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Research Article

FORMULATION AND EVALUATION OF TRAMADOL HCL SUSTAINED RELEASED PELLETS

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ABSTRACT

The present work is aimed to formulate Tramadol Hcl sustained release pellets using ethyl cellulose N50 such as hydrophobic polymer by employing the solution/suspension layer technique. The drug excipients compatibility study was carried out by Furor Transform Infrared spectroscopy (FTIR) which reveals no interaction between drug and excipients. Total 12 batches were formulated. Six formulations were prepared by using each natural polymer like ethyl cellulose N50. All the formulations were evaluated for micromeritic properties, physical evaluation, which includes particle size analysis, percentage yield, drug content, drug entrapment efficacy, percent moisture loss and swelling index, in vitro dissolution studies, scanning electron microscopy, and drug polymer interaction studies. The Optimized batch F2 was found to release the drug for 12 h (95.89%) and follows Higuchi Matrix model in dissolution studies, indicating the matrix-forming potential of natural polymer and diffusion controlled release mechanism.

Keywords: Direct compression, Ethyl cellulose, In vitro dissolution, Tramadol.

INTRODUCTION

Tramadol (Figure 1) is a non-steroidal anti-inflammatory drug, which is used in the treatment of osteoarthritis. It is used primarily to treat mild-severe pain, (both acute and chronic) fibromyalgia by the European League Against Rheumatism. After oral administration, tramadol is rapidly and almost completely absorbed. Sustained-release tablets arrive to peak concentrations after 4.9 hrs and have a bioavailability of 87% to 95% estimate with capsules. The mean elimination half-life is 6 hrs and desired dosing every 6 hours in order to maintain optimal relief of chronic pain. As a result, once-daily extended-release tablets have been formulated. Long term treatment with sustained-release tramadol once daily is usually safe in patients with osteoarthritis or refractory low back pain and is well tolerated[1-4] .Tramadol chemical name is (+) -trans-2-(Dimethyl amino methyl)-1-(m-methoxyphenyl) cyclohexanol. It is a synthetic pad of the amino cyclohexanol group, is a centrally acting analgesic with weak opoid agonist properties .To reduce the frequency of administration and to improve patient compliance, a sustained release formulation of tramadol is developed[5]. It has two different mechanisms like first it binds to the μ-opioid receptor and Second, it inhibits the reuptake of serotonin and norepinephrine[6-7]. Tramadol is used similarly to codeine, to treat moderate to severe nerve pain. It has been suggested that tramadol could be effective for alleviating symptoms of depression, anxiety, and phobias[8]. Sustained release drug delivery systems are delineated to reach a longer therapeutic effect by continuously allowed medication over an extended period of time[9].

The main objective of the present work was to develop sustained release pellets Tramadol

hydrochloride using different polymers like Polyvinylpyrilidone (Pvpk30), Hydroxy propyl methyl cellulose (HPMC), Ethyl cellulose N-15 4%, 8%, 12%, Ethyl cellulose N-50 4%, 8% and Talc[10-11]. The matrix pellets were prepared and evaluated for different physiochemical parameters such as weight variation test, moisture content test and drug content, hardness, friability, drug content and *in vitro* release[12-13].The result showed all the parameters were within the limits in case of in-vitro drug release, formulation F3 where tablets containing drug loaded pellets coated with 8% polymer load, the drug release at 2nd hour was found to be 29.26% and at 12th hour was 95.89%. Better release retarding effect was found which indicates that this range of polymer is sufficient enough to form barrier coat around the pellets from the results that formulation F3 is a better system for once-daily SR of Tramadol hydrochloride[14-16].

MATERIALS AND METHODS

Materials

Tramadol (Cygnus Chemicals Pvt Ltd, Mumbai-400607) was used as a model drug. Polyvinylpyrrolidone K30, Ethyl cellulose and Hydroxypropyl methylcellulose (PVPK 30, EC, HPMC Dow chemicals, Chennai-600020) were selected as a dispersion base. Isopropyl alcohol was selected as a good solvent, distilled water was used as a poor solvent (SD Fine Chemicals Ltd., Mumbai-400102). Sugar spheres (Signet Chemical Corporation Pvt Ltd, Mumbai) used as excipient. Talc (Choudary and company, Udaipur-324001) as an absorbent was added to promote drug dispersion and increase the bulk for compact unification of the resultant microspheres. All solvents used were of analytical grade.

