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**FORMULATION AND EVALUATION OF TRAMADOL HYDROCHLORIDE EXTENDED RELEASE TABLET BY USING HYDROPHILIC AND HYDROPHOBIC POLYMERS**

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## Abstract

The purpose of the study is to prepare extended release tablet of tramadol hydrochloride by using combination of hydrophilic polymer and wax. The hydrophilic polymers like Carbopol 934 P, polyox N 80 & HPMC K200 M & the waxes like compritol 888 ATO, cutina HR, spherizol, lubritab Type A were used. Tablets were prepared by using the wet granulation and melt granulation method. Polyox N80 & lubritab type A were selected as most promising release retarding agents in their respective groups. The drug release from only hydrophilic matrix tablet is achieved by rapid diffusion through its gel network and use of only wax is also limited due to its compression hardening and stability problems. Hence combination of hydrophilic polymer and wax has been used in the formulation of extended release tablet of tramadol hydrochloride. The two methods were selected for preparation of tablets i.e. wet granulation of hydrophilic polymer followed by wax addition method and melt granulation of wax followed by polymer addition method. All the formulations were compared with marketed formulation Ultram. Based on the comparison of similarity factor 2nd method was found to be the most promising method for the preparation of extended release tablet. The results indicated the dissolution rate was found to be directly proportional to concentration of wax as well as to concentration of hydrophilic polymer when studied at lower and higher wax levels.

**Keywords:** Extended Release, Hydrophilic polymer, Wax, Melt granulation, Wet granulation.

## Introduction

Oral route is a convenient and hence popular route for administrations of dosage forms4. The controlled release dosage forms (CDRS) are designed to retard the drug release so as to achieve a prolonged release profile1. Drug candidates having less solubility, slower dissolution rates are easy to design as CRDDS. These formulations are designed in such a way that the release pattern will be more predictable and reproducible. In contrast

drugs having high aqueous solubility and high dissolution rates are relatively difficult to design as a CRDDS2. Extended release (ER) dosage forms are most popular amongst CRDDS Common approaches in designing of SR/ER products are matrix structures; in which the drug is suspended or dissolved, use of rate controlling membranes through which the drug diffuses2. These dosage forms were achieved by incorporating various

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release retarding agents like swellable hydrophilic polymers, gums, insoluble polymers and waxes etc.

Tramadol hydrochloride is a synthetic codeine analogue and weak μ-opioid receptor agonist having an immense potential in analgesia. Tramadol HCl has been classified as a class-I substance according to bio pharmaceutics classification scheme (BCS), meaning that it is highly soluble and highly permeable. The drug is rapidly and almost completely absorbed after oral administration. The absolute bioavailability of oral dose is approximately 75%3. The half-life of the tramadol HCl is about 5-6 hours and usual oral dose is 50-100 mg/day every 4-6 hours with maximum dosage 400 mg /day4. The mean peak plasma concentration of racemic tramadol HCl occurs at two and three hours, respectively, after administration in healthy adults5. Although the drug has higher plasma half-life the steady state plasma concentration is not achieved with frequent dosing at 6 hour interval. To reduce the frequency

of administration and to improve patient compliance a sustained release formulation of tramadol HCl is desirable. Tramadol HCl requires release retarding agent to achieve constant release rate of a drug.

## Materials

Tramadol hydrochloride (Chempure, Mumbai), carbopol 934P (Lubrizol Corporation), HPMC (Methocel K 200M) (Aqualon), ( Polyox N 80 (Dow chemicals), cutina HR (Hydrogenated castor oil) (Cognis GMBH), spherizol (Stearic acid) (JRS Pharma LP), lubritab Type A (JRS Pharma LP), glyceryl behenate (Compritol 888 ATO) (Gattefosse), avicel PH101 & PH102 (FMC biopolymer) and magnesium stearate (Ferro Chemicals) (MST), talc (Luzenac Pharma).

## Methods

The trials were carried out with direct compression as well as with wet granulation approach so as to finalize the polymer, process and wax( Table.1).

