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Research Article

DESIGN, CHARACTERIZATION AND EVALUATION OF TRAMADOL HCL LOADED MICROSPHERE PREPARED BY EMULSION SOLVENT EVAPORATION METHOD

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ABSTRACT

The aim of this work was to design a controlled-release drug-delivery system for the Tramadol HCl. Tramadol HCl was encapsulated using different EC (Ethyl Cellulose), HPMC K4M (Hydroxylpropyl methyl cellulose) and CAP (Cellulose Acetate Phthalate) polymers by an emulsion solvent evaporation technique and the physicochemical properties of the formulations were characterized. Using a solvent evaporation method, white spherical microspheres were produced. The *in-vitro* drug release was studied phosphate buffer pH 6.8 for 8 hours. The formulations were then evaluated for their pharmacokinetic parameters. The entrapment efficiency of these microspheres was between 71.89 % to 85.52 %. The obtained microspheres showed good flow properties, which were evaluated in terms of angle of repose, bulk and tapped densities, Carr's index and Hausner's ratio. Particle size and drug release depend on the nature and content of polymer used. The drug release mechanism of the Tramadol HCl formulation can be explained using the zero order, First order, Higuchi model and Korsmeyer Peppas model. The controlled release of drug from Tramadol HCl microsphere provides for higher plasma drug content and improved bioavailability.

Keywords: Tramadol HCl, Opioid analgesic, Solvent evaporation, Drug release Kinetics, Microsphere, Entrapment efficiency

1. INTRODUCTION

Controlled release dosage form covers a wide range of prolonged actions that provide continuous release of their ingredients at a predetermined time. One such approach is using polymeric microsphere as carriers of drugs. As a result, the drug is localized on the targeted site. Hence, surrounding tissues are not affected by the drug. Drug release modifications have been investigated to control the time of drug release and maintain constant drug bioavailability. An optimal amount of drug delivery to the target tissue with a right period of time is very necessary so that the agent could induce little toxicity and minimal side effects. The drug release from different formulations depends on the extent of cross-linking, morphology and size of microspheres. It has been shown that reduction of either the applied dose or the frequency of administration gives better pharmacological results compared with administration of conventional doses of drugs. Usually an increase in hardness of a dosage form is accompanied by a decrease in release rate, due to a decrease in porosity. Microspheres have been widely accepted as a means to achieve an oral and parentral controlled release drug delivery system. Microspheres are better tolerated in the form of sustained release of Tramadol for their conventional counterparts and dosage. Tramadol is a synthetic codeine analog that is a centrally acting opioid analgesic and a weak μ-opioid receptor agonist. Part of its analgesic effect is produced by inhibition of uptake of serotonin and nor epinephrine. It has used in the treatment of post-surgical pain, obstetric pain, cancer pain, and chronic pain of mechanical and neurogenic origin. The absence of clinical relevant cardiovascular or respiratory side effects explains its use for post operative pain than other opioids. The half life of the drug is 5 hrs and dose is 50 -100 mg every 4 to 6 hrs. Controlled release oral drug delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects [1-3].

2. MATERIAL AND METHODS

2.1. Preparation of Microspheres (Emulsion Solvent Evaporation Method)

The polymer EC, HPMC K4M and CAP were dissolved in the mixture of propanol and acetone (60:40). The drug Tramadol HCl was dispersed in the above mixture for 15 minutes under stirring at 800 rpm. The resulting dispersion was poured slowly under stirring in to liquid paraffin (dispersion medium) containing 1% of tween 80 and stirring speed was maintained at 1200 rpm. The mixture was agitated at the room temp. (25°C) until the propanol and acetone (polymer solvent) were evaporated (4 hours). The rate of stirring was kept constant for all the methods and ratio of drug to polymer was as (D: P as 1:2, 1:3 and 1:4) labeled as F-1 to F-9. After evaporation of propanol and acetone, the liquid paraffin was decanted and microspheres were collected, washed 3 to 4 times with petroleum ether to remove any remaining oil phase. Afterwards the microspheres were dried at room temp. for 24 hours [4].

