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Formulation and Evaluation of Simvastatin Rapidmelts

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ABSTRACT

Abstract: Purpose: The aim of the present study was to formulate and evaluate simvastatin Rapidmelts by sublimation and direct compression techniques. **Method:** As simvastatin comes under class II drug, solubility of the drug should be increased before formulation. Hence, solid dispersions were prepared with β-CD and pvp k-30 by 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, croscaramellose sodium and starch 1500. 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%). **Results:** 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 6 months at 25°/60%RH and 40°/75%RH. All the prepared formulations complied with the pharmacopoeial limits. **Conclusion**: 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 sublimation method has given better result than direct compression method. That final formulation was further evaluated for *in-vivo* studies.

INTRODUCTION

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 of 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 perfect fit to 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 a 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 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 Dr. Reddy's Laboratories Ltd. Hyderabad. β-cyclodextrin, polyvinyl pyrrolidone k-30, Polyethylene glycol 4000, crospovidone, croscarmellose sodium, starch 1500, 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 solid dispersions by using co-evaparation 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	500	500	500	500	500	500
β-cyclodextrin	250	500	750			
PVP K-30				250	500	750
Water and methanol	10 ml and 10 ml for all the preparations					

Kneading method: In a mortar 50% solvent was taken, 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 mesh sieve.

Table 2: Preparation of solid dispersions by using kneading 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	500	500	500	500	500	500
β-cyclodextrin	250	500	750			
PEG4000				250	500	750
Water and methanol	Quantity sufficient for paste formation					

Evaluation of solid dispersions:

Drug entrapment efficiency:

Percentage yield was determined by weighing the dried solid dispersion and calculated with respect to the weight of the initial components according to the following formula;

% Yield = [mass of solid dispersion/(mass of drug + mass of lipidic substances)] ×100

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 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 to10 mg 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 12 mm size round Punch [2].

Table 3: Formulation of simvastatin rapid melts by Direct compression method:

Compound Name	F1	F2	F3	F4	F5	F6	F7	F8	F9
Equivalent SD	47.39	47.39	47.39	47.39	47.39	47.39	47.39	47.39	47.39
CP	4			8			12		
CCS		4			8			12	
Starch 1500			4			8			12
Mg Stearate	3	3	3	3	3	3	3	3	3
Aerosil	2	2	2	2	2	2	2	2	2
MCC	143.61	143.61	143.61	139.61	139.61	139.61	135.61	135.61	135.61
Total weight	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 12 mm round punch and die set. Simvastatin tablets were then placed in an oven at 40 ^{0}C till a constant weight is obtained[(2)]

Table 4 : Formulation of simvastatin Rapid melts by sublimation method:

Compound Name	F10	F11	F12	F13	F14	F15	F16	F17	F18
Simvastatin	10	10	10	10	10	10	10	10	10
Camphor	5	10	15						
Urea				5	10	15			
Ammonium bicarbonate							5	10	15
Crospovidone	4	4	4	4	4	4	4	4	4
Aspartame	2	2	2	2	2	2	2	2	2
Mg stearate	2	2	2	2	2	2	2	2	2
Talc	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:

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 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, 10 tablets 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 Roche friabilator and subjected to 25 rpm for a period of 4 min. Afterwards 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 then 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 900 ml phosphate buffer pH7.0 containing 0.5%SLS at a temperature of 37 ± 0.5^0C with a paddle rotation speed at 50 rpm. At specified time intervals 1, 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 min; 5 ml of 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 235 nm.

Characterization:

Fourier transform infrared Spectroscopy (FTIR):

The FTIR spectrum was obtained on a Perkin Elmer 2000 FTIR System (Perkin–Elmer, Norwalk, CT). The scanning range was 400–4000 cm^{-1} and the resolution was 4 cm^{-1}.

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 thermograms are obtained by a differential scanning calorimeter (DSC 220C, SEIKO, JAPAN) at a heating rate of 10°C/min from 10 to 200°C in the nitrogen atmosphere.

Stability Studies: In order to study the stability of the rapidmelts, 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].

***In vivo* studies:** The study was carried out in rabbits. The pharmacokinetic studies were performed for the optimized formulation of Simvastatin (F12) rapidmelts in comparison with pure drug. Simvastatin 0.9mg/ Kg body weight was used for the pharmacokinetic study. The dose was calculated based on the conversion factor of adult dose to rabbit dose as shown below [6].

