FORMULATION AND EVALUATION OF VAGINAL DRUG DELIVERY SYSTEM FOR LOCAL ACTION

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Abstract:

In this study we developed mucoadhesive vaginal drug delivery system of Propranolol for spermicidal action. Here we used Na alginate and guar gum as a mucoadhesive polymers and propyl paraben and methyl paraben used as a preservative. Various parameters were evaluated: %yield, drug content, pH, viscosity, bioadhesion strength were studied and %cumulative drug release. The % yield of the gel formulations F1-F8 was found to be in the range of 93.4±0.06 to 99.6±0.05%. The drug content of the gel formulations F1-F8 was found to be in the range of 26.37±0.04 to 28.49±0.13 mg. The viscosity of the gel formulations F1-F8 was found in the range of 9.67±0.06 to 19.02±0.13 Pas. The bioadhesion strength of the gel formulations F1-F8 was found in the range of 16.8±0.08 to 27.2±0.08 gm. Formulation containing 4 gm guar gum (F8) showed better controlled release than the other seven formulations up to 56 hrs.

Key words: Propranolol hydrochloride; Vaginal drug delivery system (VDDS); Sodium alginate; Guar gum.

Introduction:

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. 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. The vaginal route appears to be highly appropriate for bioadhesive drug delivery systems in order to retain drugs for treating largely local conditions, or for use in contraception. To prolong the residence time in the vaginal cavity, bioadhesive therapeutic systems have been developed in the form of semisolid and solid dosage forms. The most commonly used mucoadhesive polymers are synthetic polyacrylates, polycarbophil, chitosan, cellulose derivatives, pectin, tragacanth, carrageenan and sodium alginate.[1]

A gel is a semisolid system of at least two interpenetrating phases: a gelling agent and a liquid. Gels that contain water are called hydrogels, while that contain an organic liquid are

called organogels. Hydrogels in the broad sense include the matrix of water-soluble materials such as cellulose derivatives and natural gums. These pseudohydrogels swell infinitely and the component molecules dissolve from the surface of the matrix. Drug molecules are released through the spaces in the network and also by the dissolution and/or disintegration of the matrix. Mucoadhesive polymers of natural, semisynthetic or synthetic origin are able to form hydrogels. In the simplest case the drug is dispersed in a mucoadhesive polymer which swells in the presence of water and exhibits bioadhesive properties.[2]

Among all vaginal formulations, gels are easy to manufacture, comfortable and have the ability to spread onto the surface of mucous and to achieve an intimate contact with vaginal mucosa. Vaginal gels are semisolid, three dimensional, polymeric matrices comprising small amounts of solids, dispersed in relatively large amounts of liquid, yet possessing more solid-like character. Moreover, because of their high water content and their rheological properties, they present the further advantage of a hydrating and lubricating action, which is particularly useful in pathological situations characterized by dryness of the vaginal mucosa. In particular, for drugs designed for gynaecological use, a bioadhesive gel able to ensure prolonged contact between the active ingredient and the vaginal mucosa and gradual release of that ingredient over long time.[3]

Propranolol is a non-selective β blocker, has been widely used for the treatment of hypertension, but it also possesses the membrane stabilizing activity of short latency. The membrane stabilizing activity is responsible for inhibition of sperm motility, rather than its β blocking potential. 0.3 mM concentration of Propranolol hydrochloride inhibits sperm motility by 50%. Thus it produces a good contraceptive effect.[4]

Materials and methods:

Propranolol hydrochloride and sodium alginate was purchased from Balaji Drugs, Gujrat. Guar gum, methyl paraben, propyl paraben, citric acid and disodium hydrogen phosphate were obtained from Central Drug House Pvt. Ltd., New Delhi.

Methods:

Pre-formulation studies of drug including organoleptic properties, melting point and flow properties were studied.

Preparation of bioadhesive vaginal gel:

Propranolol hydrochloride gel formulations were prepared using sodium alginate and guar gum as gelling agents. Gelling agent was dispersed in small quantity of citrate phosphate buffer [0.1(M), pH 4] and stored overnight to ensure complete hydration. The drug was initially dissolved in a mixture of PVP K30 and water (5:3) and added to polymer dispersion. Methyl paraben and propyl paraben were also added slowly with continuous stirring. The final weight of the gel was adjusted to 100 gm with citrate phosphate buffer [0.1(M), pH 4] (Table 1). Entrapped air bubbles were removed by keeping the gels in vacuum desiccators.

