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### Development of Novel Controlled Release Buccoadhesive Drug Delivery Anti-Diabetic and Anti-Inflammatory Drug Combination

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#### ABSTRACT

The present research work was aimed for an innovative study to prepare buccoadhesive tablets of Glipizide and Valdecoxib with unidirectional release. In this study buccoadhesive bilayer tablets were prepared with a core layer and a backing layer. The prepared tablets were characterized for physical parameters viz., thickness, weight variation, hardness, and friability, uniformity in drug content, surface pH, water absorption, mucoadhesive performance, in vitro dissolution and in vivo studies. The fabricated mucoadhesive tablets showed good physical appearance and passed the weight variation test as per I.P specifications. The hardness and Friability of the prepared tablets indicates the compactness and mechanical strength. The uniformity in drug content in the formulated tablets indicates that the drugs were uniformly mixed with the polymers used. The surface pH of all formulated mucoadhesive tablets was almost within the salivary pH range. The water absorption studies revealed that the formulated mucoadhesive tablets with Sodium CMC exhibits high percent water absorption as compared to formulations with Poly Vinyl Pyrrolidone. The in vitro dissolution studies revealed that the release rate of Glipizide and Valdecoxib was maximum from the mucoadhesive tablet made with Carbopol 940 and PVP. The kinetic data showed that the drug release from, formulations was mainly due to diffusion and erosion mechanism. The GPV-5 formulation showed hypoglycemic actions and in vivo drug release. The accelerated stability studies revealed that GPV-5 formulation retained the physicochemical properties even after the stressed storage conditions.

**Key words:** Glipizide, Valdecoxib, buccoadhesive tablet, evaluation.

## INTRODUCTION

Glipizide is a second-generation sulfonylurea that can acutely lower the blood glucose level in humans by stimulating the release of insulin from pancreas and is typically prescribed to treat type II Diabetes. The drug is selected as model for designing sustained release because of its short biological half-life ( $3.4 \pm 0.7$  h) and to be administered 2 or 3 doses with 2.5 to 10 mg per day [1].

Valdecoxib, a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties was chosen as a model drug due to its high first pass metabolism. It undergoes both P450 and non-P450 dependent (glucuronidation) metabolism. The mechanism of action is believed to be due to inhibition of Prostaglandin synthesis primarily through inhibition of cyclooxygenase-2 (COX-2).

Buccoadhesive Glipizide and Valdecoxib tablets were prepared by using Sodium carboxy methyl cellulose (Na. CMC) and Hydroxy propyl methyl cellulose (HPMC), Carbopol and Poly Vinyl Pyrrolidone. No Glipizide and Valdecoxib buccoadhesive tablets are available commercially. So an attempt has been made to develop a combination controlled release buccoadhesive formulation of anti-diabetic drug with NSAID.

## MATERIAL AND METHODS

### Materials

Glipizide and Valdecoxib were obtained from Doctor Reddy's laboratories, Hyderabad, India. HPMC K4M, Carbopol-934P, Povidone, magnesium stearate were procured from SD fine chemicals, Mumbai, India and all other ingredients used were of analytical grade. Double distilled water was used whenever required.

## EXPERIMENTAL METHODS

### Pre formulation Studies for Drug Excipients Compatibility

#### *DSC Study*

The possibility of any interaction between drug and excipients used in formulations during tablet processing was assessed by carrying out the thermal analysis on pure drug and formulation GPV-5 using differential scanning calorimetry. The thermo grams of samples were obtained at a scanning rate of  $10^\circ \text{C} / \text{min}$  conducted over range of  $50\text{-}300^\circ\text{C}$ .

#### *FTIR Spectroscopy*

The pure drug and formulation (GPV-5) were separately mixed with IR grade potassium bromide in a ratio of (1:100) and pellets were prepared by applying 10 metric ton of pressure in hydraulic press. The pellets were then scanned over range of  $4000\text{-}400\text{cm}^{-1}$  in FTIR instrument.

#### *Scanning electron microscopy*

Tablet samples (batch GPV-5) were removed from the dissolution apparatus at predetermined time intervals and kept in oven at  $40^\circ\text{C}$  for some time; these samples were then sectioned through the undisturbed part of tablet. Further, the samples were coated with gold and visualized under a scanning electron microscope (SEM) (JEOL JSM- 6360, Japan).

