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Formulation and Evaluation of Cimetidine *In-Situ* Gelling System By Factorial Design

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ABSTRACT

The current papers offer the formulation, optimization, and evaluation of the starch-based *in-situ* gelling system of Cimetidine. The objective of the present study was to optimize the concentration of starch and concentration of $MgCl_2$ for the formulation of *in-situ* gels of Cimetidine. Starch based *in-situ* gels of Cimetidine were subjected to measurement of viscosity, pH, drug content, and Q_{80}. Entirely the preliminary batches were prepared by using different concentrations of sodium alginate (0.5% - 2%) and a constant concentration of $MgCl_2$. On source the preliminary Screening, a 3^2 full factorial pattern set about to review the consequence containing self-sustaining variables, Put concentration Containing starch (X_1) and concentration containing $MgCl_2$ (X_2) as to apprenticed probabilities like viscosity, drug content, $Q_{80,}$ and similarity factor. The best formulation C9 exhibited optimum viscosity (316 cp), drug content (99.25%), Q_{80} (90.15%), and similarity factor (73.46). The best batch exhibited good water uptake (62.44%) and there were no interactions were found during the IR study. A slow release of Cimetidine was observed and a good fit to the Korsmeyer Peppas plots was demonstrated. The correlation coefficient of the best batch is 0.9973 (Korsmeyer Peppas plots).

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INTRODUCTION

The in-situ gel-forming drug delivery may be a variety of mucoadhesive drug delivery systems. These gels are liquescent at temperature but submit to gelation in swap body fluids in pH [1]. May have a safety feature worldly belongings of room temperature dependant plus cation elicited gelation. This gelation comes to the water level of the double-helical circle zones adopted by aggregation of the double-helical losses to form a multidimensional mesh by complexation along with cations and hydrogen bonding [2]. Cimetidine, the antiulcer agent was selected as the drug which explains an H2 receptor antagonist, any patients with gastroesophageal reflux who're being treated with proton

pump inhibitors would possibly produce acid in the night.

MATERIALS AND METHODS

Cimetidine was received as freely given sampling from Glaxosmithkline, Mumbai, Sodium citrate, starch, Magnesium chloride used to be acquired from SD fine chemicals Ltd., Mumbai. All abundant chemical as well as chemical agent utilized in this study in with analytical grade.

Starch based *in-situ* gelling system of Cimetidine

Infrared studies

The Starch based *In-situ* gels of cimedtidine and other excipients was recorded using Fourier transform infrared spectrophotometer (FTIR 4100 Jasco Japan). Sample preparation was done by mixing the drug with potassium bromide (1:300), triturating it in a glass mortar. A transparent pellet of the mixture was formed and placed in the sample holder and scanned over a frequency range of 4000-400cm-1. The spectrum obtained was compared with the reported standard [3].

Method of Preparation

Starch was dissolved in ultrapure water involving sodium citrate and heat to 50^{o}C, after chilling below those 35^{o}C Suitable quantities of magnesium chloride used to be added. Cimetidine was liquefied in 0.1N HCl solution used to be additional slowly into the more than starch solution consequent to soul-stirring as to a magnetic stirrer there has been proper as well as homogeneous dispersal of the drug. Application formulations were confined to a bath sonicator for 15 minutes and after that total the sort-out solutions in pH 1.2 buffer. In batches, C1-C12 the concentration of the starch was 0.5-2 %, and also the put concentration containing $MgCl_2$ and sodium citrate stand by at 0.1% and 0.25% respectively. In CC1 to CC9 takes out 1, 1.5 along with 2% of starch as X_1 variable and takes out 0.075, 0.1 in addition to 0.125% of $MgCl_2$ as X_2 varying while concentrate sodium citrates stay constant [4].

Optimization by using 3^2 full factorial designs

The report the consequence of independent variables, i.e. Con. of starch (X_1) and the con. of $MgCl_2$ (X_2) on dependent variables [5].

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time. The polynomial terms ($X_1{}^2$ and $X_2{}^2$) are included to investigate non-linearity. The results depicted in Table 5 stand for that each one of the dependent probabilities will be strongly dependent on the chosen independent probabilities as the variety show a large variation among the CC1 to CC9 (Table 5).

Evaluations

pH

It is used to be sounded in starch primarily gels of Cimetidine, employing a digital pH meter [6].

Viscosity

The *in-situ* gel formulations were determined by using Brookfield viscometer [7].