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:

$$Y=\{P_m\text{-}Z_g\}/T_m[P+I_g]\times 100,$$

Where Y = yield, P_m = practical mass, Z_G = vaginal gel, T_m = theoretical mass, P = polymer and I_g = ingredients.[6]

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 measurements of pH of each formulation were replicated three times.[5]

Syringibility: Syringibility study was carried out by using a 22 gauze needle.[8]

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 spectrophotometerically (Model – UV-1800 Pharmaspec, Shimadzu, Japan) at 290 nm.[5]

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.[5]

Determination of spreadability:

Spreadability study was carried out by transferring the 6 gm of gel formulation to the center of a glass plate and compressed under several glass plates having wt 100±5 gm each after every 1 minute and the spread diameters recoded each time.[8]

Extrudability study:

In conducting the test, a closed collapsible tube containing above 20 gm of the gel was pressed firmly at the crimped end and a clamp was applied to prevent any rollback. The cap was removed and the gel was allowed to extrude until the pressure was dissipated.[5]

Bioadhesion measurement:

Isolated goat vaginal tissue collected from local meat shop was cleaned and then separated from the supporting muscular and connective tissues taking care to maintain integrity of mucosa by kept in saline water, and kept at 0°C till further use. Before experiments, goat vaginal tissue was thawed in normal saline. The bioadhesion measurement was performed using a modified balance method intact with freshly excised goat vaginal mucosal membrane as an *in vitro* model. The two pans of physical balance were removed.

Right pan was replaced with a 100 ml beaker and on left side, a glass slide was hanged. For balancing the assembly, a weight of 20 gm was hanged on left side. Another glass slide was placed below the hanged slide. 1 gm of gel was placed between two vaginal membrane faces. Little pressure was applied to form bioadhesion bond, and then slowly drop of water was added on right side beaker, till the gel was separated from one face of vaginal membranes attached. Volume of water added was converted to mass. That gave the bioadhesive strength of gel in gm. An initial investigation examined the reproducibility of the system using three same formulations.[8]

Partition coefficient determination:

An equal volume from n-octanol and citrate phosphate buffer pH 4 were mixed and saturated with each other for 24 hrs, after 24 hrs when the two phases were separated then it was used for further. Certain weight of either the drug or an equivalent weight of the gel was dissolved in 10 ml of the aqueous phase to give the concentration of 0.5 mg/ml. The final solution transferred to a stoppered glass bottle. The final solution transferred to a stoppered glass bottle containing 10 ml of n-octanol. The systems were agitated in a thermostated water bath at 37±1°C for 24 hrs, the phases were then separated, the aqueous phase was filtered and the concentration of the drug was determined spectrophotometrically at 290 nm against a blank solution prepared in an analogous manner. The concentration of the drug in octanol was calculated from the difference between the initial and final concentrations of the drug in the buffer phase. The partition coefficient was calculated according to Nernst equation.

$K = C_{org}/C_{aqu.}$

Where: K = partition coefficient, $C_{org.}$ = concentration of the drug in organic phase, C_{aqu} is the concentration of the drug in buffer.[7]

***In vitro* drug release:** The *in vitro* release of drug was determined from different vaginal gel formulations using a dialysis bag prepared by cellophane membrane placed in the release medium. A cellophane membrane cut to suitable size ie. 3 cm diameter, boiled in distilled water for 1 hr soaked in absolute alcohol for half an hour and stored in citrate phosphate buffer pH 4 for 24 hrs before use. 6 gm of gel formulations were packed into the cellophane membrane bags (50 mm). The release medium was 100 ml citrate phosphate buffer pH 4 containing 1% tween 80, providing sink conditions for Propranolol hydrochloride. The medium was maintained at 37°C and stirred at 100 rpm. At various time intervals (1 hr), 5 ml of dissolution fluid was collected. Levels of drug in the samples were analyzed with the UV spectrophotometer at 290 nm.[6]

Accelerated stability study:

Stability studies were performed according to ICH guidelines. The formulations were stored at room temperature and accelerated storage conditions at 45±1°C for a period of 3 months. The samples were analyzed for drug content by UV spectrophotometer at 290 nm.[5]

Results and discussion:

Table 1: Formulations of Propranolol bioadhesive gel:

Formulation code	Drug (mg)	Sodium alginate (gm)	Guar gum (gm)	Methyl paraben (gm)	Propyl paraben (gm)
F1	500	1	-----	0.4	0.6
F2		2	-----		
F3		3	-----		
F4		4	-----		
F5		-----	1		
F6		-----	2		
F7		-----	3		
F8		-----	4		

Table 2: Pre-formulation parameters of Propranolol hydrochloride:

Sl. No	**Characters**	**Inference**
1.	Nature	Crystalline powder.
2.	Colour	White
3.	Odour	Odourless
4.	Taste	Slightly bitter taste
5.	Melting point	165ºC
6.	Solubility- In water In acetone In methanol In ethanol In chloroform	 Practically insoluble Fully soluble Soluble Soluble Soluble
7.	Bulk density	0.65±0.03 gm/cc
8.	Tapped density	0.55±0.02 gm/cc
9.	Carr's index	19.23±0.12
10.	Hausner's ratio	1.24±0.03 Good flow
11.	Angle of repose	26.5º±0.05
12.	Assay	99.1%

Table 3: Physical appearance, pH, %yield and drug content of formulations F1−F8

Formul.ⁿ code	Physical appearance	pH#	%yield#	Drug content#
F1	Light reddish cream	4.09±0.11	99.6±0.05	28.49±0.13
F2	Reddish cream	4.11±0.06	98.7±0.11	27.94±0.05
F3	light brown emulsion	4.06±0.11	97.9±0.04	27.27±0.08
F4	light brown emulsion	4.11±0.08	96.4±0.06	26.52±0.12
F5	Dull white emusion	4.04±0.05	96.4±0.05	28.02±0.03
F6	Dull white ointment	4.06±0.08	97.7±0.13	27.81±0.05
F7	White thick ointment	4.09±0.06	95.6±0.02	26.85±0.11
F8	Yellowish cream	4.11±0.07	93.4±0.06	26.37±0.04

#Mean±SD (n=3)

Table 4: Viscosity, Bioadhesion strength, syringibility and extrudability study of formulations F1-F8

Formul.ⁿ code	Viscosity# (Pa*s)	Bioadhesion strength# (gm)	Syringibility	Extrudability
F1	9.67±0.06	16.8±0.08	**	*
F2	11.82±0.04	18.1±0.04	**	*
F3	14.35±0.08	19.8±0.02	**	*
F4	15.02±0.05	21.3±0.12	**	*
F5	15.11±0.05	23.1±0.11	*	**
F6	17.32±0.07	24.3±0.06	*	**
F7	18.67±0.02	26.1±0.02	*	***
F8	19.02±0.13	27.2±0.08	*	****

