Chapter-7

Thermal Analysis of Urea Inclusion Compounds

7.1 Introduction

Considerable heat evolution is observed during formation of urea inclusion compounds, the magnitude of which provides information about the physicochemical nature of formation. Similarly, urea inclusion compounds are known to decompose endothermally below the melting point of urea, with concurrent change in the crystal lattice of urea and loss in weight. Energetically, the decomposition involves the process (McAdie, 1963):

$$\text{Complex(s)} \longrightarrow \text{urea(s)} + \text{guest(liq.)}$$

The stability of a particular urea inclusion compound also depends on the energetics of the system besides the degree of structural registry between the guest and the host substructures. The energy of formation (E_F) of a urea inclusion compound is an exothermic process. It is a cumulative of the following three energy parameters:

E_L (Lattice energy): It is the difference between the lattice energies of urea molecules in the tetragonal lattice and those in the empty hexagonal lattice (present in the urea inclusion compound) respectively. This component is independent of the physical properties of the guest molecule and thus remains constant.

E_B (Building energy): In the urea inclusion compounds, there is always some vacant space between two successive guest moieties along the urea channel owing to steric constrains and van der Waals interaction between their end groups. Thus there is always some amount of empty space along the urea channel which depends on the length of the encocyte. The longer the molecular chain is, the more of the channel space is occupied and the lesser is the percentage empty space, which is a deciding factor for the urea channel to retain its hexagonal structure.

Ev (Vaporization energy of the guest molecule): This depends on the melting point of the included guest. It is a measure of the energy required to overcome the van der Waals attraction between the guest molecules in the free state so that they can be included in the urea channel.

Thus the second and third factors decide whether or not a certain guest molecule will form a stable urea inclusion complex. E.g. the second factor restricts the lower limit on the number of carbon atoms in the included n-alkane to four while the third factor does not allow n-alkane chains having more than fifty carbon atoms to get included in the urea tunnel as their melting point is then too high.

The increase of heat content on decomposition or the heat of formation of urea inclusion compounds has been determined by various methods and has been found to be closely proportional to the length of carbon main chain of the compound to be included for a homologous series (Zimmerschied *et al*, 1950). Heat of decomposition has been interpreted as due mainly to heat of fusion and difference in energy of hydrogen bonds between urea in the adduct and pure urea (Redlich et al, 1950). Higher value of heat of decomposition can be expected for urea inclusion compounds having a guest molecule possessing longer carbon chain (McAdie, 1963). Thus an estimate of heat of decomposition gives an insight into relative stability of the urea inclusion compound.

7.2 Calorimetric analysis

Determination of minimum amount of RAE required for adduction of a NNAE drug

Determination of minimum ratio of RAE and NNAE for formation of co-inclusion compounds with urea. The procedure comprised of following two stages.

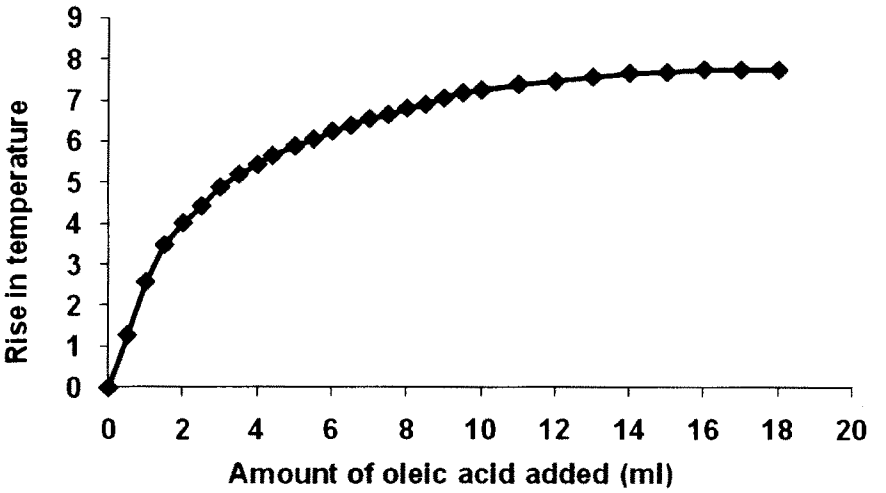
Stage I: *Determination of stoichiometric ratio between urea and endocyte, based upon measurement of temperature rise followed by addition of increments of RAE to methanolic solution of urea in the calorimeter.*

The calorimetric method proposed by Zimmerschield et al for determination of composition of urea adduct was followed employing oleic acid as RAE in urea host (Zimmerschied *et al*, 1950). A small mouthed silver Dewar flask, filled with a rubber stopper bearing a thristle funnel and a probe of thermocouple system, capable of measuring upto 0.01° C , served as calorimeter. 10 g of urea and 25 ml methanol were gently shaken in the calorimeter until equilibrium temperature was observed. Increments of 0.5 ml of oleic acid were successively introduced into calorimeter through thristle funnel. After each addition, calorimeter was shaken gently to hasten attainment of equilibrium temperature, which was then recorded. The results are presented in **Table 7.1.**

Table 7.1 Increase in temperature following addition of oleic acid to methanolic solution of urea.

Cumulative amount of oleic acid added (ml)	Temperature (°C)	Rise in temperature (°C)
0	18.51	0
0.5	19.8	1.29
1	21.2	2.59
1.5	22	3.49
2	22.54	4.03
2.5	22.95	4.44
3	23.41	4.9
3.5	23.27	5.21
4	23.96	5.45
45	24.18	5.67
5	24.41	5.9
5.5	24.58	6.07
6	24.77	6.26
6.5	24.91	6.4
7	25.08	6.57
7.5	25.18	6.6
8	25.34	6.83
8.5	25.43	6.92
9	25.58	7.07
9.5	25.71	7.2
10	25.78	7.27
11	25.92	7.41
12	25.99	7.48
13	26.1	7.59
14	26.2	7.69
15	26.22	7.71
16	26.29	7.78
17	26.29	7.78
18	26.29	7.78

Fig. 7.1 Plot showing increase in temperature following incremental addition of oleic acid to methanolic solution of urea.



From the point of intersection of the lines of extrapolation of the initial rate of temperature rise and final temperature level, the moles of oleic acid reacted with the amount of urea were calculated. Thus, the minimum amount of RAE, which can be adducted in urea was determined from the inflexion point of the curve and was found to be 2.71g of oleic acid / 10g of urea. The figure correlates well the reported value (2.65; Redlich *et al*, 1950).

Stage II. Determination of minimum ratio of RAE and drug for formation of co-inclusion compounds with urea.

The following procedure was utilized for determination of minimum ratio of RAE and each of all the NNAE drugs for formation of co-inclusion compound with urea.

A modified Zimmerschied calorimetric method (Zimmerschied *et al*, 1950) was based on measurement of temperature rise following addition of increments of RAE to methanolic solution of urea containing excess of the drug. Hence, 10 g urea, 5 g the NNAE drug and 25 ml methanol were shaken in the calorimeter until equilibrium temperature was obtained. Initially increments of 0.1 ml and later increments of 0.5 ml of RAE were successively introduced into calorimeter. The calorimeter was stirred after each addition to facilitate attainment of equilibrium. The equilibrium temperature was then recorded

after each successive addition. A plot of temperature rise vs. amount of RAE revealed the minimum amount of RAE required for formation of co-inclusion compounds of NNAE drug and RAE in urea (Madan, 1994).

The above mentioned procedure was followed for all the NNAE drugs selected in the present study and the results obtained are as follows:

7.2.1 Calorimetric analysis for urea co-inclusion compounds of amiloride hydrochloride (AH)

Increase in temperature on addition of small increments of oleic acid to methanolic solution containing 5 g of AH, 10 g urea and 25 ml methanol as per *Stage II* is presented in **Table 7.2** and data plotted in **Figure 7.2.**

Fig. 7.2 Plot showing increase in temperature following addition of successive increments of RAE to methanolic solution of urea and AH.

