World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

Check for updates

Formulation and evaluation of emulgels loaded with microspheres containing Baricitinib

P. Laxmi [1,*], G. Vijayalakshmi [2] and V. V. Basava Rao [3]

[1] *Department of Pharmaceutical Sciences, University College of Technology, Osmania University, Hyderabad-500007, India.*
[2] *Department of Chemistry, Telangana Mahila Vishwavidhyalayam, Koti, Hyderabad-500095, India.*
[3] *Department of Chemical engineering, University College of Technology, Osmania University, Hyderabad-500007, India.*

World Journal of Biology Pharmacy and Health Sciences, 2024, 18(02), 157–167

Publication history: Received on 09 November 2022; revised on 19 December 2022; accepted on 22 December 2022

Article DOI: https://doi.org/10.30574/wjbphs.2024.18.2.0261

Abstract

The main objective of the present research work was to formulate and evaluate transdermal gel loaded with microspheres of Baricitinib to increase bioavailability and to reduce the dosing frequency and to improve patient compliance. Gel loaded with microspheres of Baricitinib was prepared by taking different ratios and grades of Carbopol polymers. The prepared formulations (F1–F9) were evaluated for pre-formulation studies, percentage yield, particle size, content Uniformity, drug content entrapment efficiency and *in vitro* dissolution studies. The optimized gel loaded with microspheres of F8 formulation (drug: Carbopol 974polymer in 1:1 ratio) is more effective compared to all formulations. The prepared gel showed acceptable physical properties such as particle size of (126.5 microns), percentage yield of (96.5%), content uniformity (97.8), and drug content entrapment efficiency (90.5%). *In vitro* dissolution studies have shown 100.1% drug release in 12 h. With the optimized formulation Baricitinib emulgels are formulated using different grades and ratios of Carbopol and optimized microsphere formulation F8. The Emulgel formulation F7 showed the acceptable results with a yield of 92.3%, Drug content (100.2%), Spread ability (13.38 g.cm/s), Viscocity (112.3 cP), pH off 6.05 and it was observed that formulation F7 showed 100.2% drug release within 12 hours. All the results show that the gel loaded with microspheres of Baricitinib can be effectively used for the treatment of viral infections like small fox.

Keywords: Microspheres; Transdermal; Carobpol 974; *In-vitro* dissolution

1. Introduction

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Microspheres vary widely in quality, sphericity, uniformity of particle and particle size distribution. The appropriate microsphere needs to be chosen for each unique application. The range of techniques for the preparation of microspheres offers a variety of opportunities to control aspects of drug administration. This approach facilitates the accurate delivery of small quantity of the potent drugs, reduced drug concentration at the site other than the target site and the protection of the labile compound before and after the administration and prior to appearance at the site of action. The behavior of the drugs in vivo can be manipulated by coupling the drug to a carrier particle. The clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug are strongly influenced by the behavior of the carrier. The exploitation of these changes in pharmacodynamics behavior may lead to enhanced therapeutic effect. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion Drugs that are easily absorbed from the GIT and having a short half-life are eliminated quickly from the blood circulation. To avoid these problems oral controlled drug delivery systems have been developed as they releases the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time. A well

* Corresponding author: P. Laxmi

designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects.

2. Material and methods

Baricitinib pure drug was a generous gift from Aurobindo Pharma limited, Hyderabad, India. Carbopol 934, Carbopol 940 and Carbopol 974 were brought from Corel Pharm achem, Ahmedabad. Triethanolamine was from Signet Chemicals, Mumbai and PEG 400 was a gift sample from Signet chemicals, Mumbai. All other chemicals used were of Pharma grade.

2.1. Preformulation studies of pure drug

Pre-formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance and is characterized with the goal of designing optimum drug delivery system.

2.1.1. Particle size and size distribution

The particle size was measured with microscopic method. The particle size distribution and mean particle size diameter were automatically calculated from the particle size values obtained by using software provided. Average particle size of 500 particles was calculated. Particle size of the powder will influence the powder flow property directly.

2.1.2. Bulk density

It is the ratio of mass to the bulk volume of the powder. It is useful in the determination of compressibility index. Bulk density is significant parameter which influences the pack size of the container.

