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## FORMULATION AND EVALUATION OF ORAL MEDICATED GELLY CONTAINING CYCLODEXTRIN INCLUSION COMPLEXED WATER INSOLUBLE DRUG - GLIMEPIRIDE

Prabhakar Shirse\*

<sup>1</sup>Department of Pharmaceutics, RRKS's College of Pharmacy, Naubad, BIDAR, Karnataka-585 402

### ABSTRACT

*Glimepiride (GMP) is a Third Generation Sulphonylurea used for treatment of type 2 diabetes. Poor water solubility is the main constraint for its oral bioavailability. The rationale of this study was to enhance the solubility & dissolution of the drug by preparing its complex with  $\beta$ -CD and HP- $\beta$ -CD. In the present study attempt has been made to prepare and characterize inclusion complexes of Glimepiride with  $\beta$ -CD and HP- $\beta$ -CD. The inclusion complexes were prepared by three different methods viz. Physical, Kneading and Co-precipitation method. The inclusion complex containing GMP:  $\beta$ -CD and HP- $\beta$ -CD was further formulated into Oral Medicated Jelly by using hydrophilic polymers such as Pectin and Guar Gum in different proportions. The prepared complexes were characterized using FT-IR and DSC and finally the prepared formulations were evaluated for Physical Appearance, pH, Viscosity, Syneresis, Drug Content, Taste Masking and in-vitro Dissolution profiles. The sweeteners used for taste masking are of non nutritive type as the formulation is meant for diabetic patients. The combined polymers at specific proportions used for formulation showed best results in terms of the organoleptic properties and in-vitro dissolution profiles. The results of stability studies of best formulation revealed no change in physical appearance, drug content and in-vitro dissolution profiles, thus indicating that formulation was stable. The prepared oral medicated jelly formulations shall be successfully packed in unit dose packs to overcome the dose measurement problems by the patients.*

**Key words:** *Glimepiride, Hydroxypropyl Betacyclodextrin, Inclusion Complex, Oral Medicated Jelly, Taste Masking.*

### Correspondence to Author



Prabhakar Shirse

Department of Pharmaceutics, RRKS's  
College of Pharmacy, Naubad, BIDAR,  
Karnataka-585 402

Email: prabhakar.shirse@gmail.com

## INTRODUCTION

Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce their side effects. Solid dispersions are one of the most successful strategies to improve the drug release of poorly soluble drugs<sup>1</sup>. Presenting the compound as the molecular dispersion combining the benefits of a local increase in the solubility (within the solid solution) and maximizing the surface area of the compound that comes in contact with the dissolution medium as the carrier dissolves<sup>2</sup>. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability<sup>3</sup>. The advantage of solid dispersions over other approaches is that many of the carriers that can be applied are already extensively used in the pharmaceutical industry as excipients, so additional toxicity studies above and beyond what is required for the drug itself should not be required. The possibility of combining several carriers to produce an optimized product further extends the range of possibilities for formulation<sup>4</sup>. Many patients especially children and elderly have difficulty in swallowing tablets and capsules and consequently unable to take medicine like anti-diabetic drug as prescribed resulting in non-compliance and ineffective therapy<sup>5</sup>. Unfortunately, a high percentage of patients suffering from type-2 diabetes are elderly people showing dysphagia. The above problem becomes even more severe since the medication has to be taken lifelong everyday<sup>6, 7</sup>. Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance and convenience. One such approach led to development of oral medicated jelly.

Advantages of this drug delivery system include administration without water, convenience of administration and accurate dosing as compare to liquids, easy portability, ability to provide

advantages of liquid medication in the form of solid preparation, ideal for pediatric and geriatric patients and rapid dissolution/absorption of the drug, which may produce rapid onset of action. The patients with dysphagia can be choked by water while consuming liquid formulation which can be eliminated by administering liquid formulations with high viscosity<sup>8, 9, 10</sup>. Thus, jelly formulation containing Glimepiride was prepared. The oral medicated jelly formulations can be successfully packed in unit dose packs for the convenience of patients<sup>11, 12</sup>. Some drugs are absorbed from mouth; pharynx and esophagus as the saliva passes down in to stomach and in such cases bioavailability of drug is increased, pre-gastric absorption can result in improved bioavailability.

Glimepiride, 1-(p-(2-(3-ethyle-4-methyl-2-oxo-3-pyrroline -1-carboxamido) ethyl) phenyl) sulfonyl)-3-(trans-4-methylcyclohexyl) urea is a third-generation sulfonylurea used for oral treatment of type 2 diabetes<sup>13, 14</sup>. It causes an intensification of insulin secretion by the  $\beta$ -cells of the pancreas by closing the potassium channels and depolarizing the cell membrane; this leads to the initiation of metabolic processes which result in a release of insulin<sup>15</sup>. Glimepiride is a white or off white crystalline powder, relatively insoluble in water, but the predicated water solubility is (1.6  $\mu\text{g/ml}$ ) ( $\text{pKa}=6.2$ ). Which causes large variations in its bioavailability<sup>16</sup>. Also, during storage, the excipients may interact with the drug and affect its dissolution characteristics. There are several reports showing marked changes due to aging which adversely affect dissolution and, hence, the bioavailability of oral sulphonylurea drugs<sup>16, 17</sup>. To overcome these difficulties, several approaches have been used, namely, the formation of a complex between Glimepiride and  $\beta$ -CD, Hydroxypropyl-  $\beta$ -CD or sulfobutylether- $\beta$ -CD in presence and absence of different water soluble polymers<sup>16, 18, 19</sup>.

