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FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLETS OF PALPERIDONE BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Paliperidone is the primary active metabolite of the older Antipsychotic Risperidone. Paliperidone belongs to class II drug in BCS classification i.e., low solubility and high permeability. The aim of the present study was to improve the solubility and dissolution rate of a poorly water-soluble drug Paliperidone by using different polymers. The oral disintegrating tablets of Paliperidone developed in this investigation, releases drug within 20 minutes. Thus, we are able to achieve our objective of preparing oral disintegrating tablets of Paliperidone with minimum excipients and simple method of manufacture. Suitable analytical method based on UV-Visible spectrophotometer was developed for Paliperidone. λ_{max} of 237 nm was identified in phosphate buffer solution, pH 6.8.Prepared Paliperidone: Crosspovidone, Paliperidone: Cross carmellose sodium, Paliperidone: Sodium starch glycolate solid dispersions in different ratios by melting method. All SD formulations converted into orally disintegrating tablets using Direct compression method. Evaluation parameters like hardness, friability, weight variation and drug content indicate that values were within permissible limit for all formulations. *In vitro* drug release study was carried out and based on the results; SDF-6 was identified as the best formulation among all the other formulations. The order of enhancement of the dissolution rate super disintegrants was found to be Cross carmellose sodium> crosspovidone >Sodiumstarchglycolate.

Keywords: Antipsychotic, Solubility, Permeability, Dissolution and Disintegrating.

INTRODUCTION

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms. For many decades treatment of an acute disease or chronic illness has mostly accomplished by delivery of drugs to patients using conventional drug delivery system. Even today these conventional drug delivery systems are the primary pharmaceutical products commonly seen in the prescription. Conventional oral drug products are formulated to release the active principle immediately after oral administration to obtain rapid and complete systemic drug absorption.

Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation. Systemic drug absorption from a drug product consists of a succession of rate process for solid oral, immediate release drug products.

The rate process includes,

- Dissolution of the drug in an aqueous environments.
- Absorption across cell membranes into systemic circulation.

For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exhibits a rate limiting effect on drug bioavailability. In contrast, for a drug that has a high aqueous solubility the dissolution rate is rapid the rate at which the drug crosses or permeates cell membrane is the slowest or rate limiting step.

Together with the permeability, the solubility behaviour of a drug is a key determinant of its oral bioavailability. They have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole & chloramphenicol come immediately to mind. With the recent advent of high through put screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

Consideration of the modified Noyes – Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.

$$\frac{dc}{dt} = \frac{AD(C_S - C)}{h}$$

Where dc/dt = rate of dissolution
A = Surface area available for dissolution.
D = Diffusion coefficient of the compound
C_s = Solubility of the compound in the dissolution medium.
C = Concentration of drug in the medium at time t
h = thickness of the diffusion boundary layer adjacent to surface of the dissolving compound.

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions.

REVIEW OF LITERATURE

Chowdary KPR et al., Prepared solid dispersion of Itraconazole in lactose, microcrystalline cellulose and three superdisintegrants (Primo gel, Kollidon CL, and Ac-Di-Sol) and their formulations into tablet were investigated with an objective of enhancing the dissolution rate of Itraconazole from tablet formulation. A marked enhancement in the order of excipients to enhance the dissolution rate was Ac-Di-Sol.[22]

Shu et al., Formulated rapid oral disintegrating tablets by direct compression using co-ground mixture of D-mannitol and crospovidone. Tablet manufacturing from a physical mixture of 30%(w/v) co-ground mixture of D-mannitol and crospovidone (mixed ratio 9:1) with 65.5%(w/v) of non-ground mannitol, 4% (w/v) of crospovidone, and 0.5%(w/v) of magnesium stearate had good properties for rapidly disintegrating tablets in the oral cavity. The presumed that crospovidone acted as a grinding assistant for D-mannitol in the co-grinding process, enhancing the hardness of tablet by increasing the contact area among powder particles.[23]

