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FORMULATION, EVALUATION AND STUDY OF ANTIUROLITHIATIC ACTIVITY OF PIPERINE TABLETS

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ABSTRACT

Urolithiasis is one of the most prevalent diseases among the kidney diseases. Piperine, an alkaloid obtained from dried unripe fruits of black pepper which is showing multiple pharmacological activities can also produce significant antiurolithiatic activity. Since Piperine is slightly soluble in water solid dispersion technique was used to enhance its solubility. Four solid dispersions SD1, SD2, SD3, SD4 were prepared by using different carriers in different ratios and were evaluated for parameters such as drug content, entrapment efficacy and invitro dissolution. Based on the results, SD2 was chosen as the final solid dispersion. By using SD2 solid dispersion of Piperine six formulations F1, F2, F3, F4, F5, F6 were prepared and were evaluated for pre-compression and post-compression parameters of tablets. Based on the results, F6 was considered as the optimized formulation. Drug release kinetics studies were performed on optimized formulation F6 and it was found that the optimized formulation F6 is following first order kinetics. *In-vivo* antiurolithiatic studies were performed on male wistar albino rats using F6 tablet formulation and found its significant antiurolithiatic activity.

Keywords: Piperine, Antiurolithiatic activity, solid dispersion, Optimized formulation, Drug release kinetics

INTRODUCTION

When drug is administered orally in a solid dosage form such as tablet or capsule, it must be released from dosage form and dissolved in GI fluids before it can be absorbed. The bioavailability of many poorly water soluble drugs is limited by their dissolution rates, which are in turn controlled by the surface area that they present for the dissolution. Particle size of the drug is one of the major factors that influences dissolution rate, as solubility is intrinsically related to particle size. The larger the surface, the greater will be the interaction with the solvent which causes an increase in solubility. A unique approach of solid dispersion was first demonstrated by Sekiguchi and Obi in 1961, to reduce particle size and increase rates of dissolution and absorption. In solid dispersion technique, a eutectic mixture was prepared by melting the physical mixture of drug and water soluble carrier, followed by rapid solidification process. The active drug is released into the fluids as fine dispersed particles on exposure to aqueous fluids, because of fine dispersion of drug in the solid eutectic mixture and the rapid dissolution of soluble matrix **[1]**. The main advantage of using water soluble polymers as carriers is their non-toxicity and their general applicability to most drugs. This method can be successfully applicable for improving the solubility and stability of solid dispersions of poorly water soluble drugs, also exhibits improved wetting and decreased crystallinity **[2]**.

Piperine is an alkaloid isolated from the dried unripe fruits (pepper corns) of Piper nigrum and shows antiurolithiatic activity **[3]**. Piperine is categorized under the division of piperidine alkaloid and it is slightly soluble in water **[4]**. Chemically Piperine is (2*E*,4*E*)-5-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylpenta-2,4-dien-1-one **Figure 1**, having the molecular formula $C_{17}H_{19}O_3N_5$ **[5]**. Piperine is a solid having melting point 128°C and is optically inactive, sparingly soluble in water with cis-trans isomerism. It is weakly basic, shows high lipophilicity, and exhibits non-saturable passive absorption kinetics **[6]**. It shows significant antiurolithiatic activity along with several other pharmacological activities.

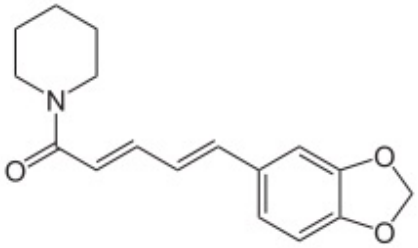

Figure 1: Chemical structure of piperine

The aim of the present work is to increase the solubility of piperine by solid dispersion

technique with different carriers, which results in increased absorption and bioavailability.

MATERIALS AND METHODS

Materials:

Piperine was bought from Shreedha phytoextracts pvt ltd, Jaipur. Other excepients such as HP β-Cyclodextrin, β-Cyclodextrin, methanol were purchased from S.D Fine chemicals. All the chemicals used for the present work are of analytical grade.

Experimental animals:

The protocol of experiment was approved by IAEC of Nirmala College of Pharmacy, Atmakur, Guntur district, Andhra Pradesh, with an approval no. 015/IAEC/NCPA/PhD/2016-17, nominated by CPCSEA. Male wistar albino rats of six to seven week old weighing 150-200g were purchased from Mahaveer enterprises, Hyderabad, Telangana. The rats were placed individually in stainless steel wire meshed plastic cages at a temperature of 23 ± 2^0C with humidity 55-60% and 12 hours light dark cycle. During the study period, the animals were fed with standard rat pellet diet, drinking water, ethylene glycol.