Drug content

Prepared starch-based *in-situ* gels of drug assayed spectrophotometrically for the drug content at the maximum wavelength with proper dilution of formulations taking suitable solvent as blank. Taking accurately weighted 50mg of prepared gel mixed in a beaker containing 100ml phosphate buffer pH 7.4 and stirred it at 75 rpm for 2 hrs [8]. Filtered it taken supernant filtrate and observed at 622 nm using UV spectroscopy and calculate drug content using the following formula.

$$\%\ Drug\ Content = \frac{Practical\ Drug\ Content}{Theoretical\ Drug\ content} \times 100$$

In-vitro drug release

The CC1 to CC9 formulations of starch based *in-situ* gels of Cimetidine [9] were carried out. The average values of Q_{80}.

Comparison containing dissolution profiles

Finding out the similarity factor (f_2) of CC1 to CC9 formulations of *in-situ* gels of Cimetidine [10].

Kinetics modelling of dissolution profiles

All the formulations of Cimetidine gels batches CC1 to CC9 were studied for their release mechanism and determined which was the perfect model for all the formulations and also determined the release mechanism for the selected batch CC5. The correlation coefficient beliefs with kinetic models [11].

Water Uptake

The study for the selected formulation of Cimetidine gels [12].

Stability study

The starch based *in-situ* formulation containing Cimetidine used to be approximate three months [13].