Lalla et al., Prepared inclusion complex of rofecoxib, an NSAID with beta cyclodextrin using ball milling technique and evaluate using DSC. Fast dissolving tablets composition with 25 mg equivalent Rofecoxib showed complete release of rofecoxib in 12 minutes as compared to 20% drug release form the conventional release marketed tablets during the same period of time.[24]

Mahaparale, et al., Prepared solid dispersion of Meloxicam by solvent evaporation method with polyvinyl, pyrrolidine(PVP), polyethylene glycol 6000 (PEG 6000) and polyethylene glycol 4000 (PEG 4000) dissolution study was carried out for all solid dispersion. All solid dispersion of Meloxicam showed higher solubility and faster dissolution than pure drug alone. Meloxicam (1:9) ratio showed highest solubility and faster dissolution than any other solid dispersion.[25]

Desai et al., Prepared orodissolving tablets of Promethazine Hydrochloride using superdisintegrants, sodium starch glycolate and croscarmellose sodium by direct compression method. The formulation containing 4% of sodium starch glycolate and 1-3% of croscarmellose sodium were found to get the best result. Thus, the tablet apart from fulfilling all official and other specifications, exhibited higher rate of release.[26]

Srinivas Babu et al., Prepared solid dispersion of Piroxicam in five superdisintegrants namely primogle, microcrystalline cellulose, crospovidone, pregeletinized starch, croscarmellose sodium and with water soluble carriers polyvinyl pyrrolidone and polyethylene glycol. Solid dispersion of piroxicam in super disintegrants gave a marked enhancement in its dissolution rate and dissolution efficiency. Solid dispersion in superdisintegrats could be used as an effective and efficient technique for enhancing the dissolution rate of piroxicam a poorly soluble drug.[27]

METHODOLOGY

Table 1: Ingredients and Manufactures

S.NO	INGREDIENTS	SUPPLIER
1.	Paliperidone	Supplied By Pharma Train, Hyderabad
2.	Crospovidone	SD Fine Chemicals, Mumbai
3.	Crosscarmellose sodium	SD Fine Chemicals, Mumbai
4.	Sodium starch glycolate	SD Fine Chemicals, Mumbai
5.	Avicel pH 102	SD Fine Chemicals, Mumbai
6.	Lactose	SD Fine Chemicals, Mumbai
7.	Talc	SD Fine Chemicals, Mumbai
8	Mg. Stearate	SD Fine Chemicals, Mumbai

Table 2: Equipment and Companies

Sl.No.	Name of the Equipment	Model
1.	Electronic weighing balance	Scale-Tec
2.	Friabilator	Roche Friabilator, Electrolab, Mumbai
3.	Compression machine	Cmd(Cadmach)
4.	Tablet hardness tester	Pfizer Hardness Tester, Mumbai
5.	UV	LabindiaUv 3000+
6.	Dissolution apparatus	Electrolab TDT-08L
7.	Vernier callipers	Cd-6"Cs

Spectrophotometer at 237 nm. The absorbance data for standard calibration curves are given in the results table.

Standard Calibration curve of Paliperidone in phosphate buffer pH 6.8 solution

Working standard

100mg of Paliperidone was weighed and dissolved in 10ml Methanol and then make up to a volume of 100ml with 6.8 phosphate buffer it gives 1000µg/ml concentrated stock solution.

Dilution 1

From the working standard solution 10ml was diluted to 100ml with 6.8 phosphate buffer it will give 100µg/ml concentrated solution.

From the dilution-1, Aliquots of 0.2, 0.4, 0.6, 0.8 and 1ml of solution were pipette out in to 10ml volumetric flask. The volume was made up to the mark with phosphate buffer pH6.8. These dilutions give 2, 4, 6, 8 and 10µg/ml concentrations of Paliperidone respectively. The absorbance was measured in the UV-visible.

II. FORMULATION OF PALIPERIDONE SOLID DISPERSIONS

Kneading method

Drug with polymers in different molar ratios (1:1, 1:2 and 1:3) was taken. First polymers is added to the mortar, small quantity of 50% ethanol is added while triturating to get slurry like consistency. Then slowly drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried at 25°C for 24 hours, pulverized and passed through sieve No. 80 and stored in desiccators over fused calcium chloride.

