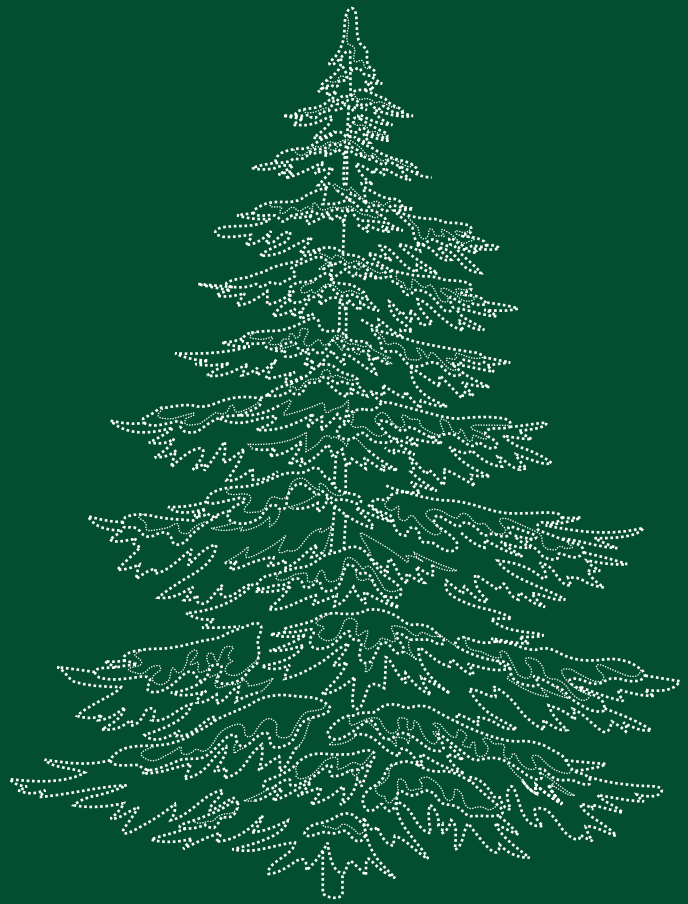


HYUNDAE Chemical Div. FECS

HYDROCEL-CR

Hypromellose

Truly

Controlled Release Polymer

Hydrophilic matrix systems designed with water-soluble polymers, such as Hypromellose, were first introduced in the early 1970's. Since then, development work has concentrated on controlled release technology, and many types of advanced polymers and techniques have become available. The hydrophilic matrix system is the simplest sustained release technology for oral dosage forms, consisting essentially of a drug and a water soluble, highly viscous polymer. It does not require any other excipient.

In the recent years, advances in this hydrophilic matrix system have allowed more controllable and reproducible drug release by controlling the chemical and physical properties of the polymer. Hydrocel-CR (Hypromellose) is especially suitable for this application, and provides a genuine consistency in the final products.

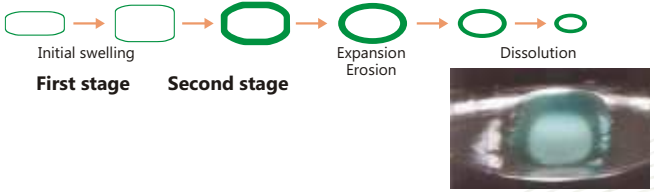
Hydrocel-CR, USP Hypromellose (HPMC), is designed for a hydrophilic matrix agent having tighter specifications, which is especially suitable for wet granulation and direct compression application.

The matrix system has several advantages as follows,

- It is very simple and easy to establish a formulation.
- The tablet is completely dissolved and thus achieves good bioavailability.
- It is easy to control the dissolution profile by selecting a specific grade.
- The matrix system is an economical method for obtaining controlled release products.

