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Taste masking of Caffeine by Inclusion Complexation of β-cyclodextrin

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ABSTRACT: Background: Caffeine is a xanthine derivative having mild CNS activity and is largely found in Coffee i.e. *Coffea arabica* and *Thea sinsensis* (Tea), which is the largest consumed drink after water in the world. **Aim:** The research work was attempted to mask the bitter taste of caffeine which is an antipsychotic, analgesic, antihypertensive and diuretic drug. **Method:** In this innovative work, β-cyclodextrin was taken in different molecular weight form in different ratio with caffeine. The caffeine was extracted by the percolation. Pure drug was dissolute in distilled water and compared with physical and kneading mixture. The chloroform solvent was taken for the drug and β-cyclodextrin complexation which was compared for phase solubility study. After solvent optimization, the temperature was optimized. The dissolution study was carried out and compared. The taste masking property was analyzed by scientific/ ethical committee. **Results:** The bitter taste of caffeine was successfully masked by the β-cyclodextrin complexation. The complexed drug was found to have different improved physical characteristics like bulk, tapped densities, Carr's index, angle of repose. XRD report showed the complexed drug to have more stabilized than pure drug. As the complex shows fuse peaks at low intensities indicating more stable and soluble, compare to the pure drug having intensed peaks showing crystalline nature, which indicates its non soluble nature. Micromeritics study of complexed pure drug revealed that the drug possessed good flow property. **Conclusion:** The β-cyclodextrin was found to masked bitter taste of caffeine and the complexed caffeine exhibited good physicochemical and dissolution properties.

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INTRODUCTIONS:

Caffeine is a central nervous system (CNS) stimulant of the methylxanthine class. It is the world's most widely consumed psychoactive drug. Unlike many other psychoactive substances, it is legal and unregulated in nearly all parts of the world. There are several known mechanisms of action to explain the effects of caffeine. The most prominent is that it reversibly blocks the action of adenosine on its receptor and consequently prevents

the onset of drowsiness induced by adenosine. Caffeine also stimulates certain portions of the autonomic nervous system [1,2]. Caffeine is a bitter, white crystalline purine, a methylxanthine alkaloid and is chemically related to the adenine and guanine bases of deoxyribonucleic acid. The coffee tree, scientifically known as *Coffea arabica*, is native to Abyssinia and Ethiopia, but grows well in Java, Sumatra, and other islands of the Dutch East Indies; in India, Arabia, equatorial Africa, the islands of the Pacific, in Mexico, Central and South America and the West Indies. The plant belongs to the large subkingdom of plants known scientifically as the Angiosperms, or Angiospermæ, which means that the plant reproduces by seeds which are enclosed in a box like compartment, known as the ovary, at the base of the flower [3,4].

MATERIALS:

The β-cyclodextrin was procured from SD Fine Chemical, Mumbai. The solvent, chloroform was purchased from Himedia Lab, Mumbai. All other chemicals and reagents were of analytical grade and procured from authorized dealer.

METHODS:

Extraction of Caffeine from coffee leaves:

Extraction is a method used for the separation of organic compound from a mixture of compound. This technique selectively dissolves one or more compounds into an appropriate solvent. The solution of these dissolved compounds is referred to as the extract. The caffeine was extracted from *Coffea arabica* by percolation method. The Caffeine was extracted from tea powder by solubilising caffeine in water in different fractions of 22 mg/ml at 25°C, 180 mg/ml at 80°C and 670 mg/ml at 100°C. The organic solvent, Chloroform was used to extract caffeine from aqueous extract of tea powder because caffeine is more soluble in chloroform (140 mg/ml) than in water (22 mg/ml). The caffeine was separated from chloroform water (caffeine) mixture by using separating funnel. The residual aqueous layer was separated from chloroform layer by using inorganic solvent, sodium sulphite as it was insoluble in organic solvent. Anhydrous sodium sulphite is an insoluble inorganic solid which will absorb water, thus drying it [5,6].

Complexation of caffeine by β-cyclodextrin:

The extracted drug caffeine was complexed with β-cyclodextrin by physical mixture and Kneading methods. The appropriate proportion (1:2) of caffeine and β-cyclodextrin kneaded complex was formed using suitable organic solvent. The prepared physical mixture and kneaded complex was dried in Hot air oven at 40 to 45 °C for 24 h. The dried mixture and complexes were passed through sieve no 40 and stored in desiccator for further study [7].

