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DEVELOPMENT AND EVALUATION OF CARBOPOL BASED SUATAINED RELEASED MATRIX TABLETS OF TRAMADOL HYDROCHLORIDE

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ABSTRACT

In the present investigation an attempt has been made to increase therapeutics efficacy, reduce frequency of administration and improve patient compliance by developing Sustained release matrix tablets of tramadol hydrochloride using carbopol as rate controlling polymer. Total four formulations ware prepared by using different drug:polymer concentration ratio and subjected to various precompression and post compression parameters. The results ware found with in pharmacopoeial standards for all formualtions. Among the formulation tablets of batch F3 found optimized showed sustained drug release for 12 h. When these dissolution profiles were subjected to various kinetic release investigations and it was observed that the mechanism of drug release was diffusion controlled with a minor contribution from polymeric relaxation. It was found that optimized formulation F3 showed no significant change in physical appearance, drug content, hardness and in vitro dissolution pattern after storage at 45 °C/75% RH for three months. From the study it was concluded that use of carbopol is good choice as rate controlling polymer for the preparation of sustained release tablets.

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INTRODUCTION

Immediate release dosage forms have no control on drug release from dosage form that generally leads to unpredictable therapeutic drug concentrations in plasma. Sustained release (SR) formulations are those which is used to overcome the drawbacks of immediate release formulations. Matrix system is the most widely used method for the development of SR dosage form due to its ease of manufacture. In matrix systems, the release of drugs from the hydrophilic polymers is controlled by a combination of mechanisms such as polymer swelling, erosion and diffusion [1]. Carbopol is hydrophilic polymer have strong binding characteristics which is widly use polymer in development of SR formulations. Their hydrophilic nature and highly crosslinked structure make them suitable candidates for SR formulations [2,3].Tramadol Hydrochloride is an opoid analgesic, which is widely used in the severe acute and in chronic pain with half life of 6-7 hours hence requires multiple daily doses to maintain adequate plasma concentrations. After oral administration, tramadol is rapidly and almost completely absorbed. Tramadol has been proved to be effective in both experimental and clinical pair without causing serious side effects. The usual oral dosage regimen of tramadol is 50 to 100 mg every 4 to 6 hrs with a maximum dosage of 400 mg/day. [4,,5]. To reduce the frequency of administration and to improve patient compliance, a sustained release formulation of tramadol is necessary . The main objective of the present work was to develop sustained release matrix tablets of water soluble Tramadol hydrochloride using carbopol as rate controlling polymer so as to release the drug in sustained manner over the period of 12 hr. Carbopols or carbomers (hydrophilic polymer) is widely used polymer in the development of sustained release and controlled preparations. Carbopol show compatibility with various active ingredients and other excipients and their hydrophilic nature and highly crosslinked structure make them suitable candidates for SR and CR formulations . The SR tablets of tramadol was prepared using varying ratios of drug and polymer like 1:0.6, 1:0.8, 1:1 and 1:1.2 were selected for the study. After fixing the ratio of drug and polymer for sustained release of drug up to desired time, the release rates were studied.

MATERIALS AND METHOD

Materials:

Tramadol hydrochloride was obtained as gift sample from Cadila Healthcare (Ahmedabad. India), Carbopol were obtained as gift samples from Leben Laboratories Pvt Ltd, Akola, Maharashtra. All other solvents and reagents were of analytical grade.

Preparation of Tramadol Hydrochloride Matrix tablets

Matrix tablet containing tramadol hydrochloride were prepared by wet granulation technique using different concentrations of carbopol 934P as rate controlling polymer. Microcrystalline cellulose was used as filler and magnesium stereate as lubricant. All the ingredients were passed through sieve no 60# and were mixed uniformly. The compositions of different excipients in formulations are listed in (Table. 1). Granules were prepared by using sufficient quantity of binder solution of PVP K 30 in isopropyl alcohol. Wet mass was passed through sieve no 16 # and dried at 45-550c for 2 hr. Dried granules were sized by passing through sieve no. 20 # and lubricated with magnesium stearate by further blending for 3 mins and finally talc was added to the blend. Compression was done on 8 station rotary tablets punching machine (Shakti) using 8mm round concave punch. [6].

Table 1: Composition of Tramadol HCl Matrix Tablets.

