CRITICAL ANALYSIS OF SUSTAINED RELEASE METFORMIN FORMULATIONS

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• **ABSTRACT :-**

Sustained-release (SR) tablets are recommended to improve patient compliance when taking metformin, which is now sold as a hydrochloride salt in the United States and other countries. Unfortunately, some patients find it difficult to swallow this large SR tablet because of its high water solubility and the high dose needed for efficacy. In order to overcome these obstacles, modifications were made to the salt production, which also affected its solubility. Metformin succinate was selected from among ten newly synthesized medicinal salts due to its decreased molecular weight and solubility. Metformin HCl and succinate were shown to be distinct substances by DSC thermograms and FT-IR spectra. Nonetheless, there was no statistically significant difference observed in other tablet parameters that are associated with effectiveness, such as permeability, density, compressibility, particle size distribution, and stability in different artificial human fluids. In this study, metformin HCl SR tablets and metformin succinate SR tablets with an excipient component lowered from 43% to 14% were created.

STRUCTURAL FORMULA OF METFORMIN :-

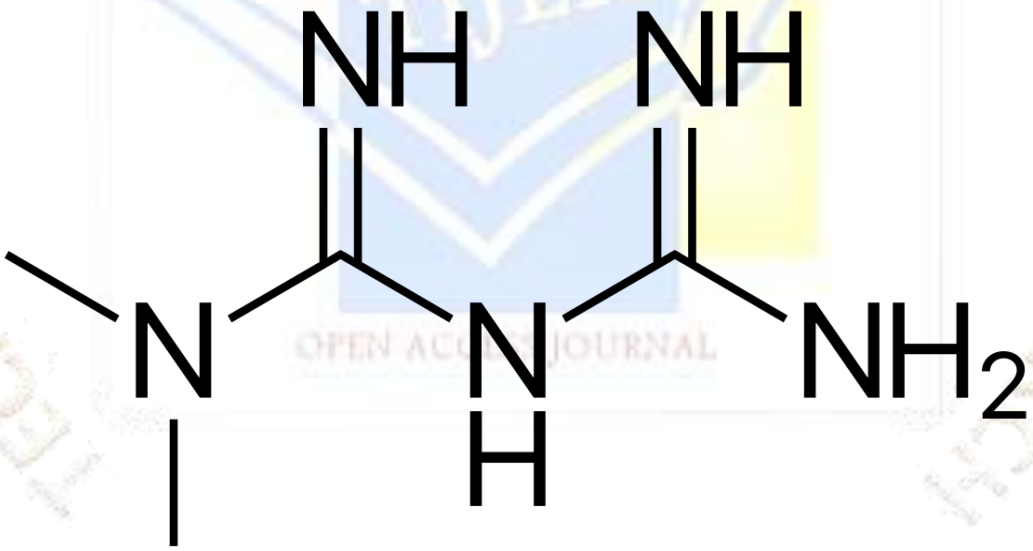


FIG. Structural formula of metformin

• **KEYWORDS** :- Metformin, sustained release, diabetes, hyperglycemia.

- **INTRODUCTION :-**

Sustained-release (SR) oral delivery systems are designed to achieve therapeutically effective concentrations of drug in systemic circulation over an extended period of time. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance.[1,2] Many innovative methods have been developed for obtaining modified drug release. From the practical view point, hydrophilic matrix tablet is one of the least-complicated approaches for developing a modified release dosage form.

Hydroxypropylmethylcellulose (HPMC) is a hydrophilic cellulose ether widely used as a pH-independent gelling agent in controlled the release preparation due to the release behavior of the drug.[3] Because of nontoxicity, easy handling and no requirement of specified technology for production of SR tablets, HPMC is often used as a release-retarding material.[4] The transport phenomena involved in the drug release from hydrophilic matrices are complex because the microstructure and macrostructure of HPMC exposed to water are strongly time-dependent. Upon contact with the gastrointestinal fluid, HPMC swells, gels and finally dissolves slowly.[5] The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution. The dissolution can be diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer.

