The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)
01–30 NOVEMBER 2022 | ONLINE

Patient-centric drug product design: case studies for special populations

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

pharmaceuticals MDPI

Isabel Martins de Almeida

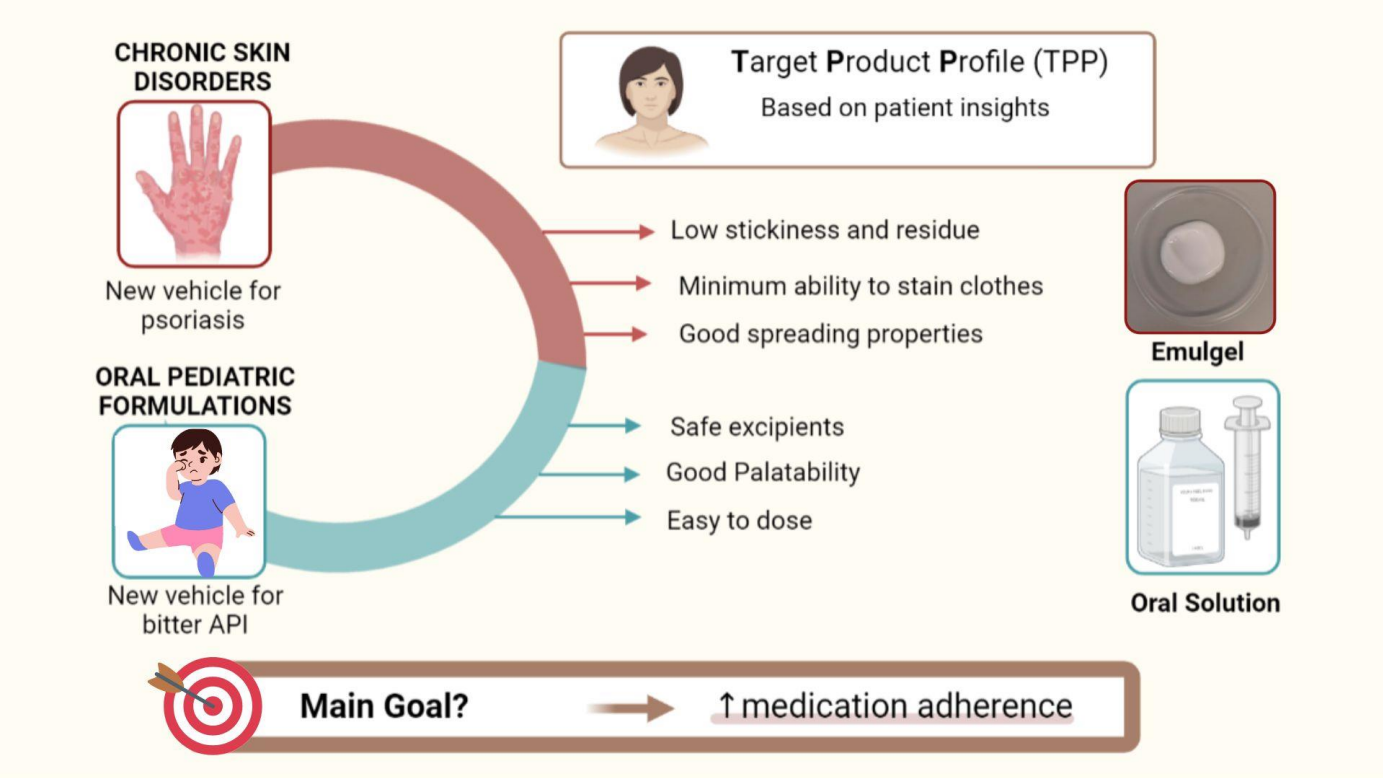
MedTech, UCIBIO, REQUIMTE & Associate Laboratory i4HB - Institute for Health and Bioeconomy
Laboratory of Pharmaceutical Technology, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Rua Jorge Viterbo Ferreira 228,Porto, Portugal;

* Corresponding author: ifalmeida@ff.up.pt

U.PORTO FACULDADE DE FARMÁCIA UNIVERSIDADE DO PORTO U.PORTO UCIBIO REQUIMTE i4HB Institute for Health and Bioeconomy

Patient-centric drug product design: case studies for special populations

Graphical Abstract



ECMC 2022
The 8th International Electronic Conference on Medicinal Chemistry
01–30 NOVEMBER 2022 | ONLINE

Abstract:
Medication non-adherence poses considerable challenges in managing chronic diseases and is associated with almost 200,000 deaths and €80-125 billion of potentially preventable direct (e.g. hospitalizations, waste of medication) and indirect (e.g. work productivity losses) costs in the European Union alone. The increasing awareness of the contribution of the acceptability of drug products by the patient to medication adherence and clinical outcomes is driving the integration of Patient Centric drug Product Design (PCDPD) into the pharmaceutical development process.
Regulatory agencies have addressed the relevancy of placing the patient in the center of pharmaceutical development. EMA has issued guideline/reflection papers for pediatric and older populations while FDA has developed a series of guidance documents on patient focused drug development with the primary goal to better incorporate the patient's voice in drug development and evaluation. PCDPD can be defined as the process of identifying the comprehensive needs of the target patient population to support the design of drug products. Three major factors are analyzed in PCDPD, namely patient, drug and drug product characteristics. This systematic approach integrates this insight which is translated to a Target Product Profile (TPP) to drive the pharmaceutical product design process. Two case studies will be presented focused on the pediatric population and on patients with a chronic skin disorder (psoriasis) which will highlight the roadmap for a successful PCDPD.

