Research Journal of Pharmacognosy (RJP) 7(4), 2020: 39-47
Received: 5 July 2020
Accepted: 12 Sep 2020
Published online: 15 Dec 2020
DOI: 10.22127/rjp.2020.238203.1609

Original article

Formulation and Finger Printing of a Poly Herbal Film-Coated Tablet for Treatment of Hemorrhoids

Sahar Dehdari[1], Homa Hajimehdipoor[2*], Somayeh Esmaeili[2], Seyed Alireza Mortazavi[3], Rasool Choopani [4]

[1]Department of Traditional Pharmacy, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[2]Traditional Medicine and Materia Medica Research Center and Department of Traditional Pharmacy, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[3]Department of Pharmaceutics, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[4]Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Background and objectives: Hemorrhoids is the most prevalent rectal disease. Despite different medical efforts, its complications are not managed well. In the present research, a popular prescription for treatment of hemorrhoids was formulated as tablet dosage form and, its HPTLC fingerprint prepared. **Methods:** *Commiphora mukul* was dissolved in *Allium ampeloprasum* juice (1:3). Then, this solution was blended with *Terminalia chebula*, *Phyllantus emblica* and *Terminalia bellirica* (1:1:1) powder. Different formulations were prepared from the mixture and the best one was selected for tablet preparation. Subsequently, the tablets were coated and their physicochemical characteristics and fingerprint pattern were obtained using silica gel plate, NP/PEG reagent and toluene: ethyl acetate: formic acid (70:15:15) as mobile phase. Laboratory stability studies were carried out as well. **Results:** Formulation C revealed excellent results in flowability studies (angle of repose: 26, carr's index: 6, hausner ratio: 1.00). It was also demonstrated acceptable results in different tests including weight variation (500 mg), hardness (8.04 kg/cm^2), disintegration time (28.50 min), friability (0.6%), dissolution (97.6% phenolics and 96.1% tannins, respectively) and the coating process. Total phenolics and tannins contents were determined as 125.8 mg/tab and 89.2 mg/tab, respectively. In fingerprinting study, characteristic spots of each species were distinguished. The film-coated tablets were stable in laboratory stability test. **Conclusion:** With reference to anti-inflammatory, astringent and wound healing roles of phenolics and tannins in hemorrhoids, the present tablets could be an appropriate candidate for hemorrhoids regarding its historical backgrounds.

Keywords: *Allium ampeloprasum*, *Commiphora mukul*; hemorrhoids; *Phyllantus emblica; Terminalia*

Citation: Dehdari S, Hajimehdipoor H, Esmaeili S, Mortazavi SA, Choopani R. Formulation and finger printing of a poly herbal film-coated tablet for treatment of hemorrhoids. Res J Pharmacogn. 2020; 7(4): 39-47.

Introduction

Hemorrhoids is the most prevalent rectal complication which is defined as enlargement and dislocation of normal rectal cushions [1,2]. Intensified pressure on rectal vascular plexus, mainly due to straining and pregnancy, seems playing the chief role in the development of hemorrhoids [3,4]. The prevalence of 39% has been reported for this disease [5]. Symptoms of

*Corresponding author: hajimehd@sbmu.ac.ir
© 2020. Open access. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/)

