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Formulation and Evaluation of Vilazodone Microspheres

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Abstract: The aim of the study was to prepare Vilazodone microspheres using Solvent evaporation method using different polymer ratio. FT-IR studies revealed that there was no chemical interaction between the drug and polymer. The average particle size of the optimized formulation was found to be 166 µm. The *in-vitro* release behavior from all the Vilazodone microspheres was found to be Higuchi drug release kinetics and produced a sustained release over a period of 12 hours with better entrapment efficiency.

Key words: Higuchi, Ethyl cellulose, Eudragit RL 100 and HPMC K4M Solvent evaporation method and microspheres.

INTRODUCTION

Oral route drug administration is by far the most preferable route for taking medications. However, their short circulating half life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of medication to achieve therapeutic effect. Rational approach to enhance bioavailability aSnd improve pharmacokinetic and pharmacodynamics profile is to release the drug in a controlled manner and site specific manner. Microspheres are small spherical particles, with diameters 1 µm to 1000 µm. They are spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature. There are two types of microspheres; microcapsules and micromatrices, which are described as, Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall. and micromatrices in which entrapped substance is dispersed throughout the matrix. Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Microsphere play an important role to improve bioavailability of conventional drugs and minimizing side effects. Ideal characteristics of microspheres: [1,2,3,4,5]

Ideal characteristics of microspheres: [6]

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.

- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability.
- Susceptibility to chemical modification.

Advantages of microspheres:

1. Particle size reduction for enhancing solubility of the poorly soluble drug.
2. provide constant and prolonged therapeutic effect.
3. provide constant drug concentration in blood there by increasing patent compliance,
4. Decrease dose and toxicity.
5. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.
6. Reduce the dosing frequency and thereby improve the patient compliance
7. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
8. Microsphere morphology allows a controllable variability in degradation and drug release.
9. Convert liquid to solid form & to mask the bitter taste.
10. Protects the GIT from irritant effects of the drug.
11. Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
12. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Limitation:

Some of the disadvantages were found to be as follows

1. The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.

Types of microspheres:

1. Bioadhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres
    i) Biodegradable polymeric microspheres
    ii) Synthetic polymeric microspheres

1. Bioadhesive microspheres: [7,8]

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water-soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

2. Magnetic microspheres: [9,10]

This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different types of

a. Therapeutic magnetic microspheres used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.

b. Diagnostic microspheres, used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

3. Floating microspheres: [11,12,13]

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, and the system is found to be floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover, it also reduces chances of dose dumping. It produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) is given in the form of floating microspheres.

4. Radioactive microspheres: [14]

Radio embolization therapy microspheres sized 10-30 nm are of larger than the diameter of the capillaries and gets tapped in first capillary bed when they come across. They are injected in the arteries that leads them to tumor of interest so all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

5. Polymeric microspheres:

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

i) Biodegradable polymeric microspheres: [15]

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature. Biodegradable polymers prolong the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However, they provide wide range of application in microsphere-based treatment.

ii) Synthetic polymeric microspheres: [16]

Synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and proved to be safe and biocompatible but the main disadvantage of these kinds of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

Method of preparation:

1. Spray Drying
2. Solvent Evaporation
3. Single emulsion technique
4. Double emulsion technique
5. Phase separation coacervation technique
6. Spray drying and spray congealing
7. Solvent extraction
8. Quassi emulsion solvent diffusion:

METHODOLOGY

PREPARATION OF 0.1N HCl (pH 1.2):

Take 8.5 ml of HCl in a 1000ml volumetric flask and make up the volume with distilled water.

Preparation of Standard Calibration Curve of Vilazodone:

- 10mg of Vilazodone was accurately weighed and dissolved in 10ml of methanol (Stock Solution –I) to get a concentration of 1000 µg/ml.
- From the stock solution-I, 1ml of aliquots was taken and suitably diluted with 0.1N HCl (Stock Solution-II) to get concentrations of 100µg/ml.
- From the stock solution-II, aliquots were taken and suitably diluted with 0.1N HCl (pH 1.2) to get concentrations in the range of 2 to 10µg/ml. The absorbance of these samples was analyzed by using UV-Visible Spectrophotometer at 231nm against reference solution 0.1N HCl (pH 1.2). The procedure repeated to pH 6.8 phosphate buffer and pH 7.4 phosphate buffer.

METHOD OF PREPARATION

Vilazodone microspheres were prepared using Ethyl cellulose, Eudragit RL 100 and HPMC K4M and distilled water as continuous phase by solvent evaporation technique. Initially dichloromethane (DCM) and methanol was mixed uniformly at room temperature, then Ethyl cellulose, Eudragit RL 100 and HPMC K4M in various proportions was dissolved in the above solution. To this mixture, a drug solution corresponding was added and mixed thoroughly and injected drop wise in to the continuous phase consisting of 100mL of SLS (Sodium Lauryl sulphate) at 250 rpm. The microspheres obtained was washed for 2-3 times with distilled water and dried at room temperature. Different concentrations and ratios of polymers used in the formulation of microspheres are mentioned in Table.

Table 7.1: Formulation chart

INGREDIENTS (MG)	FORMULATIONS								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Vilazodone	20	20	20	20	20	20	20	20	20
Ethyl cellulose (g)	0.5	1	1.5	-	-	-	-	-	-
Eudragit RL 100 (g)	-	-	-	0.5	1	1.5	-	-	-
HPMC K4M (g)	-	-	-	-	-	-	0.5	1	1.5
Dichloromethane (mL)	40	40	40	40	40	40	40	40	40
Methanol (mL)	20	20	20	20	20	20	20	20	20
Sodium lauryl sulphate (mg)	800	800	800	800	800	800	800	800	800

CHARACTERIZATION OF MICROSPHERES:

Micromeritic properties

The microspheres were characterized by their micromeritic properties such as Particle size, Bulk density, Tapped density, Compressibility index, Hausners ratio and Angle of repose.

Bulk density

In this method floating microspheres are transferred to a measuring cylinder and is tapped manually till a constant volume is obtained. This volume is bulk volume and it includes true volume of the powder and the void space among the microspheres.

$$\text{Bulk density} = \frac{\text{Mass of microspheres}}{\text{Bulk volume}}$$

Tapped density

In this method floating microspheres were transferred to a measuring cylinder & tapped for 100 times. After tapping volume of microspheres was visually examined. The ratio of mass of microspheres to volume of microspheres after tapping gives tapped density floating microspheres.

Percent Compressibility index was determined by using the formula,

Carr's Index = (tapped density – bulk density) x 100 / tapped density

Hausners ratio

Hausners ratio of microspheres was determined by comparing tapped density to bulk density using the equation

Hausner ratio = tapped density / bulk density

Angle of repose

Angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method4. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed microspheres were allowed to pass through the funnel freely on to the surface. The height and radius of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} h / r$$

Here,

θ - Angle of repose

h - Height of granules above the flat surface

r - Radius of the circle formed by the granule heap.

