WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 8, 1084-1097. Research Article ISSN 2277– 7105

DESIGN AND DEVELOPMENT OF ORAL DISINTEGRATING TABLET OF SIMVASTATIN BY USING β-CYCLODEXTRIN

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Article Received on
14 June 2016,

Revised on 04 July 2016,
Accepted on 24 July 2016

DOI: 10.20959/wjpr20168-6781

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ABSTRACT

The present study deals with the design and development of oral disintegrating tablet of Simvastatin by using β-cyclodextrin with direct compression technique using various superdisintegrants like Crosprovidone, Croscaramellose sodium and Lactose and Mannitol as diluents. Simvastatin is lipid lowering agent which inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Its absolute bioavailability is 5% and coming under the class II of biopharmaceutical classification system. The rate of absorption and/or the extent of bioavailability for such a poorly soluble drug is controlled by rate of dissolution. Hence to enhance the solubility of drug a complex of Simvastatin was prepared with β-cyclodextrin in (1:1) drug: polymer molar ratio by using kneading method and this complex was compressed into tablets. The prepared tablet were evaluated for weight variation, thickness, friability, hardness, wetting time, wetting absorption ratio, disintegration time, invitro dissolution studies, stability study, phase solubility study, DSC study and IR spectroscopy. Among all the formulations, formulation F4 prepared with Crosprovidone (45%) and lactose as diluent showed 97.84% drug release within 30 min and disintegrate within 30 sec and formulation F8 prepared with Crosprovidone (45%) and mannitol as diluent showed 98.54% drug release within 30 min and disintegrate within 28 sec. No chemical interaction between the drug and the excipients was confirmed by FTIR and DSC studies. The stability study conducted as per the ICH guidelines and the formulations were found to be stable. These results revealed that oral disintegrating tablets of poorly soluble drug Simvastatin showed enhanced bioavailability and increased solubility and hence better patient compliance.

KEYWORDS: Croscaramellose sodium, Crospovidone, Oral disintegrating tablet, Simvastatin.

1. INTRODUCTION[1, 2, 3]

Despite noteworthy advancements in drug delivery technology, the oral route remains the trendy route for the administration of drugs because of accurate dosage, low cost of therapy, self-medication, non-invasive method and ease of administration leading to high level of patient compliance. The conventional dosage forms (tablet and capsule) have wide acceptance up to 50-60% of the total dosage forms. Tablet is still most popular dosage forms existing because of ease of self-administration, compact in nature, easy to manufacture and it can be delivered in accurate dose. One drawback of solid dosage form is difficulty in swallowing (dysphasia) and chewing in some patients particularly in geriatric and pediatric patients. The problem of choking is common phenomenon in geriatric patients due to fear of choking, hand tremors, dysphasia. Oral disintegrating tablets or Mouth Fast dissolving tablets are of such examples, for the purpose of fast disintegration or dissolution in mouth with little amount of water, without water or even with saliva providing best remedy for the patient suffering from dysphasia. Moreover, this dosage form compromises an advantage of convenience of administration while travelling where there may not be an access to water which when placed in the mouth, rapidly disperse or dissolve in saliva without the need of water or chewing and can be swallowed in the form of liquid. After disintegration, the drug solution can be partially or completely absorbed from the sublingual mucosal blood vessels and bypasses the first pass metabolism of the liver, or be absorbed from the gastrointestinal tract after swallowing. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods micronization, complexation, use of surfactant and solid dispersion. The dissolution of a drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution. Simvastatin is widely used in the treatment of dyslipidemia as an adjunct to diet. It acts by specific inhibition of 3-hydroxy-3-methyl-glutaryl coenzyme-A (HMG CoA) reductase. Cyclodextrin are classical example of compounds that form stable inclusion complexes with a guest molecule to increase the solubility and bioavailability of poorly water soluble drug. In the present study, an attempt was made to develop oral disintegrating tablets of simvastatin

by using β-cyclodextrin and to investigate the effect of the superdisintegrants and diluents on the release profile of drug.

2. MATERIALS AND METHODS

2.1 Materials

Simvastatin was obtained from Wokhardt Pharma Ltd, L-1, Chikhalthana, Aurangabad as a gift sample. The Crospovidone and Talc was obtained from S.D. Fine Chemicals, Mumbai as a gift sample. β- cyclodextrin, saccharin sodium, Aerosil was obtained from Ozone International Pvt., Ltd. Magnesium stearate was obtained from Ranbaxy Fine Chemical. Ltd. Delhi. Mannitol was obtained from Qauligen fine chemical, Mumbai. Lactose was obtained from Milton Chemicals, Mumbai.

2.2 Method

2.2.1 Preparation of inclusion complexes[3, 4]

Kneading method was used to formulate the cyclodextrin complex of simvastatin.

