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Effect of Recrystallization on Size, Shape, Polymorph and Dissolution of Carbamazepine

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ABSTRACT : The recrystallization of carbamazepine was done by using two solvents and at different cooling conditions. The solvent and cooling conditions could modify the size, shape, polymorph and thereby the dissolution of original drug. The crystal shape of original carbamazepine was flaky or thin plate like. In the present work carbamazepine crystals were modified by using ethanol and acetone under four different cooling conditions. DSC study showed a change in the polymorphs under different conditions of cooling. The samples recrystallized from ethanol and acetone solutions as well as the original CBZ samples exhibited identical IR spectra, indicating that there was no change at the molecular level. A study indicated that the size, shape and the type of polymorphs in the sample effect its dissolution behaviour.

KEYWORDS: Carbamazepine, recrystallization, crystals, polymorphs, dissolution, IR spectra

INTRODUCTION

Optimal drug dissolution is crucial to the success of oral drug therapy. Slow dissolution has frequently been correlated with poor or erratic performance of oral dosage forms *in vivo*, and drugs of low aqueous solubility provide a major challenge to the designer of modern oral dosage forms[1].

Carbamazepine is used as first line monotherapy for seizures in elderly patients. The major advantages of carbamazepine include proven efficacy and less cost[2]. Carbamazepine is reported to have cognitive and behavioural advantages over other antiepileptic drugs[3]. Because of the problem with solubility, gastrointestinal absorption of carbamazepine in man is slow. Carbamazepine is insoluble in aqueous solutions, behaving as a neutral lipophilic substance and absorption may be unpredictable[4].

The crystallization technique can change the crystal properties such as habit, polymorphism and size. The nature and extent of these changes depend on the crystallization conditions including type of solvent and cooling rate as well as the presence of impurities[5].

Different crystal forms of the analgesic drug ibuprofen were prepared and characterized. Various conditions were used for the crystallization: like solvent change method, the temperature change methods, and solvent evaporation methods. Crystals were grown from different solvents. Different crystal forms with different properties were observed: cubic, needle shaped, and plate-shaped crystals were obtained. Flowability of these spherical crystals is increased. All were found to be isomorphic by DSC and X-ray analysis [6].

Spherically agglomerated crystals of tranilast (oral antiallergic agent) with improved availability *in vitro*, as well as improved micrometric properties such as flowability and pack ability, could be prepared by novel spherical crystallization technique. The agglomerates of tranilast were found to be composed of new monohydrate I, II or III, depending on the crystallization solvent and the procedure employed. With dehydration by heating, monohydrate I transformed to the stable 'a' from directly. On the other hand, monohydrates II and III converted to the amorphous and 'b' forms, respectively, followed by further transformation to the 'a' form at 110 and 150^{0}C. The amorphous and 'b' forms of agglomerates were easily prepared by storing the monohydrates under 0% RH at 30-40^{0}C. Monohydrate II and the amorphous form of the agglomerates with high surface energy could enhance the solubility and the dissolution rate of tranilast. A phase diagram of polymorphs of agglomerated tranilast

was constructed to exhibit their inter conversions under various humidities and temperatures[7].

Different polymorphs of a given compound are, different in structure and properties as the crystals of two different compounds. Solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapour pressure and stability etc., all vary with polymorphic form. In general, it should be possible to obtain various crystalline forms of a drug with different performance properties for that compound. Extensive studies on polymorphism have been conducted on steroids, barbiturates, antihistaminics and sulfonamides[8].

In the present study carbamazepine crystals were modified by using different solvents and different cooling conditions. New crystals were studied for their size, shape, polymorphism and dissolution behaviour on compression into tablet.

MATERIALS AND METHODS

Materials

Carbamazepine was provided by Amoli Organics Ltd, Mumbai, Lactose, Starch, Polyvinylpyrrolidone and methanol were procured from Merk Specialities Pvt Ltd. Mumbai, Magnesium stearate, Ethanol and Acetone were procured from Nice Chemicals, Mumbai. Sodium Cross carmellose was procured from Natinal Chemicals,Mumbai.

