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Research

Formulation and evaluation of oral mouth dissolving film of pitavastatin calcium

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Check for	Abstract
Published on: 15 Nov 2024	The aim of this study was to develop an oral mouth dissolving film (OMDF) formulation containing pitavastatin calcium, a lipid-lowering agent, for enhanced patient compliance and convenience. The films were prepared using a solvent
Published by: DrSriram Publications	casting method with a blend of suitable polymers and excipients. Various formulations were prepared and evaluated for their physical characteristics, disintegration time, drug content uniformity, and in vitro drug release profile. Optimization was conducted to achieve the desired properties of the films.
2024 All rights reserved. Creative Commons Attribution 4.0 International License.	Characterization studies including FTIR and DSC were performed to assess the compatibility between the drug and excipients. In vivo studies were carried out in human volunteers to evaluate the taste, palatability, and pharmacokinetics of the optimized OMDF. The results demonstrated that the formulated OMDF of pitavastatin calcium exhibited rapid disintegration in the oral cavity, uniform drug content, and sustained drug release profile. The optimized formulation showed good taste and palatability, indicating its potential for improving patient adherence to therapy. Overall, the developed OMDF of pitavastatin calcium presents a promising dosage form for enhanced drug delivery and patient convenience. Keywords: pitavastatin calcium

INTRODUCTION

The concept of orally disintegrating dosage forms has emerged from the desire to provide patients with more conventional means of taking their medication. Interestingly, the demand for ODF'S has enormously increased during the last decade, particularly for geriatric and paediatric patients who experience difficulty in swallowing conventional tablets and capsules. Hence, they do not comply with prescription, which results in high incidence of ineffective therapy.

The Centre for Drug Evaluation and Research (CDER), US FDA defined Fast Disintegrating Films (FDF) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter seconds, when placed up on the tongue". FDFS disintegrate and, or dissolve rapidly in the saliva without the need for water.

A solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of the water, is known as an oral fast-dispersing dosage form. Difficulty in swallowing (dysphagia) is common among all the age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules. Dysphagia is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck thyroid therapy, and other neurological disorders, including cerebral palsy. The most common complaint was tablet size, followed by surface, form and taste. The problem of swallowing tablet was more evident in geriatric and paediatric patients, as well as travelling patients who may not have ready access to water.

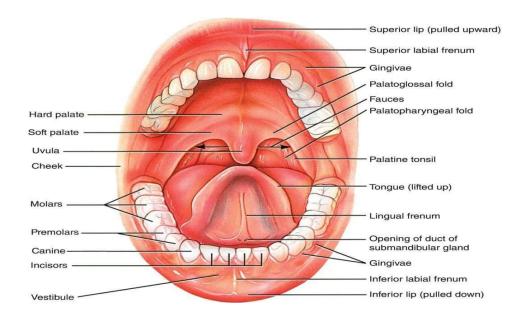


Fig 1: Structure Of Oral Mucosa

Oral mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the sub mucosa as the innermost layer. The epithelia is similar to stratified squamous epithelia, found in the east of the body in that it has a mitotically active based cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, were cells are shed from the surface of the epithelium. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as the oral mucosal thickness varies depending on the site, the buccal mucosa measures at 500-800 µm, while the mucosal thickness of the head and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100 - 200 cm. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are similar to the epidermis. The mucosae of the soft palate, the sublingual and buccal regions, however, are not keratinized. Non-keratinized epithelia, such as the floor of the mouth and buccal epithelia do not contain acyl ceramides and only have small accounts of ceramide. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulphate and glucosyl ceramides. These epithelia have been found to be consideration permeable to water than keratinized epithelia and its travel from the basal layers to the superficial layers.

Formulation Components

ODFS are fast disintegrating thin films having an area ranging from 5 to 20 cm² in which drug is incorporated in the form of matrix using hydrophilic polymer. Active pharmaceutical ingredient can be incorporated up to 15 mg along with other excipients. i.e., plasticizers, colorants, sweeteners, taste masking agents, etc. Plasticizer increases workability, spreadability and flexibility of films thereby reducing the glass transition temperature of polymers.

