KATHMANDU UNIVERSITY JOURNAL OF SCIENCE, ENGINEERING AND TECHNOLOGY
VOL. 8, No. I, FEBRUARY, 2012, pp 63-72

FABRICATION OF GLIMEPIRIDE *DATURA STRAMONIUM* LEAVES MUCILAGE AND POLY VINYL PYRROLIDONE SUSTAINED RELEASE MATRIX TABLETS: *IN VITRO* EVALUATION

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Received 08 February, 2010; Revised 29 September, 2011

ABSTRACT
The main purpose of the present work was to develop matrix tablets of Glimepiride with *Datura stramonium* leaves mucilage and Poly Vinyl Pyrrolidone and to study its functionality as a matrix forming agent for sustained release tablet formulations. Mucilage from *Datura stramonium* leaves was extracted, isolated, purified and characterized. Physicochemical properties of the dried powdered mucilage of *Datura stramonium* leaves were studied. Various formulations of Glimepiride *Datura stramonium* leave mucilage and Poly Vinyl Pyrrolidone were prepared. The formulated tablets were tested for mechanical properties, friability, swelling behavior, *in vitro* drug release pattern and the dissolution data was treated with mathematical modeling and the optimized formulation was tested for accelerated stability studies. The formulated tablets were found to have good mechanical properties, good swelling properties. The *in vitro* dissolution data was perfectly fitting to zero order and the release of drug from the formulation followed Higuchi's release. The accelerated stability studies revealed that the tablets retain their characteristics even after stressed storage conditions. From this study it was concluded that the dried *Datura stramonium* leaves mucilage and Poly Vinyl Pyrrolidone combination can be used as a matrix forming material for making sustained release matrix tablets.

Key words: Glimepiride, *Datura stramonium*, Poly Vinyl Pyrrolidone, matrix tablets, sustained release.

INTRODUCTION
Datura stramonium is an erect annual herb forming a bush up to 1.5 m tall. The leaves are soft, irregularly undulate and toothed. The flowers are trumpet-shaped, white to creamy or violet and 6 to 9 cm long [1]. No attempts have been made on this plant leaves mucilage as release retardant. Glimepiride is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus. It belongs to sulfonyl ureas drug class. Glimepiride is a weak acid with PKa of 5.3. Glimepiride is practically insoluble in water and acidic solutions but highly permeable (class 2) according to the Biopharmaceutical classification System (BCS) [2]. The oral absorption is uniform, rapid and complete with nearly 100% bioavailability. The pharmacokinetics and dosage schedule supports once daily sustained release formulations for Glimepiride for better control of blood glucose levels to prevent hypoglycemia, enhance clinical efficacy and patient compliance[3,4]. The purpose of present work was to design and evaluate sustained release matrix tablets of Glimepiride using *Datura stramonium* leaves mucilage and Poly Vinyl Pyrrolidone combination as release retardant.

MATERIALS AND METHODS
Glimepiride was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. *Datura stramonium* leaves were collected from plants growing in local areas of Anantapur, India. The plant was authenticated at the Department of Botany, Sri Krishnadevaraya University, Anantapur, India. Poly Vinyl Pyrrolidone, Micro crystalline cellulose (Avicel**)** and Magnesium stearate were procured from SD Fine chemicals (Mumbai, India). Tri chloro

acetic acid, Acetone, Ethanol (95%), diethyl ether and all other chemicals used were of analytical reagent grade and double distilled water was used throughout the experiments.

Extraction of mucilage: The fresh *Datura stramonium* leaves were washed with water. The leaves were crushed and soaked in water for 5–6 h, boiled for 30 m and left to stand for 1 h to allow complete release of the mucilage into the water. The mucilage was extracted using a multi-layer muslin cloth bag to remove the marc from the solution. Acetone (in the quantities of three times the volume of filtrate) was added to precipitate the mucilage. Later the mucilage was separated, dried in an oven at 40^0C, collected, ground, passed through a # 80 sieve and stored in desiccator at 30^0C & 45% relative humidity till use [5].

