RESEARCH ARTICLE

An Investigation on the Release Rate from Tramadol HCl-Loaded Microspheres made Using Various Polymers

Ritesh Bathe[1*], Audumbar Mali[2], Sunayana Mali[3], Jitendra Pande[4], Dipak Bathe[5]

[1]*Siddhivinayak College of Pharmacy, Warora, Maharashtra, India.*
[2]*Department of Pharmaceutics, Sahyadri College of Pharmacy, Solapur, Maharashtra, India.*
[3]*Department of Quality Assurance, Sahyadri College of Pharmacy, Solapur, Maharashtra, India.*
[4]*Department of Pharmaceutics, NRI Institute of Pharmacy, Bhopal, Madhya Pradesh, India.*
[5]*Internal Medicine SAIL, Hospital Durgapur, West Bengal, India*

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ABSTRACT

Tramadol, an opioid analgesic, is used to relieve mild to moderately severe pain. It initially binds to the opioid receptor, and then it lessens the reactivity of norepinephrine and serotonin. The polymers EC, HPMC K4M, and CAP were encapsulated using the emulsion solvent evaporation process, and formulation characterization was completed. The obtained microspheres were round and white. The phosphate buffer with a pH of 6.8 was used for the in vitro investigations of the microspheres, which were carried out for 8 hours at a temperature of 37^{o}C and 100 rpm in a 900 mL USP basket-type dissolution rate test equipment. Formulation F3 entrapped the most medication, but Formulation F6 displayed a greater yield.

The impact of the polymer's type and composition on the medication release was evident. The tramadol hydrochloride microsphere's regulated drug release results in increased plasma drug content as well as better-quality bioavailability.

Keywords: Release Kinetics, Tramadol HCl, microsphere, opioid pain medication.

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INTRODUCTION

A widely used method for achieving oral controlled medication administration is microspheres. Due to its simplicity of manufacture without sacrificing the drug's activity, the oil in oil solvent evaporation method received significantly more attention than the other procedures created for the formulation of microspheres.[1,2] Micro encapsulation using solvent evaporation processes is a common practice in the pharmaceutical sector. Also, it offers additional clinical advantages and permits regulating drug release. Tramadol is regarded as a safe, well-tolerated opioid analgesic with low risk. It might have a potency that is roughly a tenth that of morphine. Its key characteristic is that, in addition to acting as a mu-opioid agonist, it activates the descending pain inhibitory pathways, which in turn affects the effects of neurotransmitters like serotonin and norepinephrine that are involved in the modulation of pain.[3-5]

Procedure of Formulation of Microspheres[6-9]

Emulsion Solvent Evaporation Technique

The propanol and acetone mixture was used to dissolve the polymer EC, which is made up of ethyl cellulose HPMC K4M and CAP (60:40). Tramadol HCl was dissolved step-by-step for 15 minutes while being stirred at 800 rpm. The combination was quietly drizzled into liquid paraffin even though existence vigorously stirred at a speed of 1200 rpm to complete the second step of dispersion. The propanol and acetone (the polymer solvent) were stirred continuously at room temperature until they entirely evaporated. The agitation was maintained at a constant pace, and the medication with polymer ratio was labeled as (D: P as 1:1, 1:2 and 1:3) and ranged from F-1 to F-9. The microspheres were obtained by decanting the liquid paraffin after the evaporation of the propanol and acetone. The microspheres were washed three to four times with pet ether to get rid of any emollient point. Afterwards step five; the microspheres are parched for 24 hours at room temperature.

Where TMH- Tramadol HCl; EC- Ethyl Cellulose; HPMC- Hydroxyl Propyl Methyl Cellulose; CAP- Cellulose Acetate Phthalate.

Evaluation Parameters[10-13]

Percentage Yield Value

$$\% \text{ Percentage Yield Value} = \frac{W1 \times 100}{W2}$$

**Author for Correspondence: riteshbathe@gmail.com*

Table 1: Composition for tramadol HCl microsphere.[7]

Formulations	*Drug: polymer*	*Drug: polymer ratio*	*Solvent ratio propanol: acetone*
F1	TMH- EC	1–1	60–40
F2	TMH- EC	1–2	60–40
F3	TMH- EC	1–3	60–40
F4	TMH- EC- HPMC	1–0.5–0.5	60–40
F5	TMH- EC- HPMC	1–1–1	60–40
F6	TMH- EC- HPMC	1–1.5–1.5	60–40
F7	TMH- CAP	1–1	60–40
F8	TMH- CAP	1–2	60–40
F9	TMH- CAP	1–3	60–40

