Research Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2015, Volume 3, Issue 1
ISSN: 2321–3647(online)

Formulation and Evaluation of Sustained Release Matrix Tablets of Boswellia and Liquorice

Ankita Raizada[*1], Sanjula Baboota[2], Javed Ali[2], Anil Bhandari[1], V.K Purhoit[1], Hina Chadha [3]

1. Jodhpur National University, Jodhpur, Rajasthan, 342001.
2. Jamia Hamdard University, New Delhi, 110001.
3. Vishveshwarya Institute of Medical Sciences, Greater Noida, (U.P), 203207.

ABSTRACT

Various conventional dosage forms are available in the market of the plants boswellia and liquorice. The drawbacks associated with their conventional dosage forms which are fluctuation in drug blood level, patient's inconvenience, poor patient compliance, increased chances of missing the dose of a drug high dose potency etc. can be solved by formulating sustained release formulations of these herbal drugs. Different formulations of boswellia and liquorice sustained release tablets were formulated using wet granulation method. The tablets were subjected to physicochemical studies, *in vitro* drug release studies, kinetic modeling and stability studies to find out the best formulation. Drug content was carried out by HPLC fitted with a C18 column using UV detector. The in vitro release studies were conducted for 24h using USP type 2 apparatus. The dissolution profile comparison of the prepared batches was done. The dissolution data profile was fitted into zero order, first order, Higuchi and Korsemeyer-Peppas models to identify the pharmacokinetics and mechanism of drug release. *In vivo* anti-inflammatory effects of the optimized formulations were evaluated by carrageenan-induced hind paw edema method. The results of the accelerated stability study for six months revealed that storage conditions were not found to have made any significant changes. The release of formulation F-4 of boswellic acid and F-6 of liquorice was prolonged for 24h and once daily matrix tablet was formulated.

Keywords: Sustained drug delivery, Wet granulation, Anti-inflammatory, Matrix tablets, Release kinetics etc.

*Corresponding Author Email ankitaraizada24@gmail.com
Received 19 December 2014, Accepted 08 January 2015

Please cite this article as: Raizada A *et al*., Formulation and Evaluation of Sustained Release Matrix Tablets of Boswellia and Liquorice. American Journal of Pharmacy & Health Research 2015.

INTRODUCTION

Oral route has been the most popular and successfully used for sustained delivery of drugs due to convenience and ease of administration, greater flexibility in dosage form design, ease of production and low cost. Sustained drug delivery overcome the drawbacks associated with conventional dosage forms which are poor patient compliance and increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary[1,2,3]. Inflammation is a key feature in autoimmune disease. Inflammation occurs as the immune system reacts to injury, infection, environmental agents, malignancy, and cellular changes.[4,5,6,7] Any assault to living tissue, whether due to physical, chemical or microbiological origin results in inflammation, manifests by redness, heat, pain, swelling and loss of function. Ayurvedic medicines are gaining popularity among physicians and patients for better therapeutic value, effective, stable, and safe.[8,9,10,11]. *Boswellia serrata* (Salai guggul), is a moderate to large sized branching tree of family Burseraceae. Gum-resin extracts of Boswellia serrata have been traditionally used in folk medicine for centuries to treat various chronic inflammatory diseases.[12,13 ,14]The major active constituent which is present in Boswellia serrata extract as α-boswellic acid, β-boswellic acid.[15,16,17] Liquorice (syn. licorice) is an esteemed crude drug that originates from the dried roots of *Glycyrrhiza glabra* family Leguminosae. The most important compounds in Liquorice is 18-β-Glycyrrhetinicacid, has been proposed as being useful for anti-inflammatory, immunomodulatory, antitumour and expectorant properties.[18]. Boswellia has shown to be effective against a large number of inflammatory diseases such as arthritis, bronchial asthma, chronic colitis, ulcerative colitis, Crohn's disease and cancer. Boswellia has shown to be a specific inhibitor of leukotrienes. It acts by blocking the synthesis of leukotrienes, inhibits cyclooxygenase activity and prostaglandin formation therefore, inhibiting inflammation and shrinking the inflamed tissue which is the primary cause of pain and discomfort in many cases.*Boswellia Serrata*, via its active boswellic acids, appears to be a novel inhibitory of a pro-inflammatory enzyme called 5-Lipoxygenase and may possess other anti-inflammatory effects (such as nF-kB inhibition). These anti-inflammatory effects have been investigated for their benefits in osteoarthritis[19,20,21]. Researchers concluded that the anti-inflammatory effect liquorice is through the prevention of the NF-kappa B and STAT-3 activation pathways, interleukins, transcription factors, cytokines, hyaluronidase and collagenase enzymes, tumor necrosis factor (TNF) and interleukin (IL). It is reported that glycyrrhetinic acid in liquorice extract gives anti-inflammatory effect similar to glucocorticoids and mineralocorticoids[22,23].