Percentage yield

The percentage of production yield was calculated from the weight of dried microsphe-res recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical mass (Microspheres)}}{\text{Theoretical mass (Polymer + Drug)}} \text{ x } 100$$

Drug entrapment efficiency:

Weighed number of microspheres (100 mg) with phosphate buffer pH 7.4 (10 ml) was added in a vial. The solution was stirred vigorously for 24 hours with mechanical stirrer. Supernatant was collected by centrifugation and drug content in supernatant was determined by using UV spectrophotometer at wavelength 231nm. The amount of drug entrapped in the microspheres was calculated by the following formula:

$$\% \text{ Drug Entrapment Efficiency} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Swelling study:

Swelling ratio of different dried microspheres were determined gravimetrically in simulated gastric fluid pH 1.2. The microspheres were removed periodically from the solution, blotted to remove excess surface liquid and weighed on balance. Swelling ratio (% w/v) was determined from the following relationship:

$$\text{Swelling ratio} = \frac{(Wt - W0)}{(W0)} \times 100$$

Where W0 & Wt are initial weight and Final weight of microspheres respectively

***In vitro* drug release study:**

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5^0C, 50 rpm) using the USP type – I rotating basket method in simulated gastric fluid pH 1.2 (900ml) for 2 hours then replace the media with pH 6.8 phosphate buffer for 3 hours, then replace the media with pH 7.4 Phosphate buffer. A quantity of accurately weighed microspheres equivalent to 100mg Vilazodone each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined

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intervals of time and analyzed for drug release by measuring the absorbance at 231nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed simulated gastric fluid pH 1.2 maintaining sink conditions throughout the experiment.

In Vitro drug release kinetics

The release data obtained was fitted into various mathematical models. The parameters 'n' and time component 'k', the release rate constant and 'R', the regression coefficient were determined by Korsmeyer-Peppas equation to understand the release mechanism.

To examine the release mechanism of Vilazodone from the microspheres, the release data was fitted into Peppa's equation,

$$Mt / M\infty = Ktn$$

Where, Mt / M∞ is the fractional release of drug, 't' denotes the release time, 'K' repr-esents a constant incorporating structural and geometrical characteristics of the device, 'n' is the diffusional exponent and characterize the type of release mechanism during the release process.

Table 7.2: *In-Vitro* drug release kinetics

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport or non-Fickian	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

If n < 0.5, the polymer relaxation does not affect the molecular transport, hence diffus-ion is Fickian.

If n > 0.5, the solid transport will be non-fickian and will be relaxation controlled.

Other equations to study the drug release kinetics from dosage forms

a. Zero Order

$$\% R = kt$$

This model represents an ideal release in order to achieve prolonged pharmacological action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as Matrix tablets containing low soluble drugs.

b. First Order

$$\text{Log (fraction unreleased)} = kt/2.303$$

The model is applicable to hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

c. Matrix (Higuchi Matrix)

$$\% R = kt\ 0.5$$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

d. Peppas Korsmeyer Equation

$$\% R = kt\ n$$

$$\log \% R = \log k + n \log t$$

This model is widely used when release mechanism is well known or when more than one type of release phenomenon could be involved. The 'n' values could be used to characterize different release mechanisms as.

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples were mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about

12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Agilent spectrophotometer and the IR spectrum was recorded from 4000 cm-1 to 500 cm-1. The resultant spectrum was compared for any spectrum changes.

SEM (Scanning Electron Microscope) studies:

The surface morphology of the layered sample was examined by using SEM (JEOL Ltd.,Japan). The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stubs were coated with a thin layer (300A) of gold by employing POLARON - E 3000 sputter coater. The samples were examined by SEM with direct data capture of the images on to a computer.

Powder X-ray Diffraction (PXRD) Studies

The prepared mixtures were also analyzed using X-ray powder diffractometer (PXRD) which confirms the formation of the new solid phases. The difference in the 2 theta lines confirms the formation of the new solid phases as no two solids have same 2 theta lines, thus revealing the formation of new solid phases. It also reveals the information about the crystal structure, chemical composition, and physical properties of the material and also helps in structural characterization. This technique detects changes in the crystal lattice and is therefore a powerful tool for studying polymorphism, pharmaceutical salts, and cocrystalline phases. Spectra of PXRD were taken on a sample stage Spinner PW3064. The samples were exposed to nickel filtrate Cukœ radiations (40 KV, 30 mA) and were scanned from 10° to 40° , 2Ɵ at a step size of 0.045° and step time of 0.5 s.

DIFFERENTIAL SCANNING CALORIMETRY (DSC):

The possibility of any interaction between the drug and the polymer during preparation of tablets was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminum pan at a rate of 10°C/min conducted over a temperature range of 30 to 350°C under a nitrogen flow of 50 mL/min.

Zeta Potential:

Zeta capability becomes anticipated on the premise of electrophoretic mobility under an electric powered field, the use of zeta Sizer Nano ZS (Malvern Instruments, UK). For the Zeta ability measurement, Samples have been diluted as 1:40 ratio with filtered water (v/v) before analysis. zeta potential has been then measured in triplicate.

RESULTS AND DISCUSSION

8.1. PREFORMULATION STUDIES

8.1.1. SPECTROSCOPIC STUDIES

Determination of λmax

A solution of 10µg/ml of Vilazodone was scanned in the range of 200 to 400nm. The drug exhibited a λmax at 231 nm in simulated gastric fluid pH 1.2 and pH 7.4 phosphate buffer respectively. Correlation between the concentration and absorbance was found to be near to 0.998, with a slope of 0.028 and intercept of 0.004.

Calibration curve of Vilazodone in simulated gastric fluid pH 1.2

Table 8.1 shows the calibration curve data of Vilazodone in simulated gastric fluid pH 1.2 at 231 nm Fig.8.1 shows the standard calibration curve with a regression value of 0.9989, slope of 0.009 and intercept of 0.0588 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 2-10µg/ml.