Table 1: Composition of Tramadol HCl Microsphere

Formulation Code	Drug: Polymer Code	Drug: Polymer Ratio	Solvent ratio Propanol: Acetone
F1	TMH: EC	1: 2	60 : 40
F2	TMH: EC	1:3	60 : 40
F3	TMH: EC	1: 4	60 : 40
F4	TMH: EC: HPMC	1: 1: 1	60 : 40
F5	TMH: EC: HPMC	1: 1.5: 1.5	60 : 40
F6	TMH: EC: HPMC	1: 2: 2	60 : 40
F7	TMH: CAP	1: 2	60 : 40
F8	TMH: CAP	1: 3	60 : 40
F9	TMH: CAP	1: 4	60 : 40

TMH: Tramadol HCl, EC: Ethyl Cellulose, HPMC: Hydroxyl Propyl Methyl Cellulose, CAP: Cellulose Acetate Phthalate

2.2. Characterization

2.2.1. Percentage Yield Value

The percentage of production yield (wt/wt) was calculated from the weight of dried microspheres (W1) recovered from batches and the sum of the initial dry weight of starting materials (W2) as the following equation [5-8].

% Percentage Yield Value = (W1/W2) X 100

2.2.2. Drug Entrapment Efficiency

To determine Entrapment Efficiency, 100 mg accurately weighted microspheres were crushed and dissolved in a minimal amount of mixture of methanol (10 ml) in a volumetric flask, shaken it for 15 minutes. The volume was adjusted up to 25 ml with 6.8 phosphate buffer solution. The microspheres were kept to soak for overnight. After 12 hours the solution was filtered through 0.45µ membrane filter. The volume was made up to 25 ml with phosphate buffer (pH 6.8) and analyzed for drug content spectrophotometrically at 280 nm. Corresponding drug concentrations in samples was calculated from calibration plot. Drug entrapment efficiency was calculated by using following formula [5-8].

Drug Entrapment Efficiency = Estimated % Drug content in microspheres/ Theoretical % Drug content in microspheres X 100

2.2.3. Surface Morphology (Scanning Electron Microscopy):

Scanning electron microscopy has been used to determine particle size distribution, surface morphology and texture of microsphere. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using (JSM -6390), Japan. Microspheres were dusted on to double-sided carbon dust, which was placed on to a sample carrier in the shape of cylinder. After fixing the samples on the stubs, capture a photomicrograph [5-8].

2.2.4. In-Vitro drug release study

Dissolution test (*in-vitro* drug release) of microsphere: In the present study, the standard eight stations USP (apparatus, Basket) Method were employed. The microspheres equivalent to 30 mg Tramadol HCl were placed in directly in a dissolution paddle. The dissolution test was performed using 900 ml of phosphate buffer pH 6.8, at 37 ± 0.5 °C and at 100 rpm. A sample of 5 ml of the solution was withdrawn from the dissolution apparatus at certain intervals for 8

hrs, and the samples were replaced with fresh dissolution medium to maintain sink condition. The samples were filtered through 0.45µ filters. Absorbance of these solutions was measured at 271 nm. Cumulative percentage drug release was calculated using an equation obtained from a standard curve [5-8].

2.2.5. Kinetic Drug Release Study

Data obtained from *in-vitro* release studies fitted to various kinetic equations to find out the mechanism of drug release from ethyl cellulose microspheres. The kinetic models used were zero order model, first order model, Higuchi model and Korsmeyer-Peppas equation.

2.2.5.1. Zero-order release kinetics

To studies the zero-order releases kinetics the release rate data are fitted to the fallowing equation.

$F=k.t$..... (1)

Where, 'F' is the fraction of drug release, 'K' is the release rate constant and t is the release time.

2.2.5.2. First-order release kinetics

To study the first-order release kinetics the release rate data are fitted to the fallowing equation.

