A REVIEW ON MANUFACTURING AND EVALUATION OF PARACETAMOL TABLETS.

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Abstract

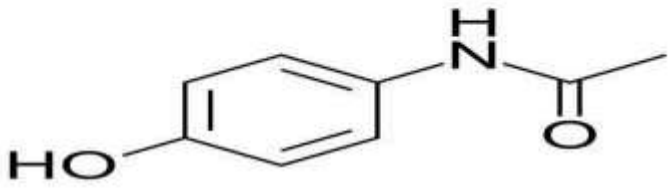
N-acylated aromatic amines (those having an acyl group, RCO- substituted on nitrogen) are important inover-the-counter headache remedies. Over-the-counter drugs are those you may buy without a prescription. Paracetamol is virtually the sole survivor of the so-called “aniline derivatives” or “aniline analgesics” which are; acetanilide, phenacetin and paracetamol (acetaminophen). Phenacetin and paracetamol are both derivatives of acetanilide. Paracetamol which is also referred to as 4-hydroxyacetanilide or para-hydroxyacetanilide to an Industrial Chemist is an important end product as well as an important precursor used in the synthesis of some other Organic compounds. As an analgesic it has gained fame because it is readily available but then its adverse effect stands pronounced when it’s not taken in its rightful dosage or when it is taken in addition to some other food or drug. This article talks about the historical changes this important compound has undergone till date, its preparation by the chemist, some reactions it undergoes in the presence of some other precursors, its Dozage, Its adverse effect as well as its usage. This is a very helpful drug which becomes a poison in the presence of other drugs such as warfarin and care should be taken when handling this drug. Paracetamol / acetaminophen is one of the most popular and most commonly used analgesic and Antipyretic drugs around the world, available without a prescription.

Keywords: Paracetamol granules, Acetaminophen,compression, friability, NSAIDS , weight variation, Hardness , Disintegration.

Introduction:-

Tablets are prepared by forcing particles into close proximity to each other by Powder compression, which enables the particles to cohere into a porous, solid specimen Of defined geometry. The compression takes place in a die by the action of two punches, The lower and the upper, by which the compressive force is applied. Powder compression Is defined as the reduction in volume of a powder owing to the application of a force. Because of the increased proximity of particle surfaces accomplished during compression, Bonds are formed between particles which provide coherence to the powder, i.e. a Compact is formed. Compaction is defined as the formation of a solid specimen of Defined geometry by powder compression.Acetanilide, phenacetin, and acetaminophen are mild Analgesics and antipyretics and are important, along with Aspirin, in many non-prescription drugs.The discovery that acetanilide was an effective antipyretic Came about by accident in 1886. At the University of Strassburg, Professor Kussmaul, of the Department of Internal Medicine, asked two assistants to give naphthalene as a Treatment for intestinal worms. Cahn and Hepp, who had been Testing naphthalene as a possible vermifuge (an agent that Expels worms) by accident, mixed up a bottle of acetanilide And the bottle of naphthalene. The patient’s worms didn’t Disappear but his fever did – dramatically. In another instance Of serendipity, it was soon in production and remained in use For several years because it was so cheap to produce. However, It had a serious side effect involving the deactivation of some Of the hemoglobin in red blood cells. However, restrictions Have been placed on its use due to kidney damage

in long-term Users. The publication of Cahn and Hepp describing their Experiments with acetanilide caught the attention of Carl Duisberg, director of research at the Bayer Company in Germany. Duisberg was confronted with the problem of Profitably getting rid of nearly 50 tons of p-aminophenol; a By-product from the synthesis of one of Bayer's other Commercial products. He immediately saw the possibility of Converting p-aminophenol to a compound similar in structure To acetanilide, by putting an acyl group on the nitrogen. It was Then believed, however, that all compounds having a hydroxyl Group on a benzene ring (that is, phenols) were toxic. Duisberg Devised a scheme of structural modification of p-aminophenol To get the compound phenacetin. Phenacetin turned out to be a Highly effective analgesic and antipyretic. A common form of Combination pain reliever, called an APC tablet, was once Available. An APC tablet contained Aspirin, Phenacetin, and Caffeine (hence, APC). Phenacetin is no longer used in Commercial pain-relief preparations. It was later found that Not all aromatic hydroxyl groups lead to toxic compounds, and Today the compound acetaminophen is very widely used as an Analgesic in place of phenacetin. 'Acetaminophen' (4-acetamidophenol) is sold as the over-the-counter analgesic "Tylenol".[1,2,3]

