Asian Journal of Pharmaceutical Technology & Innovation
ISSN: 2347-8810

Research Article

Received on: 12-12-2015
Accepted on: 01-01-2016
Published on: 09-12-2016

Corresponding Author

***Dhruv Prakash Tiwari**

Shambhunath Institute of Pharmacy, Jhalwa, Allahabad, India

Email: dhruvtiwari77@gmail.com

Formulation and Evaluation of Film Coated Tablet of Rosuvastatin

Dhruv Prakash Tiwari*, Manoj kumar Mishra

ABSTRACT

Rosuvastatin is an antilipidemic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. Hypo-lipidemic is a disorder of cholesterol level in a liver. Thus formulating Rosuvastatin into a flim coated dosage form would provide fast relief. The tablets were evaluated for the drug content, weight variation, water absorption ratio, wetting time, in vitro disintegration, hardness, friability, thickness uniformity. The tablets disintegrated in vitro within 37 to 40 seconds complete drug were released from tablet within 30 minutes. The results showed that Rosuvastatin Calcium was successfully formulated into a flim coated dosage form.

Key-words: Rosuvastatin Calcium, Hypo-lipidemic, flim coated tablets.

Cite this article as:
Dhruv Prakash Tiwari, Manoj Kumar Mishra, Formulation and Evaluation of Film Coated Tablet of Rosuvastatin, Asian Journal of Pharmaceutical Technology & Innovation, 03 (16); 2015. www.asianpharmtech.com*

INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one which immediately attains the desired therapeutic concentration of drug in plasma (or in the site of action) and maintains it constant for the entire duration of treatment. This is possible though administration of a conventional dosage form in a particular dose and at a particular frequency. The frequency of administration or the dosing interval of any drug depends upon its half-life or mean residence time (MRT) and its therapeutic index[1,2,3].

An oral coated dosage is the one which delivers the drug at a predetermined rate locally or systemically for a specified period of time Oral drug delivery system is the most popular route, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in Dosage form design than most other routes.

Sustained drug release system includes any drug delivery system which achieves slow release of drug over an period of time, and includes both prolonged and controlled drug release system.

The goal of sustained release dosage form is to maintain therapeutic blood or tissue level of the drug for extended period of time. This is generally accomplished by attempting to obtain "zero order" release from the dosage form. Zero order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system. Sustained release system generally do not attain this type of release and usually try to mimic zero order release by providing drug in slow "first order" fashion (i.e. concentration dependent[4,5].

Rosuvastatin is an antilipidemic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis. Rosuvastatin belongs to a class of medications called statins and is used to reduce plasma cholesterol levels and prevent cardiovascular disease. The drug was billed as a super-statin during its clinical development; the claim was that it offers high potency and improved cholesterol reduction compared to rivals in the class [Tripathi, 2004 and Indian Pharmacopoeia, 2010].

Rosuvastatin is a competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Rosuvastatin acts primarily in the liver. Decreased hepatic cholesterol concentrations stimulate the upregulation of hepatic low density lipoproteins (LDL) receptors which increases hepatic uptake of LDL. Rosuvastatin also inhibits hepatic synthesis of very low density lipoprotein (VLDL). The overall effect is a decrease in plasma LDL and VLDL. Invitro and invivo animal studies also demonstrate that rosuvastatin exerts vasculoprotective effects independent of its lipid-lowering properties. Rosuvastatin exerts an anti-inflammatory effect on rat mesenteric microvascular endothelium by attenuating leukocyte rolling, adherence and transmigration. The drug also modulates nitric oxide synthase (NOS) expression and reduces ischemic-reperfusion injuries in rat hearts[6]. Rosuvastatin increases the bioavailability of nitric oxide by upregulating and by increasing the stability of NOS through post-transcriptional polyadenylation. It is unclear as to how rosuvastatin brings about these effects though they may be due to decreased concentrations of mevalonic acid.

