Formulation and Evaluation of Mouth Dissolving Tablet of Pitavastatin by Solid Dispersion Method

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Abstract- *The solubility behavior of drug is one of most challenging aspect in formulation development. The purpose of the study was to improve the physicochemical properties of Pitavastatin like solubility, dissolution properties and stability of poorly soluble drug by forming solid dispersion. Solvent evaporation method was employed for the formation of the solid dispersions. Solid dispersions of Pitavastatin was prepared using carrier polyvinylpyrrolidone (PVP) K30 for the selection of an optimized solid dispersion. The results from the UV spectroscopy and FTIR spectroscopy showed that solid dispersion exist in the amorphous form, hence showed marked increase in the saturation solubility and dissolution rate of Pitavstatin than that of pure drug. Based on the physical characters and in-vitro drug release pattern, ratio 1:3 (Drug: PVP K30) solid dispersion prepared by solvent evaporation method, was selected as ideal batch for incorporation in mouth dissolving tablet. The mouth dissolving tablets of Pitavastatin were prepared by direct compression method. The prepared MDT was evaluated for hardness, friability, weight variation, wetting time, disintegration time and drug content analysis. All these properties were found to be ideal.*

Keywords- Solid dispersion, Mouth dissolving tablets, Pitavastatin, Solubility

I. INTRODUCTION

Most of the new chemical entities (NCEs) are poorly water soluble drugs [1] not well-absorbed after oral administration, which can detract them from their inherent efficacy [3, 4, 5]. Moreover, most promising NCEs, despite their high permeability are generally not well absorbed due to low solubility [6, 7]. Frequently dissolution is the rate-controlling factor in the bioabsorption of these drugs, as it is often the slowest of the various stages involved in the release of the drug from its dosage form and passage into systemic circulation. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs [6, 8]. Solid dispersion is one of the most successful strategies to improve drug release, thus increasing their bioavailability and reducing side effects [9, 10]. The Pitavastatin is the drug candidate chosen for the study. Pitavastatin is white to pale yellow fine powder, chemically (3R,5S,6E)-7-[2-Cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3,5-dihydroxyhept-6-enoic acid with a molecular weight of 421.460 g/mol and molecular formula C25H24FNO4. Pitavastatin is a blood cholesterol lowering agent. It is a inhibitor of HMG CoA reductase. It is soluble in ethanol and practically insoluble in water.

Pitavastatin, was classified according to the Biopharmaceutical Classification System as a drug with low solubility and it is presented as an immediate-release dosage form in the World Health Organization essential drug list. Thus solid dispersion technique was used to enhance drug dissolution. The mouth dissolving tablets of prepared solid dispersion were prepared to make the drug available in a soluble form in the mouth, which facilitate its absorption from the buccal cavity. The drug disperses and dissolves in the saliva which passes into the stomach. In such cases the bioavailability of the drug increases. Many elderly patients have difficulty in swallowing tablets, capsules and powders. To alleviate this problem, these mouth dissolving tablets are expected to dissolve or disintegrate in the oral cavity without drinking water. The disintegrated mass can slide down smoothly along the esophagus with the help of saliva, so even people who have swallowing or chewing difficulties can take it with ease.

II. MATERIALS AND METHODS

Pitavastatin was obtained as a gift sample from Aizant Pharma Labs (Hyderabad, India). Polyvinyl pyrrolidone K30, Agar, Gum karaya, Plantago ovata, Microcrystalline cellulose, Aspartame were of analytical reagent (AR) grade, and purchased from Thermosil Fine Chem. All other chemicals and solvents used were of analytical reagent grade.

Preparation of solid dispersion by solvent evaporation method

The solid dispersions were prepared with combination of drug: PVP K30 in 1:1, 1:2, 1:3 ratios by mean of solvent evaporation method using chloroform as solvent as given in Table 1. This solution was continuously stirred using

a magnetic stirrer until the solvent was evaporated and then dried overnight at 500C. The samples thus obtained were pulverized using mortar pestle and sieved through a 60 mesh screen.

