Formulation and evaluation of mouth dissolving tablets of rosuvastatin by taste masking with eudragit epo

Tripura sundari P* and Nikitha G

RBVRR Women's College Of Pharmacy, Osmania University, Hyderabad. 500027, India

ABSTRACT

Acceptability of any dosage form mainly depends on its taste i.e., mouth feel. Drug molecules interact with taste receptor on the tongue to give bitter, sweet or salty taste sensation, when they dissolve in saliva. This sensation of the taste is the result of signal transduction from the receptor organs for taste. In the present study, attempts were made to conceal the bitter taste of Rosuvastatin by taste masking agent employing solid dispersion technique. By employing solvent evaporation method and Eudragit EPO as carrier polymer different ratios of solid dispersions were prepared. The better ratio in which the bitter taste of drug was completely concealed was selected. The finalized ratio was compressed into mouth dissolving tablet dosage forms by using super disintegrates. The prepared solid dispersions were analysed for drug content and drug release characteristics, instrumentally by DSC, XRD, FTIR studies. The prepared powder blend of tablets was analysed for flow properties and the tablets were analysed for disintegration, dissolution and other quality control tests of tablets

Keywords: Solid dispersion; Solvent evaporation technique; Eudragit EPO; Rosuvastatin.

INTRODUCTION

Among all the routes of administration, oral route is the one which is most popularly preferred because of its ease of administration, self-medication, patient compliance. After tablets it is capsule dosage form which stands next in the line

To improve the drawbacks of oral drug delivery different drug delivery systems had come into the market. (Fischer V *et al*., 1999)

The most important drawback of oral drug delivery is Disphagia or difficulty in swallowing. This problem is going to affect nearly 35% of the general population. To solve the above mentioned problems, (Jadon RS *et al*., 2009, Mukhesh S *et al*., 2011, Vummaneni V, *et al*., 2012) pharmaceutical technologists have put in their best efforts to develop a Mouth Dissolving Tablets. These dosage forms enable the disintegration and dissolving of drug in saliva in a rapid manner in the mouth which does not require drinking of water or chewing.

Rosuvastatin is a hydroxyl methyl glutaryl (HMG-CO A) reductase selective and competitive inhibitor. It is an antilipidemic agent used in the treatment of dyslipidemia. Bioavailability of Rosuvastatin is about 20%. Oral disintegrating tablet avoids first pass effect and increase its bioavailability.

Rosuvastatin is obtained as white crystalline powder that is poorly soluble in water and has very bitter taste. Based on the physicochemical and biopharmaceutical properties, it was decided to formulate Mouth Dissolving Tablets of Rosuvastatin (Randale SA *et al*., 2010, Vishnumurthy V *et al*., 2012) enhancing its solubility by solid dispersion method which may be a better option for immediate effect and by masking its bitter taste by using Eudragit EPO. As the drug exhibits poor solubility in water and low bioavailability due to incomplete absorption, it demands for a drug delivery system to enhance its absorption.

Eudragit EPO is insoluble in salivary pH (6.8) and allows the release of the drug at the expected site (Intestine or stomach). It has high pigment binding capacity and good adhesion. It helps to seal sensitive actives and increase patient compliance by taste and odour masking. Which makes it ideally suitable for formulating solid dispersions.

MATERIAL AND METHODS

Material

Rosuvastatin was received as gift sample by Aurobindo pharma. Ltd; Eudragit EPO was received from evonik group, Mumbai. The other chemicals used are of reagent grade. (Tatsuya I et al., 1999, Khan S, *et al*., 2007, Kaur T, *et al*.,2011, Sharma D, *et al*., 2012, Mohammed EA, *et al*., 2013)

* Corresponding Author
Email: tripurakrishna@gmail.com
Contact: +91-8185067523
Received on: 18-05-2017
Revised on: 07-06-2017
Accepted on: 11-06-2017

Methods

Preparation of taste masked powder blend of Rosuvastatin by Solvent evaporation technique

Taste masked powder blend of Rosuvastatin were prepared by using Eudragit EPO by preparing solid dispersions of Rosuvastatin by solvent evaporation technique. In this method drug was taken and was dissolved in required amount of acetone. Specified amount of polymer Eudragit EPO was added, the mixture was then triturated using a mortar and pestle till the solvent used is evaporated completely. Then the powder was collected, air dried for 24hrs and it was passed through sieve no.60, the mixture was sealed and was stored in desicator until further use.

