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GINGEL: Development and Evaluation of Anti-Arthritic Gel Containing Ginger (*Zingiber officinale*)

Salonee Tawde
Vivekanand Education Society's
College of Pharmacy
Mumbai, India

Kinjal Gawde
Vivekanand Education Society's
College of Pharmacy
Mumbai, India

Deepak Mahind
Vivekanand Education Society's
College of Pharmacy
Mumbai, India

Chetan Mhaprolkar
Vivekanand Education Society's
College of Pharmacy
Mumbai, India

Kirti Sawant
Vivekanand Education Society's
College of Pharmacy
Mumbai, India

Chaitali Surve*
Dept of Pharmaceutics
Vivekanand Education Society's
College of Pharmacy
Mumbai, India

Abstract:- Arthritis is a musculoskeletal system disorder which involves destabilization of normal mechanisms. Due to changing habits of living life, the number of arthritic people will increase rapidly. Currently, the existing anti-rheumatic drugs mostly show side effects like acne, blurred vision, high blood pressure and more effective to reduce pain and improve disease conditions but still, they do not treat the disease completely. Literature available indicates that most of the people seek complementary alternative treatments (CAM). Ginger (*Zingiber officinale*) has empirically explored its use as an anti-inflammatory agent. Amongst others, the Topical route of drug delivery has built up popularity because it avoids first-pass effects, metabolic breakdown associated with oral administration and gastrointestinal irritation. Also, they are less greasy and can be easily washed off from the skin surface. The current study aimed to formulate anti-arthritic gel containing ginger extract and to evaluate its drug release activity. The topical ginger gels were prepared using Carbopol 934 as a gelling agent with varying concentrations, i.e., 0.5 %, 1 %, and 1.5 % w/w. The gel was assayed to determine percent purity and cumulative drug release. Results indicated that the 1.5 % w/w concentration of carbopol in ginger gel exhibited an adequate drug release. In conclusion, an anti-arthritic gel containing 1.5 % w/w of carbopol had a good consistency, acceptable spreadability, and showed a good drug release profile. The topical prepared herbal ginger gel is a simple, easily formulated, convenient and economical alternative that needs to be weighed in the treatment of RA.

***Keywords*:-** *Gel, Ginger, Arthritis, Topical dosage form, carbopol, drug release.*

I. INTRODUCTION

Arthritis is a musculoskeletal system disorder in which due to biological and some mechanical events occurrence causes destabilization of normal coupling between degradation and synthesis in articular cartilage. It affects various large and the small joints of the body including the knee joint, wrists, feet, back, hip, and occurs in the majority of people as it is the most typical variety of arthritis found. Typically it mostly affects weight-bearing joints like back spine and pelvis. Due to changing lifestyle and pressure due to heavy movements, there will be an exponential growth in the number of arthritis cases by the year 2030. Also, more than 25 % of the world population will have arthritis in one or other form [1].

Currently, the existing anti-rheumatic drugs available in the market are to reduce the symptoms of pain and swelling, delay the worsening of disease, minimize the disability, and eventually improve patient life and symptoms. Most of these objectives are attained by use of a combination of non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs, corticosteroids, and biological agents but an enumeration of side effects is also reported [1].

Zingiber officinale, a drug of natural origin is explored for the treatment of rheumatoid arthritis. Ginger consists of active ginger phytoconstituents such as 6-gingerol (6G), 8-gingerol (8G), 10-gingerol (10G), and 6-shogaol (6S). Ginger has broad spectra of therapeutic indications like anti-bacterial, anti-inflammatory, anti-cancer, anti-oxidant, etc., [2]. Many literature studies have proved that reactive oxygen species (ROS) have a crucial role in the pathophysiology of disease like arthritis[3]. This study emphasizes the use of drugs from the natural origin as the available therapies do not provide adequate results due to toxicity, recurrence of symptoms or side effects of synthetic drugs there is an urgent need for some alternative therapies for arthritis. Literature available indicates that an estimated 60–90 % of persons with arthritis seek alternatives like complementary alternative medicine (CAM). Among the various CAM available there has been a rapid increase of demand in herbal medicine in the last few years [1].