Kneading method

Drug and β-Cyclodextrin in the proportion of appropriate molar ratio (1:2 molar ratio) were mixed in a mortar for one hour with small quantities of distilled water and methanol/ ethanol was added intermittently to get slurry like consistency. The paste was dried in the oven at the temperature of 45°C. Dried complex were pulverized into fine powder and sifted with sieve # 80.

2.2.2 Phase solubility studies[5, 6]

Solubility studies were performed according to the method reported by Higuchi and cannors. Excess simvastatin was added to phosphate buffer pH 6.8 with 0.03% SLS containing various concentration of β-cyclodextrin in a series of 100 ml volumetric flask and the mixture was shaken for 48 hr at room temperature(25^{o}C) on a shaker (120 rev/min). Then, the samples were kept aside to achieve equilibrium. After equilibrium was reached aliquots were then filtered through whatman filter paper. The filtered samples were diluted suitably and assayed for simvastatin, by measuring the absorbance at 239 nm. The phase solubility diagram was plotted total drug concentration against concentration of β-cyclodextrin. The apparent complexation constant (K1:1) of the complex was calculated as following equation from phase solubility slope, where the intercept is the intrinsic solubility of drug in the absence of β-cyclodextrin at 25^{o}C.

$$K\ (1:1) = \frac{\text{Slope}}{\text{Intercept (1-Slope)}}$$

2.3 Evaluation parameters for the Inclusion complexes[7]

Based on the results of solubility studies, the Inclusion complex showing superior solubility was selected and subjected to further evaluation by DSC and FTIR and for drug content and *in vitro* release.

2.3.1 Differential scanning calorimetry

Thermogram of simvastatin-β-cyclodextrin inclusion complex was recorded on a TA-60 WS Thermal Analyzer (Shimadzu) as shown. The samples were hermetically sealed in aluminum pans and heated at a constant rate of 10^0C/min over temperature range of 40 to 300^0C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 50 ml/min.

2.3.2 FTIR studies

Instrument used was Shimadzu FTIR-8700 spectrophotometer. In this study, potassium bromide disc method was employed. Both pure drug and Cyclodextrin complexes were subjected to IR studies. The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded.

2.4 Preparation of simvastatin orodispersible tablets[8]

Simvastatin orodispersible tablets were prepared using the superdisintegrants Crospovidone, and Croscaramellose sodium by direct compression. According to the composition shown in Table 1, eight orodispersible formulations of simvastatin were prepared. Preweighed amount of the prepared inclusion complex equivalent to 10 mg simvastatin was mixed with all ingredients and blended with initial mixture in the mortar followed by compression of the blend using, single punch in a multistation compression machine, which is equipped with 8mm concave edge punches.

2.5 Evaluation of Oral disintegrating tablet[9,10]

After compression of desired ODTs different types of pharmacopoeial and non-pharmacopoeial physico-chemical tests were executed for all formulations as follows

2.5.1 Weight variation

Twenty tablets were randomly selected from each formulation and separately weighed (Shimadzu digital balance BL-220H) and their average weight and standard deviation were calculated.

2.5.2 Thickness Variation

From each batch six tablets were picked up randomly and their thickness was measured individually using Vernier Calipers. The mean ± SD values were calculated.

2.5.3 Crushing strength or Hardness

Crushing strength or hardness is the force required to break a tablet in diametric compression. Hardness of the tablets is determined by Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moving along the gauze in the barrel at which the tablet fractures indicates the hardness of the tablet. Six tablets from each batch were taken randomly and their hardness was determined.

2.5.4 Friability

Ten tablets from each batch were accurately weighed and placed in the drum of a friabilator (Erweka, Germany) rotated at 25 rpm for a period of 4 min, then dusted and reweighed. The percentage weight loss was calculated and taken as a measure of friability.

$$\% \text{ Friability} = \frac{\text{Initial weight- Final weight}}{\text{Initial weight}} \times 100$$

2.5.5 Water Absorption Ratio (R)

A tissue paper was folded twice and positioned in a petri dish containing 6ml of water. Preceding to placement on the petri dish the weight of the tablet was weighed using a digital balance and noted as (Wb). The wetted tablet was removed from the petri dish and reweighed (Wa). Water absorption ratio (R) was calculated according to the following equation

$$\text{Water absorption ratio (R)} = \frac{W_a - W_b}{W_b} \times 100$$

Where Wb = Weight of the tablet before water absorption

Wa= Weight of the tablet after water absorption

2.5.6 Wetting Time

A piece of tissue paper twice folded placed in a petri dish (internal diameter 10cm) containing 0.5% of a water-soluble dye nigrosine. A tablet was carefully placed on the tissue paper at 25^0C. The time period for total wetting of tablet was noted. Three tablets were selected randomly from each formulation and the average wetting time was calculated.

