IJBPAS, June, 2022, 11(6): 2652-2573

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

DEVELOPMENT OF SPRAY-DRIED MUCOADESIVE VALSARTAN NASAL MICROPARTICLES: FORMULATION, OPTIMIZATION AND EVALUATION

TUFAIL DANA[1*], SUFIYAN AHMAD[2], MD. RAGEEB[3] AND SHAIKH TANVIR[4]

1: Department of Quality Assurance, SVS Institute of Pharmacy, Mungase Malegaon, Dist. Nashik (M.S.), India

2: Department of Pharmacognosy, Gangamai College of Pharmacy, Nagaon, Dist. Dhule (M.S.), India

3: Department of Pharmcognosy, Smt. S. S. Patil College of Pharmacy, Chopda, Maharahtra, India

4: Department of Pharmaceutics, Smt. S. S. Patil College of Pharmacy, Chopda, Maharahtra, India

[*]**Corresponding Author: Dr. Tufail Dana: rageebshaikh@gmail.com**

Received 18th June 2021; Revised 19th Aug. 2021; Accepted 11th Sept. 2021; Available online 1st June 2022

https://doi.org/10.31032/IJBPAS/2022/11.6.6132

ABSTRACT

The purpose of this research was to formulate, characterize, the Valsartan Nasal Microparticles encapsulated in dried *Lipidium sativum* mucilage based spray dried mucoadhesive microspheres for treating hypertension. Factorial design has been employed for the assessment of influence of three independent variables, inlet temperature, feed flow rate and drug–polymer ratio on production yield, particle size, and in vitro drug diffusion. Microparticles were evaluated for particle size, entrapment efficiency, swelling property, in vitro mucoadhesion, in vitro drug diffusion and stability studies. The result of differential scanning thermogram of Valsartan microparticles showed the peak at 109.76 °C and polymer at 263.47 °C. This DSC study further confirmed that there was no drug-polymer interaction in microparticles. X-ray diffraction The diffractogram of isolated polymer showed the characteristic sharp peak at 9.2°, 12.5°, 17° and 27.6° due to presence of particles in geometrical shape and it indicated the polymer is crystalline in nature. From the SEM photographs, it was observed that microparticles were found to be 5 µm in size and spherical in shape having smooth surface morphology. FT-IR analysis of optimized

formulation showed that the polymer and process parameters do not alter the performance characteristic of drug, thus revealing stability of the finalized formulation. The best fit model for the drug release was found to be Zero Order Model as indicated by higher R^2 value. This proved that the formulated microparticles showed sustained release. The mechanism for drug release was followed Korsmeyer-peppas model as indicated by higher R^2 value. It predicts that the drug release is polymer concentration dependent which follows zero order model and polymer having swelling and eroding properties which follows Korsmeyer-peppas model.

Keywords: Valsartan Nasal Microparticles, differential scanning thermogram, SEM, FT-IR analysis

INTRODUCTION

Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. Conventionally, the nasal route of delivery has been used for delivery of drugs for treatment of local diseases such as nasal allergy, nasal congestion and nasal infections. Recent years have shown that the nasal route can be exploited for the systemic delivery of drugs such as small molecular weight polar drugs, peptides and proteins that are not easily administered via other routes than by injection or where a rapid onset of action is required **[1]**. Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents . In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. The nose offers easy access to a large mucosal surface well suited for drug and vaccine delivery. However, factors related to the nasal anatomy, physiology and aerodynamics that can severely limit this potential, have historically been challenging to address. It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability **[2]**. Nasal drug delivery system provides excess of easy application of drug, with the possibility of self administration by removing the chance of unwanted painful condition associated with injection form of drug delivery. Fast absorption can be achieved due to large absorption surface area and high vascularisation. Nasal route can be used as an alternative to parenteral in case of emergency therapy. Nasal drug delivery system is a

potential route for direct delivery of drug to the central nervous system through olfactory region by bypassing hepatic first pass metabolism **[3]**. Nasal drug delivery is a useful delivery method for drugs that are active in low doses and show minimal or no oral bioavailability. The nasal route circumvents hepatic first pass elimination associated with the oral delivery; it is easily accessible and suitable for self-medication. Currently, two classes of nasally delivered therapeutic agents are on the market. The first one comprises low molecular weight and hydrophobic drugs for the treatment of the nasal mucosa and sinus, including decongestants, topical steroids, antibiotics and other (OTC) products. The second class encompasses a few drugs, which have sufficient nasal absorption for displaying systemic effects. Important candidates are the compounds, generally administered by injection and hardly absorbed after oral administration, due to their instability in the gastrointestinal tract, poor absorption properties, and their rapid and extensive biotransformation **[4]**.

Microparticles are particulate dispersed and or firm particles having diameter 01-1000 μm. The drug is embedded or covered in polymer or dissolved in polymer. The microspheres or microcapsules can be obtained it is depends on the method of preparation, In Microcapsules active constituent is restricted to a hollow cover of polymeric material. In microspheres drug is equally distributed. The procedure of preparation allows managing microparticles diameter. It is important for various applications **[5]**.

Valsartan is a medicine widely used to treat high blood pressure heart failure. It's also sometimes prescribed after a heart attack. Valsartan lowers your blood pressure and makes it easier for your heart to pump blood around your body. Valsartan, a non peptide, angiotensin II receptor antagonist acting specifically on AT receptor subtype, is a drug of choice in cardiovascular disorders, particularly in hyper-tension. Its mean plasma half-life is 7.5h. The bioavailability of Valsartan after oral administration is approximately 23%. Peak plasma concentration of Valsartan occurs 2-4 hrs. after oral administration. Slow absorption of drug is attributed to the presence of food, which results in the slow onset of actio n.

Drugs that are easily absorbed from the stomach and have a short half-life are eliminated quickly from the blood circulation, require frequent dosing. To avoid this problem, the nasal microparticles have

been developed in an attempt to release the drug in sustained release manner.

The goal of designing sustained release delivery system of Valsartan is to reduce frequency of dosing thereby minimizing the occurrence of side effects and to increase the effectiveness of the drug. Hence, in the present study, attempt was made to establish an optimum method and polymer system of sustained release nasal micro particles for Valsartan.

MATERIALS AND METHOD

Valsartan was obtained as a gift sample from Unichem labs, Mumbai, Isolation of Natural Polymer: The collected Lipidium sativum was authenticated from the Botanical Survey of India, WRC, Pune, Maharashtra, India. and the plant was identified as *Lipidium sativum*. The registration no. of *Lipidium Sativum* plant is BSI/WRC/IDEN.CER./2016/796.

The mucilage of plant of family of *Cruciferae* was collected from seeds. Seed was procured form local market in the form of very small brown seeds. Seeds of *Lepidium sativum* contain mucilage around the outer layer. The major problem in isolation of mucilage is that it swells but does not separate easily from the seeds. There for effective method was developed by soaking the seeds of with 10 times its weight of distilled water and kept for 24 hr. The viscous solution was sucked by syringe with the continuous homogenizing with the help of homogenizer. The mucilage was precipitated out by addition acetone in the ratio of 1:1 by continuous stirring. The coagulated mass was dried in oven at 40 – 45 °C, powdered by passing through sieve and stored in airtight container.

Characterization of Mucilage: Characterization was performed by determining solubility, melting point, pH, loss on drying, total Ash, test for carbohydrates, test for Mucilage **[6]**.

