Chapter - 6

Chitosan Interpenetrating Polymeric Network (IPN) Beads Crosslinked With Glutaraldehyde
6.1. INTRODUCTION

Hydrophilic matrix system has become an interesting industrial method to prepare controlled release (CR) dosage forms of bioactive molecules. Its convenience and easiness to manufacture cuts down the cost of the final product. In principle, when this hydrophilic matrix is exposed to an aqueous medium it does not disintegrate, but develops into a highly viscous gelatinous surface barrier, which controls the drug release. The release of active agents from such matrices is dependent upon the nature and type of the polymer used to develop the matrix. In this direction, investigations are in active progress to use appropriate polymers to develop an effective drug delivery system. Recently, the interpenetrating polymeric networks (IPNs) have found astonishing applications in the controlled release of bioactive molecules. The release mechanism from such matrices can be evaluated precisely. The major task in these areas is to design and evaluate the suitable wall material.

IPN systems contain two polymers, each in a network form that can be crosslinked in presence of each other to give a three-dimensional network structure having a large volume to facilitate the encapsulation of drug. The release of drugs through polymeric matrices can be monitored by the addition of low molecular weight additives or by coating with another polymer.

Solid biodegradable formulations with a drug dispersed throughout the particle matrix have received much attention, not only for prolonged release but also for targeting of drugs to specific sites. An easy method to produce IPN is
to crosslink two or more polymers with a common crosslinking agent. If one of the polymers is crosslinked, then it is called a semi-IPN. According to the suspension crosslinking technique to prepare chitosan microspheres, different types of bifunctional agents (glutaraldehyde, terephthaloyl chloride, hexamethylene diisocyanate etc.) can be used as the crosslinkers\textsuperscript{16-17}. Release of an active agent from the polymer matrix depends upon the extent of crosslinking\textsuperscript{18}.

Development of chitosan IPN beads by crosslinking of chitosan with gelatin, and chitosan with egg albumin separately, using a common crosslinking agent glutaraldehyde (GA) has been discussed. The use of albumin microspheres in drug delivery was first suggested by Krammer\textsuperscript{19}. Albumin has the ability to bind and release high concentration of drugs. It is stable after synthesis with a clinically acceptable shelf-life\textsuperscript{20}. Albumin is an attractive choice as a carrier for drugs by virtue of its properties such as ready availability, lack of toxicity, favorable rate of degradation, lack of antigenicity, ease of conjugation with wide range of drugs, controllable drug release rate, biocompatibility and ability to form complexes\textsuperscript{21}.

Gelatin was selected as one of the drug carrier because of its ready availability, lack of toxicity and antigenicity, pharmaceutical acceptability and its previous use in various other formulations\textsuperscript{22}. Infact, the first research leading to the development of microencapsulation procedures for pharmaceuticals, published by Bungenburg and Kass (1931) dealt with the preparation of gelatin
microspheres\textsuperscript{23}. Since then, it has been widely used as a carrier for number of drugs such as sulphamerazine, sulphadiazine and aspirin\textsuperscript{24}. Gelatin has been used as a carrier for materials of considerable range, such as pharmaceuticals, vitamins and adhesives\textsuperscript{25}.

Gelatin is a purified protein obtained by partial hydrolysis of animal collagen. It is used in the manufacture of capsule shells or as a pharmaceutical aid in the manufacture of tablets. It acts as an encapsulating agent, suspending agent, tablet binder or as a coating agent\textsuperscript{26}.

Cefadroxil is an antibiotic and a first generation cephalosporin derivative. It is a p-hydroxy analog of cephalexin, having good activity against gram-positive bacteria and relatively modest activity against gram-negative microorganisms. In view of its short half-life (1 hour)\textsuperscript{27}, cefadroxil was developed as a controlled release dosage form.

**Polymer data**

**Gelatin\textsuperscript{36}**

<table>
<thead>
<tr>
<th>Description</th>
<th>Translucent flakes, sheets, powder or granules.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Light amber to faintly yellow.</td>
</tr>
<tr>
<td>Stability</td>
<td>Stable in air but is subjected to microbial decomposition in moisture.</td>
</tr>
<tr>
<td>Solubility</td>
<td>Partially soluble in <em>cold water</em> however swells when stirred into water, soluble in <em>hot water</em>.</td>
</tr>
</tbody>
</table>
Storage: To be stored in tightly closed containers in a dry place.

pH: Between 3.8 and 7.6.

