IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

"Enhancement Of Solubility And Drug Release Modulation From Sustained Release Tablet By Using Sago As Natural Polymer"

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Abstract:

One of the key factors in achieving the optimum drug concentration in the systemic circulation for the desired (expected) pharmacological response is solubility, the phenomenon of solute dissolving in solvent to produce a homogeneous system. The main issue in developing formulations for new chemical entities as well as for generic development is low water solubility. Over 40% of the NCEs (new chemical entities) created by the pharmaceutical sector are essentially water insoluble. A significant difficulty for formulation scientists is solubility. Any medicine that is to be absorbed must be present in solution at the absorption site. Particle size reduction, crystal engineering, salt creation, solid dispersion, use of surfactants, complexation, and other techniques are used to increase the solubility of poorly soluble pharmaceuticals. These techniques include physical and chemical drug changes as well as additional approaches.

A sulfonyl urea known glimepiride is used to treat type II diabetes. The chemical name for glimepiride is C24H34N4O5S, and it has a molecular weight of around 490.617 g/mol. It falls under the Biopharmaceutical Classification System's Class II. It is hardly soluble in various organic solvents and buffers, but entirely insoluble in water and acidic solutions. It is taken orally, is soluble in Dimethyl Sulfoxide but insoluble in water, methanol, or methylene chloride (dichloromethane) (DMSO). Given this, many generic medication manufacturers are more likely to create bioequivalent oral drug formulations. The poor bioavailability of oral dose forms, however, presents the biggest design problem. Aqueous solubility, drug permeability, dissolving rate, first-pass metabolism, presystemic metabolism, and sensitivity to efflux mechanisms are some of the

variables that affect oral bioavailability. Poor solubility and inadequate permeability are the two most common causes of low oral bioavailability.

Keywords: Glimepiride, FTIR, U. V. Spectrophotometer, Hardness tester, Dissolution apparatus

Introduction:

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. Solubility is a major challenge for formulation scientist. Any drug to be absorbed must be present in the form of solution at the site of absorption. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation, and so forth.(1)

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution. The solvent is generally a liquid, which can be a pure substance or a mixture of two liquids. One may also speak of solid solution, but rarely of solution in a gas. The extent of solubility ranges widely, from infinitely soluble (fully miscible) such as ethanol in water, to poorly soluble, such as silver chloride in water. (2)

Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining (e.g., precipitation of solids). Solubility equilibrium occurs when the two processes proceed at a constant rate. Under certain conditions equilibrium solubility may be exceeded to give a so-called supersaturated solution, which is metastable Solubility is not to be confused with the ability to dissolve or liquefy a substance, since these processes may occur not only because of dissolution but also because of a chemical reaction. For example, zinc is insoluble in hydrochloric acid, but does dissolve in it by chemically reacting into zinc chloride and hydrogen, where zinc chloride is soluble in hydrochloric acid. (3) IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units. The partition coefficient (Log P) is a measure of differential solubility of a compound in a hydrophobic solvent (octanol) and a hydrophilic solvent (water). The logarithm of these two values enables compounds to be ranked in terms of hydrophilicity (or hydrophobicity).

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.

Glimepiride:

Glimepiride is a sulfonyl urea used to treat type –II diabetes mellitus. Molecular formula of glimepiride is C24H34N4O5S with a molecular mass of about 490.617g/mol. It belongs to class-II of Biopharmaceutical classification system. It is completely insoluble in water, acidic media and slightly soluble in various buffers and organic solvents. It is administered orally; insoluble in water, slightly soluble in methylene chloride (Dichloromethane), very slightly soluble in methanol and soluble in Dimethyl Sulfoxide (DMSO). Glimepiride shows low pH dependent solubility. In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 370C, solubility of drug is slightly increased to 0.02 mg/ml. These poorly water-soluble drugs provide challenges to deliver them in an active and absorbable form to the desired absorption site using physiologically safe excipients. This poor solubility may cause poor dissolution and unpredicted bioavailability. It is practically insoluble in water and other aqueous media. However, the drawback of this potentially useful hypoglycaemic agent is that it is highly hydrophobic and practically insoluble in water.

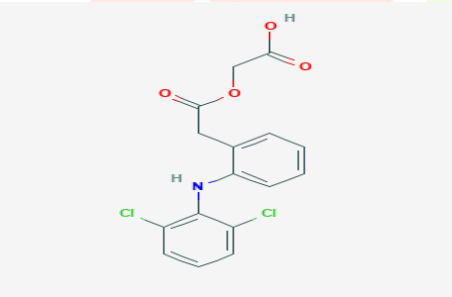


Fig. no. 01 Glimepiride

Materials and Instruments:

Following material which was of analytical grade were gifted and purchased and used as supplied by the manufacturer, without further purification. Drug used for the experimental purpose Glimepiride, Povidone, Talc, Magnesium stearate, Microcrystalline cellulose, Potassium dihydrogen Phosphate, Disodium hydrogen phosphate. Equipment's used for the experimental purpose Digital Weighing Balance, FTIR, U. V. Spectrophotometer, Hardness tester, Dissolution apparatus, Hot air oven, Friabilator.

Result and Discussion:

Preformulation study:

Preformulation testing is the first step in the rationale development of dosage forms. Preformulation testing encompasses all studies with drug in order to produce useful information for subsequent formulation of stable and suitable dosage form.

Identification and Characterization of Drug:
The characterization of drug is necessary for identification and purity of drug. In characterization of drug different physical, chemical and spectroscopic tests were performed which are given below.

Organoleptic characteristics
The organoleptic characteristics of Glimepiride such as colour, odour, and taste were studied. Colour of drug was found to be off-white and odour of the drug was identified simply by smelling.

Table.1: Organoleptic properties of Glimepiride

Description	**Standard**	**Observed**
Colour	off-white to white powder	off-white to white powder
Odor	Odourless	Odourless
Taste	Bitter	Bitter

The organoleptic characteristics of the drug were compared with the standard characteristics and both were found to be similar.

Melting point determination
Melting point of Glimepiride was determined by capillary method using Thiele's tube. The temperature at which drug goes in the liquid state was consider as a melting point of API. Practically it was found that drug get melts at 195 C. standard melting point of the API is 200ºC.

Table .2: Melting point of API

Drug name	**Melting point**	
	Standard	**Observed**
Glimepiride	200ºC	195^{O}C

The melting point of the drug was matches to the standard.

Loss on drying: -

The loss on drying of Glimepiride sample was found to be 0.5%.

FTIR study: UV Spectrophotometric method for Glimepiride:

Determination of λmax: -

Preparation of stock solution:

The stock solution of Glimepiride is prepared by dissolving 100 mg of drug in 100 ml ethanol in 100ml of volumetric flask with continuous shaking.10 ml of sample was withdrawn and diluted to 100 ml of ethanol to get 100 µg/ml of solution.