Swelling index: Mucilage content of the polymer was determined by the swelling index; hence it is useful in the evaluation of mucilage containing natural polymers. Polymer swelling capacity was determined by mixing the Polymer (1gm) with distilled water (25 ml) in a 50 ml of stoppered cylinder, and left for swelling for 23 hours, and the volume of the swollen layer was determined **[7]**.

Solubility Study of Valsartan: Accurately weighed 10 mg of Valsartan was taken in 10 ml of distilled water, methanol and phosphate buffer (pH 6.8) in 100 ml volumetric flasks and placed for 15 min. at 37 °C in sonicater. Alter 15 min., samples were filtered through Whatman filter paper No.42; aliquots were

suitably observed as clear solution and diluted for estimation by UV-Visible spectrophotometer at 250 nm **[8]**.

Drug-polymer compatibility study by FT-IR spectrophotometer: This was carried out to find out the compatibility between the drug Valsartan and the polymer *Lipidium sativum*. About 1 mg of drug and 100 mg of KBr were taken in a mortar and triturated. A small amount of the triturated sample was taken into the sample holder and scanned from 4000 cm^{-1} to 400 cm^{-1}at resolution of 4 $cm^{-1}$and 15 scans per spectrum. Samples were prepared for Valsartan, polymer *Lipidium sativum* and physical mixture of drug and polymer. The spectrums obtained are compared and interpreted for the functional group peaks **[9]**.

2.5 Preparation of spray dried microparticles of Valsartan

Three level full factorial design: The three level designs are written as 3^k factorial design. It means that 'k' factor are considered, each at 3 levels. These are usually referred to as low, medium and high levels. These levels are numerically expressed as -1, 0 and +1. A study in which there are two factors with three levels is 3^2 factorial design. This factorial design was employed for optimization of Sustained release microparticles to identify the critical factors that affect the process or product. The design was used primarily for screening significant factors, and also used sequentially to model and refine a process. A 3^2 factorial design was constructed where the concentration of Isolated polymer (X1), Temperature (X2) were selected as the independent variables. The level of these factors was selected on the basis of initial studies and observation. The dependent variables of percent drug release and entrapment efficiency were selected on the basis of preliminary studies. All other formulation and processing were kept constant throughout the study.

Full Factorial Experimental Design Layout

Variables for experimental design: Independent variable: X1 = Polymer in mg, X2 = Temperature in °C, Dependent variable: Y1 = % Entrapment efficiency, Y2 = % Drug Release.

Table 1: Coded Level Translated in Actual Units

Coded Level	Actual value	
	X1 (Drug)	X2 (Temperature)
-1	80 mg	110-50 °C
0	240 mg	120-60 °C
+1	400 mg	130-70 °C

Table 2: Formulation Table as per the Design expert Software

Sr. No.	Formulation Code	Drug Valsartan (mg)	Polymer (mg)	Inlet Temp °C	Outlet Temp °C
1	B1	80	80	130	70
2	B2	80	400	130	70
3	B3	80	80	120	60
4	B4	80	400	110	50
5	B5	80	240	110	50
6	B6	80	80	110	50
7	B7	80	240	130	70
8	B8	80	400	120	60
9	B9	80	240	120	60

The obtained results were analyzed by Design Expert Software 7.0. The results for data optimization of experimental matrix are shown in result and discussion. All the formulations were prepared as per the procedure and evaluated for various parameters given below in evaluation part **[10]**.

Evaluation parameters of Valsartan microparticles

Determination of percentage yield

The percentage yield was determined as the weight percentage of final product after drying, with respect to the initial total amount of drug polymer and other materials used for preparation of microparticles **[11]**.

$$Percentage\ Yield = \frac{actual\ yield}{theoratical\ yield} * 100$$

Drug content and drug entrapment efficiency study

For determination of drug entrapment efficiency, known amount of microparticles were added to 100 ml of phosphate buffer (pH 6.8). The resulting mixture was kept in sonicater for 30 min and then kept constant stirring overnight by using mechanical stirrer at 100 rpm. The solution was filtered using Whatman filter paper and 1 ml of this solution was appropriately diluted to 10 ml using phosphate buffer (pH 6.8) and analyzed by UV—Visible spectrophotometer. The drug entrapment efficiency was calculated using the following formula **[12]**.

$$EntrapmentEfficiency(\%) = \frac{Actualamountofdruginmicrospheres(mg)}{Druginmicrospheres(mg)} * 100$$

In-vitro drug release studies

The *in-vitro* dissolution study was performed on Electrolab TDT 06-P according to parameters

Dissolution test apparatus: USP (Type I), speed: 50RPM, volume of dissolution medium: 900 ml, dissolution Medium used: HCl 0.1 N for first 2 hrs, Phosphate buffer pH 6.8, temperature : 37 ± 0.5 ^{0}C. Aliquot (5mL) of the solution was withdrawn at regular interval of one hr. and same volume

of fresh dissolution medium was replaced to maintained volume constant.

Model Dependent Approach: In model dependent approach, analyze the mechanism of release and the release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model.

Particle size analysis: Particle size analysis was performed using a Malvern Mastersizer, Operating with mastersizer V 3.0 software **[13]**.

In-vitro mucoadhesion: The mucoadhesive property o f the Valsartan microspheres was evaluated by an in-vitro adhesion testing method known as the wash – off method. Freshly excised pieces of intestinal mucosa (4×5 cm) from sheep were mounted onto glass slides (3×1 inch) with poly cyanoacrylate glue. Two glass slides were connected with a suitable each wet rinsed tissue specimen, and immediately thereafter the support were hung onto the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given a slow, regular up and down movement in the test fluid (400mL) at 37ºC contained in a 1000 mL vessel of the machine. At the end of one hr and at hourly interval up to 8 hr, the machine was stopped and the number of microsphere still adhering to the tissue was counted. The test was performed in stomach (pH 1.2) **[14]**.

Scanning electron microscopy: The SEM was carried out to characterize the surface morphology of microparticles and this was done by using Scanning electron microscope at 20 kV at SAIF STIC, Cochin.

FTIR studies on drug loaded microparticles: The drug loaded microparticles were subjected to FTIR studies to find out the possible interactions between the drug and polymer during the time of preparation. Samples were prepared in KBr disks (1 mg sample in 100 mg KBr). The spectrums were recorded for the drug loaded microparticles using FT-IR spectroscopy.

Differential scanning colorimetry: DSC analysis was performed using a Mettler Toledo DSC, Operating with version 5.1 of star evaluation software. The samples (3-5 mg) were encapsulated in aluminium pan **[9]**.

RESULT AND DISCUSSION

Isolation: The percentage yield of mucilage was found higher with acetone, Hence the acetone was selected as precipitating agent. The percentage yield of mucilage was found to be 14.75 %.

Characterization of Mucilage

Description: The morphological and physical evaluatory study of isolated mucilage shows,

it was pale yellow to brownish in color, with characteristic odor. It was soluble in warm water, practically insoluble in ethanol, acetone, ether and chloroform. The melting range was found to be 210 °C to 220 °C. The loss on drying was found to be 17.5% and it indicated that the some amount of moisture was present in the mucilage which may interfere with other material.

The swelling index of mucilage was determined in measuring cylinder. It was found to be 18 %. There was a significant change in swelling after 24 which indicated that the mucilage had good swelling properties. The physicochemical properties of isolated mucilage are summarized in **(Table 3)**.

