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Design and Characterization of Chronomodulated Delivery of Tolbutamide for the Treatment of Diabetes Mellitus

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ABSTRACT

Background and Objectives: The study was aimed to formulate and evaluate the chronomodulated drug delivery containing Tolbutamide by releasing the drug with predetermined lag time. Tolbutamide is used to reduce blood glucose in patient with type 2 diabetes. In the present work the chronomodulated drug delivery system of Tolbutamide was designed to control early morning hyperglycemia to synchronize the circadian rhythm of Diabetes mellitus. When ingested at the bed time in the night, produce effective control of the increased blood glucose level after intake of meals by allowing the drug to release after a lag time of 5 h. The coating with Eudragit S 100 reduces the gastric irritation caused by Tolbutamide and also ensures site specific drug delivery. **Materials and Methods:** The cores tablet was prepared by using various concentrations of croscarmellose and sodium starch glycolate as superdisintegrents. The core tablet of Tolbutamide was prepared by direct compression method and then coated with Eudragit S100 as a coating polymer (dip and dry method). The powder blend of chronomodulated Tolbutamide tablet were subjected to the preformulation studies like the angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio. The prepared tablets were subjected to all quality control tests and also perform *in-vitro* dissolution study. **Results and Conclusion:** Formulation F4 show maximum drug release of 91.57% after lag time of 5 hrs. Hence it may be concluded that the newly formulated chronomodulated drug delivery systems of Tolbutamide, when ingested at the bedtime in the night, produce effective control of the increased blood glucose level.

1.1 INTRODUCTION

Chronotherapeutics is defined as a clinical practice of synchronizing the drug release or the drug delivery with body's circadian rhythm to improve the health benefits and reduce harm to the patients. [1, 2] Pulsatile drug delivery system can be defined as the rapid and transient release of a certain amount of drug molecules within a short period of time immediately after a predetermined lag time. Lag time is nothing but the time between when a dosage form is placed into an aqueous environment and the time at which the active ingredients starts to release from the dosage form. These systems are mainly designed for the diseases that show the chronopharmacological behavior and where the dose of the drug is required for extended daytime or night time activity and also for the drugs that shows the high first pass effect or have a site specific absorption in the GIT, or the drugs having high risk of toxicity. Diseases in which the pulsatile drug delivery systems are likely to be successful are asthma, cardiovascular diseases, peptic ulcer, rheumatoid arthritis, hypertension and hypercholesteremia. [3,4]

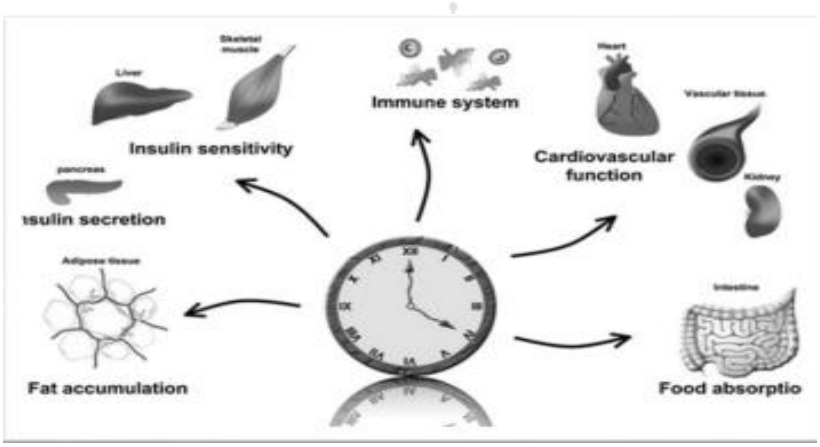

Figure 1: Disease displaying circadian rhythm [5]

1.1.1 Requirements for Ideal ChrDDS:

An ideal system should be, [6, 7]

- A time controlled and site specific delivery system.
- Self-regulatory when administered any time in a day, and should account for certain environmental factors like day-night, activity-rest status, awake-sleep.

- Easy for administration which will effectively improve patient compliance towards the dosage regimen.
- A system that havs a real time and specific triggering biomarker for a specific disease state.
- Non-toxic and it should be safe to use with approved limits.
- A system that has a feedback controlled system.
- Easy to manufacture and should be economic.

