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Formulation Development and Evaluation of Unit Moulded Herbal Semisolid Jelly useful in treatment of Mouth Ulcer

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Abstract: The primary objective of this study was conducted with a view to formulate and evaluate the unit moulded jelly containing herbal medicaments and optimization of this dosage form which will dissolve slowly when kept in contact with mouth ulcer without any irritation or inflammation and produce soothing and cooling effect. In the present investigation the aqueous extracts of *Glycyrrhiza glabra, Jasminum officinale,* and *Mentha piperita* drugs were analyzed for the preliminary studies with regards to the parameters colour, taste loss on drying, microbial profile, test for presence of heavy metals, pH and water soluble extractives. All the eight formulation (F1 to F8) under study was found to be stable and showed comparable appearance, pH, spreadability and viscosity. According to statistical analysis of the obtained results by 't' test for unpaired samples in carragenan induced rat paw edema the optimized formulation F2 containing *glycyrrhiza glabra, jasminum officinale, and mentha piperita* herbal drug extracts were shown the anti-inflammatory activity substantially equal with that of marketed preparation. The optimized formulation was found to be stable for the period of 3 months as per ICH guidelines.
Key Words: Jelly formulation, Herbal drugs, Unit moulded dosage, Carrageenan Paw edema.

INTRODUCTION

A mouth ulcer is a breach or break in the mucous membrane, which lines the inside of the mouth. It usually looks like a depression in the mucous membrane and usually has yellow or white colour. The size may vary from a millimeter or less in diameter to several centimeters. It is often painful[1].

Treatment of mouth ulcers may include soothing mouthwashes (such as salt and warm water or compound thymol glycerin mouthwash) or antiseptic mouthwashes, such as chlorhexidine mouthwash or povidone iodine mouthwash. Paracetamol is useful to relieve pain, especially for young children with viral infections causing mouth ulcers. Such young children need to be encouraged to drink to avoid dehydration. Carbenoxolone gel or mouthwash can be used[4]. These are synthetic drugs, which contain several adverse effects, so there are many herbal drugs, which are also used for treating mouth ulcers without any side effects. Polyherbal preparations are generally the mixtures of extracts, juices, pulps, secretions and exudations or powders of medicinal herbs in solid, liquid or semisolid forms with or without a suitable base.

The present study was aim towards the development of semisolid dosage form which will be unit mould containing polyherbal ingredients. For present study two herbal drugs were selected and they were moulded as a unit dosage for in the form of jellies. "Jelly is semisolid system either suspension made up of small inorganic particles or large organic molecules interpenetrated by a liquid". These are transparent or translucent non-greasy semisolid preparations meant for external application to the skin or mucous membrane. In jellies hydrated threads or granules of the dispersed phase are intimately associated with the dispersion medium. Jellies represent a more uniform type of gel structure & contain high proportion of liquid, which is usually water. Both the disperse phase & dispersion medium are continuous throughout the system, the continuity resulting from matrix formation (cross-linking gelatinous mass) [5, 6].

Box 1: Factors responsible for the mouth ulcers

- Viral infections[2]
- Toothpastes and mouthwashes that contain sodium lauryl sulfate[3]
- Mechanical trauma
- Emotional stress / Psychic stress
- Nutritional deficiencies
- Allergies and sensitivities
- Hormonal changes
- Genetics
- Infectious agents (both bacterial and viral)
- Medical conditions

Box 2: Advantages of herbal medicines[7]

- Herbal medicines have long history of use and better patient tolerance as well as public acceptance.
- Medical plants have a renewable soured, which is our only hope for sustainable supplies of cheaper medicines for the worlds growing population.
- Availability of medicinal plants is not a problem especially in developing countries like India having rich agro-climatic, cultural and ethnic biodiversity.
- The cultivation and processing of medicinal herbs and herbal products in environment-friendly.
- Prolong and apparently uneventful use of herbal medicines may offer testimony of their safety and efficacy.
- Throughout the world, herbal medicine has provided many of the most potent medicines to the vast arsenal of drugs available to modern medical science, both in crude form and as a chemical model upon which modern medicine are structured.