Pre-formulation studies:

Pre-formulation studies were performed to study the physicochemical characterization of solid and solution properties of compounds that are useful in formulating the drug into suitable form **[7]**. Melting point, Solubility studies and Drug-polymer compatability studies were carried out for Piperine. Compatability is very important aspect of pre-formulation study to assess the impact of excipients on the physical and chemical stability of the drug and eventually the performance of dosage form **[8]**. Therefore pre-formulation studies regarding the drug-polymer interaction are very crucial in selecting suitable polymers. FT-IR spectroscopy was employed to ascertain the compatibility between piperine, and the selected polymers.

Analytical method for estimation of Piperine:

UV spectroscopic method was used for estimation of piperine present in the test samples during the pre-formulation and formulation studies.1000 µg /ml Piperine stock solution was prepared by adding 10mg of piperine and 2 ml of methanol to 10ml volumetric flask, volume was made up to mark with 0.1 N HCl. 10µg /ml solution was prepared using 0.1N HCl as solvent and scanned for λ_{max} from 200-400 nm in UV/Visible spectrophotometer. Calibration curve was plotted by taking 5, 10, 15, 20, 25 and30 µg /ml concentrations. The absorbance of each solution was

measured at λmax i.e. 247 nm of piperine in UV/Visible spectroscopy against blank **[9]**.

Preparation of solid dispersions of piperine:

To select best polymer for attaining solid dispersion, solid dispersions were prepared by using β Cyclodextrin, HP β Cyclodextrin using solvent evaporation method.

Solvent evaporation method:

In solvent evaporation method, the drug and carriers were mixed in 1:0.5 and 1:1 ratios in Methanol. Solvent was removed by evaporation under reduced pressure. The mass was pulverised and passed through sieve # 100 and the obtained product was collected and stored in desiccators **[10]**.

Evaluation of Solid Dispersions:

The prepared solid dispersions were evaluated for Drug Content **[11]**, Entrapment efficacy **[12]**, *In-vitro* dissolution study **[13]**.

Formulation of piperine tablets:

Conversion of animal dose to Human Equivalent Dose [14]:

$$\text{Human Equivalent Dose (HED)}\,(\text{mg kg}^{-1}) = \text{Animal Dose}\,(\text{mg kg}^{-1}) \times \frac{\text{Animal } K_m}{\text{Human } K_m}$$

Where K_m value is different for different species and also varies with body weight.

The ratio of animal K_m to human K_m is called conversion factor

The conversion factor for rat to human is 6.2.

Animal dose is 40 mg/kg **[15]**

Direct compression method:

Equivalent weight of Piperine was added with suitable excipients and the tablets were formulated by direct compression. All the ingredients were passed through # 60 mesh sieve separately. The drug and MCC were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the remaining ingredients were mixed in geometrical order and passed through coarse sieve (#44 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3-4 kg/cm2 for all batches. The weight of the tablets was kept constant for all formulations F1 to F6 **[16]**.

Evaluation of Formulations blends for Pre-compression Parameters: [17-20]

After proper mixing of all the ingredients, the formulation blends were evaluated for pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index, Haunser's ratio.

Evaluation of tablets (Post compression parameters): [21, 22]

The compressed tablets were evaluated by performing tests such as Weight variation test, Tablet hardness, Tablet friability, In-Vitro Disintegration time, Thickness, Drug content uniformity, Dissolution studies (USP Type II Apparatus at 50 rpm).

Kinetics of drug release [23, 24]

Mathematical models were applied to determine the kinetics of drug release

a. Zero – order kinetic model – a plot of cumulative % drug released versus time (drug release rate irrespective of its concentration).

b. First – order kinetic model – a plot of log cumulative percent drug remaining versus time (drug release rate is directly proportional to concentration).

Antiurolithiatic Activity on Rats

In-vivo method:

Ethylene glycol model was used for inducing urolithiasis in rats for 28 days **[25]**. Twenty four animals were taken and divided into four groups as listed in **Table 1** and fed with drinking water and rat pellet food. The standard and test drugs were suspended in distilled water and given by oral route by using gastric tube for one time every day.

Table 1: Grouping of animals for in-vivo antiurolithiatic study

Group	Name	Fed with
Group – I	Positive control	Drinking water
Group – II	Negative control	0.75% v/v Ethylene glycol
Group – III	Standard	0.75% v/v Ethylene glycol and Cystone syrup (750 mg/kg)
Group – IV	Test	0.75% v/v Ethylene glycol and Piperine tablet (40 mg/kg)

Urine and Serum analysis:

On 28th day of study, 24 hours urine samples were collected **[26]**. Urine was stored at 20^0 C by acidifying with 1 drop of Conc. HCl. Urine calcium was determined by using commercially available kits. Urine oxalate was determined as described by Hodgkinson, 1970. Blood was collected from retro-orbital under light ether anaesthesia and the animals were sacrificed by giving high dose of anaesthetics. Serum was separated from blood by centrifugation at 10,000 g for 10 minutes. The serum collected was used for estimation of creatinine, calcium, urea, uric acid by using commercially available kits.