MATERIALS AND METHOD

Boswellia serrata gum resin powder and liquorice root were purchased from local market. Boswellic acid and 18-β-Glycyrrhetinic acid was procured from Sigma Aldrich, USA. HPLC-grade methanol and acetonitrile were obtained from Merck India. HPMC, ethyl cellulose, carbopol 971P,eudragit RS100, talc, magnesium, lactose, isopropyl alcohol and polyvinyl pyrollidone K-30 were purchased Shree Ram Chemicals, Ghaziabad. The water used was double-distilled. All other chemicals used were of analytical grade.

Preparation and standardization of boswellia extract

500gm crushed lumps of the gum exudate were extracted in 1.5lit methanol for 12 hrs. The extraction process was repeated twice with 1.5lit of methanol and residue was discarded. The total extract after filtration was concentrated. The red brown syrupy mass was obtained which was treated with 3% solution of potassium hydroxide till the pH of 9 was attained. The solution was vigorously stirred till a uniform emulsion was formed. The emulsion was then extracted with dichloromethane. The lower solvent layer is separated and discarded. To the upper aqueous fraction is added dilute hydrochloric acid solution (5%) till the pH of 3 was achieved. The precipitated acids was filtered out and washed several times with water till free of mineral acid. The product was then dried in an air oven at 40-45° to a creamish yellow powder. The amount of boswellic acid in the extract was determined by HPLC.[27]

Preparation and standardization of liquorice extract [29]

The powdered liquorice root was extracted with distilled water. The extraction temperature was maintained at 90°C with constant shaking. After boiling, the preparation was cooled for 10 min. The extract was filtered and concentrated to get a thick paste. The amount of glycyrrhetinic acid in the extract was determined by HPLC.

Preformulation Study of Boswellia and Liquorice extract-

U.V Spectrophotometric analysis[27,19]

The identity was established by comparing λ_{max} of the sample solutions with those of standard solutionsexhibit maxima at 210 and 252nm for boswellia extract and liquorice extract respectively.

HPLC analysis[27,26]

The chromatogram of the Sample solution exhibits peaks for boswellic acid and glycyrrhetinic acid at retention times that correspond to those of Standard solutions.

THIN LAYER CHROMATOGRAPHY

Thin layer chromatography of boswellia extract[2]

Solvent system was prepared by taking Toluene: Ethyl acetate: Hexane: Formic acid in the proportion of 8:2:0.5:0.3respectively on methanol extract of boswellia. The spots obtained from the extract were examined under ultra violet light of wavelength254nm and 366nm.The resolution factor (R_f) was calculated by using the formula R_f = Distance travelled by solute/Distance travelled by solvent. The R_f value was found to be 0.34 same as standard.

Thin layer chromatography of liquorice extract[30]

0.3 gr of licorice extract was dissolved in 20ml methanol. The mixture was shaken for 30minutes. The supernatant was centrifuged and decanted. The residue was taken up with 20 ml methanol and decanted after 30minutes. The supernatants were added together and evaporated to a concentrated solution. For TLC fingerprint upto 10 µl of the test solution and 5 µl of the standard solution (0.25 mg/ml) were applied manually on TLC aluminum sheet silica gel. Solvent system was development in glass chamber, saturated for 20 minutes, with a mixture of20 volumes of petroleum ether, 40 volume of benzene, 14 volume of ethyl acetate and 1volume of acetic acid. The plate was allowed to dry for 10 minutes, then it was sprayed with sulphuric acid reagent and evaluated in visible. The $R_f$of 18β-glycyrrhetinic acid in both extract and standard samples was the same equal (R_f=0.12).

Physico-Chemical Properties

Solubility determination in different pH, Solubility determination in different solvents, Partition Coefficient determination were determined.