MATERIAL AND METHODS

MATERIAL

Glycyrrhiza glabra extract, Jasminum officinale extract, Mentha piperita extract was purchased from Amsar Pvt. Ltd. Indore, India. Ciprofloxacin was gift sample from Aarti Lab. Pvt. Mumbai, India. Pectin, Tragacanth gum was purchased from Loba Chem. Mumbai, India. Gelatin, Carragenan and Nutrient agar were purchased from Research Lab. Mumbai, India. All other reagents and chemical were analytical grade. The animal experimental protocols were approved by the Institutional Animal ethical committee and conducted according to the Indian National Science Academy guidelines for the use and care of Experimental animals.

METHODS

Preliminary Study of Herbal Drugs

The aqueous extracts of *Glycyrrhiza glabra, Jasminum officinale, and Mentha piperita* were analyzed for color, loss on drying, microbial profile, heavy metals, pH and water-soluble extractive.

Evaluation of Antimicrobial Activity of Herbal Extract

The antimicrobial activity of aqueous extracts of herbal drugs was evaluated by using agar diffusion method i.e. cup plate method. This method was used to determine the zone of inhibition of the two frictions of aqueous extracts. The powdered drug extracts, 1 gm dissolved in 10 ml of sterile water to Produced solution 100 mg/ml. The 5 different concentration of the ciprofloxacin solution were prepared to contain 10, 20, 30, 40, 50 µg/ml in volumetric flask. The sterile Petri dishes were incubated with test organism and then filed with sterile nutrient agar medium keeping bore diameter of 8 mm. The Petri dishes are divided into six pats that contain the six bore mark as S_1, S_2, S_3, S_4, S_5, and one for sample under aseptic condition. In next stage, Petri dishes containing nutrient agar and test organism were impregnated with the separate extract of *J. officinale, G. glabra, and M. piperita* at concentration of 100mg/ml. Ciprofloxacin having concentration 10-50 µg/ml was used as reference standard[8]. The inoculated plates were incubated at 37 ^{o}C for all microbial strains. After 24 hr, zone of inhibition was measured and compared with that of standard .

For these purpose following ingredients was used.
Media- Nutrient agar medium.
Test organism-Staphylococcus auras, Bacillus subtillis and E.coli.
Standard antibiotic-Ciprofloxacin.

Table 1: Preliminary studies of herbal drug extracts

Sr.No	Preliminary studies			
	Parameters	***Glycyrrhiza glabra***	***Jasminum officinale***	***Mentha piperita***
1	Color	Brown powder	Brown powder	Brown powder
2	Orgnaleptic Taste	Sweet taste	Astringent	Characteristics
3	Loss on drying	4.12 % w/w	3.13 % w/w	4.00 % w/w
4 Microbial Profile	Total Plate count	580 CFU/GM	610 CFU/GM	480 CFU/GM
	Yeast & Moulds	Absent	Absent	Absent
	E. coli	Absent	Absent	Absent
	Salmonella	Absent	Absent	Absent
5 Heavy metals	As	1.0210 PPM	0.760 PPM	1.0230 PPM
	Pb	1.010 PPM	0.810 PPM	1.0890 PPM
	Cd	0.210 PPM	0.230 PPM	0.260 PPM
	Hg	0.480 PPM	0.320 PPM	0.560 PPM
6	pH	5.26	6.45	5.50
7	Water soluble extractives	79.42 %	87.40 %	86.89 %

Table 2: Formulation batches of different jelly products

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Pectin	1%	2%	----	----	----	----	----	-----
Gelatin	----	-----	2%	3%	----	----	----	------
Agar	----	-----	-----	-----	1%	1.5%	----	----
Tragacanth gum	-----	-----	-----	------	-----	-----	1%	1.5%
Citric acid	1%	1%	1%	1%	1%	1%	1%	1%
Sugar syrup	60%	60%	60%	60%	60%	60%	60%	60%
Water	30%	30%	30%	30%	30%	30%	30%	30%
Propylene glycol	3%	3%	3%	3%	3%	3%	3%	3%
Sodium benzoate	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
Peppermint water	2%	2%	2%	2%	2%	2%	2%	2%
Amaranth color	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Jasminum officinale	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Glycyrrhiza glabra	0.14%	0.14%	0.14%	0.14%	0.14%	0.14%	0.14%	0.14%
Mentha piperita	0.3 %	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%