Preparation of physical mixtures

The physical mixture of Pitavastatin, and PVP K30 were prepared by geometrical mixing method. The physical mixture of Pitavastatin with PVP K30 1:1, 1:2, 1:3 ratio were prepared by homogeneous mixing in mortal and pastel followed by sieving through 60 mesh screen.

Table 1: Composition of Pitavsatin solid dispersion prepared by solvent evaporation method

S. No.	Form	Drug::PVP K30	Method of preparation
1	F1	1:1	Solvent evaporation
2	F2	1:2	Solvent evaporation
3	F3	1:3	Solvent evaporation

Characterization of solid dispersions
Drug Content

An accurately weighed quantity of solid dispersion equivalent to 60 mg Pitavastatin was taken into 100 ml of volumetric flask. Dissolved in phosphate buffer pH 6.4 and the volume were made up with the same. An aliquot of the filtrate was diluted and analyzed spectrophotometrically (Shimadzu UV-1800 double beam Spectrophotometer) at 241 nm.

In vitro drug dissolution studies of Pitavstatin, physical mixtures and solid dispersion

In vitro dissolution studies of Pitavastatin in powder form, SDs(Solid dispersion) and PMs (Physical Mixture) were performed by using the USP XXIII type-II dissolution apparatus (Electrolab TDT-08L) employing a paddle stirrer at 50 rpm. 900 ml of pH 6.4 phosphate buffer was used as dissolution medium. The temperature of dissolution medium was maintained at 37± 0.50 C throughout the experiment. Samples of dissolution medium (5ml) were withdrawn for 20 min by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 241 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent released was calculated and plotted against time.

Drug Content

Table No 2: Drug Content in Physical Mixture and Solid Dispersions

Solid dispersion (drug to PVP K30 mass ratio)	Drug content (%)	Physical mixture(drug to PVP K30 mass ratio)	Drug content (%)
SD1:1	92.61	PM1:1	75.45
SD1:2	95.98	PM1:2	76.34
SD1:3	99.62	PM1:3	85.42

The drug content of solid dispersion of Pitavastatin was found to be 92.61 to 99.62%, it indicating good content in Solid Dispersion. The drug content of solid dispersion of Pitavastatin of optimized formulation SD 1:3 was found to be 99.62 %, indicating good content in solid dispersion

In vitro drug dissolution studies of Pitavstatin, physical mixtures and solid dispersion

The percentage release of Pitavastatin at various time intervals from the physical mixture and solid dispersions made by using various concentrations of PVP K30. It is evident that dissolution of pure drug is very low, about 30.56% of drug being dissolved in 20 min. In the 20 min SD containing 1:3 of drug and PVPK30 showed better drug release 99.45% than other ratios of SD's.

Table No 3: In vitro dissolution profile of Pitavastatin, physical mixture and solid dispersions of Pitavastatin in pH 6.4 phosphate buffer

Sr. No	Formulation	Cumulative % drug release after 20min
1	DRUG	30.56±2.45%
2	PM1:1	43.45±2.05%
3	PM1:2	47.23±1.67%
4	PM1:3	54.73±3.41%
5	SD1:1	90.74±1.34%
6	SD1:2	96.54±1.40%
7	SD1:3	99.45±1.60%

Preparation of mouth dissolving tablets

The mouth dissolving tablets of Pitavastatin were prepared by direct compression method according to the proportions given in Table 4. All the ingredients were powdered separately and passed through # 60 mesh sieve separately. The solid dispersion and directly compressible excipient were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order, in an inflated polyethylene pouch magnesium stearate and talc were added last and the tablets were compressed to get tablets of 350 mg weight.