hemorrhoids may include bleeding, inflammation, anal discharge and pain. Treatments for grades I and II can include increasing water intake, high fiber diet and topical therapies like steroids. Treatment for grades III and IV may be non-surgical or surgical intervention [1,6,7]. In spite of current medical efforts, many complications of the disease are not managed well [8]. Medicinal herbs are the valuable sources for preparing new drugs. Consumption of herbal preparations is preferred by more than 79% of the global population [9]. The usage of traditional herbal prescriptions is a robust way to prepare cheaper and more efficient herbal drugs. One of the most prescribed formulations by "Avicenna" and "Rhazes", famous Persian physicians [10,11], is "Itrifal-e moql" which consists of the dried fruits of *Terminalia chebula, Phyllantus emblica* and *Terminalia bellirica,* oleo-gum resin of *Commiphora mukul* and leaf juice of *Allium ampeloperasum* in proportion of 1:1:1:3:9 [12-14]. Nowadays, anti-inflammatory properties of all mentioned herbs [15-21], analgesic effect of *T. chebula* and *T. bellirica* [17,22-25], wound healing effect of *T. chebula* and *Ph. emblica* [26,27] and anti-bleeding property of *A. ampeloperasum* have been confirmed [28]. These pharmacological effects are very important for the management of hemorrhoids discomforts [1,29]; therefore, the described formulation seems to be a good candidate for hemorrhoids. According to Iranian traditional medicine (ITM) prescriptions, *C. mukul* should be soaked and heated in the juice of *A. ampeloperasum* until it is dissolved. Afterwards, this solution is blended with fruit powders of *T. chebula, Ph. emblica* and *T. bellirica.* Then, resultant paste should be cut into small rounded pieces by hand that is traditionally named "Hab" [12-14]. Indeed, "Hab" is a traditional dosage form that is similar to pills. Since, traditional dosage forms should be converted to modern dosage forms for better acceptance by patients and more stability and possibility of production in industrial scale, in the present investigation, coated tablets were prepared and related quality control tests were performed.

Material and Methods

Ethical considerations

The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran with the code No. IR.SBMU.RETECH.REC.1395.376.

Chemicals

Hide powder was obtained from Sigma-Aldrich, UK. Folin-Ciocalteu, all reagents, solvents and HPTLC silica gel 60 F_{254} plates (20×20 cm) were purchased from Merck, Germany.

Plant material

The fruits of *Ph. emblica* L., *T. chebula* Retz., and *T. bellerica* Retz., the oleo-gum resin of *C. mukul* (Hook. ex Stocks) Engl. and fresh leaves of *A. ampeloprasum* were purchased from herbal market, Tehran, Iran in September 2015. All samples were authenticated at the Herbarium of Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran. Samples of *Ph. emblica* (382 HMS), *C. mukul* (379 HMS), *T. chebula* (380 HMS) and *T. bellerica* (381 HMS) were kept at the Herbarium of TMRC. The juices of fresh leaves of *A. ampeloprasum* were extracted through crushing vegetable machine and then, dried using freeze drying method.

Plant material analysis

Different physiochemical tests such as loss on drying, total ash, matter insoluble in ethanol, foreign matter, alcohol-soluble extractive, water-soluble extractive and total phenolics and tannins contents were performed based on the plants monographs [30,31]. Considering that there was no monograph for *A. ampeloperasum*, its tannins content was determined.

Pre-formulation studies

Dried juice of *A. ampeloperasum* was dissolved in water to make similar concentration to primary juice. Then different formulations were made using plant powders and juice of *A. ampeloperasum.*

Formulation A

In this formulation, equal quantities of fruits powders from *T. chebula, Ph. emblica* and *T. bellirica* were blended and passed through sieve no. 20. *Commiphora mukul* was weighted equal to sum of fruits and added to *A. ampeloperasum* juice (1:3). The mixture was heated in water-bath for 2 hours. Then, the solution was filtered and the filtrate was added to the blended powder of fruits. Because of high volume of filtrate in comparison to fruit powders, this formulation looked like a paste and needed long time for drying.

Formulation B
The process was similar to formulation A, but the filtrate was heated till the volume was reduced to one-fifth of its initial volume. Next, the filtrate was added to the powders. The mixture was passed through sieve no. 18. Subsequently, it was placed in oven at 40 °C and passed through sieve no. 20 after drying.

Formulation C
This formulation was same as formulation B, but the filtrate was heated till the volume was reduced to one-fourth of its first volume. Next, the filtrate was added to powders. The granules were passed via sieve no. 12. Afterwards, the water was evaporated in oven at 40 °C. After drying, it was passed through sieve no. 14. The granule size was larger than of formulation B.

Formulation D
To achieve optimum disintegration time, cross carmellose sodium (super disintegrant agent) was added to the ingredients of formulation C in different percentages (1, 3, 5, 7 and 10%). Avicel 102 was added as filler to obtain constant tablet weight in all formulations of D series.
The described formulations have been displayed in table 1.