Preparation of tramadol hcl sustained release pellets

Make the drug blend by mixing the drug along with the occupants and apply the same blend on 24#, 30 # Pharma grade sugar with the help of sugar syrup a binder solution in a stainless steel Coating Pan with the rotation of 36 rpm. In a Cleaned stainless steel vessel, purified water then add Pharma grad Sugar in it. Heat the reaction mass to 40 - 45^{0}C under stirring to get clear syrup, clean, dry planetary mixer and load all above powdered ingredients as mentioned above in it. Slowly add Sugar syrup to the above mixture and mix well to get Wet Mass. After completion of blend powder coating slowly ethyl cellulose N^{15} and ethyl cellulose N^{50} to coated pellets up to required size pellets.

RESULTS AND DISCUSSION

Preformulation studies

Drug-exicipient interactions play a vital role with respect to biological performance and formulation stability. FTIR spectroscopy was used to study the physical and chemical interactions between drug and exicipients. The characteristic absorption peaks obtained from the drug alone and in the presence of polymer (1:1) are showen in Figure. 4 (A, B, C, D, E). From the spectra, it is clear that the main drug peaks and the frequencies of peaks observed were within the standard range. This indicates that the drug was compatible with the formulation components

The following characteristics peaks were observed with Tramadol Hcl .

C-H Stretching 3050 cm-1 (Alkanes).

C-H stretching 2900 cm-1 (aliphatic hydrocarbons)

C-H stretching 1600 cm-1 (aromatic ring hydrocarbons).

Studies on tramadol hcl pellets coated with ethyl cellulose

The formulated pellets were subjected to different parameters and results were represented in the Table 1. From the results, it was observed that the bulk density was found to be between 0.58 to 0.62 mg/ml and tapped density ranged between 0.62 to 0.660 mg/ml. The other micromeritic properties such as Carr's index, Haursner"s ratio revealed no significant differences. Angle of repose was to be between 22.78 to 24.70 indicating the good flow properties. The drug content of the all formulations was within the range of 98.59 to 99.04%, ensuring uniformity of drug content in the formulations. The percentage friability of prepared pellets within the limits (<1%).

In-vitro dissolution studies

The release profiles of Tramadol Hcl from pellet coated with ethyl cellulose was shown in Table 2 & Fig 3 A. The entire pellet disintegrates during the dissolution test, and no gel like structure remained, indicating complete dissolution at different coating levels. As the coating level increased, the drug release decreased. The reduction in the release rate with increasing coating level may be due to the increased diffusion path length with an increase in the thickness of the coat. Uncoated Tramadol Hcl pellets disintegrate rapidly in dissolution medium and release their drug content within 10 min. For instant at higher coating levels, such as 12 % coating, only about 16% of Tramadol Hcl were released in 2 HR, whereas those Pellets coated to weight increases of 8%, and 4%

released 24% and 18% of drug, respectively. It is observed from the results that the coating levels had a major effect on the ultimate rate of drug release and the duration of the release. The entire pellet remained intact during the dissolution test, indicating that the ethyl cellulose coating layer controlled the drug release. Generally, in dosage forms that have a water insoluble polymer as the rate controlling membrane, since diffusion through the membrane controls the overall release rate of the drug, the layer properties and geometry, such as coating porosity, internal structure (tortuosity), and coating thickness, may be critical factors in determining the release rate of the drug.

Kinetics of in-vitro dissolution

The drug release followed first order kinetics shown in Figure 4 B. As the graph was drawn between the log percent of drug unreleased verses time were found to be linear. To ascertain the mechanism of drug release data was subjected to higuchi shown in Figure 4 C and korsmayer peppas equations shown in Figure 4 D. From the regression coefficients the plots show highest linearity with first order, followed by higuchi model. The value of release exponent 'n' for various formulations ranged from 0.552 to 0.605 indicating that the release mechanism was non- fickian diffusion. From all the formulation F1-F5, F2 (EC^{15} 8%) has shown the initial sustaining effect by releasing 18% of the drug within 2 hours and release 95.89% of the drug at the end of the 12^{th} hour. Although F5 (EC N^{50} 8%) has given sustaining effect by releasing only 21% of the drug within 2 hours, but at the end of the 12^{th} hour it released only 95.79% of the drug. Based on the above conditions F2 (EC N^{15}, 8%) is selected as the best formulation.