Aim And Objective

The main aim of the study was to improve the solubility and oral bioavailability of a poorly soluble drug Pitavastatin Calcium by formulating it as Mouth Dissolving Film (MDF) through solvent casting method. Most of

the New Chemical Entities (NCE) that are being discovered are lipophilic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery system. Because of their low aqueous solubilty and low permeability, dissolution and or release rate from the delivery system forms the rate their absorption and systemeic availability.

The Objective of the present study is To prepare inclusion complex of Pitavastatin calcium in order to increase Solubility and to Mask the bitter taste, To Develop a Formulation of fast dissolving film and evaluate *In-vitro* is solution release.

MATERIALS AND METHODS

Instruments List Of Materials Used

Table 1: List of Chemical used

S.No	Chemicals And Reagents	Supplier
1	Pitavastatin calcium	Gift sample from zydus life sciences Ltd
2	Hydroxy propyl methyl cellulose	Orchid Pvt Ltd
3	Poly vinyl alcohol	S.D.Fine Chem Ltd
4	Beta cyclodextrin	Molychem
5	PEG 4000	Qualigens
6	Urea	Qualigens
7	Glycerin	S.D Finechem Ltd
8	Sucralose	S.D Finechem Ltd

List Of Instruments Used

Table 2: List of Instrument used

S.No	Name Of Instrument/Equipment	Manufacture
1	Electronic balance(BL-2200)	Aarson Digital Balance
2	Dissolution apparatus	Lab india DS-8000
3	UV Spectroscopy	Shimazu Corporation
4	Bath Ultrasonicator	Life care
5	Desicator	Fine chem
6	Vaccum Oven	Shavani scientific PVT.Ltd
7	Hot Air Oven	Texcare Instrument
8	Calibrated Dial Gauge	Baker precision
9	Sputter Coater	Quorum sputter coater

METHODOLOGY

Preformulation Studies

Preformulation testing is the first step in the rational development of dosage forms of drugs. It involves the application of biopharmaceutical principles to the physicochemical parameters of a drug with the goal of designing an optimum drug delivery system that is stable, bioavailable and can be mass-produced. Preformulation testing is defined as investigation of physical and chemical properties of drug substances alone and when combined with excipients.

Organoleptic Evaluation of API

Organoleptic characters of drug was observed and recorded by using descriptive terminology. Following physical properties of API were studied.

Color

Odor

Taste

IR Spectroscopic Analysis

The identification of the pure drug was performed using FT-IR spectroscopy. The IR absorption spectra of the pure drug and with different Excipients were taken using KBr pressed pellet method. The pellets

were prepared by triturating sample and KBr together (1:100 ratios) and compressed at pressure of 25000 psi in a hydraulic press to form a transparent pellet. The pellet was scanned in the range of 4000-450 cm¹ using FT-IR spectrophotometer and obtained spectra were compared with the reference.

Drug-Excipient compatibility

A drug or active principle was most often delivered to patient along with other chemical substance within a pharmaceutical formulation, which should comply with strict specification, often prescribed by law. In order to be approved a formulation should warrant well defined level of stability. Interaction between drug and Excipients can be occurred by means of several mechanisms, including adsorption, complexation, chemical interaction, pH effect, and eutectic formation, resulting in drug products with desired or undesired properties. FTIR spectroscopic analysis of drug-excipients mixture was carried out spectra were compared with reference.

V Spectroscopic Analysis

Construction of Calibration curve of Pitavastatin Calcium

Preparation of 0.1 N Hydrochloric acid

8.5 ml of concentrated hydrochloric acid was diluted with distilled water and the volume made upto 1000 ml

Preparation of Simulated Salivary fluid

Dissolve 2.38gm of disodium hydrogen phosphate 0.19 gm of potassium dihydrogen phosphate and 8gm of sodium chloride in sufficient water to produce 1000ml. The pH was adjusted to 6.8.

Determination of λ max

Standard stock solution containing Pitavastatin calcium was prepared by dissolving 100mg of pitavastatin in 10 ml of Dimethyl sulphoxide in 100 ml volumetric flask to dissolve the drug. Then the volume was made upto 100 ml using phosphate buffer of pH 6.8 to obtain a concentration of 100 μ g/ml. The stock solution is further diluted using a phosphate buffer pH 6.8 to prepare 10 μ g/ml concentration. The resultant solution was scanned in the range of 200- 400 nm in UV spectrophotometer to get absorption maximum (λ max). The wavelength of maximum absorbance considered for further studies.