Delivery of drugs to the skin is a potent and targeted therapy for local disorders. The topical drug delivery system has advantages over the oral delivery system as it avoids first-pass effects, gastrointestinal irritation, and metabolic degradation and therefore this route is gaining popularity [4]. Topical gels are the formulations that are

preferred as an appropriate delivery system for drugs because they are less greasy and can be washed off easily from skin [5]. Gels are 3D matrices that are formed by two interpenetrating systems where the gelator/gallant which are colloidal particles are homogeneously distributed throughout a dispersion medium or solvent. As compared to other topical drug delivery systems gels have higher retention time at the administered site [3].

Nevertheless, there is limited information regarding the formulation and evaluation of anti-arthritis gel containing ginger powder extract. Therefore, the current study aimed to formulate a gel containing ginger extract with elegant appearance, good spreadability, soothing and cooling effect, and good dissolution profile in the selected membrane.

II. MATERIALS AND METHODS

➢ *Materials and instruments*

Ginger extract (*Zingiber officinale*) was provided ex-gratis by M/s Merck Limited – A Procter & Gamble Company, while Carbopol 934, Propylene glycol BP, Sodium hydroxide, Potassium dihydrogen phthalate, Triethanolamine, Methanol, were obtained from M/s Loba Chemie Pvt Ltd, Mumbai. All other materials employed during the studies were of analytical grade and were used as such as obtained. The instruments used included Magnetic stirrer and Ultraviolet-visible (UV-Vis) photo-spectrometer (Make: Shimadzu).

➢ *UV-Visible photo spectrometric analysis of Ginger powder:*

The ginger powder was analyzed using a UV-Vis photo spectrometer (Make: Shimadzu). In brief, 0.5 g of ginger was weighed and diluted with phosphate buffer pH 7.4 in a 50 mL volumetric flask to get the stock concentration of 10 mg/mL. The stock solution was further diluted to different concentrations in the range of 500- 1750 mcg/mL and the solutions were analyzed at 273 nm [11,12].

➢ *Optimization of the base for the gel*

The blank gels were prepared with different concentrations of propylene glycol, i.e., 20 %, 40 %, 60 % w/w and carbopol934, i.e., 0.5 %, 1 %, 1.5 % w/w (Table 1) [6]. The required amount of carbopol was taken and sprinkled in 3 mL of water in a beaker. The dispersion was kept aside for 15 minutes for carbopol to swell. The propylene glycol was added to the beaker containing carbopol mixture and stirred for uniform mixing. Further, triethanolamine was added to adjust the pH to 7. Sodium benzoate was added to it and later, a sufficient quantity of distilled water was added in this mixture to get the final weight of the gel to 5 gram.

Sr. No.	Ingredients	F1	F2	F3	F4	F5
1	Ginger	-	-	-	-	-
2	Carbopol934	1 %	1 %	1 %	0.5 %	1.5 %
3	Propylene glycol BP	20 %	40 %	60 %	20 %	20 %
4	Triethanolamine	q.s. till pH 7	q.s. till pH 7	q.s. till pH 7	q.s. till pH 7	q.s. till pH 7
5	Sodium Benzoate	0.05 %	0.05 %	0.05 %	0.05 %	0.05 %
6	Distilled Water	q.s 5gm	q.s 5gm	q.s 5gm	q.s 5gm	q.s 5gm

Table 1:- Optimization of propylene glycol for appropriate consistency and humectant properties of the gel.

➢ *Formulation of the anti-arthritic gel*

The anti-arthritic gel was formulated by the dispersion method [4]. The required amount of carbopol was taken and sprinkled in 3 mL of water in a beaker. The beaker was kept aside for 15 minutes for the carbopol to swell. Later, a weighted amount of propylene glycol and the ginger powder was added to the beaker and stirred (Table 2, Batch G1 and G2). Alternatively, the slurry of ginger powder in propylene glycol can also be prepared and can be incorporated in the beaker containing carbopol mixture (Table 2, Batch G3). The above mixture was sonicated for 10-15 minutes using a bath sonicator. Once the ginger powder was evenly dispersed, triethanolamine was added to adjust the pH till 7. Sodium benzoate was added to it and lastly, a sufficient quantity of distilled water was added to get 5gm of ginger gel.