Drug Entrapment Efficiency

In a volumetric flask, 10 mL of methanol was mixed with 100 mg of crushed microspheres, and the mixture was shaken for 15 minutes. The volume was then modified by adding 6.8 phosphate buffer solution to bring it up to 25 mL. Overnight soaking is done with the microspheres. The mixture was filtered through a 0.45 membrane filter after 12 hours. Using phosphate buffer (pH 6.8), the volume was increased to 25 mL, and the presence of drugs was determined spectrophotometrically at 280 nm. The corresponding drug concentrations in the samples were computed from the calibration plot.

$$\text{Medicine Entrapment Productivity} = \frac{\text{Predictable \% Medicine in microspheres}}{\text{Hypothetical \% Medicine in microspheres}} \times 100$$

Surface Morphology (Scanning Electron Microscopy)

Particle size distribution, surface morphology, and microsphere texture have all been studied using SEM. Japan's (JSM - 6390) was used for the SEM experiments.

***In-vitro* Drug Release Study**

The study was conducted using the USP's standard eight stations (apparatus I, Basket). The 30 mg of drug-filled microspheres were directly inserted into a dissolving paddle. 900 cc of phosphate buffer with a pH of 6.8 was used for the dissolving investigation, which was conducted at 37 0.5°C and 100 rpm. At regular intervals throughout the course of eight hours, a mixture of the solution containing 5 mL was removed, beginning the dissolution device. To preserve the sink condition; then the samples were filtered by using 0.45 filters. By using solutions, absorbance was resolute at 271 nm. Calculated was the accumulative% of medication release.

Kinetic Drug Release Study (Table 1 and 2)

A variety of kinetic equations were fitted to the results of dissolving studies. Zero order; first order; Higuchi; and Korsmeyer-Peppas kinetic models were hired.

RESULTS ALONG WITH DISCUSSION

%Produced Value

Six formulations displayed a produced of more than 80%, while all batches displayed a produced of better than 75%.

Table 2: % produced of tramadol HCl loaded microspheres[8]

S. No.	*Batches code*	*% produced*
1	F1	80
2	F2	78
3	F3	82
4	F4	79
5	F5	82
6	F6	84
7	F7	78
8	F8	81
9	F9	83

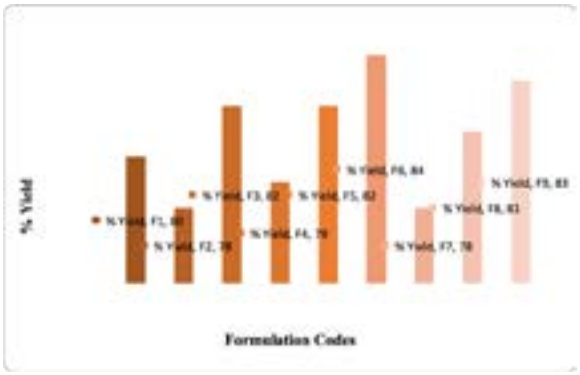

Figure 1: Histogram of %yield of tramadol

The %produced with formulation F6 is shown to be greater. Findings indicated that as polymer amounts are increased, yield percentages rise.

Drug Frame-up Efficiency

The impact of various preparation conditions was assessed on Tramadol HCl content (Table 1 and 2). All batches exhibit entrapment rates of greater than 70%, and it has been discovered that drug entrapment rises when polymer content is increased. As demonstrated in Tables 3-5, Formulation F2 demonstrates the greatest frame-up, whereas batch F4 demonstrates slightest frame-up of Tramadol HCl in the polymer.

Scanning Electron Microscopy (SEM)

Most of the tramadol HCl ethyl cellulose microspheres had smooth surfaces and were spherical. Microspheres made from cellulose acetate phthalate were discovered to be substantially less elongated in nature than those made from ethyl cellulose and HPMC K4M.

***In-vitro* Drug Release Study**

The USP basket type dissolving frequency test device was used for the *in-vitro* release investigations of medicine-loaded microspheres conducted at 37°C and 100 rpm with 900 mL of phosphate buffer (6.8 pH).

Dissolution Parameters

Medium: 900 mL of phosphate buffer at a pH of 6.8. Instrument: USP Type-I (Basket), 100 rpm, 1 to 8 hours. Max: 271 nm, temperature: 37 + 0.5°C.

