ejpmr, 2021,8(6), 175-179

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ON FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF ALLOPURINOL

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Article Received on 25/03/2021 **Article Revised on 15/04/2021** **Article Accepted on 05/05/2021**

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.

INTRODUCTION

Sustained release drug delivery system

The main goal of any drug delivery system is to deliver to quantity of a drug to a suitable region in the body and that the required drug concentration can be attained promptly and then being maintained. The drug delivery system should distribute a drug at a rate dictated by the require of the body for particular length of time. Regarding this existing points there are two important aspects to delivery system, said as, spatial placement and temporal delivery. Spatial placement connected to targeting a drug to particular organ, tissues, cells, or even sub cellular area; whereas temporal delivery system deals to controlling the rate of dosage form to the targeting region.

Sustained release tablets and capsules are mostly taken only once or twice daily, compared with immediate release tablet form that may have to take 3 or 4 times a day to attain the same required drug to produce the effect. Typically, the sustained release dosage form to furnish at once release the active component that give the what we are desired for cure of disease, followed by remaining quantity of drug should be release and maintained the therapeutic effect over a predetermined length time or prolonged period. The sustaining of drug plasma levels furnish by sustained release dose often times to eliminate the require for night dose administration, which suitable not only the patient but the care given as well.

The bulk of research can be focusing toward oral dosages that improve the temporal aspect of drug delivery. This approach is a continuously developing in the pharmaceutical industry for sustained release oral drug delivery system.

The sustained release system for oral use of administration are mostly solid and based on dissolution, diffusion or a combination of both, erosion mechanisms, in the power to directing the drug release. A delivery system containing hydrophilic and hydrophobic polymers and waxes are mixed with active component to furnish drug action for a prolonged length of time.

Merits of sustained release drug delivery system

1. Reduction in dosing frequency.
2. Reduced fluctuation in circulating drug levels.
3. Increased patient convenience and compliance.
4. Avoidance of night time dosing.
5. More uniform effect.
6. Maximum utilization of drug.
7. Reduction in GI irritation and other side effects.
8. Reduction in health care cost through improved therapy.
9. Improve bioavailability of some drugs.

Demerits of sustained release drug delivery system

1. Decreased systemic availability in comparison to immediate release conventional dosage form. This may be due to

a) Incomplete release
b) Increased first-pass metabolism, increased instability
c) Site specific absorption, pH dependant solubility,

etc.
2. Poor in vitro-in vivo correlation
3. Possibility of dose dumping.
4. Retrival of drug is difficult in case of toxicity, poisoning, or hypersensitivity reactions.

Factor affecting the design and performance of controlled drug delivery
1. Drug properties
Ø Partition coefficient
Ø Drug stability
Ø Protein binding
Ø Molecular size and
Ø Diffusivity.

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

Matrix tablets
For the manufacturing of sustained release dosage forms least complicated method involve the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix core of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. The materials which include both hydrophilic and hydrophobic polymers. A matrix system consists of active and inactive ingredients, that are homogeneously dispersed and mixed in the dosage form. It is by far the most commonly used oral controlled release technology and the popularity of the matrix systems can be attributed to several factors which will be discussed in the later section. The release from matrix type formulations governed by Fick‟s first law of diffusion.
$J = dQt/dt = - D dC/dx$
J is flux, or rate of diffusion, while Q is the amount diffused per unit of time t, and D is diffusion coefficient.

Role of matrix tablets:
1. Improved the patient compliance due to less frequent drug administration.
2. Decrease of fluctuation in steady state drug level.
3. Maximum utilization of drug.
4. Increase safety margin of drug.
5. The goal of such a system is to provide desirable delivery profiles that can achieve therapeutic plasma level.
6. To achieve the steady state blood level or tissue level i.e., therapeutically effective and non-toxic for an extended period of time.

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; Hydroxypropylmethyl 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 (Phaephyceae) 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.
- Screening of dry 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
Polyhydroxyethylemethylacrylate(PHEMA),Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone(PVP),Polyethylene-oxide(PEO), Polyacrylamide (PA).

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

iii. Biodegradable polymers
Polylactic 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, Polyacrylic 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.[14] 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

contentwas 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 after 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 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 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.

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