AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

A Comparative Assessment of Solid Dispersion and Surface Solid Dispersion Technique to Improve Solubility of Simvastatin

Rezaur Bin Islam[1], Md. Abdullah Al Masum[2*], Md. Mofazzal Hossain[3], **Anjuman Ara Alam[1], Florida Sharmin[1], S.M. Ashraful Islam[1]**

1. Department of Pharmacy, University of Asia Pacific, Dhanmondi, Dhaka-1209, Bangladesh

2. Research & Development Formulation Department, Incepta Pharmaceuticals Ltd, Savar, Dhaka, Bangladesh

3.Department of Pharmacy, University of Information Technology and Sciences, Baridhara, Dhaka-1212, Bangladesh

ABSTRACT

Practically water insoluble Simvastatin has been accused for being poorly absorbed from gastro intestinal tract. With an aim to improve the solubility and dissolution characteristics of the drug, solid dispersion and surface solid dispersion were prepared by using different water soluble and insoluble carrier at different ratio. Dispersions were made by solvent evaporation technique and undergo drug content test, compatibility by FT-IR, DSC thermal study and *in vitro* drug release study. FT-IR and DSC thermographs showed the compatibility of the drug and carrier in the incorporated ratio. All the preparations were found to improve the dissolution behavior of Simvastatin significantly compare to the binary physical mixtures and the pure drug. The suitability of solid dispersion and surface solid dispersion technique was evaluated. Also the efficacy of the carriers to improve the dissolution behavior was compared. Tablets were formulated by incorporating dispersions and were subjected to various physical tests including thickness, diameter, hardness, average weight and disintegration time. Their release pattern was compared with compressed matrix of drug and two brand products available in Bangladesh market. Their drug release pattern was further characterized with mean dissolution time (MDT), fractional dissolution time ($T_{50\%}$ and $T_{80\%}$) and percent dissolution efficiency. Tablets made of dispersion with HPMC, sodium starch glycolate and croscarmellose sodium were found to have better release rate and extent than the drug and the brand products.

Keywords: Phase homogenization; Release exponent; Mean dissolution time; Dissolution efficiency; Surfactant.

*Corresponding Author Email: almasum@inceptapharma.com

Received 21 April 2015, Accepted 27 April 2015

Please cite this article as: Masun AA *et al*., A Comparative Assessment of Solid Dispersion and Surface Solid Dispersion Technique to Improve Solubility of Simvastatin. American Journal of PharmTech Research 2015.

INTRODUCTION

Simvastatin, a well known statin, is a competitive inhibitor of Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase which is the rate limiting enzyme in cholesterol biosynthetic pathway. It is indicated in hypercholesterolaemia, mixed dyslipidaemia, atherosclerotic cardiovascular disease, diabetes mellitus and other cardioprotective disease. Simvastatin belongs to BCS class II having low solubility (1.45µg/ml) and therefore low oral bioavailability[1]. This poor aqueous solubility may result in dissolution controlled absorption and high variability in pharmacologic action. Therefore, to augment its aqueous solubility, dissolution rate and bioavailability from its oral solid formulations is vital[2], challenging and rational.

Diversified techniques have been used to improve the aqueous solubility of Simvastatin, such as the use of hydrotropic solubilizing agents[3], microemulsion[4], self-emulsifying system[5], cyclodextrin inclusion complexation[6], particle size reduction technique[7], solubilization by surfactant[8] and solid dispersions[1]. Among them, solid dispersion system has been proven promising for long. With a view to improve the solubility characteristics of Simvastatin, solid dispersion was prepared by some water soluble carriers like Lutrol F 127, polyethylene glycol 4000 & 6000 and HPMC 5 cps and surface solid dispersion was prepared by two water insoluble carriers including croscarmellose sodium and sodium starch glycolate. Their release behavior was compared with the binary physical mixture with respective polymer and their compatibility was confirmed by FT-IR and DSC thermographs. The efficacy of the carriers to improve the solubility of Simvastatin was compared and further tested by incorporating the dispersions in to compressed matrix.

MATERIALS AND METHOD

Materials

Simvastatin and Lutrol F 127 were found from Incepta Pharmaceuticals Ltd as generous gift sample. Sodium starch glycolate manufactured by Yung Zip Chemical, China and polyethylene glycol 4000 & 6000 manufactured by Clariant International, Germany were purchased. All other ingredients were of analytical grade and purchased from local market.

METHODS

Preparation of solid dispersions and surface solid dispersions

Solid dispersions (SD) and surface solid dispersions (SSD) were prepared by solvent evaporation technique according to the method of Sukanya and Kishore, 2012[1]. The SDs were prepared at weight ratio of 1:1, 1:5 and 1:10 (drug: carrier) and named as per [Table 2] using Lutrol F 127 (L_1), HPMC 5 cps (H_5), polyethylene glycol 4000 (P_4) and polyethylene glycol 6000 (P_6) as

carriers. The SSDs were prepared at same weight ratio by using water insoluble disintegrants sodium starch glycolate (SSG) and croscarmellose sodium (CCS) as carriers. Accurately weighed amount of Simvastatin and carrier were taken in a glass beaker and either dissolved or dispersed molecularly in minimum volume of Acetone to obtain a clear solution. The solution was stirred robustly for uniform mixing and evaporated at room temperature by using a blower. The viscous residues thus obtained were allowed to solidify and were kept at room temperature for 72 hrs. The solidified mass was then powdered and passed through '60' mesh screen and stored in glass vials in a desiccator.

Preparation of physical mixture

Physical mixtures (PMs) were prepared at the ratio of 1:1 by thoroughly mixing the appropriate amounts of Simvastatin and carrier for 10 min in a mortar. The mixtures were coded as per [Table 2]. The mixtures were sieved through a '60' mesh screen and stored in glass vials in a desiccator.

