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STUDY AND EVALUATION OF MICROSPHERES OF QUETIAPINE FUMARATE FOR SUSTAINED DRUG DELIVERY SYSTEM

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ABSTRACT

A basic objective of present work is to optimize the delivery of medication so as to achieve a measure of control of therapeutic effect in the face of uncertain fluctuation in the in vivo environment in which drug release takes place. Quitiapine Fumarate is antipsychotic drug which is use in the psychotic disease. Quetiapine Fumarate is one of the emerging short acting drugs, so developed formulation provides the advantage of sustained release formulation. The polymers like HPMC K100, HPMC K15, K4M were utilized in the formulation of microspheres containing Quetiapine Fumarate and evaluated for its drug release characteristics This production process is based on the solubility behaviour of HPMC, which is poorly soluble in water. Addition of an acid improves its solubility as a result of protonation of amino groups. HPMC solubility is also affected by other anions present in the solution. In the presence of phosphate, polyphosphate and sulphate ions, HPMC shows a decreased solubility. The formulation was optimised on the basis of physical characteristics, Drug release, particle size, angle of repose. *In vitro* drug release was carried out in phosphate buffer 7.4 and HCL 0.1N. Among all the formulations, F8 with shows 97.4% better controlled release at the end of 12 hrs. It has been found that the optimized formula F8 containing of HPMC K100 as drug retarding polymers shows better sustained effect for by other polymers.

KEYWORDS: Quetiapine Fumarate, Microspheres, Microencapsulation, SEM.

INTRODUCTION

The sustain drug delivery includes the application of physical and polymer chemistry. These polymers slowly release the drug in bio-system and maintain drug level within therapeutic range for longer duration. Some of the products characterize the drug permeation through the appropriate biological membrane and first pass metabolic effects prior to entry of drug into systemic circulation. The fact that the absorption and release rate of the drug from the dosage form, is one of the interesting and the most recent development in pharmaceutical field.[1]

Microencapsulation

Microencapsulation is a process whereby relatively thin coating of polymers are appliedto small particles of solids or droplets of liquids and dispersions. Microencapsulation leads to micro particles or microspheres, which are reservoir type and matrix type respectively. In either case, one or more active ingredient (core) is / are entrapped within matrix, shell or coat which is usually composed of one or morepolymers. The uniqueness of microencapsulation is size of the coated particles (1-1000µm) and their subsequent use and adaptation to a wide variety of dosage forms and product applications, which might not have been technically feasible. Microcapsule developed for use in medicine consists of solid or liquid core material containing one or more drug enclosed in coating. The core may also be referred to as the nucleus or fill and the coating as well as shell. Depending upon the manufacturing process, various type of microcapsule structure can be obtained. The most common type is the mononuclear spherical. Microcapsule usually have particle size range between 1- 2000 µm.

Reasons for microencapsulation

Drugs from many different pharmacological classes have been microencapsulated, particularly analgesics, antibiotics, antihistamines, cardiovascular agents, iron salts, tranquilizers and vitamins.

There are many reasons why drugs and related chemicals have been microencapsulated. Toxic chemicals such as insecticides may be microencapsulated to reduce hazards to operators. Also the hygroscopic properties of many core materials such as sodium chloride may be reduced by microencapsulation. Many drugs have been microencapsulated to reduce gastric irritation and other gastrointestinal (GI) tract irritation, including ferrous sulphate and potassium chloride. Sustained–release aspirin preparations have been reported to causes significantly less gastric bleeding than conventional aspirin preparation.

MATERIALS AND METHODS

Quitiapine fumerate was a gift sample from Aurobindo pharmaceuticals. Hyderabad, sodium Alginate was purchased from Qualikem fine chemicals Ltd. HPMC K15 and HPMC was purchased from Merck. All other chemicals and reagents used were of high analytical grade.

Physical characterization of Drug sample

Physical characterization of drug like Nature of drug sample, Organoleptic properties, Melting point and Solubility was checked.

