ISSN 0976 – 3333

Available Online at www.ijpba.info.

**International Journal of Pharmaceutical & Biological Archives 2011; 2(3):900-905**

***ORIGINAL RESEARCH ARTICLE***

# Formulation And Evaluation Of Sustained Release Matrix Tablets Containing Metformin Hcl And *Syzygium cumini*

**N.Aruna[1*], M.Kishore Babu[2]**

[1] *Bapatla College of Pharmacy, Bapatla, Andhra Pradesh*
[2] *Associate Professor,Department of Pharmaceutics, Bapatla College of Pharmacy, Bapatla, Andhra Pradesh, India.*

Received 02 May 2011; Revised 04 Jun 2011; Accepted 17 Jun 2011

## ABSTRACT

The purpose of the research work is to formulate and evaluate Metformin HCl sustained release matrix tablet using *Syzygium cumini* as a release rate retarding agent which is also antidiabetic in nature by means of wet granulation method. The influence of the release rate by different diluents was studied. Further the optimization of release rate of the drug was carried out by using various polymers such as HPMC K100M, Eudragit RLPO, Carbopol940, Ethyl cellulose. Tablets thus formulated were evaluated for various physical tests like weight variation, hardness, friability and results complied with in the limits. The drug release from all the formulations followed zero order kinetics and Korsmeyer-Peppas mechanism with n value > 0.5 indicating the drug released by non fickian diffusion mechanism. Formulation F6 containing HPMC K 100 M and Ethylcellulose showed the sustained drug release pattern upto 12 hrs which matched the drug release pattern of innovator. The antidiabetic activity of a formulation was evaluated with alloxan model of experimental rats. The results suggested that the *syzygium cumini* extract acted as a good release rate retarding agent and also showed promising additive antidiabetic activity with Metformin HCl.

**Key words:** Metformin HCl, *Syzygium cumini*, sustained matrix tablets, additive, antidiabetic activity.

## INTRODUCTION

Diabetes is a hereditary, chronic metabolic disease characterized by hyperglycaemia and eventual glycosuria[1]. It is caused due to the inability of tissues to carry out normal metabolism of carbohydrates, fats and proteins due to a relative or absolute lack of insulin. It occurs in two main forms. The first one is classified as type 1or insulin dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. Diabetes in this category is managed on diet and insulin. The second type is classified as type 2, non-insulin dependent diabetes mellitus (NIDDM) or maturity onset diabetes. Majority of patients in this class are obese. As a result the disease may be controlled by diet and oral hypoglycaemic agents such as Metformin HCl.

Metformin HCl is an oral hypoglycaemic agent, which belongs to the class of biguanides [2] and is now widely used as one of the mainstays in the management of type 2 diabetes. The choice of Metformin is because it does not lead to weight gain and has been shown to possess lipid-lowering properties [3]. The drug has few side effects although with chronic usage and may cause lactic acidosis and GI side effects in some patients [4]. The oral bioavailability of Metformin HCl is about 60% [5].

*Syzygium cumini* or *Eugenia jambolana* is a large evergreen tree and is used in traditional system of medicine in India as hypoglycemic [6]. Dry seeds of *Eugenia jambolana* have been reported with 11.67% alcohol soluble extractive, 3.397% inorganic, 40% of water soluble gummy fiber and 15% of water insoluble neutral detergent fibers. Hypoglycemic effect of *S. cumini (E. jambolana)* seeds is due to water-soluble gummy fiber and not because of water insoluble neutral detergent fiber and other constituents of the seeds [7]. Thus the gummy constituents of the seed can be utilized as both the excipient as a release retarding agent and also as an active constituent which possess hypoglycemic activity.

***Corresponding Author:** N.Aruna, **Email:**dr. aruna.nepalli@gmail.com,**Phone No:** +91-9440791202

The formulation of a sustained release matrix tablet thus containing Metformin HCl and *Syzygium cumini* produce additive antidiabetic activity resulting in reduction in dose of Metformin HCl and there by its dose related side effects.