Solubility Study of Valsartan: Valsartan was found freely soluble in methanol and slightly soluble in water and Phosphate buffer pH 6.6 and phosphate buffer pH 6.8 which compiles with solubility reported in Merck index.

Drug-polymer compatibility study by FT-IR spectrophotometer: FT-IR spectroscopy study was carried out separately to check the compatibility of the drug and polymer used for the preparation of microparticles. FT-IR was performed for the drug, polymer and physical mixture of drug and polymer. The spectrum obtained from FT-IR spectroscopy studies at wavelength from 4000 cm^{-1} to 400 cm^{-1} are shown in **Figure 1** and the characteristic peaks obtained are shown in **Table 4**. Drug polymer interaction were studied using FT-IR analysis and showed that there was no change in the IR spectra of pure drug Valsartan in the presence of *Lipidium sativum*. Which showed that the polymer do not alter the performance characteristic of drug, thus revealing compatibility of the selected drug with polymer. The major peaks are identical to functional groups which were listed in **(Table 4)**.

Preparation of spray dried microparticles of Valsartan

Preparation of drug-polymer solution: As *Lipidium sativum* formed a viscous solution, so for the preparation of microparticles the drug-polymer solution was prepared with the continuous stirring with variations in the rpm by using mechanical stirrer. After that 200-300 rpm was found as optimized condition.

Spray drying of drug-polymer solution

Optimization by using design expert software: The aim of the present work was to achieve optimized formulations determining the effects of some important factors and their interaction during the process preparation on microparticles physicochemical properties. Meanwhile the microparticles were being processed; the

impact of different factors had been evaluated by making changes in their quantity. Finally, two of the most significant factors had been chosen as the independent variables. In the next step, for determining the low, medium and high levels of each factor, some formulations were made, and the results are listed in **(Table 7)**. According to 3^2 factorial design, an experimental matrix was performed in which 9 experiments were performed given in **(Table 7)**.

Evaluation parameters of Valsartan microparticles

Flow property: The flow properties of all the formulations were determined by the angle of repose, bulk density, tapped density, Carr's index and Hauser's ratio values. The results are shown in **(Table 6)**. The angle of repose of all batches were found to be in the range of 22.08° to 25.19°, and Carr's index were found to be in the range of 14.33 % to 23.77%. It can be concluded that the dried mucilage has a good flow properties.

Determination of percentage yield: The percentage yield of Valsartan microparticles was found to be in the range of 46.62 to 74.06 and shown in **(Table 7)**.

Drug content and drug entrapment efficiency study

The drug content of Valsartan microparticles were found to be in the range of 40.12 % to 87.37 % and drug entrapment efficiency of Valsartan microparticles with *Lipidium sativum* was found to be in the range 24.10 % to 94.66%. The drug entrapment efficiency of the formulations was depending upon the concentration of polymer and temperature of spray drying. As the concentration of polymer and temperature varies the entrapment efficiency also varies. The entrapment efficiency increases with decrease in temperature and middle range of polymer. The increasing in temperature and decreasing in entrapment efficiency might be because of melting of drug on highest temperatures. The highest entrapment efficiency was observed for the batch of B9 that is 94.66.

In-vitro drug release studies: The *in-vitro* drug release of Valsartan microparticles was carried out by dissolution apparatus in 0.1N HCl for 2 hr and then in phosphate buffer 6.8 at 37°C ± 0.5°C was withdrawn at different time interval of 1 hr and same was replaced with equal volume of fresh medium. The mean percent cumulative drug release from microparticles was given in **Table 7**.

The release kinetics of the different formulations was shown in **Table 8**, the best fit model for the drug release was found to be Zero Order Model as indicated by higher R^2 value. This proved that the formulated

microparticles showed sustained release. The mechanism for drug release was followed Korsmeyer-peppas model as indicated by higher R^2 value.

It predicts that the drug release is polymer concentration dependent which follows zero order model and polymer having swelling and eroding properties which follows Korsmeyer-peppas model.

Experimental design and data analysis

Experimental Design of the Optimization step for Formulations

Percentage Entrapment Efficiency: Analysis of variance for experimental matrix (ANOVA)

The data were analyzed by ANOVA Test. A value of $p< 0.05$ was considered as significant. The obtained results were entered in design expert 7.0 software and a model equation was obtained to get the fit result for % Entrapment Efficiency. ANOVA result of the experimental model for percent entrapment efficiency was summarized in **(Table 11)**.

The Model F-value of 9.44 implies the model is significant. There is only a 2.58% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Effect of Polymer (One Factor)

As the concentration of polymer increases % Entrapment Efficiency also increases at their prediction points respectively.

As the temperature increases % Entrapment Efficiency also increases at their prediction points respectively upto 120 °C. The plot indicated that the temperature at medium level (120 °C) shows significant impact on percentage entrapment efficiency.

The interaction of polymer and temperature is showed in **(Figure 5)**. Factor A and B had their individual significant effects. The plot indicated as the concentration of polymer and temperature increases the entrapment efficiency also increases. As the concentration of polymer increases % Entrapment Efficiency also increases at their prediction points respectively.

Percentage Drug Release

Analysis of variance for experimental matrix (ANOVA): The data were analyzed by ANOVA Test. A value of $p< 0.05$ was considered as significant. The obtained results were entered in design expert 7.0 software and a model equation was obtained to get the fit result for % drug release.

Analysis of Variance

ANOVA result of the experimental model for percent entrapment efficiency are summarized in **Table 13**.

The Model F-value of 61.12 implies the model is significant. There is only a 0.08% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant. In this case A are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Effect of Polymer (One Factor)

As the concentration of polymer decreases % Drug release gets increases at their prediction points respectively. The plot indicated that the polymer at medium level (240 mg) showed significant impact on percentage drug release**.**

As the temperature increases, the drug release also increases at their prediction point and decreases afterwards.

The interaction of polymer and temperature is showed in **(Figure 8)**. Factor A and B had their individual significant effects. The plot indicated that polymer and temperature at medium level shows significant impact on percentage drug release**.**

Evaluation parameters of optimized Valsartan microparticles

Optimized batch was successfully evaluated and results were shown in **(Table 14)**.

The *in-vitro* Dissolution Studies of Optimized microparticles

Values of R^2 Kinetic Models for Optimized microparticles:

Scanning electron microscopy (SEM): The surface morphology of the prepared microparticles was characterized by SEM study. The morphological image is shown in **(Figure 7)**.

From the SEM photographs, it was observed that microparticles were found to be 5 μm in size and spherical in shape having smooth surface morphology.

FT-IR studies on drug loaded microparticles

This was carried out to find the possible interaction between the drug and polymers during the time of formulation of microparticles. The spectra of pure drug and drug loaded microparticles obtained from FT-IR spectroscopy studies at wavelength between 4000 cm^{-1} to 400 cm^{-1} are given in **(Figure 8)** and characteristic peaks obtained is given in **(Table 17)**.

FT-IR analysis of optimized formulation showed that there was no change in the IR spectra of pure drug Valsartan during spray drying process of formulation which shows that the polymer and process parameters do not alter the performance characteristic of drug, thus revealing stability of the finalized formulation.

In-vitro mucoadhesion: Microparticles with *Lipidium sativum* mucilage exhibit good mucoadhesion property in the *In-vitro* wash off test and the *In-vitro* mucoadhesion of optimized batch was found to be 99.84 ±1.39 % at 8 hr.

