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Research Article

Developement and Evaluation of Mucoadhesive Matrix Tablets of Glipizide Using Ispaghula

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ABSTRACT

Glipizide is an oral rapid and short acting anti diabetic medication from the sulfonylurea class. It is classified as a second generation sulfonylurea, which means that it undergoes enterohepatic circulation. Second generation sulfonylureas are both more potent and have shorter half-lives than the first generation sulfonylureas. The granules are prepared by the wet granulation method. Drug excipients interaction study did by Fourier Transform infrared spectroscopy (FTIR), and Differential Scanning Calorimetry (DSC) From results, it was concluded that there was no interference in the functional group as the principle peaks of the Glipizide were found to be unaltered in the drug-mucilage physical mixture. The thermograph of Glipizide, mixture of Glipizide with isabgol mucilage, show that there is no change in melting point which confirms that there is neither change in the crystallinity of Glipizide nor any interaction between Glipizide, isabghol mucilage used in the preparation of matrix tablet.

1. INTRODUCTION

A Mucoadhesive sustained release device can improve the effectiveness of the drug by helping to maintain a drug concentration between the effective and toxic level, inhibiting the dilution of drug in the body fluid and allowing targeting and localizing of a drug at specific site. A drug can be incorporated into a cross linked polymeric device that would adhere to a mucous substrate in the body.[1-5]

Targeting the drug or drug delivery system in a particular region of a body for extended period of time not only for local targeting but also for better control of systemic drug delivery.[5-12]

- **Adhesion** - Adhesion can be defined as bond produced by contact between a pressure sensitive adhesive and surface.[8]
- **Bioadhesion** - Bioadhesion is a state in which two materials, at least one of which of the biological in nature, are held together for an extended period of time by interfacial forces.

In a biological system four different type of bio-adhesion can be distinguish

1. Adhesion of normal cell to another normal cell.
2. Adhesion of cell to a foreign substance.
3. Adhesion of normal cell to pathological cell.
4. Adhesion of an adhesive to a biological substrate.

If the adhesive attachment is to a mucous coat, the phenomenon is referred as Mucoadhesion.

Advantages:

1. Mucoadhesion increase the intimacy and duration of contact between a drug containing polymer and mucous surface. It is believed that the Mucoadhesive nature of device can increase the residence time of a drug in body.
2. Combined effect of direct drug absorption and decrease in excretion rate for an increase bioavailability of drug with a smaller dosage and less frequent administration.
3. Another advantage of using polymer carrier for drug delivery is the prevention of first pass metabolism of certain protein drug, as drug are absorbed through the mucosal lining of tissue, can directly enter in blood stream and not be inactivated by enzymatic degradation in gastrointestinal tract.
4. Polymeric device can also allow for slow controlled release of drug and reduces the initial drug loading concentration needed.
5. Thus system also decreases the toxicity and waste of expensive drug as well as patient compliance.
6. It localizes the drug in a particular region of GI tract, thereby improving and enhancing bioavailability for those drugs with bioavailability problems.
7. The strong interaction between the polymer and the mucus lining of the tissue help to increase contact time and permit localization.

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:

- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, non-covalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site on tile self surface.

A. **Characteristics of an ideal mucoadhesive polymer**

An ideal mucoadhesive polymer has the following characteristics:

- The polymer and its degradation products should be nontoxic and should be non-absorbable from the gastrointestinal tract.
- It should be nonirritant to the mucous membrane.
- It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.
- It should adhere quickly to most tissue and should possess some site-specificity.
- It should allow daily incorporation to the drug and offer no hindrance to its release.

B. Molecular characteristics [14]

The properties exhibited by a good mucoadhesive may be summarized as follows

- Strong hydrogen bonding groups (-OH, -COOH).
- Strong anionic charges.
- Sufficient flexibility to penetrate the mucus network or tissue crevices.
- Surface tension characteristics suitable for wetting mucus/mucosal tissue surface.
- High molecular weight.

Although an anionic nature is preferable for a good mucoadhesive, a range of nonionic molecules (e.g., cellulose derivatives) and some cationic (e.g., Chitosan) can be successfully used. A short list of mucoadhesive polymers is given below:

C. Synthetic polymers:

Cellulose derivatives (methylcellulose, ethyl cellulose, hydroxy-ethylcellulose, Hydroxyl propyl cellulose, hydroxylpropyl methylcellulose, sodium carboxymethylcellulose, Polyacrylic acid polymers (carbomers, polycarbophil), Poly (hydroxyethyl methylacrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone) Poly (vinyl alcohol).

