SHAMBHUNATH INSTITUTE OF PHARMACY, JHALWA, ALLAHABAD

LECTURE NOTES
ON

PHARMACEUTICS -I

UNIT -IV

(BP-103T)

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UNIT IV

SUPPOSITORIES

Definition: Suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert localized or systemic effects.

They are used to deliver both systemically-acting and locally-acting medications.

Types:

- Rectal suppository (weigh 2gm for adult and 1gm for children).
- Vaginal suppository (weigh 3-5gm) also known as Pessaries.
- Urethral suppository also known as Bougies (weigh 4gm for males and about 2gms for females).
- Nasal suppository also known as nasal bougies (weigh about 1gm).
- Ear Cones or Aurinaria weigh about 2-3 gms.

ADVANTAGES OF SUPPOSITORIES

- Avoid first pass metabolism
- Does not cause nausea and vomiting due to gastric irritation in case of oral therapy
- Used before surgery since oral therapy is restricted
- Beneficial for patients suffering from severe vomiting
- Can be administered to unconscious patients
- Can be used as targeted drug delivery system – Localized action with reduced systemic distribution
- Get to site of action with lower dose reducing systemic toxicity
- Highly beneficial in haemorrhoids or vaginal infections
- Prolonged drug action achieved
- No pain and minimum site of action related issues

DISADVANTAGES OF SUPPOSITORIES

- Mucosal irritation
- Patient compliance
- Erratic and undesired absorption
- Placement too high into rectum may lead to first pass metabolism
- Installation may trigger defecation reaction
- GI state affects absorption:
- Diarrhea& disease states affect absorption

Suppositories Bases:

Properties of Ideal suppository base:

1. Melts at body temperature or dissolves in body fluids.
2. Non-toxic and non-irritant.
3. Compatible with any medicament.
4. Releases any medicament readily.
5. Easily moulded and removed from the mould.
6. Stable to heating above the melting point.
7. Easy to handle.
8. Stable on storage.

Types of suppositories bases:

- Cocoa butter and other fatty bases
- Water soluble and dispersible suppositories bases
- Hydrogels
- Glycerinated gelatin

Preparation of suppositories:

- Molds:-
  - Metal device used to get the required shape.
  - Made up of aluminum , brass, stainless steel, or plastics.
- Calibration of mold:-
  - It is the adjustment of mold to get suppositories of uniform weight, even though different base are used.
  - It is done prier to suppositories.
  - A set of suppositories are prepared using only the base.
  - The average weight of them is calculated & it is taken as the true weight of suppositories prepared using that mold , which is the capacity of mold.
- Displacement value:-
  - The volume of suppository from particular mold is uniform but its weight will vary because the density of medicament usually differ from the density of base .
  - To prepare product accurately , allowance must be made for the change in density of mass due to added medicament
  - The most convenient way of making this allowance is to use the displacement value-" the number of part by the weight of medicament that displace the one part by weight of base"

Suppositories are prepared by four methods:-

- ❖ Hand molding method
- ❖ Compression molding method
- ❖ Pour molding method
- ❖ Automatic molding method

(1)Hand molding method

Hand shaping suppositories is the oldest and the simplest method of preparing this dosage form. The manipulation requires considerable skills, yet avoids the complications of heat and mold preparation.

Prescribed quantity of grated powder ingredient

↓

Reduce the ingredients to fine powder in mortar

↓

Soften with diluted alcohol and smooth paste is formed

↓

Grated with theobroma oil and kneaded and triturate in the mortar

↓

Kneading and rolling method was done by hands and rolled into balls

↓

Kneaded mass is rolled between fingers into rod shaped

↓

The rods are cut into pieces and then one end point rolled to give a conical shape.

(2)Compression molding method

This method of suppository preparation also avoids heat. The suppository mass, such as a mixture of grated theobroma oil and drug, is forced into a mold under pressure, using a wheel-operated press. The mass is forced into mold openings, pressure is released, and the mold removed, opened, and replaced. On a large scale, cold-compression machines are hydraulically operated, water-jacketed for cooling, and screw-fed. Pressure is applied via a piston to compress the mass into mold openings.