Keywords: Patient-centric design, medication adherence, pediatric formulations, dermatological formulations

Introduction

MEDICATION ADHERENCE

50 % adherence rate

Patients with chronic diseases in developed countries

up to 80 %

Topical treatments

200.000 Premature deaths annually EU

€80-125 billion

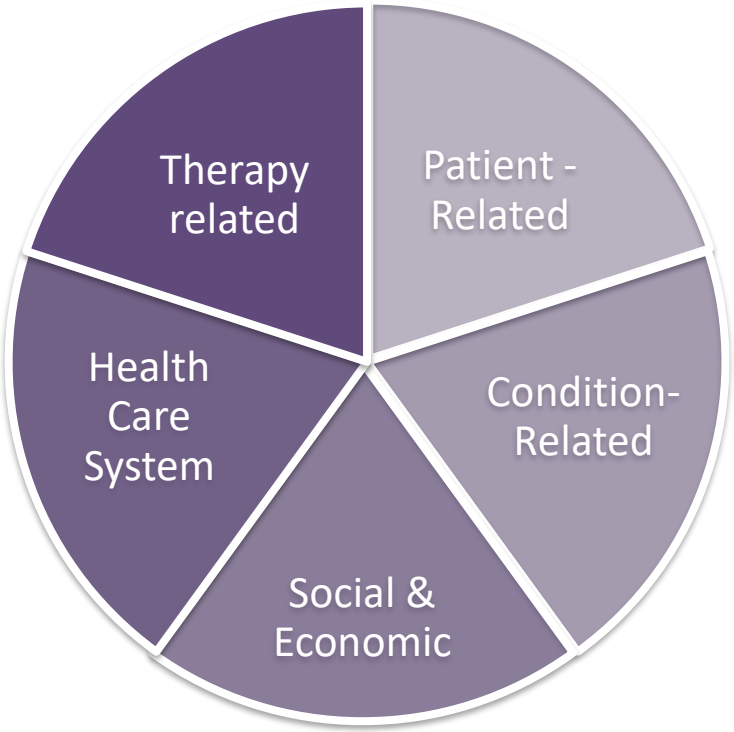
Potentially preventable and indirect costs EU

van Boven JF, et al. European Network to Advance Best Practices and Technology on Medication Adherence: Mission Statement. Front Pharmacol. 2021, 12:748702.

World Health Organization. Adherence to long-term therapies: evidence for action. 2003. Available at: http://www.who.int/chronic_conditions/adherencereport/en/

Introduction

DETERMINANTS OF MEDICATION ADHERENCE

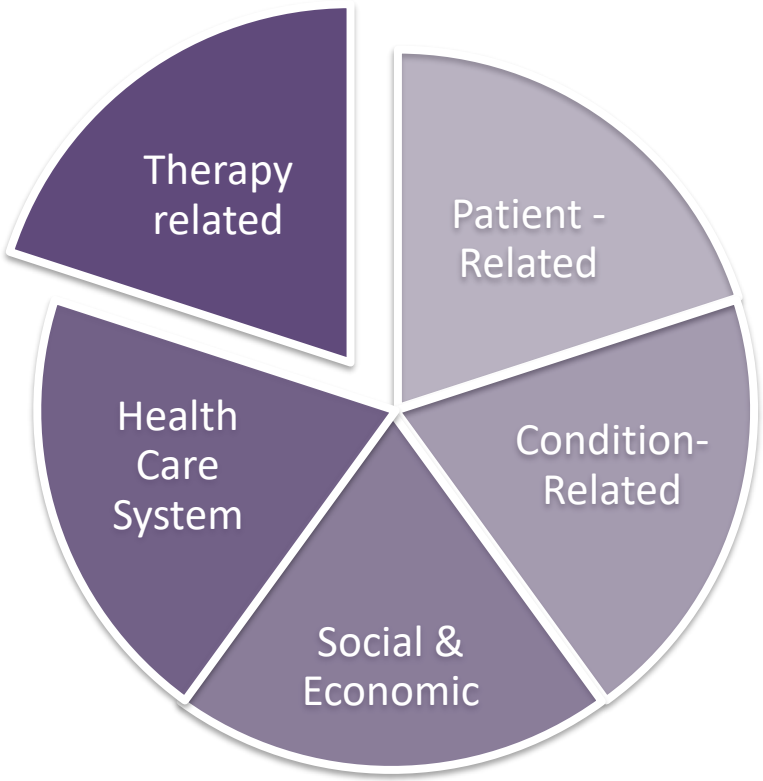


World Health Organization. Adherence to long-term therapies: evidence for action. 2003. Available at: http://www.who.int/chronic_conditions/adherencereport/en/

Introduction

DETERMINANTS OF MEDICATION ADHERENCE

PATIENT CENTRIC DRUG PRODUCT DESIGN



World Health Organization. Adherence to long-term therapies: evidence for action. 2003. Available at: http://www.who.int/chronic_conditions/adherencereport/en/

Introduction

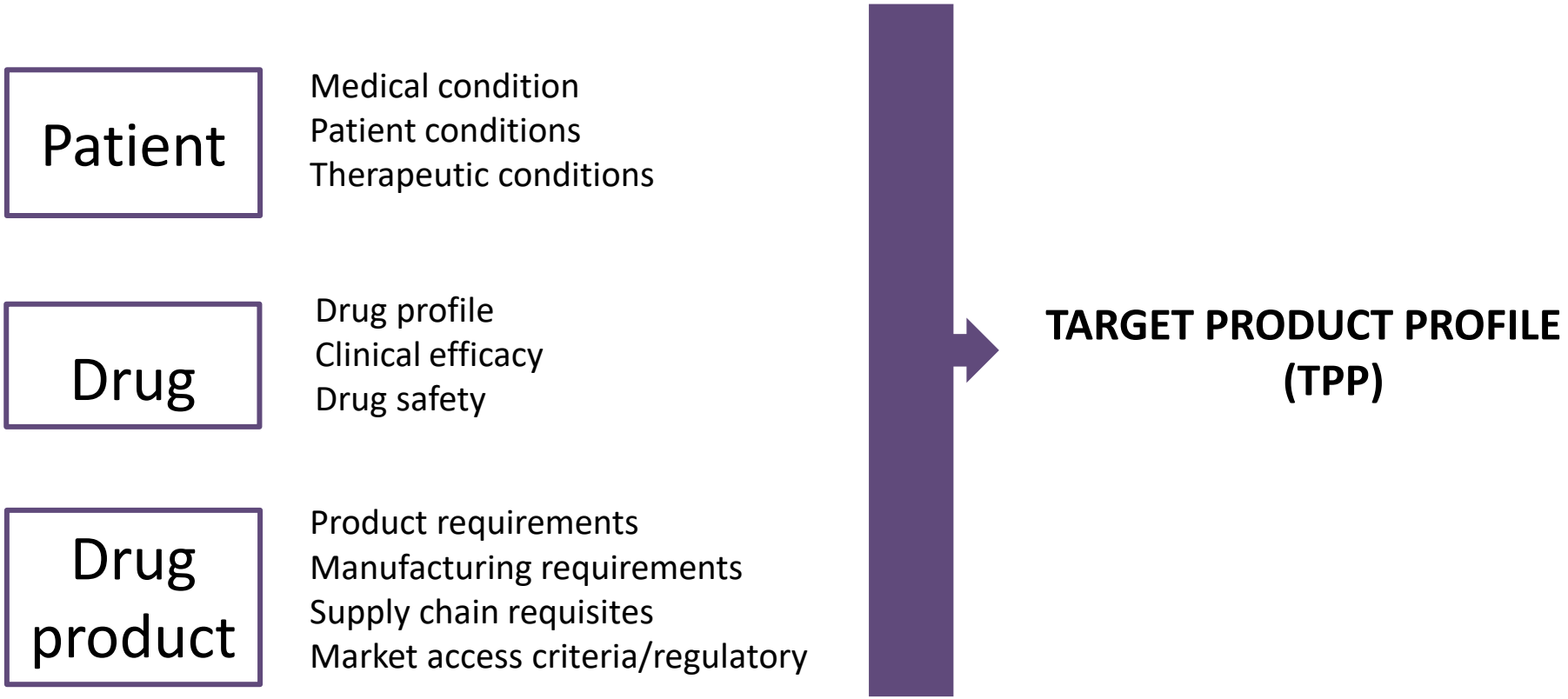
What does ***Patient centric drug product design*** means?

