Research Article

Solidified Cow Urine as a Hydrophilic Agent for Augmenting *In Vitro* Efficacy of Drugs with Solubility Limitations

Pinal H Sukharamwala[1], Basavaraj B V*[2], Nikitha S[2], Bharath S[2]

[1]Assistant professor, Department of Pharmaceutics, C.K.Pithawala Institute of Pharmaceutical Sciences and Research, Surat, India.

[2]Department of Pharmaceutics, Faculty of Pharmacy, M.S. Ramaiah University of Applied Sciences, Bengaluru, 560054, India.

***Corresponding author's E-mail:** basavaraj.ps.ph@msruas.ac.in

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ABSTRACT

The present investigation deals with the use of solidified cow urine (SCU) as a natural pharmaceutical adjuvant in pharmaceutical formulations containing drugs with low aqueous solubility and bioavailability issues. Fresh cow urine was collected and converted into solidified form by drying in a tray dryer at a controlled condition and lyophilization. Aceclofenac (BCS class II) drug with low and variable bioavailability issues was chosen as model drug. Preformulation studies were carried out to ascertain the compatibility between the CU powder and model drug. Tablets and solid dispersions were formulated by using powdered CU as a hydrophilic carrier in various ratios. Aceclofenac tablets were evaluated for both pre and post compression parameters, in vitro dissolution and SEM analysis. Solid dispersions prepared by simple kneading method were also subjected to practical yield, solubility, drug excipient compatibility, DSC and in vitro drug release studies. FTIR study indicated the compatibility between drug and powdered CU. DSC thermogram of solid dispersion showed conversion of crystalline drug into an amorphous form. The solubility of drugs from formulation was increased from 2.0 to 3.0 mg/ml compared to pure drug of 0.020-1 mg/ml. The dissolution profile of standardized tablets AF5 and solid dispersions AS2 were found to be 99.34%, and 95.44% respectively, much better drug release compared to the marketed product. In vitro toxicity studies confirmed the non-toxic nature of the CU powder. Standard tablet and solid dispersion formulations showed an acceptable physicochemical integrity on accelerated stability studies as per ICH guidelines. Thus, the SCU rich in hydrophilic contents in an appropriate concentration could be a promising natural hydrophilic excipient and solubilizer in several pharmaceutical formulations for enhanced solubility and bioefficacy.

Keywords: Solidified cow urine, bioefficacy, solid dispersion.

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INTRODUCTION

Medication items contain both active pharmaceutical ingredients and excipients. Excipients otherwise called adjuvants, used to convert pharmaceutically active substances into pharmaceuticals dosage form that can be appropriate for administration to patients. The International Pharmaceutical Excipients Council (IPEC) has characterized excipients as "Substances other than the API which have been suitably assessed for wellbeing and are purposefully incorporated into a medication".[1] Based on the safely data excipients are classified into 'new chemical excipients' and 'established excipients'.[2] Excipients play an important part in pharmaceutical field.[3] These include:

- Modulating solubility and bioavailability of API
- Enhancing strength of API in dosage forms
- Acting as emulsifying agents, tablet binders and disintegrates and so on
- Maintaining osmolarity and pH of the solvent used in liquid formulation
- Participating in the immunogenic reaction of drug substances

Adjuvants are substances that have few or no pharmacological impacts by themself however may build the potency and efficacy of different drugs when given in the meantime. According to current research articles, concentrated cow urine has a capacity to increase the bioavailability and efficacy of the bioactive molecule (antifungal, anti-microbial and anticancer medications) with which it is administered, without demonstrating any pharmacology activity of its own when use at therapeutic level.[3]

In Ayurveda, this idea is given as "yogvahi" indicates to increase the effect of poorly soluble and bioavailable drugs by increasing their oral bioavailability and diminishing their dose and consequently adverse effects. By joining the idea of ayurveda with present methods we can build up some efficient and valuable drug formulations. It is said that the CU contains "RASAYANA" tatva responsible for increasing bioavailability and immune system .[4,5] Chemical composite analysis of raw cow urine (table 1) result indicates proximity of phenol, halogenated phenol and urea which

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are responsible for bio-enhancing and immune booster properties of cow urine.[6] Use of cow urine as a pharmaceutical adjuvant is a decent decision due to its numerous medicinal and nutritional properties. Nitrogen concentration of cattle urine varies between approximately 3.0 and 10.5 g/L.