Formulation of Jelly

Eight different formulations of jelly (**See table 2**) were prepared using pectin, gelatin, agar and tragacanth gum as gelling agents in different concentrations. The various gelling agents were tried to achieve desired stiffness, slow dissolution. Excipients like propylene glycol, was tried to enhance softness, and slipperiness of the jelly. Citric acid was used to maintaining the pH. Coloring agent and flavoring agent were added to increase the aesthetic value of the jelly. The formulation contains the high amount of water, so a chance of microbial growth was high; hence sodium benzoate is used as preservative. Sugar syrup was used as a bulking agent which provide body to the jelly. All the ingredients are weight accurately. In one beaker pectin, propylene glycol, citric acid were taken and heated to dissolved pectin and citric acid with constant stirring. In another beaker sugar syrup was prepared by adding 67 gm of sugar in a beaker and make up the volume up to 100 ml. Sugar syrup was added to pectin solution and boiled for few minutes. Sodium benzoate, amaranth colour were dissolved in peppermint water. After boiling pectin solution, the scum was removed and peppermint water was added to it and mixed thoroughly and uniformly. Herbal drug extracts was weight accurately, dissolved in little amount of water and added before jelly is allowed to set, mix thoroughly. These whole solutions was transferred in to moulds and then allow it for cooling and settling undisturbed by proper covering the moulds to avoid exposure to outer environment. After the jelly is set it is wrapped in to the gelatin paper and store in dry place.

Evaluation of prepared jelly

Appearance

The prepared jelly was inspected visually for clarity, colour and presence of any particle. The test is important regarding patient compliance.

pH [9]

The pH of all the jelly was determined using digital pH meter. 0.5 g of the weighed formulation was dispersed in 50 ml of distilled water and the pH was noted. The standard pH of the jelly was 3-3.4.

Spreadability

Spreadability of formulations was determined by an apparatus suggested by Multimer[10], which was fabricated and used for the study. It consists of wooden block provided with two glass slides. Lower slide fixed on wooden block and upper slide with one end tide to glass slide and other end tide to weight pan. A jelly quantity 2.5 gm was placed between two slides and 1000 gm weight was placed over it for 5 min to press the sample to a uniform thickness. Weight 80 gm was added to pan. The time (in sec) required to separate the two slides were taken as a measure of spreadability. Sorter time interval to cover the distance of 7.5 cm indicates better spreadability.

Spreadability was calculated by using the following formula,

$S = M L / T$

Where,

S = Spreadability,

M= weight tide to upper slide

L = Length of glass slide (7.5 cm), T = Time taken to separate two slides

Determination of Viscosity[11]

Viscosity of the jelly was carried out by using (LV) Brookfield viscometer (Dial type). As the system is non-Newtonian spindle no. 4 was used. Viscosity was measured for the fixed time 2 min at 0.3 rpm. Viscosity determination of jelly was done by Brookfield viscometer (Dial type).

Factor = 20 M
M = 1000
Viscosity = Dial reading x factor

The viscosity was calculated by following relation.

Viscosity in centipoises = Dial reading × Factor

The factor in above relation is found in factor finding chart provided by manufacturer of Brookfield viscometer.

Total Microbial Counts of Prepared Jelly

The herbal preparations are more prone to microbial growth. Hence all the eight formulations (F1 to F8) were evaluated for total microbial count. The bacteria and fungi were evaluated by plate count method as total microbial count.

Pretreatment to prepared jelly samples for total microbial count

10 g of the jelly being examined were dissolved in Buffered Sodium Chloride Peptone Solution. (pH 7.0) and volume was adjusted to 100 ml with the same medium. The 9 dilutions were prepared in the range of 10:1, 10:2, 10:3, 10:4, 10:5, 10:6, 10:7, 10:8 and 10:9. The dilutions were prepared using 10 ml of previous dilutions with 9.0 ml of sterile water and shaken well. All the three samples were treated in the same way for total microbial count.