## MATERIALS AND METHODS

Metformin HCl (Harman Finochem Ltd.), Ethanolic extract of *syzygium cumini* seeds (Chemiloids), PVP (Himedia), Microcrystalline cellulose (SD Fine chemicals), HPMCK100M (Degussa Chemicals), Eudragit (Degussa Chemicals), Ethylcellulose (Himedia), Carbopol 934( Kemphasol ), Isopropyl alcohol (Fischer scientific). All chemicals and solvents used were of analytical grade.

**Preformulation studies:**

**Compatibility study of Metformin hydrochloride with Ethanolic extract of *syzygium cumini* by IR Spectroscopy:**

The physicochemical compatibility between Metformin hydrochloride & Ethanolic extract of *syzygium cumini* used in the research were carried out by subjecting to IR Spectral studies. The samples were scanned under diffuse reflectance mold and plotted the graph by KBr pellet method and spectra were recorded in the wavelength region between 4000$cm^{-1}$ to 400 $cm^{-1}$. The spectra obtained for Metformin hydrochloride, Ethanolic extract of S*yzygium cumini* and physical mixtures of Metformin hydrochloride with the Ethanolic extract of *Syzygium cumini* were compared.

**UV interference studies:**

100 mg of Metformin HCl was weighed and dissolved in 100ml of phosphate buffer pH 6.8 solution. Similarly 150 mg of powder blend containing 100 mg drug and 50 mg of powder blend containing no drug (placebo) were dissolved. All flasks were shaken for 15 min. later solutions were filtered, suitably diluted and absorbances were measured at 233 nm to verify the interference of additives.

**Formulation of Metformin HCl tablets:**

Metformin HCl sustained release matrix tablets were prepared by wet granulation technique The composition of the tablets was presented in table no.1 The components were blended for 15 minutes, moistened with IPA to form a damp mass and wet granules were produced by passing through sieve no.12. The obtained wet granules were dried at 50$^{o}$c in hot air oven till constant weight was obtained (until dried). Then the granules were then passed through sieve no.16, lubricated with magnesium stearate & talc and compressed by using a Cadmach 16 station tablet machine with flat-faced punches (16mm diameter).

**Evaluation:**

The formulated tablets were evaluated for the following parameters.

**Thickness:**

The thickness and diameter of the formulated tablets were measured by using vernier calipers and the average of 3 values was recorded.

**Weight variation:**

The formulated tablets were tested for weight uniformity. 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is with in permissible limits or not.

$$\% \text{ Weight Variation} = \frac{\text{Average weight-Individual weight}}{\text{Average weight}} \times 100$$

**Hardness:**

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Monsanto tablet hardness tester. The average of 3 values was recorded.

**Friability:**

Roche friability test apparatus was used to determine the friability of the tablets. 20 pre weighed tablets were placed in the apparatus, which was subjected to 100 revolutions. Then the tablets were reweighed. The percentage friability was calculated using the formula.

$$\% \text{ Friability} = \frac{\text{Initial weight- Final weight}}{\text{Initial weight}} \times 100$$

**Drug content:**

Twenty tablets were weighed and powdered. The quantity of powder equivalent to 100 mg of Metformin hydrochloride was dissolved in phosphate buffer pH 6.8 diluted to 100ml with phosphate buffer pH 6.8 then the solution was filtered and suitably diluted. The drug content was estimated spectrometrically at 233 nm.

***In vitro* dissolution studies:**

Dissolution rate was studied using USP type II paddle dissolution apparatus using 900 ml phosphate buffer pH 6.8 at 100 rpm. An aliquot amount of the sample was with drawn at regular time intervals and the same volume of pre-



© 2010, IJPBA. All Rights Reserved.

warmed (37±0.5$^{o}$) fresh dissolution medium was replaced. The samples were filtered, suitably diluted and drug content of Metformin hydrochloride in each sample was analyzed by using Shimadzu UV-spectrophotometer at 233 nm.

