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FORMULATION AND EVALUATION OF ATORVASTATIN ORODISPERSIBLE TABLETS

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ABSTRACT

The present study was aimed to formulate orodispersible tablets of atorvastatin by using superdisintegrants in order to enhance the bioavailability. The orodispersible tablets displaying faster disintegration providing significant advantages over traditional dosage forms. The tablets are prepared by direct compression technique by using superdisintegrants like sodium starch glycolate and cross caramellose sodium. Formulations F1 to F8 were made with varying proportions of superdisintegrants. The drugs excipients compatibility studies were performed by FTIR and DSC indicates there is no compatibility issue. All the prepared formulations passed quality control test for tablets. The *in vitro* dissolution rate of all the formulations shows improved dissolution rate. The F8 formulation shows high dissolution rate compared to other formulations. The prepared formulations significantly enhancing the solubility and dissolution rate of the drug.

KEYWORDS

Orodispersible tablets, Atorvastatin, Superdisintegrants and Cross caramellose sodium.

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INTRODUCTION

Atorvastatin an anti-hyperlipidemia drug which is used to treat increased lipid contents. Orodispersible tablets are used to administer drugs via absorption in the mouth (buccal or sublingually). Orodispersible tablets (ODT) are single unit dosage forms that don't require water to disintegrate. The traditional solid dosage forms like tablets and capsules results in chocking and difficulty in swallowing. Hence in such cases orodispersible tablets offers a better option in such case.

Orodispersible tablets provides fast onset of action. Orodispersible tablets are used to avoid first pass metabolism.

Ideal requirements of oral disintegrating tablets

- They should be able to mask the bitter taste of the drug.
- They should have negligible or no residue in the mouth after the administration.
- They should have pleasant feel in mouth.
- They will easily disintegrate and dissolve.
- Ease of administration for the patients who are mentally ill, disabled and un-cooperative.

Advantages

- Patient compliance increased, as ODT do not require any water for administration.
- Stability of dosage form is more as the medicament remains in the solid dosage form till it is consumed. Hence, it is having stability as solid dosage form and having a bioavailability as liquid forms.
- Pediatrics, geriatrics and bed ridden patients can be administered with ODT who feel difficulty in swallowing.
- ODT are advisable when fast onset of action is required.
- Higher dosage forms can be formulated when compared to the oral dissolving films.

Limitations

- Bitter taste drugs cannot be formulated as oral disintegrating tablets, as they may leave an unpleasant taste after administration.
- Proper manufacture is required, or they will leave unpleasant taste after consumption of tablet if not properly manufactured.
- Production cost is more when compared to conventional tablets.
- ODT are not suitable for the patients with mouth dryness.
- Stability to humidity is very less and the release process is unstopped if once started.

MATERIAL AND METHODS

Atorvastatin calcium was obtained as a gift sample from Yarrowchem Products (Mumbai) PVK K-30 Sodium starch glycolate Cross caramellose sodium, Aspartame Talc Magnesium stearatecrystalline cellulosewere purchased from Lobachem and Merck Private Limited.

Methodology

Preformulation studies

It is most important requirement in developing any drug delivery system. Preformulation studies were performed for drug before formulation. It includes melting point determination, compatibility studies and solubility studies[1,2].

Identification of drugs

Organoleptic properties

Organoleptic properties include color, odor and taste. These were identified by descriptive technique.

Melting point

By using capillary tube method melting point was determined.

Solubility studies

Solubility of drug is important parameters as it influences the drug therapeutic activity. So, it is very much needed to determine the solubility for a drug. The solubility of drug is determined by adding excess drug in a flask with glass stopper containing 10ml of water. The flask is agitated for 24 hours until equilibrium was achieved, and the aliquots were filtered through 0.45mm filter. The filtered samples were diluted and assayed using a UV-visible spectrophotometer against a blank.

UV Visible spectroscopic study

The absorption maxima of the sample solution are observed in between 200-400nm wavelength range using UV-Visible spectrophotometer.

Identification of ƛmax of Atorvastatin calcium

50mg of pure drug Atorvastatin calcium was weighed accurately and transferred into a volumetric flask and dissolved in 50ml of methanol (1mg/ml). 10ml of this solution is withdrawn and made up to 100ml, appropriate dilution were made with 0.05M phosphate buffer pH 6.8 to give concentration of 10µg/ml, scanned in UV range from 200-400nm and spectrum is recorded[3].

