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Research Article

A STUDY ON THE EFFECT OF DIFFERENT CELLULOSE POLYMERS ON RELEASE RATE FROM TRAMADOL LOADED MICROSPHERES PREPARED BY EMULSION SOLVENT EVAPORATION METHOD

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ABSTRACT

Sustained release microspheres of tramadol hydrochloride were formulated using a enteric polymers like cellulose acetate phthalate (CAP), cellulose acetate (CA) and ethyl cellulose (EC) by emulsion solvent evaporation technique. The microspheres were characterized for particle size, flow properties, percentage yield, scanning electron microscopy (SEM) and drug entrapment. The results obtained were found in desired ranges where the drug entrapment efficiency of microspheres was found to be ranging from 61.54% to 86.95%, size of microspheres found in the range 341µm to 608µm. The shape of the microspheres was found to be spherical by SEM. The drug excipient compatibility was determined by FTIR, DTA and XRD studies. The drug release was extended up to 12 hours with CAP and EC and maximum release retardation was found in the formulation with EC (Formulation F3). FTIR DTA and XRD results showed that tramadol is compatible with excipients. The curve fitting data revealed that the release followed first order kinetics and higuchi's and peppa's plots stated non-fickian and diffusion controlled release.

Keywords: Tramadol hydrochloride, cellulose acetate phthalate, ethyl cellulose, emulsion solvent evaporation, microspheres.

INTRODUCTION

Microencapsulation is defined as the application of a thin coating to individual core material that have an arbitrary particle size range from 5 to 5000µm[1,2]. This coating can retard the release of a drug[3], modify the availability of the core and promote sustain release, change the cores chemical properties such as solubility and reactivity and physical properties such as color, and particle size[4], alter the heat sensitivity and photosensitivity of the core[5]. Microencapsulation can improve the absorption of a drug and reduce side effects such as irritation of the gastric intestinal mucosa [6]. Cellulose acetate phthalate (CAP) and cellulose acetate (CA) are widely used as a coating material for tablets. Several researchers have investigated the use of CAP and CA as polymer[7,8,9]. Ethyl cellulose is also used as a coating material for sustaining release of the drug[10,11]. Tramadol hydrochloride is a centrally acting opoid analgesic. It is a nonselective complete agonist of µ-δ and κ-opoid receptor with a higher affinity for µ-receptors. The half life of drug is 5.5-6.5 hours [12,13]. The shorter biological half life and frequent dosing makes an ideal candidate for sustain drug release system. Therefore the objective of the work is to provide a sustained pharmaceutical composition contained tramadol in a modified release formulations and to maintain the blood levels of the active ingredients for a prolonged period of time.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride was obtained as a gift sample from Nitin Pharmaceuticals Ltd. Karnal. (A.P). Cellulose acetate phthalate, cellulose acetate was obtained as a gift sample from Nacto Pharma, Hyderabad. (A.P). Ethyl cellulose was a gift sample from Dr Reddy's, Hyderabad. (A.P). All the solvents are procured of Merck.

Methods

Preparation of microspheres

Tramadol microspheres were prepared by the emulsion solvent evaporation method. The polymers (ethyl cellulose, cellulose acetate and cellulose acetate phthalate) were dissolved in acetone; by stirring the mixture at 800rpm the author dispersed the drug particles in liquid paraffin (50% heavy+50% light) containing 1% w/w polysorbate80. The polymer solution was added slowly to the drug dispersion by means of a burette. The mixture was agitated at room temp (25°c) until the acetone (polymer solvent) was evaporated (4 hours). The rate of stirring was kept constant for all the batches and for all the methods and the ratio of drug to polymer was varied as (D: P as 1:1, 1:2, 1:3) labeled as F-1 to F-9. The liquid paraffin was decanted and the microspheres were collected, washed with petroleum ether to remove any remaining oil phase and dried under, reduced pressure for at least 12 hours. Table No.1.

Characterization of microspheres

Scanning electron microscopy (SEM)

Morphological characterization of the microspheres was carried using scanning electron microscopy (SEM-S-3700N, SHIMADZU). For SEM the double-sided sticking tape, and coated with gold film (thickness 200nm) under the reduced pressure (0.001torr).