Procedure

1 gm pure drug substance was weighed and placed in a measuring cylinder, the volume occupied by it is noted.

It is defined mathematically as:

Bulk density = mass of powder / Bulk volume

2.1.3. Tapped density

It is the ratio of mass to the tapped volume of the powder.

Procedure

1gm pure drug substance was weighed and placed in a measuring cylinder and then it is tapped on a wooden base for about 500 times and finally the volume occupied by it is noted.

Tapped density = mass of powder / tapped volume

2.1.4. Powder flow properties

The wide variety of methods for characterizing the powder flow are generated in the wide spread use of powders in the pharmaceutical industry because no single and simple test method can adequately characterize the flow properties of pharmaceutical powders. Four commonly reported methods for testing powder flow are

- Angle of Repose,
- Compressibility Index,
- Hausner's Ratio
- Shear Cell.

In the current research powder flow properties were determined by first three methods

2.1.5. Angle of repose

The angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. It is the constant, three dimensional angle (relative to the horizontal base) assumed by a cone – like pile of material. The maximum angle which is formed b/w the surface of a pile of powder and horizontal surface is called the angle of repose.

Procedure

The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

It is calculated by using the formula: $\theta = \tan^{-1}(h/r)$

2.1.6. Compressibility index/ consolidation index/ carr's index

Procedure

The bulk density and tapped density were measured and then compressibility index was calculated using the formula:

$$\text{Consolidation index [C] (\%)} = \frac{\text{Tapped density} - \text{Poured density x 100}}{\text{Tapped density}}$$

2.1.7. Hausner's ratio

Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula:

Hausner's ratio [H) = Tapped density / Poured density

The relationship between Carr's index and Hausner's ratio is given below

H = 100/100-C

2.2. Solubility studies

The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into dissolution medium and consequently, the therapeutic efficiency of the pharmaceutical product. The solubility of material is usually determined by the *equilibrium solubility method*, which employs the preparation of a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged period of time [72hrs] until equilibrium is achieved at 25 ^{0}C on mechanical shaker. After this period the solutions were filtered through 0.45µ Millipore filter and analysed spectroscopically at respected wavelength against blank sample (blank sample containing the same concentration of specific solvent used without drug). Three determinations were carried out for each sample to calculate the solubility of drug. Solvents used for solubility determination are:-Water, 4.5pH Acetate Buffer, 6.8 pH Phosphate Buffer, 7.2 pH Phosphate Buffer, 7.4 pH Phosphate Buffer, 0.1 N HCl and 0.1 N NaOH

2.3. Calibration Curve of API by UV-Visible Spectroscopic Method

2.3.1. Standard graph preparation

Accurately weighed 25 mg of drug was transferred to 25 ml volumetric flask. 5ml of methanol was added and volume was made up to 25 ml with respective buffer. (1000 micro gram/ml) – I Stock solution. From first stock solution 5ml was taken and diluted to 50 ml with buffer. (100 micro gram/ml) – II Stock solution. From second stock solution various concentrations were prepared and absorbance was taken at lamda max of each drug and a calibration curve was plotted by taking concentration on X-Axis and corresponding absorbance on Y-axis.

2.4. Development of microsphere formulations

2.4.1. Preparation of microspheres

Batches of microspheres were prepared which involved different grades of Carbopol as polymers were dispersed in purified water (10 ml) to form a homogeneous polymer mixture. The API, was added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (4% w/v) solution. The addition was done with continuous stirring at 200 rpm. The added

droplets were retained in the calcium chloride solution for 30 min to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried.

2.4.2. Formulations of Microspheres of Baricitinib

Table 1 Composition of Baricitinib Microspheres

Name of the Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Baricitinib	100	100	100	100	100	100	100	100	100
Carbopol 940	100	200	300						
Carbopol 934				100	200	300			
Carbopol 974							100	200	300
Methanol	5	5	5	5	5	5	5	5	5
Water	10	10	10	10	10	10	10	10	10
Calcium Chloride (5%)	QS	QS	QS	QS	QS	QS	QS	QS	QS

2.5. Characterization of microspheres

2.5.1. Percentage yield

The percentage of production yield was calculated from the weight of dried microspheres recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \text{Practical mass (Microspheres)}/\text{Theoretical mass (Polymer+Drug)} \times 100$$