### Preparation of mucoadhesive Tablets

Mucoadhesive tablets were prepared in 3 steps.

#### *Step-I: Preparation of Core Layer's Mixture*

Glipizide, Valdecoxib, Hydroxy propyl Methyl Cellulose, Carbopol-940, Sodium Carboxy Methyl Cellulose-H, Polyvinyl Pyrrolidone-K30 and Magnesium stearate were mixed well by using glass mortar and pestle. This mixture was used for the preparation of core layer of the tablet. The composition of core layer was shown in Table 1 [2-5].

### **Step-II: Preparation of Backing Layer's Granules**

Carbopol 934P, Poly vinyl pyrrolidone, Magnesium stearate, Saccharin sodium were mixed well using glass mortar and pestle. By gradually adding the ethanol (95%) solution to a dry mixture; a wet mass/lump was prepared. Clove oil was added to this lump and mixed properly. Then this lump was passed through the sieve (#mesh 40). Then wet granules were dried in a Hot Air Oven at a temperature 40°C for 20 min. To this dried granules, magnesium stearate lubricant was added. These granules were used for the preparation of backing layer of the tablet. The composition of backing layer was shown in Table 2 [3-5].

### **Step-III: Compression**

For this purpose an I.R. hydraulic press and Die Punch Set having diameter of 10mm was used. Firstly, the mixture of drug and polymers (weighed quantity-150mg) was compressed using a pressure of 50kg/cm<sup>2</sup> for 5 sec. Then upper punch was removed and then granules of backing layer (weighed quantity -75mg) were added over the first layer and compressed at a pressure of 200kg/cm<sup>2</sup> for 15 sec. By this way, the bilayer tablet was prepared [3-5].

## **EVALUATION OF TABLETS**

### **Physical evaluation of tablets**

#### **Thickness**

The thickness of the tablets was determined using a thickness screw gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used and average values were calculated.

#### **Uniformity of Weight Test**

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado) and the test was performed according to the official method.

#### **Hardness and Friability**

For each formulation, the hardness and friability of 10 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively.

#### **Swelling behavior of matrix tablets**

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulation GPV-1, GPV-2, GPV-3, GPV-4 and GPV-5 were studied. One tablet from each formulation was kept in a petri dish containing phosphate pH 7.4. At the end of 2 h, the tablet was withdrawn, kept on tissue paper and weighed, repeated for every 2 h till the end of 12 h. The % weight gain by the tablet was calculated by using following equation [8].

$$S.I = \{(M_t - M_0) / M_0\} \times 100$$

Where,

S.I = Swelling Index,  $M_t$  = Weight of tablet at time 't' and  
 $M_0$  = Weight of tablet at time 0.

#### **Mucoadhesive Force Measurement**

Mucoadhesive force measurement of tablets was done by modifying balance method. The right pan was replaced with a glass beaker container and on the left side beaker with a copper wire. Teflon block of 1.5 cm diameter and 3 cm height was adhered strongly with the glass beaker. The two sides were then adjusted, so that the left hand side was exactly 5 g heavier than the right. Stick the stomach on the teflon block with help of the cyanoacrylate glue and fill the beaker with acidic buffer till the tissue remains in a moist condition. Stick the tablet to beaker and put on the tissue for a 15 min. After that add water slowly in to right beaker until the tablet detaches. Weight the water required for the tablet detachment. Calculate Actual weight for detachment and force of adhesion in dyne by following equation [7].

$$\text{Actual weight for detachment (W)} = \text{weight for detachment (g)}$$

#### **Surface pH**

The surface pH of the mucoadhesive tablets was determined in order to investigate the possibility of any side effects *in vivo*. An acidic or alkaline pH may cause irritation to the buccal mucosa. A combined glass electrode was used for this purpose.

The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH  $6.5 \pm 0.05$ ) for 2h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1min [8]. The results were shown in Table 4.

