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Preparation and characterisation of B cyclodextrin aspirin inclusion complex

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Abstract

Complexation is the association between two or more molecules to form a noncovalent based complex that has higher solubility than the drug itself. From solubility standpoint, complex can be put in to two categories, stacking complexes and inclusion complexes. The aim of this work was to study the influence of β -cyclodextrin (β -CD) on the biopharmaceutical properties of aspirin. To this purpose the physicochemical characterization of aspirin- β -cyclodextrin binary systems was performed both in solution and solid state. Present study includes deals with the preparation of inclusion complex of Aspirin β -cyclodextrin as carrier and to evaluate Aspirin β -cyclodextrin inclusion complex for various parameters viz., % practical yield, drug content, *in vitro* release study, drug-excipients interaction study, etc.

Key- Words: Complex, Aspirin, B cyclodextrin

Introduction

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) orally effective in treating fever, pain, and inflammation but gastrointestinal side effects were observed. Preparation of aspirin β -cyclodextrin inclusion complexes was to increase the solubility and reduce the irritation. The complexes were prepared and preliminarily confirmed using DSC, FTIR, X-ray diffraction and dissolution test. Aspirin induces a long-lasting functional defect in platelets by permanently inactivating the COX enzyme system. Orally administered aspirin requires high and frequent dosing because it undergoes extensive presystemic metabolism. Also, chronic oral aspirin is associated with serious gastrointestinal side-effects. So as to reduce the gastrointestinal side-effects the bioavailability and the solubility of aspirin has to be increased to overcome the side effect of aspirin related to stomach and gastro intestinal tract (GIT).^{1,2}

Cyclodextrin are cyclic (α -1, 4)-linked oligosaccharides of α -D-glucopyranose, containing a relatively hydrophobic central cavity and hydrophilic outer surface. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrin are not perfectly cylindrical molecules but the toroidal or cone shaped. Based on this architecture, the primary hydroxyl groups are located on the narrow side of the cone shape, while the secondary hydroxyl groups are located on the wider edge. During the past two decades, cyclodextrin and their derivatives have been of considerable interest in the pharmaceutical field because of their potential to form complexes with a variety of drug molecules. Cyclodextrin are used to increase the solubility of water insoluble drug through inclusion complexes formulation. The hydrophobic cavity of cyclodextrin is capable of trapping a variety of molecules within to produce inclusion complexes. Many advantages of drugs complex with cyclodextrin have been reported in scientific literature which includes-increased solubility, enhanced bioavailability, improved stability, masking of bad taste or odor, reduced volatility, transformation of liquid or gas into solid form reduced side effect, and the possibility of a drug release system, etc. The solid state characteristics of the drug after preparation and during storage will depend on the processing variables as well as the characteristics of the system. When the objective of the

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formulation is to attain faster dissolution rates, presence of amorphous of the drug and improved dissolution rate would therefore be a result of presence of amorphous high energy forms of the drug as well as the ability of the cyclodextrin to form a soluble complexes with the drug, the performance of the product over the shelf life would depend on the ability of the cyclodextrin to prevent crystallization of the amorphous drug to its stable crystalline forms. However the use of cyclodextrin in the solid oral dosage forms is limited to low dose drugs with large stability constant due to mass limitations of oral dosage. In this study, an attempt was made to improve the solubility and dissolution rate of Aspirin by complexing with β -Cyclodextrin, thereby increasing its bioavailability and therapeutics efficiency. The complex of β - cyclodextrin with Aspirin was prepared by using physical mixture method, kneading method, precipitation method, solid dispersion/co-evaporated dispersion method at 1:1, 2:1, 3:1 stoichiometric ratio. The characterization of drug with β -Cyclodextrin using differential scanning calorimetry (DSC), powder X-ray diffractometry (PXRD), FTIR, *In vitro* aqueous solubility and dissolution rate profile of complexes were performed.³⁻⁵

The techniques generally employed to enhance the solubility of poorly water soluble drugs are use of surface active agent, hydrates and solvates, polymorphism, complexation, solid dispersion. Among this Complexation and Solid dispersion is a unique technique used to increase solubility, dissolution and bioavailability of poorly water-soluble drugs. Conventional methods for preparing complex include physical mixture, complex formations, and solvent evaporation techniques. Hence, in the present investigation an attempt will be made to develop inclusion complex solid of Aspirin to overcome solubility problems of drug.