Table 1: Diseases requiring the ChrDDS[8]

Disease or syndrome	Circadian rhythmicity
Allergic rhinitis	Worse in the morning/upon rising
Asthma	Exacerbation is more common during sleep
Rheumatoid arthritis	Symptoms are more on awakening
Osteoarthritis	Symptoms get worsen in the middle of a day
Angina pectoris	Variation in the ECG and chest pain are more common in early morning
Myocardial infarction	Greater chance in early morning
Stroke	High chance in the morning
Sudden cardiac death	Incidence is higher in the morning

1.1.2 Diabetes mellitus

The word diabetes has been derived from two words, diabetes (Greek) which means “siphon through” and mellitus (Latin) which means “sweetened with honey”.it is a group of metabolic diseases characterized by hyperglycemia resulting from defect in insulin secretion, insulin action or both. There are three main types of diabetes mellitus, Type I DM results from the pancreas failing to produce enough insulin. This from was previously referred to as “insulin-dependent diabetes mellitus” (IDDM) or “juvenile diabetes.” Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. This form was previously referred as “non-insulin dependent diabetes mellitus”. Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop high sugar levels. [9]

1.1.3 Circadian rhythmicity and Diabetes mellitus [10]

Diabetes has become an epidemic. In 2017, as per the International Diabetes Federation, an estimated 451 million people had diabetes. Its prevalence is increasing rapidly, and by 2030, this number is estimated to be almost double. There are many conventional dosage forms available in the market to treat the condition of diabetes. This study emphasizes on treating diabetes based on circadian rhythm. Hence, the pulsatile type of delivery system was designed and was characterized. The terminology pulsatile consists of the word "Pulse," indicating a rhythmic beat. The pulsatile system is often misunderstood as a chronotherapeutic system. It comprises the release of drug after a definite lag time followed by abrupt or prompt release.

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The circadian rhythm regulates many body functions in humans, namely metabolism, physiology, behavior, sleep patterns, and hormone production. It has been reported that more shocks and heart attacks occur during morning hours.

The patients with diabetes are reported to have high blood sugar levels after meals compared to other timings. Almost all chronotherapeutic systems intended for treating the conditions following the circadian rhythms release the drug after a lag phase in one single attempt. There is no single system developed for such conditions, which can release the drug in multiple pulses unless the formulation is intended to be taken more than once daily.

These systems are beneficial for drugs having a high first-pass effect, drugs administered for diseases that follow chronopharmacological behavior, drugs having a specific absorption site in gastrointestinal tract (GIT), targeting to the colon, and cases where night-time dosing is required. Chronotherapy targets the medication administered at the time when they are required the most.

Hence in the present research work a novel chronotherapeutic approach has been made to formulate chronomodulated release tablets of Tolbutamide with a lag time of about 5 h to control the early morning hyperglycemia in non-insulin dependent diabetic patients. Thus, this new dimensional approach of chronomodulated tablet of Tolbutamide taken at bed time,

releasing drug in the morning hours can prove to be a revolution in the treatment of early morning hyperglycemia.

MATERIALS AND METHODS

MATERIALS

Tolbutamide, Eudragit S 100 was obtained from Yarrow chem products, Mumbai. Starch glycolate, Croscarmellose sodium, Magnesium stearate, Microcrystalline cellulose, Talc, Acetone were obtained from Nice chemicals, Cochin. All the materials and reagents were of analytical grade.

2.1 PREFORMULATION STUDY OF DRUGS

Preformulation is a group of studies that focus on the physiochemical properties of a new drug candidate that is responsible for the drug performance and the development of dosage form. This property gives the framework for the drug combination with pharmaceutical ingredients in the design of a dosage form. To develop an elegant, effective, stable and safe dosage form by establishing kinetic rate profile, compatibility with other pharmaceutical ingredients and establishing the physicochemical parameter of new drug substances are the major objectives of the Preformulation studies. Following are some of the important parameters evaluated during Preformulation studies. [11]

2.1.1 Physicochemical Evaluation of Drug

2.1.2 Description study of Tolbutamide

The initial evaluation during Preformulation studies is the descriptive study which evaluates the color and odor of the substance.

2.1.3 Determination of solubility of Tolbutamide

Solubility is the analytical composition of saturated solution expressed as a proportion of designated solute in a designated solvent. Aqueous solubility is an important physicochemical property of the drug substance which determines the systemic absorption as well as the therapeutic efficacy. Based on the quantity of the solvent required to dissolve one gram of pure drug substance, the solubility of drugs can be categorized as follows. [12]

Table 2: Solubility specification

Descriptive Terms	Part of solvent requires/ Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000

2.1.4 Determination of λmax of drugs

- **Determination of λmax of Tolbutamide in 0.1N HCl**

The wavelength of maximum absorption is distinct for each drug and it is determined using a UV spectrophotometer. 5mg of the pure drug was dissolved in 50ml of 0.1N HCl then 5ml is pipette out from this solution into a 10ml standard flask and made up to the volume. The λmax was determined by using a UV spectrophotometer.