### Table No. 01: Trial batches for the selection of hydrophilic polymer and wax

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **F1** | **\*F2** | **F3** | **\*F4** | **F5** | **\*F6** | **F7** | **F8** | **F9** | **F10** |
| 1 Tramadol hydrochloride | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 2 HPMC K200M | 75 | 75 | - | - | - | - | - | - | - | - |
| 3 Carbopol 934 P | - | - | 75 | 75 | - | - | - | - | - | - |
| 4 Polyox N 80 | - | - | - | - | 75 | 75 | - | - | - | - |
| 5 Lubritab type A | - | - | - | - | - | - | 75 |  | - | - |
| 6 Cutina HR | - | - | - | - | - | - | - | 75 | - | - |
| 7 Stearic acid | - | - | - | - | - | - | - | - | 75 |  |
| 8 Compritol 888 ATO | - | - | - | - | - | - | - | - | - | 75 |
| 9 Purified water | qs | - | qs | - | qs | - | - | - | - | - |
| 10 Avicel PH 101 | 40 |  | 40 |  | 40 | - | - | - | - | - |
| 11 Avicel PH 102 | 23 | 61 | 23 | 61 | 23 | 61 | 61 | 61 | 61 | 61 |
| 12 Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 13 Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

**S.No. Ingredients Mg / tablet**

**Average weight 250 250 250 250 250 250 250 250 250 250**

**\***Indicate the trial batches of hydrophilic polymer formulated by direct compression

F1: Carbopol 934P (WG); F2: Carbopol (DC); F3: HPMC K200M (WG); F4: HPMC K200M (DC); F5: Polyox

N 80 (WG); F6: Polyox N 80 (DC); F7: Compritol 888ATO; F8: Cutina HR; F9: Sperizol; F10: Lubritab type A

### Procedure for preparation of tablets by using direct compression approach

All the ingredients were weighed and sifted through sieve (ASTM #40). The materials were blended together for 10 minutes. At last magnesium stearate was mixed for the lubrication of the blend for 5 minutes. Then blend was compressed into tablets using flat 9 mm s/c round punch.

### Procedure for preparation of tablets by using wet granulation approach

All the ingredients were weighed and sifted through sieve (ASTM #40). Tramadol HCl and avicel PH101 and polymers were blended together for 10 minutes. Then blend was granulated using purified water to get desirable granulation point. The wet granules were sifted through sieve (ASTM #16). The granules were then dried at 600 C for sufficient time to get the dried granules. The

granules were passed through sieve (ASTM # 30). avicel PH102, magnesium stearate were blended with granules for 5 minutes. The lubricated blend was compressed into tablets using flat 9 mm s/c round punch.

### Procedures for preparation of tablet by using melt granulation approach (F7- F10)

All the ingredients were weighed. Tramadol HCl and wax were sifted through the sieve (ASTM #40) separately. Wax was melted below its m.p and tramadol HCl was mixed in molten mass slowly to get uniform dispersion. The molten mass was allowed to cool at room temperature. The granules were passed though sieve (ASTM # 30). Avicel PH102 was sifted through sieve (ASTM #40). Magnesium stearate and talc were sifted through sieve (ASTM #40). Then mixed with granules for 5 minutes and compressed into tablets using flat 9 mm s/c round punch.

From the above methods carried out for the selection of polymer and wax, polyox N 80 was selected as polymer and lubritab type A was selected as hydrophobic polymer. These selected polymers were then used in combination in further study. The formulations were prepared by two methods i.e. wet granulation of polyox N 80 followed by lubritab type A addition and melt granulation of lubritab type A followed by polyox N 80 addition. These methods were then compared to select best possible method for further study.

### Selection of process sequence

**Preparation of tablets by using wet granulation followed by wax addition (F11)**

To prepare granules, tramadol HCl, polyox N 80, avicel PH101 and each of the polymers were sifted through ASTM # 40 sieve and then material was weighed and mixed intimately in polythene bag for

10 minutes. Granules were prepared by using purified water as binder. Then the granules were passed through ASTM # 16 sieve and then ASTM # 30 and dried in hot air oven for 1 hour at 400 C. Then lubritab type A, avicel PH102 and magnesium stearate, talc were added extra granularly and intimated in polythene bag for 5 minutes. The blend was compressed into tablet by using flat 9 mm round s/c punch.

