Thai Journal of Pharmaceutical Sciences (TJPS)

5th International Conference on Pharmaceuticals, Nutraceuticals and Cosmetic Science (IPNaCS 2017)

Investigation of Cellulose Ethers as Gelling Agent in High Alcoholic Formulations

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Keywords: Ibuprofen, Topical gel, Cellulose ether, Hydroxypropyl methylcellulose

Introduction

Cellulose ethers are polymers produced by chemical modification of cellulose. Mostly used cellulose ethers in pharmaceuticals are methylcellulose (MC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) and sodium carboxymethyl cellulose (NaCMC). These polymers are non toxic and non irritant to skin, less sensitive for microbial contamination than natural gelling agents and stable in wide range of pH.[1] The solubility of these polymers in binary organic and organic solvent/water systems must be investigated individually. The compatibility of the ingredients in the formulation should be determined to provide stable gel preparation. Ibuprofen was used as a model drug because its solubility in water is very low (0.21%w/w at 25°C) and its topical dose is 5%w/w. Thus the supersaturated solution in gel preparation must be obtained by the use of cosolvent which always are ethanol (or isopropyl) and propylene glycol that also act as permeation enhancers. Ibuprofen is a relatively lipophilic drug which the log P of 4.0. The pK_a is 4.54 and will ionize at physiological pH value.[2] Whitefield *et al*. reported their comparative efficacy study and found that 5%w/w ibuprofen gel showed similar efficacy to oral tablet of 400 mg taken three times per day. [3] For delivery of drug via transdermal, ibuprofen gives high flux of drug transport even in high ionized situation.[4] To formulate gel preparation of such a very high concentration of ibuprofen, cosolvent system with highly stable gelling agent was our research interests.

The objectives of this study were to find an appropriate solvent system to dissolve a sufficient amount of ibuprofen and to investigate the appropriate gelling agent from five cellulose ethers: MC, HEC, HPMC, HPC and NaCMC. The most appropriate gelling agent was selected for optimization study. The gels were evaluated for physical appearance, viscosity, drug content and physical stability.

Methods

Solubility of Ibuprofen in solvent mixtures and gelling agent compatibility study

An excess of ibuprofen was added to 50 ml of solvent mixture prepared by varying isopropyl alcohol (IPA) from 10-30%w/w, with propylene glycol (PG) at 10 or 20%w/w and water that was added up to 100%w/w. The solid-liquid mixtures were then stirred for 5 h at room temperature. Samples were then allowed to precipitate. Dissolved ibuprofen was determined by measuring absorbance after appropriate dilution and calculated from previously constructed calibration curve from analytical method validation. An appropriate solvent mixture was selected and used to perform the compatibility study with five cellulose ethers which were MC, HEC, HPC, HPMC and NaCMC by mixing 50 g of 2-4% hydrogels with 5 g of ibuprofen dissolved in 30 g of IPA and 15 g of PG and 5 g of water.

Preparation of ibuprofen gel

Firstly, stock of gelling agent was previously hydrated at the concentration of 6%w/w. Secondly, Ibuprofen was dissolved in IPA and PG then the resulted clear solution was gradually added in hydrogel and stirred gently. Poloxamer 407 (previously dispersed) or PEG 400 and alkaline solution were added after the

preparation was mixed thoroughly and the left DI water was added to give a total weight of 100 g. Table 1 demonstrates the eight gel formulations.

Table 1 The compositions of the formulations.

Ingredient	Concentration %w/w							
	Rx1	**Rx2**	**Rx3**	**Rx4**	**Rx5**	**Rx6**	**Rx7**	**Rx8**
Ibuprofen	5	5	5	5	5	5	5	5
IPA	30	30	30	30	30	30	30	30
PG	15	15	15	15	15	15	15	15
6% HPMC	30	30	30	30	30	30	30	30
Poloxamer 407	-	5	-	5	-	5	-	5
PEG 400	-	-	5	5	-	-	5	5
40% NaOH solution	-	-	-	-	1	1	1	
DI water qs to	100	100	100	100	100	100	100	100

Drug content analysis

One gram of ibuprofen gel was accurately weighed and dissolved in 100 ml of phosphate buffer pH 7.2. The solution was then diluted by pipetting 1 ml and transferred to a 50 ml-volumetric flask. The volume was adjusted with phosphate buffer pH 7.2. The drug content was measured spectrophotometrically at 221 nm against corresponding placebo gel solution in phosphate buffer pH 7.2 as blank. The absorbance was transformed to concentration by using linear regress line from analytical method validation results.

