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Research Article

Formulation Development and Evaluation of Cooling Gel Sheets for Antipyretic Effect

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ABSTRACT

Objective: The aim of the research was to develop a formulation which has no or less side effects and toxicities, stably accumulates large amount of water, is excellent in cooling effect, offers water retaining for a long duration and has superior functionality e.g. reducing fever, migraine, headache, neuralgia. **Methods**: Different formulations were formulated using different polymers like Xanthan gum, HPMC, Carbopol 934 NF, sodium CMC, Guar gum, Gelatin and Ultraze in different ratio. The formulations were evaluated for Physical Appearance, pH, Homogeneity, Viscosity, Consistency, Swelling studies, Loss on drying, Skin irritation test, Stability studies. **Results:** Formulation **C_5** was having good adhesive property and was very easy to apply on the non-woven fabric. The elasticity and viscosity were good and was clear in appearance. All the formulations were evaluated for various parameters and formulation **C_5** was most stable among all with good adhesive property, smooth and good elasticity with highest water absorbing capacity and highest cooling effect and this formulation was taken as optimized formulation. **Conclusion:** From the present investigation it can be concluded that that **C_5** formulation showed optimum homogeneity, consistency, viscosity, swelling studies and stability. Cooling gel sheets could be a potential method for reducing fever in near future which can be replacements for the old method of applying wet cloth on the forehead. The cooling gel sheets could provide cooling for maximum 6-8 hrs with a single sheet.

Keywords: Aquagel, Fever, Cooling gel Sheet, Hydrogel, Temperature

INTRODUCTION

Hydrogel (also called aquagel) is a network of polymer chains that are hydrophilic, sometimes found as a colloidal gel in which water is the dispersion medium. In 1955 Professors Lim and Wichterle of Prague, Czech Republic, synthesized the first hydrogel with potential biomedical uses which was a synthetic poly-2-hydroxyethyl methacrylate and was later on used in contact lens production[1]. They swell by absorbing water and shrink on drying[3]. In the dehydrated state most hydrogels are hard and brittle[4]. The hydrophilicity of the network is due to the presence of chemical residues such as hydroxylic, carboxylic, amidic, primary amidic, sulphonic and others that can be found within the polymer backbone or as lateral chains[5]. Hydrogels possess a degree of flexibility very similar to natural tissue, due to their significant water content[6]. Hydrogels can also be synthesized by crosslinking with an electron beam or c-irradiation[7]. Fever occurs when the thermostat resets at a higher temperature, primarily in response to an infection. To reach the higher temperature, the body moves blood to the warmer interior, increases the metabolic rate, and induces shivering. To lower the temperature of body various antipyretics like aspirin, paracetamol, ibuprofen, diclofenac sodium, indomethacin etc. are given. They have many side effects and toxicities. The "chills" that often accompany a fever are caused by the movement of blood to the body's core, leaving the

Figure 1: Prepared hydrogel

surface and extremities cold. Once the higher temperature is achieved, the shivering and chills stop. When the infection has been overcome or drugs such as aspirin or acetaminophen (Tylenol) have been taken, the thermostat resets to normal and the body's cooling mechanisms switch on, the blood moves to the surface and sweating occurs[8]. Cooling gel sheets are becoming very popular as an analgesic providing cooling relief via a patch that can be positioned against most areas of the body, but is largely used on the forehead. The excellent heat transfer ability is made possible by the gels unique structure which disperses heat freely and maintains a constant and steady cooling effect that lasts up to 8 hours. Basically it is a replacement to the traditional cooling patches used to lower down the fever.

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Table 1: Composition of hydrogel

Ingredients	Carbopol: HPMC (1:1) C_1	Carbopol: HPMC(1:2) C_2	Carbopol: HPMC(1:3) C_3	Carbopol: HPMC(1:4) C_4	Carbopol: HPMC(1:5) C_5
Carbopol 934 NF	0.8 g	0.8 g	0.8 g	0.8 g	0.8 g
HPMC (1 lakh cps)	0.8 g	1.6 g	2.4 g	3.2 g	4 g
Polyvinyl alcohol.	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g
Polyethylene glycol	1.5 g	1.5 g	1.5 g	1.5 g	1.5 g
Dimethicone	2 g	2 g	2 g	2 g	2 g
Water	100 ml	100 ml	100 ml	100 ml	100 ml
Menthol	2 ml	2 ml	2 ml	2 ml	2 ml