Cyclodextrins are cyclic oligosaccharides, containing six, seven or eight glucopyranose units ( $\alpha$ ,  $\beta$  or  $\gamma$  respectively) obtained by the enzymatic degradation of starch<sup>20</sup>. These are torus shaped molecules with a hydrophilic outer surface and

lipophilic central cavity, which can accommodate a variety of lipophilic drugs. Cyclodextrins are able to form inclusion complexes with poorly water-soluble drugs and have been shown to improve pharmaceutical properties like solubility, dissolution rate, bioavailability, stability and even palatability without affecting their intrinsic lipophilicity or pharmacological properties. Out of the three parent cyclodextrins,  $\beta$ -cyclodextrin ( $\beta$ -CD) appears most useful as a pharmaceutical complexing agent because of its complexing ability, low cost and other properties<sup>20, 21</sup>. Natural cyclodextrins have limited water solubility. However, a significant increase in water solubility has been obtained by alkylation of the free hydroxyl groups of the cyclodextrins resulting in hydroxyalkyl, methyl and sulfobutyl derivatives. The ability of cyclodextrins to form inclusion complexes may also be enhanced by substitution on the hydroxyl group.

The objective of present study is to prepare inclusion complexes of Glimepiride with cyclodextrins in different molar ratios by different methods such as physical, kneading and co-precipitation method to increase the solubility of Glimepiride for improvement of dissolution rate and bioavailability of the drug and formulate into oral medicated jelly to improve patient compliance.

## MATERIALS AND METHODS

### Materials

Glimepiride (GMP) was a gift sample obtained from M/s. Amsal Chem Pvt. Ltd. Mumbai, India. And all other excipients such as  $\beta$ -Cyclodextrin ( $\beta$ -CD), Hydroxypropyl- $\beta$ -Cyclodextrin (HP- $\beta$ -CD), Pectin, Guar Gum, Sucralose, Citric Acid, Mannitol, Sodium Citrate, Methyl Paraben Sodium, Propyl Paraben Sodium, Sunset Yellow FCF, Lemon Flavor, were procured from M/s. Yarrow Chem Products., Mumbai, India.

### Methods

#### Phase Solubility Studies

Phase solubility studies were carried out according to the method reported by Higuchi and Connors<sup>22</sup>. An excess of Glimepiride (200 mg) was added to 15 ml portions of distilled water, each containing

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variable amount of  $\beta$ -CD or HP- $\beta$ -CD such as 0, 1, 3, 6, 9, 12, and 15 x 10<sup>-3</sup> moles/liter. All the above solutions with variable amount of  $\beta$ -CD or HP- $\beta$ -CD were shaken for 72 hours. After shaking, the solutions were filtered and their absorbance was noted at 228 nm<sup>23</sup>. The solubility of the Glimepiride in every  $\beta$ -CD or HP- $\beta$ -CD solution was calculated and phase solubility diagram was drawn between the solubility of Glimepiride and different concentrations of  $\beta$ -CD or HP- $\beta$ -CD as shown in Figure 1.

#### Preparation of Cyclodextrin Inclusion Complexes

##### Physical Mixture

GMP with  $\beta$ -CD in different molar ratios (i.e. 1:1M, 1:2M) and with HP- $\beta$ -CD in ratio (i.e., 1:1M) were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 80 and stored in a desiccators over fused calcium chloride<sup>24</sup>.

##### Kneading Method

GMP with  $\beta$ -CD in different molar ratios (i.e. 1:1M, 1:2M) and with HP- $\beta$ -CD in ratios (i.e.1:1M) were taken. First cyclodextrin is added to the mortar, small quantity of 50% ethanol is added while triturating to get slurry like consistency<sup>24</sup>. Then slowly drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried at 25°C for 24 hours, pulverized and passed through sieve No. 80 and stored in desiccators over fused calcium chloride.

##### Co-precipitate Method

GMP was dissolved in ethanol at room temperature and  $\beta$ -CD & HP- $\beta$ -CD was dissolved in distilled water. Different molar ratios of GMP and  $\beta$ -CD (1:1M and 1:2 M) and GMP and HP- $\beta$ -CD (1:1 M) were taken<sup>24</sup>. The mixture was stirred at room temperature, for one hour and then slowly evaporated on a boiling water bath. The inclusion complex precipitated as a crystalline powder was pulverized and passed through sieve No. 80 and stored in a desiccator till free from any traces of the organic solvent.