The goal of sustained release dosage form is to maintain therapeutic blood or tissue level of the drug for extended period of time. This is generally accomplished by attempting to obtain "zero order" release from the dosage form. Zero order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system. Sustained release system generally do not attain this type of release and usually try to mimic zero order release by providing drug in slow "first order" fashion[7] (i.e. concentration dependent).

PREFORMULATION STUDIES[8]

Preformulation is the learning phase about a new drug molecule. It involves generating information regarding physicochemical properties of the drug molecule, its interaction with excipients, stability profile and preliminary *in-vivo* properties. Information gathered during preformulation is of immense importance for the development of stable dosage form.

Identification of Rosuvastatin calcium [9, 10]

Physical Appearance: It is off white to creamish white crystalline powder.

Melting Point Determination

A capillary melting point tube was taken. A small amount of compound was placed on a clean surface. The

compound was put into open end of the capillary tube. The capillary melting point tube was placed into the melting point apparatus. The sample was observed continuously for liquification and the melting point was recorded. Melting point of Rosuvastatin calcium was found to be in range of 120-128°C.

Solubility Studies[11]

Accurately weighed 10 mg drug was taken in 10 ml of each solvent at room temperature and sonicated for 10 minutes and examined for any undissolved particles. The results of study are shown in table 1[In House method in Akums Drugs & Pharmaceutical Ltd, Haridwar].

Table 1: Results of solubility studies of Rosuvastatin Calcium

Solvents	Solubility of Rosuvastatin calcium
Acetonitrile	Freely soluble
Distilled Water	Sparingly soluble
Acetone	Slightly Soluble
Methanol	Soluble

Partition Coefficient The partition coefficient directly influences the permeability of drug through skin, and could be approximated by measuring partition coefficient of drug in n-octanol/water. The partition coefficient of rosuvastatin in an n-octanol/water system was calculated to be 2.3[12].

K=Corg / Cwat (3.1)

Compatibility Study[13,14]

For the development of formulation compatibility study between drug and excipients is necessary for stable dosage form on basis of its physical, chemical and biological characteristics. Drug-excipients interaction study was done by taking 1:1 ratio of drug and excipients in 2ml glass vials, sealed and placed in stability chamber at 25^{0}C/60% RH, 40^{0}C/75 % RH and 60^{0}C for 21 days. The sample was analyzed for colour change and bad odours after 7, 15, & 21 days. From the results obtained, it was found that the drug is compatible with the respective excipients under evaluation based on physical observation. So chosen excipients can be used in the formulation. The result showed that very slight changes in appearance was observed indicating compatibility of rosuvastatin calcium with the chosen excipients.

FORMULATION DEVELOPMENT

Rosuvastatin calcium tablet containing 10 mg drug were prepared by non aqueous wet granulation method according to the formula mentioned in table 2. A batch size of 1000 tablets was planned for each formulation based on trial-error method and the quantity for each formulation was expressed in grams[15,16].

Table 2 Optimization of Trial Batch

Ingredients (gm/batch)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rosuvastatin calcium IP	11.54	11.54	11.54	11.54	11.54	11.54	11.54	11.54	11.54
Dicalcium phosphate (powder)	15	15	15	15	15	15	15	15	15
Microcrystalline cellulose IP	51	51	51	51	51	51	51	51	51
Lactose IP	26	26	26	26	26	26	26	26	26
Pre-gelatinized starch USP NF	16	16	16	16	16	16	16	16	16
KLUCEL EXF	3.6	3.2	2.9	3.4	3.3	2.8	2.3	2.6	3.1
Isopropyl alcohol IP (ml)	80	80	80	80	80	80	80	80	80
Magnesium stearate IP	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Colloidal silicon dioxide	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Primogel	3	3	3	3	3	3	3	3	3
Cross povidone IP	1.7	2.1	3.4	1.9	2	2.5	3	2.7	2.2
Total weight	209.89	209.89	209.89	209.89	209.89	209.89	209.89	209.89	209.89

Procedure:

Weighed quantities of Rosuvastatin calcium IP, Dicalcium phosphate (powder) IP, Lactose IP, MCC IP, Pre-gelatinized starch USP NF and KLUCEL EXF were passed through sieve 40#. Isopropyl alcohol was taken in SS container and KLUCEL EXF was added with continuous stirring to obtain binder solution. All the excipients except KLUCEL EXF were mixed and passed through sieve 24#. The mixture obtained after sieving was transferred and dry mixing was carried out for 30 min in a polyethylene bag. Binder solution was added to the tablet material at slow rate for about 15 min. After the addition of binder solution the mixture was continuously mixed to get desired mass. Additional quantity of IPA was added to get the desired consistency. The wet granules were passed through multimill using 8mm screen knives in forward orientation at slow speed. It was checked for black particles which were generated through the friction of blades. The wet granules were loaded in the dryer and air dried for 10 min. The mass was raked intermittently in the dryer and dried at 55 to 65 0C of inlet air temperature and 35 to 40°C outlet temperature for 20 to 30 min to get LOD of 2 to 3%. The dried granules were passed through the vibro sifter using sieve 18#. The granules retained on the sieve were passed through multimill using knives in forward orientation at slow speed and checked for presence of black particles. Primogel and Crospovidone IP were passed through sieve 100#. Magnesium stereate IP and Crospovidone IP were passed through sieve 40#. The sieved and dried granules were placed in the mixer along with Colloidal silicon dioxide IP, Primo gel and Crospovidone and blended for 15 min. Magnesium stereate was added into polyethylene bag and blending was carried out for 5 min. The lubricated granules were compressed on 12 station rotatory punching machine of BB tooling type having upper punch of 7.1 mm circular concave and lower punch of 7.1 mm circular concave surface with 7.1 mm circular die size[17].

Evaluation of Granules:

Table 3: Precompression results for trial batches

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density (gm/cm3)	0.337	0.335	0.341	0.321	0.325	0.338	0.333	0.331	0.339
Tapped density (gm/cm3)	0.391	0.387	0.392	0.371	0.374	0.389	0.381	0.383	0.394
Angle of repose	26.28	26.16	26.23	26.13	25.96	26.03	25.71	26.19	26.39
% compressibility	13.81	13.43	13.26	13.47	13.1	13.11	12.59	13.57	13.95
Hausners ratio	1.601	1.152	1.146	1.157	1.1507	1.1508	1.144	1.157	1.163

Evaluation of tablets[18]

All the tablets were evaluated for different parameters like hardness, thickness, friability, drug content, disintegration time and *in-vitro* drug release.

***In Vitro* dissolution study**[19]

In-vitro dissolution of tablet was studied in USP XXIV dissolution apparatus (Electrolab) employing a paddle stirrer using 900 ml of phosphate buffer of pH 6.8 as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution media was maintained at 37+0.5 °C throughout the experiment. 5 ml samples were withdrawn by means of syringe at predetermined time not less than 1 cm from the vessel wall and filtered through 0.45 micron nylon membrane filter. The samples were analyzed for drug content after suitable dilution by measuring the absorbance at 248 nm in HPLC for chromatogram recording. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Percentage amount of Rosuvastatin released was calculated and plotted against time. The results of trial batches and innovator are shown in table 5.4.

Reference solution: 0.05% w/v solution of Rosuvastatin calcium in the mobile phase was prepared. 2 ml of drug solution was diluted with 100 ml of dissolution medium.