Table 2: Composition of hydrogel

Ingredients	Carbopol: HPMC (1:9) C_6	Carbopol: HPMC: HPC (1:5:5) C_7	Carbopol:HPMC: HPC (1:5:5) C_8	Carbopol: HPMC: HPC (1:5:7) C_9	Carbopol: HPMC: HPC (1:7:7) C_{10}
Carbopol 934 NF	0.8 g	0.8 g	0.8 g	0.8 g	0.8 g
HPMC (1 Lakh cps)	7.2 g	4 g	4 g	4 g	4 g
Sodium polyacrylate	-	-	-	-	0.4 g
Polyvinyl alcohol.	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g
Polyethylene glycol	1.5 g	1.5 g	1.5 g	1.5 g	1.5 g
Dimethicone	2 g	2 g	2 g	2 g	2 g
HPC	-	4 g	4 g	5.6 g	4 g
Methyacrylic acid	-	-	0.1 g	0.4 g	0.1 g
Water	100 ml	100 ml	100 ml	100 ml	100 ml
Ethanol	-	-	2 ml	2 ml	2 ml
Menthol	2 ml	2 ml	2 ml	2 ml	2 ml

MATERIALS AND METHODS

HPMC (1 lakh cps), Carbopol 934 NF, Xanthum gum, Sodium CMC, Guar gum, Gelatin, Sodium polyacrylate, HPC (Hydroxyl propyl cellulose), Methacrylic acid, Ultraze 20, Polyvinyl alcohol, Polyethylene glycol 400, Dimethicone were obtained from Unijules Life Sciences, Nagpur. All the ingredients were of analytical grade. Different formulations were formulated using different polymers like Xanthan gum, HPMC, sodium CMC, Guar gum, Gelatin. Amongst all HPMC forms the most stable gel. The gels made from other polymers were not stable. The viscosity of the gels was low and had less water absorbing capacity as compared to HPMC.

Various Parameters of Selected Formulations

Some of the formulations were taken which were found to be stable and checked for various parameters.

Formulation **C_5** was having good adhesive property and was very easy to apply on the non-woven fabric. The elasticity and viscosity were good and was clear in appearance.

Evaluation of hydrogel

Table 3: Composition of hydrogel

Ingredients	Ultraze20: HPMC:HPC (1:7:7) C_{11}	C_{12}	C_{13} (Hot water)	C_{14}	C_{15}
Carbopol 934 NF	-	0.8 g	0.8 g	0.7 g	0.3 g
HPMC (1 Lakh cps)	5.6 g	4 g	4 g	4 g	4 g
Sodium polyacrylate	0.8 g	-	-	-	-
Ultraze 20	0.8 g	-	-	-	-
Polyvinyl alcohol.	0.5 g	0.5 g	0.5 g	0.6 g	1 g
Polyethylene glycol	1.5 g	-	-	0.5 g	1 g
Dimethicone	2 g	-	-	3 g	2.5 g
HPC	5.6 g	4 g	4 g	-	-
Water	100 ml	100 ml	100 ml	100 ml	100 ml
Methyacrylic acid	-	0.2 g	0.2 g	-	-
Ethanol	-	4 ml	4 ml	-	-
Menthol	2 ml	2 ml	2 ml	2 ml	2 ml

Table 4: Various parameters of selected formulations.

Formulation Codes	Adhesive property	Application on non-woven cloth	Elasticity	Viscosity	Clearance
C_1	+	Easy	Less	Good	Not clear
C_3	++	Not so easy	Less	High	Clear
C_5	+++	Easy	Good	Good	Clear
C_{10}	++	Difficult	Good	Less	Clear
C_{13}	++	Very difficult	Less	High	Not clear
C_{15}	++	Difficult	Less	High	Not clear

Table 5: Various physical parameters of selected hydrogel formulations

Formulation Code	Clarity	Color	Texture	Stickiness	Presence of particles
C_1	Not clear	White	Smooth	+++	No
C_3	Clear	Transparent	Smooth	++	No
C_5	Clear	Translucent	Smooth	+	No
C_{10}	Clear	Translucent	Smooth	+	No
C_{13}	Not clear	White	Rough	++	No
C_{15}	Not clear	White	Smooth	+++	No

Physical Appearance: The prepared gels were inspected visually for clarity, colour, texture, and feel upon application such as stickiness, smoothness and presence of any particle. The test is important regarding patient compliance[9,10].