#### **Matrix Erosion**

Each tablet weighed ( $W_1$ ) were immersed in a phosphate buffer pH 6.8 for predetermined time (1, 2, 4, 8 and 12 h). After immersion, tablets were wiped off by the excess of surface water by the use of filter paper. The swollen tablets were dried at  $60^\circ\text{C}$  for 24 h in an oven and kept in a desiccator for 48 h prior to be reweighed ( $W_2$ ) [9]. The matrix erosion was calculated using the formula given in the following equation.

$$\text{Matrix Erosion} = (W_1 - W_2) / W_1 \times 100$$

### **In Vivo Pharmacodynamic Studies**

#### **Selection and maintenance of animals**

Male guinea pigs either sex weighing 300-350 g were employed for the study (procured from National Institute of Nutrition, Hyderabad, India). The guinea pigs were maintained under standard laboratory conditions (temperature of  $25 \pm 2^\circ\text{C}$  and relative humidity of  $50 \pm 15\%$ ) and normal photo period was used for the experiment. Commercial pellet diet (Ratan Brothers, India) and water were provided when desired. The experimental protocol has been approved by the Institutional Animal Ethics committee and by the Regulatory body of the government (Reg. no.582/02/c/CPCSEA).

#### **Hypoglycemic study**

Two groups of guinea pigs each of 3 animals, that were fasted (water) at least 12 h before the experiments were used for the study. Prior to tablet administration, the guinea pigs were anaesthetized with pentobarbital (25 mg/kg). Before administration of dosage form, a blood sample as a control was taken from each guinea pig from jugular vein. The blood glucose level for the control and test samples was determined using the glucose-measuring instrument Medisence (Abbott Laboratories, USA). The instrument was self-calibrated, and the samples were allowed to dry before the results were read to avoid contamination of the lens. The administration region of the buccal mucosa of each guinea-pig was wiped with absorbent cotton immersed in saline and then pure Glipizide and mucoadhesive tablet (GPV-5) at a dose of 800  $\mu\text{g}/\text{kg}$  of Glipizide was administered for each guinea pig were attached to cheek to each group. Blood samples were collected at 1h intervals up to 12h and the blood glucose level was performed as per method described earlier. The % reduction in blood glucose level was measured [5].

#### **Anti-inflammatory study**

The anti-inflammatory actions were measured by comparing the maximal oedema response during 6 h. A 0.1 ml of 1% carrageenan suspension was subcutaneously given into the sub plantar tissue of the hind paw of each guinea pig. Group I normal guinea pigs treated with placebo (1% Sodium CMC), which served as normal control, Group II guinea pigs were treated with Valdecocix pure drug (2 mg/kg body weight), which serves as standard and Group III guinea pigs were treated with formulation (a dose of 2mg/kg body weight respectively). All the doses were given according to their body weight [11, 12].

#### **Accelerated Stability Studies**

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines. Optimized formulation (GPV-5) was sealed in Aluminium packaging coated inside with polyethylene, and then kept in stability chamber maintained at  $45^\circ\text{C}$  and 75% RH for 3 months. At the end of studies, samples were analysed for the drug content, *in-vitro* dissolution, floating behaviour and other physicochemical parameters [13].

## **RESULTS**

The compatibility of drug with excipients was studied by DSC, FTIR and SEM studies. The DSC graphs of Glipizide, Valdecocix and formulation were shown in Fig 1 and 2. The FTIR spectrums of Glipizide, Valdecocix and formulation (GPV-5) were shown in Fig 3, 4 and 5. The SEM of optimized tablet surface at X200 and X1000 magnification was shown in Fig 6. The prepared tablets showed uniformity in thickness and weights. The friability of formulated tablets was less than 1% and the hardness was more than  $4 \text{ kg}/\text{cm}^2$ . The formulated tablets showed uniformity in Glipizide and Valdecocix content. The surface pH and water absorption were within the acceptable limits.

The mucoadhesive strength and swelling index were found to be satisfactory. The *in vitro* dissolution showed that more than 25% of drug released at first one hour and the remaining was released for extended period of time. All these values were shown in Table 4. The swelling index of formulated tablets was shown in Fig 7.

The *in vitro* dissolution was shown in Fig 8 and 9. The optimized formulation (GPV-5) showed reduced blood glucose levels (<40%) within 3<sup>rd</sup> h and maintained till the end of 12<sup>th</sup> h Vs. Glipizide oral control and was shown in fig 10. The same formulation was tested for percent inhibition of paw oedema in guinea pigs and it was more than 40% compared to Valdecoxib pure drug and showed in Fig 11.

