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Effect of seeding on sucrose polymorphism

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ABSTRACT

The study of polymorphism in pharmaceutical compounds and their intermediates is very important and an integral part of drug development in present days. In fact, a detailed polymorphic study helps to resolve problems such as drug solubility and drug formulation techniques in drug manufacturing processes. The subject of polymorphism has received extensive academic and industrial attention. The regulatory requirements for filing new drug application (NDA) and abbreviated new drug application (ANDA) of a particular dosage form are so stringent that pharmaceutical companies are bound to study polymorphs along with their bioavailability and stability. The present study demonstrates the effect of seeding on the polymorph of sucrose which is used as a drug when complexed with iron as in Iron-Sucrose or in the form of excipient.

Keywords: PXRD, Polymorph, ANDA, NDA, Seeding

INTRODUCTION

Polymorphism is derived from greek word, *polus* meaning many and *morph*, meaning shape. In other words, it is defined as the ability of a substance to exist in two or more crystalline phases that have different arrangements or conformations of the molecules in a crystal lattice [1]. In case the difference is because of packing of the molecules, it is termed as *packing polymorphism* and if it is due to difference in conformation, it is called *conformational polymorphism*[2]. The different arrangements of atoms within the unit cell of various polymorphs can have a profound effect on the properties of the final crystallized compound [3]. In case of elements, polymorphism is termed as allotropy [4].Graphite and diamond are one of the classic examples of allotropism in carbon. In addition to elements, inorganic minerals also exhibit polymorphism e.g., ZnS is known in the forms referred to as wurtzite and sphalerite [5]. Polymorphs of $CaCO_3$ are calcite, aragonite and valerite. Polymorphism has also been reported in large biological molecules like protein molecules, arising out of change in the conformation [6]. Lysozyme is an enzyme, which crystallizes in six different forms due to difference in water content, amount of anions and packing arrangement. Besides proteins, amino acids have also been reported to show change in crystal structure, e.g., L-glutamic acid exists in two different morphs *a* and*a'* which have different shapes- rhombic and needle like [7]. Prasanna *et.al.* have studied the crystal structure of thiamine iodide hydroiodide [8].

During batch crystallization, often solvent molecules get trapped within the crystal lattice resulting in the formation of a solvate. The solvate may have high organic volatile contents entrapped that might not match with the Q3 guidelines of the FDA[9]. Therefore, the study of polymorphism in pharmaceutical compounds is very important and is an integral part of drug development in present days. The stability of polymorph is one of the main parameter to determine the expiry date of the final formulated drug. It has been reported that change in polymorph of a drug has profound effect on its solubility, dissolution rate and bioavailability. Aguiar and colleagues [10,11]at Parke Davis illustrated the effects of polymorphism on drug bioavailability and dissolution rates in the case of chloramphenicol palmitate and since then, the subject of drug polymorphism has received extensive academic and industrial attention.Prajapati*et.al.* have also reported the effect of hydrophilic polymers in solubility of Carbamazepine [12].In addition to that, Mahalakshami*et.al.* reported the effect of size and polymorph on dissolution of carbamazepine [13]. Ritonavir is one of the drug which had to be withdrawn from the market due the change in

polymorph with time that did not give the desired drug effects [14]. Aspartame is artificial sweetener which exists in five polymorphs in which the bundles like crystals are easy to handle[15].Nighute*et.al.* studied the microcrystal of Cefuroxime [16]. Single crystals of lactose have also been isolated from alcohol aqueous solution [17].

Use of sucrose in pharmaceutical industry

Sucrose is a member of carbohydrates, commonly known as table sugar or saccharose, is a white, odorless, crystalline powder with a sweet taste. Sucrose crystallizes in the monoclinic space group P21[18].It is mainly used in food industry as a preservative, a flavour enhancer, a bulking agent in other foods, a food for yeast to aid fermentation in baking and brewing, a means to raise boiling or lower freezing points in the production of ice creams, an enhancer of the texture and shelf-life of certain foods. The second major use of sucrose is in the pharma industry as a major excipient to mask the bitter taste of active pharmaceutical ingredients (API). Table 1.1 summarizes the use of sucrose in various formulations being used in pharmaindustry. Fig 1.1 and Fig 1.2 shows the use of sucrose in direct compression and wet granulation techniques, respectively used for formulation. Sucrose is major constituent in some drugs also. Sucralfate (aluminium salt of sucrose octasulphate) is used in treatment of peptic and stomach ulcers [19]. Sucrose polyesters have also been used as contrast agents in magnetic resonance imaging (MRI) [20]. Sucrose forms at least 80% part of drug in iron sucrose which is marketed under the brand name Venofer and is given to patients suffering from acute anemia. Iron sucrose which is used as drug to increase the haemoglobin level is a polymeric compound [21].