Table 6: Values of evaluation parameters of hydrogel

Formulation Code	pH	Homogeneity	Viscosity (mPas)	Consistency (mm)	Swelling (%)	Water Content (%)	% loss on drying	Skin irritation
C_1	6.57± 0.14	No lumps or aggregates, Homogenous	193661±0.34	4.4	447.16	81.72	40.87	Nil
C_3	6.78± 0.26	No lumps or aggregates, Homogenous	195061±0.21	4.2	337.5	77.14	45.23	Nil
C_5	6.52± 0.19	No lumps or aggregates, Homogenous	198671±0.27	4.0	995.23	90.80	11.46	Nil
C_{10}	6.24± 0.31	No lumps or aggregates, Homogenous	190026±0.36	4.7	451.72	81.87	21.16	Nil
C_{13}	6.38± 0.38	No lumps or aggregates, Homogenous	200674±0.29	4.8	409.80	80.38	15.46	Mild redness observed
C_{15}	6.46± 0.21	No lumps or aggregates, Homogenous	201268±0.32	4.7	382.14	79.25	60.40	Nil

pH: The pH of the hydrogels was determined by immersing pH meter to a depth 0.5 cm in a beaker containing hydrogels. The determinations were carried out in triplicate and the average of three reading was recorded[11,12].

Homogeneity: The homogeneity was inspected by visual inspection after the gel has been set in the beaker for their appearance and presence of any aggregates or lumps[12].

Viscosity: Viscosity of the gel was determined by using (LV) Brookfield viscometer (Dial type). As the system is non-Newtonian spindle no. 4 is used. Viscosity was measured for the fixed time 2 min for 1.5 rpm[9,13].

Consistency: Consistency of the gel was determined by dropping a cone attached to a holding rod from a fixed distance of 10 cm in such a way that it should fall on the center of the beaker filled with gel. The penetration by the cone was measured from the surface of the gel to the tip of the cone inside the gel. The distance travelled by cone was noted down after 10 sec[14].

Swelling studies: The weight of the equilibrium-swollen gels in water, W_f, was determined using an analytical balance. The gels were then placed in a dish, open to ambient laboratory conditions, for 2 days, and then dried under vacuum at room temperature for an additional 2 days[15]. The weight of the samples after the drying process was defined as W_i. The swelling capacity of these

Table 7: Stability study data of selected hydrogel formulations

Formulation Code	Day	Color		Homogeneity		pH		Swelling indices	
		4 ^{0}C	25 ^{0}C	4 ^{0}C	25 ^{0}C	4 ^{0}C	25 ^{0}C	4 ^{0}C	25 ^{0}C
C_1	0	White	White	+++	+++	6.57	6.57	447.16	447.16
	30	White	White	+++	+++	6.57	6.59	445.5	452.6
	60	White	White	+++	+++	6.57	6.6	445.23	454.14
	90	White	White	+++	+++	6.58	6.6	446.44	454.78
C_3	0	Transparent	Transparent	+++	+++	6.78	6.78	337.5	337.5
	30	Transparent	Transparent	+++	+++	6.77	6.8	336.15	338.12
	60	Transparent	Transparent	+++	+++	6.77	6.81	336.34	338.5
	90	Transparent	Transparent	+++	+++	6.78	6.81	336.59	339.25
C_5	0	Translucent	Translucent	+++	+++	6.52	6.52	995.23	995.23
	30	Translucent	Translucent	+++	+++	6.52	6.53	994.2	996.12
	60	Translucent	Translucent	+++	+++	6.51	6.53	994.24	996.33
	90	Translucent	Translucent	+++	+++	6.53	6.54	995.8	996.89
C_{10}	0	Translucent	Translucent	+++	+++	6.24	6.24	451.72	451.72
	30	Translucent	Translucent	+++	+++	6.24	6.24	450.13	452.2
	60	Translucent	Translucent	+++	+++	6.22	6.25	450.46	452.64
	90	Translucent	Translucent	+++	+++	6.22	6.25	452.41	452.69
C_{13}	0	White	White	+++	+++	6.38	6.38	409.80	409.80
	30	White	White	+++	+++	6.39	6.38	408.32	409.98
	60	White	White	+++	+++	6.39	6.39	408.78	410.58
	90	White	White	+++	+++	6.39	6.39	409.9	410.96
C_{15}	0	White	White	+++	+++	6.46	6.46	382.14	382.14
	30	White	White	+++	+++	6.46	6.48	381.35	383.69
	60	White	White	+++	+++	6.48	6.48	381.78	383.86
	90	White	White	+++	+++	6.48	6.49	382.12	384.78