Differential scanning calorimetry (DSC)

This was carried out to find out the possible interaction between the drug and polymer. The thermograms obtained from differential scanning colorimeter. DSC thermogram of drug shows a peak at 117 °C **(Figure 9)** and polymer *Lipidium sativum* at 263.47 °C **(Figure 10)**. The thermogram of Valsartan microparticles showed the peak at 109.76 °C and polymer at 263.47 °C **(Figure 11)**. This DSC study further confirmed that there was no drug-polymer interaction in microparticles.

Table 3: Physicochemical properties of mucilage

Sr. No.	Test	Observation
1.	Total Ash %	0.066 ±0.009
2.	Test for Carbohydrates	+ ve
3.	Test for Mucilage	+ ve
4.	Angle of repose	20.4±0.003
5.	Bulk density	0.579±0.04
6.	Tapped density	0.609±0.001
7.	Compressibility Index	0.04±0.01
8.	Hausner's ratio	1.05±0.011

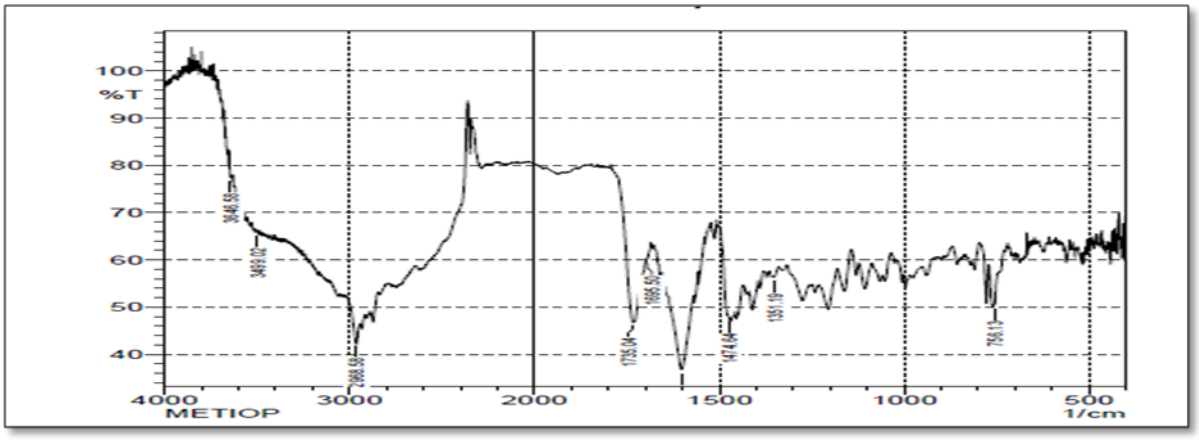


Figure 1: FT-IR spectrum of physical mixture of Valsartan and *Lipidium sativum* polymer

Table 4: IR interpretation of Physical mixture of drug and polymer

Sr. No.	IR peak cm-1	Groups
1.	756	C-H
2.	1351	C-N
3.	1477	C=C
4.	1601	C=O
5.	1695	C=N
6.	1735	C=O
7.	2968	C-H
8.	3499	N-H
9.	3646	O-H

Table 5: Formulation of batches of microparticles

Sr. No.	Drug : Polymer	Solvents	Observation
1.	1:1	Acetone	Formation of coagulation
2.	1:1	Acetone + Water	Phase Separation
3.	1:1	Water	Dried powder
4.	1:3	Acetone	Formation of coagulation
5.	1:3	Acetone + Water	Phase Separation
6.	1:3	Water	Dried powder
7.	1:1	Methanol 60% + Water 40%	Due to precipitation tube blocks
8.	1:1	IPA	Mass formation
9.	1:1	IPA 50% + water 50%	Due to precipitation tube blocks

Table 6: Flow properties of preformulation batches

Batches	Bulk density (gm/mL)*	Tapped density (gm/mL)*	Angle of repose (˚)*	Carr's Index (%)*	Hausner's ratio*
B1	0.481±0.88	0.631±0.80	23.02±1.3	23.77±0.46	1.31±0.90
B2	0.512±0.86	0.612±1.1	22.08±1.2	16.33±0.43	1.19±0.43
B3	0.508±0.89	0.632±1.2	24.09±0.76	19.62±0.69	1.24±0.82
B4	0.514±1.2	0.622±0.67	23.17±0.55	17.36±0.78	1.21±0.88
B5	0.523±0.25	0.634±0.55	25.19±0.38	17.50±0.64	1.21±0.97
B6	0.496±0.28	0.628±1.4	23.44±0.92	21.01±0.89	1.26±1.2
B7	0.526±0.56	0.614±.85	23.14±1.5	14.33±0.76	1.16±1.6
B8	0.52±0.35	0.634±0.77	24.15±1.3	17.98±0.88	1.21±0.98
B9	0.511±0.41	0.62±0.98	22.30±1.0	17.58±1.13	1.21±0.65

(* n=3 ± SD)

Table 7: Percentage yield, drug content, entrapment efficiency and release for all batches

Sr. No.	Experimental Runs	% Yield	Drug content %	% EE	% Release
1.	B1	46.62 ±0.23	40.12 ±0.62	28.39±0.065	83.31 ±0.19
2.	B2	58.95 ±0.62	44.60 ±1.46	24.10±0.087	45.05±0.215
3.	B3	61.87 ±0.19	75.49 ±1.56	86.60±0.260	79.44±0.416
4.	B4	65.62 ±1.58	61.95 ±1.38	68.93±0.070	41.30±0.255
5.	B5	66.56 ±0.45	57.55 ±2.49	80.57±0.101	49.02±0.771
6.	B6	59.87 ±1.11	65.66 ±0.26	75.98±0.045	74.02±0.033
7.	B7	46.56 ±0.36	49.89 ±0.72	21.24±0.061	50.26±0.963
8.	B8	72.5 ±0.44	81.56 ±1.86	90.48±0.292	38.75±0.271
9.	B9	74.06 ±0.72	87.37 ±0.29	94.66±0.091	52.92±0.098

(* n=3 ± SD)

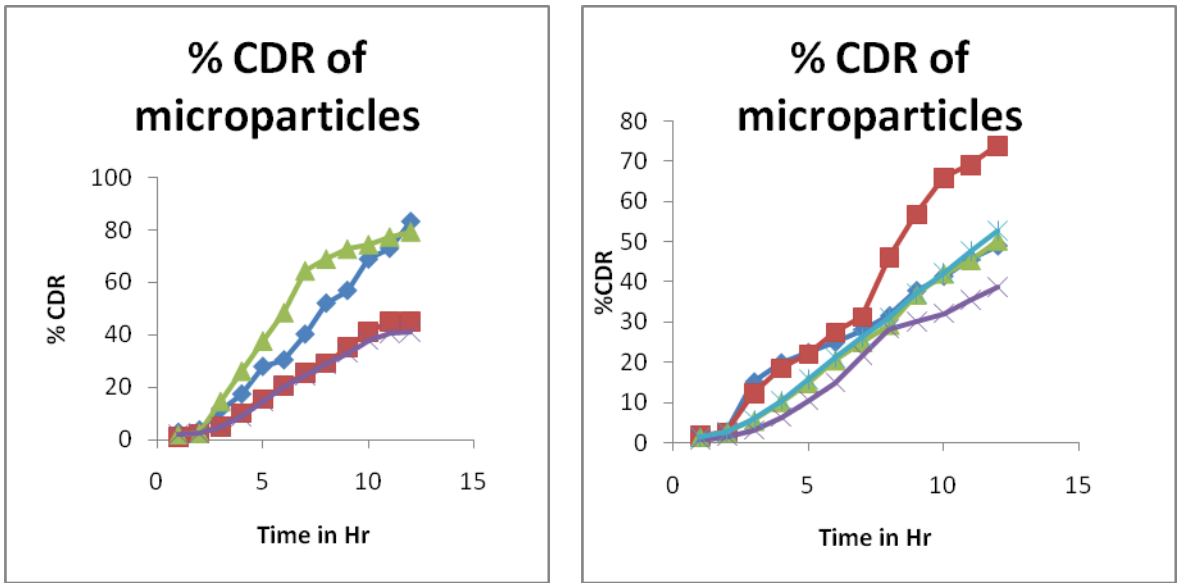


Figure 2: *In-vitro* release profile of drug in phosphate buffer 6.8 (B1 to B9)