Table 8.1: Calibration curve data for Vilazodone in simulated gastric fluid pH 1.2

CONCENTRATION (µg /ml)	ABSORBANCE
2	0.128
4	0.254
6	0.368
8	0.478
10	0.591
2	0.128

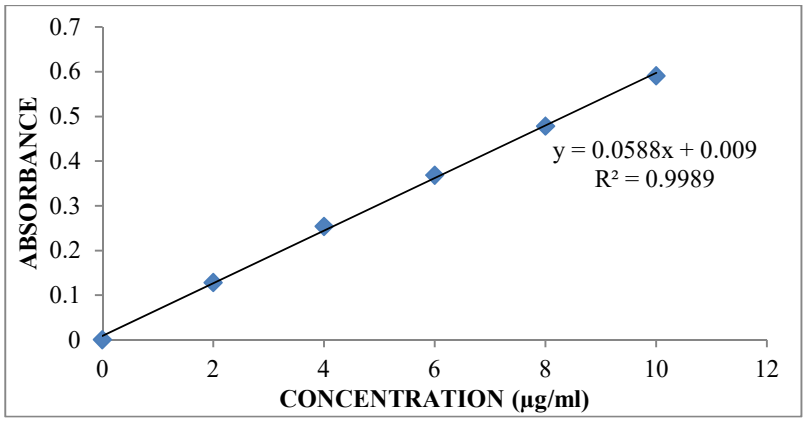


Fig 8.1: Standard graph Of Vilazodone in simulated gastric fluid pH 1.2

Calibration curve of Vilazodone in pH 7.4 phosphate buffer

Table 8.2 shows the calibration curve data of Vilazodone in pH 7.4 phosphate buffer at 232nm. Fig. 8.2 shows the standard calibration curve with a regression value of 0.9986, slope of 0.0101 and intercept of 0.0567 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 2-10µg/ml.

Table 8.2: Calibration curve data for Vilazodone in pH 7.4 phosphate buffer

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
2	0.126
4	0.231
6	0.342
8	0.452
10	0.571

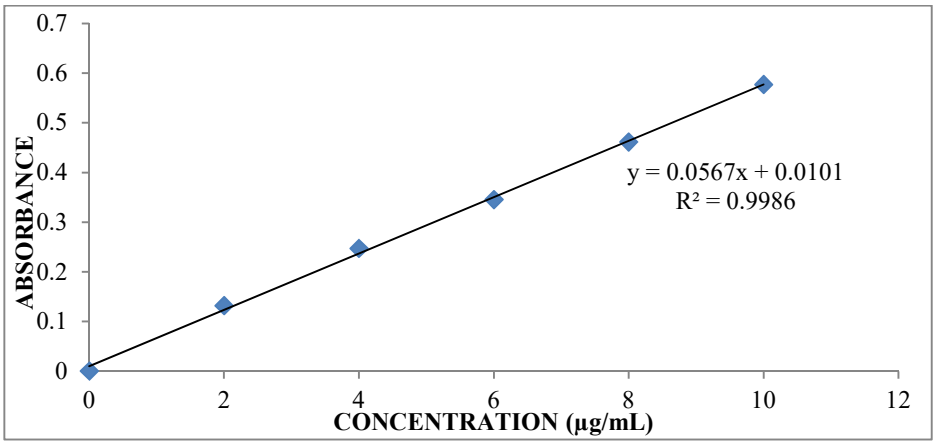


Fig 8.2: Standard graph of Vilazodone in pH 7.4 phosphate buffer

Evaluation and characterization of microspheres

Micrometric Properties

The mean size increased with increasing polymer concentration which is due to a significant optimum in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing Ethyl cellulose as a polymer had a size range of 125±0.01 µm to 187±0.05 µm. Microspheres containing Eudragit RL 100 as polymer exhibited a size range between 137±0.08 µm to 191±0.09 µm.

Microspheres containing HPMC K4M as polymer exhibited a size range between 152±0.04 µm to 191±0.01µm.

The particle size data is presented in Tables 8.3 and displayed in Figures. The effect of drug to polymer ratio on particle size is displayed in Figure. The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

The bulk density of formulation F1 to F9 containing Ethyl cellulose, Eudragit RL 100 and HPMC K4M formulation was in the range of 0.50 to 0.59 gm./cm^3 (as shown in table 8.3), tapped density 0.50 to 0.59 and Hausners ratio 1.135 to 1.237.

The car's index of formulation F1 to F9 containing different grades of Ethyl cellulose, Eudragit RL 100 and HPMC K4M 11.86 to 19.18 respectively. The angle of repose of formulation F1 to F9 containing Ethyl cellulose, Eudragit RL 100 and HPMC K4M formulation was in the range <31.45 respectively (as shown in table 8.3) The values of carr's index and angle of repose indicate good flow properties.

Table 8.3: Micromeritic property of microspheres of Vilazodone

Formulation code	Mean partical size	Bulk density (gm./cm^3)	Tapped density (gm./cm^3)	Hausener's ratio	Carr's index	Angle of repose
F1	125±0.01	0.59	0.73	1.237	19.18	31.45
F2	171±0.06	0.58	0.71	1.224	18.31	30.64
F3	187±0.05	0.58	0.70	1.207	17.14	30.05
F4	191±0.09	0.50	0.57	1.140	12.28	23.49
F5	166±0.02	0.52	0.59	1.135	11.86	23.82
F6	137±0.08	0.53	0.62	1.170	14.52	24.50
F7	152±0.04	0.55	0.64	1.164	14.06	24.68
F8	185±0.07	0.56	0.67	1.196	16.42	25.07
F9	191±0.01	0.54	0.65	1.194	16.40	25.05

Percentage yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug-polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The percentage yield was found to be in the range.

Drug entrapment efficiency

Percentage Drug entrapment efficiency of Vilazodone ranged from 72.90 to 90.45 % for microspheres containing Ethyl cellulose, Eudragit RL 100 and HPMC K4M polymer, the drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microspheres is displayed in Table 8.4, and displayed in Figures.

Table 8.4: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

Formulation code	% Yield	Drug Content (mg)	% Drug entrapment efficiency	Zeta Potential (mV)
F1	97.02	97.85	74.90	-22.12
F2	89.36	98.05	86.63	-25.81
F3	92.40	99.12	91.25	-25.52
F4	95.47	96.99	83.70	-24.25
F5	98.10	99.71	92.12	-38.55
F6	96.77	98.63	91.45	-22.83
F7	89.40	97.75	85.63	-27.59
F8	95.10	98.15	89.81	-31.11
F9	96.45	98.41	90.69	-30.80

Swelling studies

The swelling ratio is expressed as the percentage of water in the hydrogel at any instant during swelling. Swell ability is an important characteristic as it affects mucoadhesion as well as drug release profiles of polymeric drug delivery systems. Swell ability is an indicative parameter for rapid availability of drug solution for diffusion with greater flux. Swell ability data revealed that amount of polymer plays an important role in solvent transfer. It can be concluded from the data shown in Table 8.5 that with an increase in polymer concentration, the percentage of swelling also increases. Thus, we can say that amount of polymer directly affects the swelling ratio. As the polymer to drug ratio increased, the percentage of swelling increased from 12.33 to 34.26 % for microspheres containing Eudragit as polymer, 15.53 to 38.8 % for microspheres containing Carbopol 934p as polymer. The percentage of swelling of the prepared microspheres is displayed in Figures. The effect of drug to polymer ratio on percentage swelling is displayed in.

