Research Article

Formulation, development, and evaluation of tramadol Hcl sustained-release dosage form

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ABSTRACT

Aim: The aim of the investigation was to develop a new formulation of tramadol HCl. **Material and Method:** Tramadol HCl is, centrally acting analgesic, by improving the prolong action of tramadol HCl drug using hydroxypropyl methylcellulose, ethylcellulose as polymer provides a release of therapeutically active medicament over an extended period of time, for example, from about 12 to 24 h. Tablet formulation was prepared by wet granulation technique. The tablets were compressed (8 mm diameter, standard concave punches) using a rotary tablet compression machine (4 station, Rimek, Ahmedabad, India). **Result:** The prepared tablets were evaluated for weight variation, hardness, friability, drug content, in vitro dissolution, and stability studies. From the above evaluate parameters, it was concluded that batch B-1 showed good results and was found having optimized concentration of polymers and other additives to prepare a sustained-release tablet of tramadol Hcl. **Conclusion:** The developed new formulation of tramadol HCl sustained-release tablet is successful.

Keywords: Analgesic, sustained release, tablet, tramadol Hcl

Introduction

Tramadol Hcl is a centrally acting synthetic analgesic of the amino cyclohexanol group with opioid-like effects. Its mode of action is not completely understood, but it appears to act by modifying transmission of pain impulses through inhibition of noradrenalin and serotonin reuptake and also by weakly binding to mu-opioid receptors.

Due to its side effect profile in comparison with other analgesics, tramadol Hcl may have a role in patients who are intolerant of conventional opioid and other non-opioid analgesics, those who have preexisting cardiopulmonary disease, such as the elderly or obese, and those in whom codeine use is inappropriate. In the acute and post-operative settings, it may have a place in multimodal, analgesia, where opioid and non-opioid drugs are given in combination to achieve analgesia, with a reduction in the incidence and severity of side effects.[1]

Similarly, in chronic pain conditions, tramadol Hcl may be considered (as a single agent or in combination) where non-opioid analgesics have proven ineffective or where multimodal therapy might be advantageous to limit side effects (e.g., where a reduction in nonsteroidal anti-inflammatory drug dosage is desirable). The reduced constipating effect of tramadol Hcl compared with other opioids may be useful in patients with chronic cancer pain, although nausea may be a dose-limiting side effect and sustained-release morphine is more effective in severe cancer pain. Due to its extended duration of effect, the sustained-release formulation may provide convenience in ambulatory patients with chronic pain.[2,3]

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Advantages of controlled drug therapy

1. Patient compliance due to a reduction in the frequency of designing
2. Employ minimum drug
3. Minimize or eliminate local and systemic side effects
4. Obtain less potentiation or deduction in drug activity with chronic use.
5. Minimize drug accumulation with chromic dosing
6. Improves efficacy in treatment
7. Cure or control confirm more promptly
8. Improve control of condition, that is, reduce fluctuation in drug level
9. Improve bioavailability of same drugs.[4]

Materials and Methods

Materials

Tramadol hydrochloride was received from all Fine Chemicals, Chennai, as a gift sample. Hydroxypropyl methylcellulose (HPMC), microcrystalline cellulose, magnesium stearate, sodium hydroxide pellets, and talc (collected from Global College of Pharmacy, Kahnpur Khui) were used. Other materials used were of analytical grade.

Preparation of sustained-release matrix tablets

Tablet formulation was prepared by wet granulation technique. All the powders were passed through BSS-40 mesh. Required quantities of tramadol hydrochloride and other polymers (HPMC) were mixed separately and thoroughly and a sufficient volume of granulating agent (water) was added slowly. After enough cohesiveness was obtained, the mass was sieved through NO: 60 mesh. The granules were dried at 40°C for 30 min and then were passed through 22 meshes. Talc and magnesium stearate were finally added as glidant and lubricant for each batch of granules. The tablets were compressed (8 mm diameter, standard concave punches) using a rotary tablet compression machine (4 station, Rimek, Ahmedabad, India) [Table 1].