Table 8: The values of R2 kinetics models for formulation batches (B1-B9)

Runs	Zero order	First order	Higuchi	Korsmeyer-peppas	Hixon
B1	0.989	0.876	0.943	0.974	0.953
B2	0.988	0.865	0.953	0.987	0.942
B3	0.937	0.741	0.960	0.924	0.829
B4	0.986	0.864	0.958	0.986	0.935
B5	0.976	0.718	0.977	0.918	0.83
B6	0.989	0.876	0.943	0.974	0.907
B7	0.99	0.886	0.941	0.990	0.960
B8	0.976	0.885	0.943	0.986	0.942
B9	0.992	0.885	0.943	0.990	0.960

(* n=3 ± SD)

Table 9: Response of all formulated batches with respect to different factors considered

Runs	Factors		Response 1	Response 2
	X1(mg)	X2(°C)	% Release	% EE
B1	80	130	83.31 ±0.19	28.39 ±0.065
B2	400	130	45.05 ±0.215	24.10 ±0.087
B3	80	120	79.44 ±0.416	86.60 ±0.260
B4	400	110	41.30 ±0.255	68.93 ±0.070
B5	240	110	49.02 ±0.771	80.57 ±0.101
B6	80	110	74.02 ±0.033	75.98 ±0.045
B7	240	130	50.26 ±0.963	21.24 ±0.061
B8	400	120	38.75 ±0.271	90.48 ±0.292
B9	240	120	52.92 ±0.098	94.66 ±0.091

(* n=3 ± SD)

Table 10: F-value Table for percent entrapment efficiency of all formulation batches

Source	Sum of Square	Df	Mean square	F Value	p-value Prob>F
Significant	**700.87**	**4**	**175.22**	**9.44**	**0.0258**
A- Polymer	**141.81**	**2**	**70.90**	**3.82**	**0.1182**
B-Temperature	**559.07**	**2**	**279.53**	**15.05**	**0.0138**
Residual	**74.28**	**4**	**18.57**	**-**	**-**
Cor Total	**775.16**	**8**	**-**	**-**	**-**

Table 11: ANOVA values

Std. Dev.	**4.31**	**R-Squared**	**0.9042**
Mean	**61.40**	**Adj R-Squared**	**0.8083**
C.V.%	**7.02**	**Pred R-Squared**	**0.5149**
PRESS	**376.06**	**Adeq Precision**	**8.822**

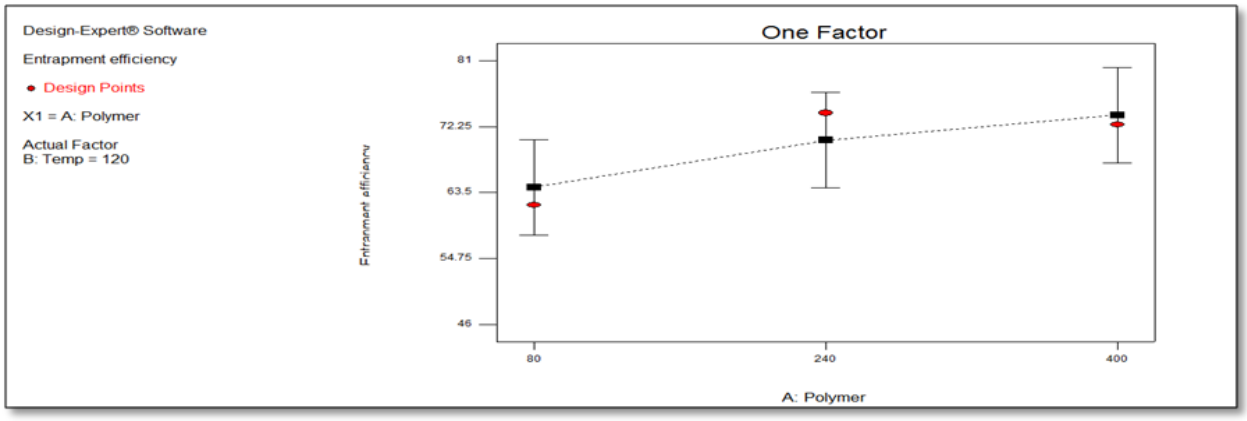
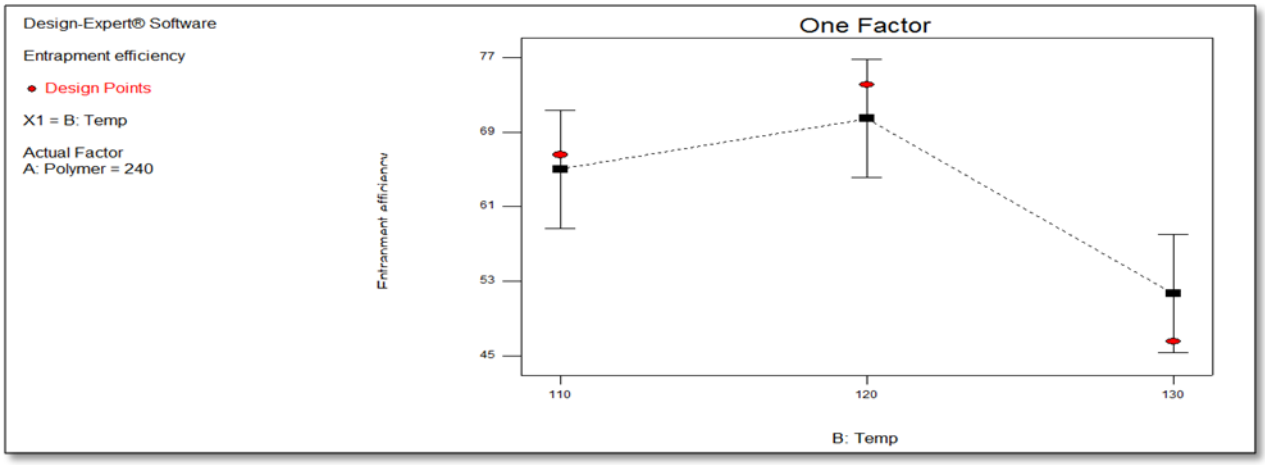