Table 3: Formulation table of Paliperidone solid dispersions

F.Code	Polymer/ Carrier	API: Polymer/ Carrier ratio
SD1	Crospovidone	1:1
SD2		1:2
SD3		1:3
SD4	Cross carmellose sodium	1:1
SD5		1:2
SD6		1:3
SD7	Sodium starch glycolate	1:1
SD8		1:2
SD9		1:3

Table 4: Formulation of oral disintegrating tablets of solid dispersions of Paliperidone

Ingredients	SDF1	SDF2	SDF3	SDF4	SDF5	SDF6	SDF7	SDF8	SDF9
Drug:Polymer	12	18	24	12	18	24	12	18	24
Avicel pH102	20	20	20	20	20	20	20	20	20
Lactose	64	58	52	64	58	52	64	58	52
Talc	2	2	2	2	2	2	2	2	2
Mg. stearate	2	2	2	2	2	2	2	2	2
Total.wt (mg)	100	100	100	100	100	100	100	100	100

EVALUATION OF TABLETS

A) Pre Compression studies

1. Angle of Repose

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose of granules was determined by the funnel method. Diameter of the powder cone was measured and angle of repose was calculated using the following equation[17].

$$\theta = \tan^{-1} (h/r)$$

Where:

θ = angle of repose

h = height in cms

r = radius in cms

Table 5: Angle of repose limits Flow Properties and Corresponding Angles of Repose

Flow Property	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

2. Dens Bulk density (BD)

It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22#sieve and transferred in 100 ml graduated cylinder. Calculate the apparent bulk density in gm/ml by the following formula[18].

Bulk density = weight of powder/ Bulk volume.

$$D_b = \frac{M}{V_0}$$

M = mass of the powder

V_0 = bulk volume of the powder.

b) Tapped density (TD)

It is the ratio of total mass of powder to the tapped volume of powder

Tapped density = Weigh of powder / Tapped volume

$$Dt = (M) / (V_f).$$

M = mass of the powder

V_f = tapped volume of the powder.

3. Carr's Index

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below:

$$\text{Compressibility index} = 100 \times \frac{\text{Tappeddensity} - \text{Bulk density}}{\text{Tappeddensity}}$$

4. Hausner's Ratio

Hausner's Ratio is a number that is correlated to the flow ability of a powder.

$$\text{Hausner's Ratio} = \frac{\text{TappedDensity}}{\text{Bulk Density}}$$

Compressibility index limits

Table 6: Scale of Flow ability (USP29-NF34)

Compressibility Index (%)	Flow Character	Hausner'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

B) Post compression studies

1. General appearance

The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

2. Average weight/Weight Variation

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

$$\%\text{weight variation} = \frac{\text{average weight - weight of each tablet}}{\text{Average weight}} \times 100$$

Table 7: Weight variation tolerance for uncoated tablets
Acceptance criteria for tablet weight variation (USP 29-NF 34)

Average weight of tablet (mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

3. Thickness

Thickness of the tablets (n=3) was determined using a Vernier callipers.

4. Hardness test

Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then

forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

5. Friability test

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting.

Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min.

The difference in the weight is noted and expressed as percentage.

It should be preferably between 0.5 to 1.0%.

$$\%\text{Friability} = [(W_1-W_2)/W_1] \times 100$$

Where, W_1= weight of tablets before test,

W_2 = weight of tablets after test

6. Disintegration

A tablet is placed in every glass tube and the basket containing these glass tubes positioned in the beaker containing the required fluid such that all tablets dip properly. The apparatus is then apparated for specified time. The tablet pass the disintegration tests then none of the drug particles remain on the mesh/wire screen i.e., the tablet must disintegrate and all the particles must pass through the mesh within the time specified in the monograph. However, the insoluble coating particles or the soft mass without palpable core are exempted.