Preparation of microparticles[2]

HPMC Microparticles were prepared according to the procedure first reported by Calvo et al. (1997b) based on the ionic gelation of HPMC with bicarbonate and alginate anions. Microparticles were prepared by using different drug to polymer ratio. Required quantity of drug was dissolved in 10 ml of mixture of methanol and dichloromethane (1:1). Polymer HPMC is separately dissolved in 2% v/v acetic acid solution. Drug solution was dispersed into the polymer solution containing emulsifier Tween 80. The Emulsion was prepared with homogenous stirring. Then Emulsion was injected drop by drop into 20% w/v sodium alginate/ sodium bicarbonate solution. Because of using sodium alginate/sodium bicarbonate, HPMC polymer is not solubilised in the solution of sodium alginate/sodium bicarbonate which leads to formation of microparticles by precipitation. Here sodium alginate and sodium bicarbonate used as cross-linking agents. These microspheres are very delicate/ sensitive. To hardening the microparticles, microparticles were kept on ice and then added into supersaturated dextrose solution. Then filterate and dried the microparticles.

HPMC was dissolved in acetic aqueous solution (2%). Calculated quantity of drug was added to the HPMC solution and sonicated for uniform distribution. 0.5%w/v of Tween 80 was added to the HPMC solution as a suspending agent.

Table 1: Formulation table.

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
Quetiapine fumarate	500	500	500	500	500	500	500	500	500	500	500	500
Na Alginate	100	200	300	400	100	200	300	400	100	200	300	400
HPMC K100	25	50	75	100	-	-	-	-	-	-	-	-
HPMC K15	-	-	-	-	25	50	75	100	-	-	-	-
HPMC K4M	-	-	-	-	-	-	-	-	25	50	75	400
$NaHCO_3$	1	1	1	1	1	1	1	1	1	1	1	1
Water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	qs
Calcium chloride solution	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%

Ionto trophic gelation method

Mix HPMC+ Polymer in water kept a side for soaking up to 24 hr. drug dissolved in pure water and mix it into the above polymer solution then this solution allow through 24guage syringe in to the 5% calcium chloride solution.

Evaluation of Microparticles

Particle size and characterization of the morphology of the microparticles

The particle size of all the batches of the formulated microparticles in a sample was measured with an optical micrometer fitted with a calibrated eye piece. Calibration of the microscope was done piror to particle size measurement of the microparticles. The mean of 100 particles was noted as particle size.

The surface morphology (roundness, smoothness and formation of aggregates) and the size of microparticles formulations were studied by scanning electron microscope (SEM). The data obtained after the observation were analyzed accordingly.

Angle of repose (θ)[3]

It is a direct measure of flow property of powders. The tangent of angle repose is equal to the coefficient of friction between the particles. Angle of repose was determined using funnel to pour the powder on the powder on the surface from a fixed height of 2cm, the radius of base of a pile was measured at 5 different point and average was taken for calculating angle of repose.

Percentage Yield[4]

The percentage yield of different formulations was determined by weighing the microparticles after freeze drying.

Drug Entrapment Efficiency[5]

The various formulations of the microparticles were subjected for drug content analysis. Suspension of the various formulations was prepared by suspending microparticles (equivalent to 150 mg of pure) in aqueous solution. Each suspension was sonicated for 30 min to separate the free drug in the supernatant from the drug incorporated in the microparticles. Concentrations of in the supernatant were determined by UV-visible spectrometry at 292 nm after suitable dilution. The amount of the drug incorporated in microparticles was calculated from the difference in drug concentrations between the

supernatant and the original given concentrations. The entrapment efficiency was calculated according to the following.

Fourier Transform Infra-red Spectroscopy (FT-IR) Analysis[6]

The Fourier transform infra-red analysis was conducted for the analysis of drug polymer interaction and stability of drug during formulation process. Fourier transform infra-red spectrum of pure and formulated microparticles were recorded. The formulation was kept for stability study before going for the FT-IR study. After the completion of the stability study formulation is used for the FT-IR study and the peaks of were observed. Infrared absorption spectra of and microparticles in the wavelength region of 450cm^{-1} to 3600cm^{-1} were recorded using FT-IR (SHIMADZU, JAPAN). Resolution used in the scans was 4 cm^{-1} and the spectra were averaged over 20 scans.

***In vitro* Release Studies[7]**

Drug release studies on the loaded HPMC microparticles were carried out using a USPXXI dissolution rate test apparatus for 30 h at a stirring speed of 100 rpm. An amount of microparticles equivalent to 150 mg of was placed in the dissolution medium Citric acid buffer pH 0.1 for 2 h. Then, after 2 h replaced phosphate buffer of pH 7.4 maintained for 30 hr at a temperature of 37± 0.5ºC. 5 ml of sample aliquot of the dissolution medium was withdrawn at different time intervals and fresh dissolution medium was simultaneously used to replace the quantity withdrawn. The samples were then filtered using a Whatmann No. 1 qualitative filter paper and assayed spectrophotometrically (Varian Carry 50 Bio, USA) at 292 nm to estimate the drug concentration. All experiments were performed intriplicate.

