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DEVELOPMENT AND CHARACTERIZATION OF MICROPARTICLES OF RAZATRIPTAN BENZOATE DRUG CARRIER SYSTEM VIA NASAL ROUTE

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ABSTRACT

Objective: Rizatriptan Benzoate is the 5H1 receptor agonist and used in treatment of migraine, cluster headache. The main objective is to develop ideal anti-migraine nasal mucoadhesive microparticles as local and systemic drug delivery system. Method: An attempt was made to formulate the nasal mucoadhesive microparticle of Rizatriptan Benzoate with excipients like mucoadhesive polymers i.e HPMC, ethyl cellulose etc., by using modified solvent evaporation method. And evaluated them for production yield, drug loading efficiency, surface morphology by SEM, drug content, particle size, *In-vitro* drug release studies. The release rates were studied using GRAPHPAD PRISM software. Result and discussion: The prepared microparticles of Rizatriptan Benzoateformulations were found to be satisfactory particle size i.e in the range of 36.96 to 53.28µm,mucoadhesion time of F5 found to be 370 min,drug content was found to be72.86 % to 81.80 % and drug release of the drug follow zero order kinetic model. Optimized formulation F5shows that the developed formulations have shown improved dissolution profile in comparison to other formulation.The developed nasal mucoadhesive microparticles are having potential to deliver of anti-migraine drugs via nasal route.

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INTRODUCTION

Intranasal therapy has been an accepted and preferredform of treatment for many diseases in the Ayurvedic system of Indian medicine.There is number of formulations available in the market like nasal drops, spray, gel, powders, nano/microparticles, ointments, microemulsions etc.[1] and these have huge advantages by compare with other route of administration, self medication is possible,it enhances the better systemic bioavailability of protein and peptide type of drugs by rapid absorption due to formulation has such bioadhesive polymers[2]and overcome the problems of first pass metabolism, degrading of drug in GIT, which is occurred in oral routeand it is needle free, overcome the problems of need of sterility, pain, discomfort which caused by parenteral route of administration, alsoit suitable for restricting and obstacles blood brain barrier so that drug can delivered in both controlled and conventional releaseby local and systemic in the biophase of CNS.[3]Although it has some limitations like high molecular weight compounds cannot be delivered through this route, irritation of nasal mucosa by drugs may occur but these can be negotiable.

Migraine

It is a primary CNS disorder,characterized by the repetition of attacks rather than a single attack, which may recur in many individuals under certain circumstances (eg, stress).Headache with focal neurological signs or symptoms like visual disturbance, numbness or tingling in the hand, tongue or side of the face, or weakness in one arm are common in this case.[4]

Microparticulate Drug Delivery System

Microparticles are particulate dispersion or solid particles with 1-1000 µm in size range. The microparticles system allows entrapping the active drug within matrix, which eliminates the environmental stability problems, minimize the adverse effects regarding drug, increase the bioavailability by sustained activity, as well as enhance the patient compliance.This article focused on study of prepared microparticles evaluation and release kinetic activity.[5]

MATERIALS AND METHODS:

Rizatriptan benzoate sample gifted by Em-cure lab (pune), hydroxypropyl methyl cellulose (HPMC), ethyl cellulose, other excipients like dichloromethane, acetonitrile, methanol, liquid paraffin,tween 80, petroleum ether, etc.

METHODOLOGY:

Before proceed for actual formulation, we used to study preformulation and compatibility studies.

Preformulation Studies:

Preformulation studies include physical tests i.e description, melting point determination[6]by digital melting point apparatus, note down thetemperature at which the drug meltsand compatibility studieswith excipients.

Compatibility Studies[7]

Compatibility of drug with different polymers and other excipients were tested by Fourier transform infrared spectroscopy (FTIR) for disappearance or shifting of drug peaks in any of the spectra.[8,9]Differential scanning calorimetry (DSC)for determine the thermo tropic and thermal behavior of the drug withexcipients.[10]X-ray diffractometer (XRD)for determine the crystallinity natureofdrug and other excipients.[11,12]

PREPARATION METHOD

Preparation of Rizatriptan Benzoate loaded Microparticles:[13,14]

The formulation chart for formulating microparticles is shown in following table.