Guar gum is a nonionic polysaccharide derived from the seeds of *Cyamopsis tetragonolobus*, family Leguminosae. In pharmaceuticals, guar gum is used in solid dosage forms as a binder and disintegrant.[6] Many researchers have reported the use of guar gum, as a hydrophilic matrix, for designing oral controlled-release dosage forms.[7–9]

Metformin hydrochloride(HCI), the only available biguanide, remains the first-line drug therapy for patients with Type 2 diabetes mellitus (T2DM), acting by decreasing the hepatic glucose output and peripheral insulin resistance.[10] The advantages of metformin are a very low risk of hypoglycemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality.[11] It is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50–60% with a relatively short plasma half-life of 1.5–4.5 h.[12,13] An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms such as abdominal discomfort, nausea and diarrhea that especially occur during the initial weeks of treatment.[14] Side-effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. A SR formulation that would maintain plasma levels of the drug for 10–16 hours might be sufficient for once-daily dosing of metformin. SR products are needed for metformin to prolong its duration of action and to improve patient compliance.

The overall objective of this study was to develop matrix SR tablets of metformin using natural gums (Guar gum) as suitable hydrophilic matrix systems compared with the extensively investigated hydrophilic matrices (HPMC) with respect to the *in vitro* drug release rate.

- **Physico-Chemical Properties of Metformin :-**

Topic	Description
Chemical formula	$C_4H_{11}N_5$
Molecular weight	129.16 g/mole
Drug class	Antidiabetic Agents
IUPAC Name	3-(diaminomethylidene)-1,1-dimethylguanidine
Synonyms	1,1-Dimethylbiguanide N,N-dimethylimidodicarbonimidic diamide
Elimination Half-life	1.5-4.5 hours
Duration of Action	4-8 hours
Plasma Peak Time	2-3 hours
p^H	6.68
p^{Ka}	12.4
Boiling point	224.1°C at 760 mmHg
Melting Point	222-226 °C
Bioavailability	(50-60)%

DOSAGE FORMS OF METFORMIN :-

There are several dose forms for metformin. Several dosage forms are available in the market, including tablets, sustained release tablets, extended release suspensions, and solutions. Each patient will require a different dosage of this medication. The average doses of this medicine for type 2 diabetes:

For oral dosage (sustained release tablet): Adults: Metformin (alone) 1000mg per day and not more than 2000mg.

Metformin with insulin, 500mg per day with meal and not more than 2500mg per day.

- (extended release suspension): Adults: 5mililiters per day taken with evening meal.
- (solution): Adults: Metformin only, 5mililiters two times Or 8.5mililiters once a day with meal. Metformin with insulin, 5mililiters once a day and not more than 20mililiters (mL) per day.

CONTRAINDICATION :-

Lactic acid accumulation in the blood can result from metformin-induced lactic acidosis. Because congestive heart failure is contraindicated for the treatment of metformin, many patients with type 2 diabetes are not allowed to take the medication.

Because metformin significantly raises plasma lactate levels, it is not recommended to start metformin treatment in patients with type 2 diabetes, including those over 70. Damage to the heart, lungs, blood vessels, and primarily the kidneys can result from elevated plasma lactate levels. Deadly consequences could result from the failure to treat lactic acidosis promptly, which would cause body parts to shut down.

PREGNANCY COMPLICATIONS :-

It is generally accepted that taking metformin while pregnant is safe. There is no evidence linking metformin to a higher risk of problems or birth defects. It's crucial for mothers of young children with polycystic ovarian syndrome to control their blood sugar levels if they have diabetes. It helps lower your risk of birth defects and other pregnancy-related complications, as well as your risk of developing complications from diabetes. Metformin is also safe to take while nursing because, although small amounts of the drug may be found in breast milk, it has no negative effects on the growth and development of the baby.