Drug- polymer compatibility

Drug and polymers i.e., excipients used in the preparation of formulations should be compatible with each other in order to achieve ideal dosage form[4,5].

Fourier Transform Infra-Red (FTIR) spectroscopy

FTIR studies are performed in order to know the chemical compatibility of drug with excipients and to determine the functional groups. KBr pellet method is used to determine the IR spectrum of atorvastatin. KBr contains moisture so, it should be heated at 100ºC before using it for baseline correction. The spectrum of pure drug and physical mixtures of drug and excipients was scanned in the range of 4000 to 400cm^{-1}. The spectrum obtained for pure drug is taken as reference and the spectrum of excipients is compared with it[6,7].

Differential scanning calorimetry

The thermograms of pure atorvastatin calcium and mixture of atorvastatin calcium and mixtures of drug and excipients were obtained at scanning rate of 10ºC per min conducted over a temperature range of 25-350ºC respectively. The physical state of drug in formulations was analyzed by using DSC.

Evaluation of powder blend

Bulk density

Measured quantity of powder blend of each formulation is taken in a measuring cylinder and shacked to remove any agglomeration. The volume occupied by the powder in measuring cylinder determines bulk volume[8]

The formula is

$$\text{Bulk Density} = \frac{\text{Weight of powder (gms)}}{\text{Volume of powder without tapings (ml)}}$$

Tapped density

Measured quantity of powder blend for each formulation is taken in a measuring cylinder and shaken to remove any agglomerates. Then the measuring cylinder was tapped till no change in volume is noted. The final volume of the powder will give the tapped density[9].

The formula is

$$\text{Tapped density} = \frac{\text{Weight of powder (gms)}}{\text{Volume of powder after tapings (ml)}}$$

Hausner's ratio

Hausner's ratio of powder determines the flow properties. Powders with Hausner's ratio less than 1.25 are said have good flow properties and those with more than 1.5 shows poor flow properties[2]. The formula is

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

Carr's compressibility Index

Carr's index is also called compressibility index[8]. The formula is given as follow

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{ X } 100$$

Angle of repose

It is also used to determine the flow properties of powder. Funnel method used to determine angle of repose. The measured quantity of the powder is taken in a funnel. The funnel is adjusted in such a way that the tip of funnel toucher the apex of the heap is measured to determine the angle of repose. Angle of repose is determined by using the formula[8].

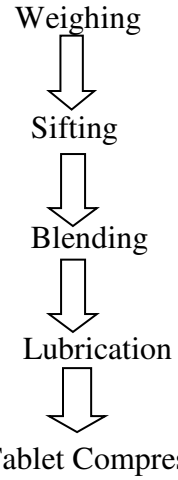
$$\text{Tan } \theta = h/r$$

Where, h is height, r is radius

Method of manufacturing oral disintegrating tablets

Direct compression

Atorvastatin oral disintegration tablets are prepared by using direct compression method with 8mm oval shaped punches and break liner on side of the tablet. Flow chart of atorvastatin oral disintegrating tablet by direct compression,



Manufacturing Process

Environment condition: Room temperature (30°C)

Manufacturing machine character: Cad Mach- Total 16 stations

Formulation of Atorvastatin calcium ODT's using sodium starch glycolate, cross caramellose sodium, as super disintegrants.

Method: Direct compression method

Formulation procedure

Ingredients such as Atorvastatin was sieved through 24 mesh and other excipients like sodium starch glycolate, cross caramellose sodium, magnesium state and micro crystalline cellulose were passed through 60 mesh. The formulation blend for each tablet is prepared and these blends are compressed by using oval shaped 8.0mm punches.

Evaluation of atorvastatin oral disintegrating tablet's

Weight variation

The tablets were selected randomly from each formulation and checked for weight variation. According to USP weight variation should be less. The following percentage deviation allowed in weight variation is[9].

Uniformity in thickness

The thickness of tablet was measured using vernier calliper or screw guage. Each tablet is taken and placed between the arms of vernier calliper and measured by sliding caliper scale[10].

Hardness test

Hardness of a tablet was determined by using Monsanto hardness tester. Hardness testing is important measurement to determine the strength and resistance to with stand mechanical shocks in manufacturing, package and shipping. Units are Kg/cm^2. Three tablets are picked from each formulation and the mean and standard deviation values were calculated[11].