Kidney histopathology studies:

Histopathology of the harvested kidney section was done to study the effect of drug in dosage form on the calculi present in kidneys and also to understand its effect on the internal structure of kidney. This study was carried out as per standard protocol. Staining of the kidney section was done as per the standard techniques of histology **[27]**.

Statistical analysis:

The results obtained were represented as Mean ± SEM. The data was analyzed statistically using One way ANOVA followed by Tukey's post test for determining the level of significance by using Graph pad prism. Difference among the obtained data were considered as significant if $p < 0.05$.

RESULTS & DISCUSSION

Pre-formulation studies:

a) Determination of Melting point:

The melting point found to be 128-130^{o}C and it is in the melting point range of pure piperine. It reflects the purity of piperine used for the study.

b) Solubility

Solubility of piperine was carried out at 25^{0}C using 0.1 N HCl, 6.8 phosphate buffer, and purified water and the results are shown in **Table 2**. From the results, we can say that Piperine has more solubility in 6.8 pH buffer solution when compared to other buffer solutions.

c) Drug-polymer compatibility studies:

Drug and polymer compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug **Figure 2** with polymers (carriers) used in solid dispersion **Figure 3** and **Figure 4**. Form the spectra it was observed that there are no major interactions between the pure drug (Piperine) and polymer (Piperine + polymer) which indicates the compatability between drug and polymer.

Analytical method development by U.V. Spectroscopy:

The λ_{max} was found to be 247nm **Figure 5**. A series of concentrations ranging from 5-30µg/ml were scanned and the absorbance values were shown in **Table 3**. The standard graph obtained was linear, with r^2 value 0.999 **Figure 6**.

Preparation of solid dispersions of piperine:

Solid dispersions of Piperine with carriers (drug polymer) HP β-Cyclodextrin, β-Cyclodextrin were prepared by using solvent evaporation method. The compositions of piperine solid dispersions are given in **Table 4**.

Evaluation of Solid Dispersions:

a) Estimation of Drug content:

The % drug content for the prepared solid dispersions of Piperine was in the range of 75.82±0.36 - 86.21±0.18 shown in **Table 5**. The % drug content was highest for SD2 which was prepared by using HP β Cyclodextrin and it was least for SD3 prepared by using β Cyclodextrin.

b) Entrapment efficacy:

The entrapment efficacy of the formulated solid dispersions was studied and the results

were shown in the **Table 5**. The entrapment efficacy of the prepared solid dispersions was found to be in the range of 76.75±0.22-88.52±0.24%, it was highest for SD2 and least for SD4.

c) *In-vitro* dissolution study:

In-vitro drug release of Piperine solid dispersions with β Cyclodextrin and H P β Cyclodextrin in various ratios were observed which shows at the end of 90 mins the formulation SD1 releases 81.16, formulation SD2 releases 84.96, formulation SD3 releases 74.54, formulation SD4 releases 78.21% and the detailed resulted were shown in **Table 6** and also represented in graphical form **Figure 7** which clearly indicates that SD2 shows more dissolution with highest percent drug release.

Formulation of piperine tablets:

Six formulations F1-F6 were prepared with different concentrations of excipients **Table 7**.

Evaluation of Formulations blend for Pre-compression Parameters

Derived properties and flow properties were studied for formulation blend F1-F6 and the results were shown in **Table 8**. The angle of repose of different formulations was ≤ 30.68 which indicates that material have good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.42g/cm^3 to 0.52g/cm^3.Tapped density was found between 0.48g/cm^3 to 0.60g/cm^3.These values indicate that the blends have good flow property. Carr's index for all the formulations was found to be between 11.53-15.518 and Hausner's ratio from 1.12-1.18 which reveals that the blends have good flow character.

Evaluation of tablets (Post-compression parameters)

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the **Table 9**. Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3.68 – 4.28 kg/cm^2. All the formulations passed the weight variation test since the % weight variation was within the pharmacopoeial limits. Friability values were found to be less than 1% in all the formulations F1 – F6 and considered to be satisfactory ensuring that all the formulations are mechanically stable. The % drug content values for all the formulations (F1-F6) were found to be in the range of 85.96±0. 97.16±0.28% and it was found to be within the limits which confirm that the drug was distributed uniformly in all the formulations.

Dissolution studies:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release. The % cumulative drug release from the formulations F1-F6 ranges from 89.78±0.16 to 99.82±0.22 and the detailed results were shown in **Table 10**. From the results it was found that F1 formulation showed least in-vitro drug release and F6 formulation showed highest in-vitro drug release **Figure 8**.

