NON-ORAL DRUG PREPARATIONS CONTAINING CYCLODEXTRIN COMPLEXES

L. Szente, J. Szejtli, M. Gál-Füzy
Biochemical Research Laboratory of Chinoin Pharm. Chem. Works Ltd.
Budapest, 1026 Endrődi S. u. 38/40, Hungary

ABSTRACT. The application of cyclodextrin complexed drugs in non-oral dosage forms results in the following advantages:

- The stability of volatile, chemically unstable drugs is significantly improved by transforming them into cyclodextrin complexes.
- The transformation of oils, liquids into crystalline, solid state provides better physical, mechanical properties, easy to handle products.
- Complex formation /encapsulation on molecular scale/ remarkably enhances the dissolution and absorption of lipophylic drugs.
- The formation of water soluble inclusion complexes makes possible the preparation of parenteral dosage forms without using organic solvents or detergents.

1. INTRODUCTION

The practically most important non-oral dosage forms containing cyclodextrin complexes can be classified as follows:

- rectal suppositories containing cyclodextrin complexes
- eye lotions with complexed drugs
- powdery inhalants formulated with cyclodextrins
- dermal application of β-cyclodextrin or its complexes
- parenteral forms containing water soluble cyclodextrin complexes.

This paper deals with the advantages of the application of cyclodextrin complexes in rectal suppositories, inhalants and parenteral dosage forms.

2. RESULTS

2.1. Suppositories containing β-cyclodextrin complexes

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Rectal suppositories containing volatile, lipophylic drugs /i.e. essential oils, terpenoids/ have certain disadvantages that need to be reduced. Neither the physical-mechanical properties of these suppositories nor the stability and rectal absorption of their active ingredients are satisfactory.

2.1.1. Physical properties of suppositories

The most significant physical-mechanical characteristics of rectal suppositories are: the point of solidification, time of melting and the break-strength.

As it is shown in Table I. all above mentioned mechanical properties of rectal suppositories are remarkably improved, when their active ingredients /menthol, camphor, eucalyptus oil/ are present as β-cyclodextrin complexes.

Table I.

Mechanical properties of suppositories studied

Sample	Point of solidification /°C/	Time of melting /sec/	Break-strength /N/
Adeps solid 2 g	28,6	558	101
20 % Me,C,E /A	26,2	234	25
2 % Me,C,E /A	27,0	468	65
2 % Me,C,E, CD/A	30,0	636	108
CD/A 2 g	29,6	564	106
Massa polyox. 2 g	-	1896	133
Me,C,E CD/M	-	2748	142
CD/M 2 g	-	2550	138

Legend: Me - menthol; C - camphor; E - eucalyptus oil; A - Adeps solidus; M - Massa polyox aetheni

/All data represent averages of 5-5 parallel measurements./

2.1.2. Stability studies of the active ingredient of the suppositories

It has been pointed out that cyclodextrin complexation significantly improves the thermal stability of volatile, oxydizable active ingredients of suppositories. The results of the heat-stability tests are summarized in table II.

Table II.

The loss of free and complexed fennel oil from suppositories at 60 °C. Fennel oil content is expresed in %

Time /days/	F /A	F CD/A	F /M	F CD/M
0	100	100	100	100
1	4	89	30	85
2	2	80	13	86
4	0	80	9	82
8	0	72	0	80

Legend: F - fennel oil; A - Adeps solidus base; M - Massa polyoxaetheni base; CD - β-cyclodextrin

2.1.3. In vitro dissolution of drugs from suppositories

For this study suppositories of different suppository bases were prepared by using free and β-cyclodextrin complexed fennel oil and indomethacin.
As table III. shows the application of cyclodextrin inclusion complexes instead of free drugs results in a remarkably enhanced absorption of lipophylic drugs even from fatty suppository bases /e.g. Adeps solidus, Butyrum caco/.

Table III.

In vitro dissolution of free and complexed substances from suppositories /in mg/ pH 7,3 t = 37 °C.

Time /hours	F /A F=50 mg	F CD /A F= 2 mg	F /M F=4,36	F /CD/M F=4,24	I /B I=10 mg	I /CD/B I=10mg
1	0,03	0,17	0,19	1,39	0	0,19
2	0,05	0,31	0,30	1,87	0,12	0,48
3	0,07	0,41	0,39	1,99	0,20	0,76
4	0,11	0,56	0,55	2,20	0,49	1,35
5	0,16	0,70	no data	no data	0,96	2,34

Legend: F - fennel oil; A- Adeps solidus base; M - Massa polyoxaetheni base
I - Indomethacin; B - Butyrum cacao base
CD- β-cyclodextrin

Preliminary in vivo rectal absorption studies on rats gave results that were in an acceptable agreement with the above in vitro data. Similar enhancement of the rectal absorption of antiinflammatory drugs due to the complex formation was observed by Uekama et al [1].

