

FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING ORAL FILM OF A LIPID-LOWERING DRUG**Mohd. Adil Khan*¹, Girijesh Kumar Pandey¹, Amit Joshi¹, B.K. Dubey², Amit Kumar Jain¹, Prabhat Jain³****¹ Technocrats Institute of Technology-Pharmacy Education and Research, Bhopal (M.P.)****²Technocrats institute of technology- pharmacy, Bhopal (M.P.)****³Scan Research laboratories Bhopal (M.P.)***Corresponding Author's E mail: Suhan404@gmail.com

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ABSTRACT

Recently, fast dissolving films are gaining interest as an alternative of fast dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds meaning the consumer can take the product without need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance. As the drug is directly absorbed into systemic circulation, degradation in gastrointestinal tract and first pass effect can be avoided. These points make this formulation most popular and acceptable among pediatric and geriatric patients and patients with fear of choking. Thus the objective of the present study was to formulate and evaluate fast dissolving oral films (FDOFs) of simvastatin to overcome the limitation of bioavailability and increase patient's compliance. Simvastatin is an anti-hyperlipidemic drug, inhibits HMG CoA reductase enzyme and short half life ($t_{1/2}$) and usually oral dose regimen (5 to 40 mg) taken to 4 times a day. In the present study oral films were prepared by solvent casting method using HPMC K15 as a film formers and PEG 400, glycerine as plasticizers and evaluated for mechanical properties, disintegration and *in vitro* dissolution. All formulations showed good mechanical properties and *in vitro* drug release. The optimized (F5) Formulation (HPMC K15, CCS and PEG 400) exhibited drug release of 98.78 % in 15 minutes which was significantly high when compared to other formulation. Fast dissolving films of Simvastatin can be considered suitable for clinical use to lower cholesterol and triglycerides level, where a quicker onset of action for a dosage form is desirable along with the convenience of administration.

Keywords: Simvastatin, Fast dissolving oral film, Bioavailability, Mechanical properties.**INTRODUCTION:**

It is estimated that 26–50% of the patient population find difficulty in swallowing tablets and hard gelatin capsules¹. These patients mainly include the elderly who have difficulty taking conventional oral dosage forms because of hand tremors and dysphagia and pediatric patients who are often fearful of taking solid oral dosage forms owing to their underdeveloped muscular and nervous systems². In addition, patients who are mentally ill, developmentally disabled, uncooperative, on reduced liquid-intake plans or nauseated and travelers who may not have access to clean water also are candidates for FDOFs^{3,4}. The traditional alternative to swallowing difficulties is formulating a drug substance in liquid dosage form.

