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# Formulation And Evaluation of Tolbutamide sustained release tablet for Diabetes Mellitus

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**ABSTRACT: -**

Tolbutamide, a first-generation sulfonylurea, is commonly used in the management of type 2 diabetes mellitus. However, its short half-life necessitates frequent dosing, leading to fluctuations in plasma drug levels. To address this limitation, a sustained release (SR) formulation of tolbutamide has been developed to provide a controlled release profile, improving therapeutic efficacy and minimizing side effects associated with peak concentrations.

This study investigates the formulation and in vitro evaluation of a tolbutamide sustained release tablet. The tablets were prepared using hydrophilic matrix systems, incorporating various excipients to optimize drug release. The formulation was characterized by in vitro dissolution testing, which demonstrated that the sustained release profile of tolbutamide was maintained over an extended period (up to 24 hours). The release kinetics followed a pseudo-zero-order model, suggesting a controlled and consistent release of the drug.

The pharmacokinetic study of the SR tablets, conducted on healthy human volunteers, showed a significant reduction in peak plasma concentration (C-max) and an extended time to reach peak concentration (T-max) compared to conventional immediate-release tablets. This provided a smoother and more prolonged therapeutic effect, resulting in improved patient compliance due to reduced dosing frequency.

Overall, the tolbutamide sustained release tablet presents a promising alternative to conventional formulations, offering better control over blood glucose levels, reduced side effects, and improved patient adherence to the treatment regimen.

These binders prolong the dissolution rate of some slightly soluble drugs and can be chosen as good candidate for sustained release.

Tablets were prepared by direct compression method using different drug-polymer concentration. FT-IR study revealed that there was no chemical interaction between the drug and polymers used.

Pre-compression and post-compression parameters complied with Pharmacopoeial limit for the tablets. Four different binders (tragacanth, gum acacia, guar gum, starch) were used in 3 different concentrations (25%, 50%, 75%) and was compared with the standard rate retardant polymer HPMC.

The in vitro release study was performed and the results indicated that the formulation TEF8 (Guar Gum 50%) was found to be the optimized formulation which can extend the release up to a period of 24 hours.

The kinetic release data showed that the optimized formulation followed zero order kinetics. From the stability studies it was clear that the formulation was stable after 2 months at accelerated condition of 40 °C+2 °C/75% RH±5% in a stability chamber.

**Keywords:** Sustained drug delivery system, physical dispersion method, ether injection method, soya lecithin, stability studies.

## Introduction: -

A sulfonylurea and first-generation potassium channel blocker, tolbutamide is an oral hypo-glycemic drug. If diet alone is ineffective for managing type 2 diabetes, this medication may be administered. The pancreas secretes more insulin when tolbutamide is present. It is not frequently used due to a higher prevalence of adverse effects compared to newer, second-generation sulfonylureas, such as Glibenclamide. Because of its quick metabolism, it usually has a brief duration of action, making it suitable for usage in elderly individuals. In 1956, it was found. [1]

Tolbutamide sustained release tablets are a formulation of the oral hypo-glycemic agent, Tolbutamide, designated to provide prolonged control of blood sugar levels in patients with Type 2 diabetes.[1]

The chemical formula for tolbutamide is N-(butyl amino) carbonyl-4-methylbenzene sulfonamide. Type-II diabetes mellitus is treated with this medication. In I.P.2, B.P.3, and Martindale [2], it is official. A few techniques for determining tolbutamide4-8 have been published in the literature. A

novel RP-HPLC technique that exhibits good reproducibility and sensitivity was created for this investigation. ICH guidelines were followed in the validation of the devised approach.[2]

By releasing the medication slowly over an extended period, these tablets aim to improve patient compliance, minimize hypo-glycemic episodes, and enhance therapeutic effectiveness. The methods, formulations, technologies, and systems for delivering a pharmaceutical chemical in the body as required to safely accomplish its intended therapeutic effects are referred to as novel drug delivery systems, or NDDS. [ 1-3]

A vesicular, colloidal structure, liposomes are made up of one or more bilayers enclosing an equal number of aqueous compartments. Liposomes are tiny, synthetic, spherical vesicles that can be made from natural, harmless phospholipids and cholesterol. In addition to being biocompatible, liposomes' size and hydrophobic and hydrophilic properties make them attractive drug delivery vehicles. The liquid inside the sphere-shaped shell contained peptides, protein, hormones, enzymes, antibiotics, antifungal, and anti-cancer compounds. [4-9] Particle sizes of liposomes vary from 30 nm to several micro-meters.