Kinetics of drug release:

The drug release from the tablets was explained by using mathematical model equations such as zero order, first order methods and it was shown in **Figure 9**. Based on the regression values shown in **Table 11**, it was concluded that the optimized formulation F6 follows First order kinetics.

Antiurolithiatic activity on rats:

In-vivo studies for antiurolithiatic activity were performed on male wistar rats of four groups and treated with water, ethylene glycol, cystone syrup (750 mg/kg), piperine tablet (40 mg/kg)

Urine and Serum Analysis

Urine and serum samples were collected from *in-vivo* models after 28 days of calculi induction treatment and samples were analyzed and the results are shown in **Table 12**.

Serum analysis was performed for the estimation of creatinine, urea, calcium and uric acid. It was found that piperine tablet (40mg/kg) has shown low levels of Creatinine, urea, uric acid and calcium and shown in **Figure 10**.

Urine samples were collected and examined for the amount of calcium and oxalate. It was found that the *in-vivo* models treated with piperine tablets (40mg/kg) has shown low calcium and oxalate content in urine which indicates significant antiurolithiatic activity ($p<0.05$) of piperine syrup and shown in **Figure 11**.

Kidney histopathology:

Kidney histopathological studies revealed that no calcium oxalate deposits were found in the kidney of negative control group (**Figure 12a**). A significant deposition of calcium oxalate crystals was observed in positive control group (**Figure 12b**). Some occasional deposition of calcium oxalate crystals and mild cystic dilatation of renal tubules were observed in group treated with standard (Cystone syrup) and final formulation of piperine tablet (**Figure 12c & 12d**) which indicates significant antiurolithiatic activity.

The solubility of Piperine was enhanced by preparing solid dispersion. Piperine tablet formulation was developed by optimizing tablet formulation. Based on the results of pre-compression and post-compression tests F6 was selected as optimized one. The optimized tablet formulation showed significant antiurolithiatic activity same as standard.

Table 2: Solubility studies of Piperine

MEDIUM	SOLUBILITY(mg/ml)	SOLUBILITY LEVEL
Water	0.056	Insoluble
0.1 N HCl	0.205	Slightly soluble
6.8 pH buffer	0.284	Slightly soluble