Table 8.5: Swelling studies

S.NO.	FORMULATION CODE	INITIAL (Wt)	FINAL (Wt)	PERCENTAGE SWELLING
1	F1	15	16.85	12.33
2	F2	15	18.92	16.13
3	F3	15	20.14	34.26
4	F4	15	17.33	15.53
5	F5	15	18.24	21.6
6	F6	15	20.82	38.8
7	F7	15	23.41	56.06
8	F8	15	27.92	86.13
9	F9	15	26.34	85.61

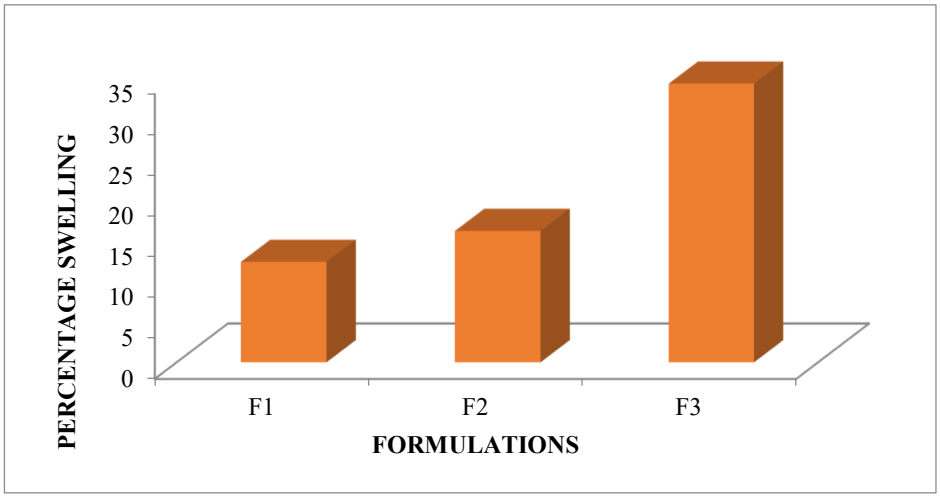


Fig 8.3: Percentage swelling of microspheres containing Ethyl cellulose

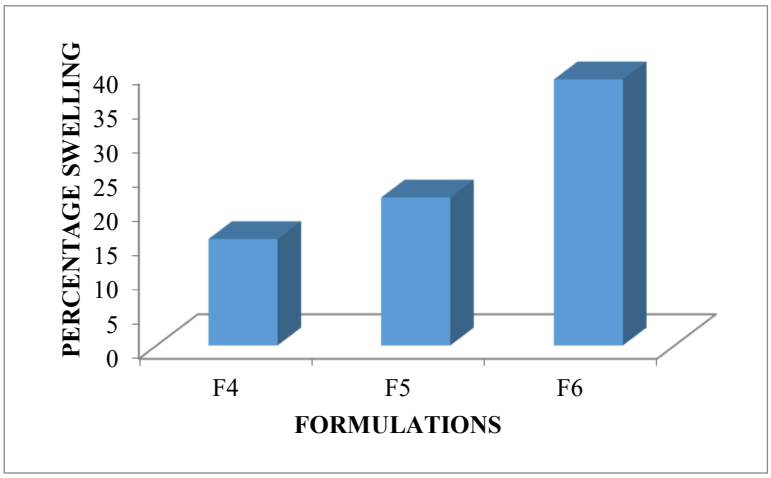


Fig 8.4: Percentage swelling of microspheres containing Eudragit RL 100

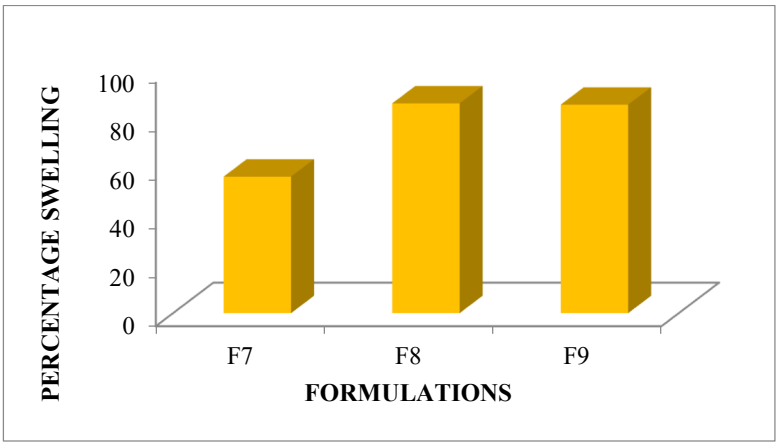


Fig 8.5: Percentage swelling of microspheres containing HPMC K4M

IN VITRO MUCOADHESION TEST

As the polymer to drug ratio increased, microspheres containing Ethyl cellulose, Eudragit RL 100 and HPMC K4M exhibited % mucoadhesion ranging from 72.75 to 96.25 %, the results of *in-vitro* mucoadhesion test are compiled in Table 8.6.

Table 8.6: *In Vitro* Mucoadhesion Test of all Formulations

S.NO.	FORMULATION CODE	No. OF MICROSPHERES		PERCENTAGE MUCOADHESION
		INITIAL	FINAL	
1	F1	20	14.55	72.75
2	F2	20	16.12	80.60
3	F3	20	18.14	90.7
4	F4	20	18.92	94.60
5	F5	20	19.25	96.25
6	F6	20	15.72	78.60
7	F7	20	17.32	86.6
8	F8	20	17.86	89.3
9	F9	20	17.89	90.01

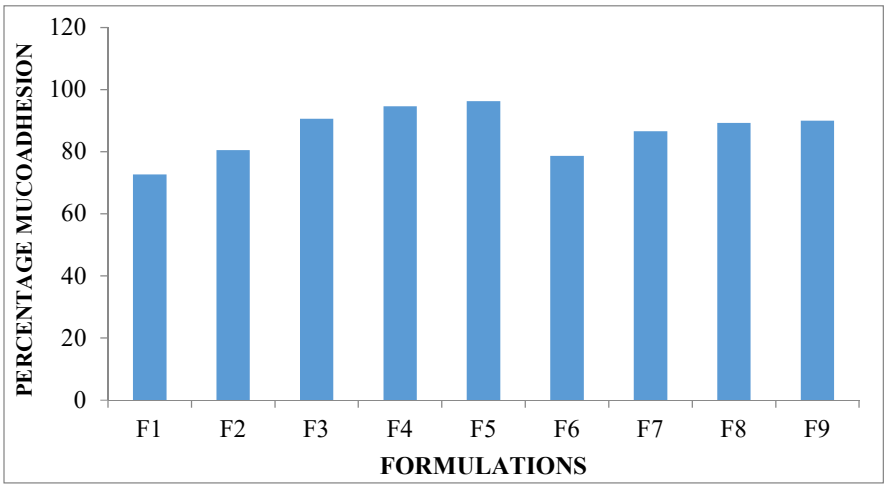


Fig 8.6: Percentage mucoadhesion of microspheres

IN-VITRO DRUG RELEASE STUDIES

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type I. The dissolution studies were conducted by using dissolution media, pH 1.2. The results of the *in-vitro* dissolution studies of formulations F1 to F9 are shown in below table. The plots of Cumulative percentage drug release Vs Time.