- 

Paracetamol
Acetaminophen

$C_8H_9NO_2$

- **Types of Tablets**

1. On the basis of drug release tablets

(a) Immediate release tablets

(b) Modified release tablets

• Extended release tablets Delayed release tablets

II. On the basis of methods of manufacturing

• Compressed tablets Molded tablets

III. On the basis of route of administration

(a) Oral tablets for ingestion:

1. Compressed tablets

2. Multiple compressed tablets

3. Delayed action tablets

4. Sugar coated tablets

5. Film coated tablets

6. Chewable tablets

7. Targeted tablet

- Floating tablet
- Colon targeting tablet

8. Dispersible tablets:

(b) Tablets used in oral cavity.

1. Buccal tablets

2. Sublingual tablets

3. Troches and Lozenges

4. Dental cones

(c) Tablets administered by other routes

1. Implantation tablets (or depot tablets)

2. Vaginal tablets (or vaginal insert)

IV. On the basis of types of dosage form ingested

(a) Tablets used to prepare solution
    1. Effervescent tablets
    2. Dispensing tablets
    3. Hypodermic tablets
    4. Tablet triturates
(b) Tablets used as such
    Example: Remaining all.

1.Compressed tablet: These tablets are uncoated, made by compression of granules and usually intended to provide rapid disintegration and drug release. These tablets, after swallowing, get disintegrated in the stomach, and its drug contents are absorbed in the gastrointestinal tract and distributed in the whole body.

2.Multiple compressed tablets: These tablets are prepared to separate incompatible (physically or chemically) ingredients or to produce repeat action/prolonged action products.Repeat action tablet: Repeat-action tablets are a type of extended-release dosage form which contain two single doses of medication, one for immediate release and one for delayed release. Typically, the immediately released drug comes from the exterior portion of the tablet and the delayed release coming from the interior portion. Essentially, there is a tablet within a tablet, with the interior tablet having a coating that delays release of its contents for a predetermined time.

3.Delayed release tablet: These are the dosage forms which release a portions of drug at a time other than promptly after administration. An initial portion may be released promptly after administration. Enteric-coated dosage forms are common delayed-release products. Sugar coated tablet: The tablet that contains active ingredient(s) of unpleasant taste may be covered with sugar to make it more palatable. This type of tablet should be administered in whole form, otherwise the patient will experience the unpleasant taste of the active ingredient.

4.Film coated tablet: The tablet that is covered with a thin layer or film of polymeric substance which protects the drug from atmospheric conditions and mask the objectionable taste and the odor of drug.

5.Buccal tablet: "Buccal tablets", which means that instead of being swallowed like a normal tablet, they should be dissolved in the mouth. They should not be swallowed whole or chewed. The tablet is placed high up along your top gum, under the upper lip either side of your mouth. The tablet will soften and stick to the gum, and will dissolve completely after a few hours.

6.Sublingual tablet: The drug which is destroyed or inactivated within the gastrointestinal tract but can be absorbed through the mucosal tissue of the oral cavity is usually given in this formulation. The tablet is required to be placed below the tongue for the slow release of drug. But for immediate effect some medicaments are formulated in such a way to dissolve within 1 to 2 minutes. Nitroglycerin is prepared in this formulation.

7.Troches or lozenges: Lozenges are solid preparations that are intended to dissolve or disintegrate slowly in the mouth. They contain one or more medicaments usually in a flavored, sweetened base. Lozenges are most often used for localized effects in the mouth. They can also be used for systemic effect if the drug is well absorbed through the buccal lining or is swallowed. Lozenges can be made by molding or by compression. The name troche is applied to compressed lozenges.