Friability

It is the phenomenon where tablet surface are damaged and show evidence for lamination or breakage when subjected to mechanical shock. It was determined by using Roche Friabilator. It is expressed in percentage (%). Six tablets were initially weighed (w initial) and transferred to Friabilator. The Friabilator was operated at 25rpm for 4 minutes for 100 revolutions. The tablets are weighed again (w final). The percentage friability calculated by[12].

$$\text{Percent friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} X\ 100$$

Disintegration Time

Six tablets were selected randomly, and disintegration test was performed using disintegration tester. The 900ml of 0.05M phosphate buffer pH 6.8 was taken in a one-liter beaker and the temperature was adjusted to 37 ± 2°C. The time taken by the tablets to disintegrate with no residues left on the mesh was recorded[8].

Drug content

Weight of six tablets was recorded initially which was then crushed using mortar and pestle. Equivalent to 5mg drug, crushed amount of powder was taken which was later dissolved in 20ml methanol and then volume was made up to 100ml with 0.1 N HCl. Above solution was bath sonicated for about 20 min. It was further diluted 10 times with 0.1 N HCl. The absorbance was determined using UV-visible spectrophotometer at 244nm and concentration was calculated.

Dissolution studies

In vitro dissolution study was performed in a USP type II dissolution test apparatus using 900ml of 0.05M phosphate buffer pH6.8 as at 37±0.5°C, 75rpm for 30 min at predetermined time intervals, samples of the dissolution medium were withdrawn, filtered through membrane of 0.45mm pore diameter and analyzed spectrophotometrically[8].

RESULTS AND DISCUSSION

Identification of drugs

Organoleptic properties

Color: White

Odor: Odorless

Melting point

The melting point of pure drug is found to be 163±1°C

Solubility studies

Pure drug saturation solubility was found to be 0.019±0.12mg/ml.

Atorvastatin standard calibration curve:

Serial of dilutions made from working standard solution with suitable buffer to get concentration from 2 to 10 micrograms/ ml and the absorbance measured at 244nm.

IR spectra of pure drug sample (ATV) gave absorption peak at 3666.68cm^{-1} and 3246.20cm^{-1} of free hydroxyl group (O-H stretch) and bounded hydroxyl group (O-Hstretch), respectively; 3361.93cm^{-1} peak of amide (N-Hstretch); 2968.45cm^{-1} peak of aromatic (C-H stretch); 2927.94cm^{-1} absorption peak of alkyl (C-H alkyl); 1649.14cm^{-1} peak of keto-amide (C=O stretch); 1581.63cm^{-1} absorption band of amide (N–H bend); 1377.17cm^{-1} peak of fluoride (C-F stretch) and 1313.52cm^{-1} absorption peak of pyrrole (C-N stretch). All characteristic peaks of atorvastatin trihydratecalcium were retained in all the physical mixtures. It was found that atorvastatin calcium is compatible with super disintegrants in the formulation.

Appearance of the tablet

White colored, round shaped, tablet with plain surface.

Physical evaluation of tablet

The results of quality control tests of the prepared tablets done as for the procedure and presented in the table.

Evaluation of tablets

Tablets prepared by direct compression method, since the materials are free flowing, we opted this method, tablets obtained are of uniform die fill tablets obtained in the range of acceptable weight variation as per the limits of pharmacopeia specifications, less than 10%.

Tablets are evaluated by using the Vernier calipers. The thickness of the tablets is found to be in the range of 5.2-6.0mm. Uniformity thickness obtained due to the uniform die fill. Tablets evaluated by using the Pfizer hardness tester. Hardness of the tablets found to be in the range 5.8-6.5Kg/cm^2. Uniform hardness due to equal compression force.

Tablets are evaluated by using the Roche Friabilator and friability of the tablets are observed in the range of 0.53-0.69.

Tablets are evaluated for disintegration time in the USP disintegration apparatus. The disintegration time was found to be in the range of 45-60 sec. The tablets are evaluated for the uniformity dispersion in which all the tablets dispersed within few seconds in purified water and all the formulations under the limit.

Tablets are evaluated for the content uniformity test all the formulations are under IP Specification.

***In-vitro* Drug Release Studies**

In-vitro release data of oral dissolving tablets of atorvastatin calcium tablets

Discussion

In-vitro drug release was conducted for the formulation using USP dissolution apparatus type - II at (50) rpm. The percentage drug release at the end of 30 min found in the range 59-89%.