However, liquid dosage forms have several limitations, such as the need for measuring, bulkiness, physical, chemical and microbial stability issues, spoilage, inaccurate dosing and organoleptic properties of drug and drug formulations⁵. Conventional solid oral formulations contributed significantly to minimizing the shortcomings of liquid dosage forms. The crushing of tablets or opening of capsules is a straightforward way for patients or caregivers to lessen the swallowing difficulties. However, serious consequences may be associated with modified release, enteric-coated and cytotoxic or hormonal medicines, as these formulations are designed for special cases⁶. Moreover, European Medical Agency does not recommend the splitting or crushing of tablets because the active pharmaceutical ingredient (API) is not evenly distributed in the tablet^{7,8}. Thus, it is very convenient to develop a formulation that disintegrates in the oral cavity and eases the swallowing process. In recent years, fast dissolving oral formulations established their importance in patient population suffering from dysphagia, stroke, thyroid disorder, Parkinson's disease, multiple sclerosis and cerebral palsy⁹. Commercially available orodispersible tablets (ODT) and orally disintegrating films or orodispersible films (ODF) are the most successful platforms for pharmaceutical product development. ODTs are solid oral dosage forms that disintegrate rapidly, typically within 30 s, with or without the administration of additional water¹⁰. They provided great comfort to patients with swallowing difficulties¹¹. Despite the benefits of ODTs, there are some challenges in their processing and handling owing to their fragility and brittleness which warrant special package for protection during storage and transportation¹². The films are flexible and not as fragile as most ODTs. Hence, there is ease in transportation, consumer handling and storage of ODFs. ODF can be defined as a dosage form that employs a water soluble polymer (generally a hydrocolloid, which may be a bioadhesive polymer), which allows the dosage form to quickly wet, adhere and dissolve to release the drug when placed on the tongue or in the oral cavity⁵. ODF alleviated patient discomforts associated with swallowing disabilities without compromising the therapeutic effect. In addition, it could ease the administration of drugs to pediatric patient population¹³. Moreover, ODF can be helpful in curtailing dose variations in younger patients, in whom liquid formulations are the most accepted way of drug delivery. Currently, solvent casting methods are commonly employed to produce ODFs, owing to its ease of production and low set up costs^{14,15}. Statins are a group of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors used in heterozygotic hypercholesteraemia and hyperlipidemia. Simvastatin, lovastatin and atorvastatin are the most used but only the first one is a prodrug. Prodrug form is better absorbed in comparison to non-modified form. The chemical structure of simvastatin, (1S,3R,7S,8S, 8aR)-8-[2-[(2R,4R)-4-hydroxy-2H-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a hexahydronaphthalen-1-yl 2,2 dimethylbutanoate. Biotransformation into an active form of simvastatin (β -hydroxyacid) takes place in the liver by ring-opening reaction of the lacton.

The inhibition of the HMG-CoA causes a decrease in LDL, low-density lipoprotein (20-40%), triglycerides (10–20 %), while it increases HDL, high-density lipoprotein (5-15%) and LDL receptor expression. Due to this fact these compounds are the most commonly prescribed drugs for the prevention of atherosclerosis and heart disease, both as a prodrug or non-modified form. The fact that they can be used after heart attack and in co-existence of diabetes as well as in kidney dysfunction gives statins the status of a first choice drug. However, overdose of statins causes an increase of amino transferases concentration which can lead to myopathy. Simvastatin is a powerful lipid-lowering drug that can decrease low density lipoprotein (LDL) levels by up to 50%. It is used in doses of 5 mg up to 80 mg. Higher doses (160 mg) have been found to be too toxic, while giving only minimal benefit in terms of lipid lowering. Its act by inhibiting 3-hydroxy-3- methylglutaryl coenzyme A HMG-CoA reductase, the rate limiting enzyme of the HMG-CoA reductase pathway, the metabolic pathway responsible for the endogenous production of cholesterol. Statins are more effective than other lipidregulating drugs at lowering LDL-cholesterol concentration but they are less effective than the fibrates in reducing triglyceride concentration ¹⁶⁻¹⁹. Initial investigations were focused on the development of placebo fast dissolving films with good peel ability, appearance and a quick disintegration time. After choosing the components for the placebo film, simvastatin loaded films were formulated. Although, fast dissolving film is an attractive dosage form for the delivery of simvastatin. Finally fast dissolving films using HPMC and CCS were formulated and evaluated.

MATERIALS AND METHODS

Materials

Simvastatin were obtained as pure sample from Aristo Pharmaceuticals Limited, Mandideep, Bhopal (MP), India as gift samples along with their analytical reports. HPMC K15M, PEG-400, SSG, CCS was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Aspartame, citric acid was obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Drug-excipient compatibility study

FTIR spectra of pure drugs, polymers used and blends were recorded on KBr disk method using Brukers Alpha Spectrophotometer with IR solution software to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with potassium bromide in a glass mortar with pestle and compressed into disks in a hydraulic press (Techno search Instruments, India). FTIR

spectra of all the samples were recorded over a spectral region from 4700 to 400 cm^{-1} using 20 scans with 4 cm^{-1} resolution.