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

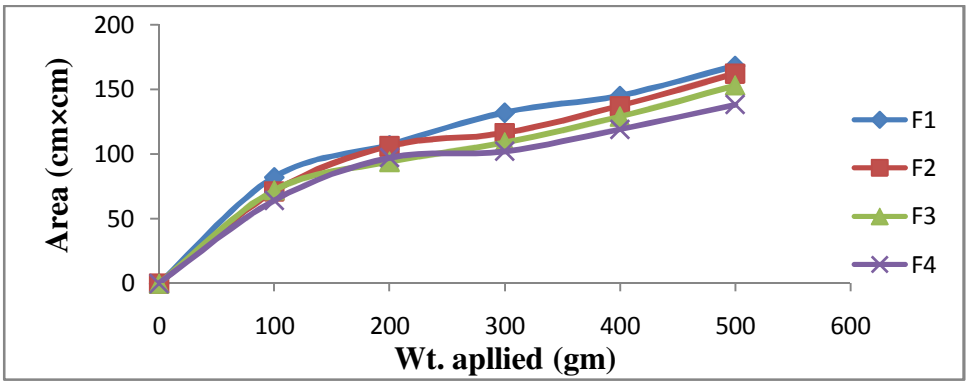

Figure 1: Spreadability of mucoadhesive vaginal gel formulations F1-F4

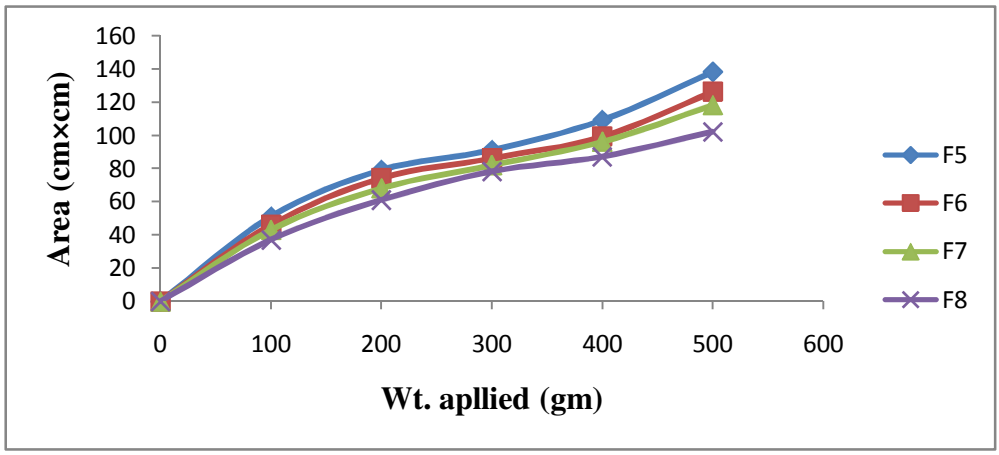

Figure 2: Spreadability of mucoadhesive vaginal gel formulations F5-F8

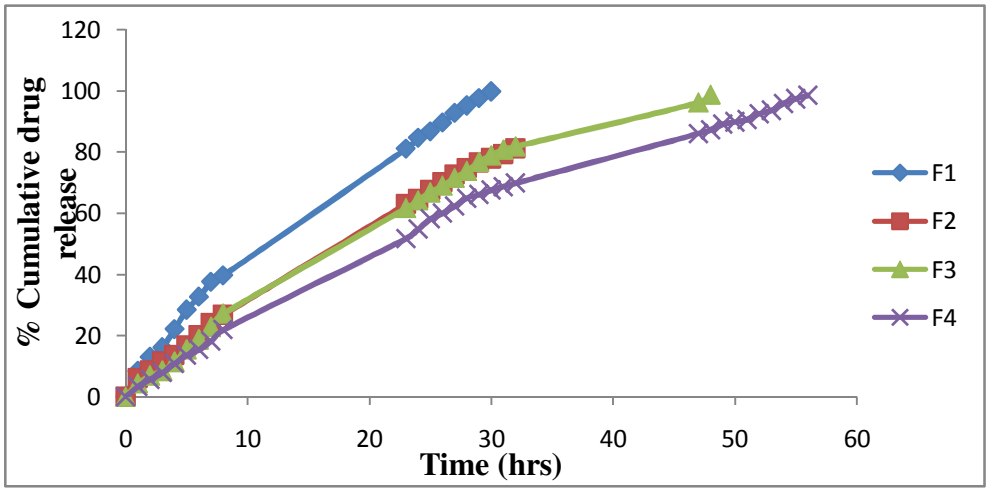

Figure 3: *In vitro* drug release profile of formulation F1–F4

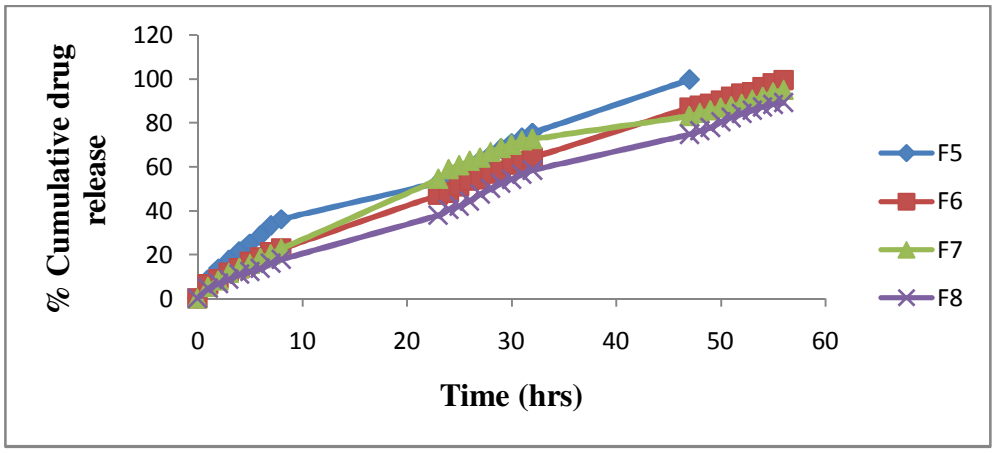

Figure 4: *In vitro* drug release profile of formulation F5–F8

Table 5: Stability studies of best forfulation

Time (months)	pH#	Syringability	Extrudability	Drug content# (mg)	%CDR
1	4.11±0.07	*	****	26.37±0.04	89.1605992
2	4.65±0.07	*	***	24.11±0.11	90.2331567
3	5.10±0.07	*	**	22.46±0.14	91.4465787

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

In this study bioadhesive vaginal gel of Propranolol hydrochloride with different amounts of sodium alginate and guar gum were prepared and prolonged release of the drug was demonstrated. The compatibility between the drug and polymers were confirmed by IR spectrophotometer. The physicochemical parameters and the release characteristics were studied. The pH, %yield and drug content of the gel formulations F1- F8 was found to be in the range of 4.04±0.05 to 4.11±0.08, 93.4±0.06 to 99.6±0.05 and 26.37±0.04 to 28.49±0.13 respectively (Table 3) from this results we can say that no significance variation observe in cange in concentration of polymers. The bioadhesion strength of the gel formulations F1-F8 was found to be in the range of 16.8±0.08 to 27.2±0.08 gm (Table 4) from this result we can say that increasing in polymers concentration bioadhesive strength increase. The optimum partition coefficient of either Propranolol hydrochloride alone or formulated into vaginal gel between n-octanol and phosphate buffer pH 4 was determined and found to be 3.12±0.14 at 37°C. It