Microbial limits: Total microbial count, not more than 1000 cfu/g.

**Egg albumin**

Synonyms: Egg white, ovalbumin, albumin.

Description: Powder.

Color: Pale yellow.

Melting point: 61°C (decomposes).

Stability: Stable.

Water solubility: Moderate.

**Drug data**

Cefadroxil is an antibacterial.

Chemical name: 7-(R)-2-amino-2(4-hydroxyphenyl)acet-amido-3-methyl-3-cephem-4-carboxylic acid monohydrate.

Molecular formula: C_{16}H_{17}N_{3}O_{5}S, H_{2}O

Molecular weight: 381.40

Chemical structure:

![Chemical structure of Cefadroxil]

Description: White to off white, crystalline powder.

Solubility: Slightly soluble in water; practically insoluble in ethanol (95%); in chloroform and in ether.
6.2. EXPERIMENTAL

Materials

The gift sample of cefadroxil was supplied by Sun Pharma, Baroda, India. The chitosan was purchased from Aldrich Chemical Company, USA. Analytical grade glutaraldehyde (GA) and acetic acid were purchased from s.d.Fine Chem. Ltd. Mumbai, India and used as received.

Methods

6.2.1. Preparation of IPN beads

The IPN network beads of chitosan with gelatin and chitosan with egg albumin were prepared by using the documented procedure with suitable modification\textsuperscript{29}. It is shown in Scheme IV. Pure chitosan (2 g) or blend of chitosan with gelatin (5% w/w of dry weight of chitosan) and chitosan with egg albumin (10% w/w of dry weight of chitosan) were dissolved separately in 1% acetic acid solution and stirred for 3 hours. To this, known amount of cefadroxil (20% w/w of dry weight of polymer) was added and mixed homogeneously. This polymeric solution was added dropwise into the mixture of methanol–HCl solution (20:1), containing 1% GA. Temperature was maintained at 25°C. Finally, the crosslinked IPN beads were separated from the mixture at selected time intervals i.e. after 5 and 10 minutes by filtration. The beads were washed with water and allowed to dry\textsuperscript{29}. 

Dose : 500 mg to 2 g daily, in divided doses.
Scheme IV

H₂N—ALBUMIN

+ CH₂OH

+ OHC—CHO

ALBUMIN

ALBUMIN

ALBUMIN

ALBUMIN

OCH₂
6.2.2. Measurement of bead size

Different samples of completely dried beads were randomly selected and their sizes were measured using a micrometer screw gauge (Sargent Co., USA) within an accuracy of ±0.01mm.

6.2.3. Swelling study

Swelling study was carried out by measuring the percentage water uptake by beads at different time intervals. Five IPN beads, exposed to glutaraldehyde for different time intervals were selected and kept on a watch glass containing distilled water. Watch glass was placed in an incubator. The beads were weighed at regular intervals of time (every 30 minutes), until a constant weight was achieved and the average value was calculated. Results are shown in Fig. 6.5.

6.2.4. Drying study

The beads formed were allowed to dry in an oven maintained at 40°C. Initial mass of the beads should be nearly equal for easy comparison. The beads were weighed at an hourly interval of time, until a constant weight was achieved. Mass measurements were done on a single pan analytical balance. In order to maintain the accuracy, experiments were carried out in triplicate. Results are shown in Fig. 6.6.

6.2.5. Drug content

The drug content was determined by incubating the known mass of beads with 5 ml of water, till the beads were swollen completely. The swollen beads were crushed using a mortar and pestle and the solution thus formed was
sonicated for 2 minutes using 60 MHz frequencies. The above solution was concentrated using rotary flash evaporator to form a thick paste, to which about 10 ml of methanol was added to extract the entire drug. The precipitated polymer was separated from methanol by centrifugation. After appropriate dilution with methanol, the absorbance of the solution was measured at 263 nm and the drug content was determined. The results are summarized in Table 6.4.