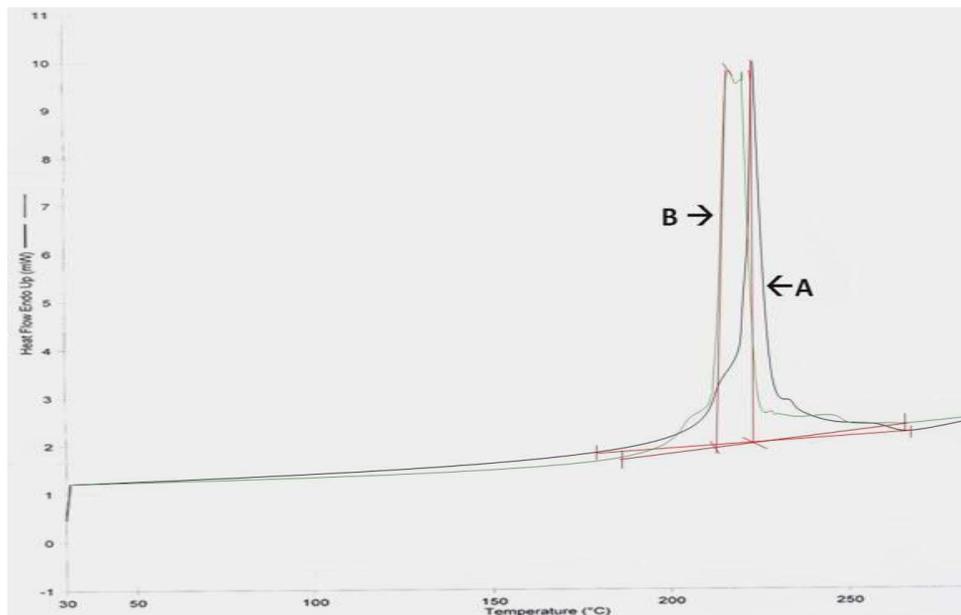


Fig.1. DSC of Glipizide Pure drug (A) and Glipizide (B) in GPV formulation

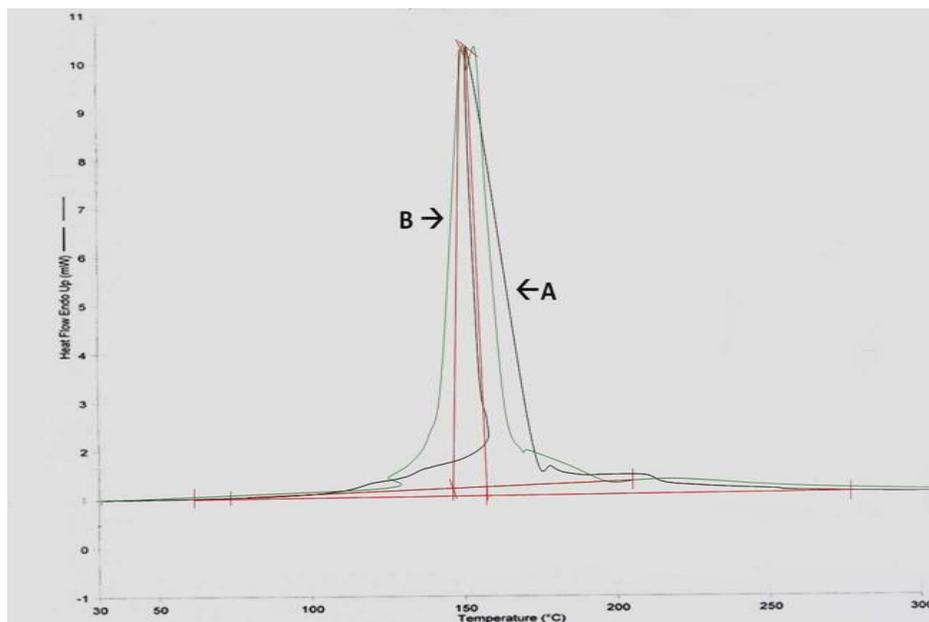


Fig.2. DSC of Valdecoxib Pure drug (A) and Valdecoxib (B) in GPV formulation

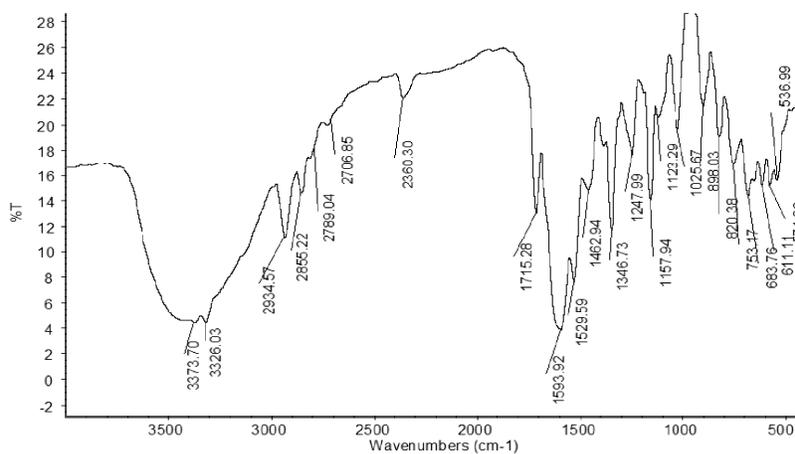


Fig.3. FTIR Spectrum of Glipizide

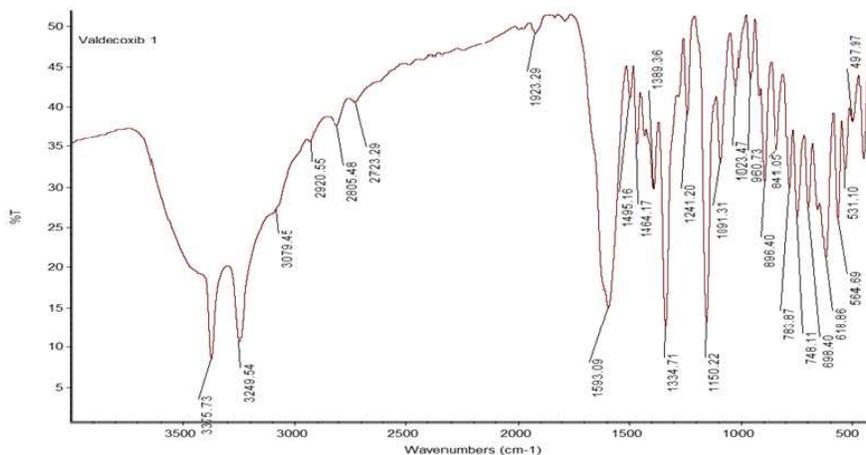


Fig.4. FTIR Spectrum of Valdecoxib

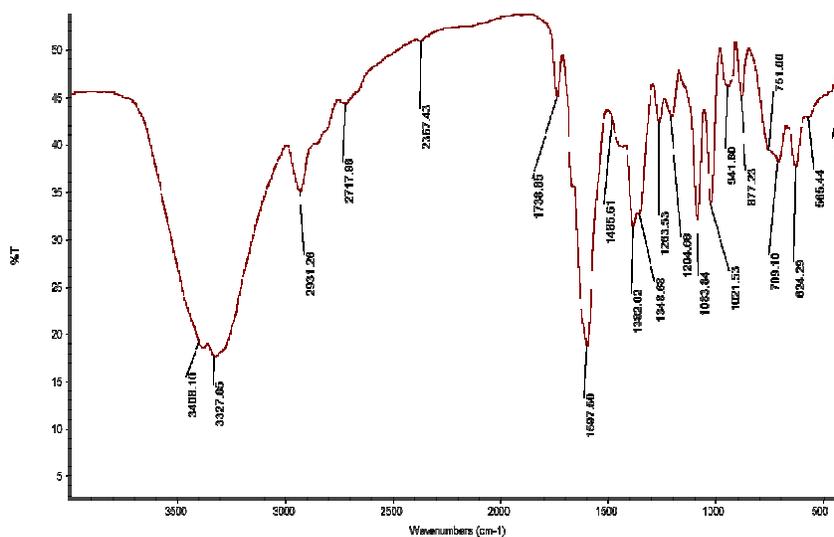


Fig. 5. FTIR Spectrum of GPV-5 formulation

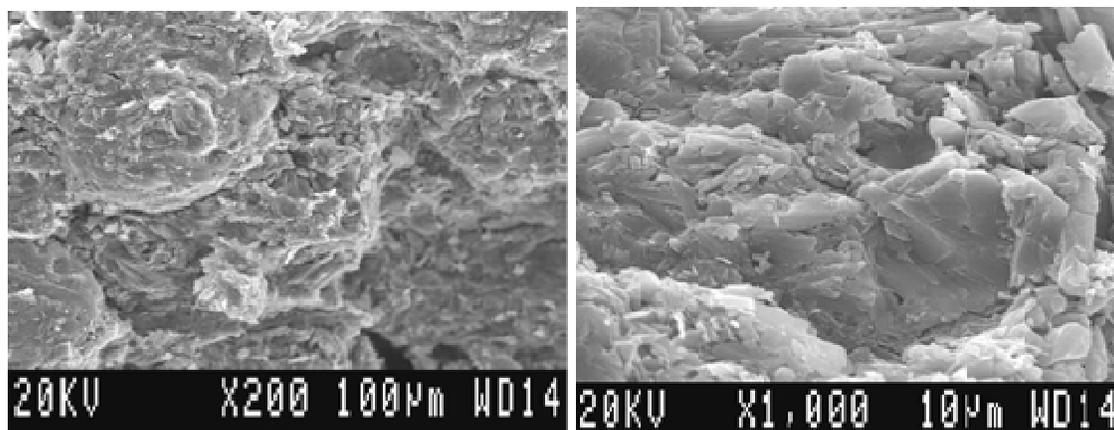


Fig.6. SEM of Formulation GPV-5 at X200 and X1000

Table 1: Composition of mucoadhesive tablets core layer