Preparation of Primary Stock Solution

The stock solution (1mg/ml) of Pitavastatin calcium was prepared by dissolving 100mg of drug in 100 ml of 0.1N HCL. A portion of stock solution was diluted to get the working standard solution.

Preparation of Sample solution

The above mentioned stock solution is taken 10 ml and made to 100ml with 0.1N HCL thus giving a concentration of $100\mu g/ml$. Aliquot of standard drug solution ranging from 2ml, 4ml, 6ml, 8ml and 10ml was taken and make upto 100ml with 0.1N HCL in volumetric flask. The resultant solution was estimated by UV Spectrophotometer at 245nm.

Formulation Development

Solubility Enhancement Of Pitavastatin Calcium

Kneading Method

In this method the Pitavastatin and BCD were taken in (1:1) ratio. Both drug and carrier was triturated for 45 minute by using a small volume of water to give a thick paste, which was kneaded up to 60 minutes and then kept for air dry. Then the dried mass was scratched, pulverized and shifted through sieve # 60 and stored in desiccators for further studies.

Melting Method

Pitavastatin solid dispersion prepared with polymer PEG 4000 in ratio, by using melting method. The formulation involves a drug and a water soluble carrier and heating it directly until polymers melts. The melted mixture is then solidified rapidly in an ice- bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved.

Solvent Evaporation Method

Pitavastatin & Urea solid dispersion was prepared by Solvent Evaporation method. Drug and carrier were prepared in ethanol in ratio 1:1 and mixed continuously a magnetic stirrer until the solvent is completely evaporated after that the mixture was kept at 35°C for 2 hours and dried under vaccum for 24 hrs Then the mixture is subsequently pulverized and screened through sieve 60 to obtain the uniform sized fine powder of drug polymer complex and it was Finally stored in a tightly closed container for further studies.

Evaluation parameters of oral fast dissolving film Appearance

The formulated films should be checked for their appearance. Film should be checked visually for their appearance. These parameters will be checked with visual infection of film by feel or touch. The observation suggests that the films are having smooth surface and they are elegant enough to see.

Thickness of films

The thickness of the film can be measured by micrometer screw gauge at three different places and average of three values was calculated. This is essential to ascertain uniformity in the thickness of the film which is directly related to the accuracy of dose in the film. The different films can be measured using a calibrated dial gauge (Baker Precision measuring instruments, China) with an accuracy of 0.001mm. Thickness was measured by placing the each film between the anvil and the presser foot of the dial gauge in 5 different locations and the average thickness was calculated.

Weight of films / weight variation

Oral fast dissolving films can be weighed on analytical balance and average weight can be determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipients and API.

Folding endurance

Folding endurance of the film is essential to study the elasticity of the film during storage and handling. The folding endurance of the film films was determined by repeatedly folding one film at the same place till it broke. This is considered to reveal good film properties. A film (2 x 2 cm) was cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance. All determination can be performed in triplicate.

pH value

The pH value was determined by dissolving one oral film in 10 ml distilled water and measuring the pH of the obtained solution. All determinations were performed in triplicate. It is necessary that strip should have nearly uniform pH value.

Dryness/Tack test

Tack is the tenacity with which strip adheres to an accessory or piece of paper that has been pressed into contact with the strip.

Content uniformity

The film will be tested for drug content by UV method at 245nm. A film of 2.2 cm diameter can be dissolved in purified water and diluted to get a concentration of $1\mu g/ml$. The absorbance will be measured at 245nm against blank. The amount of drug can be calculated using standard graph.

Disintegration time

The in-vitro disintegration time will be determined using disintegration test apparatus. 6 MDFs were placed in each of the six tubes of the basket and apparatus operated with 900 ml of purified water as the immersion fluid, maintained at $37 \pm 2^{\circ}$ C. The time in second's taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was recorded in seconds. The FDA recommends a disintegration time of 30s or less for ODTS based on the USP disintegration test was taken as a limit for MDFs also.