6.2.6. In vitro dissolution study

Dissolution studies were carried out in 900 ml phosphate buffer solution (pH 7.4) using the dissolution tester (Dissotest, Lab India) equipped with six pedals. The dissolution rates were measured at 37°C and 100 rpm speed. A 10 ml of aliquot was withdrawn from the vessel at predetermined time intervals (every 30 minutes) and replaced with an equal volume of corresponding dissolution medium. The samples were diluted appropriately before the assay. The amount of drug released was monitored by measuring the UV absorbance at 263 nm and concentration of drug was determined using the calibration curves constructed from reference standards (Fig. 6.7).

6.2.7. Stability studies

Chitosan as well as its IPN beads were placed in screw capped glass containers and stored at different temperatures (60°C, 37°C, room temperature and 5°C) and 75% RH (relative humidity) in an artificial humidifier for a period of 3 months. The samples were assayed for the drug content and observed for any physical changes at regular intervals (every week). The results are
summarized in Table 6.5, Table 6.6 and Table 6.7 for gelatin IPN, egg albumin IPN and GA crosslinked chitosan beads respectively.

6.3. RESULTS AND DISCUSSION

The IPN beads were prepared by varying the concentrations of chitosan, gelatin and egg albumin. The formation of beads was confirmed by FTIR spectroscopy and further characterization was done by assaying the drug content and rate of drug release.

6.3.1 Spectral studies

FTIR spectral data was used to confirm the chemical intactness of drug in the IPN beads. FTIR spectra of pure cefadroxil, GA crosslinked IPN and cefadroxil loaded GA crosslinked IPN were compared (Fig. 6.1). Amino groups of chitosan were converted into imine group (C=N), when treated with glutaraldehyde. The peak observed at 1647 cm⁻¹ indicated the formation of imine group (C=N) and confirmed the crosslinking of chitosan with GA (Table 6.1).

FTIR spectra of pure cefadroxil showed stretching bands at 2918 cm⁻¹ and 2850 cm⁻¹ due to the presence of -NH₂ group. The peak observed at 3221 cm⁻¹ was due to N-H stretching. The presence of C=O and -COOH groups were confirmed by the peaks observed at 1683 cm⁻¹ and 1753 cm⁻¹ respectively.

The spectra of cefadroxil loaded IPN beads exhibited bands at 2850 cm⁻¹ due to the -NH₂ group and at 1753 cm⁻¹ due to the -COOH group of the drug. A sharp peak at 1517 cm⁻¹ was due to C=C aromatic stretching. This indicates
noninvolvement of drug in any chemical interactions either with the polymer or the crosslinking agent.

Table 6.1. FTIR spectral data of chitosan derivatives

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of the compound</th>
<th>C=N</th>
<th>N-H</th>
<th>NH₂</th>
<th>O-H</th>
<th>C=O</th>
<th>-COOH</th>
<th>C=C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cefadroxil</td>
<td>--</td>
<td>3221</td>
<td>2918</td>
<td>3487</td>
<td>1683</td>
<td>1753</td>
<td>1517</td>
</tr>
<tr>
<td>2</td>
<td>GA crosslinked IPN</td>
<td>1640</td>
<td>--</td>
<td>--</td>
<td>3412</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>Cefadroxil loaded GA crosslinked IPN</td>
<td>1647</td>
<td>3252</td>
<td>2925</td>
<td>3425</td>
<td>1683</td>
<td>1753</td>
<td>1517</td>
</tr>
</tbody>
</table>
Fig. 6.1. FTIR spectra of (1) Cefadroxil, (2) GA crosslinked IPN and (3) Cefadroxil loaded GA crosslinked IPN
DSC studies

The DSC thermograms of cefadroxil, GA crosslinked IPN and cefadroxil loaded IPN beads were taken in air with a heating rate of 10°C/min and were compared (Fig. 6.2).

The polymorphism of drug and transition temperature of the polymer were studied before and after drug loading. After crosslinking with GA, the endothermic peak of chitosan shifted from 50°C to 74°C indicating the formation of IPN, which showed decomposition at 320°C (Table 6.2).