**Pharmacodynamic studies [**[8]]:

Pharmacodynamic study was carried out in Adult Male Wistar Rats weighing 180-200g obtained from the Animal House of Bapatla College of Pharmacy (1032/ac/07/CPCSEA), Bapatla. The experiment protocol (IAEC/III/09/BCOP/2011) was approved by the Institutional Animal Ethical Committee (IAEC) of Bapatla College of Pharmacy. Diabetes was induced in rats using alloxan monohydrate. A dose equivalent to 150mg/kg body weight was dissolved in ice cold saline and administered intra peritoneally to the rats. After 72 hrs the extent of diabetes induction was monitored based on blood sugar level. Blood glucose levels of > 240 mg/dl were accepted as the basal level for diabetes.

To study the additive antidiabetic activity of Metformin HCl and the ethanolic extract of *syzygium cumini*, wistar rats (150-200gm) were divided into 5 groups and were fasted for 18hrs with free access to water. To group 1 normal saline was administered and used as the negative control, for group II 500mg/kg of Metformin HCl, for group III 350mg/kg of ethanolic extract of *S.cumini*, for group IV a mixture of 500mg/kg of Metformin HCl and 350 mg/kg of ethanolic extract of *S.cumini*, for group V 850mg/kg of Metformin HCl were dissolved in water and administered orally. Four rats were used for each study and the mean was computed.

## RESULTS AND DISCUSSION

Preformulation Studies: Compatibility study of Metformin HCl and *S.cumini* were conducted by employing I.R.Spectral studies (**Fig 1.1-1.3**). Metformin hydrochloride showed characteristic peaks at C=N - (stretching) 1629.55 cm$^{-1}$,1655.59 cm$^{-1}$,1669 cm$^{-1}$ ; C-N - (stretching) 1061.62 cm$^{-1}$,1029.48 cm$^{-1}$, 1030.77 cm$^{-1}$ ; N-H – (stretching) 3397.96 cm$^{-1}$,3378.67 cm$^{-1}$,3394.1 cm$^{-1}$ and the Ethanolic extract of *S.Cumini* [9] at 2933 cm$^{-1}$, 1454.37 cm$^{-1}$,812.90 cm$^{-1}$,635.94 cm$^{-1}$. As the identical principle peaks were also observed in formulations containing the physical mixture, indicated that no interactions exist in between the Metformin HCl and *S.cumini*.

UV interference studies: Interference of the additives used in the formulation was studied and the % recovery was found to be 99.4 indicating that these ingredients are not interfere with the estimation of Metformin HCl.

The quality control tests adopted for the tablets are depicted in the (**Table 2 & 3)**. The Hardness of the tablets ranged between 7.5 Kg/Cm$^2$ to 8.1 Kg/Cm$^2$, the Thickness of the tablets ranged between 3.8.mm to 4.2.mm. The percent friability of the prepared tablets was well within acceptable limit. There was no significant weight variation observed between average weight and individual weight. The results indicated that the tablets possessed enough mechanical strength to maintain their integrity. The drug content in all the formulations was with in the range of 99.2 to 100.4%, ensuring uniformity of drug content in the formulations.

The dissolution data was showed in (**Fig.2**). The drug release followed zero order kinetics as the graph drawn in between the amount of drug release verses time was found to be linear (**Fig.3**). To ascertain the mechanism of drug release the data was subjected to Higuchi & Korsmeyer Peppas equation.Application of Korsmeyer Peppas equation to the data showed that the mechanism of drug release of Metformin hydrochloride from the matrix tablets is governed by non fickian diffusion (slope > 0.5), and the release rate was found to be influenced by the concentration of polymer employed in the preparation of tablets (**Table 4**). The comparison of the drug release from the tablets formulated with *Syzygium cumini* and Metformin HCl (F6) with commercial S.R tablet (Glycomet) was assessed by using the similarity factor f2 test. Similarity factor (*f2*) of the two formulations was found to be 68.089% indicating the no significant differences in between the selected and commercial formulation. The pharmacodynamic studies indicated that the combination of Metformin HCl and *Syzygium cumini* exhibited additive antidiabetic activity. The % of reduction in blood glucose levels was showed in (**Fig.4**), Moreover the reduction in blood glucose level was comparable with the higher dose of Metformin HCl.