Estimation of Simvastatin

The drug contents of SDs, SSDs and PMs were analyzed using a UV-spectrophotometer (UV mini 1240, Shimadzu) by dissolving equivalent samples in methanol to prepare solutions of 2 µg/ml concentration. Standard solution was prepared by dissolving 10 mg of Simvastatin in 100 ml methanol which was further diluted 50 times to produce identical concentration. The absorbance's of the above solutions were measured at 238 nm against appropriate blank solution.[9]

Fourier Transform Infrared (FTIR) spectroscopy

FTIR spectra of Simvastatin, SDs and SSDs of 1:5 ratios were taken in IR-Prestige 21, Shimadzu, Japan by scanning the samples in potassium bromide (KBr) discs. Before taking the spectrum of the sample, a blank spectrum of air background was taken. Samples were scanned over the frequency range 2000 cm^{-1} to 400 $cm^{-1.}$ The IR spectra of solid dispersions were compared with standard IR spectra of pure Simvastatin and respective carrier.

Differential Scanning Calorimetric (DSC) study

DSC analysis of the drug, carrier (HPMC 5 cps) and their SD of 1:1 ratio were carried out in Bangladesh Council of Scientific and Industrial Research (BCSIR). Samples were heated under nitrogen atmosphere on an aluminum pan at a rate of 10°C/min over the temperature range of 30°C and 300°C. Thermal data analysis of DSC thermogram was conducted by using STAR software.

Preparation of dissolution media

Buffer pH 7.0 solution containing 0.5% sodium dodecyl sulfate in 0.01 M sodium phosphate solution were selected as the dissolution media for the preparations.[9] The media was prepared by

dissolving 30 g of sodium dodecyl sulfate and 8.28 g of monobasic sodium phosphate in 6 L of water, and adjusting with 50% (w/v) sodium hydroxide solution to a pH of 7.0.

In-vitro dissolution studies

In vitro dissolution studies were performed in USP XXI six station dissolution test apparatus using 900 ml of dissolution medium. Dissolution studies were performed at a rotation speed of 50 rpm at 37^0C±0.5^oC throughout the experiment. Samples equivalent to 10 mg of Simvastain were accurately weighed and subjected to *in vitro* dissolution. Samples of 5 ml were taken at 10, 15, 20, 30, 45 and 60 minutes interval. On each interval, equal volumes of fresh dissolution medium were replaced to maintain a constant volume for drug dissolution immediately after taking samples. The concentration of Simvastatin was determined using UV spectroscopy (Shimadzu, Japan) at 238 nm.[10] The test was executed thrice for each sample.

Characterization of dissolution data

To characterize the drug release rate from the preparations in different experimental conditions MDT (mean dissolution time), $T_{50\%}$, $T_{80\%}$ and dissolution efficiency (DE) were calculated according to the following equations.[11]

$$DE = \frac{\int_{t_1}^{t_2} y \cdot dt}{y_{100} \times (t_2 - t_1)} \times 100$$

$T_{50\%} = (0.5/k)^{1/n}$

$T_{80\%} = (0.8/k)^{1/n}$

$MDT = (n/n+1).\ K^{-1/n}$

Where, *k* represents for the antilog of intercept & *n* denotes to release exponent of Korsmeyer's plot and *y* is the percentage of dissolved drug. A higher value of MDT indicates a lower drug releasing ability of the solid dispersion and vice-versa. Besides, The DE is the comparison in percentage of the area under the dissolution curve up to a certain time *t*, and the area of the rectangle described by complete dissolution in the same time. Higher the value of DE, greater is the dissolution rate.

Preparation of tablets

Tablets were prepared by direct compression with the SDs and SSDs of 1:5 ratios. The amount of SDs and SSDs were calculated according to the obtained drug content of the preparations [Table 2] and mixed with other excipients. The items were accurately weighed for 20 tablets according to the formulations summarized at Table 1. Particular attention was given to ensure thorough mixing and phase homogenization. Required amount of mixture were weighed by electronic balance and

compressed using a KBr-Press laboratory hydraulic press. The surfaces of the die and punch were lubricated each time with magnesium stearate before compression. All the preparations were stored in airtight glass containers at desiccator for further study.

Table 1 Composition of different formulations of tablets of Simvastatin, SD and SSD (in mg).

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Simvastatin	10.0	-	-	-	-	-	-
S-L_1 1:5 SD	-	62.5	-	-	-	-	-
S-P_4 1:5 SD	-	-	58.3	-	-	-	-
S-P_6 1:5 SD	-	-	-	61.3	-	-	-
S-H_5 1:5 SD	-	-	-	-	60.2	-	-
S-SSG 1:5 SSD	-	-	-	-	-	58.8	-
S-CCS 1:5 SSD	-	-	-	-	-	-	58.9
Avicel PH 102	80.0	80.0	80.0	80.0	80.0	80.0	80.0
Lactose Monohydrate	377.0	324.5	328.7	325.7	326.8	328.2	328.1
Sodium Starch Glycolate	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Magnesium Stearate	18.0	18.0	18.0	18.0	18.0	18.0	18.0
Total weight	500.0	500.0	500.0	500.0	500.0	500.0	500.0

Evaluation of Tablets

Tablets of each batch were evaluated for various physical tests including thickness, diameter, hardness, average weight and disintegration time. Randomly collected 10 tablets of each batch were evaluated for thickness and diameter by digital slide calipers, average weight by digital balance and then, they had undergone hardness test by Monsanto hardness tester. Six tablets were tested for disintegration time by Electrolab disintegration tester ED-2L at 37^{o}C±0.5^{o}C. Dissolution test was performed trice for each formulation using above stated method.

Comparison with marketed products

Simvastatin tablets marketed by two popular pharmaceutical companies of Bangladesh were purchased from drug store. Their physical characteristics were evaluated. They also subjected to dissolution test by the same method described for SDs, SSDs & PMs and their release behavior was compared against prepared tablets.

