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Original Article

Formulation and Evaluation of Gastroretentive Floating Microspheres of Rilpivirine Hydrochloride

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ABSTRACT

Background: Systems of floating drug delivery have a bulk density less than gastric fluids and thus it remains buoyant in the stomach without having any effect on gastric emptying rate for prolonged period of time. Rilpivirine is an antiviral drug is used to treat human immunodeficiency virus (HIV), to combat the spread of (HIV), delivery of long acting; antiretroviral (ARV) drugs would be very beneficial for prevention and treatment. However the poor bioavailability of the drug requires attention in improving it and the technique of floating microspheres was investigated for the same objective. **Methods:** Floating microspheres of Rilpivirine are formulated by Emulsion – solvent diffusion technique using Ethyl cellulose and carbopol as polymers. The floating microspheres were subjected to evaluation for micrometric properties, percentage yield, particle size, drug polymer compatibility, scanning electron microscopy (SEM) and *in vitro* drug release studies and kinetics of drug release. **Results:** The results show that as the polymer concentration increases, the particle size, percentage yield, *in vitro* drug release was affected of floating microspheres. The micromeritic test was performed to confirm the particle size, and SEM results confirmed their hollow structure with smooth surface. Optimized formulation has shown good percentage yield, encapsulation efficiency, drug release was 98.25% at the end of 12 hrs, the release was found to follow fickian diffusion with excellent drug release for long period of time. **Conclusion:** The results conclude that floating microspheres formulation of rilpivirine HCl could be effective tool in improving the bioavailability of drug for improved absorption.

Key words: Rilpivirine HCl, carbopol, floating, microspheres, SEM, antiretroviral.

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INTRODUCTION

The major drawback of oral drug delivery system is that not all the drug molecules are absorbed uniformly throughout the gastro intestinal tract due to the gastrointestinal tract physiology and transit time that leads to improper bioavailability and non-reproducible therapeutic effects. Hence gastroretentive delivery systems are developed which are a type of control release systems.[1] It includes floating microspheres which are defined as solid, spherical particles ranging from 1-1000 micrometer in size. They exhibit free flowing nature and powders consisting of synthetic polymers which are biodegradable. Generally prepared by incorporating drug dispersed throughout the matrix that have potential for controlled release of drugs.[2] Gastroretentive drug delivery (GRDD) is an approach to prolong the gastric residence time, therefore targeting site-specific release of drug in the upper gastrointestinal tract (GIT) for local or systemic effects.[3] Based on this criteria different approaches have been proposed to retain dosage form in the stomach.[4]

Floating microspheres are a type of gastroretentive systems that are based on non-effervescent approach. The medicament is released gradually at controlled rate, resulting in improved gastric retention with less fluctuations in plasma concentration of drug.[5] Rilpivirine (RPV) is a next-generation non-nucleoside reverse tran-scriptase inhibitor that has potent activity against wild-type human immunodeficiency virus (HIV) and mutants resistant to first-generation Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and been approved for treatment since 2011.[6] The physio-chemical and pharmacological properties of RPV have led to exploring the development of a sustained release formulations, aimed at overcoming tedious frequent dosing regimen.[7]

The present work aims at developing a floating drug delivery system of RPV, in form of microspheres using polymers carbopol and ethylcellulose. The solvent evaporation technique was employed for formulation and the formulated microspheres were evaluated to prove the attainment of desired sustained release of the drug with effective drug encapsulation.[8]

MATERIALS AND METHODS

Materials

Rilpivirine HCl was gift sample from Hetero Labs Pvt Ltd, polymers and other chemicals were purchased from S.D.Fine chemicals.

Methods

Organoleptic properties: Colour and nature, taste and odour of the drug were examined.

Identification of drug and excipient compatibility study

Procedure by FT-IR Studies: The IR spectrums of the rilpivirine HCl with excipients were taken by using alpha bruker FTIR spectrometer.[9] The transmission minima obtained in the spectra with the sample corresponded in functional groups position and relative size to those in the spectrum obtained with the standards.

UV Spectroscopic Method for Analysis of Rilpivirine HCl

Preparation of reagents: Phosphate buffer pH of 6.8 was prepared by taking 50.0 ml of 0.2M Potassium dihydrogen phosphate in a 200 ml

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volumetric flask and add the specified volume of 0.2M of sodium hydrochloride and then add water to volume.

Standard calibration curve: Stock solution of the drug was prepared by dissolving 100mg of drug in 100ml of Phosphate buffer pH of 6.8. From this stock solution 2-20µg/ml concentrations were prepared after suitable dilutions. The absorbance's of each test solutions were checked at λ_{max} of 254nm using UV-Visible spectrophotometer against buffer.