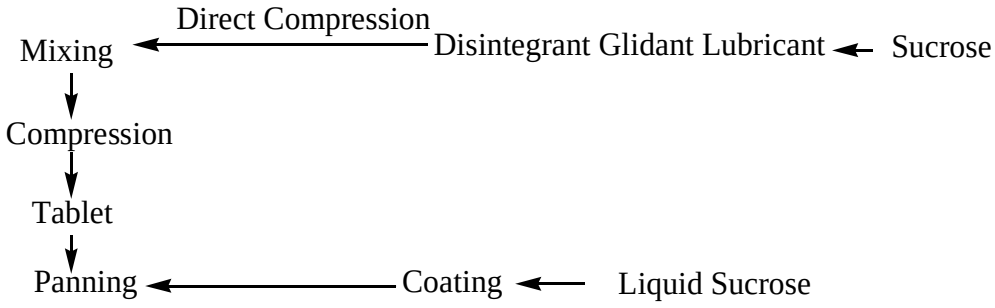

Fig 1.1 Use of sucrose in direct compression

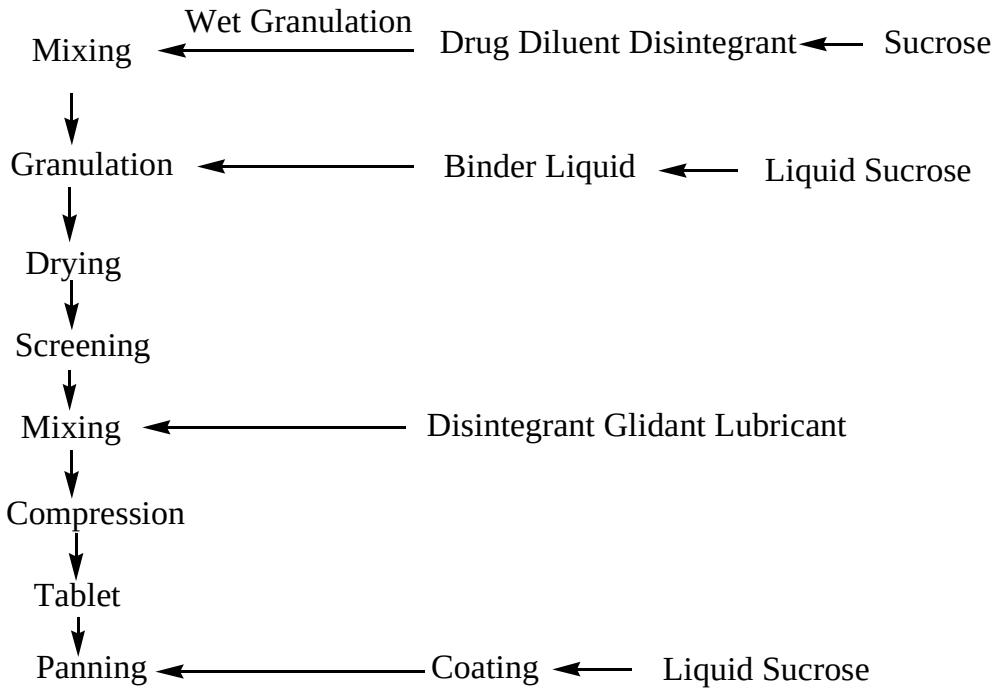

Fig 1.2 Use of sucrose in wet granulation

Table 1.1Various uses of sucrose in pharma industry

Dosage Forms	Sugar Products	Desired functionality
Medicated Confectionary	Liquid sugars, granulates sugars, glucose syrups	Glass forming diluents, controlled dissolving, stability, sweetness and taste masking
Blended Powders(cold and flu remedies)	Powdered sugar, screened sugar	Diluent, rapid dissolving, complementary particle size, sweetness, taste masking
Syrups, Elixirs	Liquid sugar, Inverts	Diluent, sweetness, preservative, demulcent, wetting agent, prevention of crystallization, viscosity (body mouthfeel), taste masking
Suspensions	Liquid sugar, Inverts	Diluent, sweetness, preservative, demulcent, wetting agent, prevention of crystallization, viscosity (body mouthfeel), taste masking, suspending agent
Tablet, Lozenges	Liquid sugar, powdered sugars, Directly compressible sugars	Compressibility (tablet forming), binder, diluent, dissolution, texture, coating, protection, sweetness, taste masking
Capsules, saches	Sugar spheres	Diluent uniformity, ability to coat, controlled dissolving, stability
Nasal, oral drops	Liquid sugar, Inverts	Viscosity and sweetness as goes in the mouth lately
Bioadhesives	Liquid sugar, Inverts	Sweetness in taste

Polymorphism in sucrose

The existence of polymorphism in sucrose is well documented in literature. It is reported to exist in crystalline and amorphous forms [22]. The melting points reported in various studies are quite varied which may be because of its existence in different polymorphic forms. The literature survey reveals that there might be at least three intermolecular arrangements within the crystals of sucrose molecules [23].Conformational polymorph of sucrose has been reported by Tu Lee *et. al.* Sucrose crystals, grown from a furfuryl alcohol-water solution at 60^{o}C exhibit a wide endothermic peak from 140 - 170^{o}C in its differential scanning calorimetry (DSC) scan whereas, commercial sucrose crystals has melting point around 187- 189^{o}C [24]. Dimorphs of sucrose have also been reported by Tu Lee *et. al.*[25]. The physiochemical properties of the sucrose thin films have been studied by Predoi*et. al.*[26], when they found that the sucrose thin films having thickness of about 449nm showed good adhesion and therefore can be used as biofilms in different bioadhesive drugs.The glass transition temperature of amorphous sucrose, 319-347K has been studied by Alexandra *et.al.* using molecular dynamics tool which proves to be good for the study of glass transition temperature of carbohydrates[27].

Literature survey has revealed the various polymorphic forms of sucrose. One of the main challenges during the crystallization of the desired polymorph is the crystallization of impurities of other polymorphs which may act as seeds for the conversion of one polymorph into another during the different stages of the drug development. The resulting polymorph may not offer the desired drug stability and efficacy. Sudha*et. al.* have reported the effect of seeding on Paracetamol [28]. Swamivelmanickam*et. al.* studied the preformulation studies of Amoxicillin trihydrate [29]. To best of our knowledge, no such results have been reported in the case of sucrose which undergoes various changes in the chemical and physical environment during the drug development process. Therefore there is a need for such type of studies. Amorphous form of a particular drug or excipient is always desired as it enhances the bioavailability. The aim of the present work is to study the effect of seeding of crystalline polymorph on the stability of amorphous form.

Experimental Section:

Crystalline Form II of sucrose was taken in a mixer grinder and grinding was continued for 1.5 hour at room temperature to get the amorphous form. To evaluate the effect of grinding time on the polymorphic behavior of sucrose, samples were taken after intervals of 5, 15, 30, 45, 60 and 90 mins and were subjected to PXRD (Fig 1.3-1.6).The PXRD was done at X'pert PRO X-ray diffractometer, PANanalytical (MPD PW3040/60 XRD; CuKα anode; λ = 1.541 A^{o}). Each sample was consolidated in an aluminium holder and scanned at 40kV and 30mA from 5^{o} to 35^{o} 2θ values using a scanning period of 0.1285^{o}/ min and a step size of 0.0084^{o}. The powder diffraction patterns were analyzed using X'Pert High score software (version 2.2.0) and plotted using OriginPro 7.5.

Further, the prepared amorphous form was contaminated with known quantities of crystalline form II in 0.5%, 1%, 1.5% and 2% amount (Table 1.2). These samples were triple packed in LDPE, HDPE and finally packed in aluminium pouch in duplicate. Each pair of contaminated sample along with the pair of pure amorphous form of sample was finally stored under dry conditions (silica gel) at lower (5^{o}C), ambent (25^{o}C), intermediate (45^{o}C) and accelerated temperature (70^{o}C) ± 2^{o}C for one month. Samples were withdrawn after 15 days intervals of time to check the effect of seeding of crystalline Form II on stability of amorphous form of sucrose at different storage conditions with time. The PXRDS of the samples have been reported from Fig 1.3-1.26.

Table 1.2 Samples prepared to study the effect of seeding

Sample ID	Form II%	Amorphous %
1	0.5	99.5
2	1.0	99
3	1.5	98.5
4	2.0	98

RESULTS AND DISCUSSION

Effect of grinding on crystallinity of sucrose:

Fig 1.3 shows the PXRD of crystalline Form II of sucrose. Fig 1.4 to Fig 1.8 shows the effect of grinding on the polymorphic transformation of Form II with time. No change was observed in the polymorph till first 15 minutes (Fig 1.4). The peak intensities were found to decrease at 30 minutes (Fig 1.5) which demonstrated the deformation of crystalline nature of Form II. Most of the characteristic peaks of crystalline Form II were found to be diminished after 45 minutes (Fig 1.6). PXRD after 60 minutes of grinding showed complete conversion of crystalline Form II into amorphous form (Fig 1.7). The sample was further grinded for extra 30 minutes to ensure the complete conversion into amorphous form (Fig 1.8).

Stability study of amorphous form of sucrose in the presence of Form II at different concentration

Fig 1.9 - 1.20 represents the PXRD graphs of amorphous form in the presence of 0.5% of crystalline Form II at different temperatures after 15 and 30 days intervals of time respectively. It is clear from the graphs that 0.5% seeding did not bring any polymorphic change in the amorphous form at 5^{o}C even after 30 days. However, some of the characteristic crystalline peaks (2θ values of 11.71, 12.76, 13.16, 18.85, 25.3) were observed in the PXRD graph at higher temperatures wherein in the intensity of the crystalline peaks were found to increase with increase in the temperature and time of storage. The crystalline peaks were found to be most prominent after 30 days of storage condition at 70^{o}C.

Seeding with 1% of crystalline morph shows same type of trend as was observed in the case of 0.5% seeding where amorphous form was found to be stable at 0^{o}C even after 30 days (Fig-1.21 and 1.22). But the observed characteristic crystalline peaks were found to be more prominent in the case of 1% seeding showing the direct relationship between rate of polymorphic transformation with increase in the concentration.