7. Wetting time and Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish (internal diameter 5 cm) containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured, the wetted tablet was then weighed.

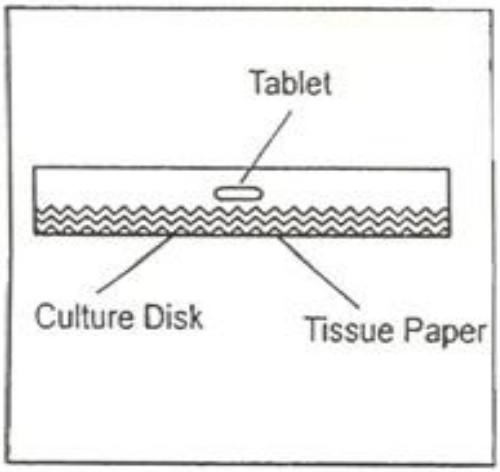

Fig. 1: Schematic representation of wetting time / water absorption determination

Water absorption ratio 'R' was determined using following equation

$$R = 100 \times \left(\frac{W_b - W_a}{W_a} \right)$$

Where, W_a is weight of tablet before water absorption and W_b is weight of tablet after water absorption

8. Assay Procedure

Weigh and finely powder not less than 20 tablets. Transfer an accurately weighed portion of the powder equivalent to about 10mg of model drug a 10 ml volumetric flask. Add approximately 6ml of 6.8 phosphate buffer and shake and sonicate for 10 min to complete the extraction. Dilute the

methanol to volume and mix. Pipette 1ml aliquot into a 10ml volumetric flask, dilute with mobile phase to volume, mix and filter. From it withdraw take 1ml aliquot and make up to mark with buffer. Calculate the quantity in mg of model drug Hydrochloride in the portion taken by the formula

Assay = test absorbance/standard absorbance*standard concentration/sample concentration*purity of drug/100*100.

9. In vitro Dissolution Study

900 ml of 6.8 Sodium phosphate buffer was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of $37^0C \pm 0.5^0C$. A tablet was placed in the vessel and was covered; the apparatus was operated up to 60mins at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} =237 nm using a UV-spectrophotometer (Lab India).

Table 8: Dissolution parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	6.8 phosphate buffer
Volume	900 ml
Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	5, 10, 15, 20, 25 and 30mins
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	237 nm

RESULTS AND DISCUSSION

Construction of Standard calibration curve of Paliperidone in 6.8 phosphate buffer

The absorbance of the solution was measured at 237nm, using UV spectrometer with 6.8 phosphate buffer as blank. The values are shown in table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml

Table 9: Standard Calibration graph values of Paliperidone in 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.092
4	0.187
6	0.272
8	0.365
10	0.457

Standard plot of Paliperidone plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown fig.