Introduction

"The process of identifying the comprehensive needs of individuals or the target patient population and utilizing the identified needs to design pharmaceutical drug products that provide the best overall benefit to risk profile for that target patient population over the intended duration of treatment."

Stegemann *et al*. Defining Patient Centric Pharmaceutical Drug Product Design. AAPS journal 18(5) 2016.

Introduction



Stegemann *et al*. Rational and practical considerations to guide a target product profile for patient-centric drug product development with measurable patient outcomes – A proposed roadmap. AAPS journal 18(5) 2016.

Introduction

PATIENT-RELATED CHARACTERISTICS	EXAMPLES
Age	Organ and body functions, social-emotional development
Visual impairment	Blindness
Motoric impairment	Arm mobility, difficulty walking, manual dexterity
Swallowing impairment	Dysphagia
Cognitive impairment	Memory loss, dementia
Poor hand sensitivity	Control of movement and strenght
Loss of hearing	
Dentition	
Health literacy	
Psychological distress	Negative perception, depressive disorders
Disease state	Comorbidities, disease disability
PK/PD	Kidney clearance
Psychosocial issues	Way of living, Employment satus, acess to caregivers

Stegemann *et al*. Defining Patient Centric Pharmaceutical Drug Product Design. AAPS journal 18(5) 2016.

Introduction

PRODUCT-RELATED CHARACTERISTICS	EXAMPLES
Route of administration	Oral, inhalation, rectal, vaginal, dermal
Product strenght concentration	
Type of dosage form	Tablet, oral solution, ointment
Site of dermal application	Arm, feet, back
Appearance	Product size, shape, colour, embossing
Swallowability	Related to tablet size, shape, coating/waxing, liquid viscosity, mouth feel
Dose to therapeutic effect	Number of tablets, total volume of liquid
Dosing regimen	Dosing frequency, duration of treatment
Packaging	Inner/outer, labelling
Container closure system	
Dosing and administration devices	Syringes, applicator
Any handlings to be conducted prior to use	Opening capsules, measuring liquids
Instructions for use	Complexity
Caregiver assistance	

Stegemann *et al*. Defining Patient Centric Pharmaceutical Drug Product Design. AAPS journal 18(5) 2016.

Introduction

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 October 2020
EMA/CHMP/QWP/292439/2017
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on the pharmaceutical development of medicines for use in the older population

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 August 2013
EMA/CHMP/QWP/805880/2012 Rev. 2
Committee for Medicinal Products for Human Use (CHMP)
Paediatric Committee (PDCO)

Guideline on pharmaceutical development of medicines for paediatric use

Introduction

FDA U.S. FOOD & DRUG ADMINISTRATION

Patient-Focused Drug Development: Collecting Comprehensive and Representative Input

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2020

Patient-Focused Drug Development: Methods to Identify What Is Important to Patients

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2022
Procedural

Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Communications, Division of Drug Information at druginfo@fda.hhs.gov, 855-543-3784 or 301-796-3400; or (CBER) Office of Communication, Outreach and Development at ocod@fda.hhs.gov, 800-835-4709 or 240-402-8010; or Office of Strategic Partnerships and Technology Innovation, Center for Devices and Radiological Health at cdrh-pro@fda.hhs.gov, 800-638-2041 or 301-796-7100.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

June 2022
Procedural

ECMC 2022
The 8th International Electronic Conference on Medicinal Chemistry
01–30 NOVEMBER 2022 | ONLINE

