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Formulation and Evaluation of Simvastatin Rapidmelts

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Keywords: Simvastatin, β-cyclodextrin, co-evaporation, kneading, direct compression, sublimation, superdisintegrants, subliming agents.

ABSTRACT

The aim of the present study was to formulate and evaluate simvastatin Rapidmelts by sublimation and direct compression techniques. As simvastatin comes under class II drug, the solubility of the drug should be increased before formulation. Hence, solid dispersions were prepared with β-CD and pvp k-30by using co-evaporation and kneading method. Among those solid dispersions prepared with β-CD(1:1.5) by using co-evaporation method has shown better drug entrapment values compared to other formulations. Those solid dispersions were formulated as rapidmelts by using direct compression. In direct compression method, rapidmelts were prepared using superdisintegrants crospovidone, croscarmellose sodium and starch1500. Those are evaluated for both pre-compression and post-compression parameters. Simvastatin rapidmelts were prepared by sublimation method using subliming agents camphor, urea, and ammonium bicarbonate. Each subliming agent is used in three different concentrations (2.5,5.0,7.5%). Rapidmelts prepared with the two methods were evaluated for weight variation, hardness, friability, %drug content and disintegration time. The best formulation was subjected to stability testing for 6months at 25º/60%RH and 40º/75%RH. All the prepared formulations complied with the pharmacopoeial limits. The results suggest that F12 formulation has given the best disintegration and dissolution results. From the result, it was concluded that rapidmelts prepared by using the sublimation method has given a better result than a direct compression method. That final formulation was further evaluated for *in-vivo* studies.

INTRODUCTION:

The oral route of administration is most convenient for drug administration. Orally disintegrating systems are dosage forms, which when placed in the mouth rapidly disperse and dissolve in the mouth without the need for water. After disintegration, the drug solution can be partially or completely absorbed by the sublingual blood vessels and bypasses first pass metabolism by the liver or be absorbed from the GIT after swallowing. Prescription ODT products initially were developed to overcome the difficulty in swallowing among pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules.

Today, ODTs will be more widely available as OTC products for the management of many conditions such as lowering cholesterol, heart problems, allergies, cold, etc. The presence of a highly porous surface in the tablet matrix is the key factor for the rapid disintegration of ODT.

Many methods were reported for solubility and dissolution enhancement of poorly soluble drug such as mechanization, complexation, solid dispersions, kneading method, etc. Solid dispersions is a technique that depends on melting or dissolution process to disperse one or more active ingredient in a carrier or matrix in the solid state. This ensures increased drug wettability and reduction of particle aggregation and hence increased drug dissolution [(5)].

Pediatric and geriatric patients may have difficulties in swallowing or chewing pharmaceutical dosage forms for oral administration. Tablets that rapidly dissolve upon contact with buccal cavity could present a solution to those problems and so there is an increased interest in fast dissolving dosage forms for buccal, sublingual and oral administration. Fast dissolving / disintegrating tablets is a perfect fit for those patients as they immediately release the active drug when placed upon the tongue by rapid disintegration. So in the present investigation rapidmelts of Simvastatin were prepared.

Simvastatin is widely used in the treatment of hyperlipidemia. It acts as an HMG-CoA reductase inhibitor. Hyperlipidemia drugs are mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. Statins generally work via nuclear receptors, Statins may have benefits other than just lowering cholesterol, they have anti-inflammatory properties, which help stabilize the lining of blood vessels. Simvastatin is practically insoluble in water and crystalline compound. Dissolution is the rate-limiting step that controls

oral absorption. Therefore, improvement in solubility and dissolution rate is essential to enhance drug bioavailability.

As Simvastatin comes under BCS class II drug solid dispersions of simvastatin were prepared by using different polymers in different ratios by using different techniques to enhance the solubility of the drug. Then those solid dispersions were formulated as rapimelts by using different superdisintegrants using direct compression method. To improve the porosity, volatile substances such as subliming agents can be used in the tableting process, which sublimated from the formed tablet. Simvastatin rapidmelts were prepared by using direct compression and sublimation techniques.

MATERIALS AND METHODS:

MATERIALS:

Simvastatin was obtained as a gift sample from Aurobindo pharma ltd, Hyderabad. β-cyclodextrin, polyvinylpyrrolidone k-30, Polyethylene glycol4000, crospovidone, croscarmellose sodium, starch1500, magnesium stearate, aerosil, microcrystalline cellulose, camphor, urea, ammonium bicarbonate, talc, aspartame, mannitol were kindly supplied by BMR Pharma and chemicals. All the other solvents used were of analytical grade.

METHODS:

Calibration Curve For Simvastatin: For this stock solution of Simvastatin (1mg/ml) was prepared. From the stock solution, 5-25 µg/ml dilute solutions were prepared. The absorbance was measured using UV- visible spectrophotometer at 235nm.

Preparation of solid dispersions:

Solvent evaporation method: Drug and polymers were mixed in different ratios(1:0.5,1:1,1:1.5) in a mortar. Methanol was added in proportion wise with constant and continuous stirring until the mixture was completely dissolved. Methanol was evaporated under constant stirring and resultant solid dispersions were collected.

