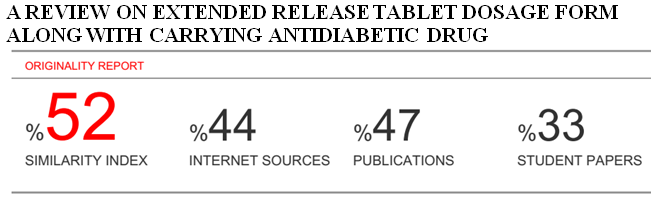
**Reviewer’s Comments**

****

**A Review on Extended Release Tablet Dosage form carrying Antidiabetic Drug**

**Abstract**

Oral medication conveyance has been referred to for a considerable length of time as the most broadly used route of administration among different routes that has been investigated for the systemic delivery of medications by means of various pharmaceutical products of various dosage form. The oral administration route for sustained release drug delivery systems has been widely explored because of more flexibility in design and high patient compliance. Metformin hydrochloride is an antidiabetic agent which improves glucose tolerance in patients with type 2 diabetes and reduces basal plasma levels of glucose.

***Keywords :*** Extended release, Polymers, Matrix tablet, in-vitro dissolution, Antidiabetic, Controlled release

**Introduction**

Oral drug delivery is favored course of administration for the greater part of the active molecule of drug due to its few points of interest like more prominent adaptability in design furthermore, high patient compliance. As a result of more prominent strength, precision in dose, production ease, formulation of tablets is favored oral dosage form. Tablet accessibility in market ranges from generally straight forward Immediate release (IR) formulation to complex sustained release (SR) or modified release dosage forms[1]

Sustained release drug delivery system was meant to discharge the medication in a delayed rate to keep up plasma drug levels. The medications having shorter half life are appropriate for the sustained release drug delivery system. The principle objective in planning Sustained release drug delivery system is to lessen dosing recurrence and along these expanding the activity.[2]

The drug molecule appears better supported sustained drug release profile in matrix frameworks by distinctive systems [3].

Type 2 diabetes mellitus is an incessant dynamic disorder described by less insulin discharge and there is increase in insulin resistance. It is generally acknowledged that it required serious and tight glycemic control to counteract various cardiovascular inconveniences. Metformin hydrochloride is an orally controlled biguanide, broadly utilized in the treatment of type 2 diabetes, a common disease that consolidates deformities of both insulin secretion from pancreas and, insulin activity. It is a hydrophilic medication which gradually and not completely taken up from the gastrointestinal tract; the absolute bioavailability is answered to be of 50 - 60% has moderately short biological half life of 1.5 - 4.5 hours. In any case, frequent dosing schedule and danger of gastrointestinal side effects make its dose measurements complicated. In this way, it is sensible to expect the necessity of sustained released metformin formulation to extend out its span of activity and to enhance patient consistence [4].

**Advantages of Sustained Release Matrix System**

i**) Patient compliance:**

Lack of compliance is mainly seen with chronicdisease which required long term treatment, as achievement of medication treatment relies upon the patient capacity to agree with the medication treatment. Patientcompliance is affected by a many factors, like knowledge of ailment process, patient confidence intreatment, and understanding of patient related to astrict treatment plan. Additionally the difficulty oftherapeutic regimens, the cost of therapy and local orsystemic side effect of the dosage form. This issuecan be set out to some degree by administeringsustained release drug delivery system.

**ii) Reduced 'see-saw' fluctuation:**

Drug concentration in the systemic circulation and tissue compartments show ‘see saw’ pattern frequently when the drug administration in conventional dosage form. The sizes of these variances fundamentally relies upon drug kinetics such as the rate ofabsorption, distribution, elimination and dosing intervals. The 'see-saw' pattern is more prominent just in case of drugs with biological half-life less than four hours, since recommended dosing intervals are rarely less than four hours. A well-designedsustained release drug delivery system can widely reduce the frequency of drug dosing and also maintain a steady drug concentration in blood circulation and target tissue cells.

