Macedonian Pharmaceutical Bulletin, 72 (Suppl 1) 103 - 104 (2026)
Online ISSN: 1857-8969
DOI: 10.33320/maced.pharm.bull.2026.72.03.049
Short communication

Replacement of solid diisopropanolamine with its 85% liquid form in a carbomer-based gel formulation

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Introduction

Topical semisolid products are dosage forms in which critical quality attributes (CQAs) are strongly influenced by formulation composition and process parameters (Mohammed et al., 2024).

The studied aqueous-alcoholic gel formulation contains two active pharmaceutical ingredients (APIs) classified as BCS class II with carbomer as gelling agent and diisopropanolamine (DIPA) as a pH-adjusting and gel-forming agent. In such carbomer-based systems, gel formation and viscosity depend on polymer neutralization, where DIPA plays a key role in establishing the gel structure formation and ensuring formulation stability (Lyapunov et al., 2015). When used in solid form, DIPA requires a melting step prior to incorporation, introducing an additional processing step that increases manufacturing complexity.

The aim of this study was to replace the solid DIPA with its liquid form (85%) in order to simplify the manufacturing process by eliminating the melting step, while maintaining the required functionality of the excipient and the quality attributes of the final product.

Materials and methods

Materials

DIPA was used in two forms: solid DIPA (BASF, Germany) and 85% liquid DIPA (Maruti Industries, India). Two APIs classified as BCS class II were obtained from Solara Active Pharma Science and Symrise, respectively. Other excipients included carbomer (Lubrizol, Belgium), propylene glycol (BASF, Germany), ethanol 96% (v/v) (Alkaloid, N. Macedonia) and purified water.

Preparation and characterization

Three production batches were produced using solid DIPA and three batches were produced with liquid DIPA 85% with reduced water content (for polymer hydration) to compensate for the water introduced with diluted excipient. All batches were manufactured under same conditions, in a vacuum homogenizer (Olsamix 300), where carbomer (3.0 g/100.0 g) was dispersed and hydrated in purified water (39.0 g/100.0 g) to form the initial polymer base, followed by addition of DIPA (8.0 g/100.0 g) to induce polymer neutralization and gel formation. For the batches produced with solid DIPA, the excipient was melted prior to incorporation. Subsequently, the APIs, previously dissolved in mixture of ethanol 96.0% (30.0 g/100.0 g) and propylene glycol (10.0 g/100.0 g) as solubilizer, were added into the homogenizer and incorporated into the gel base under mixing to obtain a homogeneous formulation.

Content uniformity of both APIs was evaluated on samples taken from six locations per batch for formulation containing solid DIPA and from nine

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locations per batch for formulation containing liquid DIPA. The assay of one API was determined using a validated high-performance liquid chromatography (HPLC) method based on peak area ratio, while the content of the second API was determined using a validated gas chromatography method (7890B gas chromatograph coupled with flame ionization detector). Results are expressed as mean value ± standard deviation of all measurements. The viscosity of each batch was determined on three measurements per batch, using a rotating RV viscometer (21 – 25 °C; spindle T-C 93; speed of 5 rpm; 1 min) and the results are expressed as mean value. The pH was measured potentiometrically (Mettler Toledo SevenCompact™ S210) on three samples per batch and mean values were reported. In addition, the appearance of the gels was evaluated visually.

Statistical evaluation

Statistical analysis was performed using an unpaired two-sample t-test assuming unequal variances, based on batch mean values. Differences were considered statistically significant at $p < 0.05$.

Results and discussion

Preliminary laboratory trials were conducted to assess the feasibility of replacing solid DIPA with its liquid form and to optimize formulation parameters. Based on these results, the formulation was further scaled up to production batches, as evaluation at larger scale is essential to confirm process robustness and the behavior of the gel under manufacturing conditions.

The production batches produced with solid DIPA showed consistent assay values for both APIs, with average values ranging from 100.1% ± 2.2% to 101.9% ± 0.4% for the first API and from 101.0% ± 1.0% to 105.9% ± 0.9% for the second API.

In the case of liquid DIPA 85%, the assay values for both APIs were similarly consistent, with average values around 101.6% ± 1.1% to 107.7% ± 0.2% for the first API and 102.9% ± 1.6% to 104.2% ± 0.8% for the second API, confirming uniform distribution of the APIs in the gel matrix.

For the batches prepared with solid DIPA, viscosity values were approximately 43 800 – 50 800 cPs, while pH values were in the range of 7.5 – 7.6 and the gels exhibited a homogeneous and transparent appearance.

Similarly, the batches produced with liquid DIPA 85% showed comparable physicochemical properties, with viscosity values around 44 000 – 53 600 cPs, pH values around 7.5 – 7.7 and acceptable visual appearance.

Statistical evaluation using an unpaired two sample t-test assuming unequal variances showed no statistically significant differences between formulations prepared with solid and liquid DIPA in terms of the assay of the first API ($p = 0.371$), the assay of the second API ($p=0.750$), viscosity ($p=0.248$) and pH ($p=1.000$). These results confirm that replacement of solid DIPA with liquid DIPA 85% did not significantly affect the evaluated CQAs of the gel formulation.

Conclusion

The replacement of solid DIPA with its liquid form (85%) was successfully achieved without affecting the CQAs of the formulation.

No significant differences were observed in assay of APIs, viscosity, pH and appearance of gels between batches prepared with solid and liquid DIPA 85%.

These findings confirm that liquid DIPA can be used as a suitable alternative to solid DIPA, enabling simplification of the manufacturing process, by eliminating the melting step, without compromising product quality.

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