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Studies on Release Performance of Proniosmes and its Tablets of BCS Class II Drug Simvastatin

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ABSTRACT

The Present investigation deals with the preparation and evaluation of proniosomes of simvastatin using non-ionic surfactant like span 60, cholesterol and maltodextrin in various proportions and evaluation of performance of prepared proniosomes in tablet dosage form. Proniosomes were prepared by slurry method. Proniosomes and tablets were evaluated for In-vitro drug release study, solid state characterization and results of dissolution study was compared with marketed formulation. Proniosomes showed very poor drug release because drug was molecularly dispersed in span 60, cholesterol and which may effect on the drug release. The prepared tablet formulation showed improvement in dissolution rate due to presence of hydrophilic carrier like a maltodextrin and other hydrophilic tablet excipients. Thus, the developed proniosomal tablet formulation of simvastatin improve dissolution rate in comparison with marketed formulation and may leads to enhancement of bioavailability of simvastatin.

Keywords: Proniosomes, Simvastatin, Span 60, Maltodextrin, Cholesterol.

INTRODUCTION

The vesicular systems are highly ordered assemblies of one or several concentric lipid bilayers formed, when certain amphiphillic building blocks are confronted with water. Vesicles can be formed from a diverse range of amphiphillic building blocks. Novel drug delivery attempts to either sustain drug action at a predetermined rate, or by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. It can also localize drug action by spatial placement of controlled release systems adjacent to, or in the diseased tissue or organ; or target drug action by using carriers or chemical derivatization to deliver drug to particular target cell type. Different types of pharmaceutical carriers such as particulate, polymeric, macromolecular and cellular are present. Particulate type carrier also known as colloidal carrier system, includes microspheres, nanoparticles, polymeric micelles and vesicular like liposomes, sphingosome, niosomes, transferosomes, pharmacosomes, virosomes [1,2].

Proniosomes are dry formulations of surfactant coated carrier, which can be measured out as needed and rehydrated by brief agitation in hot water. These “proniosomes” minimize problems of niosomes physical stability such as aggregation, fusion and leaking and provided additional convenience in transportation, distribution, storageand dosing. Proniosomes-derived niosomes are superior to conventional niosomes in convenience of storage, transport and dosing. Dry proniosomes are expected to be more stable than a pre-manufactured niosomal formulation. In release studies proniosomes appear to be equivalent to conventional niosomes. Size distributions of proniosomes-derived niosomes are somewhat better than those of conventional niosomes so the release performance in more critical cases turns out to be superior. Proniosomes are dry powder, which makes further processing and packaging possible. The powder form provides optimal flexibility, unit dosing, in which the proniosomes powder is provided in capsule could be beneficial. Dry granular type of proniosomes involves coating with water soluble carrier such as sorbitol or maltodextrin with surfactant. The result of coating process is a dry formulation in which each water soluble particle covered with thin film of surfactant. The proniosomes are reconstituted by addition of aqueous phase at temperature greater than transition temperature and brief agitation [3,4].

The 3-hydroxy-3-methylglutaryl-coenzyme (HMGCoA) reductase inhibitors or statins are clearly the most effective class of drugs for lowering LDL cholesterol. Those drugs have been associated with a beneficial on cardiovascular disorders. As such, statins have become some of the most widely prescribed (e.g. simvastatin, fluvastatin, pravastatin, atorvastatin, pitavastatin, cerivastatin). Several combination preparations of a statin and another agent, such as ezetimibe/simvastatin, are also available. According to the most recent NCEP (National Cholesterol Education Program) guidelines, the indications for the use of statins have been broadened such that patients with even low normal LDL cholesterol levels are now being treated in favorably altering the incidence of stroke and myocardial infarction [5,6].

Simvastatin is a hypolipidemic/lipid lowering agent categorized as a BCS class II i.e., low solubility high permeability [7]. In literature attempts has been made to improve bioavailability of simvastatin by various approaches like solid dispersion [8], lycopene-containing Nano formulation [9], caseinate-coated simvastatin-zein nanoparticles [10], micronisation [11], amorphous simvastatin dispersed in pHPMA [12], niosomes for pediatric transdermal drug delivery [13], Solid lipid nanoparticles for oral delivery [14].

