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Development of Novel Sustained Release Bioadhesive Vaginal Tablets of Povidone Iodine

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Iodine has long been used as an antiseptic for the prevention and treatment of vaginal infections. The present study was aimed at the development of rapidly disintegrating, bioadhesive and sustained release vaginal tablets of an iodophore, polyvinylpyrrolidone (povidone iodine), their evaluation and comparison with the marketed formulations. The formulation development included drug-excipient compatibility studies, optimization of performance parameters like disintegration time, bioadhesion and drug release profile and comparison of physical properties and performance parameters with the marketed formulation. The developed formulation provided a sustained release of polymer complexed iodine (up to 8 hrs), rapid disintegration (< 1 min.), desired bioadhesive properties and retention for a prolonged time.

Keywords vaginal delivery; iodophores; bioadhesive; sustained release

INTRODUCTION

Iodine has long been used as an antiseptic for prevention and treatment of a wide range of infections. However, its popularity as an anti-microbial agent has been limited by a number of undesirable factors like irritation, sensitization, staining properties, low water solubility and high vapor pressure (Block, Roche, Soine, & Wilson, 1986). In early 1950's, the "*taming of iodine*," i.e., complexation with inert polymers led to a class of new compounds, known as iodophores (Shelanski, 1956). Inert polymers like polyvinylpyrrolidone (Betadine®), Poloxamer (Prepodyne®), undecolynium chloride (Virac®) and poly-*N*-vinyl lactam and dextrin are often used in such iodophores. Povidone iodine, a chemical complex of poly (vinyl-2-pyrrolidinone) with elemental iodine, is the most commonly used iodophore.

Besides the antimicrobial activities, povidone iodine also possesses spermicidal activities (Shanbrom, 1996) and is also indicated for infectious vaginitis of all etiology including trichomoniasis, candidiasis, *Gardnerella* infection, specific, nonspecific, and/or mixed vaginitis. Several vaginal dosage forms of povidone iodine are available in market in different countries. These include tablets/pessaries, solutions, ointments and creams indicated for specific and nonspecific vaginitis.

The activity of povidone iodine *per se* has been related to reservoir effect for free iodine (Adham & Gilbert, 1986) and its antimicrobial effect is entirely due to the free unbound iodine. When administered in vivo, due to high vapor pressure, susceptibility to evaporation and inactivation in living tissues, the amount of free active iodine may be less than that required for activity. Hence, in order to achieve desired levels in the cervico-vaginal area, it will be advantageous to deliver iodine in small amounts in a consistent manner.

Conventional vaginal drug delivery systems have limitations of low residence time and leakage from the cavity (Robinson & Bologna, 1994) which causes messiness, discomfort and inconvenience leading to poor patient compliance and hence loss of therapeutic efficacy (Joglekar, Rhodes, & Danish, 1991). The dose of a drug in vaginal formulations is much higher than that required for desired biological activity. Most of the marketed vaginal tablets contain 200 mg povidone iodine per unit dose and semisolids contain 2% w/w povidone iodine.

Recently, there has been an increased interest in novel vaginal drug delivery systems with special emphasis on bioadhesive and sustained release systems. The sustained release bioadhesive dosage forms have advantages such as prolonged retention and constant local drug level at the site of application,

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thus reduction in dose and dosing frequency and hence, increased patient compliance (Bouckaert, Temmerman, Voorsepoels, Vankets, Remon, & Dhont, 1995).

The objective of the present study was to develop rapidly disintegrating, sustained release, bioadhesive tablets of povidone iodine, evaluation of physical and performance parameters and their comparison with marketed formulations. Stability studies were conducted for the optimized formulation.

MATERIALS AND METHODS

Chemicals, Excipients and Marketed Products

Povidone-iodine IP (Batch No. 0204011) (coded as PI), was procured from UniLab Chemicals and Pharmaceuticals Pvt. Ltd., Mumbai, India. The drug was tested for identity and was used as received. Chemicals and reagents for preparation of buffers, analytical solutions, and other general experimental purposes were obtained from various commercial sources and were of analytical grade.

All the excipients used in formulation development were either GRAS (generally regarded as safe) listed or were approved for vaginal administration, and were procured from local pharmaceutical excipient suppliers.

Marketed products used for comparison include Betadine® vaginal pessaries (Win-Medicare Limited, New Delhi, India), Pivipol® vaginal tablets (AR-Ex Laboratories Pvt. Ltd., Mumbai, India), and Wokadine® vaginal pessaries (Wockhardt Limited, Aurangabad, India).

