Development of Prolonged Delivery of Tramadol and Dissolution Translation by Statistical Data Treatment

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ABSTRACT: The present study was carried out to fabricate a prolonged design for tramadol using Kollidon SR (Polyvinyl acetate and povidone based matrix retarding polymer). Matrix tablet formulations were prepared by direct compression of Kollidon SR of a varying proportion with a fixed percentage of tramadol. Tablets containing a 1:0.5 (Drug: Kollidon SR) ratio exhibited a rapid rate of drug release with an initial burst effect. Incorporation of more Kollidon SR in the matrix tablet extended the release of drug with subsequent minimization of the burst effect as confirmed by the mean dissolution time, dissolution efficiency and f2 value. Among the formulation batches, a direct relationship was obtained between release rate and the percentage of Kollidon SR used. The formulation showed close resemblance to the commercial product Contramal and compliance with USP specification. The results were explored and explained by the difference of micromeritic characteristics of the polymers and blend of drug with excipients. Insignificant effects of various factors, e.g. pH of dissolution media, ionic strength, speed of paddle were found on the drug release from Kollidon-SR matrix. The formulation followed the Higuchi kinetic model of drug release. Stability study data indicated stable character of Batch T6 after short-term stability study.

KEYWORDS: Tramadol; Kollidon SR; Dissolution efficiency; CONTRAMAL; Model fitting

Introduction

Tramadol, a synthetic opioid of the aminocyclohexanol group, is a centrally acting analgesic with weak opioid agonist properties. It is a highly water soluble drug. Tramadol has been proved to be effective in both experimental and clinical pain without causing serious cardiovascular or respiratory side effects. (Lehmann, 1997) The half-life of the drug is about 5.5 hours and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hours with a maximum dosage of 400 mg/day (Scott et al., 2000). To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of tramadol is valuable.

Matrix systems are favored because of their simplicity, patients compliance over traditional drug delivery which has many drawbacks like repeated administration, fluctuation in blood concentration level, etc. Developing oral SR matrix tablet for highly water soluble drugs with a constant release rate has always been a challenge to the formulation technologist. Most of the highly water soluble drugs if not formulated properly may readily release the drug at a faster rate and are likely to produce toxic concentrations of the drug upon oral administration. Hydrophilic polymers have become the product of choice as an important ingredient for formulating SR formulations of highly water soluble drugs. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance (Alderman, 1984).

Oral sustained release dosage form by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms. (Amidon et al., 2000) Sustained or controlled drug delivery occurs while embedded within a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and at constant rate for desired time period (Ford et al., 1985).
The matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. It required fewer unit operations, less machinery, reduced number of personnel and processing time, and increased product stability and production rate (Reddy RK et al., 2003).

The tablets prepared in the present study by the direct compression method have advantages over the tablets prepared by wet granulation in time and energy consumption, thus making it possible to formulate tablets at a lower cost (Terashita et al., 2000). Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery (Lachman et al., 1991).

Polymers utilized as hydrophilic excipients for controlled release formulations (i.e. HPMC, alginates, xanthan gum) are well known and widely used. There are, however, some distinct disadvantages for some of these hydrogel formers, which complicate the development and production of matrix tablets: the lack of polymer flowability hampering the direct compression process, the influence of the pH value (alginates, xanthan gum), the ionic strength (HPMC) on the release profile and the poor compressibility of the hydrogel formers. This will result in tablets with a low hardness (xanthan gum, alginates).

From an economical point of view the production of sustained release tablets by direct compression shows great promise. An innovative excipient that offers good controlled release characteristics together with excellent direct compression properties is required as the essential tool for the development and manufacturing of matrix tablets (Gundert Remy, 1990).

Materials and Methods

Material

Tramadol was supplied from Cadila healthcare, Ahmedabad, India. Kollidon SR was received from Astron Research, India. Talc and Magnesium stearate (Apex Chemicals, Ahmedabad) were used as received.