2.5.2. Drug entrapment efficiency

Powdered microspheres were suspended in 10 ml of phosphate buffer (pH 6.8). After 24 h, the solution was filtered, the filtrate was centrifuged at 2000 rpm for 3 min, and then analyzed for drug content spectrophotometrically (Shimadzu UV-1800, Japan)), and the concentration of soluble drug was calculated. The amount of drug entrapped in the microspheres was calculated by the following formula,

Entrapment efficiency = (Weight of drug added formulation - weight of drug recovered from Microspheres) /Weight of drug added during formulation

2.5.3. Particle size analysis

Samples of the microparticles were analyzed for particle size by optical microscope. The instrument was calibrated and found that 1 unit of eyepiece micrometer was equal to 12.5µm. Nearly about 100 micro particles sizes were calculated under × 45 magnifications. The average particle size was determined using the Edmondson's equation:

$D_{mean} = nd/n$; Where, n – Number of microspheres observed d – Mean size range

2.5.4. In vitro release studies

The *in vitro* release of microspheres was done with phosphate buffer pH of 6.8 for 12 h using dissolution apparatus USP I Basket type at a temperature of 37.0±0.5°C. Microsphere equivalent to one dose of drug was taken, and it was inserted in the basket wrapping it with a muslin cloth (900 ml phosphate buffer pH 6.8, at 37±2°C and was adjusted to 100 rpm). The sample was taken at predetermined time intervals for 12 h. To maintain the sink condition, the samples withdrawn were replaced with an equal volume of dissolution medium at different time intervals. After suitable dilution, samples were analyzed at UV visible spectrophotometer.

2.5.5. Formulation of the microsphere-loaded emulgel

The gels with varying concentrations of different grades of Carbopol were prepared by dispersing the required quantity of Carbopol in the required quantity of distilled water with continuous stirring and kept overnight for complete

hydration. Further appropriate quantities of triethanolamine were added to the previous polymeric mixture. Optimized formulation of the drug loaded microsphere was added to the above polymeric mixture with constant stirring. Final pH of the preparation was adjusted to4.5 with 0.5 M sodium hydroxide solution. The composition of all the formulation is given in Table.

2.5.6. Formulations of Microspheres Loaded Emulgels of Baricitinib

Table 2 Composition of Baricitinib Microspheres loaded Emulgel**.**

Name of the Ingredient	**Composition (mg/unit)**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
BaricitinibMicrospheres (F4) –eqvt. to 100 mg of Baricitinib	200	200	200	200	200	200	200	200	200
Carbopol 940	100	200	300						
Carbopol 934				100	200	300			
Carbopol 974							100	200	300
Triethanolamine (%)	2	2	2	2	2	2	2	2	2
PEG 400 (%)	30	30	30	30	30	30	30	30	30
Water QS to (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000

2.6. Characterization of microsphere loaded emulgel

2.6.1. Study of the physical properties

Visual inspection

The organoleptic properties, such as color, texture, consistency, homogeneity, and physical appearance of gel containing microspheres were checked by visual observation.

Determination of pH

Determination of pH is done using Systronic digital pH meter 335. pH meter was calibrated before use using a standard buffer solution.

Viscosity

The viscosity of the formulated gel is determined by DV-E Brookfield viscometer using spindle no 64

Spread ability

One of the criteria for Emulgel is to meet the ideal quality is that it should possess good spread ability. It is the term expressed to denote the extent of the area to which gel readily spread on application to the skin or affected part. The therapeutic efficacy of a formulation also depends on its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from emulgel and placedin between the slides under the direction of a certain load. Lesser the time taken for separation of two slides, better the spread ability It is calculated using the formula:

$$S = M.L/T$$

Where,
M = wt. tied to upper slide
L = length of glass slides.
T = time taken toseparate the slides

Drug content determination

Drug concentration in emulgel was measured by spectrophotometer. Drug content in emulgel was measured by dissolving a known quantity of emulgel in solvent (ethanol) by sonication. Absorbance was measured after suitable dilution in UV/visible spectrophotometer.