### Preparation of tablet by using melt granulation followed by hydrophilic polymer addition approach (F12)

For the preparation of tramadol HCl and the lubritab type A were sifted through # 60 mesh sieve. The materials were accurately weighed. Granules of tramadol HCl and Lubritab type A were prepared by melting wax in water bath at their respective melting point and then drug was added slowly in molten wax and kept for drying at room temperature. Then molten mass was sifted though the ASTM # 30 and then these granules were mixed in weighed polyox N 80, avicel PH102 and magnesium stearate and intimately mixed in polythene bag for 10 minutes. The blend was compressed into tablets using flat 9 mm round punch.

### Table No. 02: Trials carried out to select the process sequence

**S. No. Ingredient Mg/ tablet**

 **F11 F12**

|  |  |  |  |
| --- | --- | --- | --- |
| 1 | Tramadol HCl | 100 | 100 |
| 2 | Polyox N 80 | 75 | 25 |
| 3 | Avicel PH101 | 24 | - |
| 4 | Purified water | qs | NA |
| 5 | Lubritab Type A | 25 | 100 |
| 6 | Avicel PH102 | 22 | 21 |
| 7 | Talc | 2 | 2 |

 8 Magnesium stearate 2 2

 **Average weight (mg) 250 250**

The trials shown in table (Table.2) were evaluated for dissolution study and similarity factor comparison suggested that tablets prepared by using melt granulation followed by hydrophilic polymer addition approach have significant impact on dissolution profile when compared to the tablets

prepared by using wet granulation followed by wax addition approach. Hence further trial batches were carried out using melt granulation followed by polymer addition method.

### Table No. 03: Trial batches prepared using melt granulation followed by polymer addition method

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **S. No.** | **Ingredient** | **F13** | **F14** | **F15** | **F16** | **F17** | **F18** |
| 1 | Tramadol | 100 | 100 | 100 | 100 | 100 | 100 |
| 2 | Lubritab Type A | 75 | 80 | 85 | 90 | 95 | 100 |
| 3 | Polyox N 80 | 46 | 41 | 36 | 31 | 26 | 21 |
| 4 | Avicel PH 102 | 25 | 25 | 25 | 25 | 25 | 25 |
| 5 | Talc | 2 | 2 | 2 | 2 | 2 | 2 |

6 Magnessium Stearate

2 2 2 2 2 2

**Average weight (mg) 250 250 250 250 250 250**

All the formulations (table.3) were prepared by using the same method as that of the batch F12. In all these formulations only amount of hydrophilic polymer and hydrophobic polymer i.e. wax was changed keeping all the other excipients constant and effect of change in polymer and wax was observed by carrying out dissolution studies.

### Evaluations of pre and post compression parameters

**Pre compression parameters**

The tablet blends were evaluated for pre compression parameters like bulk density, tapped density, compressibility and hausner’s ratio.

### Post compression parameters

All the tablets prepared (Batches F1- F12) were evaluated for hardness using monsato hardness tester (n = 6), friability using roche friabilator (n = 6), weight variation using digital balance (n = 10), and thickness using vernier calipers (n = 10).and weight variation (n=10).

### In vitro drug release study

Dissolution studies were carried out on all the tablet formulations in triplicates, employing ng USP basket apparatus at 75 rpm and 37 ± 0.5 0 C, using 0.1 N HCl as the dissolution medium. An

aliquot of sample was withdrawn periodically at suitable time intervals and volume was replaced with an equivalent volume of plain dissolution medium. Samples were analyzed spectrophometrically at 271 nm. Drug release data obtained during in vitro dissolution studies were analyzed using a double-beam, UV spectrophotometer, Model SHIMADZU UV1800.

### Comparison of Drug Release with Marketed Formulation

Drug release profiles of the optimized formulation were compared with marketed formulation Ultram ER each containing 100 mg of tramadol hydrochloride per tablet.

