www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(11): 520-523
© 2018 TPI
www.thepharmajournal.com
Received: 18-09-2018
Accepted: 20-10-2018

Nitin Kumar
HIMT College of Pharmacy (Harlal Institute of Management and Technology) Greater Noida, Uttar Pradesh, India

Gaurav Saxena
Gniot College of pharmacy, Greater Noida, Uttar Pradesh, India

Snigdha Shukla
HIMT College of Pharmacy (Harlal Institute of Management and Technology) Greater Noida, Uttar Pradesh, India

Mamta Seliya
HIMT College of Pharmacy (Harlal Institute of Management and Technology) Greater Noida, Uttar Pradesh, India

Akanksha Samuel
Lloyd College of Pharmacy, AKT University, Greater Noida, Uttar Pradesh, India

Correspondence
Nitin Kumar
HIMT College of Pharmacy
(Harlal Institute of Management and Technology) Greater Noida, Uttar Pradesh, India

Formulation and evaluation of contraceptive herbal gel

Nitin Kumar, Gaurav Saxena, Snigdha Shukla, Mamta Seliya and Akanksha Samuel

Abstract
Gels are semi solid, three dimensional and polymeric formulations, comprising the small amount of solid dispersed large amount of liquid. These topical formulations have been extensively studied. Vagina has been used as a mucosal drug delivery route for a long time. Gels are receiving a great deal of interested as vaginal drug delivery system. *Gossypium hirsutum* seeds (Gossypieae), *Azadirachta indica* seeds (Meliaceae), and *Trigonella foenum graecum* seed (Fabaceae) extracts were formulated in an aqueous based carbopol-934(1%w/w) gel system. Six formulations of the gel were prepared by varying the proportions of polymers. Preformulation studies on solubility, partition co-efficient, viscosity and bioadhesion were determined along with compatibility studies using a validated HPLC method. Based on these tests, formulation AA-7 was selected as best formulation and i*n-vitro* drug dissolution studies were carried out. Overall curve fitting demonstrated that the drug liberated from mucoadhesive gels AA7 followed zero-order model (R2 = 0.9929) for burst release during first hour and followed Korsmeyer–Peppas model (R2 = 0.9976) for sustained release phase during later 23 hours suggesting, non-Fickian diffusion. It could be safely concluded from the study that the herbal gel formulation (AA-7) can be developed as a tropical contraceptive subjected to further *in-vivo* studies.

Keywords: Formulation, herbal, topical contraceptive, vaginal formulation

1. Introduction
According to World Health Organization (WHO), around 80% of the world's population depends, on traditional medicine system for their primary healthcare needs. Hence, there would be considerable economic benefits in the development of indigenous medicinal plants for the treatment of various diseases [1, 2]. In India, it is reported that traditional healers use 2500 plant species and around 120 species of plants are used as regular sources of medicine. This knowledge of medicinal plants has been accumulated in the course of many centuries based on different medicinal systems such as Ayurveda, Unani and Siddha [3, 4].

There are many herbal plant which uses in treatment of several disease such as skin disease, cancer and other life style conditions like diabetes etc. There are many herbal plants which used as contraceptive agents in traditional system of medicine. *Gossypium hirsutum* seeds (Gossypieae), *Azadirachta indica* seeds (Meliaceae), and *Trigonella foenum graecum* seed (Fabaceae) have versatile ethnological uses in a variety of medical conditions. These plants parts are also reported to have contraceptive activity and may cause abortion.

Trigonella foenum-graecum from the family Fabaceae, an aromatic herbaceous plant is widely cultivated in Mediterranean countries and Asia. [5].*Gossypium hirsutum* seeds from the family Gossypieae, an aromatic herbaceous plant is widely cultivated in Mediterranean and Asia Region [6]. *Azadirachta indica* seeds from the family Meliaceae widely plant cultivated in planed and hilly region [7].

The vagina plays a major role in reproduction and it is an important organ of the reproductive system. Normally lactobacilli produce sufficient lactic acid to acidify vaginal secretions to pH 3.5–4.5. Menstrual, cervical and uterine secretions and semen act as alkalising agents and increase the pH. The pH plays also a role in amount of drug absorption and is important for drug delivery systems. Vaginal drug delivery system is an important route of drug administration. The presence of dense network of blood vessels has made the vagina an excellent route of drug delivery for both systemic and local effect. [8,9]. The vaginal route has some advantages due to its large surface area, rich blood supply, avoidance of the first pass effect, relatively high permeability to many drugs and self-insertion [10].