Authors are aware about the use of cholesterol in oral delivery of simvastatin but here simvastatin was taken as a model drug due to high lipid solubility (BCS class II drug) and used cholesterol was in small amount. In present investigation it was observed that proniosomes can retard the drug release but when tablets were prepared there was improvement in drug dissolution.

MATERIALS AND METHODS

Simvastatin was obtained as a gift sample from Lupin Research Park Pune, Cholesterol, Span-60, and maltodextrin was purchased from Loba chemie Mumbai. All other ingredients were of analytical grade.

Preparation of proniosomes by using slurry method

Proniosomes were prepared by the slurry method. Seven different ratios of surfactant to cholesterol were prepared with decreasing ratio of carrier as mentioned in Table 1. For the ease of preparation a 250 µmol stock solution of span-60 and cholesterol was prepared in chloroform solution was added to a 100 ml beaker containing the maltodextrin carrier, stirred it continuously to make a slurry. These materials were further dried overnight at room temperature. This dry preparation is referred to as proniosomes. These proniosomes were stored in a tightly closed container at room temperature for further evaluation [15,16].

Table 1: Composition of proniosomes formulation.

S. No.	Formulation code	Drug (mg)	Surfactant Span 60 (mg)	Maltodextrin (mg)	Cholesterol (mg)	Solvent (ml)
1	P1	100	200	300	200	8
2	P2	100	200	300	150	8
3	P3	100	200	300	100	8
4	P4	100	200	300	50	8
5	P5	100	50	300	150	8
6	P6	100	100	300	100	8
7	P7	100	150	300	50	8

Preparation of proniosomal tablets

Proniosomes were weighed to have an equivalent of 5 mg of simvastatin; Tablets were prepared by direct compression method. Proniosomes along with other excipients like talc, lactose, sodium starch glycolate, were mixed in a mortar. The resulting blend was lubricated with magnesium stearate and compressed on the KBR Press (round shaped, 6 mm punch) machine [Model no: M15] composition of proniosomes tablet as shown in Table 2 [17,18].

Table 2: Composition of proniosomes tablet.

Content	Batch 1 Qt (mg)	Batch 2 Qt (mg)	Batch 3 Qt (mg)	Batch 4 Qt (mg)	Batch 5 Qt (mg)	Batch 6 Qt (mg)	Batch 7 Qt (mg)
Proniosomes (Equivalent to 5 mg simvastatin)	38	32	29	23	26	25	21
Lactose	130	135	137	141	139	140	145
SSG	24	25	26	28	27	27	26
Mg Sterate	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200

Characterization of proniosomes

The prepared proniosomes and compressed tablets were characterized by using FTIR, PXRD and DSC in short, IR spectrums of drug and optimized formulation were determined on Fourier Transform Infrared Spectrophotometer. The X-ray diffraction pattern of pure drug, proniosomes was recorded by using X-ray diffractometer (Philips analytical X-ray diffractometer (Model: PW 3710) (Philips, Almelo, The Netherlands)) with copper target, having voltage of 30 kV, and current of 30 mA. The DSC thermograms of Proniosomes were recorded on the thermal analyzer of (In PerkinElmer 4000 Software: PYRIS Version-11.1.0.0488, 2009, PerkinElmer, Inc.) The thermal analysis was performed at a heating rate of 10°C /min over temperature range of 50°C to 400°C in nitrogen Atmosphere.

In vitro dissolution study

The *in-vitro* dissolution test of prepared all batches of simvastatin proniosomes and tablets were carried out by USP apparatus type II at a temperature of 37 ± 5°C in 900 ml of 0.1N HCL + 0.1% SLS as an dissolution medium at 50 rpm. 5 ml of sample was withdrawn at different time interval (5, 15, 30, 45, 60, 90 and 120 minutes) and filtered through whatman filter paper, analyzed spectrophotometrically at 239 nm and drug release was calculated. At each interval of sample was replaced by fresh medium for maintaining the sink condition.

Evaluation of tablets

The prepared tablets were evaluated for official and unofficial tests with *in vitro* dissolution study as described above.

Stability studies

The formulations (Tablets) were stored in air tight sealed vials at room temperature. Surface characteristics in proniosomes were selected as parameter for evaluation of stability, the proniosomes were sampled at regular interval of time (0, 1, 2, and 3 months), observed for color change and surface characteristics [19].

