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Formulation and Evaluation of Matrix Tablet of Tramadol Hydrochloride

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ABSTRACT

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The aim of this project was to develop once daily controlled release matrix tablets of Tramadol HCl. Controlled release matrix tablets of Tramadol HCl using different polymers viz. Eudragit RS-100, Ethylcellulose, Carbopol 934P and Polyvinyl Pyrolidone K-90 were formulated and evaluated. The tablets were prepared by wet granulation method. The tablets were evaluated for thickness, weight variation, hardness, friability, drug content and *in-vitro* dissolution studies. Different release models like zero order, first order, Higuchi etc were applied to *in-vitro* drug release data in order to evaluate the drug release mechanisms and kinetics. Three batches of matrix tablets were developed. Among these formulations, F5 formulation showed satisfactory physicochemical properties and drug content uniformity and controlled release of drug for 24 hours with maximum release of 95.73%. Matrix tablets with optimum concentration of ethyl cellulose, PVP K-90 were successfully developed and evaluated.

Keywords: Matrix tablets, Eudragit RS-100, Ethylcellulose, Carbopol 934P, PVP K-90, Tramadol HCl.

INTRODUCTION

Tramadol HCl (TmH) is a centrally acting analgesic having both opioid and nonopioid effects. TmH acts as opiate agonist, through selective binding to the μ-opioid receptor, and weak inhibition of norepinephrine and serotonin uptake. It is administered when non-steroidal anti-inflammatory drugs fail to mitigate pain. It is readily absorbed after oral administration.[1]

Its bioavailability is 68-72 %. It has a plasma elimination half-life of 4 - 6 h with a usual dosage regimen of 50-100 mg and maximum dose 400 mg (50 mg 4 times a day). Therefore, to reduce frequency of administration and improve patient compliance, a controlled release matrix dosage formulation of tramadol HCl is desirable.[2]

Controlled release dosage forms release drug at constant rate and provide plasma concentration that remain invariant with time. Controlled release technology implies a quantitative understanding of the physicochemical mechanism of drug availability to the extent that dosage form release rate can be specified. Potential development and new approach to oral controlled release drug delivery includes hydrodynamic pressure controlled system. In general, controlled release delivery attempts to; sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with a minimization of undesirable side effects associated with sawtooth kinetic pattern.[3]

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For controlled–release system, oral route of administration has attracted most attention. This is because there is more flexibility of dosing. The duration of a drug action after oral administration is mainly a function of drug related properties such as the rate of absorption and clearance as well as residence time of the delivery system at absorption site.

MATERIALS AND METHODS

Tramadol hydrochloride was obtained as gift sample from Salute Bestochem Pvt. Ltd. Haridwar, Uttarakhand, India. Eudragit RS-100 was procured from Wockhardt Research Center. Ethylcellulose, Carbopol 934P, PVP K-90, Magnesium stearate, and Talc were procured from Central Drug House (P) Ltd. New Delhi. IPA was purchased from RFCL Limited New Delhi India. All other chemicals and ingredients used for study were of analytical grade.

Preparation of matrix tablets[4]:

Tablets were prepared by wet granulation method. The drug (tramadol hydrochloride) and excipients such as Eudragit RS100, Ethyl cellulose, Carbopol 934P were mixed properly with excipients in poly bags and were granulated with PVP-K90 using isopropyl alcohol as granulating agent[5]. The wet mass was passed through sieve #25. The resultant granules were dried at room temperature. Dry granules were lubricated with magnesium stearate and talc. The matrix tablets were prepared by compression using 8 station rotary machine (Kambert Machinery). Each tablet contained 200 mg drug (Table 1).

Evaluation of the matrix tablets [5,6]:

Weight variation

The weight variation test was performed by weighing 20

tablets individually and collectively, the average weight was calculated and the deviation of the individual weight from the mean weight was calculated (Table 2).

Thickness

Thickness of the tablets was determined by using Vernier Caliper. For this purpose 20 tablets were individually measured for their thickness.

Hardness

Hardness of the tablets was determined with the help of Monsanto hardness tester.

Friability

10 tablets were weighed and rotated for 4min at one hundred revolutions per Minute. using Roche friabilator. The tablets were then reweighed and percentage friability was calculated using following formula.

%Friability = (Loss in weight/Initial weight) x 100

Drug content

The drug content of the tablets was measured spectrophotometrically. For this purpose 5 tablets were weighed and crushed in a pestle and mortar. % drug content or assay of the tablet was determined by official method.

***In-vitro* dissolution study**

In-vitro dissolution studies were carried out using USP typeII (Paddle type) dissolution test apparatus (Electrolab TDT-80L). The basket was rotated at 50 rpm and the temperature was maintained at 37.5±0.5 ^{0}C and 900 ml of dissolution medium was used. A single tablet was dropped in 900 ml of dissolution media (0.1N Hcl). The samples were withdrawn at interwal of 1, 3, 6, 9, 12, 15, 18, 21, 24 hrs and filtered through Whatman filter paper. Then test solutions were analyzed by UV Spectrophotometer by measuring absorbance at 271 nm.

Fig. 1: *In-vitro* drug release profile of F3, F4 and F6 formulations

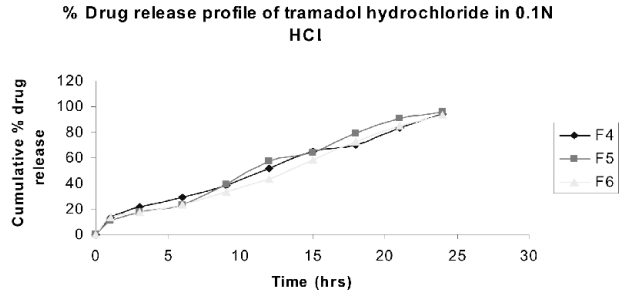

Table 1: Ingredients used in formulation of tramadol hydrochloride matrix tablets.