In vitro release study

Franz diffusion cell was used for the drug release studies. Emulgel (one unit dose) was applied onto the surface of the cellophane membrane evenly. The cellophane membrane was clamped between the donor and the receptor chamber of the diffusion cell. The receptor chamber was filled with freshly prepared PBS solution to solubilize the drug. The receptor chamber was stirred by a magnetic stirrer. The samples(1.0 ml aliquots) were collected at a suitable time interval. Samples were analyzed for drug content by UV visible spectrophotometer. Cumulative corrections were made to obtain the total amount of drug release at each time interval.

3. Results and discussion

3.1. Solubility Studies

Saturation solubility studies was done in different solvents and results are tabulated below. It was found that the drug is practically insoluble in all the solvents.

Table 3 Solubility profile in different solvents

Solvent	Solubility (mcg/mL)			
	1	2	3	Average
0.1N HCl (0.1N HCl)	14.5	15.6	15.2	15.1
pH 4.5 Acetate Buffer	16.5	17.2	16.9	16.9
pH 6.8 phosphate buffer	18.5	19.2	21.2	19.6
Double Distilled Water (pH 7.0)	17.5	17.2	17.5	17.4
pH 7.2 phosphate buffer	22.5	23.6	24.5	23.5
pH 7.4 phosphate buffer	23.5	25.6	26.9	25.3
0.1N NaOH (pH 11.0)	30.2	32.3	33.5	32.0

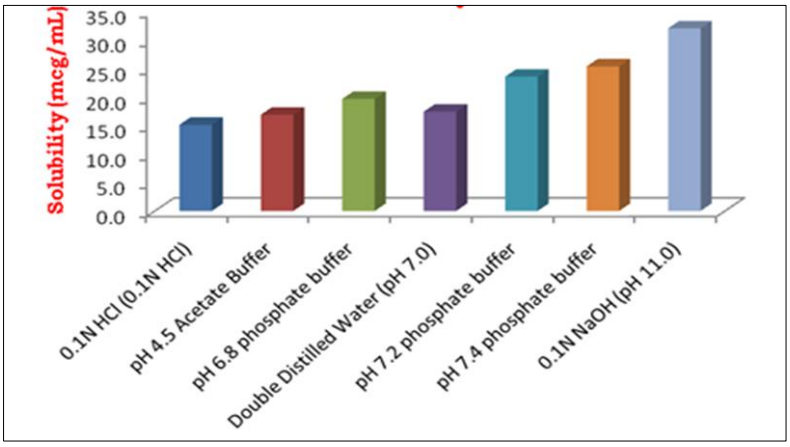

Figure 1 Saturation solubility profile of baricitinib

3.2. Calibration plot of API in different solvents

Calibration curve of API in 7.4pH and 6.8pH buffer was plotted and graphs are shown below along with absorbance values

Table 4 Calibration curve profile in 6.8PH buffer

Calibration Curve in 6.8pH Buffer				
Concentration (µg/mL)	**Absorbance at 250nm**			
	1	**2**	**3**	**Average**
0	0	0	0	0.000
10	0.124	0.126	0.125	0.125
20	0.251	0.254	0.255	0.253
30	0.336	0.338	0.337	0.337
40	0.486	0.488	0.487	0.487
50	0.651	0.655	0.654	0.653
60	0.721	0.734	0.735	0.73

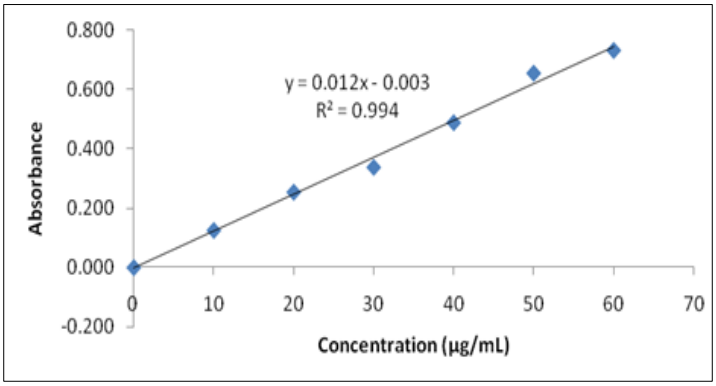

Figure 2 Calibration curve in 6.8 pH buffer

Table 5 Calibration curve profile in 7.4pH buffer

Calibration Curve in 7.4pH Buffer				
Concentration (µg/mL)	**Absorbance at 250nm**			
	1	**2**	**3**	**Average**
0	0	0	0	0.000
8	0.126	0.125	0.126	0.126
12	0.254	0.256	0.258	0.256
16	0.338	0.339	0.341	0.339
20	0.489	0.488	0.489	0.489
24	0.654	0.656	0.659	0.656
32	0.732	0.735	0.739	0.735

