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Assessing the formulation and efficacy of venlafaxine-loaded microspheres for antidepressant effects

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Abstract
Background: Depression is the one of the largest reasons of non-fatal health loss worldwide. Second-generation antidepressant drugs are the first-line therapy for pharmacological management of depression. Improvement in the use of these drugs is significant in lowering the burden of depression. Venlafaxine is a unique antidepressant drug including a wide range of antidepressant activity and a safety profile that are corresponding to serotonin selective reuptake inhibitors.
Aim: To enhance the bioavailability & half- life of Venlafaxine Hcl drug by using Ion gelation method using various grade polymers of HPMC such as HPMC K4M, HPMC K 15M, HPMC K100M & HPMC 15cps depends on their viscosity.
Objective: The development of sustained release microspheres of Venlafaxine Hcl.
Method: The solubility of venlafaxine was studied in various solvents. Microspheres with different compositions were formulated and optimized. Selected formulation of microspheres contained high viscosity grade polymer and were evaluated for parameters such as drug content, particle size and in *vitro* drug release etc. Optimized microspheres formulation was incorporated in HPMC 15CPS and was evaluated for *in vitro* and stability.
Result: The FTIR shows the detect the functional group in Venlafaxine Hcl active drug. The UV analysis of Venlafaxine Hcl shows absorbance at 226 nm. The results give prepared microspheres enhanced drug content, drug entrapment efficiency, bulk density, tapped density, Housner's ratio, carr's index, Angle of repose. In the optimized F4 (HPMC 15cps+drug) trial which release Venlafaxine Hcl. 16.9±1.2 % in 1st hr. & remaining drug released upto 16 hrs which is 96.2 ±2.45%.
Conclusion: The present study is aimed at development of a simple, rapid and useful method for identification of the venlafaxine and its metabolites in the microbial culture media. Results indicated that the microspheres has potential for sustained action of drug release and may act as a promising tool to enhance percutaneous delivery of venlafaxine.

Keywords: Sustained Release, Venlafaxine Hcl, Polymers, SNRI, Microspheres, anti-depressant, *In- Vitro* drug release

Introduction

Depression is a state of low mood and resistance to activity. It can affect person's thoughts, behavior and motivation as well as feeling of sense of well-being. The symptom of depression is called to be dysphoria, which refers to loss of interest in activity and a loss of feeling of happiness in some activities that usually bring joy to people. It is a normal temporary reaction to life events as like loss of loved one; and it also a symptom of certain mood disorders means major depressive disorder or dysthymia. Venlafaxine extended-release (XR) has been investigated in patients with major depression and in patients with major depression with associated anxiety in randomized, double-blind, multicenter trials. Off-label venlafaxine can be used for brain damage, hot flashes, diabetic neuropathy, fibro myositis, and complex pain syndromes, prevention of migraine, post-traumatic stress disorder, obsessive-compulsive syndrome, and premenstrual disorders. The purpose of a sustained release dosage form is to keep therapeutic medication levels in the blood or tissues for a longer length of time. Attempting to obtain "zero-order" release from the dose form is usually the way to go. Drug release from the dosage form that is independent of the amount of drug in the delivery system is referred to as zero-order release. Prolonged-release systems can alternatively be thought of as attempts to achieve sustained-release delivery.

Microspheres are solid, roughly spherical particles with a size range of 1-1000m. The medicine is disseminated throughout the microsphere matrix, which is made up of polymeric components. Biodegradable synthetic polymers and natural materials were used in the composition. Albumin and gelatin are natural polymers, while polylactic acid and polyglycolic acid is a manufactured polymer. The polymers used to make microspheres are selected based on their solubility, stability profile, method, safety, and cost effectiveness.

Microorganisms such as bacteria and fungi were used as in *vitro* models for the prediction of mammalian drug metabolism with successful applications. A systematic examination of microbial hydroxylation on variety of model organic compounds followed by a comparison of O- and N-dealkylation reactions led Smith and Rosazza to propose that a microbial transformation system could closely mimic most of the phase I transformations of a drug observed in mammals. The use of microorganisms as models of mammalian metabolism has been well documented for obtaining novel metabolites as new drug entities and also for producing existing metabolites in large amounts. In the present investigation, different microorganisms were used for evaluating their ability to metabolize venlafaxine. The aim of this study was to identify the microbes that can be used for production of an active metabolite of venlafaxine

O-desmethyl venlafaxine in larger quantities for further characterization as well as pharmacological and toxicological evaluation. For that, the estimation of venlafaxine and its metabolites in microbial culture media is essential.