In contrast to the results observed in the case of 0.5% and 1% seeding, amorphous form was found to be unstable even at 0^{o}C after 15 days of storage when it was seeded with 1.5% of crystalline form (Fig 1.23 and fig 1.24). However, in concordant with the results observed with seeding at lower concentration, the PXRD graphs in this case also demonstrated the direct relationship between the intensity of the peaks with increase in storage time and temperature. Fig 1.25 and 1.26depicts the comparative studies of polymorphic transformation of amorphous form in the presence of 2% crystalline form at different temperature and time respectively which shows the same trend as was observed with 1.5% seeding. All the results have been summarized in Table 1.3.

Table 1.3 Stability data of Seeding samples

Sample ID	Time (Months)	2θ values				Peak Intensity
		5^{o}C	25^{o}C	45^{o}C	70^{o}C	
Seeding0.5 %	15 days	No change	11.71, 18.85	12.76, 13.16	12.76, 13.16, 25.3	Less
	30 days	No change	11.71, 18.85	12.76, 13.16	12.76, 13.16, 25.3	Increased
1%	15 days	No change	11.71, 18.85	12.76, 13.16	12.76, 13.16, 25.3	Less
	30 days	No change	11.71, 18.85	12.76, 13.16	12.76, 13.16, 25.3	Increased
1.5%	15 days	11.71, 18.85	11.71, 18.85, 25.28	12.76, 13.16	12.76, 13.16, 25.3	Less
	30 days	11.71, 18.85	11.71, 18.85, 25.28	12.76, 13.16	12.76, 13.16, 25.3	Increased
2.0%	15 days	11.71, 18.85	11.71, 18.85, 25.28	11.71, 18.85, 19.62, 24.78, 25.28	11.71, 18.85, 19.62, 24.78, 25.28	Increased
	30 days	11.71, 18.85	11.71, 18.85, 19.62, 24.78, 25.28	11.71, 18.85, 19.62, 24.78, 25.28	11.71, 18.85, 19.62, 24.78, 25.28	Increased

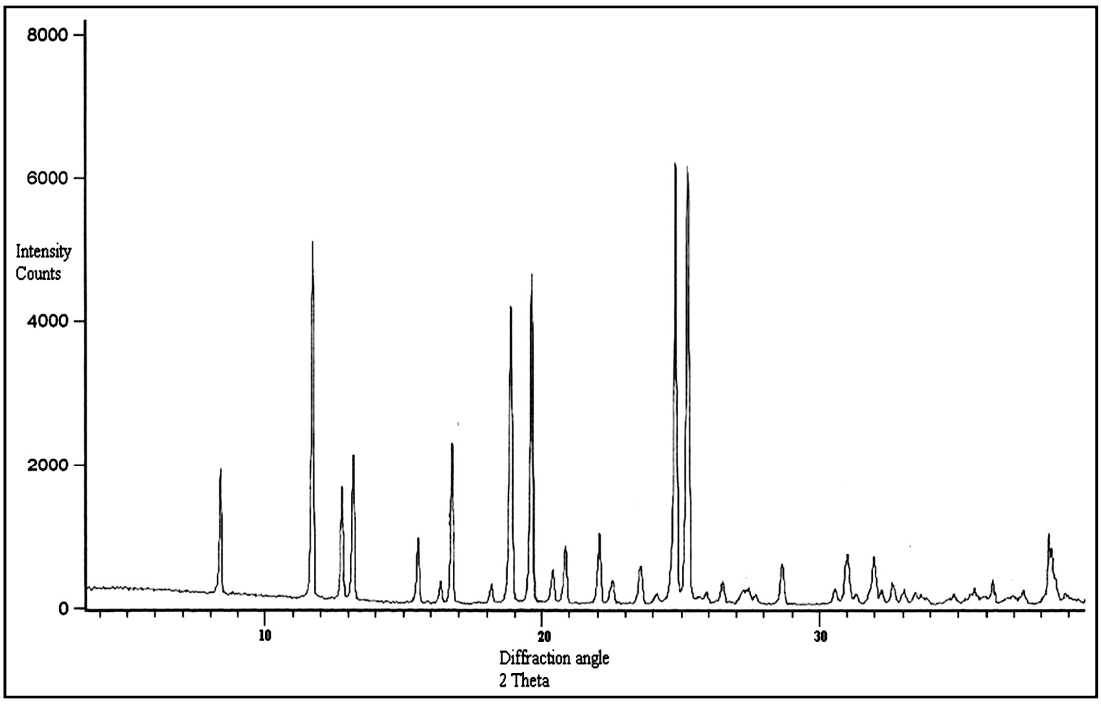

Fig 1.3 Form II for sucrose

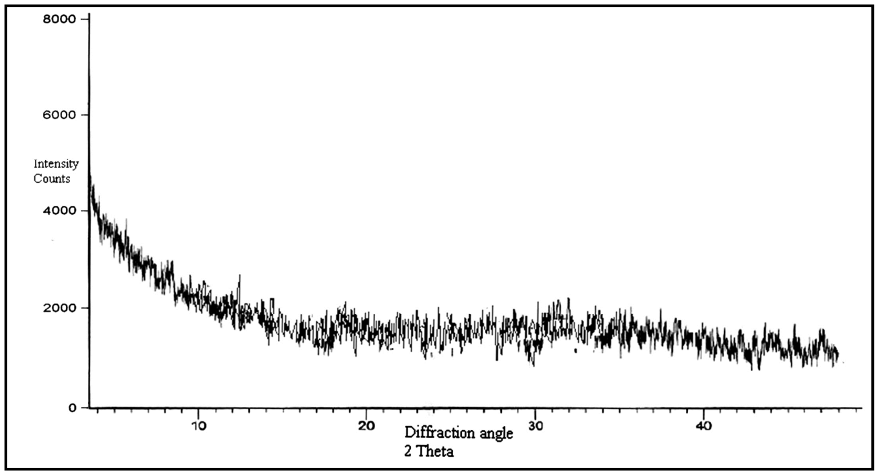

Fig 1.6 PXRD pattern of sucrose (45 mins of milling)

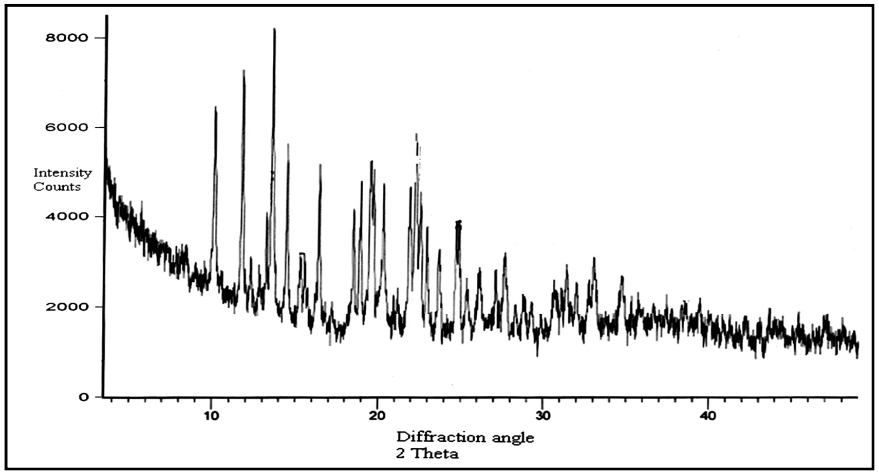

Fig 1.4 PXRD pattern of sucrose (15mins of milling)