The thermogram of cefadroxil was compared with that of the formulation. In case of cefadroxil a sharp endothermic peak was observed at 190°C corresponding to the melting point of the drug. This peak did not appear in the DSC thermogram of cefadroxil loaded IPN beads, which indicated the molecular level dispersion of drug in the formulation and its intactness in the formulation.

Table 6.2. Thermal analysis data

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of the compound</th>
<th>DSC peaks (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Endothermic</td>
</tr>
<tr>
<td>1</td>
<td>Cefadroxil</td>
<td>190</td>
</tr>
<tr>
<td>2</td>
<td>GA crosslinked IPN</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>Cefadroxil loaded GA crosslinked IPN</td>
<td>65</td>
</tr>
</tbody>
</table>

218
Fig. 6.2. DSC thermograms of (1) Cefadroxil, (2) GA cross linked IPN and (3) Cefadroxil loaded GA crosslinked IPN
TGA studies

Effect of crosslinking and drug loading on thermal decomposition of chitosan was studied by thermogravimetry. TGA experiments were carried out on cefadroxil, GA crosslinked IPN and cefadroxil loaded IPN beads (Fig. 6.3), in an atmosphere of air.

As shown in Table 6.3, the GA crosslinked IPN showed a lesser weight loss (56%) as compared to chitosan (60%) at same temperature indicating, the crosslinking reduces the rate of thermal degradation.

Cefadroxil undergoes decomposition at 200°C, above which only 0.5% of char residue remains. Higher weight loss was due to the complete decomposition of the drug above its melting point. Drug loaded beads decomposed at the same temperature as that of pure drug and showed a higher weight loss as (62%) compared to plain chitosan. Since the melting point of drug is not altered, indicates the absence of chemical interaction with the polymer.
Table 6.3. TGA data of GA crosslinked IPN

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of the compound</th>
<th>Decomposition temperature (°C)</th>
<th>Mass loss (% Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cefadroxil</td>
<td>99-190 190-308</td>
<td>6 98.52</td>
</tr>
<tr>
<td>2</td>
<td>GA crosslinked IPN</td>
<td>38-218 218-465</td>
<td>7.12 56.17</td>
</tr>
<tr>
<td>3</td>
<td>Cefadroxil loaded GA crosslinked IPN</td>
<td>50-155 155-470</td>
<td>11.671 61.922</td>
</tr>
</tbody>
</table>
Fig. 6.3. TGA curves of Cefadroxil (-----), GA cross linked IPN (- - - - -) and Cefadroxil loaded GA crosslinked IPN (-----)
Characterization of beads

The IPN beads were evaluated using SEM. Beads were spherical in shape with the particle size ranging between 800 and 900 μm (Fig. 6.4). Either the formation of network or increased exposure time to the crosslinking agent did not affect the particle size but, the drug content varied both with the type of network and the time of exposure to the crosslinking agent (Table 6.4).

6.3.2. Swelling study

Swelling study was carried out in order to find out the effect of IPN formation and the extent of crosslinking on the release rate of cefadroxil from the matrix. It was performed by monitoring the percentage water uptake (Fig. 6.5). Chitosan and its IPNs are hydrophilic in nature and hence, transport of water through such polymers depends upon the rigidity of the polymer as well as the extent of crosslinking.

It may be noted from the results (Table 6.4) that the IPN formation significantly reduces the water uptake of chitosan beads. Further, the gelatin based IPN beads were more rigid than the egg albumin IPN beads as evidenced by the smaller extent of swelling of gelatin IPN when compared to the egg albumin IPN.
Fig. 6.4. SEM View of Chitosan IPN Bead
Fig. 6.5. Effect of IPN formation on rate of water uptake

(*) GA crosslinked chitosan beads, (▲) Egg albumin IPN beads, and (●) Gelatin IPN beads
The diffusion coefficient (D) was calculated for different types of beads. The values of D for sorption were higher than those observed for desorption experiments. These data show a dependence on the IPN formation. D values for sorption were found highest for chitosan beads and lowest for gelatin IPN beads. The intermediate values were found for the egg albumin IPN beads.