The drug polymer ratio that gave the best taste masking was 1:2. The amount of polymer used in 1:2 is efficient in masking the taste of the drug.

Formulation of Mouth Dissolving Tablets employing solid dispersions

All the ingredients were weighed accurately as per given quantities and mixed well. The powder blend was passed through sieve no. 60. The powder blend was mixed thoroughly in a polybag for 10 minutes. Then it was compressed into tablets using 8.0 mm standard concave punches.

Evaluation of Pre-compression parameters of the powder Blend

Angle of repose

Angle of repose was determined by funnel method. The powder blend was poured through a funnel which can be raised in vertical direction until a maximum height of cone (h) was obtained. The heap radius (r) was measured and angle of repose (θ) was calculated using the following formula,

$$Tan\theta = \frac{h}{r}$$

Bulk Density

Bulk density (ρb) was determined by using graduated measuring cylinder. In this method the weighed quantity of powder blend was transferred into the measuring cylinder and the volume (vb) occupied by the powder was checked. The bulk density was calculated by using the formula

$$\rho b = \frac{vb}{M}$$

Tapped Density

This was calculated by transferring weighed quantity of powder blend into a measuring cylinder and tapped till there is no difference in two consecutive values of volume (vt). The tapped density (ρt) can be calculated by the given formula.

$$\rho t = \frac{vt}{M}$$

Compressibility Index

Compreesibility index indicates the ease with which the powder flows. It is calculated by using tapped density and bulk density. The formula to calculate compressibility index is

$$I = \left\{ \frac{(\rho t - \rho b)}{\rho t} \right\} \times 100$$

If the compressibility value is below 15% it represents good flow property and above 20% represents poor flow properties of the powder blend.

Hausner's Ratio (H)

Unlike compressibility index Hausner's ratio is an indirect index of powder flow properties. It can be calculated by

$$H = \frac{\rho t}{\rho b}$$

Lesser the hausner's ratio (<1.25) better will be the powder flow.

Assay of Drug polymer complex (DPC)

The content of Rosuvastatin in DPC was determined using UV-spectrophotometer. DPC equivalent to 30mg drug were dissolved in methanol. Further appropriate dilutions were done with phosphate buffer pH 6.8 to give a final concentration of 10µg/ml (10 ppm) solution. Percent drug content was calculated from the absorbance obtained at 248nm.

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectra of pure drug, polymer, and DPC (1:2) were observed using FTIR spectrophotometer (Perkin Elmer, Spectramax). KBr pellets with DPC were scanned over a range of 400 to 4000 cm-1 and the data was used for interpretation.

Differential scanning calorimeter (DSC)

The DSC thermograms of samples (pure drug, solid dispersions of Rosuvastatin) were recorded on DSC. In this generally hermetically sealed aluminium pans containing samples were heated over a range of 20 to 250^0C with a constant heating rate of 10^0C/Min under nitrogen purge.

X-Ray diffraction (XRD)

X-Ray diffraction analysis was employed to detect the crystallinity of the pure drug and the formulations, which was conducted using XRD 6000 diffractometer. The powder was placed in a glass sample holder. Samples were scanned from 5º to 50º with a step size of 0.02º and the scan speed was 3ºmin⁻¹

Scanning electron microscopy (SEM)

SEM photographs are used to examine the surface

morphology of the samples.

Bitterness evaluation by Subjective evaluation method

Bitterness evaluation is performed on ten healthy volunteers with good taste perception. the volunteers were asked to keep the samples on their tongue for 10 sec and were informed to spat out after that. They were informed to scale the bitterness on a numerical scale ranging from 0-10.

Scale: 0- Tasteless, 1- Very Slight, 2- very slight bitterness, 3- Slight bitterness, 4- slight to moderate bitterness, 5- Moderate bitterness, 6- Moderate to strong bitterness, 7- Strong bitterness, 8- Very Strong bitterness, 9-10 very strong bitterness.