Table 1: Chemical Analysis of cow urine

Sl. No.	Chemical Composition	Quantity
1	Protein	0.1037g/lit
2	Uric Acid	135.28 g/lit
3	Urea	5.5418 mmol/lit
4	Creatinine	0.9970 g/lit
5	Lactate	3.7830 mmol/lit
6	Total phenol	4.7850 mg/100ml
7	Halogenated phenol	1.3420 mg/100ml
8	Vitamin A	2.7030 mg/100ml
9	Vitamin C	216.40 mg/lit
10	Vitamin B1	444125 mh/lit
11	Lactate dehydrogenase	21.740 unit/lit
12	Alkaline phosphate	110110 k.k. unit
13	Calcium	5.735 mmol/lit
14	Phosphorous	0.5805 mmol/lit

Although many nitrogenous constituents are involved in the chemical make-up of cattle urine, urea is dominant. Urea concentration represents 52.0% to 93.5% of total urinary nitrogen and is dependent upon the amount of dietary protein consumed by cattle. The advantages of incorporating this natural substance into pharmaceutical dosage forms give several advantages like ease of formulation, increased absorption of drugs with solubility limitations, decreased dosing and most importantly absence of toxicity and economic feasibility.[6] Moreover, they can be modified in a way that they can perform on par with the pharmaceutical dosage forms available in the market.

The objective of the present work was to determine the practical feasibility of the solidified cow urine for employing as a safe and natural formulation additive for the solubility enhancement of drugs with solubility limitations (BCS 2,3 and 4).

MATERIALS AND METHODS

Materials

Morning fresh cow urine was procured from the local farmer of Bengaluru suburban region from Amrit Mahal breed. Aceclofenac was obtained commercially from Yarrow Chem Products, Mumbai. Other excipients such as talc, magnesium stearate, acacia and lactose were procured from reputed chemical suppliers and all other reagents used were of analytical grade.

Methods

Collection and drying of cow urine

The cow urine used for this study was obtained from a Karnataka breed "Amrit Mahal". Fresh early morning concentrated cow urine was collected from the healthy cow at the time of excretion and kept for in a tray dryer at 100 travel ^{o}C for 3 hours. Once liquid gets completely evaporated, a solid mass is left over as a concentrated form of cow urine. Dry residue was scraped off from the petri plates and passed through sieve no. 85 and 120 to get a fine powder. Powder sample was weighed, transferred to an amber colored airtight container and stored at room temperature.

Characterization of powder cow urine

Size of particle was measured by the optical microscope (Olympus NWF, India). Melting point was measured by melting point device (RAGAA). Solubility of solidified cow urine was tested in water, 0.1 N HCl, 6.8 pH phosphate buffer, acetone, ethanol, methanol and chloroform. Moisture content of sample was determined by the initial weight (V_o) and final volume (V) after keeping it in hot air oven at 105 ^{o}C for 3 hours. Cow urine powder was tested for toxicity by performing mutagenicity AMES test using S. typhimurium bacterial species. The Ames test is one of the most frequently applied tests in toxicology. Almost all new pharmaceutical substances and chemicals used in industry are tested by this assay. Bulk density was determined with fixed weight of sample in a measuring cylinder (g/ml). Tapped density was determined using tap density tester with 500 tap (g/ml). Angle of repose was measured by fixed height method. Carr's index and Hausner's ratio were determined using following formula:

$$Carr's\ index = Tapped\ density - bulk\ density/Tapped\ density \times 100$$
$$Hausner's\ ratio = Tapped\ density/Bulk\ density$$

Formulation of tablets

Aceclofenac each containing 100 mg tablets were prepared by direct compression method. The solidified CU was incorporated into the formulations at different proportions starting from 10 mg to 40 mg. All the ingredients given in the formula were mixed thoroughly and passed through sieve no. 44. The blends were directly compressed into tablets on a Rimek (RSB-4) Minipress, 10-station rotary tablet punching machine using 6 mm round and flat punches.[7, 8] The compositions of various formulations are shown in table 2.