Table 1: Preparation of simvastatin solid dispersions by using solvent evaporation method:

Excipients	1:0.5(SIM1)	1:1(SIM2)	1:1.5(SIM3)	1:0.5(SIM4)	1:1(SIM5)	1:1.5(SIM6)
Drug(mg)	500	500	500	500	500	500
β-CD (mg)	250	500	750			
PVP K-30(mg)				250	500	750
Water and methanol (1:1)	20ml					

Kneading method: In a mortar 50%solvent was taken, the calculated amount of polymer was added and is triturated to get slurry-like consistency. Then the drug was incorporated, remaining solvent was added and titration is continued for 1hr, air dried at 25^0C for 48hrs and the resulting dried product was pulverized and passed through a mesh sieve.

Table 2: Preparation of simvastatin solid dispersions by using kneading method:

Excipients	1:0.5(SIM7)	1:1(SIM8)	1:1.5(SIM9)	1:0.5(SIM10)	1:1(SIM11)	1:1.5(SIM12)
Drug(mg)	500	500	500	500	500	500
β-CD (mg)	250	500	750			
PEG4000(mg)				250	500	750
Water and methanol	Quantity sufficient for paste formation					

Evaluation of solid dispersions:

Drug entrapment efficiency:

Ten milligrams of each solid dispersion were weighed in glass Stoppard tubes and redispersed in 3 ml distilled water. The dispersion was then lysed with 1ml chloroform to allow for complete release for the entrapped drug. Complete extraction of the drug was facilitated by shaking the tubes for 6 hrs in water bath shaker at 37 ºC. The samples were centrifuged at 6000 rpm for 5 min and then allowed to stand for complete separation of the two phases. The collected aqueous solutions were analyzed for determining the drug concentration as previously described. Drug concentration was also used for determining % encapsulation efficiency according to the following formula[(1)]

% Encapsulation efficiency = (actual drug loading/ theoretical drug loading) × 100

Preparation of simvastatin rapidmelts:

Simvastatin rapidmelts were prepared by using direct compression and sublimation methods.

Direct compression method: Solid dispersions equivalent to10mg were taken. Rapidmelts were prepared by using superdisintegrants CCS, CP, Starch1500 (2,4,6%). All the ingredients were passed through the mesh. Then all the ingredients were mixed in geometric order and the tablets were compressed with 8 mm size round Punch [(2)].

Table 3: Composition of simvastatin rapid melts by direct compression method:

Compound Name	F1	F2	F3	F4	F5	F6	F7	F8	F9
Equivalent Solid dispersion (mg)	65.5	65.5	65.5	65.5	65.5	65.5	65.5	65.5	65.5
CP (mg)	4			8			12		
CCS (mg)		4			8			12	
Starch 1500(mg)			4			8			12
Mg Stearate(mg)	3	3	3	3	3	3	3	3	3
Aerosil(mg)	2	2	2	2	2	2	2	2	2
MCC (mg)	125.5	125.5	125.5	121.5	121.5	121.5	117.5	117.5	117.5
Total weight(mg)	200	200	200	200	200	200	200	200	200

Sublimation method: Different rapidmelts of simvastatin were prepared by using subliming agents such as camphor, urea, ammonium bicarbonate in different concentrations (2.5,5,7.5%) from the final tablet weight. All of the materials were passed through sieve No. 60 before use and the accurately weighed amounts of ingredients were thoroughly mixed and compressed into 200 mg tablets using single punch machine of 8mm round punch and die set. Simvastatin tablets were then placed in an oven at 40^0C till a constant weight is obtained[(2)].

Table 4: Composition of simvastatin rapidmelts by sublimation method:

Compound Name	F10	F11	F12	F13	F14	F15	F16	F17	F18
Simvastatin(mg)	10	10	10	10	10	10	10	10	10
Camphor(mg)	5	10	15						
Urea(mg)				5	10	15			
Ammonium bicarbonate(mg)							5	10	15
Crospovidone(mg)	4	4	4	4	4	4	4	4	4
Aspartame(mg)	2	2	2	2	2	2	2	2	2
Mg stearate(mg)	2	2	2	2	2	2	2	2	2
Talc(mg)	1	1	1	1	1	1	1	1	1
Mannitol	176	171	166	176	171	166	176	171	166

Evaluation of simvastatin rapid melts:

Precompression parameters: The various characteristics of blends conducted before compression are as follows:

The angle of Repose: Angle of repose (θ) was determined using the fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the granular cone was measured and the angle of repose was calculated using the following equation:

$$\tan \theta = h/r$$

Where h and r are the height and radius of the cone

Bulk density and Tapped density: A suitable amount of powder from each formulation, previously lightly shaken to break agglomerates formed, was introduced into a 10 ml measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from a height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted.

Bulk density = weight of the powder/bulk volume of the powder

Tapped density = weight of the powder / tapped volume of the powder

Carr's index: The compressibility index of the powder blend was determined by the Carr's index. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which its packed down.

Carr's index = (tapped density – bulk density/tapped density) X 100

Hausner's ratio: Hausner's ratio was calculated from the bulk and tapped density of Simvastatin blend powder formulation and it is expressed as:

Hausner's ratio = tapped density / bulk density

Post-compression parameters:

Hardness: The average breaking strength of tablets was determined by tablet hardness tester (Monsanto hardness tester). From each formulation, 10tablets were tested for their hardness. The mean hardness (±SD)of each formula was determined [(4)]. It is expressed in kg/cm^2.

Weight Variation: To ensure the uniformity of tablets weight variation test was carried out. Twenty tablets were randomly selected from each formulation and separately weighed. Their average weight and (±SD) were calculated[(4)].

