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DESIGN AND EVALUATION OF ORAL MEDICATED JELLY OF BARICITINIB

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ABSTRACT
Baricitinib is a novel drug used to treat rheumatoid arthritis. The present study is aimed to design and evaluate oral medicated jellies of baricitinib using gelatin, citric acid, and sugar, sodium benzoate, sodium citrate, xanthan gum. The prepared jelly was analyzed for weight variation, surface pH, content uniformity, syneresis, viscosity, *in-vitro* dissolution studies, stability studies, and *in-vivo* pharmacokinetic parameters. The *in-vitro* dissolution test of the jellies was performed in pH 7.4 buffer using USP type- II (paddle) at 50rpm. All the formulations showed more than 70% of drug release within 20mins. Except for xanthan gum and gelatin, all other variables in this study are constants. 3^2 factorial designs were employed, a total of 9 formulations were generated as a consequence. F8 is the optimal formulation with the use of contour and 3D plots. Stability studies of the formulated jellies were carried out as per ICH guidelines for 3 months of different humidity and temperature conditions. The optimized F8 formulation has given highest drug release. These oral medicated jellies avoids first-pass metabolism, rapid onset of action, and high bioavailability.

KEYWORDS: Baricitinib, Arthritis, medicated jelly, contour plots, factorial design.

1. INTRODUCTION
Medicated jellies are formulated to overcome the problems associated with other oral formulations like stability, dose wastage and dose dumping.[1,2,3] RA is a condition that is characterised by discomfort, impairment, and joint destruction brought on by a chronic autoimmune inflammation response induced by a variety of cell types and cytokines.[4] Patients who do not respond well to biologic DMARDs or who encounter negative effects require new therapies.[5] Baricitinib, a preferred JAK1 and JAK2 inhibitor has demonstrated efficacy in studies involving rheumatoid arthritis patients who did not respond well to conventional synthetic DMARDs.[6] JAK inhibitors may be useful therapeutically in inflammatory diseases because JAKs transducer intracellular signals from cell surface receptors for different cytokines and growth factors involved in inflammation and immunological function.[7]

2. MATERIALS AND METHODS
Baricitinib is a gift sample from Cipla LTD and other excipients used were procured from Merck labs, Mumbai.

CALIBRATION CURVE OF BARICITINIB
❖ Preparation of stock solution
Standard curve of baricitinib was constructed using a solvent blend of DMSO and methanol.

❖ Preparation of working standard solution
From the stock, solution pipettes out 1 ml and makeup to 10 ml diluted to 100 ml with 7.4 pH phosphate buffer in a volumetric flask. The resultant solution had a concentration of 100µg/ml & was labeled as a working standard solution.

❖ Preparation of serial dilution
From the standard stock solution about 1ml,2ml,3ml,4ml, and 5m, 6 were pipette out into a series of 10 ml volumetric flasks & the volume was made up to the mark with 6.8pH buffer and mixed to obtain solutions in the concentration range10,20,30,40,50,60 µg/ml of the drug.[8]

PREPARATION OF BARICITINIB JELLY
Medicated jelly of Baricitinib was prepared by heat and congealing method. Weighed all the required ingredients. Prepared sucrose syrup and added citric acid to prevent crystallization. Gelatin should be dissolved in water and the above mixture is added to it. Barcitinib and sodium

benzoate was dissolved in vehicle and added to the above mixture with stirring. Sodium citrate was added by stirring. Coloring and flavoring agents are added. The weight of the jelly was adjusted to 5gms. It is poured in mould and cooled until jelly is solidified. The formed jelly is packed using gelatin paper & stored in dry place.[9]

Physical examination

The medicated jelly was evaluated in terms of stickiness and grittiness by rubbing the gel between two fingers. Color, and odor, was also evaluated by physical appearance. Color, odor, and presence of particulate matter.[10]

Weight variation

The weight of each of the twenty medicinal jellies was measured using an analytical balance. The average weight and percentage weight variation were determined.[11]

Formula = Initial weight of jelly – average weight of jelly / average weight of jelly x100.

pH

pH has an impact on both flavour and stability of the jelly. At room temperature, the pH of the jelly was determined using a digital pH meter. 50 ml of distilled water was mixed with 0.5 g of jelly to form a 1% solution, and the pH of the mixture was measured.

