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Research Article

Formulation and *In vivo E*valuation of Rosuvastatin Rapidmelts by Direct Compression and Sublimation Methods

T Neelima Rani*, Y Indira Muzib

Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam (WOMEN'S university), Tirupati, Andhra Pradesh

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ABSTRACT

In the present work an investigation was successfully made to formulate and evaluate rosuvastatin rapidmelts by direct compression and sublimation techniques. In direct compression method, as rosuvastatin comes under BCS class II drug, the solubility of the drug should be increased before formulation. For that solid dispersions were prepared with β-CD, PEG2000, and PEG4000 by using coevaporation and kneading method. Among those solid dispersions prepared with β-CD (1:1.5) by using coevaporation method has given better drug entrapment values compared to other solid dispersions. Selected solid dispersions were formulated as rapidmelts by using direct compression method. In direct compression method rapidmelts were prepared by using super disintegrants like ludiflash, crosscaramellosesodium, and lycoat. Those are evaluated for both precompression and post-compression parameters. Rosuvastatin rapidmelts were prepared by sublimation method using subliming agents camphor, menthol, 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 3 and 6 months at 25ºC/60%RH and 40ºC/75%RH. All the prepared formulations compiled with the pharmacopieal limits. The results suggested that R12 formulation has given the best disintegration and dissolution results compared to all other formulations. From the result, it was concluded that rapidmelts prepared by using sublimation method have given a better result than direct compression method. That optimized formulation was further evaluated for *in-vivo* studies.

Keywords: Rosuvastatin, β-cyclodextrin, PEG2000, PEG4000, coevaporation, kneading, direct compression, sublimation, superdisintegrants, subliming agents.

INTRODUCTION

Oral route of administration is most convenient route for drug administration. According to the United States, Food and Drug Administration (USFDA) defined Rapidmelts as "A solid dosage form containing a medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for rapidmelts generally ranges from several seconds to about a minute" (Pharmatech.com). Prescription Rapid melt products initially were developed to overcome the difficulty in swallowing among pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules (Neelima rani et al.,2014).

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 on fast dissolving dosage forms for buccal, sublingual and oral administration (Pharmatech.com).

Many methods were reported for solubility and dissolution enhancement of poorly soluble drug such as micronization, complexation, solid dispersions, kneading method... etc. Solid dispersion 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 ((Nikhgalb et al.,2012). Fast dissolving / disintegrating tablets immediately release the active drug when placed upon the tongue by rapid disintegration. The presence of a highly porous surface in the tablet matrix is the key factor for the rapid disintegration of rapidmelts. So, in the present investigation rapidmelts of rosuvastatin were prepared.

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

Author for Correspondence: neelimarani.tumma@gmail.com

Table 1: Preparation of solid dispersions of rosuvastatin by using cosolvent evaporation method.

Excipients	1:0.5(ROS1)	1:1(ROS2)	1:1.5(ROS3)	1:0.5(ROS4)	1:1(ROS5)	1:1.5(ROS6)
Drug(mg)	500	500	500	500	500	500
β-cyclodextrin(mg)	250	500	750	--	--	--
PEG -2000(mg)	--	--	--	250	500	750
Water and ethanol	Quantity sufficient					

Table 2: Preparation of rosuvastatin solid dispersions by using kneading method.

Excipients	1:0.5(ROS7)	1:1(ROS8)	1:1.5(ROS9)	1:0.5(ROS10)	1:1(ROS11)	1:1.5(ROS12)
Drug(mg)	500	500	500	500	500	500
β-cyclodextrin(mg)	250	500	750	--	--	--
PEG4000(mg)	--	--	--	250	500	750
Water and ethanol	Quantity sufficient for paste formation					

Table 3: Composition of rosuvastatin rapidmelts by direct compression method.

Excipient name	R1	R2	R3	R4	R5	R6	R7	R8	R9
Equivalent SD(mg)	50.01	50.01	50.01	50.01	50.01	50.01	50.01	50.01	50.01
Ludiflash(mg)	4	--	--	8	--	--	12	--	--
CCS(mg)	--	4	--	--	8	--	--	12	--
Lycoat(mg)	--	--	4	--	--	8	--	--	12
Magnesium Stearate(mg	3	3	3	3	3	3	3	3	3
Aerosil(mg)	2	2	2	2	2	2	2	2	2
MCC(mg)	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight(mg)	200	200	200	200	200	200	200	200	200

Table 4: Composition of rosuvastatin rapidmelts by sublimation method.