Their polar head groups are orientated in the pathway of the inner and exterior aqueous phases, and they are composed of one or more lipid bilayers around aqueous units.[5]

The diagnostic and therapeutic uses of liposomes containing different drugs or markers, as well as their use as a tool, model, or reagent in the fundamental research of cell interactions, recognition processes, and the mode of action of specific substances, are the two categories of liposome applications in medicine and pharmacology. The transport of novel biotechnology products, such as recombinant proteins, cloned genes, and antisense oligonucleotides, is finding new uses thanks to developments in liposome design. Liposomal versions of daunorubicin and all-trans-retinoic acid are recent advancements that have gained. Sulfonylureas increase both basal insulin secretion and meal-stimulated insulin release. Drugs in this class vary in their dose, rate of absorption, duration of action, route of elimination, and binding site on their target pancreatic β cell receptor. Advances in liposome design are leading to new applications for the delivery of new biotechnology products, such as antisense oligonucleotides, cloned genes, and recombinant proteins.[6]

The study's objective was to create and assess tolbutamide liposomes for a long-term medication delivery system. Of the entire medication delivery market, oral drug delivery is the biggest and most established category. It is the most used and rapidly expanding method of administering drugs. In the pharmaceutical sector, it is standard procedure to use hydrophilic matrices for oral prolonged release of medications. However, if a decrease in steady state fluctuation is required, medications with a lengthy half-life are also eligible. Achieving a steady state blood level or tissue level that is therapeutically effective and nontoxic for a prolonged amount of time is the fundamental objective of therapy for many medications [1]. In the US, a maximum of 2.5 g of tolbutamide per day, administered in three doses with meals, is advised. By boosting peripheral glucose absorption and reducing hepatic glucose synthesis, tolbutamide enhances insulin sensitivity. In order to maintain an effective plasma concentration, it should be given often (500 mg three times a day) due to its shorter and variable biological half-life of 1.5–4.5 hours. Tolbutamide's high dose (1.5–2.0 g/day), low bioavailability (60%) and high incidence of gastrointestinal tract (GIT) side effects (30% case) are the main issues with chronic therapy, despite its favourable clinical response and lack of serious side effects. [3-4]

***Aim For the Tolbutamide Drug: - Formulation and Evaluation of Tolbutamide Sustained Release Tablet: -***

Tolbutamide sustained-release tablets are designed to give the oral hypo-glycemic drug Tolbutamide, which is used to treat type 2 diabetes, a longer-lasting release.

The formulation with continuous release aids in:

1) Maintain blood sugar control: The sustained-release tablets help to keep a constant level of Tolbutamide in the bloodstream by releasing the drug gradually, which prolongs its duration of effect.

2) Decrease dosage frequency: By enabling once-day dosing, the sustained-release formulation enhances patient compliance and eliminates the need for several daily dosages.

3) Minimize side effects: Sustained-release tablets may help lower the risk of adverse effects, like hypo-glycemia, by avoiding the peaks and troughs connected to immediate-release formulations.

4) The overall goal of sustained-release tolbutamide tablets is to effectively manage blood sugar levels while lowering the possibility of adverse effects and enhancing patient convenience.

***Objective for the tolbutamide drug: -***

Tolbutamide sustained-release pills are intended to:

1) Provide prolonged management of blood sugar levels: The sustained-release tablets are designed to keep a constant amount of Tolbutamide in the bloodstream by releasing the drug gradually over a long period of time.

2) Improve patient compliance: Sustained-release tablets help patients stick to their treatment plan by lowering the frequency of dose.