Syneresis

Due to a lower concentration of the gelling ingredient, syneresis occurs, which causes the jelly formulation to shrink while releasing liquid during storage. For 24 hours, all of the formulations were kept at room temperature. Formulations exhibiting syneresis were eliminated.[13]

Viscosity

The viscosity of formulations F1 to F9 was examined. A uniform-sized incision was made on the plastic polyethylene bag to allow the oral medicinal jelly to be taken out of it. Spindle number LV4 at was used to measure the viscosity of the medicated jelly. A rotational speed of 50 RPM and a temperature of 25 °C ± 1 °C. Utilizing new samples each time, the viscosity measurements were performed in triplicate.[14]

Drug content

Ten jellies were crushed, and a gel containing 10 mg of baricitinib was dissolved in 100 ml volumetric flask containing 7.4 pH buffer and was diluted as required. Absorbance was measured using a UV/Visible double beam spectrophotometer at 250 nm.[15]

***In-vitro* Dissolution Study**

Medicated jelly was artificially masticated in a 7.4 pH buffer for 5 minutes to simulate chewing activity. Then it was transferred into a USP II dissolution apparatus with a paddle speed of 50 rpm and a 7.4 pH buffer as the dissolution medium. At 10, 15, 20, and 25, 30 minutes, samples were taken and replaced with an equal volume of fresh buffer. Samples were filtered, diluted, and subjected to spectrophotometric analysis.[16]

Experimental design for optimization

The screening was done using a 3^2 factorial design to limit the number of trials required to obtain the maximum quantity of data on product attributes. The chosen independent variables were the amounts of gelatin and xanthan gum in the polymeric blend, which were altered at a total of three levels: low level (1), medium level (0), and high level (+1). As dependent variables (responses), weight variation, viscosity, and *In-vitro* data were all used. The evaluation and creation of the statistical experimental design were done using the Design-Expert® Version 11 software from Stat-Ease Inc. in the USA. For optimization, a quadratic mathematical model produced using a 3^2-factorial design was used to represent the impacts of independent variables on the answers.

Where Y is the response, b0 is the intercept, and b1, b2, b3, b4, and b5 are the regression coefficients. Y = b0 + b1X1 + b2X2 + b3X1X2 + b4X21 + b5X22. Individual effects X1 and X2 are X21 and X22 are quadratic effects, while the interaction effect X1X2 is X1. A one-way ANOVA was used to determine the model's significance ($p < 0.05$).[17,18]

9. Stability studies

The final jelly formulation completed stability experiments and was kept in high-density polyethylene containers at 30℃/65% RH for three months. After each month, samples were analyzed for appearance, pH, syneresis, and drug concentration.[19]

3. RESULTS AND DISCUSSION

Drug excipients compatability studies

About 2-4 mg of the physical combination and heated potassium bromide were introduced to the hydraulic press, mixed and formed into pellets. The pellet was put in an FT-IR sample holder for transmission mode analysis in the 4000-400cm^{-1} wave number range.

4. Evaluation Parameters

All of the formulations underwent a number of assessment tests, including those for texture, thickness, particle matter, colour, and clarity. There are no particulates discovered in any of the formulations, where all appear clean and possess pleasing colour. Formulations F8 and F9 are non-sticky**.** Drug content in the all formulations is above 90%. Among all F8 formulation was highest (99.47±0.06% in 7.4pH buffer).

***In-vitro* Dissolution Study**

The optimized formulation (F8) showed a drug release of 90.01±0.6% within 25 minutes using simulation method

and a drug release of 98.45±0.3% in 30 minutes using dissolution apparatus.

5. Stability studies

Optimized formulation F8was wrapped in aluminium foil & was stored at 25℃-30°C RH± 5% for 3 months.