Analytical Method Development and Validation

PI contains iodine in three different forms (free iodine, available iodine and the total iodine). Several different analytical techniques such as titrimetry, ultraviolet (UV) spectroscopy and high performance liquid chromatography (HPLC) are available for their estimation (Barabas & Brittain, 1998; Ohshiro, Hokama, & Hobara, 1997; United States Pharmacopeia 24 and National Formulary 19, 1999). Selection of analytical method was done from these methods for drug assay, drug compatibility studies and release studies. Since the titrimetric method is a pharmacopoeial method for PI estimation, (British Pharmacopeia, 2000; Indian Pharmacopeia, 1996; United States Pharmacopeia 24 and National Formulary 19, 1999) it was used for assay of drug contents in the formulation. UV spectrophotometry and HPLC were employed for the drug release studies and drug compatibility studies, respectively, and were validated for various parameters.

Titrimetric Method

Titrimetric method (IP 96, BP 2000 and USP XXIV) was used for determination of available iodine. The procedure involved titration of 0.02 N sodium thiosulfate with PI solution using starch as an indicator. For sample preparation one tablet ($n = 3$) was dissolved in 10 mL (for marketed formulation) and in 40 mL of water (for *in house* formulation). The resulting solution was titrated with 0.02 N sodium thiosulfate previously standardized with potassium dichromate solution. Towards the end of titration (when color of solution becomes pale yellow), 3 ml of starch solution was added. The volume of sodium thiosulfate used was recorded when solution became colorless (end point).

UV Spectrophotometric Method

A UV-Vis scan of PI in presence of potassium iodide (5% w/v initially) was recorded over a range of 200 nm to 800 nm on a UV spectrophotometer (DU 6401). Two absorbance maxima with λ_{max} at 288 nm and 355 nm were obtained. Reports have already been published for estimation of PI using both the wavelengths (Adham & Gilbert, 1986). Since spectral interferences were observed in near UV range, a λ_{max} of 355 nm (far UV region) was selected as analytical wavelength.

Sample Preparation

Stock Solution

A 100 μg/mL stock solution was prepared by dissolving 10 mg of accurately weighed PI in acetate buffer solution (pH 5.0) in a 100 mL volumetric flask.

Standard Solutions

Standard solutions of 8, 15, 30, 50, 70, and 88 μg/mL of PI (corresponding to 10–110% of drug release concentration) were prepared in triplicate by appropriate dilutions of stock solution with the buffer solution.

Method Validation

The method was validated for specificity by determining the interference (if any) in presence of excipients, present in the final formulation. Linearity was determined by analyzing six standard drug solutions (8, 15, 30, 50, 70, and 88 μg/mL) in triplicates. The correlation coefficient, percentage intercept, and percentage agreement were determined. The precision of the method was assured by calculating percentage relative standard deviation (% RSD) and percentage deviation (agreement) of three replicates (each of 30, 50, and 70 μg/mL) from standard concentrations. For intra-day variation, calibration curve was prepared thrice on same day. The procedure was further repeated on two consecutive days to determine inter-day variability. Percent RSD of slopes and intercepts were calculated. Method was validated for accuracy and recovery by determining drug content in presence of excipients (present in final formulation). For this purpose 20 mL of PI solution (10 mg/mL) was added to a dispersion of excipients to obtain a final concentration of 2 mg/mL representing a total of 200 mg in 100 mL. The dispersion was filtered and filtrate was used for estimation of PI contents after appropriate dilution. Same procedure was repeated in absence of excipients and percentage recovery was calculated to determine accuracy of the method.

Solution stability was determined at 0.2 mg/mL and 2 mg/mL (corresponding to 10–100% drug release concentrations respectively). For both concentration levels, samples were stored in triplicate at room temperature, 37°C and refrigerated conditions and were analyzed after 8 and 12 hr.

HPLC Method

A reverse phase High Performance Liquid Chromatography (HPLC) method of analysis was developed for drug-excipient compatibility studies. Briefly, the HPLC instrument (SCL-10A VP, Shimadzu Corporation, Japan) consisted of a pump (LC-10AT VP, Shimadzu Corporation, Japan), online degasser (DGU-14A, Shimadzu Corporation, Japan), an auto injector (SIL-10AD VP, Shimadzu Corporation, Japan), C_{18} column (Water Spherisorb ODS2, 250 mm × 4.6 mm, 5 µm particle size, Waters, Ireland), a column oven (CTO-10A VP, Shimadzu Corporation, Japan) maintained at 30°C, a PDA detector (SPD-M10A VP, Shimadzu Corporation, Japan) and a data integrator (Class VP, Shimadzu Corporation, Japan). The mobile phase comprised of methanol: water in the ratio 70:30 with 1% w/v potassium iodide and was filtered through 0.45 µm nylon filters. Chromatography was performed at a flow rate of 1.0 mL/min. and the UV detection was carried out at a wavelength of 355 nm.

Formulation Development

The target formulation profile was decided on the basis of evaluation of marketed formulations of PI (Betadine® vaginal pessaries, Wokadine® vaginal pessaries and Pivipol® vaginal tablets). These formulations were procured from retail pharmacy and were evaluated for characteristics such as physical properties (size, shape, color, and odor), disintegration time and behavior, hardness, bioadhesion, viscosity and pH of the dispersion. Dissolution study of PI vaginal pessaries (Betadine® and Wokadine®) was also carried out to obtain release profile of marketed formulations.

