T2174

A comparison of the dissolution properties of 2 HPMC (hypromellose) capsules filled with basic compounds in acid media

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BACKGROUND

There are two types of hypromellose capsules that are manufactured by different methods.
1) The 'cold dip' method - forming HPMC capsules at ambient temperatures and requires carrageenan as a gelling agent
2) The 'thermal gelling' method - utilizing HPMC at higher temperatures without a gelling agent

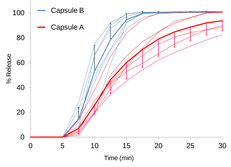
We previously compared capsules made by both methods and reported that capsules made by the 'cold dip' method were superior in terms of capsule strength and drug dissolution rate (Poster, AAPS Annual Meeting, 2010, New Orleans, W4188)[1].

PURPOSE AND HYPOTHESIS

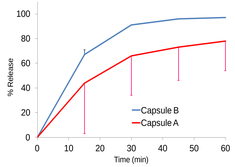
Ku *et. al.* (Int. J Pharm.,2011, 416(1), 16-24)[2] recently claimed that hypromellose capsules made by the cold dip method showed retarded dissolution profiles in the following conditions.
1) Dissolution in acidic media
2) When API is a basic compound with two different pKa's.
They speculated that the retardation was due to an interaction between carrageenan and these compounds.

In this study, we investigated dissolution from 2 types of hypromellose capsules to clarify these claims and to find out if basic groups interfere with dissolution from capsules manufactured with carrageenan.

Dissolution reported by Ku *et. al.* (2011)



Compound 1 (Structure : Not disclosed)



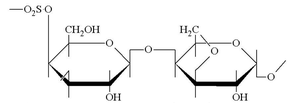
Compound 2 (Structure : Not disclosed)

Cpd	Form	P_{eff}	pKa	Fill Weight (mg)	Dissolution media	Solubility in medium (mg/mL)	Sink ratio	Paddle speed (rpm)
1	Salt	Low	4.7, 7.7 (base)	80	0.1N HCl	23.9	269	50
2	Base	High	7.9, 4.7, 3.3	100		43.3	390	

MATERIALS AND METHODS

Capsules: Size 1 hypromellolse capsules were obtained from the Japanese market:
Capsule A (Quali-V®, made by 'cold' dip method) with carrageenan/ KCl
Capsule B (Vcaps Plus®, prepared by'thermal gelling' method). without gelling agent

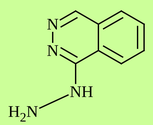
Structure of kappa-carrageenan (CA) utilized in Capsule A



Dissolution test:
Equipment: Distek Dissolution Apparatus Model 2100C with a fiber-optic UV detection system was employed. Data were collected from 6 samples and were submitted for analysis.
Conditions: Paddle method at 50 rpm in 900 mL 0.1N HCl, 34mM NaCl (1st fluid, JP16) at 37°C
JP-sinkers were used to keep capsules submerged.
Capsule contents: HPMC capsules were filled with each neat API (Hydralazine HCl : 50 mg, Pilocarpine HCl : 5 mg, Ampicillin trihydrate : 100 mg).
Solubility test: Quantified by UV after each compound was equilibrated in 0.1N HCl, 34mM NaCl at 37°C for 24 hours
Statistical analysis on dissolution profile:
Sample data were examined for statistical difference by F-test for equality of variances followed by t-test for equality of mean values. When the equality of variances was rejected, then Welch's t-test was used to investigate if the data from two groups could be regarded as equal.

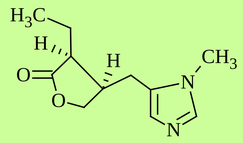
Compounds used in this study

Hydralazine



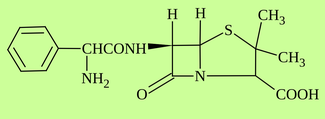
Hydrochloride, pKa = 0.5, 7.3

Pilocarpine



Hydrochloride, pKa = 1.6, 7.1

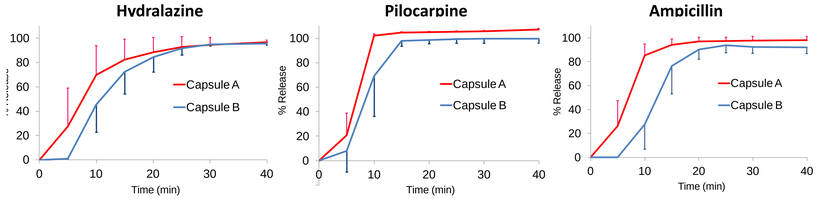
Ampicillin



Trihydrate, pKa = 2.5, 7.3

Cpd	Form	P_{eff}	pKa[5]	Fill Weight (mg)	Dissolution media	Solubility in medium (mg/mL)	Sink ratio	Paddle speed (rpm)
Hydralazine	Salt	Low[3]	0.5, 7.3	50	0.1N HCl 34mM NaCl (JP 1st)	45	810	50
Pilocarpine	Salt	High[4]	1.6, 7.1	5		418	75,240	
Ampicillin	Salt	Low[3]	2.5, 7.3	100		124	1,116	

RESULTS



- Dissolution tests in acidic media showed that Capsule A (with carrageenan) compared to Capsule B (no gelling agent) had shorter rupture times and improved dissolution rates, for the three structurally different APIs. The dissolution profiles of Capsule A were faster and with less variation especially during the initial stage of the test
- The result indicated there is no general charge interactions between carrageenan and basic groups of compounds that could interfere the dissolution in acid conditions

SUMMARY TABLE OF CAPSULE COMPARISON STUDIES

Film Strength	Capsule Strength	Disolution (Acetaminophen)	Dissolution in Acid Media (Basic compounds)
Cold dip method offered excellent results in tensile strength and film elongation	Capsule A showed superior scores for strength and brittleness	Capsule A was superior in dissolution speed with less variation in all pH media tested (water, pH1, pH4 and pH6.8)	Dissolution rate and variation of Capsule A was excellent in Acidic Media

CONCLUSIONS

- This study showed that the dissolution rate from hypromellose capsules made with carrageenan filled with basic compounds in acid media was superior to those made by the 'thermal gelling' method.
- Carrageenan that is included in these capsules appeared to act as a promoter of dissolution.

BIBLIOGRAPHY

1) Uyama T., Inui A., Kokubo T. (2010) Evaluation of the properties of HPMC capsules manufactured using different methods. Poster W4188, AAPS Annual Meeting, New Orleans, November 2010.
2) Ku MS, Lu Q, Li W, Chen Y. (2011) Performance qualification of a new hypromellose capsule: Part II. Disintegration and dissolution comparison between two types of hypromellose capsules. Int J Pharm.416(1):16-24.
3) Paixão P, Gouveia LF, Morais JA. (2010) Prediction of the in vitro permeability determined in Caco-2 cells by using artificial neural networks. Eur J Pharm Sci. 41(1):107-17
4) Zhang X, Zheng N, Rosania GR. (2008) Simulation-based cheminformatic analysis of organelle-targeted molecules: lysosomotropic monobasic amines. J Comput Aided Mol Des, 22(9):629-45
5) pKa's of Drugs and Reference Compounds. (2003) A Practical Guide to Contemporary Pharmacy Practice, 2nd edition, (Ed by JE. Thompson and L Davidow) Appendix H