6. Optimization of Data analysis

❖ **Response R1**

The formulations displayed weight variation of between 0.18 and 0.55 percent. The mathematical model is fit by the equation R1 = + 0.5189, +0.0550A, -0.0917B, +0.0000AB, -0.0683A2, -0.1283B2 that is developed. The model's F value was 12.07 and its P value was < 0.05 in the ANOVA equation, confirming the model's importance. Furthermore, the r^2 adjusted 0.8737 is in reasonable competitiveness with the r^2 predicted 0.5115. Jellies' weight variation was visible in R1's 3D response graphic.

❖**Response R2**

Reaction R2 Formulations between 45420 and 65381 exhibited viscosity. The best-fitting equation for response R1 was R2 = +61611.22, -4118.50A, +3901.83B, +898.50AB, -7110.83A2, and -584.83B, with a P value of <0.05 indicating the model's significance. The adjusted r^2 is 0.9872 faces fair competition from the expected r^2 0.9457. The 3D surface plot of R2 revealed that each formulation's viscosity.

❖ **Response R3**

The most effective model for independent variables is the one developed for response R3 = +95.78, -3.21A, -0.4733B, -1.90AB, -1.96A2, -2.20B2. Model F value 9.06, P <0.05, according to an ANOVA, was significant. Additionally, the 0.8344 r^2 corrected was similar to the 0.3188 r^2 predicted. In-vitro drug release was visible on the 3D response surface plot of R3.

❖**Check point study and design optimization**

The optimized jelly formulation (F8) was used to explore the checkpoints and was then assessed for viscosity, weight variation, and in-vitro drug release, with R1=0.364, R2=93.48, andR3=97.01%.

7. *IN-VIVO STUDIES*

Selection of animals

Animals were separated into 4 groups each group contain 4 mice.

Group 1**:** Control

Group 2: CFA

Group 3: Standard (Diclofenac jelly 100mg/kg)

Group 4: Test 4mg.

Anti-arthritic activity

The mice were housed at the animal house of Chalapathi institute of pharmaceutical sciences, lam, Guntur, AP. Animals were housed individually in an open system with recycled paper bedding. Twice weekly diets were placed in special containers on the cage floor. Relative humidity ranged between 45% and 55% humidity was measured. The environmental conditions included temperature at 23-25°C (regulated at 23°C prior to arthritis induction and 25°C post induction) Housing, handling, pain management and sample collection procedures conformed to the policies and recommendations of the Chalapathi institute of pharmaceutical sciences and Ethics Committee.

CFA (Complete Freunds Adjuvant)

CFA causes tissue necrosis, inflammation, and ulceration by suspending desiccated mycobacterium in paraffin oil and mannide monooleate. It can be administered subcutaneously in the paw or intraperitoneally in mice and rats. Onset of action will be observed after 24 hours injection. It is advised to euthanize CFA-injected animals within a week due to the rate of tissue necrosis.

Study

Group 2 was administered 0.1 ml of CFA subcutaneously to induce arthritis. Diclofenac was administered to Group 3 as normal. Group 4 received treatment with an improved F8 Jelly formulation. Using a plethysmometer to measure the volume of the paw, the results were compared after 7 days, and the data indicated that there was no sign of toxicity and that the newly developed Baricitinib jelly was just as effective to the standard one.

TABLES

Table 1: Formulation of Baricitinib jelly.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Baricitinib	4	4	4	4	4	4	4	4	4
Sucrose	15	15	15	15	15	15	15	15	15
Xanthan gum	3	2	2	3	1	3.2	1	1	3
Gelatin	0.5	0.5	1	1	0.5	1.5	1	1.5	1.5
Citric acid	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium citrate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Sodium benzoate	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Water	qs	qs	qs	qs	qs	qs	qs	qs	qs
Colour and flavour	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total weight	5gms	5gms	5gms	5gms	5gms	5gms	5gms	5gms	5gms

Table 2: Calibration curve data of Baricitinib.

