INTERNATIONAL JOURNAL OF DRUG DISCOVERY AND HERBAL RESEARCH (IJDDHR)
ISSN: 2231-6078
15(1): Jan.-March.: (2025), 45-51

Development of Topical Alum Gel By Using Multiple Trial Polymer

Research Article

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Abstract

The current study concluded that chitosan as a polymer can used for formulation of alum gel. It can be use as topical formulation for small or minor cuts on skin. This combination is useful for faster clotting time on open cut. The selection of parameters from box-Behnken design is useful for formation of optimum quality of gel. The formulation gives faster coagulation of blood as comparison to the marketed formulation, because the polymer which we used in formulation is also act as a clotting factor for blood.

Keywords: Chitosan,, polymer, box-Behnken design, alum gel.

Introduction :

It is the problem induce by the excessive blood loss inside the body, or out side the body. When the internal blood loss occurs, it called internal hemorrhage and when the blood occurs outside the body, it called external hemorrhage. The internal hemorrhage is due to damage arteries, vein, capillaries or internal organs. and the external hemorrhage is due to skin or external tissue damage.There are specific amount of calcium and other clotting factors are required for the natural arrest of hemorrhage. When the blood vessel or tissue are damaged, so the prothrombin is converted in to its active form thrombin, in the presence of calcium. then the fibrinogen transformed by thrombin in to fibrin and then curst are formed by platelets and blood to form clot.

ICH ACTIVITIES

Working with regulatory in the European Union (the European MedicinesAgency) and Japan, FDA has been instrumental in furthering quality by design (QbD) objectives through the International Conference on Harmonization ofTechnical Requirements for Registration of Pharmaceuticals for Human Use. ICH guidelines Q8 (on Pharmaceuticals Development), Q9 (on Quality RiskManagement), and Q10(on Pharmaceutical Quality System) provide someassistance for manufacturers to implement QbD into their own operations.

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TheICH Steering Committee meets twice a year to discuss the progress of its efforts.Further details are being developed by the industry organizations to assure thatquality system objectives are met by applications of experience and innovationas process understanding builds throughout the process lifecycle. This practicalinput should help ensure that quality risk management and knowledgemanagement are used to make necessary lifecycle adaptations that maintainprocess control and product quality, including evolved controls as well as rapidcorrective and preventative action (CAPA) to assure sustainable cGMPcompliance. Design decisions based on through formulation and processunderstanding as these relate to the intended use QbD. It means designing anddeveloping formulations and manufacturing processes to ensure a predefinedquality. Thus, QbD requires an understanding how formulate and processvariables influence product quality.[1-5]

Materials and Methods[6-13]

Selection of parameters trough Ishikawa approach

Ishikawa fish-bone diagram was constructed to postulate a cause-effect relationship among the probable material attributes affecting the CQAs of the formulations. it is used as key aliment for process parameters and material parameters selection factor.

Material

From this Ishikawa diagram we are selected process parameters and material parameters for our formulation of gel. Which is use for the clotting of blood on the surface of skin, induces by minor or major cuts on the skin.[14]

Method of alum gel preparation:

The excipients and API were weighed accurately by calibrated analytical weighing balance and then required quantity of Chitosan (1500 mg) was taken and mixed it in to the 40 ml of distilled water on magnetic stirrer until they uniformly mixed. The mixing was continued further for about specific time. Preservative (90mg of methyl paraben sodium and 10 mg of propyl paraben sodium) were added to the gel. Finally, the gel was neutralized by adding 4ml phosphate buffer (pH 4.5). then 250 mg of potash alum was dispersed in 6 ml of distilled water and then mixed with the gel.[1]

Selection of polymer with the combination

S. No.	Polymer combinations		Ratio
	Polymer 1	Polymer 2	
1.	Carbopol	Chitosan	1:1
			1:2
			2:1
2.	Sodium alginate	CMC	1:1
			1:2
			2:1
3.	Chitosan	Sodium alginate	1:1
			1:2
			2:1
4.	CMC	Chitosan	1:1
			1:2
			2:1
5.	Carbopol	Sodium alginate	1:1
			1:2
			2:1

Note: - we took it here 600 RPM mixing speed, 45℃ mixing temperature and 15 minutes mixing time. As a solvent we use 1% acetic acid and distilled water.