Rabbit dose per Kg body weight = Human dose × 0:07

The protocol was approved by the Institutional animal ethical committee at Sri Padmavathi Manila University, Andhra Pradesh, India. The experiments were conducted as per CPCSEA guidelines. The rabbits were acclimatized for 10 days before starting the experiment. They were fed with standard diet throughout the study. The animals were divided into two groups, each group containing four animals, group1 was given by pure drug and group 2 was administered with F12 Tablet. 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 hrs in a heparinized centrifuge tube. The pharmacokinetic parameters such as C_{max}, t_{max}, K_a, AUC and biological half life was estimated after analysis of the plasma samples.

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

HPLC assay: A gradient HPLC (Shimadzu, Class VP series) with 2 LC10AT VP pumps, variable wavelength programmable Photo Diode Array (PDA) detector, the SPD-M10A VP was used. The HPLC system was equipped with Empower software (Version 2). Samples were chromatographed on a reversed phase C18 column (5µ, 250 × 4.6 mm). 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 in 60: 40 ratio. The solution was then filtered through 0.45 µm membrane filter and degassed. The eluents were monitored using UV detection at 233 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

SD	Cosolvent method	Kneading method
SIM1	61.8	50.20
SIM2	63.4	56.65
SIM3	65.5	57.25
SIM4	49.1	52.69
SIM5	53.9	58.12
SIM6	59.9	61.29

Evaluation of rapidmelts:

Precompression Parameters: These parameters are important for the measurement of flow properties of powders. The powder has shown angle of repose values between 25-30. It indicates excellent flow of a powder. Carr's index was found to be between 10-20 and Hausner's ratio values are between 1.10-1.15. These values indicate good flow of powder. The results were shown in the tables 6 and 7.

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

Formulation Code	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	14.86.±0.12	1.17

Table 7: Preformulation parameters for rapidmelts prepared using sublimation method:

Formulation Code	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

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 averge 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:** Disintegraton 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 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 FDT formulations comply with the standards given in IP.

Table 8: Post compression parameters of rapid melts prepared using direct compression method:

Formulation Code	Hardness (kg/cm^2)	Wt.variation (mg)	% drug content	Friability (%)	Disintegration time (sec)
F1	6.4±0.01	1 9 7.3±0.01	100.74±0.12	0.71±0.10	163±1
F2	7.8±0.05	19 6.3±0.23	102.8±0.31	0.83±0.02	170±2
F3	6.9±0.12	19 8 .6±0.21	100.20±0.15	0.63±0.11	148±3
F4	7.3±0.23	19 7.2±0.11	100.31±0.21	0.72±0.12	163±1
F5	6.5±0.11	200.6±0.1	101±0.10	0.56±0.10	165±1
F6	7.1±0.12	200.5±0.12	102±0.12	0.54±0.11	156±2
F7	6.3±0.01	19 8. 6±0.14	102.3±0.12	0.69±0.12	146±2
F8	6.9±0.34	19 8.4±0.21	100.2±0.10	0.49±0.21	170±2
F9	7.2±0.31	197±0.32	101.11±0.12	0.43±0.11	153±1

Table 9: Post compression parameters of rapid melts prepared using sublimation method:

Formulation Code	Hardness (kg/cm^2)	Wt.variation (mg)	% drug content	Friability (%)	Disintegration time (sec)
F10	6.14±0.11	200.2±0.21	99±0.57	0.55±0.01	123±2
F11	6.18±0.13	201.4±0.12	100.30±0.12	0.39±0.21	142±3
F12	6.9±0.21	196.4±0.23	101±0.11	0.64±0.02	121±1
F13	7.13±0.15	198.6±0.32	100.3±0.12	0.45±0.01	127±2
F14	6.15±0.13	199.6±0.23	101±0.10	0.59±0.11	135±1
F15	5.91±0.21	200±0.11	100.2±0.21	0.53±0.12	145±3
F16	6.3±0.32	200.3±0.01	98.57±0.23	0.62±0.15	145±2
F17	6.9±0.42	197.2±0.1	100.20±0.10	0.65±0.21	125±1
F18	7.2±0.01	200.03±0.21	100.01±0.1	0.49±0.11	142±3

In vitro dissolution studies:

Formulations from F1-F9 were prepared using superdisintegrants by Direct compression method. F10-F18 were prepared by using subliming agents by sublimation method. In these two methods rapidmelts prepared by using sublimation methods has given better dissolutions compared to direct compression method. The rapidmelts prepared by using camphor 7.5% (F12) has given 100 % dissolution within 5 min.So F12 has been selected for further in vivo studies. The results were given in the tables 10 and 11.

