Macedonian pharmaceutical bulletin, 69 (Suppl 1) 61 - 62 (2023)
Online ISSN 1857 - 8969
DOI: 10.33320/maced.pharm.bull.2023.69.03.030
Short communication

Development of sprayable Carbopol gel for dermal melatonin delivery

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Introduction

Gels as dermal drug delivery systems offer many benefits, including the prolonged retention at the site of application and controlled drug release (Sastri et al., 2022). Nevertheless, patients still often prefer the use of liquid sprayable formulations due to the easier administration (Iversen and Jakobsen, 2016). The development of a sprayable dermal gel enables coupling the aforementioned advantages of gel systems with the user-friendly application mode related to liquid sprays. In the development of such gels, it is crucial to select the appropriate constituents and optimise the rheological and texture properties (Sastri et al., 2022). Statistical design of experiments (DoE) is a useful tool to optimise the essential formulation characteristics (Rathore and Winkle, 2009). Carbopol 940 is a polymer widely used in topical drug delivery systems, while polyethylene glycol (PEG) serves as a surfactant (Sastri et al., 2022). Melatonin is a neurohormone which is recently being investigated for the treatment of various skin conditions, including atopic dermatitis, seborrheic dermatitis, vitiligo and psoriasis (Rusanova et al., 2019). The aim of this work was to develop a sprayable Carbopol/PEG gel for dermal delivery of melatonin.

Materials and methods

To investigate the influence of Carbopol and PEG concentrations on the gel properties, a full factorial DoE with three levels was employed using JMP 17.0 software (JMP®, SAS Institute Inc., NC, trial version). Viscosity at shear rate of 1 s^{-1}, gel strength (observed as storage module *G*' value at shear strain of 0.1%) and firmness were investigated as responses. For the preparation of Carbopol/PEG gels, concentrated solutions of Carbopol 940 (Kemig, Croatia) or PEG 3350 (Carbosynth Ltd, UK) in purified water were mixed in appropriate ratios to obtain the final Carbopol (0.05-0.15%, *w*/*w*) and PEG (5-10%, *w*/*w*) concentrations. pH was adjusted to 5.5 with triethanolamine. Rheological properties were determined using a modular compact rheometer MCR102 (Anton Paar GmbH, Austria). Spreadability, i.e. firmness of formulations was measured by TA.XT texture analyser (Stable Microsystems, UK). Uniformity of delivered dose of the prepared gels was determined using spray pump "Topical" (Ksenomed, Croatia). Melatonin (Carbosynth Ltd, UK) was added to the optimised Carbopol/PEG gel at concentration of 0.1% (*w*/*w*, further denoted as CPM). CPM was further characterised in terms of rheological frequency sweep test and *in vitro* melatonin release using an automated Franz diffusion cells testing system Phoenix™ RDS (Teledyne Hanson, USA), with phosphate buffer pH 5.5 and 7.4 as release media. Prior to the *in vitro* release experiment, saturation solubility of melatonin in both buffers was determined. Taken samples were analysed for drug content by high performance liquid chromatography (HPLC) method.

Results and discussion

All of the prepared Carbopol/PEG formulations exhibited shear-thinning behaviour. Formulations containing 0.10 and 0.15% of Carbopol showed good structure recovery. Formulation viscosity at 1 s^{-1}, *G*' at 0.1% and firmness of the samples prepared within the DoE are shown in Table 1. Regression modelling revealed the positive influence of Carbopol concentration increase and the negative impact of PEG concentration increase on all three of the investigated responses. Considering the rheological and texture properties, as well as formulation behaviour during and after spraying by spray pump, the gel

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containing 0.10% (*w*/*w*) of Carbopol and 5% (*w*/*w*) of PEG was selected for incorporating melatonin. No change was observed in rheological behaviour and spreadability due to the presence of melatonin. Amplitude sweep test revealed no difference in storage and loss moduli before and after spraying of the formulation (Fig. 1).

Table 1. Formulations prepared according to DoE and viscosity at 1 s^{-1} (η_{1s-1}), *G*' at 0.1% and firmness (*F*) as DoE responses. Data are shown as mean±SD (n=3).

