Excipients
NISSO HPC
APPLICATION NOTE

NOTE #: CR-2012-AAPS
APPLICATION: Matrix tablet

High Viscosity Grade of Hydroxypropyl Cellulose (HPC-H) for Hydrophilic Matrix, Sustained Release Formulation

SUMMARY

High Viscosity Grade of Hydroxypropyl Cellulose (HPC) is thought as an effective controlled release (CR) material since it is a hydrophilic polymer. In this study, we investigated effects of viscosity, particle size, preparation method and difference of controlled release polymer on drug release using Theophylline as model drug. The results showed viscosity, particle size and preparation method affected the drug release, and optimization of particle size was more critical for DC method. Also, HPC was found to sustain drug release more effectively than Hydroxypropylmethyl Cellulose (HPMC) in the case of the equivalent viscosity.

INTRODUCTION

HPC is a hydrophilic polymer which is solubilised by introducing hydroxypropyl groups that hinder the hydrogen bonding of hydroxyl groups of cellulose. HPC is also thought as an effective CR material since it is a hydrophilic polymer which swells and becomes a state of hydro-gel in water, and releases drug slowly with dissolution and diffusion. In this study, we investigated effects of viscosity, particle size, preparation method (direct compression and wet granulation) and CR materials (HPC and HPMC) on tablet properties and drug release using Theophylline as model drug.

MATERIALS

Controlled Release Materials

CR Materials	Viscosity* (mPa·s)	D_{50} (μm)
HPC-M-FP (Nippon Soda Co., Ltd)	300	107
HPC-H-FP (Nippon Soda Co., Ltd)	1685	108
HPC-H-FP (Nippon Soda Co., Ltd)	3089	91
HPC-H (Nippon Soda Co., Ltd)	3040	190
HPMC 4000 (Metolose 90SH-4000SR, Shin-Etsu Chemical Co., Ltd.)	4040	90
HPMC 100000 (Metolose 90SH-100000SR, Shin-Etsu Chemical Co., Ltd.)	90200	95

*2% acqueous solution @ 20˚C

Tablet Formulation

Ingredients	%
Theophylline (Shiratori Pharmaceutical Co., Ltd.)	50
MCC (Avicel PH-101, FMC Corporation)	19
CR Polymer	30
Silica (Silysia 350, Fuji Silysia Chemical, Ltd)	0.5
Magnesium Stearate (Wako Pure Chemical Industries, Ltd.)	0.5

METHODS

Preparation of Direct Compression (DC) tablet

Powder for tablet was prepared by dry-mixing of materials except Magnesium Stearate in PE bag for 3 minutes. This was followed by addition of Magnesium Stearate and further dry-mixing for 30 seconds. Laboratory scale rotary tablet press machine (VELA5, KIKUSUI SEISAKUSHO Ltd.) was used to compress tablet at 10kN of compression force. Tablet weight was 200mg and its diameter was 8mm.

Preparation of Wet Granulation (WG) tablet

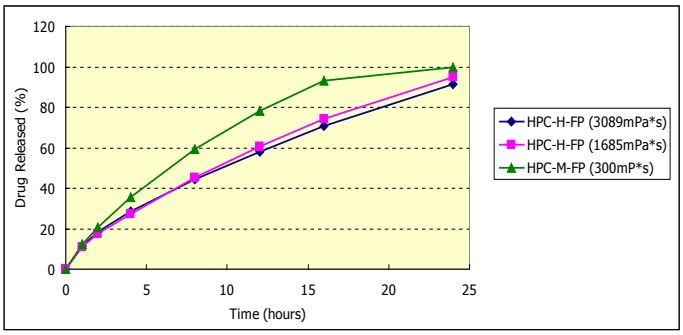
Wet granulation process was carried out in high shear mixer granulator (FS-GS-5, FUKAE PAWTEC Co., 500g Scale). All powder except Silica and Magnesium Stearate were added to the granulator and dry mixing for 1 minute. Granulation was operated for 4 minutes with pouring 30g of distilled water. The impeller and chopper were operated at constant speeds of 400 rpm and 1500 rpm respectively. The granules were predried and milled using 3mm grated screen followed by drying at 52˚C and dried with fluidized bed system (FL-LABO, FREUND Co., Ltd.) at 80˚C followed by milled using 1 mm grated screen. Powder for tablet was prepared by dry-mixing granules of 30 mesh pass and silica in PE bag for 3 minutes. This was followed by addition of Magnesium Stearate and further dry-mixing for 30 seconds. Tablet was prepared at 15kN of compression force by the same tablet machine as DC method. Tablet weight was 200mg and its diameter was 8mm.

Measurement of Dissolution Profile

Release of theophylline was measured according to JP method and concentration of theophylline at each time point was determined by measurement of absorbance at 271nm with UV spectrophotometer.