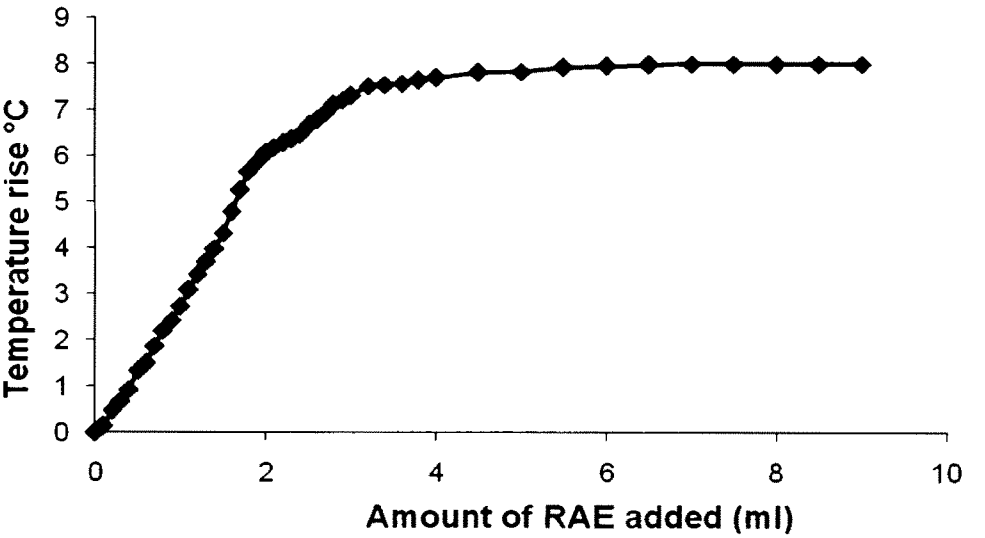


Table 7.2 Calorimetric analysis of urea – amiloride hydrochloride inclusion compounds.

Cumulative amount of oleic acid added (ml)	Temperature (°C)	Rise in temperature (°C)
0	19.43	0
0.1	19.56	0.13
0.2	19.89	0.46
0.3	20.1	0.67
0.4	20.36	0.93
0.5	20.76	1.33
0.6	20.92	1.49
0.7	21.3	1.87
0.8	21.63	2.2
0.9	21.86	2.43
1	22.16	2.73
1.1	22.51	3.08
1.2	22.84	3.41
1.3	23.14	3.71
1.4	23.42	3.99
1.5	23.75	4.32
1.6	24.21	4.78
1.7	24.68	5.25
1.8	25.09	5.66
1.9	25.29	5.86
2	25.49	6.06
2.1	25.61	6.18
2.2	25.71	6.28
2.3	25.79	6.36
2.4	25.89	6.46
2.5	26.1	6.67
2.6	26.21	6.78
2.7	26.36	6.93
2.8	26.54	7.11
2.9	26.64	7.21
3	26.74	7.31
3.2	26.95	7.52
3.4	26.98	7.55
3.8	27.01	7.58
4	27.08	7.65
4.5	27.13	7.7
5	27.24	7.81
5.5	27.26	7.83
6	27.35	7.92
6.5	27.38	7.95
7	27.41	7.98
7.5	27.42	7.99
8	27.42	7.99
8.5	27.42	7.99
9	27.42	7.99
10	27.42	7.99

Determination of minimum ratio of RAE and AH for inclusion of AH in urea

Fig. 7.2 shows an increase in temperature following addition of successive increments of oleic acid to a methanolic solution of urea and AH. While the curve for addition of oleic acid to methanolic solution of urea had a smooth sigmoid shape, in presence of drug the same curve demonstrated the following sequence of events i.e., an initial temperature rise, followed by intermediate final temperature, subsequent temperature rise and then achievement of a final temperature. The second stage of temperature rise is due to displacement of NNAE with RAE as evidenced by the fact that the overall temperature rise is similar to that of RAE alone. The point of intersection of the lines of extrapolation of the initial rate of temperature rise and intermediate final temperature allow calculation of minimum amount of RAE required for adduction of AH in urea.

Stage I: 2.71 g of oleic acid forms adduct with 10 g of urea.

Stage II: From the **Fig. 7.2**, the minimum ratio of RAE: AH for adduction of AH in urea was calculated to be 0.364:1.

On the basis of calculations of the minimum ratio of RAE: AH, urea inclusion compounds containing varying proportion of RAE and drug were prepared as per composition listed in **Table 7.3**. The modification of original Bengen' method was employed for the preparation of different inclusion compounds containing varying proportions of RAE and NNAE. Thus 10 g of finely powdered urea was dissolved in 30 ml methanol by slight heating, followed by addition of first amiloride hydrochloride and then oleic acid, in the amounts as listed in **Table 7.3.**

Table 7.3 Preparation of different urea co-inclusion of amiloride hydrochloride containing varying proportions of RAE and drug.

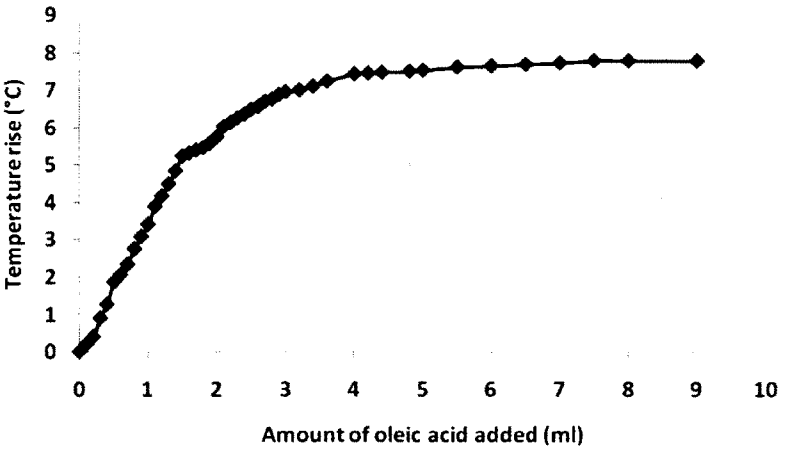
Product	RAE : Drug	AH (g)	RAE (g)
AHIC-1	0.4 : 1	1.43	0.57
AHIC-2	0.6 : 1	1.25	0.97
AHIC-3	0.8 : 1	1.11	0.89
AHIC-4	1 : 1	1	1
AHIC-5	1.2 : 1	0.91	1.09
AHIC-6	1.4 : 1	0.83	1.52

The crystals as obtained were utilized in further investigations.

7.2.2 Calorimetric Analysis for formation of urea co-inclusion compounds of enalapril maleate (EM)

Increase in temperature on addition of small increments of oleic acid to methanolic solution containing 5 g of EM, 10 g urea and 25 ml methanol is presented in **Table 7.4** and data plotted in **Figure 7.3.**

Fig. 7.3 Plot showing increase in temperature following addition of successive increments of RAE to methanolic solution of urea and EM.



Determination of minimum ratio of RAE and EM for inclusion of EM in urea

Fig. 7.3 shows an increase in temperature following addition of successive increments of oleic acid to a methanolic solution of urea and EM. The point of intersection of the lines of extrapolation of the initial rate of temperature rise and intermediate final temperature allow calculation of minimum amount of RAE required for adduction of EM in urea.

Stage I: 2.71 g of oleic acid forms adduct with 10 g of urea.

Stage II: From **Fig. 7.3**, the minimum ratio of RAE: EM for adduction of EM in urea was calculatedto be 0.446:1.

On the basis of calculations of the minimum ratio of RAE: EM, urea inclusion compounds containing varying proportion of RAE and drug were prepared as per composition listed in **Table 7.5**. The modification of original Bengen' method was employed for the preparation of different inclusion compounds containing varying proportions of RAE and NNAE (**Section 6.1**). Thus 10 g of finely powdered urea was

Table 7.4 Calorimetric analysis of urea –enalapril maleate inclusion compounds.