Purification of the Mucilage: The crude mucilage (1%) was homogenized (Potter homogenizer, Sartorius AG, Germany) with cold dilute tri chloro acetic acid solution (5%). The solution was centrifuged (3500 rpm for 20 m), neutralized with sodium hydroxide by drop wise addition and then dialyzed for 30 h against distilled water. The mucilage was precipitated by adding three volumes of 95% ethanol and washed successively with ethanol, acetone and diethyl ether[5, 6].

Drug-excipient compatibility studies

Differential scanning calorimetric (DSC) analysis: The DSC analysis was carried out using Differential Thermal Analyzer (Shimadzu DSC-60, Shimadzu Limited, Japan). A 1:1:1 ratio of Glimepiride: *Datura stramonium* leaves mucilage: Poly Vinyl Pyrrolidone were weighed into aluminum crucible and the DSC thermo grams were recorded at a heating rate of 10^0C/min in the rage 20^0C to 280^0C, at a nitrogen flow of 20 ml/m.

Fourier Transform Infrared (FTIR) spectral analysis: FTIR spectrums were recorded on samples prepared in potassium bromide (KBr) disks using FTIR spectrophotometer (Model-1601 PC, Shimadzu Corporation, Japan). Samples were prepared in KBr disks by means of a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000 cm^{-1}. The FTIR spectrums of pure Glimepiride, 1:1:1 ratio of Glimepiride: *Datura stramonium* leaves mucilage: Poly Vinyl Pyrrolidone and formulation blend (F-5) were taken.

Preparation of matrix tablets: Sustained release matrix tablets of Glimepiride with *Datura stramonium* leave mucilage and Poly Vinyl Pyrrolidone were prepared by using different drug: mucilage ratios. *Datura stramonium* leaves mucilage and Poly Vinyl Pyrrolidone were used as matrix forming materials while microcrystalline cellulose as a diluent and Magnesium stearate as a lubricant. All ingredients used were passed through a # 100 sieve, weighed and blended. The granules were prepared by wet granulation technique and evaluated for its flow properties. The granules were compressed by using 10 mm flat faced punches[89]. The compositions of formulations were showed in Table 1.

Table 1: Formulae of matrix tablets

Ingredients (mg)	**Formulation**				
	F-1	**F-2**	**F-3**	**F-4**	**F-5**
Glimepiride	2	2	2	2	2
Datura stramonium leaves dried mucilage	2.5	5.0	7.5	10.0	12.5
Poly Vinyl Pyrrolidone	5.0	5.0	5.0	5.0	5.0
Micro crystalline cellulose (Avicel)	185.5	183	180.5	178	175.5
Magnesium stearate	5	5	5	5	5
Total weight of tablet	**200**	**200**	**200**	**200**	**200**

Evaluation for granules: The granules so obtained were evaluated for flow properties viz., Angle of repose[10], Loose Bulk Density[11], Tapped Bulk Density [11], Carr's Index[12] and Hausner ratio[12].

Evaluation of tablets:
The formulated tablets were evaluated for uniformity in thickness[13], uniformity in weight[14], hardness[15], Friability[16] and uniformity in drug content[16].

Swelling behavior of matrix tablets: 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 swelling index was calculated by following equation[17].

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

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

***In vitro* drug release studies:** Release of Glimepiride from the matrix tablets was studied 900 ml phosphate buffer (pH 7.4) using United States Pharmacopoeia (USP) 6-station Dissolution Rate Test Apparatus (Model Electro lab, TDT- 06T, Mumbai, India) with a rotating paddle stirrer at 50 rpm and 37 ± 0.5^0C. A sample of Glimepiride matrix tablets equivalent to 2 mg of Glimepiride was used in each test. Samples from dissolution fluid were withdrawn at regular intervals filtered (0.45 μm) and absorbance was measured at 229 nm for Glimepiride content [18] using a UV/ visible double-beam spectrophotometer (Elico SL210, India). The drug release experiments were conducted in triplicate (n = 3).