S. No.	Excipients	Tramadol					
		F1	F2	F3	F4	F5	F6
1	Tramadol HCl	-	-	-	200	200	200
2	Eudragit RS	100	40	-	-	-	-
3	Ethyl cellulose	100	150	200	100	150	200
4	Carbopol 934P	50	50	50	50	50	50
5	PVP-K90	50	100	150	150	100	50
6	Magnesium stearate	10	10	10	10	10	10
7	Talc	10	10	10	10	10	10
8	IPA	qs	qs	qs	qs	qs	qs

Table 2: Characterization of Tramadol HCl matrix tablets

S. No.	Parameters	Formulations					
		F_1 *	F_2 *	F_3 *	F_4*	F_5*	F_6*
1	Weight variation (mg)	498.12 ±1.31	501.1 ±1.32	493.68 ±1.34	498.3±1.5	496.67 ±2.0	497.7 ±4.26
2	Hardness (kg/cm^2)	7.2 ±0.87	7.3 ±1.00	7.1 ±1.12	7.2 ±0.87	7.8 ±0.58	7.4 ±0.75
3	Thickness (mm)	3.89 ±0.1	3.88 ±0.10	3.87 ±0.12	3.90 ±0.11	4.03 ±0.03	3.88 ±0.02
4	Friability	0.6421 ±0.09	0.5137 ±0.09	0.7433 ±0.08	0.644 ±0.09	0.4137 ±0.09	0.7621 ±0.08
5	Drug content (%)	-	-	-	97.95 ± 0.37	98.07 ±0.29	98.61 ± 0.46
6	Drug release study (24hrs.)	-	-	-	94.30 ±0.75	95.73 ±0.70	93.06 ±0.72

*Average value ± SD, n=3

Table 3: Data of kinetic models for different formulations

Kinetics Model	Parameters	Formulations		
		F4	F5	F6
Zero Order	R	0.9949	0.9987	0.9956
	K_0	3.6526	3.7593	3.6683
First Order	R	0.9326	0.9460	0.9359
	K_1	0.09764	0.9479	0.09672
Higuchi Model	R	0.9528	0.9674	0.9750
	K_H	18.955	20.653	18.875
Hixson-Crowell Model	R	0.9723	0.9793	0.9669
	K_{HC}	1.0×10^{-1}	1.122×10^{-1}	1.132×10^{-1}
Peppas - Korsenmayer Model	R	0.9819	0.9766	0.9576
	n	0.6202	0.7341	0.6546

Release models and kinetics [7]

Three formulations (F4, F5 and F6) were evaluated for release kinetics by using various mathematical models such as zero order, first order, Higuchi and Hixson–Crowell .

Drug release data was fitted to different models in order to establish the release mechanism and kinetics. A criterion for selecting the most appropriate model was based on goodness of fit, high regression constant value and smallest sum of squared residuals (Table 3).

RESULTS

All the formulations were evaluated for weight variation, hardness, thickness, friability and % drug content. The weight of the formulation varied from 496.67±2.002 to 498.3±1.569 mg. Thickness of the formulation varied from 3.88±0.023 to 4.03±0.039 mm. Hardness of the tablet varied from 7.2±0.873 to 7.8±0.584 (kg/cm^2) and drug content was found to be between 97.95± 0.375 to 98.61 ± 0.462(Table2).

All formulations showed uniform thickness. The average percentage deviation of all parameters was found within the limit. The friability for all formulations were found below 1% indicating good abrasion resistance characteristics of tablets.

All formulations showed acceptable physicochemical properties and specifications for weight variation, thickness, hardness, friability and drug content. Percentage drug release of all the formulations in 0.1 N hydrochloric acid was studied for the 24 hours. The release was found to be 93.06±0.72 to 95.73±0.70 %. Formulation F5 showed maximum release over a period of 24 hrs and % drug release was found to be 95.73±0.70 %.

DISCUSSION

The results indicated that dissolution rate of tramadol hydrochloride was highest in formulation containing ethyl cellulose (150 gm), carbopol 934P (50 gm) and PVP K-90(100 gm). From the dissolution study it was clear that F5 had fast dissolution rate as compared to other formulations. So formulation F5 was found to be optimum controlled release matrix tablet with both hydrophilic and hydrophobic polymers. Combination of both types of polymers is responsible for better release of the drug in a controlled manner.

Among all model, zero order was considered as best fit model with highest value of correlation coefficient. The value of r^2 for optimized formulation F5 prepared with Ethyl cellulose, Carbopol 934P and PVP-K90 was found to be maximum (0.9987). While considering the higher correlation co-efficient values, the release data seems to better fit with zero order model.

CONCLUSION

A new oral drug delivery system for the controlled release of tramadol hydrochloride was developed. The formulations showed prolonged release for 24 hrs. The matrix tablets were made by wet granulation method. Formulation F5 was considered as the optimum formulation. The dissolution profile indicated that matrix tablet showed acid resistance and constant release of the drug at approximately zero order rates up to 24 hrs. The dissolution rate of tramadol hydrochloride was highest in formulation composed of ethyl cellulose, carbopol 934P and polyvinyl pyrolidone K-90. Hence matrix tablets with optimum concentration of ethyl cellulose, PVP K-90 were successfully developed.

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