Table 4: *In- vitro* dissolution data for uncoated tablet

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9	Innovator
0	0	0	0	0	0	0	0	0	0	0
10	24.61	26.72	31.79	25.91	26.21	32.34	34.61	32.15	26.65	33.99
20	51.12	64.23	69.88	59.99	62.91	71.81	75.82	72.92	66.26	75.51
30	77.02	89.97	97.61	81.54	86.17	98.01	100.78	98.24	88.99	100.64

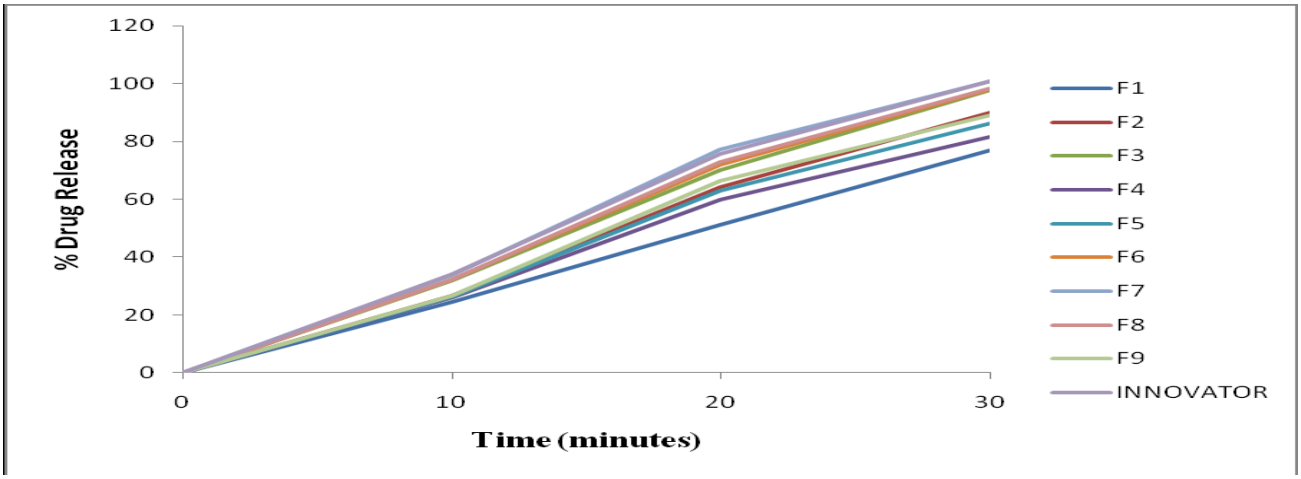

Figure 5.8 Comparative dissolution profile of Trial Batches and Innovator

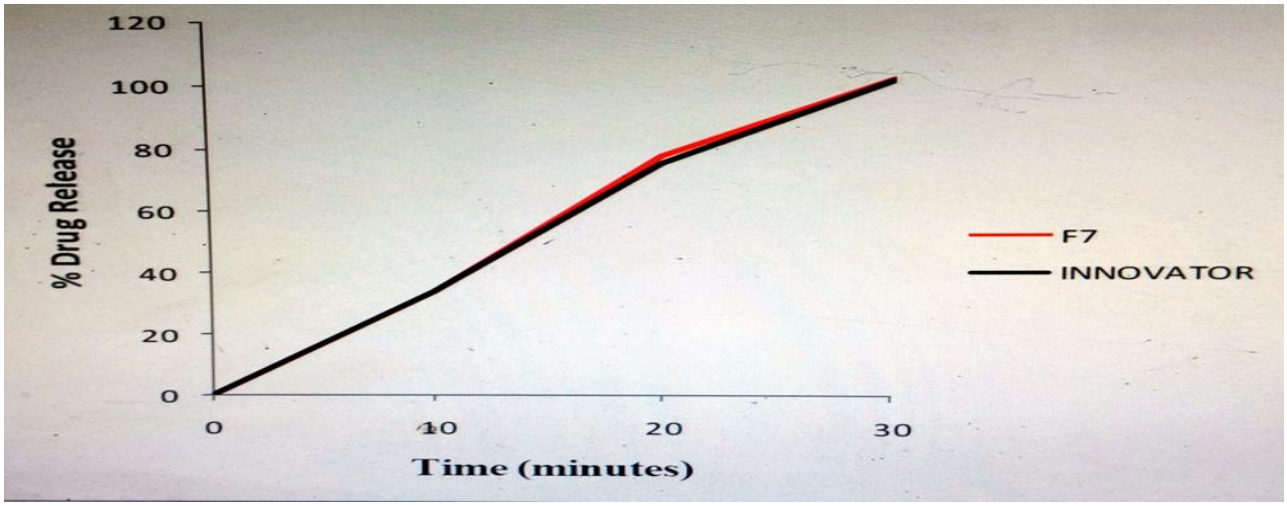

Figure Comparative dissolution profile of F7 and Innovator

Table 5: Post compression results of uncoated tablet batches

Test	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diameter	6.88± 0.01	6.84± 0.02	6.83± 0.02	6.87± 0.03	6.83± 0.01	6.86± 0.01	6.77± 0.01	6.89± 0.03	6.85± 0.01
Thickness	3.45± 0.02	3.31± 0.01	3.32± 0.05	3.32± 0.04	3.29± 0.03	3.27± 0.02	3.28± 0.02	3.31± 0.04	3.29± 0.01
% weight variation	131± 1.11	129± 2.14	132± 1.21	133± 1.18	131± 2.11	130± 1.99	128± 2.13	128± 2.09	131± 2.31
Hardness	4.5± 0.17	4.3± 0.09	4.2± 0.13	4.4± 0.18	4.4± 0.19	4.1± 0.15	3.9± 0.02	3.9± 0.21	4.3± 0.12
Friability -%w/w	0.38	0.51	0.55	0.41	0.43	0.57	0.61	0.59	0.49
Disintegration time (min)	59	41.5	41	52	49	39	30.7	34.5	48.5

Film coating[20]

The batch F7 was selected for film coating which complied with the specifications. HPMC2910 USP (HPMC E5), PEG-6000, Talcum powder, Titanium dioxide, Isopropyl alcohol Methylene blue and Ponceau 4R lake were mixed together and filtered through nylon cloth of 100# mesh.

Table 6: Coating Composition

Excipients	Quantity/batch	Functional category
HPMC 2910 USP (HPMC E5)	2.00 g	Film former
PEG 6000	0.20 g	Plasticizer
Purified talc	0.20 g	To prevent sticking of tablet