Material and Methods

Spectrophotometric method for estimation of aspirin

Determination of Aspirin λ_{max} in 7.4 pH phosphate buffer

Stock solution

Accurately weighed quantity of 100 mg Aspirin was taken in 100 ml volumetric flask and was dissolved by using 5 ml of methanol, finally the volume was made up with 7.4 pH phosphate buffers up to 100 ml to produce 1 mg/ml of solution.

Scanning

A series of concentrations i.e. 4, 8, 12, 16, 20 $\mu\text{g/ml}$ were prepared by using above stock solution and scanned between 200-400 nm. The absorption maxima of 234 nm was selected and used for further studies.

Determination of Aspirin λ_{max} in methanol

Stock solution

Accurately weighed quantity of 100 mg Aspirin was taken in 100 ml volumetric flask and was dissolved by using 5 ml of methanol, finally the volume was made up with methanol up to 100 ml to produce 1 mg/ml of solution.

Scanning

A series of concentrations i.e. 4, 8, 12, 16, 20 $\mu\text{g/ml}$ were prepared by using above stock solution and scanned between 200-400 nm. The absorption maxima of 234 nm was selected and used for further studies.

Preparation of Calibration Curve in 7.4 pH phosphate buffer

Accurately weighed amount of Aspirin equivalent to 100 mg was dissolved in small volume of 0.01M HCl, in 100 ml volumetric flask and the volume was adjusted to 100 ml with 7.4 pH phosphate buffer and further dilutions were made with 7.4 pH phosphate buffer. A series of standard solution containing Beer's Lambert's range of concentration from 4 to 15.0 $\mu\text{g/ml}$ of Aspirin were prepared and absorbance were measured at 234 nm against reagent blank. All spectral absorbance measurement was made on Shimadzu 1800 UV-visible spectrophotometer.

Preparation of Calibration Curve Aspirin in methanol⁶

A standard solution containing 1 mg/ ml of Aspirin was prepared in methanol by dissolving 50 mg of pure Aspirin in 50 ml of methanol. From this solution, working standard solutions of concentrations 2 to 12 $\mu\text{g/ml}$ of Aspirin was prepared by dilution with methanol. The absorbance of the solutions was measured at 234 nm against reagent blank. All spectral absorbance measurement was made on Shimadzu 1800 UV-visible spectrophotometer.

Methods of preparation of aspirin β -Cyclodextrin inclusion complex⁷

Preparation of inclusion complex: Inclusion complex of β -cyclodextrin & Aspirin were prepared in different ratio by various method as shown in Table 1.

Physical mixture: Physical mixtures were prepared by mixing the appropriate amount of Aspirin and β -cyclodextrin of different ratio in pestle and mortar and sieved through sieve # 60.

Precipitation method: In this method accurately weighed amount of Aspirin and β -cyclodextrin of different ratio was, dispersed in water and the solution was heated to obtain concentrated, viscous and translucent liquid. The solution was left to give a precipitation of inclusion complex. Precipitate obtained was separated and dried to get solid inclusion complex.

Kneading method: Inclusion complex of β -cyclodextrin and Aspirin in 1:1, 1:2, 1:3 ratio was

prepared by the BCD, not by dissolving but kneaded like pest with small amount of water to the drug component has been added. β -cyclodextrin was added to the mortar, and small quantities of 50% V/V ethanol were added while triturating to get slurry like consistency. Then slowly the drug was incorporated into the slurry, and trituration was continued further for 1 hrs. The slurry was then air dried at 25°C for 24 hrs. Pulverized, and passed through sieve no. 100 and stored in a dessicator over fused calcium chloride.