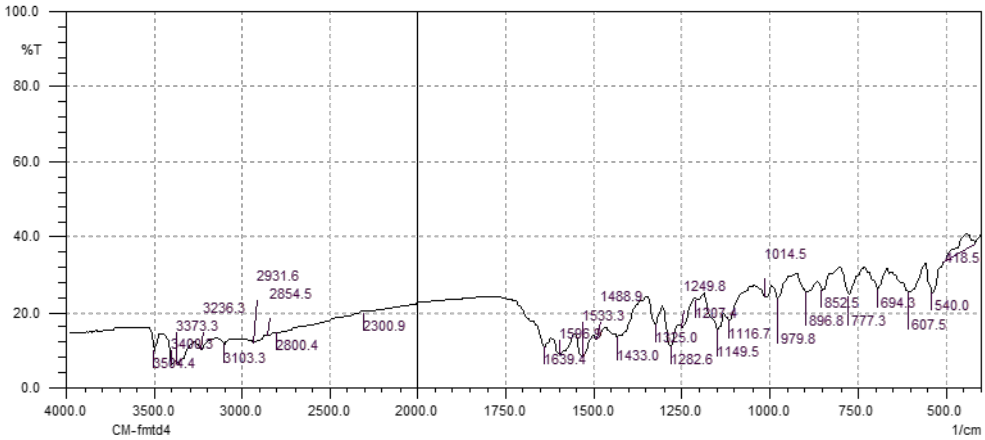

Figure 1: FTIR of pure drug

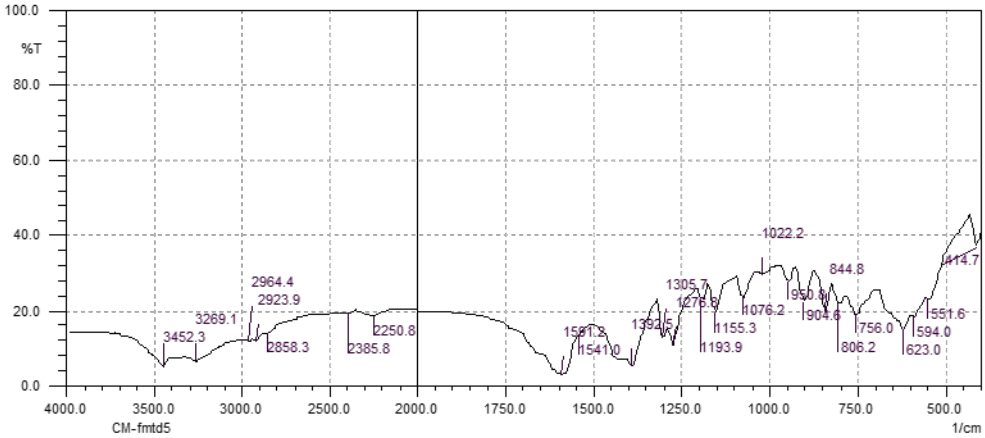

Figure 2: FTIR image of Starch

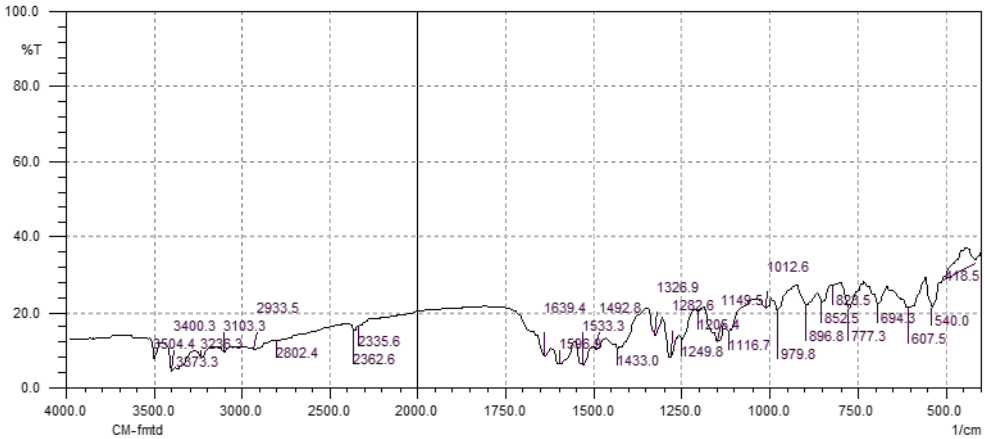

Figure 3: FTIR Spectrum for the physical mixture of drug + polymer + excipients

Table 1: Preliminary trial batches of *in-situ* gels of Cimetidine

Batch No.	Conc. of starch (%)	pH	Viscosity (cp)	Drug content (%)	Characteristic of *in-situ* gels
C1	0.5	7.6	156	81.20	The gel is not formed decently less drug content
C2	0.5	7.6	155	84.32	
C3	0.5	7.7	151	85.45	
C4	1	7.3	229	89.98	Gel formation & drug content are slightly better
C5	1	7.4	228	92.76	
C6	1	7.5	226	91.89	
C7	1.5	7.2	315	97.98	Easy formation of Gel & Good drug content
C8	1.5	7.1	318	98.98	
C9	1.5	7.1	316	99.25	
C10	2	6.8	399	95.56	Gel formation & good drug content
C11	2	6.7	399	96.11	
C12	2	6.6	399	94.12	

Note: The entire batches have been sort out using $MgCl_2$ 0.01%.

Table 2: 3^2 Full factorial design layouts of *in-situ* gels of Cimetidine

Batch No.	Variables levels in coded form		Viscosity (cp)	Drug content (%)	% Drug release (Q_{80})	Similarity factor (F_2)
	X_1	X_2				
CC1	-0	-2	226	87.99	99.32	31.21
CC2	-1	0	249	89.56	96.34	32.46
CC3	-0	+2	247	92.73	98.63	45.46
CC4	0	-2	288	97.32	98.15	51.72
CC5	0	0	317	98.54	91.26	73.71
CC6	0	+2	347	96.73	86.32	72.89
CC7	+2	-2	386	93.32	82.64	66.32
CC8	+2	0	389	95.89	78.58	68.52
CC9	+2	+2	400	93.82	90.15	73.46

Table 3: Cumulative % drug release of *in-situ* gels of Cimetidine

Time in hr.	Cumulative % drug release								
	CC1	CC2	CC3	CC4	CC5	CC6	CC7	CC8	CC9
1	50.43	46.76	41.84	27.01	19.92	17.95	16.92	13.14	12.48
2	68.21	65.67	56.88	45.39	31.35	28.03	27.71	23.92	19.88
3	88.85	84.20	75.14	62.82	43.47	39.12	38.51	33.26	29.76
4	98.14	98.00	93.13	78.38	54.73	50.52	47.11	43.36	38.56
5	99.05	98.00	97.73	94.60	65.86	62.29	59.62	52.32	49.43
6	98.07	98.00	97.73	97.03	76.33	73.07	69.62	63.70	58.34
7	99.05	98.00	97.73	97.03	83.36	82.61	78.35	74.85	69.97
8	98.07	98.00	97.73	97.03	90.18	85.03	81.04	77.48	74.70