3) Reduce hypo-glycemic episodes: Sustained-release tablets are designed to lower the risk of hypo-glycemia by avoiding the peaks and troughs that are connected to immediate-release formulations.

4) Increase therapeutic effectiveness: Sustained-release tablets are designed to increase the overall therapeutic effectiveness of Tolbutamide by offering a steady and extended delivery of the drug. Over all the objective of Tolbutamide Sustained Release Tablets is to provide effective and convenient management of Type 2 diabetes.

## Material and Methodology: -

Tolbutamide was obtained from Yarrow chem products, Mumbai. Ethyl and chloroform were acquired from Rankem Laboratories in Haryana.

The Urban Platelet Food Company in Mumbai provided the soy lecithin. The supplier of potassium dihydrogen phosphate was Merck Specialties PVT LTD, located in Mumbai. The remaining compounds were all analytical grade and didn't require any more purification.

Preparation of standard curve of tolbutamide using pH 6.8 phosphate buffer: -

To achieve a 1000 µg/ml solution, 100 mg of precisely weighed tolbutamide was dissolved in water, and the volume was increased to 100 ml using distilled water in a volumetric flask.

A stock solution of 100 µg/ml was obtained by pipetting 10 ml of the aforementioned solution into a 100 ml volumetric flask and adding phosphate buffer pH 6.8 to bring the volume up to 100 ml.

To obtain a concentration between 2 and 20 µg/ml, aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1.0 ml, 1.2 ml, 1.4 ml, 1.6 ml, 1.8 ml, and 2.0 ml were pipetted out of this stock solution into a series of 10 ml volumetric flasks and made up to mark with phosphate buffer pH 6.8.

A UV double beam spectrophotometer was then used to measure the absorbance of the resultant solution at 233 nm using phosphate buffer pH 6.8 as a blank.

Plotting concentration (µg/ml) data on the X-axis and absorbance values on the Y-axis produced the standard curve [7-8].

***Pre-formulation Studies: -***

Pre- formulation testing's goal is to produce data that will help the formulation create stable and bioavailable dose forms.

The likelihood of creating a product that is acceptable, safe, effective, and stable is increased by using pre- formulation parameters.

**A) Solubility: -**

Solubility Using a magnetic stirrer, the solubility of tolbutamide in water, methanol, and phosphate buffer pH 6.8 was assessed at room temperature.

**B) Melting Point: -**

Melting point apparatus was used to determine the melting point.

A capillary tube containing a small quantity of pure tolbutamide was placed in a melting point device, and the melting point was recorded [9].

**C) Compatibility (drug-excipients interaction) studies: -**

To ascertain any potential interactions between the drug and polymers, FT-IR spectra were obtained for the dried samples using an FT-IR 8400S (Shimadzu, Japan).

In three separate ratios (1:1, 1:2, and 1:3), the medicine in its plain form, lecithin, cholesterol, and a mixture of the drug with lecithin and cholesterol were ingested and combined with KBr.

A hydraulic press was used to compress the samples into a pellet. The pellets that had been manufactured were turned into disks. Using an FT-IR spectrophotometer, the disk was placed in the middle of the sample holding apparatus and scanned between 4,500 and 400 cm-1 [10-11].

**Formulation of liposomes loaded with Tolbutamide: -**

Tolbutamide-loaded liposome formulation Two distinct methods were used to prepare the formulation of liposomes loaded with tolbutamide: the ether injection method and the physical dispersion method both methods maintained the same cholesterol ratio while increasing the lecithin concentration by 1:1, 1:2, and 1:3 [11,12,13].

**Physical Dispersion Method: -**

The physical dispersion approach was used to create liposomes while maintaining a consistent ratio of soy lecithin to cholesterol. Using this procedure, cholesterol and soy lecithin were dissolved in chloroform.

After that, it was spread out over a conical flask with a flat bottom and left to evaporate overnight at room temperature without agitating the solution to prevent the formation of a lipid layer.

The medication was dissolved in a pH 6.8 phosphate buffer. It functions as a medium that is watery. The lipid film was then hydrated by adding the aqueous medium of flask, and the flask was gradually brought back to its upright position.