In contrast the scientific knowledge regarding the possibilities of drug delivery via the vagina is limited. To date, there are only a limited number of vaginal contraceptives are available, although various possibilities are presently being explored. The currently available vaginal delivery systems have limitations, such as leakage, messiness and low residence time, which contribute to poor subject or patient compliance.

The target for the interaction of mucoadhesive excipients is the mucus. Mucus is a mixture of large glycoproteins (mucins), water, electrolytes, epithelial cells, enzymes, bacteria, bacterial products and various other materials depending on the source and location of the mucus [11].

Beside novel drug loaded inserts which are on the market, hydrogel systems with higher retention time are existing. Many drug delivery systems are based on so called mucoadhesive polymers. Mucoadhesion is another version of the bioadhesion because the target is still the underlying tissue [12].These polymers are able to swell rapidly when placed in aqueous environment and therefore exhibiting a controlled drug release. Since the first presentation of the concept of mucoadhesion, many attempts have been undertaken to improve the adhesive properties of such polymer systems [13].

Exploring compounds having spermicidal characteristics as herbal formulation considerations will be a new direction. Moreover using such herbal formulation of more than one compound could have synergistic contraceptive potential and needs to be further explored. With this viewpoint the poly herbal gel formulation was prepared and its preformulation studies were conducted along with simultaneously exploration of its mucoadhesive potential

Material and Method

Materials

Sample Collection: Aqueous extracts of *Gossypium hirsutum* seeds (Gossypieae), *Azadirachta indica* seeds (Meliaceae), *Hibiscus rosa-sinensis* roots (Malvaceae) and *Trigonella foenum graecum* seed (Fabaceae) were gifted by Herbal extracts suppliers Noida, India.

Reagents

The cross-linking agents for the whole Carbopol 900 series are allyl ethers of either sucrose or pentaerythritol. Triethanolamine (S.D. Fine Chemicals, India) was used as neutralising agent. All the Chemicals and solvents were of analytical grade and were procured from Merck India Ltd. Carbopol 974(CP-974) was procured as a gift sample from Lubrizol (Mumbai, India).

Vaginal fluid simulant (VFS) was prepared from 3.51 gL^{-1} NaCl, 1.40 gL^{-1} KOH, 0.222 gL^{-1}, $Ca(OH)_2$, 0.018 $gL^{-1,}$ bovine serum albumin, 2 $gL^{-1,}$ lactic acid, 1 gL^{-1} acetic acid, 0.16 gL^{-1}, glycerol, 0.4 $gL^{-1,}$ urea, 5 $gL^{-1,}$ glucose and 15 gL^{-1} mucin, {pH of the mixture was adjusted to 4.5} 0.02 using 0.1 M HCl [14].

Methods

Preparation of gels

Fixed gel components consisted of 5 wt% glycerin, 0.1 wt% methylparaben and 0.05 wt% propylparaben (preservatives), totaling 6.3 wt% of the gel. DI water was used to make up the weight of the gel to 100 wt%.

HE1, HE2 and HE3 (0.1 wt%) was dispersed in glycerin (3.5 wt%) to form a homogenous paste which was then added to 1 wt%.

TFV solution in water. Required amounts of Carbopol 974P were added to the above solution and stirred with a paddle mixer at 350 rpm for 45 min to ensure complete hydration of the polymer. Stainless steel paddles (passivated316 L) and USP grade water should be used to avoid introduction of trace amounts of metal into the gel during preparation. Methylparaben (0.15 wt%) and propylparaben (0.05 wt%) were weighed and mixed with pre-heated glycerin (1.5 wt%) at 65°C until all solids dissolved. Required amount of HEC was added to the glycerin paste after cooling to room temperature. The glycerin paste was then added to the Carbopol 974P dispersion with constant stirring.

The weight ratio between the polymer and the triethanolamine used was 1:1.6.Different mucoadhesive polyherbal gel formulations of the 250 mg NAC were prepared using the following excipients: CP-974 (0.25–1.0% w/w), honey (3–5% w/w), aerosol (0.5–2.0% w/w) and water (q.s. to 50 g).The formulations were prepared using Box-Behnken experimental design and characterised for elastic modulus(G0), gel index (GI) and maximum detachment force (MDF) as defined later. The optimized formulation generated using statistical screening was prepared with three different Carbopol grades viz. Carbopol 934P (CP-934), Carbopol 974P (CP-974) and Noveon AA-1 (CP-AA1) for comparative evaluation of the rheological profile of MPGs with three polymers and for their comparative mucoadhesive potential.