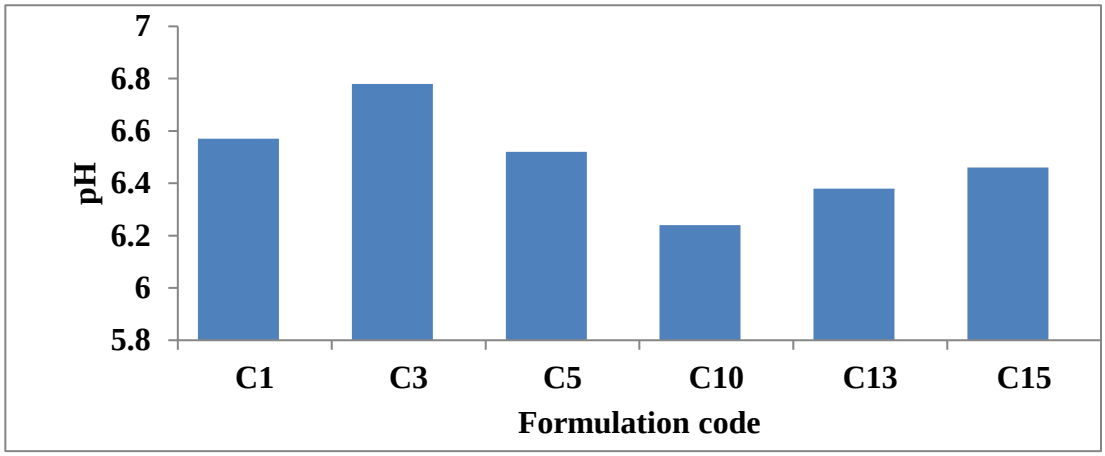

Figure 2: Comparative graph pH values of selected hydrogel formulations

hydrogels was quantified by the mass swelling ratio, Q, defined in eq.

$$Q = \frac{Wf - Wi}{Wi}$$

The water content of hydrogels were calculated after the equilibrium swelling by

$$\text{Water content} = \frac{\text{Wet weight} - \text{Dry weight}}{\text{Wet weight}} x100$$

Loss on drying: Some patches were selected and were kept for 7 days to check the loss on drying[9].

Skin irritation test: Test for irritation was performed on human volunteers. For each gel, five volunteers were selected and 1.0g of formulated gel was applied on an area of 2 square inch to the back of hand. The volunteers were observed for lesions or irritation. As the hydrogel does not contain any drug so it was directly applied to the human skin to check for any redness, abrasion or rashes[10,13]. All the tests were done in triplicates and mean of the three was taken.

Stability studies: For stability studies, formulations were stored in tight sealed ambered colored glass containers at temperatures 4 °C and 25 °C for a period of three months[10,12,16]. These formulations were regularly tested for changes in pH, color, homogeneity, swelling studies and water content.