Excipient name	R10	R11	R12	R13	R14	R15	R16	R17	R18
Rosuvastatin(mg)	40	40	40	40	40	40	40	40	40
Ludiflash(mg)	6	6	6	6	6	6	6	6	6
Menthol(mg)	5	10	15						
Ammoniumcarbonate(mg)				5	10	15			
Camphor(mg)							5	10	15
Magnesium Stearate(mg)	3	3	3	3	3	3	3	3	3
Aerosil(mg)	2	2	2	2	2	2	2	2	2
MCC(mg)	QS	QS	QS	QS	QS	QS	QS	QS	QS
Totalweight(mg)	200	200	200	200	200	200	200	200	200

Table 5: Drug entrapment efficiency values of rosuvastatin solid dispersions.

Solid Dispersion	Cosolvent method	Solid Dispersion	Kneading method
ROS1	76.50	ROS7	71.63
ROS2	78.26	ROS8	73.30
ROS3	79.98	ROS9	75.59
ROS4	65.11	ROS10	59.94
ROS5	67.02	ROS11	62.23
ROS6	70.20	ROS12	64.97

Therefore, improvement in solubility and dissolution rate is essential to enhance drug bioavailability (P.Rohini et al.,2014).

As Rosuvastatin comes under BCS class II drug solid dispersions of rosuvastatin 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 rapidmelts 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. Rosuvastatin rapidmelts were prepared by using both direct compression and sublimation techniques.

MATERIALS AND METHODS

Materials

Rosuvastatin was obtained as a gift sample from Hetero Drugs Ltd, Hyderabad. β-cyclodextrin, PEG2000, PEG4000, Ludiflash, croscarmellose sodium, lycoat, magnesium stearate, aerosil, microcrystalline cellulose, camphor menthol, ammonium bicarbonate were kindly supplied by BMR chemicals, Hyderabad and Shreeji chemicals, Mumbai. All the other solvents used were analytical grade.

Methods

Standard calibration curve of rosuvastatin

Table 6: Preformulation parameters for rapidmelts by direct compression method.

Formulation code	Angle of repose(^{0})	Bulk density(mg/ml)	Tapped Density(mg/ml)	Carr's Index(%)	Hausner's ratio
R1	27.41±0.01	0.54±0.01	0.62±0.10	12.90±0.01	1.14±0.01
R2	26.48±0.11	0.52±0.05	0.58±0.01	10.34±0.21	1.11±0.20
R3	26.61±0.05	0.51±0.10	0.58±0.05	12.06±0.11	1.13±0.03
R4	25.20±0.11	0.55±0.06	0.64±0.021	14.06±0.05	1.16±0.05
R5	26.99±0.06	0.53±0.02	0.61±0.06	13.11±0.08	1.15±0.15
R6	27.74±0.02	0.58±0.04	0.66±0.21	12.12±0.10	1.13±0.20
R7	27.88±0.10	0.57±0.10	0.65±0.24	12.30±0.20	1.14±0.11
R8	26.56±0.20	0.51±0.20	0.56±0.20	8.92±0.15	1.09±0.12
R9	28.80±0.04	0.55±0.11	0.62±0.10	11.29±0.11	1.12±0.10

Table 7: Preformulation parameters for rapidmelts by sublimation method.

Formulation code	Angle of repose (^{0})	Bulk density(mg/ml)	Tapped Density(mg/ml)	Carr's Index(%)	Hausner's ratio
R10	25.26±0.01	0.336±0.05	0.382±0.01	12.04±0.020	1.136±0.01
R11	21.89±0.05	0.324±0.01	0.379±0.10	14.511±0.01	1.169±0.02
R12	24.36±0.10	0.317±0.06	0.376±0.12	15.691±0.03	1.186±0.05
R13	24.87±0.20	0.330±0.01	0.391±013	15.60±0.05	1.184±0.10
R14	22.39±0.15	0.325±0.10	0.382±0.15	14.921±0.06	1.175±0.12
R15	23.45±0.11	0.313±0.12	0.356±0.11	12.07±0.08	1.137±0.11
R16	24.85±0.21	0.320±0.15	0.387±0.10	17.31±0.10	1.209±0.20
R17	25.59±0.01	0.310±0.20	0.368±0.20	15.76±0.11	1.187±0.11
R18	23.31±0.05	0.324±0.24	0375±0.01	13.60±0.05	1.157±0.15

Table 8: Post compression parameters for rapidmelts by direct compression method.