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Sr no.	Ingredients	G1	G2	G3
1	Ginger	5 %	5 %	5 %
2	Carbopol 934	0.5 %	1 %	1.5 %
3	Propylene glycol BP	20 %	20 %	20 %
4	Triethanolamine	q.s till pH 7	q.s till pH 7	q.s till pH 7
6	Sodium Benzoate	0.05 %	0.05 %	0.05 %
5	Distilled Water	q.s 5gm	q.s 5gm	q.s 5gm

Table 2:- Formulae table for preparation of ginger gel.

➢ *Evaluation of the Gel*

- *Organoleptic Characteristics*

The drug loaded formulations were evaluated for the parameters like homogeneity, texture, color, physical appearance and immediate skin feel by visual observation. A small quantity of gel was pressed between the thumb and index finger to check the texture and homogeneity on the basis of consistency of the formulation and presence of coarse particles. Immediate skin feel (including grittiness, greasiness, and stiffness) was also evaluated.

- *Spreadability studies*

The spreadability studies were carried out using 1gm of the gel on the butter paper. This was then placed between two parallel tiles with an upper plate bearing a weight of 1 kg. The spreading diameter of the gel was recorded as spreadability. The average diameter of the circle after the spreading of the gel was determined [7].

- *Assay*

The assay of the drug in the gel was performed by extracting the ginger constituents from 1gm of ginger gel with 25 mL of phosphate buffer (pH-7.4) for 15 minutes. The resultant mixture was filtered through a membrane filter, having pore size 0.45 µm. The absorbance of the filtrate was determined spectrophotometrically at 273 nm (Shimadzu UV-VIS spectrophotometer) after appropriate dilution with phosphate buffer pH 7.4. The above assay was performed in triplicate. The same procedure was carried on a blank reference gel. The concentration of the novel drug (ginger) was estimated from the calibration curve deduced above [8].

- *Dissolution using dialysis membrane method*

The *In vitro* drug release studies were carried out using the dialysis bag technique on a freshly prepared ginger gel sample. Blank gel prepared was used as a reference. The dissolution medium used was phosphate buffer (pH 7.4). The dialysis bags (MW cut off 60,000 daltons) were soaked in phosphate buffer (pH 7.4) overnight before use. The release experiment was performed by taking 1gm of ginger gel into a dialysis bag with the two ends fixed by a thread [9,10]. These bags were placed in the release medium under gentle stirring at 50 rpm. At regular fixed intervals, aliquots (5 mL) were withdrawn and passed through the Whatmann filter paper. To maintain sink conditions, the same volume of fresh release medium was replaced in the dissolution medium. The amount of ginger released into the filtrate was determined using a UV- Visible Spectrometer at a detection wavelength of 273 nm. All the assessments were carried out in triplicate.

III. RESULTS AND DISCUSSION

➢ *Standardization*

The ginger powder was analyzed using a UV/VIS spectrophotometer (Shimadzu) at 273 nm [11,12] . The solution of ginger powder in phosphate buffer pH 7.4 followed the Beer Lambert's law in the range of 500-1750 mcg/mL with regression coefficient (R^2) values 0.9994 and the regression equation was calculated as y= 0.0004x+ 0.0091 as shown in Fig. 1.

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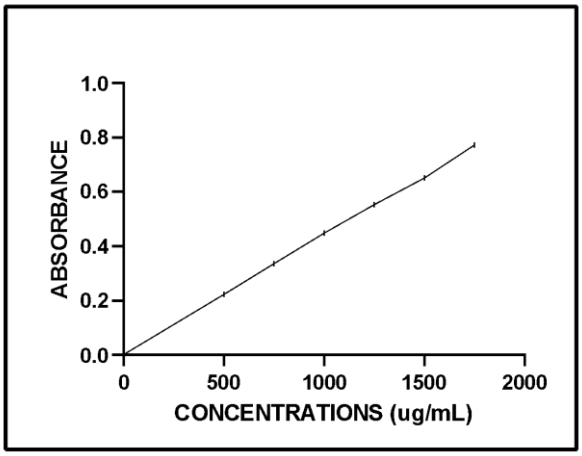

Fig 1:- Calibration curve in phosphate buffer pH 7.4: y=0.0004x+0.0091, R^2=0.9994.