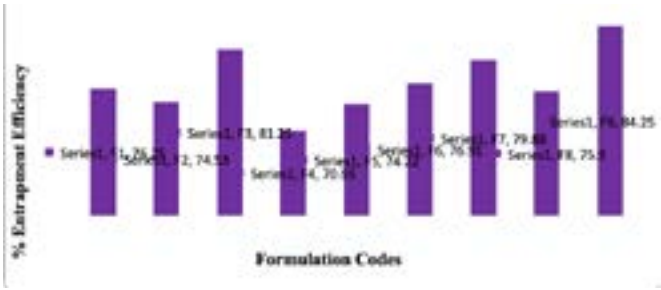

Figure 2: Histogram of % drug entrapment of tramadol.

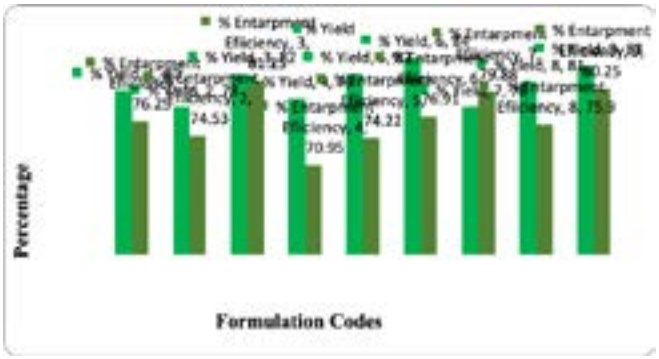

Figure 3: Contrast of %produce with %medicine entrapment of tramadol HCl encumbered microspheres.[7]

Table 3: Frame-up efficiency for Tramadol HCl encumbered microspheres

S. No.	*Batches code*	*Frame-up efficiency (%); (Mean SD; n:-3)*
I	F1	76.25 +1.085
II	F2	74.53 +1.300
III	F3	81.25 +1.200
IV	F4	70.95 + 0.818
V	F5	74.22 +1.154
VI	F6	76.91 +1.097
VII	F7	79.88 +0.780
VIII	F8	75.90 +0.956
VIIII	F9	84.25 +1.097

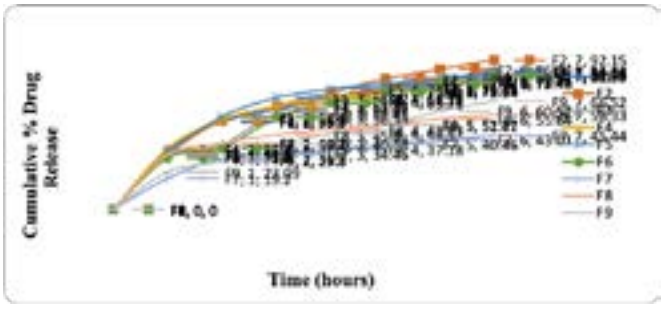

Figure 4: *In-Vitro* medicine relief of Tramadol HCl loaded microspheres.[10]

Release Kinetics

In mandate to analyze the kinetics of the relief manner of medications from grounding, the statistics were formfitting using a variety of kinetics models. The 1st order calculation explains the release from systems where the concentration of the dissolving species influences the dissolution rate. According to the Higuchi square root equation, the rate of medicine relief is associated with the degree of medicine diffusion in schemes where the solid medicine is distributed in an unsolvable environment. The applicability of each of these calculations was investigated in the current study. It has been demonstrated that diffusion has organized drug release from ethyl cellulose microspheres (Table 2, Figure 1).

Zero Order Graph

As shown in Figure 5.

First Order Graph

As shown in Figure 6.

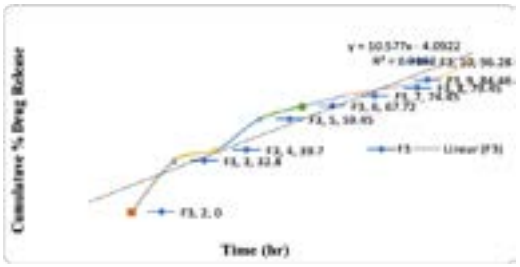

Figure 5: Zero order graph for medicine relief kinetics.[10]

Table 4: Relative readings between %yield and %entrapment efficiency[9]

S. No.	*Batches codes*	*Polymer ratio drug: polymer*	*Solvent ratio (%)*	*% Yield*	*Hypothetical medicine content (mg)*	*Applied drug content (mg)*	*Entrapment Efficiency (%)*
1	F1	1:1	60:40	80	200	152.5	76.25
2	F2	1:2	60:40	78	200	149.06	74.53
3	F3	1:3	60:40	82	200	162.50	81.25
4	F4	1:1	60:40	79	200	140.50	70.95
5	F5	1:2	60:40	82	200	141.90	74.22
6	F6	1:3	60:40	84	200	153.82	76.91
7	F7	1:1	60:40	78	200	159.76	79.88
8	F8	1:2	60:40	81	200	151.50	75.90
9	F9	1:3	60:40	83	200	160.50	80.25