**iii) Total dose reduction:**

To treat an ailing condition less measure of aggregate drug is used in Sustained release drug delivery systems. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

**iv) Improvement of deficiency in treatment:**

Ideal treatment of a disease requires an effective transfer of active drugs to the tissues, organs thatneed treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically

effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A sustained release dosage form leads to better management of the acute or chronic disease condition.

**v) Economy:**

The initial unit cost of sustained release products is typically more than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over an prolong period of time may be less. [5]

**Disadvantages of Extended Release Matrix Tablet**

* Highly expensive.
* Often poor systemic availability.
* Need for additional patient education and counseling.
* Dose dumping.
* Often poor invivo-invitro correlation. [6,7]

**Characteristics of Drug Suitable for Extended Release Tablet**

The ideal physicochemical and pharmacokinetic qualities of medications which can be defined as extended release tablet are as per the following:

a) Atomic size ought to be beneath of 1000 Dalton.

b) Aqueous solvency ought to be in excess of 0.1 mg/ml for pH 1 to pH 7.8.

c) The partition coefficient ought to be high.

d) Absorption mechanism ought to be diffusion and the general absorbability from all GI fragments discharge ought not be impacted by pH and catalysts.

e) Elimination half-life ought to be between 2 to 8 hrs.

f) Drugs ought not metabolized before absorption it cause less bioavailability.

g) Absolute bioavailability ought to be at least 75% or more.

h) Absorption rate constant (Ka) ought to be higher than discharge rate.

I) Apparent volume of distribution (Vd) ought to be substantial.

j) Total clearance ought not rely upon dosage.

k) Elimination rate constant are required for design and therapeutic concentration (Css) ought to be low and smaller (Vd).[3,4,5]

**Drugs those are undesirable for Such design:**

1. Drugs having elimination half-life under 2 hours.
2. Drugs having controlled in substantial measurement.
3. Drugs whose therapeutics list is tight.
4. Drugs having poor water solvency.
5. Drugs having long end half-life.
6. Drugs having broad first-pass clearance.[8,9]

**Ways to Achieve Extended Release Matrix Tablet:**

The reason for outlining Extend Release dosage form is to build up a dependable formulation that has various benefits of the immediate release dosage form but then retards the dose dumping. The basic standard in design of extend release tablet are to retards the absorption, bio transformation and elimination rate respectively. Different systems have been utilized in the formulation of Extend Release products. In general, extended formulations can be branched into various classifications in light of the mechanism of drug discharge.

1) Diffusion controlled release system.

2) Dissolution controlled release system.

3) Ion exchange resin drug complex.

4) Swelling controlled release.[10]

**Types of matrix systems:**

There are two types of matrix system which are as follows

**1. Slowly Eroding Matrix:**

It comprises of materials or polymers which disintegrate over a time frame, for example, waxes, glycerides, stearic corrosive, cellulosic materials and so forth. The portion of drug planned to have an prolonged activity is joined with lipid or cellulosic material and afterward granulated. Untreated drug is granulated and both are blended. [11]

Matrix System have absence of adaptability in adjusting to constantly change dose levels as required by clinical investigation result. Accordingly, new dose strength is essential. Moreover, for a few items that require novel discharge profiles (dual discharge or delayed with extended release), more complex matrix-based innovations, for example, bilayer tablets are required.

2.**Inert Plastic matrix:**

The rate controlling release ingredients of hydrophilic matrix are polymers which act by swelling when it contact with aqueous solution form a gel layer on the surface of the system. Swelling or dissolution can be the effective factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms.

**Constraints of Matrix System**

Matrix System have absence of adaptability in adjusting to constantly change dose levels as required by clinical investigation result. Accordingly new dose strength is essential. Moreover, for a few items that require novel discharge profiles (dual discharge or delayed with extended release), more complex matrix based innovations, for example, bilayer tablets are required.[13]

**Distinctive techniques used based on type of matrix system utilized in Extend Release tablet formulation:**

**A) Hydrophilic Matrix System:**

At first drug granulated with inert, insoluble matrix polymers. Granules are compacted by direct compression method. The formulated matrix tablet indicates gradual discharging of API from the inert plastic network by draining of body fluids and succeeded by the diffusion system. Inert insoluble polymers, for example, polyethylene, polystyrene,polyvinylacetate, polymethacrylate or polyamide.