Titanium dioxide	0.150 g	Pigment
Isopropyl alcohol	35 ml	Solvent
Methylene chloride	35 ml	Solvent
Ponceau 4R lake	0.08 g	Colouring agent

The uncoated, de-dusted tablets were loaded into the coating pan and the tablets were warmed up to 50oC. The Coating solution (2-3%) was sprayed over the warmed tablets using 1.5mm air nozzle spray gun for efficient coating. Hot air was passed between each application of coats. Tablets bed temperature during coating procedure should not exceed 37˚C. The tablets were dried as per parameters specified in table 7.

Table 7: Coating parameter specification

Specification	Film coated
Pan speed	2-5rpm
Atomizing air pressure	3 to 5 kg/cm2
Inlet air temperature	45 to 55 ^{o}C
Outlet air temperature	40 to 45 ^{o}C
Bed temperature	35 to 40 ^{o}C
Predrying in pan	15 min at 45 ^{o}C
Final drying in pan	1-2 hrs at 40-45^{o}C
Post drying in pan	1-1.5 hr air drying
Dry bulb temp	25 ^{o}C
Wet bulb temp	18 ^{o}C
Relative humidity	40 + 5 %

Assay of Film Coated Rosuvastatin Calcium Tablet by HPLC[21-24]:

The retention time of major peak due to Rosuvastatin calcium in chromatogram of the sample preparation correspond to that of the standard preparation as obtained in the assay Rosuvastatin.

Reference solution: A 0.05 percent w/v of Rosuvastatin calcium RS was prepared in mobile phase and diluted 5.ml of the solution to 25 ml with mobile phase.

Test solution: Accurately weighed tablet powder equivalent to 25 mg of Rosuvastatin was dissolved in 30 ml of methanol. The mixture was sonicated for 10 min and volume was made upto 100 ml. The mixture was centrifuged for 10 min and 5 ml was diluted with 25 ml of mobile phase and filtered through nylon membrane of 0.45 micron pore size.