In order to complete hydration, the conical flask was then placed on a water bath with a temperature maintained at 37± 2ºC for two hours.

The conical flask was shaken gently until the lipid layer was separated from the flask wall and a suspension of liposomes formed. After that, the liposome suspension was kept at 4ºC for a day in order to allow the liposomes to mature. For 20 minutes, the prepared liposome suspension was centrifuged at 15,000 rpm. For additional research, the precipitate was then gathered and diluted with distilled water12. The overall procedure outlined above was followed to manufacture several batches of liposomes, and Table No. 1 provides the composition needed to prepare liposomes [15-16].

**The ether injection technique: -**

The ether injection approach was used to create liposomes while maintaining a consistent ratio of cholesterol to soy lecithin. This procedure involved dissolving the cholesterol and soy lecithin in methanol and ether.

The medication was dissolved in a pH 6.8 phosphate buffer. It functions as a water-based media. 60°C was reached by heating the aqueous medium. Ether-lipid solutions are injected drop by drop into the heated aqueous medium above as part of the procedure.

When the ether comes into contact with the aqueous phase, it vaporizes, and the lipid that is disseminated mostly forms Uni-lamellar liposomes. After that, the product was gathered and kept at 4°C to allow the liposomes to mature.

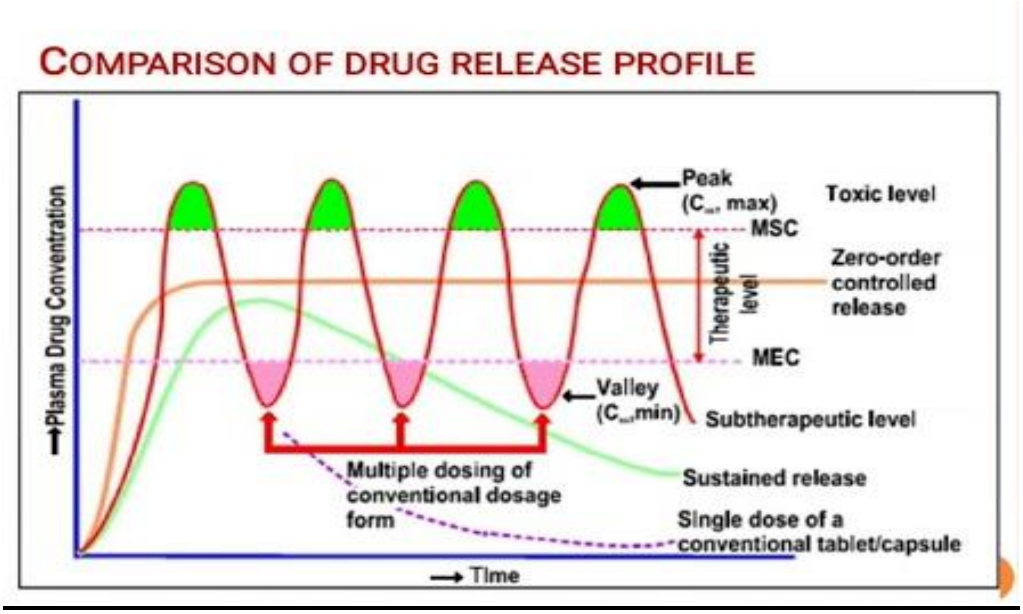
Then prepared liposomal suspension was centrifuged at 15,000 rpm for 20 mins. The precipitate was diluted with distilled water for evaluation studies. Different batches of liposomes were prepared as per the general method described above and composition for the preparation of liposomes is given in Table No. 1[17-18].