Flowability properties
The resultant powders from three series of formulations (B, C and D) were evaluated for flowability properties including angle of repose, Carr's index, and Hausner ratio. According to the results of flowability properties of powders, best formulations were selected for tablet preparation. The resulting herbal powders were compressed via 12 mm concave punch using a single stroke punching machine.

Evaluation of tablet properties
Different tests including weight variation, friability, hardness, disintegration time, thickness, diameter, dissolution test and assay of total phenolics and tannins were performed on the tablets [30,31].

Determination of total phenolics and tannins contents
For determination of total phenolics and tannins contents, 10 tablets were powdered and the weight of one tablet was dissolved in 1 litre of distilled water (stock solution). Two mL of stock solution was mixed with 1mL of folin-Ciocalteu reagent and 10 mL distilled water and diluted to 25 mL with sodium bicarbonate 29%. The samples were kept in a dark place for 30 min. Then, their absorbances at 760 nm were measured. Pyrogallol (0.125, 0.0625 and 0.0312 mg/mL) was used as the standard.
For determination of total tannins contents, 10 mL of the stock solution was added to 100 mg hide powder and shaked for 60 min. Next, the mixture was filtered and the above mentioned process was performed for the solution [30].

In vitro dissolution studies
Dissolution study was performed on 6 herbal tablets of formulation C using apparatus 2 (paddle method). The dissolution test was done with 900 mL of water, at 37 ºC, 75 rpm for 60 min. Sampling was carried out after 30, 45 and 60 min intervals and the percentage of released total phenolics and tannins compounds were determined.

Film-coating process
According to the results of physicochemical tests, the best formulations (B and C) were selected for the coating process. Both the aqueous and alcohol soluble coating methods were performed. First, aqueous film-coating process was done using pink powder of Opadry II, Colorcon®.

Table 1. Ingredients of different tablet formulations

Ingredients	Formulation codes							
	A	**B**	**C**	**D_1**	**D_2**	**D_3**	**D_4**	**D_5**
Terminalia chebula (mg)	100	100	100	100	100	100	100	100
Terminalia bellirica (mg)	100	100	100	100	100	100	100	100
Phyllantus emblica (mg)	100	100	100	100	100	100	100	100
Commiphora mukul (mg)	300	300	300	300	300	300	300	300
Allium ampeloprasum juice (mL)	900	180	225	225	225	225	225	225
Cross carmellose sodium (mg)	-	-	-	5.6	16.8	28	39.2	56
Avicell 102 (mg)	-	-	-	54.4	43.2	32	20.8	4
Mesh size	-	18,20	12,14	12,14	12,14	12,14	12,14	12,14

The existed spots in both tablet and controls with proper concentration were considered as characteristic spots for the detection of each tablet contents. The chromatogram exhibited the characteristic colored spots of herb extracts at Rf values of 0.14 (doubled yellow), 0.37-0.47 (green) and 0.82 (blue) related to *T. chebula*, dissvoled *C. mukul* in *A. ampeloprasum* and *Ph. emblica* extracts. In addition, *T. chebula* and *T. bellirica* had demonstrated some similar spots at Rf values of 0.35 (yellow), 0.55 (red) and 0.58 (yellowish red). So, HPTLC fingerprint could be considered as a reliable method for quality control assessment of the prepared tablets.

Through stability studies, no change in appearance and smell of tablets were found. Phenolics and tannins were reduced less than 5% during 3 months. However, real stability should be performed on the final package of tablets in industrial scales.

There were clinical trials with good results for some of used herbs in this tablet as well. Topical application of *A. ampeloprasum* cream twice daily for 3 weeks, improved bleeding in patients with grade I and II of hemorrhoids [28]. In addition, oral consumption of crude resin of *C. mukul* 3g/day for 4 weeks decreased some of symptoms of patients such as painful defecation and constipation [37]. Besides, pain reliever effect of *T. chebula* at the dose of 500 mg twice daily was confirmed through a randomized double blind clinical trial through hot air pain model on 12 healthy humans [23]. Hence, present tablet is a good offer for patients with symptomatic hemorrhoids due to probable synergistic effects of its ingredients. Herbal medicines have great abilities for the management of hemorrhoids and post hemorrhoidectomy complications [38]. Presence of tannins and phenolics phytocompounds in the present poly herbal tablet was confirmed through qualitative and quantitative assays. Antioxidant and anti-inflammatory effects of phenolics and tannins have been confirmed [39-43]. In addition, wound healing, astringent and antibacterial properties have been ascribed to tannins [27,44-46]. Mentioned pharmacological effects are necessary for the management of hemorrhoids [47]. Regarding the anti-inflammatory, antioxidant, antibacterial, wound healing and astringent properties of the mentioned herbs, the tablets could be good choice for clinical purpose.

