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Annals of Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iann20

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To cite this article: Ana Topete, Junmei Tang, Quankui Lin, Benilde Saramago & Ana Paula Serro (2021) *In vivo* study on the performance of therapeutic intraocular lens loaded with an antibiotic and an anti-inflammatory, Annals of Medicine, 53:sup1, S117-S117, DOI: 10.1080/07853890.2021.1896109

To link to this article: https://doi.org/10.1080/07853890.2021.1896109

Published online: 28 Sep 2021.

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DOI: 10.1080/07853890.2021.1897459

In vivo study on the performance of therapeutic intraocular lens loaded with an antibiotic and an anti-inflammatory

Ana Topete[a,b], Junmei Tang[c], Quankui Lin[c,d], Benilde Saramago[a] and Ana Paula Serro[a,b]

[a]Centro de Química Estrutural, Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal; [b]Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Egas Moniz Cooperativa de Ensino Superior, Caparica, Portugal; [c]School of Ophthalmology & Optometry, Eye Hospital, Wenzhou Medical University, Wenzhou, China; [d]Wenzhou Institute of Biomaterials and Engineering, Wenzhou, China

ABSTRACT

Introduction: Cataract treatment usually involves surgery for substitution of the opacified eye lens by an artificial intraocular lens (IOL). In the post-operatory period, antibiotics and anti-inflammatories eye drops are prescribed to prevent endophthalmitis that may occur due to bacterial infection and results in serious complications [1,2]. This drug delivery method leads to a low bioavailability of the drugs due to the ocular clearance and absorption mechanisms. Furthermore, since it requires frequent administrations, it is uncomfortable for patients and it may lead to a low compliance. Drug-loaded intraocular lenses (IOL) have been explored as potential drug release vehicles due to their prolonged time of contact with the eye and constitute a promising alternative to eye drops [3]. The main goal of this work is to evaluate the *in vivo* performance of dual drug-loaded IOLs containing an antibiotic and an anti-inflammatory.

Materials and methods: An antibiotic, moxifloxacin (MXF), and an anti-inflammatory, ketorolac (KTL) were loaded in commercial acrylic IOLs by soaking in drug solution containing the two drugs (5 mg/mL each drug) at 60 °C for 2 weeks. The effect of the drug loading on lenses properties such as the swelling capacity, optical properties (transmittance) and mechanical properties (Young's modulus) was evaluated. After sterilisation, the drug loaded lenses were used for *in vitro* drug release tests, carried out in sink conditions (PBS, 3 mL, 36 °C, 180 rpm) and *in vivo* experiments with rabbits. A mathematical model was applied to the *in vitro* results to predict the *in vivo* concentrations. In the *in vivo* tests, the lenses were implanted into the right eye of 5 Japanese rabbits. No eye drops were administered in the post-operatory period. To evaluate ocular inflammation, slit-lamp examinations were done on the days 1, 3, 7, 14 and 21. On the day 21 the animals were anaesthetised and killed humanely with air embolism. The eyes were enucleated for histological investigation, in particular the cornea and the iris were separated, sectioned with a cryostat and stained following the haematoxylin and eosin staining.

Results and discussion: It was found that the presence of drugs increases the swelling capacity of the lenses, slightly decreases the Young's modulus and does not affect the transmittance in the range 500–700 nm. *In vitro* tests show that the lenses are able to release both drugs in a sustained way. The mathematical model indicates that the *in vivo* concentration of MXF should be higher than the minimal inhibitory concentration (MIC) of *Staphylococcus aureus* and *Staphylococcus epidermidis* (two of the most common bacteria responsible for endophthalmitis), for at least 15 days and that the concentration of KTL stays above half maximal inhibitory concentration (IC50) of cyclooxygenase 1 (and cyclooxygenase 2 (2 enzymes responsible for inflammation) for 16 days. In the *in vivo* tests, the slit-lamp examinations demonstrated that after 7 days no inflammation was present on the eyes of the rabbits. The histological evaluation proved good biocompatibility of the double loaded lenses.

Conclusions: The double loaded lenses revealed to be promising devices for the post-cataract surgery prophylaxis, complying with both antibiotic and anti-inflammatory therapeutic needs.