Table 10: Cumulative % drug release for 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±0.02	29.95±0.02
15	70.33±0.82	57.64±0.05	28±0.19	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±0.02	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±0.22	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±0.27	81.96±0.25		99.55±0.21				
45			91.9±0.30						
50			99.5±0.17						

Table 11: Cumulative % drug release for 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±±0.05	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		

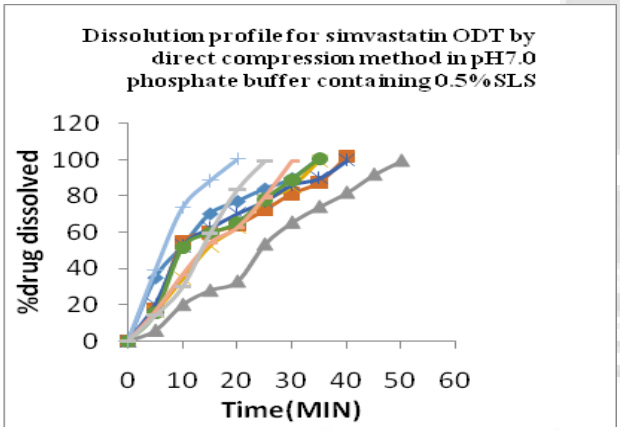


Fig 1: Dissolution profile for Simvastatin Rapidmelts by direct compression method

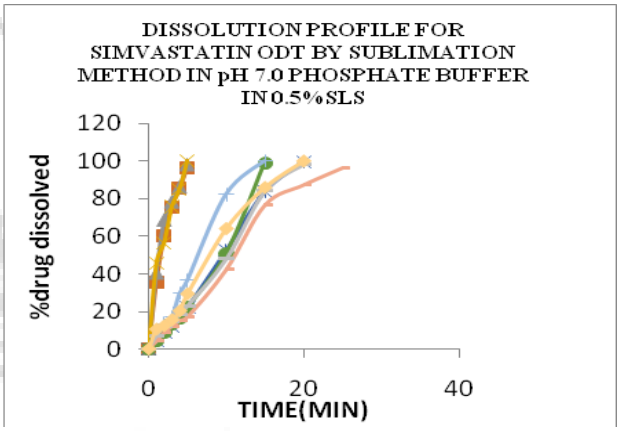
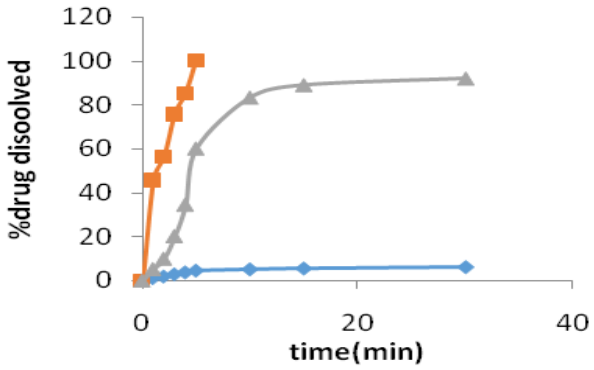


Fig 2: Dissolution profile for Simvastatin rapidmelts by sublimation method



Comparative dissolution profiles for pure drug, optimized formulation and marketed product

Drug release kinetics: The results obtained from *in-vitro* dissolution studies were fitted to zero and first order kinetics.

Table 12: Correlation Coefficient (R) values for 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	0.912	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	0.789
F14	0.958	0.760
F15	0.979	0.848
F16	0.976	0.976
F17	0.989	0.896
F18	0.978	0.811

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

Time (Min)	% Dissolution Rate	25^0C/60 % RH (Dissolution rate after storage) %		40^0C/75 % RH (Dissolution rate after storage) %	
		3 Months	6 Months	3 months	6 M onths
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}, $t_{1/2}$ and K_a were given in table 14.

Table 14: Pharmacokinetic parameters for Simvastatin Rapidmelts in Rabbits:

Pharmacokinetic parameter	Pure drug	F12
C_{max} (ng/ml)	9.6	9.9
T_{max} (min)	60	60
$AUC_{(0-9)}$ (mg.h/L)	201	217.48
Ka ($h^{-1)}$	0.29	0.27
$t_{1/2}$ (hrs)	2.4	2.5