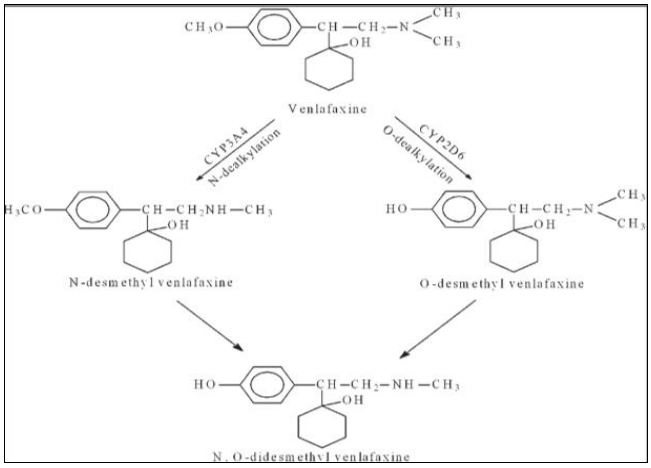
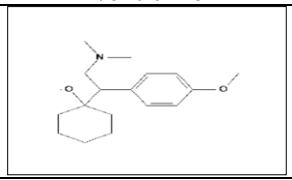


Fig 1: Mammalian metabolic pathway of Venlafaxine

In this study, a Venlafaxine loaded microsphere was formulated in order to minimize the side effects associated with the oral delivery of the drug. The formulated microspheres were then evaluated.

Materials and Methodology

Drug Profile

Drug	Venlafaxine
Chemical Structure	
IUPAC name	1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexan-1-ol
Molecular formula	$C_{17}H_{27}NO_2$
Molecular weight	277.408 g/mol
Class	Antidepressant-Agent (Serotonin-norepinephrine reuptake inhibitor)
Solubility	Water, Ethanol, Methanol.
Melting point	215-217 °C
Dosage form	Tablet, Capsule
BCS Classification	Class-I (High solubility & High permeability)
Bioavailability/Half life	45% and 5 Hr.

Mechanism of Action

Increasing serotonin levels, dopamine and nor-epinephrine in the brain by blocking transport proteins and stopping its reuptake at presynaptic terminal.

This action leads to more transmitter at the synapse and ultimately increase the stimulation of postsynaptic receptors.

Materials

Venlafaixne Hcl sample from Yarrow chemicals, Mumbai, HPMC K4M, HPMC K 15M, HPMC K100M, HPMC 15cps, Carbapol 934, Sodium Alginate & Calcium Chloride, distilled water.

Experimental method

Preparation of Std. Sodium alginate solution (2%)

2gm of Na. alginate into 250 ml flask. Add 100 ml of distilled water and a stir bar. Stir on a magnetic stirrer for about 1hr. or until solid dissolves completely. For best results allow the mixture to stand for overnight to give uniform solution.

Preparation of Std. Calcium chloride solution. (10% w/v)

Weight accurately 10gm of calcium Chloride dissolved in 100 ml of distilled water and dissolved it to give uniform solution.

Preparation of Sustained release microspheres

- Required quantities of Na. alginate & selected polymers were dissolved in purified water to form a homogenous solution.
- The drug was added to the polymer solution and mix thoroughly with help of a mechanical stirrer at 1000rpm for 1hr. To form viscous dispersion
- The resulting dispersion was then added manually drop wise into 10% w/v calcium chloride solution through a syringe with a needle.
- The added droplets were allowed to retain in $CaCl_2$ solution for 3hr to complete curing
- The microspheres were collected by decantation & washed with water & dried at 45ºc.