D. Natural polymers: [15]

Tragacanth, Sodium alginate, Karaya gum, Guar gum, Xanthan gum, Lectin, Soluble starch, Gelatin, Pectin, Chitosan. Bioadhesive polymers are classified as first generation and second generation.

E. Matrix system: [16]

Historically , the most important drug delivery system that have been the matrix because of their simplicity, ease in manufacturing high level of reproducibility, stability of raw material and dosage form, and ease of scale-up and process validation.

Table No 1. Three type of matrix system: [25]

Types of matrix	Examples
Hydrophilic matrices	Methylcellulose, Hydroxyethylcellulose, Hydroxyprorpyl methyl cellulose, sodium carboxymethylcellulose.
Fat-Wax matrices	Carnuaba Wax, Stearyl alcohol, Stearic acid, cetyl alcohol, Triglycerides.
Plastic matrices	Polyethylene, Polyvinylchloride, Ethylcellulose, Methylacrylate copolymer

Requirements of Matrix System:

The matrix materials must comply with the following conditions,

- They must comply inert and non-reactive with the drug and additives in the tablet.
- They must be able to form stable and strong matrices.
- They must be non-toxic.

Advantages of matrix systems:

- Excipients are generally cheap and are usually GRAS (generally regarded as safe).
- Capable of sustaining high drug load and high molecular weight compounds.
- Reproducible release profile.
- Easy to manufacture.
- Possible to obtain different types of release profiles: Zero order, First order, bimodal etc.
- Readily available pharmaceutical manufacturing equipment can be used.[26]

NATURAL GUMS AND MUCILAGES:

Gums and mucilages have similar constitution on hydrolysis yield a mixture of sugar and uronic acids. Gums are considered to be pathological products, while mucilages is formed by normal metabolism.[27]

Gums: Gums are amorphous translucent substances which are insoluble in alcohol and most organic solvents. It is soluble in water and gives a viscous sticky solution. Other gums are swollen by absorbing water to form a jelly-like mass. Gums are abnormal products, formed by - Injury of the plant

- Unfavourable conditions(e.g. drought)
- Breakdown of cell walls (A process of extracellular formation called gummosis).[27]

Mucilage: Mucilages are generally normal products of metabolism formed within the Cell (intracellular formation)

Functions of Mucilages,

- Storage material
- Water storage reservoir
- Protection for germinating seed.[28]

Advantages of Natural Gums and Mucilages in Pharmaceutical Formulations

The following are a number of the advantages of natural plant–based materials.

Biodegradable-Naturally available biodegradable polymers are produced by all living organisms. They represent truly renewable source and they have no adverse impact on humans or environmental health (e.g., skin and eye irritation).

Biocompatible and non-toxic-Chemically, nearly all of these plant materials are carbohydrates composed of repeating sugar (monosaccharides) units. Hence, they are nontoxic.

Low cost-it is always cheaper to use natural sources. The production cost is also much lower compared with that for synthetic material. India and many developing countries are dependent on agriculture.

Environmental-friendly processing-Gums and mucilages from different sources are easily collected in different seasons in large quantities due to the simple production processes involved.

Local availability (especially in developing countries)-In developing countries, governments promote the production of plant like guar gum and tragacanth because of the wide applications in a variety of industries. Better patient tolerance as well as public acceptance. There is less chance of side and adverse effects with natural materials compared with synthetic one. For example, PMMA, povidone.

Edible sources-Most gums and mucilages are obtained from edible sources.[29]

Disadvantages of Natural Gums and Mucilages

Microbial contamination-The equilibrium moisture content present in the gums and mucilages is normally 10% or more and,

structurally, they are carbohydrates and, during production, they are exposed to the external environment and, so there is a chance of microbial contamination. However, this can be prevented by proper handling and the use of preservatives.[30]

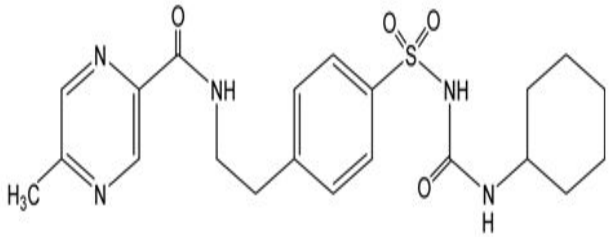
Batch to batch variation- Synthetic manufacturing is a controlled procedure with fixed quantities of ingredients, while the production of gums and mucilages is dependent on environmental and seasonal factors.[31]

Uncontrolled rate of hydration-Due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary. There is a need to develop suitable monographs on available gums and mucilages.