Formulation Of Rilpivirine HCl Floating Microspheres – Formulation design

Floating microspheres were formulated by Emulsion solvent diffusion. Weighed amount of rilpivirine HCl was mixed with carbopol and ethyl cellulose Drug and polymers are mixed in a solution of ethanol:dichloromethane at room temperature. Sodium bicarbonate was mixed to above solution. The drug polymer solution was poured slowly in 100ml of water containing 0.02% w/v Tween 80 maintained at constant temperature of 40°C and preparation was stirred at 300rpm for 1hr. The finely developed microspheres were then filtered, and dried overnight at 40°C.[10]

Evaluation of Rilpivirine HCl Floating microspheres

Microsphere Particle Size determination: The particle size of the microspheres was determined with an optical microscope under regular polarized light, and mean particle size was calculated by measuring 100 microspheres with the a calibrated ocular micrometer.[11]

Angle of repose

Angle of repose of microspheres measures the resistance to particles flow, and is determined by fixed funnel method. Where, (θ) is the angle of repose, H/D is the surface area of standing height of microspheres heap formed paper after dropping the microspheres from glass funnel.

$$\phi = \tan^{-1}(h/r)$$

Compressibility Index

Also called as Carr's index and is determined by following equation.

$$\text{Carr's Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Hausner's ratio

Hausner's ratio is found by the equation.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Drug Entrapment Efficiency

The drug content of rilpivirine HCl loaded microspheres was determined by dispersing 100mg microspheres in 10ml of ethanol, which was stirred with a magnetic bead for 8hr to extract the drug. The samples were diluted and analysed spectrometrically at 254nm and the percentage drug entrapment was calculated.[12,13]

$$\%\ \text{Drug entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} * 100$$

Percentage yield

The percentage yield was determined by:

$$\text{Percentage yield} = \frac{\text{Weight of floating microspheres}}{\text{Weight of drug and polymer}} * 100$$

In vitro Drug Release Study

In vitro drug release studies of floating microspheres were performed using USP type I dissolution apparatus in 900ml of Phosphate buffer (PH 6.8) dissolution media at 100rpm and 37°C. At each specified interval 5ml of the sample was collected and was replaced by equal volumes of fresh dissolution medium on each occasion. The sample was analyzed by UV Spectrophotometer at 254nm.

In vitro Release kinetics

The release data was fitted into various mathematical models. The parameters like 'n' and the time component 'k' release rate constant and 'R', which is coefficient of regression are determined by korsmeyer-peppas equation to have an idea on release mechanism. To examine the release mechanism of rilpivirine HCl from the microspheres, the release data was fitted into Peppa'sequation.

Percentage Buoyancy Rilpivirine HCl Floating Microspheres

In vitro floating nature can be determined by determining % buoyancy and carried our in USP type II dissolution apparatus by means of spreading floating microspheres in Phosphate buffer (pH 6.8) containing the surfactants. The media stirred at 100 rpm at 37±0.5°C. After specific interval of time, samples are collected and analysed for drug release.

Swelling Index

A 100 mg quantity of microspheres was soaked in 20 mL of phosphate buffer, pH 6.8 for 12 hr. After the 12 hr, the microspheres were then removed and excess buffer was wiped using a dry filter paper and their final weights were determined.

$$\text{Swelling Index}(\%) = \frac{\text{change in weight (mg)}}{\text{original weight (mg)}} * 100$$

RESULTS

Development of Calibration Curve of Rilpivirine HCl

The standard graph of rilpivirine HCl was constructed in phosphate buffer, linearity was observed in the absorbance values obtained, hence this curve justifies the analytical method developed for further analysis in *in vitro* testing studies.

Calibration curve is plotted as shown in Figure 1.

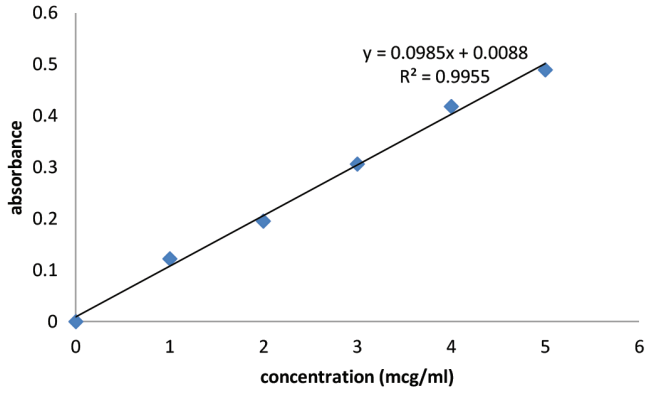

Figure 1: Calibration curve of Rilpivirine HCl.