Table 5: *In-vitro* medicine relief of Tramadol HCl loaded microspheres.[13]

Time (min)	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
0	0	0	0	0	0	0	0	0	0
1	34.7	32.02	31.82	37.12	33.53	30.02	29.53	33.39	28.04
2	52.4	52.9	38.03	54.23	56.13	36.15	33.16	41.14	38.17
3	62.14	64.3	58.43	62.35	66.83	57.18	45.23	46.33	42.19
4	67.16	73.07	68.73	67.23	73.29	66.11	52.41	49.42	51.43
5	77.57	81.42	75.49	72.54	78.42	73.89	66.34	51.23	54.24
6	79.92	85.31	79.18	77.59	81.93	77.34	74.14	56.26	59.12
7	86.18	91.16	84.47	80.85	85.03	81.13	79.23	59.68	67.24
8	94.23	97.15	96.2	86.29	88.09	88.1	81.33	63.38	70.38

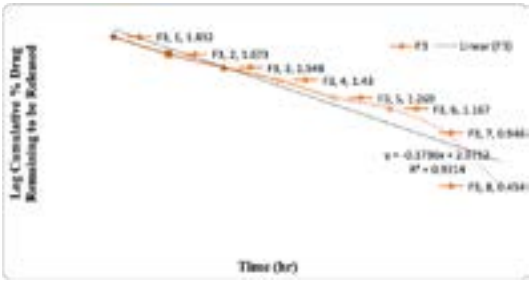

Figure 6: First Order Graph for medicine relief kinetics.[10]

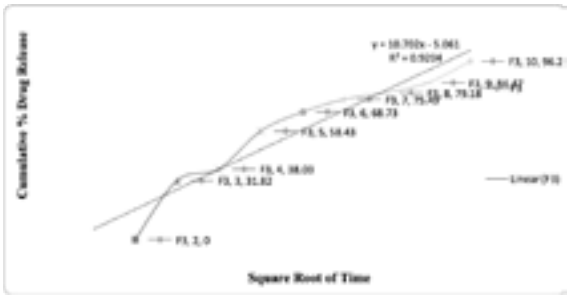

Figure 7: Higuchi Graph for medicine relief kinetics.[11]

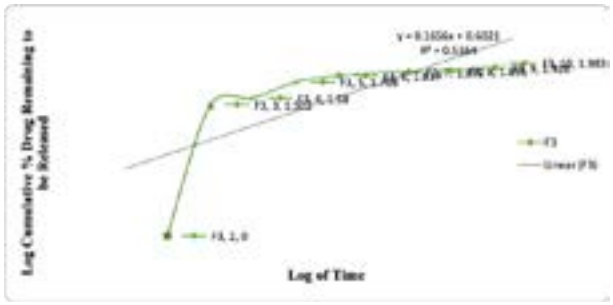

Figure 8: Korsmeyer-Peppas Kinetics Graph for medicine relief kinetics.[11]

Higuchi Graph

As shown in Figure 7.

Korsmeyer-Peppas Kinetics Graph

As shown in Figure 8.

SUMMARY AND CONCLUSION

The formulation F6 demonstrated the highest yield of all the formulations, and the F3 formulation had the highest level of drug entrapment. Maximum Tramadol Hydrochloride release from different formulations was obtained within 8 hours, and formulation F3's microspheres with the polymer ethyl cellulose showed the greatest drug release delay. The release profile unequivocally shows that the polymer utilized has an impact on the drug's rate of release. The relevant correlation coefficient was used to identify the formulation release mechanism. Higuchi's and Peppa's release plots indicated non-fickian and diffusion-controlled release, and the formulation adhered to zero order release kinetics. In the spectrum of tramadol hydrochloride, the C-H, O-H, N-H, and C=O bands were similar, indicating the drug and polymer's compatibility. The release relies on the ratio of the polymer. High entrapment efficiency and the spherical nature of the microspheres and drug particles on the surface were discovered using SEM analysis. In order to achieve a better release pattern with the aid of a comparative study of increasing polymer ratios, formulation batches of the full release of the drug with excipients were created using different ratios of tramadol hydrochloride to ethyl cellulose, tramadol hydrochloride to HPMC K4M, and tramadol hydrochloride to CAP. The tramadol hydrochloride microspheres increase medication release for 8 hours or longer, allowing for a reduction in the frequency of administration as well as a significant reduction in the adverse effects safe from repetitive administration of traditional tablets. The stability analysis indicates that the formulations may remain stable for longer.

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