**B) Fat-wax Matrix Tablet:**

The strategies include in addition of drug into fat wax. Granules are showered which get hard in air, mixing in a aqueous fluid media with or without the surfactant and dried by spray drying strategy. A suspension of drug and melted fat wax are solidify by utilizing fluidized-bed and steam jacketed blender or granulating with a solution of waxy material. In this type of matrix tablet, drug is discharged by straining and hydrolysis mechanism.

**C)Hydrophobic Matrix Tablet:**

The technique include in preparation of hydrophobic matrix tablet is direct compression of drug with plastic materials and furthermore can be granulated to required particle size to enhance blending with the drug particle.

**D) Biodegradable Matrix Tablet:**

It can be processed by utilizing polymers which involved monomers linked to one another by functional groups and have unsteady linkage in the backbone. These examples are natural polymers, for example, polysaccharides ,proteins, and manufactured polymers , altered natural polymers, for example, aliphatic poly (esters) and poly anhydrides.

**E) Mineral Matrix Tablet:**

Mineral matrices can be set up by utilizing polymers which are acquired from different types of seaweads. Example: Alginic acid which is a hydrophilic sugar.[13]

**Various Type of Polymers Used in Matrix Tablet:**

* **Hydrogels**: Poly hydroxyl ethyl methyl acrylate (PHEMA), Cross-linked polyvinyl alcohol(PVA).
* **Soluble polymers**: Poly ethylene glycol (PEG), Polyvinyl alcohol (PVA), Polyvinylpyrrolidone(PVP).
* **Biodegradable polymers**: Polylactic acid,Polyglycolic acid (PGA), Polycaprolactone (PCL), polyanhydrides, etc
* **Non-biodegradable polymers**: Polyethylenevinyl acetate (PVA), Polydimethylsiloxane(PDS), Polyether urethane (PEU), Polyvinylchloride (PVC).
* **Mucoadhesive polymers:** Polycarbophil, Sodiumcarboxy methyl cellulose, Polyacrylic acid,Tragacanth, Methyl cellulose, Xanthan gum, Guar gum etc[15,16,17]

**Evaluation Parameters for Extend Release Matrix Tablet :**

1. **Thickness and Diameter:** Thickness and diameter of tablets was determined using Vernier Caliper. Five tablets from Each batch is used, and average values were calculated.[18]
2. **Hardness of the Tablet** :Tablet hardness has been characterized as, “the force required breaking a tablet in a diametric Compression test”. For every formulation, the hardness of three tablets are examined utilizing Monsanto hardness analyzer. The tablet was set in “Monsanto hardness tester’’, the tablet was placed in Monsanto hardness analyzer vertically and the force was applied with the assistance of screw the end point was recognized by breaking the tablet.[19]
3. **Weight variation test:** Twenty tablets were randomly chosen and weighed to determine the average weight and were compared with single tablet weight. The percentage weight variation was computed according to Indian Pharmacopoeial particular. Tablets with an average weight in excess of 400 mg ought not be more than ±5 %. This is an important process which comes under quality control test as per standard in one batch all tablet ought to be in uniform weight .The weight variation test was performed with the help of digital weighing balance. From the one batch 20 tablets were chosen randomly as sample and their individual weight was identified and average weight was identified. Finally percentage deviation was figured by the utilizing following formula: [20]