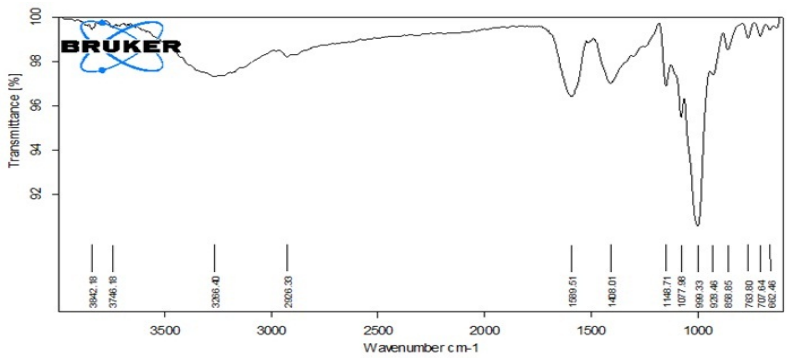

Figure 2: IR spectrum of pure Piperine

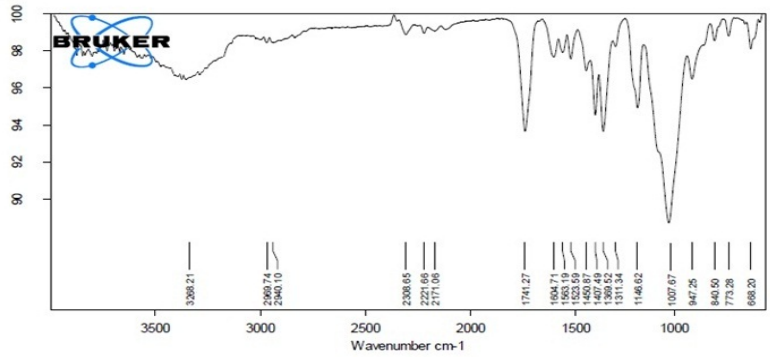

Figure 3: IR spectrum of Piperine + β-Cyclodextrin

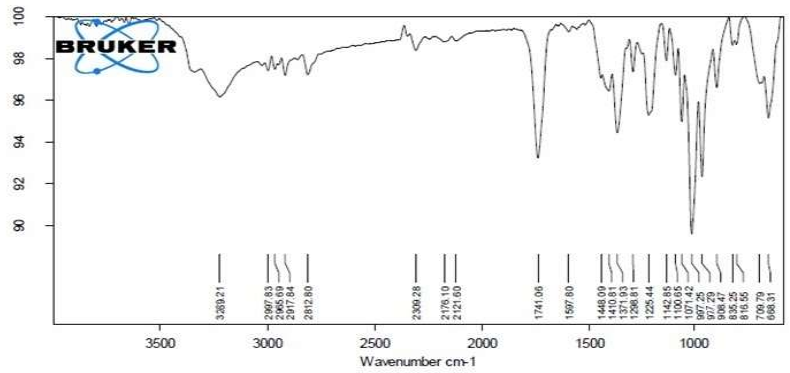

Figure 4: IR spectrum of Piperine + HP-β-cyclodextrin

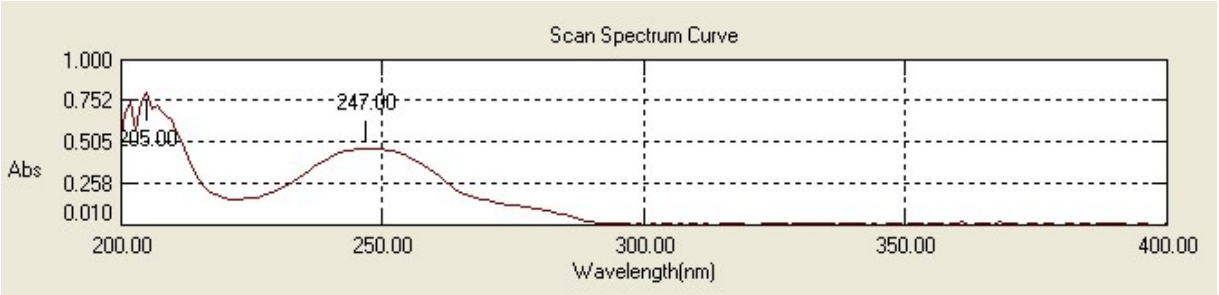

Figure 5: UV scan spectrum of Piperine

Table 3: Calibration curve data of Piperine

Concentration (ppm)	Absorbance
0	0
5	0.034
10	0.074
15	0.116.
20	0.154
25	0.198
30	0.237

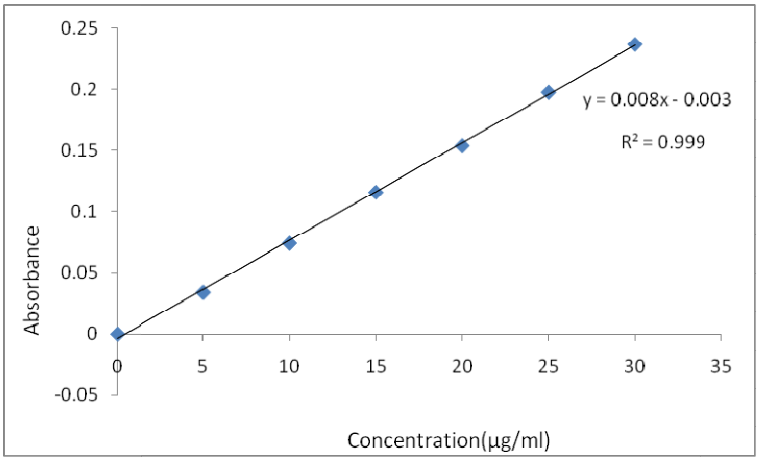

Figure 6: Calibration curve of Piperine

Table 4: Composition of different solid dispersion formulations

Formulation code	Drug: polymer	Drug : polymer ratio
SD1	Piperine: HP β-Cyclodextrin	1:0.5
SD2	Piperine: HP β-Cyclodextrin	1:1
SD3	Piperine: β-Cyclodextrin	1:0.5
SD4	Piperine: β-Cyclodextrin	1:1

Table 5: % Drug content and Entrapment efficiency of solid dispersions

Form. Code	%Drug content	Entrapment efficacy (%)
SD1	79.64±0.24	83.21±0.10
SD2	86.21±0.18	88.52±0.24
SD3	75.82±0.36	78.75±0.36
SD4	78.02±0.28	76.75±0.22

Table 6: I*n-vitro* dissolution studies for solid dispersions (SD1-SD4)

Time(Min)	Percentage drug release			
	1:0.5 (SD1)	1:1(SD2)	1:0.5(SD3)	1:1 (SD4)
0	0	0	0	0
15	37.26±0.12	42.86±0.18	32.78±0.01	35.12±0.12
30	41.22±0.26	56.85±0.12	39.92±0.06	39.98±0.04
45	52.82±0.02	63.28±0.02	47.36±0.12	49.82±0.24
60	61.21±0.01	72.48±0.24	56.28±0.08	58.22±0.22
75	78.36±0.16	80.21±0.06	64.86±0.04	74.86±0.34
90	81.16±0.22	84.96±0.18	74.54±0.26	78.21±0.10