Formulation

Compatibility study for screening potential excipients was carried out using TLC, HPLC and UV visible spectroscopy. All the polymers and active ingredients were passed through sieve no. 80 separately. Accurately weighed amount of polymers and excipients were thoroughly mixed in glass mortar pestle. The granules were prepared by wet granulation technique using isopropyl alcohol as solvent and passed them to sieve no. 20 and dried in hot air oven at 45°C. The granules were then mixed properly with magnesium stearate, talc and punched with the help of automatic punching machine to a desired hardness, shape, and size (Table-1 and 2).

EVALUATION

Flow Properties of granules

The granules were evaluated for their flow properties such as angle of repose, bulk density, tapped density, angle of repose and compressibility index.

Tablet evaluation

The Formulated tablets were evaluated for different physicochemical properties like hardness, friability, weight variation, thickness, in vitro release studies and drug content. Hardness test- Randomly sampled 5 tablets in each batch of formulation were used for the determination of hardness with the help of Pfizer tester. Determination of friability- Sample of 10 tablets of each prepared formulation dedusted prior to testing. Accurately weight tablets sample was placed in Roche friabilator, in which tablets were subjected to 100 free falls of 6 inches in rotating drum at 25 rpm and then reweighed. The percentage losses were calculated for each batch of the tablets. Determination of weight variation- 20 tablets were selected at random and weighed accurately; the average weight of the tablet was calculated. Then the deviation of individual weight from the drug weight was calculated. Determination of thickness and diameter of tablets-The individual crown to crown thickness of ten tablets was determined using vernier calipers for each batch.

***In vitro* dissolution study**

Dissolution studies of each formulation was carried out using USP type 2 dissolution apparatus for 24 hours apparatus in 900 ml of simulated pH1.2 for the first 2 h and then in phosphate buffer (pH 6.8) from 3 to 24h at 100 rpm maintaining the temperature at 37 ± 0.5°C. Samples of 5ml of each were collected at 2, 4, 6, 8, 10, 12, 16, 20 and 24hrs intervals over a period of 24h. The withdrawn sample was immediately replaced by equal volume of fresh buffer. Collected samples were analyzed spectrophotometrically carried out on a UV-Vis spectrophotometer (Shimadzu 1700 Double beam) at measured wavelength of 210nm for bowellia and 252nm for liquorice, and cumulative percent drug release was calculated. The dissolution studies were performed in triplicate for all the batches. A plot of cumulative % drug release versus time in hours was plotted(Figure 1 and 2).

Kinetic analysis of dissolution data-

The release data were fitted to five kinetic models, viz, zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell to determine drug release mechanism with the aid of Expert 7.0.3 trial software, GraphPad Instat® (GraphPad Software Inc., San Diego, CA). [24, 25]

Drug Content-

Twenty tablets of each formulation containing was accurately weighed to find out the average weight and powdered. Suitably diluted drug solutions were run on HPLC fitted with a C_{18} column using UV detector. Drug content was carried out by measuring the peak area of standard and sample solutions at 210nm and 252nm for boswellia and liquorice respectively.

Preparation of standard solutions of boswellic acid and glycyrrhetinic acid

The standard stock solution was prepared by dissolving accurately weighed 5mg of standard boswellic acid, 5mg of standard glycyrrhetinic acid were separately dissolved in 5 ml of methanol obtaining stock concentrations of 1000 µg/ml. Working standard solution are prepared by suitable dilutions in the range of 1-20 µg/ml in methanol. The peak areas were recorded and calibration curve was prepared by plotting peak areas versus concentration applied.

HPLC analysis of boswellia

HPLC system with UV detector by using mobile phase consisting of 5 % acetonitrile solution in water buffered to pH 2.7 by 10 % ortho-phosphoric acid (90:10 v/v) on using a C18 as a stationary phase with a flow rate of 1 mL/min . The peak was detected at 210nm. [27]

HPLC analysis of liquorice

The analysis have been carried out by HPLC with UV detector at 252nm were analyzed by a column C-18, with a mobile phase consisting of methanol-water (70:30, v/v, containing 1% acetic acid) and the flow rate was 1mL/min.