The formulations F1, F2, and F3 containing Eudragit showed a maximum release of 79.70 % at 12 hours, 87.91 % after 12 hours, 91.53% 12 hours respectively.

The formulations F4, F5, and F6 containing Carbopol 934p showed a maximum release of 97.29 % at 12 hours, 99.72 % after 12 hours, 86.14% 12 hours respectively.

The formulations F7, F8, and F9 containing HPMC K4M polymer showed a maximum release of 80.15% 12 hours, 76.94 % after 12 hours, 73.04% after 12 hours respectively.

Table 8.7: *In-Vitro* drug release data of Vilazodone microspheres

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	11.58	7.25	10.20	23.85	28.42	14.73	16.42	20.45	15.28
2	26.35	11.31	16.61	36.90	35.61	19.98	24.25	27.91	29.31
3	31.89	18.89	23.85	41.65	40.13	24.86	30.91	33.26	34.86
4	38.54	25.10	32.11	47.23	43.54	28.12	33.59	37.96	41.52
5	47.28	35.51	41.25	52.89	51.32	35.68	47.75	42.85	46.71
6	55.31	41.19	50.86	57.72	58.14	41.10	52.53	50.64	53.86
7	62.50	46.87	56.20	60.98	62.80	46.27	59.70	56.48	56.24
8	67.14	53.96	61.46	62.54	68.51	53.79	63.21	61.31	60.87
9	73.86	56.24	65.82	64.15	72.47	69.46	68.48	65.16	66.65
10	85.41	62.31	74.72	75.12	74.71	79.60	71.22	73.62	71.23
11	89.92	72.75	78.95	77.28	86.25	84.76	80.38	77.19	75.54
12	98.86	78.23	81.54	86.19	99.34	96.82	85.90	82.37	78.21

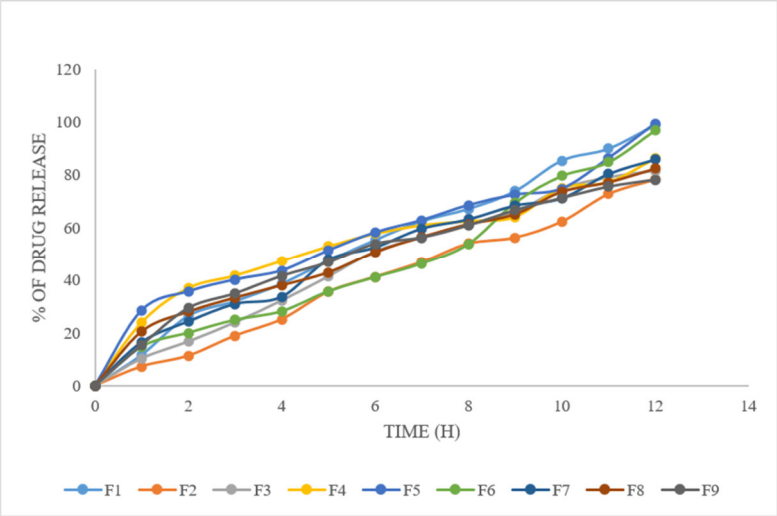


Fig 8.7: *In-Vitro* drug release profile of Vilazodone microspheres

Invitro drug release from all the formulation was found to be slow and sustained over the period of 12 hours, among other formulation F5 showed better sustained release pattern and the cumulative percentage release at the end of 12 hours was found to be 99.34 %.

In-vitro drug release kinetics

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the *in-vitro* drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled in Table 8.9. The coefficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered. The kinetic data analysis of all the formulations reached higher coefficient of determination with the peppas release kinetics whereas release exponent value (n) ranged from 0.970. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows peppas release kinetics along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

Table 8.8: Release kinetics studies of the optimized formulation (F5)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q0 1/3	Qt 1/3	Q0 1/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
28.42	1	1.000	1.454	0.000	1.855	28.420	0.0352	-0.546	71.58	4.642	4.152	0.490
35.61	2	1.414	1.552	0.301	1.809	17.805	0.0281	-0.448	64.39	4.642	4.008	0.633
40.13	3	1.732	1.603	0.477	1.777	13.377	0.0249	-0.397	59.87	4.642	3.912	0.730
43.54	4	2.000	1.639	0.602	1.752	10.885	0.0230	-0.361	56.46	4.642	3.836	0.805
51.32	5	2.236	1.710	0.699	1.687	10.264	0.0195	-0.290	48.68	4.642	3.651	0.990

58.14	6	2.449	1.764	0.778	1.622	9.690	0.0172	-0.236	41.86	4.642	3.472	1.169
62.8	7	2.646	1.798	0.845	1.571	8.971	0.0159	-0.202	37.2	4.642	3.338	1.303
68.51	8	2.828	1.836	0.903	1.498	8.564	0.0146	-0.164	31.49	4.642	3.158	1.484
72.47	9	3.000	1.860	0.954	1.440	8.052	0.0138	-0.140	27.53	4.642	3.020	1.622
74.71	10	3.162	1.873	1.000	1.403	7.471	0.0134	-0.127	25.29	4.642	2.935	1.706
86.25	11	3.317	1.936	1.041	1.138	7.841	0.0116	-0.064	13.75	4.642	2.396	2.246
99.34	12	3.464	1.997	1.079	-0.180	8.278	0.0101	-0.003	0.66	4.642	0.871	3.771