Ingredients (mg)	Formulations					
	GPV-1	GPV-2	GPV-3	GPV-4	GPV-5	GPV-6
Glipizide	10	10	10	10	10	10
Valdecoxib	20	20	20	20	20	20
Carbopol-940	47.66	28.66	57.20	47.66	28.66	57.20
Sodium Carboxy Methyl Cellulose-H	70.34	89.34	60.8	-	-	-
Polyvinyl Pyrrolidone-K30	-	-	-	70.34	89.34	60.8
Magnesium stearate	2	2	2	2	2	2
<b>Total Weight = 150 mg</b>						

Table 2: Composition of mucoadhesive tablet backing layer

Ingredients	Quantity (mg)
Magnesium stearate	33.75
Ethyl Cellulose	37.58
Clove oil	0.02
Saccharin sodium	3.65
<b>Total Weight = 75 mg;</b>	
<b>Composition same for all formulations</b>	

**Table 3: Angle of Repose, Loose Bulk Density, Tapped Bulk Density, Carr's Compressibility Index of GPV granules**

Formulations	Angle of Repose ( $\theta$ )	Loose Bulk Density ( $\text{g/cm}^3$ )	Tapped Bulk Density ( $\text{g/cm}^3$ )	% Compressibility
GPV-1	28.80 $\pm$ 4.51	0.569 $\pm$ 0.21	0.662 $\pm$ 0.02	14.05 $\pm$ 0.03
GPV-2	28.20 $\pm$ 3.52	0.571 $\pm$ 0.15	0.997 $\pm$ 0.03	14.39 $\pm$ 0.01
GPV-3	26.18 $\pm$ 3.91	0.575 $\pm$ 0.42	0.674 $\pm$ 0.03	14.69 $\pm$ 0.01
GPV-4	25.64 $\pm$ 4.51	0.569 $\pm$ 0.32	0.662 $\pm$ 0.01	14.05 $\pm$ 0.23
GPV-5	27.54 $\pm$ 0.02	0.621 $\pm$ 0.02	0.754 $\pm$ 0.02	17.29 $\pm$ 0.21
GPV-6	26.98 $\pm$ 2.93	0.591 $\pm$ 0.33	0.702 $\pm$ 0.10	15.80 $\pm$ 0.20