Cumulative amount of oleic acid added (ml)	Temperature (°C)	Rise in temperature (°C)
0	16.99	0
0.1	17.09	0.2
0.2	17.39	0.4
0.3	17.89	0.9
0.4	18.26	1.27
0.5	18.86	1.87
0.6	19.06	2.07
0.7	19.34	2.35
0.8	19.75	2.76
0.9	20.08	3.09
1	20.41	3.42
1.1	20.89	3.9
1.2	21.17	4.18
1.3	21.49	4.5
1.4	21.84	4.85
1.5	22.24	5.25
1.6	22.32	5.33
1.7	22.4	5.41
1.8	22.46	5.47
1.9	22.58	5.59
2	22.75	5.76
2.1	23.03	6.04
2.2	23.14	6.15
2.3	23.26	6.27
2.4	23.36	6.37
2.5	23.49	6.5
2.6	23.56	6.57
2.7	23.7	6.71
2.8	23.76	6.77
2.9	23.88	6.89
3	23.96	6.97
3.2	24.01	7.02
3.4	24.11	7.12
3.6	24.24	7.25
4	24.24	7.45
4.2	24.46	7.47
4.4	24.48	7.49
4.8	24.51	7.52
5	24.54	7.55
5.5	24.62	7.63
6	24.66	7.67
6.5	24.7	7.71
7	24.74	7.75
7.5	24.8	7.81
8	24.8	7.81
9	24.8	7.81

dissolved in 30 ml methanol by slight heating, followed by addition of first EM and then oleic acid, in the amounts as listed in **Table 7.5.** The crystals obtained were utilized in further investigations.

Table 7.5 Preparation of urea co-inclusion compounds of enalapril maleate containing varying proportions of RAE and drug.

Product	RAE : Drug	EM (g)	RAE (g)
EMIC-1	0.45 : 1	1.38	0.62
EMIC-2	0.6 : 1	1.26	0.75
EMIC-3	0.8 : 1	1.12	0.88
EMIC-4	1 : 1	1	1
EMIC-5	1.2 : 1	0.91	1.09

7.2.3 Calorimetric Analysis for urea co-inclusion compounds of glipizide (GLP)

Increase in temperature on addition of small increments of oleic acid to methanolic solution containing 5 g of GLP, 10 g urea and 25 ml methanol is presented in **Table 7.6** and data plotted in **Figure 7.4.**

Fig. 7.4 Plot showing increase in temperature following addition of successive increments of RAE to methanolic solution of urea and glipizide.

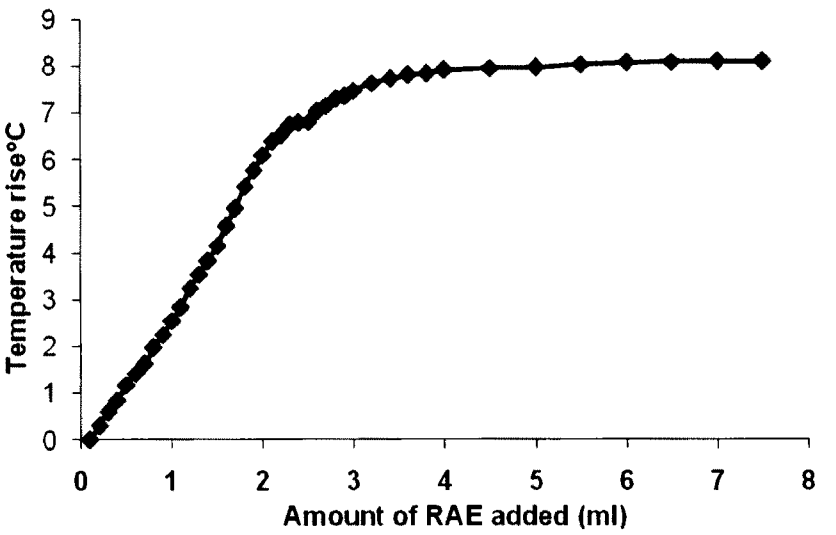


Table 7.6 Calorimetric analysis of urea inclusion compounds of glipizide.

Cumulative amount of oleic acid added (ml)	Temperature (°C)	Rise in temperature (°C)
0	23.91	0
0.1	24.21	0.2
0.2	24.35	0.44
0.3	24.51	0.6
0.4	24.76	0.85
0.5	25.08	1.17
0.6	25.32	1.41
0.7	25.53	1.62
0.8	25.87	1.96
0.9	26.16	2.25
1	26.45	2.54
1.1	26.74	2.83
1.2	27.16	3.25
1.3	27.45	3.54
1.4	27.74	3.83
1.5	28.05	4.14
1.6	28.48	4.57
1.7	28.87	4.96
1.8	29.34	5.43
1.9	29.67	5.76
2	30.01	6.1
2.1	30.29	6.38
2.2	30.42	6.51
2.3	30.64	6.73
2.4	30.7	6.79
2.5	30.71	6.8
2.6	30.93	7.02
2.7	31.06	7.15
2.8	31.2	7.29
2.9	31.26	7.35
3	31.38	7.47
3.2	31.54	7.63
3.4	31.63	7.72
3.6	31.71	7.8
3.8	31.75	7.84
4	31.83	7.92
4.5	31.86	7.95
5	31.88	7.97
5.5	31.95	8.04
6	31.98	8.07
6.5	32	8.09
7	32.01	8.1
7.5	32.01	8.1
8	32.01	8.1

Determination of minimum ratio of RAE and GLP for inclusion of GLP in urea

Fig. 7.4 shows an increase in temperature following addition of successive increments of oleic acid to a methanolic solution of urea and GLP. The point of intersection of the lines of extrapolation of the initial rate of temperature rise and intermediate final temperature allow calculation of minimum amount of RAE required for adduction of GLP in urea.

Stage I: 2.71 g of oleic acid forms adduct with 10 g of urea.

Stage II: From **Fig. 7.4,** the minimum ratio of RAE: GLP for adduction of GLP in urea is found to be 0.95:1.

On the basis of calculations of the minimum ratio of RAE: GLP, urea inclusion compounds containing varying proportion of RAE and drug were prepared as per composition listed in Table 7.6. The method employed for the preparation of different inclusion compounds was same as that mentioned in **Section 6.1**. Thus 10 g of finely powdered urea was dissolved in 30 ml methanol by slight heating, followed by addition of first EM and then oleic acid, in the amounts as listed in **Table 7.7.** The crystals obtained were utilized in further investigations.

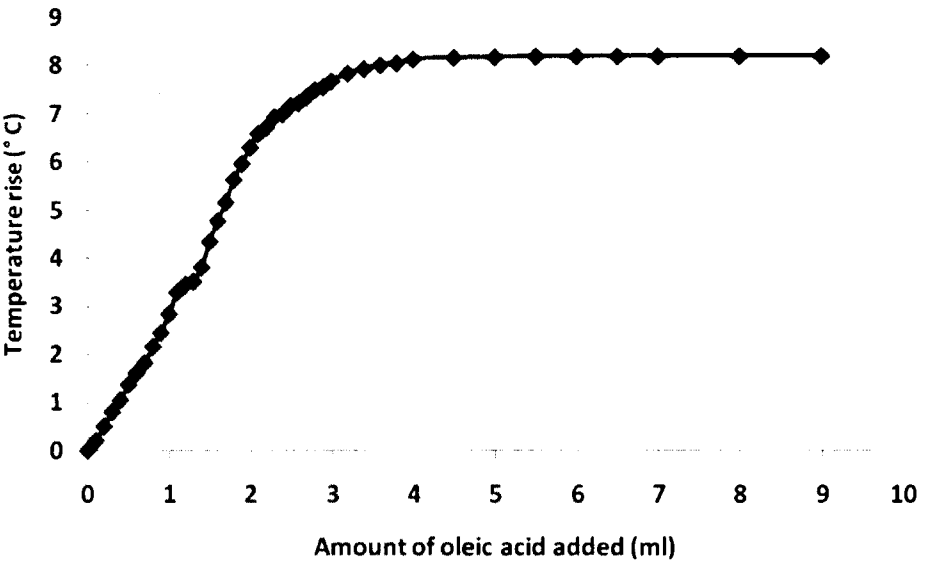
Table 7.7 Preparation of different urea co-inclusion compounds of glipizide containing varying proportions of RAE and drug.

Product	RAE : Drug	GLP (g)	RAE (g)
GLPIC-1	1 : 1	1	1
GLPIC-2	1 : 0.8	0.89	1.11
GLPIC-3	1 : 0.6	0.75	1.25
GLPIC-4	1 : 0.4	0.57	1.43
GLPIC-5	1 : 0.2	0.33	1.82

7.2.4 Calorimetric Analysis for urea co-inclusion compounds of *Cis*-RA

Increase in temperature on addition of small increments of oleic acid to methanolic solution containing 5 g of *cis*-RA, 10 g urea and 25 ml methanol is presented in **Table 7.8** and data plotted in **Figure 7.5.** The entire experiment was performed in subdued light.