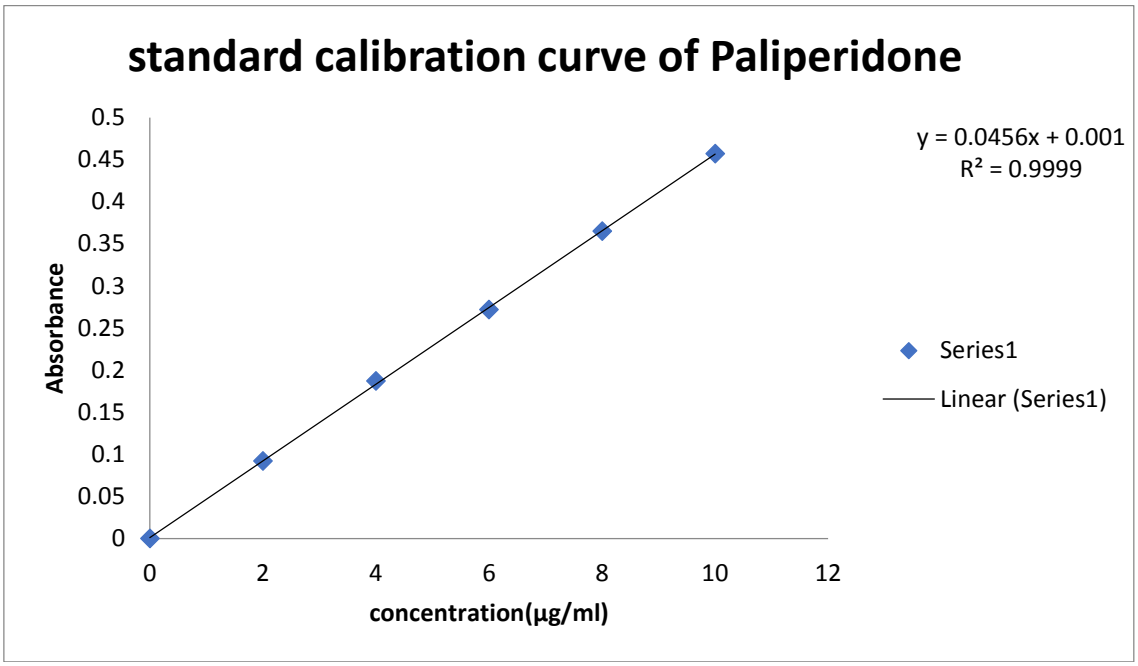

Fig. 2: Standard calibration curve of Paliperidone in 6.8 phosphate buffer

Inference

The standard calibration curve of Paliperidone in 6.8 phosphate buffershowed good correlationwith regression value of 0.999

Table 10: Pre compression studies of Paliperidone Oral disintegrating tablets

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
SDF1	0.40	0.48	16	1.2	12.73
SDF2	0.41	0.50	13.0	1.5	11.29
SDF3	0.50	0.58	13	1.16	11.58
SDF4	0.39	0.47	17.0	1.56	12.23
SDF5	0.37	0.41	9.75	1.1	12.35
SDF6	0.43	0.52	17.3	1.41	11.62
SDF7	0.44	0.50	12	1.1	9.92
SDF8	0.41	0.45	8.8	1.0	11.85
SDF9	0.50	0.58	13	1.16	11.58

Inference

- The prepared tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table.
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 to 1.56 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be 11.29 to 12.73 which indicating passable flow (i.e. incorporation of glidant will enhance its flow).

Table 11: Post compression studies of Paliperidone Oral disintegrating tablets

Formulation code	Hardness	% Friability	% Assay	Thickness (mm)	Disintegration Time	Wetting Time	Water Absorption Ratio	Weight variation
SDF1	4.0	0.61	98.84	3.2	135	152	70.41	Pass
SDF2	4.0	0.56	98.76	3.3	170	193	72.34	Pass
SDF3	3.5	0.75	98.57	3.2	122	142	75.23	Pass
SDF4	3.5	0.63	97.30	3.4	57	72	77.87	Pass
SDF5	3.5	0.84	98.76	3.1	48	61	82.56	Pass
SDF6	3.0	0.59	99.10	3.4	30	42	89.33	Pass
SDF7	3.5	0.48	99.23	3.5	40	53	85.66	Pass
SDF8	3.5	0.47	99.25	3.7	49	73	80.27	Pass
SDF9	3.5	0.72	98.48	3.2	120	137	75.13	Pass

Inference

- The variation in weight was within the range of ±7.5% complying with pharmacopoeia specifications of USP.
- The thickness of tablets was found to be between 3.1 to 3-7mm.
- The hardness for different formulations was found to be between 3.0 to 4.0 kg/cm^2, indicating satisfactory mechanical strength
- The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98 to 100 %.