$c_{Carbopol}$ (%)	c_{PEG} (%)	η_{1s-1} (mPa s)	$G'_{0.1\%}$ (Pa)	*F* (mN)
0.05	5.0	91.0±40.8	5.0±0.0	26.5±2.0
0.05	7.5	60.3±11.2	5.0±0.2	32.0±0.6
0.05	10.0	30.2±14.5	4.9±0.1	33.7±0.6
0.10	5.0	2601.1±153.1	16.2±1.0	47.4±1.1
0.10	7.5	1321.1±35.0	8.8±0.0	39.9±1.1
0.10	10.0	785.1±86.5	6.7±0.1	45.4±1.1
0.15	5.0	17928.3±662.4	80.1±0.3	129.1±4.4
0.15	7.5	11541.7±280.4	58.1±2.1	107.9±4.3
0.15	10.0	7753.3±846.0	40.5±0.1	80.4±2.0

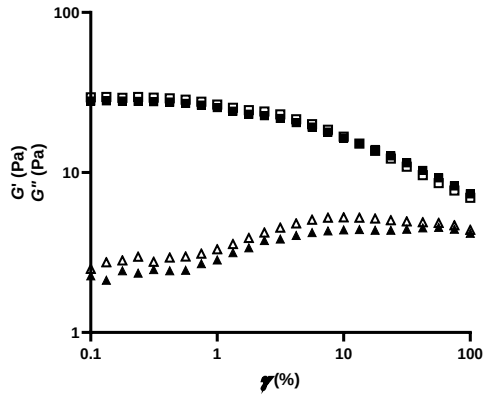

Fig. 1. Storage (*G*', squares) and loss (*G*", triangles) moduli of CPM as a function of shear strain before (filled symbols) and after (open symbols) spraying with spray pump "Topical".

Carbopol ensured prolonged melatonin release from CPM formulation compared to control (PEG/melatonin solution) in both pH 5.5 and 7.4, corresponding to the healthy and wounded skin, respectively (Fig. 2). Using f2 criteria for estimation of similarity revealed similarity between *in vitro* release profiles of melatonin from CPM at both pH values.

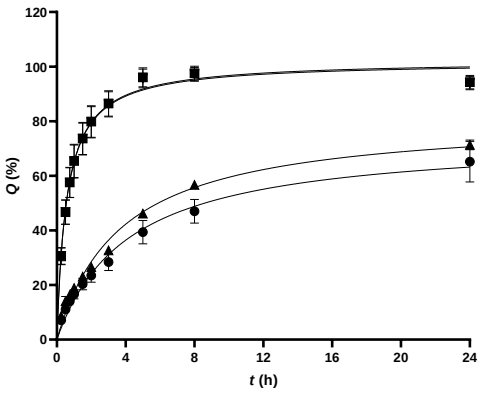

Fig. 2. *In vitro* release profiles of melatonin from CPM in PBS pH 5.5 (circle) and 7.4 (triangle) compared with the dissolution of the melatonin solution (square, the dissolution profile was almost identical at both pH 5.5 and 7.4). Data are expressed as mean ± SD (n=3).

Conclusion

Regression modelling elucidated the relationship between the Carbopol and PEG concentrations and gel characteristics, enabling the selection of optimal formulation with respect to its rheological, texture and spray properties. The addition of melatonin did not influence the formulation characteristics, proving the robustness of the developed gel. The gel structure and integrity remained intact after spraying. The formulation ensured controlled melatonin release in both pH 5.5 and 7.4. The obtained results set a firm base for further *in vitro* and *in vivo* experiments.

Acknowledgements: This work was supported in part the project FarmInova (KK.01.1.1.02.0021) funded by the European Regional Development Fund.

References

Iversen, L., Jakobsen, H.B., 2016. Patient Preferences for Topical Psoriasis Treatments are Diverse and Difficult to Predict. Dermatol Ther (Heidelb) 6, 273–285. https://doi.org/10.1007/s13555-016-0119-4

Rathore, A., Winkle, H., 2009. Quality by design for biopharmaceuticals. Nat Biotechnol 27, 26–34.

Rusanova, I., Mart, L., Florido, J., 2019. Protective E ff ects of Melatonin on the Skin : Future Perspectives.

Sastri, T.K., Gupta, V.N., Chakraborty, S., Madhusudhan, S., Kumar, H., Chand, P., Jain, V., Veeranna, B., Gowda, D. V., 2022. Novel Gels: An Emerging Approach for Delivering of Therapeutic Molecules and Recent Trends. Gels 8. https://doi.org/10.3390/gels8050316