Fabrication and In-Vitro Characterization of Colchicine Microsponge Based Gel For Topical Drug Delivery System

Lalita, Twinkle Garg*

Himalayan Institute of Pharmacy, Kala Amb, Himachal Pradesh

Himalayan Institute of Pharmacy,Kala Amb, H.P., India

***Corresponding author: Twinkle Garg**

twinklegarg2004@yahoo.co.in

ABSTRACT

The goal of any drug delivery system is to provide therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired plasma concentration of drug for a particular period of time. Colchicine is used for the treatment of gout, pseudo-gout and familial Mediterranean fever. It is known to have low therapeutic index and low oral bioavailability due to extensive first pass effect, and also associated with sever gastrointestinal side effects following oral administration. To overcome its oral intake drawbacks, colchicine loaded microsponges gels were prepared in an attempt to deliver the drug transdermally. colchicine is reported to cause local pain, inflammation at injection site and first pass metabolism, gastrointestinal (GI) side effects respectively. Hence an alternative topical drug delivery system has been proposed in the form of microspongel gel for its simplicity of application, higher patient compliance and controlling the drug release. The drug loaded microsponges were prepared employing emulsion solvent evaporation method using xanthan gum. Further the drug loaded microsponges were incorporated into carbopol base gel. The formulations were characterised on several parameters such as pH, drug content, viscosity and spreadability and stability studies and showed satisfactory results. The results from FTIR study showed no drug excipient interactions. *In vitro* drug release studies were done to check the formulations' efficacy and the results showed sustained release of drug in colchicine loaded microspongel gel formulation as compared to control gel formulation. The study concluded that the procedure for making Colchicine microspongal gel is straightforward and repeatable.

KEYWORDS: Microsponge, Gel, Colchicine, Quasi - Emulsion solvent evaporation method, Xanthan gum.

INTRODUCTION:

Microsponges are extremely small (micron range) spherical particles that are unbreakable and harmless designed for its properties of not penetrating the skin layer epidermis and absorbing skin secretions in order to lessen the skin oiliness. Spherical particles are made up of groups of smaller spheres that can contain four times as much skin secretions as they weigh. They gather in the skin's minuscule crevices and discharge the drug there over time, as the skin requires it. The microsponge system can stop components from building up too much in the dermis and epidermis. The microsponge system has the potential in reducing the irritation caused by potent medication without any interference with the potency of the medication. The microsponge delivery method has produced a new wave of novel,

highly effective, and very well-tolerated products. These products generally come in the traditional forms such as gels, lotions or creams and have a relatively large amount of API [1, 2].

Microsponges are patented polymeric delivery systems made of porous microspheres that can hold a variety of active chemicals, including sunscreen, emollients, fragrances, essential oils, and anti-infective, anti-fungal, and anti-inflammatory medications. Each microsphere, like a real sponge, is made up of a large number of interconnected voids enclosed in a non-collapsible framework. Depending on the level of smoothness or after-feel needed for the finished formula, the size of the microsponges can be adjusted; typically, they range in diameter from 5 to 300 µm [3,4].

The goal of any drug delivery system is to provide therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired plasma concentration of drug for a particular period of time. However, incomplete release of drug, shorter residence time of dosage form in the gastrointestional tract and high hepatic first pass effect leads to lower bioavailability. Such limitations of the conventional dosages forms have paved to an era of controlled and novel drug delivery systems.

Colchicine is used for the treatment of gout, pseudo-gout and familial Mediterranean fever. It is known to have low therapeutic index and low oral bioavailability due to extensive first pass effect, and also associated with sever gastrointestinal side effects following oral administration. To overcome its oral intake drawbacks, colchicine loaded microsponges gels were prepared in an attempt to deliver the drug transdermally.

In context of above principle, the microsponge drug delivery systems were prepared for colchicine using Quasi-emulsion solvent evaporation method and incorporated in Carbopol 934 for gel formulation of colchicine loaded microsponges. The prepared formulation will be characterized for several parameters such as pH, drug content, viscosity, *in vitro* drug release, and spreadability and stability studies.

