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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF SIMVASTATIN

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ABSTRACT
The objective of the present work was to formulate mouth dissolving tablet enriched with taste masking agent to provide rapid onset of action of simvastatin increasing its therapeutic efficacy and also increase the compliance amongst geriatric, pediatric and uncooperative patients. Precompression blends of the MDTs were prepared and evaluated for its micromeritic properties. The angle of repose, bulk and tapped density, Hausner's ratio and Carr's Index were determined and all indicated that the prepared blends have excellent flow characteristics. Total seven formulations of MDTs were prepared using direct compression (DCT1 to DCT4) and sublimation method (ST1 to ST3). The concentration of the super-disintegrant or the sublimating agent was varied depending on the method. All the formulations were subjected to post compression evaluation test and the results indicate that the direct compression formulation had hardness of 4 Kg/cm^2 while those prepared using sublimation had hardness of 3 Kg/cm^2, thickness of 8 mm, weight variation in the range of 3.5-5.1 %, friability of less than 1 %, drug content in the range of 97.9 to 98.5 %, wetting time from 19 to 41 seconds with water absorption ratio of more than 75 %, disintegration time of less than 30 seconds and a drug release of more than 80 % over a period of 5 minutes.

KEYWORDS: Simvastatin, mouth dissolving, sublimation, super-disintegrant, direct compression.

INTRODUCTION
Simvastatin (Figure 1) is a hyperlipimic drug that lowers the level of lipoproteins in blood. It has attaracted considerable attention due to its potential to prevent cardiovascular diseases by retarding the accelerated atherosclerosis in hyperlipoproteinemic individuals. It is indicated for the treatment of hyperlipidemia to reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C). Simvastatin is a lipid-lowering agent, which is an inactive lactone which gets hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. The maximum absorption of the drug occurs in 1.3-2.4 hours and it has a half-life of 2 to 3 hours. It has a bitter taste and requires taste masking.[1]

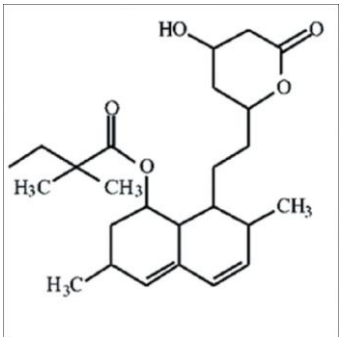

Figure 1: Structure of simvastatin.

Previously several attempts have been made to mask its taste and improve it onset of action.[2-6] The onset of action of simvastatin has been reported to be 1 hour post oral administration. Difficulty in swallowing (dysphagia) is a very general problem with patients of all age groups, especially with the pediatrics and elderly. Owing to these challenges it was envisioned that a mouth dissolving tablet enriched with taste masking agent would be a probable solution to provide rapid onset of action of simvastatin increasing its therapeutic efficacy and also increase the compliance amongst geriatric, pediatric and uncooperative patients.

MATERIAL AND METHODS

Simvastatin and Crospovidone were obtained as a generous gift from Medibios Laboratories, Tarapur; Mannitol and Saccharin were purchased from Oxford Fine Chemicals. UV-Visible Spectrophotometer Labtronics, LT-2201) was used to measure the absorbance of solution for testing drug content.

Preformulation studies[7,8]

The procured sample of simvastatin was observed for its appearance, color and taste in order to characterize the physical parameters. Melting point of the sample was determined by open capillary method. The specific optical rotation of the aqueous solution was determined using an optical polarimeter. In order to check the solubility qualitative method was used.

Calibration curve of Simvastatin in methanol[9]

An accurately weighed quantity of 100 mg simvastatin pure drug was taken in a 100 mL volumetric flask. Sufficient quantity of methanol was added to it and shaken well until the drug completely dissolved. From this, 10 mL of the solution was pipetted out and made up to 100 mL with methanol. From this 5, 10, 15, 20 and 25 mL of solutions are pipetted out in separate standard flasks and the volume was made up to 100 mL with methanol. The absorbance is measured at 231 nm in UV-Spectrophotometer.