INVITRO DISSOLUTION STUDIES OF PALIPERIDONE TABLETS

Table 12: Dissolution profile

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	6.8 Phosphate buffer
Volume	900 ml
Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	5, 10, 15, 20, 25 and 30 minutes
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	237nm

Table 13: Dissolution profile

Time (min)	Pure Drug	SDF1	SDF2	SDF3	SDF4	SDF5	SDF6	SDF7	SDF8	SDF9
0	0	0	0	0	0	0	0	0	0	0
5	10.21	21.31	30.24	31.12	36.35	36.14	49.51	25.09	34.23	41.15
10	13.14	35.68	41.37	38.53	45.34	42.32	68.74	39.33	43.25	48.52
15	20.41	49.53	52.31	50.55	58.37	62.14	89.24	51.56	58.24	62.34
20	28.25	72.31	79.93	79.96	85.33	87.37	99.94	65.61	79.56	85.22
25	33.36	89.95	92.36	92.22	95.96	99.62		79.83	92.32	97.35
30	38.52	95.32	98.12	99.34	99.11			91.39	96.01	99.34

Note: 5 ml of sample was with draw at each time point & replace the same volume of 6.8 phosphate buffer preheated to 37± 0.5 ºC

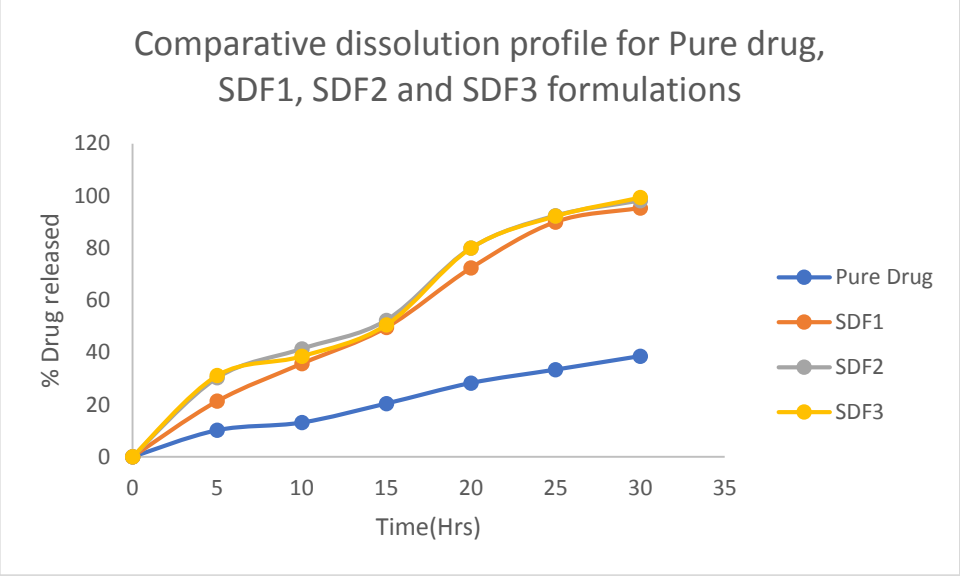

Fig. 3: Comparative dissolution profiles of Paliperidone Oral disintegrating Tablets for Pure drug, SDF1, SDF2 and SDF3 formulations