***In vivo* anti-inflammatory effects-**

The sustained anti-inflammatory effects of the optimized formulations (F-4 and F-5) of boswellia and (F-5 and F-6) of liquorice were evaluated by carrageenan-induced hind paw edema method developed in Wistar rats by Winter et al. 1965.[26] Wistar rats weighing 200– 250 g were randomly divided into groups: control, formulation (F- 4 and F-5) of boswellia and formulation (F-5 and F -6) of liquorice each containing 6 rats. The animals were kept under standard laboratory conditions, at a temperature of 25 ± 1°C and relative humidity of 55 ± 5%. Paw edema was induced by injecting carrageenan in distilled water. Dose for the rats was calculated based on the weight of the rats. Formulations were given to all animals (except in control group) half an hour before subplantar injection of carrageenan in right paw. The amount of paw swelling was determined using plethysmometer time to time and expressed as percent edema.

Stability studies

Stability studies were performed as per the guidelines of the International Conference on Harmonization after storage at 40°C/75% RH 0, 3 and 6 months. Physical appearance, drug content and dissolution pattern were determined after storage.

RESULTS AND DISSCUSSION

Prepared all formulations of boswellia extract granules bulk density and tapped density were found in the range of0.45±0.04 to0.51±0.02 and 0.48±0.03 to 0.57±0.04 respectively. The angle of repose was in the range 25.34°±0.52 to 27°.16±0.36. The compressibility index was within the

range of 10-25 hence indication of good flow property. All the tablets of each formulations of boswellia extract showed acceptable results with respect to diameter, thickness, hardness, drug content uniformity, friability and average weight. The diameter of all the formulations was found in the range of 10.42±0.26 to 10.61±0.29. All formulations showed less than 1% friability, which was within the prescribed limit. The average weight deviation percentage of 20 tablets taken from each formulation was less than ±5%. Drug content was more than 95% and within the limits. Hence all the formulations complied with the official specifications (Table-3). Prepared all formulations of liquorice extract granules bulk density and tapped density were found in the range of 0.45±0.04 to 0.50±0.02 and 0.47±0.03 to 0.56±0.02 respectively. The compressibility index was within the range of 10-25 hence indication of good flow property. All the tablets of each formulations of boswellia extract showed acceptable results with respect to diameter, thickness, hardness, drug content uniformity, friability and average weight. The diameter of all the formulations was found in the range of 10.20±0.48 to 10.32±0.43. All formulations showed less than 1% friability, which was within the prescribed limit. The average weight deviation percentage of 20 tablets taken from each formulation was less than ±5%. Drug content was more than 95% and within the limits (Table-4). By observing the *in vitro* release data it may be concluded that the release rate of drug from matrix formulations largely depends upon type of polymer and its amount. The results of dissolution studies of boswellia formulations F-1, F-2 and F-3were given relatively rapid and complete release within 20h. The higher concentration of ethyl cellulose and eudragit RS100 showed better sustained release properties (F-4 and F-5) than HPMC (F-6). The results of dissolution studies of formulations F-6 was not considered for further studies since inadequate amount of drug (6.03%) was released at 2 h. The drug release from the tablets prepared using formulation F-4 and F-5 was slow and spread over 24h.The drug release data of formulations were subjected to different models of kinetics viz. zero order, first order, Higuchi and Korsmeyer-Peppas. Regression analysis was performed and the values of R^2 suggest that the drug release follows first order kinetics and fits into Higuchi model. Drug release from formulation F-4 and F-5 was governed by diffusion through the matrix. Formulation F-4 and F-5 ($n < 0.45$) indicates Fickian type of release. Release studies of liquorice illustrate that formulation F-1and F-2 complete the drug release within 16h, F-3 sustained drug release was upto 20h and incomplete drug release with formulation F-4 at the end of 24h.Regression analysis was performed and the values of R^2 suggest that in-vitro release profiles of drugs from the formulations F-5 and F-6 of liquorice showed good fit in the Korsmeyer-Peppas model compared to other kinetics model (zero order, first order and Higuchi). Values of n between 0.5 and 1.0 can

be regarded as an indicator for the non-Fickian (anomalous transport) diffusion. For all formulations, the value of n was in the range 0.646- 0.738 indicating non-Fickian (anomalous transport) wherein the drug release mechanism is controlled by both diffusion and dissolution. Percent inhibition of edema produced by formulation treated group was calculated against the respective control group. Results of these studies were compared using one-way analysis of variance (ANOVA).

