FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILM OF SIMVASTATIN

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ABSTRACT

Simvastatin is a lipid lowering drug which is used to lower the risk of cardiovascular disease and manage abnormal lipid levels by inhibiting the endogenous production of cholesterol in the liver. Simvastatin is practically insoluble in water and undergoes extensive first-pass extraction in the liver. Thus the objective of the present research is to develop fast dissolving oral film of Simvastatin which avoid first pass metabolism and to have rapid onset of action. Oral films were prepared by solvent casting method using natural as well as synthetic film forming polymers like xanthan gum, guar gum, HPMC-K15 and HPMC-E15. The formulated films were evaluated for its appearance, thickness, uniformity in weight, surface pH, tensile strength, folding endurance, disintegration time and invitro dissolution rate. All films found to possess desirable physical and mechanical properties whereas the films based on HPMC K-15 and Xanthan gum (F2) as film former exhibited drug release of 99.42% in 18 minutes with satisfactory stability.

Keywords: **Simvastatin, Fast Dissolving Oral Films, Solvent Casting method, HPMC.**

INTRODUCTION

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration[1,2]. The fast dissolving oral film consists of a very thin strip that is just placed on the patient's tongue or any oral mucosal tissue, instantly wet by secretion the film rapidly hydrates and adheres onto the location. It then quickly disintegrates and dissolves to release the drug for oromucosal and intragastric absorption. As most of the polymers used in mouth dissolving films (MDFs) are amorphous, dispersion of drug in polymer matrix aids rapid dissolution[3-5]. These advantages enhance the patient compliance and make pharmaceutical manufacturer invest money in change of the existing products in the market to MDFs.

Dietary and lifestyle changes in recent decades have resulted in many chronic diseases such as dyslipidaemia. It constitutes a serious problem all over the world as it is considered the primary predisposing factors for many heart illnesses. Simvastatin belongs to the statins which is lipid lowering group used to control elevated cholesterol, or hypercholesterolemia. They act by inhibiting the 3-hydroxy3-methylglutryl coenzyme A[6]. Simvastatin is water insoluble crystalline powder. It undergoes extensive first pass metabolism in the liver which results in very low and variable oral bioavailability. The properties of drug like short half-life (2-3 hour), small dose size (5-80mg) and low molecular weight (418.57) makes it suitable candidate for administration by oral route[7]. This route of administration is expected to overcome the problem of poor oral bioavailability by at least avoiding the presystemic metabolism of the drug.

MATERIALS AND METHODS

Material: Simvastatin was gifted by Emcure Pharma, Pune**.** HPMC K15, HPMC E15, Xanthan gum, Gum guar, Citric acid, Sucrose, PEG-400 was supplied by Research –Lab Fine Chem industries Mumbai, Sodium starch Glycolate was supplied by Acme Pharmaceuticals, Gujarat, India.

Drug-Excipient Compatibility Study: FTIR spectra of pure drug and with excipientswere mixed thoroughly with potassium bromide (1:100) for 3-5 minutes in a mortar and compressed into disc using hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm-1 in FTIR spectrophotometer (Jasco, Japan).

Preparation of oral fast dissolving films:

The oral fast dissolving films of Simvastatin (10 mg/film) were prepared by solvent casting technique. Different viscosity grades of HPMC (K-15 and E15) as film formers, guar gum and xanthan gum as natural film forming agents and PEG 400 as plasticizer were used in the films.

***Method of preparation*[8,9]:**

- Required amount of polymer was weighed and dispersed in the solvent mixture of ethanol and dichloromethane with the help of cyclo mixer to form a homogenous viscous solution.

- Then the solution was degassed in bath sonicator for 5min.
- The bubble free solution was poured in to petriplates and dried for about 24 h. Films after drying were removed and cut into the desired size. Formulations were prepared using HPMC K-15 and E15 at different drug: polymer ratios. Plasticizer PEG 400 was used at 5ml/film. The compositions of the formulations are shown in Table1.