We have select various quantities of drug which are converted into code such as AA1, AA2,AA3,AA4,AA5,AA6,AA7,AA8 and AA9 are shown in Table No: 01.

Evaluation of bioadhesive vaginal gel

Percentage yield

The percent yield was calculated as the weight of the formulations recovered from each batch divided by total weight of drug and other all ingredients used to prepare formulations multiplied by 100. The percentage yield of each formulation was replicated three times. The yield was calculated by the following formula:

$$Y = \{P\text{m} - Z\text{g}\}/T\text{m}\,[P + \text{Ig}] \times 100$$

Where Y = yield, Pm = practical mass, ZG =vaginal gel, Tm = theoretical mass, P = polymer and Ig = ingredients.

Determination of pH

The pH of the gel was determined by a digital pH meter (MK-VI, Systronics, Ahmedabad) 1 gm of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation and constant reading was noted. The pH measurement of each formulation was carried out three times.

Syringeability

Syringeability study was carried out by using a 22 gauze needle.

Estimation of actual drug content present in vaginal gel:

About 6 gm of gel was weighed accurately and dissolved in citrate phosphate buffer pH 4 containing sodium lauryl sulphate (1% w/v). After appropriate dilutions, the drug content was analyzed spectrophotometrically (Model – UV-1800 Pharmaspec, Shimadzu, Japan) at 290 nm.

Drug content uniformity

Initially, the formulations were tested for homogeneity by visual inspection. To ensure the homogeneity of drug content

in the formulation of the gel, six tubes were sampled from the different locations of the mixer and assayed for the drug content as stated above. Studies were performed in triplicate for all the formulations [15].

Determination of Spreadability

Spreadability study was carried out by transferring the 6 gm of gel formulation to the center of a on a circle of 2 cm diameter pre marked on a glass plate and then a second glass plate was employed. Half kilogram of weight was permitted to rest on the upper glass plate for 5 min and the spread diameters recoded each time [15, 16].

Extrudability

A closed collapsible tube containing about 20 g of gel was pressed firmly at the crimped end and a clamp was applied to prevent any roll back. The cap was removed and the gel was extruded. The amount of the extruded gel was collected and weighed. The percentage of the extruded gel was calculated [17, 18].

***In vitro* release kinetics**

Dissolution studies were performed using the USP XXVIII, paddle-rotating method (Electrolab dissolution tester, Electrolab, India) at 37 °C ± 0.5 °C and 75 rpm using two dissolution media: phosphate-buffered saline pH 4.5 (PBS), and VFS. The gels were first packed into a dialysis bag and placed into the dissolution media. Dissolution studies were carried out in triplicate, maintaining the sink conditions for all the formulations. A 5 ml aliquot of sample was withdrawn at regular time intervals, filtered and assayed spectrophotometrically at 269 nm (Shimadzu 1601 UV–VIS Spectrophotometer, Japan). The cumulative% drug release was calculated for the formulations and the possible mechanism of drug release from mucoadhesive polyherbal gels postulated.

Result and Discussion

Table 1: Drug Content of Gel Formulations

Formulation code	Drug (mg)
AA1	FE: CE: NE: 40:30:30
AA2	FE: CE: NE: 30:40:30
AA3	FE: CE: NE: 30:30:40
AA4	FE: CE: NE: 50:25:25
AA5	FE: CE: NE: 25:50:25
AA6	FE: CE: NE: 25:25:50
AA7	FE: CE: NE: 60:20:20
AA8	FE: CE: NE: 20:60:20
AA9	FE: CE: NE: 20:20:60

FE= Gossypium hirsutum seeds; CE= Hibiscus rosa-sinensis roots; NE=*Trigonella foenum graecum* seed