METHOD

Recrystallization with Ethyl alcohol (ethanol)

3 grams of carbamazepine in four sets were dissolved in 30ml of ethanol at 65^0C in a 100ml beaker. Then the solutions were treated under different conditions as follows.

1. The solution was immediately transferred to freezer (CBZ-1).
2. The solution after reaching room temperature, stored in freezer(CBZ-2).
3. The solution was kept at room temperature (CBZ-3).
4. The solution was rapidly added to 900 ml of cold water stirred well and then left at room temperature (CBZ-4).The precipitated crystals from above methods were collected after 48 h by filtration and dried at 60^0C for 30 min and stored in a desiccator at room temperature.

Recrystallization with Acetone

3 grams of carbamazepine in four sets were dissolved in 30ml of acetone at 40^0C in a 100 ml beaker. Then the solutions were treated under different conditions similar to ethanol recrystallization as mentioned above. The precipitated crystals from above methods 1, 2, 3 and 4 [PA-1, PA-2, PA-3 and PA-4] were collected after 48 h by filtration and dried at 40^0C for 30 min and stored in a desiccator at room temperature.

Morphology and particle size analysis by Microscopic method

Particle size analysis was done by bright field microscopy method and Volume Surface diameters of recrystallized samples were calculated.

Differential scanning Calorimetry (DSC)

DSC thermograms of original drug and the recrystallized samples were recorded by a thermal analysis system by using DSC-60 from Shimadzu Corporation, Japan. The samples were placed in aluminium pans and were crimped, followed by heating under nitrogen flow (30 ml/min) at a scanning rate of 5^o/min from 25^o to 300^oC. Aluminium pan containing same quantity of indium was used as reference. The heat flow as a function of temperature was measured for both the drug and recrystallized samples.

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectroscopy was conducted using a Shimadzu FTIR 8300 Spectrophotometer and the spectrum was recorded in the region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample in KBr (200-400 mg) and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained. Spectra were recorded for each of the samples.

Preparation of tablets from recrystallized carbamazepine

The carbamazepine tablets from recrystallized samples were prepared by wet granulation method. Composition is shown in Table no. 1.The drug and excipients (CBZ+ Lactose+ 1% Croscarmellose sodium) were blended. Granulation was carried out by adding 5% starch paste slowly until a damp mass was formed. The mass was forced through sieve no 12, and the granules obtained were spread in hot air oven & dried at 50^0 for 4 hr. After drying the granules were passed through 22/44 # .The granules retained on 44# were mixed with 15% of fines. The dried granules were mixed with 2% croscarmellose and then lubricated, using 2% magnesium stearate. The tablets were compressed using single punch tablet compression machine.

Dissolution studies

The dissolution of carbamazepine tablets was studied using USP apparatus No. 2. The tablet sample containing 200 mg of drug was added to 900 ml of distilled water as dissolution medium. The mixture was stirred at 100 rpm at 37±0.5^{o}C. 1 ml samples were withdrawn at predetermined time intervals, diluted to 10ml and assayed at 285 nm on the spectrophotometer.

Study of release rate kinetics[9]

Different kinetic models (zero-order, first-order, Higuchi's equation and Korsmeyer's equation) were applied to interpret the drug release kinetics from matrix system with the help of Equations 1-4.

$$M_t = M_0 + k_0 t \quad \text{(1)}$$

$$Ln\, M_t = ln\, M_0 + k_1 t \quad \text{(2)}$$

$$M_t = M_0 + k_H t^{1/2} \quad \text{(3)}$$

$$M_t/M_\alpha = k_k t^n \quad \text{(4)}$$

In these equations, M_t is the cumulative amount of drug released at any specified time point and M_0 is the dose of the drug incorporated in the delivery system. k_0, k_1, k_H and k_k are rate constants for zero order, first order, Higuchi and Korsmeyer's model respectively. For the

same number of parameters, the coefficient of correlation (R^2) can be used to determine the best of the model equations.

