EFFECT OF WATER CONTENT IN KNEADING METHOD OF SOLID DISPERSION TECHNIQUE FOR SOLUBILITY ENHANCEMENT

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Abstract

Objective: The main objective of the research work was to optimize the water requirement/content used in kneading method for solid dispersion/inclusion complex formation between water insoluble drug and polymer.

Methods: Nimesulide (model drug) and β-cyclodextrin were taken in a different ratio such as 1:1, 1:3 and 1:5 and, the mixture was triturated well for half hour. Water was incorporated to the mixture in different levels like 75%, 50%, 25% w/v in divided proportions and 0% (no water addition, but the mixture was triturated continuously). After each part of water addition, the mixture was triturated well for 10 min and dried using hot air over for 30 min at 50 °C and sieved using sieve no: 44. The complexes formed were subjected for various analytical characterization studies including solubility, particle size, the angle of repose, tapped density, Carr’s index, fourier transfer infrared spectrometry (FTIR), thermo gravimetric-differential thermal analysis (TG-TDA), x-ray diffraction (XRD) studies and in vitro dissolution studies.

Results: The dissolution studies showed improvement in the release of nimesulide, which depended on the percentage level of water. The solubility of the sample was increased with increasing the concentration of the inclusion complex formed. Kneading method was proved to be a successful technique for formation of stable inclusion complex of nimesulide with β-cyclodextrin. All the formulations exhibited acceptable particle size and solubility in the range of 22.6±2 to 29±5 and 45±5 to 133±3.5 respectively.

Conclusion: Nimesulide and β-cyclodextrin complex was successfully prepared and characterized for the drug-polymer stability and interactions. The result confirmed that the liquid content in the solid dispersion prepared by the kneading method played an important role in the dissolution of the poorly soluble drug.

Keywords: Nimesulide, β-cyclodextrin, Solid dispersion, Kneading method

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INTRODUCTION

Nimesulide (NM) is one of the potent non-steroidal anti-inflammatory drugs (NSAIDs), widely prescribed for various anti-inflammatory conditions. NM has categorized under class II drugs of the biopharmaceutical classification system (BCS) that illustrate poor aqueous solubility, which is the main reason for its low and variable oral bioavailability [1-3]. NM is an acidic drug that differs from many similar compounds, by virtue of the presence of sulfoxide group rather than a carboxyl group. Chemically it is named as [4-nitro-2-(phenoxo) methane sulphoxanilide] (fig. 1).

![Fig. 1: Structure of nimesulide][2]

Pharmacologically NM is an inhibitor of cyclo-oxygenase-2 (COX-2) enzyme, and hence inhibits the synthesis of critical prostaglandins and spares cytoprotective prostaglandins. It can also inhibit the process involved in platelets aggregation [4-6]. The oral absorption of NM is dissolution rate limited, and hence enhancement in solubility and dissolution rate is required for increasing its oral bioavailability [7]. Among different methods reported for improving the solubilization of NM, the formation of an inclusion complex with cyclodextrins (CDs) (fig. 2) has been identified as the most common and successful approach. CDs exhibit a hydrophilic outer surface and lipophilic inner cavity with a cyclic torus shape, which is capable of interacting with a large variety of guest molecules to form an inclusion complex. CDs are commonly used in drug formulations as solubility enhancers because of their ability to form water soluble complexes with poorly water soluble drugs. They also have huge potential as carrier molecules in the formulation of novel drug delivery systems. The inclusion complexes can modify pharmacokinetic properties of guest molecules by fitting within the hydrophobic cavity of CDs [8, 9]. Several NSAIDs have been complexed with CDs, which resulted in high solubility and dissolution rate, decreased side effects, reduced dose, improved bioavailability and stability, lesser gastric irritation and also enhanced the palatability of the active molecules [10-13].