➢ *Formulation of the anti-arthritic gel*

Different formulation trials were conducted to evaluate the influence of various excipients on the release profile of ginger. Various batches of bases were prepared as shown in Table I to get the optimum percentage of ingredients. The gels were later evaluated for the organoleptic properties and spreadability. In this, the concentration of propylene glycol BP was varied and was incorporated to get different gels as shown in Table I. Based on the appearance and consistency, Batch F5 showed excellent results and was taken for further optimization. The gel was formulated using two different methods, viz., (A) Dispersion of the drug in the gel base, (B) Dispersion of the drug in the co-solvent, and incorporation in the gel base. Gels prepared by the former method displayed non-homogeneity and lesser consistency as well as the drug release values were erratic. On the contrary, gel prepared using the later method displayed homogeneity, good consistency, and better drug release.

➢ *Organoleptic studies*

The organoleptic properties, including color, physical appearance, phase separation, homogeneity, texture, and immediate skin feel of the selected topical formulations, are displayed in Table 3. Results showed that the topical gel formulation had a cosmetically appealing appearance and smooth texture, and they were all homogenous with no signs of phase separation.

Formulation	Physical appearance	Color	Texture	Consistency	Homogeneity	Immediate skin feel
G1	Opaque	Yellowish brown	Smooth	Poor	Homogeneous	no grittiness, not greasy
G2	Opaque	Yellowish brown	Smooth	Moderate	Homogeneous	no grittiness or greasiness
G3	Opaque	Yellowish brown	Smooth	Good	Homogeneous	no grittiness or greasiness

Table 3:- Physicochemical evaluation of selected gel formulation.

➢ *Spreadability*

Spreadability of semisolid formulations is the ability of a gel to evenly spread on the surface of the skin which plays a requisite part in the administration of a standard dose of a medicated formulation to the skin and the efficacy of topical therapy. Fig. 2 shows the spreading values, that is, diameters observed for the formulations after five minutes after spreading them on a surface resembling skin. The values represent the extent to which the formulations promptly spread on the application surface by applying a small amount of shear. The Spreadability of the formulations was inversely proportional to the concentration of the swelling agent; that is, spreadability increased with decreased carbopol concentration (Table 4). During optimization, the value of spreadability for batch F4 was found to be 6.93 cm indicating that it is easily spreadable by a small amount of shear but the consistency of the same was poor. Based on spreadability, batches F1 and F5 were preferable over F4. Also based on consistency F5 was preferred over F1.

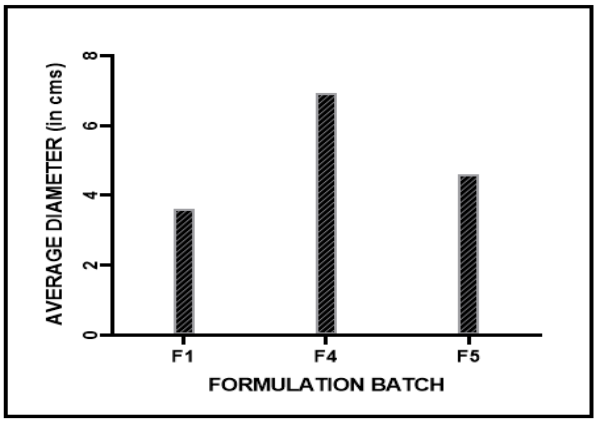

Fig 2:- Graphs representing the diameters of spreadability.

Batch Number	Average diameter (cm)
F1	3.63
F4	6.93
F5	4.6

Table 4:- Average diameters of trials F1, F4 and F5.

➢ *Assay*

All the gel formulations mustered drug content in the range of 85 % to 100 %. These results suggested that ginger powder was uniformly distributed in the carbopol matrix and the loss of drug during formulation was insignificant.