Sodium starch glycolate is used as the super disintegrants in the formulation from F_1 to F_4 at the concentration of 1.5 to 6% respectively.

Cross carmalose sodium is used as the super disintegrants in the formulation from F_5 to F_8 at the concentration of 1 to 4% respectively.

Preformulation:

- Melting point of atorvastatin calcium tablets was found to be 163ºC, which is complied with IP standard thus indicating the purity of obtained drug sample.
- The solubility of atorvastatin calcium is found in various solvents and it is found that it is soluble in methanol.
- In Preformulation studies it is found that, the wavelength of atorvastatin calcium is found to be 244nm by using UV spectroscopy in pH 6.8 buffer.

Differential Scanning Calorimetry

DSC enables the quantitative detection of all the process in which energy required or produced. The thermograms of atorvastatin calcium and physical mixture of atorvastatin calcium with sodium starch glycolate and thermograms of best formulation of sodium starch glycolate are shown in the figure. Atorvastatin showed the melting point at 163ºC. Peak of physical mixture of atorvastatin calcium and sodium starch glycolate appears at the same

position. This confirmed absence of interaction between atorvastatin and sodium starch glycolate.

Table No.1: Carr's index types of flow of powders

S.No	Carr's index	Type of flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fait to passable
4	23-35	Poor
5	33-38	Very Poor
6	>40	Extremely Poor

Table No.2: Flow properties of angle of repose

S.No	Flow type	Angle of repose
1	Excellent	<25
2	Good	25-30
3	Passable	30-40
4	Poor	40

Table No.3: Formulation table of Atorvastatin oral disintegrating tablets

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Atorvastatin(mg)	40	40	40	40	40	40	40	40
2	PVK K-30(mg)	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
3	Sodium starch glycolate (%)	1.5	3	4.5	6	--	--	--	--
4	Cross caramellose sodium (%)	--	--	--	--	1	2	3	4
5	Aspartame(mg)	10	10	10	10	10	10	10	10
6	Talc(mg)	2	2	2	2	2	2	2	2
7	Magnesium stearate(mg)	2	2	2	2	2	2	2	2
8	Micro crystalline cellulose Q.S. to	250mg	250mg	250mg	250mg	250mg	250mg	250mg	250mg

Table No.4: Average weight of tablet

S.No	Average weight of tablet	Percentage deviation
1	130mg or less	10
2	More than 130mg and less than 324mg	7.5
3	324mg or more	5

Table No.5: Concentration and absorbance values

S.No	Concentration	Absorbance ± SD
1	0	0
2	2	0.148 ±0.1
3	4	0.290 ±0.5
4	6	0.439 ±0.8
5	8	0.570 ±0.9
6	10	0.690 ±0.6

Table No.6: Evaluation of atorvastatin oral disintegrating tablet's

S.No	Formulation	Hardness Kg/cm² (n=3)	Friability % (n=6)	Disintegration on time sec (n=6)	Wetting variation(n=20)	Drug content % (n=10)
1	F1	6.3±0.12	0.53	58	251.12± 0.41	99.78±1.08
2	F2	6.2±0.13	0.63	60	249.02± 0.51	98.72±0.08
3	F3	6.1±0.15	0.66	45	250.14± 0.15	98.99±1.09
4	F4	6.5±0.14	0.65	60	249.52± 0.62	99.99±0.52
5	F5	6.2±0.08	0.67	55	248.62± 0.74	99.38±0.79
6	F6	5.8±0.11	0.60	50	249.72± 0.14	98.79±0.68
7	F7	6.4±0.17	0.62	50	250.17± 0.41	99.19±0.34
8	F8	6.5±0.11	0.69	55	249.44± 0.78	98.70±0.15