Table No.1 : Formulation Table of Rizatriptan Benzoate loaded Microparticles.

Sr. No	Formulation ratio (EC:HPMC)	Drug (mg)	Ethyl cellulose (EC) (mg)	HPMC (mg)
1	F 1(1:1)	100	150	150
2	F2(1:2)	100	150	300
3	F 3(1:3)	100	150	450
4	F 4(1:4)	100	150	600
5	F 5(1:5)	100	150	750

The active drug placed in a mixture of organic solvent to which weighed HPMC was added to form polymer solution. Ethyl cellulose was dissolved in acetone separately. Both the solutionswere mixed andadded in beaker containing liquid paraffin with tween 80by the help of syringe and continuous mechanical stirring was carried out at 2000 rpm for 2 hrs. The microparticles obtained were filtered and washed with ether. (Diagrammatic process shown in fig. no.1).

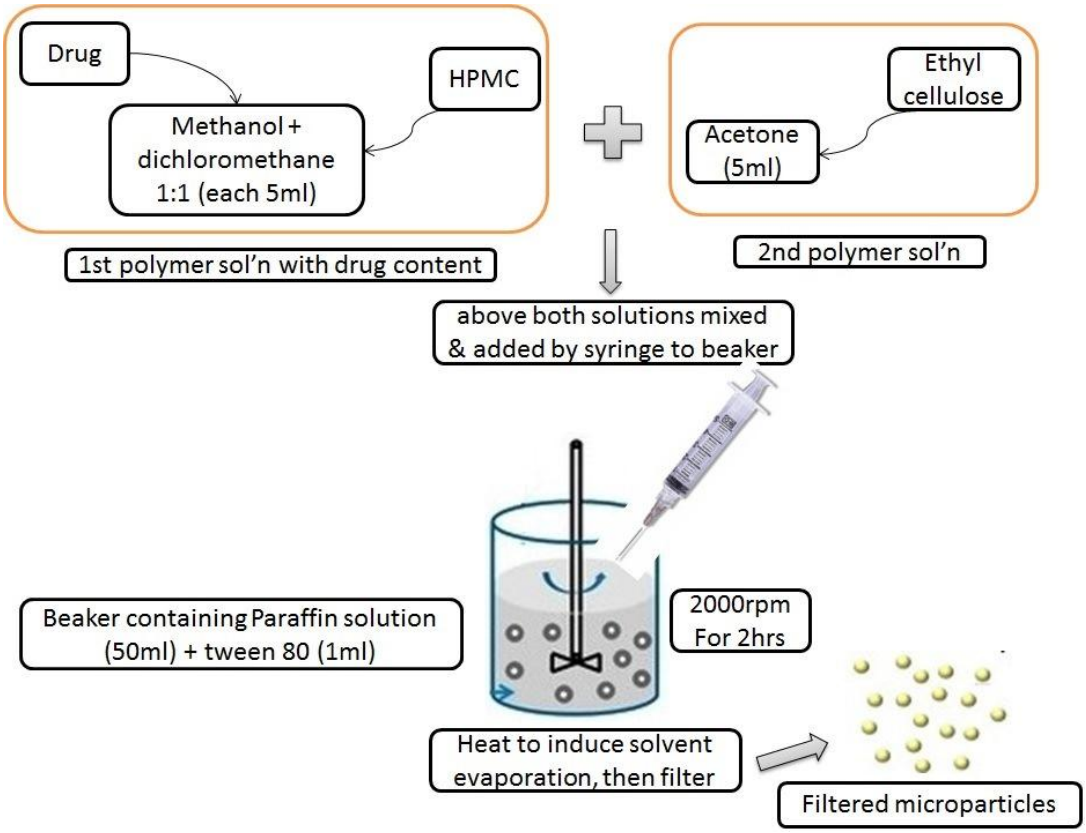


Fig. No.1:Microparticles preparation by modified emulsion solvent evaporation technique.