Particle Size analysis

All the batches prepared were analyzed for particle size where microspheres were placed on the set of standard sieves ranging from sieve No. 16# – 60#. The sieves were arranged in such a way that in descending order of the mesh size 16# on the top and 60# mesh in the bottom. The microspheres passed through the set of sieves and the amount retained on each sieve was weighed and the average mean diameter was determined.

Angle of repose

A funnel was fixed in a stand in such a way the top of the funnel was at a height of 6cms from the surface. The microspheres were passed from the funnel so that they form a pile. The height and the radius of the heap were measured and the angle of repose was calculated using the equation.

$$Ø = h/r$$

Assay of tramadol

To determine the total drug content of the microspheres, 100mg of microspheres was ground to a fine powder and dissolved in 5ml of acetone and diluted with phosphate buffer pH 7.4 to 100ml. The drug content was determined spectrophotometrically at 270nm. Three determination of the microspheres content from the same batch for each ratio and method was performed.

Encapsulation efficiency (EE)

Drug loaded microspheres were weighed and dissolved in phosphate buffer pH 7.4 and mixture was filtered. The percent entrapment was calculated using the Eq (1).

$$\text{Encapsulation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad \text{Eq (1)}$$

Table 1: Formulation and Composition

Formulation	Drug (mg)	Ethyl Cellulose (mg)	Cellulose acetate (mg)	Cellulose acetate phthalate (mg) 1:1	Drug: Polymer
F1	300	300	-	-	1:1
F2	300	600	-	-	1:2
F3	300	900	-	-	1:3
F4	300	-	300	-	1:1
F5	300	-	600	-	1:2
F6	300	-	900	-	1:3
F7	300	-	-	300	1:1
F8	300	-	-	600	1:2
F9	300	-	-	900	1:3

Table 2: % Drug Content, Angle Of Repose, Average Mean Diameter (Amd) And Wall Thickness

Formulation	%DC	Angle of repose	AMDμ	Wall thickness
F1	73.00	23.30	391.8	68.09
F2	70.53	23.01	341.66	59.30
F3	78.25	22.29	405.98	70.56
F4	61.45	28.64	591.11	102.75
F5	76.71	28.29	582.8	101.82
F6	67.40	28.09	608.27	105.72
F7	86.95	27.35	452.08	78.50
F8	80.22	26.17	457.24	79.47
F9	84.91	25.20	466.67	81.11

Table 3: Curve fitting data for all formulations from F1-F9

Formulation	First order Equation			Higuchi's Equation			Peppa's double Log Plot	
	Slope	Rate constant (K) mg. hr^{-1}	Regression coefficient (R^2)	Slope	Rate constant (K) mg. hr^{-1}	Regression coefficient (R^2)	Slope	Regression coefficient (R^2)
F1	-0.000	1.989	0.914	3.463	4.700	0.986	0.458	0.974
F2	-0.001	1.957	0.927	3.179	5.502	0.979	0.435	0.975
F3	-0.000	1.944	0.969	2.702	4.093	0.985	0.469	0.989
F4	-0.004	1.927	0.943	4.802	18.97	0.987	0.346	0.985
F5	-0.004	2.024	0.909	4.811	13.61	0.994	0.379	0.990
F6	-0.004	2.097	0.876	5.193	3.284	0.983	0.462	0.809
F7	-0.007	1.981	0.991	5.889	14.89	0.848	0.475	0.859
F8	-0.006	2.003	0.998	5.455	13.69	0.894	0.468	0.889
F9	-0.004	1.973	0.993	4.902	14.17	0.929	0.480	0.949