Methods

Preformulation Studies

Micromeritic properties

The angle of repose of tramadol and its physical mixtures with other excipients were determined by the fixed funnel method (Lieberman et al., 1990). The physical mixtures of the drug with different excipients were prepared by triturating the drug and additives in a dried mortar for 5 min. The accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto the surface. The height and diameter of the powder cone was measured and angle of repose was calculated. The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using the Density apparatus (DBK instruments, Bombay, India). The Carr's index (%) and the Hausner's ratio were calculated using following equations:

\[
\text{Carr's index } (%) = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100
\]

\[
\text{Hausner's ratio } = \frac{\text{TBD}}{\text{LBD}}
\]

Method of Preparation

Preparation of tablets

The compositions of the tablet formulations are given in Table IV. Weighed amounts of tramadol and Kollidon SR were mixed using stainless steel pestle to get a uniform mixture. The mixture was then blended with magnesium stearate and talc in a poly-bag and compressed into tablets employing the direct compression method (Cadmach, Ahmedabad, India) using 10 mm flat-faced punches.

Physicochemical characterization of tablets

The thickness and diameter of the tablets (n = 10) were determined using digital vernier calipers. The hardness of the tablets (n = 10) was determined by using the Monsanto hardness tester. The friability (%) of the tablets (n = 6) was determined using the Roche Friabilator. Weight variation tests of the tablets (n = 20) were carried out as per the official method (Lieberman HA et al., 1990). For determining the drug content, three tablets were crushed and a powder containing 100 mg of tramadol was dissolved in 100 mL of methanol. The solution was passed through a whatmann (No.1) filter and analyzed spectrophotometrically at 272.5 nm after sufficient dilution with a phosphate buffer (pH 6.8).

In-vitro Release study

The in-vitro dissolution study was carried out using the USP Type 2 dissolution apparatus. The study was carried out in 900 mL of in 0.1N HCl for the first 2 hours and then 900 mL of phosphate buffer (pH 6.8) from 3 to 24 h. The dissolution medium was kept in a thermostatically controlled water bath, maintained at 37 ± 0.5°C. The paddle was lowered so that the lower end of the stirrer was 25 mm above from the base of the beaker. The pre-weighed tablet was then introduced into the dissolution vessel and the paddle was rotated at 50 rpm. At different time intervals, 5 ml samples were withdrawn and analyzed spectrophotometrically at 272.5 nm for the drug release. At each time of withdrawal, 5 mL of fresh corresponding medium was replaced into the dissolution vessel (n = 3).
Stability study

The tablets were charged for the accelerated stability studies as per ICH guidelines (40 ± 2°C and 75 ± 5% RH) for a period of 6 months in stability chambers. They were placed in flint vials and hermetically sealed with rubber plugs and aluminum caps. The samples were taken out at 15, 30, 60 and 90 days and evaluated for the drug content and physical parameters like color change, friability, hardness and cumulative drug release (n = 3).

Statistical Data treatment

Model independent approaches [i.e., dissolution efficiency (DE) and mean dissolution time (MDT)] were used to translate the profile differences into a single value (Costa et al., 2001).

\[
DE = \frac{\int_0^t Y \times dt}{Y_{100} \times t} \times 100
\]

MDT is a measure of the dissolution rate: the higher the MDT, the slower the release rate.

\[
MDT = \frac{\sum_{j=1}^{n} t \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}
\]

where i is the dissolution sample number, n is the number of dissolution sample time, tmid is the time at the midpoint between i and i-1, and ΔM is the amount of drug dissolved between i and i-1 (Banakar, 1992). The similarities between 2 dissolution profiles were assessed by a pair-wise model independent procedure such as similarity factor (f2) (Gohel et al., 2002).

\[
f_2 = 50 \log\left\{\left[1 + \frac{1}{n} \sum_{i=1}^{n} w_i (R_i - T_i)^2\right]^{-0.5} \times 100\right\}
\]

where n is the number of pull points, wt is an optional weight factor, R is the reference profile at time point t, and T is the test profile at the same time point; the value of f2 should be between 50 and 100. An f2 value of 84 ± 0.25 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between releases profiles increases.