Post compression Evaluation parameters

Uniformity of weight/weight variation test

Uniformity of weight was performed by randomly weighing ten tablets individually and collectively on digital balance. Individual weight of tablets was determined from average weight of tablets.

Friability

The friability of tablets were measured using Roche friabilator. Six pre-weighed tablets were rotated at 25rpm for 4minutes.The tablets were then reweighed after removal of fines using 60 mesh screens and the percentage of weight loss was calculated.

% Friability = (Loss in weight / Initial weight) X 100

Tablet hardness

Hardness of the tablets was measured by Monsanto hardness tester. Hardness gives the idea about the crushing strength required to break the tablets. It is measured in Kg/Cm2.

Tablet thickness

Digital vernier calpers was used to note the thickness of prepared tablets.

Assay of tablets

Ten tablets were used to know the content of drug in the prepared tablets. The tablets were taken in mortar and were powdered by using pestle. Powder equivalent to 30 mg of Rosuvastatin was taken and dissolved in 100mL methanol. Finally a solution of 10ppm was prepared by using buffer. Percent drug content was calculated from the absorbance obtained at 248nm.

Tablet disintegration time

Disintegration time of the prepared tablets was carried out in triplicate in distilled water at 37^0C. The time taken by the tablets to disintegrate was noted.

In-vitro drug release studies

The in vitro drug release studies for the prepared tablets of Rosuvastatin were performed by dissolution testing method. Phosphate buffer of pH 6.8 at 37^0C and USP type II apparatus with 50 rpm speed were used to perform the test.10 mL of aliquots were taken at 5, 10, 15, 20, 30, 45 and 60 mins. The absorbances were noted at 248nm.

Data analysis

The data obtained from drug release studies was fitted in different kinetic models and the graphs were drawn.

Stability studies

The formulation for stability testing was selected on the basis of optimization results. The reproducible batch was subjected to stability conditions for the duration of one month at 40ºC/75%RH. Evaluation of the formulation was done for performance characteristics like appearance, hardness, assay (% drug content) and dissolution studies (%drug release).

RESULTS AND DISCUSSION

FTIR Studies

FTIR studies were carried out to investigate if there is any chemical interaction between polymer, added excipients.

DSC

In order to check chemical interaction between drug and polymer, thermal analysis was carried out by using DSC

From the results it was observed that optimized formulation followed first order release with non fickian diffusion mechanism.

DISCUSSION

Among all the prepared solid dispersions, 1:2 ratio of Drug:polymer was selected based on subjective evaluation of bitterness. This ratio was further prepared in the form of mouth dissolving tablet dosage form

The finalized ratio was evaluated for powder characteristics, pre and post compression parameters, drug release studies and compared with physical mixture and marketed preparation. The prepared solid dispersion, physical mixture of finalized formula were analysed instrumentally by FTIR, DSC, XRD and SEM studies.

Rosuvastatin pure drug had shown the dissolution of 32% in 60mins with 5.7% drug release in 5mins. Whereas the solid dispersion had shown 100% drug release within 15mins and 81.2% drug release in 5mins. Marketed tablet had shown the dissolution of 78% in 60mins with 45% drug release in 5mins. It clearly represents better drug release characteristics of the formulated solid dispersions than the physical mixture and marketed preparation.

Figure 1: FTIR of Rosuvastatin pure drug

Figure 2: FTIR of Eudragit EPO polymer

Figure 3: FTIR of Physical mixture (1:2)

Table 1: Formulation trials of taste masked powder blend of Rosuvastatin using Eudragit EPO

DPC	Prepared ratios
Rosuvastatin : Eudragit EPO	1:1, 1:2, 1:3, 1:4, 2:1

FTIR: Some characteristics peaks at 2948.97, 1489.67, 1155.89, 969.73 of pure drug were missing or stretched to other wave no. in the prepared solid dispersions which represents the interaction between drug and polymer.

DSC: The results obtained in FTIR studies were further confirmed by the DSC thermograms, which shows either disappearance or stretching of endothermic peak to other temperature which confirms the interaction of polymer with drug.

