

# UREA FROM THE CHEMIST'S POINT OF VIEW

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## Synopsis

Urea is a colourless and odourless tetragonal crystal. Due to its molecular structure (dipolaric) it can easily be dissolved in water, whereas it is almost insoluble in nonpolar substances such as chloroform or ether. In solution, urea undergoes a decomposition to carbon dioxide and ammonia. A so-called "sand paper effect" may occur, especially in preparations containing higher urea concentrations caused by the phenomenon of recrystallisation.

Therefore topical products with urea require stabilisation (either with triacetin, lactic acid or polysaccharides). Non stabilised urea containing preparations can only be used safely for periods of up to six weeks (the stabilised preparations can be stored for two or even three years).

In conclusion it can be said that urea containing formulations for cosmetic and/or dermatological purposes have to be developed with great care to provide perfect results.

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## Riassunto

L'urea é una sostanza cristallina e inodore, facilmente solubile in acqua e praticamente insolubile nei solventi apolari quali il cloroformio e l'etere. Una volta disciolta l'urea si decompone facilmente in anidride carbonica ed ammoniacca.

Data la sua poca stabilità in soluzione i preparati topici a base di urea debbono essere ben stabilizzati (sia con acido lattico che con polisaccaridi).

Si deve fare anche molta attenzione alla sua concentrazione di utilizzo per evitare il fenomeno di ricristallizzazione che provoca il cosiddetto "effetto sabbia" ben noto agli utilizzatori abituali. In conclusione si può affermare che le preparazioni cosmetiche o dermatologiche a base di urea debbono essere formulate e controllate con grande cura.

## Introduction

Jean Rouelle (1718-1778), a french apothecary, discovered urea as a natural constituent of human urine in 1773 ("Identification d'une substance savonneuse dans l'urine"). Friedrich Wöhler (1800-1882), M.D. and chemist, succeeded in synthesizing urea from ammonium cyanate. He therefore proved that no mystical "vis vitalis" is necessary to synthesise organic materials from inorganic precursors.

## Manufacture and chemistry of Urea:

Urea (U) is the diamide of carbonic acid. It is a colourless, odourless (or nearly odourless), slightly hypogrosopic prismatic crystalline substance with a cooling saline taste (2).

The world production of urea is mainly used in fertilizers and for the synthesis of plastics (altogether 40 million tons in 1980).

These large amounts of U are manufactured from ammonia and carbon dioxide under high pressure (100-200 atm) and high temperatures (170-250°C). In the laboratory U is still synthesized by the method of Dr. Wöhler.

Apart from the many favourable effects of topical urea, this substance is cheap. 1 kg of Urea pura of the quality specified in the Austrian pharmacopoeia would cost less than 50 AS.

Due to its ability to form intramolecular dipoles, U resembles the water molecule. Therefore it readily dissolves in polar solvents such as water or alcohol but it is almost insoluble in nonpolar media such as chloroform or ether.

U is a weak acceptor of protons and would give in water a solution with a pH of 7,5, at least theoretically. Deviations occur due either to the carbon dioxide content of water or to impurities and decomposition of U itself.

## Decomposition of urea (Fig. 1)

Once in solution, urea decomposes and, in simple terms, the following reactions occur. First U is converted into ammonium cyanate. The equilibrium lies completely on the side of the unchanged U. In the subsequent reaction ammonium cyanate is hydrolytically split. Other U molecules then form ammonium cyanate in order to maintain the equilibrium of the first reaction. Ammonium cyanate is split into two molecules of ammonia and one molecule of carbonic acid. Carbonic acid is a weak and instable acid ( $H^+ + HCO_3 \rightleftharpoons H_2CO_3 \rightleftharpoons CO_2 + H_2O$ ), the two molecules of ammonia react as proton ( $H^+$ )- acceptors.

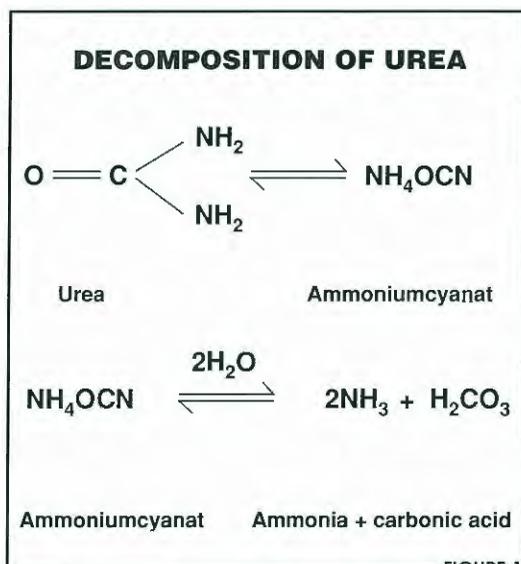


FIGURE 1

Therefore the pH constantly increases. Some factors such as the steadily increasing pH, raising of the temperature and open storage, which permits the escape of the produced ammonia and carbon dioxide, enhance the decomposition. Open storage (and high temperature in addition) favours evaporation of water. The result could be a recrystallization of U. The risk is greater with the higher initial concentrations of U. The crystals act like sand on the skin and cause irritation.