(3)Pour molding method

Molds should be filled only when they are at room temperature. A cold or frozen mold should never be used because it can cause fractures and fissures throughout the suppository. Each cavity

should be filled slowly and carefully ensuring that no air bubbles are entrapped in the cavity. To prevent layering in the suppositories, the pouring process should not be stopped until all the cavities have been filled. Molds should be allowed to set at room temperature. Refrigeration should only be used if the suppository has not congealed after 30 to 40 minutes.

Aluminum molds usually require lubrication before use. Hard rubber molds may require lubrication. One way is to use a vegetable oil spray. Other lubricants include light mineral oil when water soluble bases are being used and glycerin or propylene glycol when oleaginous bases are being used. Whichever lubricant is used, only a light coating of it is needed. If too much lubricant is used, the excess will pool in the tip of the suppository cavity.

(4)Automatic molding method

The molding operations (pouring, cooling, and removal) can be performed by machine. All filling, ejecting, and mold-operations are fully automated. The output of a typical rotary machine ranges from 3500 to 6000 suppositories.

The machine usually made up of chrome-plated brass molds are installed radially in the cooling turn able

The method of choice for commercial suppository production involves the automated filling of molds or performed shells by a volumetric dosing pump that meters the melt from a jacketed kettle or mixing tank directly into the moldsor shells. Strips of performed shells pass beneath the dosing pump and are filled successively, passed through cooling chambers (to promote solidification), sealed, and then packaged.

Packing of suppositories:

- It can be foiled in aluminum ,plastic, paper, tin strip.
- **Modern packing machine:** nearly 8000 suppositories can be wrapped per hour.
- **In packing molding:** In this ,the suppository mass is directly move into the series of molds which are made up of plastic. After cooling , excess mass is trimmed of . By this technique 12,000 to 15,000 suppositories can be produce per hour.
- **Disposable molds:** They are suitable for tropical climate. They are made up of plastic or aluminum .
- **Labeling:** “store in a cool place.” “Not to be taken orally.”

DISPLACEMENT VALUE:

The Volume of a suppository from a particular mould is always uniform but its weight varies because the densities of the medicaments usually differ from the density of base. Therefore to prepare suppository of uniform and accurate weight, allowance must be made for the change in the mass due to the added medicaments. For this purpose the displacement value of the medicament is taken into consideration.

The Displacement value can be defined as, **The quantity of the drug which displaces one part of the base**. In order to calculate total amount of base required Displacement value of the drug is used by pharmacists and suppository manufacturers.

The displacement value of any given medicament can be calculated by the method below.

Step I: Theoretical weight of total Base required. a gramme

Step II: Theoretical weight of total drug required say 40%. b gramme

Step III: Amt of Base present in medicated suppository.

(60/100)*b=c gramme

Step IV: Amt of Drug present in medicated suppository.

(40/100)*b=d gramme

Step V : Amount of base displaced by d gramme of medicament =(a-c) gramme

Displacement Value= d/(a-c)

Q. Calculate the displacement value of zinc oxide in theobroma oil suppository containing 40% zinc oxide prepared in a 1 gm mould. If it is known that 8 suppositories weigh 11.74 g?

Q. Prepare and Dispense Iodoform Suppository containing 0.9 gm of iodoform, prepared in cocoa butter. The suppository must be of 2gm and 10 suppositories are to be prepared. Displacement Value of Iodoform is 4.0.

Problem 1. Calculate the displacement value of ZnO in theobroma oil suppository containing 40% of ZnO, prepared in 1gm mould. 8 suppository weighs 11.74 gm.

Weight of 8 suppository (Theobroma oil) = a = 8×1 = 8gm.

Weight of 8 suppository (ZnO) = b = 11.74gm.

Amt. of theobroma oil in 8 suppository = $c = \frac{60}{100} \times 11.74$

$= 7.044$ gm.

Amt. of ZnO in 8 suppository = $d = \frac{40}{100} \times 11.74$

$= 4.696$ gm.

Amt of theobroma oil displaced by 4.696 gm of medicament = a - c

$= 8 - 7.044$

$= 0.956$ gm.

Displacement value = $\frac{4.696}{0.956} = 4.912$.

$\left(\text{i.e.} \Rightarrow \frac{d}{a-c}\right)$

Problem 2. Prepare and dispense Iodoform suppository containing 0.9gm of Iodoform, in cocoa butter. Suppository must be of 2gm and 10 suppositories must be prepared. Displacement value of iodoform is 4.0.