## Result and discussion

### Evaluation of pre and post compression parameters

All the pre and post compression parameters were found satisfactory and the pre compression parameters were within the limits as given in I.P. (See table.4,5,6,7)

### Table No. 04: Precompression parameters

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **S.No** | **Parameter** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** | **F10** | **F11** | **F12** |
| 1 | Bulk density | 3.15 | 3.22 | 3.18 | 3.14 | 3.20 | 3.16 | 3.10 | 3.23 | 3.19 | 3.21 | 3.19 | 3.22 |
| 2 | Tapped density | 3.85 | 3.95 | 3.90 | 3.74 | 3.89 | 3.78 | 3.71 | 3.94 | 3.80 | 3.78 | 3.79 | 3.89 |
| 3 | Carr’s index | 18.18 | 21 | 19 | 21 | 23 | 22 | 18 | 19 | 22 | 20 | 22 | 19 |
| 4 | Hausner’s ratio | 1.22 | 1.22 | 1.2 | 1.21 | 1.26 | 1.23 | 1.3 | 1.25 | 1.20 | 1.23 | 1.22 | 1.24 |

**Table No. 05: Post compression parameters**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **S.No** | **Parameters** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** | **F10** | **F11** | **F12** |
| 1 | Average Weight (mg) | 245 | 248 | 246 | 246 | 246 | 248 | 250 | 249 | 248 | 247 | 251 | 250 |
| 2 | Thickness (mm) | 0.28 | 0.30 | 0.29 | 0.28 | 0.29 | 0.30 | 0.24 | 0.26 | 0.24 | 0.25 | 0.31 | 0.33 |
| 3 | Hardness (kP) | 4.3 | 4.4 | 4.3 | 4.5 | 4.4 | 4.3 | 5.2 | 5.3 | 5.4 | 5.2 | 4.7 | 4.4 |
| 4 | Friability % | 1.01 | 0.96 | 0.81 | 0.78 | 0.99 | 0.80 | 0.82 | 0.82 | 0.79 | 0.88 | 0.78 | 0.85 |

### Table No. 06: Pre compression parameters of batches F13-18

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **S.No** | **Parameter** | **F13** | **F14** | **F15** | **F16** | **F17** | **F18** |
| 1 | Bulk density (g/cm3) | 3.15 | 3.22 | 3.18 | 3.14 | 3.20 | 3.16 |
| 2 | Tapped density (g/ cm3) | 3.74 | 3.89 | 3.78 | 3.71 | 3.94 | 3.80 |
| 3 | Carr’s index (%) | 21 | 19 | 21 | 23 | 22 | 18 |
| 4 | Hausner’s Ratio | 1.2 | 1.21 | 1.26 | 1.23 | 1.3 | 1.25 |

**Table No. 07: Post compression parameters**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **S.No** | **Parameters** | **F13** | **F14** | **F15** | **F16** | **F17** | **F18** |
| 1 | Average Weight (mg) | 248 | 246 | 246 | 246 | 248 | 250 |
| 2 | Thickness (mm) | 1.25 | 1.24 | 1.23 | 1.24 | 1.26 | 1.24 |
| 3 | Hardness (kP) | 4.5 | 4.6 | 4.7 | 4.5 | 4.3 | 4.5 |
| 4 | Friability(%) | 1.01 | 1.02 | 0.98 | 0.89 | 0.97 | 0.99 |

### In vitro dug release studies Selection of hydrophilic polymer

When drug release profiles of formulations (F1-F6) carried out for selection of the hydrophilic polymer were studied, in direct compression method carbopol 934P (F2) showed slower release profile (Table.5). In wet granulation method polyox N 80 (F5) potentially controlled drug release as

compared to other polymers. When dissolution profiles of (F2) carbopol 934P (DC) and (F5) polyox N 80 (WG) were compared for selection of the method for further studies, polyox with the wet granulation process was found to have better release retarding strength. Similarly the similarity factor comparison suggested use of polyox N 80 (F6) for further studies.