Preparation of solid dispersion

Solid dispersion of drug and solidified cow urine was prepared by kneading method. Aceclofenac with solidified CU of 1:1, 1:2 and 1:3 ratio was taken. Solidified CU was added to the mortar and trituration was carried out with a small quantity of 50 % ethanol to get slurry like consistency. Aceclofenac was incorporated into the slurry and trituration was further continued for one hour. Slurry was then air dried at 25 ^{o}C for 24 hours, pulverized and

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passed through sieve no.100. The resulting sample was stored in a desiccator until further use (Table 3) .[9]

Table 2: Formulation table for single aceclofenac tablets containing solidified CU

Ingredients	AF1 (mg)	AF2 (mg)	AF3 (mg)	AF4 (mg)	AF5 (mg)
Aceclofenac	100	100	100	100	100
Solidified CU	-	10	20	30	40
Acacia	2	2	2	2	2
Talc	4	4	4	4	4
Magnesium stearate	4	4	4	4	4
Lactose q.s.	200	200	200	200	200

Table 3: Formulation of solid dispersion

Formulations	Batch code	Ratio	Method
Aceclofenac solid dispersion using SCU	AS1	1:1	Kneading method
	AS2	1:2	
	AS3	1:3	

EVALUATION OF SCU BASED ACECLOFENAC TABLETS

All the tablets prepared were evaluated for hardness, thickness, friability, drug content, disintegration time, dissolution study as per IP. Hardness and friability of the tablets were measured using Monsanto hardness tester and Roche friabilator (25 rpm/4 min) respectively. Disintegration time of tablets was determined in a dissolution test apparatus using phosphate buffer pH 6.8 as a test fluid.[7]

Evaluation of drug content in the tablets

Twenty tablets from each formulation were weighed and triturated. Powder equivalent to 50mg was taken in a mortar, dissolved in methanol and the resulting solution was sonicated. The absorbance was measured spectrophotometrically at λ_{max} 273 nm for all aceclofenac tablets. The drug content was then calculated using standard calibration curve. [10]

In vitro drug release studies of tablets

The dissolution test was carried out using the IP apparatus II (paddle) for all the formulations in order to study the drug release profile. 900 ml of 6.8 pH phosphate buffer was used as a dissolution medium and rpm was set at 50 with 37^{o}C ± 0.5^{o}C temperature. The tablets were dropped into the 900 ml of dissolution media. At regular time period, 5 ml of sample was withdrawn and same amount of fresh buffer was replaced into the dissolution vessel to maintain the sink conditions. Dissolution study was carried out for 1 h. Amount of drug was measured spectrophotometrically at λ_{max} 273 nm for aceclofenac against 6.8 pH phosphate buffer as a blank. The percentage drug release was compared with the marketed preparation for both the drugs.[10]

Scanning Electron Microscopy (SEM)

To assess the efficacy of solidified cow urine as solubility promoter and in turn enhancing bioavailability of aceclofenac, the selected SCU based tablet was subjected to Scanning Electron Microscopy (ZEISS ultra-55, Germany) analysis. SEM analysis was done for aceclofenac tablet (AF5) before and after 1 hour of dissolution study to record the physical transformation. [11]

Evaluation of solid dispersions (SDs)

Solubility study

The excess amount of the all the SD formulations (aceclofenac SDs) was added to 100 ml of distilled water, sonicated and filtered. Suitable aliquots were withdrawn from the filtered solution and analyzed by UV spectrophotometer (Shimadzu UV-1700, Japan) at 273 nm.[12]