Chromatographic system[25-28]

The stainless steel column 25 cm x 4.6 mm of phenomenaxluna was packed with octadecylsilane bonded to porous silica (5 µm). The mobile phase was a mixture of 50 volumes of 0.2 per cent acetic acid in water, 25 volumes of acetonitrile and 25 volumes of methanol. The mixture was filtered and degased. The flow rate was adjusted to 1 ml per minute and spectrophotometer set at 248 nm. The 20 µl loop injector was used.

Equal volumes (20µl) of blank solution, reference solution (five replicate) and test solution (duplicate) were injected separately and chromatogram was recorded to measure the response of major peaks. The test is not valid unless the relative standard deviation for replicate injections is not more than 2.0 per cent.

Table 5.16 Comparison of post compression evaluation results of F7 and Innovator

Parameters and acceptance criteria	Film coated tablet F7	Innovator
Diameter (7.1mm + 0.2mm)	7.21+0.07mm	7.19+0.05mm
Thickness (3.3mm + 0.3mm)	3.32+0.007mm	3.34+0.008mm
Average weight (132mg + 7.5%)	133.45+1.1mg	133.23+1.1mg
Hardenss kg/cm2	3.9 + 0.02	4.0 + 0.09
Uniformity of weight within (+ 7.5% of average weight)	-2.3% to +2.1%	-2.2% to+2.1%
Disintegration time (NMT 30 min)	3.25 min	3.34 min
Uniformity content (85% to 115%)	96.835	96.788
%Drug release after 30 min	100.81	100.74
Assay %	100.2	99.41

Result and Discussion

In Pharmaceutical practice several approaches exist for administration of drugs to the patients. Oral drug delivery products lead the world wide drug delivery market as they are the most convenient to administer, most cost effective to manufacture and the most preferred by patients.

If the drug is given in conventional dosage form, it has to be administered several times a day, to produce the desired therapeutic effect, because of frequent dosing, fluctuations in plasma drug level occur. The pronounced fluctuations resulting from the conventional drug administration are likely to yield fluctuations of therapeutic effects, when the drug concentration falls below the minimum therapeutic level. Drug concentration can be controlled with in the narrow therapeutic range by the use of extended release systems, which will minimize the severity of side effects

New and more sophisticated sustained release drug delivery systems are constantly being developed with coating phenomena and tested. Successful fabrication of sustained release products is usually difficult and involves consideration of the physic-chemical properties of the drug, pharmacokinetic behavior of the drug, and route of administration, diseased state to be treated and most importantly placement of the drug in a dosage form that will provide the desired temporal and spatial delivery pattern for the drug

The use of sustained-release formulation for the oral administration of drugs to a patient of a drug can be maintained over a prolonged period of time without the necessity of multiple daily drug administration. Some drugs are toxic or otherwise deleterious in high concentrations in upper GIT, and thus require controlled administrations of drugs into lower GIT to the patients. Such administration results in a controlled drug concentration.

Hyperlipidemia is a common chronic lipoidal disorder that is characterized by unbalanced lipoprotein levels. Hyperlipidemia is an excess of fatty substances called lipids, largely cholesterol and triglycerides, in the blood. It is also called hyperlipoproteinemia because these fatty substances travel in the blood attached to proteins. This is the only way that these fatty substances can remain dissolved while in circulation. Hyperlipidemia, in general, can be divided into two subcategories:

Hypercholesterolemia in which there is a high level of cholesterol
Hypertriglyceridemia in which there is a high level of triglycerides, the most common form of fat.

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) currently form the mainstay of lipid-regulating therapy, and are the most effective agents for reducing serum cholesterol concentrations and cardiovascular mortality **.**

Rosuvastatin calcium is a new and highly effective inhibitor of HMG-CoA reductase that has completed Phase-III clinical development for the treatment of patients with dyslipidaemia. In clinical trials, Rosuvastatin (1–80 mg) produced reductions in LDL-C, total cholesterol (TC), and triglycerides (TG), and increases in high density lipoprotein cholesterol (HDL-C).