Preparation of MDTs of simvastatin by Direct Compression method[10]

The MDTs of simvastatin were prepared by direct compression method according the batch formula given in Table 1. All the ingredients were separately sifted through 60 mesh sieve. The drug and microcrystalline cellulose were mixed in small portions of both and blending it to get a uniform mixture. This mixture was kept aside for blending. All the other ingredients were accurately weighed and mixed in geometrical order and tablets and blended in a double cone blender. The blend was compressed to tablets of 8 mm sizes using flat round punch using compression Machine.

Table 1: Batch formula per tablet using direct compression method.

Ingredient (mg)	Formulation code			
	DCT 1	DCT 2	DCT 3	DCT 4
Simvastatin	5	5	5	5
Crospovidone	7	14	21	28
Saccharin Sodium	12	12	12	12
D-mannitol	114	107	100	93
Avicel PH-102	54	54	54	54
Methyl cellulose	3	3	3	3
Talc	3	3	3	3
Magnesium stearate	2	2	2	2
TOTAL	**200**	**200**	**200**	**200**

Preparation of MDTs of simvastatin by Sublimation method[11]

Sublimation method has been used occasionally for the formulation of MDTs. As no reported sublimation method was found in literature for formulation of simvastatin MDTs, we formulated three formulations using varying concentration of camphor as the sublimating agent. The composition of the formulation developed is presented in Table 2. Accurately weighed ingredients were sifted through sieve no.44 and thoroughly mixed for 10 minutes. All other ingredients except magnesium stearate were added to the blend and thoroughly mixed. The specified quantity of magnesium stearate was added to the mixture and was blended in double cone blender for 1 minute. The tablets were compressed using tablet punching machine. The compressed tablets were than subjected to sublimation at 50°C for 60 min.

Table 2: Batch formula per tablet using sublimation method.

Ingredient (mg)	Formulation code		
	ST1	ST2	ST3
Simvastatin	5	5	5
Crospovidone	24	24	24
Saccharin Sodium	6	6	6
D-mannitol	85	75	65
Avicel PH-102	50	50	50
Camphor	10	20	30
PVP	15	15	15
Talc	3	3	3
Magnesium stearate	2	2	2
TOTAL	**200**	**200**	**200**

Precompression evaluation the formulation blends

All the prepared blends (DCT1-4 and ST1-3) were subjected to determination of the micromeritic properties (bulk and tapped density, angle of repose, Hausner's ratio and Carr's Index) using previously reported methods.[12,13]

Evaluation of MDTs[7]

The MDTs prepared using both the methods were subjected to evaluation of the post compression parameters (tablet evaluation) according to guidelines.

Hardness Test

The hardness of the formulated tablets was tested using Monsanto type hardness tester.

Friability test

The friability test of the formulations was performed using a Roche type friability test apparatus.

Weight Variation Test

20 tablets were randomly taken and weighed to calculate the average weight of the tablets. Each of these tablets was individually weighed and the difference from average weight was calculated. The percent weight

variation was calculated to determine the deviation from the average weight.

Thickness

The thickness of randomly selected tablets from each batch of formulation was measured using a digital vernier caliper.

Drug content

Five tablets from each formulation were weighed to determine the average weight. These tablets were crushed in a mortar then the amount of powder equivalent to 20 mg of drug was transferred in 20 mL of methanol. 10ml from this stock solution was withdrawn and diluted up to 100 mL with methanol. 0.6 mL from this stock solution was pipetted out and diluted to 10 mL. Absorbance of the resulting solution was measured at 231 nm using UV spectrophotometer.

Wetting time

A piece of tissue paper folded twice was placed in a small petri dish (i.d. = 6.5 cm) containing 10 mL of water, a tablet was placed on the paper, and the time for complete wetting was measured.