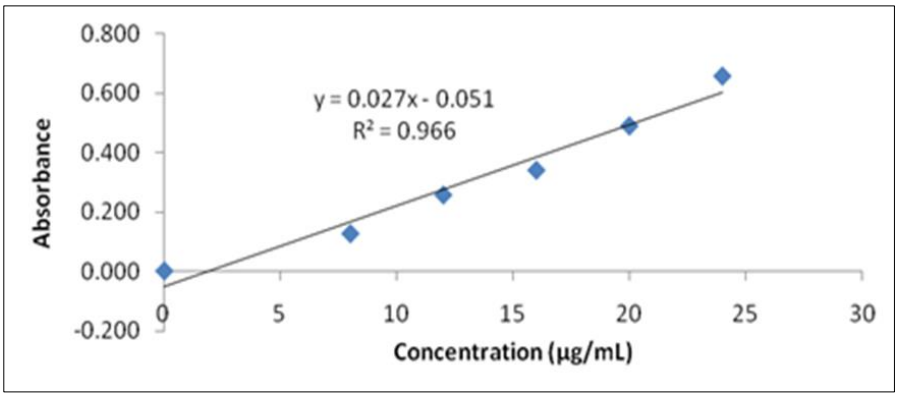

Figure 3 Calibration curve in 7.4 pH buffer

3.3. Preformulation parameters of API

The preformulation evaluation of Baricitinib API was evaluated for Particle size, Bulk density, Tapped Densit, Hausners ratio, Carrs index and Angle of repose. The reported results are given in the table below.

Table 6 Preformulation parameters

Parameter	Result
Bulk density (g/cc)	0.52
Tapped density (g/cc)	0.66
Carr's Index	26.92
Hausners Ratio	1.27
Angle of Repose	28.3
Particle Size	
D(50)	35-45µ
D(90)	90-100µ

3.4. Physicochemical characteristics of microspheres

The physicochemical characteristics of microspheres like percentage yield, Particle size, content uniformity and % entrapment efficiency were evaluated. All the formulations F1-F9 were evaluated and the results are reported below. From the results it was observed that all formulations have shown the size in micro level with entrapment efficiency of 90%.

Table 7 Characteristics of Baricitinib Microspheres

Test	F1	F2	F3	F4	F5	F6	F7	F8	F9
Percentage Yield	87.9	89.8	89.9	82.5	93.5	95.6	85.6	93.6	99.2
Particle Size (Microns) (D(90))	95.4	99.8	112.3	102.3	125.6	103.2	98.5	102.3	99.6
Content Uniformity/Assay(%)	99.9	100.2	100.1	98.6	99.5	99.2	100.2	99.8	98.9
% Entrapment Efficiency	92.5	91.5	91.6	92.6	92.6	95.6	94.5	93.6	94.5

3.4.1. In vitro dissolution study of Baricitinib Microspheres

The results of *in vitro* dissolution comparisons of Baricitinib microspheres formulations F1-F9 are summarized in Table below. The % drug release from Baricitinib microspheres formulation F8 showed was highest (100.1) and faster than

other Baricitinib microsphere formulations. From the results, it was observed that formulation F8 has shown 100% drug release within 12 hours and hence has been chosen as best formulation for converting into emulgel.