Drug excipient compatibility studies were done by isothermal testing and the ratio of drug to the excipient was similar to that expected in final formulation. For each excipient, sets of four samples (drug-excipient blend) were prepared. One set was designated as control and stored in freezer until analysis. Three sets were subjected to thermal stress (50ºC) for 3 weeks. Two sets each of pure drug and pure excipients were also prepared and stored at same conditions of temperature as that of drug and excipient blends. The procedure involved accurate weighing of PI (about 200 mg) and required amount of excipient into 5 mL vials. The vials were then mixed on a cyclomixer to ensure thorough mixing of drug with excipient and were covered with aluminium foil, capped and sealed with parafilm. The stressed samples were stored in an oven at 50°C for 3 weeks. These were visually examined at weekly intervals for any apparent change in color and physical form. Samples were then analyzed in duplicate by HPLC method for PI contents to determine any incompatibility.

Selection of suitable granulation approach was done on the basis of time taken by tablet to disintegrate in 10 mL of simulated vaginal fluid. Only the excipients found compatible with drug (based on thermal and isothermal stress testing- drug excipient compatibility studies) were used to develop prototype formulations (Garg, Tambwekar, Vermani, Garg, Kaul, & Zaneveld, 2001). Since, starch gives color reaction with iodine; starch-based disintegrating agents such as sodium starch glycolate were avoided in the formulation.

The formulation comprised of bioadhesive polymers, disintegrants as well as diluents. Bioadhesive polymers were used to provide sustained release as well as bioadhesive properties while the disintegrants were used to disintegrate the tablet. Selected polymers (polycarbophil, hydroxypropylmethyl cellulose, carboxymethyl cellulose, xanthan gum, chitosan glutamate), disintegrants (polyplasdone, Ac-Di-Sol, hydroxypropyl cellulose [low viscosity]) and diluents (lactose, Granulac, Flowlac, sorbitol, microcrystalline cellulose) were tried in different combinations. PI and all excipients were passed through 60-mesh sieve (BSS, Scientific Engineering Corporation, India). All ingredients mentioned above, except magnesium stearate and HPC as binder, were mixed together for 10 min. The mixture was granulated with aqueous dispersion of HPC as binder. Wet mass was passed through BSS sieve #16 (Scientific Engineering Corporation, India), wet granules were dried at 50°C for 8 hr and dried granules were passed through BSS sieve #22. Dried granules were mixed with magnesium stearate for 10 min and the blend was compressed in the form of almond shaped tablets having an average weight of 1.25 g using a single stroke tablet-punching machine (Cadmach CMS-15, India) with almond shaped dies and punches designed specifically for preparation of vaginal tablets. For dry granulation, no binder was added to drug polymer blend and granules were prepared using Kalweka granulator. The disintegration time of the tablets was recorded in 10 mL of water.

Optimization of disintegration time, bioadhesion and drug release was carried out during the formulation development.

Evaluation of Povidone Iodine Tablets (PIT)

Each batch of tablets was visually inspected for surface characteristics and general tablet appearance. In addition, the following tests were conducted.

Assay

The marketed and the *in house* formulations were crushed, an equivalent of 200 mg of iodine weighed and extracted with distilled water. The drug content was then determined titrimetrically. All estimations were performed in triplicate.

Weight Variation and Hardness

For weight variation, 20 tablets were weighed individually and average weight was determined. Hardness of tablets was measured on a hardness tester (Erweka Instruments, Germany).

The force required to break tablets (n = 3) along the long axis was recorded. Thickness (n = 3) was measured using vernier caliper (Digimatic, Mitutoyo, Japan).

Disintegration Time

An *in house* developed method for the measurement of disintegration time, specifically for vaginal formulations, was utilized (Garg, Vermani, Kohli, Raghupati, Tambwekar, Garg, Waller, & Zaneveld, 2002). For this purpose, a tablet was placed in a disintegration assembly containing 10 mL of normal saline maintained at 37°C and stirred at 300 rpm using a magnetic stirrer. The tablet was considered to be disintegrated when it completely dissolved or separated into component parts or became soft such that the mass had no solid core which offered resistance to pressure with a glass rod. Disintegration time and behavior of disintegration were recorded (n = 6).

Viscosity

Viscosity of the tablet dispersion was measured using Brookfield viscometer (Model DV-III+, Brookfield Engineering Labs Inc.). A tablet was dispersed in 20 mL of water and filled in a sample holder of small sample adapter. Viscosity was measured using cylindrical spindle no. SC4-21 at a speed of 30 rpm (% torque- 10–90%) at a temperature of 37°C for 1 min. The measurements were done in triplicate and the data was processed using Rheocalc-32 (version 2.1) software.