2.5.7 Drug content

Twenty tablets were weighed accurately and a quantity of tablet powder equivalent to 10 mg of Simvastatin was weighed and transferred to a 10 ml volumetric flask containing about 7 mL of 6.8 pH phosphate buffer with 0.03% sls, ultrasonicated for 5 min and volume was made up to the mark with the same. The solution was filtered through Whatman filter paper No. 41 and 1 ml of filtrate was further diluted to 10 mL with buffer. One ml of this solution was transferred to 10 ml calibrated volumetric flask and the volume was made up to the mark with the buffer. The absorbance were measured at 239 nm against phosphate buffer as blank and the amount of drug in the sample was estimated from the calibration curve.

2.5.8 In-vitro disintegration time

The in-vitro disintegration time of a tablet was determined using disintegration apparatus as per USP specifications17. One tablet in each of the 6 tubes of the basket is to be placed and the apparatus subjected to run. The assembly should be raised and lowered between 50 cycles per minute. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

2.5.9 *In vitro* Dissolution study[11, 12]

Dissolution profiles of Simvastatin tablets were determined using the USP method II with paddle speed at 50 rpm. Dissolution was performed in 900 ml pH 6.8 phosphate buffer solution with 0.03% SLS maintained at 37±0.20C. 5ml of samples were withdrawn at 5, 10, 15, 20, 25, 30 minutes time intervals. The volume of dissolution fluid was adjusted to 900 ml, by replacing each 5ml aliquot withdrawn were filtered through Whatman filter paper (no.41), 5ml diluted with 10 ml of phosphate buffer solution with 0.03% SLS and analyzed at 239 nm, using UV-Visible double beam spectrophotometer (JASCO V-630).

2.6 Stability Study[10]

Stability studies of the selected formulated tablets were carried out by keeping the tablets at room temperature and at 40^0C ± 2^0C / 75 ± 5% RH (stability chamber) for 2 month and

evaluated for physical properties and drug content during the testing period. All the parameters were compared with initial formulation.

3. RESULT AND DISCUSSION

Oral disintegrating tablets of Simvastatin were prepared by direct compression method using croscarmellose sodium and crospovidone as superdisintegrants in different concentrations. Mannitol and lactose as a diluent used with different concentrations. The solubility of the drug was increased by preparing inclusion complex of simvastatin and β-cyclodextrin (1:1 molar ratio) using kneading method and phase solubility study also be carried out for determination of amount of solubility to be increased, by plotting phase solubility diagram The phase solubility diagram for complex formation was shown in figure 1 in the phase solubility diagram, the regressed curve has a slop value 0.0103, intercept 0.0203 and correlation coefficient was R^2=0.9946. The apparent stability constant, K was calculated from the linear plot of the phase solubility diagram according to the equation was 50.50%. No chemical interaction between the drug and the excipients was confirmed by FTIR and DSC studies. Eight formulations were prepared taking above mentioned ingredients and evaluated. All the formulations were evaluated for post-compression parameters. The post- compression parameters data were given in Table 3, 4. All the formulations of Simvastatin tablets fulfilled the official requirements. The average weight of the tablets of all formulations were in the range of 300 ±2.1 to 300± 7.2 (mg ± SD). The uniformity weight of the obtained tablets were within the limit i.e. below ± 7.5%. The drug content of the tablets was in the range to 90.60% to 98.80% within the acceptable limit. Hardness of the tablets were found in the range of 3 to 3.5 Kg/cm^2. Friabilty was below 1% signifying the tablets have good mechanical properties. Wetting time and water absorption ratio of the ODTs were 17.1 to 64±4 and 32±2 to 86±5 respectively.

Disintegration study was carried out for all the formulations and the formulations shows disintegration time 28s to 52s. Among this formulation containing crospovidone (45%) shows rapid disintegration time than crosscaramellose sodium (45%). This could be due to better capillary action and wicking action with crospovidone and compared crosscaramellose. Based on the disintegration time and wetting time the superdisintegrants ranked as crospovidone (CP) >croscarmellose sodium (CCS). Increase in concentration of superdisintegrant increases the DT. The fast dissolution might be due to rapid breaking down of the tablet particles. The in vitro dissolution studies in phosphate buffer pH 6.8 for the

optimized formulations (F4, F8) are reported in Table 3 and Figure 2. Formulations containing 45% CP (F4 97.84%, F8 98.54%) showed highest dissolution. Hence around 45% w/w concentration can be optimum for crospovidone. All formulation shows dissolution time 85.89% to 98.54%. In the above study, it was observed that the formulations containing crospovidone (45%) and mannitol as diluent showed the fastest disintegration and better dissolution as compared to the formulations containing Croscaramellose sodium with lactose as diluent. Hence optimization formulations (F4, F8) containing were selected for stability study 40±2^{0}C and 75±5% RH for two months.