***Tolbutamide sustained release tablet formulation table are as follows:-***

**Formulation table 1**

| Ingredient | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Tolbutamide | 50mg | 50mg | 50mg | 50mg | 50mg |
| Starch | 10mg | 20mg | 15mg | 14mg | 18mg |
| Magnesium Stearate | 15mg | 4mg | 8mg | 20mg | 17mg |
| Lactose | 20mg | 18mg | 7mg | 6mg | 10mg |
| Talc powder | 5mg | 8mg | 20mg | 10mg | 5mg |

***FTIR Analysis: -***




**FTIR Spectra of Tolbutamide Sustained Release Tablet.**

- **Process: -**
  - **A) Tablets are prepared by three methods: -**
    - **1) Direct compression**
    - **2) Wet granulation method**
    - **3) Dry granulation metho**

**(1) Direct Compression: -**

Direct compression involves direct compressing the powdered material into tablets. Direct compression is adopted, if drug constitutes major portion of tablet [86-90] total weight (Figure 1).

Tablets containing 25% or less of drug substances can be formulated, with a suitable diluent which acts as a carrier or vehicle for the drug.

Tablets prepared by above method are subjected to compression machine which may be single station or multiple stations.[20]

**(2) Wet Granulation Method:** -This method is the most prevalent and commonly utilized approach. It consists of several steps, such as weighing ingredients, mixing, granulation, and screening the damp mixture, followed by drying, lubrication, and tablet compression.

The primary active ingredient, diluent, and disintegrant are combined, and then the mixture is sifted through a sieve. Binding agent solutions are introduced to the initial blend while stirring.

The quantity of binding agent added must be adequate to prevent excess moisture in the tablet. If the powder is insufficiently wetted, the granules may become too fragile and could break during the lubrication process, complicating tablet compression.

Tray drying is the most prevalent technique for drying tablet granules. Historically, tray drying was the most commonly utilized method for drying tablet granulations, though it may now be supplanted by fluid-bed dryers as a modern alternative.

Once the granules are dried, they are passed through a screen, typically made of 60-100 mesh nylon cloth. Following the dry granulation process, a lubricant in fine powder form is added, which is necessary for effective filling of the die cavity (Figure 1). [21,22]

**B) Dry granulation method: -**

This technique is used to prepare tablets; slugging may be employed to create the granules if the ingredients are extremely sensitive to moisture or cannot withstand high drying temperatures.

Dry granulation or twofold compression typically removes a number of processes that require the powder mass to be slugged.

The slug is created by blending the lubricant, diluent, and active substance. The remaining lubricant is then added to the granulation, well mixed, and compressed to create the tablets after the compressed slug has been sent through the mesh or mill (Figure 1).[23]


**Fig: - Processing steps in Direct Compression, Wet Granulation and Dry Granulation.**

## Evaluation of Tablet: -

**1. General appearance: -**

Consumer acceptance, lot-to-lot uniformity, and tablet-to-tablet uniformity are all dependent on a tablet's overall look, identity, and elegance. Measurements of size, shape, colour, odour, taste, and other characteristics are all part of the overall appearance control process.

**2. Size and shape: -**

It is controllable and dimensionally characterized. A tablet's thickness is merely a variable. A micro-meter or another tool can be used to measure the thickness of tablets. The thickness of tablets should be kept within a standard deviation of ± 5%.

**3. Unique identification marking: -**

These markings make use of printing, engraving, or embossing. These markings consist of the product code, product name, company name, or emblem, among others.

**4. Organoleptic properties: -**

Colour distribution must be uniform with no mottling. For visual colour comparison compare the colour of sample against standard colour.

**5. Hardness and Friability: -**

To endure the mechanical stresses of handling during manufacturing, packaging, and transportation, tablets need to have a specific level of strength, hardness, and resistance to friability. The crushing strength of tablets is often measured by hardness.

**Fig: - Pfizer type hardness tester.**


**Fig: - Monsanto hardness tester.**

***6. Friability: -***

A Roche friabilator can be used in a lab to test a tablet's friability. This consists of a plastic chamber that rotates at 25 rpm and drops the tablets into the friabilator six inches away. It then runs for 100 revolutions. They weigh the tablets again. It is deemed appropriate to compress tablets that lose less than 0.5% to 1.0% of their weigh

**Fig: - Friability Apparatus.**

 ***Drug content and release: -***

**1) Weight variation test (USP): -**

Weigh each of the twenty tablets. Determine the average weight and contrast it with the weight of each tablet. If no more than two tablets deviate from the percentage restriction and if no tablet deviates by more than twice the percentage limit, the tablet passes the USP test.