RESULTS AND DISCUSSION

Simvastatin is white to off-white powder having irregular flow property and poor aqueous solubility. Lutrol F 127, HPMC 5 cps, polyethylene glycol 4000 and 6000, sodium starch glycolate and croscarmellose sodium were used as carriers to enhance the dissolution property. All the obtained SDs and SSDs prepared by solvent evaporation technique were found granular, non sticky, free flowing and easily compressible. Binary physical mixtures also showed good flow

property. All these preparations revealed good uniformity and had yielded results from 96% to 102% of the theoretical claim in the drug content analysis. The results summarized in the Table 2.

Table 2 Result of drug content of SDs, SSDs and PMs of Simvastatin.

Sl. No.	D:C Ratio	Carrier	Code	Theoretical drug content (%)	Calculated drug content (%)
1	1:1	Lutrol F 127	S-L_1 1:1 SD	50.00	48.17
2	1:5	(L_1)	S-L_1 1:5 SD	16.67	16.01
3	1:10		S-L_1 1:10 SD	9.09	8.79
4	1:1		S-L_1 1:1 PM	50.00	51.24
5	1:1	PEG 4000	S-P_4 1:1 SD	50.00	49.01
6	1:5	(P_4)	S-P_4 1:5 SD	16.67	17.14
7	1:10		S- P_4 1:10 SD	9.09	9.24
8	1:1		S- P_4 1:1 PM	50.00	49.31
9	1:1	PEG 6000	S-P_6 1:1 SD	50.00	49.77
10	1:5	(P_6)	S-P_6 1:5 SD	16.67	16.31
11	1:10		S-P_6 1:10 SD	9.09	9.34
12	1:1		S-P_6 1:1 PM	50.00	49.68
13	1:1	HPMC 5 cps	S-H_5 1:1 SD	50.00	51.24
14	1:5	(H_5)	S-H_5 1:5 SD	16.67	16.60
15	1:10		S-H_5 1:10 SD	9.09	9.41
16	1:1		S-H_5 1:1 PM	50.00	49.32
17	1:1	Sodium Starch	S-SSG 1:1 SSD	50.00	50.78
18	1:5	Glycolate	S-SSG 1:5 SSD	16.67	17.01
19	1:10	(SSG)	S-SSG 1:10 SSD	9.09	8.88
20	1:1		S-SSG 1:1 PM	50.00	50.67
21	1:1	Croscarmellose	S-CCS 1:1 SSD	50.00	48.84
22	1:5	Sodium	S-CCS 1:5 SSD	16.67	16.97
23	1:10	(CCS)	S-CCS 1:10 SSD	9.09	8.96
24	1:1		S-CCS 1:1 PM	50.00	49.63

D:C- drug: carrier, SD- solid dispersion, SSD-surface solid dispersion, PM-physical mixture

The FT-IR spectra of Simvastatin showed characteristic peaks at 1704 cm^{-1} (lactone C=O and ester C=O stretching), at 1462 cm^{-1} (methylene and methyl bending vibration), at 1266 cm^{-1} and 1225 cm^{-1} (lactone C-O-C stretching), at 1164 cm^{-1} (ester C-O-C bending vibration), at 1068 cm^{-1} (secondary alcohol C-O stretching) and at 868 cm^{-1} for trisubstituted olefinic C-H vibration [Figure 1]. Similar peak positions were reported by Elbary et al., 2011[12]. Solid dispersions and the surface solid dispersions were found to retain the major peaks of drug. In fact, their spectra were clearly composed of vibrations and stretching peaks of drug and carrier at similar positions. Therefore, no chemical interaction or adverse impacts of the manufacturing technique on the stability of the preparations are reported in the FT-IR spectra. Absence of any interaction was also reported by Rao et al., 2010[10] and Mandal et al., 2010[9] who formulate solid dispersion of Simvastatin with

croscarmellose sodium and PEG 4000 & 6000 respectively.