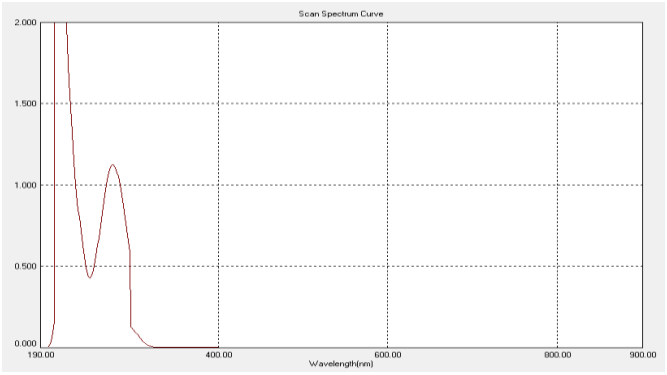


Fig.2 Spectra of Glimepiride

Calibration curve of Glimepiride in ethanol:

From the stock solution of Glimepiride, known concentration of 10µg/ml is prepared by suitable dilution with ethanol. Wavelength scanned for the maximum absorption of drug solution using UV spectrophotometer within the wavelength region of 200–800 nm against blank ethanol. Obtained spectra shows the peak with a highest absorbance is considered as absorbance maximum of the drug.

Table .3 Absorbance of Glimepiride

Sr. No	Concentration (ug/ml)	Absorbance (nm)
1	5	0.126
2	10	0.25
3	15	0.358
4	20	0.53
5	25	0.667

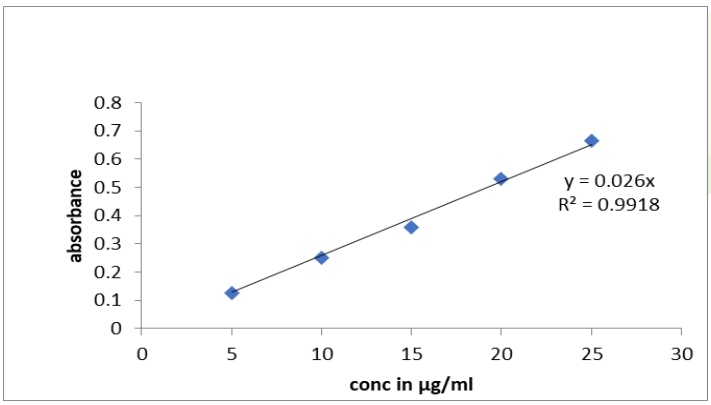


Figure .3: Calibration curve of Glimepiride using ethanol

Assay of Glimepiride: -

Table .4 Assay of Glimepiride

Parameter	% Purity	Standard
Glimepiride	97.5%	95-105%

Assy of Glimepiride was carried out by spectrometric method and % purity was found to be 97.5%

Solubility study:

Table no .5 solubility of Glimepiride in different solvent by using ASS

Sr. no	Medium	Solubility (before)	Solubility (mg/ml)(After)
1	Distilled water	0.963	1.904
2	Phosphate buffer 6.8	0.995	1.395
3	Ethanol	1.000	1.956
4	0.5M HCL	0.120	0.123

Solubility study of glimepiride was carried out by using plain sago starch and it was observed that when combined with sago starch the solubility of glimepiride increases in water.

Table no .6 Solubilty of Glimepiride in different solvent by using Plain sago starch

Sr.no	Medium	Solubility(before)	Solubilty(mg/ml) (After)
1	Distilled water	0.789	1.000
2	Phosphate buffer 6.8	0.856	1.236
3	Ethanol	0.963	1.000
4	0.5M HCL	0.127	0.126

8.1.1.8 Compatibility study: -

Preformulation compatibility studies of Glimepiride with all excipients were carried out prior to preparation nanoemulsion. The daily observations of compatibility study for 14 days were taken for colour changes, cake formation, liquefaction, and gas formation.

Table .7: - Excipients + Glimepiride Compatibility Study

Sr. no	Physical mixture	Observation			
		Color Change	Cake Formation	Liquefaction	Gas formation
1	Glimepiride + Sago starch	No	No	No	No
2	Glimepiride + Povidone	No	No	No	No
3	Glimepiride + acetylated sago starch	No	No	No	No
7	Glimepiride + Talc	No	No	No	No
8	Glimepiride + Magnesium Stearate	No	No	No	No
9	Glimepiride cellulose	No	No	No	No

Formulations and Development:

Selection of carriers or Optimization of carriers

Prepared solid dispersion and physical mixtures with different polymers with different ratio was evaluated for its solubility FTIR.

FTIR:

Compatibility by FT-IR Study: -

IR spectroscopy has been employed as a useful to identify the drug excipients interaction. IR spectroscopy of pure Glimepiride and excipients were taken before starting a compatibility study and after completion of compatibility study the IR of all samples were taken and compared with IR graph of before compatibility Study.