Total Microbial Counts of Prepared Jelly for evaluation of bacteria

The four sterile Petri dishes were used for bacterial count. Out of the four Petri dishes, one was used for control and three Petri dishes were used for different dilutions of the sample. Amongst the various dilutions 10:6, 10:7 and 10:8 dilutions of samples were used for the bacterial count in duplicate. Each diluted sample (1.0 ml) was first poured into Petri dishes; liquefied Nutrient Agar Medium (25.0 ml) was poured into the same Petri dishes at 45 ^{0}C. The Petri dishes were incubated at 30 ^{0}C for 5 days. The colonies formed were then counted.

Total Microbial Counts of Prepared Jelly for evaluation of fungi

The dilutions of samples (10:3, 10:4, & 10:5) were used for the fungal count. Sabouraud dextrose agar with streptomycin was used instead of liquefied Nutrient Agar Medium. The procedure followed was as mentioned above. The plates were incubated at 20 ^{0}C to 25 ^{0}C for 5 days. The results are shown in table 8.

Stability Studies at Various Temperatures

Stability studies of prepared jelly at different temperature condition were carried out with regards to temperature like 4 ^{0}C, 45 ^{0}C and at room temperature. The stability studies are carried out for 3 months and the formulations were analyzed for the changes in the physical parameters like appearance, pH, viscosity, sugar crystallization and stiffness at 15 days, 30 days, 60 days and 90 days.

Table 3: Comparative study for zone of inhibition of herbal drug extracts Vs Ciprofloxacin

Conc.	Average zone of inhibition in mm								
	Glycyrrhiza glabra			*Jasminum officinale*			*Mentha piperita*		
	S. aureus	***B. subtillis***	***E.coli***	***S. aureus***	***B. subtillis***	***E.coli***	***S. aureus***	***B. subtillis***	***E.coli***
S1	11	13	17	19	21	19	11	13	9
S2	13	17	23	23	25	21	13	17	13
S3	17	21	27	27	29	23	17	19	17
S4	23	26	29	29	31	27	19	21	20
S5	27	28	31	31	33	28	21	23	23
Control	00	00	00	00	00	00	00	00	00
Sample	29	31	33	33	34	29	23	25	27

S1-S5 = Standard concentration of ciprofloxacin i.e. 10-50 µg/ml
Sample = Test solution of herbal extrac*t* i.e. 10 mg/ml

Table 4: Physical properties of the prepared jelly formulations

Formulations	Appearance	pH	Spreadability (sec)	Viscosity (cps)*
F1	Transparent	3.40	30	640000
F2	Transparent	3.30	27.27	600000
F3	White	3.50	31.57	588000
F4	White	3.50	26.08	580000
F5	White	3.40	23.07	624000
F6	White	3.40	35.29	552000
F7	Creamy	3.80	21.42	566000
F8	Creamy	3.60	24	604000

***In-vivo* evaluation of jelly for anti-inflammatory activity by carragenan induced rat paw edema method**[12-14]

Among the in-vivo methods the carragenan induced rat paw edema assay is believed to be one of the most reliable and is also the most widely used method. Carragenan in the mixture of Polysaccharides composed of sulphated galactose units and is derived from lrish Sea Moss, Chondrous Crispus. Albino rats (Strain Wister) of either sex about 150 – 225 gm were used. The animals were housed under standard laboratory conditions, maintained on a natural Light and Dark cycle and had free access to food and water. Animals were acclimatized to laboratory conditions before the test. Each animal was used twice.

Acute edema was induced in the right hind paw of rats by injecting 0.1 ml of freshly prepared 1 % aqueous solution of carrageenan in the plantar region of the right hind paw. The volumes of the hind paw were measured using plethysmometer at 60, 120 and 180 min after carrageenan challenge. Inflammation was expressed as the percentage change in paw volume. 50 mg of respective formulation were weighed and applied to left hind paw of each rat prior to one hour before Carragenan injection.

