TASTEMASKING OF CAFFEINE BY BETACYCLODEXTRINE AND FORMULATION EVALUATION OF NANO SUSPENSION

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ABSTRACT

Caffeine is a drug isolated from Coffea arabica. The pure drug is an alkaloid categorized as Xanthine. Caffeine broadly used as CNS stimulant, analgesic, antipyretic and antipsychotic drug. As the pure drug is an alkaloid derivative it has bitter taste. Here the research work is an attempt to mask the bitter taste of drug by complexation. Betacyclodextrin polymer is used here as the complexing agent to mask taste of bitterness. The complexation resulted in enhancement of bioavailability and physical parameters.The most important property of a dosage form is its ability to deliver the active ingredient to its site of action in an amount sufficient to elicit the desired pharmacological response. Bioavailability is a measurement of the extent of a therapeutical active drug that reaches the systemic circulation and is available at the site of action. Accordingly, the absorption of an intravenously administered drug is instantaneous and complete. However, for reasons of convenience and stability, most drugs are administered orally after first being formulated in to dosage forms, usually tablets, capsule, nanosuspensions, naoemulsions etc. Various physicochemical, physiological, formulation and manufacturing variables affect the bioavailability of the drug from these orally administered dosage forms. Among the various factors that affect the bioavailability, it has now been recognized with certainly that dissolution behavior and the factor affecting such performance are of paramount importance in the design and evalution of nanosuspension. As early as 1955 parrot and coworker's stressed that the release of a drug from the primary particle and its subsequent availability to the body is goverened by the dissolution rate of the particle. The properties of the dosage form that modify the dissolution rate must necessarily influence the blood level of the drug, and thus may function as the controlling factor in determining the magnitude of the pharmacological response elicited and sometimes even of determining whether or not such a response is exhibited at all. The pharmaceutical and medical literature is replete with report showing variability in clinical response among orally administered drug product that contains chemically equivalent amounts of a drug. Those drugs are usually of limited aqueous solubility and the variation has generally been attributed to differences in the rate of dissolution.

Keywords: Repaglinide, β-cyclodextrin, XRD, Complexation.

MANUSCRIPT

INTRODUCTION

A Caffeinated nanosuspension is a versatile formulation combining conventional and innovative features. It comprises 100% pure drug nanoparticles with sizes in the nano-scale range, generally stabilized by surfactants or polymers. Nanosuspensions are usually obtained in liquid media with bottom-up and top-down methods or by their combination. They have been designed to enhance the solubility, the dissolution rate and the bioavailability of drugs via various administration routes. Due to their small sizes, Caffeine nanosuspensions can be also considered a drug delivery nanotechnology for the preparation of nanomedicine products.

EXPERIMENTAL METHOD

Illuriation on micromeritics study of pure drug.

Experiment	Result
Bulk density	0.1742 gm/ml
Tapped density	0.2632 gm/ml
Carr's index	33.82%
Hausner's ratio	1.51
Angle of repose	33.52^0