Solid dispersion/co-evaporated dispersion method:

The inclusion complex of β -cyclodextrin & Aspirin was prepared by dissolving the drug in methanol and β -cyclodextrin was dissolve in water separately. The β -cyclodextrin solution is then added to the drug solution and stirred to attain equilibriums. Then resulting solution was evaporated to dry.

Table 1: Formulation ingredients, preparation method of Aspirin β -cyclodextrin Inclusion Complex

Batch Code	Composition	Method	Ratio
F1	β -cyclodextrin + Aspirin	Physical mixture	1:1
F2	β -cyclodextrin + Aspirin	Physical mixture	1:2
F3	β -cyclodextrin + Aspirin	Physical mixture	1:3
F4	β -cyclodextrin + Aspirin	Precipitation method	1:1
F5	β -cyclodextrin + Aspirin	Precipitation method	1:2
F6	β -cyclodextrin + Aspirin	Precipitation method	1:3
F7	β -cyclodextrin + Aspirin	Kneading method	1:1
F8	β -cyclodextrin + Aspirin	Kneading method	1:2
F9	β -cyclodextrin + Aspirin	Kneading method	1:3
F10	β -cyclodextrin + Aspirin	Solid dispersion/c o- evaporated dispersion method	1:1
F11	β -cyclodextrin + Aspirin	Solid dispersion/c o-	1:2

		evaporated dispersion method	
F12	β -cyclodextrin + Aspirin	Solid dispersion/c o- evaporated dispersion method	1:3

Evaluation of Aspirin - β -Cyclodextrin inclusion complex⁸⁻¹²

Physical Appearance

All the batches of Aspirin - β -cyclodextrin inclusion complex were evaluated for colour and appearance.

Percent Practical Yield (PY)

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Inclusion complex were collected and weighed to determine practical yield (PY) from the following equation.

$$PY (\%) = \frac{\text{Practical Mass (SD) / Theoretical Mass (Drug + Carrier)] \times 100}{}$$

Drug Content

The Physical mixture and solid dispersion equivalent to 25 mg of model drug were taken and dissolved separately in 25 ml of methanol. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbance of solutions were determined at 234 nm by UV spectrophotometer. The actual drug content was calculated using the following equation as follows:

$$\% \text{ Drug content} = \frac{[M \text{ act} / \text{Melt solvents}] \times 100}{\text{Actual Aspirin content in weight quantity of inclusion complex}} \times 100$$

Theoretical amount of Aspirin inclusion complex

In-Vitro Dissolution Study

Dissolution studies were performed assuring sink condition according to the paddle method (USP) using USP XXIII apparatus type-II (electrolab TDT-O9T). The dissolution medium was 900 ml 7.4 pH phosphate buffer kept at 37°C \pm 0.5°C. The inclusion complex containing 100 mg of Aspirin was taken in a muslin cloth and tied to the rotating paddle kept in the basket of dissolution apparatus, the basket was rotated at 100 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed spectrophotometrically at 234 nm using Shimadzu-1800 UV-visible spectrophotometer, the samples withdrawn were replaced by fresh buffer solutions. Each preparation was tested in triplicate and then means values were calculated.

Infrared spectroscopy (IR)

FT-IR spectra of pure Aspirin, β -cyclodextrin, with its inclusion complex were obtained by Perkin-Elmer FT-IR spectrophotometer using potassium bromide (KBr) pellets. KBr pellets were prepared by gently mixing the sample with KBr (1:100). The sample was scanned from 4,000 to 400 cm^{-1} .

Differential scanning calorimetry (DSC)

Thermal analysis of Aspirin, β -cyclodextrin, and the inclusion complex were carried out using differential scanning calorimetry method. Samples were examined using a Shimadzu TGA-50 DSC instrument (Shimadzu Corporation, Japan). Samples equivalent to approximately 8 mg Aspirin were placed in aluminum pans and heated from 25 to 200°C with a heating rate of 10°C/min.