Drug content analysis

Preparations equivalent to 50 mg was weighed accurately and transferred to 50 ml volumetric flask and dissolved in methanol. After suitable dilution, the absorbance of the above solution was measured at 273 nm for aceclofenac SDs using methanol as blank solution. The drug content of all solid dispersion formulations was calculated using standard graph of the drug.[13]

Fourier Transform Infrared (FTIR) spectroscopy

FTIR analysis was done for intact aceclofenac, cow urine and solid dispersion AS2 where the samples absorption spectra were recorded using PerkinElmer FTIR Spectrophotometer at wave number range of 4000 - 400 cm^{-1}.[14]

Differential Scanning Calorimetry (DSC)

The thermal properties of intact aceclofenac, cow urine and solid dispersions AS2 were determined using a thermal analyzer (Mettler-Toledo, Mumbai). Each sample in a small amount was placed on an aluminum pan and heated at a constant rate of 10 ^{o}C/min over a temperature range from 30°C to 300°C.[14]

In vitro drug release studies of solid dispersions

All SDs formulations were subjected for dissolution studies using 6.8 pH phosphate buffer as dissolution medium. Aliquots of sample were withdrawn at 10, 20, 30, 40, 50 and 60 minutes time intervals and analyzed for drug release by measuring the absorbance at 273 nm for aceclofenac SDs using UV-visible spectrophotometer. The volume withdrawn at each time intervals was replaced with same quantity of fresh medium to maintain the sink condition.[15]

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RESULTS AND DISCUSSION

Cow urine powder

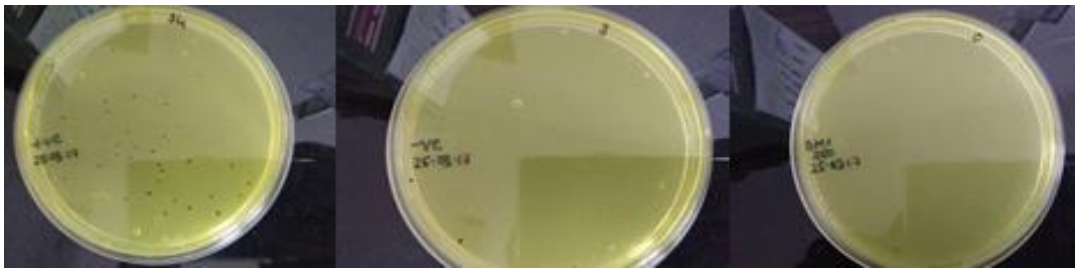
Cow urine was converted into solidified form by 2 different drying equipment: tray dryer and lyophilizer. Cow urine powder was found to be brown, amorphous and hygroscopic in nature. Powder sample was examined under optical microscope. The powder analysis images from the optical microscopy revealed that the particles were of irregular shape with an average diameter of 450 µm. The properties of solidified CU are summarized in table 4.

The percentage yield was calculated to get an idea about the selection of appropriate method of processing and conversion. From the values covered in the table 4, it can be concluded that tray dyer gives more yield compared to lyophilizer method. Derived properties of the powder were determined by recording the bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose which falls under the category of "fair to passable", indicating the need of lubricant addition to increase flow properties for compression.

AMES test utilizes a histidine auxotroph of salmonella typhimurium. It determines if a sample is a mutagenic or not. Appearance of many colonies of the microbe on the minimal plate after addition of the test sample is an indication that the sample is a mutagenic. In the current study as compared with the negative control (3 colonies) sterile saline water and positive control (34 colonies) Hydroxylamine, the sample was found non-mutagenic as there was absence of any colony on the compared positive control with the reference of negative control (figure 1).