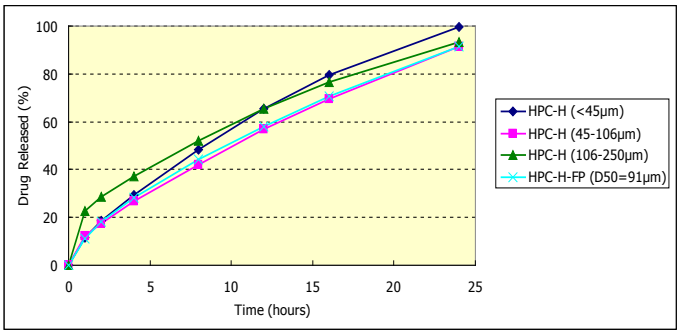
RESULTS AND DISCUSSION

Fig. 1: Effect of Viscosity (DC method)



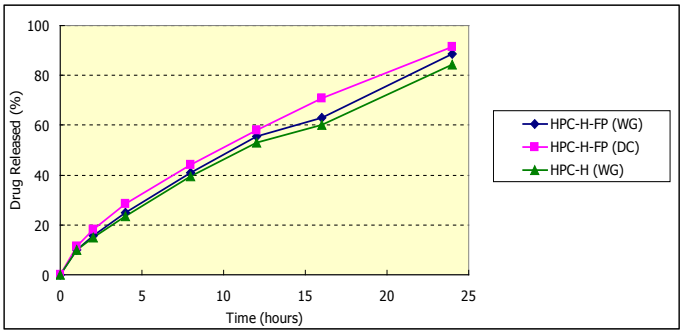
(Fig 1) Drug release from tablet prepared by HPC-M-FP was much faster than HPC-H-FP since its viscosity was much lower. However, a difference in drug release profile viscosity of HPC-H-FP (1685mPa*s vs 3089mPa*s) was not observed.

Fig. 2: Effect of Particle Size



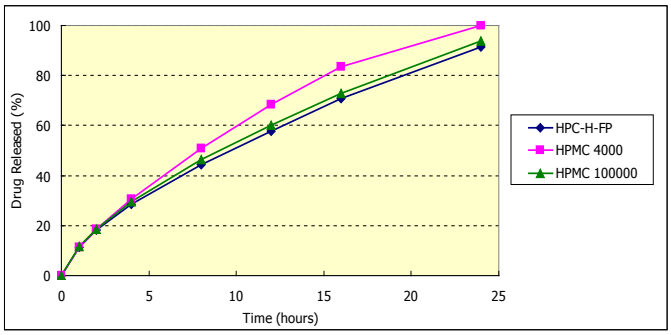
(Fig. 2) In the case of bigger particle size, initial drug release rate was faster since disintegration of tablet may start before hydro-gel formation due to poor tablet hardness. In the case of finer particle size, harder tablet hardness could be obtained and initial drug release could be sustained. However, diffusion and dissolution of hydro-gel was also faster due to smaller size of gel. As a result, drug release became faster gradually. The results showed ideal range of particle size was 45-106µm and HPC-H-FP was found to be within the range.

Fig. 3: Effect of Preparation Method



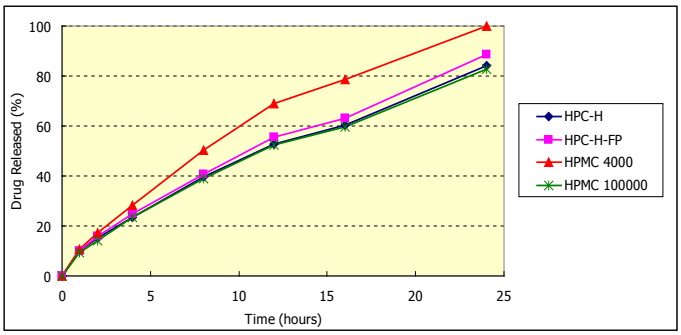
(Fig. 3) The result showed drug release from WG was sustained a little more than DC. The reason seems formation of hydrophilic matrix of granule level is more effective to sustain drug release than the one of tablet level. Also, effect of particle size was not seen in the case of WG method.

Fig. 4: Effect of CR Polymer (DC Method)



(Fig. 4) In the case of DC method, HPC-H-FP sustained drug release more than HPMC 4000, and showed equivalent release control performance to HPMC 100000 while its viscosity was much lower.

Fig. 5: Effect of CR Polymer (WG Method)



(Fig. 5) In the case of WG method, much difference was not seen in comparison of drug release from tablet prepared by HPC-H and HPC-H-FP. Also, Both HPC-H and HPC-H-FP showed equivalent release control performance to HPMC 100000. Drug release from tablet prepared by HPMC 4000 was much faster than the others.

CONCLUSIONS

- The results showed drug release rate depended on viscosity and particle size and effect of particle size was more critical in the case of DC method.
- The result showed ideal range of particle size might be 45-106µm and in the case of bigger particle size, initial drug release became faster, and in the case of finer particle size, drug release rate became faster gradually while initial was sustained well.
- Particle size was found to affect on drug release in the case of WG method.
- HPC was found to sustain drug release more effectively than HPMC in the case of the equivalent viscosity.
- In both DC and WG method, HPC-H was found to have equivalent control release performance to HPMC 100000 while its viscosity is much lower.

Head Office
Nippon Soda Co., Ltd
2-1 2-Chome, Ohtemachi
Chiyoda-ku, Tokyo 100-8165 Japan
(T) +81-3-3245-6159
info@nippon-soda.co.jp

U.S./Canada
Nisso America Inc.
88 Pine Street, 14th Floor
New York, NY 10005 USA
(T) +1-212-490-0350
info@nissoamerica.com

Europe
Nisso Chemical Europe, GmbH
Berliner Allee 42, 40212
Duesseldorf, Germany
(T) +49-(0)-211-1306686-0
info@nisso-chem.de