Stability Studies

Accelerated Stability study as per ICH guidelines (for a new dosage form) at $40^0 \pm 2^0$ / 75 %±5% RH for three months was conducted. The optimized formulations were stored in above mentioned conditions. After definite time intervals they were tested for their physical appearance, percentage drug content, and in vitro dissolution profile. These formulations were tested at time 0 and end of each month for 3 months.

RESULT AND DISCUSSION

Morphology and particle size analysis by Microscopic method

As can be seen (Figure no. 1) the crystal shape of carbamazepine (original sample) was flaky or thin plate like with even edges. The crystals obtained from ethanol by methods 1,2 and 3 were polyhedral or hexagonal prisms (Figure no. 2a,b,c),where as, those prepared by method 4 were acicular or needle like (Figure no. 2d).The crystals obtained from acetone by methods 1,2 and 3 show thin plate like shape with irregular edges (Figure no. 3a,b,c) , those by method 4 were needle shaped (Figure no.3d).

It can be concluded that the crystal size generally decreases at fast cooling due to incomplete growth of a large number of small crystals (Table no.2). The difference in the shapes of the crystals from ethanol and acetone can be due to interaction between solvent and drug.

DSC (Differential Scanning Calorimetry)

DSC (Differential Scanning Calorimetry) thermograms for the samples recrystallized from each solvent system at different conditions are shown in Figure no.4 & 5. The DSC thermograms of CBZ-1, CBZ-2, CBZ-4, PA-1, PA-2, and PA-3 showed two endotherms, one at higher melting point (Form I)and another at lower melting point (Form III). Carbamazepine exhibits enantiotropic polymorphism and there exists a transition temperature below the melting point of either of the polymorphs at which both these forms have the same free energy. Above the transition temperature, the higher melting Form I has lower free energy and is more stable. Below the transition temperature, however, the lower melting Form III is more stable since it has the lower free energy. The transition temperature of carbamazepine enantiotropic forms has been reported to be around 71^0C (Behme and Brooke, 1991).Hence at room temperature, Form III is the most stable form. Therefore the formulation containing CBZ-1, CBZ-2, CBZ-4, PA-1, PA-2, and PA-3 possess the most stable carbamazepine enantiomer (Form III).

IR spectra

Comparison of FT-IR spectrum of original drug with that of crystallized carbamazepine (figure no.6&7) did not reveal any distinctive changes. Both original and crystallized carbamazepine powders except CBZ-4 and PA-4 exhibited identical FT-IR spectra with absorption bands at 3466 cm^{-1} & 3161 cm^{-1} (-N-H stretching), 1677 cm^{-1} (-C=O stretching), 1605 and 1593 cm^{-1} (range of -C=C- and –C=O vibration and -NH deformation (Table no 3) . In CBZ-4 and PA-4 the shift of the peak towards lower wave number from 3466.20 cm^{-1} to 3439.19 $cm^{-1}$is due to hydrogen bonding between the free -NH of CBZ and the oxygen of water[129].As cold water is added in the process of recrystallization of the samples CBZ-4 and PA-4, it interacts through strong hydrogen bonds with the carbamazepine amide group, thereby altering the IR peaks corresponding to –NH valence vibration.The spectral differences between the polymorphs were only too subtle to differentiate the different polymorphs by FTIR indicating that there are not any changes at the molecular level.

Dissolution Studies

The dissolution profiles of carbamazepine crystals obtained from both the solvents are shown in Figure no.8-11. The lowest dissolution rate was observed for tablets prepared by crystals obtained by method 3 (CBZ-3 and PA-3).Crystals obtained by method 4 from either ethanol or acetone (CBZ-4 and PA-4) showed the highest dissolution rate (Table no.4). The results indicate particle size may significantly affect dissolution and thereby oral absorption of carbamazepine. The release profile of tablets from CBZ-3, PA-1, PA-2, PA-3 and PA-4 matches with release data of marketed product. In addition the release profiles of PA-2 and PA-3 satisfy the release requirement of USP as shown in Table no.4.