Morphological study on optimized pellets

The morphological studies carried by using the scanning electron microscopy. In this study the pellet was observed under different magnifications.The scanning electron microscopy (Fig 5) shows the pellets being the spherical in shape. The surface depression was observed. The ethyl cellulose shows more rough surface which is due to the density of the matrix and it justifies sustained action.

Stability Studies

Optimized formulation was packed and stored in ICH certified stability chambers maintained at (25°C and 60%±5% RH II) 40and 75%±5% RH for three months. The results are shown in Table 3 and 4. It was found to be there is no changes in the physical and chemical parameters of Tramadol Hcl Pellets of formulation F2 after three months at 25°c/60%±5% RH, 40°c /75%±5% RH. There is no significant difference in the percentage of drug release of Tramadol Hcl Pellets of formulation F2 after three months at 25°c/60%±5% RH, 40°c /75%±5% RH. Tramadol Hcl sustained release pellets were formulated by the powder layer method by using ethyl cellulose as rate controlling polymer. The drug and excipient compatibility studies were performed by using IR Spectroscopy and found that they were compatible. All formulations were prepared into pellets and analyzed for the parameters such as percentage of drug content, friability, bulk density, tapped density, compressibility index, Hausner's ratio, angle of repose and the results were found to be within the limits. In-vitro dissolution studies for all formulations were carried out in 0.1N Hcl for 12 hrs and the percentage of drug release was calculated. The order of drug release for all the formulations followed first order kinetics and the mechanism of drug release governed by Higuchi. The diffusion coefficient value 'n' was found to be range of 0.5-0.85; it indicates that the drug release mechanism follows non-fickian transport (diffusion mechanism).The stability studies were conducted for optimized formulation (F2) as per ICH guidelines at 25^0C±2/60±5% RH and 40^0C±2/75±5% RH for 3 months and no changes were observed.

CONCLUSION

The present investigation focused on the improvement of absorption and oral bioavailability of tramadol Hcl along with sustained action. To meet the above criteria extended release tablets of tramadol Hcl was formulated with hydrophobic rate controlling polymers such as ethyl cellulose as key excipients. The hydrophobic polymers selected were more reliable as they released the drug slowly, extending it over a long period of time. Alternating concentrations of ethyl cellulose have a significant influence on the release rate of the drug. The drug release from all the formulations followed first order kinetics and Higuchi's mechanism. The in-vitro dissolution profiles of F2 were found to be better formulation. Therefore, it may be concluded that the extended release formulations are suitable delivery system for tramadol hcl and may be used for effective management in GERD.

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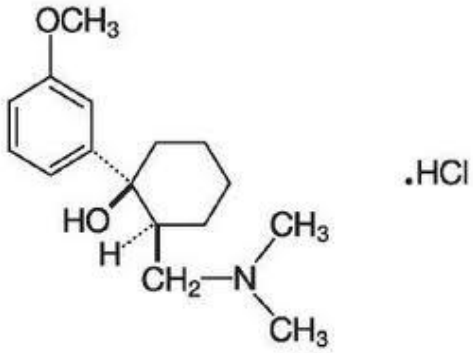


Fig. 1: Chemical Structure of Tramadol Hydrochloride

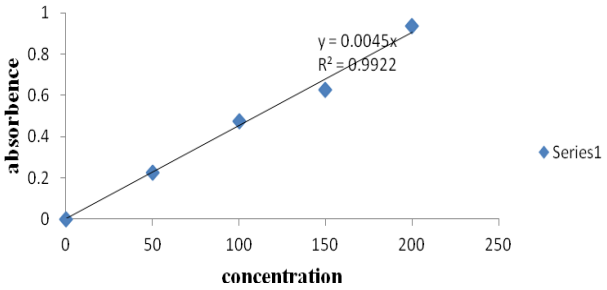
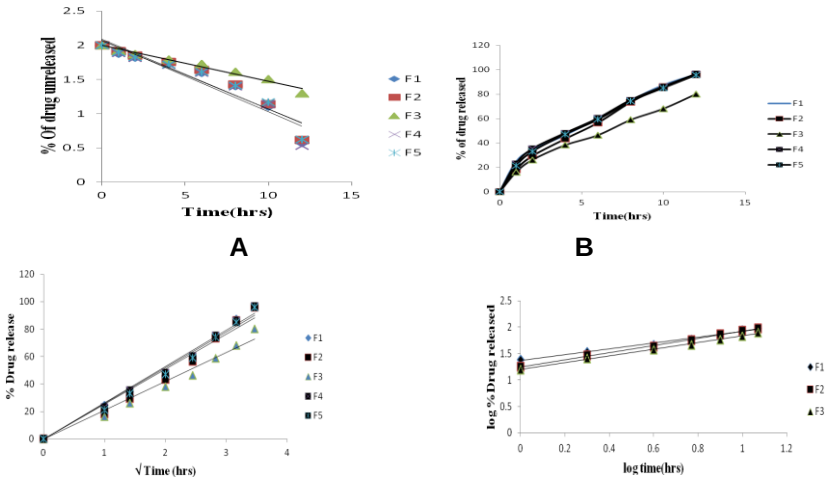