Model Fitting

The method of Bamba et al. was adopted to ascertain the kinetics of drug transport. In-vitro drug release data of optimized batch A3 were analyzed by different kinetic models to evaluate the drug release mechanism of tramadol. FORTRAN software, developed in-house, was used. The least value of the sum of the square of residuals (SSR) and Fisher’s ratio (F) were used to select the most appropriate kinetic model (Bamba, et al., 1979; Gibaldi et al., 1967; Korsmeyer et al., 1983; Higuchi, 1961; Langenbucher, 1972).

Result and Discussion

Preformulation Studies

Micromeritics

In the present study, the direct compression method was adopted for tabletting. For direct compression, the mixture of drug and polymer should have good flow and compression properties. The plain powder of tramadol exhibited an angle of repose value of 31.40 ± 0.025°, indicating poor flow property. It was further supported by a high Carr’s index value of 27.83 ± 0.046% and Hausner’s ratio of 1.39 ± 0.054. Kollidon SR is a novel directly compressible material. The characterizations of kollidon SR samples were done with respect to micromeritical properties and were compared with standard literature values. Further, micrometical study was carried out for a mixture of tramadol and kollidon SR and also for the physical mixture of tramadol, Kollidon SR, talc and magnesium stearate (Table 2). Kollidon SR has excellent compressibility and endows tablets with enormous hardness and low friability. This is due to the combination of the very plastic polyvinyl acetate and the also strongly binding povidone. The excellent flowability and compressibility of Kollidon SR makes this excipient particularly suitable for the manufacture of sustained release tablets obtained by direct compression. The required content of Kollidon SR in the tablet depends on the solubility of the active ingredient.

<table>
<thead>
<tr>
<th>TABLE 1 Formulation of tramadol tablets.</th>
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<tbody>
<tr>
<td>BATCH</td>
</tr>
<tr>
<td>Tramadol (mg)</td>
</tr>
<tr>
<td>Drug: Kollidon SR</td>
</tr>
<tr>
<td>Talc (%)</td>
</tr>
<tr>
<td>Mg-Stearate (%)</td>
</tr>
<tr>
<td>Tablet weight (mg)</td>
</tr>
</tbody>
</table>
In-vitro Drug Release

Kollidon SR is a polyvinyl acetate and povidone based matrix retarding agent. It is particularly suitable for the manufacture of pH-independent sustained-release matrix tablets by direct compression. Polyvinyl acetate is a very plastic material that produces a coherent matrix even under low compression forces. When the tablets are introduced into gastric or intestinal fluid, the water soluble povidone is leached out to form pores through which the active ingredient slowly diffuses outwards. Kollidon SR contains non ionic groups and is therefore inert to drug substances. The sustained-release properties are unaffected by ions or salts. The drug release of tramadol from the matrix tablet containing Kollidon SR was indicated by MDT, \( f_2 \) and DE. Batch T1 containing 1: 0.5 drug to kollloidin SR ratio showed MDT 2.58 ± 0.53 hrs, which exhibited no control on release, also, the value of similarity factor was found to be 24.33 ± 0.45, which also supported to reject batch T1. Batch T2 exhibited 3.29 ± 0.73 hrs of MDT which was far better than of Batch T1, but was not up to mark. The in-vitro dissolution data revealed that drug release retardation was proportional to polymer concentration. Upon enhancing Kollidon SR content in tablet subsequent drug releases extension was found in Batches T3-T7. The values of MDT for batches T3, T4, T5, T6 and T7 were found to be 4.52 ± 0.32, 5.54 ± 0.59, 6.92 ± 0.24, 8.34 ± 0.58 and 7.09 ± 0.54 respectively. Batch T6 revealed an \( f_2 \) value 84 ± 0.25, which showed the highest similarity among all experimental batches.