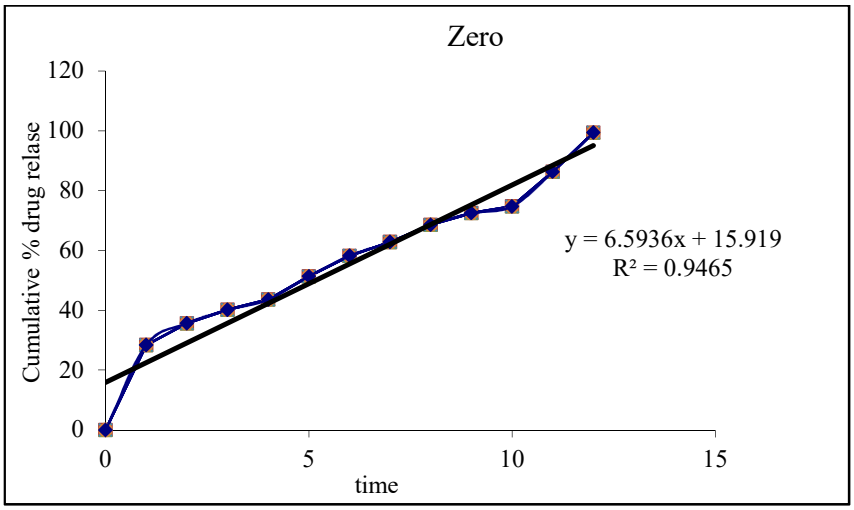


Fig 8.8: Zero order release kinetics

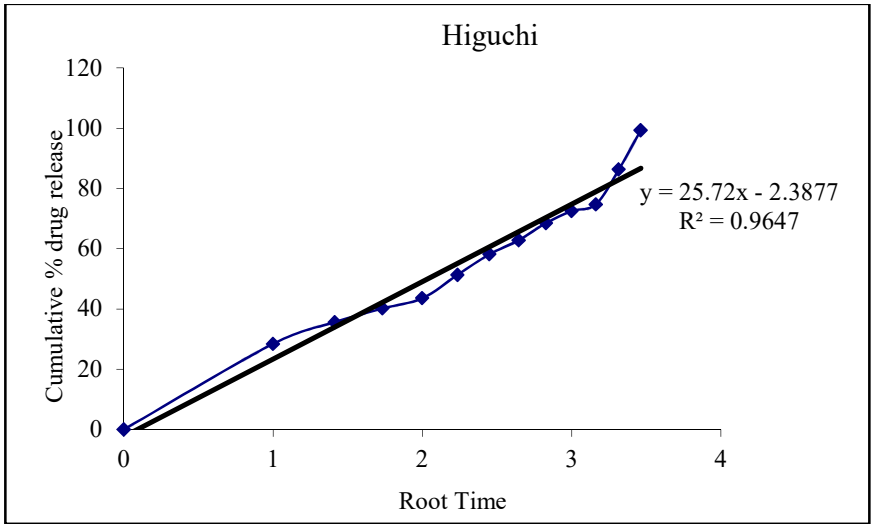


Fig 8.9: Higuchi release kinetics

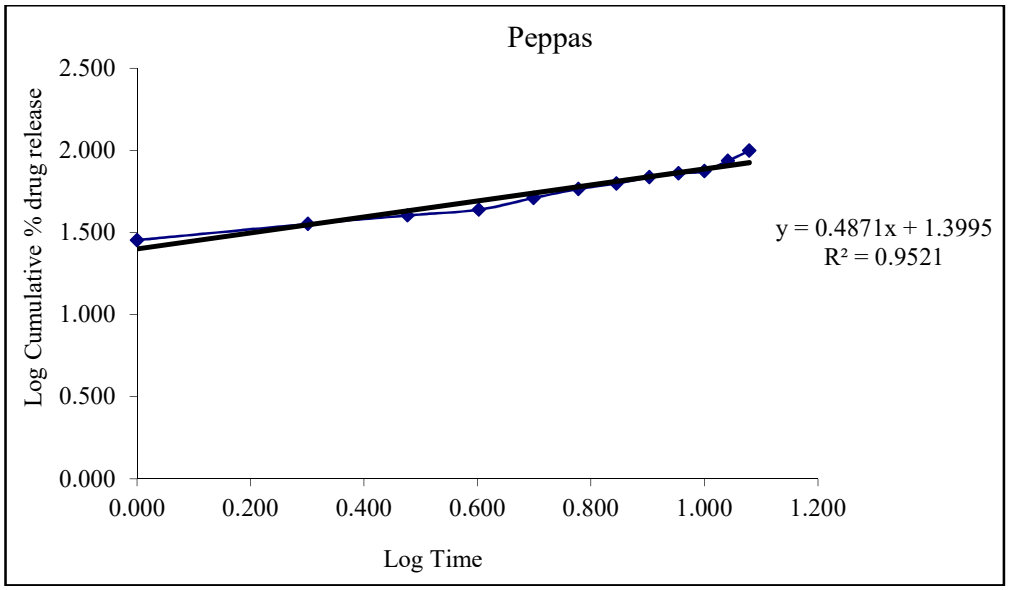


Fig 8.10 : Kors mayer peppas release kinetics

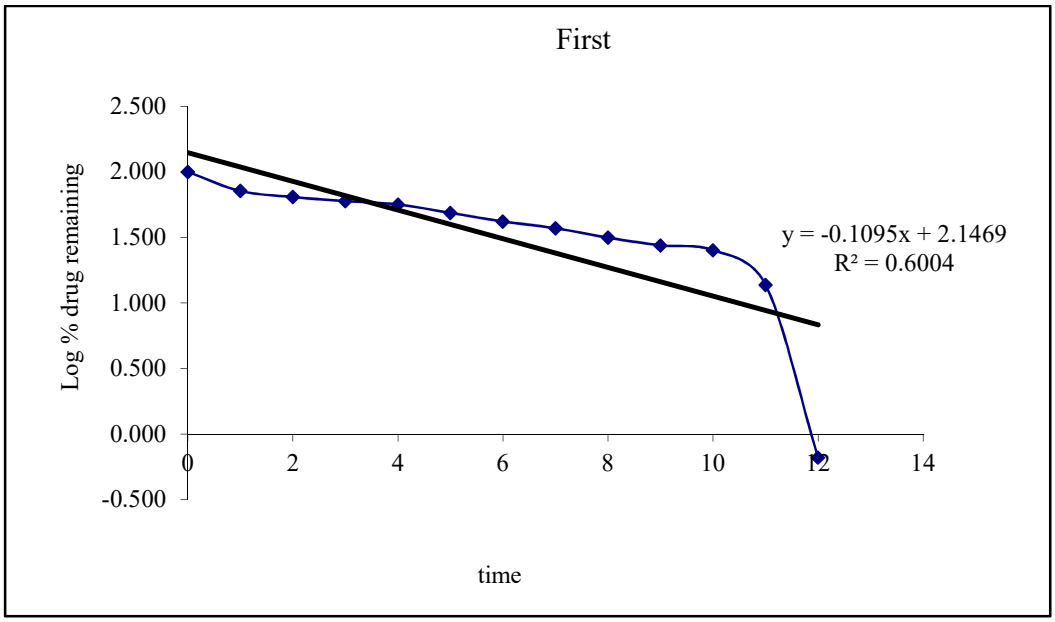


Fig 8.11: First order release kinetics

Optimised formulation F5 was kept for release kinetic studies. From the above graphs it was evident that the formulation F5 was followed Higuchi release mechanism.