Table 2: Formulation of Mouth dissolving tablets of Rosuvastatin using Direct compression Technique

Ingredients	F1	F2	F3
DPC	120	120	120
Crospovidone	5	10	15
Talc	2	2	2
Magnesium stearate	2	2	2
Starch	10	10	10
Total weight (mg)	140	145	150

Table 3: Pre compression properties of Rosuvastatin

Optimized ratio	Angle of repose	Bulk density(g/ml)	Tapped density(g/ml)	Hausner's ratio	Carr's index	Drug content
1:2	27.01±0.7	0.66 ± 0.03	0.73 ± 0.03	1.32 ±0.02	14.46±0.4	96.5

Table 4: Wave numbers of Rosuvastatin pure drug and in solid dispersion

Stretching / Bending	In pure drug	In solid dispersion
O-H stretch Carboxylic acid	2948.97	2973.68
C-C stretch Aromatics	1489.67	1281.46
C-O stretch Alcohols, Esters	1155.89	1214.83
C-H bend Alkenes	969.73	838.94

Table 5: Post compression parameters of Rosuvastatin

Parameters	Result
Hardness	2 kg/cm²
Friability	0.16
Disintegration time (sec)	12 Sec
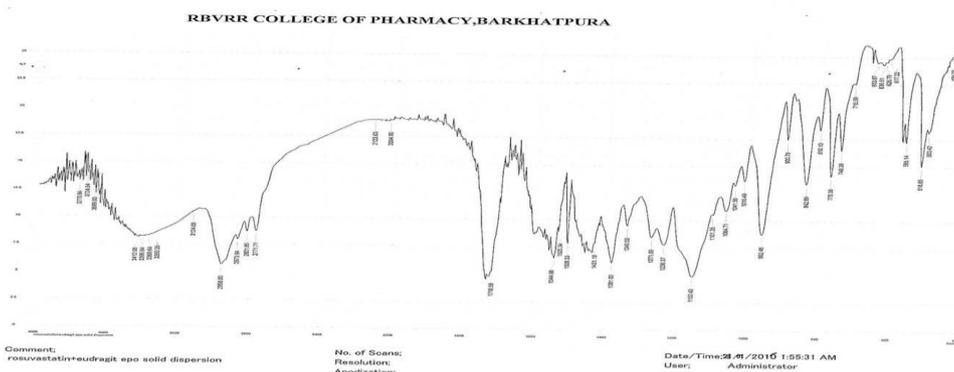
Figure 4: FTIR of Solid dispersion (1:2)

(A) Rosuvastatin pure drug   (B) Rosuvastatin solid despersion   (C) Rosuvastatin physical mixtu
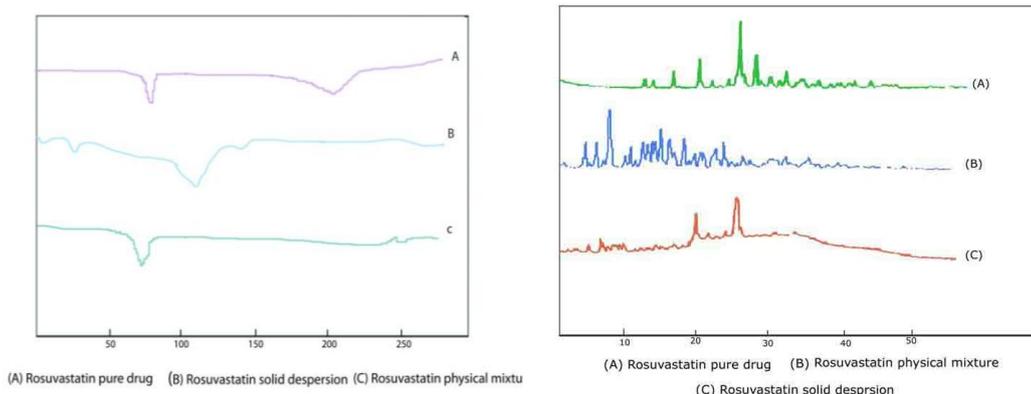
Figure 5: Overlay of DSC thermograms

(A) Rosuvastatin pure drug   (B) Rosuvastatin physical mixture
(C) Rosuvastatin solid desprsion