Preparation of oral films

Drug (Simvastatin) containing fast dissolving films were fabricated by the solvent casting method. The optimized amount of HPMC was dissolved in 5ml of water and stirrer continuously for 1 hour, optimized amount of plasticizer and drug were dissolved in 95 % ethanol and then added to the polymeric solution, polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm, 10 films area and was dried at controlled room temperature (25-30°C, 45 % RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use. Formulations were prepared using HPMC K15, PEG-400, SSG and CCS at different drug: polymer ratios. The compositions of the formulations were shown in table 1.

Table 1 Formulation of simvastatin oral fast dissolving films

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6
API	240	240	240	240	240	240
HPMC K 15	400	600	800	400	600	800
Glycerin	-	-	-	-	-	-
PEG-400	150	150	150	150	150	150
SSG	150	200	250	-	-	-
CCS	-	-	-	150	200	250
Aspartame	50	50	50	50	50	50
Citric acid	100	100	100	100	100	100
DM water qs to (ml)	-	-	-	-	-	-

Evaluation

The formulations were evaluated by the following tests.

Thickness

Randomly 10 films were selected and thickness was measured using vernier calliper at three different places.

Weight variation

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Drug content analysis

The patches (n = 3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 225nm.

Folding endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of moisture content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight.

***In vitro* dissolution study**

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at $37\pm 0.5^\circ\text{C}$; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery ($2.5\times 2.5\text{ cm}^2$) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through $0.45\text{ }\mu\text{m}$ membrane filter and the concentration of the dissolved simvastatin was determined using UV-Visible spectrophotometer at 225nm. The results were presented as an average of three such concentrations.

Stability studies

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at $40\pm 2^\circ\text{C}$ temperature and $75\pm 5\%$ relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of film was found to slightly decrease at higher temperature.

Physical appearance and texture analysis of the films

These parameters were checked simply with visual infection of films and by feel or touch.

***In vitro* disintegration**

The film of (4.15cm^2) size (unit dose) was placed on a petridish containing 10 ml of distilled water. The time required for the film to break was noted as cursive *in vitro* disintegration time.

Measurement of mechanical properties

Microprocessor based advanced force gauge tensiometer (DS 2 series) equipped with a 50 kg load cell was used to determine the mechanical properties of OFDFs. Film of 60x10 mm² was fixed between two clamps separated by a distance of 3 cm²⁰. The lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip broke. The force and elongation of the film at the point when the strip broke was recorded. The tensile strength and percent elongation values were calculated using the following formula.

$$\text{Tensile strength} = \text{load at breakage} / \text{film thickness} \times \text{film width}$$

$$\% \text{ Elongation} = \text{increase in length} \times 100 / \text{original length}$$

RESULTS AND DISCUSSION

The FTIR spectra of the pure drug and excipients were recorded in between 400 to 4000 wave number (cm⁻¹). No peaks are observed which interfere with the main drug peaks Fig 1 & 2. Solubility of simvastatin was freely soluble in methanol and ethanol, slightly soluble in 0.1N HCL, Sparingly Soluble in water, 0.1N NaOH, soluble in chloroform and 6.8 pH phosphate buffers. The melting point of simvastatin was 136-138°C and λ_{max} of simvastatin was found to be 225 nm in 6.8 pH phosphate buffer solution by using U.V. spectrophotometer (Labindia-3000+). The general appearance, assay, weight variation and thickness of all the films were within acceptable limits table 2. The results for tensile strength, folding endurance, disintegrating time and % of moisture were shown in table 3. Tensile strength value of optimized formulation (F5) was 1.012±0.063kg/cm². The folding endurance of the optimized oral fast dissolving formulation (F5) was 120.35 ± 6.45. The formulations containing CCS were showing good results compared to SSG. The assay values of all the formulations were ranging from 96.45 to 98.65%. The disintegration time was ranging between 105 to more than 145sec. The final formulation shows better drug release (98.78%) compared to other formulation within 15 m (Fig. 3). The cumulative percentage (%) drug release profile and the assay of the F5 formulation films indicates that the drug remain stable under the ASC without any significant change in its release profile and the drug content. From the stability studies it was clearly observed that the drug showed good stability after subjecting to accelerated stress conditions and the polymers shown significantly compatibility with the drug. The kinetic data of optimized formulation F5 was given in table 4 and fig 4. it was fallow first order drug release.