![Fig. 2: Structure of β-cyclodextrin][12]

Kneading is one of the common methods used in solid dispersion technique for the enhancement of solubility and dissolution rate of...
poorly soluble drugs. The process involves reduction of particle size at the molecular level through complexation of the freely water soluble chemically inert carriers with the guest molecule (drug). The formed product could result in better therapeutic effect due to improved solubility and increased bioavailability. During the kneading process, the addition of few drops of water to the triturated drug and inert polymer mixture helps in complete complexation between drug and polymer. The addition of water aids in dissolving the freely water soluble carrier which allows the drug to enter into the molecular domain, followed by titration helps in reducing particle size up to sub-micron level. Thus, the combination of complexation and size reduction may double the effect for the enhancement of solubility [14, 15]. The aim of the present study was to prepare NM complexes with CDs by kneading method and study the effect of water level added in the solid dispersion process for the enhancement of solubility of the drug.

MATERIALS AND METHODS

Materials

Nimesulide was purchased from Chatan and Chatan Ltd., Chennai, India. β-cyclodextrin was procured from SD Fine Chem Ltd., Mumbai, India. All other chemicals and reagents used were of analytical grade.

Table 1: Optimization of water in kneading method for nimesulide and β-cyclodextrin complexation

| S. No. | Formulation code | Drug (g) | Carrier (g) | Water (% w/v) |
|-------|------------------|----------|-------------|---------------|
| 1     | KN1              | 1        | 1           | 25            |
| 2     | KN2              | 1        | 1           | 75            |
| 3     | KN3              | 1        | 1           | NW            |
| 4     | KN4              | 1        | 1           | 25            |
| 5     | KN5              | 1        | 3           | 50            |
| 6     | KN6              | 1        | 3           | 75            |
| 7     | KN7              | 1        | 3           | NW            |
| 8     | KN8              | 1        | 5           | 25            |
| 9     | KN9              | 1        | 5           | 50            |
| 10    | KN10             | 1        | 5           | 75            |
| 11    | KN11             | 1        | 5           | NW            |
| 12    | KN12             | 1        | -           | -             |
| 13    | PT13             | 1        | -           | -             |
| 14    | NP14             | 1        | -           | -             |

KN 1-12–Kneaded complex of nimesulide and cyclodextrin, NW–No Water added, NP–Nimesulide pure drug (unprocessed) and PT–Nimesulide pure drug in triturated form

Physical and derived properties of kneaded mixture

Angle of repose

In order to evaluate the flow properties of the formulations prepared by the kneading method, angle of repose, bulk density, tap density and Carr's index were calculated.

Angle of repose (θ) was determined using funnel method to assess the flow behaviour of the sample. The powder sample was poured through a funnel placed at the height of about 3 cm from the base plane and allowed to form a heap. The height and diameter of the formed heap were noted and angle of repose was calculated using the formula [18].

\[ θ = \tan^{-1}(h/r) \]

Where, h = height; r = radius of the heap. The experiment was conducted in triplicate and the mean±standard deviation was estimated.

Bulk density

The triturated final sample was accurately weighed and poured into a clean, dry measuring cylinder and the bulk volume was noted. The cylinder was then tapped 300 times from a constant height and the tapped volume was recorded. The bulk density and tapped density were calculated with respect to the known weight of the sample taken for the analysis, using the formula [18, 19].

\[ \text{Bulk density} = \frac{\text{Weight of substance}}{\text{Bulk volume}} \]

Carr's index

Carr's index is a measure to indicate the nature of the sample and its suitability to convert as tablets by tablet compression process. The stability and dose specificity of the kneading mixture could be improved by formulating as tablets. Carr's index was calculated from the values of bulk density and tapped density of the formulation using the formula [19].

\[ \text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Bulk density}} \times 100 \]

Solubility test

The solubility of the kneaded samples was analysed and compared to the pure drug by shake flask method using the thermostatic shaker. About 1 mg of NM and the kneaded mixture was placed in 5 ml sample tube and 2 ml of distilled water was added to each separately. The tubes were placed on the shaker and continued shaking (Incubator shaker Edison, NJ, USA) for 24 h at 150 rpm at room temperature. The samples were taken out and then centrifuged at 4500 rpm at 4 °C for 10 min. The supernatant of each sample was collected separately, suitably diluted and the concentration of drug was measured using UV spectrophotometer (Evolution 201, Thermo Scientific, USA) at 397 nm [20].
In vitro dissolution studies