##### Drug Content Estimation

50 mg of complex was accurately weighed and transferred to 50 ml volumetric flask and volume was made up to the mark with methanol. From this 1ml was taken in 10 ml volumetric flask and the

volume is adjusted up to the mark with same solvent. The absorbance of the solution was measured at 228 nm using appropriate blank. The drug content of GMP was calculated using calibration curve<sup>25</sup>.

#### **IR Spectroscopy**

The IR spectra of GMP and their complexes were obtained by KBr pellet method by JASCO FT/IR-5300 spectrometer.

#### **Differential Scanning Calorimetry (DSC)**

The samples were analyzed by DSC using a Mettler Toledo SR System. The samples were placed into pierced aluminum container.

#### **In-vitro Dissolution Studies for Glimepiride – Cyclodextrin Inclusion Complexes**

*In-vitro* dissolution of GMP inclusion complex was studied in USP XXIV dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of phosphate buffer of pH 7.4 was used as dissolution medium at 50 rpm. The temperature of  $37 \pm 0.5^\circ\text{C}$  was maintained throughout the experiment. Complex equivalent to 50 mg of GMP was used in each test. 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 228 nm after suitable dilution with phosphate buffer<sup>26</sup>. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. The amount of GMP released was calculated and plotted against time and compared with pure drug. The results drug content and dissolution profiles of different formulations are shown in Table No.3 & 4 respectively.

#### **Preparation of Glimepiride - Cyclodextrin Inclusion Complexed Oral Medicated Jelly**

The Best batch obtained from Kneading method with 1:1M ratio of inclusion complex of GMP- HP-  $\beta$

-CD was prepared into oral medicated jelly containing 2 mg of GMP.

1. Weighed accurately all the required ingredients in separate polyethylene bags.
2. Taken 50 ml of purified water and heated up to  $90^\circ\text{C}$  then dispersed dry Guar Gum & Pectin powder in the water. Maintain the temperature of water at  $90^\circ\text{C}$  while dispersion.
3. The dispersion was stirred using suitable magnetic stirrer for the period of 25 min maintained at the temperature of  $90^\circ\text{C}$  to facilitate hydration of Guar Gum.
4. Then Mannitol was added to the solution obtained at above step (3) under continuous stirring. Maintain the temperature of solution at  $90^\circ\text{C}$  while addition.
5. GMP- HP-  $\beta$  -CD Complex was added to the above step (4) under continuous stirring.
6. Then Sucralose, Citric acid, Methyl Paraben Sodium, Propyl Paraben Sodium were added to the above step (5) under continuous stirring.
7. Dissolved Sodium citrate in 10 ml of purified water and added to the above step (6) under continuous stirring.
8. Dissolved Sunset Yellow color in 10 ml of purified water and added to the above step (7) under continuous stirring.
9. Dissolved Lemon flavor in 10 ml of solution obtained from above step (8) and added to the above step (8) under continuous stirring.
10. Adjusted the final weight of the batch with required quantity of Purified water.
11. Packed the resultant solution in polyethylene mould provided with airtight seals.
12. Allowed to cool to room temperature to form jelly like texture.

The compositions of different formulations used for the preparation of oral medicated jelly are shown in Table No. 5.

Table No. 4  
*In-vitro* Drug Dissolution Profile of Glimepiride – Cyclodextrin Inclusion Complexes

TIME(Min)	PERCENT DRUG RELEASE									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F0
0	0	0	0	0	0	0	0	0	0	0
5	12.91	17.01	21.22	15.11	19.11	23.9	14.05	17.12	21.11	20.1
10	17.99	21.37	32.32	19.79	27.31	33.51	20.14	27.41	31.29	40.7
15	28.11	29.72	40.91	30.95	39.15	44.25	31.72	34.54	41.91	77.2
20	35.72	45.77	53.21	42.15	51.57	55.47	45.13	49.14	54.14	11.65
25	47.91	57.41	62.25	50.67	61.72	69.21	52.59	56.27	61.15	16.04
30	59.25	65.92	74.61	62.95	70.97	77.69	64.17	67.11	73.29	20.34
45	70.77	72.98	83.29	72.11	83.01	86.61	74.77	77.91	84.39	23.34
60	81.52	83.79	92.11	84.43	91.01	97.41	81.15	85.01	94.52	29.39

Table No. 5  
 Formula for Preparation of Glimepiride Oral Medicated Jelly

Sr. No.	Ingredients (%w/w)	Formulation Code			
		GOJ-1	GOJ-2	GOJ-3	GOJ-4
1	GMP : HP- $\beta$ -CD Complex (equivalent to 2 mg of GMP)	8.32	8.32	8.32	8.32
2	Guar Gum	0.2	0.3	0.4	0.5
3	Mannitol	20	20	20	20
4	Sodium Citrate	0.2	0.3	0.4	0.5
5	Citric Acid	0.05	0.05	0.05	0.05
6	Sucralose	0.25	0.25	0.25	0.25
8	MethylParaben Sodium	0.2	0.2	0.2	0.2
9	Propyl Paraben Sodium	0.02	0.02	0.02	0.02
10	Sunset Yellow FCF	QS	QS	QS	QS
11	Lemon Flavour	3.00	3.00	3.00	3.00
12	Purified Water %upto	100	100	100	100

## Evaluation of Oral Medicated Jelly

### Physical Appearance

Texture and clarity of the oral medicated jelly was evaluated in terms of stickiness and grittiness by mildly rubbing the gel between two fingers. Odour can also be evaluated by physical observation.