Formulation code	Hardness (kg\cm^2)	Average weight (mg)	Drug content(%)	Friability(%)	*Invitro* disintegration time(sec)	Wetting time(sec)
R1	3.96±0.01	199.36±0.05	96.78±0.01	0.25±0.10	79±2	38.4±2
R2	4.02±0.10	198.30±0.02	97.13±0.02	0.31±0.02	85±5	44.8±5
R3	4.10±0.11	198.89±0.14	96.23±0.20	0.19±0.06	94±3	40.8±4
R4	3.88±0.05	199.12±0.11	98.45±0.14	0.36±0.01	62±6	26.8±2
R5	3.95±0.02	197.82±0.15	97.60±0.11	0.49±0.08	70±8	31.6±4
R6	4.05±0.15	199.02±0.06	99.65±0.16	0.22±0.09	82±1	30.4±±5
R7	4.23±0.12	198.56±0.02	98.54±0.11	0.15±0.10	46±5	18.4±1
R8	3.87±0.05	197.78±0.20	97.02±0.13	0.30±0.12	65±2	26.4±6
R9	3.99±0.20	198.80±0.03	99.23±0.11	0.61±0.11	77±1	25.4±4

Table 9: Post compression parameters for rosuvastatin rapidmelts by sublimation method.

Formulation code	Hardness (kg\cm^2)	Average weight (mg)	Drug content(%)	Friability (%)	*Invitro* disintegration time(sec)	Wetting time(sec)
R10	4.96±0.01	199.96±0.05	95.56±0.01	0.87±0.03	94±1	34.4±4
R11	4.52±0.10	198.89±0.11	96.59±0.02	0.69±0.05	83±5	26.8±2
R12	4.87±0.11	201.3±0.02	99.78±0.23	0.42±0.01	68±1	20.4±4
R13	5.02±0.05	200.02±0.11	96.63±0.11	0.19±0.12	115±2	38.4±3
R14	4.36±0.02	199.77±0.13	98.80±0.10	0.77±0.11	97±4	29.6±1
R15	4.88±0.15	196.58±0.15	99.56±0.11	0.89±0.02	85±3	24.4±6
R16	5.11±0.12	198.80±0.12	98.11±0.12	0.71±0.06	106±2	35.8±3
R17	4.97±0.05	199.30±0.20	97.89±0.05	0.56±0.04	89±1	26.6±4
R18	4.49±0.20	198.89±0.21	98.96±0.06	0.91±0.10	74±2	22.4±4

A solution of rosuvastatin containing the concentration of 10µg/ml was prepared in 6.8 pH buffer and UV spectrum was taken. The solution was scanned in the range of 200-400nm.10 mg drug was taken accurately in 10ml volumetric flask. It was dissolved in 6.8 pH buffer to gives 1000 µg /ml. The standard stock solution was then serially diluted with 6.8 pH buffer to get 5 to 30 µg/ml of rosuvastatin. The absorbance was measured against 6.8 pH buffer as blank at 243 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Table 10: Cumulative %drug release for formulations prepared using direct compression method.

Time (min)	R1	R2	R3	R4	R5	R6	R7	R8	R9
0	0	0	0	0	0	0	0	0	0
5	30.21±0.01	16.36±0.02	18.50±0.01	28.9±0.10	21.65±0.10	25.98±0.20	42.5± 0.01	38.58± 0.02	38.98± 0.01
10	49.25±0.05	44.24±0.03	25.25±0.12	48.54±0.15	51.15±0.12	33.65±0.01	58.90± 0.05	58.98± 0.20	47.65± 0.10
15	65.55±0.10	50.54±0.04	30.54±0.20	55.65±0.05	60.25±0.11	48.96±0.15	73.66± 0.06	65.55± 0.03	55.52± 0.23
20	70.62±.05	60.54±0.20	45.23±0.05	68.72±0.20	65.33±0.20	52.25±0.10	88.38± 0.20	72.73± 0.10	65.56± 0.15
25	78.11±0.15	70.30±.12	56.35±0.10	78.29±0.03	72.34±0.15	63.5±0.13	100.26± 0.05	85.59± 0.15	70.54± 0.12
30	85.25±0.20	78.64±0.1	67.59±0.13	91.95±0.15	85.81±0.13	72.56±0.05	---	99.55± 0.06	75.96± 0.11
35	99.89±0.06	85.39±0.01	78.50±0.05	99.69±0.11	96.55±0.12	83.65±0.12	---	---	----
/40	----	98.88±0.03	87.54±0.04	----	99.59±0.02	95.95±0.03	-----	---	---
45	----	----	93.5±0.01	----	----	99.99±0.05	---	----	----
50	----	---	98.98±0.20	----	----	----	----	---	----

Table 11: Cumulative %drug release for formulations prepared using sublimation method.