All values mentioned as mean  $\pm$  S.D; Number of trials (n) = 3

**Table 4: Evaluation of post compression Parameters for GPV tablets**

Formulation	Thickness (mm)	Hardness ( $\text{kg/cm}^2$ )	Friability (%)	Weight Variation (mg)	Assay (%)	
					Glipizide	Valdecoxib
GPV-1	2.98 $\pm$ 0.33	3.83 $\pm$ 1.29	1.83 $\pm$ 0.02	225.82 $\pm$ 12.05	100.95 $\pm$ 10.25	99.49 $\pm$ 9.23
GPV-2	3.07 $\pm$ 2.39	3.50 $\pm$ 0.50	1.73 $\pm$ 0.03	225.29 $\pm$ 9.17	101.27 $\pm$ 18.94	101.71 $\pm$ 11.19
GPV-3	3.09 $\pm$ 1.39	3.16 $\pm$ 0.23	1.25 $\pm$ 0.02	226.25 $\pm$ 10.55	99.24 $\pm$ 6.85	100.05 $\pm$ 12.36
GPV-4	3.01 $\pm$ 0.12	5.22 $\pm$ 0.39	0.39 $\pm$ 0.03	225.81 $\pm$ 9.98	98.94 $\pm$ 9.91	101.45 $\pm$ 10.65
GPV-5	3.10 $\pm$ 0.09	6.50 $\pm$ 0.50	0.46 $\pm$ 0.01	224.86 $\pm$ 1.78	100.25 $\pm$ 1.29	100.05 $\pm$ 2.25
GPV-6	3.02 $\pm$ 0.06	5.83 $\pm$ 0.29	0.66 $\pm$ 0.02	225.06 $\pm$ 12.44	100.91 $\pm$ 10.11	100.97 $\pm$ 11.65

All values mentioned as mean  $\pm$  S.D; Number of trials (n) = 3

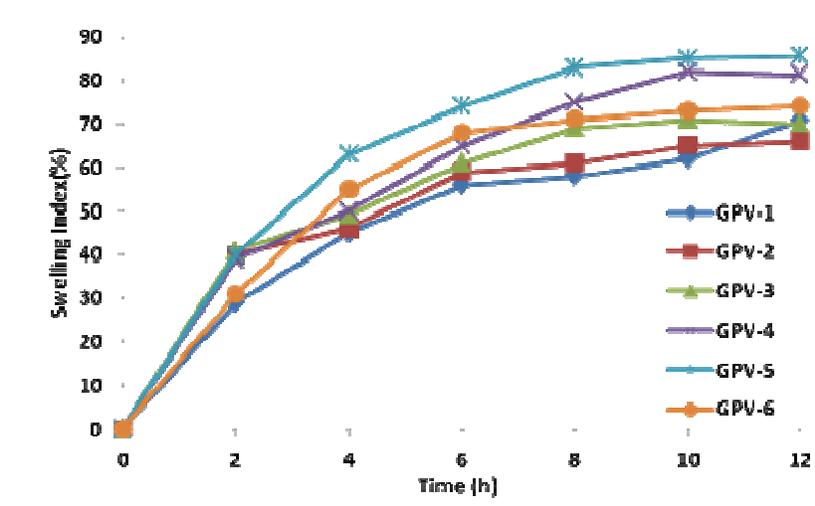


Fig.7. Swelling Index of GPV mucoadhesive tablets

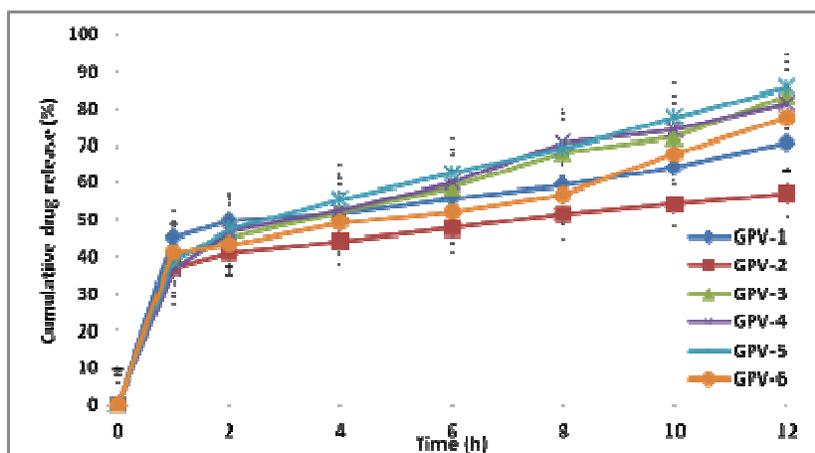


Fig.8. Zero order plots for GPV tablets (Glipizide)