RESULTS AND DISCUSSION

FTIR analysis

FT-IR spectra of Simvstatin showed all possible peaks of functional group at wavelength 3553 cm^{-1} indicates free OH stretching vibration, 3011, 2959 and 2872 cm^{-1} indicates aliphatic CH stretching and at 1714 cm^{-1} indicates stretching vibration of ester and lactone carbonyl functional group [1]. All characteristic peaks were observed for simvastatin in physical mixture. FT-IR spectra of proniosomes showed the peak at 3546 cm^{-1}, 2927 cm^{-1}, 1699 cm^{-1} for, OH stretching vibration, CH stretching vibration and stretching vibration of ester and lactone carbonyl functional group respectively. In the FT-IR spectra of proniosomal tablet showed all possible peaks of functional groups at wavelength 3523, 3325, 3264 cm^{-1} indicates free OH stretching vibration, the peaks at 2900 cm^{-1} indicates aliphatic CH stretching and at 1696 cm^{-1} indicates stretching vibration of ester and lactone carbonyl functional group as shown in Figure 1 and Table 3. The overlay spectra of proniosomal tablets showed peaks same as that of pure drug no significant shifting pattern was observed. It indicates that there was no interaction between drug and excipients [20].

Table 3: Principle peaks observed in overlay of FTIR spectra.

S. No	Type of peak	Standard peak	Observed peak			
			Pure drug	Physical mixture	Proniosomes	Tablet
1	O-H Stretching	3000-3700	3546	3546	3374	3523
2	C-H stretching	2700-3300	2952, 2930, 2872	2919	2927	2900
3	Esters and Lactone Carbonyl group	1600-1700	1698	1696	1699	1696

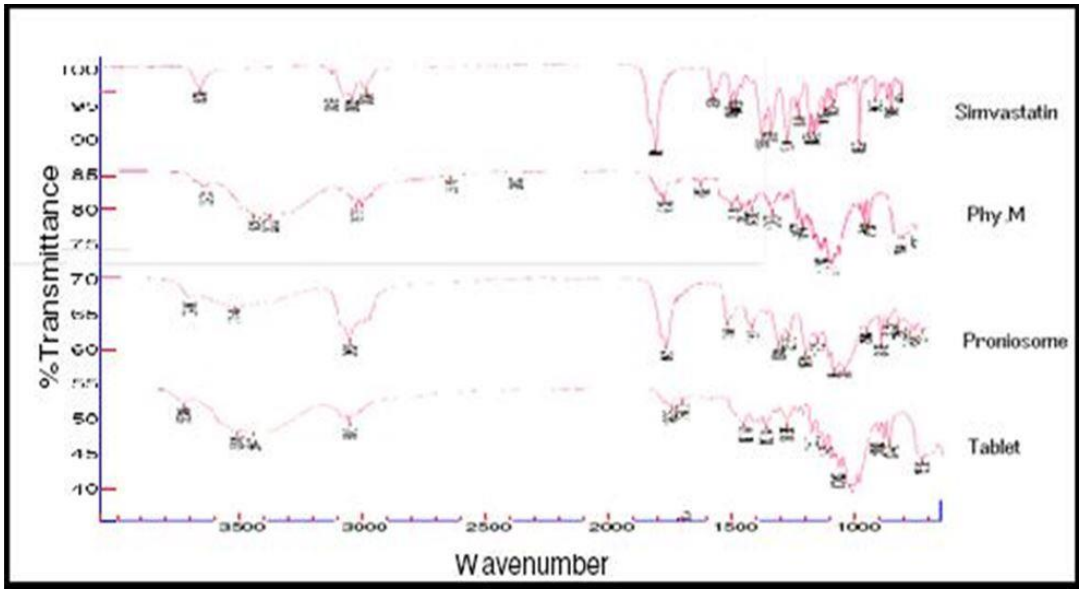

Figure 1: FTIR spectral analysis of formulation.