Table 1: Formulation table

Sr no	Ingredient mg/ml	Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Simvastatin (mg)	10	10	10	10	10	10	10	10	10
2	HPMC K15(mg)	600	600	600	-	-	-	600	600	600
3	HPMC E15(mg)	-	-	-	600	600	600	-	-	-
4	Xanthan gum(mg)	20	30	40	-	-	-	-	-	-
5	Guar gum(mg)	-	-	-	20	30	40	20	30	40
6	Citric acid(mg)	2	2	2	2	2	2	2	2	2
7	Vanillin(mg)	1	1	1	1	1	1	1	1	1
8	SSG(mg)	2	2	2	2	2	2	2	2	2
9	Sucrose(mg)	1	1	1	1	1	1	1	1	1
10	PEG400(ml)	5	5	5	5	5	5	5	5	5
11	Water(mg)	10	10	10	10	10	10	10	10	10

Evaluation of Simvastatin Films [10-17]

Fast dissolving film should be stiff, flat and should not curl on the edges. Mechanical property of the fast dissolving film plays an important role in deciding all these things. Therefore, the prepared mouth dissolving films were evaluated for the following parameters.

Physical Appearance and Surface texture: Physical appearance was checked by visual inspection and surface texture was evaluated by touch or feel of the film.

Uniformity of Weight: Each film was individually weighed on analytical balance and average weight of 3 films was determined. A large difference in weight denotes the nonuniform distribution of drug in the film.

Thickness of Film: The thickness of different films was measured using a standard Vernier Caliper. Thickness was measured by placing each film between the anvil and the presser foot of the dial gauge in 5 different locations and the average thickness was calculated.

Folding Endurance: Folding endurance was determined by repeatedly folding the film at the same position without breaking was noted for 3 films of same batch.

Surface pH: The surface pH of OFDF was determined to investigate the possibility of any side effects in *in vivo* studies. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was ensured to keep the surface pH as close to pH 6.8 (oral cavity pH). The pH of oral film was usually determined by wetting the film with distilled water in a petridish and noting pH by touching the film surface with a pH paper.

Drug content: The films of 2×2 cm^2 were cut, placed in 100 ml volumetric flask, dissolved with methanol and volume was made up to 100 ml. The absorbance of the diluted solution was measured at 238 nm.

Disintegration time: Test was performed using disintegration test apparatus. 2×2 cm^2 film was placed in the basket, raised and lowered it in such a manner that the complete up and down movement at a rate equivalent to thirty times a minute. Time required when no traces of film remain above the gauze was noted.

In-vitro dissolution study: The in vitro dissolution study was carried out for the formulations F1 to F9 was done in USP type-I apparatus using pH 6.8 phosphate buffer at 37^0C±0.5ºC and 75rpm. The measurement of % drug release was carried out at 238 nm using UV spectrophotometer.

Accelerated Stability Studies for Optimized Formulation: Accelerated stability studies were carried out according to ICH guidelines. The Optimized formulations F_2 was assessed for accelerated stability study. Each film (2 × 2 cm^2) was wrapped in a butter paper followed by aluminum foil and placed in an aluminum pouch, which was heat-sealed at the end. Stability study was carried out at 40 ± 2 °C and 75 ± 5% RH for 3 months. Samples were withdrawn every month and evaluated for its physical appearance, *in-vitro* disintegration time and % drug release.

RESULTS & DISCUSSION

Drug-Excipient Compatibility Study: IR spectra of Simvastatin and dry mix of drug, HPMC and xanthan gum are given in Figure 1a & 1b. FTIR scan of a physical mixture of drug and excipients exhibited peaks similar to that of the pure drug, indicating that there was no interaction between the drug and the excipients.