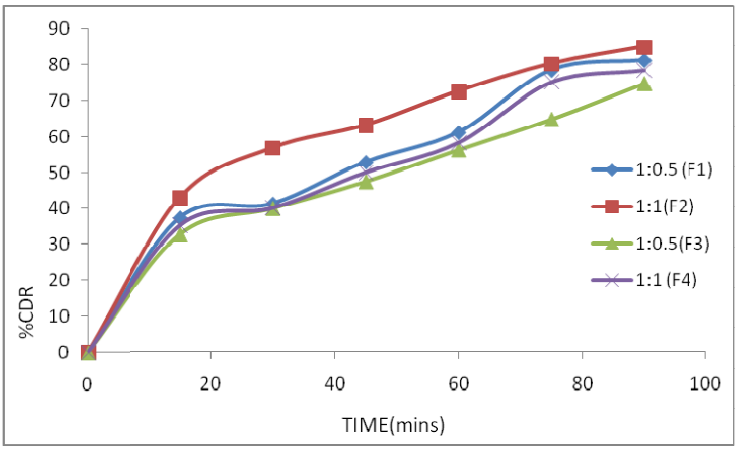

Figure 7: I*n-vitro* drug release profile for drug: β -Cyclodextrin(F1-F2) & HP β -Cyclodextrin (F3-F4)

Table 7: Different formulations of piperine tablets F1-F6

INGREDIENTS	F1	F2	F3	F4	F5	F6
Piperine(mg)	390	390	390	390	390	390
Lycoat (mg)	4	5	6	-	-	-
SSG (mg)	-	-	-	4	5	6
MCC(mg)	25	24	23	25	24	23
Magnesium Stearate	3	3	3	3	3	3
Talc	3	3	3	3	3	3
TOTAL(mg)	425	425	425	425	425	425

Table 8: Pre- compression parameters for formulations blend

Formulation	Derived properties		Flow properties		
	Bulk density (Mean±SD)	Tapped density (Mean±SD)	Angle of repose (Mean±SD)	Carr's index (Mean±SD)	Haunser's ratio (Mean±SD)
F1	0.50±0.01	0.58±0.01	27.38±0.30	14.28±0.02	1.14±0.06
F2	0.48±0.01	0.54±0.02	28.42±0.39	11.53±0.26	1.11±0.03
F3	0.44±0.04	0.50±0.01	23.02±0.68	12.58±2.08	1.12±0.05
F4	0.48±0.02	0.56±0.01	27.26±0.96	14.81±1.28	1.11±002
F5	0.54±0.16	0.62±0.03	31.68±0.73	13.33±1.86	1.15±0.04
F6	0.51±0.02	0.60±0.06	28.26±0.36	15.51±1.96	1.16±0.05

Table 9: Characterization Piperine tablets

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegration time (Sec)	% Drug content
F1	425.6±0.02	3.4±0.02	3.6±0.01	0.68±0.02	82.18±0.02	85.96±0.24
F2	424.7±0.06	3.5±0.04	4.2±0.03	0.62±0.06	61.16±0.05	89.65±0.02
F3	424.2±0.07	3.7±0.06	3.5±0.02	0.79±0.08	50.36±0.06	91.62±0.16
F4	425.8±0.04	3.4±0.01	3.9±0.01	0.65±0.02	62.08±0.08	93.02±0.24
F5	424.6±0.03	3.2±0.01	3.7±0.01	0.59±0.08	38.29±0.02	96.71±0.34
F6	425.4±0.02	3.5±0.02	4.1±0.06	0.48±0.06	32.12±0.07	97.16±0.28

Table 10: % Cumulative drug release of formulations F1-F6

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	32.54±0.10	36.41±0.14	38.38±0.42	33.81±0.04	38.77±0.16	41.65±0.14
10	45.30±0.26	48.71±0.02	50.85±0.22	46.29±0.19	50.28±0.20	54.17±0.16
15	58.12±0.42	63.64±0.14	68.23±0.10	60.80±0.06	66.48±0.04	71.31±0.02
30	75.23±0.28	79.84±0.22	85.53±0.06	72.25±0.10	81.85±0.08	89.46±0.12
45	83.68±0.02	89.52±0.34	91.26±0.10	86.29±0.22	92.28±0.12	96.10±0.28
60	89.78±0.16	93.59±0.28	96.74±0.21	91.87±0.14	97.17±0.28	99.82±0.22