Concentration (µg/ml)	Absorbance (nm)
10	0.135
20	0.248
30	0.461
40	0.612
50	0.741
60	0.986

Table 3: Physical evaluation tests of jellies.

Formulation code	Clarity	Colour	Particulate matter	Texture	Stickness
F1	Clear	Red	No	Smooth	Sticky
F2	Clear	Red	No	Smooth	Sticky
F3	Clear	Red	No	Smooth	Slightly sticky
F4	Clear	Red	No	Smooth	Slightly sticky
F5	Clear	Red	No	Smooth	Sticky
F6	Clear	Red	No	Smooth	slightly sticky
F7	Clear	Orange	No	Smooth	Slightly sticky
F8	Clear	Pink	No	Smooth	Non sticky
F9	Clear	Pink	No	Not smooth	Non sticky

Table 4: Results of Weight variation, Viscosity and pH, Syneresis.

S.No	Formulation code	(%)Weight variation	Viscosity (cps)	pH	Syneresis
1	F1	0.51±0.12	51420	6.14±0.05	Yes
2	F2	0.49±0.05	56330	6.28±0.02	Yes
3	F3	0.72±0.07	60953	6.51±0.09	Yes
4	F4	0.62±0.04	54159	6.62±0.04	Yes
5	F5	0.39±0.14	55402	6.33±0.05	Yes
6	F6	0.31±0.18	62381	6.68±0.03	No
7	F7	0.36±0.23	58500	6.54±0.16	Yes
8	F8	0.21±0.05	60785	6.85±0.02	No
9	F9	0.27±0.03	55397	6.72±0.11	No

Table 5: Drug content of Jellys.

S.No	Formulation	% Drug content
1	F1	92.79±0.34
2	F2	96.48±0.12
3	F3	93.67±0.23
4	F4	95.28±0.02
5	F5	96.38±0.15
6	F6	94.11±0.21
7	F7	95.25±0.05
8	F8	99.47±0.06
9	F9	97.92±0.14

Table 6: Cumulative %drug release of oral medicated Jellys.

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
0	0	0	0	0	0	0	0	0	0
5	9.02±01	9.84±0.3	8.24±0.4	11.77±0.8	8.78±0.1	8.2±0.2	15.43±0.3	18.05±0.7	10.54±0.2
10	24.07±0.9	20.38±0.4	17.35±0.1	23.58±0.6	17.36±0.3	24.66±0.8	35.81±0.5	39.26±0.5	18.47±0.4
15	39.22±0.6	39.47±0.5	33.68±0.7	41.73±0.2	39.81±0.5	34.72±0.6	47.43±0.2	55.12±0.6	41.51±0.6
20	55.04±0.3	60.85±0.3	56.28±0.8	57.9±0.3	54.33±0.6	57.88±0.5	59.88±0.4	78.18±0.8	63.49±0.8
25	72.08±0.5	75.99±0.6	68.09±0.3	66.03±0.7	69.75±0.5	70.14±0.3	70.56±0.3	90.01±0.6	78.39±0.3
30	90.45±0.8	93.48±0.7	85.73±0.5	77.43±0.6	84.31±0.3	88.24±0.7	89.37±0.5	98.45±0.3	88.56±0.6

Table7: Stability studies data.

Parameter	After 1st month	After 2nd month	After 3rd month
Appearance	Smooth	Smooth	No change
pH	3.52±0.042	3.46±0.04	3.21±0.09
Viscosity(cps)	60340	58600	57190
Temp^{0}C	25	25	25

Table 8: *In vivo* data.