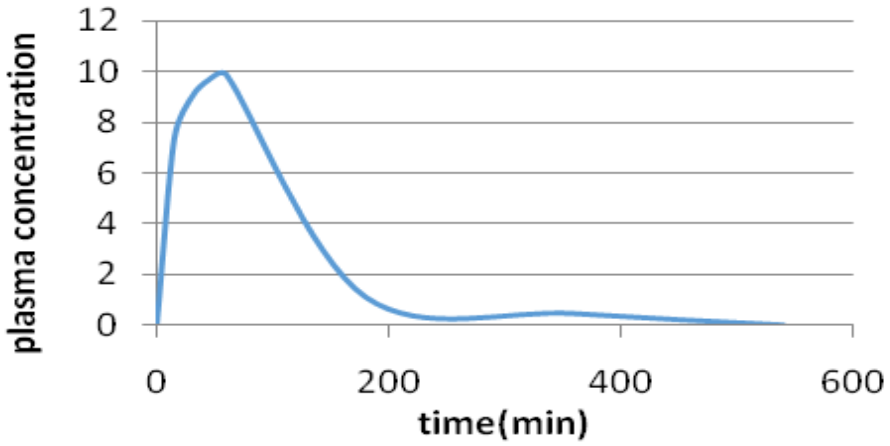


Fig 4: Plasma concentration profile

Characterization:

FTIR studies: The results obtained with IR studies showed that there was no interaction between the drug and other excipients used in the formulation. Fourier transform infrared spectroscopy analysis was performed to pure drug and optimized formulation and presented in Fig 11and 12.

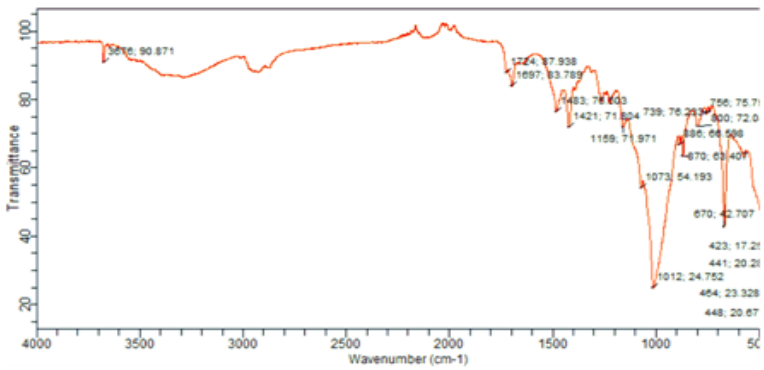


Fig 5: FTIR for Simvastatin pure drug

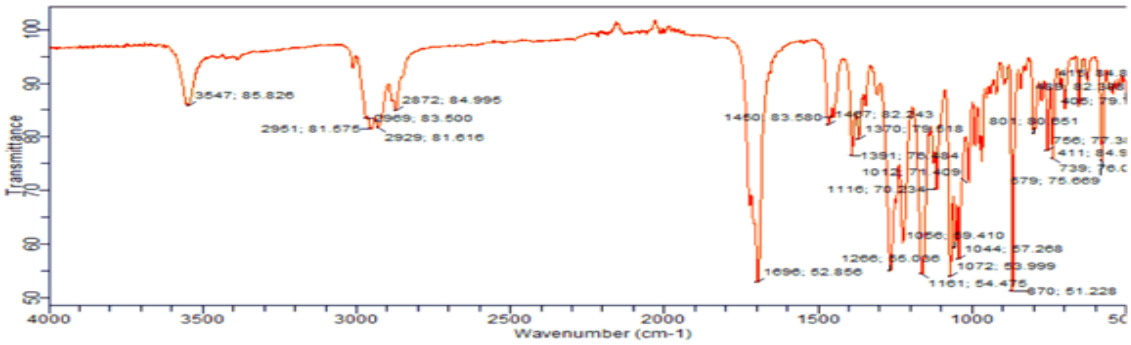


Fig 6: FTIR for Simvastatin formulation

DSC analysis: DSC thermograms for pure drug and optimized formulation were given in the fig 7 and 8. Peaks indicating that there was no interactions between drug and excipients.