Fig. 7.5 Plot showing increase in temperature on addition of small increments of RAE to methanolic solution of urea and *cis*-RA.



Determination of minimum ratio of RAE: cis-RA

On the basis of results obtained in the above experiment, minimum amount of RAE required for adduction of drug is calculated as follows:

Stage I: 2.71 g of RAE forms adduct with 10 g of urea.

Stage II: The minimum ratio of RAE: *cis*-RA required for adduction of *cis-RA* in urea was calculated to be 0.392 : 1.

On the basis of calculations of minimum ratio of RAE: drug, urea inclusion compounds containing varying proportion of RAE and drug were prepared (**Table 7.9**) and utilized in further investigations.

Table 7.8 Calorimetric acnalysis of urea inclusion compounds of *cis*-RA.

Cumulative amount of oleic acid added (ml)	Temperature (°C)	Rise in temperature (°C)
0	23.71	0
0.1	23.91	0.2
0.2	24.21	0.5
0.3	24.51	0.8
0.4	24.76	1.05
0.5	25.08	1.37
0.6	25.32	1.61
0.7	25.53	1.82
0.8	25.87	2.16
0.9	26.16	2.45
1	26.55	2.84
1.1	26.94	3.23
1.2	27.16	3.45
1.3	27.3	3.59
1.4	27.74	4.03
1.5	28.05	4.34
1.6	28.48	4.77
1.7	28.87	5.16
1.8	29.34	5.63
1.9	29.67	5.96
2	30.01	6.3
2.1	30.29	6.58
2.2	30.42	6.71
2.3	30.64	6.93
2.4	30.7	6.99
2.5	30.87	7.16
2.6	30.93	7.22
2.7	31.06	7.35
2.8	31.2	7.49
2.9	31.26	7.55
3	31.38	7.67
3.2	31.54	7.83
3.4	31.63	7.92
3.6	31.71	8.0
3.8	31.75	8.04
4	31.83	8.12
4.5	31.86	8.15
5	31.87	8.16
5.5	31.88	8.17
6	31.88	8.17
6.5	31.88	8.17
7	31.88	8.17
8	31.88	8.17
9	31.88	8.17

Table 7.9 Preparation of different urea co-inclusion compounds containing varying proportions of *cis*-RA and RAE.

Product	RAE : Drug	*Cis*-RA (g)	RAE (g)
UIOA-1	0.4 : 1	1.42	0.58
UIOA-2	0.6: 1	1.25	0.75
UIOA-3	0.8 : 1	1.11	0.89
UIOA-4	1 : 1	1	1
UIOA-5	1.4 : 1	0.83	1.17
UIOA-6	1.8 : 1	0.71	1.29

7.2.5 Calorimetric analysis for urea co-inclusion compounds of nicorandil (NRD)

Increase in temperature on addition of small increments of oleic acid to methanolic solution containing 5 g of NRD, 10 g urea and 25 ml methanol is presented in **Table 7.10** and data plotted in **Figure 7.6.**

Fig. 7.6 Plot showing increase in temperature on addition of small increments of RAE to methanolic solution of urea and nicorandil

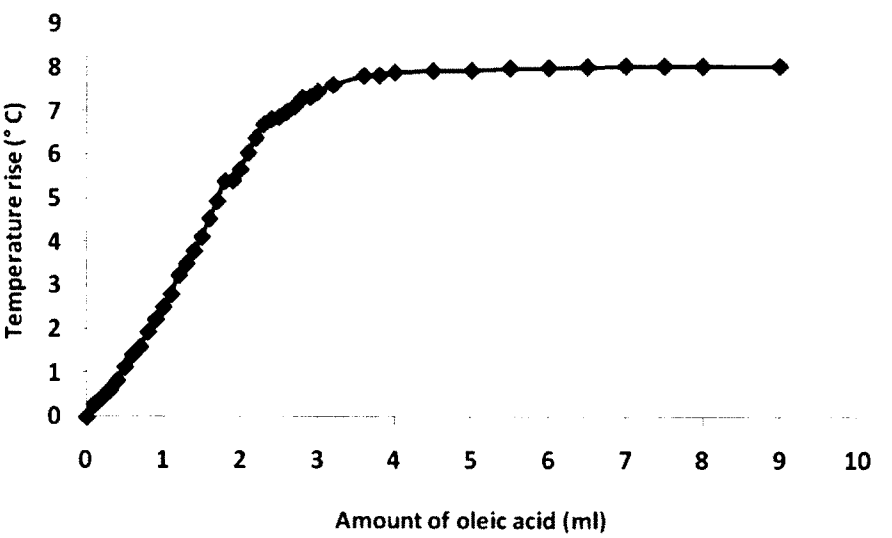


Table 7.10 Calorimetric analysis of urea inclusion compounds of nicorandil.

Cumulative amount of oleic acid added (ml)	Temperature (°C)	Rise in temperature (°C)
0	22.71	0
0.1	23.00	0.29
0.2	23.15	0.44
0.3	23.32	0.61
0.4	23.54	0.83
0.5	23.85	1.14
0.6	24.13	1.42
0.7	24.31	1.60
0.8	24.65	1.94
0.9	24.94	2.23
1	25.22	2.51
1.1	25.52	2.81
1.2	25.95	3.24
1.3	26.22	3.51
1.4	26.51	3.80
1.5	26.83	4.12
1.6	27.25	4.54
1.7	27.65	4.94
1.8	28.11	5.4
1.9	28.18	5.47
2	28.36	5.67
2.1	28.76	6.05
2.2	29.10	6.39
2.3	29.41	6.70
2.4	29.53	6.82
2.5	29.48	6.77
2.6	29.70	6.99
2.7	29.82	7.11
2.8	30.02	7.31
2.9	30.04	7.33
3	30.16	7.45
3.2	30.32	7.61
3.6	30.53	7.82
3.8	30.54	7.83
4	30.61	7.90
4.5	30.65	7.94
5	30.66	7.95
5.5	30.71	8.00
6	30.72	8.01
6.5	30.74	8.03
7	30.76	8.05
7.5	30.76	8.05
8	30.76	8.05
9	30.76	8.05

Determination of minimum ratio of RAE : NRD

On the basis of results obtained in the above experiment, minimum amount of RAE required for adduction of drug is calculated as follows:

Stage I: 2.71 g of RAE forms adduct with 10 g of urea.

Stage II: The minimum proportion of RAE: NRD required for adduction of NRD in urea was calculated to be 0.603 : 1.

On the basis of calculations of minimum ratio of RAE:NRD, urea inclusion compounds containing varying proportion of RAE and drug were prepared (**Table 7.11**) and utilized in further investigations.

Table 7.11 Preparation of urea co-inclusion compounds containing varying proportions of RAE and nicorandil.

Product	RAE : Drug	NRD (g)	RAE (g)
NRDIC-1	0.7 : 1	1.18	0.82
NRDIC-2	0.85 : 1	1.08	0.92
NRDIC-3	1 : 1	1	1
NRDIC-4	1.15 : 1	0.98	1.02
NRDIC-5	1.3 : 1	0.87	1.13

7.3 Thermal analysis of urea co-inclusion compounds

Urea, which is known to form stable inclusion compounds with long linear compounds, also forms inclusion compounds with slightly branched molecules. Since formation of inclusion compound is dependent upon linearity of guest component, therefore any increase in branching or decrease in linearity will reduce the propensity of adduct formation. *Since the formation of urea inclusion compounds is exothermic in nature, therefore, their stability is naturally related to heat of decomposition.* Thus, branching of guest molecules leads to not only decrease in the possibility of adduct formation, but also to distortion of host lattice in the event of formation of an adduct. *Any distortion of host lattice will weaken the host structure with a corresponding decrease in the heat of decomposition.*

All the inclusion compounds containing varying proportions of RAE and NNAE drugs were subjected to thermal analysis in order to determine heat of decomposition of the inclusion compounds and to study effect of the relative proportion on stability of the inclusion compounds.