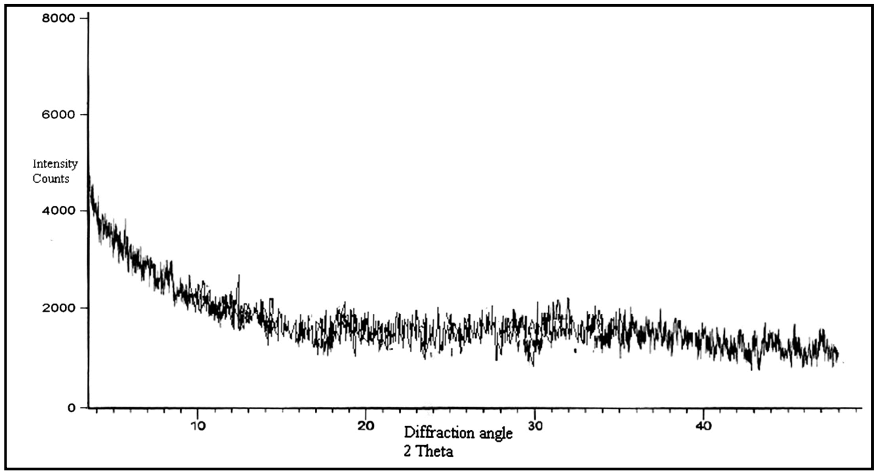

Fig 1.5 PXRD pattern of sucrose (30mins of milling)

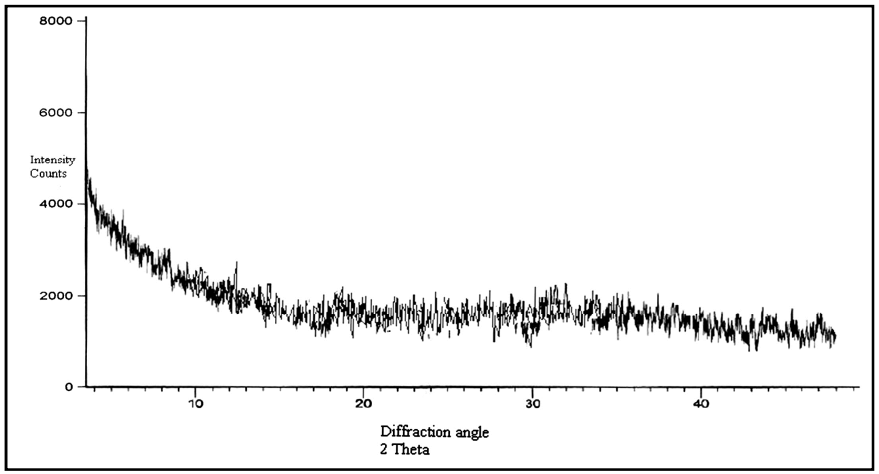

Fig 1.7 PXRD pattern of sucrose (60 mins of milling)

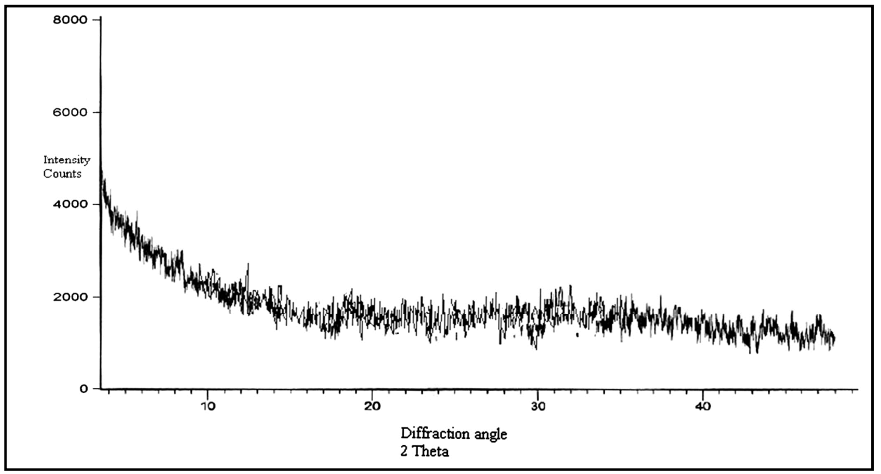

Fig 1.8 PXRD pattern of sucrose (90 mins of milling)

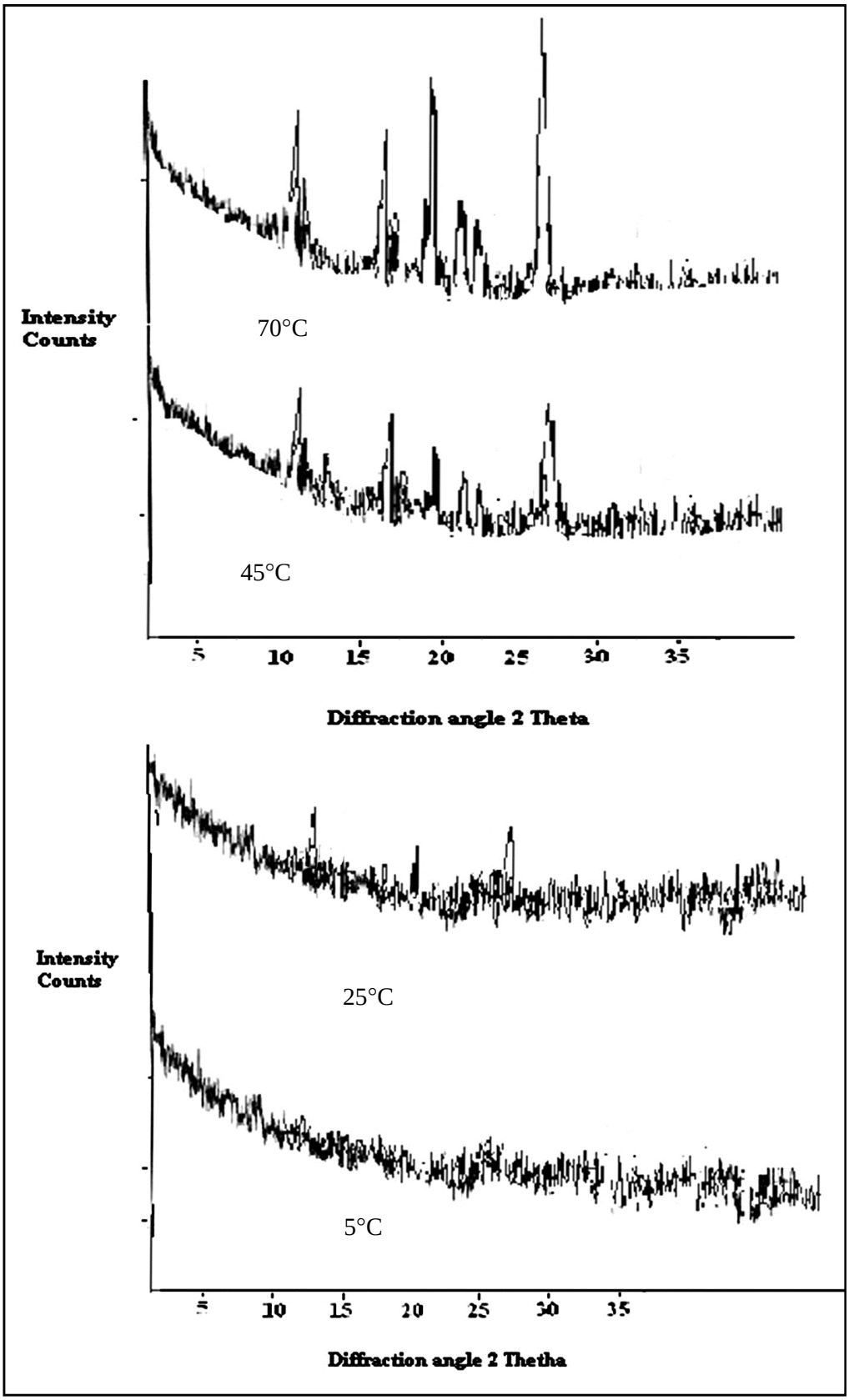

Fig 1.26 PXRD pattern's of amorphous samples with 2.0% Form II (1 month)