Friability: To evaluate the friability 10 tablets from each batch were collected and weighed. The tablets were placed in the Rochefriabilator and subjected to 25rpm for a period of 4min. Afterward, the tablets were dusted and once again reweighed. The percentage loss in weights was calculated and taken as a measure of friability[(4)].

***In-vitro* disintegration time**: The *in-vitro* disintegration studies were carried out using a digital tablet disintegration test apparatus. One tablet was placed in each of the 6 tubes of the basket assembly and the disk was added to each tube. This assembly was then suspended in a 1-liter beaker containing water with its temperature being maintained at 37±2°C. The basket was then moved up and down through a distance of 5 to 6 cm, at the frequency of 28 to 32 cycles per minute. The time required for the complete disintegration of the tablet was recorded. It is expressed in seconds.

***In-vitro* dissolution studies**: The dissolution profiles of simvastatin from rapidmelts were determined in a dissolution tester, apparatus II. All tests were conducted in 900ml phosphate buffer pH 7.0 containing 0.5%SLS at temperature of 37±0.5^{0}C with a paddle

rotation speed at 50rpm. At specified time intervals, 1,5,10,15,20,25, 30,35,40,45 and 50min; 5mlof dissolution medium was withdrawn and replaced with an equal volume of medium to maintain a constant total volume. Samples were filtered through a 0.45 µm Milliporefilter and assayed for drug content spectrophotometrically at 235nm.

Wetting time: The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10-cm diameter were placed in a Petri dish with a 10-cm diameter. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. The wetting time was measured in seconds.

Drug – Excipient compatibility study:

Fourier transform infrared Spectroscopy (FTIR):

The concentration of the sample in potassium bromide should be in the range of 0.2% to 1%. The pellet is much thicker than a liquid film, hence a lower concentration in the sample is required (Beer's Law). Too high a concentration usually causes difficulties obtaining clear pellets. The IR beam is absorbed completely, or scattered from the sample which results in very noisy spectra.

Differential Scanning Calorimetry (DSC):

Drug – excipients compatibility was evaluated using differential scanning calorimeter. The endotherms of pure drug and optimized formulation were recorded separately. The DSC can be used to obtain the thermal critical points like melting point, enthalpy specific heat or glass transition temperature of substances. The sample and an empty reference crucible are heated at constant heat flow. A difference of the temperature of both crucibles is caused by the thermal critical points of the sample and can be detected.

Stability Studies: In order to study the stability of the rapid melt, representative samples of the were packed in amber colored airtight glass containers and they were stored in stability chambers maintained at 25°C/60 % RH and 40° C/75 % RH. The physicochemical properties of these samples were analyzed at 0, 3 and 6 months. At each time point, one container was taken out from the respective storage conditions and subjected to content uniformity and dissolution rate studies [7, 8].

Pharmacokinetic evaluation of simvastatin optimized formulation in rabbit plasma: Pharmacokinetic study:

Healthy rabbits (New Zealand Albino) of either sex weighing 2.5-3.0 were selected and housed with CPCSEA (1722/RO/Ere/13/CPCSEA) guidelines, fasted overnight and had free access to drinking water.

Experimental design:

Animals were separated into three experimental groups, each group consisting of three animals (n=3). The test formulation of the batch (F12) was compared with (reference/ marketed formulation) with the following treatment schedule under the fasted condition:

Group I - (Normal Control) – Received placebo.

Group II- (Positive control) – Marketed formulation

Group III- Simvastatin formulation (F12) used as a test.

The optimized formulations were administrated via oral gauge at a dose 0.513 mg/kg. Blood samples (each of about 1-2ml from each animal) were withdrawn from marginal ear vein at regular time intervals after administration. During each period, approximately 1 ml of blood was collected from a marginal ear vein of rabbit into microcentrifuge tubes containing EDTA. Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 3, 6, 9, 24 hrs in a heparinized centrifuge tube.

Extraction of Plasma:

The samples were centrifuged immediately and the plasma separated was stored at -20^{0}C till the time of analysis. The drug was extracted from the plasma. To 10µl/ml of plasma 50µl/ml of 10µg/ml of the drug, the solution was added in a stoppered test tube. This was kept in a cyclone mixer for 15min.To that 2ml of acetonitrile was added and vortexed for 2min and centrifuged at 3200rpm for 15min. The aqueous layer was collected and drug concentration was determined using RP-HPLC.

HPLC assay:

A water alliance2695 separation module equipped with a UV detector employed throughout the study. Column employed in this method was BDS C18(4.6×5 mm). The samples were injected with an automatic detector. The 10 µl volume of sample was injected. The input and output operations of the chromatographic system were monitored by waters empowered software. The flow rate selected was 1.0mL per min. The detection was done at 235nm. The temperature and run time were monitored at 25ºC and 10min respectively. A calibration curve was constructed between concentration and peak area obtained with the respective concentration of the solution. The mobile phase was prepared prior to the experiment by taking buffer and acetonitrile in60: 40 ratio. The solution was then filtered through 0.45 µm membrane filter and degassed. The eluents were monitored using UV detection at 235 nm.

RESULTS AND DISCUSSION:

Drug entrapment efficiency: From the drug entrapment values it was observed that solid dispersions prepared with coevaparation method were better entrapped compared to kneading method.