SIDE EFFECTS :-

When someone has an allergic reaction to metformin, they should seek emergency medical attention. Metformin users may experience lactic acidosis, which can be lethal. Get emergency medical help when Metformin show mild symptoms such as :

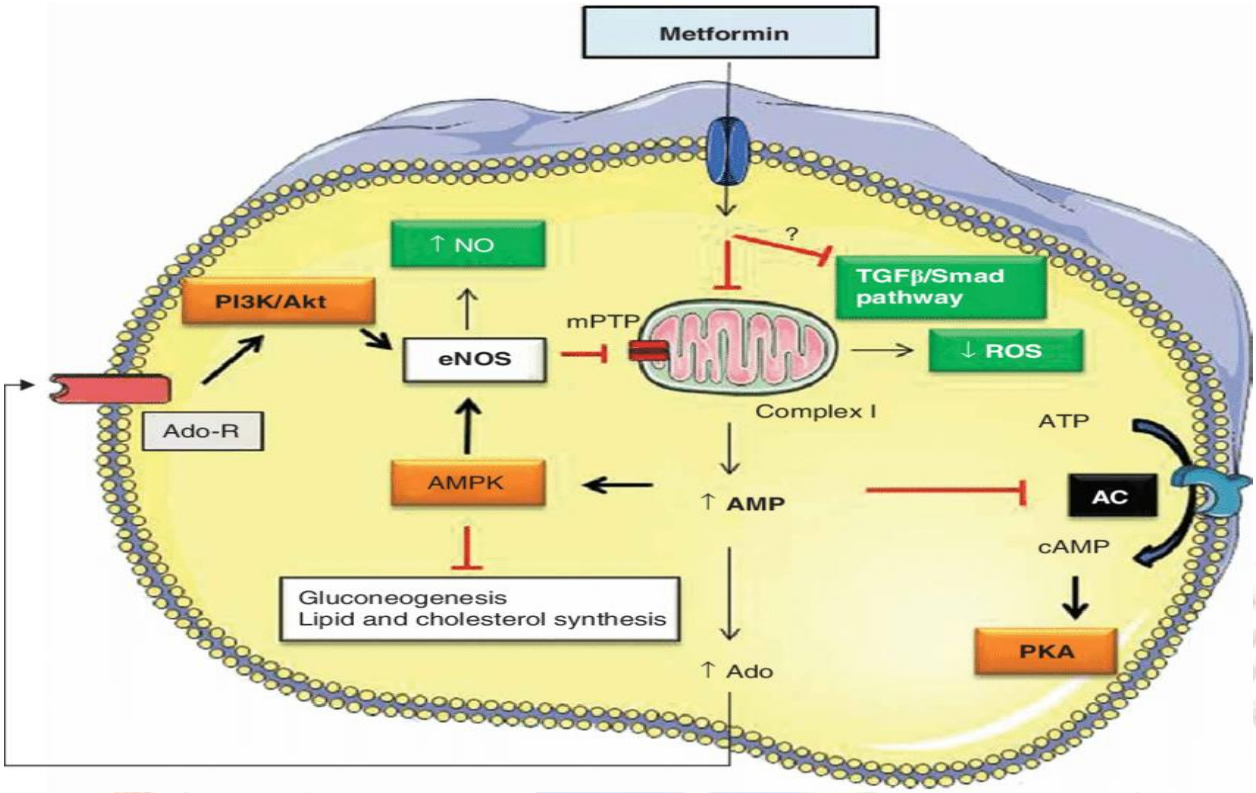
More common :

- Feeling dizzy, light-headed, tired or very weak
- Trouble breathing
- Unusual muscle pain
- Feeling cold
- Stomach pain , vomiting
- Diarrhoea
- Difficult urination

Less common :

- Anxiety
- Blurred vision
- Increasing hunger
- Increasing sweating

MECHANISM OF METFORMIN :-



FORMULATION :-

In the formulation of sustained release tablets, certain additives or the choice of excipients is crucial in addition to the primary API (Active Pharmaceutical Ingredient), which is metformin HCL. Formulation expertise is needed to produce a product that will be stable, transportable, and handleable even though the tablet manufacturing process is relatively complex and every batch should ensure stability. Excipients of various kinds could be used in a variety of ways to formulate metformin sustained release tablets. Table 3 below includes a list of common excipients needed for tablet preparation.