Table 4: Composition Pitavstatin mouth dissolving tablets

INGREDIENTS (mg)	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9
Pitavastatin solid dispersion PVP K30(1:3)	240	240	240	240	240	240	240	240	240
AGAR	10	15	20	-	-	-	-	-	-
Gum karya	-	-	-	10	15	20	-	-	-
Plantago ovata	-	-	-	-	-	-	10	15	20
MCC	30	30	30	30	30	30	30	30	30
Aspartame	5	5	5	5	5	5	5	5	5
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Purified Talc	3	3	3	3	3	3	3	3	3
Mannitol	60	55	50	60	55	50	60	55	50
Total	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

Evaluation of flow properties of final powder blend of different batches

Angle of Repose

The angle of repose is measure of extent of interparticle forces or index of flow. The angle of repose was determined by fixed funnel method in which the funnel was secured with its tip at a given height above a graph paper placed on a horizontal flat surface. The powdered blends were poured carefully through the funnel until apex of conical pile just touches the tip of funnel. The radius of the base of the cone was measured. The angle of repose was measured using the following equation.

$$\text{Angle of repose "Q"} = \text{Tan}^{-1}\left\lfloor \frac{H}{R} \right\rfloor$$

Where, H = Distance between tip of funnel and the base, R = Radius of the base of the cone.

Bulk Density and Tapped density

The bulk density of final powdered blend was determined by pouring 10 gram of final blend of a given batch into a 250 ml graduated glass cylinder which was kept at an angle of 45 degree to horizontal while pouring. The cylinder was straightened up and the volume occupied by the material was noted down. The bulk density was calculated by dividing the weight by the occupied volume. After noting the bulk density the glass cylinder containing final blend was tapped initially 500 times followed by 750 times and lastly 1250 times if needed and final tapped volume was determined (USP 30 NF 25). The tapped density was calculated by dividing the weight by the final tapped volume.

$$\text{Bulk density} = \frac{M}{V_1}$$

$$\text{Tapped density} = \frac{M}{V_2}$$

Where M = mass of test sample, V1 = unsettled apparent volume and V2 = final tapped volume.

Compressibility index and Hausner ratio

The Carr compressibility index and Hausner ratio of the powdered blend were computed on the basis of tapped density and bulk densities.

$$\text{Carr compressibility index} = \frac{(\text{Tapped density} - \text{bulk density}) \times 100}{\text{Tapped density}}$$

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of carvedilol mouth dissolving tablets

The prepared mouth dissolving tablets were evaluated for various official specifications.

Hardness

The crushing strength of the tablets (hardness) was measured using a Monsanto hardness tester. The force required to crush the tablet was measured in Kg / cm2. The test was done in triplicate for each batch.

Friability

The friability of a sample of 10 tablets was measured using a Roche Friabilator. Ten preweighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated using formula:

$$\% \text{ Friability} = \frac{(W_i - W_f) \times 100}{W_i}$$

Where Wi = initial weight of tablets Wf = final weight of tablets

Weight variation

20 tablets of each batch were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight.

Wetting time

The wetting time of the tablets was evaluated by the use of a piece of double folded tissue paper placed in a petridish containing 6 ml of water. A preweighed tablet was placed on this paper and the time for complete wetting of tablet was noted as wetting time.

In vitro dispersion time

The tablet was added to 10 ml of water and time required for complete dispersion was measured. Three tablets from each formulation batches were randomly selected and in vitro dispersion time was performed.

Drug content analysis

Twenty tablets were accurately weighed and finally powdered. The quantity of powder equivalent to 12.5 mg of carvedilol was taken and dissolved in 100 of methanol. The samples were filtered through a 0.45µm millipore filter and samples obtained were suitably diluted. Each diluted samples were than analyzed spectrophotometrically at 284 nm.