6. Illustration

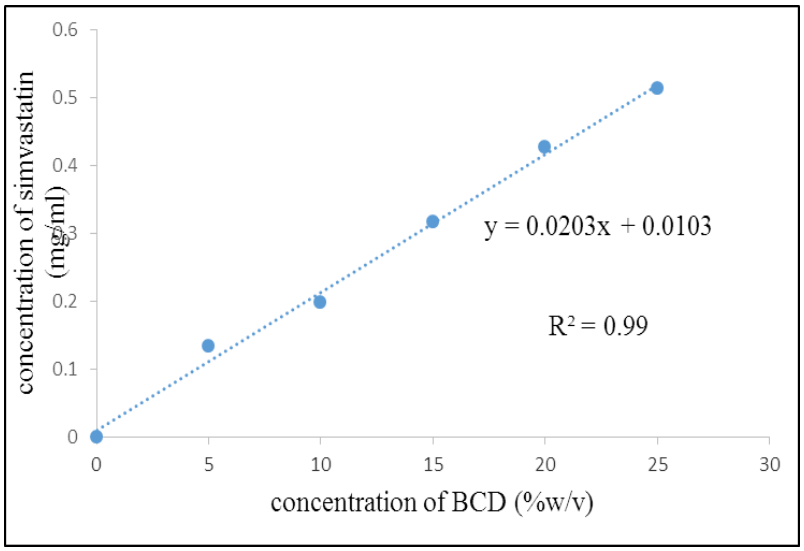

Fig.1: Phase solubility diagram of simvastatin and β-cyclodextrin β-CD, y = 0.0203x, R^2 value= 0.9946

Table 1: Formulae of Simvastatin oral disintegrating Tablets

(All quantities in mg)

Sr. No.	Formulation	Friability (%)	Weight Variation(mg ± SD)	Thickness (mm± SD)	Hardness (kg/cm.sq±SD)
1.	F1	0.36	300 ±2.3	2.1±0.2	3
2.	F2	0.20	300 ±6.4	2.1±.0.1	3.5
3.	F3	0.31	300 ±4.0	2.3±0.1	3.5
4.	F4	0.42	300 ±5.2	2.2±0.4	3.5
5.	F5	0.28	300 ±5.3	2.1±0.3	3.5
6.	F6	0.65	300± 7.2	2±0.4	3
7.	F7	0.50	300 ±4.3	2.2±0.4	3
8.	F8	0.72	300 ± 2.1	2.1±0.2	3

(*)Amount of complex equivalent to 10 mg of Simvastatin (with β- cyclodextrin).

Table 2: Evaluation Parameters of the Formulation

Sr.No	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
1.	Amount of simvastatin*	37.1	37.1	37.1	37.1	37.1	37.1	37.1	37.1
2.	Crosspovidone	0	15	30	0	45	15	30	45
3.	Croscaramellose sodium	45	30	15	45	0	30	15	0
4.	Lactose	207.9	207.9	207.9	207.9	-	-	-	-
5.	Mannitol	-	-	-	-	207.9	207.9	207.9	207.9
6.	Aerosil	3	3	3	3	3	3	3	3
7.	Saccharin sodium	3	3	3	3	3	3	3	3
8.	Magnesium stearate	3	3	3	3	3	3	3	3
9.	Talc	1	1	1	1	1	1	1	1
10.	Total weight of tablet	300	300	300	300	300	300	300	300

Table 3: Evaluation Parameters of the Formulations

Sr. No.	Formulation	Diameter mm ± SD	Wetting time (s)	Water absorption ratio	Disintegration Time (sec)	% drug content	% drug Release in 30 min
1.	F1	10±0.00	24±4	48±5	52	91.46	96.61%
2.	F2	10±0.00	17±1	57±3	50	90.60	85.89%
3.	F3	10±0.00	20±5	74±1	35	94.26	90.22%
4.	F4	10±0.00	62±3	35±4	30	97.40	97.84%
5.	F5	10±0.00	26±1	60±2	50	92.53	97.55%
6.	F6	10±0.00	20±4	78±3	50	91.89	86.57%
7.	F7	10±0.00	24±2	86±5.	32	94.12	91.05%
8.	F8	10±0.00	64±4	32±2	28	98.80	98.54%