Time(min)	R10	R11	R12	R13	R14	R15	R16	R17	R18
0	0	0	00	0	0	0	0	0	0
5	34.21± 0.01	40.32±0. 20	51.47±0. 01	28.08±0. 02	35.36±0. 01	40.01±0. 02	30.21±0. 02	37.79±0. 10	48.20±0. 05
10	59.86± 0.10	65.59±0. 12	72.30±0. 02	42.30±0. 05	59.78±0. 12	62.05±0. 05	55.46±0. 05	60.21±0. 02	73.66±0. 10
15	74.45± 0.11	87.60±0. 10	98.69±0. 05	61.03±0. 10	78.80±0. 05	82.11±0. 20	73.56±0. 20	81.49±0. 05	96.29±0. 11
20	89.96± 0.05	99.58±0. 10	----	79.68±0. 11	89.60±0. 10	98.67±0. 10	86.49±0. 11	99.60±0. 11	-------
25	97.90± 0.06	-------	-------	87.89±0. 06	100.01±0 .1	----	100.23±0 .1	------	-------
30	--------	-----	-------	98.80±0. 04	-------	-----	-----	------	-------

Table 12: Comparative dissolution profile for the pure drug (rosuvastatin), optimized formulation and marketed product.

Time(min)	Pure Drug	R12	Marketed Drug
0	0	0	0
5	12.36±0.21	51.47±0.01	14.65±0.20
10	15.23±0.25	72.30±0.02	25.12±0.01
15	20.13±0.52	98.69±0.05	39.52±0.12
20	25.46±0.14	----	50.12±0.20
25	30.12±0.32	-------	61.02±0.12
30	39.25±0.05	-------	72.05±0.10
35	45.26±0.20	--------	80.02±0.05
45	64.28±0.15	-----	89.26±0.29

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. Ethanol was added in proportion wise with constant and continuous stirring until the mixture was completely dissolved. Ethanol was evaporated under constant stirring and resultant solid dispersions were collected (Nikhgalb et al.,2012).

Kneading method

In a mortar, 50% solvent was taken to that add the calculated amount of polymer and is triturated to get slurry-like consistency. Then the drug was incorporated, remaining solvent was added and trituration is continued for 1hr, air dried at 40 ºC for 48hrs and the resulting dried product was pulverized and passed through a sieve (Aftabmodi et al.,2006).

Drug entrapment efficiency (hasanain.Sh.Mahmood et al.,2016)

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 the complete release of 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. % Entrapment efficiency was calculated according to the following formula.

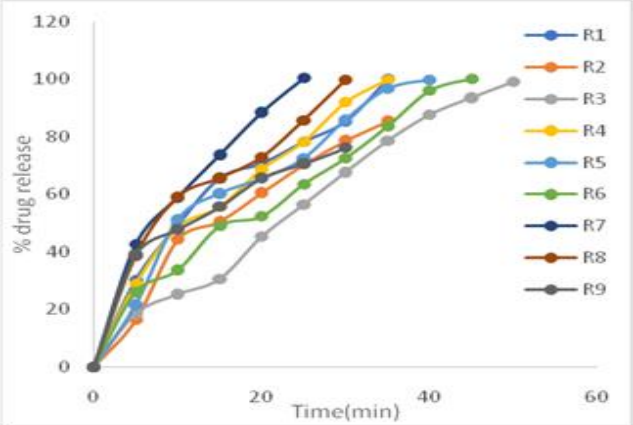

Figure 1: Cumulative % dissolution profiles for rosuvastatin rapidmelts by direct compression method.