In vitro dissolution study of tablets

The in-vitro dissolution study of tablets was carried out using USP II dissolution apparatus (Paddle method). The in- vitro dissolution media used was 0.1 N HCl. The mouth dissolving tablet of formulation batch was dropped into 900 ml of dissolution media maintained at a temperature of 37±0.5°C and stirred at a specified rpm i.e. 50 rpm. 10 ml aliquots of dissolution medium were withdrawn at time interval of 5, 10, 15, 30, 45, 60 minutes which was replaced with 10 ml of fresh dissolution medium kept at 37± 0.5°C. The samples withdrawn were filtered through 0.45 □m millipore filters, diluted and assayed at 284nm using a UV-visible double beam spectrophotometer.

III. RESULTS AND DISCUSSION

Solubility study

Solubility of the Pitavastatin was determined in water

Table 5: Solubility data of Pitavastatin in water

Solvent	Solubility (mg/ml)
Water	0.0394 ±0.035

UV ABSORPTION MAXIMA OF PITAVASTATIN

UV scanning was done in Shimandzu double beam UV/VIS spectrophotometer using 10 µg/ml drug solutions in the wave length range of (200-400 nm).

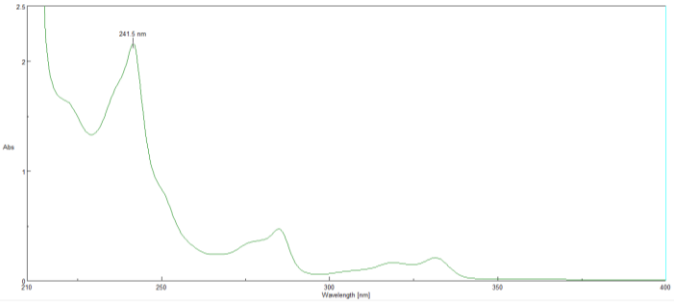

Figure no. 1: UV Absorption Spectra of Pitavastatin

Preparation of calibration cure

Table no. 6: Standard Calibration Curve Pitavastatin in 0.1 N Hcl

Sr. No	Concentration (µg/ml)	Absorbance (λ max = 241nm)
1.	0	0
2	2	0.247
3	4	0.448
4	6	0.603
5	8	0.827
6	10	0.982

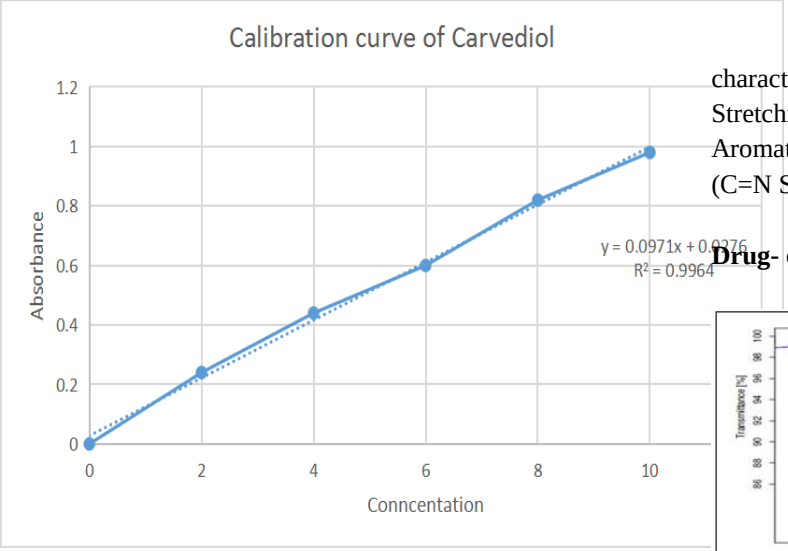

Figure No. 2: Standard Calibration Curve Pitavastatin in 0.1 N Hcl

FT-IR Absorption Spectrum

FT-IR spectra of drug samples were recorded using FT-IR spectrophotometer (FT-IR 8400S, Shimadzu).