### Rheological Measurement

Viscosity of oral medicated jelly was measured using Viscometer spindle number LV4 at the rotation of 50 rpm at room temperature. The viscosity measurements were made in triplicate using fresh samples each time<sup>12</sup>.

### pH of the Oral Medicated Jelly

The pH of oral medicated jelly was measured using digital pH meter at room temperature<sup>27</sup>. The pH of the final gel has got influence on the taste &

stability of the oral jelly.

### Syneresis

Syneresis means contraction of gel upon standing and separation of water from the gel. Syneresis is more pronounced in the gels where lower concentration of gelling agent is used. Gels were kept under scrutiny for signs of syneresis. The gels showing signs of syneresis were rejected and not considered for further studies<sup>28</sup>. Syneresis is one of the major problems associated with low acylated guar gum gels.

### Taste Masking

Five grams of optimized formulation containing 2 mg Glimepiride was given to taste panel experts and they were told to keep the gel in mouth for 5 s. The volunteers were instructed not to swallow the

gel. They were asked to comment on the bitterness, aftertaste, sweetness, and flavor of the gel. Mouth feel in terms of grittiness was also checked. Bitterness and aftertaste were graded from non-bitter and nonsaline (-) to slightly saline and bitter (+) to bitter and saline (++) to very bitter and strong saline (+++). Sweetness was graded from less sweet (+) to sweet (++) to very sweet (+++). Flavor and mouth feel were assessed from less (+) to moderate (++) to good (+++) <sup>29</sup>.

#### **Drug Content**

Two grams of Glimepiride soft gel was accurately weighed on an electronic balance and then transferred to 1000 ml volumetric flask. Then, 900 ml of pH 6.8 phosphate buffer was added to dissolve the gel. From that solution, pipet out 1 ml of the sample and diluted up to 50 ml with pH 6.8 phosphate buffer. Samples were analyzed spectrophotometrically at 228 nm by UV spectrophotometer after filtering the sample through 0.45  $\mu$  filters. The gels comply with the test if not more than one of values thus obtained is outside the limits of 85-115% of the average value and none is outside the limits 75-125%. <sup>12</sup>.

The evaluation results of all the four oral medicated jelly formulations are shown in Table No. 6.

#### ***In-vitro* Dissolution Studies for Glimepiride - Cyclodextrin Inclusion Complexed Oral Medicated Jelly**

*In-vitro* dissolution was studied in USP XXIV dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of phosphate buffer of pH 7.4 was used as dissolution medium. The stirrer was adjusted rotate at 100 rpm. The temperature of dissolution media was previously warmed to  $37 \pm 0.5^\circ\text{C}$  and was maintained throughout the experiment. 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 228 nm after suitable dilution with phosphate buffer pH 6.8. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Percentage amount of GMP released was calculated and plotted against time.

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The 5 gm of ready to use oral medicated jelly containing 2 mg of Glimepiride was used for the dissolution test <sup>30,31</sup>.

The comparative profiles of *in-vitro* dissolution studies of Glimepiride Cyclodextrin Inclusion Complex oral medicated jelly are shown in Table No.7

#### **Stability Studies**

The optimized formulation was subjected for two month stability study according to ICH guidelines. The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. The samples were kept at different temperatures (0-8°C and Room Temperature) for four weeks. The samples of soft gel were observed weekly for pH, viscosity, and physical appearance. All the tests were performed after allowing the samples to be equilibrated at 25°C for two hours <sup>12</sup>. A physically stable medicated oral jelly retains its viscosity, color, clarity, taste, and odor throughout its shelf-life. Medicated oral jelly was checked for syneresis during storage. A freshly made sample should serve as a reference standard for subjective evaluations.