MATERIAL AND METHODS:

Materials

Colchicine was received as gift sample from Heliox Pharma. Other excipients like Xanthan gum, ethyl cellulose, sodium hydroxide and Carbopol 934 etc. were obtained from laboratory.

Experimental Methods

Preparation of Colchicine Microsponges

The xanthan gum-facilitated W/O/W emulsion solvent evaporation method was used to create the microsponges. A separate ratio of doubly distilled water was used to dissolve 100 milligrammes of the drug, and acetone was then added to the solution. To achieve a concentration of 0.2% (w/v), xanthan gum was gently incorporated into the acetone/water mixture. An aqueous solution of xanthan gum can have up to 40–50% of acetone introduced to it without the gum precipitating. Xanthan gum was utilised in this novel method because of this reason. Using a rotor-stator homogenizer at 2000 rpm for 5 minutes, the internal aqueous phase was emulsified into a 25 ml 1% (w/v) solution of ethyl cellulose in dichloromethane that contained 0.5% (w/v) Span 80. To create a W/O/W type emulsion, the created water-in-oil (W/O) emulsion was then added to 60 cc of water that contained 0.6% (w/v) Tween 80 while being continuously mechanically stirred at 1300 rpm. For an additional 1.5 hours, the stirring was done with a three-blade propeller to enable the organic solvent to evaporate. Filtration was used to

isolate the resulting micro sponges, and drying by air was the last step [5-7]. The chemical makeup of various micro sponges was listed in table 1.

Table 1: Composition of Colchicine loaded Microsponges

Sr. No	Formulation Code	Drug (mg)	Xanthan gum (%) (w/v)	Ethyl cellulose (%) (w/v)	Acetone: water (ml)
1	F1	100	0.2	1	2:8
2	F2	100	0.4	1	2:8
3	F3	100	0.6	1	2:8
4	F4	100	0.2	2	2:8
5	F5	100	0.2	3	2:8
6	F6	100	0.2	4	2:8
7	F7	100	0.2	3	1:9
8	F8	100	0.2	3	3:7
9	F9	100	0.2	3	4:6

Evaluation of Colchicine microsponge [8-11]

Percentage yield

The percent production yield of the prepared microsponge formula was determined using the formulae:

$$\text{Percentage yield} = \frac{\text{Practical mass of Microsponge}}{\text{Theoretical mass (polymer + Drug)}} \text{X100}$$

Particle size measurement

An optical lens was used to measure the microsponge's particle size.

Scanning Electron Microscope (SEM) study

SEM was used to examine the surface morphology of the microsponge compound.

Preparation of Colchicine microsponges gels

Formulations of microsponges carrying medication were added to the gel base, which was made up of distilled water up to 10 ml, 1% and 2% Carbapol 934, sodium benzoate (50 mg), propylene glycol (0.75 ml), triethanolamine (enough), and propylene glycol [12-15]. The composition of drug loaded microsponge gel is depicted in table 2.

Table 2. Composition of Different Colchicine microsponge gels

Sr. No	Ingredients	Formulation Code		
		F10	F11	F12
1	Microsponge equivalent to Colchicine (mg)	100	100	100
2	Carbopol 934 (%w/v)	1	1.5	2
3	Sodium benzoate (mg)	50	50	50
4	Propylene glycol (ml)	0.75	0.75	0.75
5	Triethanolamine (mL)	q.s	q.s	q.s
6	Distilled water (mL)	10	10	10

Evaluation of Colchicine microsponges gels [15-19]

Visual Appearance

The newly created gels were examined visually, and the prepared formulae were examined for physical characteristics (e.g., colour and homogeneity).

pH determination

The pH of the Colchicine microsponges gel compositions was measured using a digital pH metre. The pH was tested in triplicate and the average readings were then calculated.

Rheological studies

Rheological experiments were conducted using a viscometer. Three readings were taken in total and the average readings were then calculated.