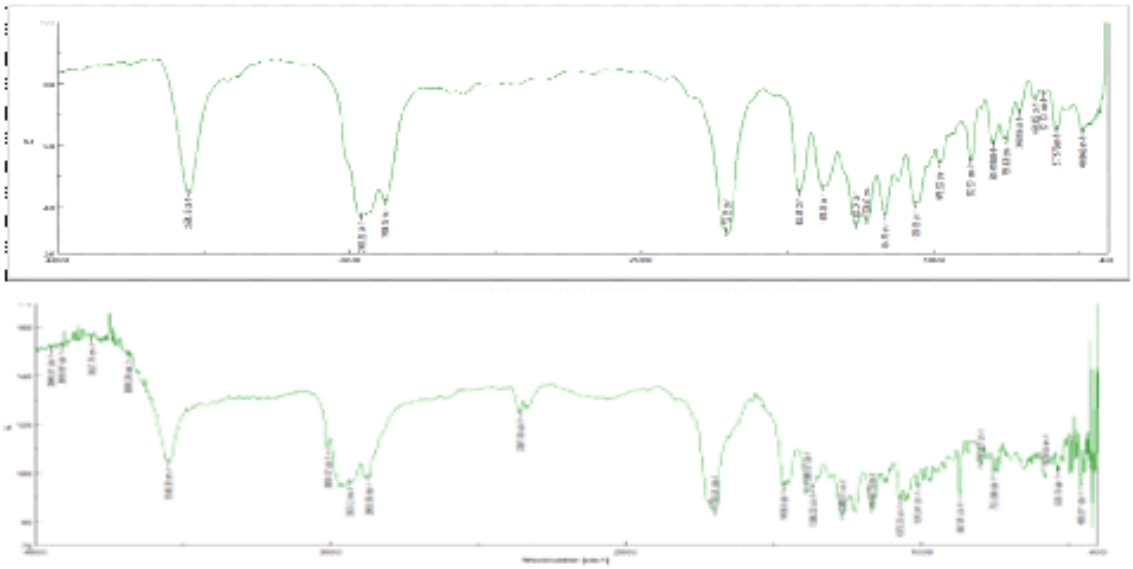

Figure 1(a): FTIR spectra of pure Simvastatin (b): FTIR spectra of Simvastatin with HPMC K15 & Xanthan gum

Evaluation of Simvastatin Films

Physical Appearance and Surface texture: Physical appearance was checked by visual inspection and surface texture was evaluated by touch or feel of the film. The organoleptic characteristics such as appearance, surface texture and odour were observed for films of Simvastatin. They were found to be clear and free from foreign materials and air bubbles without odour. Figure 2 indicates the formulated Simvastatin mouth dissolving films.

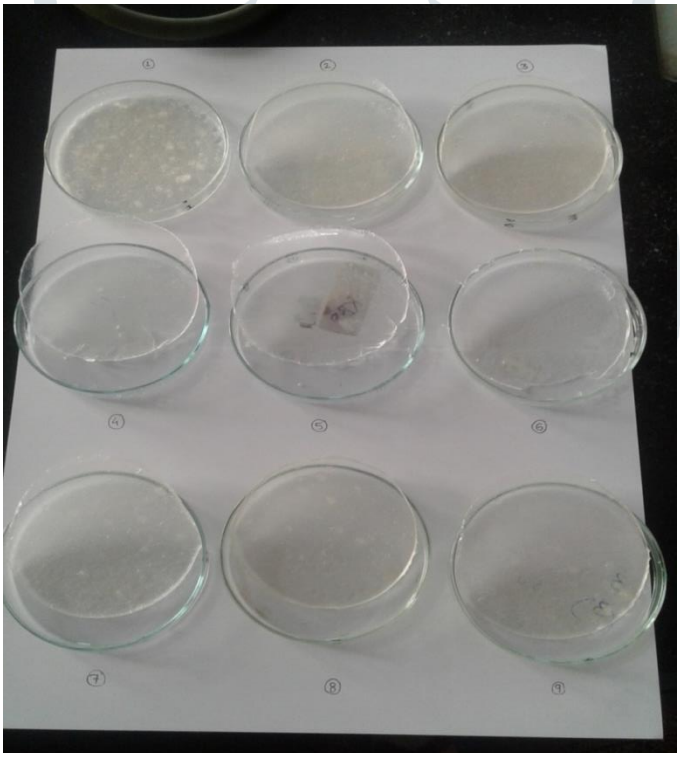

Figure 2: Simvastatin Oral Films F1 to F9

Uniformity of Weight: All the batches were uniform in weight with no significant difference in the weight of the individual formulations from the average value. Weight variation was found to be in the range of 0.0261±0.052 to 0.355±0.036 mg for films prepared.

Thickness of Film: It is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose distribution in the film**.** The thickness of the films gradually increased with increase in the amount of the polymer and was found in the range of 0.014 to 0.053mm.

Folding Endurance: For formulations F1-F3, folding endurance was in the range of 97-186, F4-F6 was in the range of 55-67 and F7 to F9 was in the range of 175-162. The observed folding endurance data of the films developed with various viscosities and concentrations of film formers indicated that the increase in viscosities and concentrations of the film lead to increase in the folding endurance of the films.

Surface pH: The surface pH of the film should be similar to that of saliva i.e. 6.8 as it is being kept in the oral cavity for dissolution for avoiding the irritation. The pH of Simvastatin film was measured in triplicate

for each sample and found in the range from 6.75 – 6.85 with an average of around pH 6.80 which indicates that pH range was well within the targeted pH and suitable in oral cavity.