Bioadhesion

Bioadhesion was measured on the basis of work done to break the adhesive bond between formulation and model membrane. Bioadhesive strength (BS) of vaginal formulations towards sheep vagina was measured using a calibrated Texture Analyzer (Model TA-XT2i, Stable Micro Systems, Garg et al., 2002). The analyzer was equipped with a 5 kg load cell and custom-made probes modified to hold model membranes horizontally. The sample was dissolved /dispersed in 3 mL of normal saline and 0.5 g was applied between model membranes. The model membranes used include cellophane membrane [hydrated with simulated vaginal fluid (SVF_M)] and the sheep vaginal mucosa. The membrane was mounted on custom made probes, which were previously calibrated to move at predetermined rate. During measurement, upper probe was lowered at a rate of 0.1 mm/sec, at a constant force of 0.25 N, until a contact with the membrane was obtained. The force was maintained for 5 min and the upper probe was allowed to rise upwards at a rate of 0.1 mm/sec. Each experiment was repeated five times. BS i.e. force required to separate membranes was taken as an indicator of bioadhesion.

The cellophane membrane, as the model membrane, was prepared by hydrating the cellophane with simulated vaginal fluid (SVF_M) for at least half an hour. The sheep vaginal mucosa was obtained from sheep vaginal tissue (*Ovis aries*, nondescriptive local breed) obtained immediately after the sacrifice of animals at slaughter house. Vaginal tissue was cleaned and separated from supporting muscular and connective tissues taking care to maintain the integrity of mucosa. The isolated tissue was frozen at –20°C until further use. Before experimentation, tissue was thawed in normal saline containing 0.1% w/v sodium azide as preservative. After thawing, vaginal tube was incised longitudinally and tied with a thread to the modified probes with its mucosal side exposed. Institutional Animal Ethics Committee (IAEC) NIPER approval was obtained for the use of isolated sheep vaginal tissue.

Retention Time

In vitro retention time was evaluated by using an *in house* developed assembly (Vermani, Garg, & Zaneveld, 2002). Intact sheep vaginal tissue was suspended in vertical position inside the assembly and the temperature was maintained at 27°C and humidity at 75% relative humidity (RH) to protect the tissues from drying out. An intact tubular piece of sheep vaginal tissue (approximately 10 × 3.5 cm; thawed in normal saline containing 0.1% w/v sodium azide) was suspended vertically with the help of a loop of wire and a stand. Tissue was surrounded with a cotton pad moistened with normal saline, further surrounded by aluminum foil in order to keep the tissue moist for the duration of experiment. A tablet was dispersed in 5 mL of SVF_M and introduced into isolated vaginal tube by means of a 10 mL syringe. A balance was placed below the suspending tissue to measure weight of tablet dispersion falling down under the effect of gravity. The weight of dispersion that fell from the vaginal cavity, as a function of time was recorded and the percent retained was determined based on percentage of dispersion expelled from the vaginal tract and calculated as:

$$\text{Percent retained} = 100 - \text{percent expelled}$$

The experiments were performed in triplicate.

Spreadability

Spreadability of tablet dispersion was measured using an *in house* assembly. The assembly consisted of two glass plates one of which was stationary. The other glass plate was placed over the stationary plate and connected by means of a nylon wire through a pulley to the texture analyzer. A tablet was dispersed in 3 mL of normal saline and 0.5 g of the dispersion was placed over a mark on the lower glass plate. The upper glass plate was placed gently and a weight of 20 g was placed above it. The plates were allowed to slide at a rate of 1 mm/sec for a total distance of 50 mm. The spreadability (n = 6) was measured as the maximum force required to slide the upper plate.

Drug Release Studies

A modified USP type II dissolution apparatus (paddle type) was used to carry out dissolution studies. For routine studies, 100 mL of buffer solution with 1% w/v potassium iodide was

used as the dissolution media; the temperature was maintained at 37.0 ± 0.5°C and the agitation rate was 50 rpm. Dissolution was run for 8 hours with sampling points at 0.5, 1, 2, 3, 4, 6, 8, hr for *in house* formulation, whereas, for the marketed vaginal pessaries the dissolution was carried over a period 8 hr with sampling points at 5, 15, 30, 45, 60, 90, 120, 240, 360, and 480 min. and were analyzed by UV spectrophotometric method at a wavelength of 355 nm. The experiments were performed in triplicate and the results were expressed in terms of cumulative percentage release vs. time.

Accelerated Stability Studies

The optimized formulation was studied for accelerated stability as per ICH requirements for Zone IV countries. Tablets were packed in 0.03 mm aluminium foil with polyethylene coating and stored in stability chamber maintained at 40 ± 2°C/ 75 ± 5% RH and were evaluated for visual changes, hardness, disintegration time, viscosity and release behavior (n = 3 each), bioadhesive force and strength (n = 5 each) at 1, 3, and 6 months.