In-vitro dissolution studies

The *In-vitro* dissolution study was carried out in 500 ml pH 6.8 phosphate buffer using (USP) XIV basket apparatus II at 37± 0.5°C and at 50 rpm. Each square cut film sample (dimension: 2cm x 2cm) was submerged into the dissolution media and appropriate aliquots were withdrawn at 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 minute time intervals and again replaced with same volume of dissolution media. The sample were filtered through whatman filter paper for all the batches and analysed spectrophotometrically at 272 nm (Model UV-1800 UV-Visible spectrophotometer, Shimadzu, Japan). Sink conditions were maintained throughout the experiment. The dissolution test was performed in triplicate for each batch.

RESULT AND DISCUSSION

Preformulation study

Organoleptic Evaluation of Pitavastatin Calcium (API)

API white to off white crystalline powder, odourless, and tasteless.

Analytical development

IR Spectroscopic Analysis

The IR absorption spectra of the Pitavastatin Calcium were taken in the range 4000- 400 cm⁻¹ using KBr disc method. The major peaks were reported evaluation of purity.

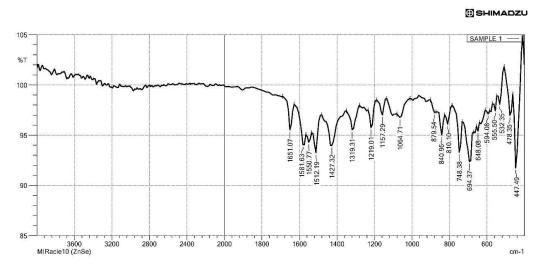


Fig 2: FTIR Spectra Of Pitavastatin Calcium

Drug-excipient compatibility FTIR compatibility study

Excipient compatibility was determined using FTIR spectroscopy. The prepared placebo and final blend were subjected to FTIR study. FTIR spectra or result were tabulated below,

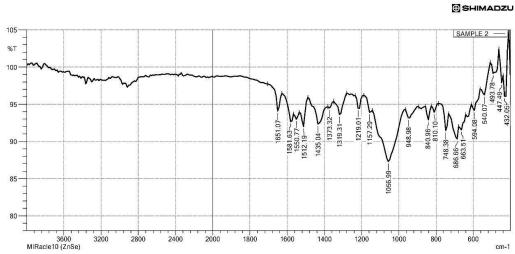


Fig 3: FTIR Spectra result

S.NO	Wave Number in cm ⁻¹	Group Assigned
1	1651.07	C=C Stretching (Aromatic)
2	1581.63	NO2 Stretching
3	1550.77	NO2 Bending

4	1512.19	NO2 Stretching
5	1319.31	C-F Stretching
6	1219.01	C-O-C Stretching
7	840.96	C-H Bending
8	748.38	C-Br Stretching
9	594.0	O-H Deformation

FTIR Spectrum of API showed the characteristic functional groups of drug along with their wave numbers. Result indicates that, there is no interaction between drug and Excipient used in the formulation.

UV Spectroscopic Analysis Construction of Calibration curve of Pitavastatin Calcium

 λ MAX of Pitavastatin calcium was determined with solutions of Simulated Salivary fluid and 0.1 N Hcl. The observed spectrum was given below,

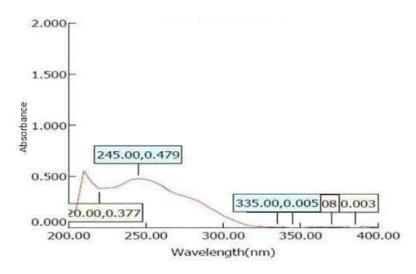


Fig 4: UV Spectrum Of Pitavastatin Calcium (λ max – 245 nm)

The λ max of Pitavastatin Calcium is 245 nm.