% Inhibition = % Edema (Control) - % Edema (Formulation)/ % Edema (Control) X 100

Statistical analysis was performed. P-values less than 0.05 were considered statistically significant. The results obtained from *in-vivo* study shows that the formulation F-4 of boswellia and formulation F-6 of liquorice are good source for anti-inflammatory activity. (Table-5 and 6)

After storage at 40°C/75% RH for 3 and 6 months there was no considerable changes found in physical change (appearance, friability and hardness), drug content and in-vitro drug release profiles of formulation F-4 of boswellia and formulation F-6 of liquorice. The results obtained from accelerated stability studies indicate that F-4 tablets of boswellia drug content was obtained 100.26 % at 0 month, 99.89 % at 3 month and 98.19 % at 6 month. Furthermore, drug content of formulation F-6 of liquorice was found 99.82 % at 0 month, 99.70 % at 3 month and 98.42 % at 6month.

Table 1: Composition of formulation of sustained release matrix tablets of Boswellia (mg/tablet)

S. No	Name of ingredient	F-1	F-2	F-3	F-4	F-5	F-6
1	Boswellia extract	250	250	250	250	250	250
2	Ethyl cellulose	125	--	--	150	--	--
3	Eudragit RS100	--	125	--	--	150	--
4	HPMC K15M	--	--	125	--	--	150
5	Microcrystalline cellulose	20	20	20	--	--	--
6	PVP K30	63	63	63	63	63	63
7	Magnesium stearate	7	7	7	7	7	7
8	Talc	5	5	5	5	5	5
9	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
	Total wt(mg)	475	475	475	475	475	475

Table 2: Composition of formulation of sustained release matrix tablets of Liquorice (mg/tablet)

S. No	Name of ingredient	F-1	F-2	F-3	F-4	F-5	F-6
1	Liquorice extract	250	250	250	250	250	250
2	Carbopol 971P	100	--	--	120	--	--
3	Sodium CMC	--	100	--	--	120	--

4	HPMC K15M	--	--	100	--	--	120
5	Lactose	20	20	20	--	--	--
6	PVP K30	70	70	70	70	70	70
7	Magnesium stearate	5	5	5	5	5	5
8	Talc	5	5	5	5	5	5
9	Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
	Total wt(mg)	450	450	450	450	450	450

Table 3: Parameters of Boswellia matrix tablets formulations

Formulation	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug Content (%)	Avg. Weight (mg)
F1	10.46±0.13	4.24±0.04	6.82±0.21	0.20±0.01	98.68±1.02	474.24±0.97
F2	10.50±0.17	4.12±0.03	6.73±0.24	0.22±0.01	98.62±0.95	476.21±1.18
F3	10.45±0.14	4.32±0.03	7.01±0.21	0.38±0.02	99.17±0.41	473.14±0.67
F4	10.42±0.26	4.22±0.02	6.94±0.40	0.21±0.04	100.26±0.97	476.10±0.97
F5	10.53±0.21	4.17±0.08	7.04±0.04	0.21±0.03	99.05±0.63	475.93±1.96
F6	10.61±0.29	4.17±0.06	7.13±0.24	0.24±0.02	100.59±0.22	472.99±1.63

Table 4: Parameters of Liquorice matrix tablets formulations

Formulation	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug Content (%)	Avg. Weight (mg)
F1	10.20±0.48	4.10±0.18	7.01±0.12	0.20±0.01	99.61±0.83	451.09±0.78
F2	10.24±0.63	4.96±0.16	7.19±0.12	0.23±0.03	98.22±1.04	448.91±0.49
F3	10.32±0.43	4.13±0.31	6.98±0.14	0.17±0.02	99.10±0.74	449.33±1.75
F4	10.25±0.25	4.11±0.24	7.36±0.18	0.13±0.04	99.96±1.34	452.35±1.36
F5	10.24±0.29	4.26±0.17	6.87±0.26	0.21±0.02	100.10±0.94	450.91±0.57
F6	10.30±0.92	4.24±0.13	7.41±0.22	0.30±0.04	99.82±0.97	448.86±0.98

Table 5: Percent inhibition of edema produced by formulation F-4 and F-5 of boswellia