The rate of drug dissolution from the formulated solid dispersion was studied by dissolution method. The powder samples were dried and sieved and then filled in hard gelatin capsule shells (size no. 1). The capsules were placed in the basket of USP type-I dissolution apparatus (Lab India, Mumbai) containing 900 ml of distilled water as the media. The dissolution set up was maintained at 50 rpm speed and 37 °C±2 °C for 60 min. At predetermined time intervals such as 10, 20, 30, 40, 50 and 60 min, the samples were withdrawn and the media was replaced with warm fresh distilled water after each withdrawal, to maintain the sink conditions. The collected samples were suitably diluted and the concentration of drug released at each time point was calculated using the linear standard calibration curve method. The experiment was conducted in triplicate and the mean±standard deviation was recorded.

Powder X-ray diffraction

Samples of NM-CD complex prepared by kneading method with different levels of water were evaluated by X-ray powder diffraction analysis. The pure NM and kneaded samples were individually loaded in the sample cavity of the X-ray diffractometer (Ultima-3, Rigaku) and the diffraction patterns were obtained using Cu radiation. The system was used with diverging and receiving slits of 0.05° and 0.2°, respectively. The pattern was observed with 40 kV of tube voltage and 30 mA of tube current and scanned over the 2θ range of 10°-80° [21].

Drug content

The accurately weight quantity of kneaded powder sample was taken equivalent to the drug dose filled in a capsule and dissolved in 50 ml of methanol. The sample was diluted suitably and the absorbance was measured using UV-visible spectrophotometer at 397 nm. The percentage of drug content was calculated by using the standard calibration method [21].

\[
\% \text{ Drug Content} = \frac{\text{Sample Absorbance}}{\text{Standard Absorbance}} \times 100
\]

Fourier transforms infrared spectroscopy (FTIR)

FTIR (Perkin-Elmer system 200 FT-IR spectrophotometer) analysis was performed in order to find out the interaction between the drug and the polymers and thus the stability of drug could be confirmed. IR analysis of the sample reveals the presence of the characteristic functional group in the pure samples and the possible interaction in the mixture samples that could be compared to the original spectrum. It was performed by KBr pellet technique in which the samples were mixed with previously dried, saturated potassium bromide, and then pressed under a hydraulic pressure of 150 kg/cm² to form thin transparent disc pellet. The disc was placed in the IR sample holder and scanned over a range of 3600 to 400 cm⁻¹ at ambient temperature [22, 23].

Table 2: Solubility, particle size and drug content of the formulations

| S. No. | Formulation code | Solubility (mg/ml) | Particle size (µm) | Assay (%) |
|-------|-----------------|--------------------|-------------------|-----------|
| 1     | KN1             | 72.5±3             | 23.8±1.5          | 105.9±1   |
| 2     | KN2             | 91.5±3             | 24.2±2            | 102.7±3   |
| 3     | KN3             | 79.25±5.5          | 24.6±4            | 95.9±4    |
| 4     | KN4             | 68±2.5             | 26.3±3            | 95.4±5    |
| 5     | KN5             | 95.25±5            | 26.6±8            | 96.1±2    |
| 6     | KN6             | 130.75±9           | 24.6±2            | 106±4     |
| 7     | KN7             | 107.25±4           | 26.4±2            | 109.4±1   |
| 8     | KN8             | 86±5.6             | 29.8±5            | 96.9±5    |
| 9     | KN9             | 118.25±5           | 24.6±4            | 95.3±4    |
| 10    | KN10            | 133.75±2.5         | 25.8±3            | 97.7±2.5  |
| 11    | KN11            | 124.25±10          | 23.8±2            | 95.6±53   |
| 12    | KN12            | 103.75±3.8         | 29.5              | 110.1±1   |
| 13    | PT13            | 52.5±4             | 22.6±2            | 97.6±4    |
| 14    | NP14            | 45.3±4±5           | 23.4±3            | 96.8±3    |

KN 1–12–Kneaded complex of nimesulide and cyclodextrin, NP–Nimesulide pure drug (unprocessed) and PT–Nimesulide pure drug in triturated form. The data is given as mean±SD (n=3)
Physical properties