© 2010, IJPBA. All Rights Reserved.

**Fig 1.1: FTIR Spectra Of *Syzygium Cumini***

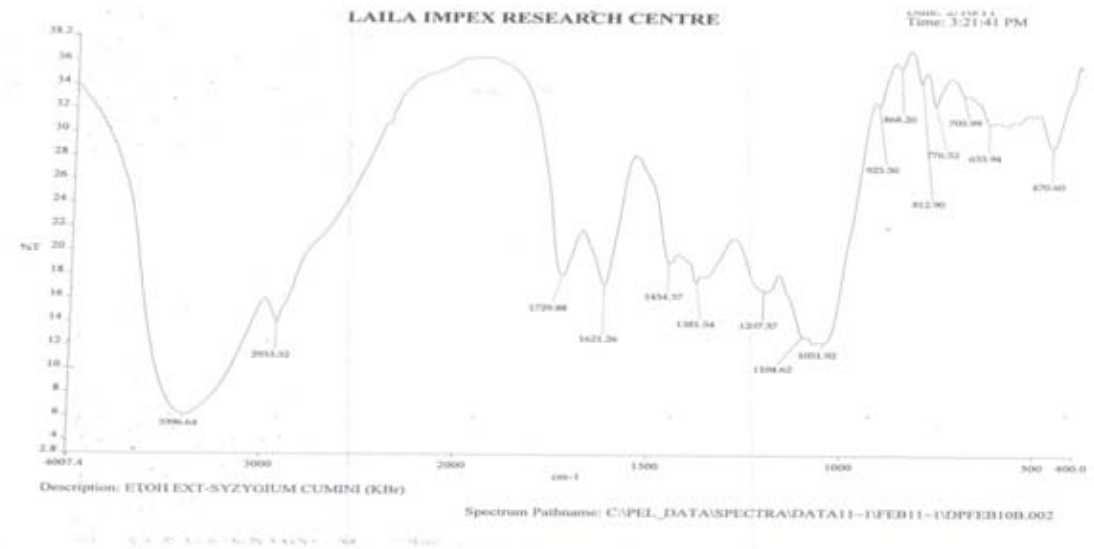
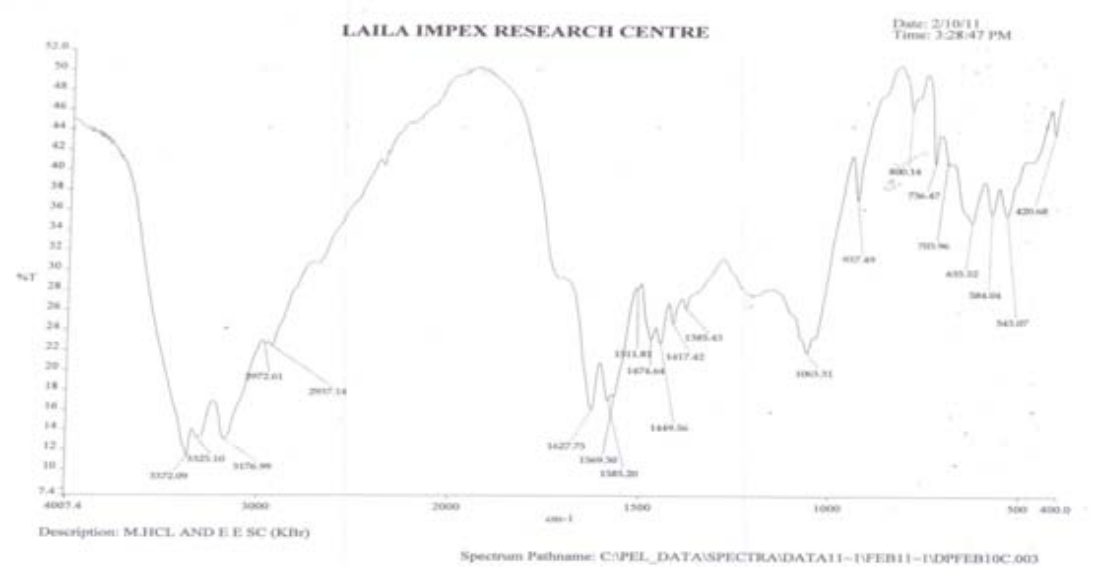