Table 5: Drug Entrapment efficiency values

Solid dispersion	Cosolvent method	Solid dispersion	Kneading method
SIM1	61.8	SIM7	50.2
SIM2	63.4	SIM8	56.65
SIM3	65.5	SIM9	57.25
SIM4	49.1	SIM10	52.69
SIM5	53.9	SIM11	58.12
SIM6	59.9	SIM12	61.29

Evaluation of rapidmelts:

The parameters such as angle of repose, bulk density, tapped density, Carr's index, Haussner's ration are important for the measurement of flow properties of powders. For the formulations, F1-F18 angle of repose values obtained were the powder has shown the angle of repose values between 25-30℃. It indicates an excellent flow of all formulations. Carr's

index was found to be between 10-20(%) and Hausner's ratio values are between 1.10-1.15. These indicate the good flow of powders from F1-F18. The results were shown in the **Tables 6 &7**.

Table 6: Precompression parameters for simvastatin rapid melts prepared by using direct compression method:

Formulation Code	The angle of repose(º)	Bulk density (mg/ml)	Tapped density (mg/ml)	Carr 's index(%)	Hausner's ratio
F1	27.23±0.12	0.60±0.01	0.75±0.01	20.32±0.01	1.26
F2	26.46±0.01	0.60±0.11	0.74±0.21	18.78±0.05	1.23
F3	28.36±0.11	0.62±0.13	0.74±0.11	15.35±0.02	1.18
F4	29.21±0.32	0.59±0.15	0.73±0.15	18.76±0.11	1.23
F5	29.56±0.01	0.62±0.14	0.75±0.10	16.38±0.13	1.20
F6	25.62±0.05	0.61±0.13	0.71±0.05	14.19±0.15	1.17
F7	27.35±0.10	0.61±0.01	0.77±0.13	10.39±0.01	1.26
F8	28.76±0.12	0.61±0.02	0.75±0.23	18.40±0.21	1.23
F9	29.01±0.11	0.63±0.32	0.74±0.32	14.8±0.12	1.17

Table 7: Precompression parameters for simvastatin rapidmelts prepared using the sublimation method:

Formulation Code	The angle of repose(º)	Bulk density(mg/ml)	Tapped density(mg/ml)	Carr 's index(%)	Hausner's ratio
F10	27.2±0.01	0.35±0.10	0.45±0.21	22.22±0.12	1.29
F11	28.3±0.11	0.32±0.11	0.43±0.02	25.58±0.11	1.34
F12	25.7±0.12	0.35±0.21	0.42±0.05	16.67±0.05	1.20
F13	28.3±0.11	0.36±0.02	0.46±0.10	21.74±0.10	1.28
F14	29.3±0.20	0.36±0.05	0.49±0.11	26.53±0.11	1.36
F15	28.5±0.01	0.38±0.12	0.48±0.15	20.83±0.21	1.26
F16	26.5±0.10	0.45±0.11	0.53±0.21	15.09±0.05	1.18
F17	24.3±0.01	0.38±0.21	0.48±0.01	20.83±0.03	1.26
F18	27.3±0.20	0.35±0.02	0.47±0.10	25.53±0.05	1.34

Mean±SD, n=3

Post-compression parameters:

Weight variation*:* All the formulations were evaluated for uniformity of weight. The average weight of all the formulations was found to be in the range of 197±0.32 to 201.4±0.12 mg.

Hardness: All the formulations were evaluated for hardness using Monsanto hardness tester. The average hardness was found to be between 6-7.5kg/cm^2.

Friability: Rapidmelts were evaluated for their % friability using Roche friabilator. The average % friability was found to be below 1 %. It indicates good mechanical strength of the powder.

In-vitro **Disintegration time:** Disintegration time was found to be between 120-170 sec. These results indicate that increasing the concentration of superdisintegrants and sublimating agent in the tablets results in the formation of more pores form on tablets that are less likely to break up or dissolve easily in water.

Drug content: All the formulations were evaluated for drug content according to the procedure described in the methodology. The assay values for all the formulations were found to be in the range of (98.57±0.23 to 102.8±0.31). According to IP standards, the tablets must contain not less than 95 % and not more than 105 % of the stated amount of the drug. Thus, all the rapidmelts comply with the standards given in IP.

Table 8: Post compression parameters of simvastatin rapidmelts prepared using direct compression method:

Formulation Code	Hardness (kg/cm^2)	Average weight (mg)	%drug content	Friability (%)	Thickness (mm)
F1	4.4±0.01	1 9 7.3±0.01	100.74±0.12	0.71±0.10	2.0±0.10
F2	4.8±0.05	19 6.3±0.23	102.8±0.31	0.83±0.02	2.02±0.01
F3	3.2±0.12	19 8 .6±0.21	100.20±0.15	0.63±0.11	1.9±0.20
F4	3.6±0.23	19 7.2±0.11	100.31±0.21	0.72±0.12	1.6±0.30
F5	4.5±0.11	200.6±0.1	101±0.10	0.56±0.10	2.2±0.11
F6	3.8±0.12	200.5±0.12	102±0.12	0.54±0.11	2.10±0.21
F7	3.1±0.01	19 8. 6±0.14	102.3±0.12	0.69±0.12	2.03±0.26
F8	3.9±0.34	19 8.4±0.21	100.2±0.10	0.49±0.21	2.06±0.20
F9	4.2±0.31	197±0.32	101.11±0.12	0.43±0.11	2.14±0.12