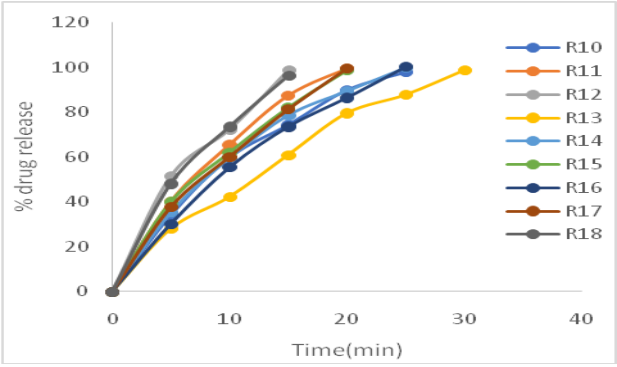

Figure 2: Cumulative % dissolution profiles for rosuvastatin rapidmelts by sublimation method.

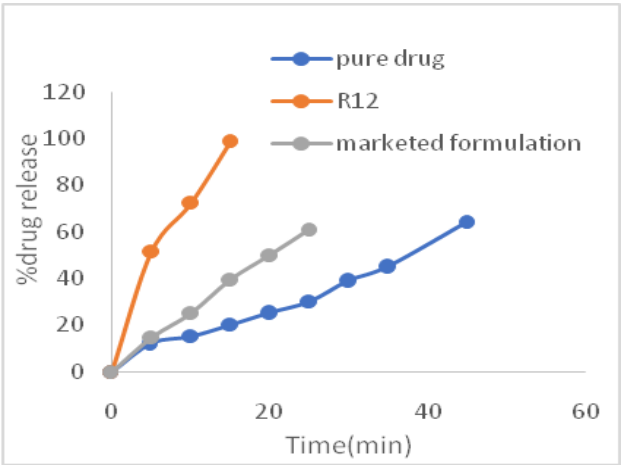

Figure 3: Comparative Dissolution profile for rosuvastatin pure drug, optimized formulation and marketed formulation

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

Preparation of Rosuvastatin Rapid melts

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

Direct compression method

For the preparation of rapidmelts by this method solid dispersions were equivalent to 40mg were taken and were prepared by using superdisintegrants CCS, ludiflash, lycoat (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 8mm size round punch.

Sublimation method

Different rapidmelts of rosuvastatin were prepared by using subliming agents such as camphor, menthol, 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. Rosuvastatin tablets were then placed in an oven to generate a porous matrix due to the removal of volatilizable component(P.Klyankar et al.,2015).

Precompression Parameters (P.Rohini et al.,2014)

The various characteristics of blends to be 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/volume of the packing

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

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 rosuvastatin blend powder formulation and it is expressed as:

Hausner's ratio = tapped density / bulk density

Post Compression Parameters

Hardness

Hardness is defined as the resistance of the tablet against the applied force till it breaks. Hardness indicates the ability of a tablet to withstand mechanical shocks while packaging, handling, and transportation. The hardness of

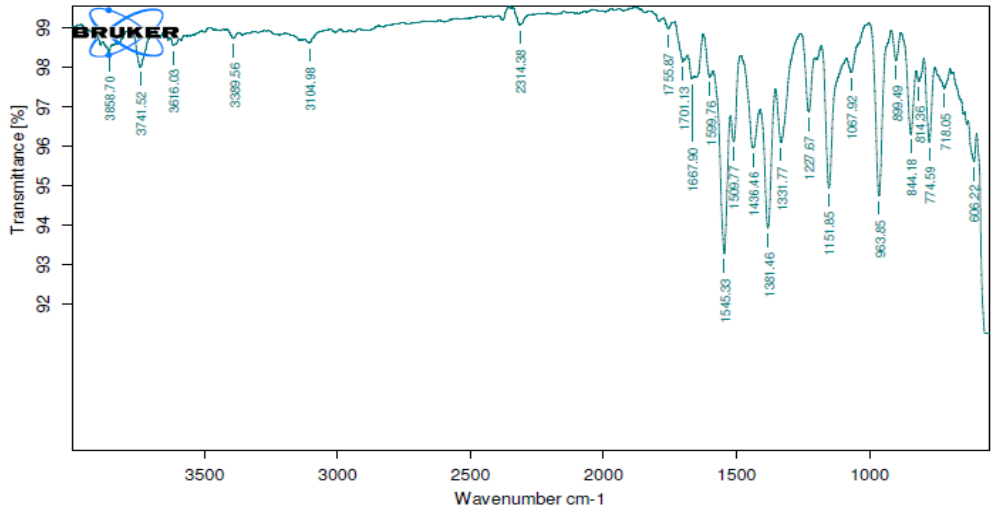

Figure 4: FTIR PURE ROSUVASTATIN.