Table 1: Formulation of tramadol HCl, SR tablets

Name of the Ingredient	Category	Batch code		
		B-I	B-II	B-III
Tramadol HCl (in mg)	Centrally acting analgesic	200.00	200.00	200.00
HPMC (in mg)	Polymer	20.00	40.00	60.00
Microcrystalline cellulose (in mg)	Diluent	166.00	146.00	126.00
Distilled water (in ml)	Granulating agent	q. s	q. s	q. s
Magnesium stearate (in mg)	Lubricant	8.0	8.0	8.0
Talc (in mg)	Glidant	6.0	6.0	6.0

HPMC: Hydroxypropyl methylcellulose

Preformulation study

Bulk density and tapped density[5]

The bulk density and tapped density of the drug were determined using the United States Pharmacopeia (USP) method. The specific weighed quantity of drug was added in the measuring cylinder. Their volume was noted down to calculate bulk density. After tapping, the volume was again noted down to calculate the tapped density. The bulk and tapped densities of drug were determined by the following formula -

Bulk density (g/cm^3) = Weight of powder/Bulk volume

Tapped density (g/cm^3) = Weight of powder/Tapped volume

Angle of repose[5]

This parameter is useful to measure resistance of particles to movement. The static heap of powder, when only gravity acts on it, will tend to form a conical round. One limitation exists; the angle to horizontal plane cannot exceed a certain value and this is known as angle of repose (θ).

The angle of repose was determined by the following equation tan (θ) = 2 h/D

Where, h = Height of bed powder and D = Powder bed diameter. Values of θ usually range between 20° and 40°. At θ values >50°, powder flows with difficulty [Table 2].

Table 2: Relationship between angles of reposes and flow property

Angle of repose (θ)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Poor

Hausner ratio[6]

Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula:

Hausner ratio = Pt/Pb

Where, Pt = tapped density and Pb = bulk density. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Compressibility[7]

Compressibility means a reduction in the bulk volume of the material as a result of displacement of gaseous phase.

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Untapped density}}{\text{Tapped density}} \times 100$$

The Carr's index is indicator of compressibility. The values <20% show good compressibility and above it show poor compressibility [Table 3].

Evaluation parameters

Weight variation[8]

A total of 20 tablets were selected randomly and weighed. Average weight of the tablet was used determined. The tablets were weighed individually and the weight variation was determined. The tablets meet the test if not more than two tablets are outside the limit and if no tablet differs by >2 times the limit. The weight variation limits for tablets differ depending on average tablet weight. The limits are specified in the following Table 4.

Hardness[9]

The resistance of tablets to shipping or breakage under conditions of storage, transportation, and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Pfizer hardness tester. The hardness was measured in terms of kg/cm^2.

Table 3: Compressibility index

Compressibility index	Flow
5-15	Excellent
12-16	Good
18-21	Fair
23-35	Poor
35-38	Very poor
40>	Extremely poor

Table 4: Limits for weight variation

Average weight of tablets	Maximum % difference allowed
80 mg or less	10
80-250 mg	7.5
More than >250 mg	5

Friability[10]

Friability is the measure of tablet strength. Veego friabilator was used for testing the friability. For this test, 10 tablets were weighed and placed in friabilator which was operated for 100 revolutions for 4 min at the speed of 25 rpm. The tablets were then dusted and reweighed. The friability of tablets was calculated and was found to be <1% using the following formula:

$$\text{Friability } (\%) = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Drug content[11]

For estimation of the drug content, 10 tablets were taken, crushed and drug equivalent to that amount in the formulation is taken and dissolved in respective media. Then, a suitable concentration of the solution was taken, and its absorbance was measured with the help of ultraviolet-visible spectrophotometer in the λ max 270. Then, the respective concentration was calculated from the standard graph.