Drug content: The drug content was found in the range of 89.06 to 98.16% implying uniform distribution of drug in the films.

Disintegration time: The data of disintegration time indicates that increasing the concentrations of polymer along with different viscosities tends to increase the disintegration time. Disintegration time for all the formulations were in a range of 23.00±1.03 to 48.19±1.07sec. It was observed that as the concentration of polymer increased, the thickness of film increased and thereby time taken for the film to disintegrate increased.

Table 2: Evaluation parameters of films

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness of film(mm)	0.044 ±0.01	0.014 ±0.001	0.043 ±0.006	0.052 ±0.003	0.047 ±0.004	0.050 ±0.007	0.043 ±0.004	0.045 ±0.009	0.053 ±0.004
Weight variation mg)	0.194± 0.014	0.185± 0.089	0.355± 0.036	0.205± 0.035	0.3131 ±0.068	0.0272 ±0.026	0.0261 ±0.052	0.234± 0.059	0.185 ±0.51
Folding endurance	97±19	183 ±11	186 ±10	55±5	64±3	67±3	175 ±66	163 ±23	162.3 ±16
pH of the Film	6.63 ±0.2	6.76 ±0.1	6.63 ±0.3	6.86 ±0.1	6.66 ±0.2	6.73 ±0.4	6.76 ±0.3	6.43 ±0.2	6.63 ±0.5
Drug content	93.40 ±1.65	98.16 ±1.57	92.31 ±3.91	89.06 ±0.36	96.23 ±0.91	95.42 ±1.38	93.75 ±1.1	95.98 ±1.68	92.70 ±1

In-vitro Dissolution Study: The data reveals that the percentage of drug release at the end of 18th min was between 90.85 to 99.42% for formulations F1 to F9. All formulations exhibited essentially similar release pattern. Formulation F2 showed a maximum percentage drug release of 99.42%. This could be attributed to the higher rate and extent of swelling of the larger proportion of the hydrophilic polymer.

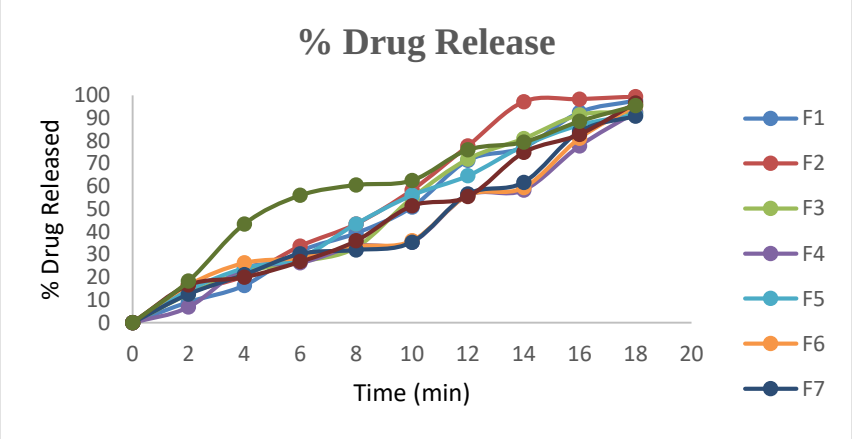

Figure 3: Drug release from simvastatin oral fast dissolving films

Accelerated Stability Study

Accelerated Stability Study: To determine the change in performance of dosage form on storage, stability study of optimized formulations (F2) were carried out at 40 ± 2 °C and 75 ± 5% Rh for 3months. Samples were withdrawn after each month and evaluated for physicochemical properties. It was concluded that formulations F2 was stable and retained its original properties with minor differences. There was no physical change in appearance and flexibility. Moreover, there were no major changes in disintegration time and drug content. Hence, the formulations were found to be stable.