FTIR of Glimepiride API

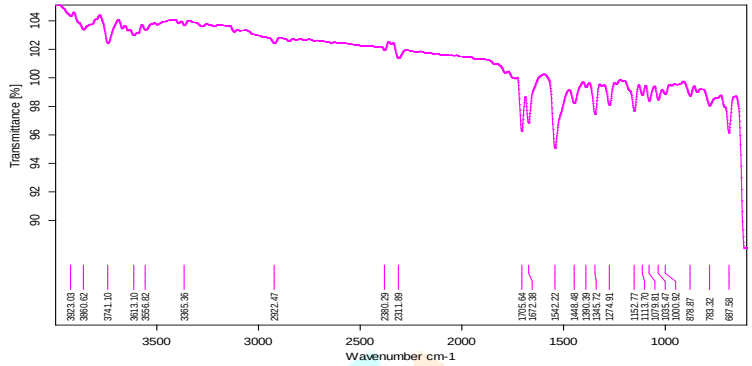


Fig.4 FITR of Glimepiride

FTIR of Sago Starch Plain

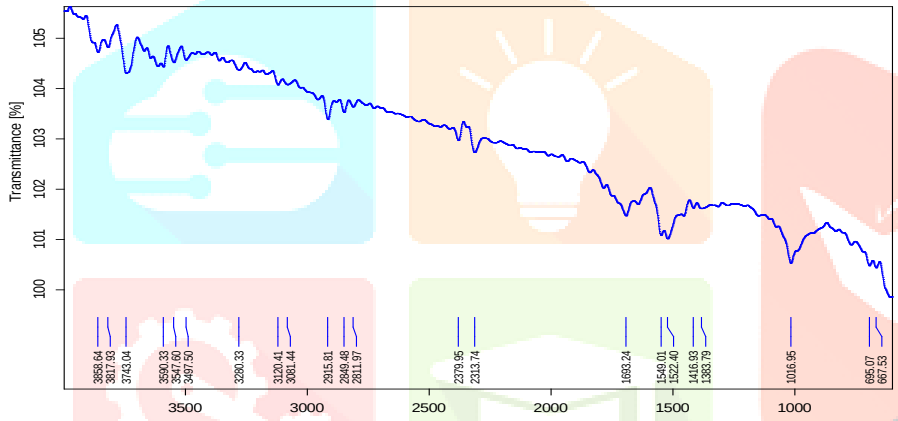


Fig.5 FTIR of Sago starch Plain

FTIR OF Acetylated Sago Starch

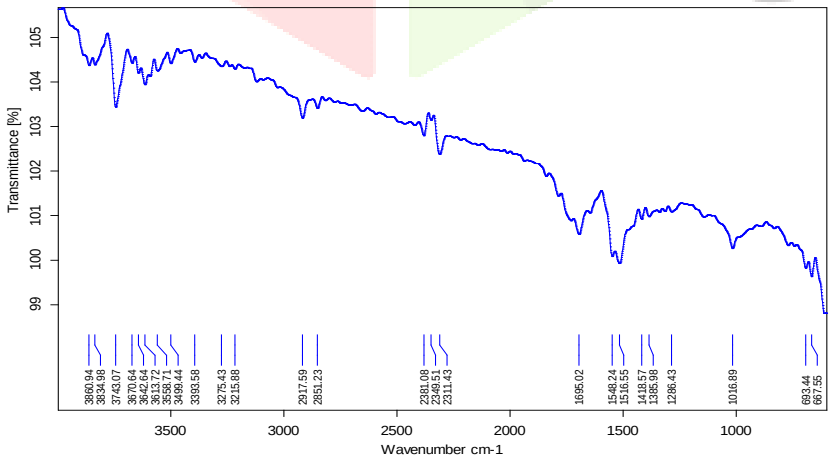


Fig.6 FTIR of ASS

FTIR of Glimepiride + Plain sago starch

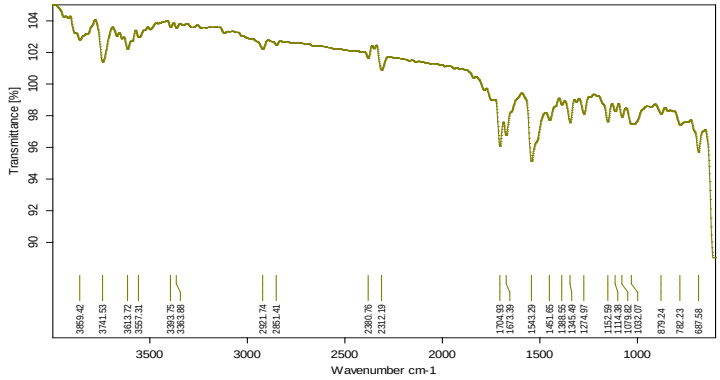


Fig.7 FTIR Glimepiride +Plain sago starch

FTIR of Glimepiride +Acetylated Sago starch

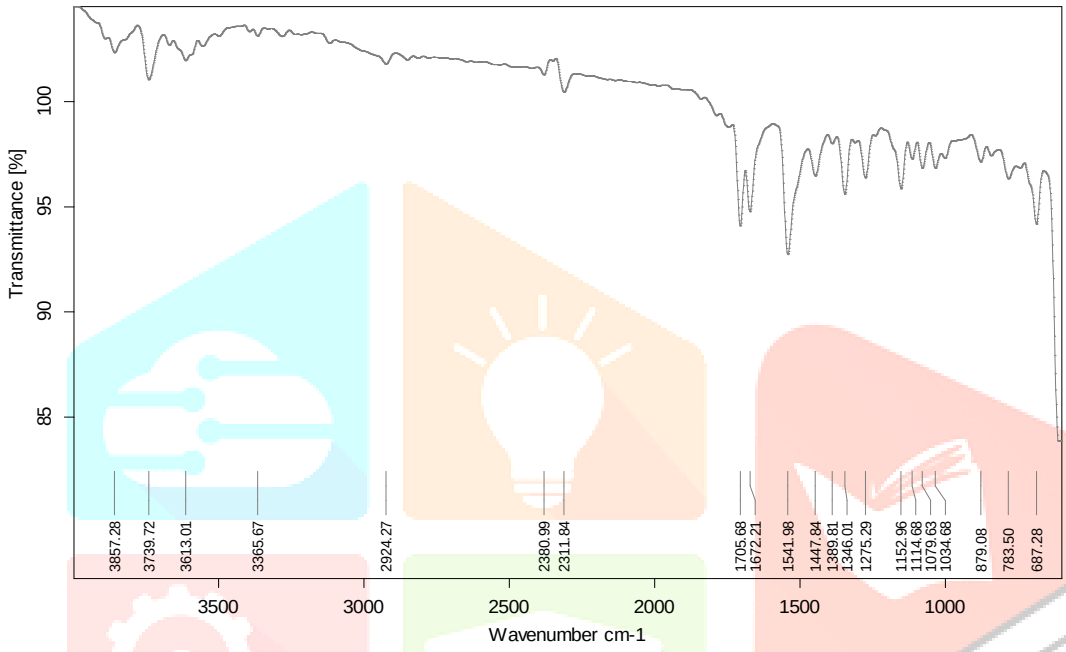


Fig.8. FTIR Glimepiride + ASS

FTIR of Glimepiride + Avicel

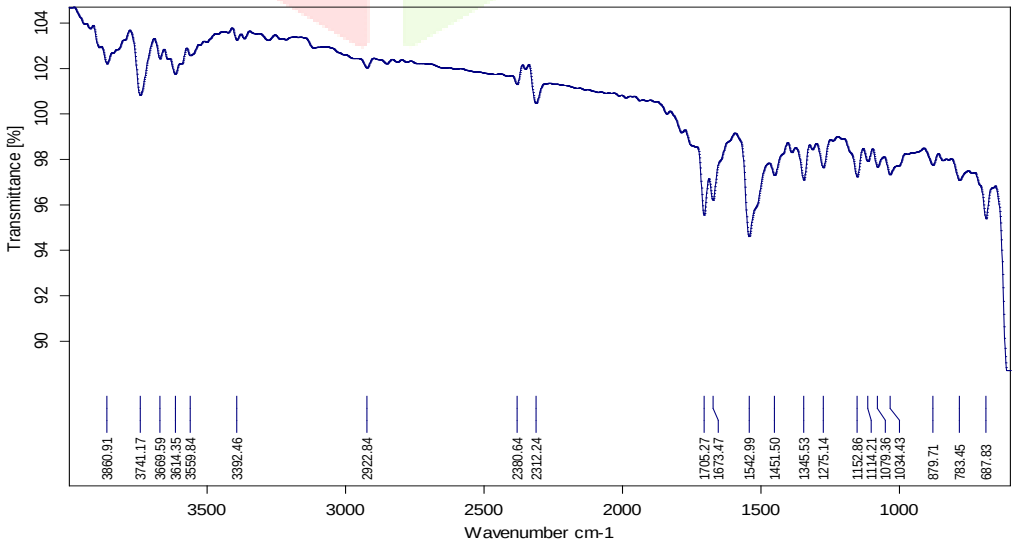


Fig.9 Glimepiride + Avicel

FTIR of Glimepiride + Magnesium stearate

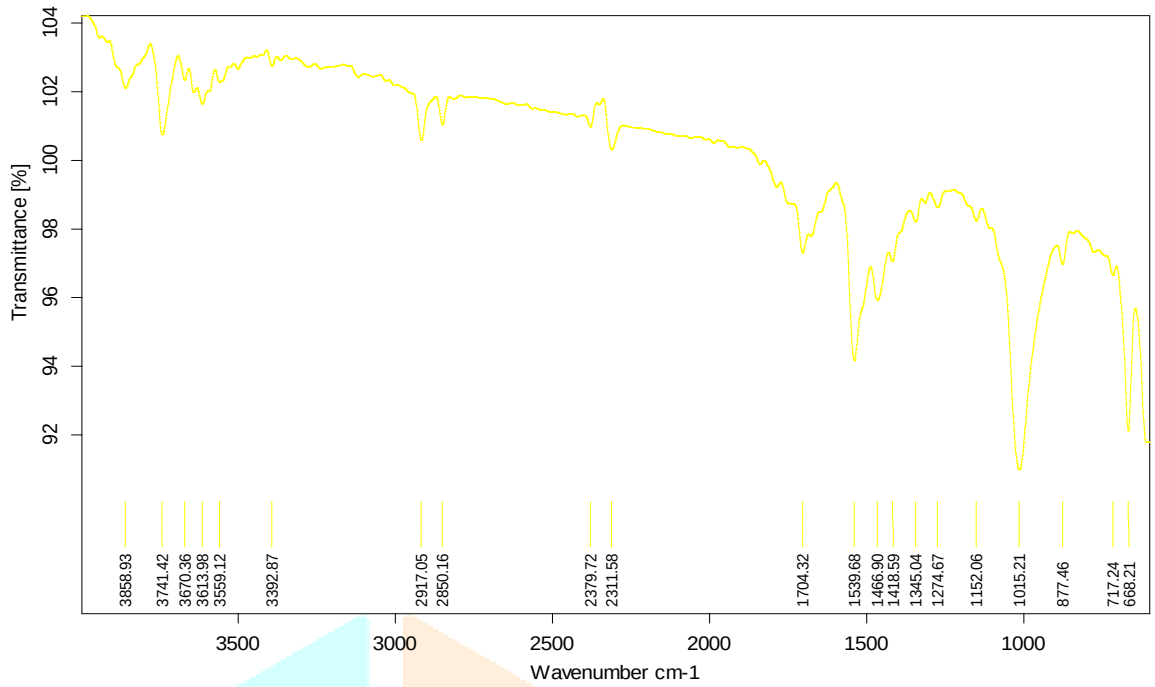


Fig.10 Glimepiride + Mg.stearate

FTIR of Glimepiride +Talc

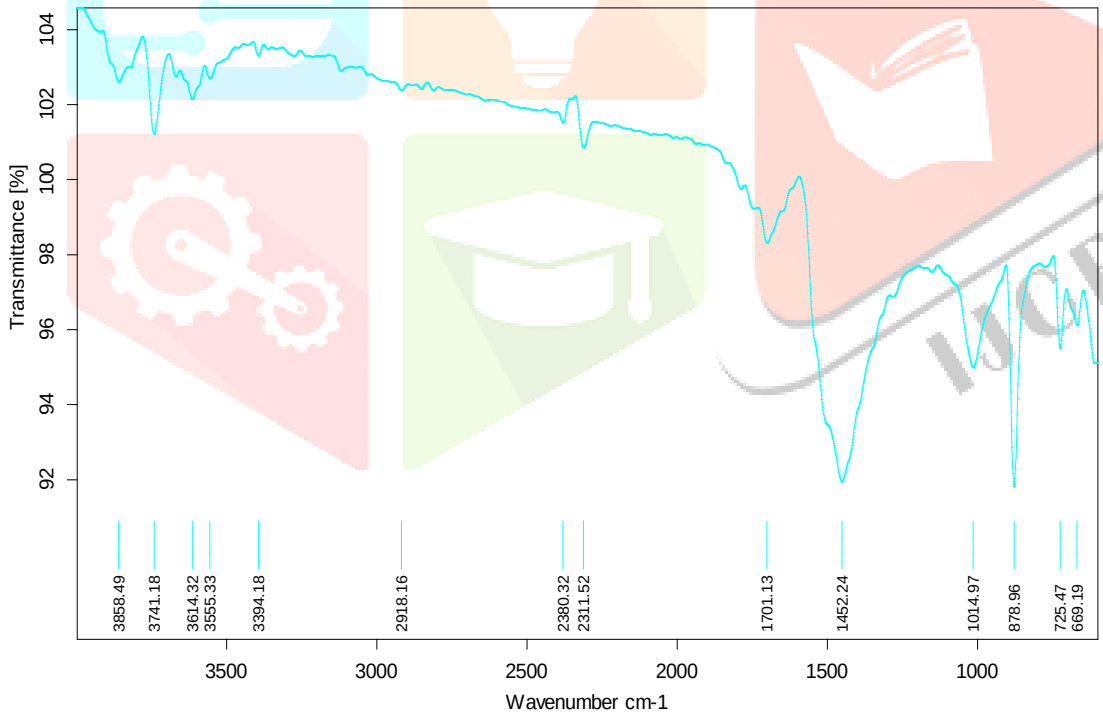


Fig.11 FTIR Glimepiride +Talc

When graphs of IR after compatibility study were compared with graphs of IR of drug and excipients before compatibility. It shows that all the characteristic peaks of Glimepiride were present in spectra after compatibility study with and without moisture. Hence from IR study it can be concluded that the drug Glimepiride was compatible with all excipients which was used in the formulation and development.

Precompression Study:

Bulk Density:
The bulk density of various powder blend prepared with different ingredients was measured by using graduated cylinder. The bulk density was found in the range from 0.483gm/ml -0.495 gm/ml. The results are presented in Table 8.8.

Tapped Density:
The tapped density of various powder blend prepared with different ingredients was measured by using graduated cylinder. The tapped density was found in the range from 0.564gm/ml-0.584 gm/ml. The results are presented in Table 8.8.