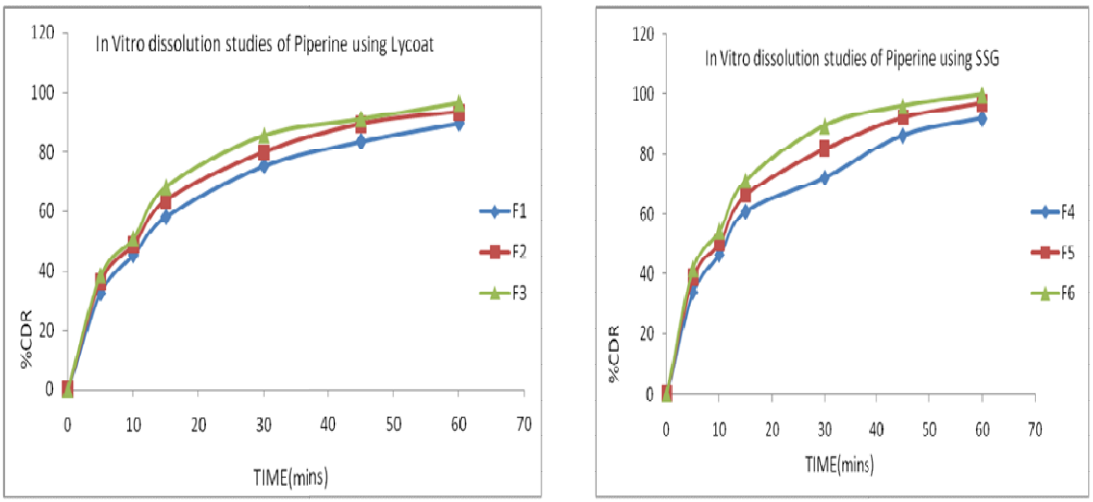

Figure 8: *In-vitro* drug release of F1-F3 and F4-F6

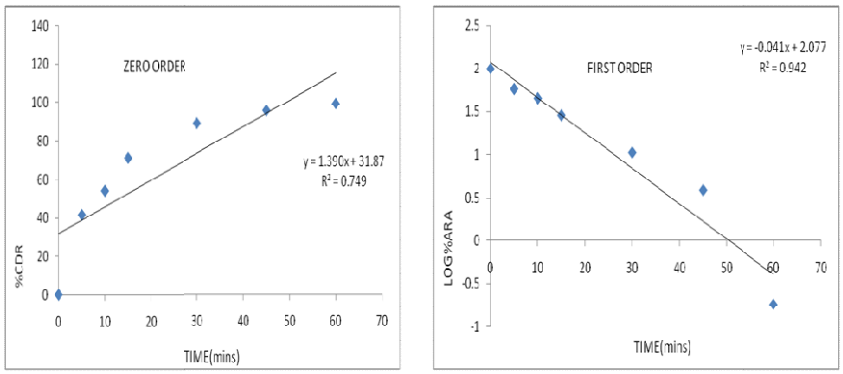

Figure 9: Zero order and First order plot of F6

Table 11: Order of kinetic values of optimized formulation F6

order of kinetics	Zero Order	First Order
Regression values	0.749	0.942

Table 12: Effect of Piperine tablet on various urinary and serum parameters in ethylene glycol induced urolithiasis

Sample	Normal Control	Ethylene Glycol	Cystone Syrup (750 mg/Kg)	Piperine tablet(40 mg/Kg)
Serum creatinine	0.55±0.05	2.33±0.09$^{\#}$	1.02±0.14**	1.06±0.23**
Serum urea	16.52±0.44	32.69±0.83$^{\#}$	23.69±.72**	21.05±1.07***
Serum calcium	8.12±0.15	16.47±0.26$^{\#}$	8.14±0.03**	7.81±0.55**
Serum uric acid	4.14±0.26	8.36±0.56$^{\#}$	3.16±0.41**	3.24±0.43**
Urine oxalate	6.26±0.34	13.23±0.45$^{\#}$	5.11±0.42**	5.41±0.43***
Urine calcium	6.09±0.40	10.62±0.37$^{\#}$	7.21±0.44**	8.13±0.34***

*****P < 0.001 when compared to ethylene glycol control**
****P < 0.01 when compared to ethylene glycol control**
***P < 0.1 when compared to ethylene glycol control**
 # P < 0.1 when compared to normal control