Reduced viscosity on storage-Normally, when gums and mucilages come into contact with water there is an increase in the viscosity of the formulations. Due to the complex nature of gums and mucilages (monosaccharides to polysaccharides and their derivatives), it has been found that after storage there is reduced in viscosity.[30,31]

DRUG PROFILE:-Glipizide [33, 34]

STRUCTURE :



Molecular Formula : $C_{21}H_{27}N_5O_4S$

Figure 1- IUPAC Name: N-[2-[4[(cyclohexyl) carbonyl 7] amino] sulfonyl] phenyl] ethyl]-5-Methyl pyrazine carboxamide.

2. MATERIALS AND METHODS

1. **Glipizide (**Aristo pharmaceuticals Pvt. Ltd., Mandideep, Raisen, M.P.)
2. **Lactose Monohydrate (**Loba Cheime Pvt. Ltd, Mumbai) SS Batch No: V229906
3. **Magnesium stearate (**Chemie Pvt. Ltd, Mumbai) Batch No.62289
4. **Starch (**Loba Cheime Pvt. Ltd, Mumbai) Batch No: S048410
5. **Acetone:** Loba Cheime Pvt. Ltd, Mumbai (Batch No: LG037810)

2.1 Granulation method

Tablets were prepared by varying concentration of mucilage as release retardant and concentration of all the excipients were kept constant as shown in Table

Procedure:

Weighed amount of prepared granules were taken, to it lubricants and fines were added and uniformly mixed. The prepared mixtures were taken for compression using 8mm concave punch

2.2 Preparation of granules:

Drug and excipients were weighed accurately as per composition given in table no 14 & 15 and powdered to obtain uniform Particle size using mortar and pestle. The powder was thoroughly mixed to obtain uniform mixing of drug and excipients. To the above mixture required amount of starch paste was added to form damp mass. The quantity required to form sufficient damp mass was weighed and recorded. Then prepared damp mass was passed through sieve no #16 and the granules. The prepared granules were kept for drying in hot air oven at 50-60º.Then dried

granules were collected, separated from fine by sieving. Separated granules were weighed and analyzed for true density, angle of repose, bulk density and Carr's index.

Evaluation for Granules: Prepared granules were evaluated for different physical parameters such as angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio. The Experiment was repeated with other two samples and average values were taken.

2.3 Evaluation of Tablets[35-40]

2.3.1 Drug Content

Ten tablets were taken and triturated in a glass mortar. The powdered tablet equivalent to 4 mg of solid dispersion of drug was dissolved in a 100 ml acid buffer pH1.2 and the drug content was determined spectrophotometrically at 227.8 nm. Drug content of different batches of tablets is shown in Table 11.

2.3.2 Hardness

Tablets require a certain amount of strength or hardness and resistance to friability to withstand mechanical shock of handling in manufacturing, packing and shipping.

Hardness was measured using automatic hardness tester Model No: C- WWTDH500N Campbell electronics, Ahmedabad. Mean of three values with standard deviation for each formulation is shown in Table 12.

2.3.3 Friability

Friability was evaluated as the weight loss of tablet equivalent to 100 mg, tumbled in a friabilator (model E2, electro lab, Bombay) for 4 min at 25 rpm. The tablets were deducted, and loss in weight caused by fracture or abrasion was recorded as percentage friability**.** Results are shown in Table 16.

The percentage friability was measured using the formula,

$\%F = \{(W - W_0)/W_0\} \times 100$……(9)

Where, % F = Friability in percentage.

W_0 = Initial value of tablet.

W = Weight of tablet after test.

2.3.4 Thickness and Diameter

Method - Three samples were selected randomly from each batch and thickness was measured using Campbell tablet tester (Model No. C-WWTDH 500 N)**.**Similarly one tablet from each batch was tested for diameter. Results shown in table No.16

Table 2: Composition of Glipizide Tablets using polymers

Batch	Ingredients	Formulation Code		
		GI1	GI2	GI3
1	Glipizide	10	10	10
2	DFM	-	-	-
3	IM	75	100	125
4	HPMC K4M	-	-	-
5	Lactose	105	80	55
6	Starch Paste	q.s	q.s	q.s
7	Magnesium stearate	5	5	5
8	Talc	5	5	5

Where- I, Isapgol; q.s, quantity sufficient.