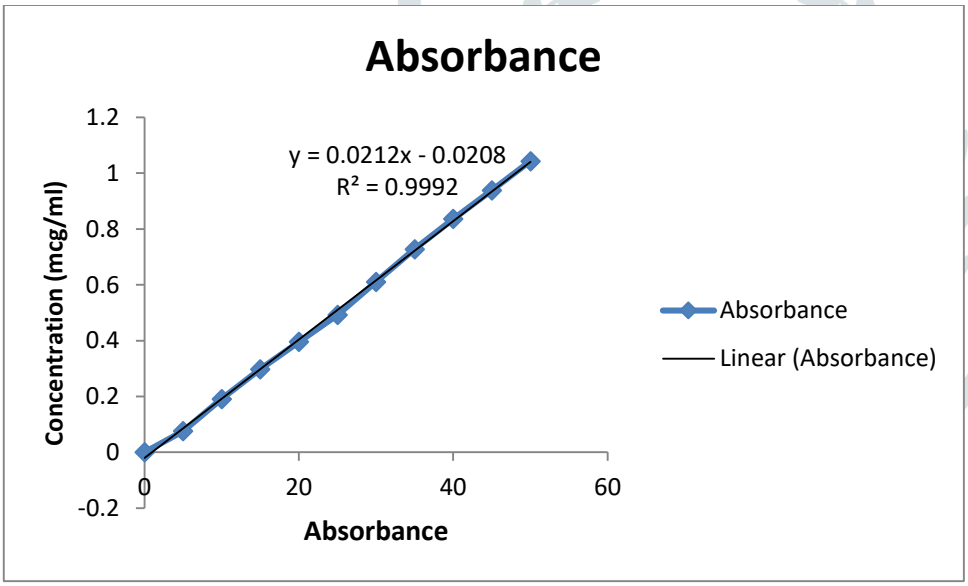
Sieve analysis of caffeine bulk drug

Sieve no.	Retained amount of drug (in mg)	Percentage retained (%)
22	0.926	46.3
30	0.330	16.5
44	0.176	8.8
60	0.168	8.4
80	0.016	0.8
100	0.101	5.05
120	0.010	0.5
Total	1.727	86.35

Spectroscopy analysis of caffeine

The first step in formulation study is to be established then analytical method so that all future measurement can be quantitative. 100mcg/ml solution of caffeine was prepared in different mediums e.g. pH 7.4 buffer and water. All the prepared solution were scanned for λ_{max} against the corresponding medium as blank in the spectral range of 200-400nm. The spectrums were recorded and from the spectrum $\lambda_{max}$was determined. Then linearity was checked by preparing calibration curve by taking different diluted solutions in the respective mediums.

Spectroscopy	Determination of using 1mg/ml solution in medium	λ_{max}
	Distilled water	273nm



Calibration curve of Caffeine with distilled water

Dissolution study of pure drug:

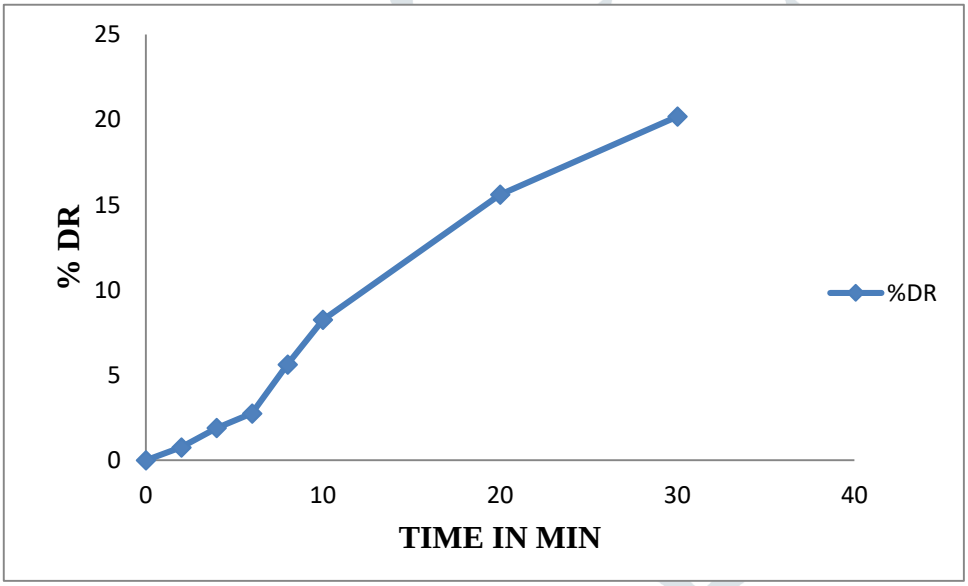
Dissolution study of pure drug (Caffeine) was carried out with distilled water using following method.