	% Inhibition of edema							
Formula	**1h**	**3h**	**6h**	**9h**	**12h**	**16h**	**20h**	**24h**
F-4	29.12±0.35	42.69±0.56	65.02±0.25	65.30±1.21	68.82±0.84	67.89±0.32	67.91±0.46	67.81±0.98
F-5	16.34±1.41	36.91±0.83	51.61±0.79	50.18±1.93	50.19±1.63	49.97±0.68	49.05±0.74	49.00±1.07

Table 6: Percent inhibition of edema produced by formulation F-5 and F-6 of liquorice

	% Inhibition of edema							
Formula	**1h**	**3h**	**4h**	**9h**	**12h**	**16h**	**20h**	**24h**
F-5	22.19±0.97	44.79±1.63	65.93±1.35	66.93±0.83	65.82±0.47	65.65±1.35	65.36±0.64	65.04±0.36
F-6	28.77±0.83	46.37±0.73	70.64±1.03	68.44±1.31	69.04±0.93	69.01±0.78	69.15±0.35	68.88±1.92

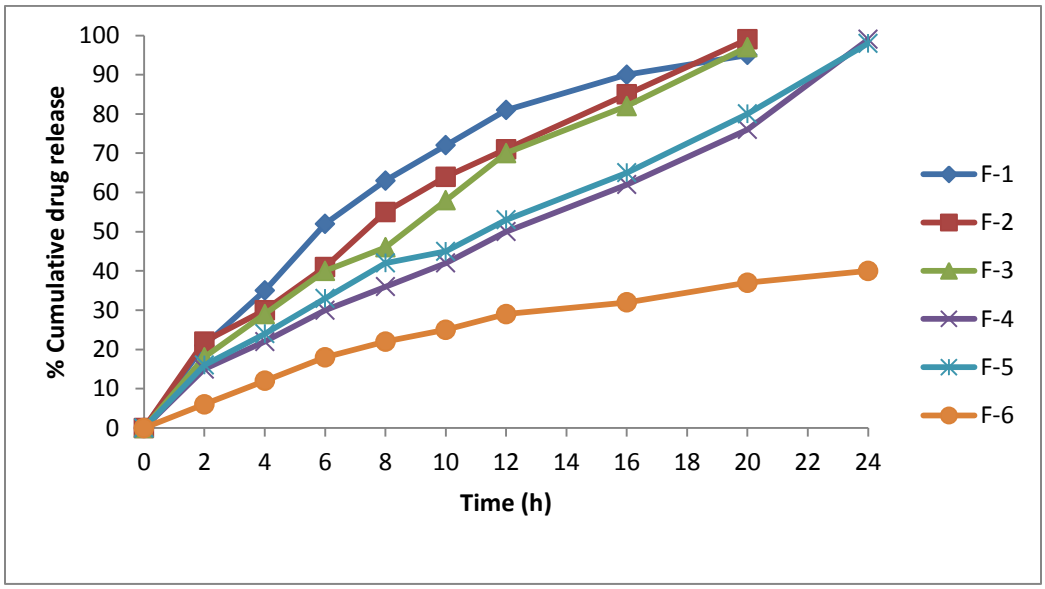

Figure 1: Comparison of in-vitro drug release study of boswellia sustained release formulations F-1 to F-6.