Drug release kinetics: To analyze the mechanism of drug release from the prepared formulations, the data obtained from *in vitro* release studies were subjected to Zero order[19], First order[19], Higuchi's[20], Korsmeyer Peppa's[21] and Hixson Crowell models[19].

Scanning Electron Microscopy: The optimized formulation (F-5) was selected for Scanning Electron Microscopy (SEM) analysis. The tablet surface morphology was studied at zero time and 4^{th} h of dissolution.

Accelerated Stability Studies of optimized matrix tablets: The promising formulation (F-5) was tested for a period of 3 months at accelerated storage conditions (temperatures of 40^0C with 75% RH) and the drug content was estimated[22].

RESULTS AND DISCUSSION

The thermo gram of Glimepiride showed a short endothermic peak at 209.13^0C (Figure 1). The thermo gram of formulated matrix tablets with *Datura stramonium* leaves mucilage and Poly Vinyl Pyrrolidone showed an endothermic peak at 193.20^0C (Figure 2) indicating a slight change in terms of shifting towards the lower temperature. Thus these minor changes in the melting endotherm in the drug could be due to the mixing of the drug and excipients which lower the purity of each component in the mixture (may not indicate the potential incompatibility).

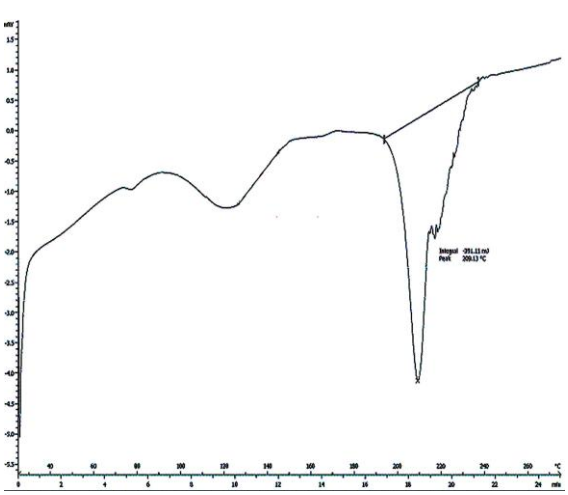

Fig.1: DSC thermo gram of Glimepiride

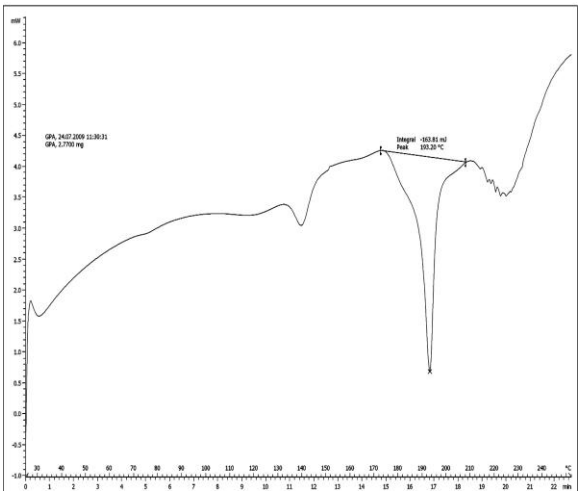

Fig.2: DSC thermo gram of Glimepiride: Datura stramonium mucilage: Poly Vinyl Pyrrolidone (1:1:1)