8.Dental cone: A tablet form intended to be placed in the empty socket following a tooth extraction, for preventing the local multiplication of pathogenic bacteria associated with tooth extractions. Implantation tablets: A small tablet that is prepared for insertion under the skin by giving a small surgical cut into the skin which is stitched after the insertion of the tablet. This tablet must be sterile one. The drug used in this preparation is usually water insoluble and the tablet provides a slow and continuous release of drug over prolonged period of time ranging from 3 to 6 months or even more. Contraceptive tablet is formulated as implant.

9.Vaginal tablet/Pessary: Pessaries are solid medicated preparations designed for insertion into the vagina where they melt or dissolve. Moulded pessaries are cone shaped and prepared in a similar way to moulded suppositories. Compressed pessaries are made in a variety of shapes and are prepared by compression in a similar manner to oral tablets.

10.Effervescent tablets: The tablet that contains acid substances and carbonate or hydrogen carbonate that react rapidly in the presence of water to release carbon dioxide. Sodium bicarbonate, citric acid and tartaric acid are added to the active ingredients to make the tablet effervescent. This preparation makes the tablet palatable.

11.Dispensing tablet: These tablets are prepared for providing an accurate and convenient quantity of drug that can be incorporated readily in compounding other dosage form. Tablets are solely designed to provide a convenient quantity for administration as a dosage form, because sometimes they contain very potent drugs which may prove fatal.

12.Hypodermic tablet: It is a compressed or molded water-soluble tablet that contains a specified amount of medication and is intended for hypodermic administration, Tablet triturate: These are powders moulded into tablets. Moulded tablets are flat, circular disc and usually contains a potent substance which is mixed with lactose, dextrose or some other suitable diluent. The apparatus used for the preparation of tablet triturates is made of stainless steel or plastic.[4]

Procedure for tablet preparation :-

- **Wet Granulation Method :-**

1. Weigh and pass paracetamol powder through 100# sieve.

2. Mix paracetamol and starch powder uniformly in mortar and pestle.

3. Prepare 10% starch paste in boiling water and stir until it becomes translucent.

4. Add starch paste dropwise in mortar to get cohesive mass. Record quantity of starch paste used for granulation.

5. Screen prepared cohesive mass through 12# granulating sieve and collect it on granulating tray.

6. Dry granules in tray at 500C for 30 min. Pass 50 % dried granules through 16# sieve to get uniform particle size and continue drying for 30 min.

7.Weigh granules equivalent to 500 mg of paracetamol.

8.Check setting for the tablet machine. Fill weighed granules into the die cavity.

9.Apply optimum pressure on upper punch so as to granules gets compressed.

10.After compression eject the prepared tablet and subjected to hardness test.

11.If tablet have sufficient hardness then repeat the procedure to prepare next tablet.[5]

Sr no.	Ingredients	Quantity given (1 tablet)	Quantity Taken (40 tablets)	Role of ingredients
1.	Paracetamol I. P	500 mg	20gm	Antipyretic, Analgesics
2.	Starch Paste	10 %	10ml	Binding Agent
3.	Starch Powder	12.5 mg	0.25gm	Binding agent

4.	Magnesium stearate	5%	5gm	Lubricant
5.	Talc	1%	1gm	Glidant
6.	Methyl Paraben	0.01%	0.01gm	Preservative

(I) **Binders (or adhesives):** Binders or adhesives are the substances that promote cohesiveness. It is utilized for converting powder into granules through a process known as Granulation.

- **Commonly used binders are:** Acacia, Tragacanth, Methyl cellulose, Hydroxy propyl methyl cellulose, Starch paste, Sodium alginate etc.
- **Direct compression (DC) Binders:** Directly compressible binders are required in direct Compression of tablets. It exhibit adequate powder compressibility and flowability. Examples: Microcrystalline cellulose, pregelatinized starch etc.

(II) Disintegrants:

Disintegrants are agents added to tablet (and some encapsulated) formulations to promote the breakup of the tablet (and capsule "slugs") into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. Examples of disintegrants are Microcrystalline cellulose, Starch 1500, Methyl cellulose etc.

- Super Disintegrants: These derivatives are developed to have greater effectiveness even at low concentrations. Super-disintegrants function principally by swelling on absorbing water. It swells upto ten fold within 30 seconds when it comes in contact with water. Examples: Crosscarmellose, cross-linked cellulose etc.