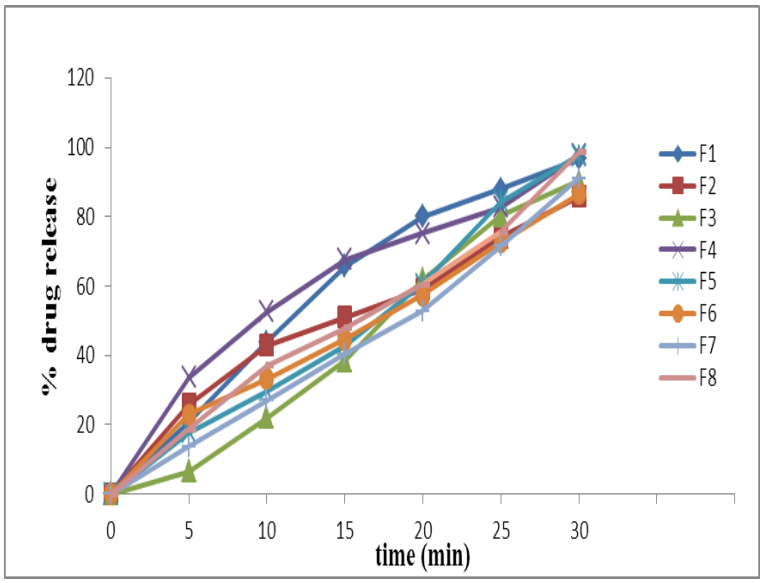

Fig 2: Comparative Dissolution profile of all batches Formulated

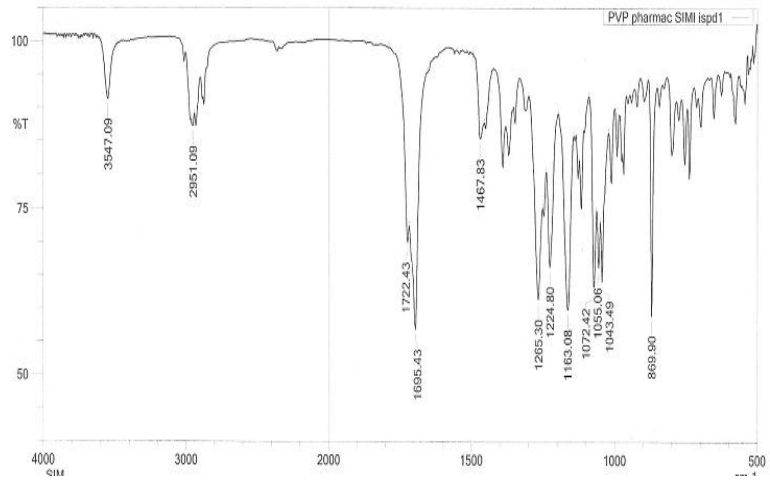

Fig 3: FTIR Spectrum of Simvastatin

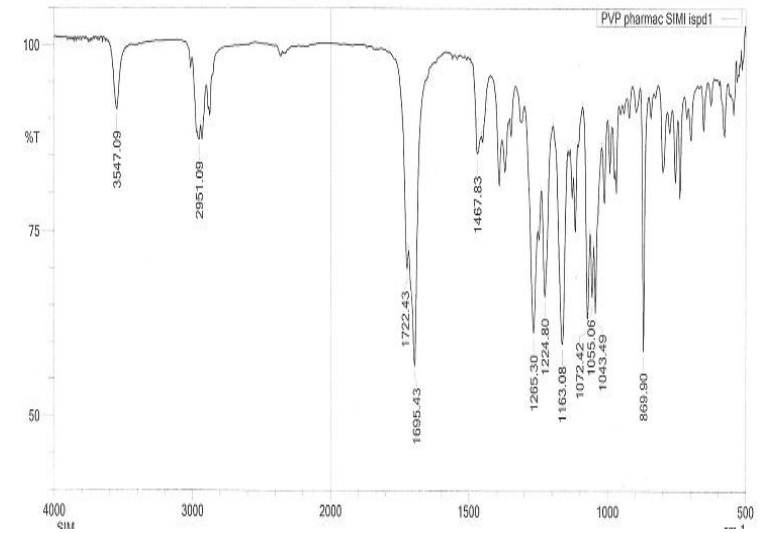

Fig 4: FTIR Spectrum of β-cyclodextrin