Mean±SD, n=3

Formulation Code	*In vitro* Disintegration time(sec)	Wetting Time(sec)
F1	163±1	39.6±2
F2	170±2	48.4±5
F3	148±3	42.3±1
F4	163±1	26.4±6
F5	165±1	39.6±2
F6	156±2	32.8±1
F7	146±2	18.5±4
F8	170±2	24.8±9
F9	153±1	21.4±1

Table 9: Post compression parameters of simvastatin rapidmelts prepared using the sublimation method:

Formulation Code	Hardness (kg/cm^2)	Average weight(mg)	Drug content (%)	Friability (%)	Thickness(mm)
F10	3.94±0.11	200.2±0.21	99±0.57	0.55±0.01	2.0±0.10
F11	4.18±0.13	201.4±0.12	100.30±0.12	0.39±0.21	2.1±0.20
F12	4.0±0.04	196.4±0.23	101±0.11	0.64±0.02	2.0±0.11
F13	3.85±0.15	198.6±0.32	100.3±0.12	0.45±0.01	1.5±0.15
F14	4.11±0.13	199.6±0.23	101±0.10	0.59±0.11	1.9±0.22
F15	4.4±0.21	200±0.11	100.2±0.21	0.53±0.12	2.05±0.14
F16	4.6±0.32	200.3±0.01	98.57±0.23	0.62±0.15	2.11±0.21
F17	4.1±0.42	197.2±0.1	100.20±0.10	0.65±0.21	2.16±0.10
F18	4.2±0.01	200.03±0.21	100.01±0.1	0.49±0.11	2.11±0.25

Formulation code	*Invitro* disintegration time(sec)	Wetting Time (sec)
F10	123±2	14.2±1
F11	142±3	10.8±5
F12	121±1	8.6±2
F13	127±2	20.4±3
F14	135±1	16.3±7
F15	145±3	14.8±2
F16	145±2	28.6±1
F17	125±1	23.8±3
F18	142±3	18.4±5

In-vitro dissolution studies:

***In-vitro* dissolution studies:** Formulations from F1-F9 were prepared using superdisintegrants (CCS, CP, SSG) by direct compression method. F10-F18 were prepared by using subliming agents (Camphor, Urea, ammonium bicarbonate) by a sublimation method. In the direct compression method, superdisintegrants will act by swelling the drug and results in faster disintegration and dissolution. In the sublimation method subliming agents will act by increasing the porosity of drug results in faster wetting and dissolution and increases bioavailability. In these two methods, rapidmelts prepared by using sublimation methods has given better dissolution compared to the direct compression method. The rapid melt prepared by using camphor 7.5% (F12) has given 100% dissolution within 5min. So F12 has been selected for further *in-vivo* studies. The results were given in the **Tables 10&11.**

Table 10: Mean (±SD) Percent cumulative drug release for simvastatin formulations prepared using direct compression method:

Time(Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	34.94± 0.5	17.36± 0.19	5.96±0 .15	16.1± 0.01	20.21± 0.10	15.46± 0.01	38.98± 0.32	16.65± 0.01	14.04± 0.01
10	52.52± 0.7	54.42± 1.25	20.20± 0.21	34.4± 0.5	52.52± 0.12	51.80± 0.20	73.66± 0.12	306.84 ±01	29.95± 0.02
15	70.33± 0.82	57.64± 0.05	28±0.1 9	52.5± 0.36	62.25± 0.15	59.64± 0.32	88.38± 0.01	54.42± 0.32	59.4±0 .21
20	77.22± 0.1	64.15± 0.32	33.0±0 .01	62.7± 0.15	70.33± 0.32	65.10± 0.25	100.26 ±0.2	62.73± 0.12	83.39± 0.32
25	84.11± 0.2	72.23± 0.45	53.4±0 .25	77.2± 0.18	777.22 ±0.2	71.87± 0.10	---	79.59± 0.19	99.07± 0.15
30	89.81± 0.4	81.26± 0.02	65.5±0 .15	85±0. 19	86.24± 0.45	89.09± 0.15	---	99.55± 0.17	---
35	100.73 ±0.1	87.43± 0.17	74.1±0 .11	99.3± 0.01	89.81± 0.25	100.7± 0.22	---	---	---
40	---	101.68 ±0.2	81.96± 0.25	---	99.55± 0.21	---	---	---	---
45	---	----	91.9±0 .30	---	---	---	---	---	---
50	---	---	99.5±0 .17	---	---	----	---	----	---

Table 11: Mean (±SD) Percent cumulative drug release for simvastatin formulations prepared using sublimation method:

Time (Min)	F10	F11	F12	F13	F14	F15	F16	F17	F18
0	0	0	0	0	0	0	0	0	0
1	35.4±0.01	40.5±0.02	45.8±0.01	4.35±0.01	4.45±0.01	6.48±0.05	4.25±0.01	7.25±0.01	10.46±01
2	60.2±0.03	68.7±0.05	56.4±0.02	8.78±0.05	9.02±0.02	13.45±0.01	8.79±0.02	12.26±0.2	12.36±0.02
3	75.4±0.02	78.5±0.05	75.8±0.05	12.24±0.02	13.4±0.05	16.89±0.02	12.22±0.05	14.45±0.02	15.46±0.03
4	85.4±0.5	86.4±0.02	85.1±0.03	18.54±0.01	16.54±0.01	29.54±0.05	15.14±0.03	18.45±0.03	20.24±0.05
5	96.22±0.02	98.36±±0.1	100.2±0.1	22.11±0.02	22.1±0.01	36.36±0.01	17.12±0.05	23±0.02	29.24±0.01
10	----	----	-------	52.52±0.03	50.6±0.02	81.9±0.02	42.3±0.02	48±0.02	63.9±0.1
15	----	----	-----	83.9±0.05	99±0.01	99.78±0.05	76.74±0.05	84.3±0.05	85.77±0.02
20	----	----	-----	99.31±0.02	-----	----	87.43±0.1	98.36±0.01	99.78v0.1
25	---	----	-----	----	-----	----	96.46	----	----