Figure 6: Overlay of XRD graphs

Table 6: r2 values for the prepared solid dispersion

Formulation	Zero order r² value	First order r² value	Higuchi r² value	Peppas 'n' value
Rosuvastatin:Eudragit EPO (1:2)	0.6116	0.9542	0.9179	1.9961
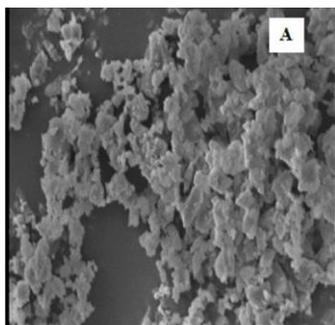
Figure 7: SEM Rosuvastatin pure drug
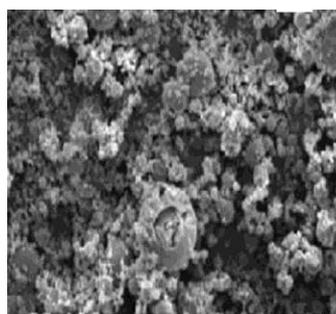
Figure 8: SEM Eudragit EPO polymer

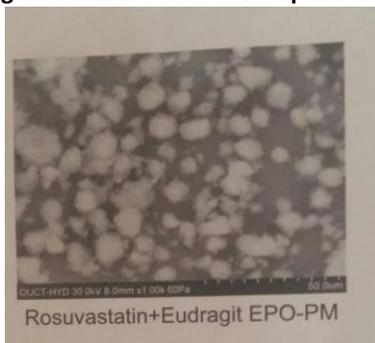Rosuvastatin+Eudragit EPO-PM

Figure 9: SEM of physical mixture (1:2)

Rosuvastatin+Eudragit EPO-SD

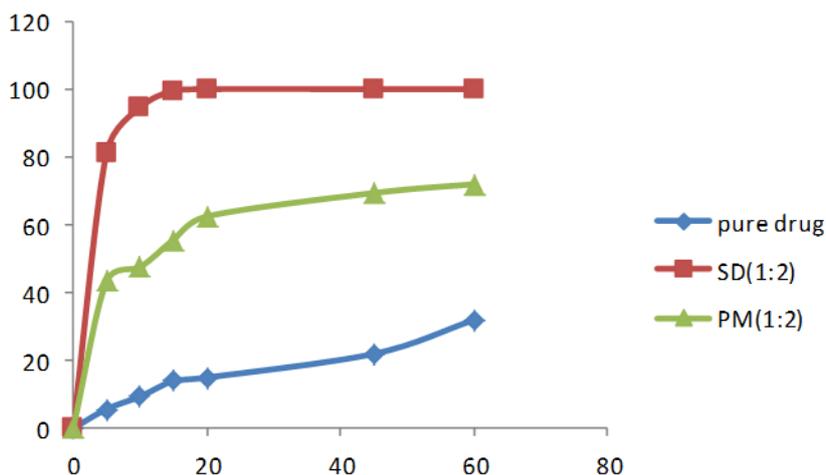**Figure 10: SEM of Solid dispersion (1:2)**

Figure 11: Cumulative %drug release profile of various preparations

Table 7: Evaluation of stability batch of prepared MDTs

Parameters	Before stability studies	After stability studies (1-month)	After stability Studies (2-month)	After stability Studies (3-month)
Hardness	2	2	2	2
Friability	0.16	0.17	0.18	0.19
Disintegration time (sec)	12	13	14	14
% drug release	100%	99%	99%	100%

Table 8: Parameters for stability study batch of Rosuvastatin MDT

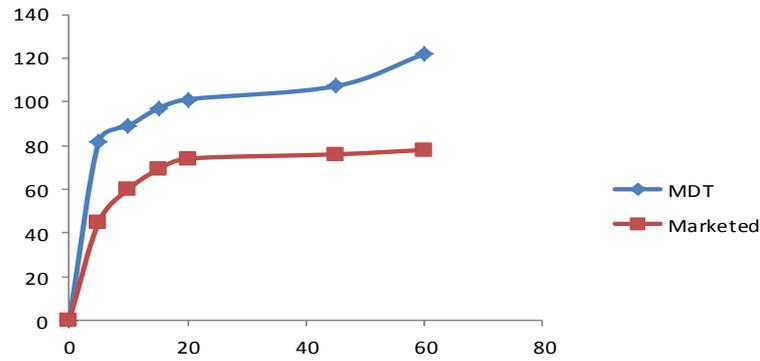| Sr.no	Tests	Specifications	Initial	$40^0C \pm 2^0C$/ 75% RH $\pm5\%$ RH 3 Months
1.	Appearance	White in colour, round, plain on both sides.	Complies	Complies
2.	Hardness	2	2	2
3.	Disintegration time	Not more than 1 minute	12	14