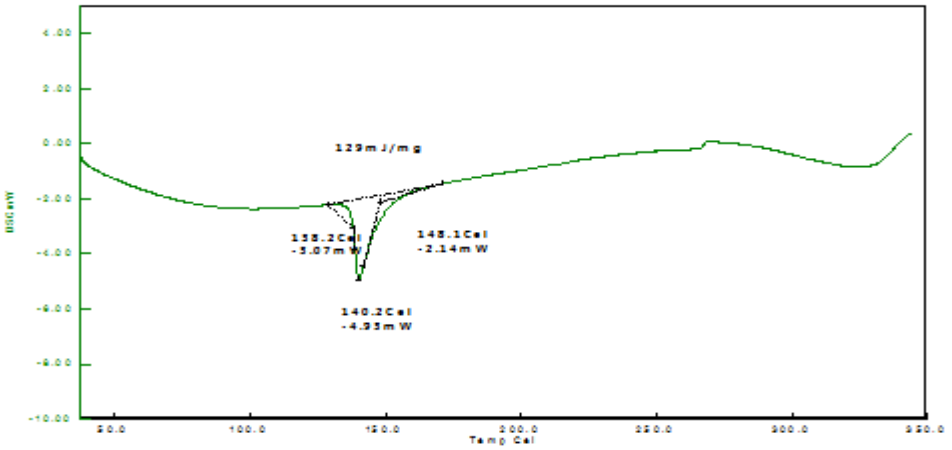


Fig 7: DSC for Simvastatin formulation

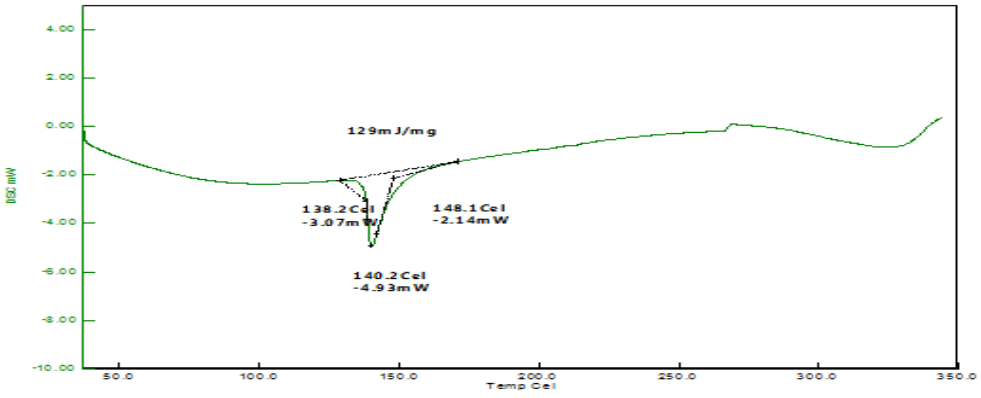


Fig 8: DSC for pure drug

CONCLUSION

The present study was done on rapidmelts of Simvastatin using direct compression and sublimation methods. Drug wavelength was determined and 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, 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 marketed formulation and F12 was selected for further *in vivo* studies. From the result, it was concluded that rapidmelts prepared by using sublimation method has given better result than direct compression method. So sublimation method would be an effective method for the preparation of rapidmelts.

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REFERENCES

1. Hammady T, El-Gindy A, Lejmi E, Dhanikula RS, Moreau P, Hildgen P. Characteristics and properties of nanospheres co-loaded with lipophilic and hydrophilic drug models. Int. J. Pharm. 2009, 18,369(1-2), 185-95.
2. Ahmed AbdElbary, AdelA.Ali,HebaM.Aboud. Enhanced dissolution of meloxicam from orodispersible tablets prepared by different methods. Bulletin of Faculty of Pharmacy, Cario University,(2012)50, 89-97.
3. A. Mahesh, Nalini Shastri and M.Sadanandam, Development of Taste Masked Fast Disintegrating Films of Levocetirizine Dihydrochloride for Oral Use, Current Drug Delivery, 2010, 7, 21-27.

4. Shweta Guptaa, M Saquib Hasnainb , S S Agarwala, Formulation and evaluation of oral disintegrating tablets of itopride hydrochloride using ion exchange resins as drug carrier, Asian Journal of Pharmaceutical Sciences 2012, 7 (3): 207-218.
5. T. Neelima Rani and Y. Indira Muzib, Rapid Melts: A Review, International Journal Of Pharmaceutical And Chemical Sciences, Vol. 3 (1) Jan-Mar 2014,118-130.
6. Ghosh MN (2005) Fundamentals of experimental pharmacology, 3rd edn. Sk Ghosh Publications, Kolkata, pp 192–194.
7. Grimm W (1998) Extension of the International Conference on Harmonisation Tripartite Guidelines for stability testing of new drug substances and products to countries of Climatic Zones III and IV. Drug Dev Ind Pharm 24:313–325. doi:10.3109/036390 49809085626.
8. ICH (2003) Harmonised tripatite guideline: stability testing of new drug substances and products ICH Q1A(R2). ICH Expert Working Group, Europe, Japan and USA.