The observations of stability studies are shown in Table No.8

## **RESULTS AND DISCUSSION**

### **Phase Solubility Studies**

The complexation of GMP with  $\beta$ -CD and HP- $\beta$ -CD was investigated by Phase Solubility Studies. The phase solubility diagram for complex formation is shown in Figure: 1. The aqueous solubility of GMP was increased linearly as a function of concentration of CD. The phase solubility diagram can be classified as type AL according to Higuchi and Connors. It is assumed that the increase in solubility observed was due to the formation of a 1:1 M inclusion complex. The solubility constant ( $K_c$ ) was calculated from the slope of the linear plot of the phase solubility diagram according to equation,

$$K_{a,b} = \frac{\text{slope}}{S_0 (1-\text{slope})}$$

Where  $S_0$  is the solubility of the drug in absence of

CD. The calculated Kc value was  $32.95 \text{ M}^{-1}$   
and  $= 42.57 \text{ M}^{-1}$  with  $\beta$ -CD and HP- $\beta$ -CD

respectively.(Table No.2, Fig.1)

Table No. 2

Phase Solubility Studies of Glimepiride:  $\beta$ -Cyclodextrin Complexes and Glimepiride: HP- $\beta$ -Cyclodextrin Complexes

Concentration of $\beta$ -CD (mM)	Concentration of GMP (mM)	Concentration of HP- $\beta$ -CD (mM)	Concentration of GMP (mM)
0	0.04	0	0.04
3	0.043	3	0.045
6	0.047	6	0.05
9	0.051	9	0.055
12	0.055	12	0.06
15	0.059	15	0.065

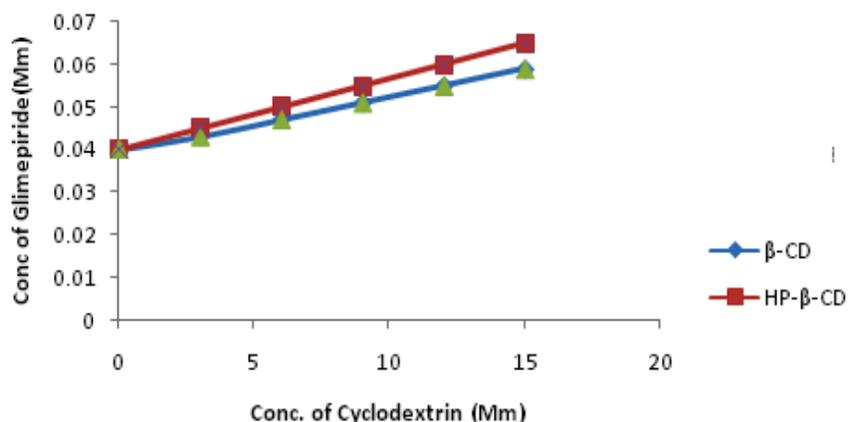


Fig. 1: Phase Solubility Diagram of Glimepiride with  $\beta$ -CD and HP- $\beta$ -CD

Drug Content Estimation in Glimepiride-Cyclodextrin Inclusion Complexes

The inclusion complexes prepared by physical mixture and kneading method showed nearly 100

% drug content. But the inclusion complexes prepared by Co-precipitate method were found to be slightly less. The comparison results are shown in Table No.: 3

Table No. 3

Drug Content Estimation of Glimepiride in the  $\beta$ -CD and HP- $\beta$ -CD Inclusion Complexes

Formulation Code	Percent Drug Content $\pm$ SD
F <sub>1</sub>	98.07 $\pm$ 0.39
F <sub>2</sub>	98.21 $\pm$ 0.63
F <sub>3</sub>	98.37 $\pm$ 0.27
F <sub>4</sub>	99.19 $\pm$ 0.51
F <sub>5</sub>	99.39 $\pm$ 0.19
F <sub>6</sub>	99.57 $\pm$ 0.72
F <sub>7</sub>	97.61 $\pm$ 0.19
F <sub>8</sub>	97.77 $\pm$ 0.72
F <sub>9</sub>	98.15 $\pm$ 0.36

### IR Spectroscopy

IR Spectra of pure drug and inclusion complexes tablets of GMP with  $\beta$ -CD and HP- $\beta$ -CD prepared by different methods are given in Fig. 6. As clearly seen from the spectra, the characteristic peaks of

GMP at 709, 1082, 1444, 1674, 1705, 2360 and 3369 were modified significantly as a result of complex formation. The comparison graphs are shown in Fig. 2.

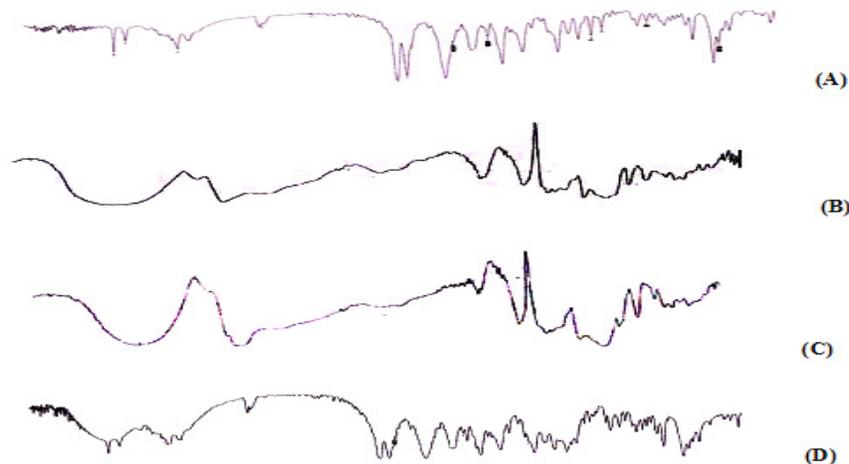


Fig. 2: F.T.I.R. Spectra of (A)GMP, (B)  $\beta$ -CD, (C)HP- $\beta$ -CD and (D) F6 Complex