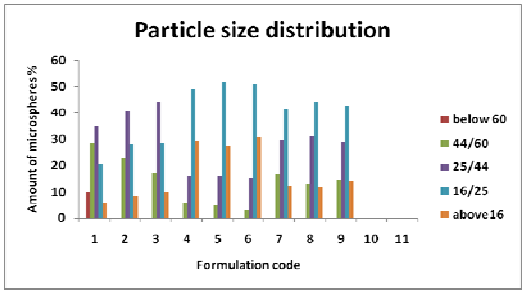

Fig. 1: Histogram Stating Particle Size Distribution of Microsphere

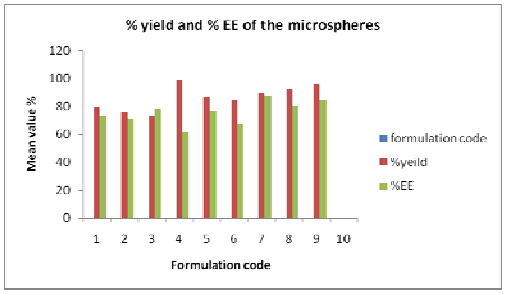

Fig. 2: Histogram Stating % Yield and Encapsulation Efficiency

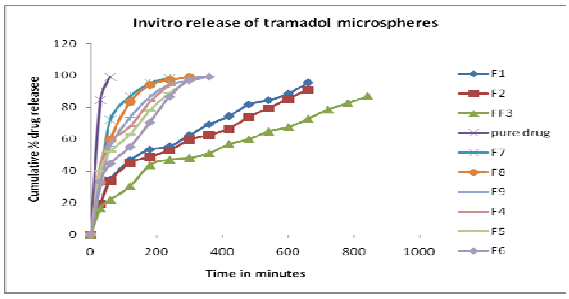

Fig. 3: Cumulative Drug Release of Tramadol Microsphere Formulations

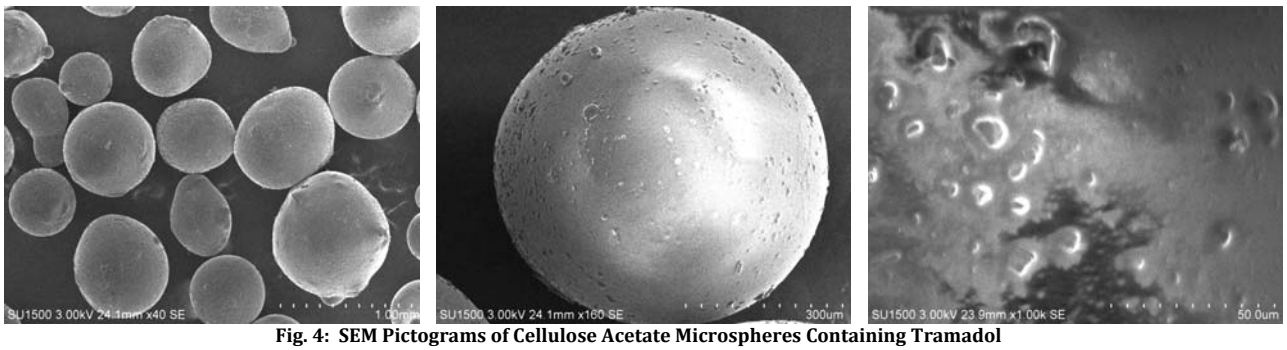

Fig. 4: SEM Pictograms of Cellulose Acetate Microspheres Containing Tramadol