Table 2: PH, Drug Content, Viscosity of Gel Formulations

Formulation	PH	Drug content	Viscosity
AA1	4.05±0.22	14.2±0.23	8.12±0.05
AA2	4.01±0.21	16.1±0.24	8.45±0.03
AA3	3.99±0.22	15.2±0.25	8.23±0.05
AA4	4.01±0.11	18.9±0.33	9.87±0.03
AA5	4.06±0.11	17.9±0.32	9.66±0.04
AA6	4.02±0.14	18.3±0.34	9.33±0.03
AA7	3.99±0.12	16.7±0.22	8.55±0.06
AA8	4.01±0.13	17.1±0.23	8.43±0.05
AA9	4.02±0.11	16.4±0.22	8.23±0.06

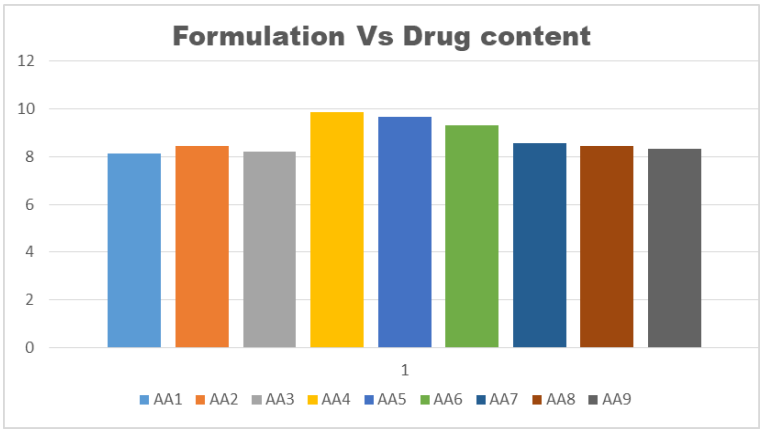

Fig 1: Comparison of Drug Content in Different Gel Formulations

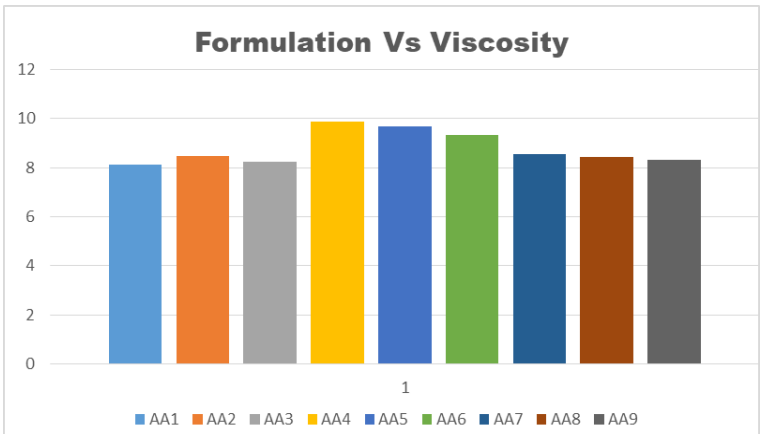

Fig 2: Comparison of Viscosity in Different Gel Formulations

Table 3: Bioadhesion Strength, Syringeability and Extrudability of Gel Formulations

Formulation code	Bioadhesion strength (gm)	Syringeability	Extrudability
AA1	14.5±0.4	*	**
AA2	12.4±0.6	*	**
AA3	10.7±0.3	*	**
AA4	15.2±0.6	**	*
AA5	12.4±0.8	**	*
AA6	11.3±0.5	**	*
AA7	17.2±0.6	***	**
AA8	12.3±0.4	**	**
AA9	10.6±0.6	**	*

Mean ±SD (n=3), *-poor, ** good, *** very good,

In this study, gel formulations of herbal extracts were prepared, and compatibility between the drug and polymers were confirmed by IR spectrophotometer. The prepared gels were brown in color with slight aromatic odor. The physicochemical parameters and the release characteristics were evaluated. The pH, and drug content of the gel formulations AA1-AA9 was found to be in the range of 3.99 to 4.06, and 14.2 to 18.3 respectively Table No: 02. The bioadhesion strength of the gel formulations AA1 – AA9 was found to be in the range of 10.7 to 17.2 Table No: 03. After 1:1 dilution of gels with VFS the pH of the gels was found in the range of 5.0–5.5.