When considering the bulk and tap densities, only small variations of tablet weight are expected. This was confirmed by an evaluation of the tablet properties (Table 3). A high content uniformity was achieved. The direct compression resulted in tablets with an extremely high hardness and a low friability. According to the chemical composition and the adjusted particle size distribution, the marked dry binding capacity in combination with the good flow properties, are regarded as additional benefits when using Kollidon SR as a sustained release excipient. Moderate swelling of the tablets was observed, but the tablet shape remained intact due to the water insoluble polyvinyl acetate. The drug release profile from kollidon matrix was not affected by pH (Fig. 2). Addition of 0.25% NaCl did not change the in-vitro drug released profile, which proved that, there is no any significant effect of ionic strength on drug release (Fig. 3).

### Table 2
Micromeritics properties of tramadol and mixtures of tramadol and excipients.

<table>
<thead>
<tr>
<th>Composition</th>
<th>Angle of repose (°)</th>
<th>CI (%)</th>
<th>Hausner's ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>31.40 ± 0.025</td>
<td>27.83 ± 0.046</td>
<td>1.39 ± 0.054</td>
</tr>
<tr>
<td>K- SR</td>
<td>23 ± 0.028</td>
<td>10 ± 0.032</td>
<td>1.11 ± 0.043</td>
</tr>
<tr>
<td>T+ K- SR</td>
<td>24 ± 0.038</td>
<td>17.64 ± 0.053</td>
<td>1.23 ± 0.014</td>
</tr>
<tr>
<td>T+ K- SR + Talc + M</td>
<td>22 ± 0.073</td>
<td>15.83 ± 0.036</td>
<td>1.17 ± 0.053</td>
</tr>
</tbody>
</table>

All values are expressed as Mean ± SD, n=3. CI=Carr’s Index; T=Tramadol; K-SR= Kollidon SR; K-SR* = reported values in literature; M=Magnesium stearate

### Table 3
Physicochemical evaluation of tablets.

<table>
<thead>
<tr>
<th>Batch</th>
<th>Thickness* (mm)</th>
<th>Hardness** (kg/cm²)</th>
<th>Friability** (%)</th>
<th>Weight Variation *** (%)</th>
<th>Drug content* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>4.21 ± 0.035</td>
<td>6.79 ± 0.523</td>
<td>0.72 ± 0.035</td>
<td>3.46 ± 0.053</td>
<td>98.33 ± 0.047</td>
</tr>
<tr>
<td>T2</td>
<td>4.31 ± 0.063</td>
<td>6.68 ± 0.12</td>
<td>0.67 ± 0.025</td>
<td>2.58 ± 0.038</td>
<td>99.29 ± 0.052</td>
</tr>
<tr>
<td>T3</td>
<td>4.36 ± 0.072</td>
<td>6.98 ± 0.399</td>
<td>0.59 ± 0.064</td>
<td>2.67 ± 0.024</td>
<td>98.73 ± 0.036</td>
</tr>
<tr>
<td>T4</td>
<td>4.49 ± 0.026</td>
<td>6.33 ± 0.525</td>
<td>0.75 ± 0.028</td>
<td>3.21 ± 0.027</td>
<td>97.92 ± 0.071</td>
</tr>
<tr>
<td>T5</td>
<td>4.43 ± 0.061</td>
<td>6.82 ± 0.649</td>
<td>0.64 ± 0.042</td>
<td>2.58 ± 0.062</td>
<td>98.55 ± 0.026</td>
</tr>
<tr>
<td>T6</td>
<td>4.53 ± 0.052</td>
<td>6.39 ± 0.664</td>
<td>0.44 ± 0.054</td>
<td>3.09 ± 0.041</td>
<td>99.21 ± 0.026</td>
</tr>
<tr>
<td>T7</td>
<td>4.59 ± 0.034</td>
<td>6.27 ± 0.429</td>
<td>0.55 ± 0.061</td>
<td>2.83 ± 0.063</td>
<td>99.85 ± 0.026</td>
</tr>
</tbody>
</table>

All values are expressed as Mean± SD; *n = 3; **n = 6; ***n = 20.
Table 4 Statistical parameters of formulation batches.