Introduction

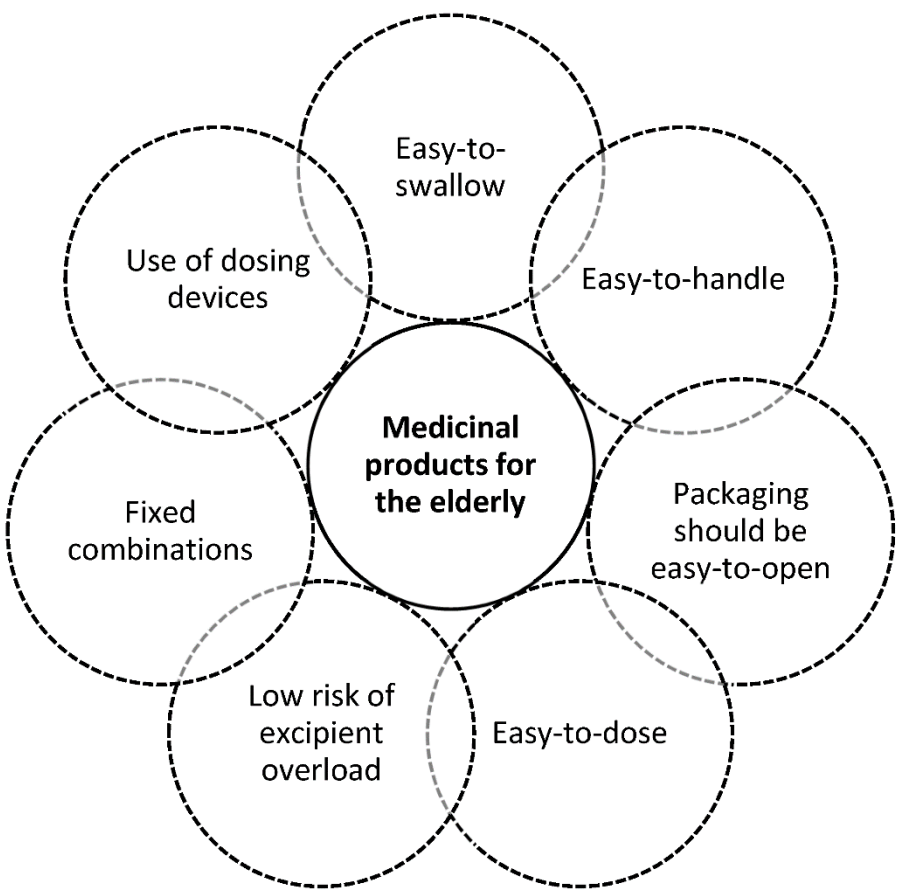
Special populations

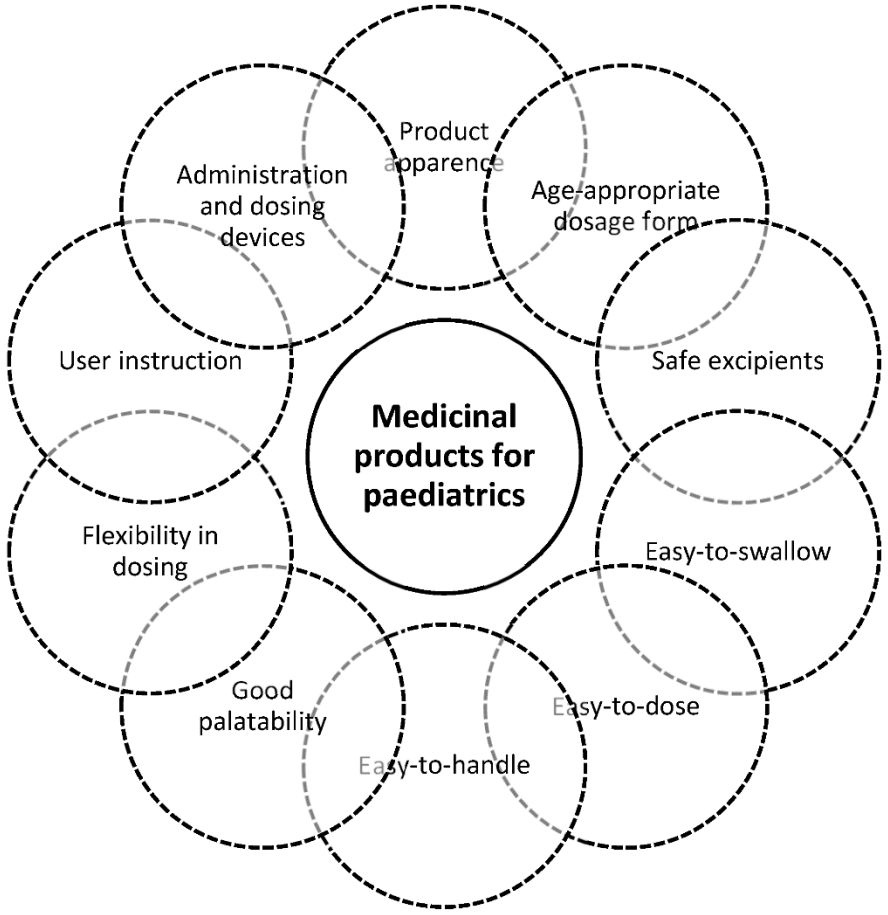
Paediatrics

Geriatrics

Dermatological patients

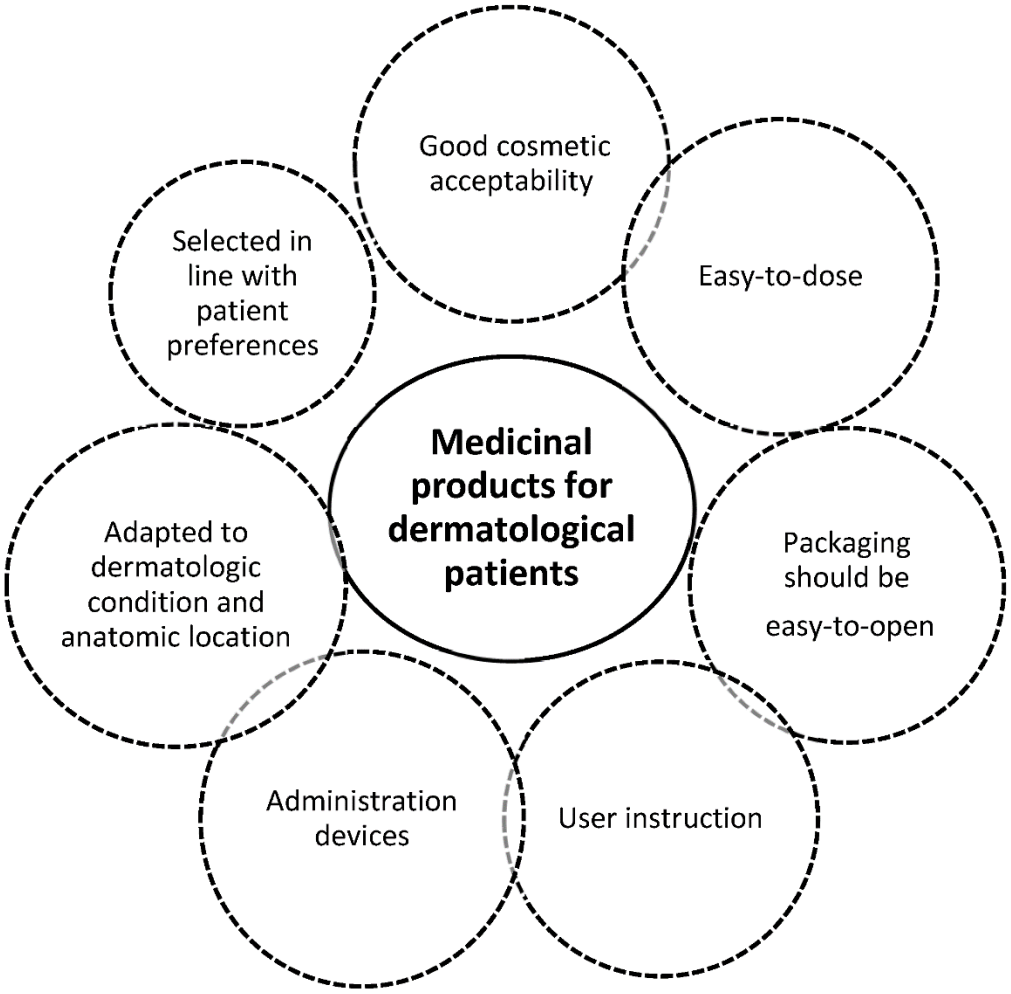
Introduction





Menditto E, Almeida IF et al. Patient centric pharmaceutical drug product design-the impact on medication adherence. Pharmaceutics. 2020; 12(1):44.