Weight of cocoa butter for 10 suppository = $2 \times 10 = 20$gm.

Weight of iodoform for 10 suppository = $0.9 \times 10 = 9$gm.

Displacement value = 4.0.

Amt. of base displaced = $\frac{9}{4}$

$\Rightarrow 2.25$gm.

Qty of cocoa butter = $20 - 2.25$

$= 17.75$gm.

Formula = Iodoform = 9.0gm.

cocoa butter = 17.75gm.

Evaluation:

The various evaluation tests for suppositories are:

1. Test of appearance

All the suppositories should be uniform in size and shape. They should have elegant appearance. Individual suppositories should be examined for cracks and pits due to entrapment of air in the molten mass.

2. Test of physical strength

In this test, tensile strength of suppositories is measured to assess their ability to withstand the rigors of normal handling.

The apparatus used is called as breaking test apparatus. It consists of a double-wall chamber. Through the walls of the chamber, water is pumped. The inner chamber consist of a disc which holds the suppositories. To this disc, a rod is attached. The other end of the rod consists of another disc on which weights are placed.

Procedure

On the first disc the test suppository is placed. On the second disc a 600 g weight is placed. At 1 minute interval, 200 g weights are added till the suppository crumbles. All the weights used are added which gives the tensile strength. Likewise, few more suppositories are tested and the average tensile strength is calculated. Tensile strength indicates the maximum force which the suppository can withstand during production, packing and handling. Large tensile strength indicates fewer tendencies to fracture.

3. Test of dissolution rate

It is the amount of dosage form that gets dissolved in body fluid in unit time. It is a measure of the rate of drug release from the suppository.

Two types of apparatus are available for testing the dissolution rate. They are:

(a) **Suppository dialysis cell** - Lipophilic suppositories are tested using suppository dialysis cell, which is also called as modified flow-through cell.

(b) **Stationary basket** - Rotating paddle apparatus (USP dissolution test apparatus). Hydrophilic suppositories are tested using stationary basket - rotating paddle apparatus.

4. Test of melting range

It is a measure of the thermal stability of the suppository.

It is the time taken by the entire suppository to melt in a constant temperature water bath. The test is conducted using the tablet disintegration apparatus. The suppository is immersed in a constant water bath. Finally the melting range is recorded.

5. Test of softening time

Softening time is the time for which the suppository melts completely at a definite temperature. This test measures the softening time of suppositories which indicates the hardness of the base.

Method

The apparatus consists of a cellophane tube tied at the two ends of a condenser. The two ends of the cellophane tube are open. Water is circulated through the condenser at a definite rate. As a result, after some time the upper half of the tube opens wide and the lower half collapses. A suppository is dropped into the water in the condenser. The time period in which the suppository melts completely is noted as the softening time.

6. Test of uniformity of drug content

This test is to assess the uniformity of the mixed suppository mass. Different suppositories are assayed for the drug. All the suppositories should contain the same labeled quantity of the drug.

7. Test of drug uptake

Both in-vitro and in-vivo tests should be conducted to assess the amount of drug absorbed into the systemic circulation.

(a) **In-Vitro test**

The test conditions should be similar to those inside the human body. The dissolution apparatus is used which consists of simulated gastric and simulated intestinal fluids. Definite number of suppositories are placed in the apparatus. Aliquot portions of the dissolution medium are withdrawn at definite intervals of time and drug uptake is measured.

(b) **In-Vivo test**

This test is carried in animals or human volunteers. The suppository is placed in the intended body cavity. At regular intervals of time, blood samples are collected and the amount of drug present is determined.

PHARMACEUTICAL INCOMPATIBILITIES

Definition

When two or more ingredients of a prescription are mixed together the undesired change that may take place in the physical, chemical or therapeutic properties of the medicament is termed as *incompatibility*.

Classification

Incompatibilities are of three types:

1. Physical incompatibility
2. Chemical incompatibility
3. Therapeutic incompatibility

PHYSICAL INCOMPATIBILITY

Usually, this is due to immiscibility or insolubility. It can cause unsightly, non-uniform products from which removal of an accurate dose is very difficult.