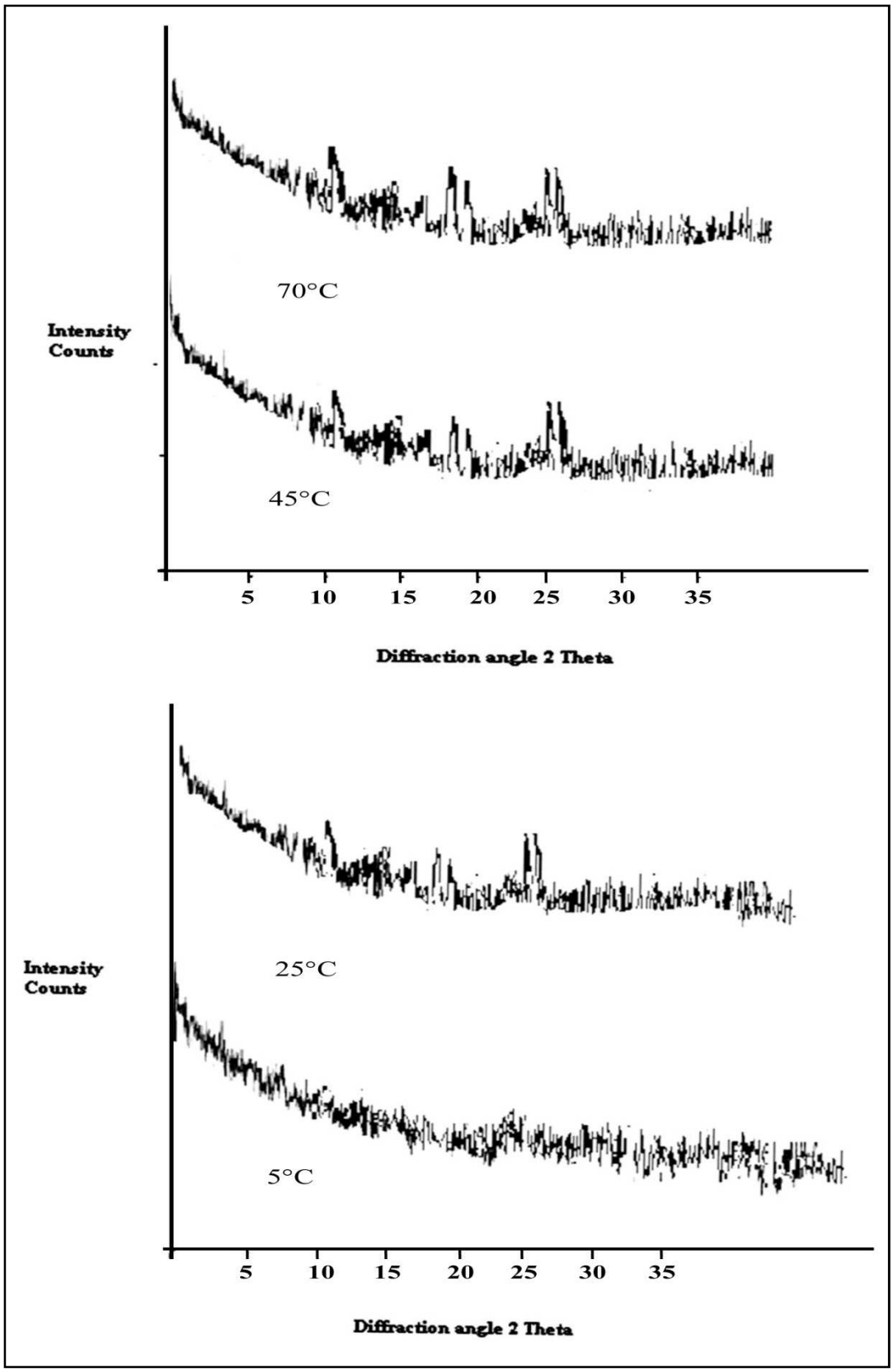

Fig 1.24 PXRD pattern's of amorphous sample with 1.5% Form II (1 month)