Compressibility Index:
A flow property plays an important role in pharmaceuticals especially in tablet formulation because improper flow may cause more weight variation. Values of Carr's Index (Compressibility) below 15% usually give rise to good flow properties but readings above 25% indicate poor flow properties. The compressibility index of various powder blend prepared with different ingredients using bulk density and tapped density data was calculated. It was found in the range 10.40 to 17.29 % and hence they exhibit better flow property. The results are given in Table 8.8.

Hausner's Ratio:
Hausner ratio is an indirect index of ease of powder flow. Lower hausne'r ratio (>1.25) indicates better flow properties than higher ones (< 1.25). The hausne'r ratio of various granules prepared with different ingredients was calculated by using bulk density and tapped density data. It was found in the range of 1.11 to 1.23 which indicates better flow property. The results are given in Table 8.8

Angle of Repose:
The angle of repose for all formulations was in the range of 27^o – 33^o so it shows good flow property.

Table 8: Pre Compression Characterization of Tablets

Batches	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's ratio	Carr's Index (%)	Angle of Repose (θ)
A1	0.483	0.584	1.20	17.29	27.02^0
A2	0.483	0.564	1.16	14.36	28.81^0
A3	0.475	0.586	1.23	11.11	28.81^0
A4	0.495	0.564	1.23	11.87	30.11^0
B1	0.483	0.555	1.14	12.97	26.50^0
B2	0.483	0.564	1.16	14.36	27.02^0
B3	0.475	0.564	1.18	15.78	28.36^0
B4	0.495	0.555	1.11	10.40	32.21^0

Post compression evaluation:

Weight variation:

The theoretical average weight of the various formulated tablets is 350 mg and weight variation of various formulation are depicted in Table No 8.9. The percentage deviation of the weight was within 5% as per monograph.

Hardness:

The hardness of various tablet formulation was shown in Table No 8.9. The hardness of the tablet was found in the ranges from 2.5 to 3.1 Kg/ cm^2 So, it was the sufficient hardness for tablet transporting and packing.

Thickness:

The thickness of the various tablet formulation was shown in Table No 8.9. The thickness of the tablet was found in the ranges from 4 to 4.2 mm. It was important for packing of tablet and acceptance.

Friability:

The friability of the various tablet formulation was shown in table no 8.9. The friability of the tablet was found in the ranges from 0.61 to 0.92%. The values are within limit of the official monograph i.e., not more than 1%.

Drug content:

The content of the various formulations was analyzed by UV spectrometric method. It was very important for the release percentage from the amount present in the tablet. The percentage of drug found in the tablet ranges from 97.08 to 100.8% and was within the limits. The drug content of various formulations was shown in table no 8.9.

Batch Code	**Hardness (Kg/cm^3)**	**Friability (%)**	**Thickness (mm)**	**Weight variation (%)**	**Drug Contents (%)**
A1	4.1±0.216	0.1	4.07±0.08	200±14.25	97.5
A2	4.2±0.2	0.76	4.075±0.08	200±15.37	100.8
A3	4.8±0.141	0.3	4.05±0.05	200±16.12	100
A4	4.2±0.1	0.66	4.05±0.05	200±17.5	99.1
B1	4.4±0.19	0.0.1	4.05±0.08	200±13.6	100.8
B2	4.2±0.14	0.3	4.05±0.05	200±14.3	98.3
B3	4.00±0.19	0.46	4.05±0.08	200±15.5	97.08
B4	3.9±0.12	0.78	4.05±.0.05	200±12.3	99.58

In vitro drug release study:

In vitro drug release profile for all formulations were carried out by using 0.5M HCL for 2hrs and in phosphate buffer ph 6.8 as dissolution medium till the drug get release.

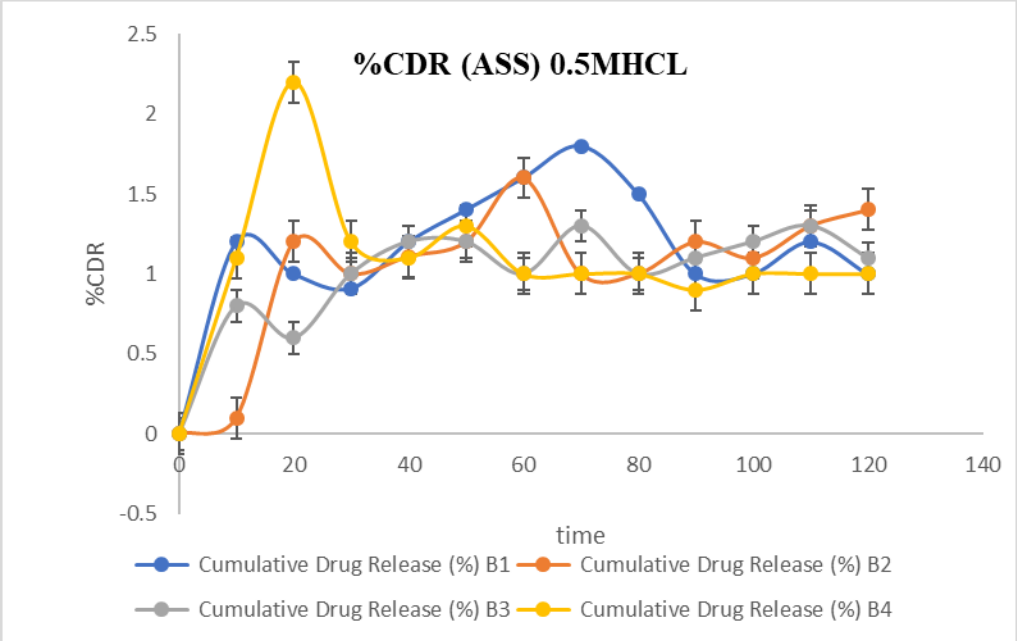
Table .10(A): Dissolution study of formulation 0.5M HCL (2 HRS)

Time (min)	Cumulative Drug Release (%)			
	B1	B2	B3	B4
10	1.2±15.43	0.1±10.32	0.8±11.13	1.1±1.52
20	1±7.57	1.2±4.85	0.6±1.68	2.2±1.69
30	0.91±5.29	1±2.70	1±1.78	1.2±2.38
40	1.2±2.15	1.11±1.15	1.2±2.28	1.1±2.58
50	1.4±2.15	1.2±1.15	1.2±1.72	1.3±1.16
60	1.6±2.15	1.6±1.15	1±1.68	1±2.03
70	1.8 ±13	1.0±10.32	1.3 ±2.3	1 ±1.45
80	1.5±5.2	1 ±2.6	1 ±2.2	1±1.32
90	1 ±2.3	1.2 ±2.69	1.1±2.1	0.9 ±1.36
100	1 ±2.6	1.1 ±3.5	1.2±2.3	1 ±4.5
110	1.2±1.8	1.3±5.6	1.3±6	1 ±1.1
120	1 ±1.9	1.4±1.2	1.1±3.3	1 ±1.23