Figure 3: Effect of polymer concentration on entrapment efficiencies



Fiure 4: Effect of temperature on entrapment efficiency

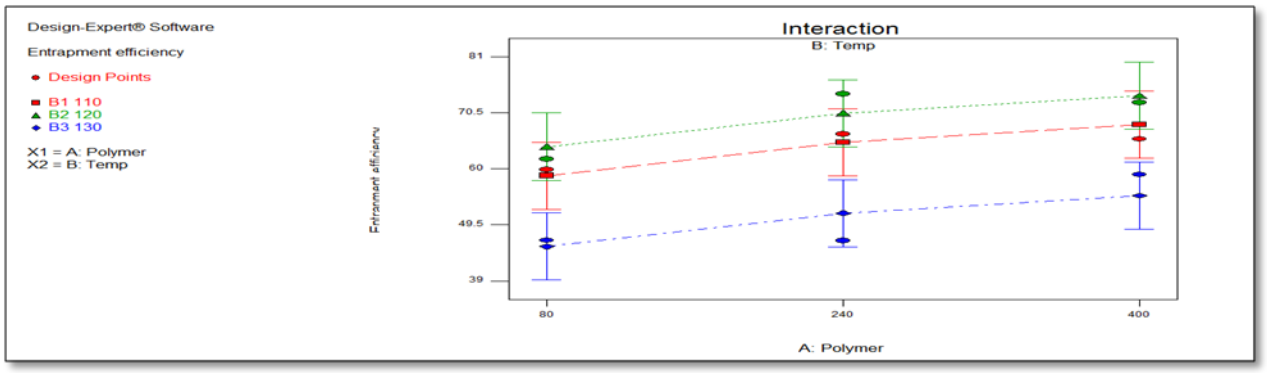


Figure 5: Interaction plot of Polymer and Temperature

Table 12: F-value Table for percent drug release of all formulation batches

Source	Sum of Square	Df	Mean square	F Value	p-value Prob>F
Significant	2295.5	4	573.97	61.12	0.0008
A- Polymer	2261.85	2	1130.93	120.43	0.0003
B-Temperature	34.02	2	17.01	1.81	0.2754
Residual	37.56	4	9.39	-	-
Cor Total	2333.43	8	-	-	-

Table 13: ANOVA result

Std. Dev.	3.06	R-Squared	0.9839
Mean	57.12	Adj R-Squared	0.9678
C.V.%	5.36	Pred R-Squared	0.9185
PRESS	190.16	Adeq Precision	18.381

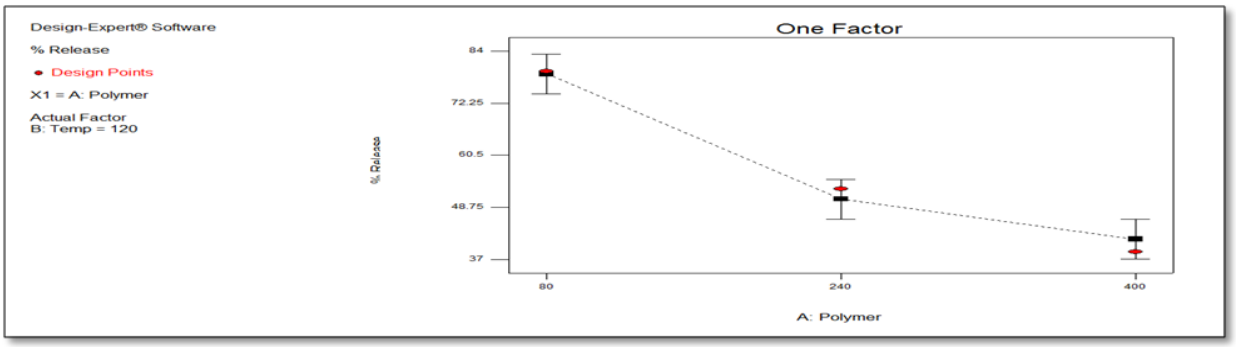


Figure 6: Effect of polymer concentration on drug release

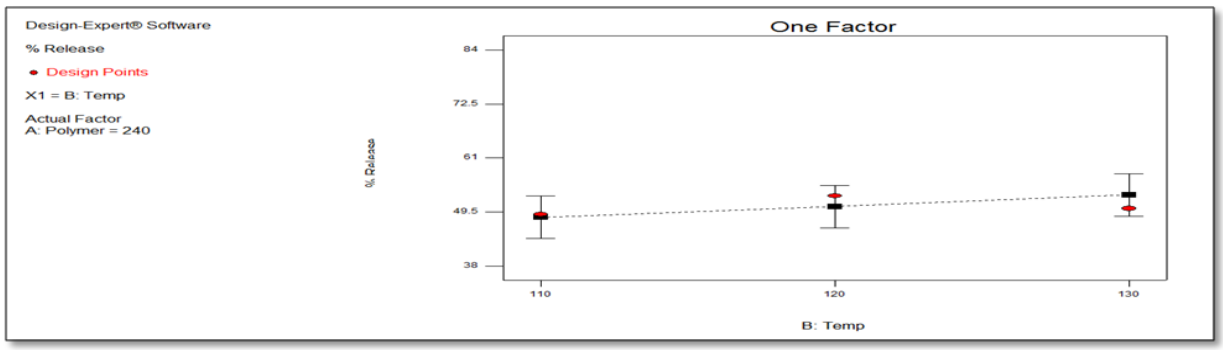


Figure 7: Effect of temperature on drug release

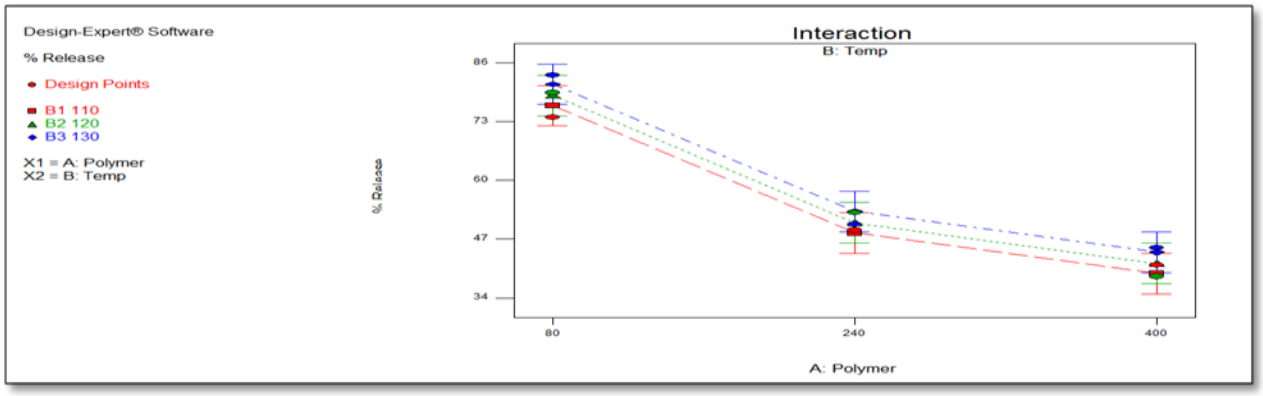


Figure 8: Interaction plot of polymer and temperature with respect to drug release

Table 14: Flow properties and percent yield of optimized batch

Sr. No.	Parameters	Results
1	Percentage yield (%)	72.96 ±0.913
2	Mean particle size	D 10= 13 micron
		D 50= 20 micron
		D 90= 27 micron
3	Bulk density(gm/mL)*	0.418 ±0.108
4	Tapped density (gm/mL)*	0.379 ±1.003
5	Angle of repose (°)*	21.00 ±0.009
6	Carr's Index (%)*	23.97 ±0.19
7	Hausner's ratio*	1.13 ±0.070

(* n=3 ± SD)