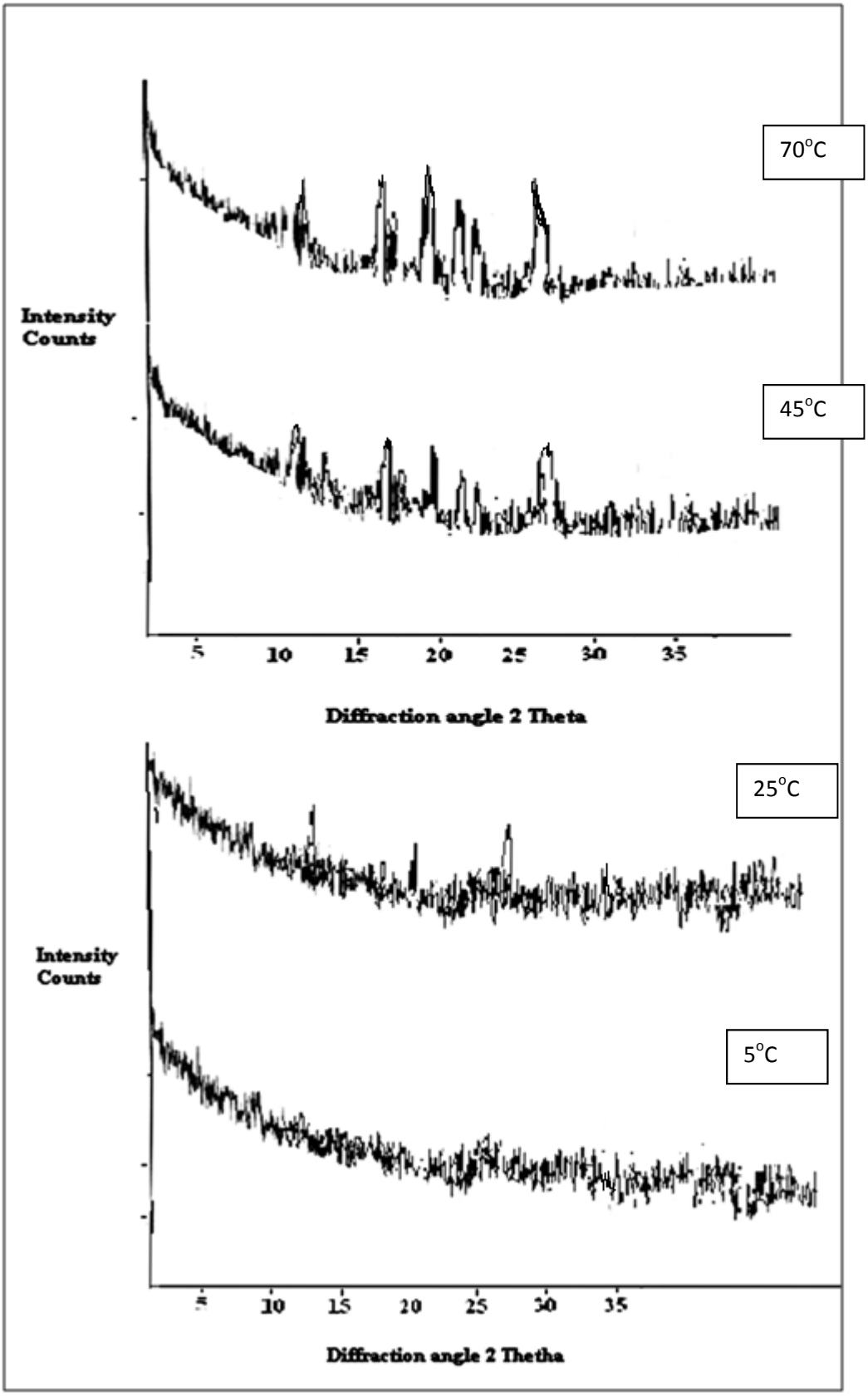

Fig 1.22 PXRD pattern's of amorphous sample with 1.0% Form II (1 month)

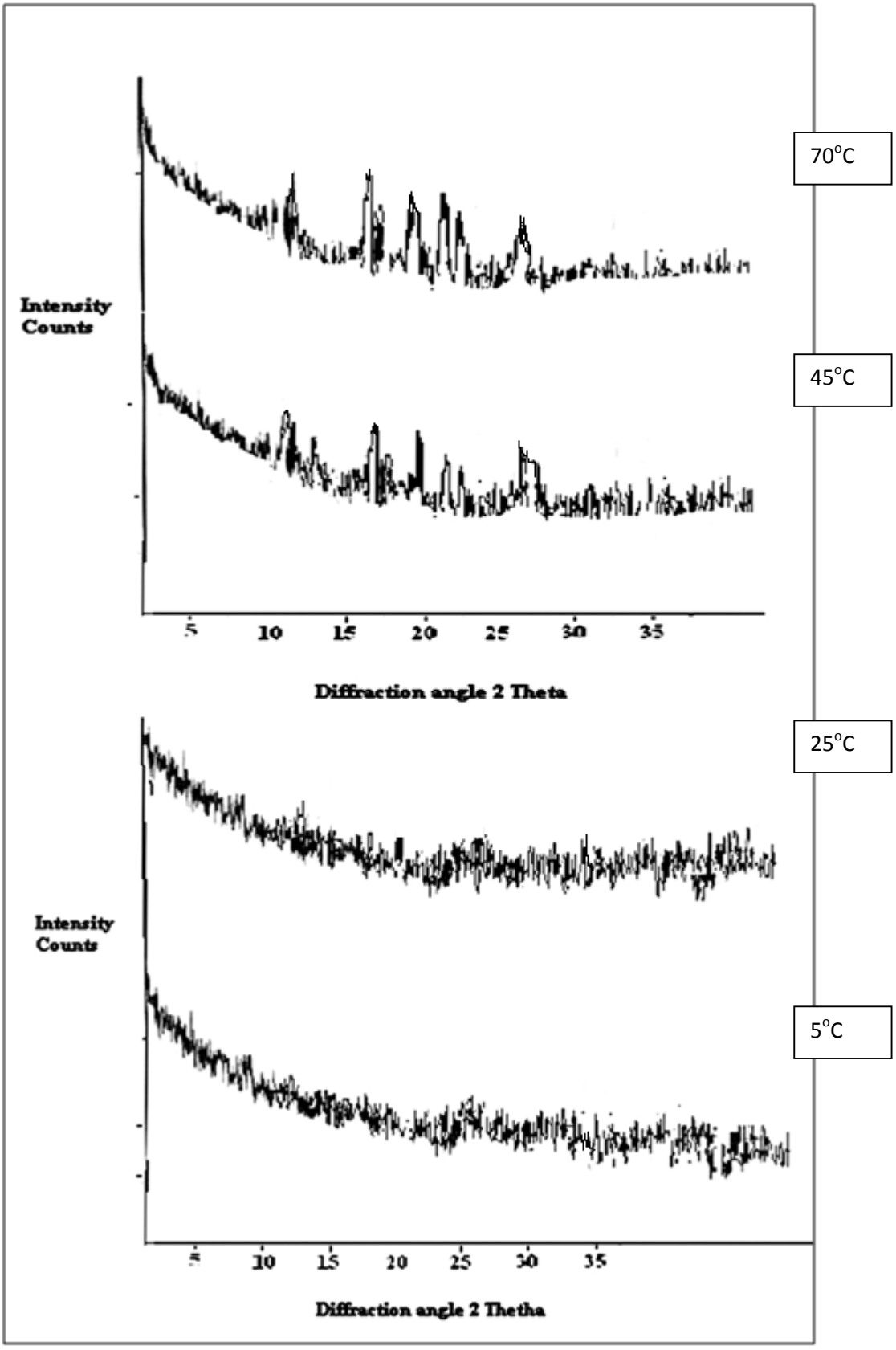

Fig 1.20 PXRD pattern's of amorphous sample with 0.5% Form II (1 month)