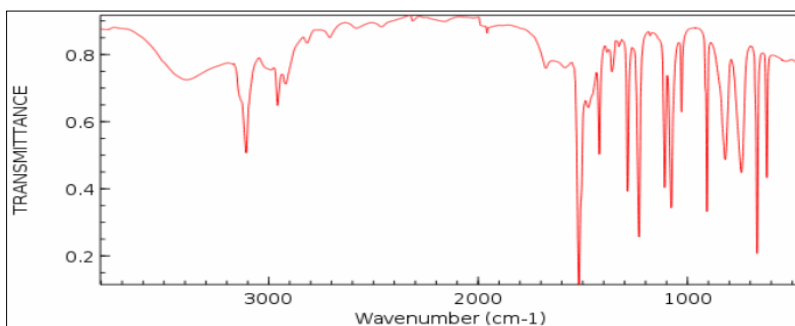


Fig. 1 FT-IR Spectrum of pure drug

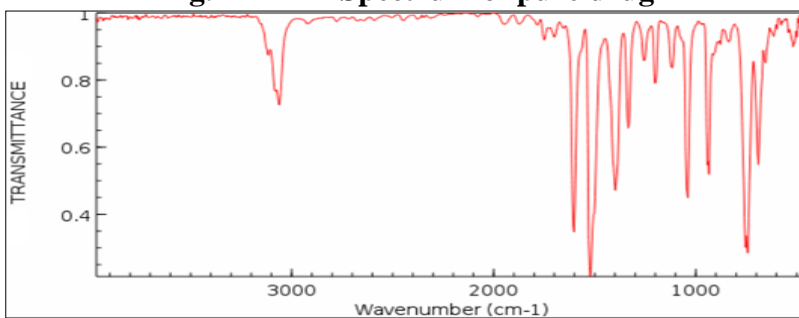


Fig. 2 FT-IR Spectrum of drug and excipients

Table 2 Result of general appearance, thickness, weight variation and % Assay

F. Code	General Appearance	Thickness in μm	Weight(mg) Mean \pm S.D	% Assay
F1	Translucent	92 \pm 4	92 \pm 4	96.45 \pm 2.12
F2	Translucent	95 \pm 6	98 \pm 3	97.89 \pm 1.45
F3	Translucent	96 \pm 5	95 \pm 4	96.45 \pm 1.21
F4	Translucent	98 \pm 8	92 \pm 5	97.25 \pm 1.78
F5	Translucent	96 \pm 7	96 \pm 4	98.65 \pm 1.32
F6	Translucent	98 \pm 8	95 \pm 3	97.85 \pm 1.74

Table 3 Result of folding endurance, disintegrating time, tensile strength &% of moisture content

F. Code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength kg/cm^2	%o Moisture Content
F1	104.33 \pm 9.87	120 \pm 10	0.985 \pm 0.065	0.521 \pm 0.45
F2	106.25 \pm 4.56	145 \pm 11	0.965 \pm 0.045	0.458 \pm 0.32
F3	100.33 \pm 7.67	113 \pm 15	0.978 \pm 0.078	0.325 \pm 0.36
F4	112.02 \pm 8.55	115 \pm 13	0.985 \pm 0.045	0.748 \pm 0.41
F5	120.35 \pm 6.45	105 \pm 14	1.012 \pm 0.063	0.658 \pm 0.25
F6	118.66 \pm 5.29	135 \pm 15	1.054 \pm 0.078	0.741 \pm 0.74