**Fig 1.2: FTIR Spectra Of Metformin Hcl**


**Fig 1.3: FTIR Spectra Of Metformin Hcl With *Syzygium Cumini***








© 2010, IJPBA. All Rights Reserved.

**Table 1 Composition Of Sr Matrix Tablets Containing Metformin Hcl And *Syzygium Cumini***

| S.No | Composition in milligrams | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|---|
| 1 | Metformin HCl | 500 | 500 | 500 | 500 | 500 | 500 |
| 2 | Ethanolic extract of *S.Cumini* | 350 | 350 | 350 | 350 | 350 | 350 |
| 3 | PVP K30 | 100 | 100 | 100 | 100 | 100 | 100 |
| 4 | MCC | 150 | 150 | 150 | 150 | 150 | 150 |
| 5 | HPMC K100M | - | 100 | 60 | 60 | 60 | 60 |
| 6 | Carbopol 940 | - | - | 40 | - | - | - |
| 7 | HPC | - | - | - | 40 | - | - |
| 8 | Eudragit RLPO | - | - | - | - | 40 | - |
| 9 | Ethylcellulose | - | - | - | - | - | 40 |
| 10 | Talc | 5 | 5 | 5 | 5 | 5 | 5 |
| 11 | Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 |
| 12 | Total wt. | 1010 | 1060 | 1210 | 1210 | 1210 | 1210 |

**Table 2 Characterisation Of Granules**

| Formulation | Bulk density (gm/ml) | Tapped density(gm/ml) | Carr's index | Hausner ratio | Angle of repose(º) |
|---|---|---|---|---|---|
| F1 | 0.311 | 0.339 | 8.59 | 1.090 | 22.43±0.06 |
| F2 | 0.294 | 0.324 | 9.25 | 1.102 | 22.84±0.06 |
| F3 | 0.350 | 0.378 | 7.407 | 1.080 | 21.67±0.07 |
| F4 | 0.336 | 0.364 | 7.692 | 1.083 | 21.93±0.05 |
| F5 | 0.333 | 0.353 | 5.665 | 1.060 | 20.98±0.04 |
| F6 | 0.315 | 0.337 | 6.528 | 1.069 | 21.25±0.04 |

*gm- gram, ml- millilitres

**Table 3 Physical Properties Of Sr Tablets Containing Metformin Hcl And *Syzygium Cumini***

| Formulation | Weight variation (%) | Hardness | Thickness (mm) | Friability (%) | Drug content |
|---|---|---|---|---|---|
| F1 | 2.95±0.33 | 7.8±0.15 | 4.0±0.04 | 0.54±0.06 | 99.8±0.10 |
| F2 | 3.52±0.29 | 8.1±0.23 | 3.8±0.02 | 0.51±0.10 | 99.2±0.06 |
| F3 | 2.46±0.19 | 7.4±0.28 | 4.2±0.05 | 0.62±0.09 | 100.4±0.08 |
| F4 | 3.09±0.30 | 7.5±0.17 | 4.1±0.06 | 0.58±0.12 | 99.6±0.12 |
| F5 | 2.24±0.25 | 7.9±0.10 | 3.9±0.02 | 0.53±0.15 | 99.6±0.08 |
| F6 | 2.75±0.16 | 7.6±0.19 | 4.1±0.04 | 0.59±0.15 | 99.4±0.10 |

*kg- kilogram, cm- centimeter, mm- millimeter
*All values are expressed as mean ± SD(n=3).