Table 15: Percent cumulative drug release for optimized batch

Time (Hr)	% CDR
1	1.37 ±0.098
2	2.59 ±0.78
3	5.49 ±0.094
4	10.23 ±0.009
5	16.00 ±0.569
6	20.83 ±0.079
7	26.27 ±0.113
8	30.50 ±0.876
9	36.83 ±0.791
10	42.65 ±0.375
11	48.24 ±0.159
12	51.82 ±0.959

(* n=3 ± SD)

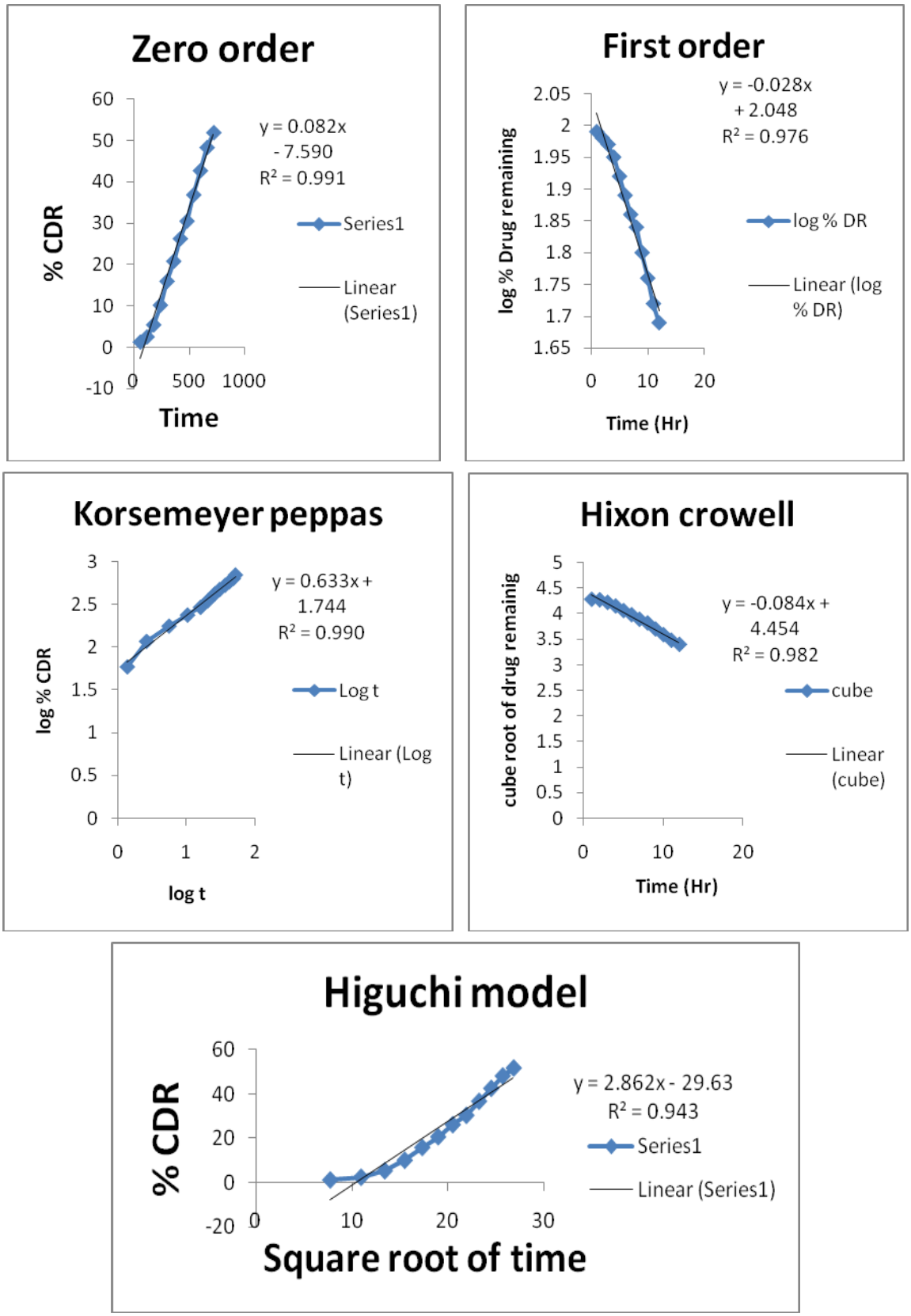


Figure 6: Zero order, First order kinetics, koresemeyer peppas, Hixon Crowell model, Higuchi model for optimized batch

Table 16: R^2 of all kinetics models for optimized batch

Batch	Zero order	First order	Korsmeyer Peppas	Higuchi	Hixon- Crowel
Optimized	0.991±0..19	0.976 ±1.27	0.990±0.597	0.982 ±0.02	0.943 ±0.94

(* n=3 ± SD)

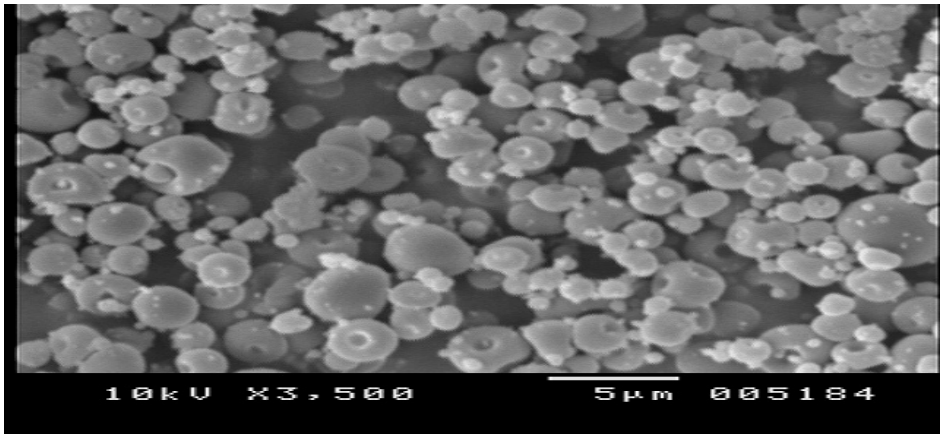


Figure 7: SEM of microparticles (optimized batch)

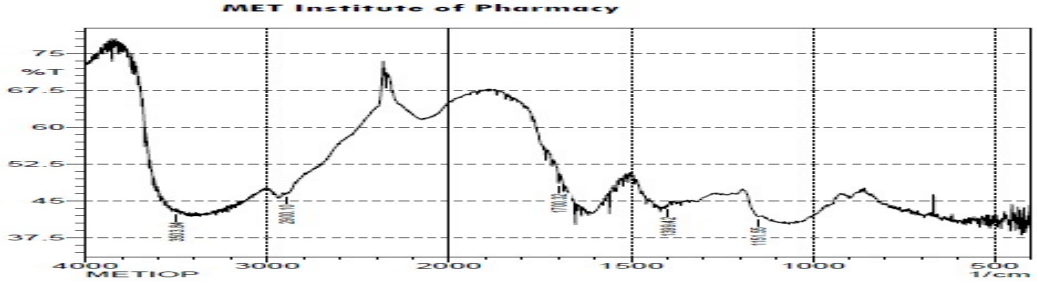


Figure 8: FT-IR spectrum of drug loaded finalized formulation

Table 17: Interpretation of FTIR spectrum of drug loaded final formulation

Sr. No.	Peak in cm^{-1}	Functional Group
1	763.84	Mono substituted benzene ring
2	1422.58	Amide
3	1529.62	Aromatic ring
4	1649.21	Ketones
5	1716.72	Amide
6	2508.53	Alkane
7	3404.51	Hydroxyl Group

