The Pharma Innovation

ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

Received: 11-03-2013
Accepted: 12-05-2013

Vol. 2 No. 4 2013
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION - JOURNAL

Formulation and Evaluation of Ciprofloxacin Microspheres for Nasal Drug Delivery

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The aim of the study was to evaluate ciprofloxacin-hydrochloride loaded microspheres using copolymers synthesized from acrylic and methacrylic acid esters as a the retardant material for nasal administration.. Microspheres prepared by emulsion solvent diffusion method using an acetone and dichloro methane system. Formulation parameters and processing parameters like ratio of drug to polymer (1:1, 1:1.5, 1:2 and 1:3) concentration of aerosol, volume of water and stirring speed were optimized. Aerosil was used as the inert dispersing carrier to increase the dissolution rate. The prepared microspheres characterized for their micromeritic propertics and drug loading, as well as Differential scanning calorimetry and scanning electron microscopy. The *In vitro* release studies performed in Phosphate buffer PH 7.4. The prepared microspheres should white, free flowing and spherical in shape. The drug-loaded microspheres showed 86-96% of entrapment and release contected up to 8-10 hr.

Keyword: Ciprofloxacin Hydrochloride, *In vitro* Release Studies, Emulsion Solvent Diffusion Method, Microspheres for Nasal Administration.

1. Introduction

Intranasal delivery is suitable for the local and systemic delivery of diverse therapeutic compounds. Among the non-invasive routes, nasal administration offers promising potential as a viable alternative for the delivery of some drugs.[8] Hence, a surge of interest led to many investigations involving the nasal cavity as a feasible site for the administration of much therapeutic agents. The nasal route is conventionally used for drug delivery for treatment of local diseases . In the recent years, this route has received special attention as a convenient and reliable method for the systemic delivery of drugs, especially those that are ineffective by oral route due to their metabolism in the gastrointestinal tract being prone to first-pass effect and must
be administered by injection The objective of the present study is to prepare the sustained release microspheres of ciprofloxacin by improving the entrapment efficiency and patient compliance and thereby decreasing the toxicity, dosing frequency, cost of the drug, avoiding the first pass metabolism, and maintain the optimum therapeutic drug level for prolonged period. Ciprofloxacin is a broad-spectrum antibiotic active against gram positive and gram negative bacteria[6]. All type of microspheres that has been used as an nasal drug delivery are water soluble but absorbed water into sphere matrix, resulting in swelling of spheres[12]. The eudragit

microspheres system was effective as an absorption enhancer for ciprofloxacin. The quassi emulsion solvent diffusion of ciprofloxacin microspheres is simple, suitable, and reproducible method to obtained ciprofloxacin microspheres.

2. Materials and Methods

Ciprofloxacin is procured by Vital therapeutics, secundrabad, Eudragit S100 gift sample from Evonik Roehm Pharma polymers, Mumbai, Aerosil purchased from Yerrow chem., Products, Mumbai, Acetone, Dicholo methane purchased from Merck Pvt. Ltd Mumbai.

2.1 Standard Graph of Ciprofloxacin In Phosphate Buffer PH 7.4

100 mg of ciprofloxacin was taken in 100 ml of phosphate buffer (PH 7.4). Aliquots of 10 ml from stock solution was taken and diluted to 100 ml with phosphate buffer to get 2, 4, 6, 8 and 10 mcg/ml. The absorbance of the solution was measured at 271 nm on a spectrophotometer.

2.2 Peparation of Ciprofloxacin Microspheres[1,3.4,5]

2.2.1 Quasi Emulsion Solvent Diffusion Method

Microsphere was prepared by quasi-emulsion solvent diffusion method. The spherical crystallization technique has been accepted as a useful technique for a particle design for pharmaceuticals.

Weighed amount of ciprofloxacin was dissolved with Eudragit S 100 in a mixed solution of acetone and Di choloro methane. Then aerosol was suspended uniformly in the drug polymer solution under vigorous agitation. The resultant drug-polymer suspension was poured into 150 ml distilled water containing (0.02-0.15%) of sodium deodile sulphate (poor solvent). Under agitation (400-700) and thermally controlled at 38 c.