Table 1: Composition of Venlafaxine Hcl sustained release microspheres

Sr. No	Ingredients	F1	F2	F3	F4	F5
1	Venlafaxine Hcl (mg)	500	500	500	500	500
2	Sodium alginate (mg)	400	400	400	400	400
3	HPMC K4M (mg)	100	-	-	-	-
4	HPMC K15M (mg)	-	100	-	-	-
5	HPMC K100M (mg)	-	-	100	-	-
6	HPMC 15cps (mg)	-	-	-	100	-
7	Carbapol 934 (mg)	-	-	-	-	100
8	$Cacl_2$ (%w/v)	10	10	10	10	10
9	Distilled Water (ml)	QS	QS	QS	QS	QS

Fig 2: Prepared venlafaxine HCl microspheres

Evalution studies

Solubility study

It was important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in drugs.

Analytical methods

Determination of λ max

The absorption maximum of the standard solution was scanned between 200- 400 nm regions on Jasco V-630 UV-Visible spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

Development of standard curve of Venlafaxine Hydrochloride in 0.1N NaOH

Preparation of 0.1N NaOH

0.1N NaOH was prepared according to I.P. 1996.40.00 gm of pellets of NaOH was diluted with fresh distilled water to produced 1000 ml.

Preparation of stock solution of Venlafaxine Hydrochloride in 0.1 N NaOH

Accurately weighed 10 mg of Venlafaxine Hydrochloride was dissolved in little quantity of 0.1 N NaOH up to volume 100 ml (stock solution)

Procedure: From the stock solution, aliquots of 0.5, 1, 1.5, 2, 2.5 ml were transferred to 10 ml volumetric flasks and final volume was made to (diluted upto) 10 ml with 0.1N NaOH to form 5, 10, 15, 20, 25 µg/ml conc. Absorbance values of these solutions were measured against blank (0.1N NaOH) at 226 nm using UV-Visible spectrophotometer.

Identification by FTIR spectroscopy

Venlafaxine Hydrochloride discs were prepared by pressing the Venlafaxine Hydrochloride with potassium bromide and the spectra between 4000^{-1} to 500^{-1} cm was obtained under the operational conditions. The absorption spectra obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

Identification by melting point: Melting point of the drug was obtained by the melting the drug in melting point apparatus.

Determination of bulk density and tapped density

An accurately weighed quantity of the powder was carefully poured into the graduated cylinder and the volume was measured then the graduated cylinder was closed with lid, set into the density determination apparatus (Bulk density apparatus, Electrolab, Mumbai). The density apparatus was set for 500 taps and after that, the volume was measured and continued operations till the two consecutive readings were equal.

Compressibility index (Carr's Index) & Hausner Ratio

The Compressibility index and Hausner's ratio are measures for the property of a powder to be compressed. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, they are frequently greater inter particular interaction. A greater difference between the bulk and tapped densities will be observed. These differences are directly related to the compressibility index and the Hausner Ratio. The compressibility index and Hausner ratio may be calculated using measured values for bulk density and tapped density as follows:

Table 2: Acceptance criteria of flow properties

Sr. No.	Flow Properties	Angle of Repose (θ)	Comp. Index (%)	Hausner ratio
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair	36-40	16-20	1.19-1.25
4.	Passable	41-45	21-25	1.26-1.34
5.	Poor	46-55	26-31	1.35-1.45

Angle of repose

The flow properties of the drug are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces of the drug are determined by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan \theta = h/r$

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

Where,

h = height of pile

r = radius of the base pile

θ = angle of repose

Percentage yield

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula.

$$\text{Percentage yield} = \frac{\text{Practical yield of microspheres} \times 100}{\text{Theoretical yield of Microspheres}}$$

Drug content estimation

A number of microspheres (Powder) equivalent to 25 mg of Venalfaxine Hcl in 1000 ml of distilled water. Then the resultant dispersion was kept 24 hr. for complete Solubilization of drug and filtered through Whatman filter paper. Then to pipette out 1ml of resultant solution in 10 ml volumetric flask volume make upto 10 ml with distilled water and observed spectrophotometrically at 226 nm.