Table 11: Dissolution study of formulation Phosphate buffer 6.8

Time (min)	Cumulative Drug Release (%)			
	B1	B2	B3	B4
150	3.19±1.52	5.65±4.77	8.01±11.28	10.65±4.77
180	22±1.69	22.23±3.94	28.72±5.53	31.23±3.94
210	29.20±2.38	30.94±3.64	31.70±7.24	38.94±3.64
240	36.41±2.58	32.96±2.14	35.70±4.37	48.96±2.14
270	44.37±1.16	39.91±2.50	40.27±1.67	55.91±2.50
300	47.38±2.03	45.49±0.81	43.23±1.52	60.49±0.81
330	51.64±11.13	50.65±4.77	48.01±11.28	62.65±4.77
360	54.08±1.68	56.23±3.94	58.72±5.53	65.23±3.94
390	58.48±1.78	58.35±14.84	58.64±11.13	66.13±16.53
420	60.63±2.28	62.29±2.98	60.08±1.68	68.05±6.02
480	62.16±1.72	67.29±2.08	62.48±1.78	68.27±3.46
540	64.16±1.68	70.44±2.18	65.63±2.28	70.45±1.79

600	70.64±11.13	75.48±2.18	68.16±1.72	72.55±1.79
660	71.08±2.70	77.48±2.18	75.16±1.68	75.55±1.79
720	78.79±1.15	79.35±14.84	77.64±11.13	77.73±16.53
780	79.79±1.15	80.13±16.53	80.08±1.68	80.25±6.02
840	79.79±1.15	80.25±6.02	82.48±1.78	83.27±3.46
900	80.06±5.29	81.27±3.46	85.63±2.28	90.45±1.79
960	82.40±2.15	85.45±1.79	88.16±1.72	92.55±1.79
1020	85.40±2.15	86.55±1.79	88.55±1.79	95.55±1.79
1080	90.40±2.15	92.55±1.79	96.55±1.79	98.55±1.79



It was observed that the Sustained release tablets of glimepiride prepared by using Acetylated sago starch shows the minor drug release in 0.5m HCL for 2 hrs .From above observation it shows that the tablet do not degrade in the HCL for 2 hrs.

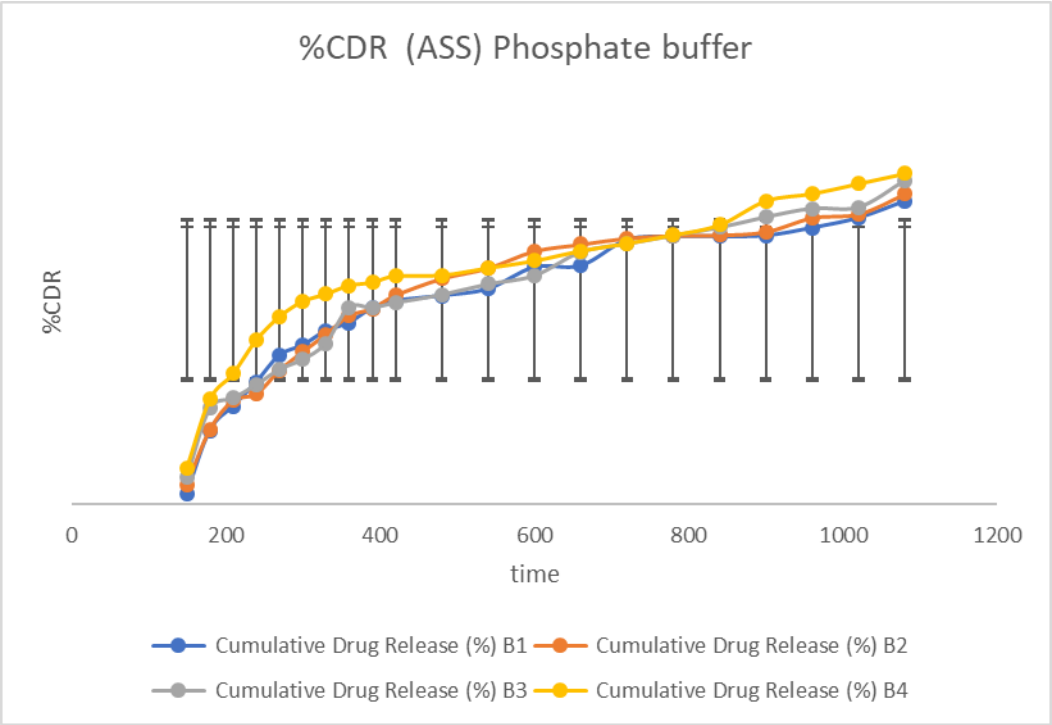


Table 12: Dissolution study of formulation 0.5M HCL (2 HRS)

It is observed that the tablets of Glimepiride sustained release prepared by using acetylated sago starch shows the slow release in first 13 hrs and then slightly get increases.

PLAIN SAGO

Time (min)	Cumulative Drug Release (%) plain sago			
	Ps A1	**Ps A2**	**Ps A3**	**Ps A4**
10	1.2±15.43	0.1±10.32	0.8±11.13	1.1±1.52
20	1±7.57	1.2±4.85	0.6±1.68	2.2±1.69
30	0.91±5.29	1±2.70	1±1.78	1.2±2.38
40	1.2±2.15	1.11±1.15	1.2±2.28	1.1±2.58
50	1.4±2.15	1.2±1.15	1.2±1.72	1.3±1.16
60	1.6±2.15	1.6±1.15	1±1.68	1±2.03
70	1.8 ±13	1.0±10.32	1.3 ±2.3	1 ±1.45
80	1.5±5.2	1 ±2.6	1 ±2.2	1±1.32
90	1 ±2.3	1.2 ±2.69	1.1±2.1	0.9 ±1.36
100	1 ±2.6	1.1 ±3.5	1.2±2.3	1 ±4.5
110	1.2±1.8	1.3±5.6	1.3±6	1 ±1.1
120	1 ±1.9	1.4±1.2	1.1±3.3	1 ±1.23