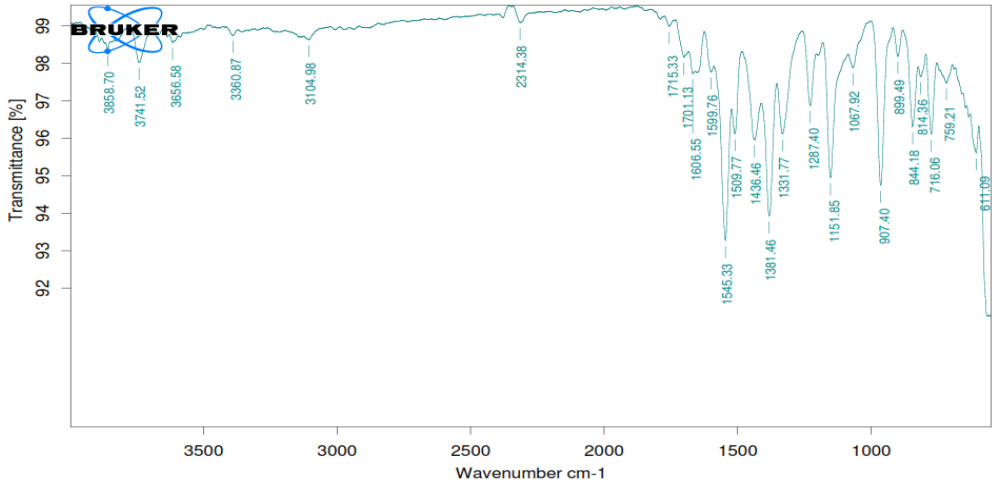

Figure 5: FTIR OPTIMIZED ROSUVASTATIN.

Table 13: Stability Studies.

Time(Min)	Initial	25^0C/60 % RH (Dissolution rate after storage) %		40^0C/75 % RH (Dissolution rate after storage) %	
0months		3Months	6Months	3Months	6Months
0	0	0	0	0	0
5	51.47±0.01	49.45±0.02	52.01±0.05	51.41±0.01	51.46±0.02
10	72.30±0.02	72.31±0.03	72.35±0.01	72.34±0.01	72.30±0.02
15	98.69±0.05	97.62±0.05	100.69±0.02	98.69±0.01	98.61±0.03

the tablets was determined using Monsanto hardness tester. 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.

Friability

Friability of the tablet determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablet at the height of 6 inches in each revolution. A preweighed sample of tablets was placed in friabilator and was subjected to 100 revolutions. Tablets were dusted. After 100 revolutions the tablets were reweighed. Then calculate friability by the given equation.

F= (1-Wo/W) 100

Wo = weight of the tablet before the test, W = weight of the tablet after the test.

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 tissue paper. The time required for water to reach the

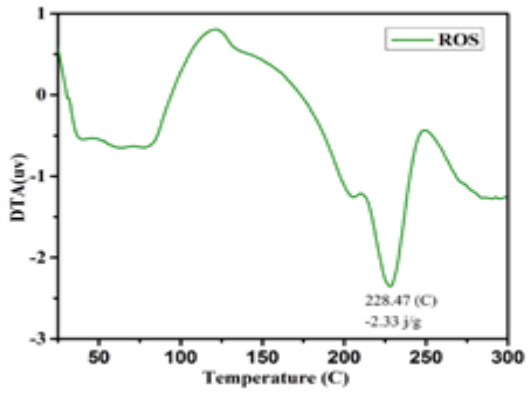

Figure 6: DSC for rosuvastatin pure drug.

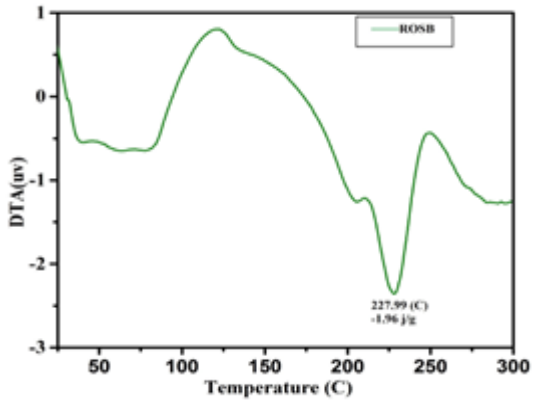

Figure 7: DSC for rosuvastatin optimized formulation.