CHARACTERISTIC EVALUATION OF PREPARED MICROPARTICLES[15-19]

Percentage Yieldof Production:

The percentage yield was calculated using the following formula:

$$\% \text{ yield} = \frac{\text{Practical Mass (Microparticles)}}{\text{Theoretical Mass (Polymer + Drug)}} \times 100$$

Particle Size Analysis:

Optical microscopy is used for the particle size determination.

Determination of Drug loading Efficiency:

Drug loaded microparticles (100 mg) were dissolvedin 10 ml of 0.1 N HCL and keep for 12 hrs. Filter thecontent present in the solution was determined at 226nm using a UV visible spectrophotometer. Drug loading in the microparticles was estimated by using following formula:

$$L = Qm / Wm \times 100$$

Where, L – the percentage loading of microparticles,
Qm- quantity of the drug,Wm- weight of microparticles.

Dug content:

Prepared microparticles of drugs were assayed spectrophotometrically for the drug content at the maximum wavelength by proper dilution with solvent 0.1 N HCL.

$$\% \text{ Drug Content} = \frac{\text{Practical Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Mucoadhesive Time:

A small piece of sheep nasal mucosa was tied on to a glass slide using thread. Microparticle were spread on and the glass slide hung on groves of a USP tablet DT apparatus, operated in a manner that regular up down movements in the beaker containing phosphate buffer pH 6.4. Note down the time required for complete washing of microparticles.

In Vitro Drug Release Studies:

It was performed using USP (type 2) dissolution apparatus. Around 10 mg of sample was placed in tea bag and tested in simulated nasal electrolyte solution (SNES)with 30 rpm speed with 37ºC. Withdrawn sample (1ml) at predetermined time intervals (3, 6, 10, 25, 35, 50, 70, 90, 120, 180, and 240 min) and for each withdrawal replaced the corresponding volume with fresh SNES. Samples were filtered and assayed spectrophotometrically at 226 nm.

RESULTS AND DISCUSSION:

Preformulation Studies

Description:

TheRizatriptan Benzoate sample was found to be white to off-white, crystalline solid.

Melting Point of Rizatriptan Benzoate:

The melting point by literature is 178°C.After estimation it was found to be 176-180°C.

Compatibility study

IRStudy:

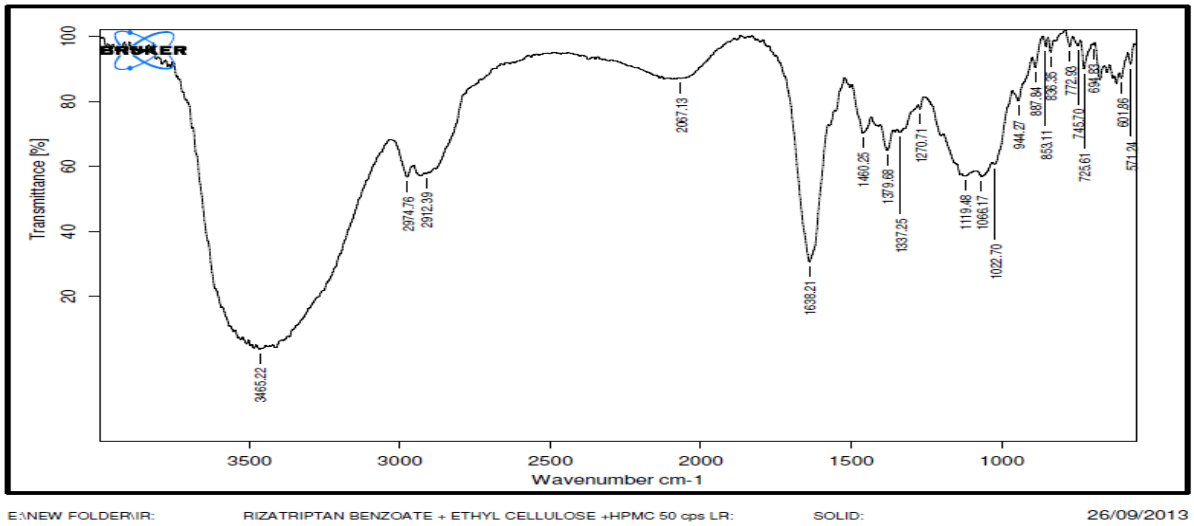


Fig. No. 2: IR of physical mixtureof Rizatriptan Benzoate + Ethyl Cellulose+ HPMC.

IR spectral peaks of the pure drug and drug in combination with polymers are observed in fig. no.2,which indicate that there is no interaction between Rizatriptan Benzoate and polymers when compared with the infrared spectrum of pure drug as all functional group frequencies were present.

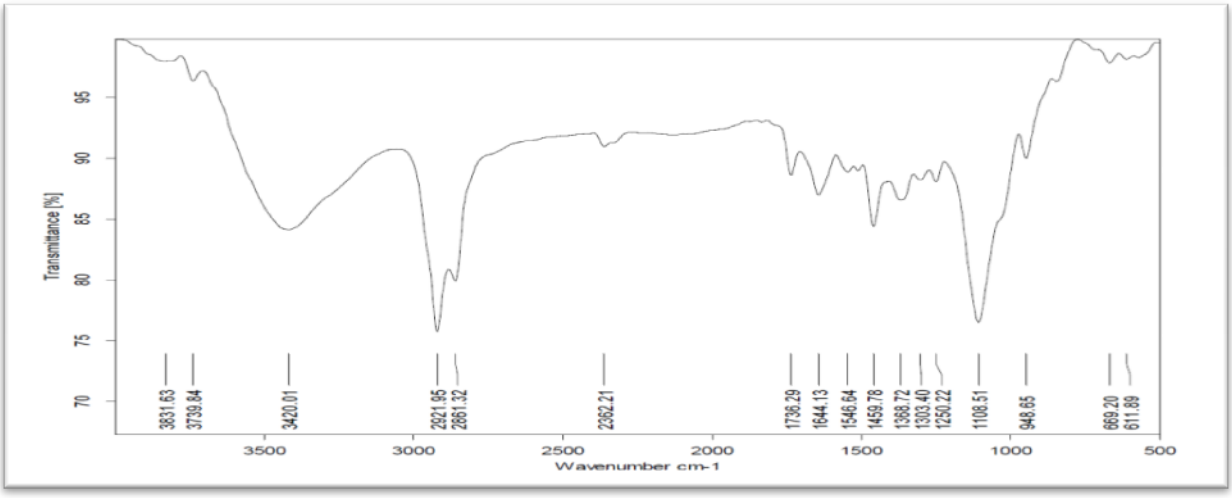


Fig. No. 3: IR of Rizatriptan Benzoate formulation.

The IR spectrum obtained of Rizatriptan Benzoate Formulation shows characteristic absorption peaks observed in fig. no.3

DSC study:

By using DSC analysis of drug and polymer, the nature of the drug inside the polymer matrix can be assessed.