Figure 1 illustrates the schematic dissolution profile of the matrix tablet. After administration, hydrophilic matrix tablets made with Hyrocel-CR hydrate to form a gel layer, which regulates the drug release pattern. The most important aspect of this matrix system is the homogeneity of HPMC particle distribution in the tablet. The selection of Hydrocel grades affects the initial wetting, swelling, hydration and gel strength. In the first stage, usually within 30 to 60 minutes after administration, before the completion of the gel layer, the polymer particles on the tablet surface become partially hydrated. Sometimes surface erosion or excess dissolution can be observed in tins period. In the second stage, the gel layer is completed, and a steady dissolution of the active ingredient occurs.

Figure 1. Schematic dissolution profile of the matrix tablet



General information on major factors

Factors affecting the drug release are shown in table 1 and next page

Table 1. General Information on major factors affecting the drug release

• Solubility of drug	Solubility in water
	pH dependency
• HPMC properties	Substitution type of HPMC
	Viscosity of HPMC (related to molecular weight)
	Particle size
	Particle shape (related to bulk density)
• Composition	HPMC content in the tablet
	Tablet size
	Other excipients
• Preparation	Direct compression or wet granulation
	Compression force
	Tablet shape
	Film coating

Hydrocel includes several types with different levels of substitution. Chemical name and CAS registry numbers are listed below.

Table 2. Types of Hydrocel

Type	Methoxy (%)*1	Hydroxypropoxyl (%)*1	Name in the USP	CAS registry number Chemical name
AW	28.0—30.0	7.0—12.0	Hypromellose, Substitution type 2910	9004-65-3 Hypromellose, Hydroxypropyl Methylcellulose
BW	27.0—30.0	4.0—7.5	Hypromellose, Substitution type 2906	
CW	19.0—24.0	8.0—12.0	Hypromellose, Substitution type 2208	

*1: the ranges are expressed as the USP specification.

General information on major factors

- Drug solubility is one of the most influential factors for designing a drug release pattern. Highly water-soluble drugs require higher amounts of HPMC in the tablet.
- Suitable types of HPMC are the Hydrocel AW and CW grades, especially CW-CR grades, which have a characteristic of quick hydration and gel formation.
- The higher viscosity of HPMC or amount of HPMC in the tablet can decrease the drug release rate. Generally, an optimum content of Hydrocel in the tablet is at least 20%. If the content is below 20%, there is a risk for initial erosion or excess dissolution in the first stage.
- Preparation method also affects the dissolution profile due to the difference of HPMC particle distribution in the tablet. In the case of wet granulation, most of the water can be taken up by Hydrocel, resulting in the separation of Hydrocel and the other components. (i.e. large particles with high Hydrocel content and ungranulated drug in the fine particle fraction.) Direct compression methods can avoid such processing factors.

How to adjust the dissolution profile

In case dissolution is too fast:

- Increase the content of Hydrocel in the tablet formulation.
- Select higher viscosity grade of Hydrocel.
- Increase the tablet size.

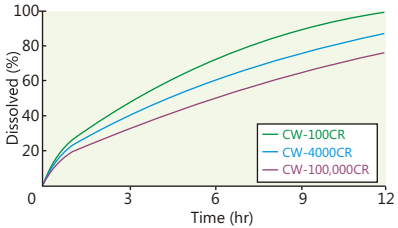
In case dissolution is too slow: Opposite adjustments of too fast dissolution.

Effect of drug solubility

For a highly water-soluble drug: Drug release is regulated by diffusion through the gel layer. In the first 30 minutes an excess amount of drug in the gel layer can release. The dissolution profile is shown in Figure 2.

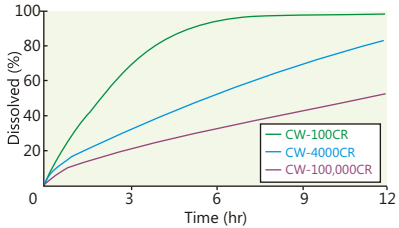
For a poorly water-soluble drug: Drug release is regulated by erosion of the matrix tablet. The dissolution curve is comparatively linier as compared with highly soluble drugs. The dissolution profile is shown in Figure 3.