$F= 100\times (1-e^{-kt})$ ..... (2)

Where, 'F' is the fraction of drug release, 'K' is the release rate constant, 'e' is exponent coefficient and't is the release time.

2.2.5.3. Higuchi release model

To study the Higuchi release model the release rate data are fitted to the fallowing equation.

$F= K.t^{1/2}$..... (3)

Where,

F' is the fraction of drug release and 'K' is the release rate constant.

2.2.5.4. Korsmeyer and Peppas release model

To study the Korsmeyer and Peppas release model the release rate data are fitted to the fallowing equation.

$Mt/M\infty=K.tn$..... (4)

Where,

$Mt/M\infty$ is the fraction of drug release, 'n' is the diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form [9].

3. RESULTS AND DISCUSSION

3.1. Percentage Yield Value

All Batches showed a % yield of greater than 75%, whereas six batches showed a yield of more than 80%. % yield is found to be higher with formulation F6.Results showed that % yield increases with increase in the amount of polymer.

Table 2: % Yield of Tramadol HCl loaded micro-spheres

Sr. No.	Formulation Code	% Yield
1	F1	82
2	F2	85
3	F3	84
4	F4	76
5	F5	81
6	F6	83
7	F7	77
8	F8	82
9	F9	85

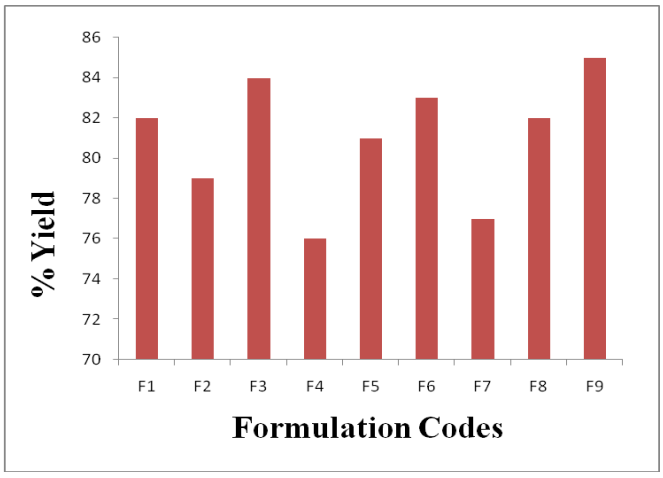

Fig. 1: % Yield of Tramadol HCl loaded micro-spheres.

3.2. Drug entrapment efficiency

The influence of different preparation condition on Tramadol HCl content was evaluated. All batches show % entrapment more than 70 % and it is found that entrapment of drug increases with an increase in the amount of the polymer. Formulation F2 shows maximum entrapment whereas formulation F4 shows minimum entrapment of the Tramadol HCl in the polymer as shown in Table 3.

3.3. Scanning Electron Microscopy (SEM)

Results showed that ethyl microspheres of Tramadol HCl were predominantly spherical in shape with smooth surface. Ethyl cellulose and HPMC K4M based microspheres were found to be much more elongated in nature than microspheres prepared by using cellulose acetate phthalate.

Table 3: Entrapment efficiency of Tramadol HCl loaded microsperes

Sr. No.	Formulation Code	Entrapment efficiency (%) (Mean SD, n=3)
1	F1	77.24 ±1.085
2	F2	85.52 ±1.400
3	F3	82.24 ±1.300
4	F4	71.89 ± 0.815
5	F5	73.24 ±1.152
6	F6	74.95 ±1.085
7	F7	78.64 ±0.764
8	F8	74.08 ±0.53
9	F9	84.53 ±1.05

Table 4: Comparative studies % yield and % entrapment efficiency

Formulation codes	% Yield	Theretical drug content (mg)	Practical Drug content (mg)	Entrapment Efficiency (%)
F1	82	200	157.30	77.24
F2	79	200	164.28	75.52
F3	84	200	155.63	82.24
F4	76	200	140.28	71.89
F5	81	200	149.68	73.24
F6	83	200	159.34	74.95
F7	77	200	162.37	78.64
F8	82	200	158.20	74.08
F9	85	200	160.97	84.53