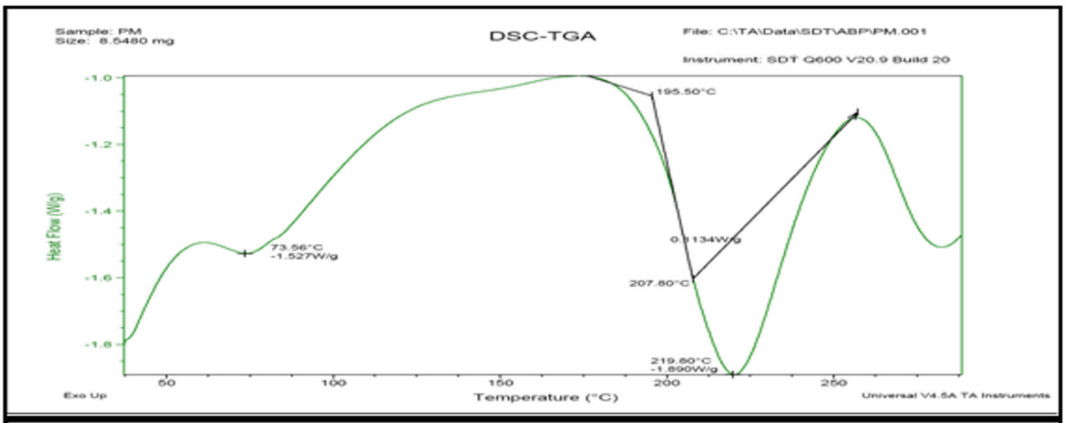


Fig. No.4: DSC of Rizatriptan Benzoate Formulation.

The results of DSC analysis observed in fig. no.4, showed that the sharp endotherm of pure drug at 178˚C, HPMC and Ethyl cellulose were 202˚C and 214˚C. The integrity of drug was unaffected when developed in to microparticle, this is confirmed by DSC of formulation where the composite melting peaks of pure drug, HPMC and ethyl cellulose were found to beat 195˚C, 207˚C and 219˚C indicating compatibility between drug polymer and processing conditions.

X-Ray Diffractometry study ofPowder sample:

It is powerful technique for identification of crystalline nature of drug and its combination with polymer, excipients.

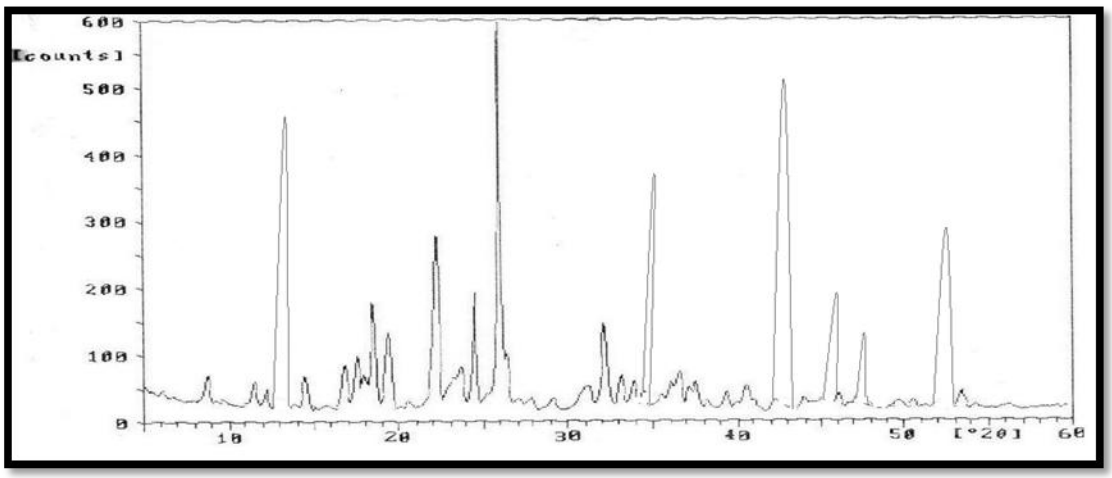


Fig No. 5: XRD of Rizatriptan Benzoate formulation.

The internal structures of Rizatriptan Benzoate, HPMC and Ethyl Cellulose are shown in X-ray diffraction pattern of the selected formulation F5is shown in fig. no.5. The graphical data indicated that the initial crystalline behaviour of Rizatriptan Benzoate has been altered marginally in the formulation. This may be causedby the effect of amorphous nature of polymer and may be due to less availability of drug for diffraction pattern in the formulation.