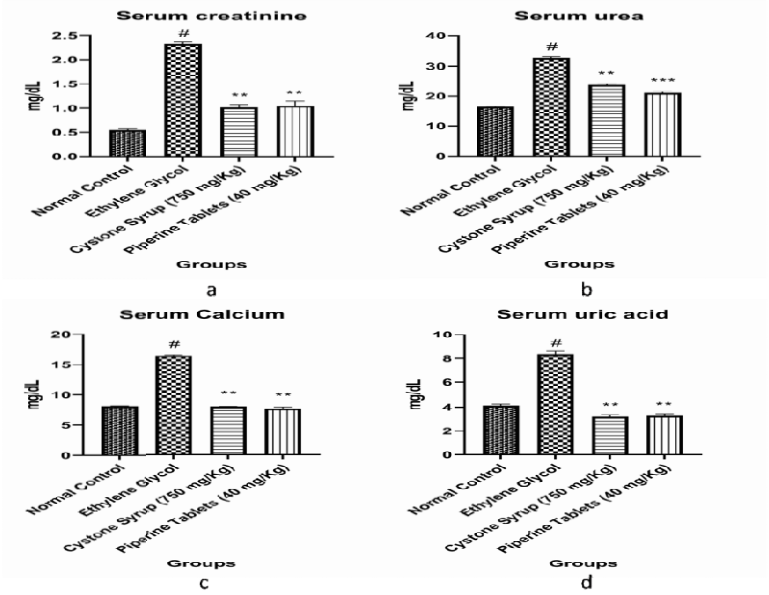

Figure 10: Estimation of a) Serum Creatinine b) Serum Urea c) Serum Calcium d) Serum Uric acid levels by serum analysis in *in-vivo* antiurolithiatic activity

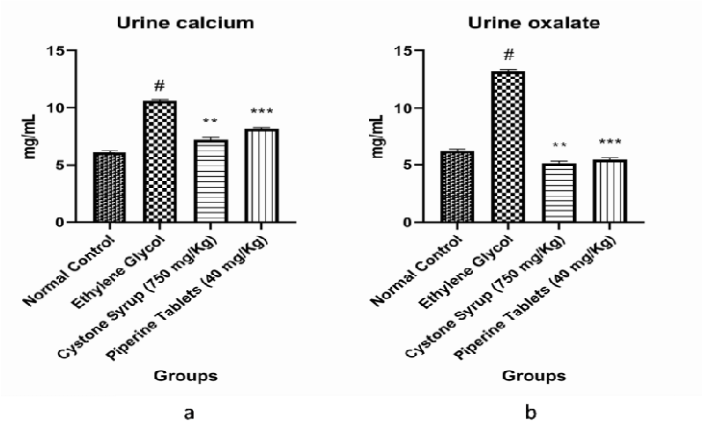

Figure 11: Estimation of a) Urine calcium and b) Urine oxalate levels by urine analysis in *in-vivo* antiurolithiatic activity

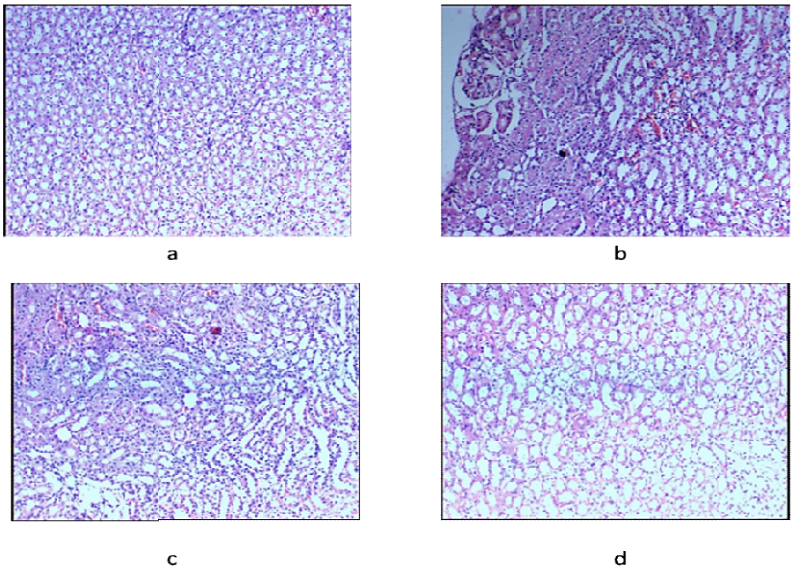

Figure 12: Histopathology in a) Normal control b) Ethylene glycol control c) Cystone syrup (750 mg/kg) treated animal d) Piperine tablet (40 mg/kg) treated animal

CONCLUSION

The present study deals with formulation and evaluation of piperine tablets. Four solid dispersions SD1, SD2, SD3 and SD4 were prepared by taking two different polymers β-cyclodextrin and HP β-cyclodextrin in different ratios. Based on the results obtained for evaluation tests done solid dispersion SD2 was chosen as the final solid dispersion. Six formulations F1-F6 were prepared by taking different excepients in different amounts and were evaluated for pre-compression and post-compression parameters. Based on those results F6 was chosen as optimized formulation. Kinetic studies were done on the optimized formulation F6 and was concluded that it follows first order kinetics.

In-vivo studies were done on the final F6 formulation by using male wistar rats to

reconfirm its activity. The results revealed that the final F6 formulation of piperine tablet has shown significant antiurolithiatic activity as standard cystone syrup. So it was concluded that the final F6 formulation of piperine tablet was good, stable and shows significant antiurolothiatic activity.

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