### Table No. 08: In vitro drug dissolution of batches F1-12

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Time in hrs** | **%Target Drug****release** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6 F7****% drug release** | **F8** | **F9** | **F10** | **F11** | **F12** |
| 0.5 |  | 20 | 30 | 55 | 29 | 36 | 17 | 30 | 34 | 33 | 28 | 26 | 28 | 23 |
| 1 |  | 30 | 39 | 59 | 43 | 50 | 37 | 40 | 40 | 49 | 38 | 37 | 36 | 30 |
| 2 |  | 45 | 56 | 98 | 59 | 59 | 50 | 49 | 54 | 64 | 51 | 53 | 50 | 50 |
| 3 |  | 60 | 68 | - | 73 | 81 | 68 | 60 | 63 | 73 | 61 | 65 | 64 | 63 |
| 4 |  | 70 | 75 | - | 80 | 84 | 80 | 69 | 69 | 80 | 64 | 75 | 75 | 73 |
| 6 |  | 85 | 788 | - | 89 | 90 | 94 | 77 | 71 | 86 | 77 | 87 | 86 | 91 |
| 8 |  | 95 | 84 | - | 92 | 94 | 96 | 81 | 80 | 89 | 88 | 94 | 96 | 101 |
| 12 |  | 100 | 101 | - | 100 | 99 | 100 | 101 | 100 | 98 | 100 | 102 | 100 | 102 |
|  | **F2 value** |  | 52.96 | ND | 47.52 | 39.87 | 56.63 | 58.00 | 50.18 | 42.39 | 58.33 | 61.10 | 55.01 | 56.30 |
| **Table No. 09: In vitro drug dissolution of batches F13-18** |
| **Time in hrs** | **Target drug release** | **F13** | **F14** | **F15** | **F16** | **F17** | **F18** |  |
| 0.5 | 20 | 17 | 22 | 18 | 18 | 23 | 18 |  |
| 1 | 30 | 25 | 39 | 28 | 26 | 28 | 29 |  |
| 2 | 45 | 37 | 48 | 39 | 36 | 45 | 38 |  |
| 3 | 60 | 55 | 65 | 54 | 50 | 59 | 57 |  |
| 4 | 70 | 65 | 74 | 62 | 60 | 68 | 72 |  |
| 6 | 85 | 78 | 88 | 85 | 82 | 91 | 88 |  |
| 8 | 95 | 88 | 93 | 82 | 90 | 95 | 98 |  |
| 12 | 100 | 101 | 99 | 101 | 100 | 101 | 100 |  |
| F2 value | NLT 50 | 54.68 | 54.96 | 55.31 | 55.85 | 56.83 | 59.88 |  |

**Selection of the hydrophobic polymer**

When dissolution profiles (F7-F10) for the formulations carried out for selection of wax were studied the results showed that lubritab type A controlled the drug release as compared to other waxes (Table.6). Similarity factor also suggested

that Lubritab type A was promising release retardant among the waxes. The dissolution profiles of wet granulation followed by wax addition approach (F11) and melt granulation process followed by polymer addition approach (F12) were comparable with dissolution profile of reference

product Ultram (Table.8) . Similarity factor (ƒ2) was used to compare differences in drug release profile, which suggested that melt granulation

followed by polymer addition process (F12) was found best possible method for further study.



### Fig. No. 01: Comparison of dissolution profiles between optimized formulation F18 and Ultram

When the dissolution profiles over the period of 12 hours for the formulations (F13, F14, F15, F16, F17 and F18) were studied (Table.9), the results suggested that the dissolution rate was found to be directly proportional to concentration of wax as well as hydrophilic polymer when studied at lower and higher wax levels. The dissolution profile of the formulation F18 was comparable with the reference product with maximum similarity factor value of 59.88.The comparison between dissolution profile of formulation F18 and ultram also suggested that Formulation F18 was comparable to drug release pattern as that of Ultram (Fig 1).This observation can be attributed to weakening of the drug-wax matrix strength because of presence of channel formation due hydrophilic polymer in contact with media. However, the study does impart a significant conclusion and measure of controlling the drug release profile by changing the ratio of wax to hydrophilic polymers.

## Conclusion

Tramadol HCl is highly water soluble drug, it has half life is 5.5 hrs. Hence requires administration every 6 hrs. to maintain therapeutic level. Thus study was designed to extend the drug release for 12 hrs by using hydrophilic polymer, polyox N 80 and wax, Lubritab type A as release retarding agents. Use of only hydrophilic polymer is limited due to rapid diffusion and use of only waxes is also limited due to compression problems, over hardening of waxes and stability problems. Hence,

combination of polymer as well as waxes has been used in formulation of ER matrix tablets. Accordingly, the formulations were prepared by using melt granulation followed by polymer addition method. The optimized formulations exhibited excellent controlled release properties using combination of hydrophilic polymer and hydrophobic excipient. The results indicated the dissolution rate was found to be directly proportional to concentration of wax as well as to concentration of hydrophilic polymer when studied at lower and higher wax levels

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