Spreadability Study

The spreadability of gel was measured using a laboratory-made apparatus consisting of two glass slides, the top slide attached to a balance by a hook and the lower slide attached to a wooden plate. 1gm of gel was applied to the lower slide, while weight was applied to the top slide. The upper slide moved linearly in the direction of the weight when weight was applied, and the time it took for the upper slide to fully displace was recorded.

Drug content

The drug concentration of each sample of Colchicine microsponges gel formulation was determined separately by mixing 1 g of the gel with 100 mL of water. The resulting solutions were filtered through a 0.45 mL filter to produce transparent solutions. The drug concentration was measured spectrophotometrically using water as a blank.

***In vitro* drug release studies**

A Franz diffusion cell was used to examine the drug release characteristics from Colchicine microsponges gel and control gel. After computing drug release, an image illustrating drug release in relation to time was created. Each formulation's release studies were done in triplicate.

RESULT AND DISCUSSION:

Preparation of Colchicine microsponges

Different polymer rations were tested during the preparation of colchicine microsponges. Analysis of the prepared microsponges' delivery systems' stability, release effect, and better impact was done. Colchicine microsponges were made using the emulsion solvent evaporation technique because it is straightforward and repeatable.

Evaluation of Colchicine microsponges

Microscopic examination and Surface appearance

The colchicine loaded microsponges revealed that some formulas had spherical shapes, others had irregular structures, and still others displayed agglomeration formation. The results are depicted in table 3.

Table 3. Microscopic examination of Colchicine Microsponges (F1-F9)

Sr. No	Formulation Code	Appearance
1	F1	Microsponge not form
2	F2	Irregular Shape microsponge formed
3	F3	Agglomeration structure was formed
4	F4	Spherical microsponge formed
5	F5	Spherical microsponge formed
6	F6	Irregular and Spherical microsponge formed

7	F7	Spherical microsponge formed
8	F8	Spherical microsponge formed
9	F9	Irregular and Spherical microsponge formed

Percentage yield

The percentage yield of all formulation was found to be in a range of 86.560 ± 0.139 to 93.280 ± 0.507. The results are depicted in table 4.

Percentage Drug Entrapment

The drug entrapment was discovered to be in the range of 56.37 ± 0.101 to 82.0 ± 0.101%. According to research, formulation F8 has the highest rate of drug entrapment. The results are depicted in table 4.

Particle size measurement

The particle size range for all formulations was between 15.7 and 26.7 microns. These findings clarify why the microsponges had similar sizes when the polymer concentration was changed. The results are depicted in table 4.

Table 4. Evaluation of Colchicine Microsponge (F2-F9)

Sr. No.	Formulation Code	% Yield	% EE	Particle Size (µm)
1	F2	90.22 ± 0.166	68.47 ± 0.154	15.7 ± 0.577
2	F3	86.56 ± 0.139	58.52 ± 0.116	16.7±0.577
3	F4	87.96 ± 0.753	56.37 ± 0.101	18 ± 0.000
4	F5	89 ± 0.420	69.64 ± 0.101	21 ± 0.000
5	F6	87.26 ± 0.976	70.51 ± 0.058	26.7 ± 0.577
6	F7	88.64 ± 0.567	75.37 ± 0.101	22.7 ± 0.577
7	F8	93.28 ± 0.507	82 ± 0.101	19.3 ± 0.577
8	F9	88.83 ± 0.602	76.07 ± 0.101	24 ± 0.000

Value is expressed as mean ± SD; n = 3

Scanning electron microscope (SEM) study

The SEM images are displayed in figure 1. Colchicine microsponges made using the improved formulation (F8) were discovered to be spherical in shape.