Figure 12: Comparision of % drug release of prepared MDT and Marketed tablet
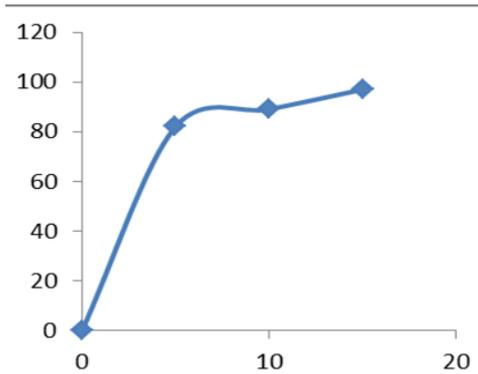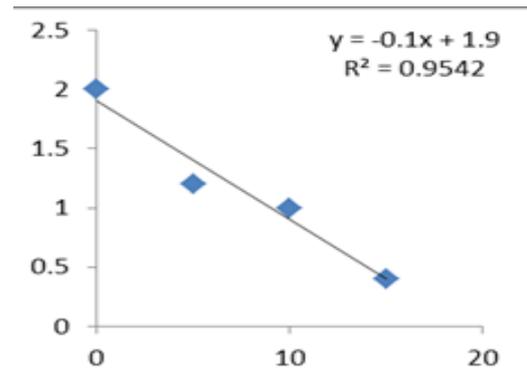

Figure 13: Zero order plot of prepared MDT

$y = -0.1x + 1.9$
$R^2 = 0.9542$

Figure 14: First order plot of prepared MDT

$y = 28.553x$
$R^2 = 0.9179$
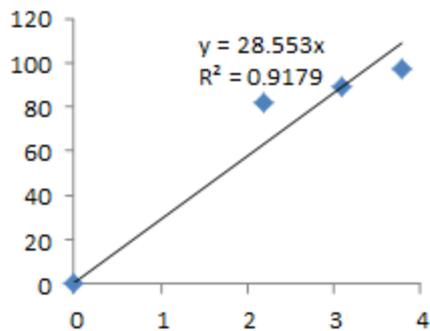
Figure 15: Higuchi plot and Peppas plots of prepared MDT
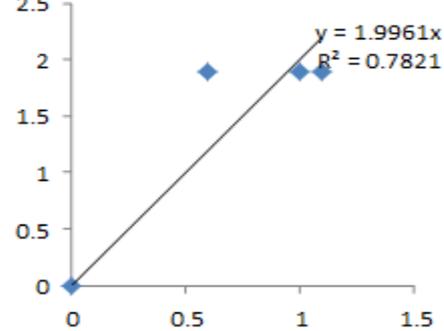

$y = 1.9961x$
$R^2 = 0.7821$

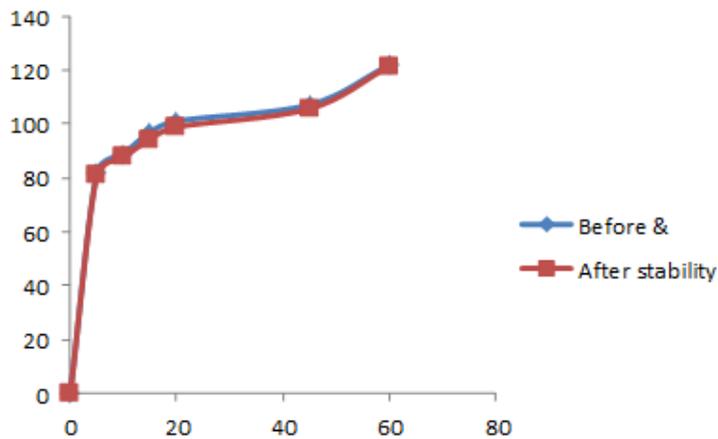**Figure 16: Higuchi plot and Peppas plots of prepared MDT**

Figure 17: Drug release studies of Rosuvastatin from the prepared MDTs Before and After stability studies

XRD: The results obtained in XRD are in line with DSC, which shows clearly the reduction in crystallinity of drug in solid dispersions.