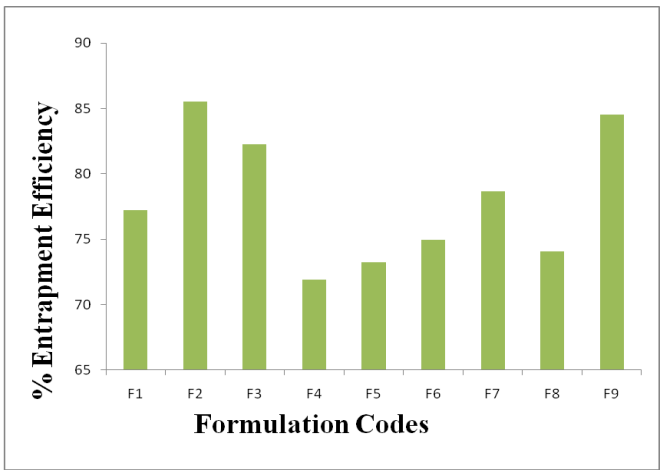

Fig. 2: % Drug Entrapment of Tramadol HCl loaded microspheres

3.4. *In-Vitro* drug release study

The *in-vitro* release studies of drug loaded microspheres were carried out at 37°C and 100 rpm using phosphate buffer (pH 6.8) 900 ml in a USP basket type dissolution rate test apparatus. An accurate weighed amount of microspheres (containing approx 50 mg of the drug) were added to dissolution medium and at pre-set interval 10 ml aliquots were withdraw and replaced by an equal volume of fresh dissolution medium. Aliquots following suitable dilution were analyzed specto-photometrically at 271 nm. Dissolution studies were performed for period of 8 hours.

Dissolution parameters:

Medium: 900 ml of pH 6.8 phosphate buffer,

Apparatus: USP Type-I (Basket), Speed: 100 rpm, Time point: 1 to 8 hrs, Temperature: 37°C±0.5°C, λ Max: 271 nm.

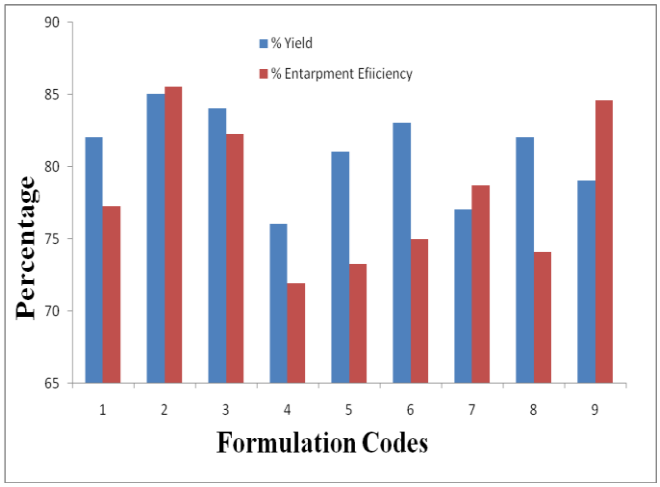

Fig. 3: Comparison of % Yield and % Drug Entrapment of Tramadol HCl loaded micro-spheres