Results and Conclusion

In the present investigation, an attempt was made to improve the solubility and dissolution rate of a drug Aspirin by complexation method using β -cyclodextrin as carrier. Inclusion complex was prepared by Physical mixture, Precipitation method, Kneading method and Solid dispersion/co-evaporated dispersion method. The prepared inclusion complex were evaluated for number of parameters like DSC, FTIR, XRD, percent practical yield, drug content uniformity studies, and In-vitro drug release studies etc.

Table 2: Standardization of Aspirin

Characteristics test (performed)	Standard as per the manufacturer sheet (Aspirin)	Observation
Description	White crystalline powder	Complies
Melting range	131.00 – 136.80°C	132°C
Solubility	Water Ethanol Methanol PBS pH 7.4	Soluble Freely soluble Freely soluble Soluble
Identification	As per Indian Pharmacopoeia	Positive

Table 3: Standard calibration data of Aspirin in pH 7.4 phosphate buffer

Conc. (mcg/ml)	Absorption (nm)
0	0.00
2	0.075
4	0.15
6	0.204
8	0.27
10	0.34
12	0.42

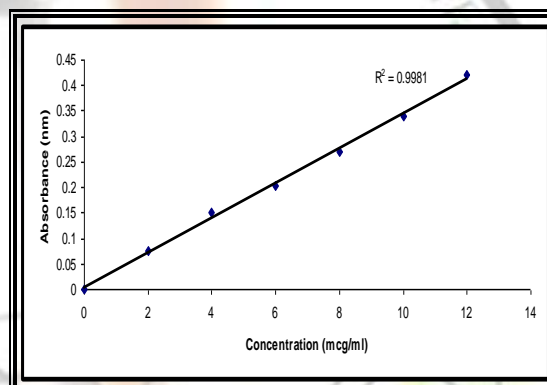


Fig. 1: Standard calibration curve of Aspirin in pH 7.4 phosphate buffer

Table 4: Standard calibration data of Aspirin in Methanol.

Conc. (mcg/ml)	Absorption (nm)
0	0.000
4	0.081
8	0.149
12	0.221
16	0.281
20	0.355

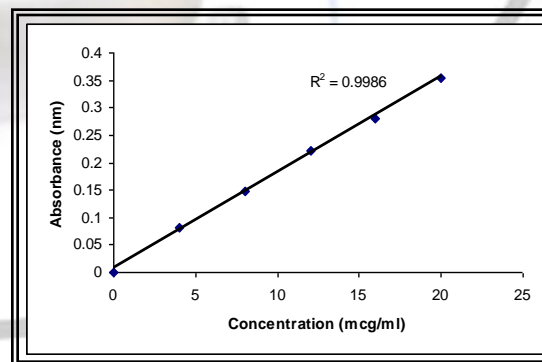


Fig. 2: Standard calibration curve of Aspirin in Methanol

Table 5: Physical parameters of Aspirin β -cyclodextrin inclusion complex

Formulation Code	Physical Appearance	
	Colour	Appearance
F1	White	Powder (Crystalline)
F2	White	Powder (Crystalline)
F3	White	Powder (Crystalline)
F4	White	Powder (Crystalline)
F5	White	Powder (Crystalline)
F6	White	Powder (Crystalline)
F7	White	Powder (Crystalline)
F8	White	Powder (Crystalline)
F9	White	Powder (Crystalline)
F10	White	Powder (Crystalline)
F11	White	Powder (Crystalline)
F12	White	Powder (Crystalline)

Table 6: Drug content uniformity studies and percentage practical yield of Aspirin β -cyclodextrin inclusion complex