SEM: The microphotographs clearly evidenced the transformation of crystalline drug into amorphous dispersion form, which is why the solubility and there by dissolution of the drug were enhanced in the prepared solid dispersions.

Stability studies: The drug release studies conducted on stability batch revealed that the drug release pattern was not modified upon standing. There is no evidence for the conversion of amorphous form of the drug in the dispersions back to its original crystalline form which explains the enhancement in solubility and dissolution rate of drug.

CONCLUSION

Eudragit EPO was found to be efficiently masking the bitter taste of Rosuvastatin. Mouth dissolving tablets prepared by using prepared solid dispersions showed better drug release profiles in comparison to marketed products. The stability studies performed up to 3months at 40ºc, 75%RH proved that the drug release parameters were within limits which confirms the stability of solid dispersions and mouth dissolving tablets prepared employing solid dispersions.

REFERENCES

British Pharmacopoeia 2014 Volume I. London: Stationery Office; 2014. General monographs and general chapters, page no-944-945.

Drug information. Novartis products leaflet. Available from:-http://www.pharma.us.novartis.com. [Internet]. Accessed on 16th January, 2014.

Fischer V, Johanson L, Heitz F, Tullman R, Graham E, Baldeck JP, Robinson WT: 1999, The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor fluvastatin: effect on human cytochrome P-450 and implications for metabolic drug interactions. Drug Metab Dispos. 1999 Mach 1999; 27(3): 410-6.

http://www.drugbank.ca/drugs/DB01095. [Internet]. Accessed on 16th January, 2015.

Jadon RS, Nayak S, Amlan S. 2009, Taste masking of Lornoxicam by polymer carrier system and formulation of oral disintegrating tablets. International Journal of Drug Delivery; 2009; 1; 27-31.

Kaur T, Gill B, Kumar S, Gupta GD. 2011, Mouth Dissolving Tablets: A novel approach to drug delivery- Review Article. International Journal of Current Pharmaceutical Research; 2011; 3(1): 1-7.

Khan S, Kataria P, Nakhat P, Yeole P. 2007, Taste Masking of Ondansetron Hydrochloride by Polymer Carrier System and Formulation of Rapid-Disintegrating Tablets. Pharm Sci Tech; 2007; 8 (2):1-7.

Mohammed EA, Dr Shaimaan N, Hammad AL. 2013, Formulation and evaluation of rosuvastatin orodispersible tablets: A Research article. International Journal of Pharmacy and Pharmaceutical Sciences; 2013; 5(2):339-346.

Orange book Food and Drug Administration. Available from:- www.accessdata.fda.gov/scripts/cder/ob.

Randale SA, Dabhi CS, Tekade AR, Belgamwar VS, Gattani SG, Surana SJ. 2010, Rapidly disintegrating tablets containing taste masked metoclopramide hydrochloride prepared by extrusion-precipitation method: A Research article. Chem. Pharm. Bull; 2010; 58(4): 443-445.

Sharma D, Chopra R, Bedi N. 2012, Development and evaluation of paracetamol taste masked orally disintegrating tablets using polymer coating technique: A Research article. International Journal of Pharmacy and Pharmaceutical Sciences; 2012; 4(3):129-134.

Taste Masking: an important pharmaceutical technology for the improvement of organoleptic property of pharmaceutical active agents. European journal of biological sciences; 2011; 3(3): 67-71.

Tatsuya I, Yoshiteru W, Naoki U, Mitsuo M. 1999, Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter-taste-masked granules by the compression method. Chem. Pharm. Bull; 1999; 47(10):1451-1454.

Vishnumurthy V, Nagpal D. Taste masking technologies: An overview and recent updates.2012, International Journal of Pharamaceutics and Biomedical Sciences; April- June 2012; 3(2); 510-520.

Vummaneni V and Nagpal D. 2012, Taste Masking Technologies: An Overview and Recent Updates. International Journal of Research in Pharmaceutical and Biomedical Sciences; April – June 2012; 3(2).