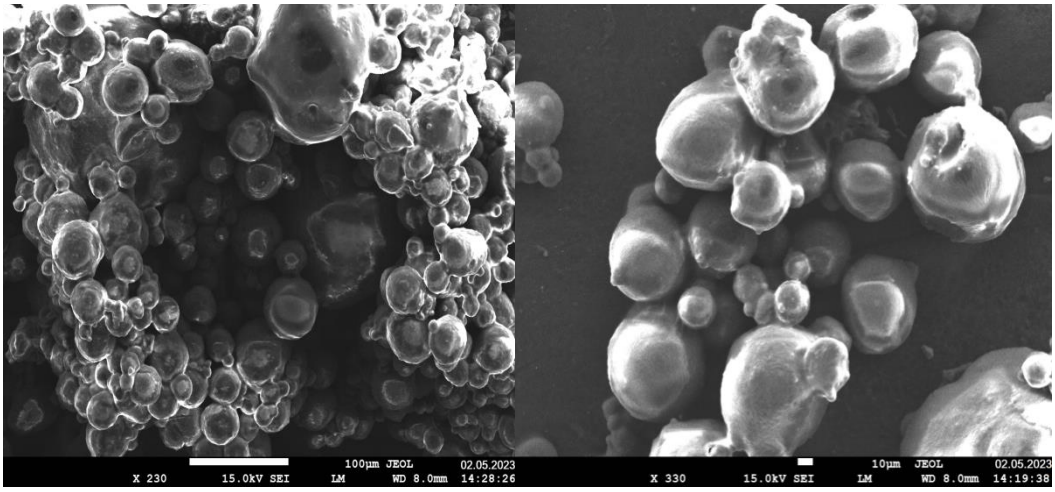

Figure 1. SEM Image of Formulation F8

Incorporation of Colchicine microsponge into gel for topical drug delivery

After successfully dispersing the formulation in carbopol 934 various concentrations, the gel of the optimised F8 formulation was created and used for further characterization.

Evaluation of Colchicine microspongel gel

Physical Appearance

The prepared gel's consistency was visibly assessed, and it was discovered to have a smooth appearance. Batches F10, F11, and F12 of the formulation displayed acceptable homogeneity and no lumps. So, additional research was done using those samples. Table 5 and Figure 2 displays the appearance of the gel formed (F10).

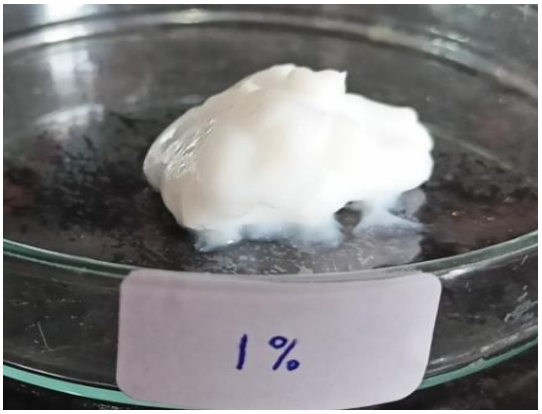

Figure 2. Visual Appearance of Colchicine microspongel gel (F10)

Table 5. Visual Appearance of Colchicine microspongal gel

Sr. no.	Formulation code	Visual Appearance
1	**F10**	Milky white gel formed
2	**F11**	Milky white gel formed
3	**F12**	Milky white gel formed

pH determination

The pH of every formulation was determined to be between 6.73 and 6.85 as depicted in table 6.

Rheological studies

The viscosity of all the formulation was in range of 1001 ± 0.58 to 1024.67 ± 0.51 as depicted in table 6.

Spreadability Study

The Spreadability of all the formulation was in range of 32.822 ± 0.23 and 35.244 ± 0.22 as depicted in table 6.

Drug content

The drug concentration gels were discovered to range from 92.171 ± 0.101 to 97.296 ± 0.101% as depicted in table 6. All formulations' drug content percentages were determined to be satisfactory. Thus, it was determined that the technique used for gel compositions was appropriate.

Table 6. Evaluation of drug loaded microspongel gel

Sr. No.	Formulation code	Ph	Viscosity (cps)	Spreadability (g.cm/sec)	% Drug Content
1	**F10**	6.85 ± 0.01	1001.00 ± 0.58	35.244 ± 0.22	97.296 ± 0.101
2	**F11**	6.75 ± 0.01	1010.33 ± 0.51	32.822 ± 0.23	94.382 ± 0.101
3	**F12**	6.73 ± 0.01	1024.67 ± 0.51	33.750 ± 0.23	92.171 ± 0.101

Value is expressed as mean ± SD; n = 3

FTIR Study

As seen Figure 3 demonstrated spectrum of formulation (F10), peaks were obtained at 2975cm^{-1} (OCH_3 Stretching), 1045.86cm^{-1} (C-O Stretching) and 1647.45cm^{-1} (C-C stretching). The FT-IR spectra of final formulation F10 maintained some of the Colchicine peaks with slight shifting.