Classification:

(A) Immiscibility

(B) Insolubility

(C)Liquefaction

(A) <u>Immiscibility</u>

1) Oils are immiscible with water and hence combination of oily drugs with water produces a product possessing two separate layers.

Remedy: This problem can be overcome by emulsification or solubilization.

2) Care must be taken when concentrated hydroalcoholic solutions of volatile oils such as *spirits and concentrated waters,* are used as adjuncts (e.g. as flavouring agents) in aqueous preparations. Large globules of oils may be separated.

Remedy: To prevent the formation of large globules, the hydroalcoholic solution should either be gradually diluted with the vehicle before admixture with the remaining ingredients or poured into the vehicle with constant stirring.

3) Addition of high concentrations of electrolytes to mixture in which the vehicle is a saturated aqueous solution of a volatile oil causes the oil to separate and collect as a surface layer.

e.g. This happens in *Potassium Citrate Mixture B.P.C.* in which large quantity of soluble solids salts out the lemon oil.

Remedy: To disperse the droplets evenly, quillaia tincture is added as a wetting agent.

(B) Insolubility

1) Liquid preparations containing indiffusible solids such as chalk, aromatic chalk powder, succinyl sulfathiazole and sulphadimidine (in mixtures) and calamine and zinc oxide (in lotions) tend to separate out - a thickening agent is necessary to obtain a uniform product from which uniform doses can be removed.

2) Some insoluble powders such as sulphur and certain corticosteroids (*hydrocortisone acetate*) and antibiotics are difficult to wet with water.

Remedy: Wetting agents

e.g. *saponins* for sulphur containing lotions

and *polysorbates* in parenteral suspensions of corticosteroids and antibiotics are used to distribute the powder and prevent formation of a slowly dispersing, solid stabilised foam on shaking.

3) When a resinous tincture is added to water the water insoluble resin agglomerate forms indiffusible clots.

Remedy: This is prevented by slowly adding the undiluted dispersion of protective colloid (*Tragacanth mucilage*).

e.g. Lobelia & Stramonium tincture which should be mixed with tragacanth mucilage and stirred constantly. This will produce a stable preparation.

4) High concentrations of electrolytes cause cracking of soap emulsions by salting out the emulsifiers.

C) Liquefaction

When certain low melting point solids are powdered together a liquid or soft mass is produced due to lowering of the melting point of the mixture to below room temperature. Thus an **eutectic mixture** is formed

Any two of the following exhibits this type of behaviour, camphor, menthol, phenol, thymol and chloral hydrate, also sodium salicylate with phenazone.

e.g. Rx

Thymol	250 mg
Camphor	2 mg
Menthol	2 mg

Make powder.

Comments: If these ingredients are triturated together, they will form an eutectic mixture.

Method-I:

All the ingredients are triturated.

An eutectic mixture (liquid) will be formed. The liquid is triturated with enough absorbent powder e.g. light kaolin or light magnesium carbonate, to give a free flowing powder.

Method-II:

Each ingredient is triturated separately with small amount of adsorbent or diluent and then these powders are lightly mixed (by tumbling action) and packed.

The diluent largely prevents contact between the ingredients and adsorbs any liquid that may be produced.

e.g. Rx

Chloral hydrate	250 mg

Prepare capsules. Supply 10 capsules.

Label: Take the capsules at night time.

Comment: Chloral hydrate is hygroscopic in nature. It will absorb moisture and soften the hard gelatin capsule shells and the shape of the capsule may change physically.

Remedy: An equal quantity of light magneisum oxide should be mixed with chloral hydrate.

Other adsorbents those may be used are kaolin, talc, starch etc.

CHEMICAL INCOMPATIBILITY

Chemical incompatibilities are generally caused by pH change, a double decomposition reaction or complex formation.

Precipitate yielding interactions

Two ingredients may produce precipitation after reaction in a solution.

Solubility of the unionized acid or base

1. Alkaloids
2. Other weak bases
3. Barbiturates
4. Other weak acids

1. ALKALOIDS

- Alkaloids are weak bases. They are almost insoluble in water.
- Salts of alkaloids are soluble in water.
- If these salts are dispensed with alkaline preparations or substances then free alkaloid may be precipitated.