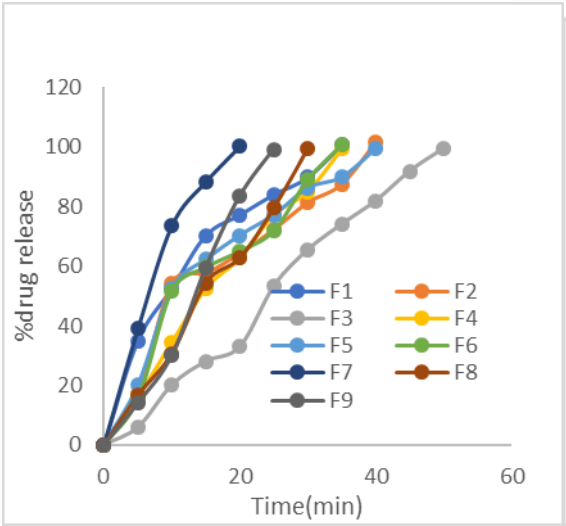

Fig. 1: Dissolution profile for simvastatin rapidmelts by direct compression method

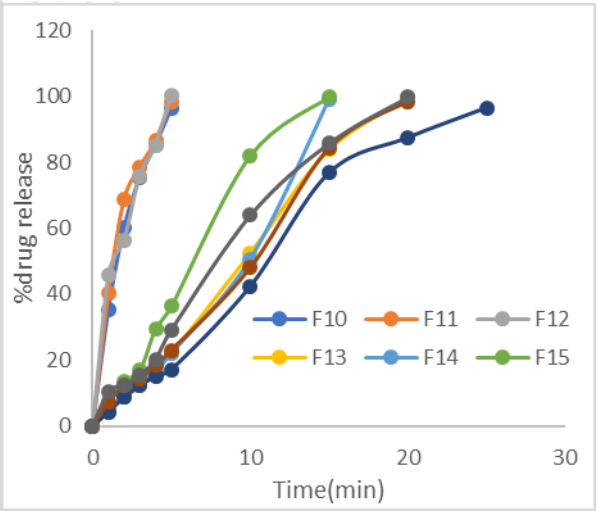

Fig. 2: Dissolution profile for simvastatin rapidmelts by a sublimation method

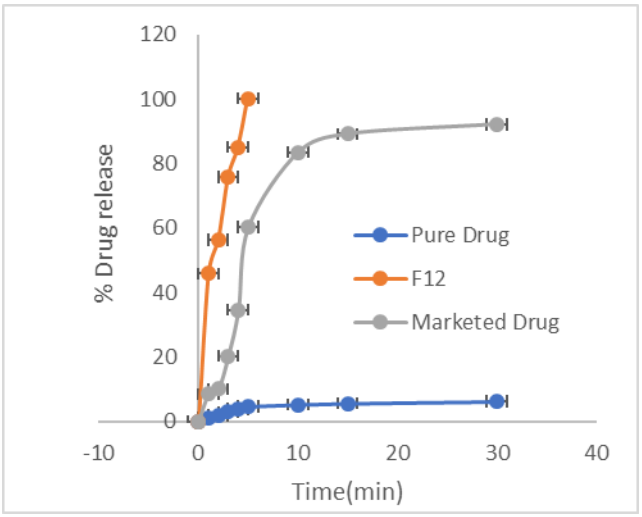

Fig. 3: Comparative dissolution profiles for pure drug, optimized formulation and marketed product

Table 12: Drug release kinetics for simvastatin dissolution data:

Product code	Zero order	First order
Pure drug	0.569	0.028
F1	0.797	0.997
F2	0.854	0.971
F3	0.989	0.934
F4	0.982	0.933
F5	0.827	0.990
F6	0.900	0.920
F7	0.912	0.989
F8	0.993	0.956
F9	0.964	0.884
F10	0.886	0.994
F11	0.814	0.885
F12	0.854	0.985
F13	0.991	0.799
F14	0.958	0.798
F15	0.979	0.848
F16	0.976	0.976
F17	0.989	0.896
F18	0.978	0.811

The values of correlation coefficients (r) and kinetic parameters obtained by fitting the data to popular drug release models are given in **Table12.** The drug release from these formulations appeared to follow more of the first order kinetics, indicated by r values (0.798-0.997) compared to those of zero order release kinetics (0.797-0.993).

Stability studies: Stability studies revealed that there is no significant changes were observed throughout the study. So we can say that formulation has good stability.