Acknowledgments

This article was a part of Ph.D. thesis (Sahar Dehdari, No. 171), Traditional Pharmacy which was granted by School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran (No. 160).

Author contributions

Homa Hajimehdipoor and Somayeh Esmaeili designed and supervised the study. Seyed Alireza Mortazavi coordinated formulation part and Rasool Choopani contributed in traditional information extraction. Sahar Dehdari performed the experimental part and prepared the manuscript. All the authors contributed in revising the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

References

[1] Moult HP, Aubert M, Parades VD. Classical treatment of hemorrhoids. *J Visc Surg*. 2014; 7(2): 1-7.

[2] Lohsiriwat V. Approach to hemorrhoids. *Curr Gastroenterol Rep*. 2013; 15(3): 13-16.

[3] Abramowitz L, Godeberge P, Staumont G, Soudan D. Clinical practice guidelines for the treatment of hemorrhoid diseases. *Gastroen Clin Biol*. 2001; 25(6-7): 674-702.

[4] Lohsiriwat V. Hemorrhoids: from basic pathophysiology to clinical management. *World J Gastroenterol*. 2012; 18(17): 2009-2017.

[5] Riss S, Weiser FA, Schwameis K, Riss T, Mittlböck M, Steiner G, Stift A. The prevalence of hemorrhoids in adults. *Int J Colorectal Dis*. 2012; 27(2): 215-220.

[6] Jeffrey L, Barnett MD, Peter C, Gary R, Lichtenstein H. Technical review on the diagnosis and treatment of hemorrhoids. *Gastroenterology*. 2004; 5085(04): 1463-1473.

[7] Lohsiriwat V. Treatment of hemorrhoids : a coloproctologist's view. *World J*