The flow properties of the kneaded formulations were calculated by using the angle of repose, bulk density, tap density and Carr's index (table no. 3) and compared with the pure drug. Bulk property of the powders depends on its particle size, which interferes with the powder flow behaviour [28]. The unprocessed pure drug exhibits poor flow behaviour because of excessive cohesive forces and non-uniform particle size. However, the triturated pure drug has shown better flow property. Similarly, in case of the kneaded mixture without the addition of water, the angle of repose value was >30, which indicated poor flow due to the improper complex formation and non-uniform distribution of the drug in the carrier. In case of the kneaded complex with the addition of water, the angle of repose <30 indicated good flow property, wherein water played an important role for the formation of uniform inclusion complex [29, 30]. Accordingly, the tapped density, bulk density and Carr's index were observed to be suitable for processing the complex mixture into a single solid dosage form like tablets by compression process or filling as a compact powder in capsules.

Table 3: Physical properties of NM-CD kneaded samples compared to pure drug

| S. No. | Formulation code | Angle of repose (θ)  | Tapped density (gm/ml) | Bulk density (gm/ml) | Carr's index |
|-------|-----------------|----------------------|------------------------|----------------------|-------------|
| 1     | KN1             | 15±0.331             | 0.617±0.046            | 0.27±0.005           | 55.3±4.11   |
| 2     | KN2             | 16±0.816             | 0.695±0.057            | 0.277±0.023          | 59.3±5.73   |
| 3     | KN3             | 16±0.209             | 0.565±0.021            | 0.328±0.027          | 41.66±6.24  |
| 4     | KN4             | 31±0.500             | 0.62±0.023             | 0.314±0.012          | 49.13±4.05  |
| 5     | KN5             | 30±0.318             | 0.60±0.026             | 0.338±0.008          | 43.50±3.53  |
| 6     | KN6             | 30±0.723             | 0.56±0.046             | 0.359±0.019          | 36.0±2.12   |
| 7     | KN7             | 30±0.828             | 0.66±0.066             | 0.357±0.036          | 45.3±3.59   |
| 8     | KN8             | 38±0.789             | 0.592±0.026            | 0.305±0.013          | 45.00±4.08  |
| 9     | KN9             | 28±0.546             | 0.659±0.021            | 0.417±0.016          | 36.7±0.56   |
| 10    | KN10            | 27±0.424             | 0.605±0.021            | 0.506±0.126          | 36.7±1.25   |
| 11    | KN11            | 25±0.942             | 0.702±0.024            | 0.466±0.013          | 33.5±3.98   |
| 12    | KN12            | 46±0.854             | 0.658±0.021            | 0.36±0.027           | 44.6±5.25   |
| 13    | PT13            | 13±0.236             | 0.63±0.047             | 0.264±0.018          | 23.7±3.43   |
| 14    | NP14            | 42±1.220             | 0.429±0.017            | 0.537±0.026          | 19.94±6.32  |

KN 1-12–Kneaded complex of nimesulide and cyclodextrin, NP–Nimesulide pure drug (unprocessed) and PT–Nimesulide pure drug in triturated form. The data is given as mean±SD (n=3).

In vitro dissolution studies

The in vitro dissolution study results of the various ratio of kneading method complex (NM-CD) are shown in fig. 3, 4 and 5. The unprocessed pure drug sample showed the very slow dissolution of less than 20% at the end of 60 min. In case of the pure drug in triturated (PT) form and also the kneaded mixture of drug: carrier with no water (NW) content, the dissolution of the drug was poor. The data showed a significant increase in the percentage drug release with an increase in the water level of the formulation from 25 to 50% w/v in all the three ratios of drug: carrier mixture (1:1, 1:3 and 1:5). However, at 75% w/v water addition in the mixture, the dissolution of the drug was not varied notably which was due to the saturation solubility level of the drug: carrier mixture, as reported in the solubility study results. The results proved that the percentage of water added in the kneading mixture played a crucial role in the in vitro release of the drug from the mixture. Water helps to form a strong inclusion complex of drug with CDs at the optimum solvent concentration. Based on the results obtained, the formulation prepared with 50% w/v water level were considered as the optimum formulation and selected for further characterization studies.