Kinetic modeling[8]

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained.

Stability Study[9]

Samples from each batch were withdrawn after the definite time intervals and the residual amount of drug in the vesicles was determined. Stability data of three formulations were further analyzed for significant difference by paired t-test.

All the batches of acyclovir microparticles were tested for stability. The preparations were divided into 3 sets and were stored at 5-8^{0}C (refrigerator) 292C and at 40^{0}C. After 15, 30 and 60 days drug content of all the formulations was determined by the method discussed previously in entrapment efficiency section.

RESULT AND DISCUSSION

Iontropic gelation and Emulsification and iontropic gelation methods are rapid and simple techniques for producing Quetiapine fumarate-loaded HPMC microparticles with small size and good reproducibility from batch to batch. This production process is based on the solubility behaviour of HPMC, which is poorly soluble in water. Addition of an acid improves its solubility as a result of protonation of amino groups. HPMC solubility is also affected by other anions present in the solution. In the presence of phosphate, polyphosphate and sulphate ions, HPMC shows a decreased solubility. For this reason, sodium bicarbonate and sodium alginate were chosen for microparticle formulations, leads to a poorly soluble HPMC derivative, whereby microparticle formulation become possible.

The FT-IR spectra of the pure Quetiapine fumarate and formulation were recorded to check interaction between drug and polymers. Before FT-IR examination formulation is kept for the stability testing. The characteristic peak due to pure Quetiapine fumarate has appeared in the spectra without any markable change in the position. It indicates that there was no chemical interaction between Quetiapine fumarate and HPMC.

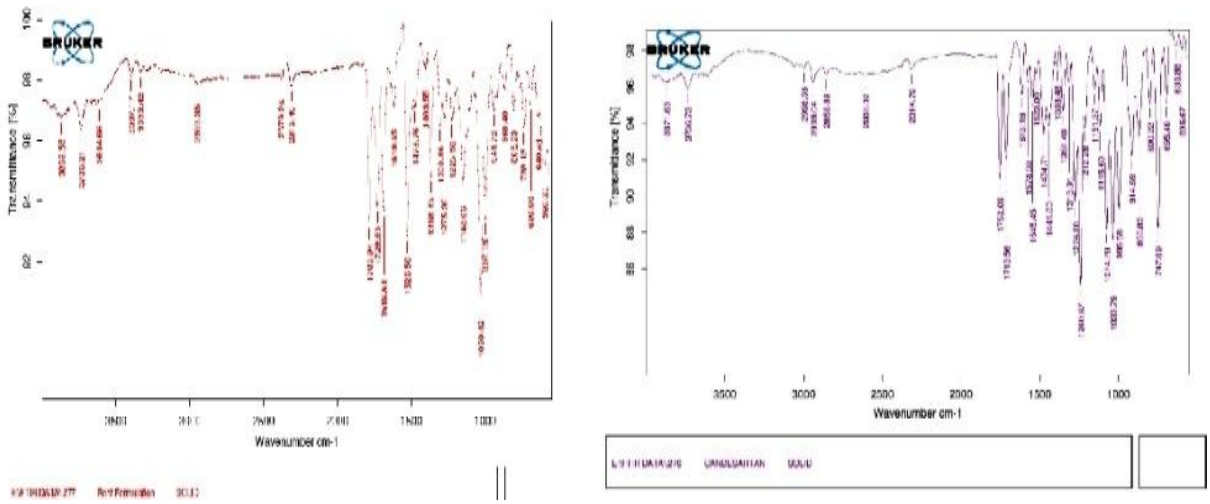

Figure 1: FTIR of (A) Quetiapine Fumarate (B)HPMC K100.

The surface morphology (roundness, smoothness and formation of aggregates) and the size of microparticles formulations were studied by scanning electron microscope (SEM). The data obtained after the observation were analyzed accordingly.