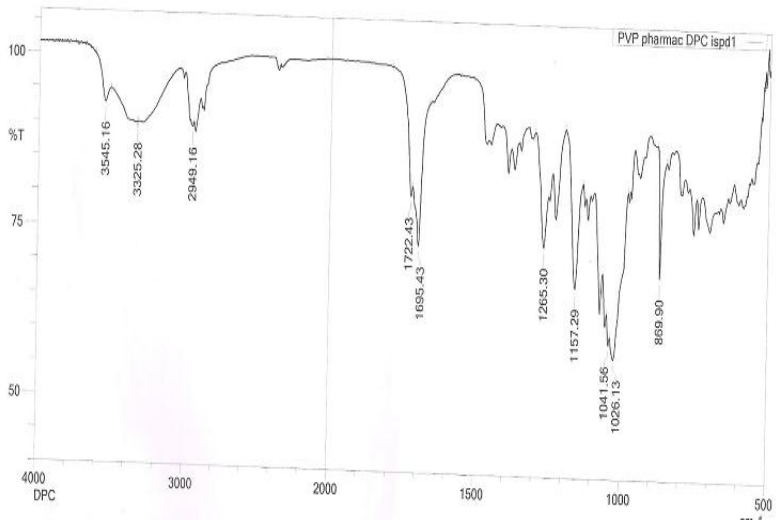

Fig 5: FTIR Spectrum of Drug+β-cyclodextrin complex

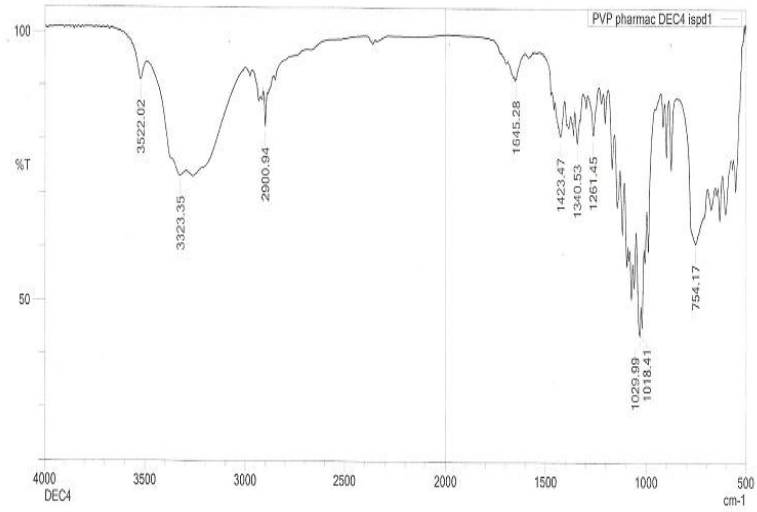

Fig 6: FTIR Spectrum of simvastatin drug loaded formulation (4)

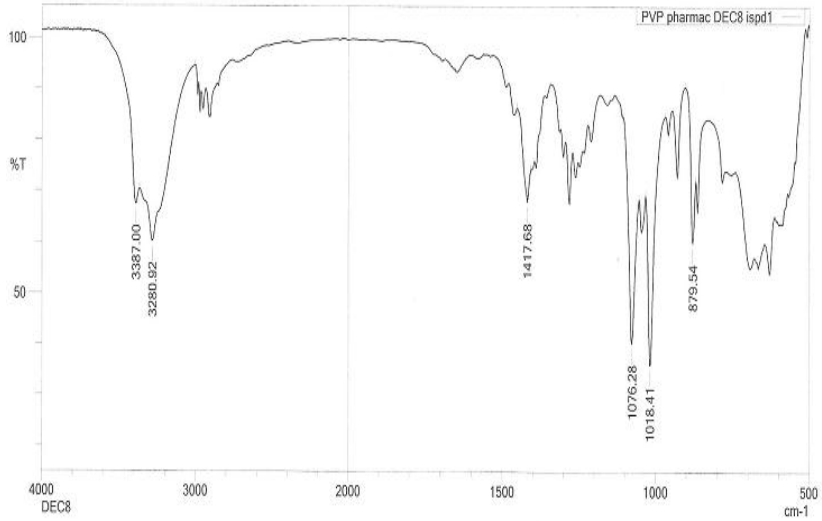

Fig 7: FTIR Spectrum of simvastatin drug loaded formulation (8)