TIME (min)	CONTROL	CFA (0.1ml)	STANDARD (Diclofenac 100mg/kg)	TEST(4mg)
0	1.47±0.048	1.52±0.048	1.60±0.041	1.475±0.048
5	1.70±0.041	1.97±0.048	1.87±0.085	1.700±0.041
15	1.65±0.065	2.37±0.063	2.07±0.085	1.950±0.065
30	1.72±0.048	2.77±0.085	1.97±0.085	2.125±0.075
60	1.70±0.041	3.07±0.095	1.92±0.048	2.025±0.063

FIGUTRES

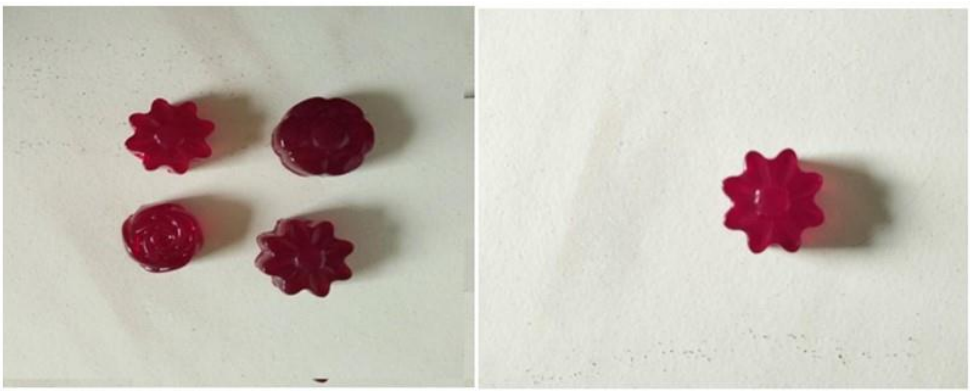

Figure .1: Jellies of Baricitinib

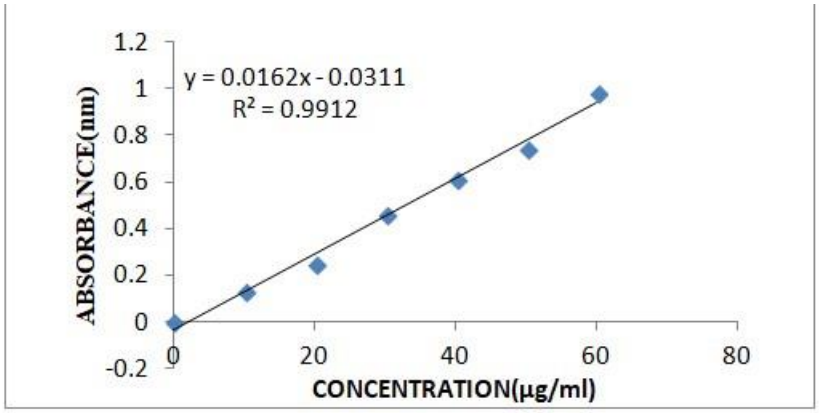

Figure 2: Calibration curve of Baricitinib

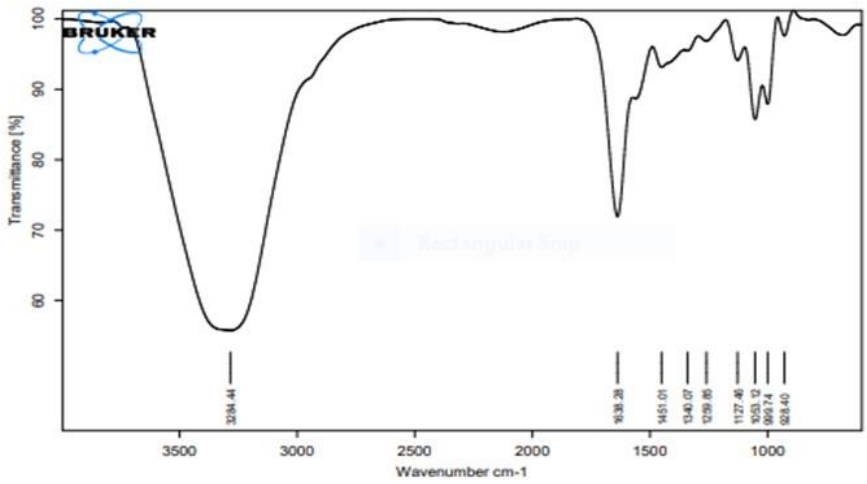

Figure .3: FT-IR spectrum of pure drug Baricitinib

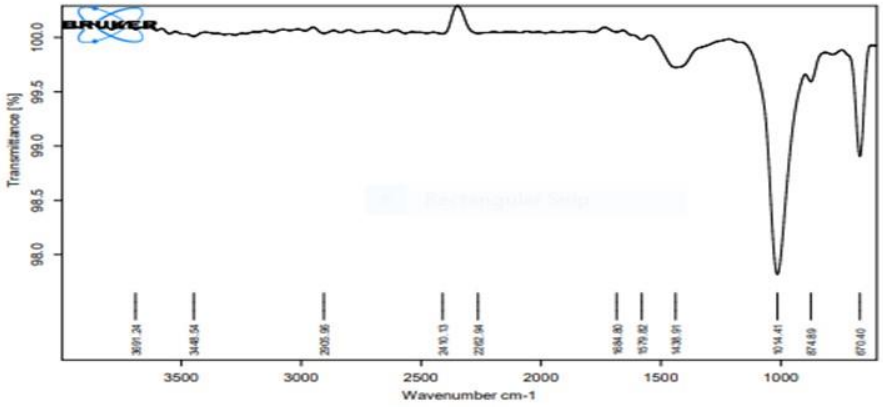

Fig .4: FT-IR spectrum of physical mixture (Baricitinib+Gelatin+Xanthan gum)