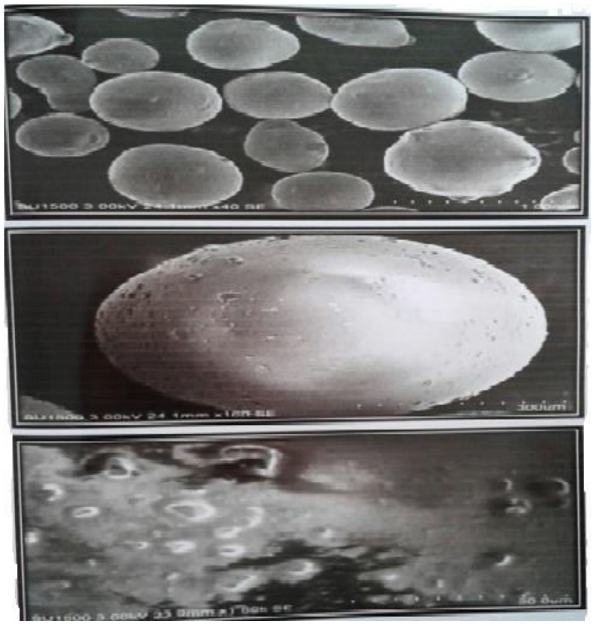

Fig. 4: SEM picture of ethyl cellulose and HPMC K4M microspheres of Tramadol HCl

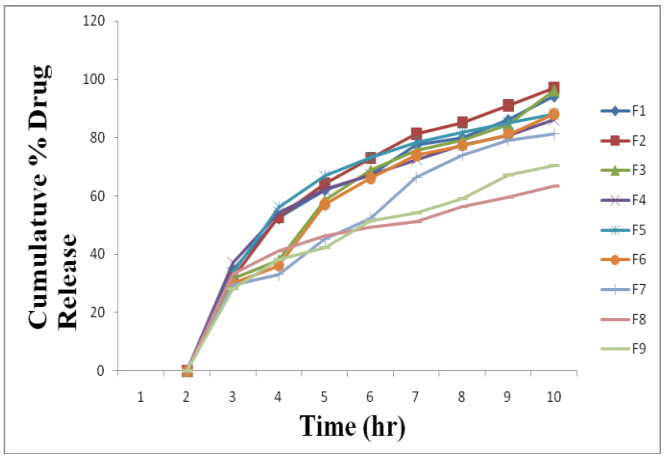

Fig. 5: *In-Vitro* drug release of Tramadol HCl loaded microspheres

3.5. Release Kinetics

In order to describe the kinetics of the release process of drugs from sustained release preparation, the data were fitted with different kinetics models. The first order equation describes the release from systems when dissolution rate is dependent on the concentration of the dissolving species. The Higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion. The applicability of all these equations was tested in the present work. The release of drugs from ethyl cellulose microspheres is found to be diffusion controlled release.