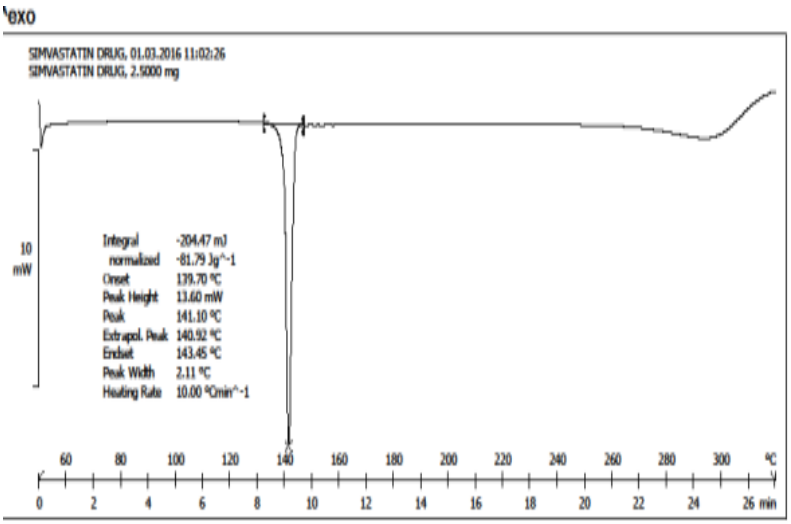

Fig 8: DSC graph of Simvastatin

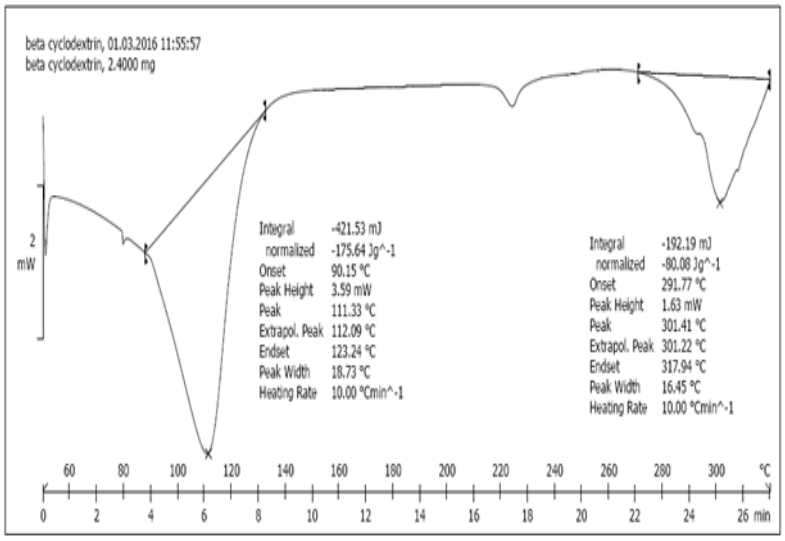

Fig 9: DSC graph of β-cyclodextrin

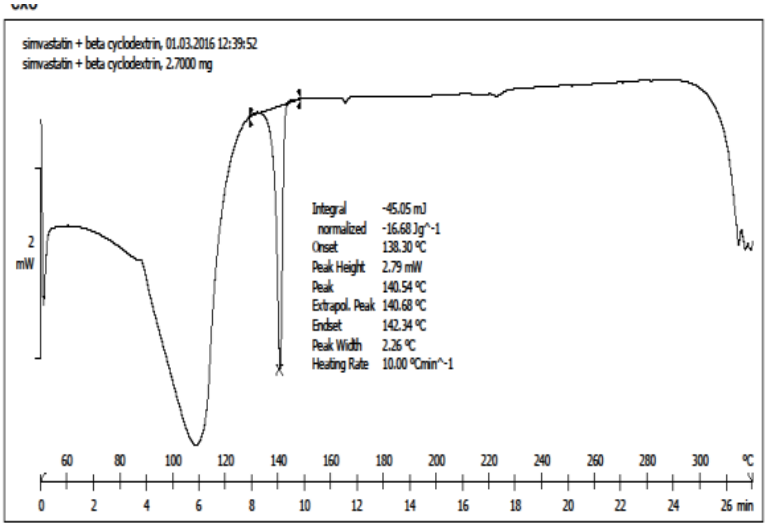

Fig 10: DSC graph of Simvastatin+ β-cyclodextrin complex

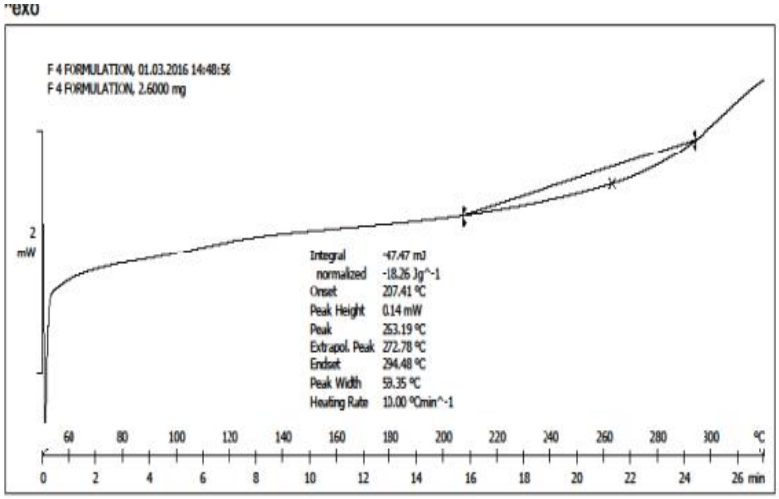

Fig 11: DSC graph of simvastatin drug loaded formulation (4)