**2) Content Uniformity Test: -**

Choose 30 tablets at random. Ten of these were tested separately. If nine out of ten tablets have at least 85% and no more than 115% of the drug's listed content, and the tenth tablet has at least 75% and no more than 125% of the labelled content, the tablet passes the test. The remaining 20 tablets will be tested separately if these requirements are not fulfilled, and none of them may fall outside the 85–115% range.

**3) Disintegration Test (USP): -**

The U.S.P. apparatus for disintegration testing comprises six 3-inch glass tubes with a 10-mesh screen at the bottom and an open top. In order to measure the disintegration time, one tablet is put in each tube, and the basket rack is set up in a 1-liter beaker of water, simulated gastric fluid, or simulated intestinal fluid at 37 ± 2 0 C so that the tablet stays 2.5 cm below the liquid's surface when it moves upward and stays no closer than 2.5 cm from the beaker's bottom when it moves downward. Move the tablet basket up and down at a frequency of 28 to 32 cycles per minute over a distance of 5 to 6 cm.

Placing perforated plastic disks on each tablet will stop them from floating. The test states that the tablet must break up and that every particle must go through the 10-mesh screen within the allotted time. Any residue that is left over ought to have a soft bulk. Time of disintegration: Tablet without coating: 5 to 30 minutes Tablet coated: 1-2 hours.


**Fig: - Disintegration Test Apparatus.**

## Dissolution Test (USP): -

**Apparatus 1: -**

One tablet is positioned inside a tiny wire mesh basket that is fastened to the shaft's bottom and is connected to a variable speed motor. A 100 ml flask containing a dissolution medium (as described in the monograph) is submerged in the basket. The flask has a hemispherical bottom and is cylindrical. A continuous temperature bath keeps the flask at 37±0.50C. To measure the amount of medication in solutions, the motor is set to rotate at a predetermined speed, and fluid samples are taken periodically.

**Apparatus 2: -**

It is identical to apparatus 1, with the exception that a paddle is used in place of the basket. Before stirring, the dosage form is given time to drop to the bottom of the flask. The U.S.P. for the dissolution test outlines the assay technique, the type of apparatus to be used, the shaft's rpm, the test time limit, and the dissolution test medium and volume. The percentage of the stated amount of medication dissolved within the allotted time is used to express the test tolerance.[23]