- **Determination of λmax of Tolbutamide in pH 6.8 phosphate buffer**

The λmax of Aspirin was determined by using UV spectrophotometer. 5mg of the Tolbutamide was dissolved in 50ml of pH 6.8 phosphate buffer and 5ml of this solution was pipette out into a 10ml standard flask and made up to the volume. The wavelength of maximum absorption was finally noted. [13]

2.1.5 Preparation of Standard plot of Tolbutamide

- **Standard plot of Tolbutamide in 0.1N HCl**

Accurately weighed 10 mg of Tolbutamide was dissolved in 60 ml 0.1N HCl and volume was made up to 100ml in the volumetric flask using 0.1N HCl to prepare the stock solution (100µg/ml). From this stock solution, 0.5 ml solution was withdrawn and diluted up to 10 ml in a volumetric flask (5µg/ml). In the Same way solutions of 2, 4, 6, 8 and 10 µg/ml were prepared. The absorbance of each solution was measured at 246nm using 0.1N HCl as a reference standard.

➢ **Standard plot of Tolbutamide in pH 6.8 phosphate buffer**

Accurately weighed 10 mg of Tolbutamide was dissolved in 60 ml phosphate buffer (pH 6.8) and volume was made up to 100 ml in the volumetric flask using phosphate buffer (pH 6.8) to prepare the stock solution (100µg/ml). From this stock solution, 0.5 ml solution was withdrawn and diluted up to 10 ml in a volumetric flask (5µg/ml). In the Same way solution of 2,4,6,8 and 10 µg/ml was prepared. The absorbance of each solution was measured at 248nm using phosphate buffer (pH 6.8) as a reference standard. [14]

2.1.6 Determination of melting point of Tolbutamide

The temperature at which the first particle starts to melt and the last particle completely melts is regarded as the melting range and this is called as its melting point. The capillary tube was placed in an electrically operated melting point apparatus and the temperature at which the drug melts was recorded. This was performed thrice and average value was noted. [15]

2.1.7 Drug-polymer compatibility studies

In the preparation of tablet formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studied regarding the drug-polymer interaction is therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Tolbutamide and the selected polymers. The pure drug, polymers, and drug with excipients were scanned separately.

3.1 Preparation of chronomodulated Tolbutamide tablet [16]

3.1.1 Procedure for preparation of Tolbutamide core tablet

The tablets were prepared by direct compression method. The drug, diluents and superdisintegrents were passed through sieve No 40. All the above ingredients were properly mixed together. Talc and magnesium stearate was passed through sieve No 80, mixed and blended with initial mix. The powder blend was compressed using multiple punch tablet compression machine. Each tablet contains 500 mg of Tolbutamide.

3.1.2 Procedure for preparation of chronomodulated Tolbutamide coated tablet

The coating solution was developed by dissolving Eudragit S 100 (20%) in acetone and isopropyl alcohol mix solvents and then Polyethylene glycol (2%). The resulting solution was adjusted with acetone and isopropyl alcohol mixed solvents. The core tablets were coated

using dipping and drying method and increase in weight percent after coating was determined as the coating level.

Table 3: Formulation design of chronomodulated Tolbutamide tablet.

Sl. No	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1	Tolbutamide	500	500	500	500	500	500
2	Microcrystalline cellulose	123	122	121	120	119	118
3	Cross carmellose	1	1.5	2	-	-	-
4	Sodium starch glycolate	-	-	-	1	1.5	2
5	Talc	1	1.5	2	2.5	3	3.5
6	Magnesium Stearate	2	2	2	2	2	2
	Total	627	627	627	627	627	627

Precompression parameters

The FTIR, Angle of repose, Bulk density, Tapped density, Compressibility index, Hausner's ratio were determined for all formulations of powdered blend. Table 2.

4.1 Precompression parameters [17]

4.1.1 Angle of repose

Fixed funnel and free standing cone method are used to measure the static angle of repose "Ɵ". It is the maximum angle possible between the surface of a pile of powder and the horizontal plane. A paper was placed on a flat horizontal surface and above which the funnel was clamped with its tip 2 cm height. The powder blend was poured separately through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameters of the base of the powder cones were determined and the tangent of the angle of repose was calculated using the equation,

$$\tan Ɵ = h/r$$

h = height of granule pile

r = radius of tablet granules

Angle of repose (Ɵ) = $\tan^{-1}$ (h/r)

Table 4: Flow property according to the Angle of repose

Flow property	Angle of repose
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65

4.1.2 Bulk density

Bulk density is ratio of total mass of powder to the bulk volume of the powder. Bulk density is expressed as g/cm3. The bulk density of a powder primarily depends on particle size distribution, particle shape and tendency of particles to adhere together. Required quantity of powder sample was in a measuring cylinder and the volume, Vb, occupied by each of the samples without tapping the measuring cylinder was noted and this gives you the bulk density. The bulk density was calculated using the following equation;