The FTIR spectrum of Glimepiride showed characteristic peaks at wave numbers were 3344.3 (3300-3500) (N-H), 2900.7 (2850 – 3000) (C-H), 2900.7 (3300 - 2500 (O-H), 1427.2 and 1342.4 (1350 –1550) (N=O), 1072.3 (1220 -1020) (C-N) and 1033.8 (1000 –1300) (C-O) (Figure 3). Infrared absorption spectrum of *Datura stramonium* leaves mucilage and Poly Vinyl Pyrrolidone (1:1) spectrum shows prominent peaks at wave numbers 2920.0 (2850 – 3000) (C-H), 3379.1 (3300 – 3500) (NH), 1029.1 (1000 – 1300) (C-O) (Figure 4). The major FTIR peaks observed in matrix tablets were 3344.3 (3300-3500) (N-H), 2900.7 (2850 – 3000) (C-H), 2900.7 (3300 - 2500 (O-H), 1427.2 and 1342.4 (1350 –1550) (N=O), 1072.3 (1220 -1020) and (C-N) 1033.8 (1000 –1300) (C-O). (All these values were represented as cm^{-1}). This indicates that there were no chemical incompatibility between Glimepiride and the polymers (*Datura stramonium* leaves mucilage and Poly Vinyl Pyrrolidone) used.