Method: 500ml of medium was placed in the dissolution vessel and temperature was maintained to $37^0 \pm 0.5^0$ C. 100 mg of caffeine was added to dissolution medium and paddle was used at a stirring rate of 50 rpm. 2ml sample was taken from the dissolution medium at regular time intervals. After each sampling,

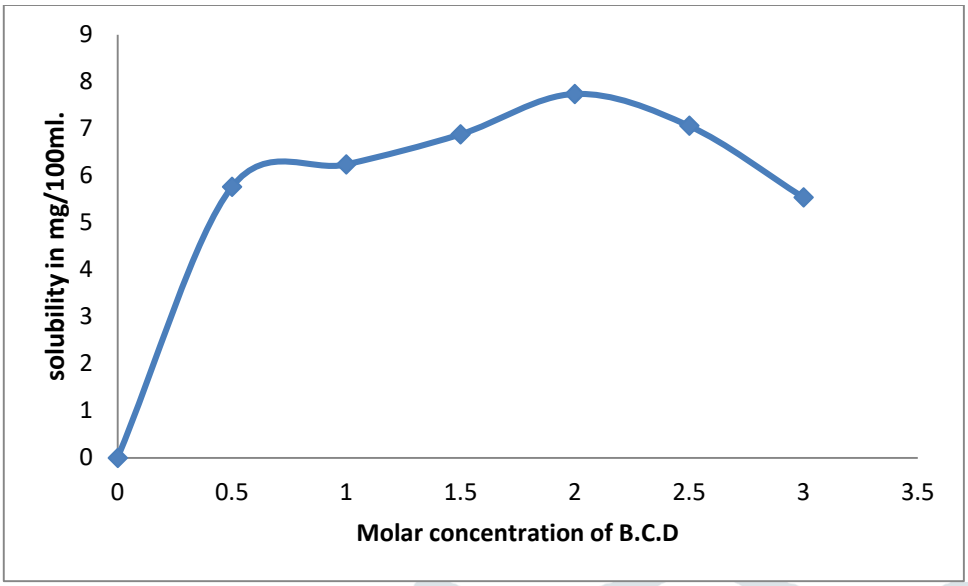
medium was added to maintain a constant volume of dissolution medium. The sample were then analyzed for the drug content at respectively λ_{max} 273nm, using UV-Visible spectrophotometer.

Dissolution data of pure drug in distilled water

Sl.NO.	Time	%DR
1	0	0
2	2	0.76
3	4	1.9
4	6	2.75
5	8	5.63
6	10	8.25
7	20	15.6
8	30	20.18



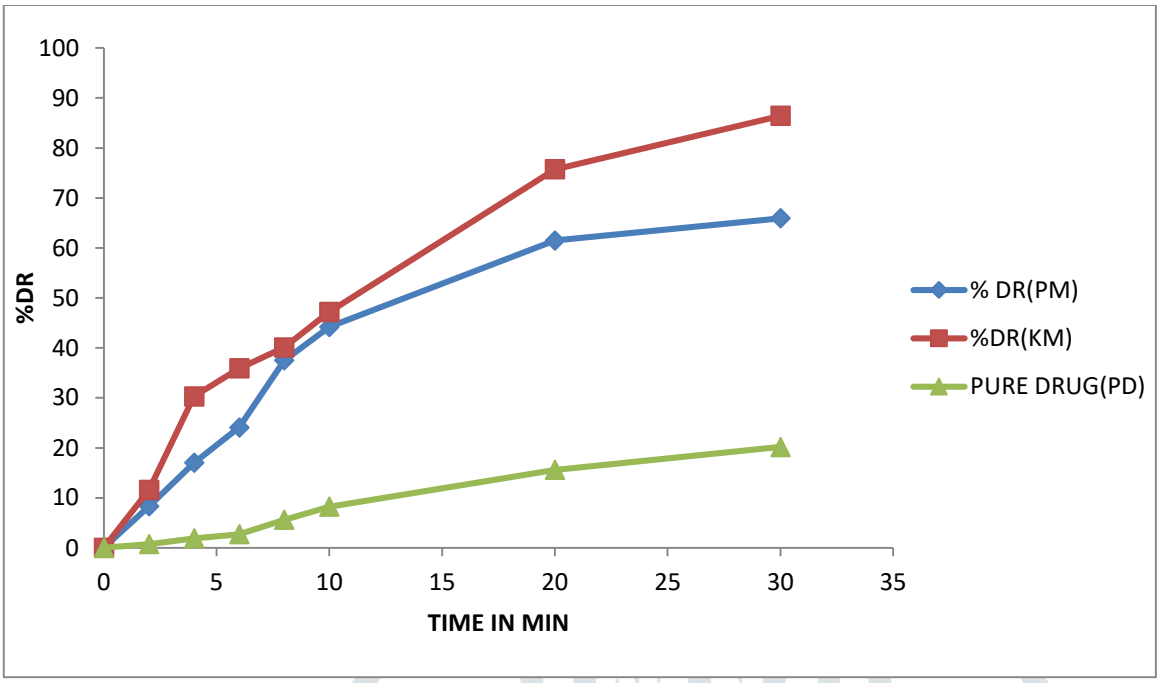
Phase solubility study of Caffeine with β- CD complex