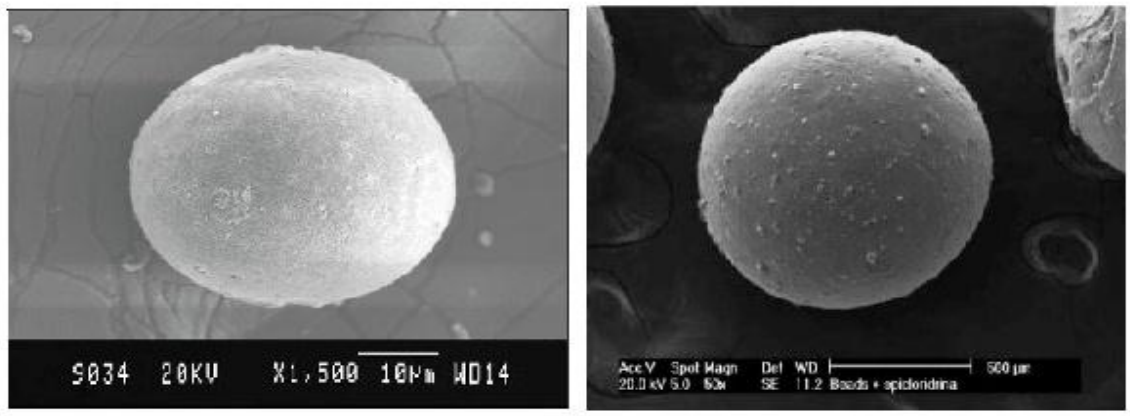

Figure 2: SEM images and particle size of optimised formulation.

Release studies were carried out by using two different release media. HCl pH 0.1 and Phosphate buffer of pH 7.4 were used in order to evaluate the influence of the pH inside gastric and intestine on Quetiapine fumarate release from HPMc microparticles. In Figure, Quetiapine fumarate release profiles from Quetiapine fumarate-loaded HPMC microparticles of pH 0.1 and 7.4 buffer solutions.

As can be seen from the figures, an initial burst effect was observed from all HPMC microparticles (between 13 and 22% of loaded Quetiapine fumarate). After this initial burst, all studied microspheres released Quetiapine fumarate at a lower rate. Quetiapine fumarate release from the was pH dependent (faster release at pH 0.1 than at pH 7,4). This is attributed to the higher solubility of the polymer at lower pH. In fact, as proposed earlier, HPMC microparticles can also provide pH responsive release profile by swelling in acidic environment of the gastric fluid. When comparing the release profiles from cross-linked (with SS/SC) and with & without adding calcium chloride. By addition of the cations like calcium chloride, the drug release was diminished hence it was more controlled. we see that at pH 7.4 the release of Quetiapine fumarate is substantially decreased in the crosslinked particles. It has been proposed before that addition in HPMC particles can be used as a method to modulate release kinetics of drugs, as demonstrated for theophylline. However, the difference between the release kinetics of Quetiapine fumarate from the two types of HPMC particles is more or less diminished (or is a lot smaller) at pH 3.0, possibly due to the rapid swelling and

increased solubility of this polymer a low pH, which results in a very fast release of particle-loaded Quetiapine fumarate from all HPMC microparticles during the first 4-5 hours of incubation. F8 with shows 97.4% better controlled release at the end of 12 hrs. It has been found that the optimized formula F8 containing of HPMC K100 as drug retarding polymers shows better sustained effect for by other polymers.