7.3.1 Method

Thermal analysis of all the drugs and their urea co-inclusion crystals was performed using a DSC Q10 V 9.0 (275), Waters Ltd. TA system with a differential scanning calorimeter equipped with a computerized data station. The samples were lightly ground to give finer crystals (which allows for better sample to pan contact). Aluminum pans and lids were used to contain the samples. The mass of the empty pan and lid was determined, the sample added and then the mass was determined again. The pan was then sealed with a press that crimped the lid tightly to the pan.

All samples (~3mg) were heated at scanning rate of 10°C/min from 40 °C to 300 °C/ 200 °C in an atmosphere of nitrogen gas by passing at a flow rate of 60 ml/min. An empty aluminium pan was used as the reference pan. DCS was calibrated using Indium metal with a melting endotherm at 156.89 °C.

7.3.2 Thermal analysis of urea co-inclusion compounds of AH

Results for DSC thermograms of different AHIC adduct containing varying proportions of RAE and AH are summarized in **Table 7.12** and overlay of thermograms is presented in **Fig. 7.7**. In all these thermograms, a low-temperature endotherm corresponding to complex decomposition and to the release of tetragonal urea was observed. Heat of crystalline transition was plotted against quantity of RAE added per g of AH (**Fig. 7.8**).

The plot clearly indicates that an increase in amount of RAE in the adduct, makes the adduct more stable (r^2= 0.996). Since AH is an aromatic moiety with substitutions in the ring, it is presumably too wide to fit inside the hexagonal tunnels formed by urea host. However, in presence of the RAE, AH is assumed to get co-included with RAE. This would in turn lead to local distortion of the urea tunnel structure in the vicinity of aromatic ring, the extent of steric strain on host lattice being proportional to the amount of NNAE incorporated. The same observation was made regarding X-ray diffractogram of AHIC crystals.

Table 7.12 Heat of decomposition of urea inclusion compounds of amiloride hydrochloride containing varying proportions of RAE and drug.

Product	RAE : Drug	Heat of decomposition (J/g)
AHIC-1	0.4 : 1	15.06
AHIC-2	0.6 : 1	20.23
AHIC-3	0.8 : 1	24.57
AHIC-4	1 : 1	30.23
AHIC-5	1.2 : 1	36.99
AHIC-6	1.4 : 1	41.58

Fig. 7.7 DSC thermograms of RAE- AH -Urea co-inclusion compounds containing varying proportions of RAE and AH.

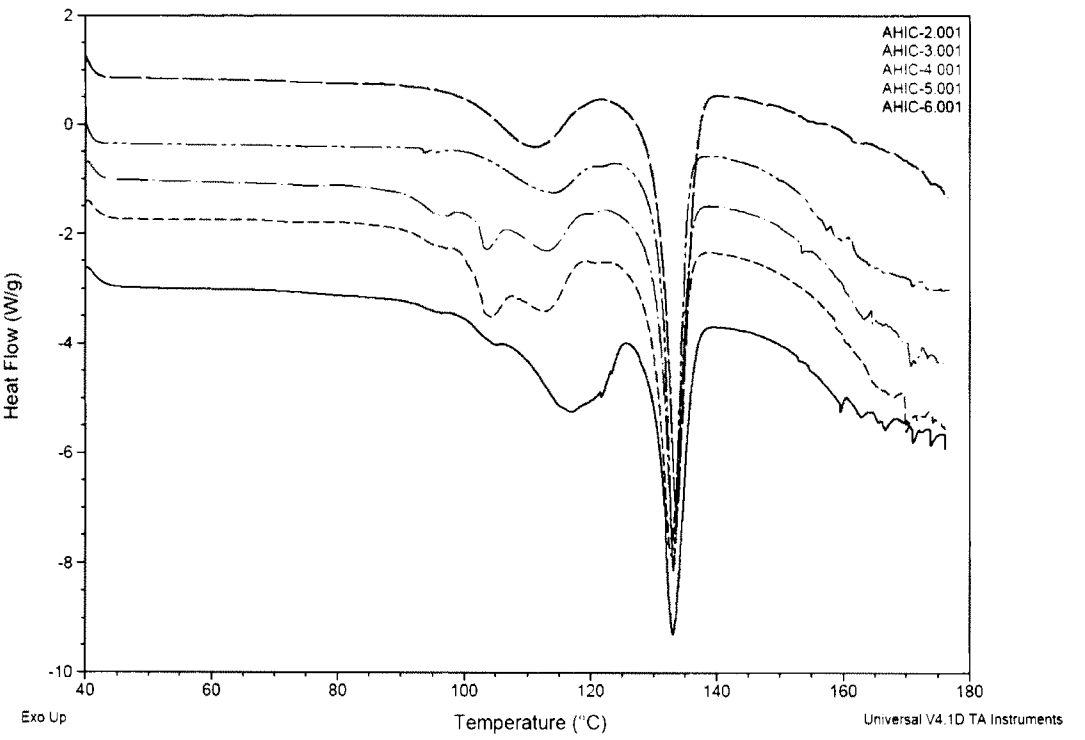
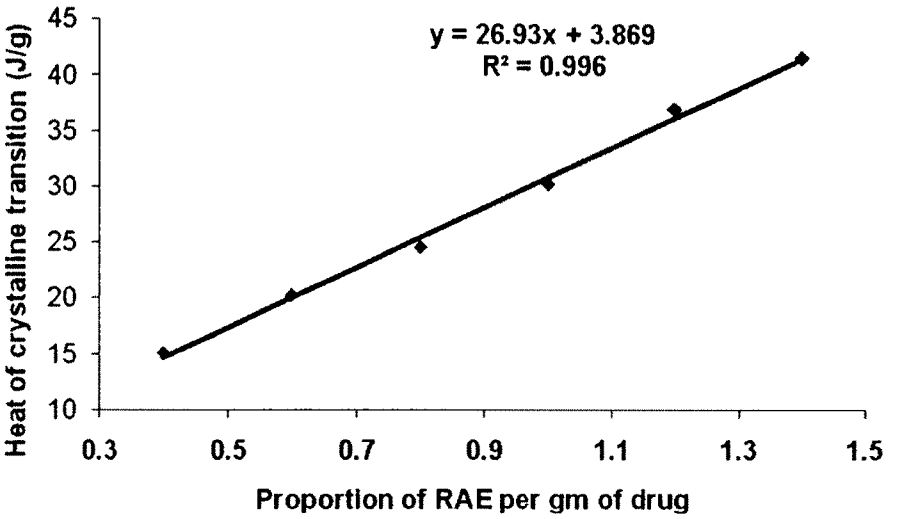


Fig. 7.8 Plot showing change in heat of decomposition for different urea inclusion compounds containing varying proportion of RAE and AH.



7.3.3 Thermal analysis urea co-inclusion compounds of EM

Results for DSC thermograms of different EMIC adduct containing varying proportions of RAE and EM are summarized in **Table 7.13** and overlay of thermograms is presented in **Fig. 7.9**. Heat of crystalline transition was plotted against quantity of RAE added per gram of EM (**Fig. 7.10**).

As evident from **Fig. 7.9**, enalapril melting endotherm at ~ 151°C was absent all the thermograms indicative of absence of the crystalline form of EM. Presence of a low-temperature endotherm in all the thermograms corresponds to the decomposition of hexagonal inclusion compound and to release of guest molecules and solid tetragonal form of urea. Heat of decomposition/ crystalline transition was found to increase linearly with change in quantity of RAE added per g of EM (r^2= 0.969). This clearly reveals that as the amount of RAE in the inclusion compound is increased, heat of crystalline transition increases indicating improved stability of the co-inclusion compound. Formation of urea inclusion compounds is exothermic in nature, which clearly indicates that the resulting compounds are stable. However, substituents in the guest moiety, which do not form part of a linear chain, will naturally lead to distortion and weakening of host structure comprising of narrow channels with consequent decrease in heat of decomposition of urea inclusion compounds. EM having an aromatic moiety with

substitutions in its molecular structure is presumably too wide to accommodate inside the channels formed by urea host. However, in presence of RAE, some proportion of enalapril maleate is included in urea. This is expected to lead to occasional distortions in the host cell in the vicinity of aromatic ring, the extent of steric strain on host lattice being proportionate to the amount of NNAE incorporated. However, distortion of urea host lattice by aromatic groups somewhat weakens the host lattice as evidenced by gradual decrease in heat of decomposition with corresponding increase in relative proportion of drug.