The absolute bioavailability of Rosuvastatin calcium tablets administered a single dose after a meal was approximately 20% relative to intravenous infusion. The Formulation of sustained film coated Rosuvastatin calcium expected to reduce the frequent exposure of dose to upper GIT and thus facilitate in proper distribution to liver rather than skeletal muscles leading to improved patient compliance, maintain therapeutic action.

Stability studies of sustained release tablets were carried out by keeping the formulations at 40^0C /75% RH in stability chamber for three months. From the results obtained, it can be concluded that formulation in the form of tablet has achieved the objective of sustained drug release, patient compliance and cost effectiveness as a single daily dose of the drug.

REFERENCES

1. Abbaspour, M.R. Sadeghi, F. AfrasiabiGarekani, H., 2008.Design and study of ibuprofen disintegrating sustained-release tablets comprising coated pellets *.J .Pharm. Sci.* vol. 68, pp. 747–759.
2. Ahmed, A. G. and Tadros, M. 2010. Design and in vitro/in vivo evaluation of novel nicorandil extended release matrix tablets based on hydrophilic interpolymer complexes and a hydrophobic waxy polymer*, Int. J. of Pharm,* vol. 69, pp. 1019–1028.
3. Ashanmugarathinam1, d.vidhyeswari1 and a.puratchikody formulation, characterization and *in-vitro* evaluation of acrylic polymer loaded aceclofenac microspheres.
4. Barmpalexis, B. Kanaze, F. Kachrimanis, K.andGeorgarakis, E. 2010. Artificial neural networks in the optimization of a nimodipine controlled release tablet formulation. *European Journal of Pharmaceutics and Biopharmaceutics*, vol.74, pp. 316–323.
5. Brahmankar, D. M. and Jaiswal, S. B.,2009. *Biopharmaceutics and pharmacokinetics - A treatise* .second edition 2009, ISBN 978-81-85731-47-6, VPBN 32.
6. Brouillet, F. Bataille, B. Cartilier, L. 2008, High-amylose sodium carboxymethyl starch matrices for oral, sustained drug-release: Formulation aspects and *in vitro* drug-release evaluation. *Int.J.Pharm*. vol. 356.pp. 52–60
7. Cao, Q.R., Kim, T.B., and Lee, J.B., 2007, Photoimages and the release characteristics of lipophilic matrix tablets containing highly water-soluble potassium citrate with high drug loadings. *Int.J.Pharm.*vol 339,pp. 19–24.
8. Chansanroj, K., Petrovic, J., Ibric, s.,and Betz, G., 2011, Drug release control and system understanding of sucrose esters matrix tablets by artificial neural networks. *Euro.J.vol*36.pp.315-318.
9. Corti, G., Cirri, M., Maestrelli, F., Mennini, N.,and Mura, P., 2008, Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl-b-cyclodextrin.*pharm. tech.*vol. 68.pp. 303–309.
10. Corti, G., Cirri, M., Maestrelli, F.,andMennini, N.2008 Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl-b-cyclodextrin. *European Journal of Pharmaceutics and Biopharmaceutics.*vol. 68.pp.303–309
11. Fukuda, M., Peppas, N.A.,andMcGinity, J.W., 2006, Properties of sustained release hot-melt extruded tablets containing chitosan and xanthan gum. *Int. J.Pharm*.vol. 310.pp. 90–100.
12. Furlanetto, S., Cirri, M., Maestrelli, F., Corti,G.,and Mura, P. ,2006, Study of formulation variables influencing the drug release rate from matrix tablets by experimental design.*pharm. Tech*.vol. 62.pp. 77–84.
13. Fukuda, M., Peppas, N.A.,andMc, Ginity J.W., 2006, Floating hot-melt extruded tablets for gastroretentive controlled drug release system. *J.C.R.*vol. 115 ,pp. 121–129.
14. Gaikwad,D.,Limkar,A., Sangeeta,Bobe,K.,Patil,M.,Khade,T.,Gavitre,B., Kulkarni,V.,and Gaikwad,U.,2009, Formulation and Evaluation of Sustained Release Tablet of
15. Aceclofenac by Film Coating. *International Journal of Research in Pharmaceutical and Biomedical Sciences.* ISSN: 2229-3701.
16. Ghosh, S.,andBarik, BB.,2010 Formulation and *in Vitro* Evaluation of Once Daily Sustained Release Formulation of Aceclofenac**.** *Trop J Pharm Res,*vol. *9 (3).pp.* 265
17. Hayashi,T., Kanbe, H., Okadaa, M., Kawase, I ., Ikeda, Y. Y., Onuki, Y.,and Kaneko, T . Sonobe, T.,2007*In vitro* and *in vivo* sustained-release characteristics of theophylline matrix tablets and novel cluster tablets,*International Journal of Pharmaceutics*.vol. 341.pp. 105–113.
18. Takahashi,M. Onishi, H. Machida, Y.2004, Development of implant tablet for a week-long sustained release *Journal of Controlled Release* ,vol.100 , 63–74.