Bulk density = Weight of sample/ Bulk volume (Vb)

4.1.3 Tapped density

It is defined as the ratio of total mass of the powder to the tapped volume of the powder. The tapped density can be measured by pouring a specified quantity of powder sample through a glass funnel into a 50ml graduated cylinder. The cylinder is tapped from a height of 2cm until a constant weight is obtained. After 100 taps, the volume occupied by the powder is measured and this is called as the tapped volume the tapped density was calculated using the formula;

Density = Weight of sample/ Tapped volume (Vt)

4.1.4 Hausner's ratio

This is measured as the ratio of tapped density to the bulk density. This can be expressed using the equation,

Hausner's ratio = Tapped density/ Bulk density

4.1.5 Compressibility index

Compressibility is the ability of the powder to reduce its volume under pressure. This was calculated by using the equation;

Compressibility index = (Tapped density- bulk density)/ tapped density*100

Table 5: Flow property of powder based on the 1) Angle of repose, 2) Compressibility index, 3) Hausner's ratio

Angle of repose	Compressibility index	Hausner's ratio	Flow property
25-30	<10	1-1.1	Excellent
31-35	11-15	1.12-1.18	Good
36-40	16-20	1.19-1.25	Fair
41-45	21-25	1.26-1.34	Passable
46-55	26-31	1.35-1.45	Poor
56-65	32-37	1.46-1.59	Very poor
>66	>38	>1.60	Very, very poor

5.1 Post compression parameters of chronomodulated tolbutamide tablets [18]

5.1.1 Hardness

Three tablets are randomly picked and hardness was determined. Hardness can be measured using the Monsanto Hardness tester and can be expressed in kg/cm^2.

5.1.2 Thickness

The thickness of tablet was measured by vernier calipers.

5.1.3 Weight variation

Twenty tablets were collected randomly and weighed individually. The individually weighed tablets were compared with an average weight for the determination of weight variation. The uniformity of weight is determined according to I.P specification. As per USP specification, not more than two of the individual weight should deviate from average weight by more than 5% and none deviate more than twice that percentage. The percentage of deviation was calculated using the equation;

% Deviation= (Individual weight-Average weight / Average weight) *100

Table 6: Weight variation specification as per IP (2007)

Average weight of tablets (mg)	Percentage difference (%)
125 or less	10
125-250	7.5
More than 250	5

5.1.4 Friability

The Friability of the tablets can be tested using Roche friabilator. It is expressed in percentage (%). Initially 6 tablets were weighed (Wi) and were transferred into the Roche friabilator and operated at 25 revolutions for 4 minutes. The tablets were again weighed (Wf). Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered as acceptable. The percentage friability was then calculated using the equation;

$$\% \text{ friability (F)} = \frac{\text{(Initial weight (Wi) – Final weight (Wf))}}{\text{Initial weight (Wi)}} \times 100$$

5.1.5 Disintegration test

Disintegration test was performed using an altered disintegration method with six tablets (n=6). The USP disintegration test apparatus was maintained at a temperature of 37±0.5°C. The test was performed using 0.1N HCl and 6.8 pH phosphate buffer respectively.

5.1.6 Drug content

Drug content uniformity is determined by estimating the API content in an individual tablet. Limit of content uniformity is 85-115 percent. 20 tablets were weighed individually then placed in a mortar and powdered with a pestle. An amount of powdered Tolbutamide (100mg) was dissolved in 100ml of suitable buffer (6.8 pH phosphate buffer). The absorbance was measured at 248nm after suitable dilution.

5.1.7 *In-vitro* Drug release studies [19]

Dissolution parameters

Medium: 0.1N HCl (pH 1.2), Phosphate buffer (pH 6.8)

Apparatus: USP dissolution apparatus II (Paddle type)

RPM: 50

Temperature = 37 ± 0.5°C

Volume: 900ml

The dissolution studies of the chronomodulated tablets containing Tolbutamide was carried out using 900 ml of 0.1N HCl for 2h followed by pH 6.8 phosphate buffer solution. The set condition was 37±0.5°C, 50 rpm, and paddle type USP II apparatus. Aliquots were withdrawn for every one hour interval and were replaced immediately with the same volume of fresh buffer medium. Aliquots, following suitable diluents were assessed spectrophotometrically at 248nm.