Physicochemical characterization of complex

Parameters	Complex	Pure drug
Bulk density	0.294 gm/ml	0.1742 gm/ml
Tapped density	0.384 gm/ml	0.2632 gm/ml
Compressibility index	23.43%	33.82%
Angle of repose	30.068^0	33.52^0
Hausner's ratio	1.306	1.51

Comparative dissolution data of Kneading mixture, physical mixture, pure drug with distilled water



Preparation and Evaluation of nanosuspension

Nanosuspensions were prepared by the solvent evaporation technique. Caffeine was dissolved in 10 ml ethylacetate (organic phase) at room temperature. This was poured into 40 ml of water containing different amount of SLS, PVPK 30 and PEG maintained at room temperature. Continuous stirring at 7500 rpm for 6-7 minute by using magnetic stirrer. The addition of the organic solvent was done with the help of syringe positioned with a needle directly in to the aqueous surfactant (at a rate of0.5 ml/min). the solution was stirred for 5-6 minute at 20,000-25,000 rpm(magnetic stirrer) and then was subjected to the sonication for 10 minute (probe sonicator). The suspension was then stirred for 1 hour to induce diffusion of organic solvent in to the continuous phase. The prepared nanosuspension was left stirring at room temperature to evaporate the organic solvent.

Drug	F1	F2	F3	F4
Caffeine(gm)	0.13	0.13	0.13	0.13
Ethyl acetate(ml)	10	10	10	10
SLS(mg)	4	4	4	4
PVP K 30(mg)	50	25	50	25
PEG(mg)	30	15	30	15
Distilled Water	40	40	40	40

Particle size, zeta potential and its morphology

Particle size and zeta potential was determined by photon correlation spectroscopy (PCS) using a Beckman coulter. This analysis yields the mean diameter. All the data presented are the mean values of three independent samples produced under identical production conditions. Partical morphology was examined by Scanning Electron Microscopy.

Entrapment efficiency

This method is suitable for determining entrapment efficiency of nanosuspension when fairly high concentration of free drug is present in the supernatant after centrifugation. 10ml portion of the freshly prepared cooled nanosuspension was centrifuged at 10,000 rpm for 10 minute using centrifuge. The supernant was removed and the amount of unicorporated drug was measured by taking the absorbsance of supernatant was removed and the amount of unicorporated drug was measured by taking the absorbance of supernatant solution at 273 nm by using UV spectrophotometer.

Total drug content:

An aliquote (0.5ml) of the nanosuspension was evaporated to dryness. The residue was dissolved in methanol and filtered with a 0.45µm filter. Total drug content was determined by UV spectrophotometer at 273nm.