RESULTS AND DISCUSSION

Analytical Method Development and Validation

Titrimetric Method

The percentage recovery of PI from marketed formulation and from *in house* formulation was compared using titrimetric method and a good percentage agreement was found between labeled claim and calculated amount. This method could not be used for the release studies as it was not able to give an accurate end point for samples with very small amounts of the drug. The titrimetric method was therefore, used only for assay of the drug contents as specified in USP/IP/BP (British Pharmacopeia, 2000; Indian Pharmacopeia, 1996; United States Pharmacopeia 24 and National Formulary 19, 1999).

UV Spectrophotometric Method

Method Validation. The method was found to be specific for PI in presence of tablet excipients. There was no shift in λ_{max} in the presence of excipients. A standard curve was constructed by plotting area under the curve against concentration of PI. Linearity of the method was observed in the concentration range of 8–88 µg/mL demonstrating its suitability for analysis in this range. Regression analysis showed, equation, y = 0.0098x + 0.01, with a correlation coefficient, (r^2 = 0.9998) and the value of percentage intercept (< 2% of response at 100% test concentration), indicating functional linearity between concentration of PI and absorbance. Results of repeatability are given in Table 1. UV spectroscopic method passed the intermediate precision of intra-day and inter-day variability as % RSD of slopes of calibration curves, when analyzed on same day (n = 3) and on 3 consecutive days, was within 2%. Results of intra-day and inter-day precision are given in Table 2.

TABLE 1
Results of Precision and Repeatability Test for PI by UV Method

Drug Concentration (µg/mL)	% Agreement	% RSD
30	100.84	1.75
50	100.67	1.14
70	100.84	1.24

TABLE 2
Results of Intra-Day and Inter-Day Precision

Parameter	Intra-Day Precision	Inter-Day Precision
Slope		
Average	0.0097	0.0098
% RSD	0	0.59
Intercept		
Average	0.014	0.012
% RSD	2.26	1.66

Recovery and accuracy of the method was established by spiking approach. The recovery value of 97.77% with 1.1% RSD value indicates that the method is accurate for PI in the presence of excipients. Analysis of samples shows that there was no change in drug content after 8 and 12 hr of storage at refrigerator, room temperature and 37°C (Table 3). % RSD and % agreement was calculated and the data suggests that solutions were stable under test conditions.

HPLC Method

The retention time for PI was found to be 3.2 min under the specified conditions and the method was found to be linear at the concentration range of 0.4 to 0.6 mg/mL. The correlation coefficient (R^2 = 0.999) and percentage agreement (99.18–100.28%) indicates functional linearity between concentration of PI and the area under the curve.

Appropriate method for drug analysis was selected from the three analytical methods for drug assay, drug compatibility studies and release studies. Although, titrimetric method is a pharmacopoeial method for PI estimation, (British Pharmacopeia, 2000; Indian Pharmacopeia, 1996; United States Pharmacopeia 24 and National Formulary 19, 1999), it could not be used for the release studies, since, the drug present in the formulation was very small and hence, resulted in inaccuracy of end point. Thus, this method was used for determination of assay of drug contents in the formulation.

UV spectrophotometry method deals with direct estimation of PI present in the solution. An added advantage of this method was addition of potassium iodide to PI solution that

TABLE 3
Solution Stability of PI

Time		8 hr			12 hr		
Storage Condition	Conc. (mg/mL)	Mean Absorbance	RSD	% Agreement	Mean Absorbance	RSD	% Agreement
Refrigerator	0.2	0.0863	1.39	98.28	0.0870	2.68	99.16
RT		0.0866	2.44	98.59	0.0861	1.01	97.97
37°C		0.0859	1.88	97.75	0.0856	3.536	97.35
Refrigerator	2.0	0.8000	0.22	99.92	0.7981	0.001	99.68
RT		0.7976	0.423	99.61	0.7910	0.011	98.77
37°C		0.7977	0.413	99.62	0.7870	0.011	98.27

increases stability of the PI solution. Potassium iodide converts free iodine present in solution to tri-iodide and higher polyiodide. Therefore, this method was employed for the drug release studies.

HPLC method was employed for drug compatibility studies and since it is more sensitive method as compared to UV spectrophotometric, this method was used for estimation of drug contents in drug-excipient compatibility samples.

Formulation Development

Formulation development was based on the evaluation for different physico-chemical properties of batches made with different excipient combinations and methods. Drug excipient compatibility studies indicated, on visual observation, no change in color and physical form. Results from thermal stress testing at 50°C for three weeks are summarized in Table 4. All the excipients were found to be compatible with the drug.

Initial trials were conducted to find the suitability of dry and wet granulation method for formulation development. Trials were conducted with different blends of disintegrants or superdisintegrants. The approach was to granulate drug and polymer together and then compress it with other excipients. With this approach, wet granulation was tried but binder solution was not able to granulate the powder blend which may be due to higher polymeric contents of powder blend. Subsequently, dry granulation approach was tried and the tablets showed good disintegration behavior and a DT of less than two minutes. Hence, this approach was used further for formulation development.