5.1.8 Stability studies

Stability studies were performed at a temperature of 40°c at 75%RH, over a period of three months (90days) on the promising chronomodulated tablet of Tolbutamide. Sufficient number of tablets (15) were packed in amber colored screw capped bottle and kept in stability chamber maintained at 40°±1°c&RH.sample were taken at monthly intervals. At the end of three months period hardness, dissolution test and % drug content studies were performed to determine the drug release profiles and drug content. [20]

6.1 RESULT AND DISCUSSION

6.1.1 Physical description of API

Table 7: Physical description of API

Sl. No.	API	Colour	Odor	Nature
1	Tolbutamide	White	Odorless	Non hygroscopic crystalline powder

The color, odor and the nature of the API were same as that mentioned in the BP and USP.

6.1.2 Solubility

The solubility of Tolbutamide was checked in different solvents. It was practically insoluble in the water. But the solubility profile changes in the organic solvents.

6.1.3 λmax determination

- **Determination of λmax of Tolbutamide in 0.1N HCl**

The UV range between 200-400nm was scanned for absorption maxima of Tolbutamide using Schimadhzu UV-1700 series.

Table 8: λmax of Tolbutamide in 0.1N HCl

Sl. No.	λmax in 0.1N HCl
1	243nm

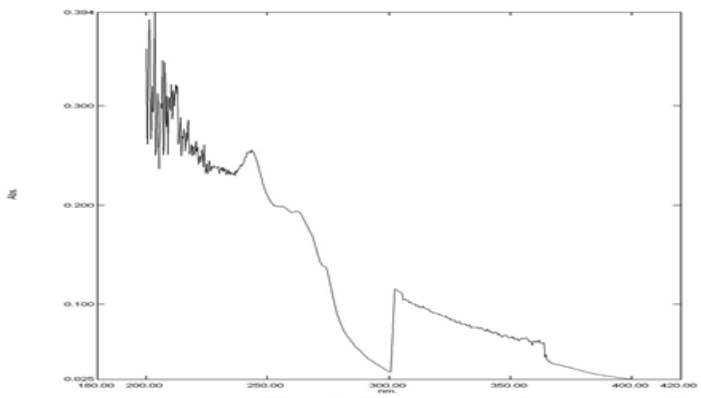

Figure 2: λ max of Tolbutamide in 0.1N HCl

- **Determination of λmax of Tolbutamide in pH 6.8 phosphate buffer**

Table 9: λmax of Tolbutamide in pH 6.8 phosphate buffer

Sl. No	λmax in pH 6.8 phosphate buffer
1	248nm

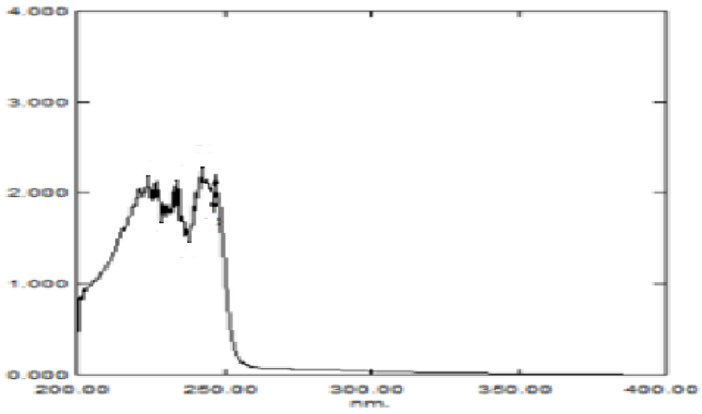

Figure 3: λmax of Tolbutamide in pH 6.8 phosphate buffer

The λmax of the Tolbutamide was found to be 243nm in 0.1N HCl and 248nm at pH 6.8 phosphate buffer. Since the Tolbutamide is formulated as chronomodulated release, the λmax of pH 6.8 phosphate buffer is used for calculations. The obtained λmax value was same as that of the reference value.