Table 4: Physical properties of the solidified cow urine prepared

Properties	Result
% Yield	Tray dryer: 4 % Lyophilizer: 0.9%
Melting point	180 – 200 °C
Solubility	Freely soluble in water, 0.1 N HCl, 6.8 pH phosphate buffer; Soluble in methanol, ethanol, acetone; Insoluble in chloroform
Bulk density	0.714 g/ml
Tapped density	0.909 g/ml
Carr's index	21.45 %
Hausner's ratio	1.27
Angle of repose	37.99°
Loss on drying	< 0.3 %



(a) (b) (c)

Figure 1: AMES test result (a) Positive control shows 34 colonies (small grainy structures) (b) Negative control shows 3 colonies (c) Dry CU sample shows absences of colonies

SCU based aceclofenac tablets

The physical properties of the prepared tablets are summarized in the table 5. All the tablets were found to have satisfactory hardness results in the range between 3.0 kg/cm^2 to 3.5 kg/cm^2. The actual weight of the tablets was 200 mg and the weight variation range was between 185 mg to 215 mg (±7.5 %) complying with the pharmacopoeial limit. Friability test resulted in 0.58% to 0.79 %, within the pharmacopoeial limit of <1 % indicating that all the tablets were mechanically stable with considerable resistance to chipping and abrasion during handling, packaging or transportation. Tablets employing cow urine powder disintegrated within 6-7 min. so all the prepared aceclofenac tablets revealed better quality in terms of hardness, weight variation, friability, drug content, and disintegration time fulfilling the official (IP) specifications of uncoated tablets.

The drug release from all the aceclofenac formulation was in the range of 58.43 % - 99.34 % (figure 2). The highest drug release was found to be 99.34 % with AF5 formulation of aceclofenac with 40 mg of SCU. The results indicated that as the solidified cow urine concentration increases, proportionately enhances the drug release from the formulation increases owing to an increased concentration of hydrophilic contents in the SCU. The drug release from all the tablet formulations showed a faster release when compared to marketed product.

The surface morphology of aceclofenac tablet (AF5) was determined before and after the dissolution study. The morphology of the aceclofenac AF5 tablet sample showed a relatively smooth non porous surface (figure 3) before the

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dissolution but prevalence of uniform porous structure across the post dissolution sample was clearly evident indicating the possible scientific justification for an improvised solubility. The liquid aliquot of the aceclofenac tablet (AF5), containing cow urine powder showed pore formation on particle surface which may be due to wetting, imbibition or penetration into the tablets leading to a rapid release of the drug (figure 3) with an enhanced solubility.

Table 5: Post compression physical parameters of SCU blended aceclofenac tablets

Formulation code	Hardness (kg/cm²)	Weight variation test (mg)	Friability (%)	Disintegration time (sec)	Drug content (%)
AF1	3.4 ± 0.045	193.33 ± 9.42	0.66 ± 0.04	598 ± 5.08	90.89 ± 0.05
AF2	3.5 ± 0.026	191.66 ± 10.67	0.71 ± 0.03	454 ± 4.14	98.18 ± 0.06
AF3	3.3 ± 0.159	188.33 ± 6.87	0.67 ± 0.05	425 ± 6.25	96.41 ± 0.21
AF4	3.4 ± 0.089	191.66 ± 6.84	0.58 ±0.05	410 ± 5.85	98.64 ± 0.06
AF5	3.3 ± 0.112	193.33 ± 8.58	0.63 ± 0.02	389 ± 4.87	98.29 ± 0.02

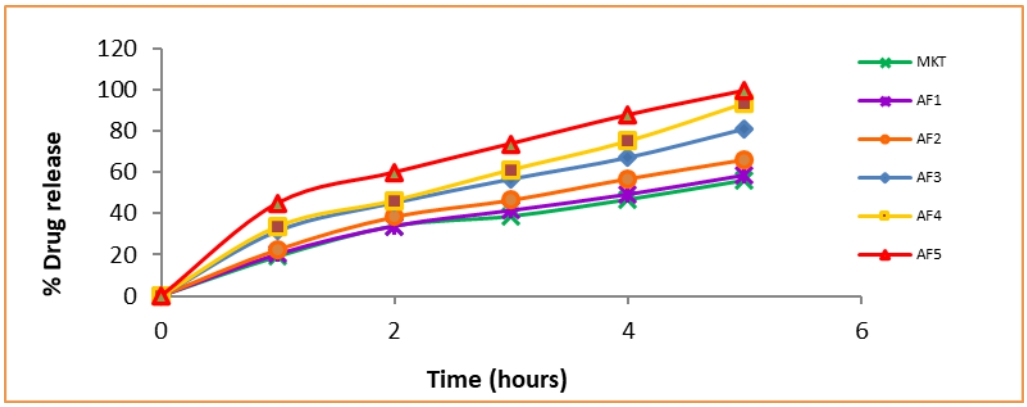

Figure 2: Dissolution profile of SCU based aceclofenac tablets along with marketed formulation