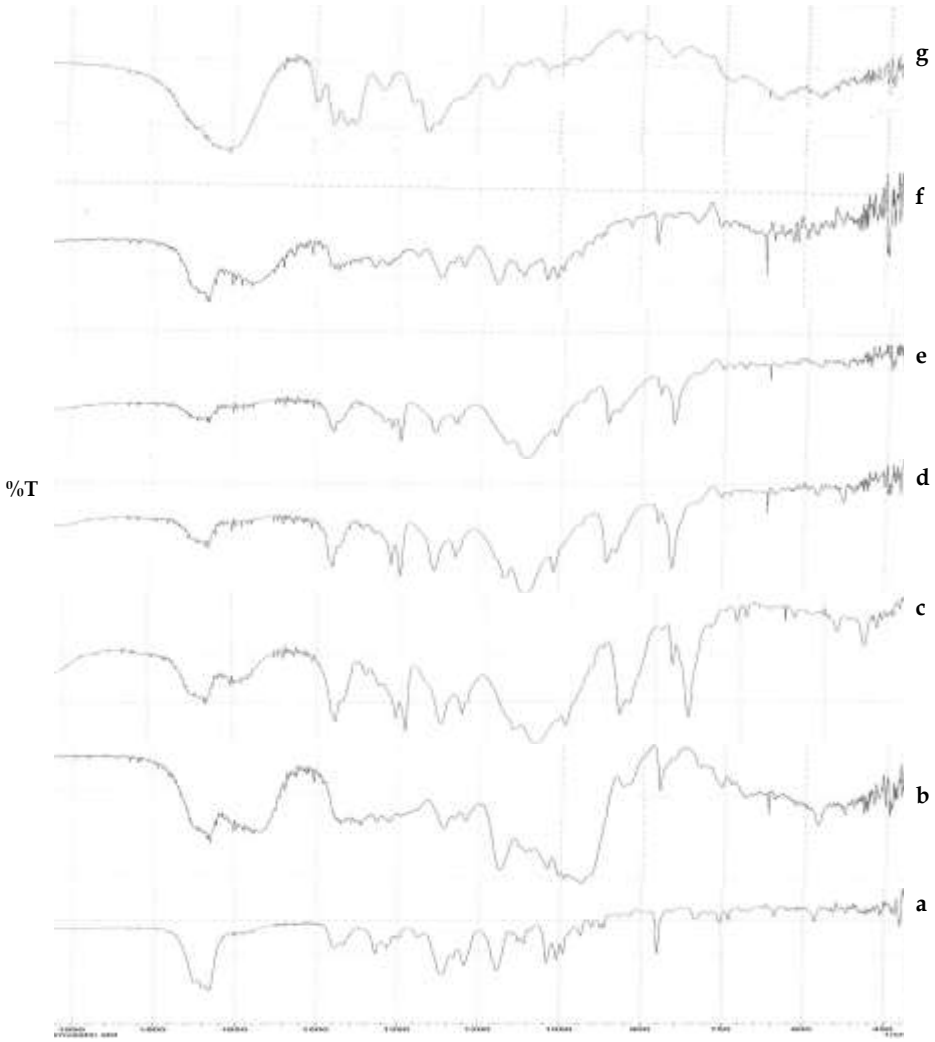

Figure 1:FT-IR spectra of a) Simvastatin, b) S-SSG 1:5 SSD, c) S-P_4 1:5 SD, d) S-P_6 1:5 SD, e) S-L_1 1:5 SD, f) S-H_5 1:5 SD and g) S-CCS 1:5 SSD.

DSC thermogram of Simvastatin showed a sharp endothermic peak at 140.67ºC corresponding to melting of drug [Figure 2 a]. Onset of melting started on the temperature of 137.50ºC and ended at 143.51ºC. The carrier hydroxypropyl methyl cellulose was found not to have any specific melting position as like other polymers and an endothermic peak was seen in the thermogram having peak on 100.65ºC that started from 66.66ºC and continued to 117.56ºC. In the thermogram of solid dispersion of drug and carrier, two major peaks are found having position on 131.30ºC and 137.46ºC respectively. First one is probably for the polymer and second one stands for the drug peak. Thus no chemical interaction or alteration is found form the DSC data.

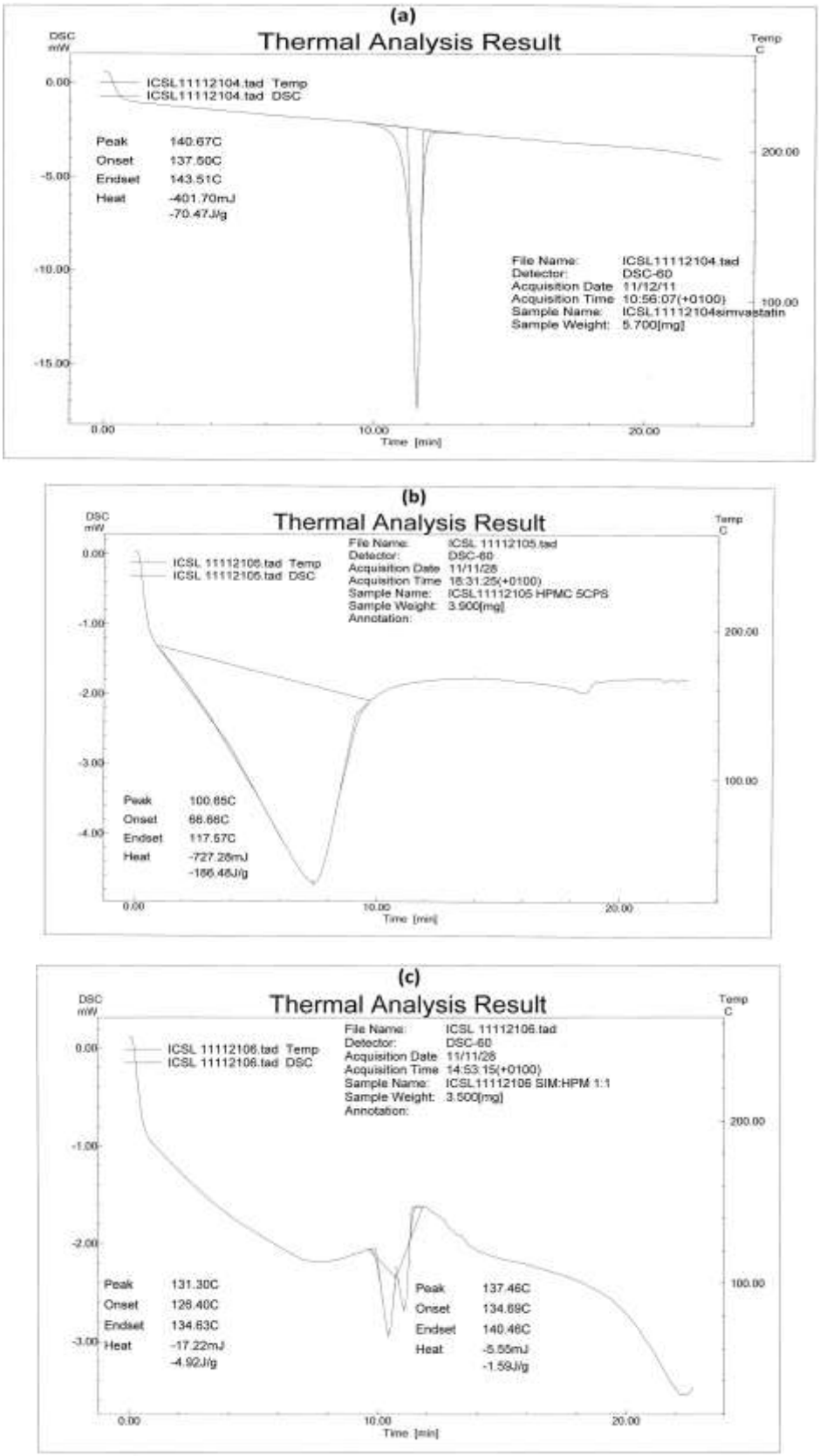

Figure 2: DSC thermograph of a) Simvastatin, b) HPMC 5 cps and c) S-H_5 1:1 SD.