COMPATIBILITY STUDIES

Drug polymer compatibility studies were carried out using Fourier Transform Infra-Red spectroscopy to establish any possible interaction of Drug with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug.

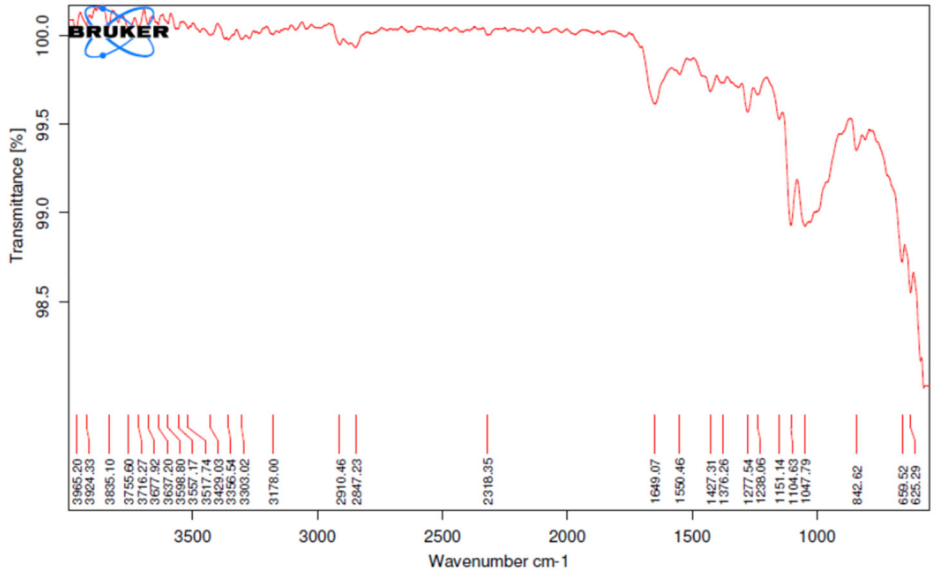


Fig 8.12: FT-IR spectra of Pure drug

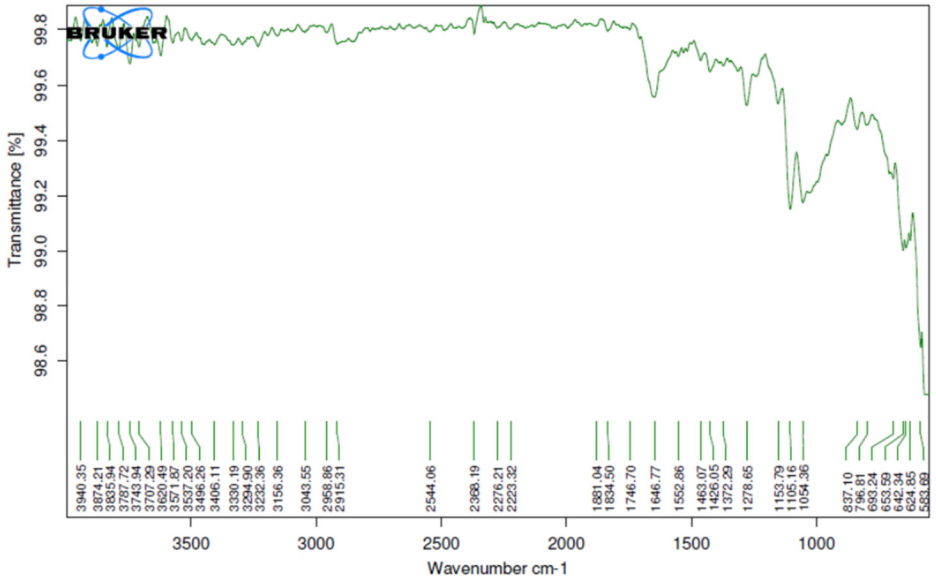


Fig 8.13:FT-IR spectra of Optimised formulation

SEM :

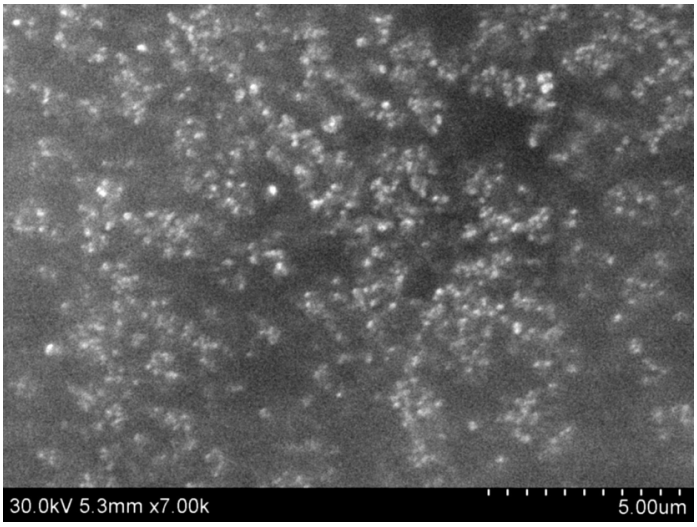


Fig 8.14: SEM of Optimised formulation

SEM was used to examine the morphologies and surfaces of the Vilazodone (Fig). The surface morphology of the microspheres was found in plain Vilazodone powder made up of irregularly shaped crystals with rough surface. The particles of formulation F5 appeared a numerous uniform spherically shaped particles 166±0.02 µm with smooth surfaces of drug-loaded microspheres could be seen with the solvent evaporation technique similar findings have been reported.