### Differential Scanning Calorimetry (DSC)

The thermal behavior GMP -HP- $\beta$ -CD complex was studied using DSC in order to confirm the formation of complex. DSC thermo gram of GMP, HP- $\beta$ -CD and F<sub>6</sub> complex are shown in Fig. 7. The DSC thermo gram of GMP showed an endothermic

peak at 214°C corresponding to its melting point. The thermo gram of F<sub>6</sub> showed endothermic peak at 237°C which is different from the pure drug, which gives clear evidence that there is formation of the complex. The comparison graphs are shown in Fig. 3.

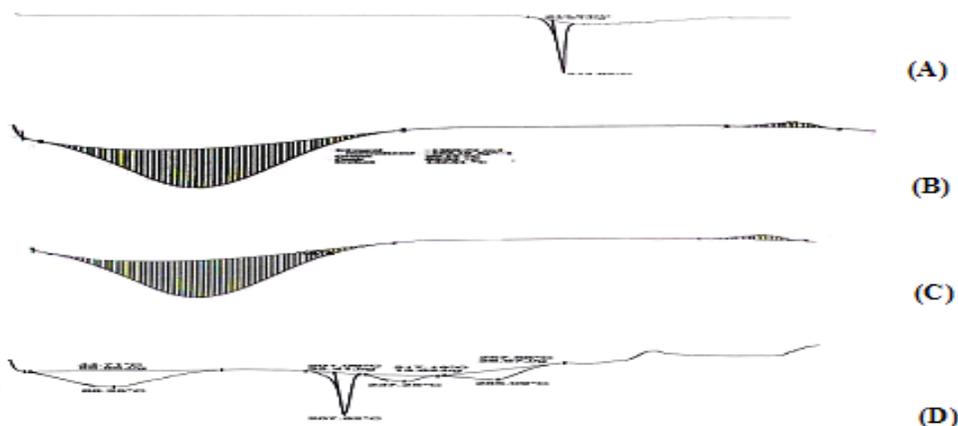


Fig. 3: DSC Thermograms of (A) GMP, (B)  $\beta$ -CD (C) HP- $\beta$ -CD and (D) F6 Complex

### *In- vitro* Dissolution Study in GMP Inclusion Complexes

The dissolution characteristics of GMP (pure drug) and inclusion complexes are shown in Fig. 4, 5 and 6. The inclusion complexes produces pronounced enhancement in its dissolution rate than pure drug.

The inclusion complexes prepared with HP- $\beta$ -CD shows higher dissolution rate than the inclusion complexes prepared with  $\beta$ -CD. Among these the complexes, the complex prepared with HP- $\beta$ -CD i.e. formulation F<sub>6</sub> shows higher dissolution rate than the other methods, so same has been chosen for

preparation of Fast Dissolving Tablets. The Comparative results are shown in table No.:4 and

the comparison graphs are shown in Fig. 4.

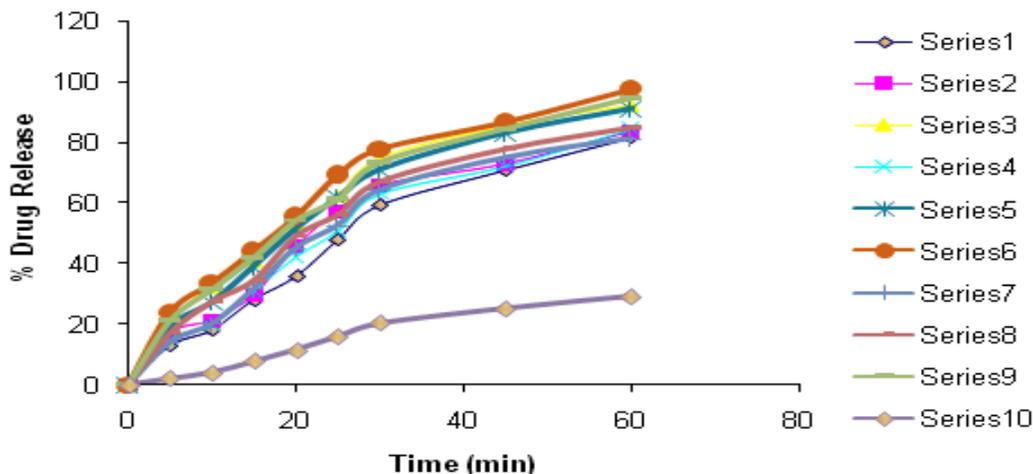


Fig. 4: Plot of *In- vitro* Drug Dissolution Profile of Glimepiride – Cyclodextrin Inclusion Complexes (F<sub>0</sub>, F<sub>1</sub>, F<sub>2</sub>, F<sub>3</sub>, F<sub>4</sub>, F<sub>5</sub>, F<sub>6</sub>, F<sub>7</sub>, F<sub>8</sub> & F<sub>9</sub>)