Dissolution profile of inclusion complex and solid dispersion Cumulative drug release pivastatin calcium

TIME (minutes)	Pure Drug	PEG
2	7.9	22.4
5	12.9	26.8
10	14.8	35.7
15	20.5	44.8
30	28.4	60.3

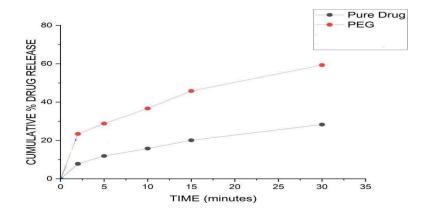


Fig 5: Comparitive invitro drug release profile of batches

From the above result, it was observed that among the Inclusion complex and solid dispersion prepared, inclusion complex with PEG showed rapid rate of dissolution in SSF. Also, it showed rapid and complete release in 0.1N Hcl. Hence inclusion complex of Pitavastatin PEG was selected for further formulation development.

Preparation of thin placebo films

To select and optimize the polymer concentration, placebo films were prepared with polymers HPMC 3cps, HPMC 15cps and polyvinyl alcohol. Among the polymers selected PVA films and HPMC 3cps (150 and 200 mg) are not completely coming out petri dish after drying. Other casted films were evaluated for *invitro* dispersion timeand the results are tabulated below.

Formulation	Concentration	Invitro Dispersion
		Time (Sec)
HPMC3cps	250 mg	28.2 ± 0.4
HPMC15cps	150 mg	15.2 ± 0.1
HPMC15cps	200 mg	18.0 ± 0.5
HPMC15cps	250 mg	22.3±0.2

From the above mentioned results it was observed that 150 mg of HPMC 15cps showed least dispersion time. Hence 150 mg of HPMC 15 cps was selected for further trials.

Formulation and Evaluation of Pitavastatin calcium MDF

WeighT (Mg)	Thicknes S (Mm)	Folding Enduranc E	Disintegratio N Time(Sec)	Invitro Dispersio N On Time(Sec)	Drug Conten T (Mg)
84±1.25	130±3.68	6.0±1	27.0±0.8	28±0.8	98.6±0.7

Physical appearance and surface texture of films

These parameters were checked with visual infection of film and by feel or touch. he observation suggests that the films are having rough surface.

Uniformity of weight

The weight of prepared film was determined using electronic balance and the average weight of the film was given in the table. The weight of MDF were about 84 ± 1.25 mg. The calculated standard deviation value was very low which suggest that the prepared film was uniform in weight.

Thickness

The thickness of MDF were about 130±3.68 µm also the calculated standard deviation values are very

low which suggest that the prepared film were uniform in thickness.

Folding endurance

Folding endurance is the next of ease of handling in the film which reveals good film properties. The folding endurance of film prepared MDF were about 6.0±1.

Surface pH

Surface pH was determined by the film were allowed in contact with 0.5 ml of distilled water. The surface pH of the MDF was close to neutral pH. Consideration the fact that acidic or alkaline pH may cause irritation to the oral mucosa and influenced the degree of hydration of polymer, the surface pH of the MDF was close to salivary pH was possible, by the proper selection of the polymer for developing the fast films.

Drug content

The drug content of Pitavastatin calcium MDF was in the range of 98.6%. The drug content and content uniformity were found within pharmacopeial limit. Both the result suggesting that drug was uniformly dispersed throughout all films.

Invitro dispersion time and Disintegration Time

The *invitro* dispersion time of the MDF were about 28 ± 0.8 sec and disintegration time of 27.0 ± 0.8 . The FDA recommends a disintegration time of 30s or less for ODTS based on USP disintegration test. The observed disintegration values of MDF were well below the limit and passes the test for disintegration.

In-vitro dissolution study

The formulated Pitavastatin calcium MDF were evaluated for dissolution study in simulated salivary fluid and 0.1 N Hcl to simulate the release in mouth and to in gastric environment respectively. The dissolution profile was compared with commercially available immediate release tablets (Pitavastatin 4 mg).