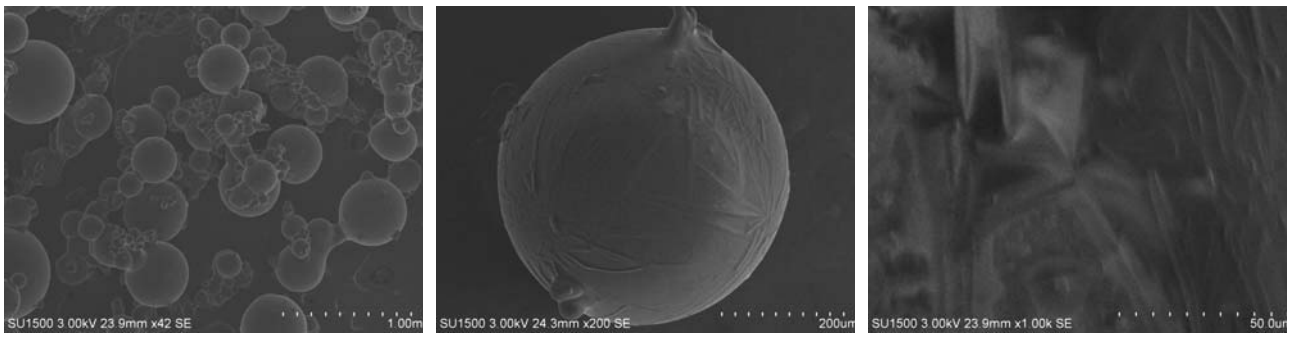

Fig. 5: SEM Pictograms of Cellulose Acetate Phthalate Microspheres Containing Tramadol

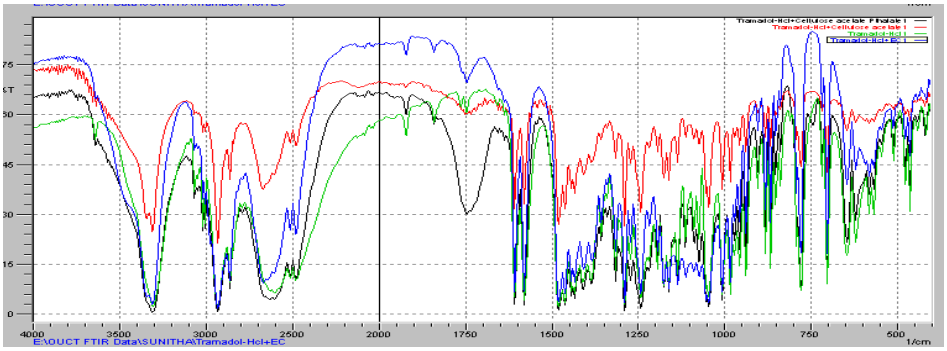

Fig. 6: FTIR overlay graphs of the pure drug tramadol and the formulations

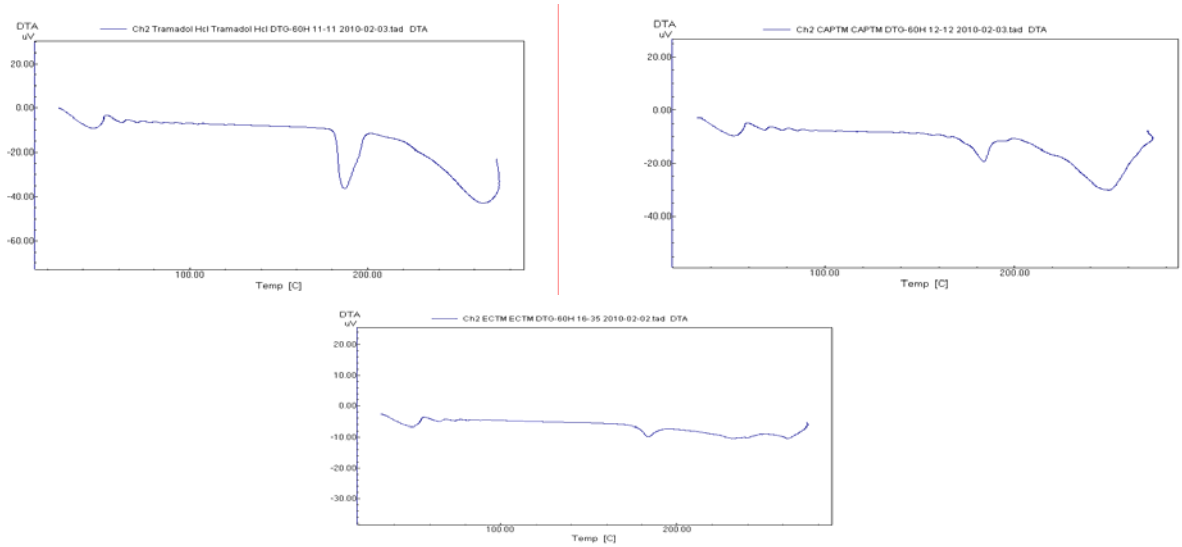

Fig. 7: DTA Thermograms of Tramadol Pure Drug, Drug+Cap And Drug+Ec

Wall thickness

The wall thickness of the prepared microspheres was calculated using the Eq (2).