RESULTS AND DISCUSSION

- Organoleptic characteristics of pure drug (caffeine) showed that the drug is white coloured, odourless, crystalline and bitter in taste.
- The spectroscopy study using UV- Visible spectrophotometer of caffeine in distilled water maximum wavelength was found to be 273nm.
- From the compressibility index and angle of repose values it was concluded that the pur drug having poor flow properties.
- From phase solubility study the drug : BCD ratio of 1:2 has optimum complexation takes place.
- Higher percentage of drug complexation was obtained with kneading method than with physical mixture.
- Higher percentage of drug complexation was obtained with kneading mixture using 20 ml methanol.
- Higher percentage of drug complexation was obtained with kneading method when the complex was dried at 45^0 c.
- After taste masking by beta cyclodextrine complexation, it was reported by volunteer to be masked bitter taste It was concluded with high dissolution rate and better micromeritics property.

- The dissolution study was carried out for pure drug, physical mixture, and kneading mixture in distilled water and is found to be 20.18%, 65.94%, and 86.43% in 30 minutes respectively.

Melting point

Melting point was measured with the use of Thieles tube apparatus by using paraffin oil, thermometer, thread and burner. The melting point of the plain caffeine drug was found to be 235^0 C.

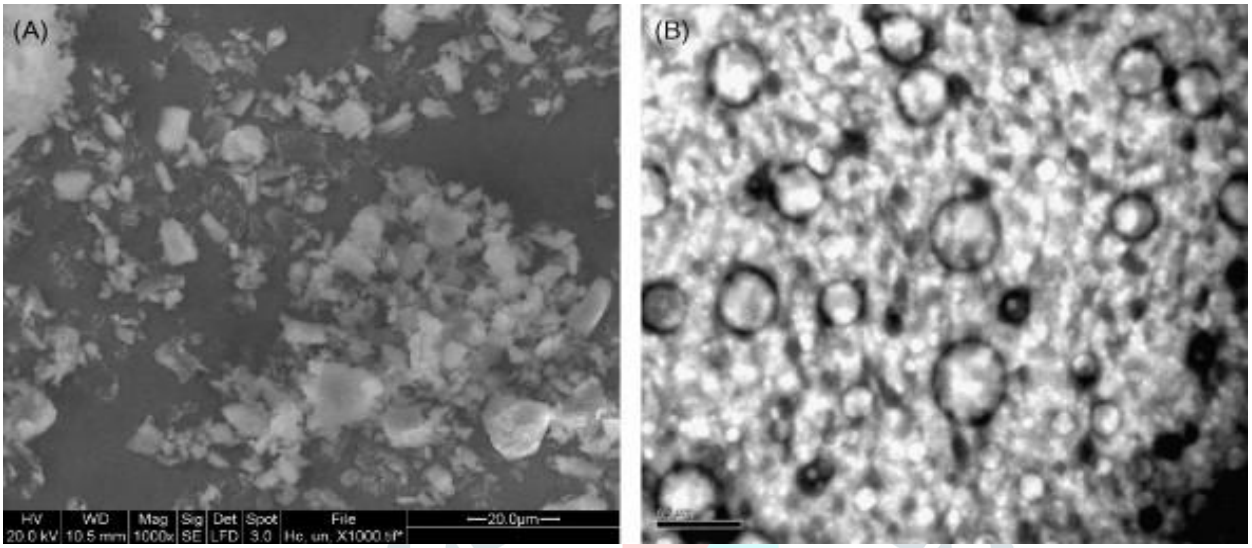


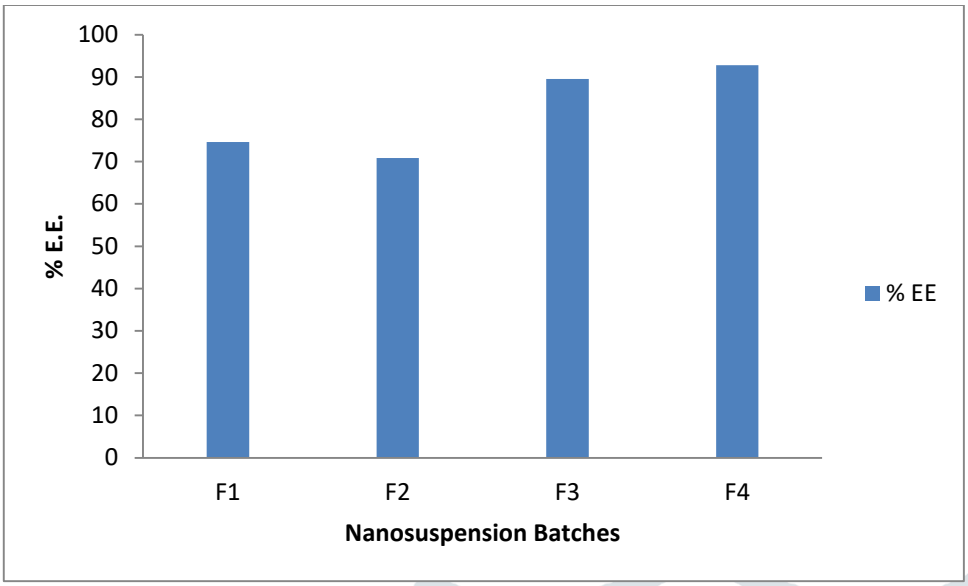
Fig A SEM of Pure drug, Fig B TEM of complexed Nanosuspension

Zeta potential

It is generally acknowledged that a zeta potential of approximately ± 20 mV is required. Zeta potential analysis was performed to get information about the surface properties of the nanocrystal. The zeta potential of the prepared caffeine nanosuspension was ± 23.43 mV.

Entrapment efficiency

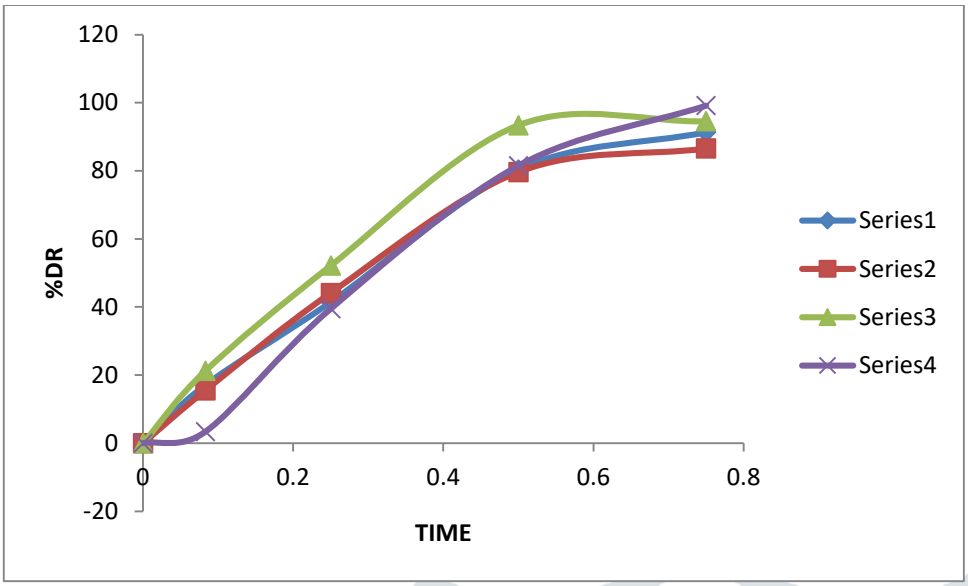
Entrapment efficiency of all formulation was found to be greater than 70%. Formulation 4 shows 92.78% entrapment efficiency.