X-Ray Diffraction Studies (PXRD)

The diffractogram of pure simvastatin shows typical and sharp peak at angle of (2Ɵ) 10.91, 14.88, 15.63, 17.19, 17.66, 18.79, 22.08, 25.91 with peak intensities at 1672, 2206, 2118, 6253, 3560, 3019, 2271, 1237 respectively which is indicates that the crystalline nature of pure drug. The crystallinity was determined by using comparing representative peaks heights in diffraction pattern of the co-crystals with those of reference. The relative degree of crystallinity was calculated by using following equation.

$$RDC = I_{sam} / I_{ref}$$

Where, I_{sam}- Is the peak height of the sample under investigation and Iref- is the peak height at the same angle for reference with highest intensity. In case of proniosomes and prepared tablets of proniosomes showed the peak intensity 1133 and 1116 at 2Ɵ of 17.19 and 17.66 respectively. The proniosomal tablet formulation showed the peak intensity 450 and 465 at 2Ɵ 17.19 and 17.66 respectively. From these it showed that there was decrease in crystallanity of drug in proniosomes and proniosomal tablet [21]. The RDC value for prepared proniosomes and tablet are shown in Table 4 and overlay of XRD are shown in Figure 2.

Table 4: RDC value for prepared Proniosomes and tablets.

S. No.	Formulation	Angle (2θ)	RDC
1	Proniosomes	17.19	0.18
		17.66	0.31
2	Tablet	17.19	0.071
		17.66	0.13

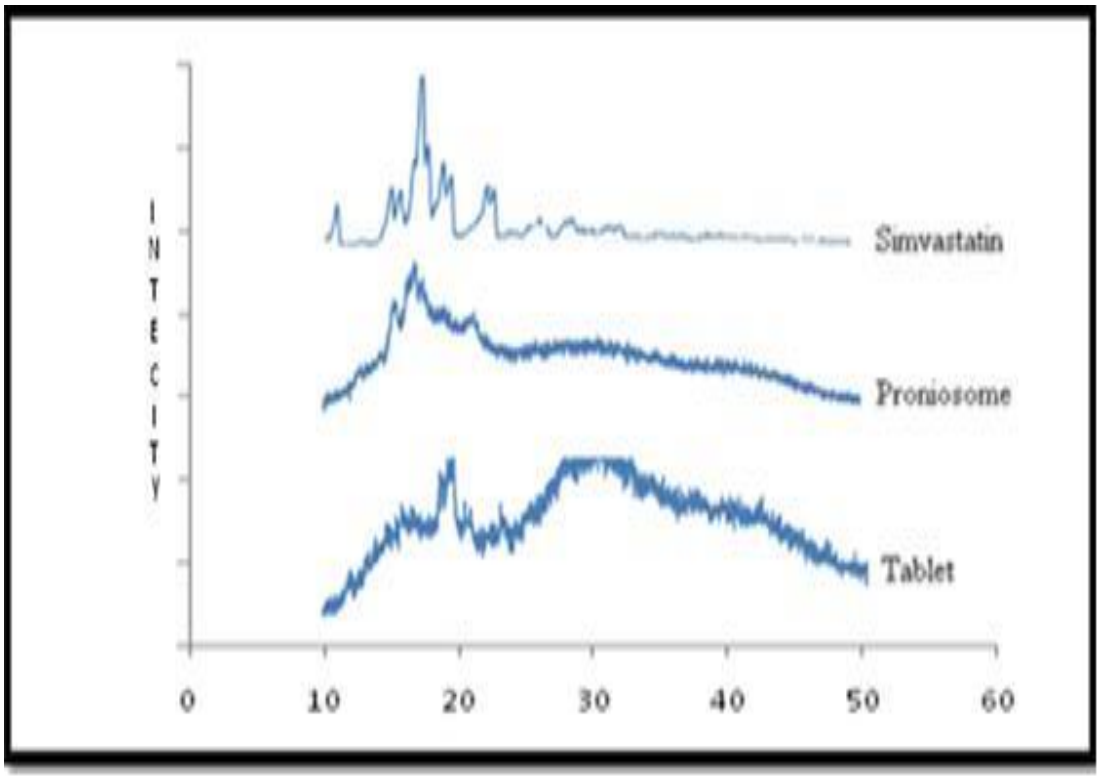

Figure 2: PXRD analysis of formulations.

DSC analysis

One of the most classic applications of DSC analysis is the determination of the possible interaction between drug entity and the excipient in its formulation. The DSC thermogram of pure drug (Simvastatin) showed an intense endothermic peak at 138.11°C. This is in consistent with the characteristics of simvastatin melting point ranging from 136°C to 140°C.