Gel viscosity

The viscosity of the gel preparations was measured by using a Brookfield Viscometer (DV-II+). The gels were rotated at 3 rpm using spindle no.S34 at controlled room temperature (27°C-30°C).

Measurement of pH

One gram of each formulation was dispersed in 5 ml of DI water and mixed well. The pH of the gel preparations was determined by using pH meter. The measurement of each formulation was done in triplicate.

Stability study

The formulations were stored in accelerated stability chamber at 45°C/75%RH. Stability was evaluated by visual inspection of appearance and analysis of the drug content after 6 months.

Results

Solubility of Ibuprofen in solvent mixtures and gelling agent compatibility study

Spectrophotometric method for determining ibuprofen in solvent mixture and in formulation was developed and validated. Ibuprofen showed maximum absorption wavelength at 221 nm in phosphate buffer pH 7.2. The correlation coefficient was found to be 0.9996 which showed good linear relationship between concentration and absorption. Table 2 shows the results of the proposed method validation. The assay method was selective, accurate and linear over the studied range. The proposed method can be used for the drug assay in the routine formulation study.

Table 2 Results of method validation.

Parameters	**Results of method validation**		**Acceptance criteria**
Linearity and Range	Concentration range	0.25 – 1.50 mg%	Range = 80 –120% of the test concentration R^2 should be > 0.9990
	Regression equation	Abs = 0.4551 Conc. + 0.0001	
	Correlation (r^2)	0.9996 ± 0.0001	
Accuracy	%Test concentrations	50 -150% (0.5, 1.0, 1.5 mg%)	%Recovery should be 98-102 %RSD not more than 2.0%
	%Mean recovery	100.94 ± 0.93	
	%RSD	0.88 ± 0.43	
Precision (Intraday)	Analyst 1 (n=6), Rx4	Mean %assay : 102.09 ± 0.42	%RSD not more than 2.0%
		%RSD: 0.41	
	Analyst 2 (n=6), Rx8	Mean %assay :105.59 ± 0.77	
		%RSD: 0.73	

Table 3 Solubility of ibuprofen in ternary mixtures.

Ternary mixtures (IPA:PG:water)	Solubility (%w/w) (mean±SD)	Dielectric constant (ε)
10:10:80	0.03 ± 0.00	67.8
20:10:70	0.34 ± 0.02	61.8
30:10:60	4.43 ± 0.33	55.8
10:20:70	0.35 ± 0.02	63.2
20:20:60	0.89 ± 0.08	57.2
30:20:50	8.76 ± 0.08	51.1

The solubility of ibuprofen in the various solvent systems is shown in Table 3. The maximum solubility (8.76 ± 0.08 %w/w) was found in the solvent mixture containing IPA:PG:DI water at 30:20:50 that the dielectric constant value is 51.1. To dissolve 5%w/w of ibuprofen, the %IPA should be up to 30% while the %PG should be around 10%. To ensure the solubility of the drug after formulating with other excipients subjected to add for increase the efficacy of the formulation, 30%w/w of IPA and 15%w/w of PG were selected to use for further development. In this system the dielectric constant is equal to approximately 53.3. The dielectric constants of IPA, PG and water used for calculation are 18.3, 32 and 78.5, respectively.[5]

The compatibility with various hydrogels is shown in Table 4. At the beginning of the addition of ibuprofen solution into each hydrogel, it was miscible. Higher amount of the solvent mixture added, the MC, NaCMC and HPC gels became more turbid and the gelling agent was separated out of liquid. Both HEC and HPMC were still clear but only HPMC could completely mix up with the drug solution containing such a high concentration of IPA.

Table 4 Compatibility of various hydrogels with ibuprofen in ternary mixtures (IPA:PG:DI water = 30:15:5).