Therefore topical preparations containing urea should be made airtight after each usage and stored at normal room temperature or below. Before application it should be made sure that no sandiness has developed (4).

### **Stabilization of Urea:**

The above mentioned facts explain why industrially produced topical preparations containing urea must be stabilized.

Stabilization reduces and delays disintegration and keeps the pH constant over longer periods (2).

One possibility for stabilizing U is the addition of triacetin. Triacetin is an ester of glycerol with three molecules of acetic acid. As soon as pH increases, the ester bonds are hydrolytically split and the released acetic acid will keep pH constant. Another possibility is the addition of lactic acid, which is as effective as acetic acid. Moreover, lactic acid is part of the NMF of the skin and will therefore increase one of the effects of U. However stabilization with lactic acid can lead to burning sensations.

At present the most sophisticated method of stabilization is the adsorption of U to polysaccharides (for instance corn or rice starch). There are no problems with local tolerance, and the pH in these formulations can be adjusted as desired.

### **Urea containing preparations for topical use upon special prescription:**

Some problems arise if one prescribes an U containing topical preparation. Generally spoken this task is easier the lower the required U concentrations and the higher the required water content are. Before introducing U into the formulation the crystals have to be pul-

verized. The use of an ointment mill will cause disappearance of sandiness (4).

For cosmetic and dermatological purposes such as augmentation of the skin-moisture, general skin protection and therapy of scaly lesions, 3-5% U in an O/W emulsion are recommended (5,6). This will have an immediate effect on the upper horny layers (Fig. 2 and 3).

<b>UREA IN O/W</b>	
Urea purae	5,0
NaCl	5,0
Tween 80	20,0
Aquae dest.	40,0
Vas. alb. ad	100,0

FIGURE 2

<b>UREA IN O/W</b>	
Urea purae	3,0
Allantoin	0,2
Karion F liqu.	3,0
Vas. flav.	10,0
Lanette N	15,0
Guajazulen 25%	0,04
Aquae dest.	100,0

FIGURE 3

For the treatment of pronounced dermatological disturbances such as psoriasis vulgaris, different forms of ichthyosis, atopic dermatitis and extremely dry skin, 10% U in W/O should be applied (5,6). U in W/O has not such a distinct immediate effect but has a longer lasting beneficial action due to its deeper penetration into the

skin (Fig. 4). For painless onycholysis, 40% U concentrations are necessary. The surrounding skin should be protected with a paste.

<b>UREA IN W/O</b>	
Urea purae	10,0
NaCl	10,0
Aquae dest.	20,0
Ungt. alc. lanae aqu. ad	100,0

FIGURE 4

After 5-10 days of occlusion the nail can be removed (7). As shown in Fig. 5, U in this case is incorporated into a vehicle, which consists only of various lipids. It is not dissolved but merely suspended. Therefore sandiness is inevitable. No improvement will be brought about by ointment mills as their use will lead to separation of the different parts of the vehicle (4).

<b>ONYCHOLYSIS WITH UREA</b>	
Urea purae	40,0
NaCl	5,0
Aquae dest.	20,0
Ungt. alc. lanae aqu. ad	100,0
Occlusion (5-10 d)	

FIGURE 5

### ***Industrially produced urea containing preparations for topical use:***

Industrially manufactured products have some distinct advantages over those upon special prescription. They have a guaranteed stability over 2-3 years on an average, whereas the prescribed products can only be used for 4-6

weeks. The quality of manufactured creams, ointments or lotions is good and constant.

Urea itself shows some antimicrobial action (5). Therefore little or no preservative need be added, and it is well known, that preservatives are rather disadvantageous from the allergological point of view.

In summary it can be said, that urea is a somewhat difficult substance to incorporate into good and stable topical formulations. Therefore urea containing preparations for cosmetological and dermatological purposes need to be developed with the utmost care to guarantee perfect results.

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