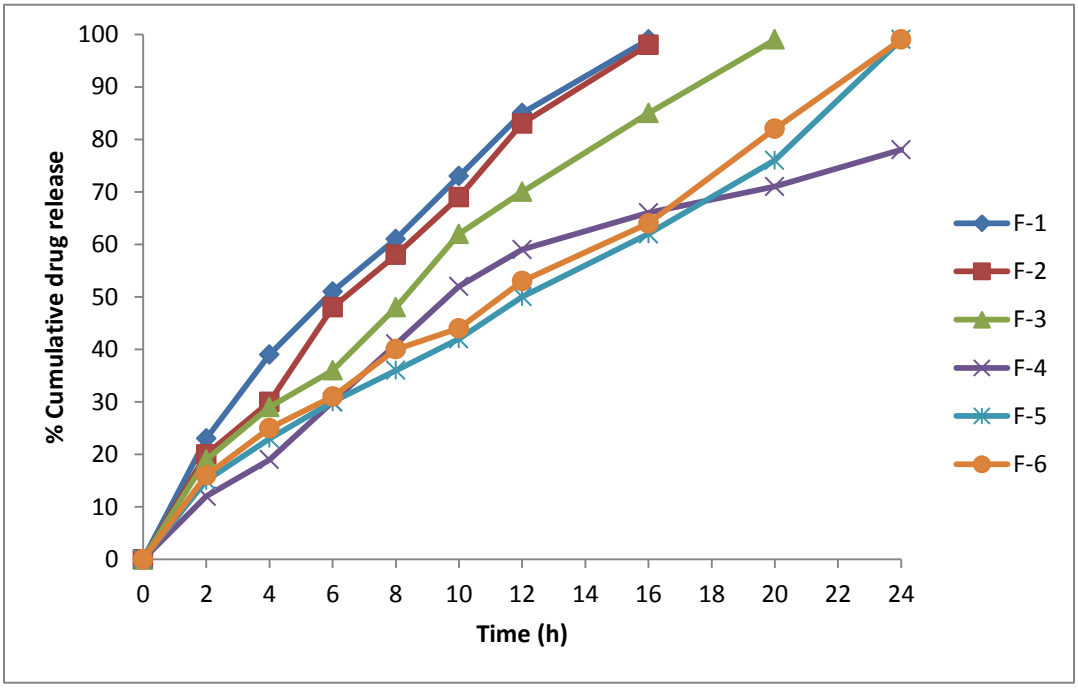

Figure 2: Comparison of in-vitro drug release study of liquorice sustained release formulations F-1 to F-6.

CONCLUSION

Studies revealed that all the physicochemical parameters comply with the official standards. The in vitro release studies exhibits the release up to 98%, over a prolonged period of time which confirms the extended release profile of formulation, having better bioavailability as well as decreased dosing frequency with reduced doses.

ACKNOWLEDGEMENT

We are thankful to honorable director and head of department (pharmacy)of the Vishveshwarya Institute of Engineering and Technology, Greater Noida (U.P) for providing the all facilities to carry out this research work.

REFERENCES

1. Martini L, Close M, Gravell K. Use of a hydrophobic matrix for the sustained release of a highly water soluble drug. Drug Dev Ind Pharm2000; 26 (1): 79- 83.
2. Reja M, Quadir MA, Haider SS. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. J Pharm Sci. 2003; 692: 274-91.
3. Trapti Rastogi, Dr. S. S. Khadabadi. Design, development and evaluation of matrix tablet containing indigenous medicinal plants. International Journal of Pharmaceutical Sciences and Research.2011; 2(11): 2806- 11.
4. Andhare M.D, Deokate U.A. Khadabadi SS, Hadke S.P., Deore S.L. Comparative Estimation of (α + β) Boswellic Acid and Curcumin from Marketed Herbal Antirheumatic Tablets. Asian Journal of Chemistry2010; 22(8): 5883-90.
5. Smolen J. S., Steiner G. Therapeutic strategies for rheumatoid arthritis. Nature Reviews Drug Discovery 2003; 2(6):473–88.
6. M. Feldmann, Pathogenesis of arthritis: recent research progress. Nature Immunology 2001; 2 (9): 771–3.
7. SiddiquiM. Z. Boswellia Serrata, A Potential Anti-inflammatory Agent: An Overview. Indian J Pharm Sci. 2011; 73(3): 255–61.
8. Rafie Hamidpour, Soheila Hamidpour, Mohsen Hamidpour, Mina ShahlariJ Tradit. Frankincense (Boswellia Species): From the Selection of Traditional Applications to the Novel Phytotherapy for the Prevention and Treatment of Serious Diseases. Complement Med2013; 3(4):221–26.
9. Shah SA, Rathod IS, Suhagina BN, Pandya SS, Parmar VK. A simple high-performance liquid chromatographic method for estimation of boswellic acids from the market formulation containing boswellia serrata extract. J Chromatogr Sci. 2000; 46:735–8.
10. Safayhi H, Rall B, Sailer ER, Ammon HP. Inhibition by boswellic acids of human leukocyte elastase. J Pharmacol Exp Ther. 1997; 281:460–3.