Cellulose ethers	Compatibility	Appearance
HEC	✓	Incompletely miscible
HPMC	✓✓	Completely miscible and clear
MC	×	Undergo syneresis and turbid
NaCMC	×	Undergo syneresis and turbid
HPC	××	Undergo syneresis and highly turbid

Evaluation of ibuprofen gel

All of ibuprofen gels were clear, smooth and homogeneous at the initial time of preparation. Formulation Rx1, Rx3 and Rx5 became slightly turbid after storing in room temperature for a few days. Table 5 shows the individual evaluation data of ibuprofen gels after preparation.

The pH values of the gels strongly varied with the adding of sodium hydroxide. Rx1-Rx4 had pH values between 3.69 ± 0.02 to 4.37 ± 0.01 while Rx5-Rx8 had pH values between 7.17 ± 0.01 to 7.51 ± 0.01. Sodium hydroxide was added to make ibuprofen ionized and dissolved.

Viscosities of the gels were found to vary from 5758 ± 65 to 14738 ± 50 cps depended on the exact composition of the ingredients in each formula. The formulations containing both poloxamer 407 and PEG 400 had the higher viscosities (Rx4 and Rx8).

The %drug contents were evaluated and found to be in the official limits (99.26 – 105.09%LA).

Table 5 Evaluation data of ibuprofen gels after preparation.

Gel property	Rx1	Rx2	Rx3	Rx4	Rx5	Rx6	Rx7	Rx8
Clarity	Translucent	Clear	Translucent	Clear	Translucent	Clear	Clear	Clear
pH	3.69 ± 0.02	4.01 ± 0.02	3.98 ± 0.01	4.37 ± 0.01	7.51 ± 0.01	7.41 ± 0.01	7.17 ± 0.01	7.32 ± 0.01
Viscosity (cp)	5881 ± 60	6720 ± 58	7178 ± 54	10332 ± 43	5758 ± 65	9378 ± 40	7580 ± 61	14738 ± 50
%Assay	99.26	99.73	102.72	101.72	101.01	100.48	101.89	105.09

Stability study

Stability of all gel formulations was carried for physical appearance and %drug contents. The %assays for ibuprofen stored at 45°C/75%RH for 6 months were found no significant loss. Rx1, Rx3 and Rx4 became highly turbid, Rx2 was clear but the gel was not homogeneously disperse. Rx5-Rx8 were homogeneously disperse and clear. Change in color was not found. From the study, it obviously revealed that HPMC was excellently compatible with the solvent mixture, with or without poloxamer 407 and PEG 400. The stability failure in appearance occurred from the solubility of the drug itself.

Discussion

Ibuprofen is a weak acidic drug which the pKa is about 4.54. Without adding sodium hydroxide, the pH values of the formulations were reflected from the nature of the dissolved drug and others ingredients. As a result of the chemical structure causes ibuprofen is freely soluble in alcohols thus a very high proportion of IPA is needed to dissolve up to 5% of the drug. Propylene glycol was used as cosolvent and as well as drug permeation enhancer. Poloxamer 407 and PEG 400 were optimized to use as stabilizers either in the formulation or the film after applying onto the skin to protect the precipitation of the dissolved drug into crystal. From the experiment, it was found that the final pH of the formulation played an important role of the stability. The neutral pH was required to force the drug ionized and dissolved. At room temperature, Rx5, the formula without both stabilizers became slightly translucent due to some precipitate of ibuprofen but Rx5 stored in the stability chamber was lastingly clear. The adding of poloxamer 407 or PEG 400 helped to stabilize the dissolved drug but just in minor accountability.

Conclusion

Cellulose ether hydrogels have many favorable properties such as low-cost, non-toxic, biocompatible, less sensitive to microbial contamination and good in film forming. In this study, HPMC possessed more preference in highly transparent and miscible with high concentration of alcohol and wide range of pH. The solvent system consisting of isopropyl alcohol:propylene glycol:water at 30:15:5 with other necessary ingredients had been proved to be compatible with HPMC. Considering the stability study, the physical appearance of Rx5-Rx8 was stable up to 6 months.

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