List of Excipients and Its Function for Formulating a Tablet :

Excipient	Function	Examples
Binder	It gives a firmness to the tablet ingredients.	Lactose monohydrate, Microcrystalline cellulose (MCC), Acacia, Hydroxypropyl cellulose, Carboxymethyl cellulose etc
Filler	Filler is added to handle the active ingredient when it is too small to handle conveniently	Microcrystalline cellulose (MCC) ,
Diluent	Provides bulk in tablet granules	Lactose, Sorbitol, Mannitol-D, Xanthan gum etc.
Lubricant	Reduce the adhesion between the preparation and the mold	Magnesium stearate, Calcium stearate,Talc
Glidants	Reduce friction between drug particle and improve flow properties	Aerosil (Colloidal silicon dioxide), Cornstarch, Talc etc.
Disintegrant	Aids in the disintegration of tablet in gastro-intestinal tract (GIT)	Hydroxypropylmethyl cellulose (HPMC), Crospovidone (polyplasdone),
Superdisintegrant	Improves the disintegration process	Kollidon CL, Sodium starch glycolate
Coating polymers	Used in sustained release tablet coating as it helps in resistance to disintegrate kin gastric fluids.	Cellulose acetate, phthalate, Hydroxypropylmethyl cellulose (HPMC)
Flavouring agents	Gives flavor to non-patient compliance drugs	Peppermint oil, Ethyl vanillin etc.

EVALUATION OF TABLET :-

[1] Weight variation test :-

Tablet weight is influenced by a number of variables, including powder flow characteristics, machine speed, head pressure, and compression machine tooling. Inconsistencies in the density and particle size distribution of powders or granulates frequently contribute to weight variation during compression. There should be as little variance in weight and dosage between tablets as possible. One in-process test parameter that guarantees dosage unit consistency during compression is weight uniformity. Twenty tablets were selected at random from the batch, each weighted separately, and the average weight was determined. Every tablet's weight was contrasted with the average weight, and the deviation's degree was calculated. The test criteria are satisfied if the weight differences between no more than two individuals are greater than 5% and none greater than 10%.

FIG. Weight variation test

[2] Tablet hardness :-

The pharmaceutical industry uses a laboratory process called tablet hardness testing to determine a tablet's breaking point, structural integrity, and how it changes over time "under conditions of storage, transportation, packaging, and handling before usage." After formulate every tablets are important hardness testing.

FIG. Digital Tablet Hardness Tester

[3] Friability tester :-

The pharmaceutical industry uses a laboratory process called friability testing to determine whether tablets will remain stable during transportation. A rotating wheel with a baffle is used to continuously drop a sample of tablets over a predetermined amount of time. The upper site table's friability was determined and reported as a percentage (%). Twenty tablets, each batch's weighted separately (Winitial), were placed in the friabilator and spun 100 times at 25 rpm. The tablets underwent a reweighting process (Winitial), and the formula below was utilized to determine the percentage friability (F) for every batch .

FIG. Friability tester

[4] Dissolution test :-

The process of releasing a medication from a tablet into solution one unit of time under controlled conditions is called dissolution testing. Dissolve test media include stimulated intestinal fluid, purified water, and others. Use of organic solvents is not advised. Widely used are USP Apparatus I (basket) and USP Apparatus II (paddle). shows an illustration of a dissolution tester.