Entrapment efficiency of the drug

The microspheres equivalent to 10mg of Venlafaxine Hydrochloride were weighed and dispersed in Distilled water. The resulting mixture was shake on mechanical shaker for about 24 hours. The solution was then filtered and drug content was estimated by UV spectrophotometry.

Encapsulation Efficiency = $(W_1/W_2) \times 100$

W_1 = Actual Weight of Drug in Sample

W_2 = Microspheres Sample Weight

***In-vitro* drug release study**

In *vitro* drug release studies of the prepared microspheres were carried out employing dissolution test apparatus (TDL-08L, Vigo (DT6D) (Electro lab Mumbai) in 900 ml of phosphate buffer pH 7.4 maintained at 37 ± 0.5ºC & 50 rpm. At specified time intervals (0,1,2,3,4,5,6,7,8,9,10,11,12 & 14, 16 hr), an aliquot of 5 ml sample was withdrawn with replacement of fresh medium to maintain the sink condition. The sample were filtered through Whatman filter paper and analyzed spectrophotometrically at absorbance 226 nm. From the drug contain, the cumulative percentage drug release vs. Time was plotted to compare the in *vitro* drug release form the prepared the microsphere formulation.

Stability Study

Stability tests are much simpler and needed less frequently for coarse dispersion, where particle sizes and phase changes must be followed. To overcome the problem of metastable formation which are not thermodynamically stable and takes long time to separate, thermodynamic stability test is recommended. Stability was carried out as per ICH guidelines.

Result and discussion

Solubility Profile

Table 3: Solubility profile of venlafaxine Hcl.

Sr. No.	Solvent	Solubility
1	Distilled water	Soluble
2	Methanol	Freely Soluble
3	Ethanol	Sparingly Soluble
4	Acetone	Practically Insoluble
5	Dichloromethane	Practically Soluble

Determination of λ max in 0.1N NaOH

The absorption maximum for Venlafaxine Hydrochloride in 0.1N NaOH was found to be 226 nm and absorption maximum was shown in Figure 2.

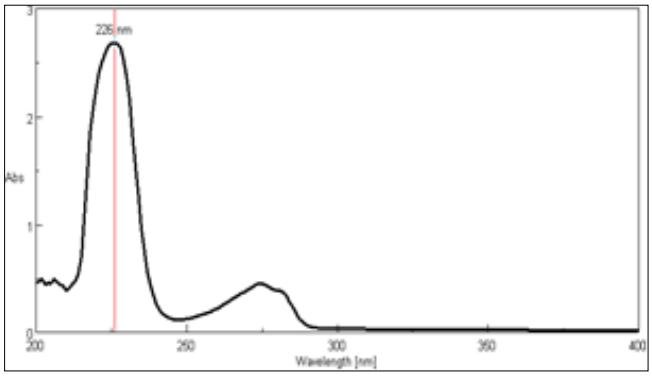


Fig 3: Calibration curve of venlafaxine hydrochloride in 0.1n NaOH

Preparation of standard graph of Venlafaxine Hydrochloride in 0.1N NaOH

Absorbance was obtained in various concentrations of Venlafaxine Hydrochloride in 0.1N NaOH Absorbance was obtained in various concentrations of Venlafaxine Hydrochloride in 0.1N NaOH were given in Table 5 and shown in Figure 4. The graph of absorbance vs. concentration for Venlafaxine Hydrochloride was found to be linear in the concentration range of 5-25 µg /ml. The calibration curve parameters shown in Table 6. So, the drug obeys Beer- Lambert's law in the range of 5-25 µg/ml.

Table 4: Spectrophotometric Data of concentration and absorbance for Venlafaxine Hydrochloride in0.1N NaOH

Sr. No	Concentration(µg/ml)	Absorbance
1	0	0.000
2	5	0.3244
3	10	0.4941
4	15	0.6923
5	20	0.9001
6	25	1.1115