The formulation containing CBZ-1, CBZ-2, CBZ-4, PA-1, PA-2, and PA-3 possess the most stable carbamazepine enantiomer (Form III) compared to tablets from CBZ-3 and PA-4 containing only Form I isomer which is unstable at room temperature due to the higher free energy. The optimized formulation PA-2 and PA-3 contains stable carbamazepine enantiomer.

Release rate kinetics:

High values of correlation coefficient (R^2: 0.9150-0.9915) were obtained when fitted to Higuchi equation compared to first order, zero order and Korsmeyer equations (Table no.5). From these results, the Higuchi model seems the best-fitted model, which indicates a dissolution-controlled release.

Stability Studies of Optimized formulation

From the results shown in Table no.6 & 7, it can be inferred that the physical appearance of the tablets, remained unchanged at the end of 1st, 2nd & 3rd month. There is slight fall in the dissolution profile, slight increase in the friability, hardness and disintegration time. But since the change in the profile is within the limits it can be concluded that the tablets were stable during the stability study.

Table no.1: Composition of Carbamazepine tablet

Ingredients	Quantity/tablet (mg)
Carbamazepine	200
Lactose	100
Starch paste 5%	Quantity sufficient
Croscarmellose sodium 1%+2% (intra-and extra granularly)	2 + 4
Magnesium Stearate 2%	4

Table no.2: Effect of recrystalizing solvents on Particle size of carbamazepine

Sample(Ethanol)	Particle size (µm)	Sample(Acetone)	Particle size (µm)
CBZ-1	246.04	PA-1	299.11
CBZ-2	276.13	PA-2	348.72
CBZ-3	297.67	PA-3	391.60
CBZ-4	199.05	PA-4	274.29

Table no .3: FTIR wave numbers of different recrystallized samples of carbamazepine

Samples	FTIR Wave numbers (cm^{-1})
CBZ(Original)	3466.20, 3161.43, 1678.13, 1604.83, 1595.18
CBZ-1	3466.20, 3161.43, 1676.20, 1604.83, 1595.18
CBZ-2	3466.20, 3161.43, 1678.13, 1604.83, 1595.18
CBZ-3	3466.20, 3161.43, 1678.13, 1604.83, 1595.18
CBZ-4	3439.19, 3192.30, 1683.91, 1606.91, 1595.18
PA-1	3466.20, 3161.43, 1676.20, 1604.83, 1595.18
PA-2	3466.20, 3161.43, 1676.20, 1604.83, 1595.18
PA-3	3466.20, 3161.43, 1676.20, 1604.83, 1595.18
PA-4	3439.19, 3194.23, 1683.91, 1606.76, 1595.18

Table no.4: Comparison of release from different formulations of carbamazepine

Formulations	% Release in 3 h	% Release in 6 h	% Release in 12 h	Particle size(µm)
USP	10-35	35-65	65-90	—
CBZ-N	47.13	58.79	80.95	—
PA-1	42.89	59.32	80.99	299.11
PA-2	30.99	48.87	85.43	348.72
PA-3	31.11	44.26	82.71	391.60
PA-4	47.46	57.65	78.92	274.29
CBZ-1	54.49	64.60	86.66	246.04
CBZ-2	50.71	54.76	85.96	276.13
CBZ-3	47.55	66.362	84.2	297.67
CBZ-4	59.17	69.96	86.22	199.05

Table no.5: Kinetic Values Obtained from Different Plots of optimized formulation.

Tablets	Korsmeyer plot			Higuchi plots.		First order plots	Zero order plots.
	K	n	R^2	K	R^2	R^2	R^2
45#	20.1429	0.5377	0.453	19.713	0.9559	0.9245	0.8176
60#	19.2885	0.6016	0.524	24.330	0.9915	0.9864	0.9023
CBZ-3	20.7778	0.5561	0.472	23.084	0.9802	0.9581	0.8767
PA-1	18.5225	0.5778	0.509	22.516	0.9873	0.9797	0.9256
PA-2	19.3865	0.4826	0.403	21.785	0.9150	0.9035	0.9563
PA-3	9.93573	0.8392	0.777	24.958	0.9591	0.9492	0.9827
PA-4	10.4303	0.8997	0.784	26.414	0.9777	0.9818	0.9175