(III) Lubricant and Glidants :-

- Lubricants are intended to prevent adhesion of the tablet materials to the surface of dies and punches, reduce inter particle friction and may improve the rate of flow of the tablet granulation. Examples: Magnesium stearate, Talc etc.

(IV) Preservatives :-

- Methyl paraben is a type of paraben. Parabens are chemicals that are often used as preservatives to give products a longer shelf life. They're added to food or cosmetics to prevent the growth of mold and other harmful bacteria.
  Example :- Methyl Paraben, propyl Paraben. [6]

Process of tablet formation can be divided into three stages :-

- **Die filling**

This is normally accomplished by gravitational flow of the powder from a hopper via the die table into the die. The die is closed at its lower end by the lower punch.

- **Tablet formation**

The upper punch descends and enters the die and the powder is compressed until a tablet is formed. During the compression phase, the lower punch can be stationary or can move upwards in the die. After maximum applied force is reached, the upper punch leaves the powder, i.e. the decompression phase.

- **Tablet ejection**

During this phase the lower punch rises until its tip reaches the level of the top of the die. The tablet is subsequently removed from the die table by a pushing device.

- **Single punch tablet machine**

A single-punch press possesses one die and one pair of punches. The powder is Held in a hopper which is connected to a hopper shoe located at the die table. The hopper Shoe moves to and fro over the die, by either a rotational or a translational movement. When the hopper shoe is located over the die, the powder is fed into the die by Gravitational powder flow. The amount of powder filled into the die is controlled by the Position of the lower punchy. When the hopper shoe is located beside the die, the upper Punch descends and the powder is compressed. The lower punch is stationary during Compression and the pressure is thus applied by the upper punch and controlled by the Upper punch displacement. After ejection, the tablet is pushed away by the hopper shoe as It moves back to the die for next tablet.[7]

- **Prerequisite**

1. Compression

2. Compaction

3. Consolidation

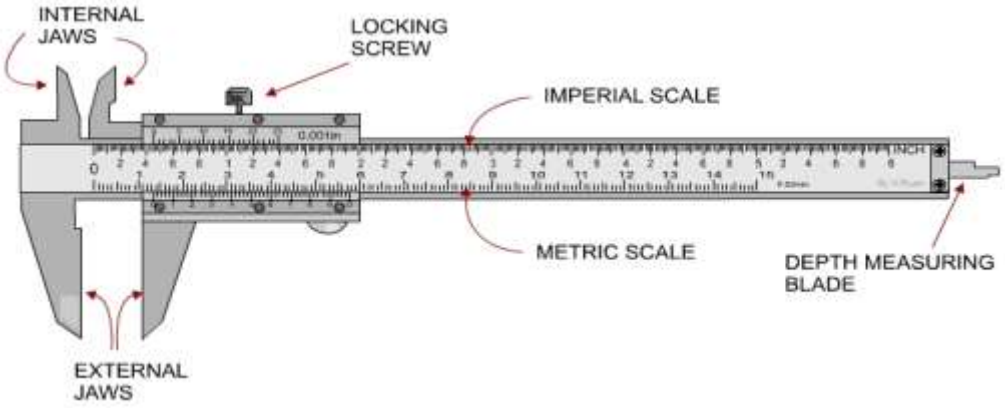
4. Deformation

Evaluation of Paracetamol Tablets :-

1.Physical Properties :- [3]

Parameters	Observations
Colour	**White**
Odour	**Odourless**
Taste	**Slightly Bitter**

2. Thickness and Diameter by vernier calliper



Tablet thickness should be controlled within 5% or less of a standard value. The crown thickness of individual tablets is measured with a micrometer. The crown thickness of individual tablets is also determined for the purpose of determining the density of tablet compacts. Mostly tablet have uniform diameter unless they have prepared by using different dies. Small variation in tablet thickness and diameter significantly affects hardness and dissolution profile of tablet. The tablet diameter and thickness is measured by using vernier calliper. Least count of measuring instrument is the ratio of smallest division on main scale and total number of divisions on vernier scale or thimble scale.[8]