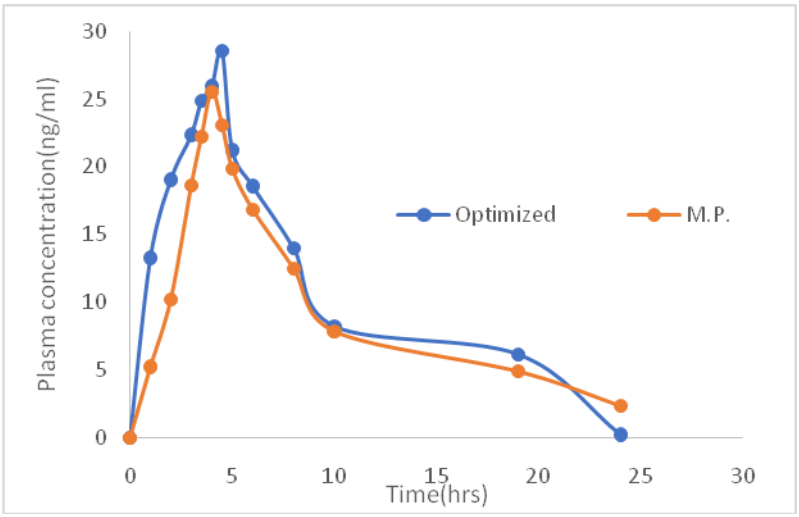

Figure 8: Mean plasma concentration-time profile of rosuvastatin following the oral administration of optimized and marketed formulation.

upper surface of the tablets was noted as the wetting time. The wetting time was measured in seconds (Biswajit basu et al.,2011)

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 rapidmelts were determined in a dissolution tester, apparatus II. All tests were conducted in 900 ml phosphate buffer pH 7.0 containing 0.5% SLS at a temperature of 37±0.5 ºC 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 Millipore filter and assayed for drug content spectrophotometrically at 243nm.

Drug – Excipient compatibility study

DSC

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 is 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.

FT-IR studies

The concentration of the sample in KBr 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) (R.M.Sarfaraz et al.,). Too high a concentration usually causes difficulties in obtaining clear pellets. The IR beam is absorbed completely, or scattered from the sample which results in very noisy spectra.

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

Table 14: Pharmacokinetic parameters for rosuvastatin rapidmelts in rabbits:

Pharmacokinetic parameter	Marketed Formulation	Optimized Formulation(R12)
C_{max}(ng/ml)	25.54	28.52
T_{max}(hrs)	4	4.5
AUC $_{(0-24)}$ (ng.h/ml)	210.86	240.91
Ke(/hr)	0.110	0.200
Biological half life($t_{1/2}$) (hrs)	6.27	3.450

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 (Bhupendra et al.,2010).

In vivo evaluation

In vivo experiments were carried out in male rabbits. Healthy rabbits (New Zealand Albino) of either sex weighing 2.5-3.0 kg were selected and housed with CPCSEA guidelines, fasted over night and had free access to drinking water. Animals were separated into three experimental groups, each group consisting of three animals (n=3). The test formulation of batch (R12) was compared with (reference/ marketed formulation) with the following treatment schedule under fasted condition:

Group I - (Normal Control) – Received placebo.

Group II- (Positive control) – Marketed formulation

Group III- Rosuvastatin formulation (R12) used as test.

The optimized formulations were administrated via oral gauge at a dose 2.05mg/kg of rosuvastatin. Blood samples (each of about 1-2ml from each animal) were withdrawn from marginal ear vein at regular time intervals after administration. The collected blood samples were immediately centrifuged at 5000rpm in ultra-cooling centrifuge for 10min at 4^0C. The supernatant plasma sample was separated and stored in a clean screw capped 5ml polypropylene plasma tubes at -20ºC in a deep freezer, until further analysis.

Estimation of drug from rabbit plasma

The stored plasma samples were processed at room temperature, 250 µl of plasma was added to 500 µl of acetonitrile to precipitate the proteins. The samples were vortexed on vortex mixer for 15min, followed by centrifugation at 10000 rpm for 15min. The respective samples were injected into the HPLC column.