Fig. 2: Calibration Curve of the Tramadol Hydrochloride



A B

C D

Fig. 3: Dissolution Profile of Tramadol Hydrochloride with various Concentrations of (A). Ethyl cellulose, (B) First order, (C) Higuchi and (D) Korsmayer Peppas

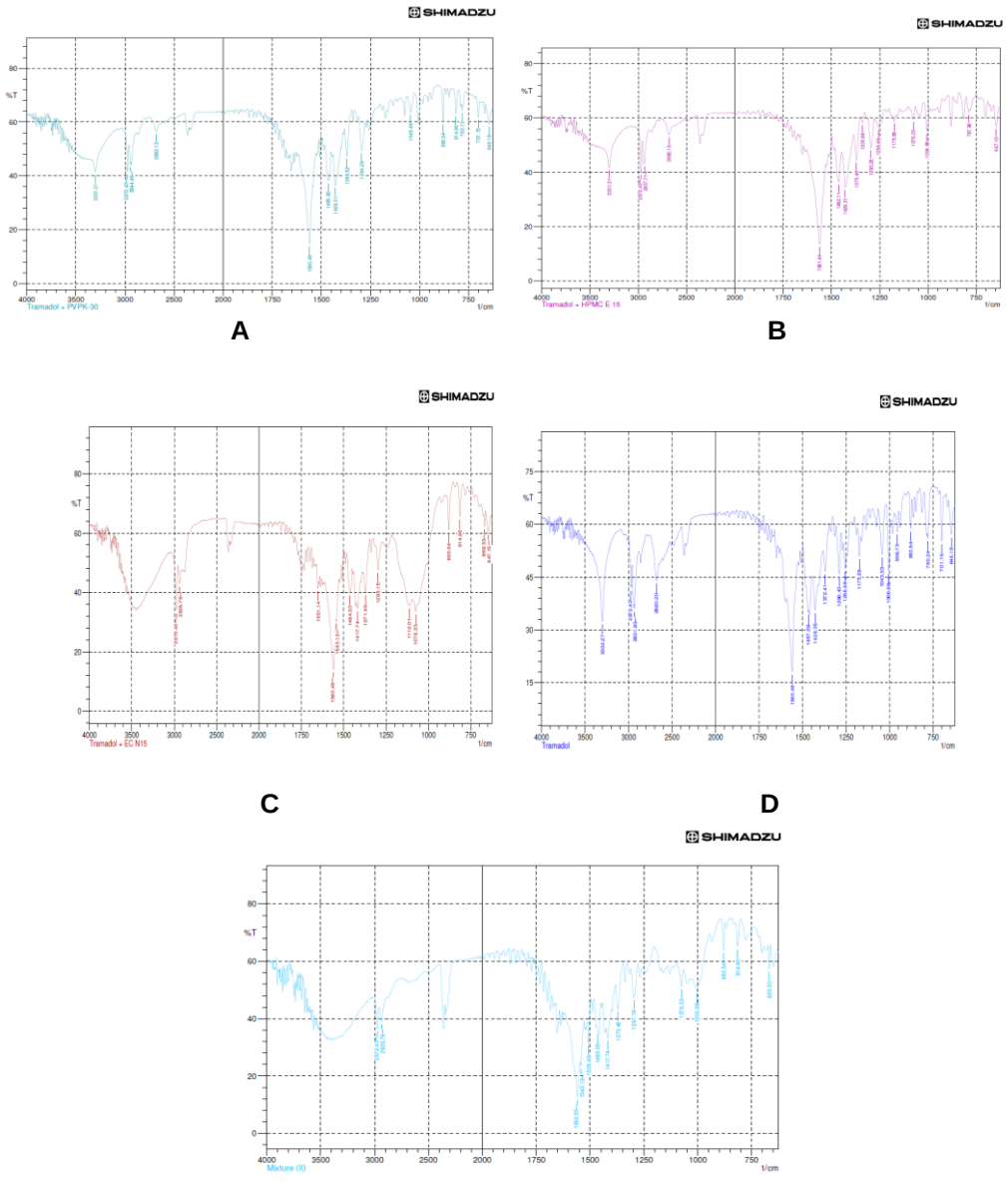


Fig. 4: Infrared Spectrum of Tramadol Hydrochloride with different Polymers like (A) PVPK-30, (B) HPMC E 15, (C) ECN 15, (D) ECN 50 and (E) Mixture (II)