Combinations of polymers were tried to attain sustained release. The final formulation consisted of povidone iodine (16%), xanthan gum, chitosan glutamate, polyplasdone, Granulac, HPC and magnesium stearate. Xanthan gum and chitosan glutamate were used for imparting bioadhesiveness. A previous study conducted on these individual polymers showed good bioadhesion in vaginal simulated enviroments (Vermani et al., 2002). Polyplasdone was used as disintegrant since it has high capillary activity and high hydration capacity and thus exhibits good ability for rapid disintegration. HPC was used as binding agent, Granulac as diluent and magnesium stearate as lubricant.

TABLE 4
Percentage Recoveries of PI From Drug-Excipient Compatibility Study (Thermal Stress at 50°C for 3 Weeks)

Drug/excipients	Visual Observations	Recovery (%)
Drug	No change	98.99
Drug+Granulac	No change	97.21
Drug+Polyplasdone	Powder was light in color compared to control, no change in physical form	98.79
Drug+Ac-Di-Sol	No change	98.88
Drug+hydroxypropyl cellulose (low viscosity)	No change	100.92
Drug+xanthan gum	No change	94.11
Drug+chitosan glutamate	No change	94.27
Drug+magnesium stearate	No change	99.05

Evaluation of Povidone Iodine Tablets (PIT)

Assay

The assay contents of tablets were found to be 100.1 (0.97% RSD)

Weight Variation and Hardness

Weight variation of all batches was recorded, and all the batches passed the test (< 4%), according to the IP limits. The hardness of final batch was found to be 4.8 kP (*SD* = 0.77).

Disintegration Time

Dispersion of a formulation in vaginal fluid is important for its biological activity as well as to avoid inconvenience to the users. An ideal vaginal formulation should disperse very rapidly in the vaginal cavity. Official disintegration test for vaginal preparations requires a large volume of disintegrating fluid (4 L of water), whereas the vaginal cavity contains only a small volume (0.2–1.0 mL) of fluid (Owen & Katz, 1999). Hence disintegration of tablets was studied in 10 mL of the medium. Though even this amount seems to be more considering the fluid in the vaginal cavity, subject variations, physiological conditions of the subject, size of the dosage form and feasibility of experimentation in the lab, limited the volume to 10 mL and not lesser. The disintegration time of *in house* developed formulation (PIT) was found to be significantly less as compared to marketed formulation. The results are shown in Figure 1.

Viscosity

Viscosity is important for the retention of the formulation. Higher the viscosity, more likely the formulation is to be retained for longer period in the vaginal cavity. Viscosity of the PIT was found to be 3189.58 cp (spindle no.: SC4-21, % torque 55.3, shear stress, 257.15 D/cm^2, shear rate 0.93 sec^{-1}). The higher viscosity of the formulation might be due to high polymeric contents used. Using one-way Analysis of variance (ANOVA) the viscosity of *in house* tablets was found to be significantly higher than that of marketed formulation at $P < 0.05$ levels. The physico-chemical properties of PIT in comparison with marketed counterparts have been presented in Table 5. A picture of the dispersion of a single unit of PIT in 10 mL of water, in an inverted beaker has been presented in Figure 2, showing the viscous and the gel like structure formed after dispersion of the tablet.

Bioadhesion

The major limitation of vaginal dosage forms is leakage and expulsion from the cavity due to muscular contractions and self-cleansing action of vaginal tract. This limitation leads to discomfort, poor patient compliance and failure of desired therapeutic effects. Therefore, the optimal formulation should have minimal leakage and remain in vagina for prolonged period of time. This is obtained by incorporating bioadhesive properties in the formulation. In vitro method to measure bioadhesion is based on the principle of measuring the force required to break the adhesive bond between a model membrane (excised sheep vagina) and the test formulations. Bioadhesive strength of PIT was compared with that of marketed tablets of povidone iodine and found to be significantly higher (Figure 3).

Retention Time

Retention of a formulation at the site is directly related to bioadhesion and governs the release and activity of a formulation. Retention behavior of PIT and marketed formulations was studied and compared. Total weight of tablet dispersion expelled from the vertically suspended sheep vagina was recorded as function of time. Only 0.9 ± 0.7% of *in house* formulation was found to fall out of the vaginal cavity over a period of 24 hr where as in case of marketed formulations > 90% of applied formulation was expelled in less than 2 hr (Figure 4). Higher retention time of PIT is attributed to the incorporation of bioadhesive polymers in the formulation, which is likely to be reflected in better retention on in-vivo use of the formulation.