6.3.4. Drying study

In order to optimize the drying conditions, some samples of chitosan and its IPN beads were selected such that the initial mass should be nearly equal. Results of drying (Fig. 6.6) indicated that the IPN beads take longer time for drying than the plain chitosan beads. The gelatin IPN beads exposed to the crosslinking agent for 5 minutes required more time than those of the egg albumin IPN beads. This may be due to an increased rigidity of the polymer wall after formation of IPN, thereby showing a decreased desorption rate of the liquid from the beads.

The drying data were further analyzed to calculate the diffusion coefficient, D. Desorption values were smaller compared to sorption which is attributed to the slow drying of the beads (Table 6.4). However, the D values for desorption did not show any systematic dependence on the type of IPN chosen. In majority of cases, the lower D values were observed for the IPNs as compared to the chitosan beads.
Fig. 6.6. Effect of IPN formation on rate of drying

(*) GA crosslinked chitosan beads, (▲) Egg albumin IPN beads, (●) Gelatin IPN beads
6.3.5. Drug content

The results of % entrapment efficiency are presented in Table 6.4. GA crosslinked chitosan beads showed least drug content as compared to egg albumin IPN and gelatin IPN beads. Gelatin (5%) IPN beads with 5 minutes exposure to GA showed maximum and GA crosslinked chitosan beads (exposed to GA for 10 minutes) showed the minimum drug entrapment efficiency.

With the increase in time of exposure to the crosslinking agent, the IPN network becomes more rigid, which in turn results in minimum leaching of drug from the beads to the external medium. Whereas excess exposure to the crosslinking agent leads to decreased drug content due to less availability of intermolecular space within the IPN matrix. Hence the most suitable method of IPN formation with maximum drug content would be by exposing to the crosslinking agent for 5 minutes.

6.3.6. In vitro dissolution study

The dissolution study was carried out using phosphate buffer solution (pH 7.4) in a dissolution tester (Dissotest, Lab India) equipped with six paddles. The temperature was maintained at 37°C. Amount of drug released from the beads was subjected to a number of physical and chemical parameters including those related directly to the release medium, the release conditions (temperature and stirring rate) and those resulting from a change in the characteristics of the CR devices (beads).
Table 6.4. Results of % Drug content of cefadroxil-loaded GA crosslinked IPN beads

<table>
<thead>
<tr>
<th>Name of the Polymer</th>
<th>Time of exposure to GA (min)</th>
<th>% Drug content</th>
<th>$D_{\text{sorption}} \times 10^{-6}$ (cm$^2$/s)</th>
<th>$D_{\text{desorption}} \times 10^{-8}$ (cm$^2$/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitosan</td>
<td>5</td>
<td>83.71 ± 0.11</td>
<td>5.37</td>
<td>9.11</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>82.41 ± 0.03</td>
<td>2.05</td>
<td>7.02</td>
</tr>
<tr>
<td>Chitosan + 5% gelatin</td>
<td>5</td>
<td>88.22 ± 0.52</td>
<td>1.57</td>
<td>5.91</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>86.11 ± 0.11</td>
<td>1.23</td>
<td>3.86</td>
</tr>
<tr>
<td>Chitosan + 10% gelatin</td>
<td>5</td>
<td>84.84 ± 0.08</td>
<td>0.75</td>
<td>3.32</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>83.94 ± 0.12</td>
<td>0.51</td>
<td>2.64</td>
</tr>
<tr>
<td>Chitosan + 5% egg albumin</td>
<td>5</td>
<td>84.35 ± 0.84</td>
<td>1.74</td>
<td>6.11</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>83.65 ± 0.24</td>
<td>1.66</td>
<td>5.96</td>
</tr>
<tr>
<td>Chitosan + 10% egg albumin</td>
<td>5</td>
<td>83.61 ± 0.50</td>
<td>1.05</td>
<td>6.02</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>82.96 ± 0.12</td>
<td>0.98</td>
<td>5.81</td>
</tr>
</tbody>
</table>
Fig. 6.7. Effect of IPN formation on drug release

(♦) Chitosan beads, (●) Egg albumin IPN beads,
(▲) Gelatin IPN beads
In order to study the effect of the nature of network on the release kinetics, beads containing 20% w/w of (dry weight of polymer) cefadroxil were selected and the results are depicted in Fig. 6.7.