FIG . Dissolution apparatus

MANUFACTURING TECHNIQUES OF TABLET :-

- Wet granulation
- Dry granulation
- Direct compression

[1] wet granulation :-

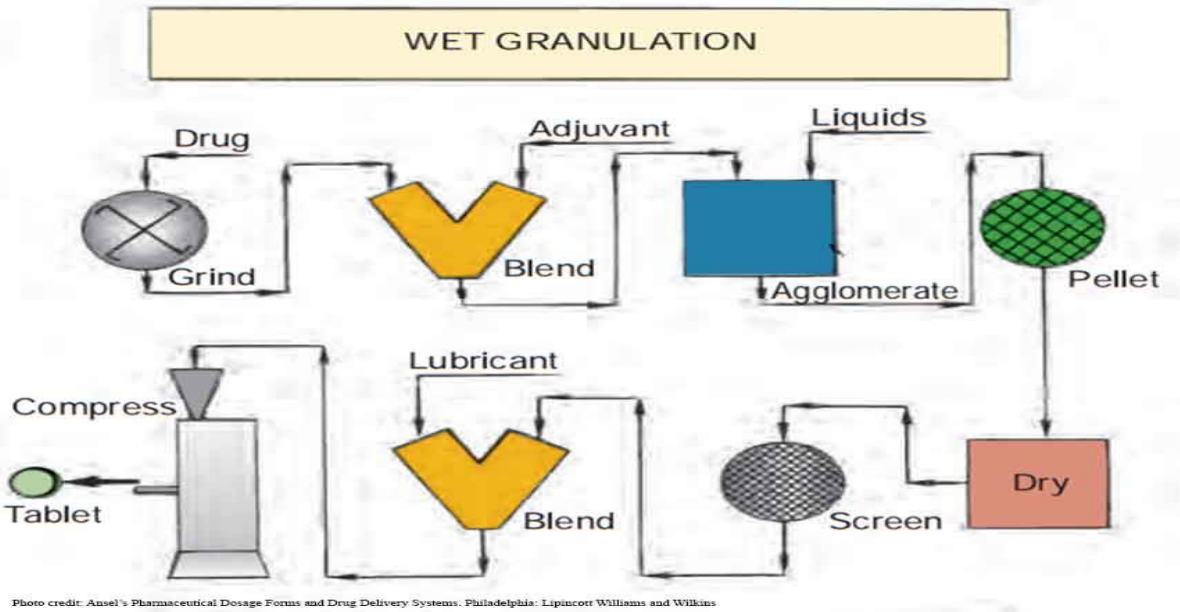
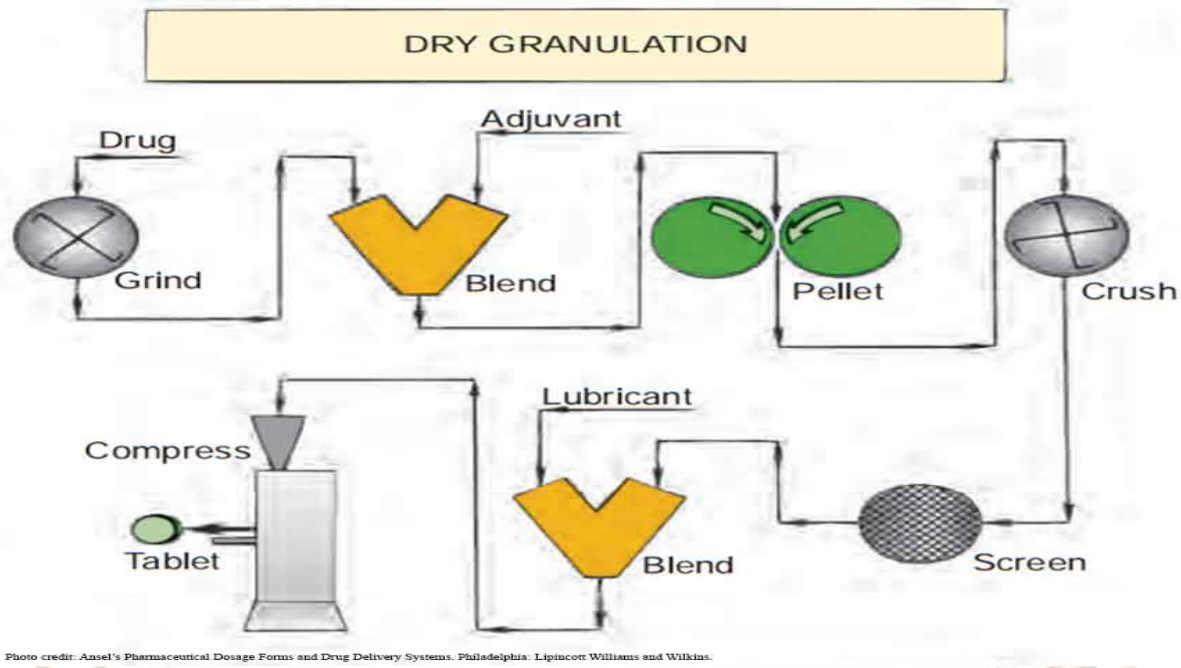