Introduction



Menditto E, Almeida IF et al. Patient centric pharmaceutical drug product design-the impact on medication adherence. Pharmaceutics. 2020; 12(1):44.

Results and discussion

CASE STUDIES

CHRONIC SKIN DISORDERS

applied sciences

Article

Design of an Emulgel for Psoriasis Focused on Patient Preferences

Rita Sanches Oliveira [1], Diva Ferraz da Silva [2], Sandra Mota [2,3], Jorge Garrido [4,*], Ermelinda Manuela Garrido [4], José Manuel Sousa Lobo [2,3] and Isabel Filipa Almeida [2,3,*]

ORAL PEDIATRIC FORMULATION FOR BITTER API

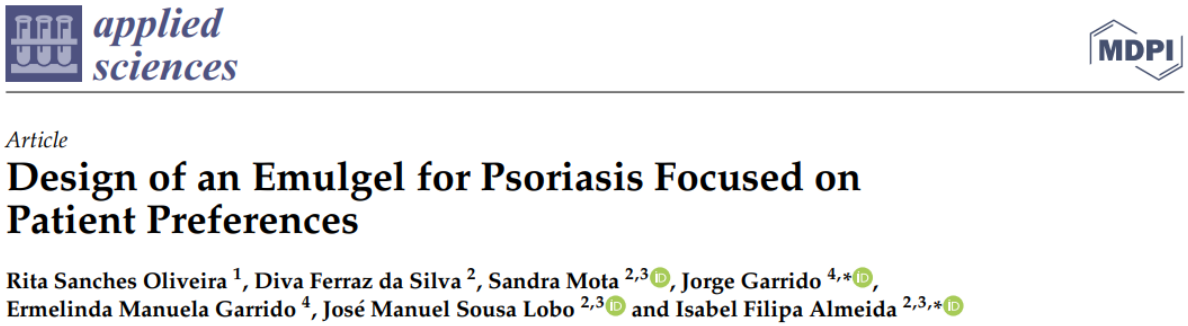
Article

Overcoming challenges in pediatric formulation with a patient-centric design approach

John Dike N. Ogbonna [1,2], E. Cunha [3*], Anthony A. Attama [1], Kenneth C. Ofokansi [1], H Ferreira [4], S Pinto [5], J Gomes [5], Ítala M.G. Marx [6,7], António M. Peres [6,7], JM Sousa Lobo [8,9] and Isabel Martins de Almeida [8,9*]

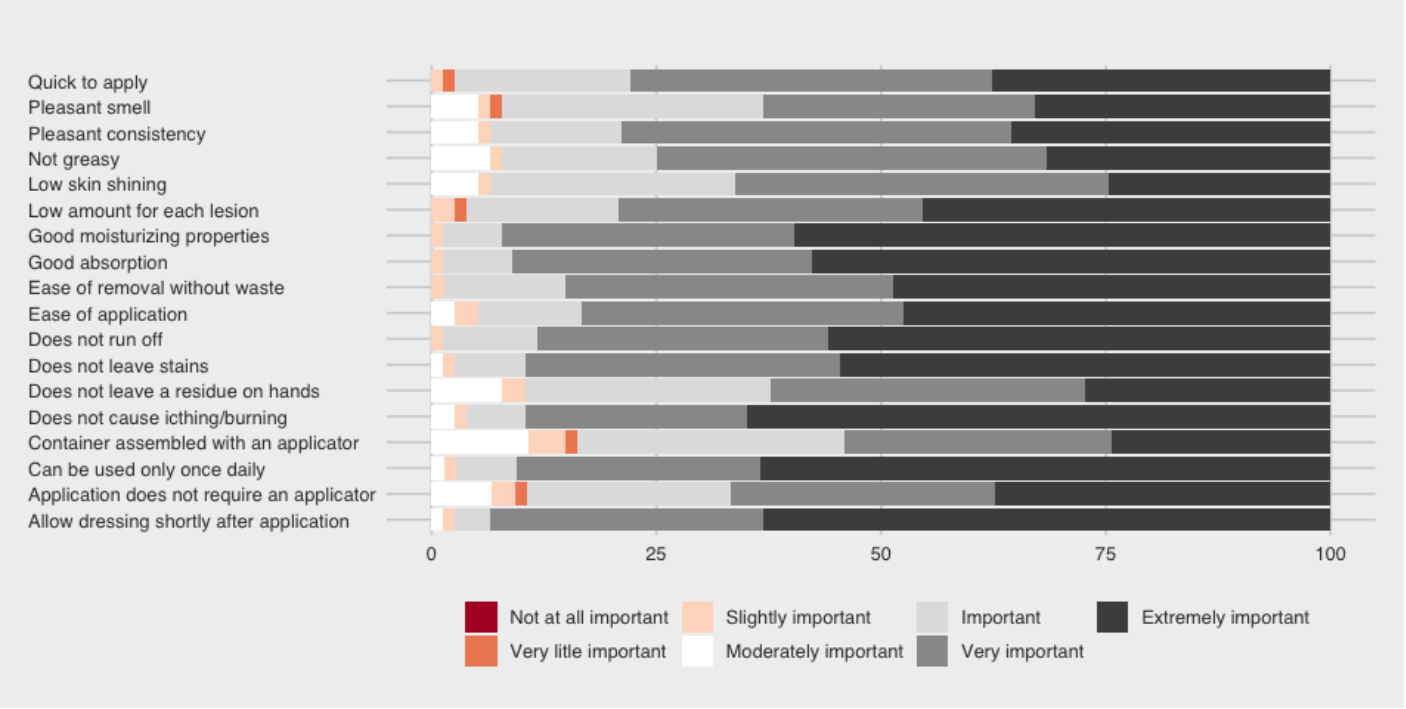
Results and discussion

CHRONIC SKIN DISORDERS



Results and discussion

Patient preferences for topical attributes of anti-psoriatic medicines N= 79



Vasconcelos V, Almeida IF et al. Patient preferences for attributes of topical anti-psoriatic medicines. *J Dermatolog Treat*. 2019; 30(7):659-663.