2.3.4 Thickness and Diameter

Method - Three samples were selected randomly from each batch and thickness was measured using Campbell tablet tester (Model No. C-WWTDH 500 N)**.** Similarly one tablet from each batch was tested for diameter. Results shown in table No.16

Table 3: Composition of Glipizide Tablets using combination of polymers:

Batch	Ingredients	Formulation Code									
		G1	G2	G3	G4	G5	G6	G7	G8	G9	G10
1	Glipizide	10	10	10	10	10	10	10	10	10	10
2	DFM	25	50	50	-	-	-	12.5	25	12.5	12.5
3	IM	-	-	-	25	50	50	12.5	12.5	25	12.5
4	HPMC K4M	50	25	25	50	25	25	25	12.5	12.5	12.5
5	Lactose	105	105	80	105	105	80	130	130	130	142.5
6	Starch Paste	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
7	Magnesium stearate	5	5	5	5	5	5	5	5	5	5
8	Talc	5	5	5	5	5	5	5	5	5	5

*Weights are given for one tablet in mg, q.s; quantity sufficient.

Table 4: Physical properties of Granules

Formulation	Bulk density (g/cc)	Tapped density(g/cc)	Carr's index	Angle of repose	Hausner's ratio
G1	0.25±0.01	0.303±0.05	17.49±0.035	24.6±0.30	1.212±0.016
G2	0.256±0.014	0.277±0.057	14.58±0.37	25.68±0.32	1.243±0.18
G3	0.243±0.016	0.29±0.059	12.27±0.038	27.75±0.31	1.139±0.19
G4	0.26±0.017	0.28±0.058	10.34±0.037	28.24±0.35	1.115±0.16
G5	0.243±0.015	0.294±0.58	10.71±0.038	28±0.37	1.12±0.017
G6	0.23±0.017	0.277±0.054	17.00±0.037	29.74±0.39	1.16±0.021
G7	0.25±0.018	0.29±0.053	16.96±0.038	27.51±0.36	1.19±0.018
G8	0.238±0.017	2.285±0.054	17.24±0.039	27.2±0.34	1.21±0.018
G9	0.256±0.016	0.312±0.058	16.49±0.035	28.45±0.37	1.134±0.013
G10	0.238±0.014	0.27±0.059	17.94±0.032	26.91±0,38	1.235±0.017

3. RESULT AND DISCUSSION:

3.1 Fourier Transform Infrared Spectroscopy (FTIR):

By Potassium Bromide Disc Method: Glipizide was mixed thoroughly with potassium bromide. This Physical mixture was compressed and converted in a circular disc. The disc was then placed in the scanning slot of FTIR and scanned to obtain FTIR of Glipizide.

Observation: Spectrum of Glipizide matched with that of reported spectrum of Glipizide as given in Clarkes Analysis of Drugs and poisons.

3.2 Reported FTIR Spectrum of Glipizide:

3.2.1 UV Absorption Spectrum of Glipizide in Acid Buffer pH 1.2

10 µg/ml solution of Glipizide was prepared and was subjected to scanning under UV visible spectrophotometer, between 200-400 nm.

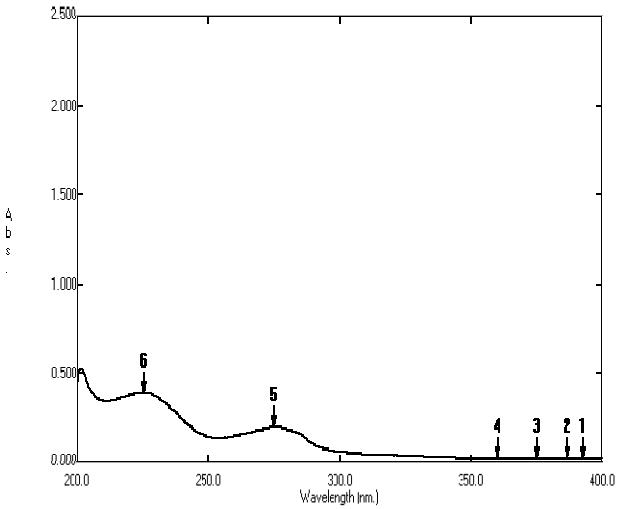


Figure No 2: UV Absorption Spectrum of Glipizide in Acid buffer pH 1.2

Observation:

3.2.2 Fourier Transform Infrared Spectroscopy:

To see the drug polymer interaction, FTIR studies were carried out. Pure Glipizide, Linseed mucilage, Isapgol mucilage, HPMC K4M, physical mixture of Glipizide, Linseed mucilage, Isapgol seed mucilage, HPMC K4M were analyzed using KBr disc method. FTIR spectra are shown in following Figures 3-5.