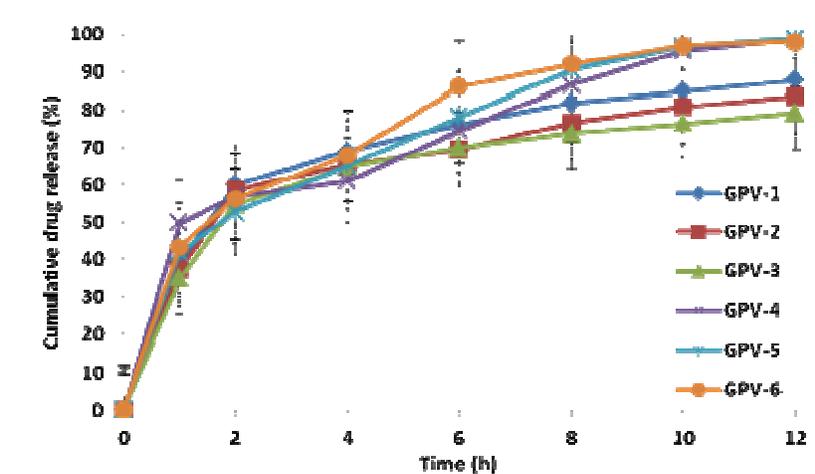


Fig.9. Zero order plots for GPV tablets (Valdecoxib)

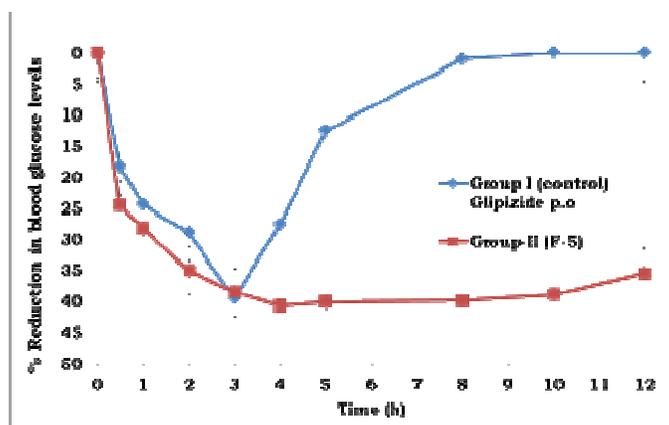


Fig.10. Reduced blood glucose levels (%) of optimized formulation (GPV-5) Vs. Glipizide oral control

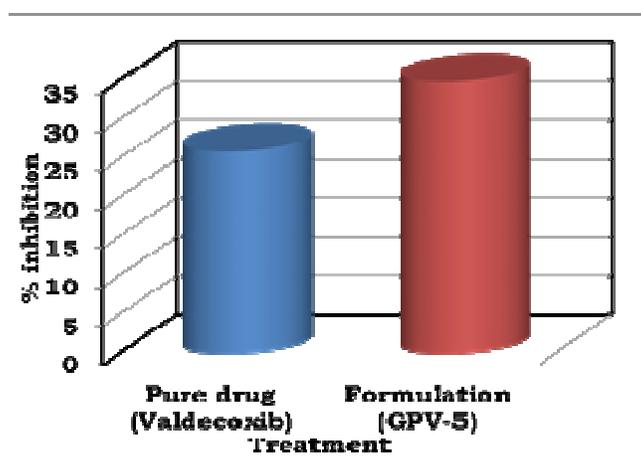


Fig.11. Percent inhibition of paw oedema with GPV-5 formulation Vs. Valdecoxib pure drug

Parameter	Before stability studies	After stability studies
General Appearance	bi layered	bi layered
Thickness (mm)	3.10±0.09	3.10±0.09
Hardness (kg/ cm <sup>3</sup> )	6.50±0.50	6.50±0.45
Friability (%)	0.46±0.01	0.46±0.01
Weight (mg)	299.86±1.78	299.86±1.72
Drug Content (%)	100.25±1.29 (Glipizide)	No change in drug content (Glipizide)
	100.05±2.25 (Valdecoxib)	No change in drug content (Valdecoxib)
Surface pH	6.05 ± 0.208	6.05 ± 0.195
Mucoadhesive Strength (g)	22.39 ± 0.241	22.39 ± 0.241
<i>In vitro</i> drug release at 12 <sup>th</sup> h (%)	Complete release (Glipizide)	Complete release (Glipizide)
	Complete release (Valdecoxib)	Complete release (Valdecoxib)
All values mentioned as mean ± S.D; Number of trials (n) = 3		

Table 5: Selected Formulations for Stability Studies GPV-5 mucoadhesive tablets stored at 40<sup>0</sup>C/75% RH

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