Selection of polymer with the alum -

S. No.	Polymer	Concentration (mg)	Solvent (ml)	Alum (%)
1.	Carbopol	1000	Distilled water (50 ml)	1
				0.5
				0.2
2.	Sodium alginate	1500	Distilled water (50 ml)	1
				0.5
				0.2
3.	CMC	1000	Distilled water (50 ml)	1
				0.5
				0.2
				0.15
				0.1
4.	Chitosan	1500	1% Acetic acid (50ml)	1
				0.5
				0.2

Note: - we took it here 600 RPM mixing speed, 45℃ mixing temperature and 15 minutes mixing time

Selection of process parameter-

S. No.	Stirring time (min)	Stirring speed (RPM)	Stirring temperature (°c)	Responses
1	15	200	45	Gel was not properly formed
2	20	200	45	Gel was properly formed
3	25	200	45	Gel was formed
4	30	200	45	Gel was formed

5	20	400	45	Gel was formed with slightly high viscosity
6	20	600	45	Gel was formed with optimum viscosity
7	20	800	45	Gel was formed with slightly low viscosity
8	20	600	55	was formed
9	20	600	65	was formed n optimum iscosity
10	20	600	75	was formed slightly low iscosity

QbD approach :

Identification of the QTPP, CQAs of the films and the risk analysis of CQAs

Defining the QTPP according to the guidelines given by the International Council of Harmonization (ICH) the Expert Working Group that represented the starting point of this research study. The QTTP revealed the CQAs, represented by the physical characteristics of the gel that should be in appropriate limits in order to ensure the desired quality of the final product.

Design of experiments

A Design of experiments (DoE) was used for understanding of the formulation and the process. In order to stability of the manufacturing process and its basic parameters. In this we select the starting formulations and the factor variation limits, a few preliminary studies were performed (data not shown).

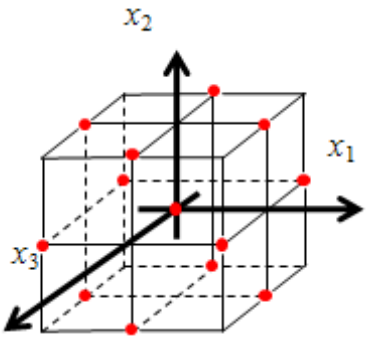

Fig. 3. box-Behnken design

The Design expert 6.6.1 software was used to develop a Box Behnken (BB) experimental design. The BB DoE was particularly chosen due to the following reasons:

1. it gives economical numberin term of runs required.
2. the experiments are based on the midpoint of each edge of the cube
3. it is mostly used three or four quantitative factors, employing three level factorial design.

The effects of the independent variables and their responses were evaluated by the analysis of coefficients. Based on these results, the design space and optimal formulations were further calculated by design expert software.

In general, the experimental work which is defined in the QbD approach illustrates the whole range of interactions between the chosen inputs and the studied responses, whereas the design space is defined as "the multidimensional combination and interaction of input variables that have been demonstrated to provide the assurance of quality"[11]

Obtained process parameters:

	Lower limit	Upper limit
Stirring time	10 minutes	30 minutes
Stirring speed	400 RPM	800 RPM
Stirring temperature	45 °c	75°c

Obtained runs in Box-Behnken design:

Run	Factor 1 A:stiring time min	Factor 2 B:stiring tem... degree celcius	Factor 3 C:stiring speed RPM	Response 1 viscosity centipoise	Response 2 spreadibility gm-cm/min	Response 3 swelling index -
1	20.00	75.00	400.00			
2	20.00	45.00	800.00			
3	10.00	75.00	600.00			
4	30.00	60.00	800.00			
5	10.00	60.00	800.00			
6	20.00	75.00	800.00			
7	30.00	75.00	600.00			
8	10.00	60.00	400.00			
9	30.00	60.00	400.00			
10	30.00	45.00	600.00			
11	20.00	45.00	400.00			
12	10.00	45.00	600.00			

Result and Discussion

Trials of gel in combination:
In the formulation of combinations of gel. no gel was formed properly in their combinations, some of them are segregated, separated and some are form plagues. In combination of sodium alginate and CMC the gel was properly formed but after the addition of alum in to them, the gel was separated.