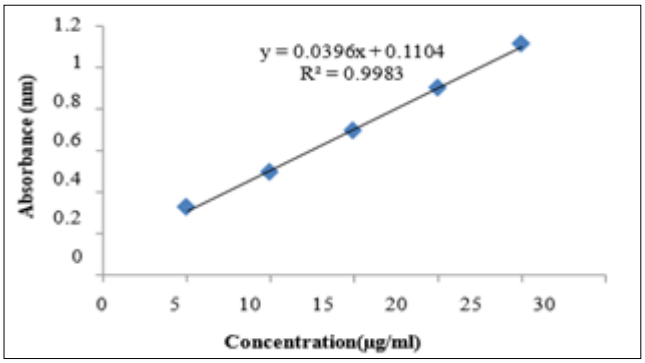


Fig 4: Standard graph of Venlafaxine Hydrochloride in 0.1N NaOH

Table 5: Data for calibration curve Parameters for 0.1 N NaOH

Sr. No	Parameters	Values
1	Absorbance maximum (λmax) nm	226 nm
2	Correlation coefficient (r)	0.9983
3	Slope (m)	0.0396
4	Intercept (c)	0.1104
5	Regression equation	y = 0.0396x+1.110

Identification by FTIR spectroscopy

The FTIR spectrum of Venlafaxine Hydrochloride was showed in Figure 05.

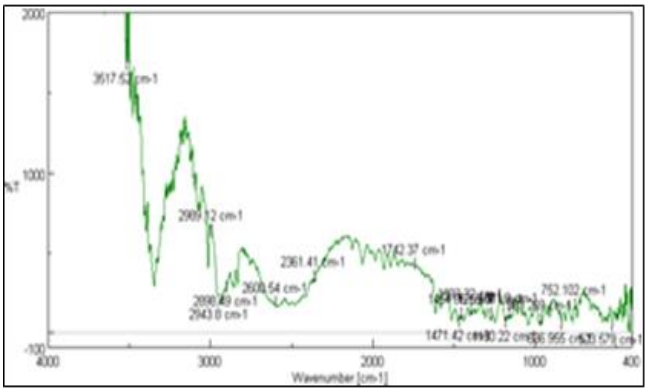


Fig 5: FTIR spectrum of Venlafaxine Hydrochloride

Melting point

Melting point values of Venlafaxine Hydrochloride sample was found to be range 215ºC to 216ºC. The reported melting point for Venlafaxine Hydrochloride was 215.3ºC. Hence, experimental values were in good agreement with official values.

Table 6: Data of Characterization of the microspheres

Sr. No.	Formulation code	Bulk Density	Tapped Density	Carr's Index	Hausner ratio	Angle of repose
1	F1	0.65±0.01	0.70±0.02	0.071±0.65	1.07±0.07	21º98'±0.31
2	F2	0.84±0.05	0.92±0.02	0.086±0.50	1.09±0.06	23º27'±0.62
3	F3	0.90±0.019	0.98±0.05	0.081±0.76	1.09±0.07	23º97'±0.37
4	F4	0.74±0.015	0.82±0.02	0.097±0.35	1.10±0.01	22º5'±0.52
5	F5	0.70±0.04	0.76±0.03	0.078±0.15	1.08±0.03	23º74'±0.43

Percentage Yield, Drug Content and Entrapment Efficiency:

The percentage yield, Drug Content and Entrapment Efficiency of Sustained release microspheres were found to various polymer. The maximum yield of microspheres was 88% in HPMC 15cps polymer, 83% in HPMC K100M polymer and 81% in Carbapol 934. Better yield of microspheres was obtained from HPMC 15cps. Drug content and Entrapment efficiency was high in HPMC 15 cps containing formulations when compared to HPMC K100M and Carbapol 934 formulations. All the formulations were Percentage Yield, Drug content and Entrapment efficiency data was showed in Table 08.

Table 7: Percentage yield, Drug content and Percentage Entrapment efficiency

S. No.	Formulations	% Yield	% Drug content	% Entrapment
1	F1	80	50	66
2	F2	78	48	64
3	F3	83	60	80
4	F4	88	70	93
5	F5	81	43	66

In-*vitro* Dissolution Studies

In-vitro drug released profiles of Venlafaxine Hydrochloride microspheres were performed in each formulation using phosphate buffer (pH 7.4) up to 16 hours. It was represented in Table 09 and showed in Figure 6.