**Percentage deviation =(Individual weight –Average weight) 100 Average Weight**

1. **Determination of drug content**: The drug content of metformin hydrochloride was determined with the help of ph 7.4 phosphate buffer solution .tablets were placed in 100 ml of ph 6.4 phosphate buffer solution individually . It was kept for 24 hours in room temperature and filtered. 1ml. of solution was withdrawn and diluted up to 10 ml with the help of ph 6.4 phosphate buffer solution and absorbance was recorded by uv –visible spectrophotometer at 233 nm. Finally the drug content was determined by using calibration curve.[21]
2. **Drug-Excipient interaction study:**The infrared (IR) spectra are recorded using an FTIR spectrophotometer by the KBr pellet method in the wavelength region between 7800 and 350 cm-1. The infrared spectra of metformin HCl pure drug, & physical mixture of optimized formulation may be recorded between 400-4000 cm-1 on FT-IR spectroscopy.[22]

**Invitro Dissolution Testing**

In vitro dissolution testing is a vital instrument for assessment of the best formulation. Dissolution testing is likewise used to characterize the biopharmaceutical attributes and to distinguish conceivable hazard, for example, potential nourishment impacts on bioavailability or interaction with different drugs. For extended release matrix tablet, to achieve special pharmacokinetic profiles, the major discussion ought to be done on solubility attributes (sink) and physiological condition specification.

* **Test Duration**

Minimum 80% dissolution ought to be accomplished with in the trial period. Test duration to the dosage duration is supported when time gaps in vitro and in vivo are in a 1:1 relationship. On the off chance that the dissolution came to beneath of 80%, it might be acknowledged, if, the test span was not less than 24 hours.[23]

* **Specification of Test**

For ER formulation, The International Pharmaceutical Federation (FIP)- Guideline and European Pharmacopeia suggested not less than 3.

For Extend Release formulation, The International Pharmaceutical Federation (FIP)- Guideline and European Pharmacopeia suggested not less than 3.

a) After 1-2 hours/ 20-30 % to give confirmation against premature drug discharge.

b) Cycle 50 % to characterize dissolution design.

c) Minimum 80 % is required to assure relatively quantitative discharge. (FIP: < 80 % be justified / at least 24 hours).

**Conclusion**

The focus of this review article has been on the formulation of extended release matrix tablets, benefits and drawback,various types of polymers can be utilized, technique of preparation and assessmentparameters. Above discussion ends up on the conclusion that matrixtablets are helpful to overcome the patientincompliance and effectiveness of dosage form in evokingdesired therapeutic response related problemslinked with conventional dosage forms. Costadequacy and once-daily dose are the beneficial pointsalong with various other advantages.So, this extend release formulation can be a suitable formulation which an antidiabetic drug can be incorporated and better pharmacological action can be achieved.

**Acknowlegement**

Authors wish to thanks the authority of Shri Ram Murti Smarak College of Engineering and Technology (Department of Pharmacy), Bareilly, for providing library and other facilities to complete successfully this review study.