In vitro dissolution studies were performed for the pure drug, each solid dispersion, surface solid

dispersion and physical mixture. Simvastatin was dissolved only 31.66% upon 60 minutes dissolution in buffer media. At the same time all the preparations were found able to improve the release behavior significantly for each ratio. Even the physical mixtures at 1:1 ratio enhanced the dissolution property of the drug prominently [Figure 3], [Figure 4]. Physical mixture of Simvastatin with Lutrol F 127 was found to release highest amount of drug (79.97% in 1 hour), whereas, PM with PEG 4000 discharged the lowest (56.69% incorporated drug). All the SDs and SSDs showed higher drug release than their respective physical mixture. It might be due to the size reduction and better dispersion of drug into carrier achieved by the dispersion technique.

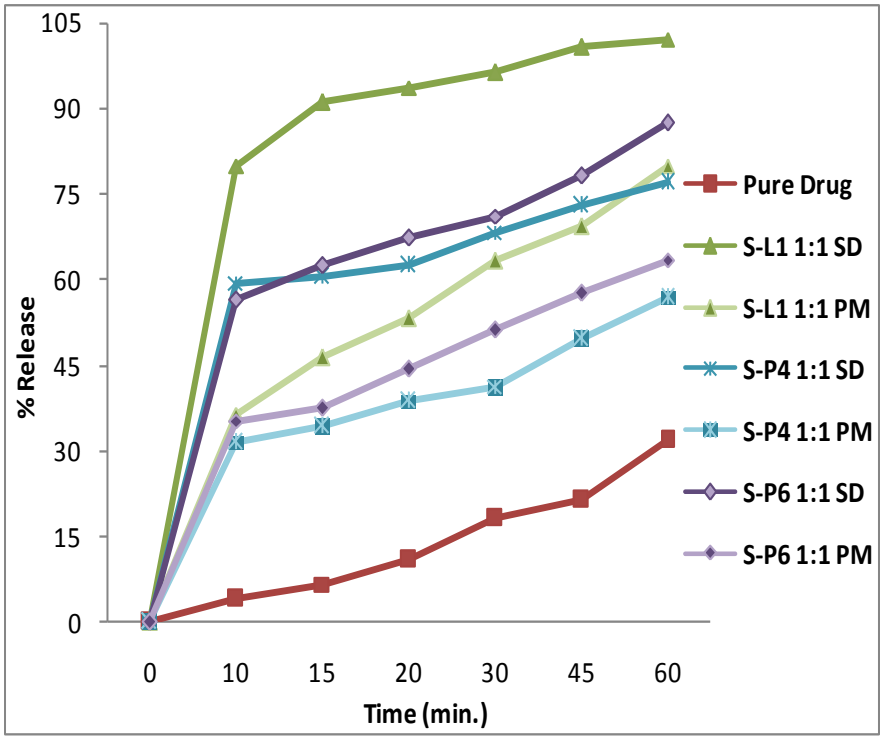

Figure 3: *In vitro* release of Simvastatin from SDs and PMs with Lutrol F 127, PEG 4000 and 6000 at ratio of 1:1.

At 1:1 ratio, all the soluble and insoluble carriers were found to contribute on improvement of dissolution criteria of Simvastatin. Among the soluble carriers, Lutrol and HPMC were found mostly effective in increasing the rate and extent of drug release [Figure 3]. In the window of only 15 minutes, S-L_1 1:1 SD and S-H_5 1:1 SD were found to release 91.10% and 85.59% of incorporated drug, while the drug itself dissolved only 6.62% in the same time. On the other hand, both water insoluble carrier CCS and SSG were found to improve the dissolution behavior of Simvastatin unprecedentedly. SSD with CCS and SSG at ration of 1:1 were found to liberate 98.74% and 76.40% drug in only 15 minutes [Figure 4].

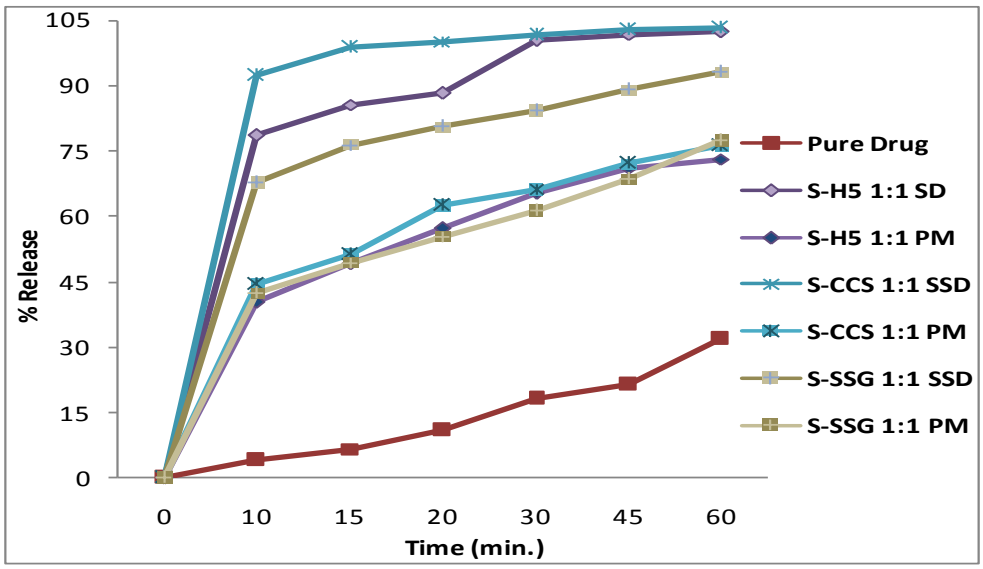

Figure 4: *In vitro* release of Simvastatin from SDs/SSDs and PMs with HPMC 5 cps, CCS and SSG at ratio of 1:1.