was also observed that with increase in polymer concentration the syringibility becomes difficult but the extrudability improved. In %CDR it was found that formulation containing 4 gm guar gum (F8) showed better controlled release than the other seven formulation up to 56 hrs, it is due to increase in polymers concentration.

Conclusion:

In conclusion, *in vitro* drug release of Propranolol hydrochloride 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 56 hrs. The formulation F8 having 4% 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 Propranolol hydrochloride for effective contraception.

References:

1. Hussain A, Ahsan F. The vagina as a route for systemic drug delivery. J Controlled Release 2005;103: 301-13.
2. Patil SA, Rane BR, Bakliwal SR, Pawar SP. Pragmatic hydrogels. Int J Res App Pharm 2011; 2(3): 758-66.
3. Bonferoni MC, Giunchedi P, Scalia S, Rossi S, Sandri G, Caramella C. Chitosan gels for the vaginal delivery of lactic acid: relevance of formulation parameters to mucoadhesion and release mechanisms. AAPS Pharm Sci Tech 2006; 7(4): 1-8.
4. Tasdighi E, Azar ZJ, Mortazavi SA. Development and *in vitro* evaluation of a contraceptive vaginoadhesive propranolol hydrochloride gel. Iranian J Pharm Res 2012; 11(1): 13-26.
5. Nayak SB, Rout PK, Nayak UK, Bhowmik BB. Development and characterization of bioadhesive gel of microencapsulated metronidazole for vaginal use. Iranian J Pharm Res 2010; 9(3): 209-19.
6. Chatterjee A, Bhowmik BB, Thakur YS. Formulation, *in vitro* and *in vivo* pharmacokinetics of anti-HIV vaginal bioadhesive gel. J Young Pharm 2011; 3(2): 83-89.
7. Ramadan AA. Formulation and evaluation of bioadhesive gels containing miconazole nitrate. J App Sci Res 2008; 4(9): 1052-65.
8. Yellanki SK, Narella NK, Goranti S, Deb SK. Development of metronidazole intravaginal gel for the treatment of bacterial vaginosis, effect of mucoadhesive natural polymers on the release of metronidazole. Int J Pharm Res Dev 2010; 2(3): 1-6.