Fourier transforms infrared spectroscopy

Infrared spectra of the pure drug and inclusion complexes of NM with β-CDs (1:1, 1:3 and 1:5) prepared by kneading method are given in fig. 6, 7, 8 and 9, respectively. The pure drug exhibited the characteristic peaks as the identity of the specific functional groups present in it. The sharp peaks observed at 3283 cm⁻¹, 1589 cm⁻¹, 1153 cm⁻¹ and 1273 cm⁻¹ indicated the N-H stretching of amide, aromatic NO₂ stretching, S=O stretching of sulphoxide and C-O-C stretching between the aromatic rings, respectively. Also, the presence of CH₃ and aromatic rings were confirmed by the corresponding stretching and bending vibrations. In case of all the kneaded inclusion complex samples (1:1, 1:3 and 1:5), the guest drug molecules present within the CDs cavity showed less intense peaks compared to the pure drug alone. The characteristic peaks of the drug were observed for the presence of N-H, NO₂, S=O and C-O-C groups in the inclusion complex. The broad peak between the range of 3300 cm⁻¹ and 3500 cm⁻¹ showed the formation of intermolecular and intra molecular hydrogen bonding between the drug and β-CD [30-32]. These bonds were responsible for the mild interactions and formation of a stable complex of drug and carrier, without significant chemical reactions.

Fig. 3: In vitro drug release profile of kneading complex of NM with CD at 1:1 ratio (n=3)
Fig. 4: *In vitro* drug release profile of kneading complex of NM with CD at 1:3 ratio (n=3)

Fig. 5: *In vitro* drug release profile of kneading complex of NM with CD at 1:5 ratio (n=3)

Fig. 6: FTIR spectrum of pure drug

Fig. 7: FTIR spectrum of kneaded complex of NM with CD at 1:1 ratio
Thermal analysis

NM and β-CDs complex prepared by the kneading method was subjected to TG-DTA analysis and the results are given in fig. 10 and 11. Pure powder drug showed a sharp endothermic peak at 150.10 °C, the characteristic melting point of the drug. Further increase in the temperature resulted in the exothermic peak at around 335 °C and a corresponding sudden weight loss in the TG curve at the same temperature, which indicated the decomposition temperature of the drug.
In case of the kneaded complex of drug: carrier, the endothermic peak of the drug was slightly shifted and hence the melting point was observed at 148.36 °C. The slight shift was probably due to a weak interaction between the host and guest molecules [31]. Additionally, the thermal properties of cyclodextrin were recorded, wherein the endothermic peak at around 82 °C represented the melting point of the polymer. Finally, the sample showed the decomposition temperature at 310 °C with corresponding sudden weight loss in the TG curve.

**Powder X-ray diffraction studies**

The XRD study results are displayed in fig. 12 and 13 for the pure drug and the kneaded complex formulation, respectively. The pure drug exhibited sharp peaks at 21.800, 22.740 and 23.260 with high intensity, which reflected the crystalline character of pure nimesulide. In case of the kneaded complex, the characteristics of both the drug and polymer were observed. Since the drug was encapsulated as inclusion complex in the carrier, the crystallinity of the drug was slightly altered. However, the sharp peaks in the formulated complex indicated the purity and crystal character of drug and the carrier [33, 34].

**CONCLUSION**

The solubility of the poorly aqueous soluble drug nimesulide was improved by the inclusion complex with β-cyclodextrin as a carrier. The effect of varying the percentage of water addition in the kneading process was comparatively explained. The formulation prepared with 50% w/v water addition exhibited a significant increase in the solubility and dissolution of the drug release. The flow and physical property of the prepared kneaded granules with improved angle of repose, tab density and Carr’s index confirmed the suitability of the mixture to convert into single unit solid dosage forms. The FTIR, TG-DTA and XRD studies confirmed the stability of the kneaded complex formulation without significant chemical alterations of the drug. The carrier compatibility and mild interactions in the formulation were also revealed. The formulated inclusion complex of nimesulide improved the solubility and flow properties to enhance the kinetic behaviour of the drug.

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**CONFLICT OF INTERESTS**

The authors declare that there is no conflict of interest.

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