Ingedients (mg)	F1	F2	F3	F4
Tramadol HCl	100	100	100	100
Carbopol 934P	60	80	100	120
PVP K 30	10	10	10	10
Magnesium Stereate	2	2	2	2
Talc	2	2	2	2
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.
Microcrystalline Cellulose	76	56	36	16

EVALUATION OF MATRIX TABLETS

Evaluation of granules :

Angle of Repose

Flow property of the granules was evaluated by determining the angle of repose and the compressibility index. Static angle of repose was measured according to fixed funnel method and free standing cone method of Banker and Anderson[7]. The angle of repose was calculated using the equation,

$$\text{Tan } \theta = h/r \quad \ldots\ldots\ldots\ldots (1)$$

Bulk density/Tapped density

Loose bulk density (LBD) and Tapped bulk density (TBD) were determined for the prepared granules. LBD and TBD was calculated using the formula,

$$\text{LBD} = \text{Wt of Powder} / \text{Vol. of Powder} \quad \ldots\ldots\ldots\ldots\ldots (2)$$

$$\text{TBD} = \text{Wt of Powder} / \text{Tapped Vol. of Powder} \quad \ldots\ldots\ldots (3)$$

Compressibility Index[8].

Carr's Compressibility Index for the prepared granules was determined by the equation,

Carr's Index (%) = TBD – LBD/TBD x 100 … … (4)

The results of precompression parameter for all the tablets formulation was shown in table 2.

Table 2: Precompressional parameters of all granules.

Formulation	Bulk density (g/ml)	Tapped Density (g/ml)	Angle of repose (θ)	% Compressibility	Hausner Ratio
F1	0.446	0.520	30.81	15.56	1.13
F2	0.373	0.532	29.58	15.68	1.17
F3	0.352	0.510	28.16	15.22	1.16
F4	0.372	0.562	32.17	15.52	1.19

Evaluation of Tablets :

Tablets from all the formulations were evaluated for its various properties like hardness by using Pfizer hardness tester , friability by using Roche friabilator and weight variation by using electronic balance. Drug content was determined by selecting 20 tablets from each formulation. Tablets were crush in morter and pestle and power equivalent 100 mg of drug was taken and diluted to 250ml with sufficient amount of phosphate buffer pH 6.8. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 271nm. The results were given in Table 3.

In Vitro Dissolution studies :

The in vitro dissolution studies was carried out in 900 ml of phosphate buffer, pH 6.8 using USP XXII Dissolution test apparatus employing paddle stirrer. One tablet was placed inside the dissolution medium and the paddle was rotated at 50 rpm. 5 ml samples were withdrawn at specific time intervals and the same volume was replaced to maintain sink conditions. The samples were analyzed for drug content spectrophotometrically at 271nm.

Stability Studies :

To assess the drug and formulation stability, stability studies were done according to ICH guidelines.[9] Optimized formulation F3 were kept in the humidity chamber maintained at 45°C and 75% RH for 3 months (Yorco Scientific Industries, India). At the end of studies, samples were analyzed for the drug content, in vitro dissolution, and other physicochemical parameters.

Drug release kinetics studies : .[10,11]

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

RESULT AND DISCUSSION

The susained release matrix tablets tramadol were formulated in four different formulation F1 to F4 by using carbopol 934P polymer using wet granulation technique (Table 1). The values of pre-compression parameters evaluated were within prescribed limit and indicated good free flowing property (Table 2). Angle of repose ranged from 28.16 to 32.17 and the compressibility index ranged from 15.22 to 15.68. The results of angle of repose indicates good flow property of the granules and the value of compressibility index further showed support for the flow property. The prepared tablets of all the formulations were evaluated for their post compression parameters like hardness, friability, weight variation, drug content and in-vitro drug release.(Table 3). The measured hardness of tablets of each formulation ranged between 5.23±0.21to 5.5±0.16 kg/cm^2. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits. The drug content estimations showed values in the range of 97.35±0.96 to 99.62±2.12% which reflects good uniformity in drug content among different formulations. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

Table 3: Postcompressional parameters of all formulations.