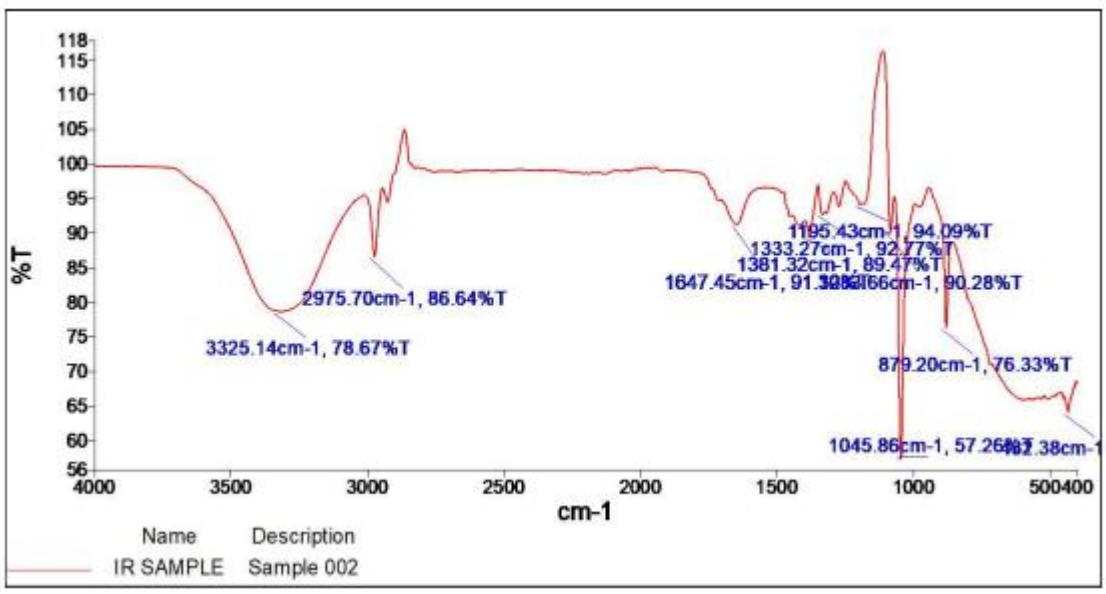

Figure 3. FTIR Spectra of Formulation F10

***In vitro* drug release studies**

Colchicine microspongal gel and control gel formulation's *in-vitro* drug release was detailed in Figure 4. Within 4 hours, the control gel's discharge reveals 99.091 ± 0.909%. In contrast, the drug release the gel formulations F10, F11 and F12 exhibited, respectively, 80.939 ± 0.105%, 72.152 ± 0.052%, and 66 ± 0.091% in the phosphate buffer saline (pH 7.4) after 24 hours. Drug-loaded gel formulation F10 which contains 1% carbopol 934 showed 24-hour maximal drug release of 80.939 ± 0.105%. Figure 4 depicted the in vitro drug release of Colchicine microspongal gel & control gel formulation.