Results and discussion

Frequency of patients that rated the attribute at least as very important

DOMAIN	ATTRIBUTE	%
Formulation	Allow dressing shortly after application	93
Formulation	Good moisturizing properties	92
Application	Once daily regimen	91
Formulation	Good absorption	91
Formulation	Does not leave stains	90
Formulation	Does not cause itching/burning	90
Application	Does not run off	88
Container	Ease of removal without waste	85
Application	Ease of application	83
Formulation	Pleasant consistency	79
Application	Low amount for each lesion	79
Application	Quick to apply	78
Formulation	Not greasy	75
Formulation	Low skin shining	67
Container	Application does not require an applicator	66
Formulation	Pleasant smell	63
Formulation	Does not leave a residue on hands	62
Container	Container assembled with an applicator	51

Vasconcelos V, Almeida IF et al. Patient preferences for attributes of topical anti-psoriatic medicines. *J Dermatolog Treat*. 2019; 30(7):659-663.

Results and discussion

Target Product Profile (TPP)

Low skin residue

Quick absorption

Minimum clothes staining

Moisturizing properties

EMULGEL

Benchmarking

Ointment, Cream, Solution

Anti-inflammatory drug: Bethametasone dipropionate

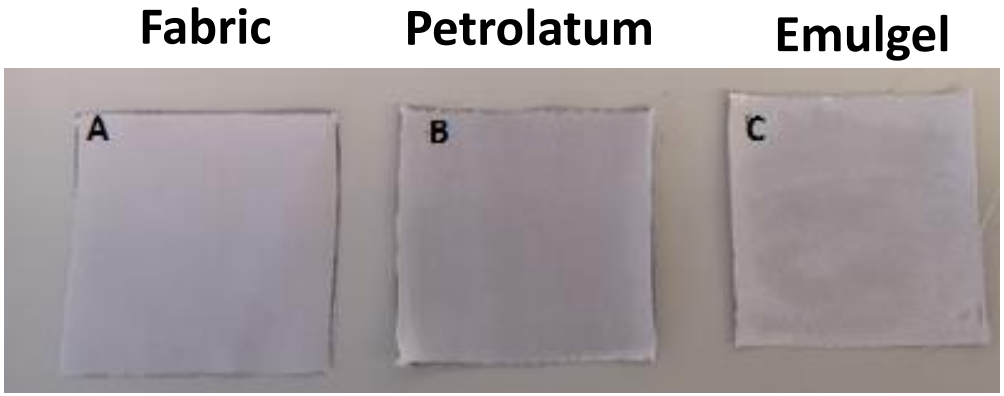
Results and discussion

TPP

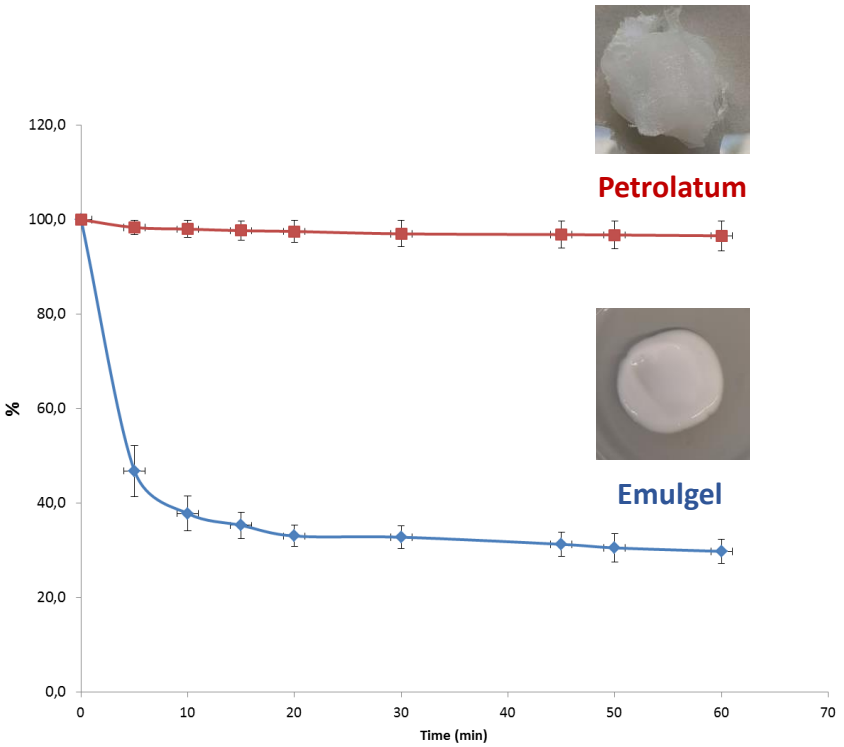
- Low skin residue → Low amount of lipophilic ingredients
- Minimum clothes staining → Low amount of lipophilic ingredients
- Quick absorption → Non petrolatum-derived ingredients; Aqueous external phase
- Moisturizing → Humectants; Hyaluronic acid

COMPOUND	wt %
Betamethasone dipropionate	0,064
Almond oil	9.0
Tween® 80	1.0
Glycerin	7.5
Sodium hyaluronate	1.0
Carbopol® 980	0.7
Methylparaben solution	3.0
Triethanolamine	qs pH 6
Water	qs 100