K→ rate constant, R→ correlation coefficient, n→ Slope

Table no.6: Stability study data of PA-2

Test	Initial	1 month	2 months	3 months
Friability %	0.49	0.58	0.68	0.79
Disintegration time(min)	5.3	6	7.5	8.2
Hardness(KP)	4.5	4.9	5.5	6.7
%Dissolution in 12 hrs	85.43%	82.12%	80.38%	78.18%
Appearance	NCA*	NCA*	NCA*	NCA*

NCA*→ No change in the appearance

Table no.7: Stability study data of PA-3

Test	Initial	1 month	2 months	3 months
Friability %	0.68	0.68	0.81	0.87
Disintegration time(min)	5.0	5.9	7.4	8
Hardness(KP)	4.5	4.9	5.5	6.7
%Dissolution in 12 hrs	82.71%	79.81%	77.21%	75.6%
Appearance	NCA*	NCA*	NCA*	NCA*

NCA*→ No change in the appearance

Figure no.1: Morphology of carbamazepine (Pure sample)

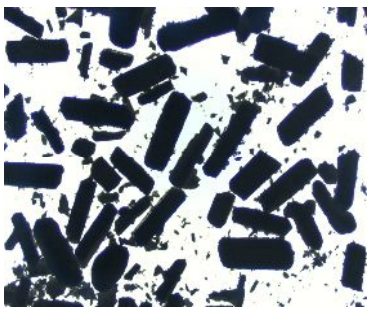
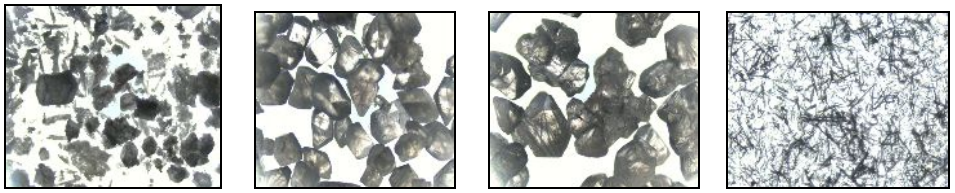


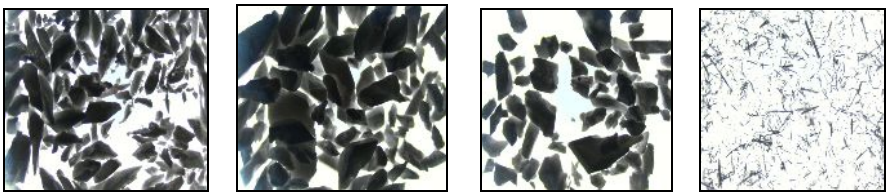
Figure no. 2: Morphology of recrystallized sample of carbamazepine from ethyl alcohol



a b c d

a-CBZ-1; b-CBZ-2; c-CBZ-3;d-CBZ-4

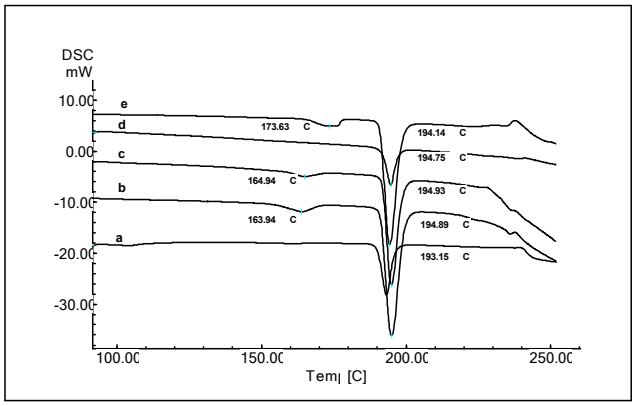
Figure no. 3: Morphology of recrystallized sample of carbamazepine from acetone