6.1.4 Preparation of standard plot

- **The Standard plot for Tolbutamide in 0.1N HCl**

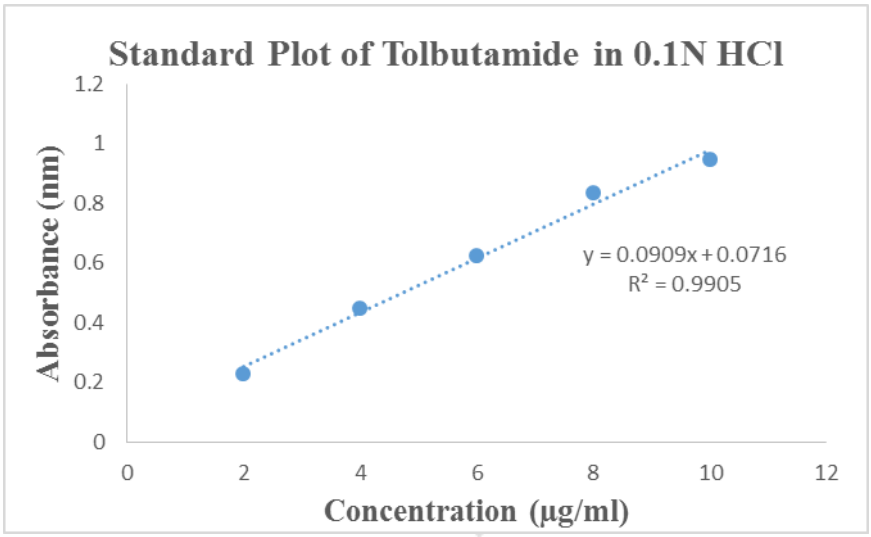

Figure 4: Calibration curve of Tolbutamide in 0.1N HCl

- **The Standard plot of Tolbutamide in pH 6.8 phosphate buffer**

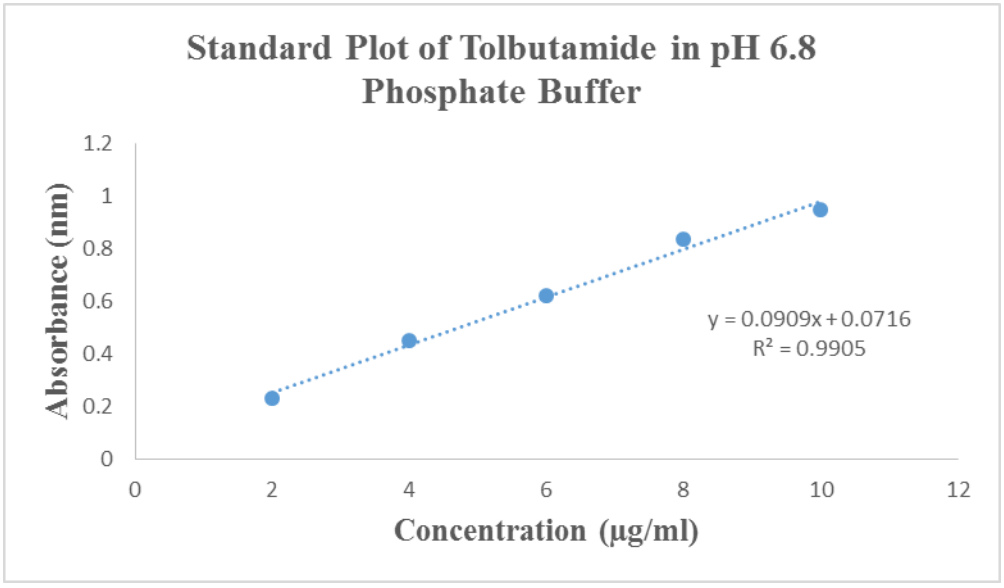

Figure 5: Calibration curve of Tolbutamide in pH 6.8 phosphate buffer

The calibration concentration range in 0.1N HCl and pH 6.8 buffer was increased in a linear manner and a straight line was observed in both the curves.

6.1.5 Compatibility Studies

FT-IR spectrum was used to study the possible interaction between API (Tolbutamide) and excipients. Each polymer included for the formulation was mixed with the drug, polymer and mixture was analyzed by IR Spectroscopy. Infrared spectra matching approach was used for the detection of any possible chemical reaction between drug and excipients. The characteristics peak due to pure Tolbutamide has appeared in the spectra without any makeable changes in the position.it indicates that there was no chemical interaction between Tolbutamide and polymers.