19. Tanaka, N. Imai, K. Okimoto, K. Ueda, S. Tokunaga, Y. Ohike, A. Ibuki,R, Higaki, K. and Kimura, T. 2005. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine. *J.C.R* ,vol.108, pp.386–.39
20. Masaki, A., Sayaka ,K.,Yuichi, O., and Yukiharu, N., 2004. Development and evaluation of a novel dry-coated tablet technology for pellets as a substitute for the conventional encapsulation technology. *International Journal of Pharmaceutics* ,Vol. 336, Issue 1, pp. 99–107
21. Toyohiro, S., Hiromu, K., Hiroshi, N., Kazuhiro, S., and Masahiro, H., 2004 .Time-release compression-coated core tablet containing nifedipine for chronopharmacotherapy. *International Journal of Pharmaceutics* Vol.280, Issues 1–2, pp. 103–111.
22. Takeshi, G., Norifumi, T.,Takaaki, Y., Shuji, S., and Kobayashi, A., 2004.Pharmaceutical design of a novel colon-targeted delivery system using two-layer-coatedtablets of three different pharmaceutical formulations, supported by clinical evidence in humans. *Journal of Controlled Release* ,Vol 97, Issue 1, pp. 31–42.
23. Holte, K., Onsøyen, E., Myrvold.,and R. Karlsen,j. 2003, Sustained release of water-soluble drug from directly compressed alginate tablets, *E. J of Pharmaceutical Sciences.*vol. 20, pp.403–407.
24. JeongH,S.,and Park, K., 2008, Development of sustained release fast-disintegrating tablets using various polymer-coated ion-exchange resin complexes. *Int.J.Phar..*vol. 353.pp. 195–204.
25. Jiménez-Martínez, I., Quirino-Barred, T.,andVillafuerte-Robles, L.,2008 Sustained delivery of captopril from floating matrix tablets. *International Journal of Pharmaceutics* .vol.362.pp. 37–43.
26. Kannan,S., Manivannan, R., KugalurGanesan, K., KakkatummalNishad,P., and Senthil Kumar,N.2010. Formulation and Evaluation of Sustained Release Tablets of Aceclofenac using Hydrophilic Matrix System. *International Journal of PharmTech Research CODEN (USA)*: IJPRIF ISSN : 0974-4304 .Vol.2, No.3. pp. 1775-1780.
27. Kohari. N., yatabe. H., Eseki. K., and Miyajaki, K., 1991. a new type of a pH independent controlled release tablet , *Int.J.Phar.*vol. 68.pp.255-264
28. Kikuchi, S., and Takayama, K., 2011, Multivariate statistical approach to optimizing sustained-release tablet formulations containing diltiazem hydrochloride as a model highly water-soluble drug. *Int.J.Phar*.vol. 386pp. 149–155.