➢ *In vitro dissolution studies*

In vitro dissolution studies of ginger gel were done by the dialysis membrane method. The cumulative release profile of ginger gel was monitored for 2 h 30 minutes at 37 °C.As seen in Table 5 and Fig. 3, the G1 batch shows a % cumulative release of more than 95 % in 60 minutes. This can be attributed to the fact that the drug was not uniformly dispersed in the carbopol gel matrix of 0.5 % and did not show a sustained release over 2 h and 30 minutes. Therefore, batch G1 did not meet the dissolution criteria. The G2 batch shows a % cumulative release of 83.65 % at the end of 2 h and 30 minutes. This can be attributed to the fact that an increase in carbopol concentration from 0.5 % to 1 % led to a sustained release of the drug over the given time interval but batch G2 did not show maximum release i.e. more than 85 %. This can be possible because the drug was directly incorporated in the gel base so the dissolution medium was not able to solubilize the drug effectively. Therefore, batch G2 did not meet the dissolution criteria. The G3 batch shows a % cumulative release of 99.895 % at the end of 2 h. This can be attributed to the fact that the method by which the gel was formulated i.e. first the slurry was prepared in propylene glycol and then was incorporated in carbopol gel base helped the drug to easily cross the dialysis membrane and gave maximum release. Also the dissolution medium was effectively able to solubilize the drug from this formulation and the increase in the concentrations of carbopol gave better results. Therefore, batch G3 met the dissolution criteria and was selected as the final formulation for arthritis.

TIME	G1	G2	G3
15	53.175 ± 4.856	43.675 ± 4.856	46.675 ± 4.856
30	60.4925± 12.156	36.7925± 12.156	53.343± 12.156
45	74.76± 6.457	62.285± 6.457	71.61± 6.457
60	98.4025± 8.962	81.502± 8.962	84.778± 8.962
90	95.02± 2.767	89.845± 2.767	90.73± 2.767
120	104.238± 14.156	77.8375± 14.156	99.895± 14.156
150	115.93± 16.459	83.68± 16.459	94.088± 16.459

Table 5:- Table showing % cumulative release of batches G1, G2 and G3.

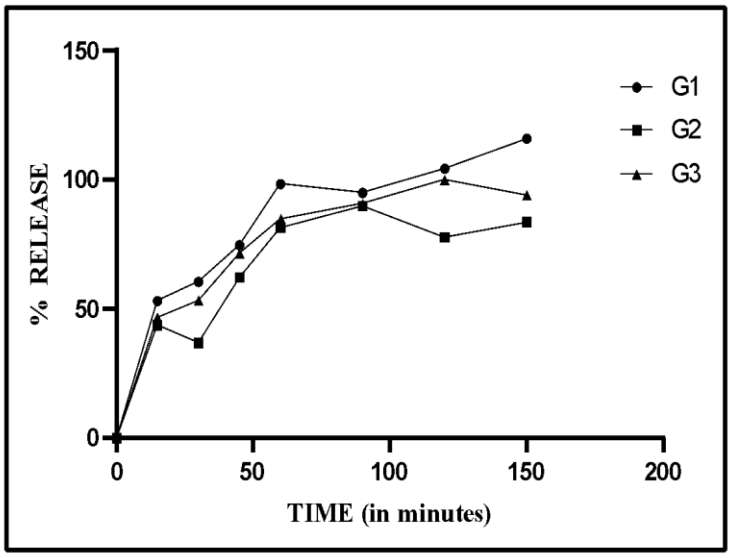

Fig 3:- Graph representing dissolution profiles of batches in phosphate buffer of pH 7.4.

IV. CONCLUSION

An anti-arthritic gel containing 5 % of the ginger extract was successfully developed. The developed gel showed good consistency, homogeneity, good skin feel, and left a soothing trail on the applied skin surface. It exhibited a good drug release of more than 99 % in less than 2h, percent assay was in the range of 85 % to 100 %. The prepared topical herbal ginger gel is a simple, easily formulated, convenient and economical alternative that needs to be weighed in the treatment of rheumatoid arthritis.

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