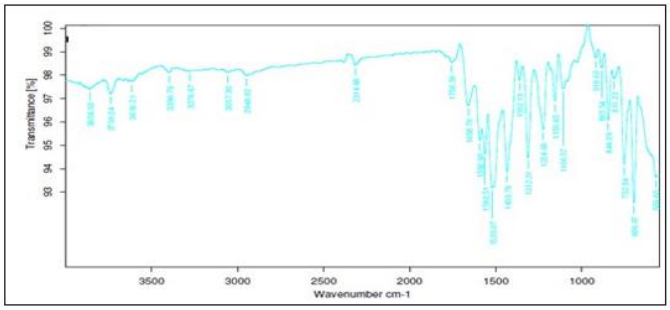

Figure No. 3: FT-IR Spectra of Pitavastatin

Table no. 7: Interpretation of FTIR Spectrum of Pitavastatin

Sr.no.	Reference Peak Wavenumber(cm^{-1})	Observed Peak Wavenumber(cm^{-1})	Functional Group
1	3300 – 3350	3571.54	O-H stretching
2	3050 – 3000	3738.06	O-H Stretching
3	3000 – 2500	2962.18	C=N Stretching
4	1600 –1450	1437.40	C-H Stretching
5	1350 –1260	1321	C=N Stretching

The IR spectrum of Pitavastatin in figure 10.1 is characterized by Principal absorption at 3571 .54 cm-1 (O-H Stretching), 3738.06 cm-1 (O-H Stretching), 1437.40 (CH-Aromatic Stretching) 2962.18 (C=N Stretching) and 1321 (C=N Stretching).

Drug- excipient compatability

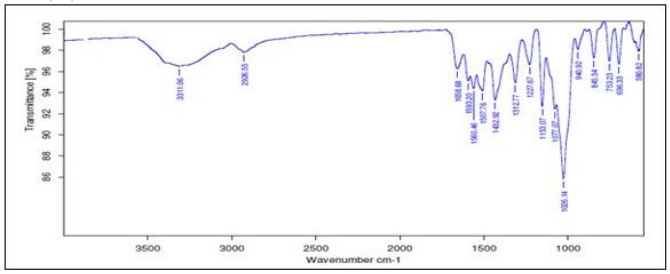

Figure No. 4: FT-IR of Compatibility Study of Drug with Excipients

Table 8: Interpretation of FTIR Spectrum of Drug Excipient compatibility

Sr.no.	Reference Peak Wavenumber(cm^{-1})	Observed Peak Wavenumber(cm^{-1})	Functional Group
1	3300-3350	3309	O-H stretching
2	3500 – 3000	3070.78	O –H Stretching
3	3000 – 2500	2916.47	C –H Stretching
4	1600 – 1450	1504.53	C=N Stretching
5	1500 -1000	1257.63	C-H stretching of tertiary amine
6	1340 – 1530	1450.52	C=N Stretching

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and superdisintegrants were studied. The characteristic absorption peaks of Pitavastatin were obtained at 3571.54 cm-1, 3738.06 cm-1, 1417.40 cm-1, 2962.18 cm-1and 1321cm-1. The peaks obtained in the spectrum of each formulation correlates with the peaks of pure drug of Pitavastatin. This indicates that the drug was compatible with the formulation components.

Evaluation of flow properties of final powder blend of different batches

Table No 9: Precompression Parameters

Formulation code	Bulk Density (g/ml)	Tapped density (g/ml)	Angle of repose (degree)	Carr's Index (%)	Hausner's ratio
PF1	0.49	0.57	26.40	14.04	1.16
PF2	0.48	0.55	26.06	12.72	1.14
PF3	0.46	0.53	23.38	13.20	1.15
PF4	0.43	0.49	24.72	12.24	1.13
PF5	0.41	0.47	24.94	12.76	1.14
PF6	0.39	0.44	25.48	11.36	1.12
PF7	0.47	0.64	26.21	26.56	1.16
PF8	0.51	0.61	25.74	16.39	1.19
PF9	0.46	0.56	23.02	17.85	1.11

Precompression parameters

Angle of Repose

The angle of repose for the entire formulations blend was found to be in the range 23.020 to 26.400. Formulations with Plantago Ovata and Gum Karaya as disintegrants showed angle of repose values ≤30o where as formulation containing Agar showed angle of repose values > 30o indicating only fair flow property of the powder blend.