Percentage Production Yield:

From the study % production yield of developed formulations was found to independent of concentration of polymers employed in the development of microparticles.The result data shown in table no.2

Drug Loading Efficiency:

The drug loading efficiency of Rizatriptan Benzoate microparticle were successfully increased with HPMC polymers and decreased with ethyl cellulose polymer which range 66.88%-85.8%. The result data shown in table no.2

Drug Content Uniformity:

The percentage of drug content for formulated microparticles was found to be 72.86 % to 81.80 %. It complies with official specifications. All the formulation showed uniform drug content which was in accordance with percent drug loading study.The result data shown in table no.2

Shape and Surface Morphology:

Morphology of the microparticle was determined by SEM, and was foundspherical and their surface was smooth anddevoid of cracks giving them good appearanceshown in Fig. no.6.The SEM dataobtained on the drug-loaded microparticle are shown in table no.2.

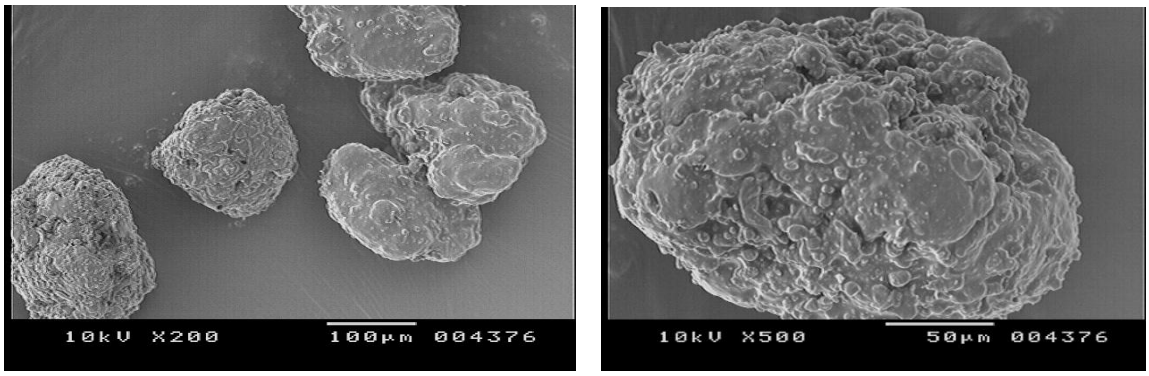


Fig. No. 6: SEM images ofRizatriptan Benzoate loaded microparticles formulation F5.

Particle Size:

The mean particle size of the microparticles was found in the range of 36.96 to53.28µm. According to literaturethe size should be between 10 to 100µm,which is appropriate for administering via nasal route. The speed of the stirrer increases the particle size decreases, thus in this studythe starring speedwas kept constant at 2000rpm,and observed that increase in speed causes breaking of the droplets resulting in non-uniform microparticles. The resultdata shown in table no.2

Mucoadhesive Time:

The increase amount of HPMC showed the more mucoadhesive strength of microparticles. For F1 mucoadhesion time was 91 min while F5 was 370 min. The high mucoadhesive time is due to more concentration of HPMC which is having excellent mucoadhesive property.This high mucoadhesion time is advocated for prolonged time of attachment of formulation to mucous membrane**.**The result data shown in table no.2

Table No.2: Characteristic evaluation of Rizatriptan BenzoateMicroparticles.

Formulation Code	F1	F2	F3	F4	F5
% Production Yield	87.6±2.1	69.9±1.5	87.4±1.8	92±2.8	85±2.1
Drug loading (%)	66.88±1.8	72.76±2.1	78.44±2.9	80.66±3.2	85.8±1.7
Drug Content (%)	78±1.6	80.98±1.4	77.21±2.2	72.86±2.4	81.80±2.4
Particle Size (µm)	53.28±1.4	36.63±1.9	39.96±1.5	43.29±2.1	43.29±2.3
Mucoadhesive time (min)	91±4	108±5	159±7	287±5	370±8

*Each value represents mean ± SD of three observations.