Table 4: Regression analysis of *in-situ* gel of Cimetidine

Parameters	B0	B1	B2	B11	B22	B12	Multiple Regression
Viscosity	314.25	86.7	17	-4	-3.6	2	0.887
Drug content (%)	88.53	2.40	0.37	-0.18	-5.5	-1.83	0.898
Q80 (%)	91.67	-11.26	-2.28	-1.37	-3.8	0.65	0.981
Similarity factor (f2)	75.82	9.12	0.50	-3.26	-20.7	-3.71	0.972

Table 5: Release kinetics of *in-situ* gels

Batch no.	Regression			
	Zero-order	First order	Higuchi	Krosmeyer peppas
CC1	0.8172	0.5212	0.9388	0.8212
CC2	0.8588	0.6112	0.9735	0.8411
CC3	0.9222	0.6112	0.9883	0.8538
CC4	0.9968	0.8282	0.8625	0.9865
CC5	0.9842	0.9934	0.9977	0.9864
CC6	0.8987	0.8789	0.9884	0.9836
CC7	0.8988	0.8714	0.8931	0.9868
CC8	0.9841	0.8765	0.8868	0.9817
CC9	0.9872	0.8976	0.9728	0.9716

Table 6: Water uptake study of Cimetidine gel batch C5

Time in min.	Weight after Decantation (gm)	Difference in weight (gm)	Percentage water uptake (%)
30	55.45	0.30	4.2
60	55.74	0.59	7.02
90	56.25	2.10	21.13
150	57.32	3.17	31.96
180	57.69	3.53	35.66
240	58.54	4.38	44.22
270	58.92	4.77	48.10
360	60.05	5.90	59.56
390	60.62	6.46	65.23
450	61.17	7.01	70.78
480	61.33	7.18	72.45

Table 7: Stability of Cimetidine gel for best formulation C5

The period for sampling	pH	Viscosity (cp)	Drug content (%)
Initial	7.1	316	99.25
One month	7.1	316	99.25
Two month	7.2	317	99.26
Three month	7.2	317	99.27

RESULTS AND DISCUSSION

IR study

The infrared spectrophotometer studies were carried CC5 of Cimetidine gel. IR spectrum for the pure drug, starch, physical mixture there was no strong interaction the functional groups of API with the Additives are shown in Figures 1, 2 and 3 respectively.

Preliminary trials

The formulations of C1 to C12 were preset out to review the consequence of polymer put concentration on spectacular viscosity, drug content, pH, and the physical properties of the gel in pH 1.2 buffer. The con. of starch used to be varying from 0.5, 1, 1.5, and 2 % [Table 1].

3^2 full factorial design

In the present study, a 3^2 full factorial design was employed to study the effect of independent variables, i.e. con. of starch (X_1) and the con. of $MgCl_2$ (X_2) on dependent variables [Table 2]. The selected independent probabilities show a large variation among the CC1 to CC9. Fitted equations touching on the responses i.e. viscosity, drug content $Q_{80,}$ and similarity factor to the transforming factor are shown in Table 4. The viscosity of solutions varied from 226 cp to 400 cp which was measured at 150 rpm [Table 2].

Factorial for drug content

The drug content varying delight in 87.99% to 98.54% in batches CC1 to CC9 *in-situ* formulations of Cimetidine and displayed to more excellence multiple regression as 0.898 [Tables 4 and 2].

The factorial equation for Q_{80}

The drug let loose at eight hours in all the batches CC1-CC9 varied from 78.58% to 99.32% (Table 3) and showed good multiple regression as 0.981 (Table 4).

The factorial trial equation for similarity factor

The similarity factor of CC1 to CC9 formulation varying from 31.21 to 73.71 [Table 2] and displayed a very good coefficient of 0.972 [Table 4].

Water uptake study

The water uptake studies depend on TGA used to be the best formulation C5 [Table 6].

Stability Study

Short-term stability of *in-situ* gel going from Cimetidine revealed which no alterations started at three months at normal room temperature and humidity condition [Table 7].

CONCLUSION

The overall *in-situ* gel formulation displayed well viscosity, drug content, and release order this report review which oral of misty solutions involving starch leads to the formation of *in-situ* gel, such formulation will be homogenously unfrozen once administered orally become gel on the vocalization site. The results of a 3^2 full factorial design conspicuous therefore the rarefaction going from starch based $MgCl_2$ considerably wonder affected sensational dependent probabilities.

Conflict of Interest

The authors attest that they have no conflict of interest in this study.

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