**References**

1. RohiniDiwedi et al,2012;, Preparation and *In Vitro* Evaluation of Sustained Release TabletFormulations of Metformin Hcl, *Asian J Pharm Clin Res,*Vol.5(1), pp. 45-48.
2. M. VijayaLaxmi, Vamshi Krishna. J, 2014;: Formulation and Evaluation of Aceclofenac Matrix Tablets using Ethyl Cellulose and Cellulose Acetate Phthalate: *JGTPS,*Vol.5(3) pp. 1804-1810.
3. Brahmankar DM and Jaiswal SB. 1995,Biopharmaceutics and Pharmacokinetics; “A Treatise” VallabhPrakashan,; 1st Ed.: pp.347- 352.
4. Dunn, C J. and Peters, D. 1995. Metformin: a review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* Vol. 49 pp. 721-749.
5. Zalte H.D. and Saudagar R.B.,2013, Review on Sustained Release Matrix Tablet, *International Journal of Pharmacy and Biological Sciences* , Vol. 3,Issue 4, pp.17-29.
6. Hoffman .,1998A. Pharmacodynamics aspects of sustained release preparations. *Adv Drug DelivRev*.;Vol.33 pp.185-199.
7. Munday DC, Cox PJ. 2000, Compressed xanthan and karaya gum matrices: Hydration, erosion and drug release mechanisms. *Int J Pharm*.;Vol.203 pp.179-192.
8. Bhargava A, Rathore R P S, Tanwar Y S, Gupta S, Bhaduka G. 2013,Oral sustained release dosage form an opportunity to prolong the release of drug*. Int J Adv Res Pharm Bio Sci*.; Vol.3,Issue1 pp.7-14.
9. Chauhan M J, Patel S A. 2012 ,Aconcise review on sustained drug delivery system and its opportunities*. Am J Pharm Tech Res*.Vol.2 Issue 2, pp.227-238.
10. Venkatraman S, Davar N, Chester A. ,2000 An overview of controlled release systems. Donald L Wise, Marcel Dekker Inc Vol.2 .pp.431- 465.
11. Sujja A J, Munday DL, Cox PJ, Khan K, 1998, Relationship between swelling, erosion and drug release in hydrophilic natural gum mini matrix formulations. *Eur J Pharm Sci* Vol.6 Issue 3 pp.207-217.
12. Boniferoni MC, Rossi S, Ferrari F, Bartoni M, et al. 1995, Viscoelastic properties of gels*. Int J Pharm Sci* Vol.117 , pp.41-48.
13. Patel KK, Patel MS, Bhatt NM, Patel LD, Pathak NL, Patel KJ. 2012, An overview: extended release matrix technology. *Int J Pharm ChemSci*Vol.1 Issue 2 pp. 828.

14) Pundir S, Badola A, Sharma 2013, D. Sustained release matrix technology and recent advance in matrix drug delivery system. *Int J Drug Res Tech* Vol. 3 Issue1 pp.12-20.

15) Jaimini M, Kothari A. 2012,Sustained release matrix type drug delivery system: *Rev J of Drug Delivery Ther*.;Vol.2,Issue 6 pp.142-148.

16)Lieberman H A, Lachman L, kanig J L. The theory and practice of industrial pharmacy. 3rd Edition. Varghese publishing house; 2014.

17)Kumar S, Kant S,Prashar B. 2012 ,A review on sustained release drug delivery system*. Int J Inst Pharm life Sci.*Vol. 2 Issue.3 pp.356-376.

18)Kumar N., Roy Mahasweta, Kumar B., Puri Pooja, Hasan M., 2016, Formulation and Evaluation of Sustained Released Metformin HCl Tablet Using Natural Polymers, *International Journal of Pharmacy & Pharmaceutical Research* , Vol. 6 issue 2 pp. 217-237.

19)Prajapati Bhupendra, Patel Rakesh, Patel Dhaval, Shah Payal , 2013 , Metformin hydrochloride sustained release tablet using different matrixing tablet, *e-Journal of Science & Technology (e-JST),* Vol.4 Issue 8, pp. 61-72.

20)BookyaPadmaja, Raparla Ramakrishna, Prasad Sriramula1Harikishan, Tarrigopula Sunitha, Vanga Sridhar ,2018, Formulation and Evaluation of Metformin hydrochloride sustained-Release Oral Matrix Tablets ,*Asian Journal of Pharmaceutical and Clinical Research* Vol 11, Issue 3, pp. 342-345

21) MohantySangeeta, Pal Abhisek, Chandra Si Sudam, 2017, Evaluation of Sustained Release Tablet of Metformin in Alloxan Induced Diabetic Rat, *International Journal of Pharmaceutical Sciences Review and Research ,*Vol. 47 , pp.133-140.

22) Satyanarayana T., Rajitha V., Suresh Kumar P., Ravinder K., Shaji G. and Saranya P., 2012, Formulation and evaluation of Metformin HCl extended release tablets ,*Pelagia Research Library*,Vol-3,Issue-1, pp. 58-63.

23) Barbara S, Martin S, Hoechst MR. Dissolution tests for ER product. Available from: URL:dx.doi.org/10.14227/DT050498