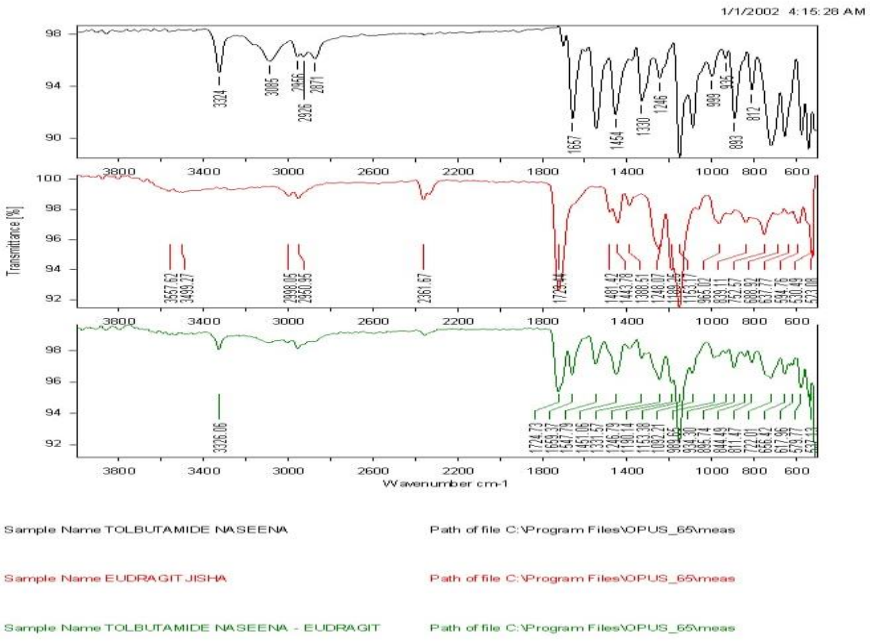

Figure 6: FTIR spectra of Tolbutamide, Eudragit S 100 and Tolbutamide

6.1.6 Assessment of Melting point

Table 10: Melting point of Tolbutamide

Sl. no	Parameter	Observed value	Reference value
1	Melting point	128.6°C	128.5-129.5°C

The melting point was checked with melting point apparatus. The melting point value was found to128.6°C be same as that mentioned in the monograph.

6.1.7 Precompression parameters

The powder blend of chronomodulated Tolbutamide tablet was subjected to the Preformulation studies like angle of repose, bulk density, tapped density, Carss' index, Hausner's ratio. The results of these Preformulation studies indicated that the powder blend shows good flow properties. The tablet was subjected to various evaluation studies.

Table 11: Precompression studies of Tolbutamide powder blend

Parameters	F1	F2	F3	F4	F5	F6
Angle of repose (°)	26.56	26.18	25.25	24.91	25.42	25.81
Bulk density (g/cm^3)	0.442	0.486	0.529	0.501	0.498	0.483
Tapped density (g/cm^3)	0.506	0.556	0.593	0.564	0.559	0.542
Compressibility index	12.64	12.58	10.78	11.17	10.91	10.88
Hausner's ratio	1.144	1.144	1.12	1.125	1.122	1.122

7.1 Formulation of chronomodulated tablet of Tolbutamide

The chronomodulated tablet of Tolbutamide was prepared using the direct compression method. Effect of the Sodium starch glycolate and Croscarmellose sodium concentrations on the release profile of the pulsatile release layer of Tolbutamide were investigated.

Figure 7: Prepared Chronomodulated Tablet of Tolbutamide

8.1 Post compression parameters

The hardness was found to be very high in F1 formulation, when compared to other five beaches. But a satisfactory result in hardness was found in F4 formulation. All the formulated tablets were passed weight variation test as the weight variation was within the IP limits of ±5% of the weight. Friability of all tablets were in the acceptable range (<1%). The friability of the formulations was in the range of 0.42±0.025- 0.59±0.021.

The drug content was in the range of 90.05-98.97%. The drug content was increased in F4 formulation due to the optimum amount of super disintegrant that results in increased drug content value. There is no disintegration occuring 0.1N HCl and the disintegration in pH 6.8 was found to be the range of 117-124sec. When compared to other trial batches F4 was found to be more satisfactory, due to the presents of sodium starch glycolate (super disintegrant).

Table 12: Post compression studies of Tolbutamide powder blend

Sl. no	parameters	F1	F2	F3	F4	F5	F6
1	Hardness (Kg/Cm²)	5.9±0.59	5.7±0.67	3.9±0.21	4.7±0.45	5.1±0.42	4.1±0.14
2	Thickness (mm)	3.49±0.022	3.48±0.026	3.51±0.035	3.53±0.032	3.47±0.039	3.57±0.038
4	Friability (%)	0.51±0.012	0.59±0.021	0.57±0.014	0.42±0.025	0.53±0.021	0.58±0.024
5	Drug content (%)	90.05	91.44	92.34	98.97	94.33	93.65
6	Disintegration time(Sec)	121	122	124	117	118	120

In-vitro drug release studies revealed that the release of tolbutamide from different formulations varies with characteristics and composition of polymers. All the tablets, belonging to the six formulations showed a chronomodulated pattern of drug release. The comparison of the drug release profile of all formulations showed that formulation F4 shows maximum drug release of 97.57%.The stability studies showed that there was no significant difference in appearance, hardness, % friability, % drug content and %drug release when stored at 40°C/75% RH for 3 months.

