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# Formulation and Evaluation of Mucoadhesive Liquid Pessaries of Acyclovir Sodium

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**ABSTRACT**

The present work is an attempt to formulate and evaluate In-situ gelling mucoadhesive liquid pessaries. The model drug chosen for the study was Acyclovir. Muco adhesive polymers such as Sodium alginate, Poly Vinyl Pyrrolidine (PVP), Carbopol and Methyl cellulose were used. Poloxamer 188 was the polymer used for gelation purpose. Poly ethylene glycol (PEG 6000) was used to modify gelation temperature. Mucoadhesive liquid pessaries of acyclovir were prepared by using cold method. Combinations of poloxamer, carbopol, sodium alginate, poly vinyl pyrollidine and methylcellulose were investigated as vehicles for different formulations. The prepared pessaries were evaluated for gelation temperature, mucoadhesive force, gel strength, spreadability and drug diffusion. Amongst the formulations prepared Acyclovir sodium mucoadhesive liquid pessaries prepared using 0.2% of Carbopol-934 shows the better mucoadhesive force (19500 dynes/cm$^2$), Spreadability (5.5 cm), and gel strength (80) with gelation temperature of 37°c.

**Keywords:** In-situ gelling, Muco adhesive liquid pessaries .

## INTRODUCTION

During the past 20 years, advances in drug formulations and innovative routes of drug administration have been made. The administration of drugs by transdermal or trans mucosal routes offers the advantage of being relatively painless. A conventional pessary is a medicated solid dosage form which melts or softens at body temperature. It is a favorable dosage form for infants, children and unconscious patients. (Zempsky WT *et al*., 1997) One major advantage of pessaries over other oral dosage forms is that the drugs given by pessaries do not undergo first pass effect in the gastro intestinal tract and the liver. Moreover, the pessaries are less painful and are most acceptable than parenteral forms. To solve the problems of conventional solid pessaries it would be desirable to develop a mucoadhesive liquid pessary which, Forms a gel at body temperature, has suitable gel strength not to be leaked out from anus after administration and, has a suitable bioadhesive force so as not to reach the end of the colon (Choi HG *et al*., 1998).

Liquid suppository is a liquid dosage form, which on insertion into the rectum (rectal suppository), Vagina (Vaginal suppository) or urethra (urethral suppository) converts into a gel (Frietas *et al.,* 1998).

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## MATERIALS AND METHODS

Acyclovir sodium was a gifted sample from Strides arcolabs Bengaluru. Poloxamer 188, Carbopol 934, Sodium alginate were obtained as gift samples from S.D. fine chem. Ltd, Mumbai. PVP K-30, Methyl cellulose, PEG 6000 were obtained as gift samples from Bross scientifics.

### PREPARATION OF INSITU GELLING SYSTEM

**Temperature induced gelling by cold method**

Acyclovir sodium and various amounts of excipients (given in the table 1) except poloxamer 188 were completely dispersed in distilled water with continuous agitation at room temperature. The mixtures were then cooled to 4° C to get a clear solution. Then poloxamer 188 was added slowly with continuous stirring. The dispersions were then stored in a refrigerator at 4° C overnight.

### EVALUATION OF PREPARED FORMULATIONS

**Measurement of gelation temperature**

Gelation temperature was assessed using the tube tilting method (Pisal *et al.,* 2004). 2 ml aliquot of gel was transferred to test tubes immersed in a water bath at 4°C and sealed with aluminum foil (Ramadan *et al.,* 2008). The temperature of water bath was increased in

increments of 1°C and left to equilibrate for 5 min at each new setting. The samples were then examined for gelation.

**Measurement of gel strength**

The gel strength was determined according to the method adopted by (Kim *et al*., 1998). 50 g of pessary was put in a 100 ml graduated cylinder and gelled in a thermostat at 37°C. The apparatus for measuring the gel strength (weight 35 g) was then placed into the liquid suppository. The gel strength was determined by the time in seconds the apparatus took to penetrate (sink) 5 cm down through the gel.