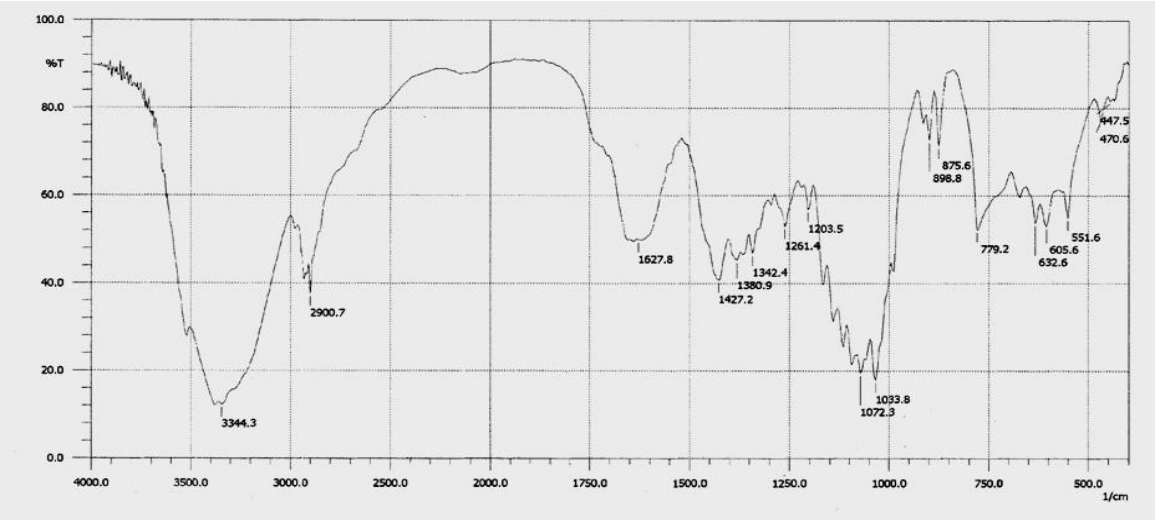

Fig.3: FTIR spectrum of Glimepiride

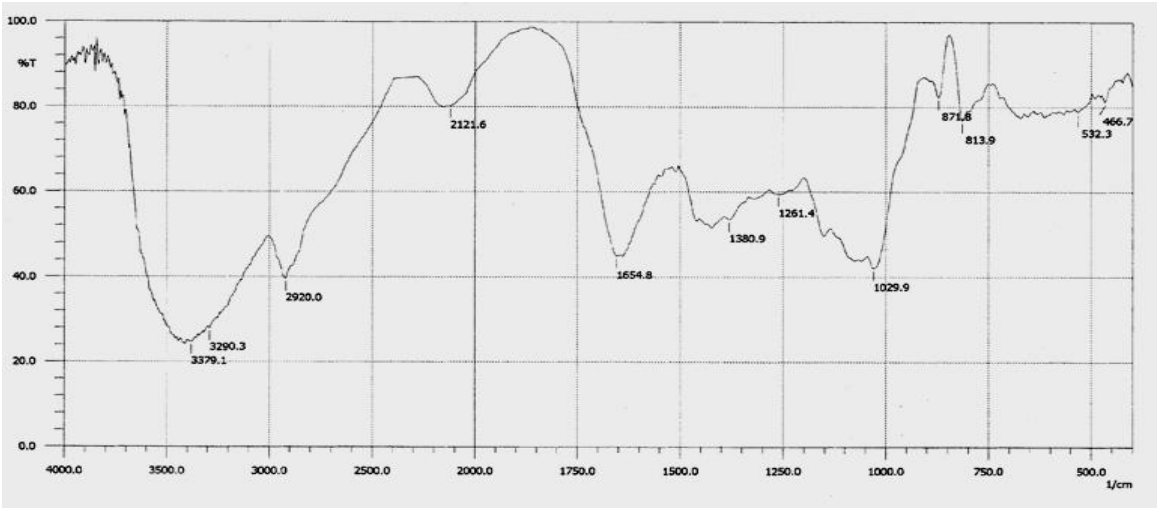

Fig.4: FTIR spectrum of Datura stramonium leaves mucilage: Poly Vinyl Pyrrolidone (1:1)

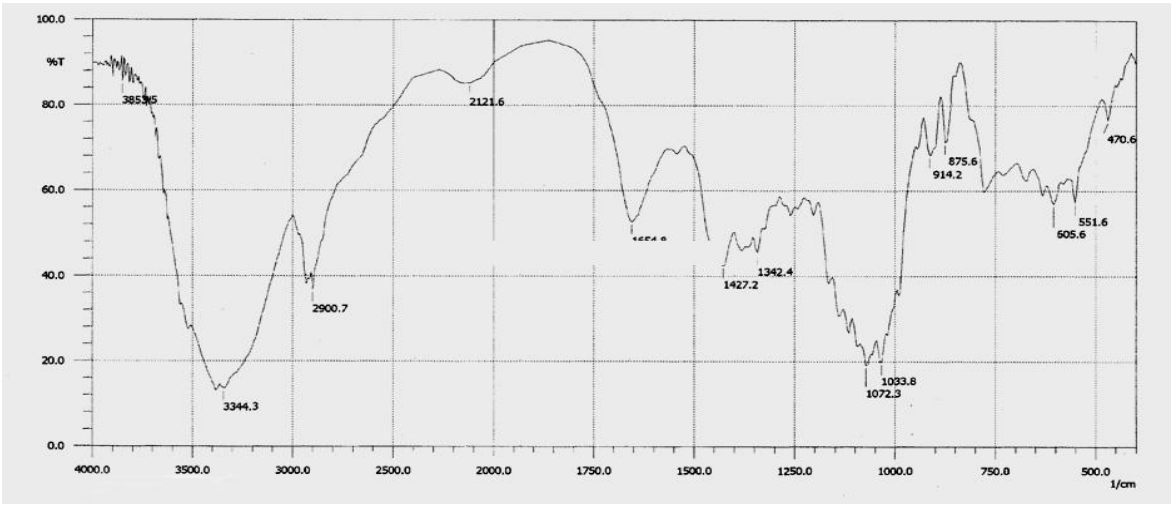

Fig.5: FTIR spectrum of formulation (F-5) blend

The Angle of repose of granules was found to be $27.83^0 \pm 1.266$ indicates that the granules had excellent flow properties. The Loose Bulk density and Tapped Bulk density were found to be 0.58±0.014 and 0.79±0.154 g/ml respectively which was used to calculated the Carr's index and Hausner ratio. The values of Carr's index and Hausner ratio were found to be 26.58±2.160 % and 1.25±0.120 respectively. All the values of flow properties were showed in Table 2.These trials were conducted in triplicates (n=3).