Table No.7: *Invitro* Studies

S.No	Time(min)	F1	F2	F3	F4	F5	F6	F7	F8
1	5	25.78±0.5	30.98±0.2	30.89±0.5	35.99±0.5	27.99±0.5	32.89±0.2	35.78±0.2	40.80±0.5
2	10	32.80±0.6	32.89±0.3	50.68±0.6	51.20±0.6	36.88±0.6	37.99±0.3	40.99±0.2	57.65±0.6
3	15	44.89±0.4	50.10±0.6	56.99±0.4	57.99±0.4	43.78±0.4	40.12±0.5	45.67±0.5	69.90±0.4
4	20	50.36±0.8	60.45±0.5	63.16±0.7	63.55±0.8	50.89±0.5	49.78±0.6	50.98±0.6	74.67±0.5
5	25	58.00±0.3	65.65±0.9	75.66±0.8	73.78±0.6	53.78±0.6	56.89±0.6	57.90±0.1	85.89±0.5
6	30	60.12±0.2	72.76±0.1	85.33±0.7	80.99±0.5	59.89±0.5	60.99±0.8	65.90±0.4	88.99±0.6

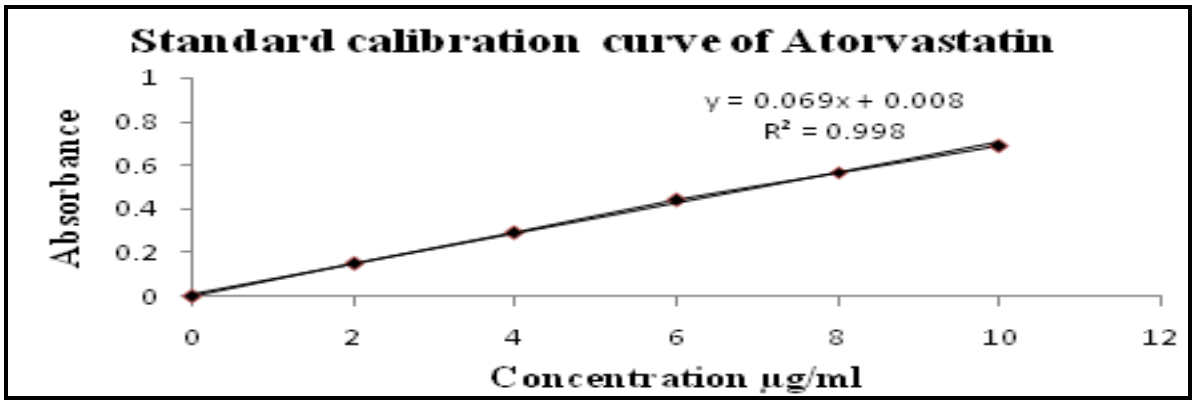


Figure No.1: Atorvastatin calibration curve

FTIR studies

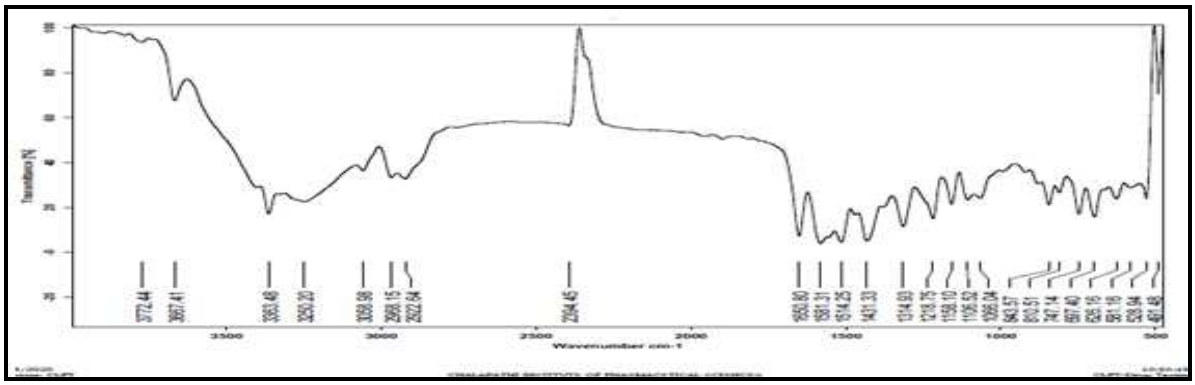


Figure No.2: FTIR spectra pure drug Atorvastatin

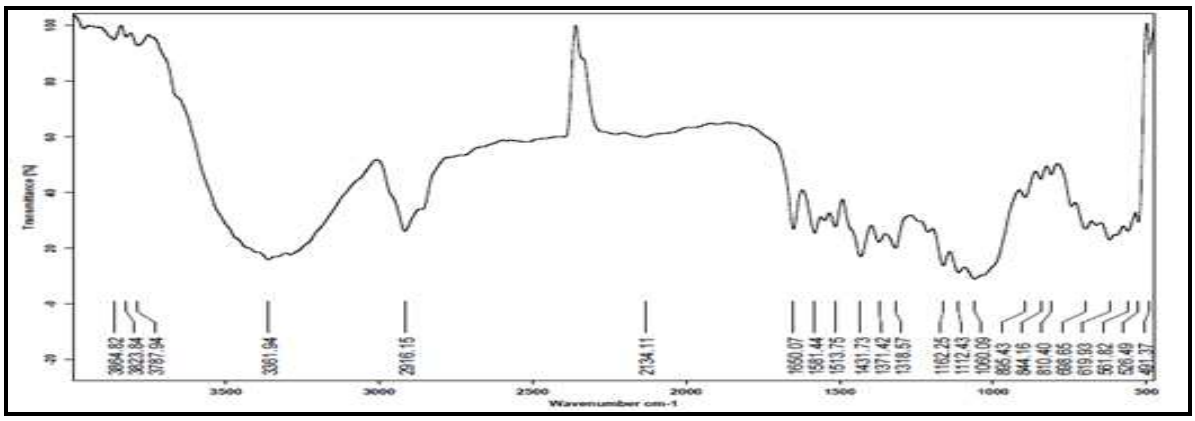


Figure No.3: FTIR spectra of Atorvastatin and physical mixtures of formulation containing SSG

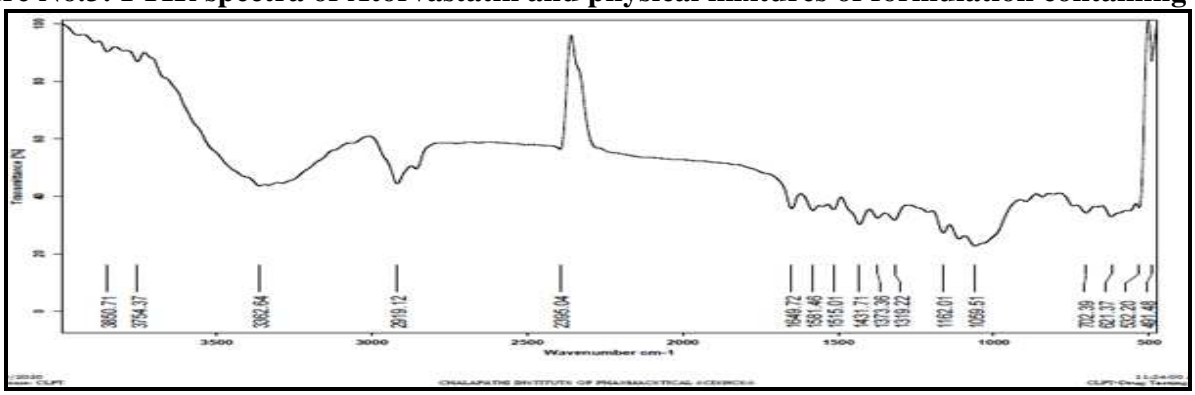


Figure No.4: FTIR spectra of Atorvastatin and physical mixture of formulation containing CCS