Figure 2. Dissolution profile: High solubility in water



Formulation: Chlorphniramine maleate ___ 191 mg
Hydrocel-CR _____ 286 mg
Mg-stearate _____ 3 mg
Total _____ 480 mg/Tab

Figure 3. Dissolution profile: Low solubility in water



Formulation: Chlorphniramine maleate ___ 382 mg
Hydrocel-CR _____ 95 mg
Mg-stearate _____ 3 mg
Total _____ 480 mg/Tab

Compression: 11.3 mm flat, 480 mg/Tab, 80 MPa
Dissolution: According to the USP paddle method; paddle rotation: 10min-1; 900 mL of purified water, test perion: 12 hours; detection: UV.

Effect of substitution type

Substitution type of Hydrocel affects hydration speed of HPMC particles and gel strength, which can influence the dissolution profile (Figure 4).

Effect of viscosity

Viscosity of HPMC affects gel strength or erosion rate of the gel in the second stage, and hydration speed in the first stage. The higher the viscosity, the stronger the gel strength and the slower the hydration speed (Figure 3). By selecting the viscosity grade the dissolution profile can be easily controlled.

Effect of particle size

Large particles require longer hydration time, and in this period particles can swell certain volume (Figure 5). Hydrocel-CR has controlled particle size around 99% passing through 100 mesh, which is an ideal particle size for matrix application.

Effect of HPMC content

The content of HPMC in the matrix tablet significantly affects the initial erosion of the tablet in the first stage (Figure 5a, 5b, 5c). To avoid such a risk the content of HPMC should be 20% or higher.

Figure 4. Effect of various substitution types

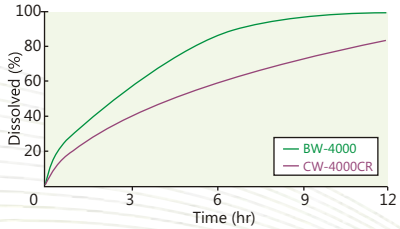


Figure 5a. Effect of HPMC content / CW-100CR

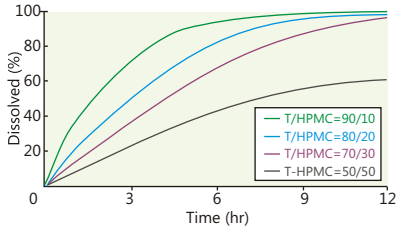


Figure 5b. Effect of HPMC content / CW-4000CR

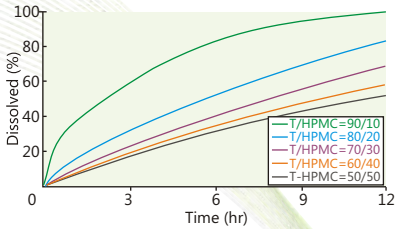
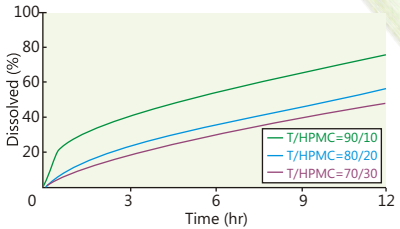


Figure 5c. Effect of HPMC content / CW-100,000CR



Compression & Dissolution conditions are the same in the previous page.

Formulation: Theophulline
Hydrocel-CR } 477 mg
Mg-stearate 3 mg
Total 480 mg/Tab

Summery of the major parameters

Increasing the parameters listed in the column of the table below could influence the drug release or tablet properties are summarized in the following table. For example, selecting a higher viscosity grade will increase initial erosion but decrease drug release in the second stage, and no change in tablet hardness.

Table 3. Summerized table for factors affecting the drug release from direct compression tablet

	Firs stage Initial erosion	Second stage Dissolution speed	Tablet hardness (before administration)
Formulation			
HPMC content ↗	Decrease	Decrease	Increase
Powder properties			
Average particle size ↗	Increase	Increase	Decrease
Bulk density ↗	Increase	Increase	Decrease
Chemical properties			
HPO content (CW) ↗	Decrease	Increase	No change
Viscosity ↗	Increase	Decrease	No change

Hydrocel includes several types of Hypromellose (USP). You may consult for the details of the other types and grades in separate brochure of Hydrocel.