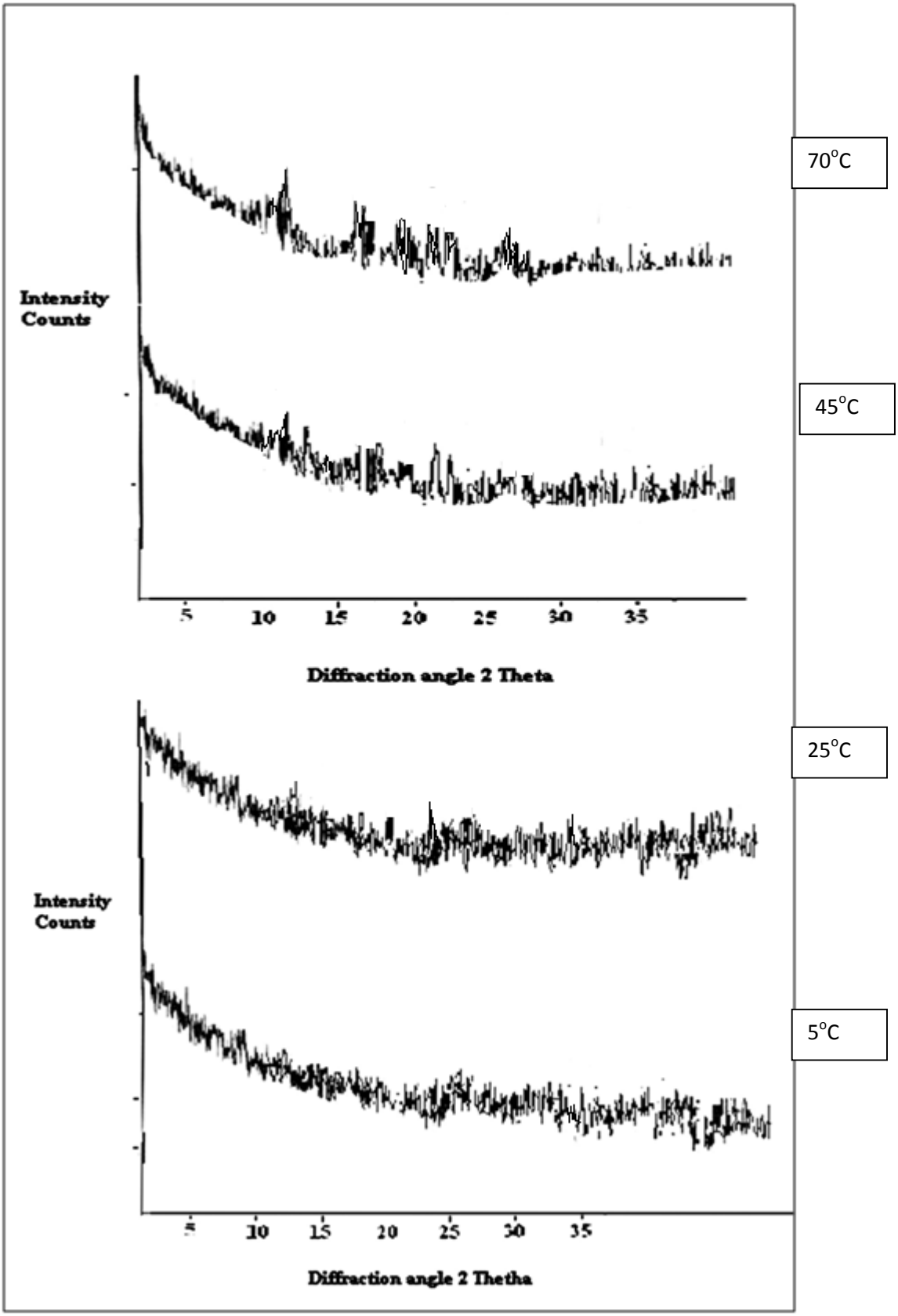

Fig 1.25 PXRD pattern's of amorphous sample with 2.0% Form II (15 days)

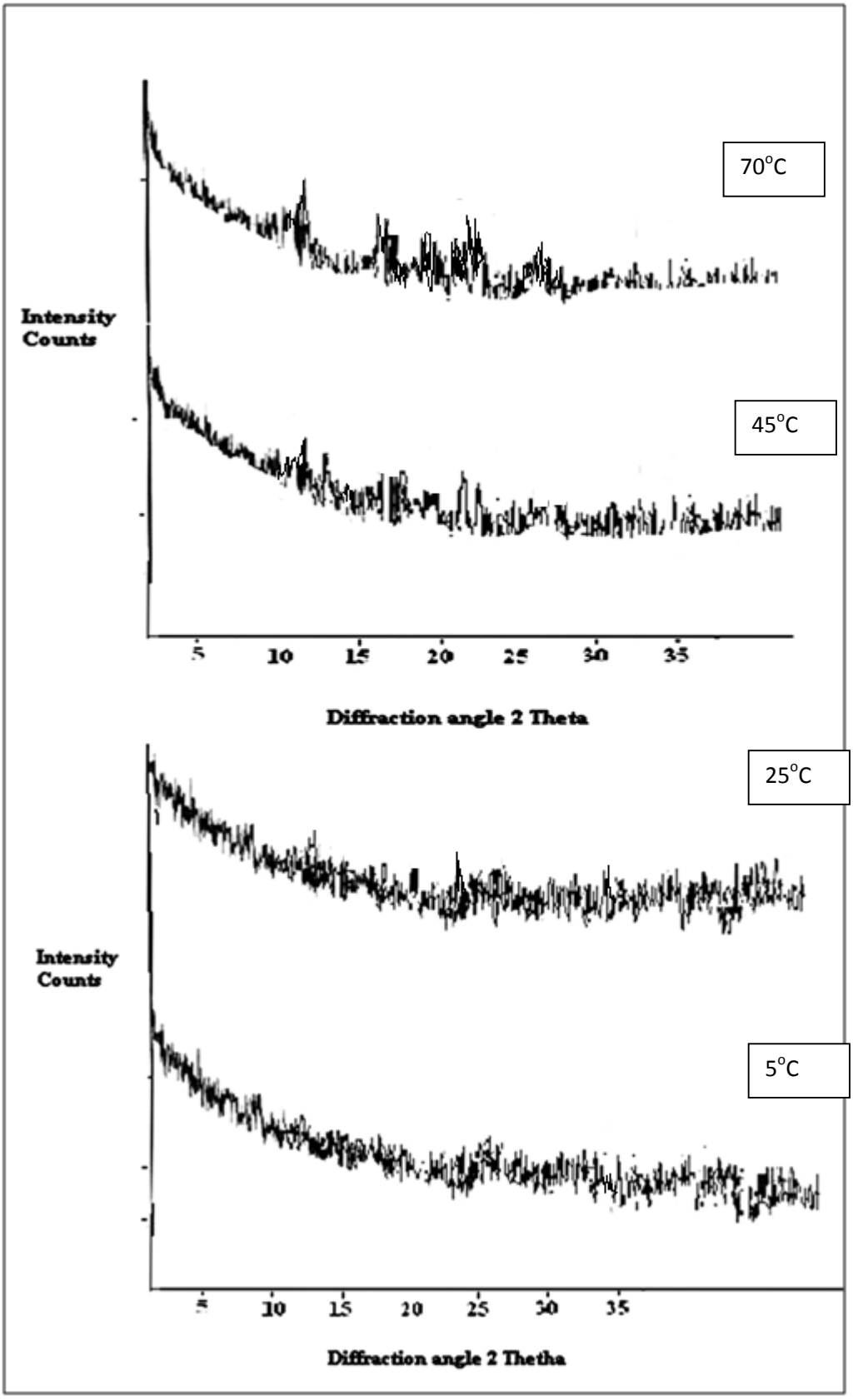

Fig 1.23 PXRD pattern's of amorphous sample with 1.5% Form II (15 days)