After agitation the system mixed for 20 min., 15 ml of poor solvent was added slowly, and agitation was continued for another 40 min until the translucent quasi-emulsion droplets turned into opaque microspheres. The solidified microspheres were recovered by filtration and washed with water. The resultant microspheres were dried in an oven at 5^0 C for 6 hrs. Formulation containing drug polymer ratio (eu RSPO) 1:1, 1:2, 1:3 were coded as F1, F2, F3. While formulation containing drug (Eu.S100) . 1:1, 1:1.5, 1:2, 1:3 were coded as B1, B2, B3, B4 microsphere dried at room temperature were then weighed and the yield of microspheres prepation was calculated using following formula

Table 1: standard ciprofloxacin in phosphate buffer PH 7.4

S.No.	Concentration(mcg/ml)	Absorbance (mcg/ml)	Absorbance (mcg/ml)	Absorbance (mcg/ml)	Avg absorbance (mcg/ml)
1.	2	0.149	0.138	0.162	0.148
2.	4	0.321	0.316	0.329	0.322
3.	6	0.474	0.487	0.470	0.477
4.	8	0.619	0.611	0.631	0.620
5.	10	0.751	0.749	0.755	0.751

2.2.2 Drug Interation Study[2,3]

Drug and polymer interaction studies are carried out by UV-spectroscopy, Scanning electron microscopy and different scanning calorimetric.

3. Result and Discussion

3.1 Encapsulation Effiency[12,13]

Drug loaded microspheres' (100 mg) were suspended in buffer solution followed by sonication for about 20 mins. It was shaken for another 20 mins in a rotary shaker for the complete extraction of drug from the microspheres. The resultant solution was filtered through 0.45 mcg membrane filter. Drug content

was determined by UV visible spectrophotometer at 271 nm.

Encapsulation efficiency was carried out with two polymers, Eu.S100 and Eu RSPO. Encapsulation efficiency found to be increase with polymer concentration in the formulations, it was observed with both polymers. In the formulation prepared with Eudragit RSPO, the percentage of encapsulation efficiency ranged from 83-85%. In formulation F1 with drug polymer ratio of 1:1 resulted as 84.8% of encapsulation efficiency similarly with formulation F2 and F3 containing drug polymer ratio 1:1 and 1:3 found to be 83% and 85% respectively

Eudragit formulations B1 and B4 drug loading capacity found to be 90.2 to 95.1%. In the ratio of drug to polymer resulted in encapsulations efficiency of 87.7% with increasing the Eudragit S100 ratio to B2(1:1.5) B3 (1:2) and B4 with encapsulation efficiency of 90.2, 93.5 and 95.1 was observed.

Encapsulation efficiency was increased with increase in polymer concentration in the formulation. Encapsulation efficiency of 63-85% was observed in the microspheres prepared with Eudragit RSPO(F1,F2,F3) .And that of 86-96% was observed in the microspheres prepared with Eudragit s100(B1,B2,B3,B4). It is so because the higher the polymer to drug ratio, the higher probability of the drug surrounded by polymer, which acts as a barrier to prevent from diffusion of drug into the external medium. However, the encapsulation efficiency depends on the polymer proportions.