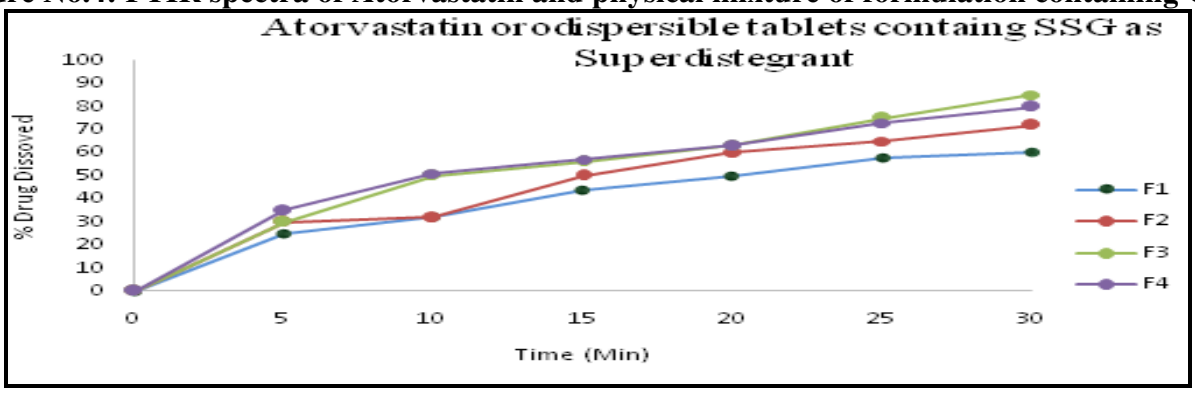


Figure No.5: *In vitro* drug release profile of F1-F4

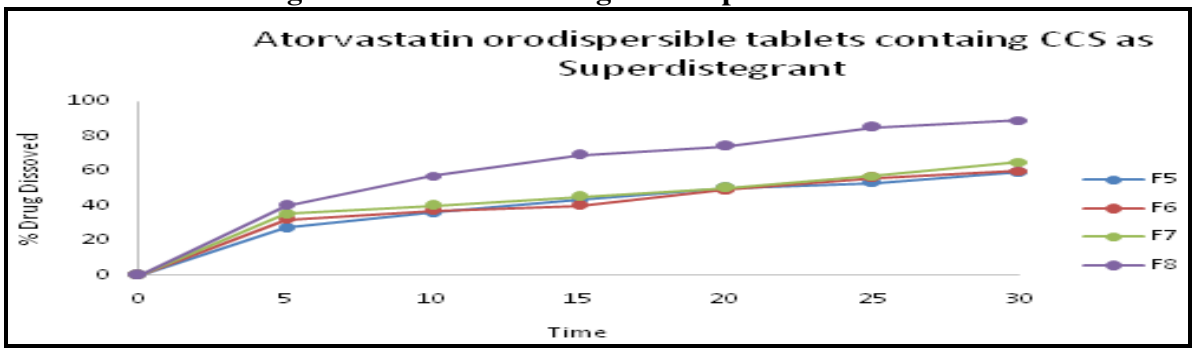


Figure No.6: *In vitro* drug release profile of F5-F8

CONCLUSION

The concept of formulating orodispersible tablets of atorvastatin calcium offers a suitable, practical approach to achieve fast release of drug. Absorption of these tablets takes place directly in to the systemic circulation, which avoids the first pass metabolism of atorvastatin calcium which ultimately results in the improvement of the bioavailability. In the present work, orodispersible tablets of atorvastatin calcium tablets successfully prepared by direct compression method using different super disintegrants in different concentrations like sodium starch glycolate, croscaramellose sodium and other excipients like magnesium stearate as lubricant and talc as glidants. All the pre-compression parameters like angle of repose, bulk density, Carr's index studied. The compressed tablet subjected to tests like hardness, drug content, friability and weight variation and *in vitro* dissolution studies.

- The drug and excipient compatibility studies like FTIR and DSC performed and the results shown that there are no physical interaction between excipients and drugs.
- Oral disintegrating tablets of atorvastatin calcium were stable without any chipping, picking or sticking.
- The drug content was uniform in all the formulations, which shows the uniformity of the content.
- Eight formulations prepared viz F1-F8, in which F8 formulations shows highest drug release 88.99%, which contains 4% croscaramellose.
- The optimized formulation F8 was found to be complying with all properties of tablets and other formulations were satisfactory.
- Formulation F8 containing croscaramellose can be effectively used in the clinical formulation of oral disintegrating tablet of atorvastatin calcium, especially in case of sudden hypertension.
- By studying above results, croscaramellose was most suitable super disintegrants for the formulation of oral disintegrating tablets of atorvastatin calcium.
- The present study is an attempt to develop an oral disintegrating tablet of atorvastatin calcium tablets with super disintegrants, which disintegrates in a matter of seconds in the oral cavity, thereby reducing the time of onset of the pharmacological action.
- Direct compression method is used for the formulation of oral disintegrating tablets, microcrystalline cellulose is used as diluents, SSG and Croscaramellose sodium were used as super disintegrants and magnesium stearate is used as flow promoter.
- The result of drug excipient compatibility by FTIR and DSC shows that there are no drugs and excipients interactions. The pre compression parameters like angle of repose, bulk density and tapped density were determined. The post compression parameters like thickness, hardness, friability and *in vitro* release time were determined and they were found to be within the IP limits.
- Hence, from the results of disintegration time and dissolution studies it was concluded that formulation F8 was found to be the most suitable formulation. This can be used in the hyper lipidemia treatment especially in sudden increase in lipid contents in body.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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