Table 13: Stability Studies of simvastatin optimized formulations

Time(Min)	Initial	25ºC/60 % RH (Dissolution rate after storage) %		40ºC/75 % RH (Dissolution rate after storage) %	
0months		3Months	6Months	3months	6 Months
0	0	0	0	0	0
1	45.8±0.01	46.08±0.16	45.6±0.15	45.8±0.15	45.9±0.31
2	56.4±0.02	55.9±0.37	56.5±0.55	56.4±0.03	56.6±0.12
3	75.8±0.05	75.8±0.15	75.9±0.22	75.8±0.80	75.9±0.13
4	85.1±0.03	85.3±0.02	85.2±0.02	85.1±0.01	85.1±0.01
5	100.2±0.1	100.3±0.1	100.2±0.2	100.2±0.02	100.1±0.01

***In-vivo* studies:** The plasma concentration-time profiles following oral administration of final formulation are given in **Fig: 10**. The data obtained from plasma concentration profiles AUC, C_{max}, T_{max}, $t_{1/2}$,$K_{a,\ MRT}$, t_a, V_d, K_e were given in **Table 14.**

Table 14: Pharmacokinetic parameters for simvastatin rapidmelts in rabbits:

Pharmacokinetic parameter	Marketed Formulation	Optimized Formulation(F12)
C_{max}(ng/ml)	8.2	9.72
T_{max}(hrs)	1	3
AUC $_{(0-24)}$ (ng.h/ml)	48.22	97.14
K_e(/hr)	0.247	0.149
Biological half-life($t_{1/2}$) (hrs)	2.8	4.63
Ka(/hr)	2.07	7.55
MRT	5.03	7.98
t_a(hrs)	2.22	0.610
Vd(lit)	0.839	0.639

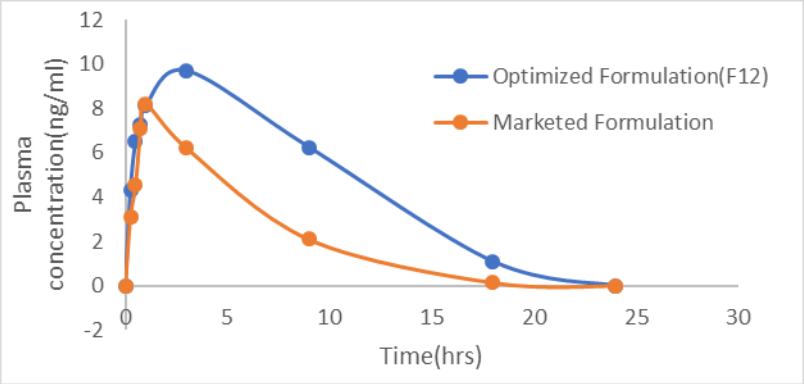

Fig. 4: Mean plasma concentration-time profile of simvastatin following the oral administration of the optimized and marketed formulation

Drug-excipient compatibility studies:

FTIR studies:

FTIR spectrum of simvastatin exhibited peaks at 3547cm^{-1}for amide N-H stretch,1696cm^{-1}for aldehyde C=O stretching,756cm^{-1} for aromatic C=H bending. The same peaks of the drug were observed in the FTIR spectra of the rapidmelts. Thereby ruling the absence of drug-polymer interaction from the obtained results. So further studies were performed based upon these results. Fourier transform infrared spectroscopy analysis was performed to pure drug and optimized formulation and presented in **Fig. 5 & 6.**

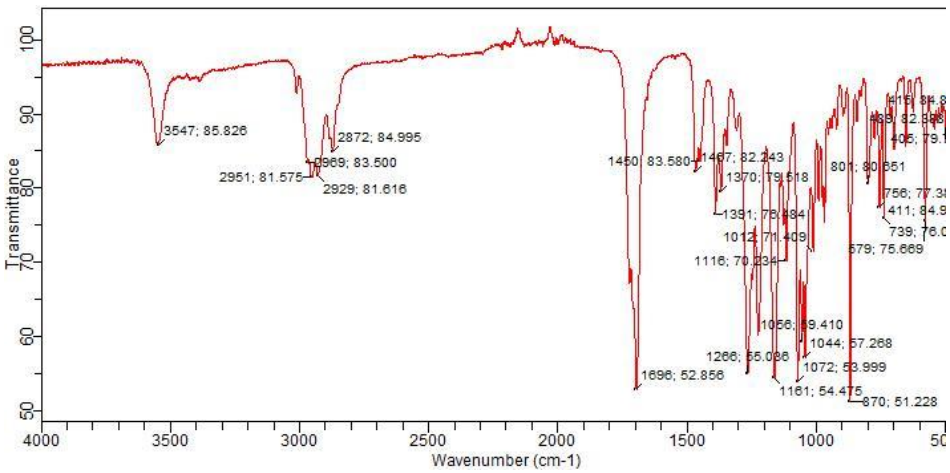

Fig. 5: FTIR spectrum for simvastatin pure drug

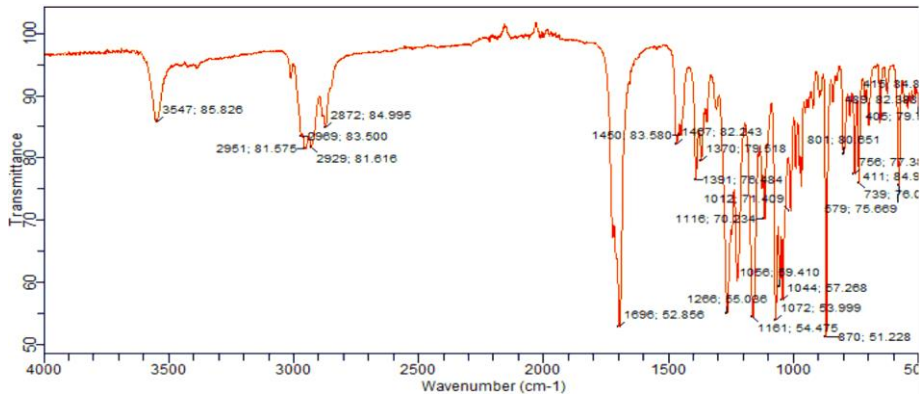

Fig. 6: FTIR spectrum for simvastatin formulation

DSC Study:

DSC thermograms for pure drug and optimized formulation were given in the **fig7&8.** The DSC thermogram of simvastatin exhibiting a sharp endothermic peak at 140.2^{0}C corresponding to the melting point of the drug simvastatin. The simvastatin rapidmelts also exhibited an endothermic peak similar to simvastatin, indicating that there was no change in the crystallinity of simvastatin, this indicates the drug-polymer compatibility. Peaks indicating that there were no interactions between drug and excipients.