$$h = \frac{\check{r}\,(1-P)\,d_1}{3(Pd_2 + (1-P)\,d_1} \qquad \text{Eq (2)}$$

Fourier transform infrared Spectroscopy (FT-IR)

The FT-IR spectra acquired were taken from dried samples. An FTIR-8400S (SHIMADZU, IR Prestige-21) spectrometer was used for the analysis in the frequency range between 4000 and 400 cms^{-1}.

X Ray Diffractometer (Shimadzu XRD 7000)

XRD studies were performed on the samples by exposing them to cu kα radiation (40kv 30mA) and scanned from range 10-80°C, 2θ at a step size of 0.020°C, preset time of 0.4 sec and scan speed was 3°C/min. Sampling pitch 0.020 degrees .All formulations including pure drug was used for XRD analysis.

***In vitro* drug release studies**

In vitro dissolution studies were performed using (USP type II dissolution apparatus). The rotating basket method specified in USP-XXI at 75 rpm. The microspheres were weighed and tied in the

muslin bag and placed in the basket. The dissolution medium (900ml) consisted of 0.1M hydrochloric acid for the first 2 hours and then changed to phosphate buffer pH 7.4 from the 3rd hour. The temperature was maintained at 37°C. An aliquot of (5ml) sample was withdrawn at specified time interval and replaced with an equivalent volume of dissolution fluid. Drug content was determined by UV-Visible spectrophotometer (Schimazdu UV 1700 E 23) at 270nm. The release studies were conducted in triplicate.