Table No 5: Interpretation of FTIR spectra of Glipizide

Sr. No	Characteristic peak (Wave number)	Group Responsible
1	3332.05	Assymetric N-H Streching
2	2941.24	Assymetric aliphatic C-H stretching
3	2854.45	Symmetric aliphatic C-H Streching
4	1650.95	Aromatic C=C stretching
5	1689.53	C=O Streching
6	1527.52	N-H Streching
7	1444.58	C-H deformation
8	3600-3100	OH stretching

3.2.2 Differential scanning calorimetry (DSC)

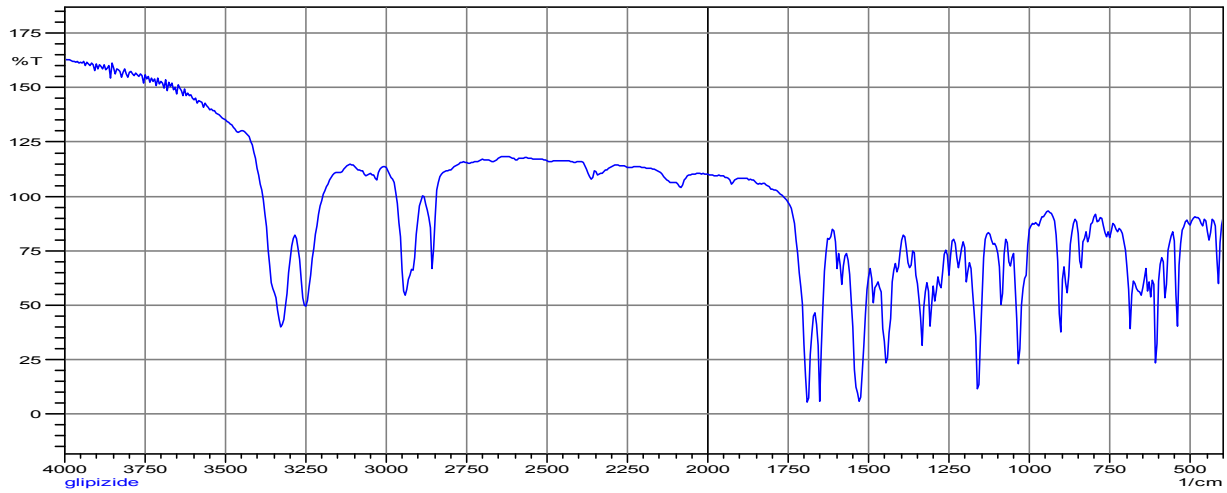
Thermal analysis was carried out using a differential scanning calorimeter (DSC Mettler Toledo DSC 821^{e}, Japan). The samples were placed in an aluminum – sealed pan and preheated to 200 ^{o}C.

The sample was cooled to room temperature and then reheated from 40 to 600 ^{o}C at a scanning rate of 10 ^{o}C/min. In DSC the amount of heat put into the system is exactly equivalent to the amount of heat absorbed or liberated during a specific transition. (transition energy).

Table No. 6: Post Compression parameters of Glipizide Tablets.

Formulations	Hardness (Kg/cm2)	Friability (% W/W)	Thickness (mm)	Diameter (mm)	% Drug content
G1	4.45 ± 0.09	0.72 ±0.026	3.111±0.05	8.02±0.025	94.10±0.05
G2	5.13 ± 0.05	0.84±0.001	3.345±0.07	8.03±0.024	98.73±0.057
G3	4.31 ± 0.06	0.87±0.005	3.322±0.08	8.03±0.023	96.57±0.059
G4	4.62 ± 0.05	0.88±0.007	3.456±0.05	8.04±0.023	95.59±0.062
G5	5.04 ± 0.07	0.92±0.02	3.777±0.09	8.01±0.027	93.65±0.065
G6	3.11 ± 0.08	0.85±0.004	3.654±0.04	8.04±0.024	97.36±0.073
G7	4.38 ± 0.06	0.89±0.002	3.656±0.03	8.03±0.026	93.78±0.059
G8	4.69± 0.04	0.74±0.028	3.333±0.02	8.03±0.024	94.68±0.055
G9	4.41± 0.05	0.83±0.006	3.345±0.06	8.03±0.028	94.52±0.052
G10	4.27±0.09	0.91±0.019	3.256±0.04	8.04±0.035	91.94±0.054