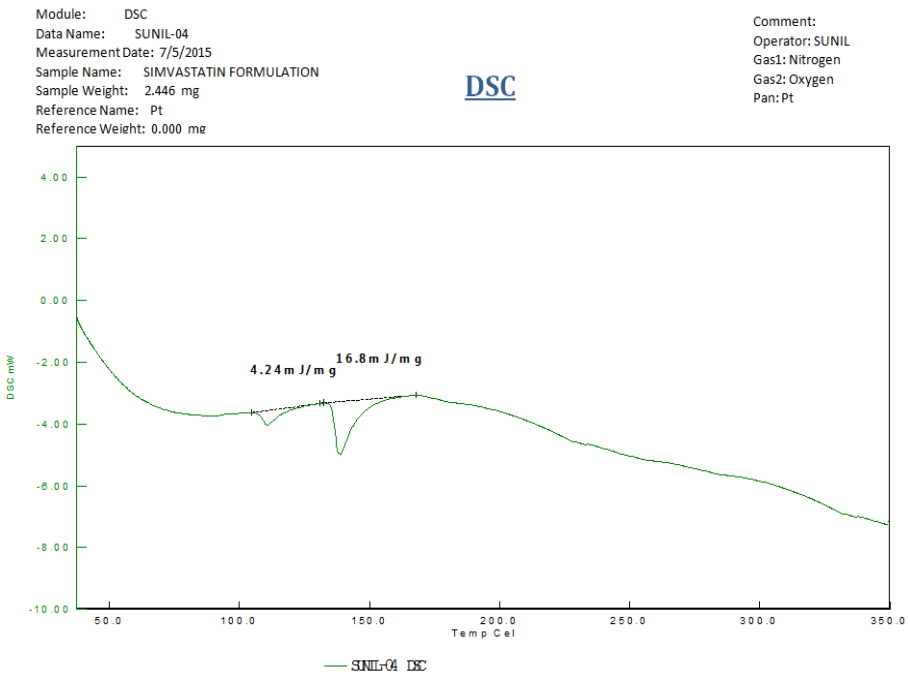

Fig. 7: DSC thermogram for pure drug

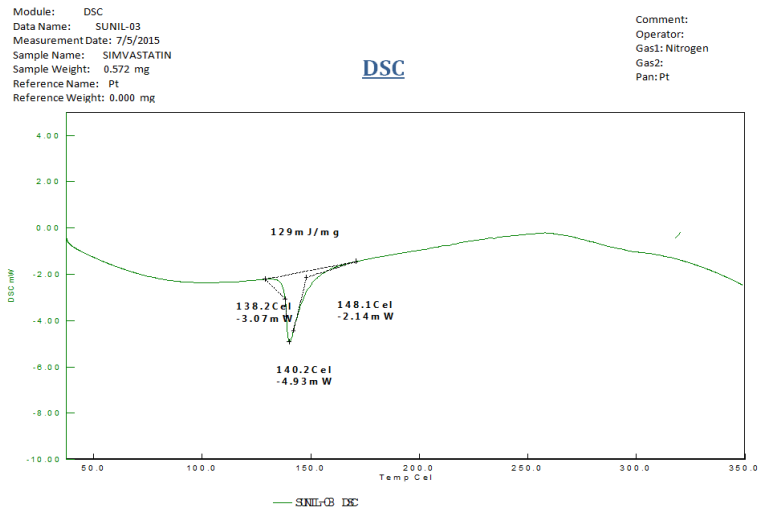

Fig. 8: DSC thermogram for simvastatin formulation

CONCLUSION:

The present study was done on rapidmelts of Simvastatin using direct compression and sublimation methods. Drug wavelength was determined and the standard graph was plotted at 235 nm. As Simvastatin comes under BCS class II solubility of Simvastatin was enhanced by preparing solid dispersions. The prepared solid dispersions were formulated as rapidmelts using direct compression method. In the sublimation, method rapidmelts were prepared by using subliming agents. The prepared blends were evaluated for precompression studies such as bulk density, tapped density, Carr's index, Haussner's ratio, the angle of repose. They were found to be within limits. After completion of precompression studies required powder blend was weighed and compressed using tablet compression machine. They were kept for post-compression studies such as weight variation, hardness, friability, in-vitro disintegration and dissolution studies. From dissolution studies, rapidmelts prepared by using camphor (7.5%) has given maximum drug release within 5 min. The optimized formulation(F12) was compared with the marketed formulation and F12 was selected for further in-vivo studies. From the result, it was concluded that rapidmelts prepared by using the sublimation method have given a better result than a direct compression method. So, the sublimation method would be an effective method for the preparation of rapid melt.

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