3. Hardness of paracetamol tablets (Mosanto Hardness Tester)

Hardness is a force required to break a tablet across the diameter. The hardness of the tablet is an indication of its strength. This is a valuable test which might influence tablet disintegration and dissolution rate.The test measures crushing strength property defined as the compressional force Applied diametrically to a tablet which just fractures it. Hardness is a property which is Dependent on density and porosity of the material on one hand and pressure of the Compression on the other. The resistance of tablet to chipping, abrasion or breakage Under condition of storage, transportation and handling factor before use depends on Hardness of tablet. Hardness adjustments are made throughout tablet run to determine the Need for pressure adjustment for tableting machine. If tablet is too hard, it will into Disintegrate, will require period of time or meet the dissolution specification. If too soft, it Will not

withstand during subsequent processing such as coating, packaging and Transportation. There are no hard and fast

rules about hardness of tablets but from practical point of view degree of hardness that does not interfere with their disintegration time is considered suitable. Generally a hardness of 5 kg is taken as minimum of uncoated tablets for insuring mechanical stability. Among a large number of measuring devices, the most favored ones are Monsanto tester, Pfizer tester, and Strong cobb hardness tester.The principle of measurement involves subjecting the tablet to an increasing load untilthe tablet breaks or fractures. The load is applied along the radial axis of the tablet. Oral tablets normally have a hardness of 4 to 8 or 10 kg; however, hypodermic and chewable tablets are much softer (3 kg) and some sustained release tablets are much harder (10-20 kg).[9]

4. Weight Variation of Paracetamol tablets

The test ensures that all the tablets in a batch are of same potency, within reasonable limits. Weight variation may basically occur due to the depth of the die cavity, bulk density of granules or powder, uniformity of particulate flow, wide variation in granule size and improper lubrication. Even with a proper granulation having uniform flow, a volume fill is not as accurate as a fill based on weight. Therefore, tablet weight variations must fall within certain specifications established by the IP.Each tablet in a batch should be uniform in weight and the weight variation if any, should be generally within □10% for tablets weighing 80 mg or less, □7.5% for tablets weighing more than 80 mg and up to 250 mg, and □5 % for tablets weighing 250mg or more.Hence, all finished batches, 20 tablets are weighed collectively and individually. From the collective weight average weight per tablet is calculated. The weights of individual tablets are the compared to ascertain whether they are within permissible limits or not.[10]

5. Friability Test of Paracetamol tablets by Roche friabalator

Roche friability (D.R. Jadge et al.,2014) is used to measure the friability of the tablets. It rotates at rate of 25 rpm. 10 Tablets are weighed collectively and placed in the chamber of the friability. In the friabilator the tablets are exposed to Rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotation (4 minutes) the

tablets Are taken out from the friabilator and intact tablets are again weighed collectively. Percentage friability is determined by Using this following formula.

Friability = (W1-W2/W1) *100

Where as W1= weight of the tablets before test

W2= weight of the tablet after test. [11]

6. Disintegration Test of Paracetamol tablets

Boavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physical – chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet.The drug will dissolve at a slower rate from a nondisintegrating tablet due to exposure of limited surface area to the fluid. The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration.Disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants.Disintegration is defined as the state in which any residue of the tablet, except fragments of insoluble coating remaining on the screen of the test apparatus consists of a soft mass having no palpably firm, unmoistened core. This disintegration test is provided to determine whether tablets disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions. The apparatus consists of a basket rack assembly supporting six glass tubes. These tubes are held vertically by two superimposed transparent plastic plates with six holes having same diameter as the tubes. Woven wire gauge made os stainless steel is attached to the underside of the lower plate. The upper and the lower plates are held in position by vertical metal rods at the periphery and a metal rod in the centre of the upper plate for attachment to mechanical device. The assembly should be raised and lowered between 28 to 32 times per minute in the liquid at 37°C.[12]

7. Dissolution Test of Paracetamol tablets

Dissolution means mass transfer from the solid surface to the liquid medium. Dissolution test is intended to measure the time required for given drug in oral solid dosage form into solution under a specific set of conditions and all particles to pass through mesh-10 screen. This test is performed in two ways ie. in-vivo and in-vitro:

• In-vivo dissolution test is performed in healthy living subjects.