gastroenterol. 2015; 21(31): 9245-9252.
[8] Rahimi R, Abdollahi M. Evidence-based review of medicinal plants used for the treatment of hemorrhoids. *Int J Pharmacol*. 2013; 9(1): 1-11.
[9] van Andel T, Carvalheiro LG. Why urban citizens in developing countries use traditional medicines: the case of suriname. *Evid Based Complement Altern Med*. 2013; Article ID: 687197.
[10] Zargaran A, Mehdizadeh A. Avicenna (980–1037 AD). *J Neurol.* 2012; 259(2): 389-390.
[11] Zarshenas MM, Mehdizadeh A, Zargaran A, Mohagheghzadeh A. Rhazes (865-925 AD). *J Neurol*. 2012; 259(5): 1001-1002.
[12] Nazem Jahan MA. Qarabadin-e Azam. Tehran: Iran University of Medical Sciences, 2004.
[13] Shafaee Esfehani MM. Qarabadin-e Shafaie. Tehran: Iran University of Medical Sciences, Research Institute for Islamic and Complementary Medicine, 2004.
[14] Aghili Khorasani MH. Qarabadin-e kabir. Tehran: Ostad Allah Qoli Khan Qajar publisher, 1855.
[15] Bag A, Kumar Bhattacharyya S, Kumar Pal N, Ranjan Chattopadhyay R. Anti-inflammatory, anti-lipid peroxidative, antioxidant and membrane stabilizing activities of hydroalcoholic extract of *Terminalia chebula* fruits. *Pharm Biol*. 2013; 51(12): 1515-1520.
[16] Evangeline S, Sundaram V, Manian RP, Kulanthaivelu K, Balasundaram S. Antioxidant, antibacterial and anti-inflammatory activity of *Acalypha indica* and *Terminalia chebula*: an in-vitro analysis. *Res J Pharm Biol Chem Sci.* 2015; 6(3): 388-396.
[17] Jami SI, Sultana Z, Ali E, Begum MM, Haque M. Evaluation of analgesic and anti-inflammatory activities on ethanolic extract of *Terminalia chebula* fruits in experimental animal models. *Am J Plant Sci.* 2014; 5(1): 63-69.
[18] Reddy TC, Aparoy P, Babu NK, Kumar KA, Kalangi SK. Kinetics and docking studies of a COX-2 inhibitor isolated from *Terminalia bellerica* fruits. *Protein Peptide Lett*. 2010; 17(10): 1251-1257.
[19] Ihantola-Vormisto A, Summanen J, Kankaanranta H, Vuorela H, Asmawi ZM, Moilanen E. Anti-inflammatory activity of extracts from leaves of *Phyllanthus emblica. Planta Med*. 1997; 63(6): 518-524.
[20] Francis JA, Raja SN, Nair MG. Bioactive terpenoids and guggulusteroids from *Commiphora mukul* gum resin of potential anti-inflammatory interest. *Chem Biodivers.* 2004; 1(11): 1842-1853.
[21] Adao CR, Da Silva BP, Parente JP. A new steroidal saponin with antiinflammatory and antiulcerogenic properties from the bulbs of *Allium ampeloprasum* var. *porrum*. *Fitoterapia*. 2011; 82(8): 1175-1180.
[22] Kumar CU. Evaluation of the analgesic activity of standardized aqueous extract of *Terminalia chebula* in healthy humaan participants using hot air pain model. *J Clin Diagn Res.* 2015; 9(5): 1-4.
[23] Jong BS, Jae YJ, Jae YP, Eun MJ, Sang IL, Sung SC, Do YP, Eun WC, Dong SS, Jong SL, Tae GLee. Anti-arthritic and analgesic effect of NDI10218, a standardized extract of *Terminalia chebula*, on arthritis and pain model. *Biomol Ther*. 2012; 20(1): 104-112.
[24] Sireeratawong S, Jaijoy K, Khonsung P, Soonthornchareonnon N. Analgesic and anti-inflammatory activities of the water extract from *Terminalia chebula* Rezt. *Afr J Trad Complement Altern Med*. 2015; 11(6): 77-82.
[25] Khan AU, Gilani AH. Antisecretory and analgesic activities of *Terminalia bellerica*. *Afr J Biotechnol*. 2010; 9(18): 2717-2719.
[26] Suguna L, Singh S, Sivakumar P, Sampath P, Chandrakasan G. Influence of *Terminalia chebula* on dermal wound healing in rats. *Phytother Res*. 2002; 16(3): 227-231.
[27] Chularojmontri L, Suwatronnakorn M, Wattanapitayakul SK. *Phyllanthus emblica* L. enhances human umbilical vein endothelial wound healing and sprouting. *Evid Based Complement Altern Med*. 2013. Article ID 720728 .
[28] Mosavat SH, Ghahramani L, Sobhani Z, Haghighi ER, Heydari M. Topical *Allium ampeloprasum* subsp *iranicum* (leek) extract cream in patients with symptomatic hemorrhoids: a pilot randomized and controlled clinical trial. *J Evid Based Complement Altern Med*. 2015; 20(2): 132-136.
[29] Altomare DF, Giannini I. Pharmacological treatment of hemorrhoids : a narrative review.

Expert Opin Pharmacother. 2013; 14(17): 1-7.

[30] Editorial Board. British Pharmacopoeia. London: The Stationary Office, 2015.

[31] Editorial Board. United States Pharmacopeia 39, National Formulary 34. Rockville: USP Convention, 2016.

[32] Ibn Sina HAA. Al Qanun Fi al-Tibb (Canon of medicine). Beirut: Alamy Le- Al-Matbooat Institute, 2005.

[33] Rhazes. Al Havi (Liber Continent). Tehran: Academy of Medical Sciences, 2005.

[34] Patel S, Jayvadan K, Patel RK. To study proximate analysis & biological evaluation of *Triphala guggulu* formulation. *Int J PharmTech Res.* 2012; 4(4): 1520-1526.