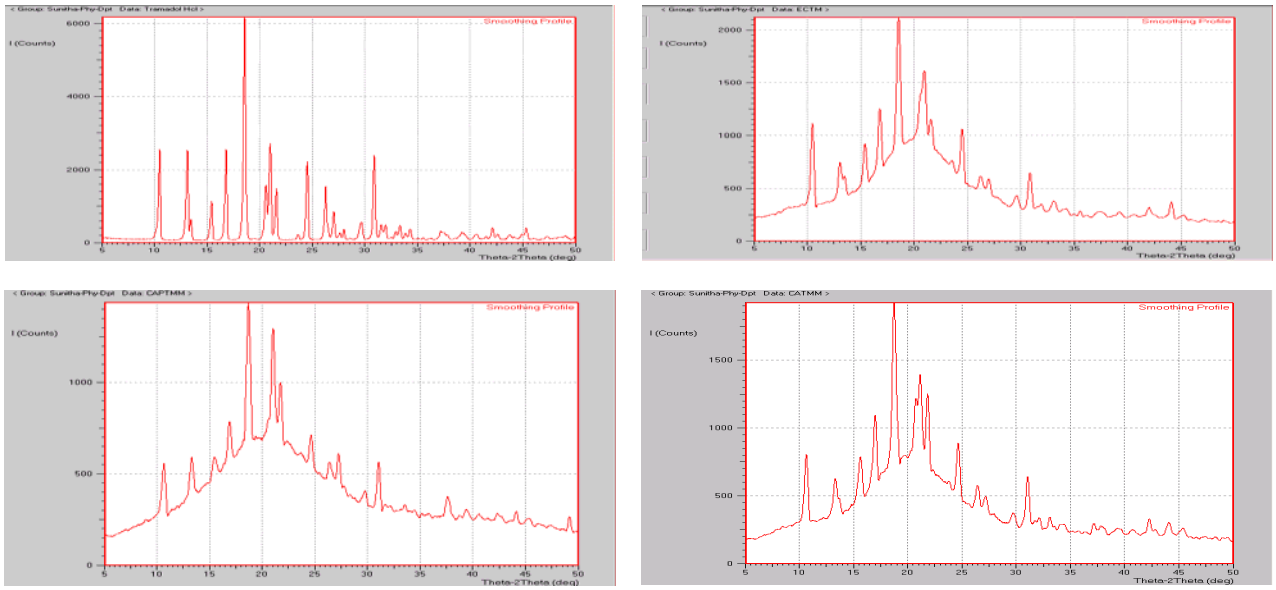

Fig. 8: XRD Graphs of the Pure Drug Tramadol and the Formulations

RESULTS

Prepared microspheres were found to be discrete, spherical and free flowing and have nearly uniform size (SEM) Figure 4 & 5. Table 2. Among all formulations the formulation F5 showed maximum percentage yield and F7 formulation showed highest drug entrapment. Figure2. The average mean diameter of the microspheres was found to be ranging between 341µm to 608µm. Fig. 1. The IR spectra of the pure drug and microspheres with polymers were compared and the characteristic peak for microspheres in spectra was found to be super imposable to that of the pure drug and no extra peaks were found which gave evidence that there was no drug polymer interaction. Figure 6. The FTIR spectrum of the physical mixture of drug and polymer showed no significant shift or reduction in intensity of peaks of tramadol. A broad band of bonded -OH of tramadol was observed from 3096cm^{-1} to 3045.97 cm^{-1} in pure drug also found in samples and a sharp prominent peaks found at 2848cm^{-1} because of -C-H stretching indicating presence of methyl group and at 1610 cm^{-1} and 1575 cm^{-1}due to -C=O stretching indicating keto group and these peaks are found prominent and clear in sample spectra also. The DTA thermograms proved the compatibility of the drug and polymers used where no deviations were found in the graph of the drug with polymer in comparison with pure drug and the mid points of the peak was found at same temperature in between 190ºC -195ºC. Figure 7.

Maximum release of tramadol hydrochloride from various formulations was achieved with in 12-14 hours and maximum retardation of drug release was in microspheres with the polymer ethyl cellulose i.e. formulation F3. Figure 3. The release mechanism of the tramadol formulation was determined by comparing their respective correlation coefficients. Drug release from microspheres prepared by using ethyl cellulose gave good sustained release when compared to other polymers. From the release profiles it can be understood that the polymer used influences the rate of release of the drug. XRD patterns of tramadol exhibits sharp peaks at 2θ scattered angle 10.57, 18.62, 21.04 and with corresponding peak intensities of 1679, 4212, 1792 linear counts respectively. Figure 8. This indicates crystalline nature of the drug. The peak intensities for formulation were also measured at the same 2θ scattered angles of 10.7, 18.8, 21.1 and the corresponding linear counts were found to be 343, 924, 540 in case of cellulose acetate 186, 607, 499 in case of cellulose acetate phthalate microspheres, 522, 977, 633 in case of ethyl cellulose microspheres formulations.

Based on the peak intensities it shows that the degree of crystallinity of drug was reduced in presences of the polymers and the decrease of crystallinity of the drug is in the following order of CAP>CA>EC. The DTA of the pure drug is showing a sharp peak indicating the high crystalline nature of the drug. In case of the microspheres with cellulose acetate phthalate the DSC shows a sharp peak indicating that the degree of crystallinity is also high. But, in case of the ethyl cellulose microspheres the degree of crystallinity is reduced found the following order EC<CAP<Pure drug. In case of cellulose acetate phthalate and ethyl cellulose microspheres there is a lowering of melting point because of the entrapment of drug in the polymer.

DISCUSSION

The formulation followed first order release kinetics, higuchi's and peppas release plots stated non-fickian and diffusion controlled release. Table No. 3. The release mainly depended on the ratio of the polymer in tramadol spectrum C-H, O-H, N-H, and C=O bands were found the same bands were also found in the spectra of all formulations indicating that there was no drug-polymer interaction. Good entrapment efficiency was observed. SEM demonstrated the spherical nature of the microspheres and the presence of the drug particles on the surface.

CONCLUSION

The tramadol microspheres sustained drug release for 12 hours or longer thereby it could be capable of reducing the frequency of administration and the dose-dependent side effects with the repeated administration of conventional tablets. No drug polymer interaction was found and formulations remained stable over a long period of time.

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