Characterization of caffeine and β-cyclodextrin physical mixture and kneaded complex:

Micromeritic study:

The micromeritic properties of pure drug (caffeine), β-cyclodextrin physical mixture and kneaded complex was determined by measuring tapped, bulk densities, angle of repose, Carr's index and Hausner's ratio [8-10].

Bulk Density: The definite mass of drug was weighed using Electronic Digital balance. The volume of weighed powder drug was measured using measuring cylinder. The measured volume was treated as Bulk volume. The bulk density was calculated using equation as mentioned below.

$\rho_b = M/V_b$ ……. (1)

Where, ρ_b is bulk density in g/cc, M is mass of drug in g and V_b is bulk volume in cc.

Tapped Density: The same weighed mass of drug was tapped using digital bulk density apparatus for 1000 taps in a cylinder and the changes in volume were measured. This volume was treated as tapped volume. The tapped density was calculated using equation as mentioned below.

$\rho_t = M/V_t$ …….. (2)

Where, ρ_t is tapped density in g/cc, M is mass of drug in g and V_t is tapped volume in cc.

Carr's Index (Compressibility Index): The Carr's index (CI) of drug powder was calculated to characterize flow properties by using following equations as given below.

$CI\ (\%) = [(V_b - V_t)/ V_b] \times 100$ …….(3)

$CI\ (\%) = [(\rho_t - \rho_v)/\rho_t] \times 100$ …….(4)

Hausner's Ratio: The Hausner's ratio of drug powder was calculated to characterize flow properties by using following equation as given below.

Hausner Ratio $= \rho_t/\rho_v$ ……..……..(5)

Angle of Repose: The Angle of repose was determined using falling funnel method. The microcapsules were poured through a vertically placed of height (h). Radius (r) of the heap was measured and the angle of repose (Q) was calculated by using the formula,

$\theta = \tan^{-1} (h/r)$ ……..(6)

Solubility study:

The solubility study of pure drug caffeine was carried out in distilled water and 0.1N HCl as per standard procedure.

Table 1. Micromeritic data of caffeine pure drug and β-cyclodextrin complex.

Parameters	Pure drug	Drug-β-CD complex
Bulk density (g/cc)	0.1742	0.294
Tapped density (g/cc)	0.2632	0.384
Carr's Index (%)	33.82	23.43
Hausner's Ratio	1.52	1.301
AOR (°)	33.52	30.064
Flow comment	Poor	Good

CD – Cyclodextrin and AOR – angle of repose.

Drug Content study:

The drug (Caffeine) content in physical mixture and kneaded complex of caffeine and β-cyclodextrin was carried out by dissolving in 0.1N HCl. The mixture was kept over Rotary shaker. After 1 h, the solution was double filtered using Whatman Filter paper 4. The Caffeine content in the filtrate was determined spectrophotometrically using UV-Visible Spectrophotometer at 273 nm. From regression equation, the drug content in percentage was calculated by using following equation as given below [11,12].

Drug content (%) = (PDC/TDC)×100 …(7)

Where, PDC and TDC are practical and theoretical drug content in mg.

Table 2. *In vitro* drug release data of caffeine and β-cyclodextrin complex.

Sl. No.	Time (min)	Pure drug	Physical mixture	Kneaded complex
		Cumulative % drug release		
1	2	0.76	8.3	11.58
2	4	1.9	17	30.29
3	6	2.75	24.1	35.89
4	8	5.63	37.5	40.09
5	10	8.25	44.21	47.2
6	20	15.6	61.48	75.74
7	30	20.18	65.94	86.43

Dissolution study:

The *in vitro* dissolution study of pure drug caffeine, physical mixture and kneaded complex of caffeine and β-cyclodextrin was carried out using USP XXXI paddle type (II) Dissolution apparatus using 0.1N HCl as dissolution medium of volume 900 ml and bath temperature was maintained at (37±1)°C throughout study. Paddle speed was adjusted to 75 rpm. At specific interval of time (2, 4, 6, 8, 10, 20 and 30 min), sample was withdrawn with replacement of 5 ml fresh medium. The dissolution study was continued for 20 min. The collected drug solutions were analyzed for caffeine content by using UV-Visible spectrophotometer at 273 nm. The concentration of drug in solution was calculated from regression equation of standard calibration curve of regression co-efficient (r^2) 0.999 [13-15].

Taste masking study:

The taste masking property was analyzed by scientific/ ethical committee. Human volunteer was tasted the pure drug caffeine, physical mixture and kneaded complex of caffeine and β-cyclodextrin [16].