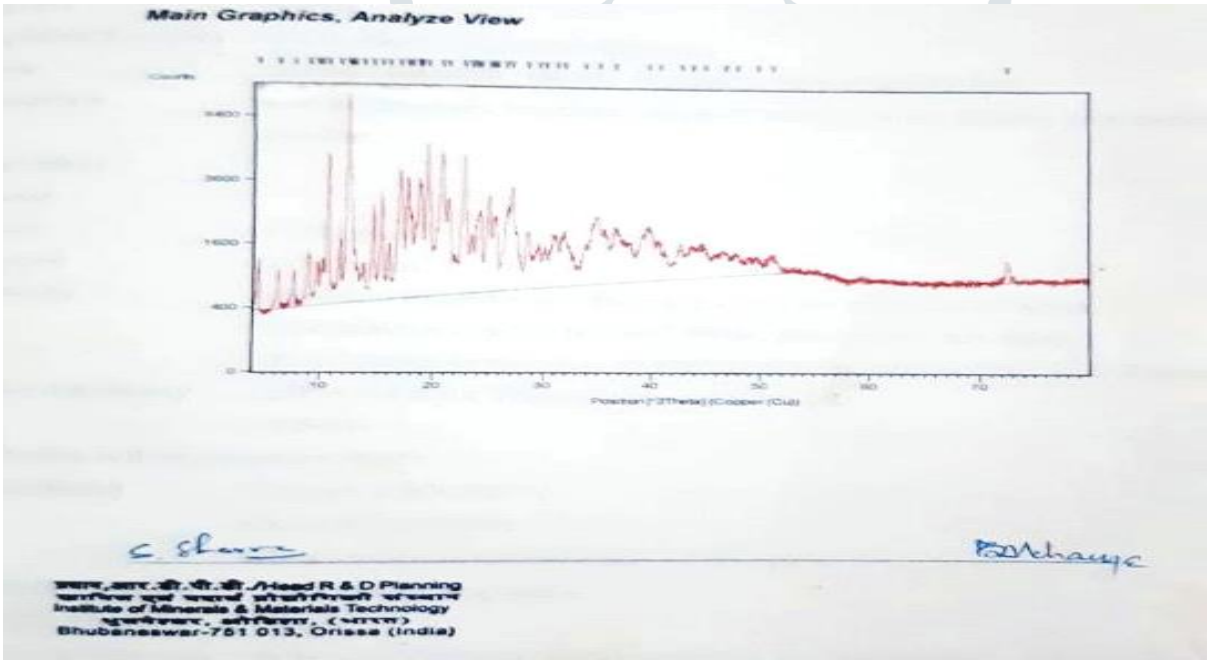
COMPARATIVE ZERO ORDER RELEASE KINETICS OF DIFFERENT FORMULATION

TIME	% DR			
	F1	F2	F3	F4
0	0	0	0	0
0.083(5 min)	17.04951	15.473	21.19888	3.360379
0.25(15 min)	41.40595	44.12672	52.13779	39.48446
0.5(30min)	80.37625	79.65732	93.38967	81.4892
0.75(45min)	91.33664	86.53421	94.53555	99.13119

COMPARATIVE ZERO ORDER RELEASE KINETICS OF DIFFERENT FORMULATION



X-ray Diffraction Study



Analgesic effect of complexed BCD caffeine

Experimental design

Animals were randomly assigned to a con-trol (saline solution) or a treated group (caffeine).

Tail flick

An analgesiometer method was used to perform the tail-flick test. The light from a project bulb situated beneath the platform where the animal was placed, was focused through a small hole on the ventral part of the tail at a point about 4 cm from the tip. Withdrawal of the tail exposed a photocell to the light, which turned off the thermal stimulus and automatically stopped the clock. The intensity was regulated so that the

reaction time var-ied between 2 and 4 s. The analgesia was tested before and 15, 30 and 45 min after treatment. Each value was derived from the mean of three consecutive readings in which the light was focused on three adjacent points of the tail.

CONCLUSION

Nanosuspensions are being formulated on certain drug (Caffeine). The result obtained with nanosuspension of caffeine that was developed and evaluated in the present study are encouraging. The formulation (F4) chosen in the study has given the better result. After making complexation with BCD at the dissolution rate been found to be 99.13. TheXRD report of complex showing it fused peak below 2500 shows its amorphous characteristics. After taste masking by beta cyclodextrine complexation, it was reported by volunteer to be masked bitter taste It was concluded with high dissolution rate and better micromeritics property. The anti microbial effects and analgesic effect found to be satisfactory.

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