3.5.1. Zero Order Plot

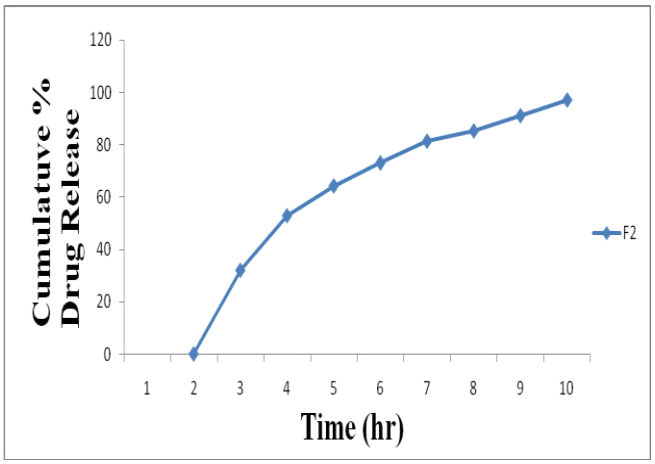

Fig. 6: Zero Order Plot for drug release kinetics for microspheres F2

3.5.2. First Order Plot

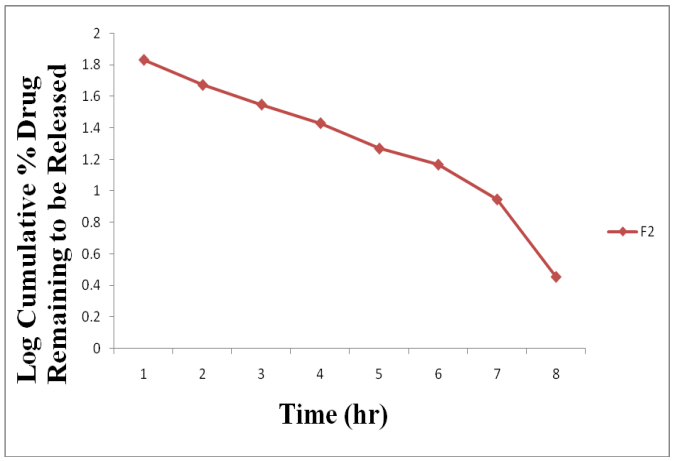

Fig. 7: First Order Plot for drug release kinetics for microspheres F2

3.5.3. Higuchi Plot

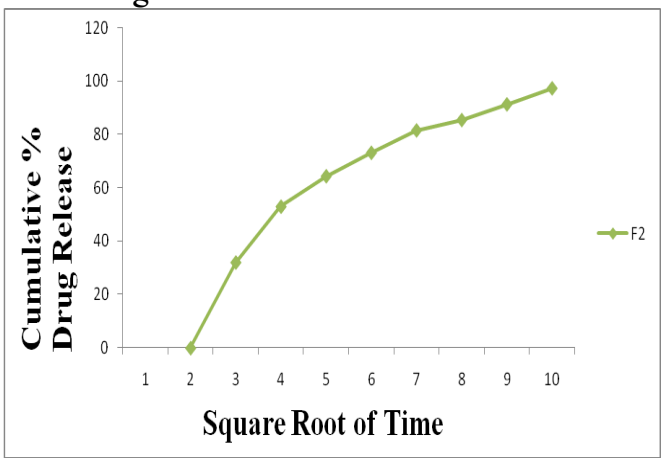

Fig. 8 Plot for drug release kinetics for microspheres F2

3.5.4. Korsmeyer-Peppas Kinetics

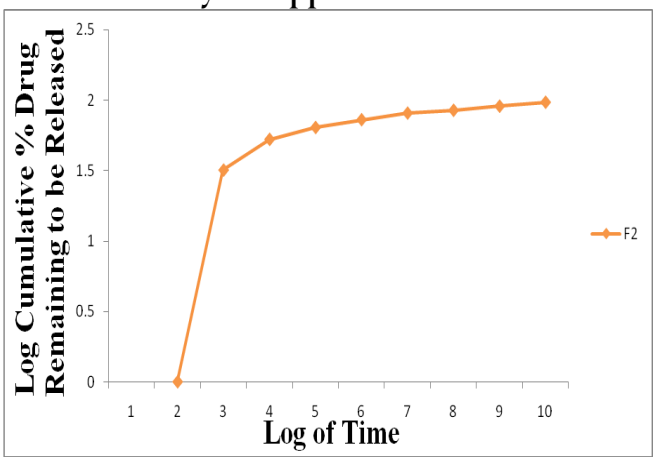

Fig. 9: Kinetics for drug release kinetics for micro-spheres F2

4. CONCLUSION

The EC, HPMC K4M, CAP microspheres of Tramadol HCl were successfully prepared by evaporation solvent evaporation method and confirmed that it is a best method for preparing Tramadol HCl loaded microspheres from its higher percentage yield. The formulation F2 has highest milligram of drug content followed by other formulations. The percentage of encapsulation of nine formulations was found to be in the range of 63.38 to 97.15. Higher percentage of loading was obtained by increasing the amount of Tramadol HCl with respect to polymer. The particle size of a microsphere was determined by optical microscopy and all the batches of microspheres show uniform size distribution. The prepared microspheres had good spherical geometry with smooth as evidenced by the scanning electron microscopy. The *In-vitro* dissolution studies showed that Tramadol HCl microspheres formulation F2 showed better sustained effect (97.15 %) over a period of 8 hours than other formulations.

5. ACKNOWLEDGEMENT

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