Water Absorption ratio

A piece of tissue paper was folded twice and placed in a Petri dish containing 6 mL of 0.5% v/v amaranth solution (as a coloring agent) in water. A tablet was placed gently on the tissue paper, and the wetted tablet was reweighed. The water absorption ratio R was determined according the following equation.

$$R = \frac{W_a - W_b}{W_b} \text{ X } 100$$

In vitro disintegration time

The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. One tablet was placed in each of the 6 tubes of the basket and a perforated disc was placed over each tablet. The assembly was raised and lowered at 30 cycles per minute in the pH 6.8 buffer maintained at 37±2°C. The time required for complete disintegration of the tablet with no palpable mass remaining in the apparatus was recorded.

In-vitro dissolution

The USP type II paddle apparatus with a paddle speed of 50 rpm was used for dissolution testing for the formulated MDTs. The dissolution media used consisted of 900 mL of 0.1 N HCl. 5 mL of samples were collected at time points of 5, 10, 15, and 30 min and the media was replenished with the same volume of fresh media. The free drug concentration was estimated using a UV spectrophotometer at a wavelength of 231 nm.

RESULTS AND DISCUSSION

Preformulation Study

The physical characterization of the drug obtained as gift sample was carried out in order to confirm the identity of the drug and the results of physical characterization, melting point and qualitative solubility studies are presented in Table 3.

Table 3: Physical characterization of simvastatin.

S. No	Test	Specification	Observation
1	Color	White or off-white	White
2	Taste	Bitter	Bitter
3	Appearance	Crystalline powder	Powder
4	Melting Point	135-138°C	137-139°C
5	Solubility	Insoluble in water, soluble in ethanol, and dichlormethane	Insoluble in water, soluble in ethanol, soluble in chloroform

Calibration curve of simvastatin

The λmax of Simvastatin was determined by scanning a 10µg/mL solution of the drug using UV sprectrophotometer from 200-400 nm. The λmax was found to be 231 nm and was hereafter used for determination of the drug in solution. The absorbance of 5 to 25 µg/mL solutions was measured at 231 nm by UV spectrophotometer (Figure 2).

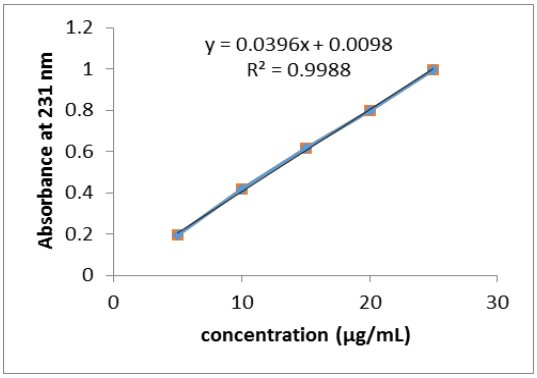

Figure 2: Calibration curve of simvastatin.

Precompression Parameters of the formulation blends

The angle of repose is a measure of the frictional forces in the loose powder blend that may hinder the flow

property of the blend making it unsuitable for feeding through the hopper of the tablet machine. The angle of repose of all the formulation blends ranged from 23°28' to 27°18'. A θ value of less than 30° of powder or blends is known to exhibit excellent flow properties.[14] The results of precompression evaluation of the formulation blends are presented in Table 4. From the results it is evident that all the blends possessed the capability to flow freely and may present no hindrance in compression or tabletting process. The values of Hausner's ratio and Carr's Index are found to be within the specifications of good flow property of powders.[15]

Table 4: Precompression parameters of blends.

Formulation Code	Bulk density (g/cm^3)	Tap density (g/cm^3)	Angle of repose (°)	Carr's Index (%)	Hausner's Ratio
DCT1	0.281	0.325	23.28	13.54	1.16
DCT2	0.287	0.329	24.22	12.77	1.15
DCT3	0.293	0.341	25.31	14.08	1.16
DCT4	0.299	0.344	27.18	13.08	1.15
ST1	0.291	0.329	24.27	11.55	1.13
ST2	0.294	0.337	24.33	12.76	1.15
ST3	0.304	0.339	24.45	10.32	1.12

Evaluation of MDTs

The tablets formulated after compression were evaluated for various quality control tests of solid dosage forms (tablets) in order to ensure that all the products meet the requirements of mouth dissolving tablets.