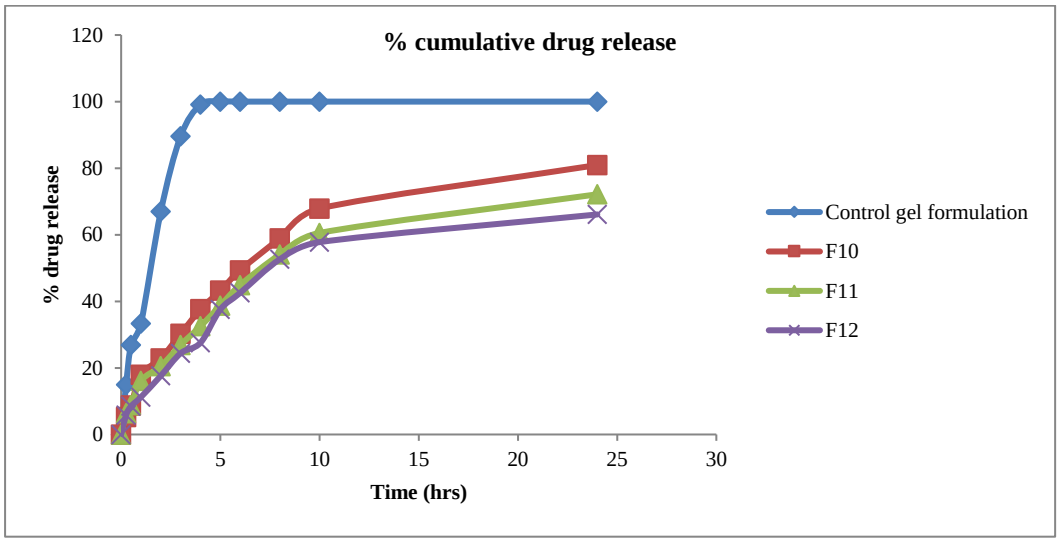

Figure 4. Percentage drug release of Colchicine microspongal gel & control gel formulation

Drug release Kinetics

The *in vitro* data was fitted to the zero order, first order, Higuchi, and Korsmeyer-Peppas models in order to determine the rate and process of drug release with precision. The findings demonstrated that the F10 formulation's drug release adhered to the Korsmeyer-Peppas order as depicted in figure 5, which explains the sustained mechanism used by Colchicine microspongal gel.

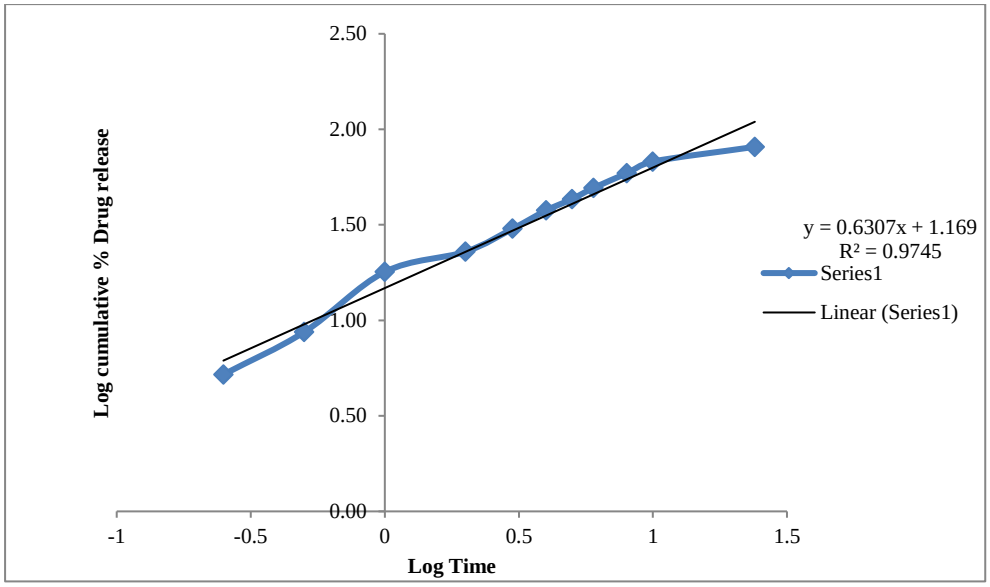

Figure 5. Korsmeyer peppas order graph of formulation F10

CONCLUSIONS:

In conclusion, Colchicine loaded microspongel gel prepared by Emulsion solvent evaporation technique using carbopol 934 as gelling agent, formulation F10 emerged as the overall ideal formulation based on several parameters such as appearance, drug content, pH, rheological properties and *in vitro* drug release characteristics. Hence it can be concluded that the microsponge drug delivery system of Colchicine is a better option for drug delivery with improved patient compliance and straightforward and repeatable.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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