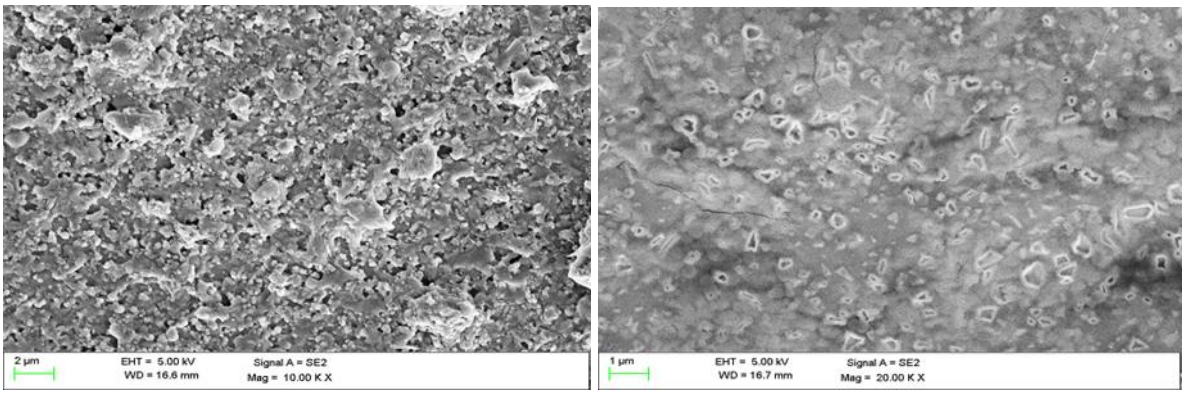

Figure 3: Surface Morphology of aceclofenac tablet AF-5 before dissolution and after dissolution strikingly indicating the change in the surface morphology of the solid particles

The result of solubility test and drug content is given in table 6. According to these results, the solubility of solid dispersion increased compared to an intact drug. The improvement of solubility occurred due to the kneading process by co-grinding that reduced the particle size with an increased surface area. Drug content was found to be between 87.65% and 96.18% (w/w). All the SDs showed the presence of high drug content and low standard deviations of results.

The FTIR results of intact solidified cow urine, intact aceclofenac, intact famotidine, solid dispersion AF2 (figure 4). The spectrum of Aceclofenac showed characteristic bands at 3319 cm^{-1} (N-H stretching), 3282 cm^{-1} (O-H stretching), 1714 cm^{-1} (C=O stretching) and 1344 cm^{-1} (O-H in plane bending). The aforementioned peaks were also shown by physical mixture, solid dispersion and optimized batch. These confirm the stability of the drug. The IR spectrum did not show any new functional groups formed, which indicated compatibility between drug and carrier.

The DSC of Thermogram of solidified cow urine, intact aceclofenac, solid dispersion AF2, is shown in (figure 5. (A), 5(B), 5(C)) shows a sharp endothermic peak at 154 ^{o}C and 164 ^{o}C which corresponds to the aceclofenac. Such endothermic peak signifies that the drugs used were in pure

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amorphous state. Solidified CU depicted a major broad peak with the melting point at 179 °C. Extra peaks can be obtained due to presence of volatile substances and low molecular weight components. The melting peaks in the drug-carrier systems demonstrated reduction in intensities, proving that the crystalline drug is converted to amorphous state.