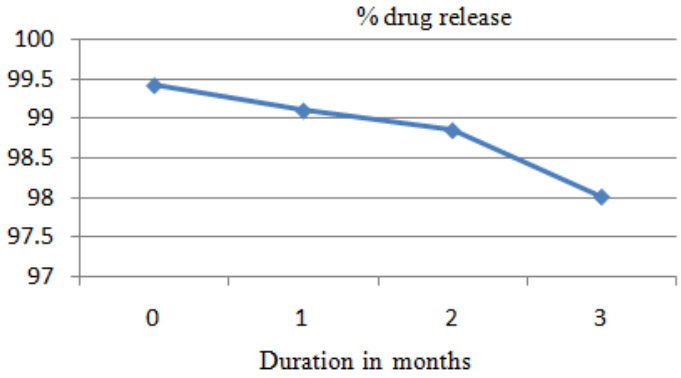

Figure 4: Stability of best formulation F2

CONCLUSION

Oral fast dissolving films loaded with simvastatin were formulated successfully by solvent-casting method. FTIR studies suggested that characteristic bands of simvastatin was not affected by polymer. Formulated films were homogenous and transparent with a neutral surface pH. Formulation F2 disintegrated in 26 seconds and released 99.42% of drug within 18 min was considered as the best formulation. From the results, it can be concluded that fast dissolving films of Simvastatin using HPMCK 15and xanthan gum as film polymer and PEG400 as plasticizer can be prepared successfully.

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CONFLICT OF INTEREST: Conflict of interest declared none.

REFERENCES

1. Sharma D.A, Salunkhe K.S, Chaudhari SR. Fast dissolving oral films: a review. International journal of pharmaceutical research and development, 2013;5(2)
2. Hosny K.M and Khames A: Preparation and evaluation of Simvastatin Orodispersible Tablets containing Soy polysaccharide and Potassium polacrillin as Novel Superdisintegrants. *Int J Pharm Sci Res* 2013: 4(9); 3381-3389.
3. Kadam V.S, Bharkad V.B, Shete G.A, Jameel A, Shendarkar G.R. and Jadhav V Formulation and evaluation of fast dissolving oral film of metoclopramide HCL. World journal of pharmacy and pharmaceutical sciences 2017; 1-8.
4. Patil P, Shrivastava S.K. Fast dssolving oral films an innovatve drug delivery system 2014; 33(7):1-8.
5. Yatin D.K, Dipen A.T, Amit V.P, Vipul P.P. Formulation and evaluation of fast dissolving sublingual film of metoprolol succinate ; Int. J. Pharma. Sci, 2013; 4(3): 140-54.
6. Pedersen TR, Tobert JA. Simvastatin: a review; Expert opinion on pharmacotherapy. 2004 5 (12): 2583-2596.
7. Murtaza G., Solubility enhancement of simvastatin: a review. Acta Poloniae Pharmaceutica, 2012; 69(4):581-590.
8. Malke S, Shidhaye SS, KadamV.J. Formulation and evaluation of oxacarbazine fast dissolve tablets; Indian J. Pharm. S. 2007; 69(2): 211-214.
9. Rajendra Prasad A, Prasanthi S, Ganesh Kumar Y, Shantha Kumari K. Development and validation of uv spectroscopy method for simvastatin in pH 6.8 phosphate buffer. Int. J. of Pharmacy and Analytical research 2015, 4(1): 16-20.
10. Deepthi A, Venkateswara Reddy B, Navaneetha K. Formulation and evaluation of fast dissolving oral films of zolmitriptan; American Journal of Advanced Drug Delivery 2014; 2(2): 153-163.
11. Mishra S, Kumar G, Kothiyal P. Formulation and evaluation of buccal patches of simvastatin by using different polymers; The Pharma Innovation 2012; 1(7):87-92.
12. Rao P.S and Reddy T.R.M. Development and evaluation of mouth dissolving films containing selegiline; International journal of pharmaceutical sciences and drug research, 2018; 10(4), 315-21.
13. Ali M.S., Vijendar C., Kumar S. D., Krishnaveni J. Formulation and evaluation of fast dissolving oral films of diazepam. J Pharmacovigilance 4: 210.
14. Sandeep I A, Bhavana N, Sankeerth P.T, Nandhini P., Nadendla RR. Formulation and evaluation of loperamide oral films; International Journal of Scientific & Engineering Research; 2017; 8(10): 370-380

15. Reddy P.S., Murthy K.R.; Formulation and evaluation of oral fast dissolving films of poorly soluble drug ezetimibe using transcutol Hp. Indian J of Pharmaceutical Education and Research. 2018; 52 (3):398-407.
16. Raza S.N., Kar A.H., Wani T.U.,Khan N.A: Formulation and evaluation of mouth dissolving films of Losartan potassium using 3^2 factorial design. Int. J Pharm Sci & Res 2019; 10(3): 1402-1411.
17. Senthilkumar K., Vijaya C. Formulation development of mouth dissolving film of etoricoxib for pain management Advances in Pharmaceutics 2015; 1-11.