Bulk Density

The bulk density of mixed blend varies between 0.39 to 0.51 gm/ml, indicating good packaging capacity of tablets.

Tapped Density

The tapped density of mixed blend was found in the range of 0.44 to 0.64 gm/ml, indicating good packing capacity of tablets.

Compressibility Index

Carr's index was found to be in the range 11.36% to 14.06% that indicated all formulation has good flow properties.

Hausner's Ratio

Hausner's ratio was found to be in the range 1.12 to 1.16 and that indicated that all formulation has good flow properties.

Post compression parameters

Table No.10 : Post Compression Parameters

Sr. No.	Formulation Code	Hardness* (kg/cm^2) ±SD	Friability (%)	*In vitro* dispersion time (s)*±SD	Percent drug content* ±SD	Weight variation	Disintegration time (sec)
1	**PF1**	3.03 ± 0.05	0.32	32.96 ± 1.46	81.35± 0.63	352.87± 0.56	33.7
2	**PF2**	2.83 ± 0.05	0.37	33.70 ± 1.45	83.02± 2.01	354.70± 0.08	33.65
3	**PF3**	2.83 ± 0.05	0.38	32.88 ± 0.63	80.45± 1.11	351.87± 0.46	32.81
4	**PF4**	2.7 ± 0.10	0.33	32.16 ± 0.92	89.94± 0.20	350.87± 0.39	30.33
5	**PF5**	2.46 ± 0.05	0.36	30.08 ± 0.75	87.84± 0.96	352.17± 0.57	29.65
6	**PF6**	2.33 ± 0.05	0.31	28.11 ± 0.66	90.41± 0.80	350.49± 0.11	27.04
7	**PF7**	2.34 ± 0.05	0.33	24.56±0.31	93.41± 0.80	352.87± 0.32	25.21
8	**PF8**	2.37 ± 0.05	0.37	24.12 ± 0.91	95.41± 0.80	350.71± 0.51	23.59
9	**PF9**	2.63 ± 0.05	0.32	22.08 ± 0.52	98.41± 0.80	350.87± 0.53	22.08

Wetting Time and Water Absorption Time

Table No 11: Data for Wetting Time and Water Absorption time

Sr. No	Formulation code	Wetting time Sec (±SD)	Water absorption ratio % (±SD)
1	PF1	52.48± 0.86	59.33± 2.89
2	PF2	54.15± 0.38	57.22± 2.46
3	PF3	51.86± 0.30	57.33± 1.12
4	PF4	54.69± 0.49	54.71± 1.51
5	PF5	56.54± 0.21	63.26± 1.86
6	PF6	57.47± 0.26	60.41± 1.93
7	PF7	52.33± 0.26	61.47± 0.26
8	PF8	51.67± 0.71	63.56± 0.31
9	PF9	47.47± 0.56	67.47± 0.26

Wetting Time was found to be in the range 47.47 to 57.47 sec. From all formulations, PF9 (20 mg Plantago Ovata) has minimum wetting time.