<table>
<thead>
<tr>
<th>Batch</th>
<th>DE (mean ± SD)</th>
<th>MDT (mean ± SD)</th>
<th>F2 (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>24.61 ± 0.47</td>
<td>2.58 ± 0.53</td>
<td>24.33 ± 0.45</td>
</tr>
<tr>
<td>T2</td>
<td>19.29 ± 0.72</td>
<td>3.29 ± 0.73</td>
<td>29.30 ± 0.19</td>
</tr>
<tr>
<td>T3</td>
<td>16.56 ± 0.36</td>
<td>4.52 ± 0.32</td>
<td>36.61 ± 0.26</td>
</tr>
<tr>
<td>T4</td>
<td>12.32 ± 0.41</td>
<td>5.54 ± 0.59</td>
<td>47.60 ± 0.53</td>
</tr>
<tr>
<td>T5</td>
<td>9.99 ± 0.29</td>
<td>6.92 ± 0.24</td>
<td>61.86 ± 0.47</td>
</tr>
<tr>
<td>T6</td>
<td>8.30 ± 0.82</td>
<td>8.34 ± 0.58</td>
<td>84.00 ± 0.25</td>
</tr>
<tr>
<td>T7</td>
<td>7.45 ± 0.11</td>
<td>7.09 ± 0.54</td>
<td>57.36 ± 0.53</td>
</tr>
</tbody>
</table>

Table 5 Results of the model fitting of batch T6.

<table>
<thead>
<tr>
<th>Kinetic Model</th>
<th>R²</th>
<th>F-Value</th>
<th>SSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hixon-crowell</td>
<td>0.95</td>
<td>9.4093</td>
<td>103.50</td>
</tr>
<tr>
<td>Korsmeyer</td>
<td>0.99</td>
<td>14.6831</td>
<td>146.83</td>
</tr>
<tr>
<td>Weibull</td>
<td>0.97</td>
<td>11.5767</td>
<td>115.77</td>
</tr>
<tr>
<td>Zero-order</td>
<td>0.92</td>
<td>80.3211</td>
<td>883.53</td>
</tr>
<tr>
<td>First-order</td>
<td>0.76</td>
<td>338.9991</td>
<td>3728.99</td>
</tr>
<tr>
<td>Higuchi model</td>
<td>0.99</td>
<td>6.9106</td>
<td>76.02</td>
</tr>
</tbody>
</table>

Fig. 1 *In-vitro* drug release profiles.
Stability Study
At the end of the testing period, the matrix tablets were observed for changes in physical appearance, analyzed for drug content, and subjected to in-vitro drug release studies. No visible changes in the appearance of the matrix tablets were observed at the end of the storage period. The drug content was found to be 99.4 ± 0.053%. At the end of 24 hours of dissolution testing, the amount of tramadol released from T6 matrix tablets before storage was 99.83 ± 0.035 whereas that released from the T6 formulation after storage was 99.27 ± 0.026. There was no significant difference in the mean amount of tramadol released from T6 matrix tablets after storing for 3 months at 40°C/75% RH (t test, p <0.05).

Model Fitting
The in-vitro drug release data of batch T6 were analyzed for establishing the kinetics of drug transport. Model fitting was done using an in-house program developed by the authors. Zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull models were tested. The best fit was shown by Higuchi model with least sum of square of residuals (SSR = 76.02) and Fisher’s ratio (F = 6.91).
Conclusion

Kollidon SR, a new excipient for drug delivery matrices, possesses good controlled release properties. The release profiles of tramadol tablet formulations with kolloidin SR were not influenced by different dissolution media or ionic strength. The excellent flow properties and the dry binding activity of kolloidin SR provides easy handling and effective development and production of sustained release tramadol tablets.

Acknowledgment

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References