Each value represents mean (n=3) ± SD



Reported FTIR Spectrum of Glipizide

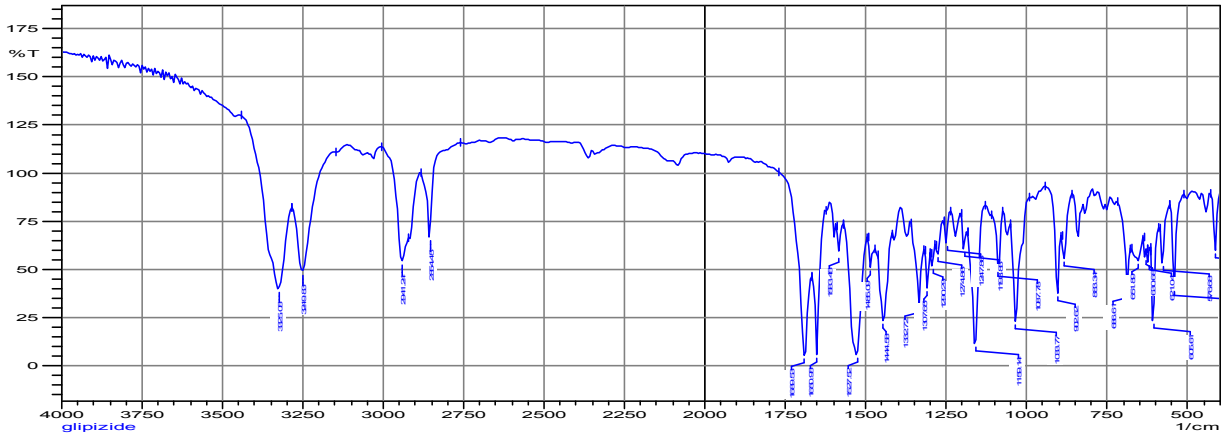


Figure No 3 : FTIR Spectra of Glipizide

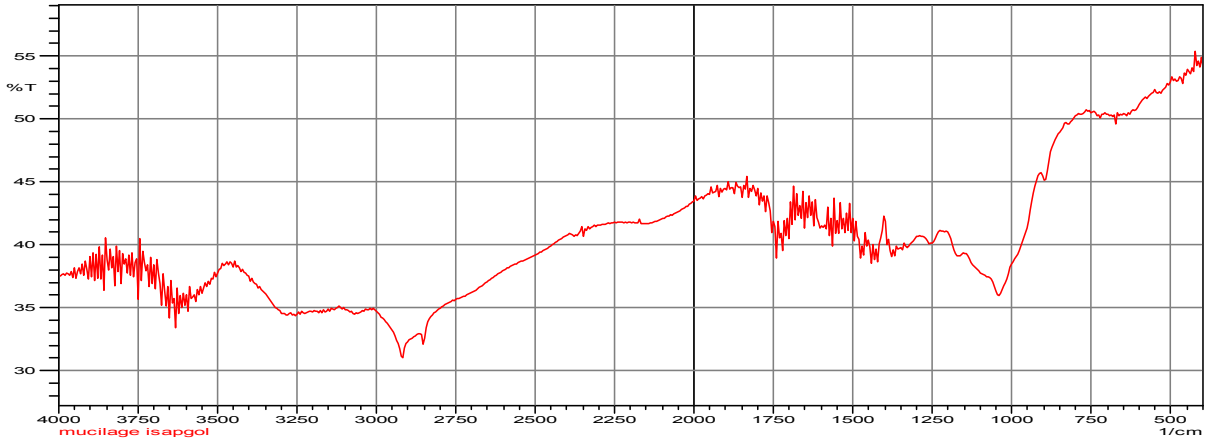


Figure No. 4 : FTIR Spectra of Isapgol mucilage

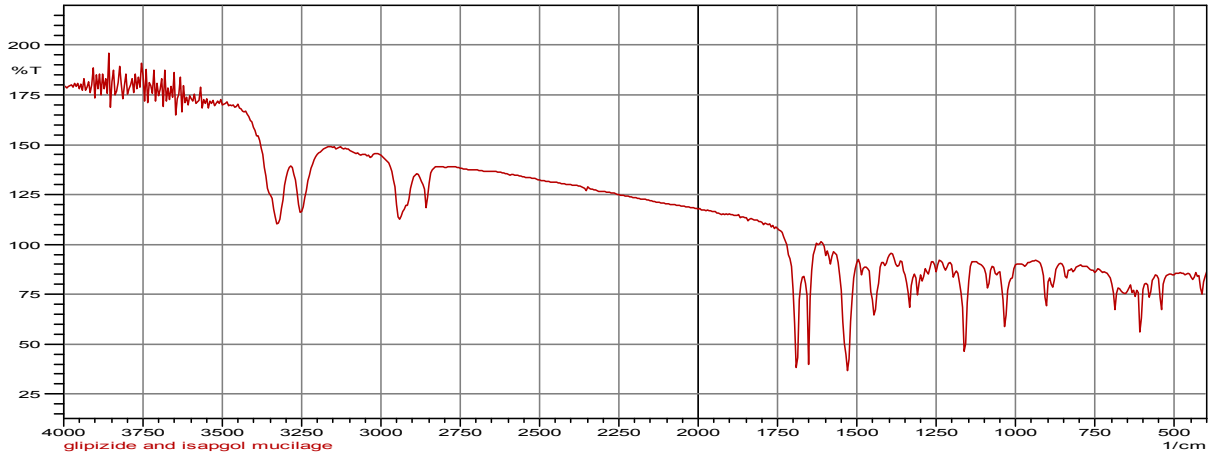