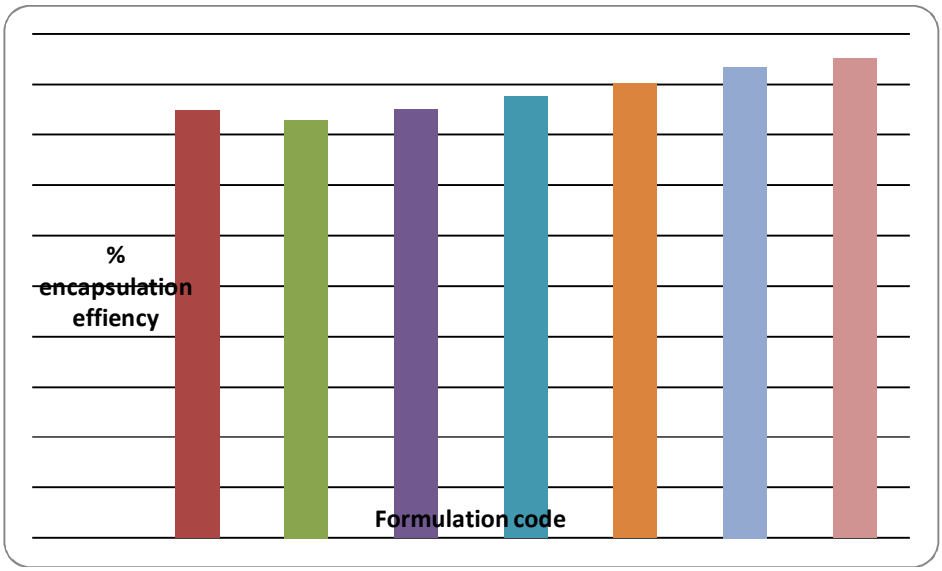

Fig 1: Effect of drug to polymer ratio in entrapment efficiency

Table 1: Effect of drug to polymer ratio in entrapment efficiency

Formulation code	% encapsulation efficiency
F1	84.8
F2	83
F3	85
B1	87.7
B2	90,2
B3	93.5
B4	95.1

3.2 Particle Size Determination[7,9,12,14,15]

The formulated microspheres were evaluated for the paricle size with the optical microscope. The increase in the viscosity with increase in polymer concentration leads to an increase of the emulsion drop let size.. However, the particle size was observed in the microspheres prepared with Eudragit S100.

Table 3: Effect of drug to polymer ratio on mean particle size

S.No.	Formulation code	Range of Particle Size(mcg)	Mean SD(mcg)
1	F1	13.6-21.5	17.55
2	F2	12.2-20.7	16.45
3	F3	15.5-23.1	19.3
4	B1	12.3-19.8	16.05
5	B2	14.1-20.5	17.3
6	B3	18.2-20.1	19.15
7	B4	10.5-18.5	14.05

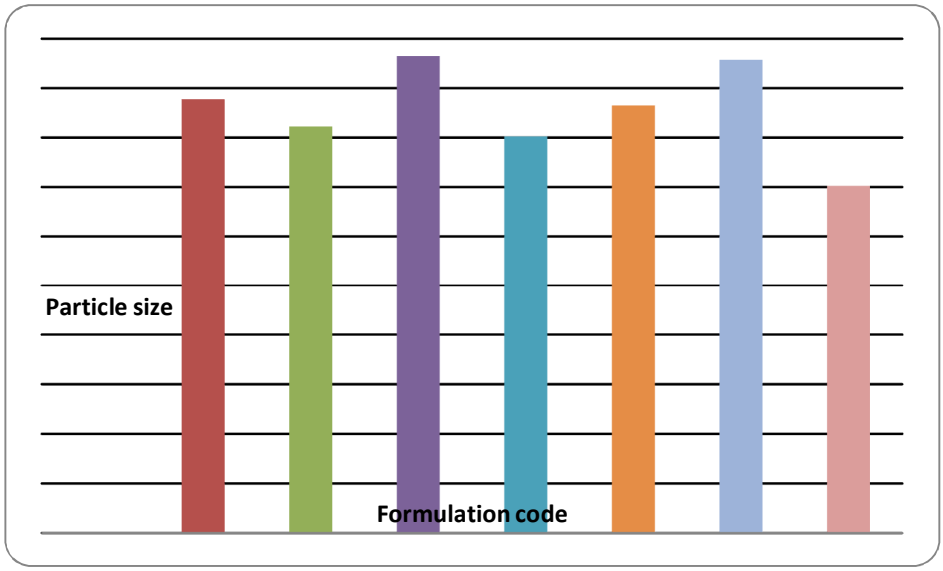

Fig 2: Effect of drug to polymer ratio on mean particle size

3.3 *In vitro* Drug Release Study[11,16,18,19]

The release rate ciprofloxacin from the microspheres could be modulated with adjusting the ratio of Eudragit S100 to aerosol in the formulation. There is relatively minor increase in the drug release rate when the ratio of the amount aerosol to ciprofloxacin was increased from 1:1.5 to 1:2. The *In vitro* drug release profile with formulations B1, B2, B3 and B4 are found to release 80%, 82.5%, 88.2%, and 98%. These *In vitro* release studies indicated that ciprofloxacin had been highly dispersed at the ratio, so as an amorphous state. As dispersing carriers, aerosol could improve apparent solubility and dissolution rate of ciprofloxacin efficiently.