Time (Min)	Reference Ir Tablet	Pitavastain Calcium Mdf
2	14.5	26.1
5	18.3	30.6
10	23.8	40.3
15	27.5	49.4
30	35.6	65.2

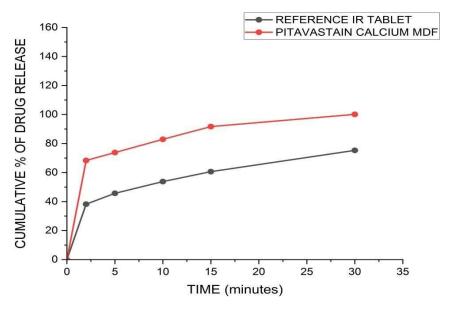


Fig 6: Comparative Dissolution Profile Of Mdf And Reference Product In SSF

Comparative dissolution profile of reference ir tablet and mdf

TIME (minutes)	Reference Ir Tablet	Pitavastain Calcium Mdf
2	38.2	68.3
5	45.7	73.8
10	53.8	82.9
15	60.6	91.7
30	75.3	100.1

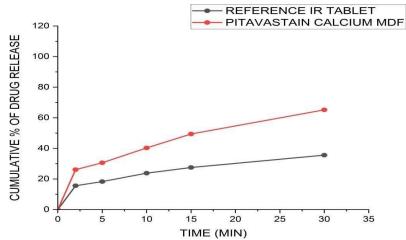


Fig 7: Comparative Dissolution Profile Of Mdfand Reference Product

The dissolution profile of Pitavastatin calcium MDF was compared with immediate release tablets of Pitavastatin calcium. The results indicate that the MDF showed rapid and extented release when compared to immediate release dosage form.

SUMMARY

Pitavastatin calcium is an Anti-hyperlipidaemic drug used for the treatment of high cholesterol level, prevention of cardiovascular disease and for cardiovascular risk reduction. But major disadvantage associated with Pitavastatin calcium is poor solubility and bioavailability. Hence enhancing the solubility of Pitavastatin calcium is inevitable to get an improved bioavailability. Mouth Dissolving Film (MDF) have better patient acceptance and compliance, may offer improved bioavailability of poorly soluble drug like Pitavastatin Calcium and improves efficacy compared with conventional dosage form. As the MDF dissolves in saliva, it may pass through enterohepatic circulation and thus prevents first pass metabolism, as it is absorbed in mouth.

In the present work, analytical method was developed for Pitavastatin Calcium using UV-spectrophotometer at λ max 245 nm. It obeys the lamberts law between 2 to 10 μ g/ml. FTIR study for API, placebo and blend was performed and the result confirms that the drug is compatible with other excipients.

The solubility of Anti-hyperlipidaemic drug Pitavastatin Calcium has been increased or enhanced by preparing 1:1 ratio of PEG inclusion complex and solid dispersion using water soluble carrier. Among the inclusion complex and solid dispersion, Pitavastatin Calcium with PEG inclusion complex showed increased solubility and rapid dissolution. To select a suitable polymer and concentration, placebo films were prepared with HPMC (3cps&15cps) and PVA in three different concentrations (150 mg, 200 mg and 250 mg per petridish). Among the trials taken, 150 mg of HPMC 15cps showed least *in-vitro* dispersion time. Hence it was selected for further formulation of MDF with selected Drug-PEG inclusion complex.

The prepared MDF were evaluated for physicochemical characteristics like uniformity of weight, thickness, folding endurance, surface pH, drug content, disintegration time, *invitro* dispersion time, *invitro* dissolution time. The Pitavastatin Calcium showed excellent weight uniformity and thickness. MDF showed neutral surface pH. The disintegration time of MDF's were below 9 sec which fulfils the FDAs disintegrating time of 30 sec for ODT. Since marketed MDF is not available, *in-vitro* dissolution study in simulated salivary fluid and 0.1 N Hcl were compared with marketed IR tablet (Pivasta 4 mg). The result indicated that dissolution rate of MDF was superior than IR tablet.

CONCLUSION

The formulation of Mouth dissolving Film of Pitavastatin Calcium complies all the requirements of mouth dissolving Film as per USP standards. It was successfully formulated. The molecular inclusion complex of Pitavastatin Calcium prepared in this study was found to have higher dissolution rates compared to commercially available immediate release tablets of Pitavastatin Calcium. Solubility enhancement, faster disintegration of Pitavastatin calcium MDF and pregastric absorption may enhance the bioavailability. On commercialization of this patient-friendly dosage form after required clinical studies, may result in a great patient compliance and a more effective treatment.

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