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Original Research Article

Design and Evaluation of Extended-Release Matrix Tablet of Tramadol Hydrochloride

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Abstract: The impartial concerning this study was to cultivate extended-release matrix pellet of Tramadol hydrochloride using various combinations of hydrophilic polymers (HPMC, Carbopol, Xanthum Gum). The form tablets were prepared by direct compression method. The pre and post compression description of blend and tablet were judged. The in-vitro dissolution studies revealed that the blend of HPMC and Carbopol in different aggregation showed hinder release of 63% at the end of 12th hour and in addition to 94.24% at the end of 24th moment, thereby appearance good release pattern necessary for ER tablet and shown good kinetic release connected of diffusion and deterioration. Hence hydrophilic polymer HPMC and Carbopol was found to extended release of very water-soluble drug, Tramadol hydrochloride.

Keywords: Tramadol hydrochloride; hydrophilic polymer; extended-release matrix tablet.

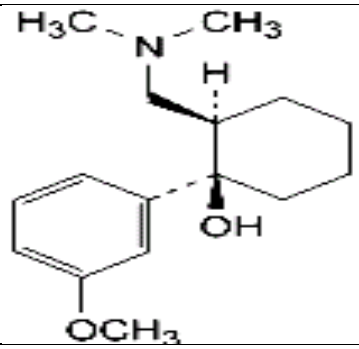
INTRODUCTION

Sustained release constitutes any dosage form that provides medication over an extended time period. In general, the sustained release dosage form is to maintain therapeutic blood or tissue level of drug for a prolonged period usually accomplished by attempting slow first order fashion. Successful fabrication of extended release products is usually difficult & and involves consideration of physicochemical properties of drug, pharmacokinetic behavior of drug, route of administration, disease state to be treated and, most importantly, placement of the drug in dosage form total will provide the desired temporal and spatial delivery pattern for the drug. The slow first order release obtained by an extended release preparation is generally achieved by the release of the drug from a dosage form. In some cases, this can be achieved by retarding the release of drug from a dosage form and in some cases; this is accomplished by a continuous release process [1, 2]. The basic rationale for extended drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action become more to design properly.

POTENTIAL ADVANTAGES OF EXTENDED DOSAGE FORMS

- Patient compliance due to reduction in the frequency of dosing.
- Employ minimum drug.
- Minimize or eliminates local and systemic side effects.
- Obtain less protentiation or deduction in drug activity with chronic use.
- Minimize drug accumulation with chronic dosing.
- Improves efficacy in treatment.

Rate controlled dosage form, and less, or not at all, a property of the drug molecules inherent kinetic properties [3]. Tramadol Hydrochloride is a centrally acting synthetic opioid analgesic. The mode of action is not clear, even though the parent and M1 metabolite of Tramadol binds to μ opioid receptors and results in weak inhibition and reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In several animal tests Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone [4].

Drug (Tramadol hydrochloride) description [5-6]	
IUPAC Name	(±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol Hydrochloride
Structure	
Molecular formula	$C_{16}H_{25}NO_2$. HCl
Molecular Weight	299.8
Description	White, bitter, crystalline and odorless powder
Solubility	It is readily soluble in water and ethanol
Therapeutic category	Opioid analgesic

In the present study, the objective is to develop matrix extended-release tablets of highly water-soluble Tramadol Hcl by using different polymers like Ethyl Cellulose, HPMC, Carbopol and Xanthan Gum. Since anti- inflammatory agent should be frequently administered to control inflammation level and once-daily dose of Tramadol ER results in less frequent fluctuations in plasma concentrations than equivalent daily doses of short-acting Tramadol, it may benefit patients experiencing pain throughout the dosing interval. Hence, the plan of work is to formulate Tramadol Hcl extended release matrix tablets which can provide constant effective level over a period of 24 hours.

MATERIAL AND METHOD

Material

Tramadol Hcl was obtained as gift sample from Milton Drugs Pvt. Ltd, Puducherry. Ethyl Cellulose, HPMC, MCC, Aerosil & Magnesium stearate was procured from Rankem Limited, Mumbai whereas Carbopol and xanthan gum were procured from Himedia, Mumbai.

Preformulation Studies

Preformulation can be defined as an investigation of physical and chemical properties of a drug substance alone. The overall objective of preformulation studies is to generate information useful to the formulator in developing stable and bioavailable dosage forms.

Drug Excipient Compatibility Studies

Compatibility study was carried for pure Tramadol Hydrochloride and combination of Tramadol Hydrochloride with excipients. FTIR (ATR- Bruker) was used for study in the spectrum range 400-4000cm^{-1}.