[35] Savarikar SS, Barbhind MM, Halde UK, Kulkarni AP. Pharmaceutical and analytical evaluation of triphalaguggulkalpa tablets. *J Ayurveda Integr Med.* 2011; 2(1): 21-25.

[36] Kulkarni A, Chimangude P, Wagh V, Kolatkar A. Formulation and evaluation of triphalaguggulkalpa tablets for optimum disintegration time. *Int J Pharm Sci Rev Res*. 2015; 34(1): 270-275.

[37] Yousefi M, Mahdavi MRV, Hosseini SM, Bahrami A, Davati A, Kamalinejad M, Faghihzadeh S. Clinical evaluation of *Commiphora mukul*, a botanical resin, in the management of hemorrhoids: a randomized controlled trial. *Pharmacogn Mag*. 2013; 9(36): 350-356.

[38] Dehdari S, Hajimehdipoor H, Esmaeili S, Choopani R. Scientific Evaluation of the prescribed herbs by Avicenna for the management of post hemorrhoidectomy complications. *Galen Med J*. 2017; 6(3): 166-184.

[39] Zhong X, Shi Y, Chen J, Xu J, Wang L, Beier RC, Hou X, Liu F. Polyphenol extracts from *Punica granatum* and *Terminalia chebula* are anti-inflammatory and increase the survival rate of chickens challenged with *Escherichia coli*. *Biol Pharm Bull.* 2014; 37(10): 1575-1582.

[40] Lee HH, Paudel KR, Kim DW. *Terminalia chebula* fructus inhibits migration and proliferation of vascular smooth muscle cells and production of inflammatory mediators in RAW 264.7. *Evid Based Complement Altern Med.* 2015: Article ID 502182.

[41] Bandyopadhyay SK, Chatterjee A, Chattopadhyay S. Biphasic effect of *Phyllanthus emblica* L. extract on NSAID-induced ulcer: an antioxidative trail weaved with immunomodulatory effect. *Evid Based Complement Altern Med.* 2011; Article ID 146808.

[42] Hossen SMM, Sarkar R, Mahmud S, Aziz NMA. Medicinal potential of *Phyllanthus emblica* (Linn.) fruits extracts: biological and pharmacological activities. *J Pharm Res Int.* 2014; 4(12): 1486-1499.

[43] Nampoothiri SV, Prathapan A, Cherian OL, Raghu KG, Venugopalan VV, Sundaresan A. In vitro antioxidant and inhibitory potential of *Terminalia bellerica* and *Emblica officinalis* fruits against LDL oxidation and key enzymes linked to type 2 diabetes. *Food Chem Toxicol*. 2011; 49(1): 125-131.

[44] Li K, Diao Y, Zhang H, Wang S, Zhang Z, Yu B, Huang S, Yang H. Tannin extracts from immature fruits of *Terminalia chebula* Fructus Retz. promote cutaneous wound healing in rats. *BMC complement Altern Med*. 2011; 11(1): 86-90.

[45] Palit M, Hegde SK, Bhat Sh. Effectiveness of mouthrinse formulated from aqueous extract of *Terminalia chebula* on salivary *Streptococcus mutans* count and pH among 8- to 12-year-old school children of karnataka : a randomized clinical trial. *Int J Clin Pediatr Dent.* 2016; 9(4): 349-354.

[46] Andarkhor P, Sadeghi A, Khodadoost M, Kamalinejad M, Gachkar L, Abdi S, Zargaran A. Effects of *Terminalia chebula* Retz. in treatment of hemorrhoids: a double – blind randomized placebo – controlled clinical trial. *Eur J Integr Med.* 2019; 30: 100935.

[47] Andarkhor P, Khodadoost M, Kamalinejad M, Talaie R, Gachkar L, Zargaran A. Twelve vegetables used for prevention and treatment of hemorrhoids in Persian Medicine. *J Tradit Chin Med.* 2019; 39(4): 466-473.

Abbreviations

ITM: Iranian traditional medicine; NP: Natural product; PEG: polyethylene glycol