ABSTRACT

The purpose of the review is to formulate and evaluate Allopurinol sustained release matrix tablet using different polymer as a release rate retarding agent which is also Xanthine Oxidase Inhibitors in nature by means of granulation method. The influence of the release rate by different diluents was studied. Formulation containing HPMC K 100 M and Methyl cellulose showed the sustained drug release pattern upto 12 hrs which matched the drug release pattern of innovator. Tablets thus formulated were evaluated for various physical tests like weight variation, hardness, friability and results complied with in the limits. Thus Xanthine Oxidase Inhibitors owing to the presence of its water soluble gummy constituents retards the release of the drug and also possess the antigout activity. Thereby sustained release matrix tablets thus formulated using polymer and Allopurinol exhibits.

KEYWORDS: Allopurinol, Sustained Matrix drug, additive, Xanthine Oxidase Inhibitors.
Factor affecting the design and performance of controlled drug delivery

1. Drug properties
   - Partition coefficient
   - Drug stability
   - Protein binding
   - Molecular size and
   - Diffusivity.

2. Biological properties
   - Absorption
   - Metabolism
   - Elimination and
   - Biological half life
   - Dose size
   - Route of Administration
   - Target sites
   - Acute or chronic therapy
   - Disease condition

Classification of matrix tablets

On the Basis of Retardant Material Used
Matrix tablets can be divided in to 5 types.

1. Hydrophobic Matrices (Plastic matrices):
   In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion.

2. Lipid Matrices
   These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices
   Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

   The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups, A.Cellulose derivatives
   Methylcellulose 400 and 4000cPs, Hydroxyethylcellulose; Hydroxypolymethyl cellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.

   B. Non cellulose natural or semi synthetic polymers:
   AgarAgar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.
   Polymers of acrylic acid: Carbopol-934, the most used variety.

4. Biodegradable Matrices
   These consist of the polymers which comprised of monomers linked to one another through functional
groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices
These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophyceae) by the use of dilute alkali.

On the Basis of Porosity of Matrix
Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Nonporous systems can be identified.

1. Macro porous Systems
In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2. Micro porous System
Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusing molecules size.

3. Non-porous System
Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

Method of Preparation of Matrix Tablet

A. Wet Granulation Technique:
- Milling and mixing of drug, polymer and excipients.
- Preparation of binder solution.
- Wet massing by addition of binder solution or granulating solvent.
- Screening of wet mass.
- Drying of the wet granules.
- Blending with lubricant and disintegrant to produce “running powder”.
- Compression of tablet.

B. Dry Granulation Technique:
- Milling and mixing of drug, polymer and excipients.
- Compression into slugs or roll compaction.
- Milling and screening of slugs and compacted powder.
- Mixing with lubricant and disintegrant.
- Compression of tablet.

C. Sintering Technique
Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat. Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled. The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering. The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release.

Polymers used in matrix tablet

i. Hydrogels
Polyhydroxyethylmethacrylate(PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone(PVP), Polyethylene-oxide(PEO), Polycrystalimide (PA).

ii. Soluble polymers
Polyethylene glycol (PEG), Polyvinyl alcohol(PVA), Polyvinylpyrrolidone (PVP), Hydroxypropylmethylcellulose (HPMC).

iii. Biodegradable polymers
Polyactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters.

iv. Non-biodegradable polymers
Polyethylene vinyl acetate (PVA), Polydimethylsiloxane(PDS), Polyetherurethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).

v. Mucoadhesive polymers
Polycarbophil, Sodium carboxy methyl cellulose, Polycrylic acid, Tragacanth, Methyl cellulose, Xanthan gum, Guar gum, Karaya gum, Locust bean gum.

Evaluations of tablets

Thickness
The thickness of the tablets were determined using a Digital Caliper (Mitutoyo, Digimatic Caliper, New Delhi, India) 20 tablets from each batch were used and average values were calculated.

Weight variation test
To study the weight variation, 20 tablets of each formulation were selected at random and determine their average weight. Not more than 2 of the individual weights may deviate from the average weight by more than the % deviation and none should deviate by more than twice that percentage (Limit for not more than 130 to 324 mg is 7.5 %.).

Drug content
Twenty Tablets were weighed individually and the drug was extracted in water. The drug content was determined by filtering the solution through 0.45 μm. The drug
content was analyzed after suitable dilution by spectrophotometrically at 276 nm.

**Hardness and friability**
For each formulation, the hardness and friability of 20 tablets each were determined using the Monsanto Hardness Tester and Roche Friabilator.

**History of Allopurinol Drug**
Allopurinol is the most frequently used urate-lowering agent that exerts its activity by nonselectively inhibiting xanthine oxidase. It is indicated for the treatment of hyperuricemia in gout, in patients with recurrent flares, tophi, and/or typical radiographic changes. Allopurinol is initiated at a daily dose of 100 mg; the dose is increased every 2-5 weeks until reaching a serum uric acid level <360 μmol/L (6.0 mg/dL). The drug should be continued for a lifelong period because maintaining low-level serum uric acid decreases tophi and the frequency of flares. Allopurinol can be started already during an acute gout attack without the risk of aggravating symptoms. If the attack has already resolved, the drug should be initiated at least 1 week of colchicine or NSAID “priming” to reduce the risk of an allopurinol-induced exacerbation. Despite common practice of reducing the dose in patients with renal insufficiency, formal evidence supporting such an approach is limited. Allopurinol is associated with a low incidence of severe AEs. Increased liver function tests are observed in up to 5% of patients, as well as dose-dependent gastrointestinal and variable CNS side effects. Isolated maculopapular skin rash may be seen in about 2%. An infrequent but severe complication is the allopurinol hypersensitivity syndrome, comprising a desquamative erythematous rash, fever, eosinophilia, and multiple organ damage, including renal and hepatic failure. Most cases occur within 60 days after initiation. Given that azathioprine is metabolized by xanthine oxidase, concurrent treatment with allopurinol should be avoided because of an increased risk of bone marrow suppression. Febuxostat is a selective xanthine oxidase inhibitor used when allopurinol is ineffective or contraindicated, as in renal impairment. Its safety profile is similar to that of allopurinol. The usual daily doses range from 40 to 120 mg.

**CONCLUSION**
Thus Xanthine Oxidase Inhibitors owing to the presence of its water soluble gummy constituent possess the release of the drug and also possess the antigout activity. Thereby sustained release matrix tablets thus formulated using polymer and Allopurinol exhibits additive antigout immunosuppressive activity which can be comparable with the higher dose of allopurinol resulting in reduction in dose of allopurinol and there by its dose related side effects.

**REFERENCES**