Drug-excipients compatibility by FTIR

The IR spectrum of RPV is characterized by typical absorption bands at about, 1649 cm^{-1}(C=O stretch), 1430 cm^{-1}(C-H bending), 1330 cm^{-1}(-CH wagging) and 1190cm^{-1} (symmetric C-N stretching).[14] There is a decrease of peak intensities observed in optimum formulation and all other peaks of RPV were smooth indicating strong physical interaction of the drug with excipients, same being depicted in Figures 2 and 3.

Percentage yield, Drug Content, Entrapment efficiency, *in vitro* buoyancy of microspheres of Rilpivirine HCl

The percentage yield of different formulation was in range 49-88% as shown in the Table 2. The maximum percentage yield was found in F_4. The drug Entrapment efficiency was estimated and the results were in the range of 61-91%. The microspheres formulations F1 to F6 exhibited good floating ability range from 68-92% (Table 2).

The Scanning Electron Microscopy (SEM)

The micrographs of the microspheres exhibited hollow structure with very smooth surface and exhibited ranges of sizes. Outer surface of microspheres was seem to be smooth, dense whereas the internal surface was found to be porous. The clear morphology with the size ranges is seen in Figure 4.

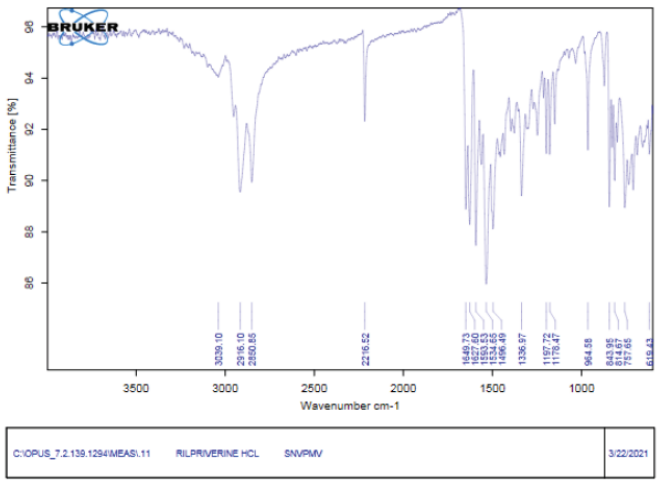

Figure 2: FTIR results of Rilpivirine HCl.

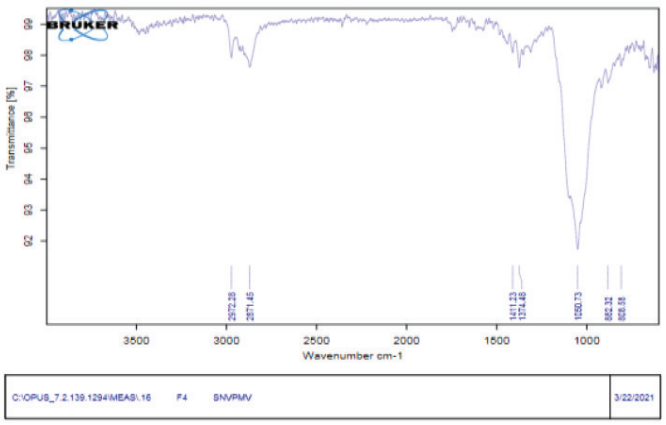

Figure 3: FTIR results of formulation.

Table 1: Formulation of Rilpivirine HCl Floating microspheres.

Formulation Code	Ingredients						
	Drug (mg)	Ethyl cellulose (mg)	Carbopol (mg)	Ethanol /ml	Dichloro methane/ ml	Sodium bicarbonate (mg)	Tween 80 (%)
F1	50	100	100	10	10	100	0.02
F2	50	100	200	10	10	100	0.02
F3	50	100	300	10	10	100	0.02
F4	50	100	400	10	10	100	0.02
F5	50	100	500	10	10	100	0.02
F6	50	100	600	10	10	100	0.02

Table 2: Percentage yield, Drug Content, Entrapment efficiency, Drug release, *in vitro* buoyancy of microspheres of Rilpivirine HCl.

FormulationNo.	Percentageyield	Drug Content in%	Entrapment Efficiency (%)	%Buoyancy	Swelling index
F1	87	56	66	67	45.4
F2	84	67	75	78	67.4
F3	96	74	62	86	78.2
F4	98	97	93	94	92.4
F5	84	88	79	65	56.2
F6	83	85	82	78	60.2

In vitro drug release studies

Optimized formulation from the above physical tests (F_4) showed high release of drug when compared to formulations with other ratio (F_1, F_2, F_3, F_4, F_5, F_6). The graph of cumulative % V/s time (min) for all formulations was plotted in Figure 2.

