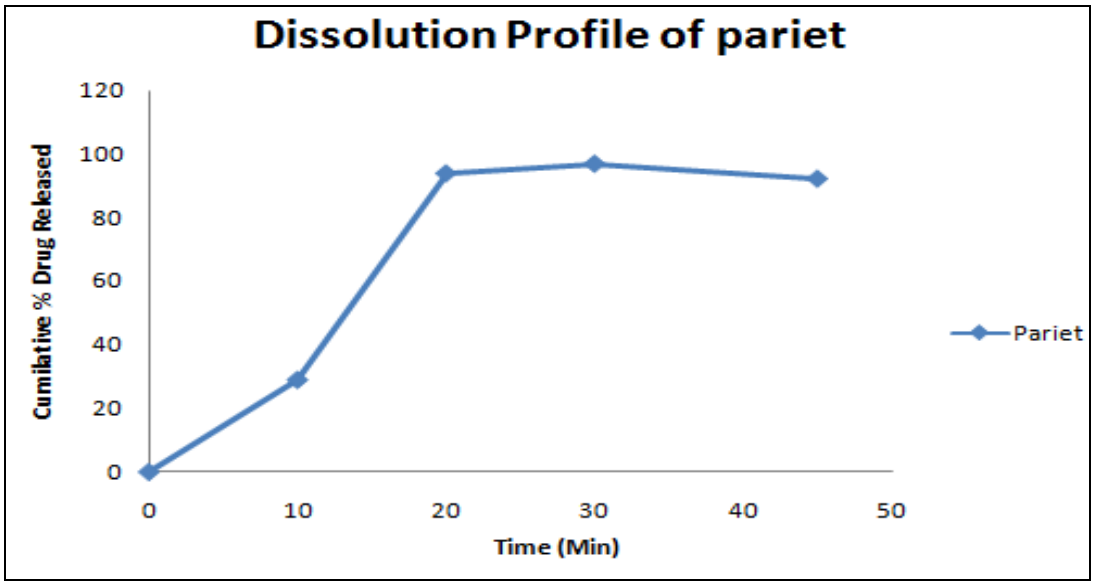

FIG. 6: DISSOLUTION PROFILE FOR PALIPERIDONE DR TABLETS: (INNOVATOR)