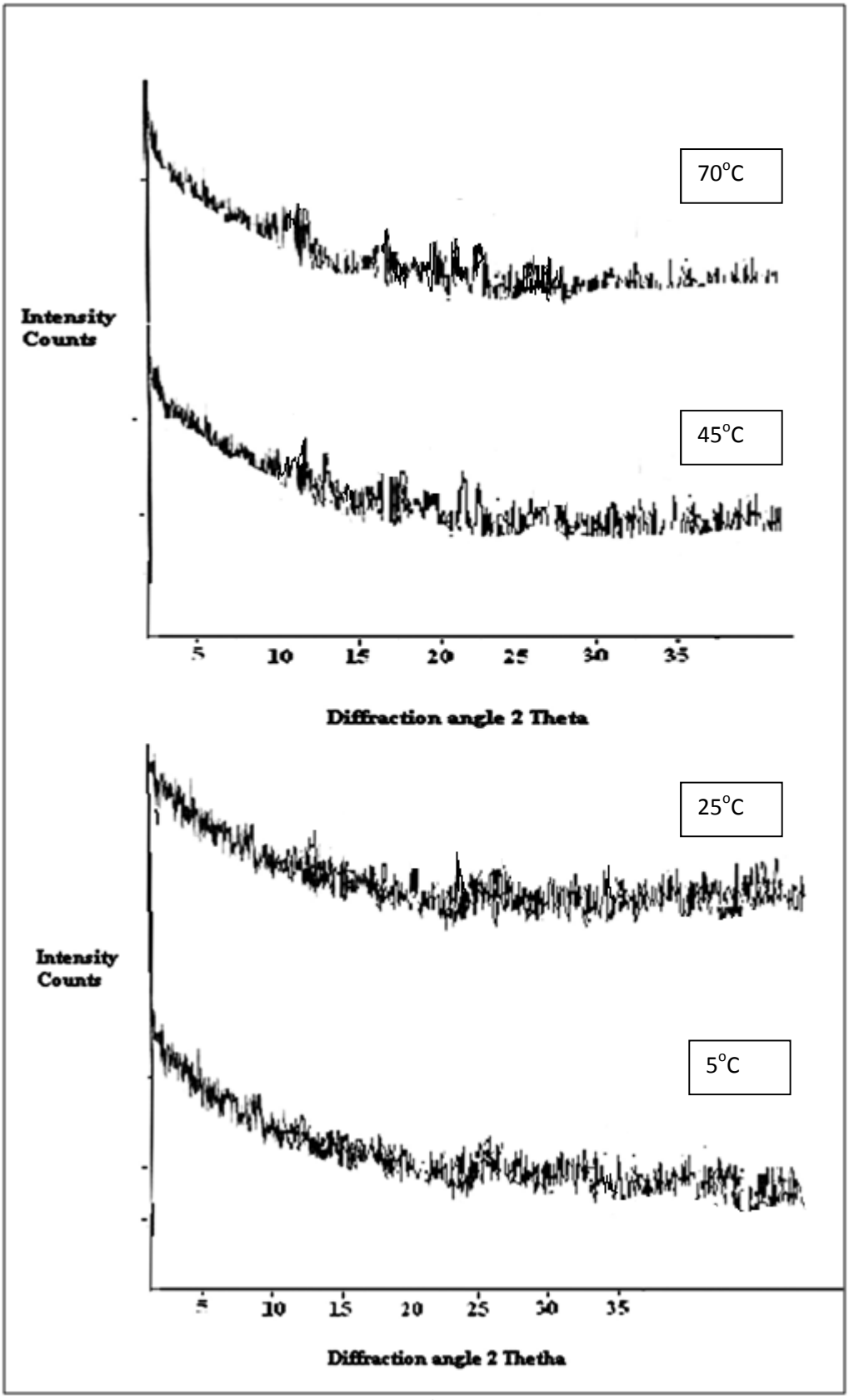

Fig 1.121 PXRD pattern's of amorphous sample with 1.0% Form II (15 days)

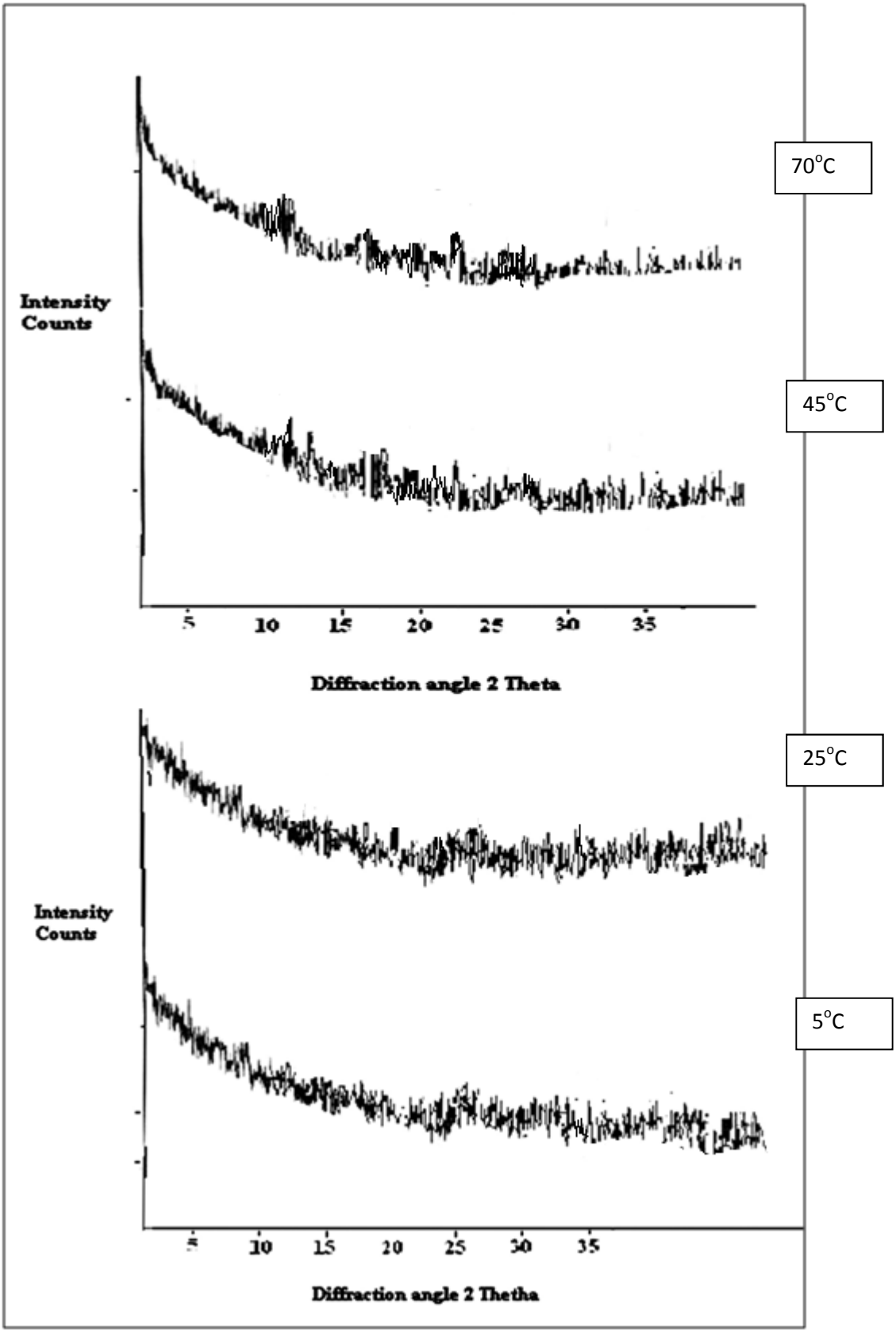

Fig 1.9 PXRD pattern's of amorphous sample with 0.5% Form II (15 days)

CONCLUSION

The present study clearly reveals the transformation of amorphous form of sucrose into crystalline Form II in the presence of later as seed at different concentrations. Further, there exist a direct relationship between the rate of transformation with concentration of seed and temperature of storage. The study depicts that amorphous form is resistant to any polymorphic change in the presence of up to maximum 1% crystalline seed at 5^{o}C. However, seed concentration above 1% leads to transformation of amorphous to crystalline form even at lower temperature. This polymorphic transformation supports that crystalline Form II is thermodynamically more stable than the amorphous form which results in observed transformation. Therefore to use the amorphous form of sucrose which may result in its enhanced bioavailability, it should be free from even a minute amount of crystalline form as an impurity. The present data can be helpful in drug formulation at different stages and finalizing the storage condition for the drugs containing sucrose as one of the excipients to have desirable effect of its amorphous form on the overall performance the drug.

The study in sucrose clearly reveals that the most stable form dominates over all forms. It is always necessary to isolate pure forms for longer stability. If mixtures are isolated then the more thermodynamically stable form will act as a seed for the lesser stable form. The storage conditions must be clearly defined in order to use a metastable form. The comparison study of manual as well as inbuilt seeding study clearly reveals that it is not necessary that any contamination from outside is doing the polymorphic transformation. The presence of polymorphic form of starting material can act as a seed for such polymorphic transformations. There is always a need to identify the pure and stable form as whether be a drug or excipient it has to go through a lot of changes of temperature, mechanical stress to give the final product, so polymorph stability is required to be studied.

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