The alkaline preparations those are generally incorporated with alkaloidal salt solutions are

(i) Aromatic Ammonia Solution
(ii) Strong Ammonium Acetate Solution
(iii) Ammonium bicarbonate
(iv) Sodium bicarbonate

However, if the alkaloidal salts are taken in low concentration then this problem does not occur because all alkaloids (free base) are slightly soluble in water.

e.g. *Nux vomica and Alkali Mixture*

2. BARBITURATES

The derivatives of barbituric acid are almost insoluble in water, but their sodium salts are soluble. These soluble salts are occasionally prescribed in mixture (liquid).

Incompatibility Solutions of the salts are very alkaline and are incompatible with
acids,
acidic salts (e.g. ammonium bromide) and
acidic syrups (e.g.. lemon syrup)

In presence of these acidic ingredients the insoluble barbituric acid derivative will precipitate. This precipitate can neither be re-dispersed nor suspended satisfactorily with thickening agents.
Remedy When precipitation is likely, it is preferable to substitute the chemically equivalent amount of the corresponding insoluble barbituric acid derivative which can be suspended easily with thickening agent.

3. OTHER WEAK ACIDS

Sulfonamides are weak acids in unionized form and their solubility is less.
Incompatibility In presence of acid or acidic salts the unionized form may be precipitated.
Remedy Sulfonamide salts and the acidic ingredients are dissolved in separate amount of vehicle. With one portion tragacanth mucilage is prepared and the other portion is suspended in it.

Double decomposition

1. ALKALOIDAL SALTS WITH SOLUBLE IODIDES

Alkaloidal salts will react with soluble iodides and may precipitate insoluble iodide salts of alkaloids.

Alklaoidal salts	Soluble iodide
Emetine hydrochloride Methadome hydrochloride Strychnine hydrochloride Papaverine hydrochloride	Potassium iodide

Incompatibility

Emetine-HCl + KI $\rightarrow$ Emetine-HI + KCl

Solubility of Emetine-HI is less hence may precipitate.
Example: Potassium iodide is used as expectorant in some alkaloid containing cough mixtures.
Remedy: If the alkaloid concentration is very low then precipitation does not occur.

2. ALKALOIDAL SALTS WITH TANNINS

Incompatibility:

Alkaloidal salts + tannins $\rightarrow$ Alkaloidal tannates$\downarrow$

N.B. One advantage of this reaction is in case of alkaloidal poisoning strong tea (or tannic acid solution) is used to precipitate the alkaloids.
Remedy: Method-B (suspended with the help of tyragacanth mucilage) is used to suspend the precipitate.

3. SOLUBLE BARBITURATES WITH AMMONIUM BROMIDE

Incompatibility

e.g. Phenobarbitone-Na + NH_4Br $\rightarrow$ Phenobarbitone$\downarrow$ + NaBr + NH_3.

Remedy: NH_4Br is an acidic salt; i.e. it is providing the necessary H^+ to phenobarbitone-Na. So NH_4Br is replaced with sodiumbromide (NaBr).
N.B. Phenobarbitone is barbituric acid derivative. Bromide ion (Br^-) has sedative action.

4. GAS PRODUCTION

Incompatibility

Carbonates + Acid or $\rightarrow$ $CO_2\uparrow$
Or, bicarbonates acidic drugs

Remedy:
The ingredients are mixed in a wide mouthed mortar and left until effervescence has ceased. If the rate of reaction is slow it is hastened by using hot vehicle.

THERAPEUTIC INCOMPATIBILITY

Usually this incompatibility arises when one or more drugs produces response or intensity different from that intended in the patients.

Classification

A) Over doses

B) Under doses

C) Improper consumption by the patient

D) Contra-indicated drugs

A) Over doses: This can be subgrouped as follows:

Excessive single dose

Sometimes a single dose may become overdose depending on the health of the patient e.g. a normal dose (taking body weight as 70 kg for an adult male) may be overdose for a lowly built person. However it should not be more than 2 to 3 normal dose.

Remedy: The pharmacist should consult the physician and clarify the dose.

e.g. 1 Rx

Atropine sulphate	6 mg
Phenobarbital	360 mg

Make capsules.

Label: One capsule to be taken three times a day before meals.

Comments: In this prescription the doses of both atropine sulphate and phenobarbital are 12 times the normal doses. The physician intended for 12 capsules to be dispensed but he has mistaken or may be it is an incomplete prescription. Hence, before dispensing the pharmacist should consult the physician again.

