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Short communication

The effect of temperature and co-povidone as a solubilizer on the solubility of levomepromazine maleate in 70% (v/v) ethanol as a solvent

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Introduction

Poorly water-soluble APIs present many challenges during both originator and generic drug development. Considering that they constitute a big portion of the existing APIs on the market, and an even bigger portion of the new APIs currently in the pipeline (Salunke et al., 2022), exploring the ways in which their solubility can be improved is essential.

One of the most common strategies for improving the solubility of APIs is the use of appropriate solubilizers (Reintjes (ed.), 2011).

Levomepromazine maleate (LM) is a typical phenothiazine antipsychotic used in the treatment of schizophrenia, and major depressive disorder. It is also known for its strong anti-emetic and sedative effects, which allowed it to find use in palliative care (Dietz, 2013; Green, 2024). LM is a BCS class II drug and it is slightly soluble in water and ethanol.

The aim of this study was to evaluate the effect of temperature and co-povidone as a solubilizer on the solubility of LM in 70% (v/v) ethanol as a solvent.

Materials and methods

Levomepromazine maleate from Euroapi (France) and Kollidon VA-64 from BASF (Germany) were used in all experiments. 70% (v/v) ethanol was prepared by mixing the appropriate amount of Absolute ethanol from Alkaloid (N. Macedonia) and purified water.

The temperature of experimental runs was maintained using a magnetic stirrer (IKA RET CONTROL/T, Germany) and controlled using a mercury-free glass laboratory thermometer (Thermo-Fischer Scientific, USA).

All experiments were performed by dissolving the appropriate amount of co-povidone in 3 mL of 70% (v/v) ethanol, followed by adding the appropriate amount of LM and gradually adding more solvent until complete dissolution was achieved and there were no visible particles left.

A reduced combinatorial design of experiments approach was used, with 26 experimental runs and 3 central points (N=29, DF=22). The analysis of data was performed with the MODDE Pro v.13.1 software. The relationship between the factors and the response was established using multiple linear regression.

Three multilevel factors were included in the design: amount of the LM (0.25 g and 0.50 g); amount of the solubilizer co-povidone (0 g, 0.25 g, 0.50 g and 0.75 g) and temperature (25 ºC, 40 ºC and 60 ºC), with the 3 central points (0.38 g LM, 0.38 g co-povidone, 42 ºC temperature). The amount (mL)

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of the solvent 70% (v/v) ethanol required to fully dissolve the API was followed as a response.

Results and discussion

The aim of the design was to evaluate the relationship between the factors and the response as well as to analyze their effects and the statistical significance.

Before analyzing the data, the model was assessed for adequacy with the summary of fit data.

The ANOVA terms indicate good model fitting (R^2=0.9766; R^2Adj=0.9703, R^2-R^2Adj=0.0063), and statistical significance of the model (Q^2=0.9489; R^2-Q^2=0.0277). Model validity is also high (0.6120), indicating a valid model with a non-significant Lack of Fit (p=0.212). The reproducibility of the model is also adequate, with a value of 0.9858, and the model error (RSD=0.0328) shows satisfactory precision.

The coefficient and effect analysis show that all three factors have statistically significant effects on the response variable.

The amount of API as a factor has a significant ($p=1.52*10^{-14}$) positive effect (+0.1168) on the response variable. Higher API load leads to an increased amount of 70% (v/v) ethanol required for complete dissolution.

The amount of solubilizer has a significant ($p=1.42*10^{-9}$) negative effect (-0.0860) on the response. Higher amount of co-povidone used leads to a decreased amount of solvent needed.

The temperature also has a strong, very significant ($p=9.47*10^{-17}$) negative effect (-0.1795) on the response. Higher temperature reduces the amount of 70% (v/v) ethanol required for complete dissolution.

The interaction between API amount and co-povidone amount shows a significant ($p=6.36*10^{-4}$) positive effect (+0.0343) suggesting that at higher API levels, the beneficial effect of co-povidone becomes weaker than expected, leading to an increased solvent requirement.

The interaction between API amount and temperature shows a significant (p=0.0358) negative effect (-0.0177) suggesting that at higher API levels, the beneficial effects of increased temperature become more pronounced, leading to a decreased amount of 70% (v/v) ethanol needed.

The interaction between solubilizer and temperature is not statistically significant (p=0.552).

Temperature has the strongest effect on improving the solubility of LM. Co-povidone also shows a beneficial effect, which appears to plateau at higher API loads, indicating diminishing returns for increases in its amount.

The improvement can be best illustrated by the 3.2x reduction of the amount of solvent needed from 23 mL (for 0.50 g LM, 0 g co-povidone, 25 ºC) to 7 mL (for 0.50 g LM, 0.75 g co-povidone, 60 ºC), and 3.7x reduction from 17 mL to 4.5 mL for the same conditions at the 0.25 g LM level.

Conclusion

The results show that both increased temperature and use of co-povidone as a solubilizer significantly improve the solubility of levomepromazine maleate in 70% (v/v) ethanol.

Increases in API load hinder the effect of co-povidone, but the temperature effect becomes more pronounced.

A combination of medium levels of co-povidone with higher temperature appear to be an optimal way to help solubilize levomepromazine maleate, especially at higher amounts.

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References

Dietz, I. et al., 2013. Evidence for the use of levomepromazine for symptom control in the palliative care setting: a systematic review. BMC Palliat. Care 12, 2. https://doi.org/10.1186/1472-684X-12-2

Green, B. et al., 2004. Focus on levomepromazine. Curr. Med. Res. Opin. 20, 1877–1881. https://doi.org/10.1185/030079904X12708

Reintjes, T. (Ed.), 2011. Solubility Enhancement with BASF Pharma Polymers. BASF SE, Ludwigshafen. http://www.pharma-ingredients.basf.com

Salunke, S. et al., 2022. Oral drug delivery strategies for development of poorly water-soluble drugs in paediatric patient population. Adv. Drug Deliv. Rev. 190, 114507