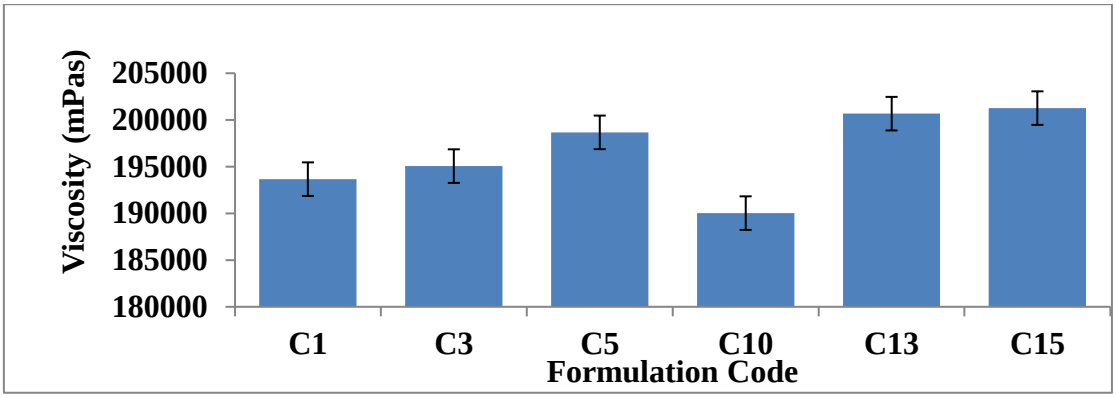

Figure 3: Comparative graph of viscosity of selected hydrogel formulations

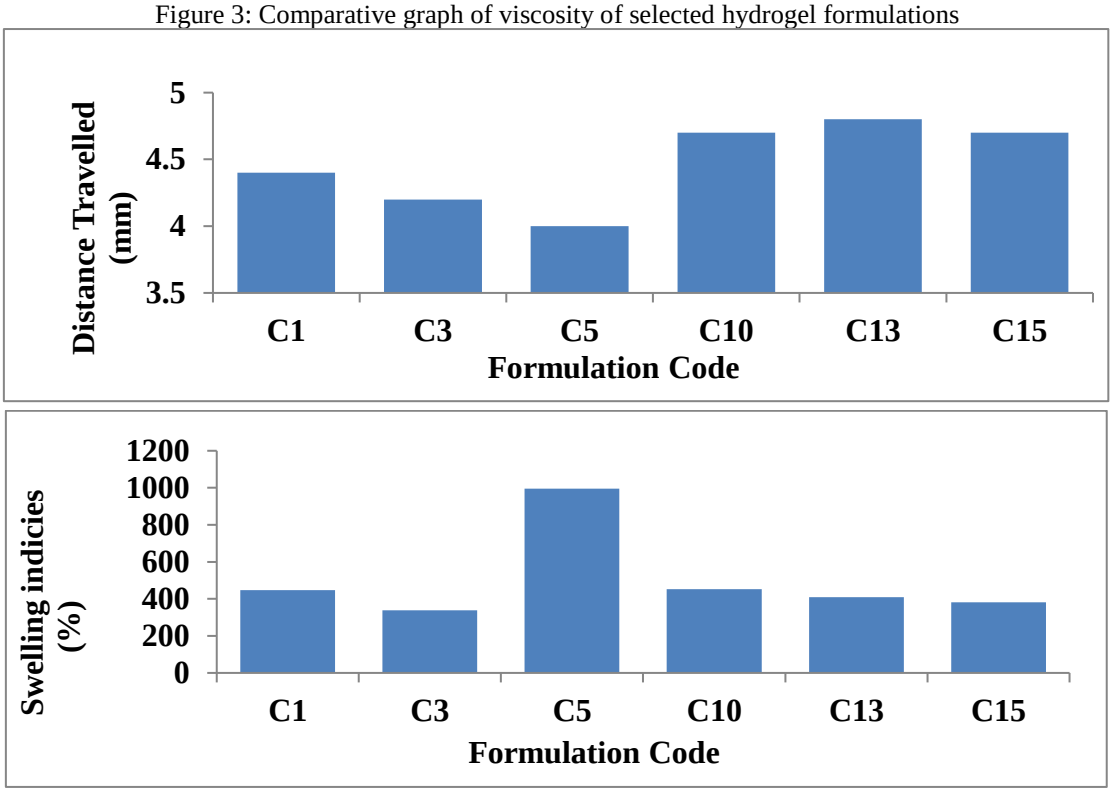

Figure 5: Comparative graph of swelling Indices of selected hydrogel formulations

RESULTS AND DISCUSSION

Formulations C_1 to C_6: Stickiness reduced as concentration of HPMC increased more adhesive mass was formed. While the viscosity of the formulation increased as the concentration of HPMC increased. The water absorbing capacity of gel also improved with the increase in HPMC concentration.

Formulation C_7: Adhesive property increases but the gel was very thick. Stickiness was not so much. The gel formulated was having very high viscosity.

Formulation C_8: Adhesive property increased than the previous, thickening also increased and the gel formed was very difficult to apply on the cloth.

Formulation C_9: Adhesive property further increased but not elasticity. The gel was not having good water absorbing capacity.

Formulation C_{10}: The gel was having good adhesive property but was very viscous.

Formulation C_{11}: The gel was having good adhesive property to skin but not elastic and the gel was not clear.

Formulation C_{12} - C_{15}: The adhesiveness further increased but not elasticity. The gels formed were not stable and were having low water absorbing capacity.