**Figure 2: Dissolution Profiles Of Sr Tablets Containing Metformin Hcl And Syzygium Cumini**

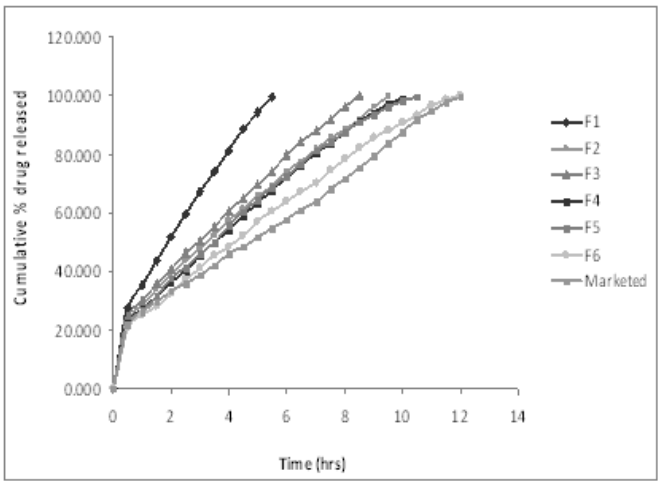



**Figure 3: Zero Order Plots Of Sr Matrix Tablets Containing Metformin Hcl And *Syzygium Cumini***

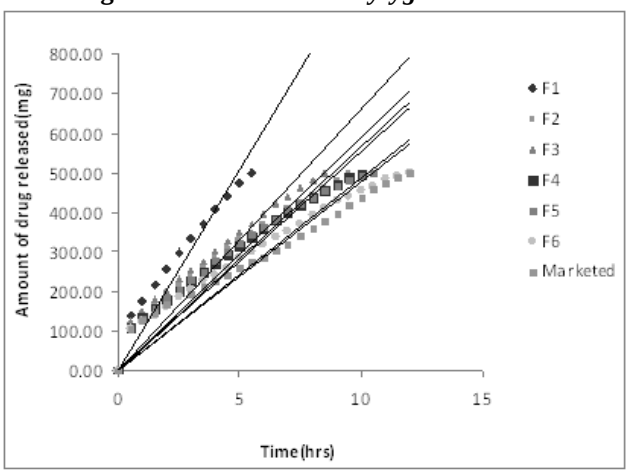



**Table 4 Dissolution Kinetics Of Sr Tablets Containing Metformin Hcl And *Syzygium Cumini***

| Formulations | Correlation coefficient | | | | Release rate constant ($mg/ml.hr^{-1}$) | Exponential coefficient | $T_{50}$ (hrs) | $T_{90}$ (hrs) |
|---|---|---|---|---|---|---|---|---|
| | Zero order | First order | Higuchi | Peppas | | | | |
| F1 | 0.9390 | 0.8539 | 0.9916 | 0.9930 | 20.3175 | 0.5583 | 2.5 | 4.4 |
| F2 | 0.9201 | 0.8476 | 0.9916 | 0.9923 | 11.7973 | 0.5284 | 4.2 | 7.6 |
| F3 | 0.9253 | 0.7353 | 0.9887 | 0.9904 | 13.1811 | 0.5246 | 3.8 | 6.8 |
| F4 | 0.9350 | 0.8955 | 0.9862 | 0.9883 | 11.2850 | 0.5490 | 4.4 | 8.0 |
| F5 | 0.9235 | 0.8514 | 0.9915 | 0.9925 | 11.0686 | 0.5520 | 4.5 | 8.1 |
| F6 | 0.9366 | 0.7637 | 0.9869 | 0.9879 | 9.5171 | 0.5515 | 5.3 | 9.5 |