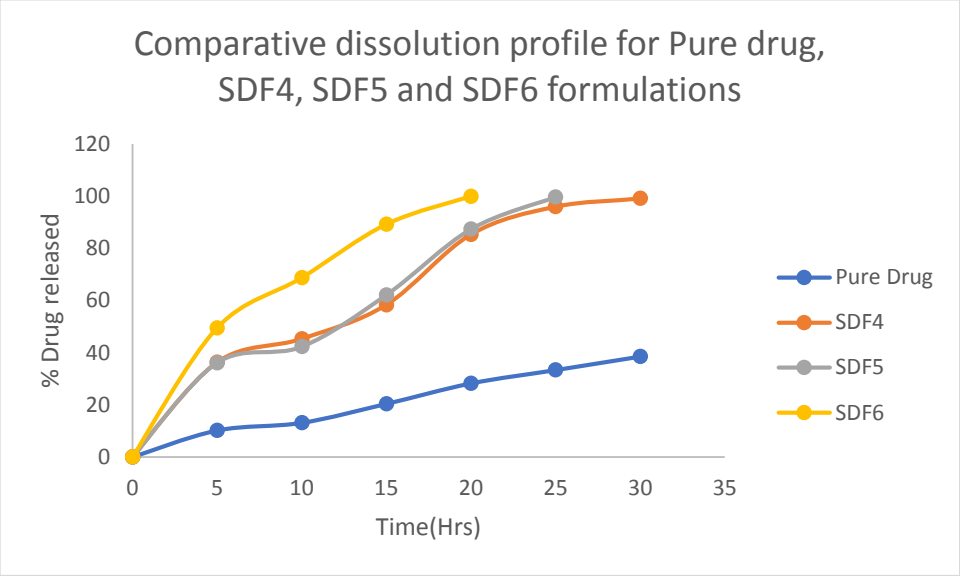

Fig. 4: Comparative dissolution profiles of Paliperidone Oral disintegrating Tablets for Pure drug, SDF4, SDF5 and SDF6 formulations

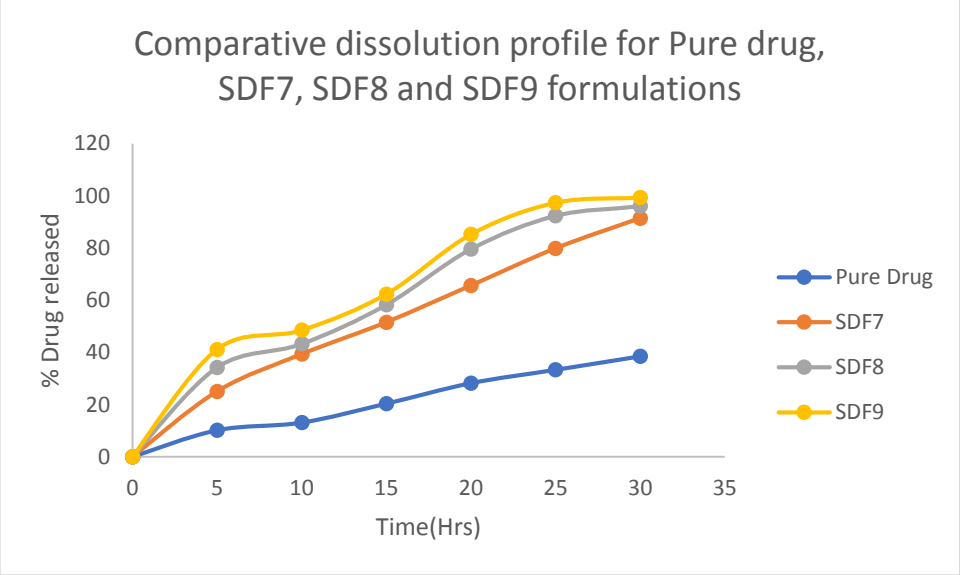

Fig. 5: Comparative dissolution profiles of Paliperidone Oral disintegrating Tablets for Pure drug, SDF7, SDF8 and SDF9 formulations