The rate of release of cefadroxil was much faster from the chitosan beads compared to its IPN beads. Further, the release of cefadroxil from the gelatin IPN is slow as compared to the egg albumin IPN. About 80% of cefadroxil was released from chitosan matrix in six hours whereas, only about 63% and 75% release occurred for the gelatin and egg albumin containing IPNs, respectively. Chitosan polymer might have become denser after the formation of IPN, thereby resulting in the decreased diffusion of drug.

6.3.7. Stability study

The beads were observed for any change in color or appearance and drug content, at regular intervals of time during storage. The results are summarized in Table 6.5, Table 6.6 and Table 6.7 for gelatin IPN, egg albumin IPN and GA crosslinked chitosan beads respectively.

IPN beads of plain chitosan, chitosan with egg albumin as well as chitosan with gelatin, were found to be stable at all the different temperature conditions. Maximum amount of drug was retained in gelatin IPN beads and least drug content was observed in chitosan IPN beads.
Table 6.5. Stability studies of Gelatin IPN beads

<table>
<thead>
<tr>
<th>Time in weeks</th>
<th>Percentage drug content at</th>
<th>Change in color and appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60°C</td>
<td>37°C</td>
</tr>
<tr>
<td>0</td>
<td>99.94±0.01</td>
<td>99.98±0.53</td>
</tr>
<tr>
<td>2</td>
<td>99.44±0.17</td>
<td>99.60±0.42</td>
</tr>
<tr>
<td>4</td>
<td>99.25±0.52</td>
<td>99.21±0.72</td>
</tr>
<tr>
<td>6</td>
<td>98.79±0.23</td>
<td>98.90±0.76</td>
</tr>
<tr>
<td>8</td>
<td>97.63±0.60</td>
<td>98.79±0.18</td>
</tr>
<tr>
<td>10</td>
<td>97.02±0.42</td>
<td>98.66±0.25</td>
</tr>
<tr>
<td>12</td>
<td>96.85±0.26</td>
<td>98.56±0.15</td>
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</table>

Table 6.6. Stability studies of Egg albumin IPN beads

<table>
<thead>
<tr>
<th>Time in weeks</th>
<th>Percentage drug content at</th>
<th>Change in color and appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60°C</td>
<td>37°C</td>
</tr>
<tr>
<td>0</td>
<td>100.0±0.03</td>
<td>100.0±0.04</td>
</tr>
<tr>
<td>2</td>
<td>99.50±0.14</td>
<td>99.76±0.12</td>
</tr>
<tr>
<td>4</td>
<td>99.10±1.31</td>
<td>99.54±0.54</td>
</tr>
<tr>
<td>6</td>
<td>98.90±0.3</td>
<td>99.12±0.67</td>
</tr>
<tr>
<td>8</td>
<td>97.80±0.1</td>
<td>99.01±0.23</td>
</tr>
<tr>
<td>10</td>
<td>96.70±0.21</td>
<td>98.7±0.07</td>
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<tr>
<td>12</td>
<td>96.50±0.24</td>
<td>98.57±0.12</td>
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Table 6.7. Stability studies of GA crosslinked chitosan beads

<table>
<thead>
<tr>
<th>Time in weeks</th>
<th>Percentage drug content at</th>
<th>Change in color and appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60°C</td>
<td>37°C</td>
</tr>
<tr>
<td>0</td>
<td>99.91±0.01</td>
<td>99.95±0.53</td>
</tr>
<tr>
<td>2</td>
<td>99.74±0.17</td>
<td>99.81±0.42</td>
</tr>
<tr>
<td>4</td>
<td>99.5±0.52</td>
<td>99.62±0.72</td>
</tr>
<tr>
<td>6</td>
<td>98.97±0.23</td>
<td>99.35±0.76</td>
</tr>
<tr>
<td>8</td>
<td>97.93±0.60</td>
<td>99.29±0.18</td>
</tr>
<tr>
<td>10</td>
<td>97.14±0.42</td>
<td>98.77±0.25</td>
</tr>
<tr>
<td>12</td>
<td>96.91±0.26</td>
<td>98.65±0.15</td>
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References


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