The physical mixture showed endothermic peak with low intensity. The peak was observed at the 147.64°C and 210°C respectively. The second peak was observed at 210°C due to presence of maltodextrin in formulation which is having melting point 240°C as per literature [22]. In case of DSC thermogram of proniosomes there was no any peak, because drug was molecularly dispersed in proniosomes and it is in dissolved or solubilized form during heating [23]. The DSC thermogram of tablet formulation showed melting endotherm at 144.32°C this might be due to recrystallization or solidification of drug due to applied compression force. The second peak observed at 207°C due to presence of maltodextrin as shown in Figure 3 [22].

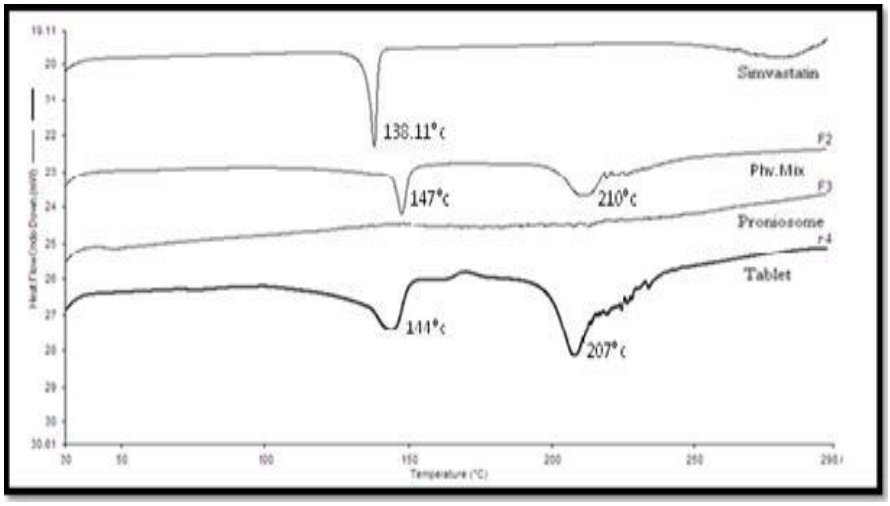

Figure 3: DSC spectra's of simvastatin and formulations.

In vitro dissolution study of proniosomes

Dissolution study reveals that there was no any significant change in drug dissolution as compare to pure drug. All the formulations showed less than 3% drug release at the end of 2 hrs. It is supported by DSC, that drug was in a solubilized state it may be difficult to release from the lipoid matrices of cholesterol and span 60.

Characterization of proniosomes loaded tablets

The disintegration time for all seven batches was found in the range of 4 to 5 min. The optimized batch F5 passes the IP limit for disintegration time. The prepared proniosomes tablet shows hardness in the range of 2.5 to 4 kg/. Friability for prepared proniosomes tablets within range of 0.11% to 0.19% this passes the IP limit of less than 1% as shown in Table 5.

Table 5: Characterization of proniosomes tablets.

Formulation	F1	F2	F3	F4	F5	F6	F7
Average Weight (mg)	200.00 ± 1.73	199.34 ± 0.57	200.35 ± 0.53	198.67 ± 0.57	200.00 ± 1.73	200.67 ± o.57	199.34 ± 1.52
Size (mm)	6 ± 0.1	6 ± 0.1	6 ± 0.1	6 ± 0.1	6 ± 0.1	6 ± 0.1	6 ± 0.1
Disintegration time (min)	4 to 5	4 to 5	5 to 6	4 to 5	5 to 6	4 to 5	5 to 6

Thickness (mm)	2 ± 0.1	2.1 ± 0.1	2.3 ± 0.1	2 ± 0.1	2.2 ± 0.1	2.1 ± 0.1	2 ± 0.1
Hardness (kg/cm^2)	3 ± 1	4 ± 10	3 ± 1	4 ± 1	3.5 ± 1	4 ± 1	2.5 ± 1
Friability (%)	0.11	0.11	0.15	0.16.	0.19	0.14	0.17

Dissolution study of proniosomes loaded tablets

From the drug release study of formulation F1 to F7 drug release was found to be 0.084 to 71.31% within 120 min, as compare to the drug release of proniosomes and marketed tablets of simvastatin (Zoc or 5 mg), the prepared tablet formulation showed improvement in drug release due to presence of hydrophilic carrier like a maltodextrin and other hydrophilic tablet excipient which may have diluted the lipid matrices. At the end of 30 minutes in case of prepared tablets, there was decrease in drug release this might be due to phase transformation or crystallization of dissolved drug [24-26] on line monitoring of this by PXRD is essential. % drug released from marketed tablets and prepared tablets as shown in Figures 4 and 5 respectively.