Results and discussion

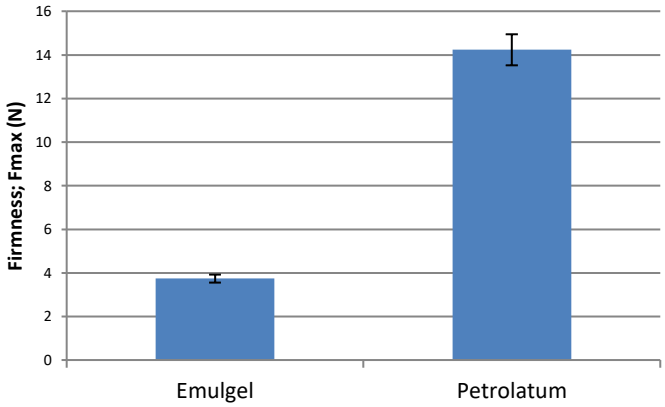


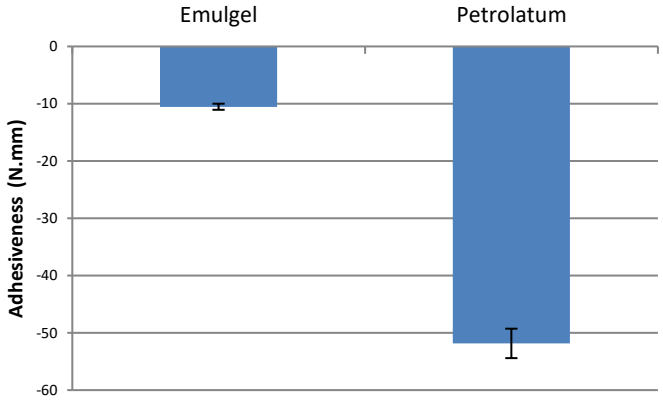
FABRIC STAINING



EVAPORATION RATE

Results and discussion

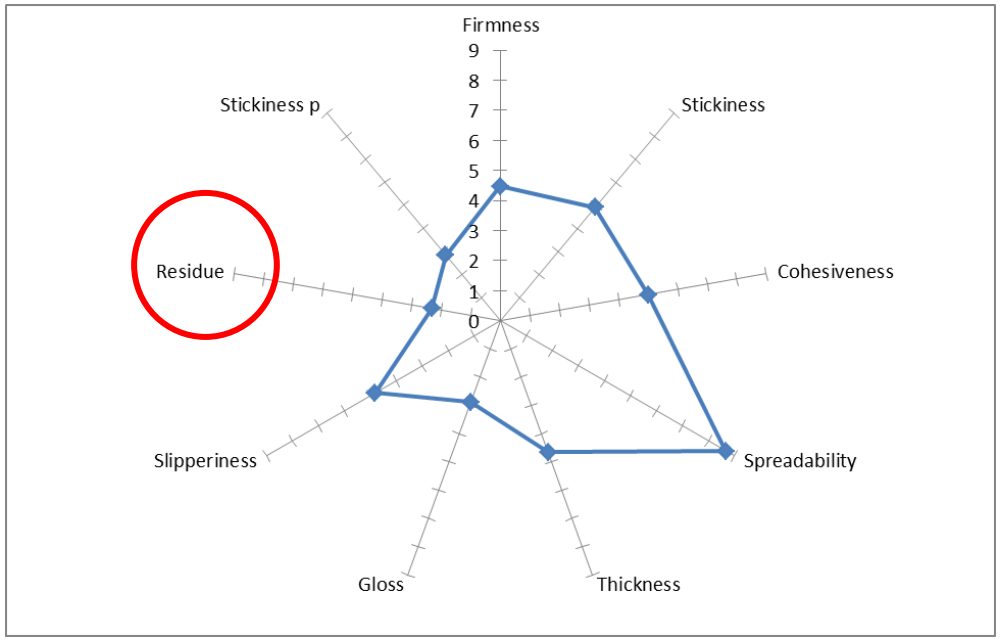


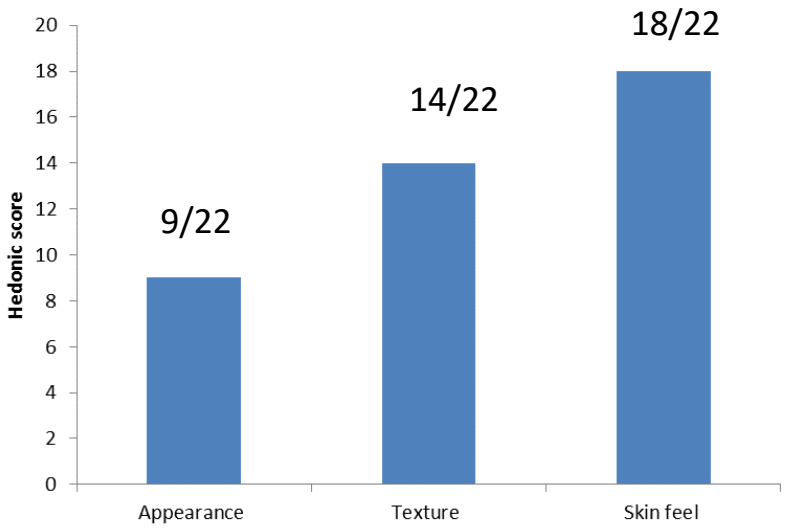


Firmness and adhesiveness (20ºC, mean values ±SD, n = 3)

TEXTURAL PROPERTIES

Results and discussion





-2 Dislike very much *to* **2** Like very much

EXPLORATORY SENSORY ANALYSIS N=11

Results and discussion

CASE STUDIES

ORAL PEDIATRIC FORMULATION FOR BITTER API

Article

Overcoming challenges in pediatric formulation with a patient-centric design approach

John Dike N. Ogbonna [1,2], E. Cunha [3*], Anthony A. Attama [1], Kenneth C. Ofokansi [1], H Ferreira [4], S Pinto [5], J Gomes [5], Ítala M.G. Marx [6,7], António M. Peres [6,7], JM Sousa Lobo [8,9] and Isabel Martins de Almeida [8,9*]

ECMC 2022
The 8th International Electronic Conference on Medicinal Chemistry
01–30 NOVEMBER 2022 | ONLINE

Results and discussion

ORAL PEDIATRIC FORMULATION FOR BITTER DRUGS
(Ranitidine as model of bitter API)

Target Product Profile (TPP)

- Good palatability (sugar-free)
- Easy to dose
- Dosing flexibility
- Safe excipients
- Easy preparation in a hospital setting