General name	Hypromellose, substitution type 2208 USP/BP/pH.Eur/JP/IP	
Type	CW	CW-CR
Description and solubility	Confirms	
Characters	Confirms	
Identification (A-C)	Confirms	
Identification (A-F)	Confirms	
pH	5.5-8.0	
Viscosity	See table side	
Loss on drying	Not more than 5.0%	
Residue on ignition	Not more than 1.5%	
Residue on ignition	Not more than 1.0%	
Heavy metals	Within the limit (Not more than 0.001%)	
Appearance of solution	Confirms	
Chlorides	Not more than 0.5%	
OVI	Confirms	
Methoxy content	19.0-24.0%	
Hydroxypropoxy content	4.0-12.0%	8.0-12.0%
Particle size	—	99% passing through 100 mesh
Starting raw material	Wood pulp & Cotton linters	Wood pulp

Hydrocel-CR has a tighter specification for substitutions with controlled particle size as compared with regular Hydrocel, which is exclusively suitable for matrix applications, especially for wet granulation and direct compression.

Table 5. Available grades and viscosity specifications

Hypromellose		Labelled
CW	CW-CR	Viscosity
	O	100
O	O	4,000
O	O	15000
O	O	100,000
O	O	200,000

Nomenclature

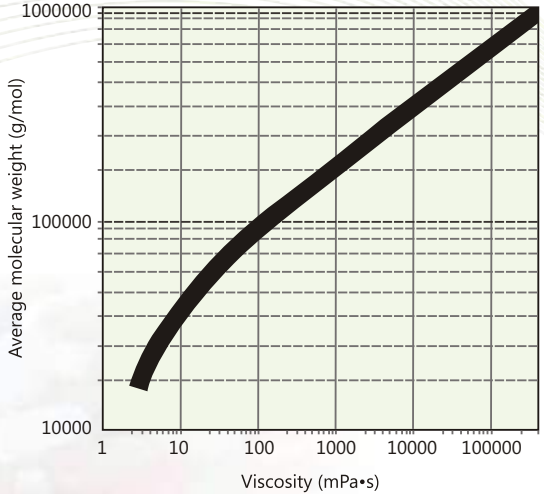
Substitution type	Labeled viscosity	Our Grades
2910	**15**	**AW**
2906	**4000**	**BW**
2208	**100,000**	**CW**

Please refer separate brochure of Hydrocel about the detailed solution properties.

Solution properties

The molecular weight of water-soluble polymer is closely related to their viscosities. The relationship is shown in Figure 6.

Figure 6. Molecular weight (Mw) vs. Viscosity

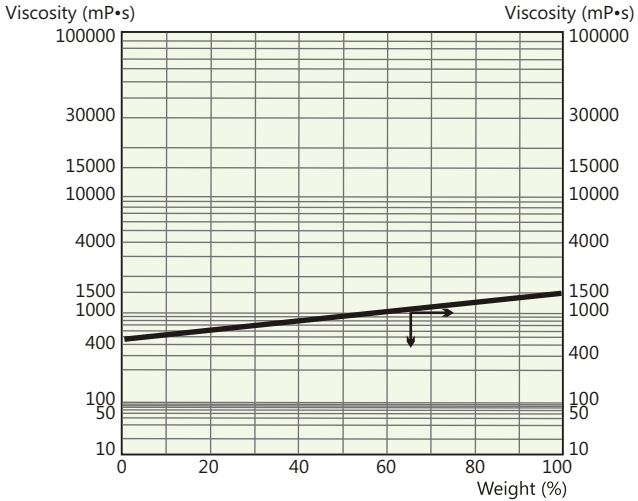


Note:
The viscosity in horizontal axis is expressed as capillary method of measurement according to the ASTM (USP method)

The desired viscosity can be obtained by the blending of different viscosity grades according to the instruction as follow. The blending chart has a special scale in viscosity for justification.

To achieve viscosity at 1000 mPas in Fig. 7, for example, the combination of 35% of a 400 mPa grade and 65% of 1500 mPas grade would give a 1000 mPas product.