Dissolution data

Table No. 12: Dissolution study data for PF1-PF9

Time (min)	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9
0	0	0	0	0	0	0	0	0	0
2	20.18±0.46	23.31±0.92	25.20±0.88	27.01±0.16	30.27±0.11	35.11±0.23	36.70±0.96	39.70±0.96	43.94±0.91
4	24.88±0.65	28.93±0.54	32.15±0.17	29.17±0.89	33.32±0.94	37.53±0.89	38.55±0.68	44.55±0.97	48.47±1.12
6	33.07±0.46	36.55±0.98	40.83±0.97	32.01±0.16	34.27±0.11	39.53±0.89	42.86±0.85	56.86±0.85	59.31±0.67
8	42.88±0.65	49.61±0.17	52.00±0.05	40.01±0.16	45.27±0.11	48.11±0.23	48.06±0.93	59.06±0.73	62.05±0.80
10	54.34±0.49	59.05±0.43	62.17±0.07	45.17±0.89	48.32±0.94	51.53±0.89	54.83±0.97	61.83±0.37	65.18±0.76
12	59.67±0.33	63.05±0.78	67.30±0.93	56.53±0.35	59.20±0.56	62.14±0.35	63.63±1.37	64.63±1.37	67.80±0.85
14	67.59±0.33	69.61±0.17	72.00±0.05	69.05±0.78	71.18±0.35	73.45±0.51	72.12±0.74	76.12±0.74	79.52±0.59
16	75.70.±0.34	79.05±0.43	82.17±0.07	78.68±0.20	84.84±0.34	86.29±0.76	79.19±0.92	83.19±0.92	90.63±1.20
18	83.84±0.53	85.05±0.78	87.30±0.93	87.37±0.88	89.33±0.17	90.39±1.27	88.27±0.98	90.67±0.98	94.70±0.94
20	89.54±0.22	91.06±0.12	92.14±0.33	91.24±0.17	92.08±0.89	94.87±0.82	95.75±0.15	96.34±0.38	98.43±0.56

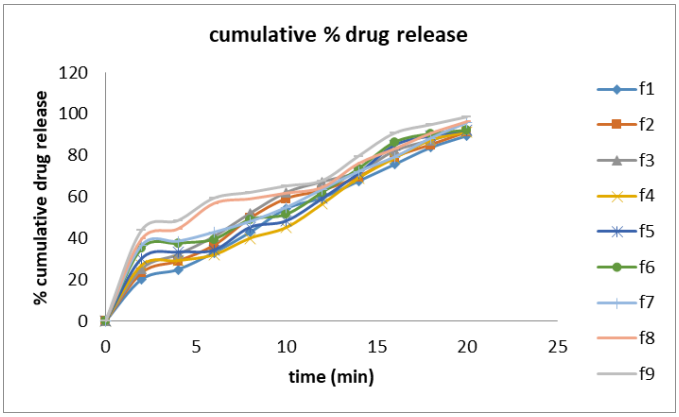

Figure No.5: Dissolution study data for PF9

The in vitro dissolution study of all formulations (PF1-PF9) gives maximum drug release of 99.43% W/V for formulation PF9 at the end of 20 min. all the formulations were within the limits for various post compression parameters like hardness, friability, weight variation and drug content. Here, PF9 had given less disintegration time and better drug release after 20 min.

Hence, PF9 having Plantago Ovata as disintegrants was selected as the best formulation.

IV. CONCLUSION

The results of the present study demonstrate that solid dispersion technique was employed to formulate mouth dissolving tablets of Pitavastatin, a poorly water-soluble drug, for the improvement of solubility and dissolution velocity. Pitavastatin solid dispersion prepared by solvent evaporation method using PVP k30 carrier. The Solid dispersion containing 1:3 ratio was selected as best among all ratio's and further used for formulation development. The values of Pre-compression parameter evaluated, were within prescribed limits and indicated good free flowing properties. The PF9 formulation with disintegrating time 22.08 secs and 99.45 % percent of drug release within 20 min compare to other remaining formulations so it is selected as an optimized formulation. Stability Study of optimized formulation PF9 was carried out for 3 months at 40°C+2°C and 75± 5% RH and tested for its physical changes, percent drug content, and in-vitro dispersion time. These formulations showed no significant variation in any parameters and found to be stable. It was concluded that the mouth dissolving tablet of Pitavastatin solid dispersion (containing PVP in 1:3 ratio) is successfully formulated using Plantago ovata as a superdisintegrants.

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