**Determination of the mucoadhesive force**

The mucoadhesive force, the detachment stress of the liquid suppositories was determined using a modification of the mucoadhesive force-measuring device used by (Choi *et al*., 2000). A section was cut from the fundus of rabbit rectum and instantly secured with the mucosal side out into each glass vial. The vials were stored at 36.5°C for 10 min. 1 vial connected to the balance and the other fixed with the poloxamer gel added and the height was adjusted so that the gel is placed between the mucosal sides of both vials. Water from a burette was allowed to fall in a beaker at a constant rate of 10 mg/sec. Increasing weight of water added gradually would detach the 2 vials. Mucoadhesive force, the detachment stress (dyne/cm²), is determined from the minimal weights of water that detached the 2 vials.

**Dissolution test**

Dissolution test was carried out using USP dissolution apparatus. 5 g Acyclovir sodium liquid suppositories was placed in a semi-permeable membrane tube. Both sides of the tube were firmly tied at its end to prevent leakage. It was then placed in dissolution tester at 36.5°C at 100 rpm using 900 ml phosphate buffer (pH 4.5) as the dissolution medium. At predetermined intervals, 5 ml samples were withdrawn and filtered. 5 ml of fresh buffer were added to the dissolution medium. The drug content of each sample was determined spectrophotometrically at 252 nm. (Valentina *et al.,* 2000).

**Measurement of spreadability**

1 gm of gel was placed on a slide and another slide was placed above that. A weight of 5 gm was placed on the slide and measure the distance spreaded by the gel using a scale after 5 minutes which gives its spreadability.

## RESULTS AND DISCUSSION

**Table.1 Composition of Different Formulations**

| Composition | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | F15 | F16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acyclovir sodium | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| PF-127 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| Methyl cellulose | 0.8 | 0.8 | 0.8 | 0.8 | - | - | - | - | - | - | - | - | - | - | - | - |
| Sodium alginate | - | - | - | - | 0.8 | 0.8 | 0.8 | 0.8 | - | - | - | - | - | - | - | - |
| PVP K-30 | - | - | - | - | - | - | - | - | 0.8 | 0.8 | 0.8 | 0.8 | - | - | - | - |
| carbapol | - | - | - | - | - | - | - | - | - | - | - | - | 0.2 | 0.2 | 0.2 | 0.2 |
| PEG 6000 | - | 0.2 | 0.3 | 0.4 | - | 1.3 | 1.4 | 1.5 | - | 2.0 | 2.1 | 2.2 | - | 2.2 | 2.3 | 2.4 |
| Distilled water | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |

**Table.2 Evaluations of the prepared formulations**

| S.No | Formulation code | Gelation temperature ($^0$c) | Muco adhesive force (dyne/cm$^2$) | Gel strength | Spreadability (cm) |
|---|---|---|---|---|---|
| 1 | F1 | 28 | 4700 | 18.5 | 6.2 |
| 2 | F2 | 33 | 4000 | 8 | 7 |
| 3 | F3 | 34 | 3900 | 5 | 7.5 |
| 4 | F4 | 36 | 3200 | 4 | 8 |
| 5 | F5 | 26 | 21000 | 59 | 4 |
| 6 | F6 | 32 | 16300 | 44 | 4.7 |
| 7 | F7 | 33 | 15100 | 37 | 4.8 |
| 8 | F8 | 35 | 12900 | 31 | 5 |
| 9 | F9 | 25 | 9400 | 71 | 3 |
| 10 | F10 | 31 | 6700 | 36 | 4.9 |
| 11 | F11 | 33 | 6300 | 32 | 5 |
| 12 | F12 | 36 | 5300 | 29 | 5.2 |
| 13 | F13 | 35 | 19500 | 80 | 5.5 |
| 14 | F14 | 37 | 16200 | 69 | 5.3 |
| 15 | F15 | 38 | 15000 | 53 | 5 |
| 16 | F16 | 39 | 14300 | 41 | 5.2 |