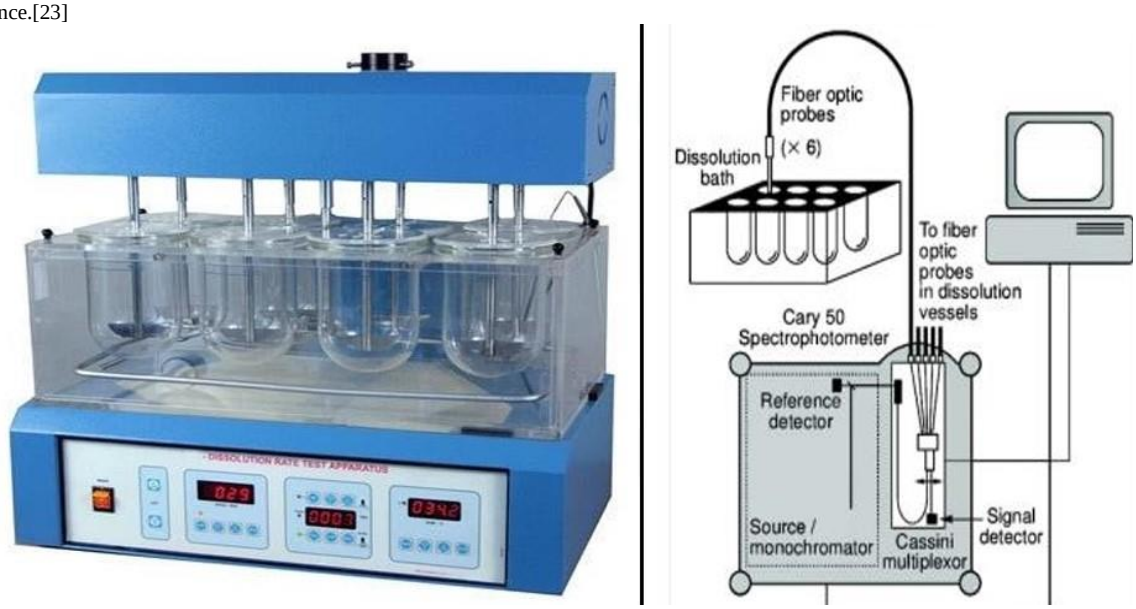



**Fig: - Dissolution Test Apparatus.**

## Result and Discussion: -

***Pre formulation tests:***

**Table 2: Pre-formulation Test results**

| Sr. No. | Test | Result |
|---|---|---|
| 1 | Colour | White |
| 2 | Odour | Odourless |
| 3 | Taste | Tasteless |
| 4 | Angle of repose | 38.72° |
| 5 | Bulk Density | 0.23g/ml |
| 6 | Tapped Density | 0.5 gm/cm$^3$ |
| 7 | Carrs index | 4% |
| 8 | Solubility | Sparingly soluble in water |
| 9 | Melting Point | 127°C |

**Table 3: -: Pre compressional parameters of Tolbutamide tablets**

| Sr. No. | Formulation | Angle of repose | Bulk density gm/cc | Tapped density gm/cc | Carrs index | Hausners ratio |
|---|---|---|---|---|---|---|
| 1 | F1 | 24.37±1.732 | 0.3±0.006 | 0.37±0.002 | 18.91±0.13 | 1.23±0.002 |
| 2 | F2 | 26.39±0.093 | 0.36±0.007 | 0.42±0.05 | 14.285±0.10 | 1.17±0.09 |
| 3 | F3 | 23.61±2.312 | 0.32±0.001 | 0.42±0.07 | 23.809±0.17 | 1.13±0.09 |
| 4 | F4 | 22.41±1.025 | 0.36±0.043 | 0.44±0.09 | 18.181±0.21 | 0.73±0.04 |
| 5 | F5 | 25.21±1.992 | 0.330±0.006 | 0.4±0.09 | 17.05±0.19 | 1.21±0.03 |

**Table 4: - Post compressional parameters of Tolbutamide tablets**

| Batch no. | Hardness kg/cm$^2$ ±SD, n=6 | Friability ±SD, n=10 | Weight variation n=20 | Thickness (mm) ±SD, n=6 | Drug content (%), (±SD), n=3 |
|---|---|---|---|---|---|
| F1 | 6.28 ±0.01 | 0.32 ±0.01 | 1.91 | 5.13 ±0.02 | 99.70 ±0.45 |
| F2 | 6.76 ±0.36 | 0.76 ±0.01 | 1.20 | 5.06 ±0.02 | 98.18 ±0.85 |
| F3 | 6.23 ±0.01 | 0.82 ±0.01 | 1.77 | 5.15 ±0.02 | 98.81 ±0.83 |
| F4 | 5.36 ±0.35 | 0.49 ±0.01 | 2.15 | 5.18 ±0.02 | 99.04 ±0.45 |
| F5 | 6.41 ±0.36 | 0.59 ±0.01 | 2.34 | 5.21 ±0.02 | 98.88 ±0.62 |

## Conclusion:

The development of a sustained release formulation of Tolbutamide was achieved successfully, allowing for a controlled and extended therapeutic effect that decreases the dosing frequency and promotes better patient adherence. By meticulously selecting matrix-forming polymers and refining formulation parameters, the resulting tablets demonstrated favourable physical characteristics, consistent drug content, and a prolonged drug release profile throughout the specified duration. In vitro release studies showed a sustained release pattern that corresponds with the desired pharmacokinetic requirements for effective management of type 2 diabetes mellitus. In summary, the Tolbutamide sustained release tablets represent a promising option compared to traditional immediate-release formulations, potentially enhancing therapeutic results and reducing side effects related to fluctuations in plasma levels.

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