Table 7.13 Heat of decomposition of urea inclusion compounds of enalapril maleate containing varying proportions of RAE and drug.

Product	RAE : Drug	Heat of decomposition (J/g)
EMIC-1	0.45 : 1	23.83
EMIC-2	0.6 : 1	29.95
EMIC-3	0.8 : 1	31.33
EMIC-4	1 : 1	38.29
EMIC-5	1.2 : 1	42.96

Fig. 7.9 DSC thermograms of urea co-inclusion compounds containing varying proportions of RAE and EM.

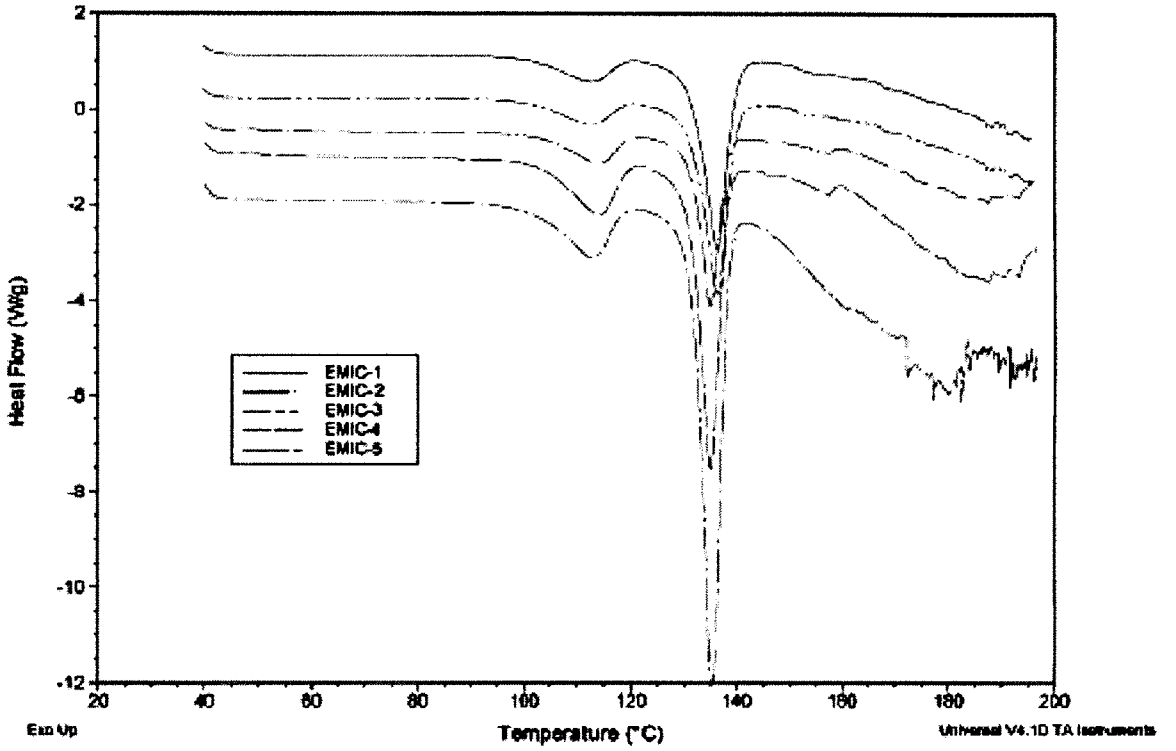
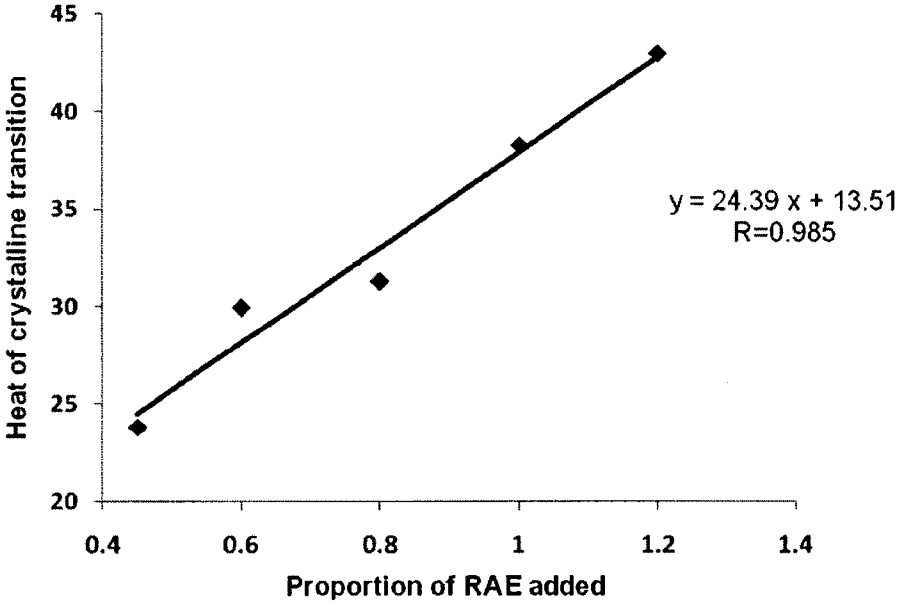


Fig. 7.10 Plot showing change in heat of decomposition for different RAE-EM inclusion compounds containing varying proportion of RAE and EM.



7.3.4 Thermal analysis of urea co-inclusion compounds of GLP

Results for DSC thermograms of different GLPIC adduct containing varying proportions of RAE and GLP are summarized in **Table 7.14** and overlay of thermograms is presented in **Fig. 7.11.**

As evident from **Fig. 7.11**, thermograms of all the inclusion compounds containing varying proportion of GLP and RAE, exhibit a low-temperature endotherm corresponding to collapse of complexed urea was observed and absence of melting endotherm for GLP is also noticeable. **Fig. 7.12** exhibits plot of heat of crystalline transition against proportion of GLP per g of RAE. The plot clearly indicates that as proportion of GLP per unit weight of RAE is increased, the stability of co-inclusion compound reduces (r^2= 0.9461). GLP being a highly substituted aromatic moiety is presumably too wide to fit inside the hexagonal tunnels formed by urea host. However, in presence of RAE, GLP is assumed to get co-included with RAE, which, in turn, would lead to local distortion of the urea tunnel structure in the vicinity of aromatic ring, the extent of steric strain on host lattice being proportionate to the amount of NNAE incorporated.

Table 7.14 Heat of decomposition for urea inclusion compounds of glipizide containing varying proportions of RAE and drug.

Product	RAE : Drug	Heat of decomposition (J/mg)
GLPIC-1	1 : 1	14.42
GLPIC-2	1 : 0.8	20.98
GLPIC-3	1 : 0.6	30.56
GLPIC-4	1 : 0.4	47.71
GLPIC-5	1 : 0.2	48.75

Fig. 7.11 DSC thermograms of glipizide-RAE-Urea co-inclusion compounds containing varying proportions of drug and RAE.