## Evaluation of Oral Medicated Jelly

### Physical Appearance

The evaluation results of different batches of Glimepiride oral medicated jelly are shown in Table No.6. All the batches were found to be transparent in appearance. The jelly of batch number GOJ-3 was found to be non-sticky and non-gritty while the gel of batch number GOJ-4 was slightly sticky. The non-gritty nature of the batch number GOJ-3 may be due to the suitable concentration of Guar Gum and Sodium Citrate but batch number GOJ-4 was sticky due to higher concentration of both Guar Gum and Sodium Citrate.

### Consistency

Guar Gum has a good gelling power hence it can produce gels at low concentration. The batch numbers GOJ-1 and GOJ-2 exhibited fluid like consistency while the jelly of batch number GOJ-4 were thick in consistency. As the consistency of gels depends on the concentration of the polymer, batch number GOJ-3 showed acceptable consistency. These visual inspection results are supported

by the viscosity measurements. The results are shown in Table No.6

### Viscosity

The results of evaluation of oral medicated jelly of

batch number GOJ-1 to GOJ-4 are shown in Table No.6. The batch numbers GOJ-1 and GOJ-2 were low because of its fluid like consistency while the viscosity of the batch number GOJ-3 was found to be appropriate because of its consistency. But, viscosity of batch number GOJ-4 was thick in consistency, sticky and gritty; it may fail to give good mouth feel. The viscosity of the batch number GOJ-3 was found to be acceptable due to its consistency. The consistency and viscosity of the oral medicated jelly are related to each other because both are dependent on concentration of Guar Gum, Sodium Citrate and other added co-solute.

Effect of concentration of added co-solute such as Mannitol and Sucralose on the viscosity and consistency of the oral medicated jelly was same because it was constant in all the batches. It is clearly evident from the observed results that changes in the viscosity and consistency of oral medicated jelly is greatly because of change in concentration of Guar Gum and slightly because of change in concentration of Sodium Citrate. Free carboxylate groups are present in the structure of Guar gum therefore it is anionic in nature and thus it would undergo ionic gelation in the presence of both divalent and monovalent cations such as

Ca<sup>++</sup>, Mg<sup>++</sup>, K<sup>+</sup>, Na<sup>+</sup>, and H<sup>+</sup> from acid <sup>32</sup>. However, its affinity for divalent cations such as Ca<sup>2+</sup> and Mg<sup>2+</sup> is much stronger than monovalents such as Na<sup>+</sup> and K<sup>+</sup> <sup>33</sup>.

### pH

The pH of the jelly preparation in the form of solution just before gelation is adjusted preferably to 4 to 7. This is because when pH is below 4 jelly preparation liable to cause syneresis and stability of the preparation deteriorates in some cases. When the pH is 6 or more close to neutrality, the

jelly preparation is far more excellent in stability. Therefore, the pH of the formulated gels was adjusted and maintained in between 5 and 7 with help of buffering agents such as citric acid and sodium citrate. The amount of citric acid was kept minimum, i.e., just to adjust the required pH. Sodium citrate was selected as a salt to contribute cation because it also act as sequestrant, buffering agent and helps in maintaining mechanical property of the gel <sup>34</sup>. The pH of gels of batch numbers GOJ-1 to GOJ-4 are shown in Table No.6

Table No. 6  
Evaluation of Oral Medicated Jelly

Formulation Code	Clarity	Consistency	Texture	pH	Viscosity (cps - centipoises)
GOJ-1	Transparent	Fluid	Nonsticky - Nongritty	5.62	2437
GOJ-2	Transparent	Fluid	Nonsticky - Nongritty	5.71	5432
GOJ-3	Transparent	Acceptable	Nonsticky - Nongritty	5.77	7132
GOJ-4	Transparent	Slightly Thick	Nonsticky - Slightly gritty	5.63	8151

### Syneresis

Syneresis is more pronounced in the gels where lower concentration of gelling agent is used. Syneresis was not noticed at room temperature probably due to binding of free water by co-solute <sup>35</sup>. The batch numbers GOJ-2 & GOJ-2 showed slight syneresis on standing, thus it was not considered for further studies. The batch number GOJ-3 showed very less degree of syneresis at room temperature and in refrigerator also (2-8°C). Syneresis was observed after 24 hrs of jelly preparation.

### Drug Content

The drug content of all the batch number GOJ-3 was found to be 97.5 ±1.5 of Glimepiride which is well within acceptable limits.