Photo credit: Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lipincott Williams and Wilkins

[2] dry granulation :-



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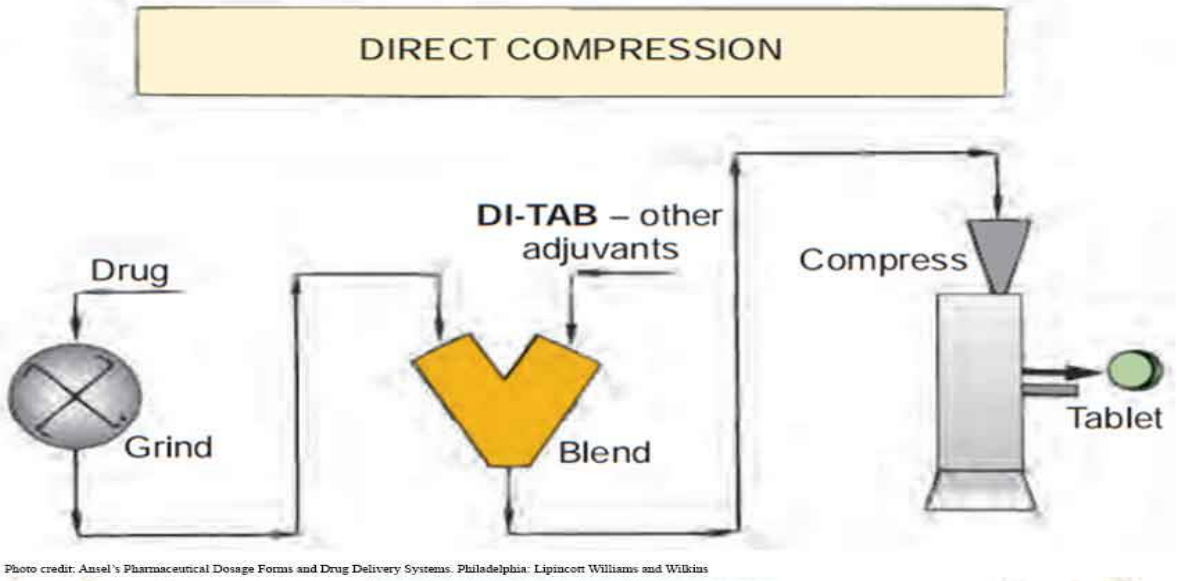
[3] direct compression :-



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TABLET CHARACTERISTICS :-

Regarding uniformity of drug content, all of the tablets with varying formulations displayed results that were satisfactory. All formulations were found to be within pharmacopoeia limits when tablet weights were determined, with the exception of F4, F5, and F7. When pressing tablets, a simple punch with an identical radius was utilized for every formulation, and there were no appreciable variations in the tablet's radius**.** The tablets' friability, which was well within the permitted 1% range, showed that their surfaces could tolerate mechanical shock or attrition while being stored, transported, and used up until they were eaten.[19] The produced tablets had a high degree of uniformity in the drug content across batches, with a high variance in weight and a drug content of over 95%.

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