Method

Tramadol Hydrochloride ER table were prepared by direct compression method with different polymer like Ethyl Cellulose, HPMC, Carbopol and Xanthan Gum in various drug**:** polymer ratio as show in Table No1. Tramadol Hydrochloride was passed through sieve #40. Ethyl Cellulose, HPMC, Carbopol, Xanthan Gum, MCC was passed through sieve # 40. The above sieved materials were mixed thoroughly by tumbling method in a polythene bag. The dry blend was lubricated with aerosil and magnesium stearate. Then the lubricated dry blends were subjected to punching using a tablet punching machine-10, B tooling 12mm round punches. Parameters like average weight, hardness and friability were checked during compression as in process quality measures [7].

Table 1: Formulation of Tramadol Hydrochloride matrix tablets using different ratios of polymers (F1-F9)

S. No.	INGREIDENT (in mg)	FORMULATION								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Tramadol hydrochloride	100	100	100	100	100	100	100	100	100
2	Ethyl Cellulose	75	75	75	75	75	75	75	75	75
3	HPMC	75	-	-	50	25	50	25	-	-
4	Carbopol	-	75	-	25	50	-	-	50	25
5	Xanthan Gum	-	-	75	-	-	25	50	25	50
6	MCC	150	150	150	150	150	150	150	150	150
7	Aerosil	3	3	3	3	3	3	3	3	3
8	Magnesium steareate	7	7	7	7	7	7	7	7	7
9	Total Weight	410	410	410	410	410	410	410	410	410

Characterisation of Blends

Angle of repose, Bulk density, Tapped density & Carr's index were determined as per standard procedure [8].

Evaluation of Tablets [9]

The thickness and diameter of the tablets were found out using Vernier Caliper and the results were expressed in millimeter. A ± 5% may be allowed depending on the size of the tablet. Tablets require a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by Monsanto hardness tester. Ten tablets from the batch were used for hardness studies and results are expressed in Kg/cm^2. The uniformity of weight was determined according to I.P specification. Friability test was performed in Roche Friabilator apparatus. Tramadol Hydrochloride tablet was tested for their drug content. The tablet was finely powdered in a mortar and pestle. Tablet equivalent to 100 mg of Tramadol Hydrochloride was accurately weighed and transferred to a 100 ml standard flask. To the drug powder, methanol was added and made up to the volume with distilled water. It was shaken thoroughly for 30 minutes to ensure complete solubility of the drug. 10ml of the resultant liquid was pipetted out in another standard flask and volume was made up to 100ml with distilled water. The absorbance of the final solution was measured at 274 nm in a UV-Visible spectrophotometer (Shimadzu). The amount of drug and the percentage purity of each formulation were evaluated. Tablet dissolution was assessed using standard USP dissolution apparatus type II. Different kinetic equations (zero order, first order, higuchi's equation, Korsmeyer equation) were applied to intercept the release from matrix system.

RESULT AND DISCUSSION

All the organoleptic character of Tramadol Hydrochloride was studied and it was found that all the character complies with IP standards. The hygroscopic characters for Tramadol Hydrochloride were performed according to the procedure. The powder of Tramadol Hydrochloride doesn't have the hygroscopic nature and so there was no need of specific environment for the drug. At ambient condition results showed no change in the weight of the powder. The density of Tramadol Hydrochloride was found 0.63 g/ml .True density was found 0.55g/ml. The results are shown in table no-3.The measurement of free flowing powder can also be done by Carr's index. The Carr's index for all the formulations was found to be 12.2, which reveals that the blends have fair flow character. The results are shown in table no-2. The angle of repose for Tramadol Hydrochloride was done as per the procedure. The angle of repose of Tramadol Hydrochloride was found to be 38.91 ±0.4.1. Which indicates that Tramadol Hydrochloride have fairly good flow property. The results are shown in table no-3. The tablets of different formulations of Tramadol Hydrochloride were subjected to various evaluation tests, such as hardness, thickness weight variation, friability and drug content. All the result is shown in Table no-5. The thickness of the tablets was found out using Vernier Caliper and the thickness found to be in the range of 4.02-4.62mm.