RESULTS AND DISCUSSIONS:

The micromeritic study data of pure drug caffeine, physical mixture and kneaded complex of caffeine and β-cyclodextrin is given in Table 1. The Carr's Index was found to be 33.82 and 23.43 % respectively for pure drug and complexed mixture. The angle of repose was found to be 33.5 and 30.1° respectively for pure drug and complexed mixture. The result revealed that the pure drug possessed poor flow property, where as caffeine and β-cyclodextrin complexed mixture possessed good flow property. Solubility study of caffeine in distilled water and 0.1N HCl was found as 15.78 and 84.29 mg/ 100 ml respectively. The drug content of physical mixture and kneaded complex of caffeine and β-cyclodextrin was 83.82 and 85.62 % respectively.

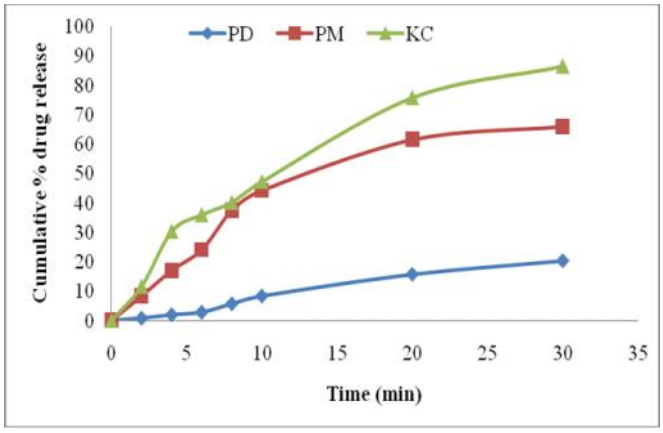

Fig 1. Cumulative % drug release data of caffeine and β-cyclodextrin complex.

PD – Pure drug, PM – Physical mixture and KC – Kneaded complex.

The *in vitro* dissolution data of pure drug caffeine, physical mixture and kneaded complex of caffeine and β-cyclodextrin is given in Table 2 and Fig 1. The pure drug caffeine released 20.2 % of drug in 30 min, where as physical mixture and kneaded complex of caffeine and β-cyclodextrin released 65.94 and 86.43 % respectively in 30 min. The dissolution study data revealed that the drug release profile of caffeine was significantly increased when caffeine was complexed with β-cyclodextrine. The phase solubility study showed 5.76, 6.24, 6.88, 7.74, 7.06 and 5.54 mg/ 100 ml with molar concentration of β-cyclodextrin 0.5, 1, 1.5, 2.0, 2.5 and 3 respectively. The X-Ray Diffraction study revealed that the complexation of caffeine and β-cyclodextrin was confirmed as shown in Fig 2. The taste masking data from human volunteer showed that the bitter taste of pure drug caffeine was significantly masked in physical mixture and kneaded complex of caffeine and β-cyclodextrine.

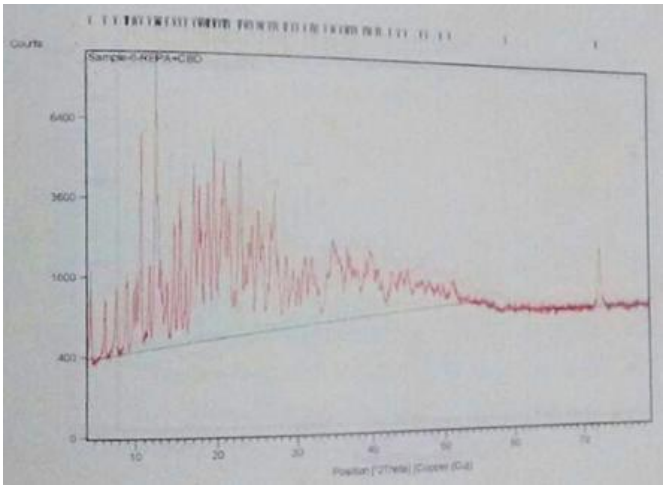

Fig 2. X-Ray Diffraction study data of caffeine and β-cyclodextrine complex.

CONCLUSION:

It could be concluded that the physical mixture and kneaded complex of caffeine and β-cyclodextrin significantly masked the bitter taste of caffeine. The physical mixture and kneaded complex of caffeine and β-cyclodextrin considerably increased the solubility as well as dissolution profile of caffeine. Thus caffeine and β-cyclodextrin complex could be successfully used in suitable dosage form as CNS stimulant in state of persistent depression.

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