### Taste Masking

The results of taste evaluation of the batch number GOJ-3 are found to be satisfactory. All the ten volunteers perceived the jelly as non-bitter. The probable reason is that the gelling agents can lower diffusion of bitter substances from the gel to the taste buds. However, the volunteers reported a slight bitter aftertaste. Mannitol was selected as a

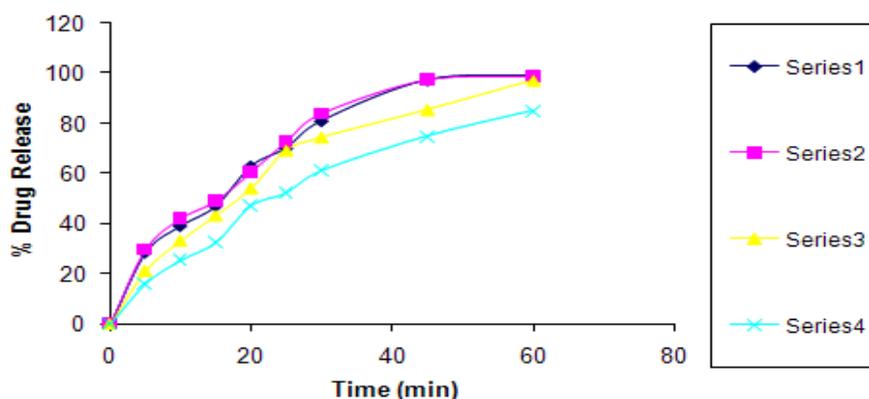
sweetener in jelly to mask the taste of Glimepiride. As it is an antidiabetic formulation, Sucralose was selected as an auxiliary sweetener because it is non-nutritive and 300-1000 times sweeter than the sucrose <sup>35</sup>. Lemon flavor was selected because to certain extent it helps in masking the bitter taste of drug and also improves patient acceptance.

### In-vitro Dissolution Studies

The results shown in reveal that jelly of the batch number GOJ-3 exhibited acceptable consistency and viscosity. Thus, it was subjected to dissolution study to draw any conclusion and their percentage drug release at different time intervals has been shown Table No. 7

Figure 5 shows that 97% of drug release from batch number GOJ-3 took in 60 min where as it shows 85% in case of batch number GOJ-4. There was no significant difference between release profiles of the GOJ-3 and GOJ-4, but release profile of batch GOJ-4 does not meet the in house specification. Also, viscosity of the batch GOJ-4 exceeded in house specification and it showed slightly gritty structure which may decrease the mouth feel, thus batch GOJ-3 was chosen as the optimized batch.

The comparative results are as shown in Table No.7



**Fig.5 : Plot of in- vitro Drug Dissolution Profile of different batches of Oral Medicated Jelly**

**Table No. 7**

*In- vitro Drug Dissolution Profile of different batches of Oral Medicated Jelly*

TIME(Min)	PERCENT DRUG RELEASE FORMULATION CODE			
	GOJ-1	GOJ-2	GOJ-3	GOJ-4
0	0	0	0	0
5	28.52	29.72	21.19	16.12
10	39.19	42.15	33.23	25.41
15	47.14	49.15	43.32	32.54
20	63.11	60.67	54.12	47.14
25	70.36	72.95	69.36	52.27
30	81.19	84.11	74.52	61.11
45	97.45	97.55	85.51	74.91
60	99.32	99.11	97.21	85.01

### Stability Studies

The results of short-term stability studies indicated insignificant changes in pH, viscosity, and appearance in the optimized formulation with time. Precipitation of drugs in the soft gels was not observed in any of the gels. Also, insignificant

syneresis was not observed in any of the samples at both temperatures. Therefore, it is recommended that soft gel should be stored at about 25°C. The observations are shown in Table No. 8

**Table No.8**

**Short Term Stability studies parameters for Optimized Batch (GOJ-3) of Oral Medicated Jelly**

Time	at Room Temperature (i.e. 33±2 °C)			at 0-8°C		
	Percent Drug Content	Viscosity (cps- centipoises)	pH	Percent Drug Content	Viscosity (cps- centipoises)	pH
First day	99.14	7134	5.77	99.21	7132	5.77
1 <sup>st</sup> week	99.27	7149	5.78	99.43	7142	5.76
2 <sup>nd</sup> week	99.51	7155	5.77	99.54	7149	5.78
3 <sup>rd</sup> week	99.34	7160	5.78	99.55	7152	5.77
4 <sup>th</sup> week	99.24	7165	5.76	99.31	7157	5.76

**CONCLUSION**

This study shows that there is significant improvement in solubility and dissolution rate of Glimepiride by its complexation with HP-  $\beta$  -CD in 1:1 M ratio prepared by kneading method.

In Medicated oral jelly prepared from cyclodextrin inclusion complexed Glimepiride, it was found from the observed results that the optimized batch number GOJ-3 was substantially stable at both room temperature and also at low temperature, thus storage at room temperature is possible. The results of GOJ-3 also showed good taste masking with acceptable mouth feel and it was able to release 97% of drug in 60 min. Finally, it was found that the batch number GOJ-3 meets all in house specifications.

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