a b c d

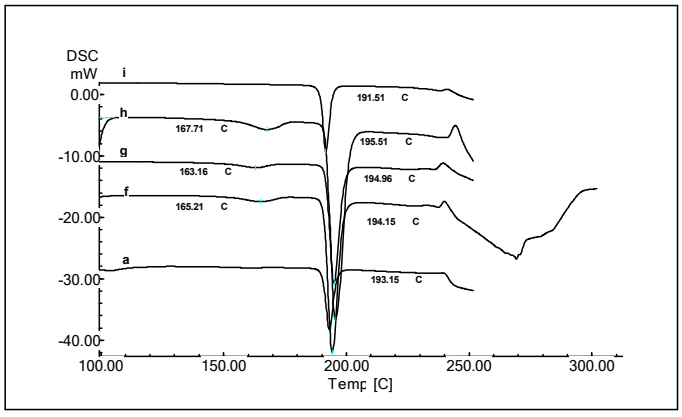
a-PA-1; b-PA-2;c-PA-3;d-PA-4

Figure no.4: DSC thermograms of crystals of carbamazepine from ethyl alcohol



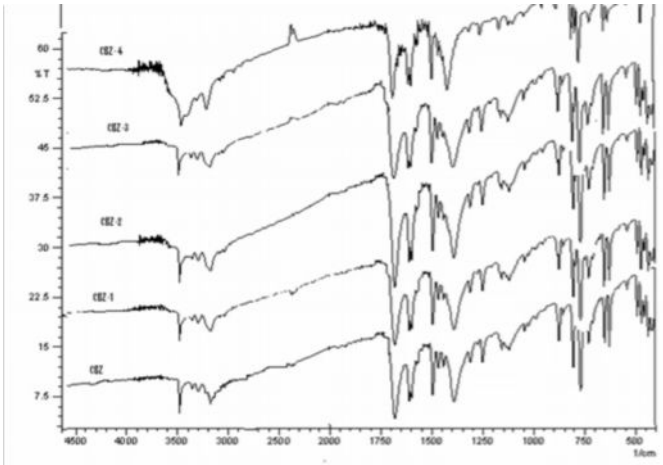
a-CBZ (original), b-CBZ-1, c-CBZ-2,d-CBZ-3, e-CBZ-4

Figure no.5: DSC thermograms of crystals of carbamazepine from acetone



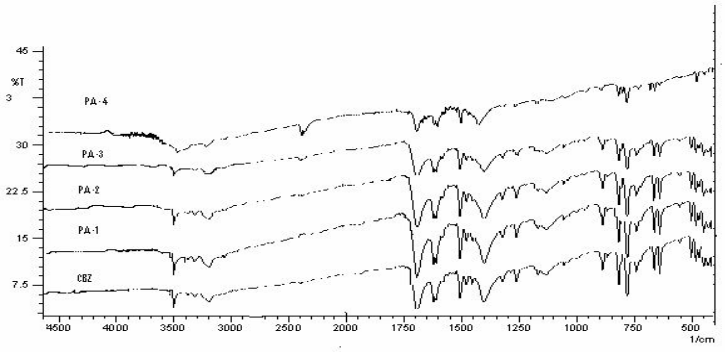
a-CBZ (pure), f-PA-1, g-PA-2, h-PA-3, i-PA-4

Figure no.6: Comparison of IR spectrum of crystals from Ethyl alcohol with original sample



CBZ → pure sample, CBZ-1 → Crystals from method 1, CBZ-2 → Crystals from method 2,
CBZ-3 → Crystals from method 3, CBZ-4 → Crystals from method 4

Figure no.7: Comparison of IR spectrum of crystals from acetone with original sample



CBZ → Original sample, PA-1 → Crystals from method 1, PA-2 → Crystals from method 2, PA-3 → Crystals from method 3, PA-4 → Crystals from method 4.