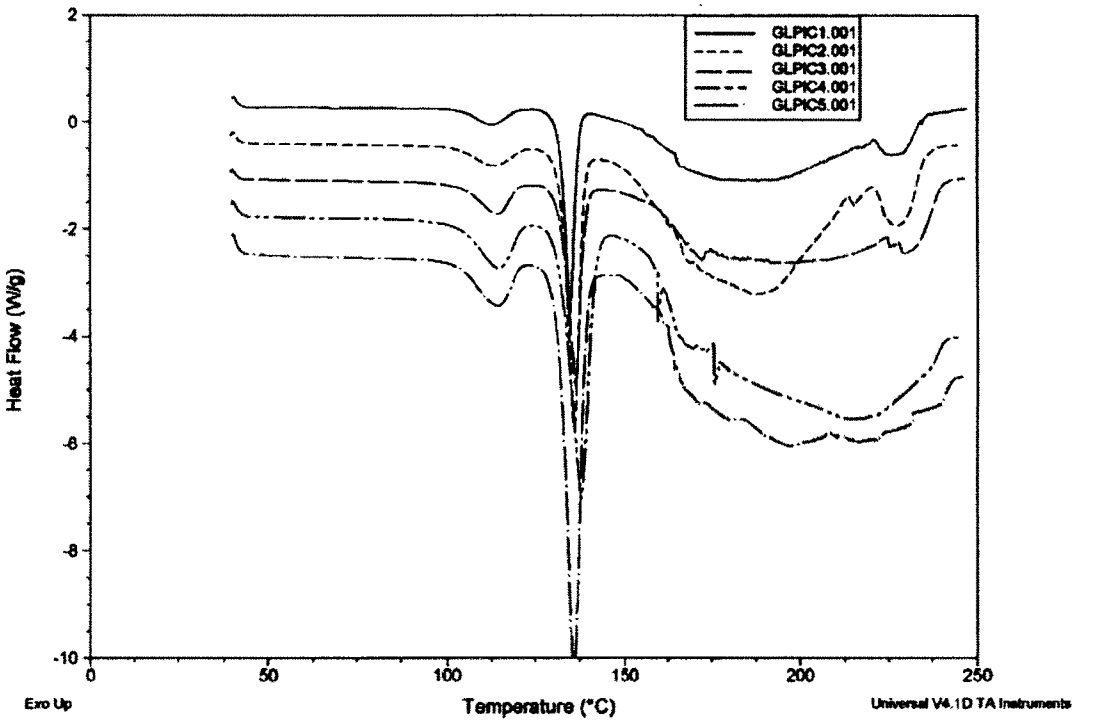
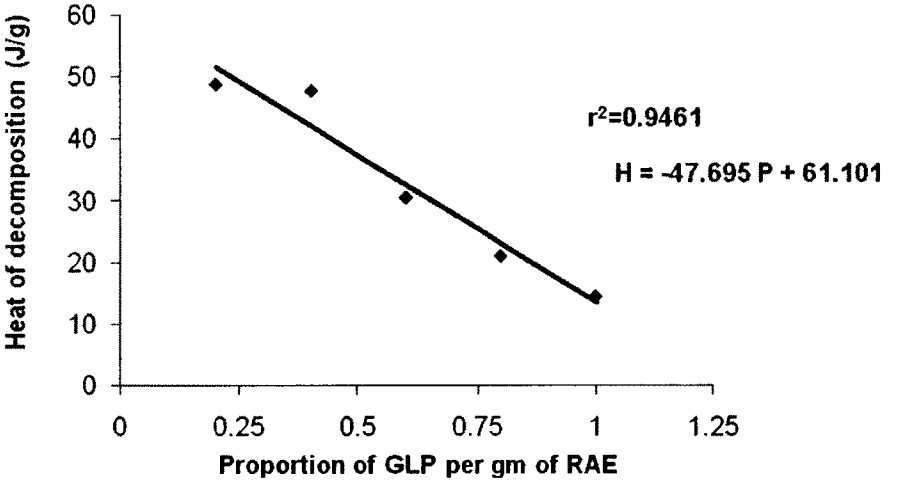


Fig. 7.12 Plot showing change in heat of decomposition for different RAE-glipizide urea inclusion compounds with varying proportion of RAE and glipizide.



7.3.4 Thermal analysis of urea co-inclusion compounds of *cis*-RA

Results for DSC thermograms of different UIOA adduct containing varying proportions of RAE and cis-RA are summarized in **Table 7.15** and overlay of thermograms is presented in **Fig. 7.13**. In all these thermograms, a low-temperature endotherm corresponding to complex decomposition and to the release of tetragonal urea was observed. Heat of crystalline transition was plotted against quantity of RAE added per unit weight of cis-RA (**Fig. 7.14**).

The plot clearly indicates that an increase in amount of RAE in the adduct, makes the adduct more stable (r^2= 0.982). Since *cis*-RA is a cyclic moiety with substitutions in the ring, the cyclohexane ring attached to linear chain in the molecular structure of the drug is presumably too wide to fit inside the hexagonal tunnels formed by urea host. However, in presence of the RAE, *cis*-RA is assumed to get co-included with RAE. This would in turn lead to local distortion of the urea tunnel structure in the vicinity of aromatic ring, the extent of steric strain on host lattice being proportional to the amount of NNAE incorporated. The same observation was made regarding X-ray diffractogram of UIOA crystals.

Table 7.15 Heat of decomposition of urea inclusion compounds of *cis*-RA containing varying proportions of RAE and *cis*-RA.

Product	RAE : Drug	Heat of decomposition (J/g)
UIOA-1	0.4 : 1	23.52
UIOA-2	0.6: 1	25.65
UIOA-3	0.8 : 1	31.47
UIOA-4	1 : 1	36.51
UIOA-5	1.4 : 1	39.27
UIOA-6	1.8 : 1	48.2

Fig. 7.13 DSC thermograms of RAE-*cis*-RA -urea co-inclusion compounds containing varying proportions of drug and RAE.

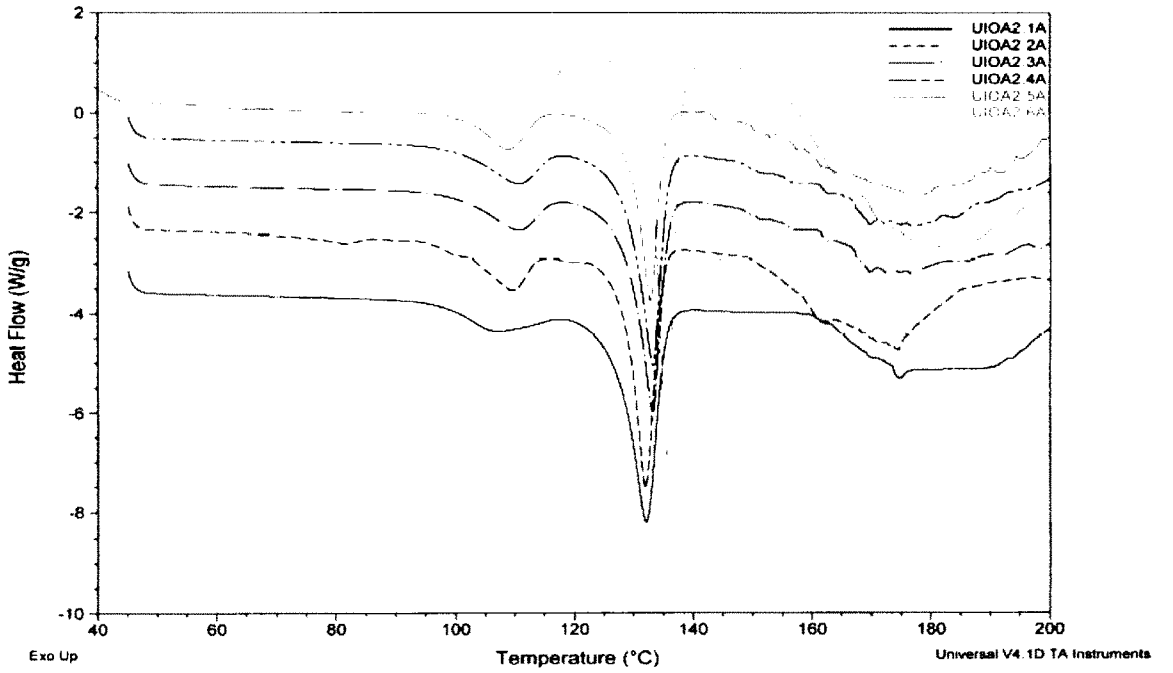
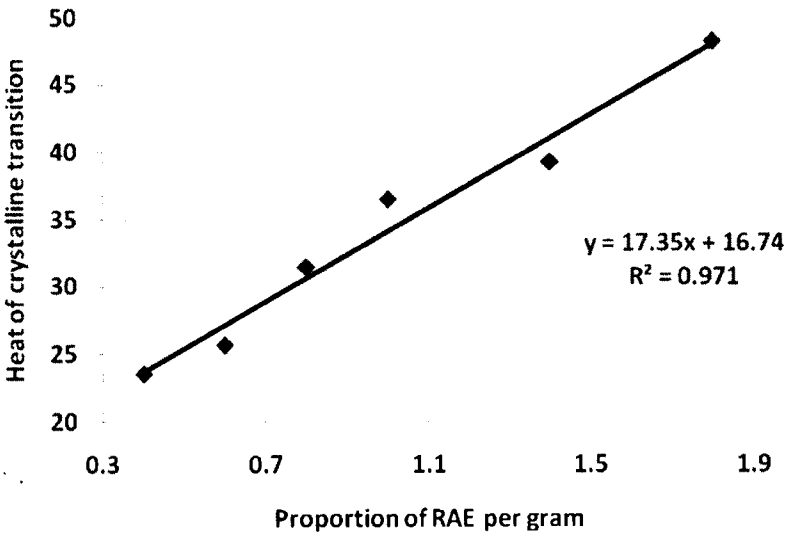


Fig. 7.14 Plot showing change in heat of decomposition for different RAE- *cis*-RA urea inclusion compounds with varying proportion of RAE and drug.