Table 18: *In-vitro* mucoadhesion of optimized batch

Sr. No.	Time in Hr	% Mucoadhesion
1	1	60.81 ±0.95
2	2	83.39 ±1.52
3	4	92.03 ±0.92
4	6	96.86 ±1.06
5	8	99.84 ±1.39

(* n=3 ± SD)

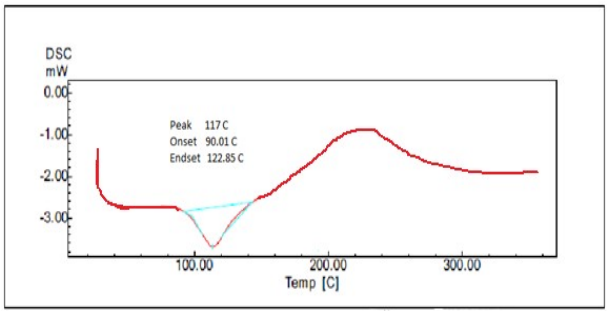


Figure 9: DSC thermogram of Valsartan,

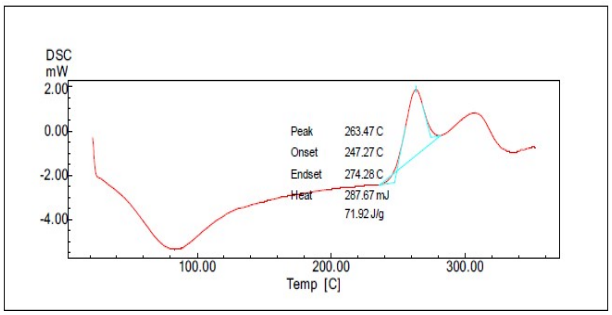


Fig 10. DSC thermogram of Lipidium sativum

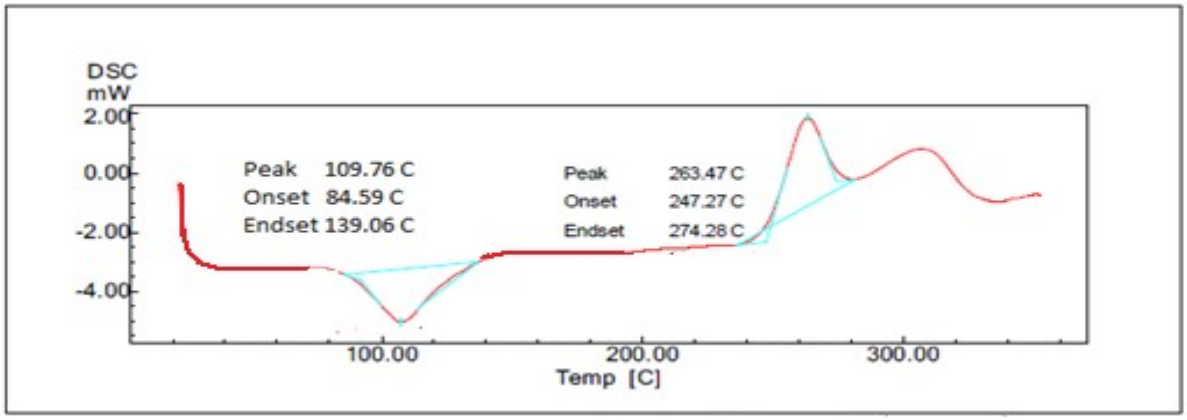


Figure 11: DSC thermogram of formulation

CONCLUSION

It was concluded that the mucilage isolated from seeds Lipidium sativum showed the presence of carbohydrates and was found acceptable for all the tested Oraganoleptic properties. From solubility analysis it was found to be sparingly soluble in warm water, Inorganic solvents like methanol and chloroform it is insoluble. In the present study, attempts were made to develop control release microparticles of Valsartan with Lipidium sativum by using spray drying method. From the release study of microparticles formulation it was concluded that the release was controlled up to 24 hrs.

FUTURE SCOPES

NDDS aim for designing dosage form in recent years, convenient to be manufactured and administered, free of side effect offering controlled release. This formulation reduces the frequency of dosing, thereby minimizing the side effect and increase the effectiveness of drug.

The future trends in innovation of drug delivery system will be continue to bring together different technological discipline and formulation aspects to create novel

technologies. The futuristic discipline for microparticles may be development of natural polymers based microparticles. The application of nanotechnology to the formulation to further enhance the acceptance and performance of these dosage forms. The Valsartan microparticles can be used for the nasal sprays.

CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

[1] Waugh A, Grant A. (2006). The Respiratory System, Ross And Wilson Anatomy and Physiology in Health and Illness, 10th Ed. London: Churchill Livingstone pp. 240-241

[2] Michael I U. (2005). Nasal Mucoadhesive Drug Delivery Background, Application, Trends And Future Perspectives, Advanced Drug Delivery Reviews, 1640-1665.

[3] Lansely AB, Martin GP.(2010) Nasal Drug Delivery In: Hillery A.M., Andrew W. L., Swarbrick J (Eds.), Drug Delivery And Targeting To Pharmacist And Pharmaceutical Scientist., CRC Press, Taylor And Francis Group, New York, 261-263.

[4] Akhtar A, Prajapati Ak, Devender K, Kumar N, A. (2012). Novel Intranasal Drug Delivery System: Review, Novel Sciences International Journal of Pharmaceutical Science, 550-556.

[5] Ns Dey, S. Majumdar, M. E. B. Rao. (2009). Multiparticulate Drug Delivery Systems for Controlled Release, Tropical Journal of Pharmaceutical Research, 1826-1837.

[6] Rishabha Malviya, Pranati Srivastava, G.T. (2011). Kulkarni, Applications of Mucilages in drug delivery - A Review, Advances In Biological Research, 1-7.

[7] Gavini. (2006). Nasal Administration of carbamazepine using chitosan microspheres: In Vitro/ In Vivo Studies, International Journal of Pharmaceutics, 9-15.

[8] Aulton ME. (2007). Pharmaceutics: The Design and Manufacture Of Medicines, 3rd Edition, Hungary, USA: Churchill Livingstone, 127-134, 337-349, 484-498, 555-563.

[9] Pavia D. L. (2010). Spectroscopy, 4th Edition, New Delhi: Cengage Learning India Pvt Ltd, pp. 15-104.

[10] Bolton S. And Bond C. (2010). Pharmaceutical Statistics: Practical And Clinical Applications, 5th Edition, New York, USA: Informa Healthcare, pp. 182-221.

[11] Sanehi P.K. *et al*., (2010), Design And Evaluation Of Sustained Release Chitosan Coated Microcapsules, International Journal Of Pharma And Bio Sciences, pp. 1-10.

[12] Huh Y. (2010). Preparation And Evaluation Of Spray Dried Hyaluranic Acid Microspheres For Intranasal Delivery Of Fexofenadine Hydrochloride, European Journal Of Pharmaceutical Scinces, pp. 1-15.

[13] Chatwal G.R., Anand S.K. (2010). Instrumental Methods of Chemical Analysis, 1st Edition, Mumbai, India: Himalaya Publishing House, pp. 2318-1331.

[14] Akram Khan. (2014). Formulation and evaluation of mucoadhesive microspheres of valsartan, Indo American Journal of Pharmaceutical Research, 3634-3641.