Figure 7. Blending chart for intermediate viscosity



1) Theophylline (Direct compression)

Direct compression is the simplest technique to prepare matrix tablets. This essentially consists of drug substance and Hydrocel.

Drug substance, which usually shows poor flowability, is primarily granulated in a fluidzied-bed granulator.

1-1) Formulation of tablet

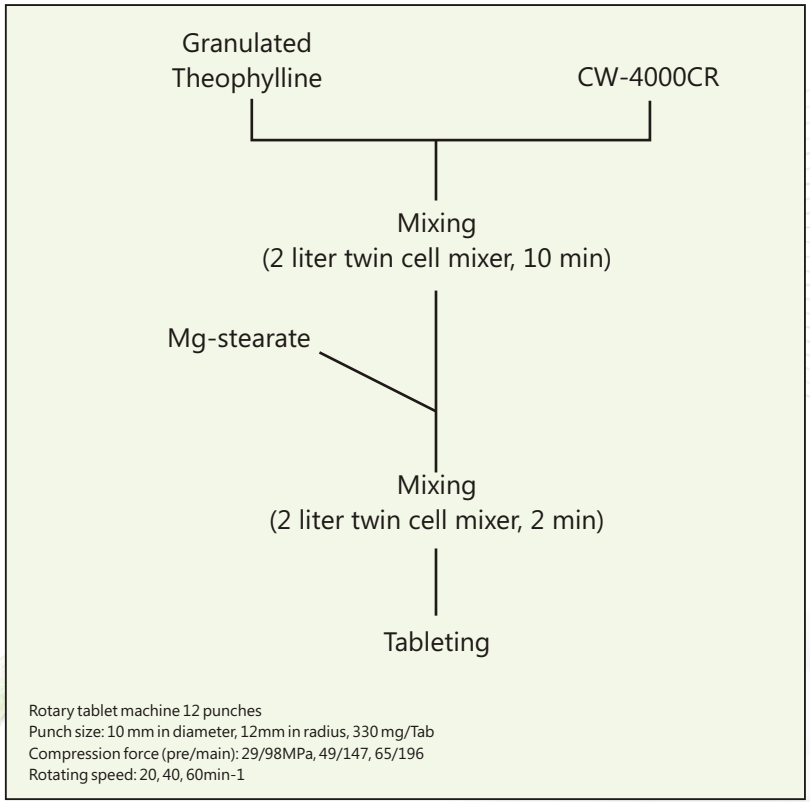
Ingredient	mg/Tablet
Theophylline*	264
CW-4000CR	64.5
Mg-stearate	1.5
Total	330 mg/Tab

*Theophylline powder was granulated by a fluidized bed.
Mixing rat; Theophylline 97%, Hydrocel AW63%

Fluidized-bed granulation
Machine: Fluidized-bed Flowcoate FLO-5 (Fruend)
Charge: 3 kg of Theophylline
Supply drying air temperature: 80°C
Exhaust air temperature: 35°C
Binder solution: Hydrocel AW6 7% aq.soln.
Spray feed rate: 60 g/min
Powder properties of granule
Bulk density: 0.34 g/mL
Tapped density: 0.47 g/mL
Average particle size: 170 μm

The resultant Theophylline powder showed good flowability and mixing ability to Hydrocel powders.

1-2) Mixing procedure of the powders for compression



Rotary tablet machine 12 punches
Punch size: 10 mm in diameter, 12mm in radius, 330 mg/Tab
Compression force (pre/main): 29/98MPa, 49/147, 65/196
Rotating speed: 20, 40, 60min-1

1-3) Results

Figure 8. Dissolution profiles of Theophylline tablets in different buffer solutions and water