In vivo, vaginal formulations experience the dilution with vaginal fluids. The likelihood exists that the rheological behavior and mucoadhesiveness of the formulations might be affected by dilution with environmental fluids [19]. Volume of vaginal fluids is reported to be about

0.75 ml [14] and the mucoadhesive gels would be applied in volumes of 1–3 ml, resulting in dilution when thoroughly mixed. To mimic the situation in the vagina, we diluted the gel formulations with VFS (1:5), and tested the influence of the dilution on *G`* (elastic modulus) and mucoadhesion in terms MDF. The dilution with simulated vaginal fluid reduced the elastic modulus, which can be ascribed to the breaking of gel structure on excessive dilution. MDF (maximum detachment force) was almost unchanged or slightly higher with dilution and suggests that the dilution may in fact help in the better wetting of the polymer and hence formation of strong mucoadhesive bonds either by physical entanglements and/or chemical bonds.

Overall curve fitting showed that the drug release from mucoadhesive gels followed zero-order model (R2 = 0.9929) for burst release during first hour and followed Korsmeyer–Peppas model (R2 = 0.9976) for sustained release phase during later 23 hours. This is further supported by the fact that combinations of polymer hydration, drug dissolution and polymer erosion determine the drug release from hydrophilic gels. Water-soluble drugs are released primarily by diffusion of dissolved drug molecules across the hydrated gel layer, while poorly soluble drugs are primarily released by polymer erosion mechanism [20].

Conclusion

In conclusion, *in vitro* drug release of herbal formulation from the bioadhesive gel formulations showed that the films containing higher concentration of polymers released the drug slowly as compared to the formulations containing lower concentration of polymers. The formulations maintained the sustained drug release for a period of more than 58 hrs. The formulation AA6 having 6% guar gum concentration was selected as the best formulation. The results of the study give a rational guideline for formulating a sustained release vaginal drug delivery system of herbal formulation for effective contraception.

The flow properties of semi-solid vaginal dosage forms might be of use to predict the spreading and coating of the formulations over the vaginal epithelia. Especially for the mucoadhesive polyherbal gels (MPGs), the rheological characteristics need to be controlled and understood since the multi-component gels might exhibit complex flow behaviors due to the possible interaction among the components.

Reference

1. Azaizeh H, Fulder S, Khalil K, Said O. Fitoterapia. 2003; 74:98-108.
2. Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS. Diabetes Care. 2003; 26:1277-1294.
3. Chopra A, Doiphode VV. Medical Clinics of North America. 2002; 86:75-89.
4. Muthu C, Ayyanar M, Raja N, Ignacimuthu S. J Ethnobiol Ethnomed. 2006; 2:43.
5. Altuntaş E, Özgöz E, Taşer ÖF. J Food Engineering. 2005; 71:37-43.
6. Al-Fatimi M, Wurster M, Schröder G, Lindequist U. J Ethnopharmacol. 2007; 111:657-666.
7. Khillare B, Shrivastav TG. Contraception. 2003; 68:225-9.
8. Ghosh R, Kamboj VP, Singh MM. Contraception, 2001; 64(4):261-269.
9. Rakoff AE, Feo LG, Goldstein L. Am. J Obstet. Gynecol. 1944; 47:467-494.
10. Hussain A, Ahsan F. J Controlled Release. 2005; 103:301-13.
11. Burgos MH, Linaires CER. Ultrastructure of the vaginal mucosa, In: E.S.E. Hafez, T.N. Evans (Eds.), The Human Vagina, North Holland Publishing Company, Eirldhown, The Netherland, 1978, 204-18.
12. Bonferoni MC, Giunchedi P, Scalia S. AAPS Pharm Sci. Tech. 2006; 7:141.
13. Jiao Y, Pang X, Liu M, Zhang B, Li L, Zhai G. Colloids and Surfaces B: Biointerfaces. 2016; 140:361-372.
14. Owen DH, Katz DF. Contraception. 1999; 59:91–95.
15. Bhalaria M, Naik S, Misra AA. Indian J Exp. Biol. 2009; 47(5):368-75.
16. Sera UV, Ramana MV. The Indian Pharmacist. 2006; 73:356-360.
17. Nappinnai M, Pakalapati S, Arimilli R. Indian Drugs. 2006; 43:513-15.
18. Shinde U, Pokharkar S, Modani S. Ind. J Pharma Sci, 2012; 74(3):237-247.
19. Hassan EE, Gallo JM. Pharm. Res. 1990; 7:491-495.
20. Pham AT, Lee PI. Pharm. Res. 1994; 11:1379–1385