Trial of polymer with alum:
In the trial of polymer with alum Carbopol and sodium are separated and segregated after addition of alum in to it. CMC can form a gel with alum but with minor amount of alum (0.1%). Which will give blood clotting time but too far which is 6 minute 26 second. which almost equal to the normal blood clotting time (8 minutes). at last, the gel was formed with Chitosan and alum (.5%).

Trial for process parameter
In the trial of process parameters, we found that for 20 minutes, 600 RPM, at 65^0C we can form the gel with optimum viscosity.

Spreadibility study:
The spreadibility of the alum gel was measured by spreading of 0.5 g of the gel on a circle of 2 cm diameter premarket on a glass plate which is situated on cm graph paper and then a second glass plate was placed on it. Hundred gram of weight was permitted to rest on the upper glass plate for 5 min. The diameter of the circle after spreading of the gel was determined.

Spreadibility of gel = M × L / T

Where, M is weight which is placed on plate, L is diameter of circle after spreading the gel, Tis time taken for spreadibility.[16]

Viscosity study:
The viscosity measurement of the alum gel was performed with a Viscometer. The gel was rotated at 100 rotations per minute (RPM). At this speed, the corresponding dial reading was noted in centipoise. [16]

Swelling index:
These tests were carried out according to the methodology proposed by Bourtoom et al. Specifically, the dry polymer was initially immersed on measuring balance than it dissolvesin distilled water at different RPM for different time, in order to equilibrate them. The excess moisture was then completely removed by heated them at different temperature. Finally, the samples were weighted and the degree of swelling calculated by using the following equation:

$$\text{Swelling degree (\%)}: \frac{We - Wo}{Wo} \times 100$$

where We represents the weight of the polymer at absorbing equilibrium (completely swelled gel), while Wo is the weight of the dry polymer before swelling (initial dry weight).[11]

Obtained responses after evaluation:

Run	Factor 1 A: stirring time minutes	Factor 2 B: stirring temp. Celsius	Factor 3 C: stirring speed RPM	Response 1 viscosity cent. poise	Response 2 spreadibility g.cm/s	Response 3 Swelling index
1	30.00	45.00	600.00	4949	144	36.3
2	10.00	60.00	400.00	3389	154	37.6
3	30.00	60.00	400.00	3992	164	32.7
4	20.00	75.00	800.00	3275	206	34.9
5	30.00	75.00	600.00	3909	122	31.7
6	10.00	60.00	800.00	6559	126	36.9
7	20.00	75.00	400.00	5969	140	36.4
8	20.00	45.00	800.00	6288	126	36.8
9	10.00	75.00	600.00	5411	128	37.0
10	30.00	60.00	800.00	5447	100	33.5
11	20.00	45.00	400.00	4793	114	36.1
12	10.00	45.00	600.00	5135	120	37.1