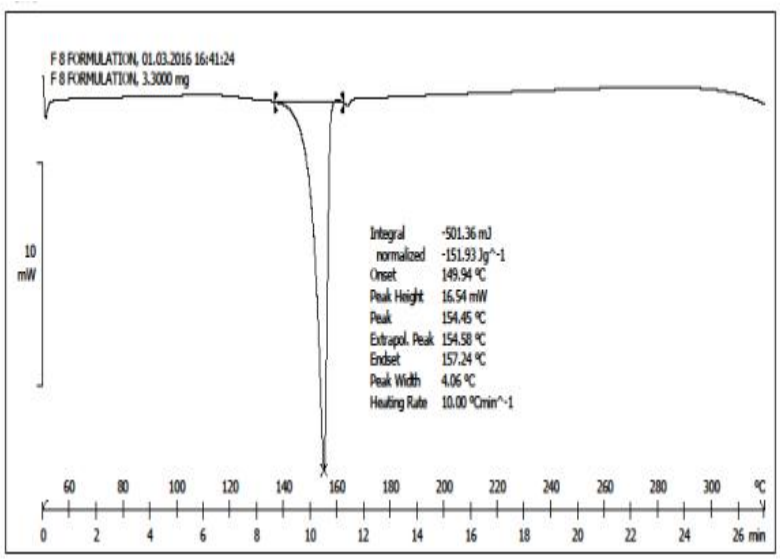

Fig 12: DSC graph of simvastatin drug loaded formulation (8)

Table 4: Stability Parameters of 2 month

Formulation	Study conditions specification	Month	% Drug Content
F4	$40^0C \pm 2^0C/75\% \pm 5\%$ RH	Initial	97.40%
		Month 1	97.34%
		Month 2	96.78%
F8	$40^0C \pm 2^0C/75\% \pm 5\%$ RH	Initial	98.80%
		Month 1	97.72%
		Month 2	96.59%

4. CONCLUSIONS

Enhancement of solubility of simvastatin was observed in the ßCD complex, where simvastatin form 1:1 molar inclusion complex by Kneading method improved dissolution rate as well as solubility of the drug.

It may be conclude that Oral disintegrating tablets prepared by direct compression of drug-ßCD complex using crospovidone as superdisintegrant and mannitol as diluents and containing simvastatin inclusion complex in β-cyclodextrin provides optimum water solubility and hence, drug bioavailability.

5. REFERENCE

1. Aulton M. E., Pharmaceutics: The Science of Dosage form Design, Churchill Livingstone, 2nd Edition, 2001; 345: 378-379.

2. Himanshu Gupta, Recent Trends in Oral Drug Delivery: A Review, Recent Patents on Drug Delivery & Formulation 2009; 3: 162-173.
3. Karemore M. N. Formulation and evaluation of fast dissolving tablet of Antihypertensive drug. International Journal of Pharmacy & Technology, April-2012; 4(1): 4000-4010.
4. Nayak, A., Manna, K. (n.d.). Current developments in orally disintegrating tablet technology. J Pharm Educ Res., 2011; 2(1): 21- 34.
5. D.K. Sanghi and Rakesh Tiwle. Phase solubility study of hydrophobic drug domperidone using a novel technique inclusion complex with β- cyclodextrin. International Journal of Pharmaceutical Research & Analysis, 2014; 4(3): 157-162.
6. KR Bobe. Formulation evaluation of fast dispersible tablet of atorvastatin by using cyclodextrin complexation method. International Journal of Drug Formulation & Research, 2011; 2(1): 167-192.
7. Kambham venkatswarlu, K. B, Chandrasekhar. Formulation and evaluation of Lacidipine oral disintegrating tablets: Enhancement of solubility and dissolution rate. International Journal of Life Science & Pharma Research, April 2016; 6(2): 16-26.
8. Khaled M Hosny. Preparation and Evaluation of Orodispersible Tablets Containing Hydroxylbutyl-β-Cyclodextrin-Simvastatin Solid Dispersion. Trop J Pharm Res, August 2013; 12(4): 469-476.
9. Chandra Sekhar Patro. Formulation and evaluation of valsartan oral disintegration tablets. Pharmanest-An International Journal of Advances in Pharmaceutical Sciences, 2013; 4: 978-990.
10. Ravi Sankar. V. Formulation and In-Vitro Evaluation of Ropinirole Oral Disintegrating Tablets. Cre. J. Pha. Res, 2015; 1(2): 76-83.
11. Bhavisha Rabadiya. Development and validation of spectroscopy method for simvastatin in different dissolution media. *IJPRBS*, 2013; 2(3): 25-41.
12. Shivanand Shiralashetti. Influence of method of preparation on solubility, physicochemical properties and in-vitro release profile of Simvastatin- cyclodextrin inclusion complexes: A comparative study. International Journal of Chem Tech Research, 2010; 2(1): 562-571.