Higher ratio of SDs and SSDs were also found impressive to improve the dissolution pattern of Simvastatin [Figure 5], [Figure 6]. The set of preparations at 1:5 ratio, were found to release the drug from 79.28% to 102.29% within 60 minutes dissolution. PEG 4000 was found to be the best carrier of this group to quicken the dissolution rate (90.57% drug release in only 10 minutes). Improvement of release characteristics continued in the preparations at 1: 10 ratio.

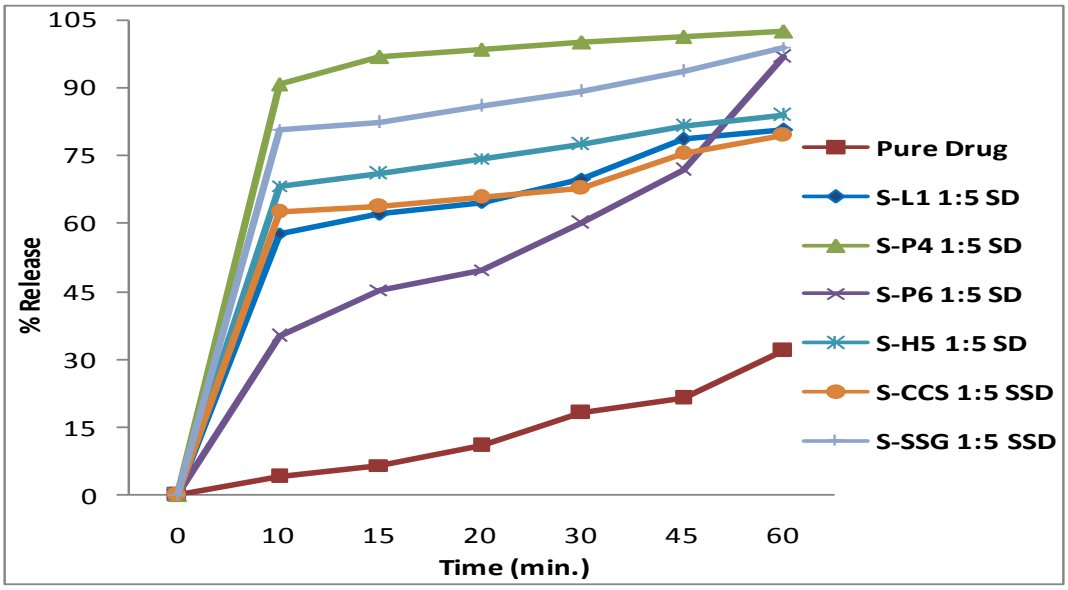

Figure 5: *In vitro* release of Simvastatin from SDs/SSDs at ratio of 1:5.

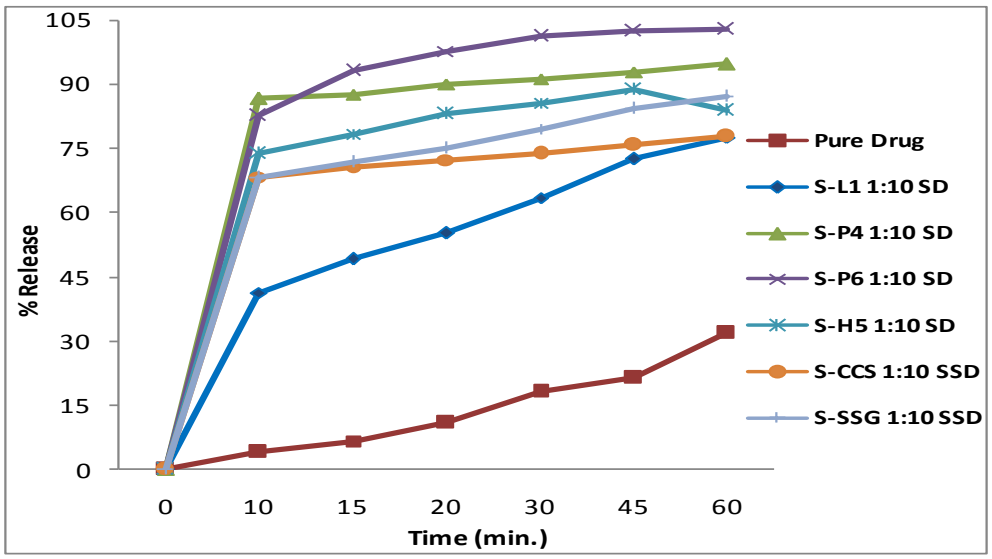

Figure 6: *In vitro* release of Simvastatin from SDs/SSDs at ratio of 1:10.

Overall observation on the drug release data of all the preparations, reduced release rate with increase of the carrier content was found for Lutrol, HPMC and CCS. SDs with Lutrol F 127 were found to release 102.17%, 80.70% and 77.49% of drug when incorporated in 1:1, 1:5 and 1:10 ratio respectively. Preparations with HPMC and CCS also have similar decreasing release fractions. This might be due to the saturation of the media with the carriers and for those, 1:1 ratio could be the best choice. On the contrary, PEG 6000 improved the dissolution rate and extent on the basis of increased loading of the carrier in the dispersion. Solid dispersion S-P_6 1:1 SD released 87.43% at 1:1 ratio, while 96.79% and 102.70% drug were liberated from 1:5 and 1:10 ratio respectively. Preparations with PEG 4000 and SSG showed increasing order of drug release at addition of more carrier (1:5), but the extent of release lessened on further carrier loading in 1:10 ratio.