The comparative dissolution test result of intact drug and solid dispersions is shown in the figure 6. The percentage release of intact aceclofenac and solid dispersions with different ratio 1:1, 1:2, 1:3 dissolved after 60 minutes were 59.42%, 81.89%, 94.44% and 86.21% respectively. The increase in dissolution rate was in the order of 1:2 > 1:3 > 1:1 in solid dispersions. As the concentration of carrier was increased, the dissolution rate of drug was found to decrease might be due to formation of viscous layer around the drug particles.

Table 6: Result of aceclofenac solid dispersion solubility test and drug content

Samples	Solubility (mg/ml)	Drug content %
Pure drug Aceclofenac	0.020 ± 0.003	100.00 ± 0.02
AS1	1.051 ± 0.008	94.89 ± 0.018
AS2	1.805 ± 0.002	96.84 ± 0.01
AS3	2.139 ± 0.008	93.42 ± 0.037

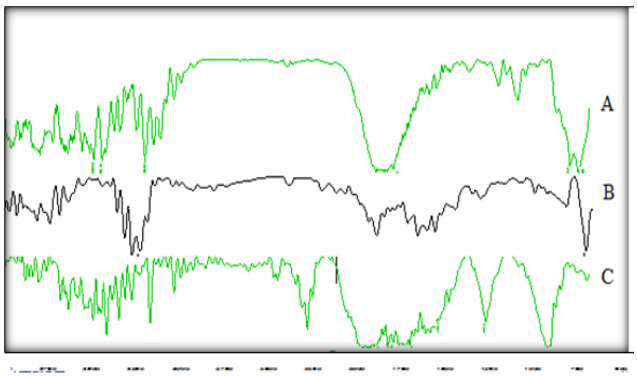

Figure 4: Fourier transform infrared spectrum of (A) solidified cow urine, (B) intact aceclofenac, (C) solid dispersion AF2

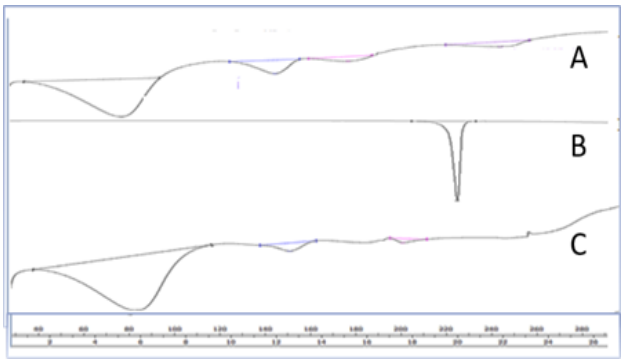

Figure 5: Thermograms of (A) solidified cow (B) intact aceclofenac (C) solid dispersion AF2

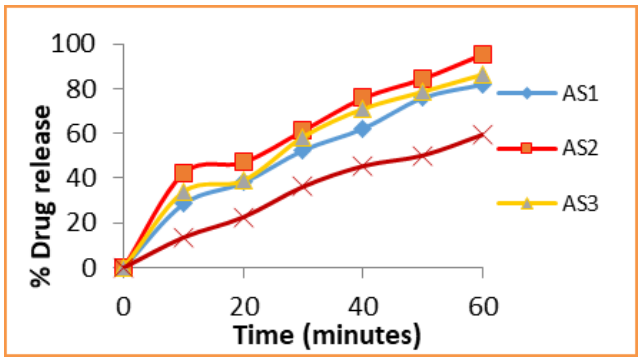

Figure 6: Comparative *in vitro drug* release profile of aceclofenac SD with pure drug

CONCLUSION

The use of highly concentrated cow urine in the solidified form as a pharmaceutical additive significantly increased *in vitro* solubility and drug release from the tablet and solid dispersion formulations compared to the marketed brand. Accordingly, the present study propounds that cow urine powder has an inherent ability to enhance the solubility of drugs with poor aqueous solubility. Upon further exploration, it could be proposed as a potentially natural and safe pharmaceutical excipient for drugs with bioefficacy issues as bioenhancer with multiple benefits in the development of effective formulations for clinical applications.

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