DISCUSSION

In the FTIR studies, there is no additional peaks seen, indicating absence of any chemical interaction. The drug Entrapment determination also showed that the drug was uniformly distributed throughout the preparation.[15] *In vitro* buoyancy test was carried out to estimate buoyancy of prepared microspheres. The microspheres formulations F1 to F6 exhibited good floating ability range from 68-92% (Table 2). The swelling index values indicate excellent absorption of gastric fluids by the polymers to form a swell able polymer sponges which released the drug in sustained effect over long periods of time.[16] Drug content of different formulation was in range 39% -91%. Maximum drug content was found in F4. The microspheres contained planned dose of the drug effectively in optimum ratios of polymers and proper stirring time so as to release drug in sustained manner. (Table 2) The angle of repose of different formulation was in range 2.6-1.7, Bulk and tapped densities showed good pack ability of floating microspheres. The particle size of different formulation was in range 118-122%. The tap density of different formulation was in range 0.20-0.25. Bulk density of formulation was in range 0.23-0.152 as shown in Table 3. Release studies of all the formulations of microspheres were conducted in phosphate buffer saline pH 6.8 solution. It was observed

Table 3: **Micrometric properties of floating microspheres of Rilpivirine HCl.**

Formulation	Particle size (µm)	Tapped density (gm/cm³)	Bulk density (gm/cm³)	Angleof repose (degree)	Compressibility Index (%)
F1	158.06	0.261	0.132	2.2	33
F2	118.06	0.250	0.120	2.3	32
F3	143.06	0.251	0.120	2.4	30
F4	144.04	0.252	0.121	1.5	21
F5	151.01	0.250	0.134	1.2	32
F6	136.08	0.262	0.121	1.8	22

Table 4: **Release Kinetics of Optimised Formulation of R^2 value.**

Formula code	Zeroorder	Firstorder	Higuchi	Korsemeyer	
	R^2	R^2	R^2	R^2	n
F4	0.9336	0.9153	0.959	0.9825	0.814

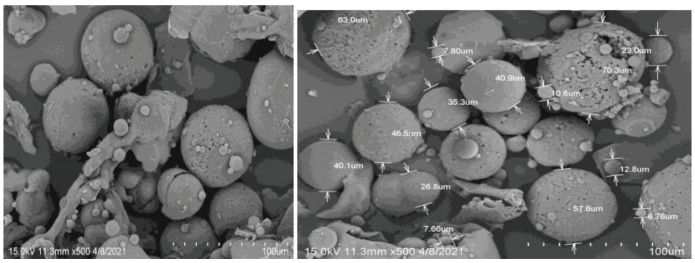

Figure 4: SEM photographs of optimized formulation.

that ratio of drug, ethyl cellulose and carbopol, influences the drug release pattern.[17] The mechanism of drug release can be analyzed and kinetics of drug release from dosage form can be determined by fitting to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer- Peppas model. The values are depicted below. The (R^2) was used as an indicator of the best fitting for each of the models. The kinetic data analysis of all the formulations reached higher coefficient of determination with the Korsmeyer-Peppas model (*R2*=0.914 to 0.996) whereas release exponent value (n) ranged from 0.498 to 0.743. From the coefficient of determination and release exponent values, it can be suggested that mechanism of release follows korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion. The formulation of microspheres follows non-fickian diffusion (anamolous). The drug release was found to be by both diffusion as well as erosion. The possible mechanism of action is by Non-fickian (koresmeyer peppas model) and Higuchi matrix model. Morphology of floating microspheres was observed by scanning electron microscopy. Outer surface of microspheres was seem to be smooth, dense whereas the internal surface was found to be porous. Shell of microspheres also exhibited slight porous nature, could be reason of the evaporation of solvent within shell of the microspheres after causing smooth and dense area.

CONCLUSION

The drug absorption within the GIT is a variable process. This research is undertaken with an aim to plan, formulate and evaluate the novel delivery systems –the floating microspheres. This novel system helps in prolonged gastric retention with extended time for the drug absorption. In this study the floating microspheres of rilpivirine HCl are prepared and evaluated. They are prepared using the ethyl cellulose in combination with carbopol polymers. The best formulation from the 6 batches (F1 to F6), found to be efficient with good recovery yield, percent drug entrapment and release of drug, was F4 with drug release of 98.46%.Floating microspheres are evaluated for surface morphology and the surface is found to be smooth. The *in vitro* drug release kinetics is performed using zero-order, first-order, Higuchi and korsemeyer models. From the R^2 value obtained from korsemeyer peppas method i.e., 0.9825 it is observed that the release of drug is slow and follows Fickian diffusion model.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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