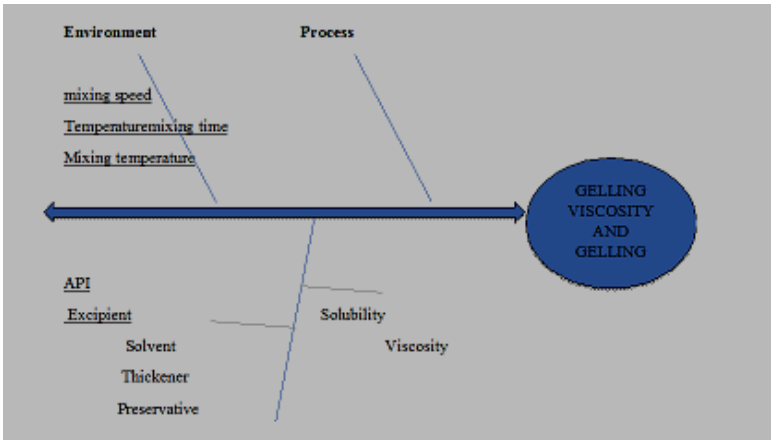

Fig :1 Selection of parameters trough Ishikawa approach

Obtained graphs of variables and their responses: -

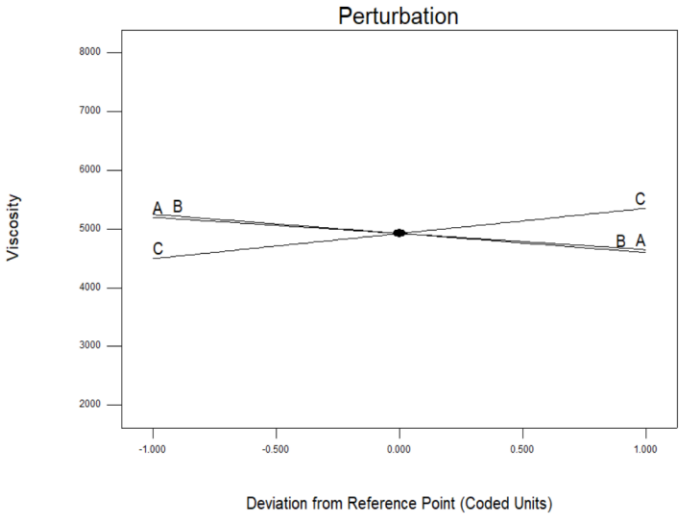

Fig. 2. Viscosity graph with respect to process parameters

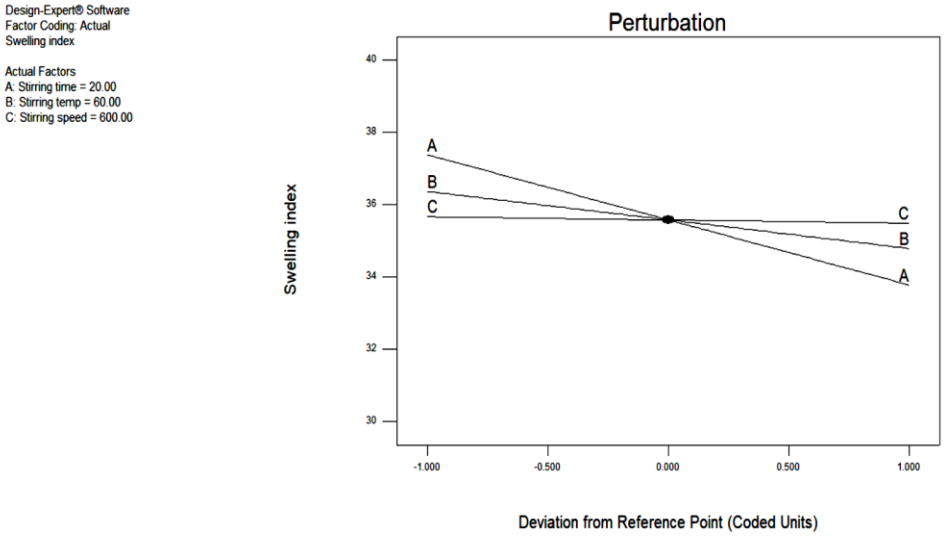

Fig. 3. Swelling index with respect to process parameters

Comparison with market formulation:

	Alum chitosan gel	**Marketed (Mancode) gel**
Components	API – alum Polymer – chitosan Excipients – methylparaben, 1% acetic acid solution	API – alum Polymer – carbomer Excipients – Aloe vera,menthol, witch hazel,spearmint, etc…
Uses	Blood clotting, wound healing	After shaving gel,moisturizer, acne remover, etc…
Viscosity	3657 centipoises	3923 centipoises
Spreadibility	132-gram cm/sec	140-gram cm/sec
Blood clotting time	1 minutes 50 second	3 minutes 30 second

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