11. Goyal S, Sharma P, Ramchandani U, Shivastanva SK, Dubey PK. Novel anti-inflammatory topical herbal gels containing withania somnifera and boswellia serrata. Int J Pharm Biol Arch. 2011; 2:1087–94.
12. Feldmann. Pathogenesis of arthritis: recent research progress. Nature Immunology 2001;2 (9):771–773.
13. Muller-Ladner, T. Pap, R. E. Gay, M. Neidhart, S. Gay.Mechanisms of disease: the molecular and cellular basis of joint destruction in rheumatoid arthritis.Nature Clinical Practice Rheumatology2005; 1(2): 102–10.
14. Smolen S., Steiner G.Therapeutic strategies for rheumatoid arthritis. Nature Reviews Drug Discovery2003;2(6): 473–88.
15. Scott L., Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. The New England Journal of Medicine 2006; 355(7): 704–12.
16. Lubberts, Koenders M, Vanden Berg WB. The role of T cell interleukin-17 in conducting destructive arthritis: lessons from animal models. Arthritis Research and Therapy2005; 7(11):29–37.
17. McInnes IB, Schett G., Cytokines in the pathogenesis of rheumatoid arthritis. Nature Reviews Immunology2007;7(6): 429–42.
18. Mesut Sancar, Thaer Hantash1, Betul Okuyan. Comparative effectiveness of Glycyrrhiza glabra vs. omeprazole and misoprostol for the treatment of aspirin-induced gastric ulcers. African J Pharmacy and Pharmacology2009; 3(12):615-20.
19. Qurishi Y, Hamid A, Zargar MA, Singh SK, Saxena AK. Potential role of natural molecules in health and disease Importance of boswellic acid. J Med Plants Res. 2010;4: 2778–85.
20. Siemoneit U, Koeberle A, Rossi A, Dehm F, Verhoff M, Reckel S. Inhibition of microsomal prostaglandin E2 Synthase-1 as a molecular basis for the anti-inflammatory actions of boswellic acids from frankincense. Br J Pharmacol. 2011; 162:147–62.
21. Cuaz-Perolin C, Billiet L, Bauge E, Copin C, Scott-Algara D, Genze F. Anti-inflammatory and antiatherogenic effects of the NF-kB inhibitor Acetyl-11-keto-B-Boswellic acid in LPS-challenged ApoE-/- Mice. Arterioscler Thromb Vasc Biol. 2008; 28:272–7.
22. Kataria R, Hemraj, Singh G, Gupta A, Jalhan S, Jindal A et al. Pharmacological activities on Glycyrrhiza glabra– a review. Asian J Pharm Clin Res 2013; 6(1):5-7.
23. Kaur R, Kaur, Dhinds AS. Glycyrrhiza glabra: a phytopharmacological review. IJPSR2013; 4(7):2470- 7.

24. Yamamura Y, Kawakami J, Santa T. Pharmacokinetic profile of glycyrrhizin in healthy volunteers by a new high-performance liquid chromatographic method. J Pharm Sci.1992; 81: 1042-6.
25. Raghuram RK, Srinivas M, Srinivas R. Once-daily sustained- release matrix tablets of nicorandil: formulation and in vitro evaluation. AAPS PharmaSciTech 2003;4: 61-9.
26. Pravin V. Gomase, Priti S. Shire, Sayyed Nazim, Amol B. Choudhari. Development and evaluation of polyherbal formulation for anti-inflammatory activity. J. Nat. Prod. Plant Resour. 2011; 1 (1): 85-90.
27. M.D. Wandhare, U.A. Deokate, S.S. Khadabadi, S.P. Hadke, S.L. Deore. Comparative Estimation of (α + β) Boswellic Acid and Curcumin from Marketed Herbal Antirheumatic Tablet.Asian Journal of Chemistry. 2010; 22(8): 5883-90.
28. Gupta P.K., Chandola H.M , Harisha C.R. , Shukla V.J., Varun B. Gupta, Pankaj Nariya. Pharmacognostical and phyto-chemical evaluation of oleo gum- resin of shallaki (boswellia serrata roxb.). Journal of pharmaceutical and biomedical sciences. 2011; 6 (16): 1-5.
29. Minglei Tian, Hongyuan Yan and Kyung Ho Row.Extraction of Glycyrrhizic Acid and Glabridin from Licorice. International Journal ofMolecular Sciences. 2008; 9: 571-7.
30. Somayeh Esmaeili, Farzaneh Naghibi, Mahmoud Mosaddegh, Nazli Nader. Determination of 18 β-Glycyrrhetinic Acidin Glycyrrhiza glabra L. Extract by HPLC. Iranian J Pharma Res 2006; 2: 137-41.