Figure No.5 :FTIR Spectra Of physical mixture of glipizide and Isapgol mucilage

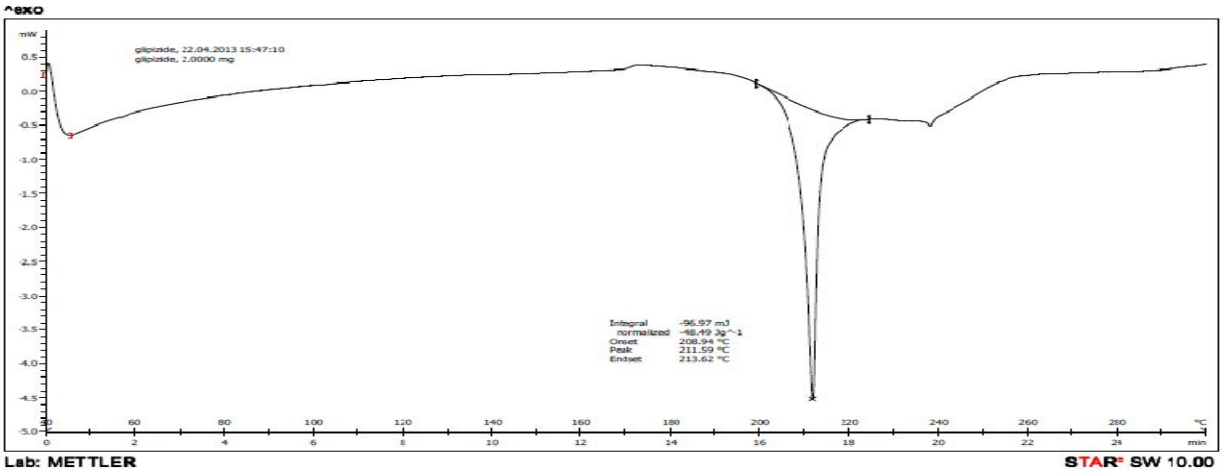


Figure. No 6 : DSC thermogram of Glipizide

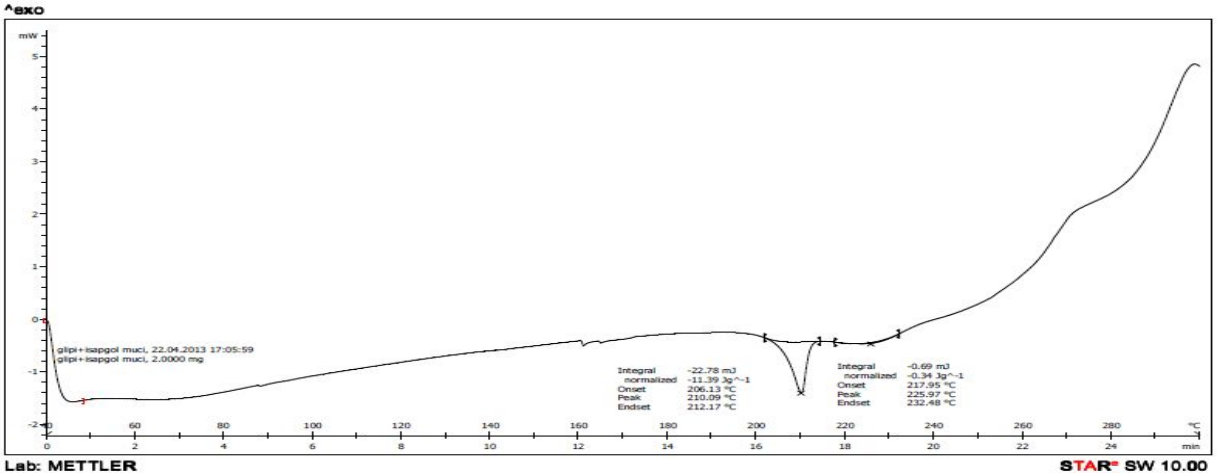


Figure No 7: DSC thermogram of Physical mixture of Glipizide and Isapgol mucilage

Table No. 7: Evaluation of formulations G2 kept for stability at 40^0C /75%RH.