FC	Drug Content uniformity (%)				% Practical Yield
	1 st	2 nd	3 rd	Mean \pm SD	
F1	92.6	90.3	89.5	90.8 \pm 21	85.50
F2	89.4	90.1	91.4	90.3 \pm 69	90.70
F3	98.1	97.4	95.6	97.0 \pm 01	89.25
F4	91.5	89.9	85.4	88.9 \pm 15	90.50
F5	80.4	82.4	86.6	83.1 \pm 33	93.66
F6	90.1	87.4	89.6	89.0 \pm 03	94.10
F7	89.4	90.1	89.6	89.7 \pm 01	92.35
F8	91.1	92.4	90.9	91.4 \pm 06	95.10
F9	92.2	93.01	92.11	92.4 \pm 40	94.09
F10	94.5	96.7	92.6	94.6 \pm 12	93.75
F11	98.4	98.9	98.1	98.4 \pm 16	96.05
F12	96.8	97.08	96.58	96.82 \pm 20	94.05

Inclusion complex of Aspirin were prepared by different method using carrier as β -cyclodextrin. In the present work, total 12 formulations were prepared and their complete composition is shown in Table . The entire Inclusion complexes prepared were found to be fine and free flowing powders. The results of percent practical yield studies are shown in Table 6. The %

Practical yield of the prepared Inclusion complex was found to be in the range of 85.50 – 96.05 %.The maximum yield was found to be 96.05% in F11. The actual drug content of all the 12 formulations is shown in Table 6. The drug content of the prepared Solid dispersions was found to be in the range of 83.1 – 98.4 % indicating the application of the present methods for the preparation of Solid dispersions with high content uniformity. The maximum % drug content was found to be 98.4% in F11.

Table 7: Dissolution profile of aspirin pure drug

Time (min)	Abs. (nm)	Conc. in 900 ml	% drug release	Cum. % drug release	Cum. % drug remain
		In mg.			
0	0.000	0.000	0.000	0.00	100.00
20	0.148	339.55	15.28	15.28	84.72
40	0.215	300.22	28.63	28.79	71.21
60	0.105	175.77	36.45	36.70	63.30
80	0.151	86.88	40.35	40.61	59.39
100	0.169	102.88	45.16	45.24	54.76
120	0.186	49.33	47.32	47.46	52.54