Tablet was prepared by using 1:5 ratio of all the SDs and SSDs and the pure Simvastatin. Tablets were compressed by direct compression technique and evaluated for thickness, diameter, average weight and disintegration time; the results are presented in [Table 3]. Tablets obtained from all the preparations had smooth surface and their thickness and diameter were found not to vary too much but to remain closer to the average value. Hardness of the prepared tablets was found within 5-6 Kg/cm^2 for all the formulations. Average weights of the tablets were found within range. Disintegration time of the obtained tablets was found below 5 minutes for all the formulations. Brand products were found to have tablet weight of 142 and 172 mg with disintegration time of less than two and four minutes respectively.

Table 3 Evaluation of physical parameters of Simvastatin tablets.

Formulation	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Average weight (mg)	Disintegration time (min.)
F-1	13.1±0.01	2.8±0.01	6.0±0.03	518±1.1%	4.9
F-2	13.1±0.02	2.8±0.02	5.5±0.05	518±1.0%	4.3
F-3	13.1±0.02	2.7±0.02	5.1±0.07	518±1.0%	4.1
F-4	13.1±0.01	2.8±0.01	5.6±0.06	518±1.1%	4.1
F-5	13.1±0.02	2.8±0.01	5.1±0.04	518±0.9%	3.3
F-6	13.1±0.01	2.8±0.01	5.7±0.04	518±1.0%	2.6
F-7	13.1±0.02	2.9±0.01	5.4±0.04	518±0.9%	2.9
Brand A	7.7±0.04	3.5±0.04	5.2±0.01	142±0.4%	1.3
Brand B	5.7±0.03	3.8±0.02	8.1±0.03	172±0.3%	3.3

Tablets from all the formulations and the brand products were subjected to dissolution study. Dissolution was performed by the same method in buffer media. All the tablets were found to have better release profiles than the tablet made of pure Simvastatin (F-1). Simvastatin was released only 28.69% from the compressed matrix of formulation F-1 after 60 minutes of dissolution. Whereas, tablets made of solid dispersions can liberate more than 95% in the same time frame. 95.67%, 99.43%, 102.25% and 99.33% drug was found to be released in 1 hour dissolution from formulation F-2, F-3, F-4 and F-5 [Figure 7]. Surface solid dispersions were also found effective after preparing tablet dosage form to release the drug at a greater quantity and faster rate. Tablets made of SSG and CCS (formulation F-6 and F-7) were found capable of releasing 80.50% and 79.84% incorporated drug only in 10 minutes, which in turn discharge 99.27% and 96.32% in 1 hour respectively. Dissolution study was also performed for the brand products. 92.62% and 92.78% drug release were found from the two marketed products in 1 hour that comply with the USP tolerance limit for Simvastatin tablet eg. not less than 75% in 30 minutes.

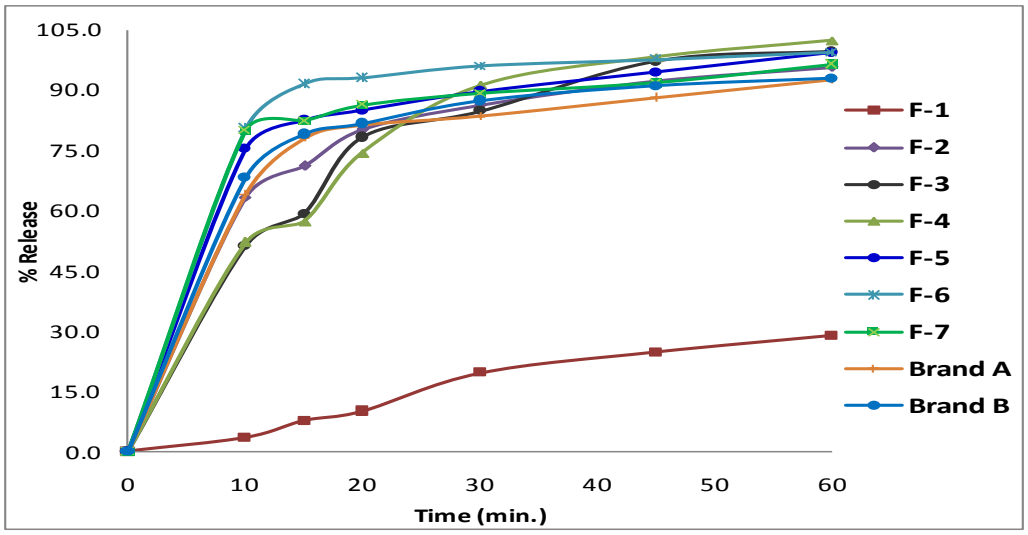

Figure 7:Drug release study from Simvastatin tablets and brand products.

With an objective of more characterization of the drug release profiles of prepared tablets, MDT (mean dissolution time), $T_{50\%}$, $T_{80\%}$ and percent dissolution efficiency (DE) were calculated. MDT value of tablets made of solid dispersions and surface solid dispersions were found significantly lower than that of the drug alone. These lower values of MDT denote to the increased drug release rate from the prepared dispersion systems. Formulation F-6 was found to have the lowest MDT value (4.74 minutes), whereas F-1 (prepared with pure drug) had a value of 79.24 minutes. Brand products available in Bangladesh were found to have satisfactorily lower value of MDT than the F-1. Formulation F-5, F-6 and F-7 containing SD/SSD with HPMC, SSG and CCS were found to have lower MDT value than those of two brand products. It indicates the suitability of dispersion system to improve dissolution of poorly soluble drugs. $T_{50\%}$ and $T_{80\%}$ also denote the same.