Table 2: Flow properties of granules

Parameters	**Value**
Angle of repose (^{0})	27.83±1.266
Bulk density (g/ml)	0.58±0.014
Tapped density (g/ml)	0.79±0.154
Carr's index (%)	26.58±2.160
Hausner's ratio	1.25±0.120
Number of experiments (n) =3	

The thickness of formulated matrix tablets was ranged from 2.85±0.035 to 3.48±0.074 mm and the hardness was ranged from 6.50±1.45 to 8.10±1.40 kg/cm^2, which was more than 5 kg/cm^2 and passes the hardness test. The loss on friability was ranged from 0.44±0.03 to 0.85±0.05 % (less than 1%). The formulated tablets were found to have good hardness and minimal weight loss on friability indicates that the tablets can with stand the mechanical shocks during their handling and transport. The drug content in the formulated tablets was ranged from 99.5±2.56 to 100.5±3.67 %. These trials were conducted for five times and shown in Table 3. The formulated tablets showed increase in swelling index as the concentration of *Datura stramonium* leaves mucilage increased (Figure 6).

Table 3: Physical properties of formulated matrix tablets

Formulation	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**	**Drug content (%)**
F-1	3.16±0.065	7.50±1.25	0.50±0.02	100.2±3.95
F-2	2.88±0.103	8.10±1.40	0.85±0.05	101.2±5.25
F-3	3.05±0.050	6.80±1.35	0.44±0.03	99.5±2.56
F-4	3.48±0.074	6.50±1.45	0.62±0.06	99.9±2.16
F-5	2.85±0.035	7.40±1.30	0.73±0.07	100.5±3.67
Number of trials (n) = 5				

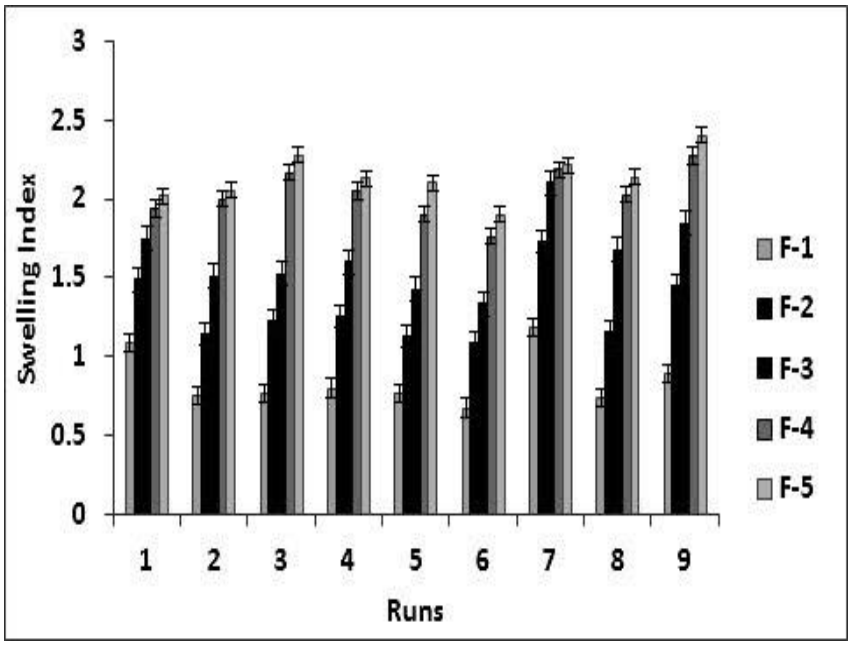

Fig. 6: Swelling behavior of matrix tablets

The drug release rate was faster in F-1 and slower in F-5. The release of Glimepiride was sustained as the proportion of *Datura stramonium* leaves mucilage increased and the overall time of release of the Glimepiride from the matrix tablet was also increased. The release of Glimepiride form the optimized formulation (F-5) showed zero order release and the formulations gave slope (n) and regression coefficient (r) values, which were 0.006705, 0.995252 respectively and shown in Table 4. The *In-vitro* drug release profile of Glimepiride from formulated matrix tablets was further studied using first order, whose slope and regression coefficient values of F-5 were -0.001762 and -0.982312 respectively and

represented in Table 4. The slope and regression coefficient values of F-5 for Higuchi model were 3.308515 and 0.993936 respectively, for Korsmeyer Peppa's they were 0.304558 and 0.968565 and for Hixson-Crowell's Model they were -0.00092 and -0.992141 respectively. These values were represented in Table 5 and shown in Figures 7, 8, 9, 10 and 11. The *in vitro* drug release data was perfectly fitted to zero order release and Higuchi's matrix models. Drug releases from matrix tablets were by drug dissolution, drug diffusion or a combination of both.