Data analysis

The total area under plasma concentration- time curve ($AUC_{0-\infty}$), the maximum plasma concentration (C_{max}), and time to reach the maximum plasma concentration (T_{max}) were selected as parameters for pharmacokinetic evaluation. The C_{max} and T_{max} were obtained directly from the experimental data of plasma concentration versus time. $AUC_{0-\infty}$ was obtained by adding the AUC_{0-24h}, which was calculated by the trapezoidal rule.

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.

Evaluation of rapidmelts

Precompression Parameters

The precompression parameters are important for the measurement of flow properties of powders. The powder has shown angle of repose values between 20-30^0.It indicates excellent flow of a powder. Carr's index was found to be between 8-15and Hausner's ratio values are between 1.10-1.15. These values indicategood flow of powder. The results were shown in the Tables 6 and 7.

Post compression parameters

Weight variation

All the formulations wereevaluated for uniformity of weight. The average weight of all the formulations wasfoundto be in the range of 197.82±0.15to201.3 ±0.02 mg.

Hardness

All the formulations were evaluated for hardness using Monsanto hardness tester. Theavergehardness was found to be between 3.88-5.02kg/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 46-106sec. 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 (95.56±0.01 to 99.78±0.23) mg. 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.

Invitro dissolution studies

Formulations from R1-R9 were prepared using superdisintegrants (ludiflash,CCS ,Lycoat) by direct compression method. R10-R18 were prepared by using subliming agents (camphor, menthol, ammonium bicarbonate) by sublimation method. In these two methods rapidmelts prepared by using sublimation methods has given better dissolution compared to direct compression method. The rapidmelts prepared by using menthol 7.5% (R12) has given 100% dissolution with in 5min. Hence R12 has been selected for further *invivo* studies. The results were given in the Tables 10&11. Comparative dissolution values for pure drug, optimized formulation (R12) and marketed formulation were given in Table12.

Stability studies

Hence, based upon evaluation parameters and drug release profiles R12 was selected as optimized and

subjected to stability studies and stored at 25°C/60 % RH and 40°C/75 % RH (ICH,2003). The samples were withdrawn at 0, 3, 6 months and rosuvastatin rapidmelts were found to be stable. When the samples were withdrawn after 3 and 6 months (for both conditions) no color change was observed. The amounts of rosuvastatin (%) in the rapidmelts stored under conditions according to ICH guidelines are given in Table 13. Stability studies revealed that there is no significant changes were observed throughout the study. So we can say that formulation has good stability.

Characterisation studies

FTIR studies

From the Fig.4 FTIR spectra the drug, exhibited peaks at 3858$cm^{-1}$for amide N-H stretch,3104cm^{-1} for =C-H,1545$cm^{-1}$for C=C stretching,1331.77$cm^{-1}$for C-N stretching and 774cm^{-1} for aromatic C=H bending. The same peaks of the drug were observed in the FTIR spectra of the rapidmelts in Fig5. Thereby ruling the absence of drug-polymer interaction from the obtained results. Fourier transform infrared spectroscopy analysis was performed to pure drug and optimized formulation and presented in Fig 4&5.

DSC studies

The thermogram of pure drug rosuvastatin has given endothermic peak at 227.9 ^{0}C. The Thermogram of rapidmelts has given endothermic peak at 228.47^{0}C.DSC thermograms for pure drug and optimized formulation were given in Fig 6&7. Peaks indicating that there were no interactions between drug and excipients.

In vivo studies

The plasma concentration- time profiles following oral administration of final formulation were given in Fig:8. The data obtained from plasma concentration profiles AUC, C_{max}, T_{max}, and bioavailability were given in Table 14.

CONCLUSION

Rapidmelts are also known as oral disintegrating tablets(or)fast dissolving tablets. These are mainly intended to be placed in the oral cavity where they dispersed before being swallowed. This is the promising dosage form for the use in pediatrics and geriatrics. The rapidmelts will provide accurate dosing and shows good chemical and physical stability with lower doses. By comparing two methods rosuvastatin rapidmelts prepared with sublimation method has given better dissolution compared to direct compression method. The subliming agents with drug have given good *in vitro* dissolution behavior due high porosity resulted by subliming agents. Formulation R12 was selected as best formulation among all and subjected to *in vivo* kinetic studies. Pharmacokinetic parameters (C_{max}, Tmax, AUC, Ke, $t_{1/2}$) for the best formulation (R12) were calculated and results shows more potentiality than marketed formulation. From the result it was concluded that sublimation method was found to be one of the best methods for the formulation of rapidmelts.

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