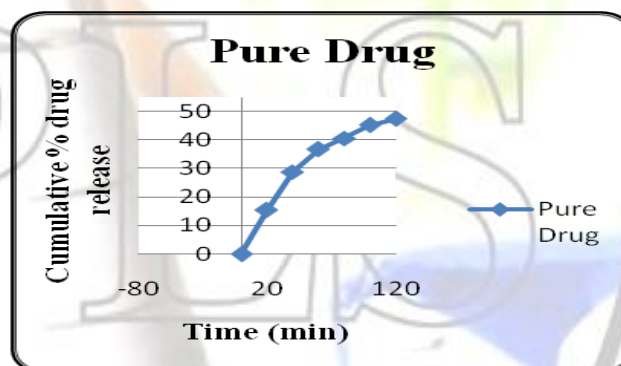


Fig. 3: Release profile of aspirin pure drug

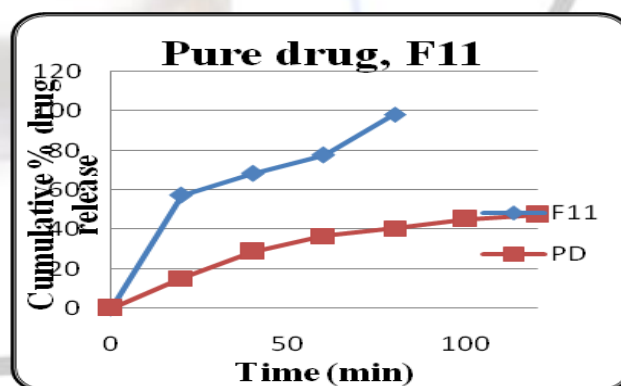


Fig. 4: Release profile of aspirin from pure drug and for formulation F11

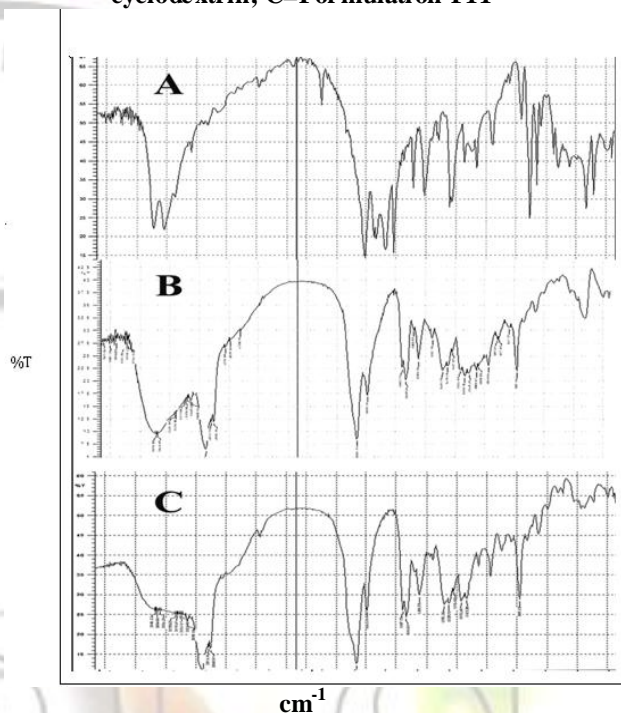
Table 8: *In-vitro* drug release profile of Aspirin β -Cyclodextrin inclusion complex F11

Time (min)	Abs. (nm)	Conc. in 900 ml	% drug release	Cum. % drug release	Cum. % drug remain
		In mg.			
0	0.000	0.000	0.000	0.000	100.0
20	0.225	1274.0	57.33	57.33	42.67
40	0.264	242.8	68.19	68.26	31.74
60	0.299	209.3	77.57	77.68	22.32
80	0.372	462.2	98.41	98.48	1.52
100	--	--	--	--	--
120	--	--	--	--	--

Drug release from Inclusion complex was faster than pure drug. Cumulative percent drug released after 80 minutes were 41.50, 47.28, 41.77, 48.35, 56.44, 91.19, 92.86, 88.17, 84.97, 87.64, 98.48, and 89.86 for F1 to F12, respectively, while it was 40.61% in 80 minutes for pure drug Aspirin. *In vitro* release study revealed that there was a marked increase in the dissolution rate of Aspirin from all inclusion complexes when compared to pure Aspirin itself. From the *in-vitro* drug release profile, it can be seen that formulation F-11 containing β -cyclodextrin (1:2 ratio of drug: β -cyclodextrin) show higher dissolution rate i.e. 98.48% compared with other formulations. In all above formulations, the drug Aspirin is in the free state and available for absorption.

The drug Aspirin was taken for the study which exhibited characteristics peaks at 3310 and 3410 cm^{-1} may be due to the molecular water present is determined. The C = O of the amine absorption is notice in 1650 cm^{-1} . In line with the structure of the molecule taken for the study. The polymer taken in this study is β -cyclodextrin which contains number of secondary hydroxyl group and primary —OH group. These two functionalities present in the molecules have shown a broad peak around 3400 cm^{-1} corresponding to primary and secondary —OH groups. C—H absorption is notice at 2873 and 2895 cm^{-1} . Strong absorption peak is also notice at 1695 cm^{-1} . These data are in conformity with structure of the β -cyclodextrin. When these two constituents, Drug and polymer β -cyclodextrin used for the required formulation. The IR spectrum of which has shown the presence of all the functionalities present in the drug as well as β -cyclodextrin suggests these during the preparation of formulation chemical reaction between two has not taken place. The formulated product is just take physical mixture none of the functional groups absorption is not affected. The formulation done by taking drug and the polymer in 1:2 ratio. Hence this formulated is a physical mixture of all the two

constituents but not the reaction product of any constituents.