Comparative gas-chromatographic studies, following the heat treatment proved, that the thermal stability of the volatiles /e.g. eucalyptus oil/ entrapped into β-cyclodextrin greatly surpassed that of the traditionally applied ones. /See Fig.1./

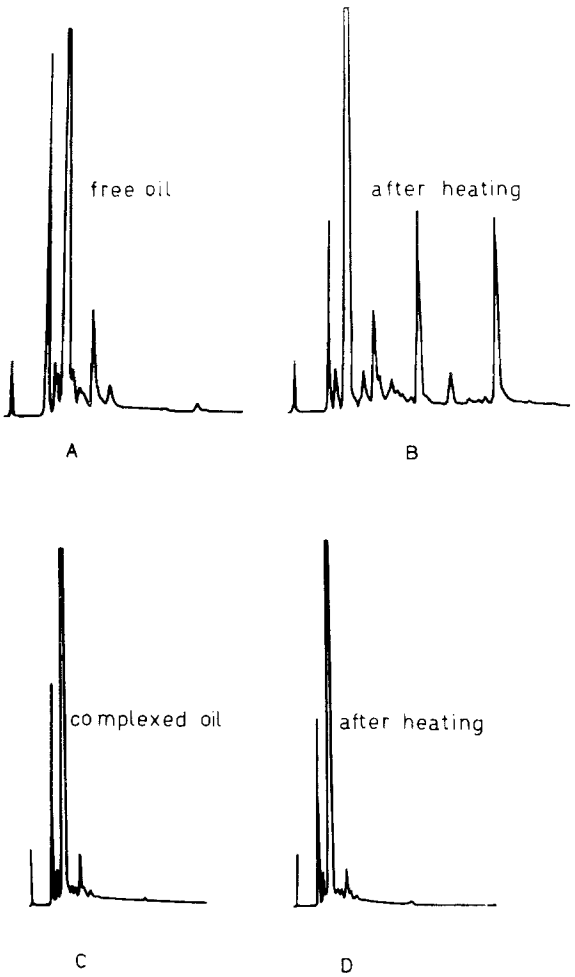

Fig.1. Comparative gas-chromatograms of free and complexed eucalyptus oil of suppositories before and after heat treatment /60 °C for 4 days/.

2.2. Powdery inhalant containing β-cyclodextrin complexes

Volatile, pharmacologically active constituents /methol, camphor, eucalyptus oil/ of a liquid inhalant were transformed into a microcrystalline powdery formulation by β-cyclodextrin complexation.

The complexation procedure provided an easy to handle, easy to store formulation for the oily product and improved the chemical stability of the volatiles, too.

Thermoanalytical studies proved, that the escape of the volatiles from cyclodextrin inclusion complexes took place at a significantly higher temperature, while the free volatiles easily evaporated. /See Fig.2./

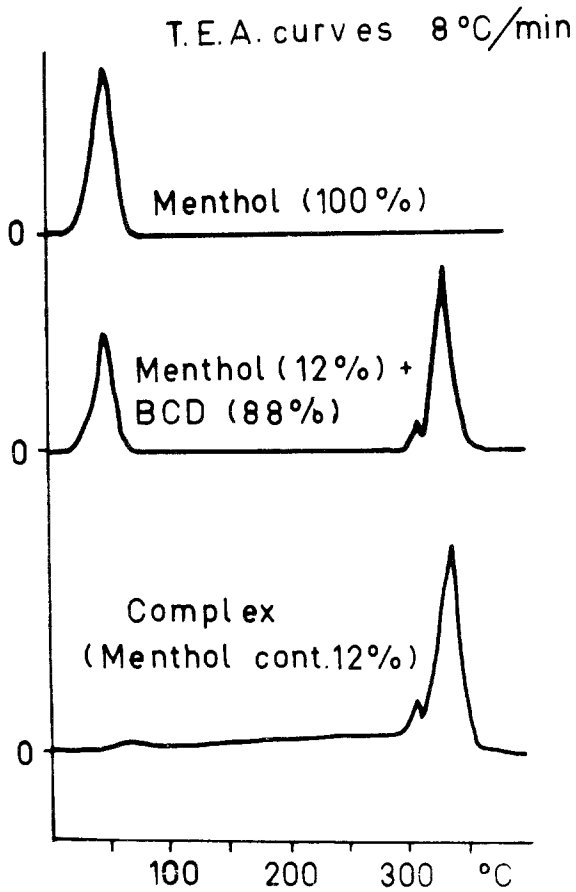

Fig.2. TEA assay of free and complexed menthol

The powdery inhalant was found to be stable in dry state, however when it contacted with water /especially hot water/

an immediate release of the entrapped volatiles took place. The release of the volatile constituents from the powdery inhalant was found to be much longer lasting, than that of the traditional preparation, under normal inhalation conditions.

2.3. Parenteral dosage forms containing cyclodextrins

Among cyclodextrin and its highly water soluble derivatives heptakis-2,6-di-O-methylated-β-cyclodextrin seems to have the most effective solubilizing and complexing property.

Its solubilizing power was tested by solubility studies involving a lot of poorly water soluble substrates of different chemical structure. The enhancement of water solubility of these substances in 10 % aqueous dimethyl-β-cyclodextrin solution was found to be 3-800 fold. See table IV.

Table IV.
Solubility of lipophylic drugs in water and in 10 % aqueous dimethyl-β-cyclodextrin solution /t= 25 °C/.

Substances tested	Solubility in mg/ml in water	in dimethyl-βCD	enhancement
alprenolol /base/	0,70	9,6	13 x
propanolol /base/	0,42	15,0	35 x
dobutamine /base/	0,78	20,0	25 x
retinoic acid	2,2	380	172 x
hidrocortisone	0,37	23	56 x
progesterone	0,016	13	812 x
theophylline /base/	6,0	19,1	3 x
naphtalene	0,005	2,96	580 x
anthracene	0,003	0,26	86 x
tetracene	0	0,33	

This remarkable solubilizing potency of dimethyl-β-cyclodextrin may be of practical interest, since it enables the easy preparation of aqueous injections of lipophylic drugs with the avoidance of use of any organic solvents or detergents.

REFERENCE

1. Uekama, K.: Yakugaku Zasshi 100 /9/. 903. 1980.