**Table.2 Drug release studies**

| S. no | Time | % drug release | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | F15 | F16 |
| 1 | 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 2 | 5 | 11.09 | 12.02 | 13.50 | 14.00 | 6.09 | 9.04 | 9.99 | 13.16 | 13.19 | 13.92 | 14.00 | 14.90 | 11.08 | 9.02 | 9.39 | 8.21 |
| 3 | 10 | 23.05 | 23.66 | 2550 | 26.07 | 12.64 | 18.98 | 19.54 | 25.25 | 24.65 | 25.86 | 27.10 | 28.17 | 21.34 | 19.78 | 19.44 | 17.26 |
| 4 | 15 | 34.87 | 35.43 | 36.60 | 38.74 | 22.66 | 29.72 | 30.05 | 37.86 | 38.57 | 39.43 | 41.40 | 42.84 | 32.65 | 29.62 | 28.15 | 26.85 |
| 5 | 30 | 47.80 | 48.56 | 49.86 | 51.43 | 28.79 | 35.12 | 36.54 | 50.22 | 51.50 | 52.96 | 56.46 | 57.53 | 38.78 | 35.14 | 34.44 | 32.21 |
| 6 | 45 | 55.43 | 56.66 | 59.75 | 60.48 | 36.99 | 44.25 | 45.22 | 59.32 | 61.23 | 62.26 | 68.85 | 69.88 | 47.98 | 45.22 | 45.12 | 43.33 |
| 7 | 60 | 65.02 | 65.09 | 67.86 | 69.53 | 41.43 | 52.81 | 54.93 | 67.96 | 68.82 | 69.09 | 75.96 | 76.63 | 56.42 | 53.85 | 52.83 | 50.97 |
| 8 | 75 | 72.2 | 72.86 | 76.43 | 77.32 | 44.77 | 59.68 | 60.56 | 75.05 | 75.20 | 77.16 | 82.33 | 83.42 | 64.76 | 60.67 | 59.46 | 57.14 |
| 9 | 90 | 80.09 | 81.43 | 85.30 | 85.98 | 49.06 | 66.00 | 68.64 | 79.32 | 79.39 | 80.73 | 86.20 | 87.88 | 72.04 | 67.02 | 66.54 | 64.22 |
| 10 | 100 | 86.00 | 87.50 | 91.50 | 92.60 | 53.00 | 71.02 | 74.56 | 82.46 | 84.34 | 85.90 | 91.14 | 92.54 | 77.02 | 72.02 | 71.34 | 68.22 |

**Fig.1 *IN VITRO* DRUG RELEASE OF F13**

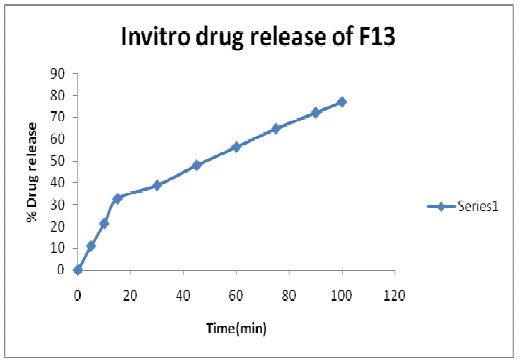
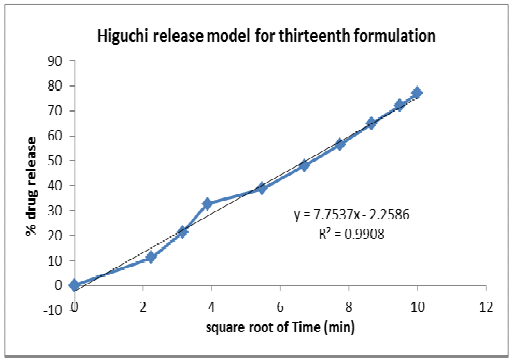



**Fig.2 Higuchi release model of F13**




## CONCLUSION

The cold method employed in the preparation of insitu gelling and mucoadhesive liquid pessaries was found to be effective. All the formulations except those which do not contain PEG 6000 meet the requirement of gelation temparature as per IP specifications. The formulation containing sodium aginate has shown highest mucoadhesive force of 21,000 dynes/cm$^2$. The formulation having carbopol 934 showed highest gel strength of 80 sec. Spreadability of all the formulations meets the requirement as per IP specifications. The formulation containing methyl cellulose showed more spreadability. Among all the formulations prepared, F4 consisting of methyl cellulose showed good drug release.

When comparison was made among the formulations regarding gelation temparature, gel strength, mucoadhesive force and spreadability, F13 was found to be the optimized formulation. Higher mucoadhesive force of formulation will lead to retention of liquid suppository in vagina. Ultimately the availability of acyclovir sodium will be improved.

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