Table 13: Dissolution study of formulation Phosphate buffer 6.8

Time (min)	Cumulative Drug Release (%) plain sago			
	A1	**A2**	**A3**	**A4**
150	2.19±1.52	2.65±4.77	4.01±11.28	7.65±4.77
180	15±1.69	16.23±3.94	18.72±5.53	22.23±3.94
210	22.20±2.38	25.94±3.64	26.70±7.24	26.94±3.64
240	29.41±2.58	30.96±2.14	31.70±4.37	35.96±2.14
270	35.37±1.16	36.91±2.50	37.27±1.67	38.91±2.50
300	40.38±2.03	40.49±0.81	43.23±1.52	50.49±0.81
330	51.64±11.13	52.65±4.77	52.01±11.28	55.65±4.77
360	54.08±1.68	56.23±3.94	58.72±5.53	65.23±3.94
390	58.48±1.78	58.35±14.84	58.64±11.13	60.13±16.53
420	58.63±2.28	59.29±2.98	60.08±1.68	61.05±6.02
480	62.16±1.72	63.29±2.08	62.48±1.78	63.27±3.46
540	64.16±1.68	66.44±2.18	66.63±2.28	68.45±1.79
600	68.64±11.13	69.48±2.18	68.16±1.72	70.55±1.79
660	71.08±2.70	72.48±2.18	73.16±1.68	75.55±1.79
720	75.79±1.15	76.35±14.84	77.64±11.13	77.73±16.53
780	77.79±1.15	78.13±16.53	80.08±1.68	80.25±6.02
840	79.79±1.15	80.25±6.02	80.48±1.78	81.27±3.46
900	80.06±5.29	81.27±3.46	81.63±2.28	83.45±1.79
960	83.40±2.15	85.45±1.79	88.16±1.72	92.55±1.79
1020	84.40±2.15	82.55±1.79	80.55±1.79	82.55±1.79
1080	87.40±2.15	80.55±1.79	89.55±1.79	90.55±1.79

It was observed that sustained release tablets of Glimepiride by using plain sago showed release faster in 13 hrs as compared to tablets prepared by using Acetylated sago starch.

Kinetic modeling

The *in-Vitro* release data was applied to various kinetic models to predict the drug release kinetic mechanism. The release constant was calculated from the slope of appropriate plots and the regression coefficient (r^2) was determined. The correlation coefficient (r^2) of Glimepiride was in the range of 0.548 - 0.975 for Sustained Releaset tablet. It was found that the *in-vitro* drug release ofsustained release tablet was best explained by Higuchi model according to regression coefficients (r^2) value. The value of n was 0.975 i.e. 0.5< n <1.0 for B1 formulation, indicated that drug release is by Non-Fickian or anomalous mechanism**.**

Fig.14 Zero order kinetics for ASS:

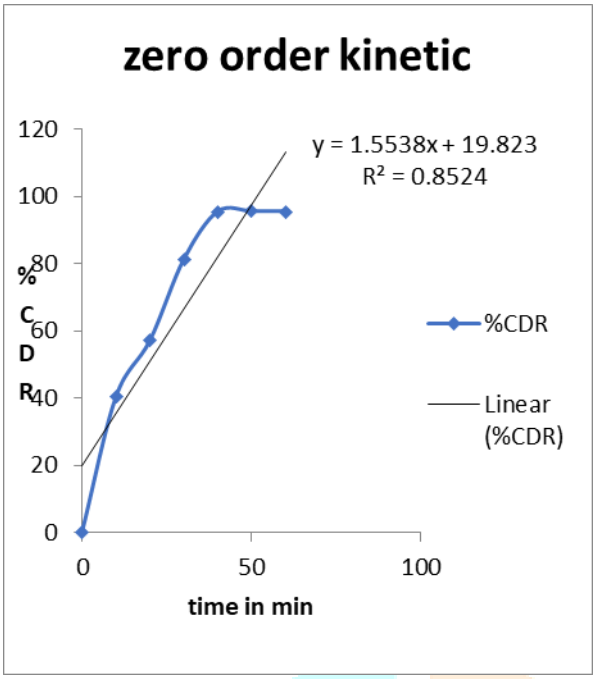


fig. 15 Zero order kinetics for Plain sago

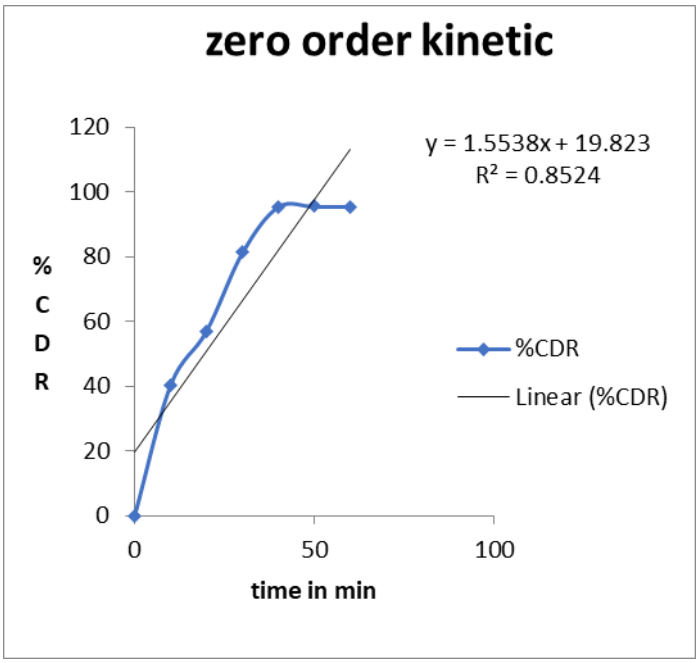


Fig.16 Higuchi model for ASS

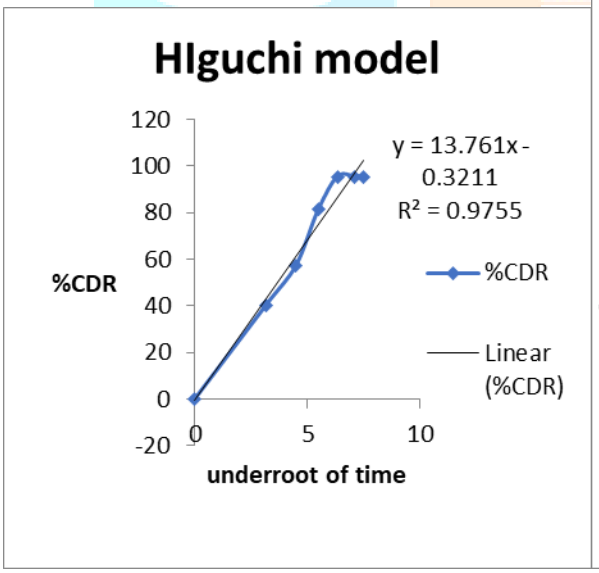


Fig.17 Higuchi model for Plain saago

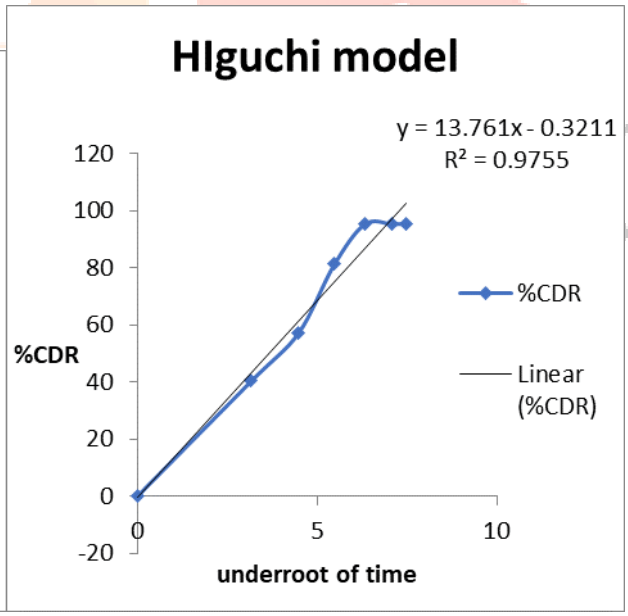


Fig 18 Korsmeyer-Peppas model for ASS

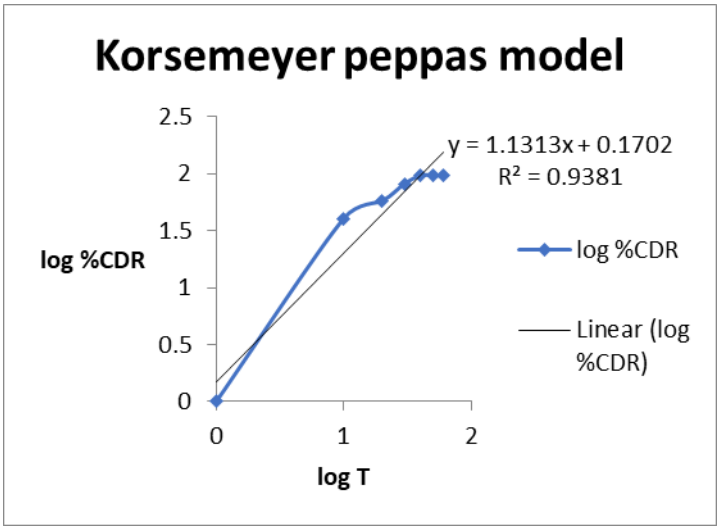


Fig.19 Korsmeyer peppas model for Plain sago

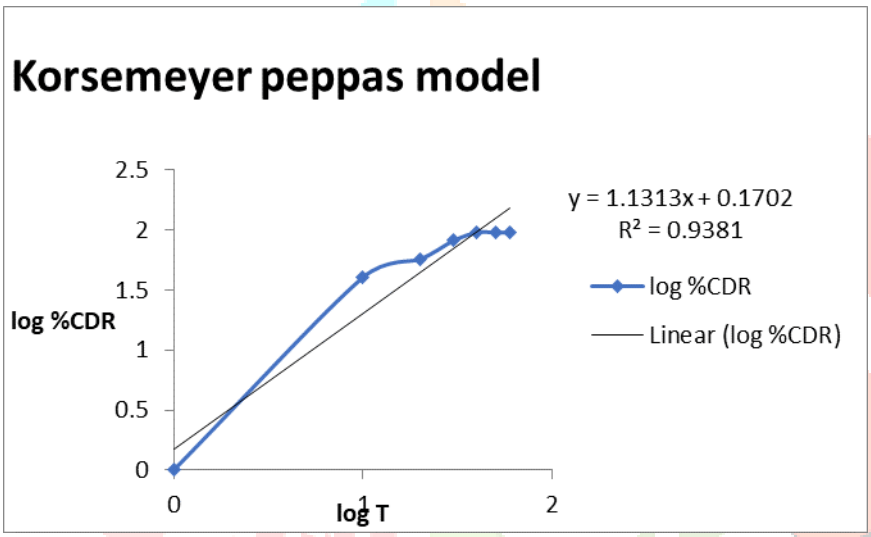


Fig. 20 First order kinetics for ASS

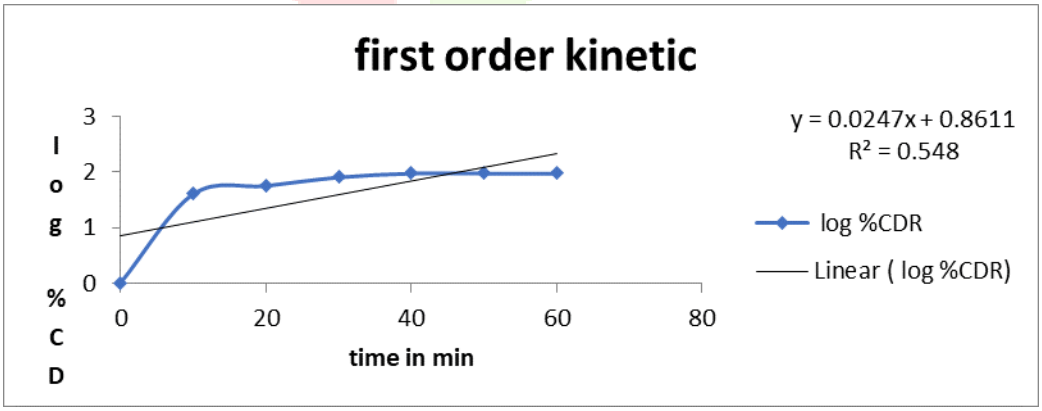
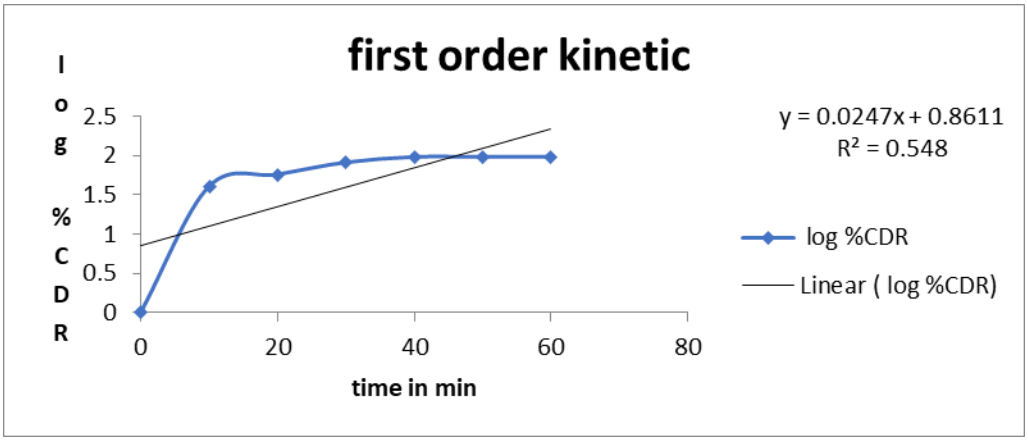


Fig.21 First order kinetics for Plain sago



All kinetics modeling for both Acetylated sago starch sustained release tablet of Glimepiride and for the tablets prepared by using plain sago starch were studied.

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