Statistical Analysis

The anti-inflammatory effect was expressed as percent edema inhibition. The formula for the same is as below.

$$\% \text{ Edema inhibition} = \frac{\text{Mean paw edema of control} - \text{Mean paw edema of test}}{\text{Mean paw edema of control}} \times 100$$

Mean paw edema + standard deviation (S.D.) and percent edema inhibition with reference to control was calculated.

Comparative Study with Marketed preparation

The optimized formulation F-2 was subjected to compare with the marketed formulation containing Chlorhexidine Gluconate Gel with respect to inhibition percentage of edema.

Table 5: Effect of aging and temperature on the optimized jelly formulation

Days	Temp ^{0}C	Appearance	Viscosity (Cps)	pH	Stiffness	Sugar crystallization
15	4 ^{0}C	Transparent	642500	3.30	N0	N0
	Room temp.	Transparent	640000	3.30	YES	NO
	45 ^{0}C	Transparent	635500	3.30	NO	NO
30	4 ^{0}C	Transparent	631200	3.25	NO	YES
	Room temp.	Transparent	622500	3.25	YES	NO
	45 ^{0}C	Transparent	612300	3.22	NO	NO
60	4 ^{0}C	Transparent	602800	3.19	NO	YES
	Room temp.	Transparent	612500	3.18	YES	NO
	45 ^{0}C	Transparent	605500	3.15	NO	YES
90	4 ^{0}C	Transparent	596500	3.15	NO	NO
	Room temp.	Transparent	586500	3.14	YES	NO
	45 ^{0}C	Transparent	576300	3.12	NO	YES

Table 6: Control reading of formulation by rat paw edema method

Marking	Wt. (gm)	Sex	Paw vol^m Initial	Paw volume (ml)			Edema (ml)		
				1 hr	2 hr	3 hr	1 hr	2 hr	3 hr
Head	200	M	4.0	2.95	2.80	2.20	1.05	1.20	1.80
Back	160	M	3.9	2.85	1.90	2.10	1.05	2.0	1.80
Tail	180	F	3.7	2.90	2.20	2.30	1.8	1.5	1.40
RFL	225	M	3.8	2.75	2.40	2.0	1.05	1.40	1.80
LFL	200	F	3.9	2.80	2.50	2.10	1.10	1.40	1.80

Table 7: Anti-inflammatory activity of jelly formulation F2 by carragenan induced rat paw oedema method

Marking	Wt. (gms)	Sex	Paw vol^m Initial	Paw volume (ml)			Edema (ml)		
				1 hr	2 hr	3 hr	1 hr	2 hr	3 hr
Head	180	M	4.3	5.2	5.3	5.4	0.9	0.9	0.9
Back	190	M	4.2	5.0	5.0	5.0	0.8	0.8	0.8
Tail	180	F	4.7	5.6	5.5	5.0	0.9	0.8	0.8
RFL	200	M	4.5	5.8	5.4	5.2	0.9	0.9	0.9
LFL	190	F	4.6	5.0	5.2	5.4	0.7	0.8	0.8

Table 8: Comparative studies of anti-inflammatory activity of optimized formulations F2 with marketed preparation

Formulation	1^{st} hour % Edema Inhibition	2^{nd} hour % Edema Inhibition	3^{rd} hour % Edema Inhibition
F2	41.57	64.33	75.74
MF	44.14	70.6	80.16

MF = Marketed Formulation: Chlorhexidine Gluconate Gel
F-2 = Formulation 2

RESULTS AND DISCUSSION

The aqueous extracts of *Glycyrrhiza glabra, Jasminum officinale, and Mentha piperita* were analyzed for color, loss on drying, microbial profile, heavy metals, pH and water-soluble extractive. All the herbal extracts i.e. *Glycyrrhiza glabra, Jasmines officinale, and Mentha piperita* are brown in color and sweet, astringent, characteristics in taste. The loss on drying of all the herbal drugs was found within the standard limit. In microbial profile the total plate counts of all the three herbal extracts were found 580 CFU/GM, 610 CFU/GM, and 480 CFU/GM respectively. Yeast and mould, E.coli and salmonella are absent in all herbal drugs extracts. Heavy metal study for As, Pb, Cd and Hg was found in limit. The pH and water soluble extractive of all herbal extracts was found within the limit. The results was shown in table no.1

The in-vitro anti-microbial activity was calculated in terms of inhibition zone diameter (mm). The organisms *Staphylococcus aureus, Bacillus subtillis* and *Escherichia coli* are used. All herbal drugs are showed the antimicrobial activity in terms of comparison with ciprofloxacin as standard antibiotics. (See table 3)

All the eight batches of prepared jelly are subjected to the evaluation for the appearance, pH, viscosity, spreadability and skin irritation test. The appearance of formulation F1 and F2 was transparent in nature and the other formulations shows creamy white in appearance.