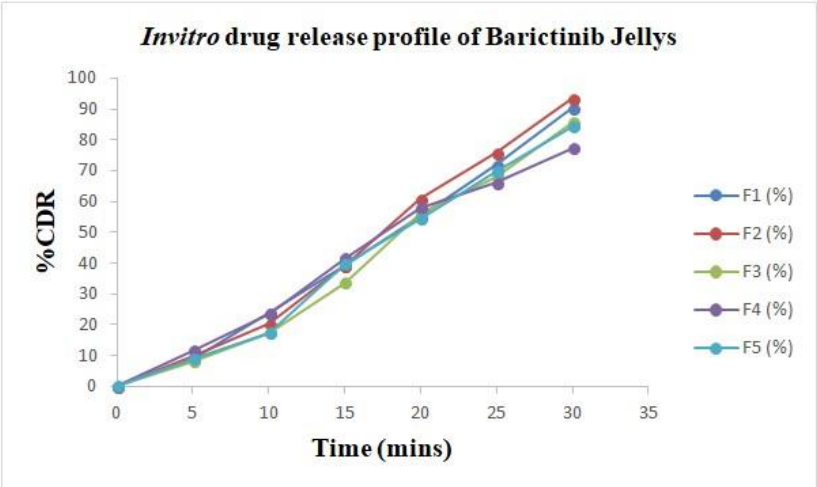

Fig 5: *In-vitro* Drug Release Studies of oral medicated Baricitinib Jellys

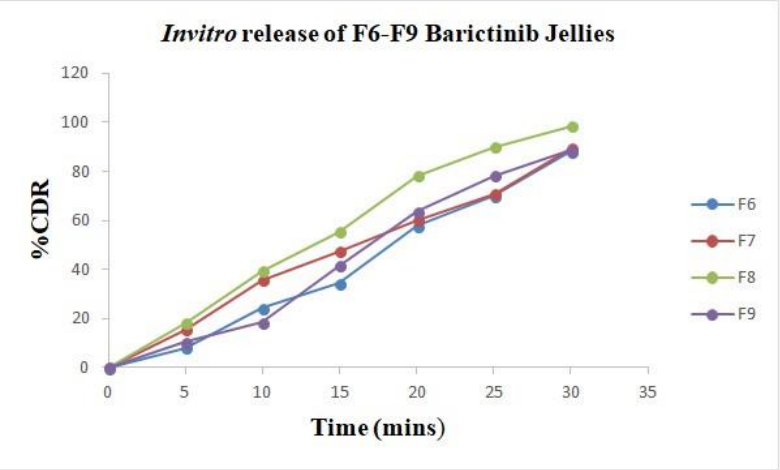

Fig 6: *In-vitro* Drug Release Studies of Baricitinib Jellys

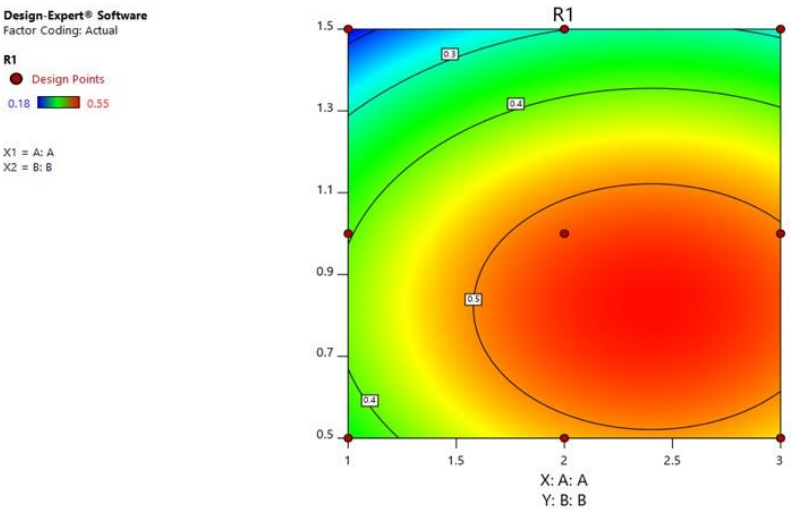