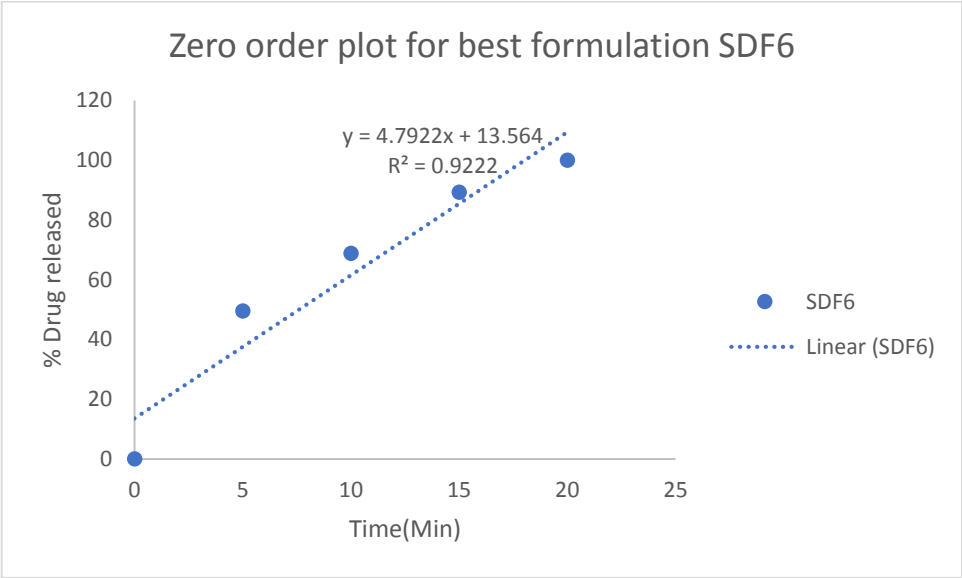

Fig. 6: Zero order plot for best formulation SDF6

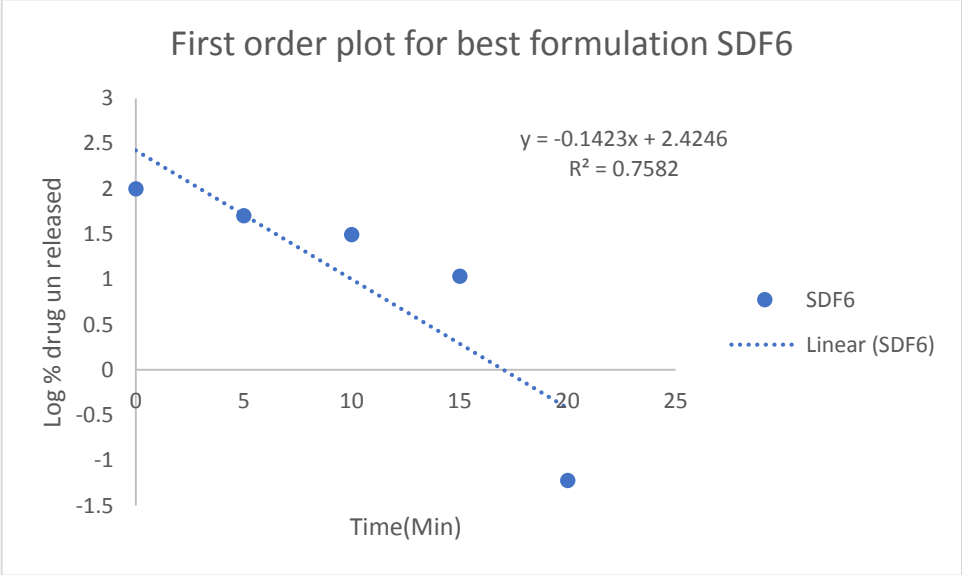

Fig. 7: First order plot for best formulation SDF6

Table 14: R^2 value and n result table

Formulation code	R^2 values	
	Zero order	First order
SDF6	0.922	0.758

Inference

- Among the different super disintegrates cross carmellose sodium was showing highest drug release within 20 minutes.
- SDF6 was showing the satisfactory results.
- SDF6 formulation follows zero order.

SUMMARY AND CONCLUSION

1. Suitable analytical method based on UV-Visible spectrophotometer was developed for Paliperidone. λ_{max} of 237 nm was identified in phosphate buffer solution, pH 6.8.
2. Prepared Paliperidone: Crospovidone, Paliperidone: Cross carmellose sodium, Paliperidone: Sodium starch glycolate solid dispersions in different ratios by melting method.
3. All SD formulations converted into orally disintegrating tablets using Direct compression method.

4. Evaluation parameters like hardness, friability, weight variation and drug content indicate that values were within permissible limit for all formulations.
5. *In vitro* drug release study was carried out and based on the results; SDF-6 was identified as the best formulation among all the other formulations and *In vitro* release profiles was 99.94% within 20 minutes.
6. The order of enhancement of the dissolution rates upper disintegrants was found to be Cross carmellose sodium>crospovidone>Sodiumstarchglycolate.

   The oral disintegrating tablets of Paliperidone developed in this investigation, releases drug within 20 minutes. Thus, we are able to achieve our objective of preparing oral disintegrating tablets of Paliperidone with minimum excipients and simple method of manufacture.

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