In vitro dissolution studies

Dissolution profiles of tramadol HCl from tablets were determined in triplicate at 37 ± 0.5°C using the USP dissolution apparatus Type II (LABINDIA, Disso 2000). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 50 rpm. Samples (5 ml) were withdrawn with replacement at predetermined time interval of 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, and 12 h and filtered through a 0.45 µm prefilter. The filtered samples were then diluted with dissolution medium and the absorbance measured at λ max 270 nm (Shimadzu UV1601) (Raval, Patel, 2011).[12]

Results and Discussion

The result of the angle of repose indicates excellent flow properties of the granules 25.36. This was further supported by Hausner's ratio (1.10) and compressibility index (14.55). In general, compressibility index up to 15% results in excellent flow properties. The bulk densities and tapped densities of the granules prepared were found in the range of 0.522 and 0.636, respectively. All the results indicate that the granules possessed good flow and compressibility properties [Tables 5-7].

Table 5: Result for angle of repose, bulk density, tapped bulk density, compressibility index, and Hausner's ratio

Parameter	Batch code		
	B-I	B-II	B-III
Angle of repose (°)	25.36	24.6	23.2
Loose bulk density (g/cm^3)	0.522	0.546	0.538
Tapped bulk density (g/cm^3)	0.636	0.639	0.648
Compressibility index (%)	14.55	17.924	16.975
Hausner's Ratio	1.10	1.09	1.10

Table 6: Result for average weight, hardness, and friability

Parameters	Batch codes		
	B-I	B-II	B-III
Average weight	200.1mg	199.48mg	201.4mg
Hardness (kg/cm^2)	5.5	5	5.5
Friability (%)	0.35	0.43	0.57
Drug content (%)	98	96	95

Table 7: *In vitro* drug release behavior of formulation batches with HPMC

Time	Batch code		
	B-I	B-II	B-III
0.5	19.263	8.4772	2.114
0.75	24.401	14.171	4.357
1.0	28.224	20.884	8.689
1.5	31.112	22.047	13.869
2.0	34.254	26.932	18.590
4.0	47.429	30.548	22.716
6.0	58.749	39.399	26.954
8.0	65.944	59.805	35.697
10.0	76.327	70.613	47.625
12.0	86.767	81.173	61.011

HPMC: Hydroxypropyl methylcellulose

The tablets of different formulations were subjected to various evaluation tests such as hardness, friability, and uniformity of weight, drug content, and *in-vitro* dissolution. The hardness of all the formulations was in the range of 5.00–5.5 kg/cm². Tablet hardness and friability is absolute indicator of strength. Conventional compressed tablets that loss <1% of their weight are generally considered acceptable. In the present study, the friability for all the formulations was <1% indicating that the friability is within the prescribed limits. In weight variation test, the pharmacopoeial limit for tablets of >200 mg is ± 5%. The average deviation of all tablet formulations was found to be within the above limit, and hence, all formulations passed the test of uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of tablets and the percentage of drug content was >95%.

The *in vitro* drug release characteristics were studied in multimedia to know the proper release pattern throughout the different pH conditions of the

GIT. In the present study, the *in vitro* drug release was studied in pH 7.2 phosphate buffer for a period of 12 h using Electrolab dissolution Apparatus.

Conclusion

The aim of the present work was to develop the sustained-release matrix formulation of tramadol hydrochloride and investigate the effects of polymer on *in vitro* drug release has been carried out in the pharmaceuticals laboratories in GCP.

Matrix tablets were prepared by wet granulation method using different concentration of HPMC in the concentration of 1:1, 1:2, and 1:3.

Tablets were subjected to *in vitro* drug release in 0.1 N HCl (pH 1.2) for first 2 h followed by phosphate buffer (pH 7.2) for remaining hours.

It was observed that B-1 formulation contains the highest concentration of HPMC (1:1) exhibited the best release profile and able to sustain the drug release for prolong period of time.

Three formulations were prepared, but among these the B-1 was chosen as the best formulation because of the percentage drug release of the tablet 86.76%.

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