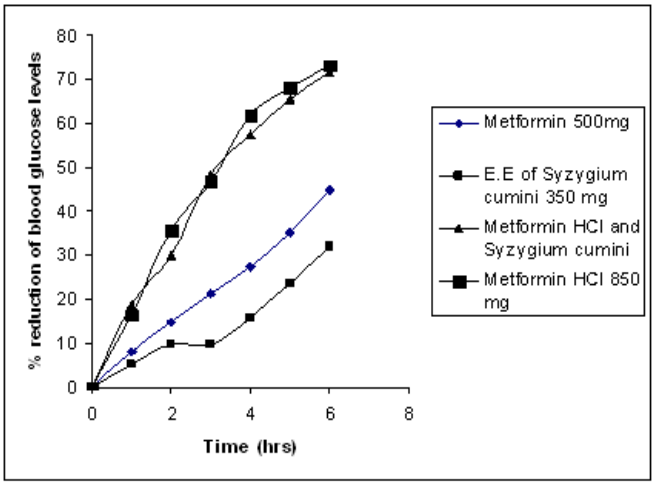
*mg- milligram, ml- milliliters, hrs- hours





© 2010, IJPBA. All Rights Reserved.

**Fig 4: Blood Glucose Levels Of Rats Given Different Formulations Of Metformin Hcl**




## CONCLUSION

Thus *syzygium cumini* owing to the presence of its water soluble gummy constituents retards the release of the drug and also possess the antidiabetic activity, Thereby sustained release matrix tablets thus formulated using *S.cumini* and Metformin HCl exhibits additive antidiabetic activity which can be comparable with the higher dose of Metformin HCl resulting in reduction in dose of Metformin HCl and there by its dose related side effects.

## ACKNOWLEDGEMENTS

The authors are thankful to the Management of Bapatla Education Society, Bapatla for providing the adequate laboratories facilities in the execution of this work.

## REFERENCES

1. Aguwa CN, Omole OK. Diabetes mellitus. In: Aguwa CN, editor. Therapeutic basis of clinical pharmacy in the tropics, 2nd ed. Enugu, Nigeria: Snaap Press (Nig) Ltd; 1998. p. 231–48.
2. O'Neil MJ, editor. Metformin the Merck index, 13th ed. Rahway: Merck & Co. Inc; 2001. p. 5966.
3. Parhofer KG, Laubach E, Geiss HC, Otto C. Effect of glucose control on lipid levels in patients with type 2 diabetes. Dstch Med Wochenschr 2002; 127:958–962.
4. Cayley Jr WE. Inappropriate prescription for metformin. J Am Med Assoc 2002; 287:2504–5.
5. Goodman & Gilman's: The pharmacological basis of therapeutics, 9th edition, The MC Graw- Hill Health professions Division; 1996
6. Modi D.C, J.K. Patel, Shah B.N and Nayak B.S. Pharmacognostic studies of the seed of Syzygium cumini Linn. An International Journal of Pharmaceutical Sciences.2010; 1 (2): 20-26.
7. Jadhav V.M, Kamble S.S , Kadam V.J . Herbal medicine: *Syzygium Cumini: A* Review. Journal of Pharmacy Research 2009; 2(8):1212-1219.
8. Michael U. Adikwu , Yukako Yoshikawa, Kanji Takada. Pharmacodynamic–pharmacokinetic profiles of Metformin hydrochloride from a mucoadhesive formulation of a polysaccharide with antidiabetic property in streptozotocin-induced diabetic rat models. Biomaterials 2004; 25: 3041–3048.
9. Sapana S. K, Jadhav V.M, Kadam V.J. A simple spectrofluorometric estimation of 3-hydroxy
Androstane [16, 17-c] (6' methyl, 2'-1-hydroxy –isopropene-1-yl) 4, 5, 6 h pyran in *Syzygium cumini* (jamun) seeds. Journal of Pharmacy Research 2009;2(8):1326-1329





© 2010, IJPBA. All Rights Reserved.