Table 4: Kinetic Values for dissolution Profile of Glipizide Matrix Tablets

Formulations	**First Order values**		**Zero Order values**	
	Slope (n)	**Regression Co-efficient (r)**	**Slope (n)**	**Regression Co-efficient (r)**
F-1	-0.000751	-0.978462	0.003559	0.990394
F-2	-0.000492	-0.996843	0.002955	0.992511
F-3	-0.001564	-0.972614	0.005966	0.996615
F-4	-0.001531	-0.992591	0.006498	0.988149
F-5	-0.001762	-0.982312	0.006705	0.995252

Table 5: Kinetic values for Glipizide matrix tablets

Formulation	**Higuchi's values**		**Korsmeyer Peppa's values**		**Hixson Crowell's values**	
	Slope (n)	**Regression Coefficient (r)**	**Slope (n)**	**Regression Coefficient (r)**	**Slope (n)**	**Regression Coefficient (r)**
F-1	1.725046	0.971738	0.162456	0.930212	-0.000431	-0.983553
F-2	1.865816	0.996448	0.171559	0.955678	-0.000322	-0.995742
F-3	3.103433	0.985042	0.287578	0.947332	-0.000643	-0.995174
F-4	3.227632	0.993489	0.313169	0.974429	-0.000831	-0.994412
F-5	3.308515	0.993936	0.304558	0.968565	-0.000921	-0.992141