Drug Release Profile:

In vitro study the formulationF1 shows 75.54% while F5 shows 95.19% drug release. It evident that, as the amount of hydrophobic polymer (EC) increases, drug release decreases. The increase in the amount of EC may increase the density of the polymer matrix at higher concentration which may result in an increased diffusion path length and hence a decrease in the overall drug release matrix. The result data shown in table no.3, and observed in fig. no.7.

Table No. 3: In vitro drug release data.

Time in min.	Formulation F1	Formulation F2	Formulation F3	Formulation F4	Formulation F5
0	0	0	0	0	0
3	4.78±0.2	3.4±0.4	3.93±0.5	4.78±0.5	2.6±0.4
6	6.65±0.6	5.53±0.6	5.81±0.6	5.53±0.2	3.4±0.5
10	10.7±0.4	8.71±0.5	9.29±0.3	9.29±0.4	5.53±0.6
20	12.29±0.3	12.1±0.8	12.57±0.4	12.57±0.6	6.65±0.2
25	14.72±0.8	16.22±0.7	17.07±0.8	14.72±0.4	17.07±0.8
35	18.2±0.7	21.86±0.3	21.86±0.7	16.22±0.9	21.86±0.9
50	22.8±1.5	22.8±1.4	34.25±0.9	18.2±0.7	22.8±1.5
70	29.84±1.2	31.99±1.6	41.19±1.4	22.8±1.6	40.07±1.1
90	38.57±1.4	40.07±1.2	50.25±1.8	39.22±1.4	50.25±1.9
120	56.49±2.6	59.02±2.6	62.77±2.4	56.49±1.2	62.77±2.6
180	76.95±2.4	79.11±2.4	74.33±2.1	79.11±1.8	84.37±2.4
240	85.68±2.6	89.8±2.2	93.09±2.5	93.47±1.4	96.38±2.8

*Each value represents mean ± SD of three observations.

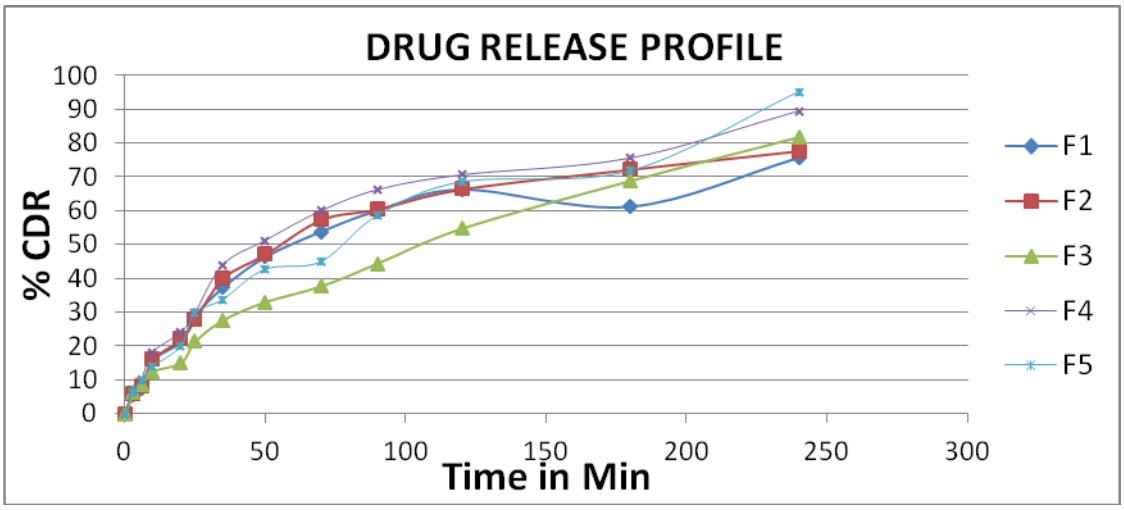


Fig. No. 7: Drug release profile of Rizatriptan Benzoate.