Correct prescription

Rx

Atropine sulphate	6 mg
Phenobarbital	360 mg

Make capsules. Supply 12 capsules.

Label: One capsule to be taken three times a day before meals.

e.g. 2 Rx

Strychnine sulphate	20 mg
Iron and ammonium citrate	500 mg

Prepare capsules. Supply 12 capsules.

Label: One capsule to be taken three times a day after meals.

Comment: 10 times overdose of strychnine hydrochloride than that of normal. The pharmacist should consult the physician and obtain the permission to change the dose.

Corrected prescription

Strychnine sulphate	2 mg
Iron and ammonium citrate	500 mg

Prepare capsules. Supply 12 capsules.

Label: One capsule to be taken three times a day after meals.

Excessive daily dose

In this case the daily dose of drug is exceeded .

e.g.1 Rx

Codeine phosphate	15 mg
Ammonium chloride	500 mg

Prepare capsules and supply 24 capsules.

Label: Two capsules to be taken every hour for cough.

Comment: The U.S.P. recommends that the prescribed dose should be taken after every four hours and not every hour. Hence the physician should be consulted.

Additive and synergistic combinations:

There are certain drugs possessing similar pharmacological activity. If these drugs are combined together, they may produce additive or synergistic action. In such case advice of the physician is necessary.

e.g. Rx

Amphetamine sulphate	20 mg
Ephedrine sulphate	50 mg
Syrup q.s.	100 ml

Let a mixture be made

Label: Take 25 ml every four hours.

Comment: Both of the drugs are sympathetic stimulants and they are prescribed in their full dose. The formulation will produce additive overdose effect. Hence, The dose of individual drug should be reduced.

(B) Under dose In this type of incompatibility, effect of one drug is lessen or antagonised by the presence of another drug. This can be exemplified by combination of following types of drugs:

1. **Stimulants** like nux-vomica, strychnine sulphate, caffeine etc. with **sedatives** like barbiturates, paraldehyde etc.
2. **Sympathomimetic** or **adrenergic** like ephedrine, nor-adrenaline with **sympatholytic** drugs like ergotamine.
3. **Sympathetic stimulants** like methamphetamine with **parasympathetic stimulants** like pilocarpine.
4. **Purgatives** like castor oil, liquid paraffin etc with **antidiarrheal** agents like bismuth carbonates.
5. **Acidifiers** like dilute hydrochloric acid and **alkalisers** like sodium bicarbonate, magnesium carbonate.

e.g. Rx

Aspirin 300 mg

Probenecid 500 mg

Prepare capsules.

Label: One capsule a day for gout.

Aspirin is an NSAID given to reduce the pain and swelling in case of gout attack. Probenecid blocks the active reabsorption of uric acid from the lumen of nephron, but salicylates (aspirin) blocks this action of probenecid. Hence, both of the drugs are antagonistic to each other, so its combination is therapeutically useless.

(C) Improper consumption by the patient:

In certain prescription some special directions should be written. If the patients are nor advised the drugs may not produce the desired action due to low bioavailability.

e.g. Rx

Tetracycline hydrochloride 250 mg

Prepare capsules. Supply 10 capsules.

Label: Take one capsule every six hourly.

Comments: Calcium present in milk inactivates the tetracycline, hence a patient may not get any therapeutic effect if he/she takes the capsule with milk.

Remedy: The pharmacist should advise the patient to take the capsule with water and not with milk. The patient should not take antacid containing calcium salts.

(D) Contra-indicated drugs

Certain drugs should not be given in particular disease condition

e.g.

(i) corticosteroids are contraindicated in patients with peptic ulcer.

(ii) Vasoconstrictors are contraindicated in hypertensive patients

(iii) Some drugs should not be given in asthmatic patients e.g. barbiturates, morphine etc.

(iv) If a person is allergic to a drug (e.g. penicillin injection) then it should not be given to the patient.

(v) Certain combination of drugs are contraindicate:

Rx

Sulphadiazine	0.25 g
Sulphamerazine	0.25 g
Ammonium chloride	0.50 g

Prepare capsules

Label: Take two capsules six hourly for cough.

Comment: In this prescription ammonium chloride is a urinary acidifier and it could cause deposition of sulphonamide crystals in the kidney.