Fig 7: Contour plot R1 (%weight variation)

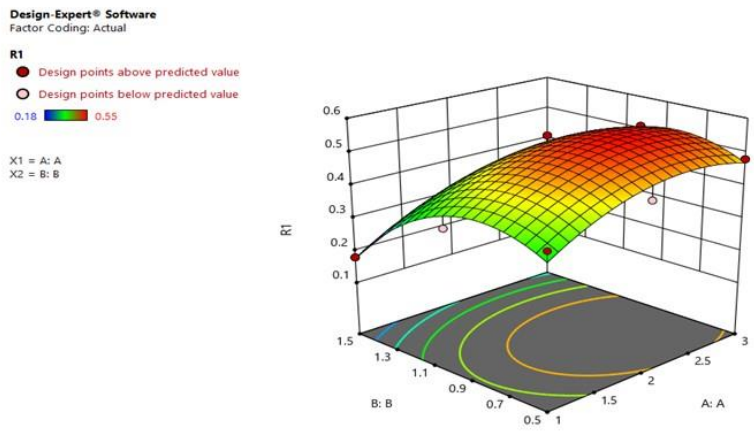

Fig 8: 3D Response surface plot R1 (%weight variation)

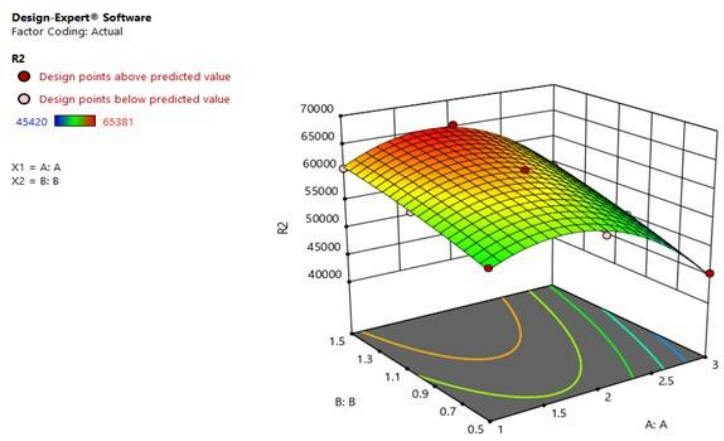

Fig 10: 3D Response surface plot R2 (viscosity) (cps)