ORAL SOLUTION WITH A SUITABLE TASTE-MASKING STRATEGY

Results and discussion

ORAL PEDIATRIC SOLUTION

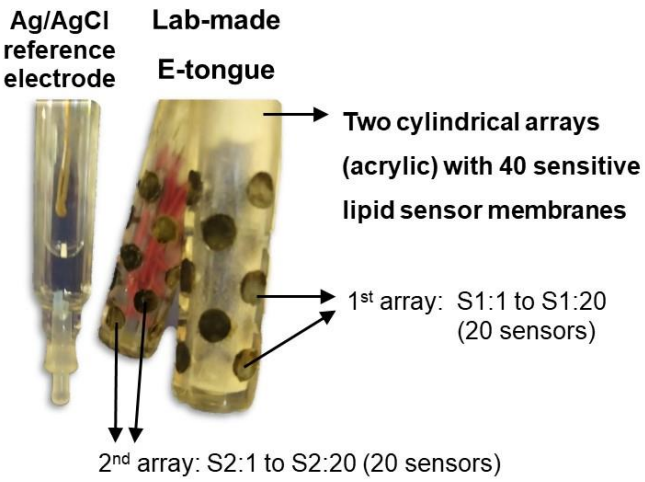
CHARACTERISTIC	TARGET	COMMENT
Concentration	25 mg/mL	Allows a low administration volume
pH	4.5-5.5	pH of maximum stability of Ra-HCl
Chemical and microbiological stability	At least 30 days	Comparison between solution in closed recipient and solution with once daily sample removal (in-use stability)
Flavor	Bubble gum	One of the preferred flavors for children
Taste masking strategy	Sweeteners and sodium chloride	Synergistic effect of aspartame and sodium saccharine Sodium chloride affords bitterness masking
Viscosity	Very fluid	Appropriated for administration with a syringe
Excluded excipients	Sugar-free, alcohol-free and paraben free	Parabens and alcohol are not recommended for pediatric formulations. Sugar-free formulation is non-cariogenic and suitable for children with diabetes and hereditary fructose intolerance
Preparation	Simple, with low energy consumption	Feasible in a hospital pharmacy setting

Results and discussion

ORAL PEDIATRIC SOLUTION

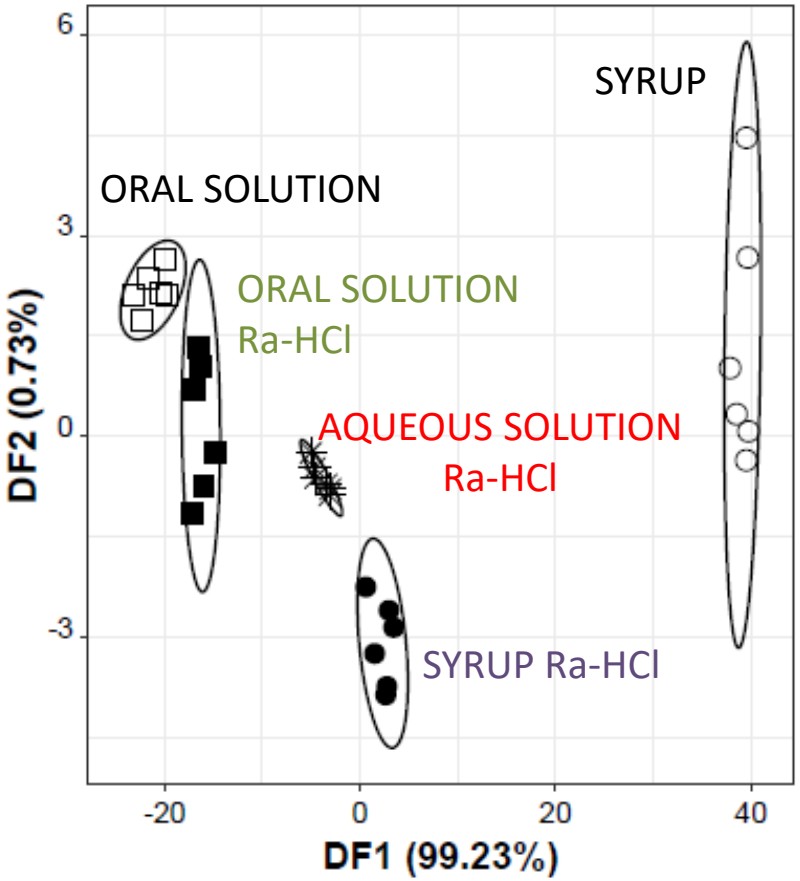
Compound	wt %
Sodium saccharin	0.6
Sorbic acid	0.1
Potassium sorbate	0.1
Sorbitol 70%	5
Citric acid	0.1
Aspartame	0.3
Sodium chloride	0.1
Sodium citrate	0.5

Results and discussion



E-tongue

ORAL PEDIATRIC SOLUTION



Conclusions

ROADMAP

NO **Does it match TPP?** YES

Patient preferences/needs	TPP	Drug product design/preparation	Drug product characterization	Usability and patient acceptability
Scientific literature Questionnaires	Patient Drug Drug product	Production environment	Relevant features from the patient perspective	Questionnaires/sensory analysis Comparison with standard treatment

? Does the use of medicines designed to match patient preferences and needs translate into higher treatment adherence?

PATIENT CENTRIC ANTI-PSORIATIC TOPICAL FORMULATION DESIGN

Jorge Garrido

Rita Oliveira

Sandra Mota

Marta Pedroso

Diva Silva

Isabel Almeida

José Manuel Sousa Lobo

PATIENT CENTRIC PEDIATRIC ORAL FORMULATION DESIGN

John Ogbonna

Anthony Attama

Keneth Ofokansi

Susana Pinto

Joana Gomes

Isabel Almeida

Helena Ferreira

José Manuel Sousa Lobo

António Peres

Ítala Marx

Edite Cunha

Acknowledgments

COST Action CA19132 – “European Network to Advance Best practices & technoLogy on medication adherencE

This work was supported by national funds from FCT—Fundação para a Ciência e a Tecnologia, I.P., Portugal, in the scope of the project UIDP/04378/2020 and UIDB/04378/2020 of the Research Unit on Applied Molecular Biosciences—UCIBIO, the project LA/P/0140/2020 of the Associate Laboratory Institute for Health and Bioeconomy—i4HB, the project UIDB/00690/2020 and UIDP/00690/2020 of CIMO and the project LA/P/0007/2020of the Associate Laboratory SusTEC, the project UIDB/00081/2020 of IMS-CIQUP and by the Federal Government of Nigeria NEEDS Assessment grant-2018. Ítala M.G. Marx also acknowledges the Ph.D. research grant (SFRH/BD/137283/2018) provided by FCT. S. Mota acknowledges the research fellowship (NORTE-01-0247-FEDER-047239) fully supported by national funding by project 47239 - Cork2Cosmetic (NORTE-01-0247-FEDER-047239).

ECMC 2022
The 8th International Electronic Conference on Medicinal Chemistry
01–30 NOVEMBER 2022 | ONLINE