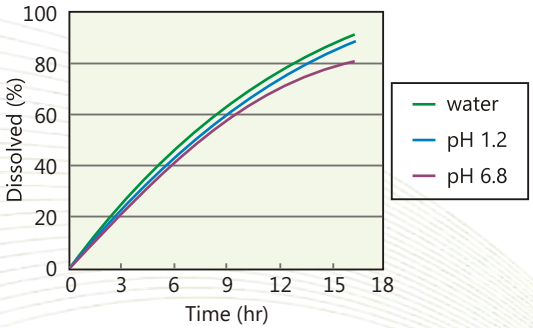


Figure 9. Dissolution profiles of Theophylline tablets with several rotation speed levels

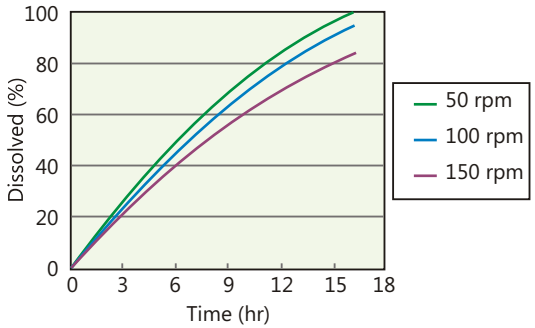


Figure 10. Dissolution profiles of Theophylline tablets at different compression force

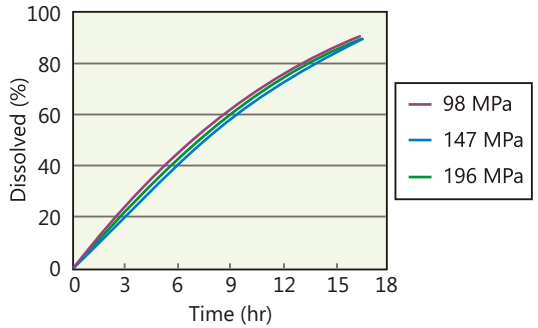


Figure 11. Tablet weight deviations between CW-4000CR and regular product

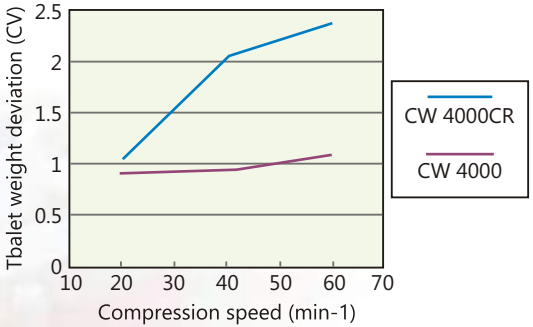


Figure 12. Tablet hardness of Theophylline direct compression tablet at different turn table speed (CW-4000CR)

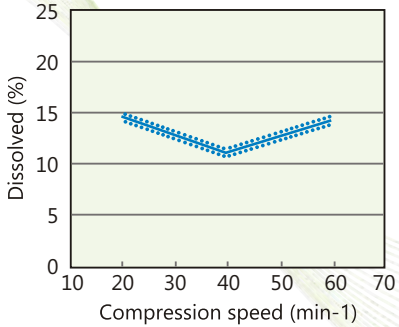
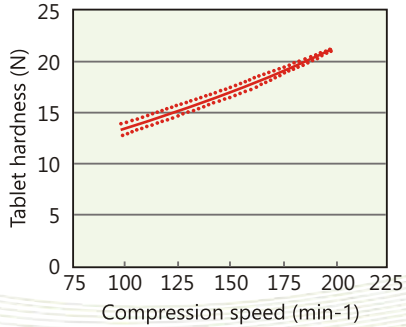


Figure 13. Tablet hardness of Theophylline direct compression tablet at different compression force (CW-4000CR)



Dissolution test: According to the USP method (Paddle method)
Dissolution medium: Purified water, pH1.2, pH6.8, 900mL
Paddle rotation: 100 (50, 150) min^{-1}
Test periods: 16 hours

In this section, important precaution for handling Hydrocel are brought to your attention. Before using Hydrocel, be sure to read the "Material Safety Data Sheets (MSDS)"; these sheets contain detailed information about safety.

Definition fo symbols

Warning Error in operation may result in death or server injury of the user.
Caution Error in operation may result in injury or property damage.