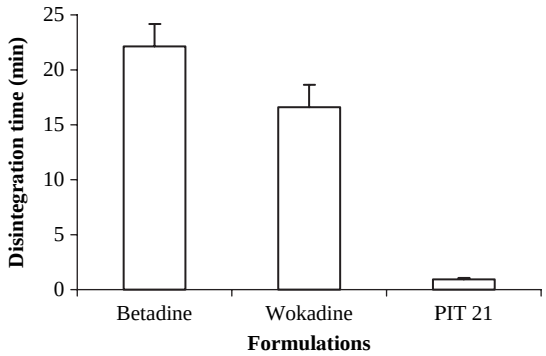

FIGURE 1. Comparison of disintegration time (M ± *SD*, *n* = 6) of marketed tablets of PI and PIT.

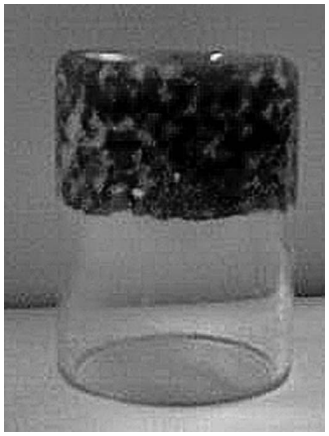

FIGURE 2. An inverted figure containing dispersion of PIT (1 unit in 10 ml of water).

TABLE 5
Physicochemical Properties of *in house* Developed Vaginal Tablets of Povidone Iodine (PIT) in Comparison With Marketed Vaginal Tablets of Povidone Iodine

Characteristics*	PIT	Betadine®	Wokadine®
Appearance	Brown, spotted surface	Light brown, spotted surface	Light brown, spotted surface
Size (L × W × T, in mm^3)	22.8 × 13.0 × 7.1	22.2 × 13.2 × 5.5	24.1 × 13.6 × 6.0
Shape	Almond	Almond	Almond
Weight (g)	1.25	1.35	1.38
Hardness (kP)	6.9	17.6	11.6
Disintegration mechanism	Fast disintegrating	Effervescence	Fast eroding
Viscosity (cPs) (tablet dispersion)	27650	2.72	2.46

*Mean (n=3).

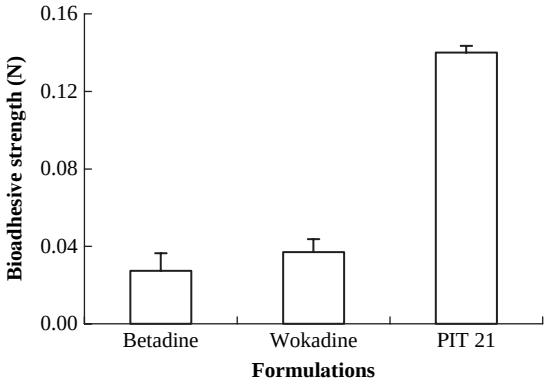

FIGURE 3. Comparison of bioadhesive strength ($M \pm SD$, n = 5) of marketed tablets of PI and *in house* developed PIT.

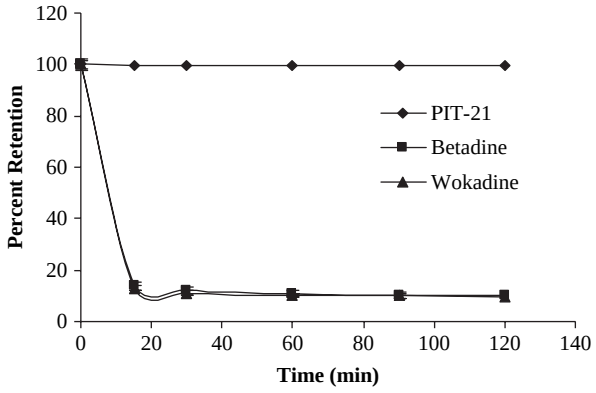

FIGURE 4. Comparison of retention behavior ($M \pm SD$, n = 3) of marketed tablets of PI and *in house* developed PIT.

Spreadability

Spreading force required for *in house* formulation dispersion was found to be 19.6 ± 1.12 g in comparison to 0.67 ± 0.30 g (n = 6) for marketed formulation (Betadine tablet®). Higher spreading values for *in house* formulation were attributed to its higher bioadhesion. Since marketed formulations possess little bioadhesive properties their dispersions are easier to spread, hence, spreading force required is less.

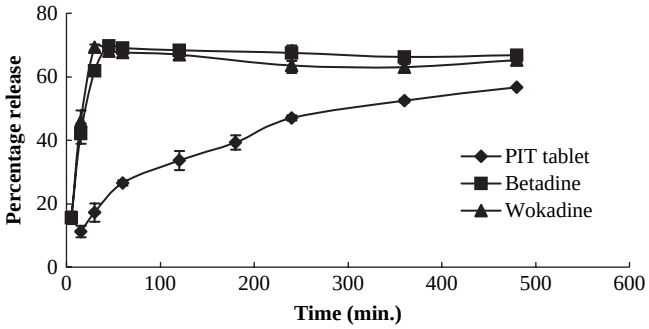

FIGURE 5. Comparison of dissolution profiles ($M \pm SD$, n = 3) of marketed tablets of PI and *in house* developed PIT.