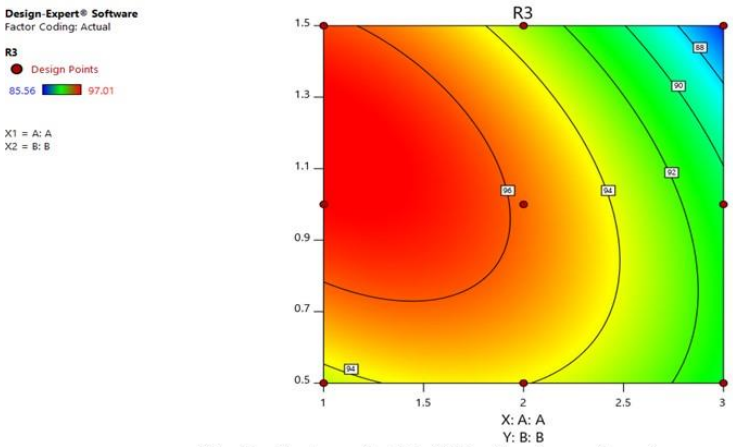

Fig .11: Contour plot R3 (%*In-vitro* drug release)

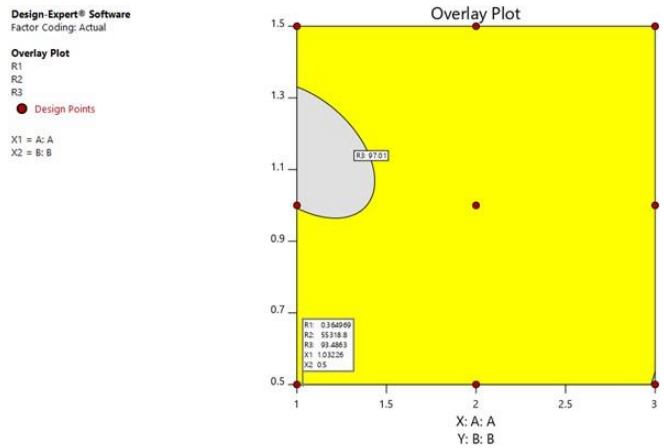

Fig. 13: Overlay plot

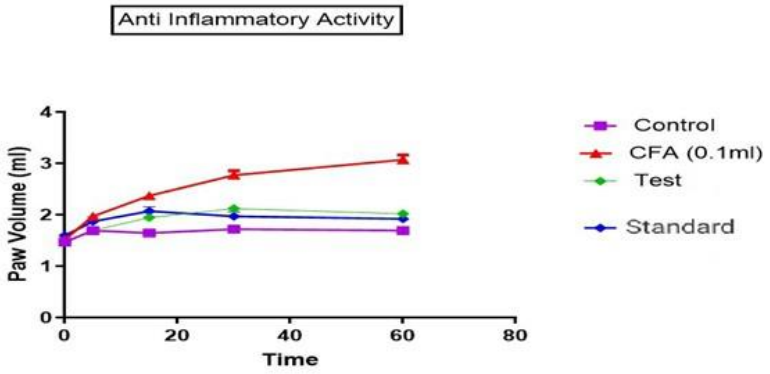

Fig .14:Anti-inflammatory activity graph

CONCLUSION

Oral medicated jellies from Baricitinib were prepared by heating and congealing method. Jellies which contain combination of gelling agents (gelatin+ Xanthan gum) showed better activity. Gelatin and xanthan gum were taken as a variables and each variable having 3 levels so by using 3^2 factorial design 9 formulations were designed with the application of DOE software. All the 9 formulations were assessed for various tests and by considering obtained data from all tests along with *in-vitro*, F8 formulation showed better, quick and constant drug release. *In-vivo* studies were carried out with F8 formulation and results was compared with standard product. Formulation showed better *in-vitro & in-vitro* correlation. Accelerated stability studies were carried out for 3 months during the study there is no noticeable change throughout the stability study period. Baricitinib jelly can be an advantageous in order to treat rheumatoid arthritis successfully like other marketed formulations. The noticeable advantage is first pass metabolism was avoided and the patients having problem of dysphagia can easily consume oral medicated jellies.

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