The formulation F2 shows the pH within the range of standard pH range (3-3.3) of the jelly and the other formulations shows higher pH. The results of pH measurement are indicated in table 4. The spreadability results were calculated in the unit of time

among the various jelly formulations. All the formulation has shown better Spreadability. The formulation F2 shows the good spreadability. The results of spreadability are revealed in table 4. The viscosity of all formulations (F1 to F8) was determined using Brookfield viscometer (dial type). The results indicated that formulations were found uniform in consistency. Viscosity of formulation F2 is found optimum as it dissolved in the solution of pH 6.8 buffers up to six minute. The results of viscosity measurement are indicated in table 4. From the observations of various parameters that the formulation F2 containing 2% Pectin as gelling agent showed acceptable values as compared to the others. Hence, it is selected for further evaluation.

All the eight formulations were analyzed for the total microbial count. The results indicated that the total microbial count in all formulations has no colonies found and all formulations are free from microbial contamination. The stability study results demonstrated no change in colour, appearance, pH, viscosity, sugar crystallization and stiffness. The pH, viscosity was also unaffected. The results are recorded in table 5. The result indicated that jelly is stable at room temperature over a period of three month. The anti-inflammatory effect of test formulation and marketed formulation on carrageenan induced rat paw edema was summarized in tables 8. According to statistical analysis of the obtained results by 't' test for unpaired samples, a significant inhibitory effect was observed for each of the formulations tested versus the control. The optimized formulation F2 containing *glycyrrhiza glabra, jasminum officinale, and mentha piperita* herbal drug extracts showed the anti-inflammatory activity.

Fig 1: Zone of inhibition of Glycyrrhiza glabra against S. aureus, B. Subtillis and E.coli.

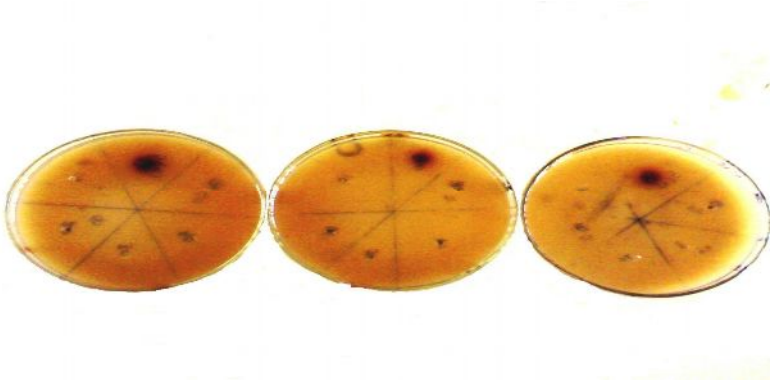

Fig 2: Zone of inhibition of Jasminum officinale against S. aureus, B.Subtillis and E.coli.

Fig 3: Zone of inhibition of Mentha piperita against S. aureus, B. subtillis and E.coli.

CONCLUSION

The present study demonstrates the herbal extracts of *glycyrrhiza glabra, jasminum officinale, and mentha piperita* were successfully formulated in the jelly formulations. All drugs extracts, which are used in the dose range are safe for consumption and can be swallowed without any risk of systemic side effects. The antimicrobial activity study of all herbal extracts is observed that, the extracts are active against organism *Staphylococcus aureus, Bacillus subtillis and Escherichia coli.* The prepared formulation will be a substitute over the other preparation available in the market in near future. The prepared jelly formulation showed good anti-inflammatory activity as compared with that of market preparation.

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