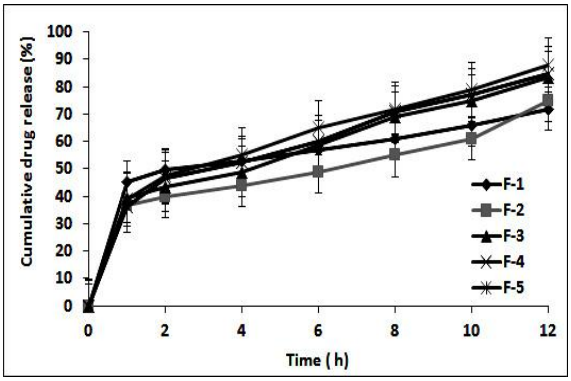

Fig. 7: Zero order release plots

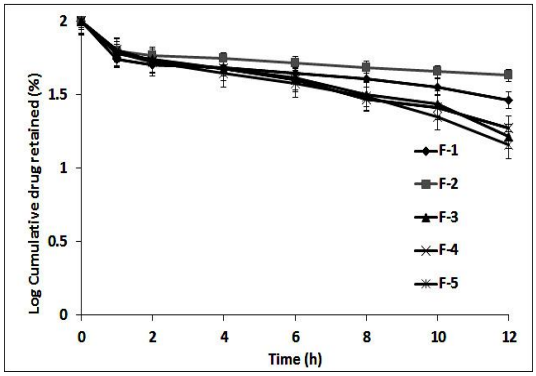

Fig. 8: First order release plots

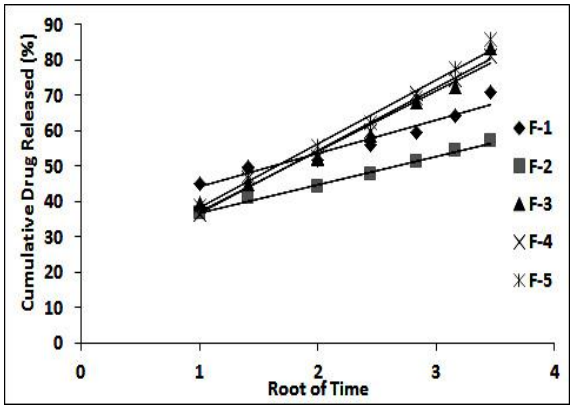

Fig. 9: Higuchi plots

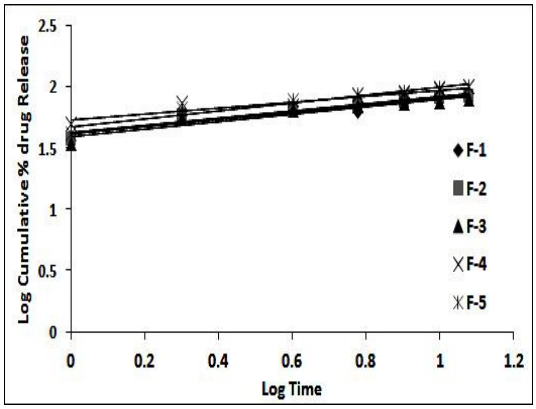

Fig.10: Korsmeyer Peppa's plots

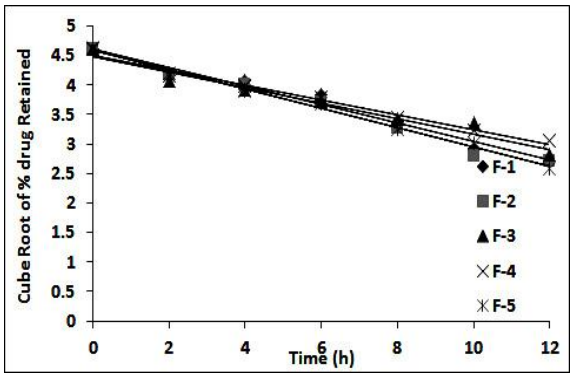

Fig.11: Hixson Crowell's plots

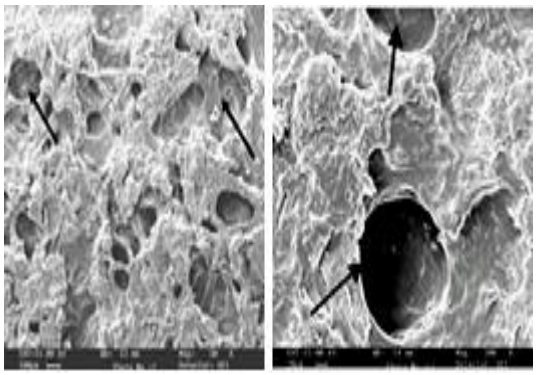
Fig.12: Surface morphology of matrix tablet (F-5) at zero time and at 4th h of dissolution

The surface morphology of optimized formulation (F-5) at zero time and at 4th h of dissolution were observed which indicates that the release of drug from dosage form by diffusion mechanism. The SEM photographs of tablet (F-5) were shown in Figure 12.

The accelerated stability studies further proved the formulation (F-5) was stable even at accelerated storage conditions. The physicochemical properties of F-5 tablets, before and after stability studies were shown in Table 6.

Table 6: Summary of physical properties of F-5 before and after accelerated stability studies

Parameter	**Before stability studies**	**After stability studies**
Thickness (mm)	2.85±0.035	2.85±0.027
Hardness (kg/cm^2)	7.40±1.30	7.40±1.10
Friability (%)	0.73±0.07	0.72±0.08
Drug content (%)	100.5±3.67	100.5±4.35
Number of trials (n) = 5		

CONCLUSIONS

The present study revealed that *Datura stramonium* leaves mucilage and Poly Vinyl Pyrrolidone combination appears to be suitable for use as a release retardant in the manufacture of sustained release matrix tablets because of its good physicochemical and swelling properties and suitability for matrix formulations. The *in vitro* dissolution data, mathematical modeling and accelerated stability studies revealed that the dried *Datura*

stramonium leaves mucilage in combination with Poly Vinyl Pyrrolidone can be used as a release retardant for making sustained release matrix tablets.

ACKNOWLEDGMENT
The authors are thankful to Dr. Reddy's Laboratories (Hyderabad, India) for providing the pure drug sample.

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