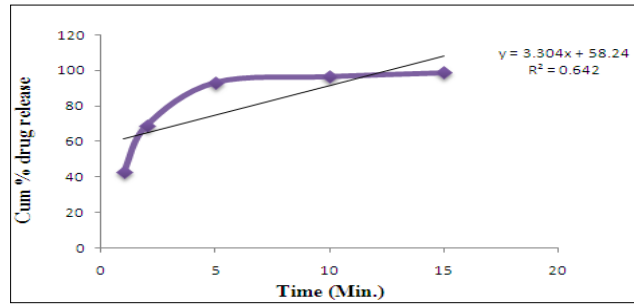
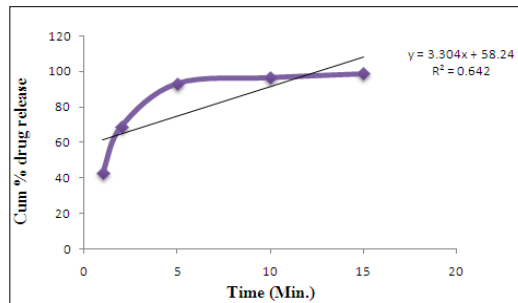


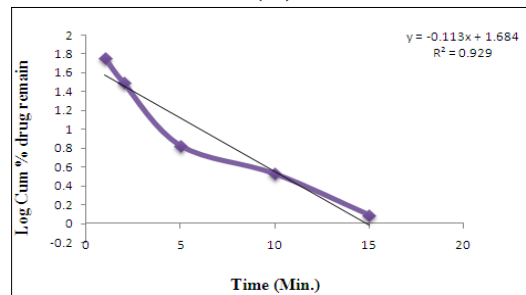
Fig. 3 Graph of *In vitro* drug release study of optimized formulation F5

Table 4 Kinetics data of Optimized Formulation F5

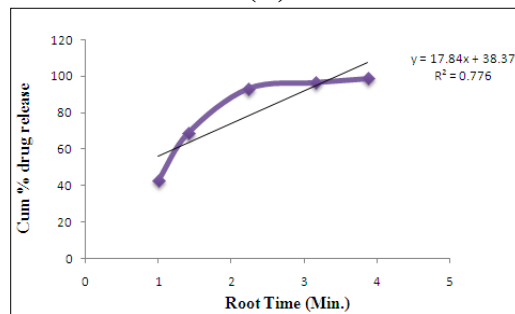
Formulation	Regression Coefficient	Zero order	First order	Higuchi	Peppas
F5	r^2	0.642	0.929	0.776	0.878



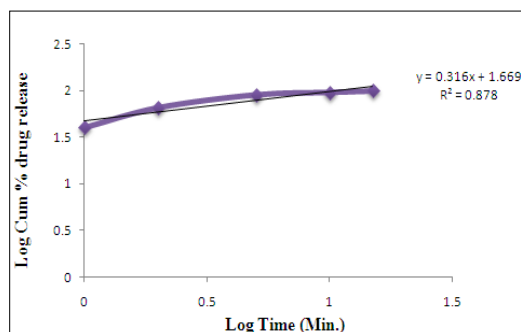
(A)



(B)



(C)



(D)

Fig.4 (A) Zero order (B) First order (C) Higuchi release (D) Korsmeyer-Peppas release kinetics of optimized formulation F5

CONCLUSION

From present study it can be concluded that oral fast dissolving films are superior in drug release. The films prepared by HPMC and PEG 400 had shown good mechanical strength, drug release, disintegration time and stability. F5 formulation is considered as the best according to the obtained results with less disintegrating time and complete drug release in 15 min. Percent drug release and disintegration time was taken as responses for study which were found within the accepted ranges. As the concentration of CCS was increased, both the disintegration and the drug release rates increased. The disintegration and release rates were found to be faster for films prepared with lowest concentration of HPMC along with maximum concentration of superdisintegrants. Simvastatin administered in the form of fast dissolving films will be potential novel drug dosage form for pediatric, geriatric and also for general population by providing faster release and better patient compliance.

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