Formulatins	Hardness* (Kg/cm2)	Friability* (%)	Weight variation* (%)	Thicknes* (mm)	Drug Content* (%)
F1	5.48±0.14	0.76±0.14	248.97±1.4	4.25±0.61	97.35±0.96
F2	5.23±0.21	0.62±0.10	248.90±1.9	4.28±0.57	98.10±0.58
F3	5.5±0.16	0.64±0.23	250.03±1.3	4.30±0.51	99.62±2.12
F4	5.43±0.19	0.65±0.19	249.65±1.8	4.40±0.83	97.68±1.19

*All values are expressed as mean ± SD, (n=3)

In Vitro Dissolution studies

All the formulations were subjected to In vitro dissolution studies. The influence of concentration of polymer on drug release were studied. The results of in vitro percentage release at different time intervals is plotted against time to obtain release profile (Fig.1). The % drug released from the formulation F1 containing drug polymer ratio 1:0.6 was 100.7% within 10 hrs. showing that drug release could not be sustained up to 12 hrs. formulation F2 was prepared employing the drug polymer ratio 1:0.8 showed 91.81% drug release at the end of 12 hr. while the formulation F3 and F4 having drug polymer ratio 1:1 and 1:1.2 showed drug release 99.58% and 86.82% respectively at the end of 12 hrs. From the study conducted it was observed that as the polymer concentration increases, the drug release was decreased. The initial burst release was observed in all the formulations due to the greater hydration at the tablet surface. From the in vitro drug release studies, it was concluded that formulation F3 having the drug polymer ratio 1:1 showed good release retardant effect, releasing the drug in sustained manner up to 12 hrs, when compared to other formulations.

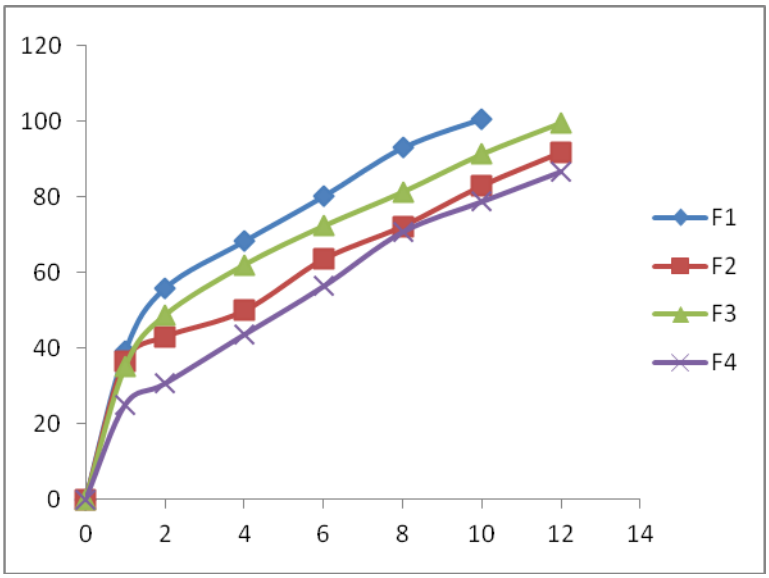

Fig.1 In vitro drug release profile of all formulations (Time in Hr Vs Cumulative % Drug release).

Release Kinetics Analysis :

To analyze the mechanism of the drug release rate kinetics of the dosage form, the drug release data of batch F3 was fitted to various models like Zero order, first order, Higuchi's model and Korsmeyer's model (Table 3). Optimized formulation F3 fitted best for Higuchi model with regression value 'r^2' was 0.997. Further to know the exact mechanism of drug release data of batch F3 was fitted to Korsmeyer's model. Slope value ($0.5<n<1.0$) suggest that the release of tramadol from matrix tablets followed Fickian transport mechanism.

Table 4: Drug release kinetic parameters of optimized formulation F3.

Model	R^2	Slope
First order	0.767	-0.160
Zero Order	0.876	7.0
Higuchi model	0.997	25.34
Korsemeyer-Peppas model	0.997	0.406

In view of the potential utility of the formulation, stability studies were carried out on optimized formulation F3 at 45 °C and 75% RH for three months. The protocols of stability studies were in compliance with the guidelines of ICH for stability testing of products intended for the global market. After storage, the formulation was subjected to a drug assay, hardness and in vitro dissolution studies. The stability study showed no significant change after storage at 45 °C and 75% RH for three months indicating that formulation (F3) was stable.

CONCLUSION

The present study was carried out to develop the sustained release matrix tablets of tramadol using carbopol as rate controlling polymer to provide an effective and safe therapy for acute and chronic pain, with a reduced dose and reduced length of treatment. In vitro dissolution studies of optimized F3 tablets formulation showed sustained release of tramadol for 12 h. Thus, results of the current study clearly indicating that Carbopol 934P are suitable drug release rate-controlling polymers for tramadol and promising alternative to the conventional dosage form.

BOTTAM LINE

Carbopol has much potential as rate controlling polymer in the development of sustained release matrix tablets.

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