Dissolution efficiency of Simvastatin of all the formulations increased markedly corresponding to the formulation F-1. After only 10 minutes of dissolution, dissolution efficiency of all the formulations was found from 25.61% to 40.25%, whereas formulation F-1 had the DE of 1.65% only. At the same interval, the brand products were found to have a DE value of 32.01% and 34.05% [Table 4]. It reveals that all the preparations were able to significantly enhance drug release rate and extent corresponding to the pure drug. In addition, three of them (formulation F-5, F-6 and F-7) were found clearly better than the marketed products also. The improvement further continued to later period as indicated by the % DE value at 60 min.

Table 4: Successive fractional dissolution time, MDT values and % DE of Simvastatin tablets.

Formulation	MDT	$T_{50\%}$	$T_{80\%}$	$\%DE_{10\ min}$	$\%DE_{60\ min}$
F-1	79.24	81.44	120.92	1.65	16.09
F-2	12.04	3.16	24.40	31.62	76.79
F-3	14.75	8.64	29.78	25.61	75.45
F-4	13.93	8.84	27.80	26.01	76.86
F-5	7.99	0.53	13.54	37.72	81.58
F-6	4.74	0.05	5.67	40.25	86.09
F-7	8.65	0.10	10.48	39.92	81.13
Brand A	12.79	1.67	24.05	32.01	75.62
Brand B	11.19	1.09	20.18	34.05	77.82

Formulation F-5, F-6 and F-7 were formulated with dispersions of Simvastatin with HPMC, sodium starch glycolate and croscarmellose sodium respectively. All of these three carriers are well known for their swelling characteristics that render the matrix disintegrated and allow water penetration that in turn increase the solubility and dissolution behavior of the drug. Though HPMC has a variety of viscosity grade, its surfactant activity reduces the contact angle and increases wetting of drug particles and hence, enhance the solubilization and dissolution of drug particles [13].

Similarly, both SSG and CCS have very fine particles that permit the drug to deposit on a larger surface up on evaporation of solvent, which causes improved wettability that finally results in enhancement in dissolution. Rao et al., 2010[10] also reported the same and also, they claimed the affinity between the hydrophilic inert carriers and the dissolution fluids facilitates rapid penetration which further enhances the dissolution process.

Solid dispersion system once again has been proved to be a successful mean of improving solubility characteristics. Marketed products available in Bangladesh were of good quality and found to meet the compendial requirement. Tablets made of dispersion system were found able to release the drug instantaneously from a 500 mg matrix without using any surfactant. HPMC, sodium starch glycolate and croscarmellose sodium were found to enhance the dissolution of Simvastatin remarkably, far better than pure Simvastatin and also superior than the available brand products.

CONCLUSION

Solid dispersion and surface solid dispersion of Simvastatin were prepared with a view to enhance the solubility and dissolution characteristics of the drug. Both water soluble and insoluble carriers were proven effective to improve the dissolution behavior of the drug markedly. Surface solid dispersion technique was found more suitable than the solid dispersion technique for Simvastatin. Some formulations were found to have better dissolution rate corresponding to the pure drug and brand products.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. Mala Khan for DSC analysis at Bangladesh Council of Scientific and Industrial Research (BCSIR).

REFERENCES

1. Sukanya M, Kishore VS. Design and development of solid dispersions of Simvastatin for enhancing the solubility. Am J PharmTech Res 2012; 2(4): 733-740.
2. Murtaza G. Solubility enhancement of simvastatin: a review. Acta Polo Pharm-Drug Res 2012; 69(4): 581-590.
3. Sable PN, Chaulang GM, Bhosale AV. Novel spectrophotometric estimation of izetemib, losorton and simvastatin using hydrotropic solubilizing agents. Int J ChemTech Res 2009; 1:1393-1397.
4. Margulis-Goshen K, Magdassi S. Formation of simvastatin nanoparticles from microemulsion. Nanomed Nanotech Bio Med 2009; 5(3): 274-281.

5. Patil P, Patil V, Paradkar A. Formulation of a self-emulsifying system for oral delivery of simvastatin: *In vitro* and *in vivo* evaluation. Acta Pharm 2007; 57: 111–122.
6. Shiralashetti S, Patil A, Patil J. Influence of method of preparation on solubility, physicochemical properties and *in vitro* release profile of Simvastatin- cyclodextrin inclusion complexes: A comparative study. Int J ChemTech Res 2010; 2(1): 562-571.
7. Patil MS, Bavaskar KR, Girnar GA, Jain AS, Tekade AR. Preparation and optimization of simvastatin nanoparticle for solubility enhancement and *in vivo* study. Int J Pharm Res Dev 2011; 2(12): 219-226.
8. Ding Z, Hao A, Zhang P. Surface properties and solubility of simvastatin in the micelles of polyglycerol diisostearate ethoxylates. J Disp Sci Technol 2007; 28 (4): 495-500.
9. Mandal D, Ojha PK, Nandy BN, Ghosh LK. Effect of carriers on solid dispersions of simvastatin (sim): physico-chemical characterizations and dissolution studies. Der Pharm Lettre 2010; 2(4): 47-56.
10. Rao M, Mandage Y, Thanki K, Bhise S. Dissolution improvement of Simvastatin by surface solid dispersion technology. Dissolution Technologies 2010; 5: 27-34.
11. Masum MAA, Sharmin F, Islam SMA, Reza MS. Enhancement of Solubility and Dissolution Characteristics of Ibuprofen by Solid Dispersion Technique. Dhaka Univ J Pharm Sci 2012; 11(1): 1-6.
12. Elbary AA, Ibrahim HK, Hazaa BS. Formulation and evaluation of color targeted tablets containing Simvastatin solid dispersion. Drugs and Therapy Studies 2011; 1(16): 62-67.
13. Pattewar SV. Solubility enhancement of poorly aqueous soluble drug-simvastatin by using HPMC E3LV. Int J Pharm Pharm Sci 2012; 4(2): 498-502.