The hardness of tablet was measured by Monsanto hardness tester. Ten tablets from the batch were used for hardness studies and results showed they were in between 6.1-6.6 Kg/cm^2. This is appropriate for matrix tablet. The uniformity of weight was determined according to I.P specification and results showed that all the formulation passes the test. The Friability of all the formulation was below 1% as per IP specification. Tramadol Hydrochloride matrix tablet was tested for their drug content and all the formulation showed drug content more than 95%. The blends of matrix tablet were prepared and Pre compression parameters like the angle of repose, bulk density, tapped density and Carr's index was characterized. The angle of repose for the blend of Tramadol Hydrochloride and excipients was done. The angles of repose of different formulations were found between 23.91± 0.4 to 28.45± 0.47. The angle of repose of different formulations was ≤ 28.45 which indicates that material had excellent flow property. So it was confirmed that the flow property of blends were free flowing. All the values were mentioned in the table no-5. The bulk density of blend of Tramadol Hydrochloride and excipients were found between 0.57 g/ml to 0.66 g/ml. True density were found between 0.54g/ml to 0.65/ml. The measurement of free flowing powder can also be done by Carr's index. The Carr's index for all the formulations was found to be 17.2-19.7 which reveals that the blends have fair flow character. The results are shown in table no-4. Characterization of Tramadol Hydrochloride blends (Pre compression parameters) was tabulated in table 5.The comparative in-vitro release profile of formulation F1-F9 was tabulated in table 6 and shown in fig.1.The release kinetic result was tabulated in table 7.

Table 2: Average weight of tablet

S. No.	Average weight of tablet	Percentage
1	80 mg or less	± 10%
2	More than 80mg and less than 250mg	± 7.5%
3	250 mg or more	± 5%

Table 3: Preformulation studies

S. No.	Drug	Hygroscopicity	Bulk density	True density	Carr's index	Angle of repose
1	Tramadol Hydrochloride	-	0.63±0.02	0.55±0.009	12.2	38.91±0.4.1

Table 4: Characterization of Tramadol Hydrochloride blends (Pre compression parameters)

Batch	Angle of repose (0)	Bulk density (g/ml)	True density (g/ml)	Carr's index
F1	26.07 ± 0.8	0.67	0.54	19.2
F 2	25.25 ± 0.6	0.69	0.54	18.5
F 3	28.45 ± 0.47	0.61	0.51	17.2
F 4	25.12 ± 0.6	0.64	0.57	18.5
F 5	26.10 ± 0.5	0.61	0.57	17.7
F 6	23.91 ± 0.4	0.68	0.55	19.2
F 7	27.46 ± 0.5	0.66	0.53	18.4
F8	27.01 ± 0.7	0.67	0.52	18.2
F9	25.92 ± 0.8	0.65	0.54	19.7

Table 5: Characterization of Tramadol Hydrochloride matrix tablets

Batch	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Average Weight (mg)	Content Uniformity (%)
F1	4.62 ± .012	6.2 ± 0.5	0.4 5± 0.005	412 ± 2	100.2 ±2.4
F 2	4.02 ± 0.09	6.2 ± 0.3	0.32 ± 0.0041	416 ± 2	98.2 ± 1.6
F 3	4.25 ± 0.16	6.4 ± 0.5	0.19 ± 0.003	422 ± 4	98.7 ±2.2
F 4	4.19 ± 0.07	6.6 ± 0.2	0.21 ± 0.002	394 ± 2	101.2 ±2.4
F 5	4.11 ± 0.05	6.1 ± 0.3	0.54 ± 0.004	400 ± 4	102.3 ±1.3
F 6	4.32 ± 0.19	6.2 ± 0.2	0.49 ± 0.011	398 ± 2	101.5 ±1.6
F 7	4.26 ± 0.22	6.2 ± 0.2	0.74 ± 0.006	418 ± 3	98.2 ±1.2
F8	4.22 ± 0.11	6.5 ± 0.4	0.46 ± 0.004	416 ± 3	99.2 ±1.8
F9	4.42 ± 0.002	6.5 ± 0.2	0.42 ± 0.003	398 ± 3	98.23±1.4