Parameter	0 Month	1 Month	2 Months	3 Months
Appearance	White Colour	White Colour	White Colour	White Colour
Thickness (mm)	5.13 ± 0.05	5.09 ± 0.01	5.07 ± 0.02	5.05 ± 0.01
Hardness (Kg/cm^2)	3.345± 0.07	3.226± 0.05	3.224± 0.04	3.186±0.04
Friability (%)	0.84±0.03	0.81 ± 0.05	0.79± 0.03	0.74± 0.03
Drug content (%)	98.73±0.05	97.63± 0.03	97.42±0.05	97.33± 0.01

* Results are mean of three observations ± S.D.

3.3 Scanning Electron Microscopy:

Tablet samples (G2) were removed from the dissolution apparatus at predetermined time intervals and sectioned through an undisturbed portion of the gel formed at the flat face of the tablet. The specimen was then positioned on the sample holder so as to present a cross – under scanning electron microscope (SEM) (Model No. 6380 – A).

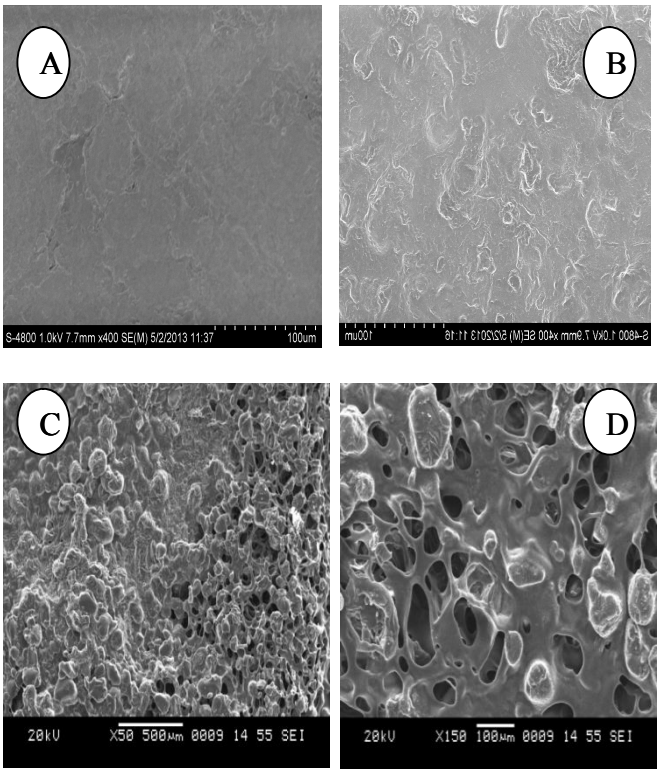


Figure 8 : SEM photomicrographs of optimized matrix tablet (batch G2) showing surface morphology after A -0 hrs, B- 4hrs, C- 6 hrs and D- 12 hrs of dissolution study.

3.4 Stability Study

Formulation G2, gave desirable release therefore were selected for stability studies. Thirty tablets of Formulation G2 were wrapped in aluminum foil of thickness 0.04 mm and stored at 40 ± 2^0C temperature with relative humidity of 75 ± 5%. The sampling was done after every one month and evaluation was done for appearance, thickness, hardness, friability, drug content and cumulative % drug release.

4. CONCLUSION

The use of natural gums and mucilages for pharmaceutical application is attractive because they are economical, readily available, non-toxic and capable of chemical modification, potentially biodegradable with few exceptions, also biocompatible.

Mucoadhesive matrix tablet of , Isapgol mucilage were prepared by wet granulation. The drug release from the tablet depends upon polymer erosion and drug diffusion.

The mucoadhesive matrix tablet prepared from showed a good control in drug release pattern for 12h From the present investigation it can be concluded that combination of natural polymers isapgol mucilage and synthetic polymer l could be succesfully employed for formulating sustain release formulation.

5. CONFLICT OF INTEREST

The author declares no conflict of interest.

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