The hardness of all the tablet formulations using direct compression method was 4 Kg/cm^2 whereas for formulations with sublimation method the hardness was 3 Kg/cm^2 indicating uniform hardness and sufficient mechanical strength. The thickness of all the tablets was found to be around 8 mm and uniform exhibiting the uniformity of flow of the blends in to the die cavity of the punching machine. The weight variation for all the formulations was found to be in the range of ±7.5% specified by the pharmacopoeias for tablets of average weight less than 324 mg. All the formulations exhibited friability of less than 1 % indicating good mechanical strength in the tablets. The drug content of each formulation was determined by using the method described in section 4.6.5 and it was found that all the formulations contained drug content in the range of 97.9 to 98.5 % (Table 5).

Table 5: Post compression parameters of MDT formulations.

Formulation Code	Hardness (Kg/cm^2)	Thickness (mm)	Average Weight variation (%)	Friability (%)	Drug content (%)
DCT1	4	8	4.9	0.51	98.20
DCT2	4	8	5.1	0.62	97.90
DCT3	4	8	4.7	0.43	98.50
DCT4	4	7	4.9	0.56	98.10
ST1	3	7	3.5	0.29	98.40
ST2	3	8	4.2	0.44	97.90
ST3	3	8	3.9	0.51	97.90

The wetting time and water absorption ratio are the indicator of the efficiency of the superdisintegrants. They exhibit the capacity of the disintegrants to absorb water and wet the tablet completely within the shortest time duration. The quick wetting and high water absorption ratio help in swelling of the MDTs and its rapid disintegration and dissolution in the oral cavity. The wetting time of the formulations ranged from 19 to 41 seconds with water absorption ratio of more than 75 % for the formulations (Table 6). The results reveal that all the formulations possessed the ability to quickly disintegrate and dissolve.[16] All the formulations exhibited of less than 30 seconds in the *in vitro* test ranging from 18.9 to 27.1 seconds.

In vitro dissolution study was performed to evaluate the release profile of the drug from various formulated MDTs. The results of the study are used to relate the percentage of drug release from its dosage form as a function of time. The addition of super-disintegrants to the formulation aids in the quick disintegration of the formulation promoting the quick dissolution of the particles which in turn enhances the release of drug from the dosage form ultimately causing enhance bioavailability and quick onset of action of the drug. All the formulations were found to release more than 80 % of the drug within a period of 5 minutes. While DCT1 exhibited the lowest release of drug (83.4 %), the highest amount of drug was released from ST3 (94.3 %).

The release rate was found to be higher in the formulations prepared by sublimation method as compared to those formulated by direct compression method. The higher porosity formed in the tablets during the sublimation process may be responsible for quicker disintegration and higher release of drug from the formulations.

Table 6: Wetting, water absorption, disintegration and drug release of MDTs.

Formulation Code	Wetting time (seconds)	Water absorption ratio	Disintegration time (seconds)	Drug release (%)
DCT1	41	75.1	27.1	83.40
DCT2	38	79.6	25.3	86.80
DCT3	32	82.3	22.4	89.10
DCT4	25	87	20.6	92.40
ST1	25	76.3	24.3	89.40
ST2	21	83.3	22.1	91.60
ST3	19	88.5	18.9	94.30

The tablets prepared by direct compression method exhibited relatively poor dissolving capabilities compared to those prepared by sublimation method. Crospovidone containing tablets usually present high capillary activity and pronounce hydration and oppose gelling thereby causing rapid disintegration and drug release. On the other hand tablets prepared by sublimation method have the lowest hardness and their porous structure is responsible for rapid water uptake, thereby facilitating the wicking action of methyl cellulose in bringing about faster disintegration.[17]

CONCLUSION

It can be concluded from the study that mouth dissolving tablets of simvastatin could be easily formulated using super-disintegrants and sublimating agents in order to achieve a rapid onset of drug action and peak plasma concentration over short period of time. The MDTs formulated using could be highly beneficial for the better compliance in elderly patients.

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