Table 8: *In-vitro* drug released profiles of Venlafaxine Hydrochloride Sustained release microspheres

Time in hours	% Drug release				
	F1 %	F2 %	F3 %	F4 %	F5 %
0	0	0	0	0	0
1	20.54±1.2	12.13±1.0	19.36±1.06	16.9±1.2	7.05±1.4
2	28.4±1.1	19.3±1.1	28.6±1.45	26.4±1.02	16.24±1.4
3	36.02±1.3	24.03±1.2	35.37±1.41	34.1±1.4	21.68±1.2
4	45.4±1.2	28.25±1.2	41.57±1.2	41.1±1.9	25.64±1.09
5	53.54±1.06	36.86±1.1	47.2±1.1	48.25±1.0	28.3±1.3
6	59.4±1.5	39.75±1.2	52.3±1.4	54.56±1.6	30.31±0.8
7	63.3±1.1	43.03±1.3	56.68±1.5	61.27±1.0	35.22±1.1
8	68.05±1.4	46.68±1.2	63.2±1.1	68.29±1.0	41.04±0.9
9	73.14±1.2	50.3±1.8	68.23±1.7	75.73±0.7	48.3±1.1
10	80.52±1.1	54.36±1.4	72.2±1.8	82.64±1.0	54.14±1.2
11	86.4±1.43	63.03±1.2	78.4±1.2	88.4±1.3	63.12±1.24
12	92.13±2.03	75.2±1.23	84.3±1.4	90.04±1.6	72.2±1.1
14	93.6±1.4	81.68±1.03	90.12±0.95	93.03±2.30	84.02±0.8
16	93.3±2.03	89.5±1.67	93.04±1.05	96.2±2.45	88.6±0.91

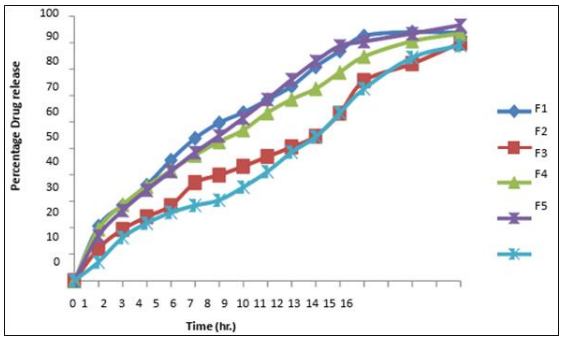


Fig 6: Std. graph of in-*vitro* drug release of formulations (F1-F5)

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Conflict of interest

The author declares that they have no conflict of interest.

Conclusion

1. Sustained release microspheres of Venlafaxine HCl were successfully prepared by ionic gelation method and conformed that it was a best method for preparing microspheres from its high percentage yield, drug content and Entrapment Efficiency.
2. The identification of drug was carried out by FTIR spectroscopy and melting point. The physicochemical parameters such as appearance, solubility Study were performed by suitable method. The analytical profile of drug was evaluated for determination of absorption maximum, development standard graph.
3. Sustained release microspheres were obtained by ionic gelation method for all the formulation from F1 to F5. By using various grade of HPMC polymer.
4. All formulations were evaluated for the percentage yield, drug content, Entrapment Efficiency, Bulk Density, Tapped Density, Carr's Index, Hausner Ratio, Angle of Repose & In *vitro* drug released profile.
5. In the present study, Venlafaxine Hcl was used as a model drug for the formulation of Microspheres for oral delivery.
6. Microspheres were prepared by ionic gelation method. The formulation was optimized using different polymers as like (Few grades of HPMC).
7. The formulation of microspheres in that Identification & characterization of drug was performed. That includes physical characterization, UV- analysis, Infrared analysis (FTIR).
8. The formulations were characterized for drug content, Entrapment Efficiency dissolution profile. The % drug contain was found to be 88% and Entrapment Efficiency was found to be 93%. The F4 shows maximum drug content and Entrapment Efficiency.
9. *In-vitro* drug dissolutions study was performed on type II dissolution apparatus and due to drug release was found to be 88.6 to 96.2 %.
10. The significant enhanced dissolution rate was observed; hence the formulation can show improved bioavailability and reduced dose frequency by ion gelation method for microsphere formulation.

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