Warning

When a large amount of Hydrocel dust is present in the air, a dust explosion may occur in the presence of flames or electrostatic sparks. (Minimum explosive dust condition: 30 g/m^3). In place where dust may accumulate, utilize local exhaust ventilation systems which are explosion-proof. Dust must be kept away from ignition sources such as fire, or electrostatic sparks.

Warning

A void mixing Hydrocel with peroxides or other oxidizing agents as Hydrocel reacts vigorously with them, add heat or 4 flames may be generate.

Warning

Never use the material in medicine or medical tools that come into contact with human blood, such as medicines given by injection.

Caution

As Hydrocel is easily flammable, take the following points into account.

Keep the material away from heat, sparks and flames. In the event of fire, use water spray, dry chemical powder, or carbon dioxide gas to extinguish it.

When Hydrocel burns, carbon dioxide and some poisonous substances, such as carbon monoxide, methanol, acetaldehyde, fromic acid, acrolein, etc. are formed. Use the appropriate protective equipment.

When storing large quantities, comply with local, state, provinicial or national regulations.

Caution

As the dust from Hydrocel may cause irritation to the skin, eyes, and throat, use protective glasses, a protective mask, and protective gloves when handling large quantities. In case of eye contact, flush eyes with water for at least 15 minutes while keeping the eyelids open.

In case of skin contact, wash off thoroughly with flowing water or soapy watery. If inhaled, immediately move to fresh air and gargle with fresh water. If a large amount of Hydrocel dust is inhaled, and the throat or nose shows signs of abnormality, immediate medical attention should be sought.

HYUNDAE Chemical Div.

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For more information, additional literature & product samples please contact us

PIOMA GROUP

Head Office & Worldwide Distribution Centre :
101-103, Shyam Kamal 'D'
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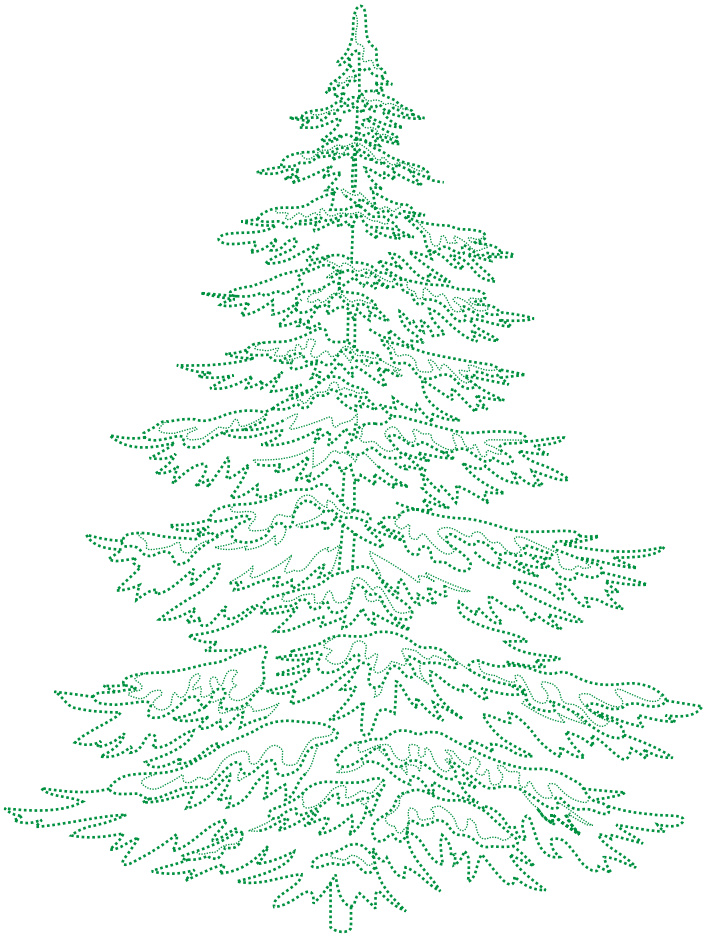

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