7.3.5 Thermal analysis of urea co-inclusion compounds of nicorandil

Results for DSC thermograms of different NRDIC adducts containing varying proportions of RAE and nicorandil are summarized in **Table 7.16** and overlay of thermograms is presented in **Fig. 7.15**. Heat of crystalline transition was plotted against quantity of RAE added per gram of nicorandil (**Fig. 7.16**).

Table 7.16 Heat of decomposition of urea inclusion compounds of nicorandil containing varying proportions of RAE and drug.

Product	RAE : Drug	Heat of decomposition (J/g)
NRDIC-1	0.7 : 1	21.55
NRDIC-2	0.85: 1	26.31
NRDIC-3	1 : 1	29.51
NRDIC-4	1.15 : 1	30.16
NRDIC-5	1.3 : 1	35.22

Fig. 7.15 DSC thermograms of RAE-nicorandil-urea co-inclusion compounds containing varying proportions of RAE and nicorandil

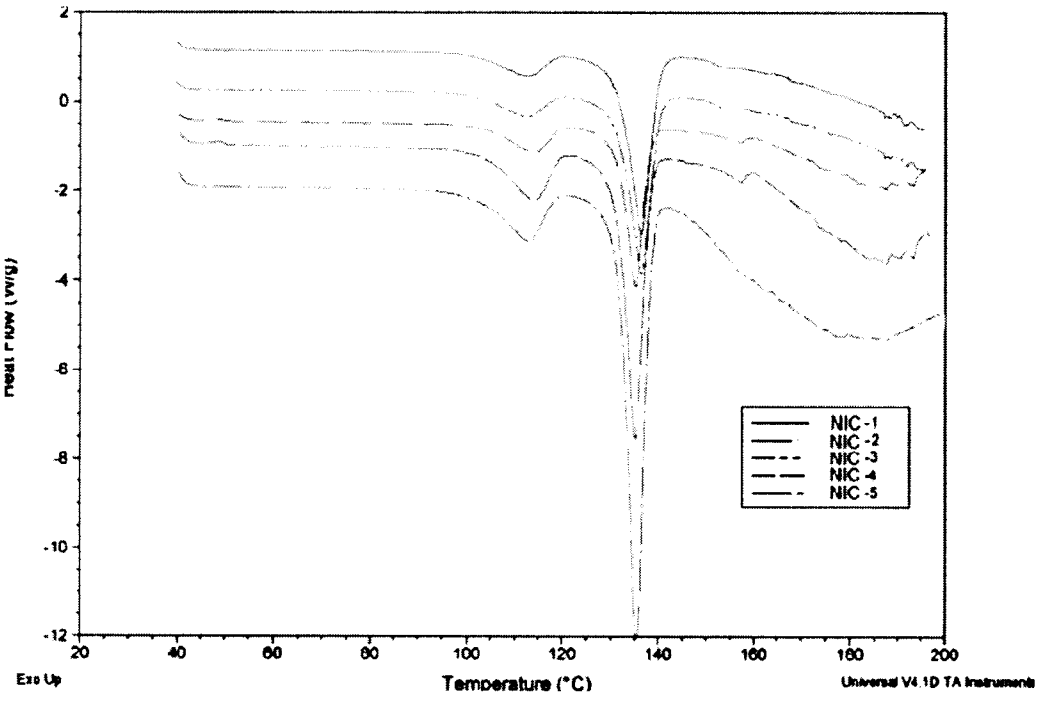
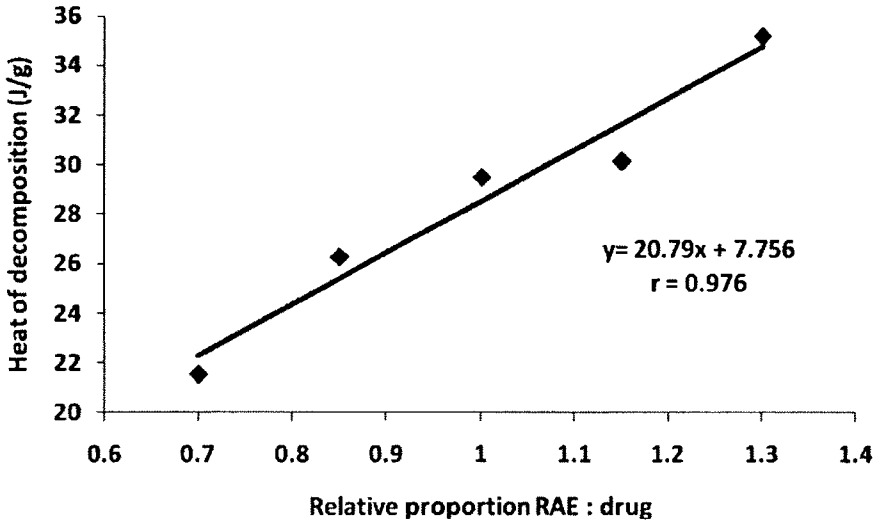


Fig. 7.16 Plot showing change in heat of decomposition for different urea inclusion compounds containing varying proportion of RAE and nicorandil.



As evident from **Fig. 7.15**, NRD melting endotherm at ~ 95.5 °C was absent all the thermograms indicative of absence of the crystalline form of the drug. Presence of a low-temperature endotherm in all the thermograms is attributable to the decomposition of urea inclusion compound and to the release of guest molecules and solid tetragonal form of urea. Heat of decomposition/ crystalline transition was found to increase linearly with change in quantity of RAE added per g of nicorandil (r^2= 0.953). This clearly indicates that an increase in the amount of RAE in the inclusion compound leads to corresponding increase heat of crystalline transition leading to improved stability of the co-inclusion compound. Since formation of urea inclusion compounds is exothermic in nature, the resulting compounds are more stable than the pure uncomplexed form of urea. However, substituents in the guest moiety, which do not form part of a linear chain, will naturally lead to distortion and weakening of host structure comprising of narrow channels with consequent decrease in heat of decomposition of urea inclusion compounds. NRD with an aromatic moiety with substitutions in its molecular structure is presumably too wide to accommodate inside the channels formed by urea host. However, in presence of RAE, some proportion of NRD is included in urea. This is expected to lead to occasional distortions in the host cell in the vicinity of aromatic ring, the extent of steric strain on host lattice being proportionate to the amount of NNAE incorporated. However,

distortion of urea host lattice by aromatic groups somewhat weakens the host lattice as evidenced by gradual decrease in heat of decomposition with corresponding increase in relative proportion of drug.

7.4 Conclusion

Urea is a well-known adductor for linear long chain organic compounds. In the present study, normally non-adductible endocytic drugs have been successfully included in urea through a modified technique. The minimum proportion of RAE required for adduction of all NNAE drugs was determined by a modification of original procedure proposed by Zimmerschied for estimation of composition of urea inclusion compounds. Thus different urea inclusion compounds containing varying proportions of all the drugs and RAE were prepared. All these inclusion compounds were subjected to thermal analysis by DSC to determine heat of decomposition, which is an indication of stability. Influence of relative proportion of RAE and NNAE drug on heat of decomposition/crystalline transition was investigated. An increase in proportion of RAE led to corresponding increase in ΔH. This could ultimately correspond to increased stability of the resulting urea co-inclusion compound.