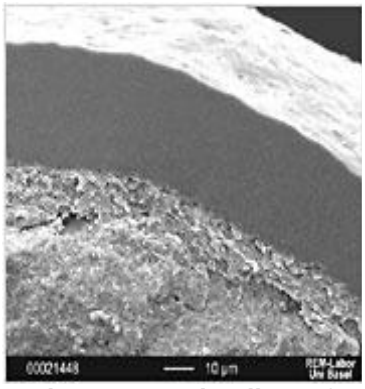


Fig. 5: Coated Pellets of Tramadol Hydrochloride

Table 1: Micromeritic properties

Formulation code	Bulk density (gm/c)	Tapped density (gm/cc)	Hausner's ratio	Angle of repose	Carr's index
F1	0.58±0.0013	0.602±0.0012	1.037±0.0015	18.77±0.0012	3.65±0.0023
F2	0.58±0.0018	0.620±0.0024	1.060±0.0013	22.78±0.0011	6.45±0.0024
F3	0.625±0.0021	0.630±0.0026	1.00±0.0015	19.79±0.0016	1.58±0.0014
F4	0.6±0.0016	0.620±0.0025	1.030±0.0017	20.30±0017	3.03±0.0023
F5	0.625±0.0024	0.660±0.0023	1.050±0.0016	24.70±0.0013	6.06±0.0024

Table 2: Kinetics studies

Formulation code	Zero order	First order	Higuchi	Peppas	K value (mg/HR)	$T_{50\%}$	$T_{90\%}$	Slope (n)
F1	0.961	0.911	0.982	0.987	8.019	4.314	10.306	0.552
F2	0.980	0.973	0.989	0.997	7.991	4.625	10.443	0.677
F3	0.972	0.909	0.991	0.995	6.678	5.230	13.211	0.630
F4	0.959	0.900	0.976	0.995	8.048	4.152	10.442	0.568
F5	0.965	0.913	0.988	0.996	7.982	4.235	10.568	0.605

Table 3: Dissolution profiles of Tramadol HCl pellets from formulations F3 at 25°C/60%± 5% RH (mean ± s.d., n=3)

Parameter	Initial	After 1 month	After 2 months	After 3 months
0	0	0	0	0
1	18.1803±0.365	18.1802±0.365	18.1801±0.365	18.1800±0.365
2	29.2681±0.380	29.2680±0.380	29.2680±0.380	29.2680±0.380
4	43.2358±0.385	43.2356±0.385	43.2351±0.385	43.2353±0.385
6	56.4128±0.388	56.4127±0.388	56.4125±0.388	56.4123±0.388
8	73.2316±0.365	73.2315±0.365	73.2313±0.365	73.2311±0.365
10	86.1806±0.360	86.1805±0.360	86.1804±0.360	86.1802±0.360
12	95.8980±0.387	95.8976±0.387	95.8978±0.387	95.8979±0.387

Table 4: Dissolution profile of Tramadol HCl pellets from formulation F3 at 40°C/75%±5% RH (mean ±s.d S, n=3)

Parameter	Initial	After 1 month	After 2 months	After 3 months
0	0	0	0	0
1	18.1803±0.365	18.1802±0.365	18.1801±0.365	18.1800±0.365
2	29.2681±0.380	29.2680±0.380	29.2680±0.380	29.2680±0.380
4	43.2358±0.385	43.2356±0.385	43.2351±0.385	43.2353±0.385
6	56.4128±0.388	56.4127±0.388	56.4125±0.388	56.4123±0.388
8	73.2316±0.365	73.2315±0.365	73.2313±0.365	73.2311±0.365
10	86.1806±0.360	86.1805±0.360	86.1804±0.360	86.1802±0.360
12	95.8980±0.387	95.8976±0.387	95.8978±0.387	95.8979±0.387

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