CONTACT Ana Topete anactopete@gmail.com

Acknowledgements

The authors acknowledge funding from Fundação para a Ciência e Tecnologia (FCT) [projects UID/QUI/00100/2013 and PTDC/CTM-BIO/3640/2014] and support from PhysIOL for providing the materials for IOLs

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DOI: 10.1080/07853890.2021.1896109

Slimming using magistral formulas: what are the risks?

Dulce Laúdo[a], Tânia Fernandes[a] and Ana I. Fernandes[a]

[a]PharmSci Lab, Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Egas Moniz Cooperativa de Ensino Superior, Caparica, Portugal

ABSTRACT

Introduction: Magistral formulas (MF) are prepared by the pharmacist for a given patient according to a prescription and following technical and scientific compounding standards. MF are often used in weight loss regimens and contain blends of drugs (D) and plant (P) extracts. Associations potentiate interactions and related adverse effects, compromising effectiveness and risking the patient's health [1,2]. Thus, the purpose of this work is to give an overview of MF intended for slimming, prescribed by doctors, in a perspective of efficacy and safety.

Materials and methods: Slimming MF (prescribed to overweight women, as hard gelatine capsules, once or twice daily) were obtained in pharmacies and analysed in terms of labelled drug/bioactive composition and dosage, therapeutic indication/claim, recommended daily dose (RDD), side effects/interactions and contraindications. Written consent for data use was obtained.

Results: MF did not contain unlawful ingredients [3]. Actives were used mostly in sub therapeutic doses (Table 1). Weight loss is a result of (a) side effect of D-III/IV (off-label use), (b) water loss due to therapeutic action (D-I/IX and P-V/VII/VIII), or (c) claimed appetite reduction (P-VI/X/XI).

Discussion and conclusions: Off-label uses of drugs and efficacy of sub therapeutic doses are questionable. D-II,III present risk of abuse and dependence. Combination of laxatives (MF 1, 2 and 6) is not recommended, increasing the chances of electrolyte imbalance and dehydration, and reducing absorption of ansa diuretics. Clinical data to support the claims and posology of botanicals is scarce and contradictory; moreover, potential side effects/interactions are at times unknown and adulteration/contamination is a risk. Of note is the potential for interaction of P-V (inhibiting several isoenzymes of CYP450) and the association of D-I/P-V may cause hypovolemia and hypocaliemia. Even if no additional interactions were found between molecules, combinations may increase the risk of adverse events. Severe/fatal interactions may occur with other drugs (e.g. D-II + opioids; D-III + MAO inhibitors), so knowledge of patient's clinical history and related medication is of the utmost importance, when prescribing and counselling. Indeed, evaluation of safety and efficacy of MF is a shared responsibility of doctor and pharmacist and requires robust scientific data, especially regarding botanicals. Slimming medication alone, without lifestyle changes, is not effective in the long term and may pose a health risk, as pointed out in this study.

CONTACT Ana I. Fernandes aifernandes@egasmoniz.edu.pt

Table 1. MF labels composition and dose (mg).

Active ingredient (AI)	MF1	MF2	MF3	MF4	MF5	MF6	MF7	Main therapeutic indication / claim	Usual posology in major pathology
Furosemide[I]	20	25		18	18	30		Diuretic	20–80/120 mg/day
Chlordiazepoxide[II]	8	8		8	8	10		Anxiolytic	30 mg (3 times/day)
Bupropion[III]	120	100		140	150	130		Antidepressant	150 mg (2 times/day)
Metformine[IV]	280		250	300	300	260		Antidiabetic	500 mg (2/3 times/day)
Artichoke[V]	110	400						Laxative	500 mg/day*
Bitter orange *(Citrus aurantium)*[VI]	150			200	200	200	200	Appetite reducer	50–100 mg/day*
Centella asiatica L.[VII]		400	400				750	Anti-cellulite, venotonic	60–120 mg/day*
Cascara Sagrada (*R. purshiana*)[VIII]		100		130		120		Laxative	150–325 mg/day*
Phenolphthalein[IX]	65	100			90	85		Laxative	30–200 mg/day
Glucomannan (*A. konjac*)[X]							500	Appetite reducer	1000–13,000 mg/day*
Slimalluma *(Caralluma fimbriata)*[XI]		300	250					Appetite reducer	500 mg (2 times/day)*

Roman superscripts identify the substance in the text.
*RDD not well established.