Table 8 *In vitro* drug release profile of Baricitinib Microspheres

Time	Mean % Release of Baricitinib								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	55.4	37.6	26.5	42.6	30.6	20.2	35.7	25.6	15.9
2	75.9	59.6	46.7	65.9	50.2	40.3	61.8	37.5	32.4
4	97.9	78.1	65.9	87.6	67.2	55.7	77.5	46.9	42.3
6	100.2	97.6	72.8	93.5	85.7	62.5	85.4	59.7	52.6
8	100.1	100.2	89.3	100.2	99.2	81.6	99.2	72.8	67.8
10	100.2	100.4	100.1	100.2	100.2	97.8	100.2	89.2	82.6
12	100.1	100.1	100.3	100.1	100.1	100.1	100.1	100.1	92.3

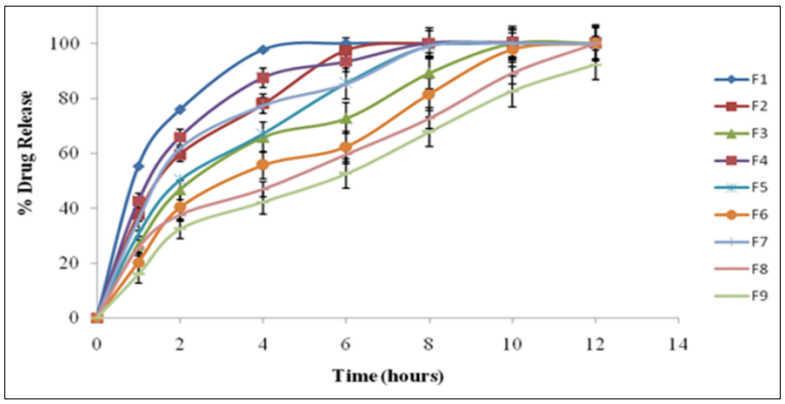

Figure 4 % drug release of baricitinib microsphere

Table 9 Physicochemical Parameters of formulations

Formulation	% Yield	% Drug Content	Spreadability (g.cm/s)	Viscosity (cP)	pH
F1	96.5	97.8	12.45	98.5	6.25
F2	92.5	99.5	11.87	201.2	6.45
F3	92.4	100.2	11.34	312.6	6.65
F4	97.5	98.7	12.56	101.2	6.12
F5	93.6	98.6	11.59	205.6	6.25
F6	94.5	99.6	11.24	332.5	6.38
F7	92.3	100.2	13.38	112.3	6.05
F8	96.5	97.8	12.47	225.6	6.28
F9	93.5	99.2	11.39	345.8	6.54

The prepared formulations (F1-F9) were evaluated for pH, Viscosity (cP), Spreadability (g.cm/s), %Drug content and % yield. The optimized emulgel formulation F7 (drug: Carbopol 974 in 2:1 ratio) is more effective compared to other formulations. The Emulgel formulation F7 showed the acceptable results with a yield of 92.3%, Drug content (100.2%), Spreadability (13.38 g.cm/s), Viscosity (112.3 cP), pH of 6.05 and it as observed that formulation F7 showed 100.2% drug release within 12 hours. From the results, it was observed that all the formulations have shown similar results with similar pH range

3.5. *In vitro* dissolutions of baricitinib emulgels

The results of *in vitro* dissolution comparisons of Baricitinib Emulgel formulations F1-F9 are summarized in Table below.From the results, it was observed that formulation F7 has shown 100.2% drug release within 12 hours.

Table 10 *In vitro* drug release profile of Baricitinib Microspheres loaded Emulgels

Time	Mean % Drug Release of Baricitinib Emulgels								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.6	15.4	11.4	18.2	13.2	9.6	22.6	16.5	13.2
2	32.5	28.4	24.6	30.3	26.4	22.4	34.5	29.3	25.6
4	41.2	38.5	33.5	39.1	36.7	29.7	43.5	41.2	34.6
6	50.3	45.9	41.6	48.2	41.2	39.7	52.6	47.2	43.2
8	65.9	61.3	56.9	63.4	58.3	53.1	69.2	63.5	58.1
10	81.3	75.6	71.6	79.2	71.9	67.3	85.9	77.8	73.4
12	90.3	85.6	81.3	88.1	81.6	79.5	100.2	87.9	83.5