Table 13: Result of in-vitro drug release of Tolbutamide tablet

SL No	Time (hr.)	% Drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	51.08	56.02	55.35	65.13	57.15	58.43
3	2	60.41	62.55	66.15	73.22	68.12	66.02
4	3	81.43	85.82	86.42	89.87	86.02	82.35
5	4	90.57	91.02	92.94	97.57	95.12	93.37

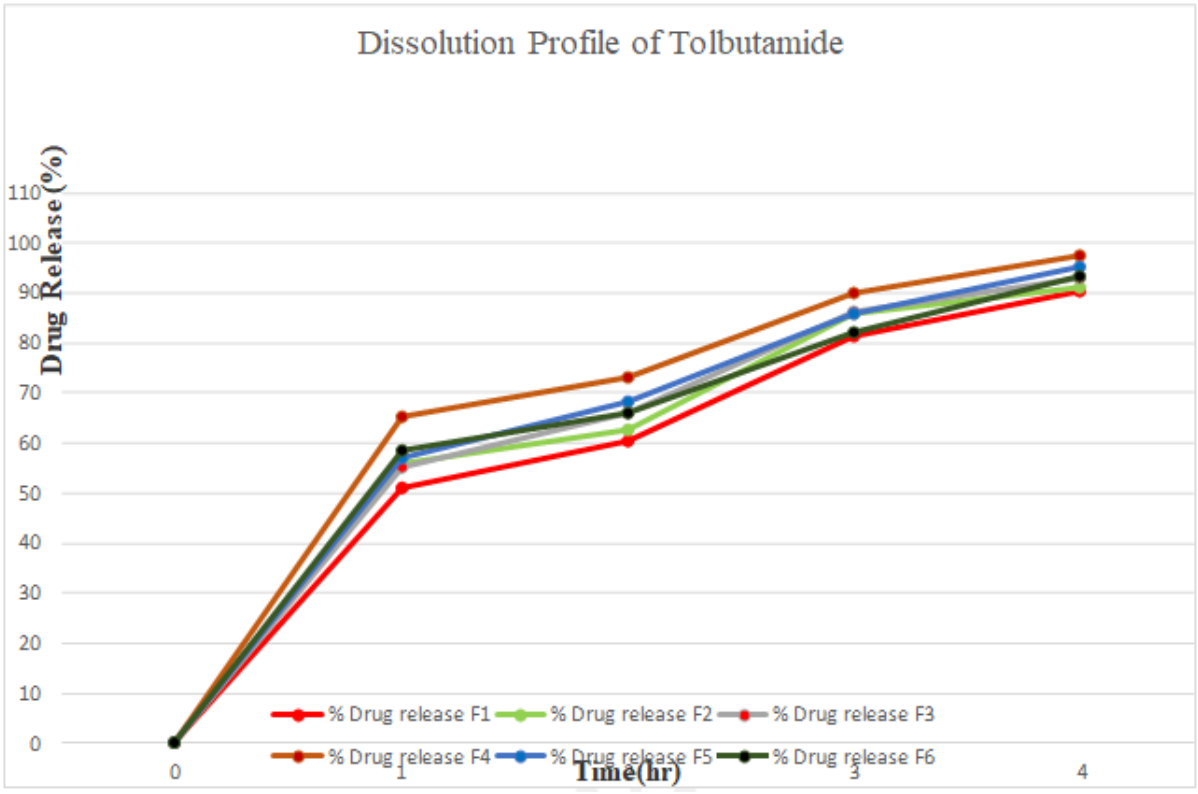

Figure 8: Dissolution profile of chronomodulated Tolbutamide tablet

9.1 DISCUSSION

The solubility of Tolbutamide were checked in different solvents. It was practically insoluble in the water. But the solubility profile changes in the organic solvents.. The results of these Preformulation studies indicated that the powder blend shows good flow property. The satisfactory result in hardness was found in F4 formulation. All the formulated tablets were passed weight variation test as the weight variation was within the IP limits of ±5% of the weight. The friability of the formulations was in the range of 0.42±0.025- 0.59±0.021.The drug content was in the range from 90.05-98.97%. The drug content was increased in F4 formulation due to the optimum amount of superdisintegrents that results in increased drug content value. There is no disintegration occur in 0.1N HCl and the disintegration in pH 6.8 was found to be the range of 117-124sec. When compared to other trial batches F4 was found to be more satisfactory, due to presents of sodium starch glycolate (super disintegrant).

Formulation F4 show maximum drug release of 97.57%.The stability studies showed that there was no significant difference in appearance, hardness, % friability, % drug content and %drug release when stored at 40°C/75% RH for 3 months.

9.2 CONCLUSION

The present study demonstrates the successful preparation of chronomodulated drug delivery system of Tolbutamide with an aim to lower the blood glucose in the early morning. The optimized formulation exhibited release profile closed to the predicted profile. Thus, the developed formulation can be considered as one of the promising preparation for the relief of early morning hyperglycemia.

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