• In-vitro dissolution test is performed in a dissolution apparatus under stimulated biological conditions.[13]

Pharmacological Activity of Paracetamol Tablets :-

1.Fever and Body Temperature

It is well known that paracetamol is antipyretic. It reduces fever in multiple species. A central site of antipyretic action against induced fever was demonstrated in rabbits by direct injection into the organum-vasculosum-lamina-terminalis (OVLT) located in the anterior wall of the third intra-cerebral ventricle. It is less well known that paracetamol can also lower a febrile body temperature. For example, several studies, employing different methods and routes of administration, have shown that paracetamol produces hypothermia in mice when the drug is administered intravenously (160mg⁄kg, 2.5°C decrease), intraplantarily (100–300mg⁄kg with 0.4–2°C decrease respectively) or intra-cerebrovascularly (dose, 0.25°C decrease). The data in humans are mixed. Effective and rapid reduction in brain temperature (2°C) was reported with a single 1000 mg dose of paracetamol in patients with subarachnoid haemorrhage or head trauma and oral or suppository paracetamol given 6g daily to stroke patients lowered a febrile body temperature by 0.3°C, a decrease attributed with reducing relative risk by 10–20%. However, oral paracetamol (650–1300mg) was reported to not lower core body temperature in normothermic cardiac or stroke (3900mg daily) patients. Thus, paracetamol-induced hypothermia appears to be clinically insignificant when given at therapeutic daily dose <4g.[14]

2. Inflammation

Paracetamol has been reported to suppress various inflammation-related substances in animals and in inflamed dental tissue (1000 mg pretreatment and 4000 mg post-surgery in patients with two-third molar extractions), but paracetamol is generally not considered to display very effective anti-inflammatory action in the clinical setting. For example, paracetamol given i.p. or orally at 100mg⁄kg (62), i.v. at 100–300mg⁄kg or intrathecally at 200 micro g⁄kg reduced inflammatory pain, but had no effect on edema and in a randomized, double-blind, placebo-controlled trial no significant improvement was seen in the paracetamol (1000mg four times daily) group when assessed 2 and 12 weeks into treatment. The relatively poor anti-inflammatory effect of paracetamol is a characteristic distinction from the NSAIDs and might be a reflection of different mechanism of action.[15]

3. Platelet Aggregation

Because of the common impression that paracetamol lacks clinically relevant anti-platelet action, it is often used to avoid the bleeding risk associated with aspirin and other NSAIDs. There is some evidence of anti-platelet activity of paracetamol in human blood samples using in-vitro and ex-vivo assays, but other studies suggest a lack of anti-platelet action. Such an action, when present, is believed to be reversible (shorter acting), in contrast to the irreversible action of aspirin and NSAIDs. At least two recent clinical trials report that paracetamol did not interrupt platelet aggregation when given at 1000mg (73) or 3000mg i.v. Paracetamol might or might not interact with NSAIDs on this endpoint. The relatively poor inhibition of platelet aggregation by paracetamol is another characteristic distinction from the NSAIDs that might be a reflection of a different mechanism of action.[16]

- **Conclusion:-**

As a result of this study we have concluded that all the six brands of Paracetamol tablets meet the criteria laid in the Official monographs and though they differ slightly in terms of various parameters like weight variation, hardness, Friability, shows its complete release at in the range of 4 to 7 mins. All marketed paracetamol tablets of 500 mg were all Under specified IP limits.Various stories are heard about this very helpful at the Same time deadly drug. While some appreciate it for its Relief of muscle and joint pain, cold and flu symptoms, Common headache, antipyretic, anti-inflammatory functions, Others curse it for its ability to lead to renal and hepatic Complications in the human body. Paracetamol is one drug Known and recognized by many but its chemistry is known By a select

few. This article has brought to light the chemical Properties of Paracetamol which can be used as a pre-cursor In the production of other chemical substances. One of its Chemistry that should be taught to all is the drug interaction Of this very powerful drug. In the presence of other drugs like Warfarin, it causes excessive bleeding; patients should also Stay away from Alcohol when taking this drug. Its adverse Effects that results from overdozage should not be taken Lightly as it can lead to range of sicknesses from skin rashes, Vomiting to even a damaged liver or kidney, therefore the Right dosage should be given to the patient and the patients Should adhere to it.

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