Fig. 5: FTIR Spectra of A=Aspirin, B= β -cyclodextrin, C=Formulation F11

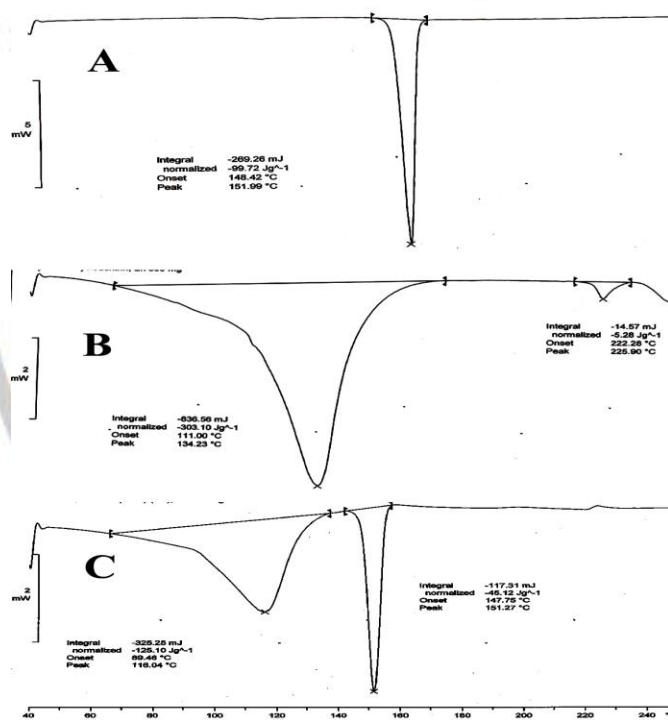
IR spectrum of the individual compound and complex (F11) exhibited the identical peaks in comparison of the IR of the previous compound supporting our conclusion that no chemical reactions have taken place.

The drug Aspirin subjected for DSC study, it started melting at 148.4°C and completed at 151.9°C, suggesting that these narrow range of melting is due to the present of single compound in the pure form. The carbohydrate polymer β -cyclodextrin is taken for DSC measurement this polymer has given rang to wide range to melting process started at 111°C to 134°C. This is the characteristics behavior of the carbohydrates. When the formulation obtained by the drug and β -cyclodextrin for DSC study two melting ranges are obtained in one peak, melting process started at 89.4°C and reach the peak at 116.0°C in an another peak process started at 147.75°C reach the peak at 151°C, suggesting that, when these two molecules (Drug and β -cyclodextrin) used for the formulation product obtained is nothing but a physical mixture of the two. In all above formulations, the drug Aspirin is in the free state and available for absorption.

The data obtain from the study of Aspirin β -cyclodextrin inclusion complex in which the β -cyclodextrin is used as a complexing agent. The following points can be concluded: The dissolution rate

of Aspirin from inclusion complex i.e., F1-F12 was significantly higher than that of pure drug, inclusion complex prepared by Solid dispersion/co-evaporated dispersion method showed faster drug release than the other method, IR studies indicated that no chemical interaction between drug and polymer took place during preparation of inclusion complex of aspirin and β -cyclodextrin, DSC studies indicated that Aspirin was homogeneously distributed within the carrier in an amorphous state and no drug crystallized out of the dispersion suggesting that drug and polymer exist in the form of a mixture rather than the reaction product., *In-vitro drug* release of Aspirin β -cyclodextrin inclusion complex of 1:2 (F11) showed higher drug release, the IR study showed that there was no chemical interaction between Aspirin and polymer β -cyclodextrin. From overall formulation, F-11 is the best formulation containing 1:2 ratio of β -cyclodextrin and Aspirin.

Fig. 6: Differential Scanning of Calorimetric thermogram of A = Aspirin, B = β -cyclodextrin and C = Formulation F11



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