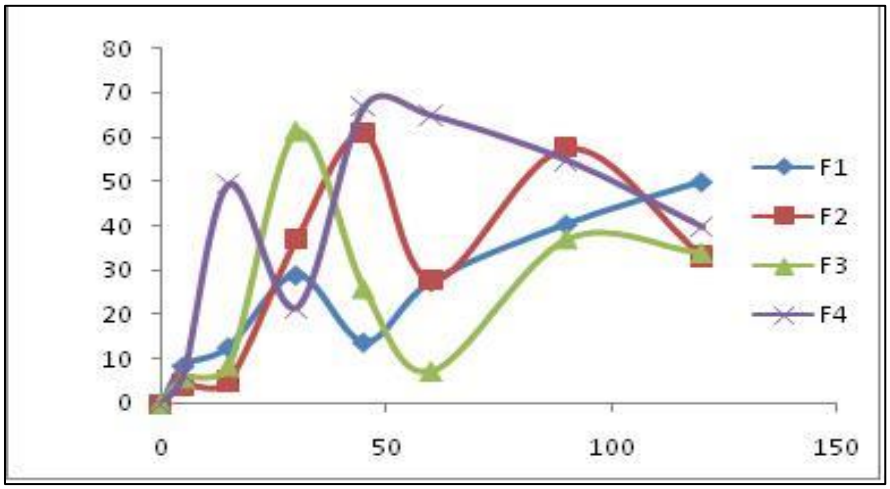

Figure 4: *In vitro* dissolution profile of proniosomes loaded formulations of simvastatin.

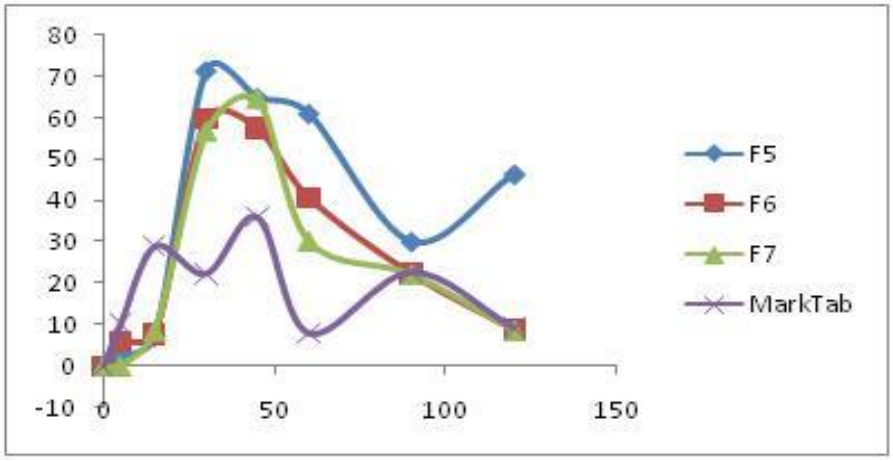

Figure 5: Comparative dissolution profile of simvastatin, marketed formulation and proniosomes loaded tablets.

Stability studies

Stability study of the proniosomes tablet formulation was conducted in air tight sealed vials at room temperature for three month. The formulation was analyzed for Surface characteristic and color change. From the results, it was revealed that proniosomal tablet showed no any change in surface characteristic and color after three month

CONCLUSION

In the present investigation proniosomes were successfully formulated by using span 60, cholesterol and maltodextrin and evaluated for its drug release study. Hence there is feasibility of delivery of simvastatin through the proniosomal tablet. Thus, the developed proniosomal tablet formulation may help to improve the dissolution rate and may enhance the bioavailability of Simvastatin.

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