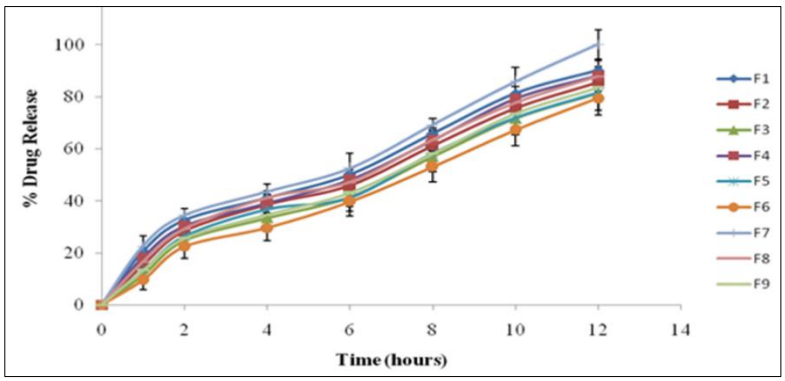

Figure 5 % drug released of baricitinib microsphere loaded emulgel

4. Conclusion

Baricitinib emulgel formulations were formulated and evaluated. From this study it was concluded that the optimized formulation of Baricitinibemulgels were formulated using Carbopol 974 in the ratio of 2:1 (Drug loaded Microspheres F8 : Polymer). The formulations F7 showed acceptable results. The optimized Baricitinibemulgel formulation F7 is more effective compared to other formulations. The Emulgel formulation F7 showed the acceptable results with a yield of 92.3%, Drug content (100.2%), Spreadability (13.38 g.cm/s), Viscosity (112.3 cP), pH of 6.05 and it as observed that formulation F7 showed 100.2% drug release within 12 hours.

Compliance with ethical standards

Acknowledgments

I here express my gratitude to my supervisors Dr. G.Vijaya Lakshmi and Professor V.V. Basava Rao.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Mythri, G.; Kavitha, K.; Kumar, M.R.; Jagadeesh Singh, S.D. Novel muco adhesive polymers—A review.J. App. Pharm. Sci.2011,1, 37–42.

[2] Patwekar, S.; Baramade, M.K. Controlled release approach to novel multiparticulate drug delivery system. Int. J. Pharm. Pharm. Sci.2012,4, 757–763.

[3] Dey, N.S.; Majumdar, S.; Rao, M.E.B. Multiparticulate drug delivery systems for controlled release. Trop. J.Pharm. Res.2008,7, 1067–1075.

[4] Sachan, K.N.; Pushkar, S.; Jha, A.; Bhattcharya, A. Sodium alginate: The wonder polymer for controlled drugdelivery.J. Pharm. Res.2009, 2, 1191–1199.

[5] Nagpal, M.; Maheshwari, D.; Rakha, P.; Dureja, H.; Goyal, S.; Dhingra, G. Formulation development and evaluation of alginate microspheres of ibuprofen.J. Young Pharm.2012, 4, 13–16.

[6] Drugbank. Baricitinb. Available online: https://www.drugbank.ca/drugs/DB11817 (accessed on 5 March 2019)

[7] Wu, P.; Nielsen, T.E.; Clausen, M.H. FDA-Approved Small-molecules Kinase Inhibitors. Trends Pharmacol.Sci.2015, 36, 422–439.

[8] Okyar A, Özsoy Y, Güngör S. Novel formulation approaches for dermal and transdermal delivery of non-steroidal anti-inflammatory drugs. In: Lemmey A. (Ed). Rheumatoid arthritis–treatment. Intech, Croatia, 2012, pp. 25-48. [CrossRef]

[9] Pena LE. Gel dosage forms: theory, formulation and processing. In: Osborne DW, Amann AH. (Eds). Topical drug delivery formulations. Marcel Dekker, New York, 1990, pp. 381-388.

[10] Steven P, Stanos DO. Topical agents for the management of musculoskeletal pain. J Pain Symptom Manag. 2007; 33(3): 342-355.

[11] Sunil KY, Manoj KM, Anumapaa T, Ashutosh S. Emulgel a new approach for enhanced for topical drug delivery. Int J Curr Pharm Res. 2017; 9(1): 15-19.

[12] Hardenia A, Jayronia S, Jain S. Emulgel: an emergent tool in topical drug delivery. Int J Pharm Sci Rev Res. 2014; 5(5):1653-1660.