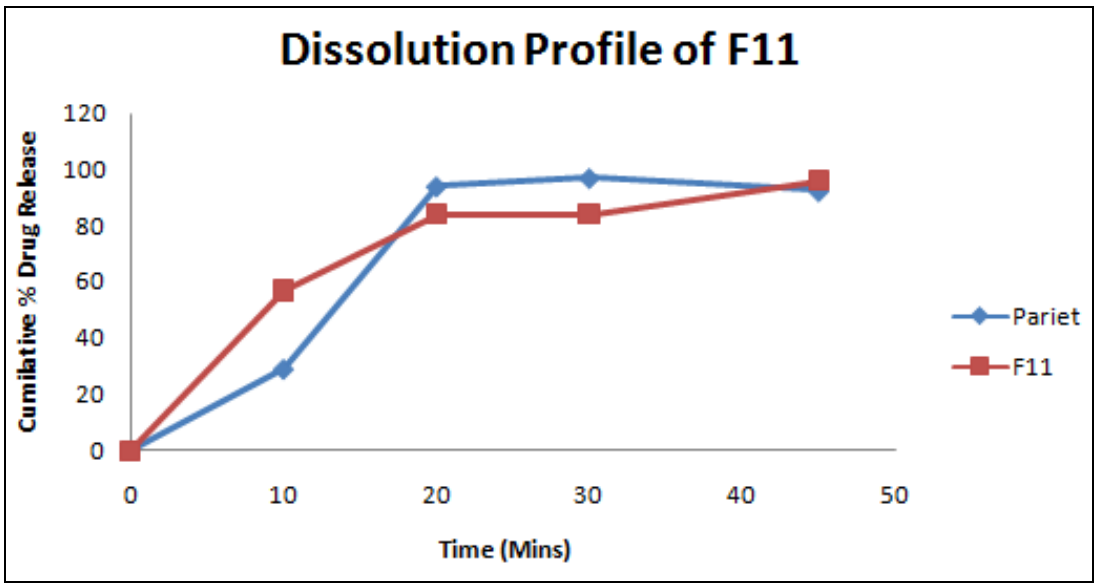

FIG. 7: DISSOLUTION PROFILE OF FORMULATION 11

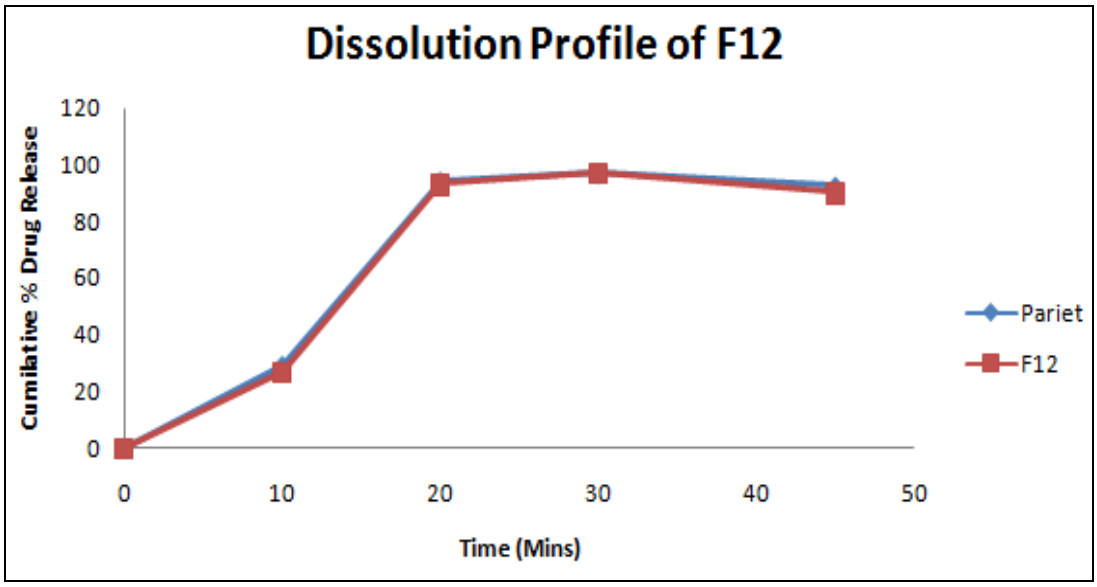

FIG. 8: DISSOLUTION PROFILE OF FORMULATION 12

TABLE 18: COMPARATIVE DISSOLUTION PROFILE FOR PALIPERIDONE 20MG DR TABLETS (PARIET) AND PREPARED FORMULATIONS F1 TO F6

S. no.	Time (min)	F1	F2	F3	F4	F5	F6	Pariet
1	0	0	0	0	0	0	0	3
2	10	1	0	14	0	1	0	29
3	20	96	57	99	64	64	55	94
4	30	97	98	98	96	83	87	97
5	45	84	85	89	87	98	98	92.3

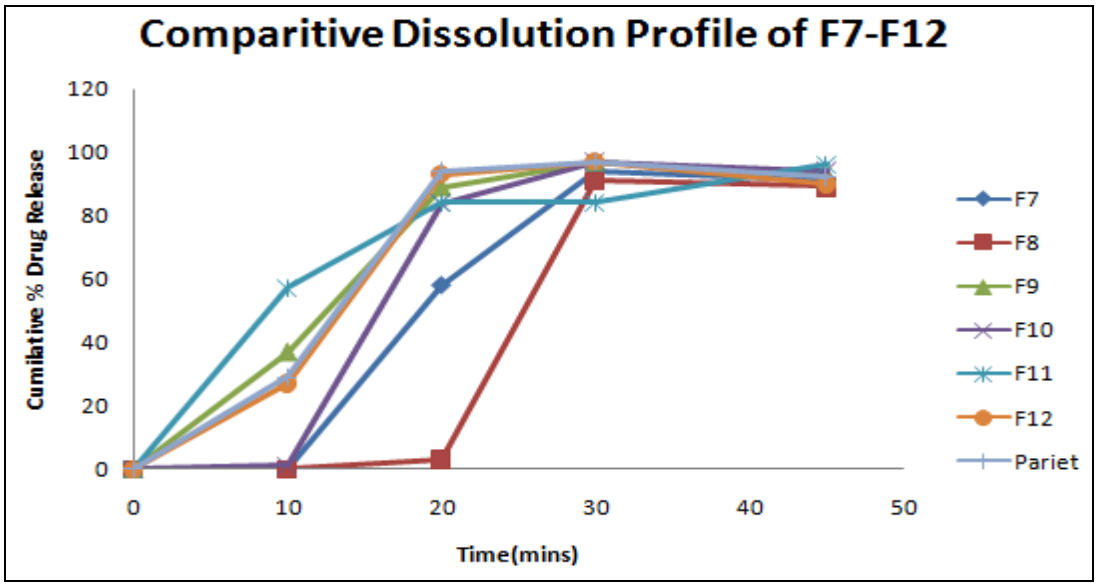

FIG. 9: COMPARATIVE DISSOLUTION PROFILE FOR PALIPERIDONE 20MG DR TABLETS (PARIET) AND PREPARED FORMULATIONS F1 TO F6

Stability Studies:

TABLE 20: STABILITY DATA FOR F11

Batch number and stability condition	Description	Assay (%)	Acid release in 0.1N HCl (%)	Dissolution study in pH 8.0 buffer
Room temperature (Initial)	Light yellow colored enteric coated tablets	99.30%	1.90%	94.38%
40 °C / 75% RH (1 month)	Light yellow colored enteric coated tablets	98.29%	2.09%	92.23%
40 °C / 75% RH (2 months)	Light yellow colored enteric coated tablets	97.3%	2.20%	92.01%
25°C/60% RH (1month)	Light yellow colored enteric coated tablets	99.05%	2.04%	93.04%
25°C/60% RH (2months)	Light yellow colored enteric coated tablets	98.69%	2.12%	91.36%

TABLE 21: STABILITY DATA FOR F12

Batch number and stability condition	Description	Assay (%)	Acid release in 0.1N HCl (%)	Dissolution study in pH 8.0 buffer
Room temperature (Initial)	Light yellow colored enteric coated tablets	99.72%	1.28%	97.38%
40°C / 75% RH (1 month)	Light yellow colored enteric coated tablets	99.43%	1.54%	93.23%
40 °C / 75% RH (2 months)	Light yellow colored enteric coated tablets	99.30%	2.26%	92.14%
25 °C/60% RH (1month)	Light yellow colored enteric coated tablets	99.47%	1.32%	95.98%
25 °C/60% RH (2 months)	Light yellow colored enteric coated tablets	99.35%	2.00%	94.92%

Similarity Factor and Dissimilarity Factor Calculation: The similarity factor (f_2) was defined by CDER, FDA, and EMEA as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference release profiles." Dissimilarity or difference factor (f_1) describes the relative error between two dissolution profiles. It approximates the percent error between the curves. The percent error is zero when the test and reference release profiles are identical and increases proportionally with the dissimilarity between the two profiles.

There are several methods for dissolution profile comparison. f_2 is the simplest among those methods. Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors f_1 & f_2.

$$f_1 = \{ [\sum_{t=1}^{n} | R_t - T_t |] / [\sum_{t=1}^{n} R_t] \} . 100$$

$$f_2 = 50. \text{Log} \{[1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100\}$$

Where 'R_t' and 'T_t' are the cumulative percentage dissolved at each of the selected n time points of the reference & test product, respectively. The factor f_1 is proportional to the average difference between the two profiles, whereas factor f_2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. The similarity factor f_2 and its significance is shown in the following table.

TABLE 22: SIMILARITY FACTOR F2 AND ITS SIGNIFICANCE

S. No.	Similarity factor (f2)	Significance
1.	<50	Test and reference profiles are dissimilar.
2.	50 -100	Test and reference profiles are similar.
3.	100	Test and reference profiles are identical.
4.	>100	The equation yields a negative value.

TABLE 23: F_2 VALUE CALCULATION

Dissolution Profile Comparision					
Time (mins)	**Innovator (R)**	**F12 (T)**	**(R-T)**	**$(R-T)^2$**	**f_2 value**
0	0	0	0	0	
10	29	27	2	4	
20	94	93	1	1	
30	97	97	0	0	89
45	92.3	90	2.3	5.29	
Total	220	217	3	10.29	

DISCUSSION: The objective of the study is to formulate and evaluate Paliperidone Delayed-Release tablets compared to the innovator product. Twelve formulations of enteric coated tablets of Paliperidone were developed by preparing core tablets using microcrystalline cellulose as diluent and sodium starch glycolate as super disintegrant and stabilizer in different proportions and varying the compositions of sub coating and enteric coating using pigment yellow, myvacet, and HPMC K 100M. The core tablets were prepared by Direct compression method. The results indicated that the finished product formulation F12 fulfilled all the specifications of the physical properties and *In-vitro* release and are comparable to the innovator product. Formulation F1 to F11 was failed due to various reasons like less acid resistance compared to the innovator or increased impurities profiles during stability or less *in-vitro* drug release compared to the innovator. Even though all the formulations are releasing the drug, but those are not comparable to the innovator product.

Formulation F12 fulfilled all the specifications prescribed for Paliperidone delayed-release tablets and comparable to the innovator product [36-39].

SUMMARY AND CONCLUSION: The Paliperidone is a proton pump inhibitor which is used in the treatment of Dopamine Antagonist.

In this study, Paliperidone enteric coated tablets were prepared by using HPMC K 100 M as an enteric coating polymer. Twelve formulations of enteric coated tablets of Paliperidone were developed by preparing core tablets using Microcrystalline cellulose as diluent and Sodium starch glycolate as super disintegrant and Stabilizer as in different proportions and varying the compositions of sub coating and enteric coating using Pigment yellow, Myvacet, and HPMC K 100M.

The core tablets were prepared by Direct compression method. F12 was found to be best of all the formulations showing drug release matching the innovator product so to that formulation all the quality control tests were done for confirmation. Stability study is carried out for 3 months at 25 °C; 60% RH: and 40°C; 75% RH, according to ICH guidelines. The tablets were tested for acid release during the stability period and confirmed that results were found within limits. The identified formula shall be utilized for the formulation development and other studies for the successful launching of the product.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

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