Kinetic Release Data for All Formulationsof Microparticles:

For studying the release kinetics, all formulations fit in the mathematical models. The drug release data obtained of all formulations were plotted in the following modes of data treatment, and shown in fig. no.8,9,10.

Zero Order Kinetics: - Time V/S. % Cumulative Drug Release.

First Order Kinetics: - Time V/S. Log % Cumulative Drug Remaining.

Higuchi Plot: - Square Root Of Time V/S. % Cumulative Drug Released.

Fig.08Comparative zero order release kinetics Rizatriptan Benzoate formulation F1 to F5.

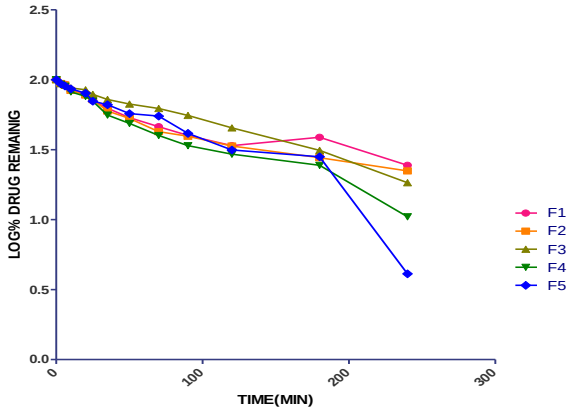
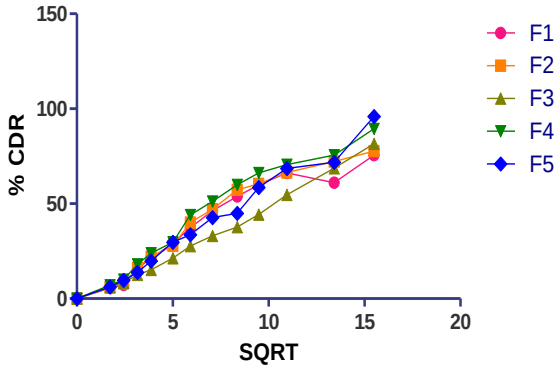


Fig.09 Comparative first order release kinetics Rizatriptan of Benzoateformulation F1 to F5.



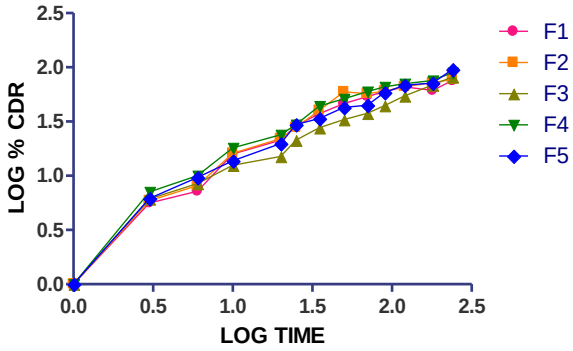


Fig. no. 10 : Comparative Higuchi release kinetics data Of Rizatriptan Benzoate microparticle formulation F1 to F5.

Results of kinetic data showed that release pattern of drug from developed in microparticulate system is by Higuchi's classical diffusion model where release of drug is dependent on partially on drug loaded into microparticulate system and due to polymer relaxation.Slope values for Peppa's model were found to be more than 0.7 which indicates non-fickianrelease process and was of anomalous type which further confirmed drug release pattern is due to polymer relaxation.

CONCLUSION

By studied the all parameters, it has been concluded that HPMC is better mucoadhesive polymer than ethyl cellulose for the formulation of mucoadhesive microparticles of anti-migraine drugs for intranasal administration.Increase in the mucoadhesive polymer led to increase in mucoadhesion. In-Vitro studies showed that formulation F5 showed better release than other formulation.Its possibility shows improvement of bioavailability. Thus, the formulated microparticles seem to be a potential candidate as intranasal controlled drug delivery system for symptomatic therapy of migraine.

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