Table 4: *In vitro* drug release data for ciprofloxacin formulations

Time(min)	B1	B2	B3	B4
0	0	0	0	0
30	61.2	61.2	66.2	79.5
60	67.2	67.2	69.5	85.6

120	71.5	72.6	74.3	90.4
240	75.4	77.8	80.2	98.09
360	80.2	82.5	88.2	95.35
480	78.2	78.2	78.2	95.7
600	70.1	71.1	69.3	92.5

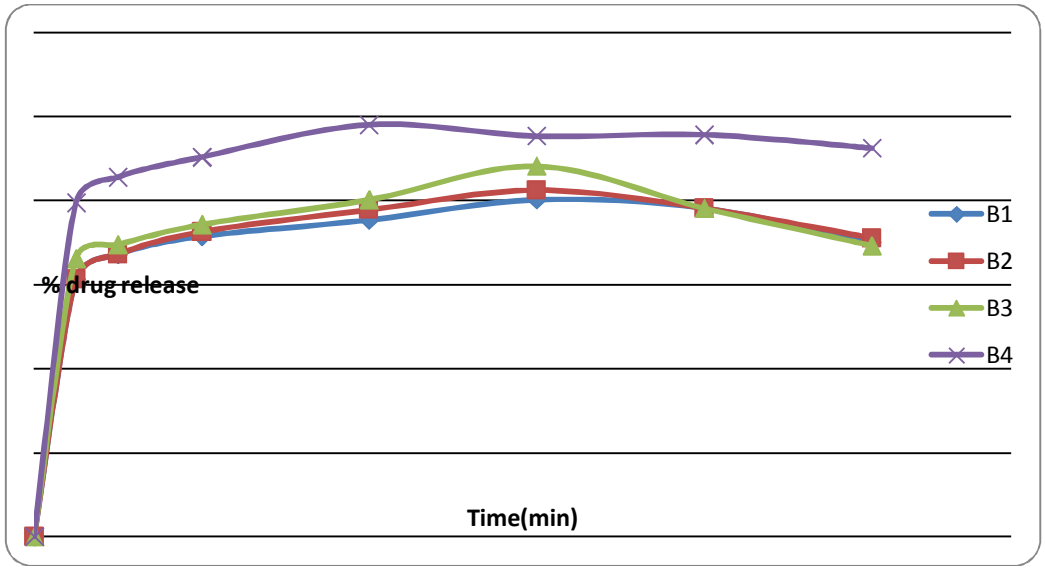

Fig 3: *In vitro* drug release data for ciprofloxacin formulations

3.4 Drug Release Models[15,16,17,18]

Data obtained from *In vitro* release studies were evaluated kinetically table present the co-relation co efficient of formulations calculated according to zero order first order, and Higuchi kinetic models. The formulation B4 followed Higuchi square root of time dependent model provided an ideal drug release rate, which is confirmed by comparing all formulation co relation co efficient for Higuchi model.

Table 5: *In vitro* release kinetic parameters of ciprofloxacin microsphere

Types of model	B1	B2	B3	B4
Zero order	0.6882	0.5627	0.6921	0.6806
First order	0.7632	0.6251	0.7362	0.8838
Higuchi model	0.8345	0.7924	0.912	0.9216

3.5 Ex-Vivo Permeation Studies[17,18]

Ex-vivo permeation study carried out by taking 25 ml of diffusion media in a receptor compartment and 100 mg of microspheres suspension in donor compartment, samples collected at different time points and subjected for analysis. The amount of ciprofloxacin permeated at different time points was calculated using the strait line equation of standard graph.

4. Conclusion

The present study investigates the feasibility of nasal delivery of ciprofloxacin microspheres formulated with various methods with acrylic acid co polymers and evaluates the mechanistic aspects of nasal route. The result based on *In vitro* drug release studies microspheres prepared with 3% Eudragit S100 found to be an optimized formulation. The optimized formulation released 98% of the ciprofloxacin with in 6 hrs, and found to follow Higuchi model of drug release. In near future this route of administration will become

the alternative route of administration to the oral route for administering microspheres.

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