Table 6: Comparative In-Vitro release from f1 to f9 batch

Time in Hrs.	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	13.51 ± 0.69	5.41 ± 3.82	16.12 ± 0.87	11.21 ± 0.95	5.41 ± 0.56	11.75 ± 0.69	7.56 ± 0.94	16.5 ± 1.56	11.58 ± 1.23
2	16.27 ± 1.03	14.23 ± 1.81	27.08 ± 0.99	20.46 ± 1.54	11.53 ± 0.94	15.26 ± 0.95	12.64 ± 1.21	19.59 ± 2.36	20.49 ± 0.95
3	25.36 ± 0.69	21.70 ± 2.16	33.43 ± 1.32	31.87 ± 1.32	24.99 ± 0.84	20.85 ± 0.92	21.41 ± 1.09	21.88 ± 1.54	25.64 ± 0.56
4	30.00 ± 1.04	28.32 ± 1.46	43.02 ± 0.89	37.95 ± 0.84	30.13 ± 0.69	25.69 ± 0.83	29.45 ± 0.94	26.72 ± 0.91	31.23 ± 1.45
5	47.27 ± 1.05	33.78 ± 1.55	48.66 ± 0.98	47.76 ± 0.91	34.99 ± 1.51	29.32 ± 0.82	35.64 ± 0.76	39.16 ± 1.69	40.70 ± 1.98
6	59.53 ± 0.71	35.24 ± 1.77	55.12 ± 1.47	54.32 ± 1.11	40.99 ± 1.64	40.23 ± 1.24	45.43 ± 0.73	46.88 ± 1.54	49.92 ± 2.12
8	69.75 ± 1.51	39.28 ± 1.21	65.14 ± 1.25	60.72 ± 1.45	49.71 ± 1.22	55.21 ± 1.64	64.23 ± 0.81	56.43 ± 1.97	60.69 ± 2.04
10	81.76 ± 0.92	42.35 ± 0.99	79.56 ± 1.89	65.78 ± 0.77	57.75 ± 0.64	69.54 ± 0.95	76.21 ± 0.88	66.85 ± 2.36	71.43 ± 1.54
12	86.23 ± 1.89	45.32 ± 0.86	92.35 ± 1.21	73.33 ± 0.92	63.80 ± 0.76	80.65 ± 0.53	88.65 ± 0.91	76.21 ± 1.54	81.26 ± 1.24
24	101.68 ± 0.65	74.31 ± 1.04	101.07 ± 0.82	101.45 ± 0.64	95.24 ± 0.95	101.23 ± 0.97	99.56 ± 1.32	99.64 ± 0.86	101.47 ± 0.81

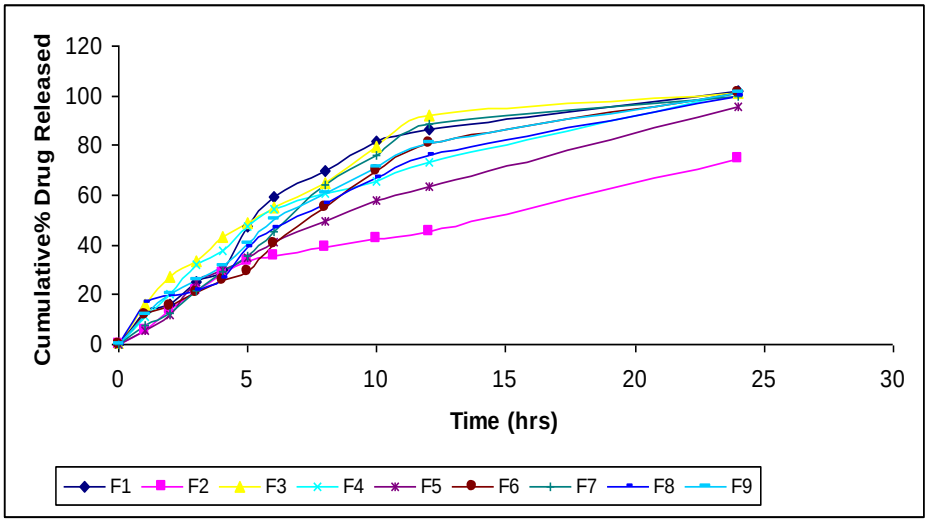


Fig. 1: Comparative In-vitro release of F1 to F9 batch

Table 7: Release kinetic study

Formulation	Zero order	First order	Higuchi's equation	Korsmeyer
F 1	0.813	0.625	0.942	0.961
F 2	0.917	0.591	0.977	0.965
F 3	0.820	0.660	0.939	0.972
F 4	0.888	0.613	0.982	0.963
F 5	0.936	0.634	0.995	0.950
F 6	0.895	0.751	0.954	0.960
F7	0.819	0.631	0.929	0.959
F8	0.908	0.761	0.967	0.955
F9	0.881	0.690	0.971	0.969

CONCLUSION

A total of nine formulations (F1-F9) of Tramadol matrix tablet, with different concentration of hydrophobic and hydrophilic polymer were used with other excipients. The tablets were punched by direct compression method after subjecting the

blend to preformulation studies like Angle of repose, Bulk density, Tapped density, Carr's Index. The results obtained were satisfactory. Post compression parameters like Hardness, Weight variation, Friability, Drug content analysis and *In-vitro* dissolution studies were also carried out and tabulated. The *in-vitro* dissolution studies were carried out in 0.1N HCl buffer and pH 7.4 Phosphate Buffer for 24-hours and it was found that among the formulated batch, F5 showed a retarded release of 63.8% at the end of 12th hour and extends the release to 95.24% at the end of 24th hour. Formulated batch F2 showed even lesser release of 45.32% at the end of 12th hour and a release of 74.31% at 24th hour but this batch fails to attain substantial therapeutic level, whereas the other batches showed sustained action but failed to show an extended action at the end of 24th hour. Hence the formulated batch of F5 was optimized as the best batch.

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