The stickiness reduces, and more adhesive mass is formed as the concentration of HPMC increases. All the formulations were evaluated for various parameters and formulation **C_5** was most stable among all with good adhesive property, smooth and good elasticity with highest water absorbing capacity and highest cooling effect and this formulation was taken as optimized formulation. The gel formed was clear, translucent and smooth. It has very less stickiness and does not have presence of any particles. The pH of the formulation was in range suitable for the skin preparations i.e 6.52. The gel showed good homogeneity with absence of lumps. Viscosity of the formulation is 198671 mPas which can be easily applied on the non-woven cloth. The gel had good consistency this means the application on cloth is easy. Upon swelling

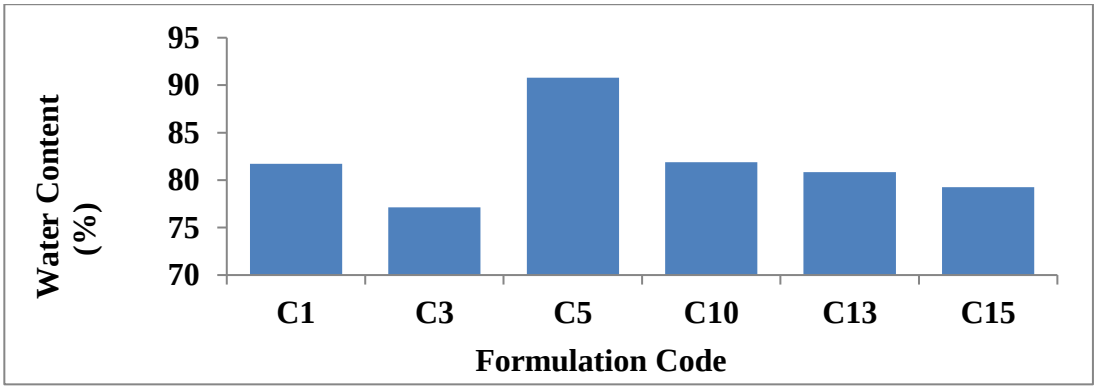

Figure 6: Comparative graph of water content of selected hydrogel formulation

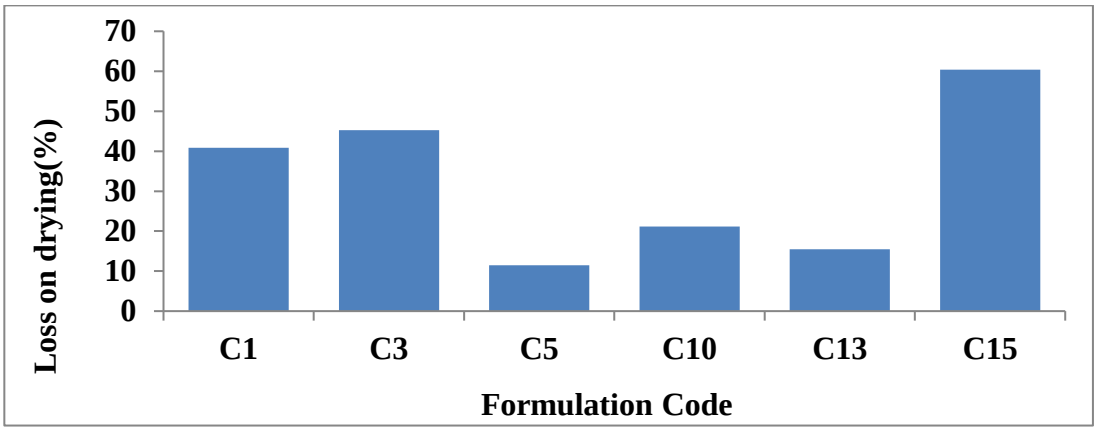

Figure 7: Comparative graph of loss on drying of selected hydrogel patches

studies the gel showed the swelling index of 995.23 % and the water content of the gel is 90.80 %. The sheet was kept in storage for 7 days and showed less % loss on drying as low as 11. 46 %. The gel was applied to human skin to check for any redness or abrasions and no redness or abrasions were observed. During the stability studies this formulation showed minimum deviations from the previous results.

CONCLUSION

Hence from the present investigation it was observed that **C_5** formulation showed optimum homogeneity, consistency, viscosity, swelling studies and stability. The formulation C_5 contained the highest water content.

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