Drug Release Studies

The dissolution studies of the formulations were conducted using modified USP Type II apparatus. Studies have been reported to carry out the drug release from vaginal formulations using dissolution media volume ranging from 10 mL to 1000 mL (Ceschel, Maffei, & Borgia, 2001; Valenta, Kast, Harich, & Bernkop-Schnurch, 2001). Some reports have also suggested use of 100 mL of the dissolution media for these studies for the vaginal formulations (Acarturk & Altug, 2001). The release profiles of marketed formulations and that of *in house* formulations were compared. The marketed formulations released the drug immediately with 80% release in an hour. On the other hand, PIT exhibited a prolonged release profile, releasing only 60% in 8 hr (Figure 5). The color of solution of marketed tablets in water faded after one and half hours indicating the evaporation of free iodine from solution whereas

TABLE 6
Comparison of Physicochemical Properties of PIT Before and After 6 Months of Accelerated Stability Studies

Parameter	Initial Values	After Exposure
Visual observation	Brown spotted surface	Slight yellowish in color
Hardness (kP)*	5.9 ± 1.1	4.89 ± 1.5
Disintegration time (s)*	60.6 ± 4.5	65 ± 7.5
Viscosity (cP)*	3189.5 ± 461	2868.75 ± 27.24
Bioadhesive force (N)#	0.1422 ± 0.048	0.1112 ± 0.018
Work of adhesion (Ns)#	1.5 ± 0.28	0.7808 ± 0.0780
Assay*	99.9 ± 1.94	98.9 ± 0.97

*Values expressed as $M \pm SD$, $n = 3$.
#Values expressed as $M \pm SD$, $n = 5$.

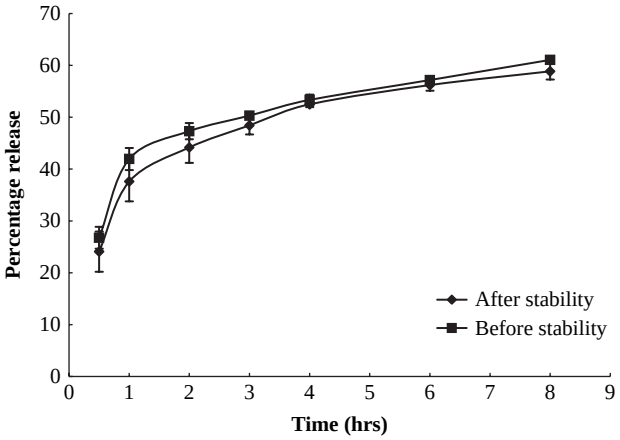

FIGURE 6. Dissolution profile of *in house* developed PIT before and after accelerated stability testing.

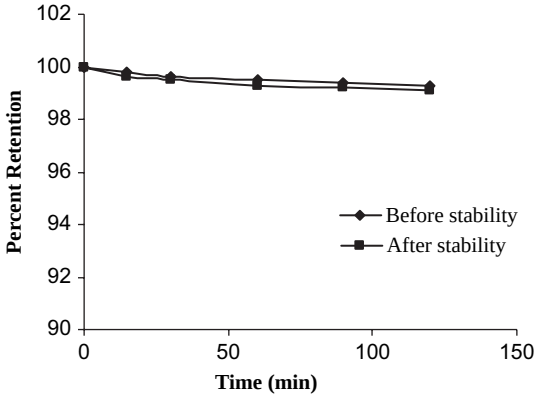

FIGURE 7. Retention profile of *in house* developed PIT before and after accelerated stability testing.

the color of dispersion of tablets of present invention in water persists for more than 4 hr, indicating the presence of free iodine in the dispersion for prolonged duration.

Accelerated Stability Studies

The stability studies were performed at 40°C and 75% RH and were analyzed at 1, 3, and 6 months and the results have been summarized in Table 6. Using one-way ANOVA, no statistically significant difference was found between the parameters evaluated except the work of adhesion. The dissolution and retention profiles of the formulation were found to be similar at the end of the stability studies (Figures 6 and 7). Since, the results were found to be comparable at the end of the stability testing; the formulations were found to be stable at the end of stability studies.

CONCLUSIONS

In the present study, novel bioadhesive and sustained release vaginal tablets of PI (containing 200 mg PI per unit) were developed. The tablets disintegrated rapidly (< 1 min in vitro), possessed significant bioadhesion and retention properties in simulated vaginal conditions, released PI over a period of 8 hrs or more and possessed acceptable mechanical and other physico-chemical properties. The dosage form developed is expected to take care of a lot of problems associated with the delivery of iodine to the vagina. Further, with appropriate in vivo studies and in vitro–in vivo correlation needs to be established.

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