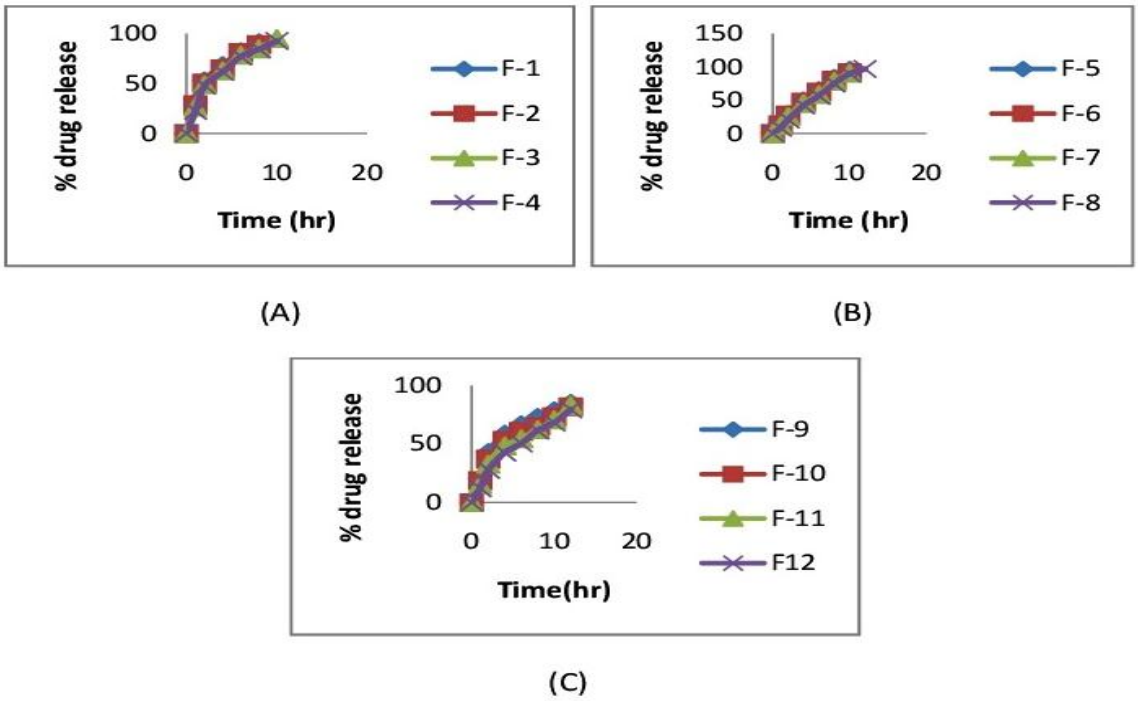

Figure 3: In vitro dissolution of formulation (A) F1 to F4 (B) F5 to F8 (C) F9 to F12.

The various kinetic models were applied to *in vitro* release data for prediction of the drug release kinetic mechanism. The release constants were calculated from the slope of appropriate plots, and the regression coefficient (r^2) was determined. It was found that the *in vitro* drug release of microparticles was best explained by First order kinetics as the plots shows highest linearity. The correlation coefficient (r^2) was 0.9877 for f8 formulation as shown in Table. For formulation correlation coefficient (r^2) is found to be 0.9566, indicating that the drug release was nearly dependent of concentration, followed by Higuchi's (r^2 = 0.9161).

In the current study, drug release kinetic according to korsmeyer-peppa's model is also followed. The values of release rate exponent (n), calculated as per the equation proposed by peppa's, and all the slope values range.9945 revealed the fact that the drug release follows a super case II transport.

Table 2: Kinetic modelling study of formulation F1 to F12.

Code	EE %	Zero order R^2	Higuchi model	First order
F-1	69.11	0.9859	0.8269	0.9811
F-2	71.55	0.9865	0.8568	0.9919
F-3	72.67	0.9844	0.9045	0.9813
F-4	84.45	0.9835	0.9283	0.9816
F-5	67.91	0.9872	0.7941	0.9816
F-6	71.6	0.9858	0.7919	0.9879
F-7	86.64	0.9829	0.9161	0.9891
F-8	90.18	0.9877	0.9161	0.9887
F-9	56.56	0.9923	0.8612	0.9812
F-10	59.81	0.9918	0.8913	0.9823
F-11	74.62	0.9928	0.8913	0.9823
F-12	76.5	0.9898	0.9121	0.9719

EE- Entrapment Efficiency

Stability study is the important part of the study for any pharmaceutical formulation. There are procedures given for the stability study in ICH guidelines.

Table 3: Short term stability study data of optimized drug.

Duration	Parameter studied	Formulation code
0	Drug content	82.11
	% Drug release	62.16
1	Drug content	80.54
	% Drug release	61.54
2	Drug content	79.83
	% Drug release	60.59
3	Drug content	79.05
	% Drug release	59.74

The short term stability study was performed as per ICH guidelines using selected Quetiapine fumarate loaded HPMC micro particles for a period of 3 months. The microparticles were periodically evaluated for drug content and in vitro drug release. The evaluated parameters did not show any significant change during the time course of storage confirmed that the prepared Quetiapine fumarate-loaded HPMC microparticles.

CONCLUSION

From the result it can be concluded that Quetiapine Fumarate was successfully formulated using ionotropic gelation method of HPMC with bicarbonate and alginate anions. Microparticles were prepared by using different drug to polymer ratio.

Method employed was simple and economical, without using any toxic solvent. Result of drug entrapment and physicochemical properties exhibited good results.it was found thet microspheres prepared were spherical as indicated by SEM studies. Compatibility studies were done by FTIR. Optimized formulation and marketed formulation shows comparable drug release profile.

From the present data it is concluded that prepared formulation controlled the drug release in a satisfactory way, which in turn demonstrate the potentiall use of HPMC K100 polymer for the development of controlled drug delivery system.

The optimised formulation Batch no.(F8) provide sustained in vitro release of drug over an extend period of 6 hrs.

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