XRD:

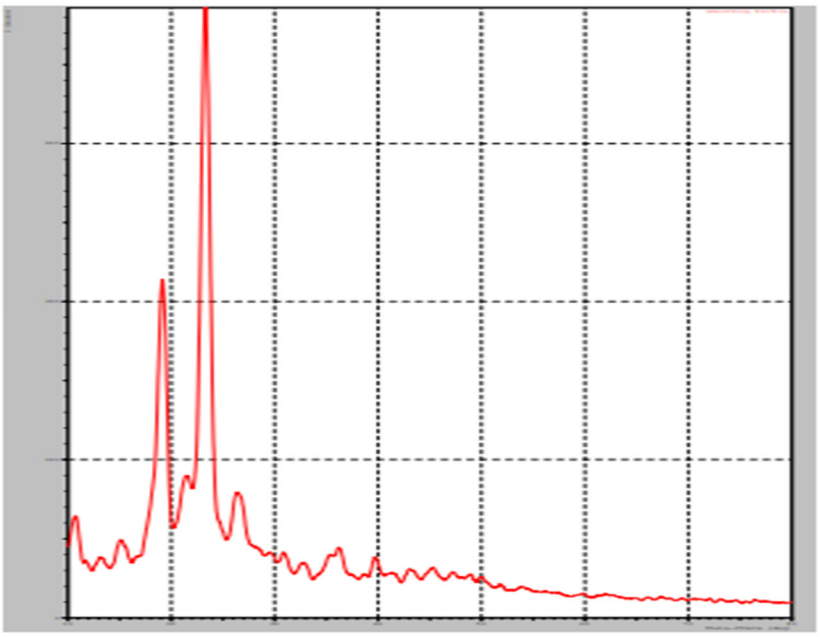


Fig 8.15: Graph: XRD graph of optimized formulations

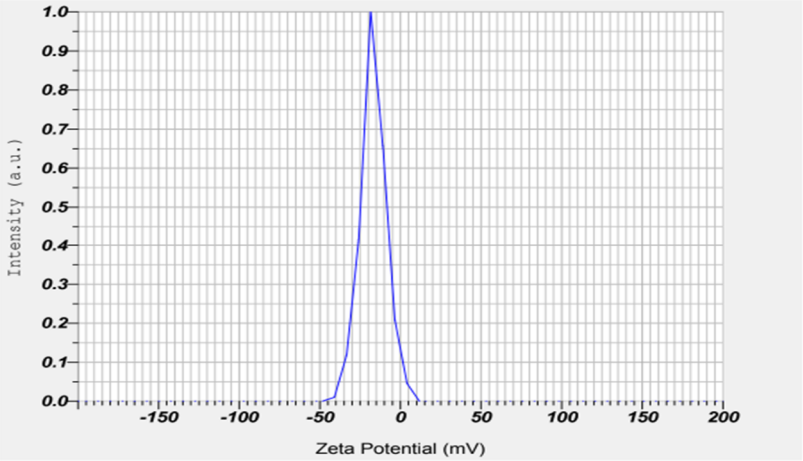
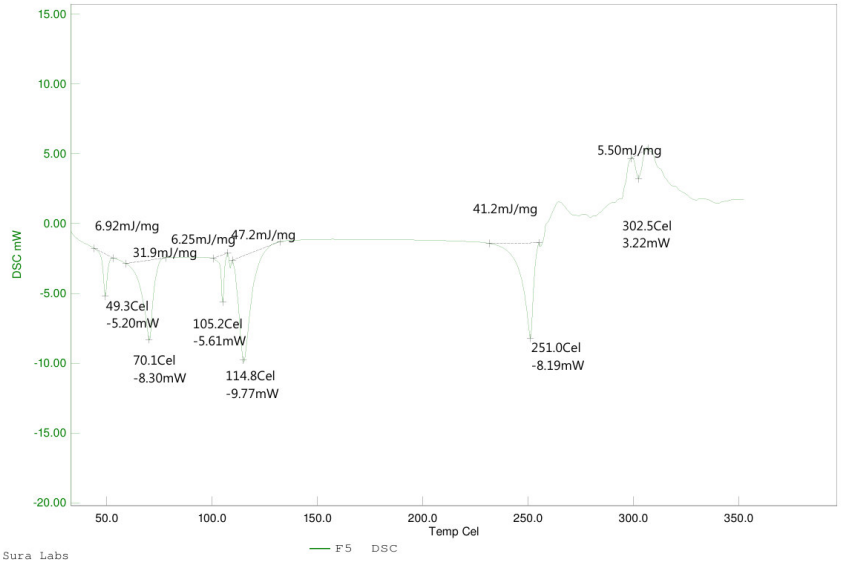


Fig 8.16: Zeta potential of optimized Formulation

The assessment of the zeta potential values (properly related to the double electric layer on the surface of colloidal particles) of a microsphere. Stronger repulsive forces are produced by extreme positive or negative zeta potential values, although repulsion between particles with similar electric charges prevents particle agglomeration and hence simple redispersion. A minimum zeta potential of -38.55 mV is required for simultaneous electrostatic and steric stabilization. The zeta potential study of microsphere formulations F5 were found to be in the range of -38.55 mV) respectively, the zeta potential measurement indicates negatively charged due to double layer repulsion between the droplets and also it depends upon the pH and concentration, which indicates good physical stability of microspheres.



Graph 8.17: DSC graph of pure drug

Upon analysis of the drug Excipient mixture for their physical characteristics no color change was observed. Based on the chemical evaluation it was found that there was no significant change observed indicating that the drug is compatible with the added ingredients.

10. SUMMARY

- An attempt was made to formulate Vilazodone loaded microspheres using Ethyl cellulose, Eudragit RL 100 and HPMC K4M as a mucoadhesive polymer by Solvent evaporation method.
- In the present study F1 to F9 formulations were prepared using Ethyl cellulose, Eudragit RL 100 and HPMC K4M as a polymer (1:1, 1:2, and 1:3) in different ratios.

- The FTIR study was carried out for the drug, polymer, physical mixture and optimized formulation F5. In FTIR study, all characteristic peaks in the spectra appeared without any remarkable changes showing that there is no chemical interaction between the drug and polymer used in the preparation of microspheres.
- The mean particle size study was carried out by using microscopic analysis and found that the range for all formulations was varied from 125±0.01 to 191±0.09 μm due to change in drug and polymer ratio.
- The drug content for all the formulations was found to be in the range of 96.99 to 99.71 %. The formulation F5 had the highest drug content.
- The entrapment efficiency of all formulations was found to be in the range of 74.90 to 92.12 %.
- The *in vitro* mucoadhesion study was conducted for all the formulations and the results were found in the range of 73.05 to 99.72%.
- The *in vitro* drug release study was carried out for all the formulations and the formulation F5 (1:1) showed sustained release of 99.34% at the end of 12 h.
- The release rate followed Higuchi drug release kinetics.

CONCLUSION

The aim of present study is to develop formulation of Vilazodone microspheres. Vilazodone microspheres were prepared through solvent evaporation technique. In the preliminary screening, from the FTIR spectra, it was observed that similar functional groups appear for the drug and the formulation. Hence it shows that there was no chemical interaction between drug and polymer used. The formulations F1 to F9 prepared by solvent evaporation technique. F5 Selected as an optimized formulation, because of better entrapment efficiency and *in vitro* drug release of about 99.34 % in 12hours. It follows Higuchi drug release kinetics. Hence it can be concluded that Vilazodone can be prepared in the form of microspheres by solvent evaporation technique to improve the drug targeting efficiency and also to prolong the duration of action.

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