Figure no.8: Comparative dissolution study of Tablets containing CBZ-1, CBZ-2 and marketed sample

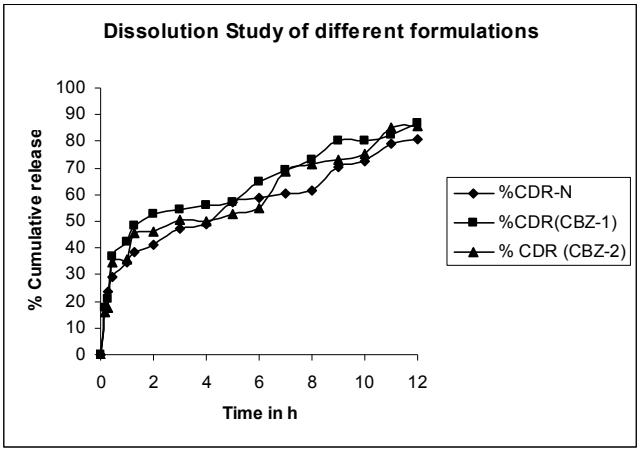


Figure no.9: Comparative dissolution study of Tablets containing CBZ-3, CBZ-4 and marketed sample

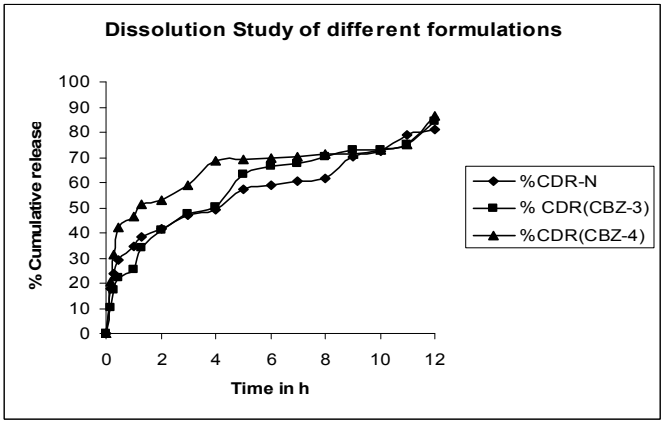


Figure no.10: Comparative dissolution study of Tablets containing PA-1, PA-2 and marketed sample

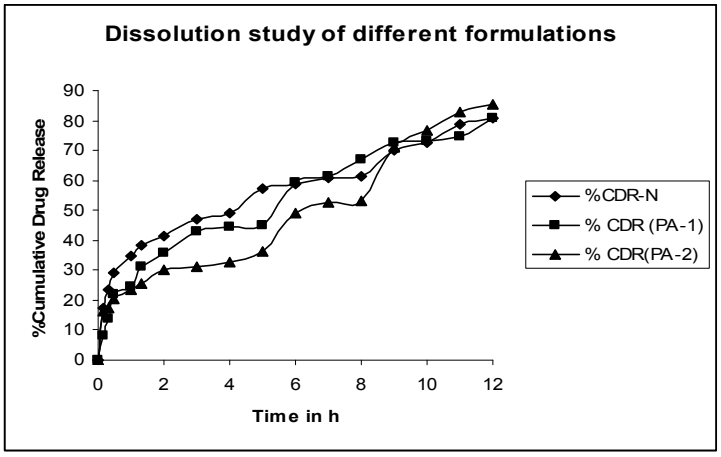
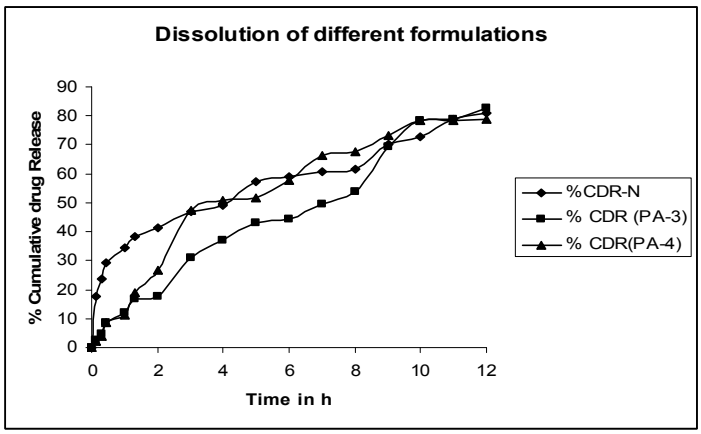


Figure no.11: Comparative dissolution study of Tablets containing PA-3, PA-4 and marketed sample



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