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FORMULATION AND EVALUATION OF ACYCLOVIR LOADED DRUG BALLS FOR THE TREATMENT OF HERPES LABIALIS

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ABSTRACT: The purpose of analysis work was to develop and optimize drug balls of erythromycin estolate for oral tissue layer delivery of drug for quick delivery of drug and better bio-availability with the aim to treatment of infectious disease. Sodium alginate primarily based drug balls containing Acyclovir were ready by specific methodology. metal alginate, alkyl radical polysaccharide were elite on the premise of formulation of drug balls, mucoadhesive force, In-vitro drug unharness. A thirty two factorial design was utilized for preparation of drug balls whereby the concentration of sodium alginate, concentration of alkyl radical polysaccharide were elite as freelance variables whereas in vitro drug unharness and proportion permeation were the dependent variables. Drug balls were evaluated with relation to the share mucoadhesion, drug content, in-vitro drug unharness and permeation studies. F4 formulation was optimized with mucoadhesive force, permeation potency and In-vitro drug release. Drug balls were characterised by FTIR and DSC study. Stability study revealed that the formulation was found to be stable.

KEYWORDS: Acyclovir, Herpes Labialis, Antiviral, drug, In-vitro diffusion, drug balls.

I. INTRODUCTION

The most favored course to the affected person is oral direction and clinician alike within the amongst numerous routes of drug transport. However there are several disadvantages of oral management of medicines like degradation by enzymes in GI tract and hepatic frist skip. Further of this absovative mucosa taken into consideration as capacity website for drug taking.

Tranmucosal direction of drug delivery such as linings of mucosal, rectal, ocular, vaginal and oral cavity. It has many reward more than oral management for systemic drug delivery of medicines.

Mucosal medication delivery crosswise over mucosal coating of oral cavity offers an unmistakable preferred standpoint over the oral dosing course by maintaining a strategic distance from intestinal and hepatic first-pass effect.

MATERIALS AND METHODS

Acyclovir was purchased from Balaji chemicals Pvt.Ltd,Gujrat. Ethanol and Tween 80 were available from the central chemical store of Rajiv Academy For Pharmacy, Mathura. Distilled water was prepared freshly and used whenever require. All other chemicals used in the study were of analytical reagent grade.

Melting point determination

Capillary fusion process was used for determination of melting point. Capillary tube was fused at one end and sufficient quantity of drug sample was placed from the open end. The capillary then subjected to digital auto melting point instument. The temperature at which drug melted was recorded and compared with the literature value of Acyclovir.The above method was done in triplicate to average melting point.

UV Spectrophotometry

A) Acyclovir solution of 0.001% w/v was prepared in saliva. For absor ption maxima the solution was scanned in the range of 200-400 nm to determine absorption maxima (X). The observed absorption maxima was recorded and compared with literature value.

Calibration curve in Saliva

Stock solution of Acyclovir was prepared in saliva of concentration 10^g/ml. Aliquots of stock solution of drug were taken into a number of 10 ml volumetric flasks and diluted with saliva to get final concentration in a range of 1-6^g/ml. Absorbance of resulted samples were measured in a range 200-400 nm.

Calibration curve in ethanol-tween80 mixture(1:1)

Stock solution of Acyclovir was prepared in ethanol-tween80 mixture (1:1) of concentration 10^g/ml. Aliquots of stock solution of drug were taken into a number of 10 ml volumetric flasks and diluted with ethanol-tween80 mixture (1:1) to get final concentration in a range of 1-6^g/ml. Absorbance of resulted samples were measured in a range 200-400 nm.

Validation of analytical method

The analytical method has been validated in accordance with the category 1 test guidelines of the USP and the guidelines of ICH Q2A. The calibration curve linearity was determined in the range of 1-6p,g / ml for absorbance (y) versus concentration (x) of Acyclovir

Table 1- Formulation design for Acyclovir loaded drug balls

Formulation code	Amount of the drug(mg)	Sodium alginate (mg)	Ethyl cellulose (mg)	Sodium citrate (mg)	Ethanol: Tween80 (1:1)(ml)	Glycerol (ml)	Water (ml)	$Cacl_2$ solution
F1	250	33.33	50	8.33	0.33	1.33	3.33	2%
F2	250	33.33	16.66	8.33	0.33	1.33	3.33	2%
F3	250	33.33	33.33	8.33	0.33	1.33	3.33	2%
F4	250	50	50	8.33	0.33	1.33	3.33	2%
F5	250	50	16.66	8.33	0.33	1.33	3.33	2%
F6	250	50	33.33	8.33	0.33	1.33	3.33	2%
F7	250	66.66	50	8.33	0.33	1.33	3.33	2%
F8	250	66.66	16.66	8.33	0.33	1.33	3.33	2%
F9	250	66.66	33.33	8.33	0.33	1.33	3.33	2%

Preparation of Acyclovir loaded drug balls

After fusion and trituration, polymer (EC), sodium citrate and glycerin were mixed together and kept for 24 hours for hydration, the preparation was performed in varied batches. Then the drug was dissolved in mixture of ethanol and tween80(1:1) and added to the above hydrated phase Then the volume of glycerol and mixture was stirred at 50 rpm with three blade stirrer for 30 min to obtain a homogeneous dispersion of the drug. Now in another beaker, dissolve sodium alginate in distilled water. Now combine the solution of sodium alginate and above to formulate the drug solution. Now 10gm of calcium chloride dissolved in 500ml distill water in another beaker

Using a deep spoon take 5ml of drug solution and dip in calcium chloride solution the drug balls will start to formulate After completion of formation of drug balls remove drug balls from calcium chloride solution and put in distilled water to stop the process.

EVALUATION OF COMPLEX

In vitro drug release

The drug release from drug balls were determined by dialysis method , the drug ball of a batch was putted in beaker, containing 200ml artificial saliva. It was performed at 37+2^{o}C and 100rpm. Samples were collected at interval of 0, 10min, 20min, 30min, 45min, 1h, 1. 5 h, 2h, 3h, 4h, 5h, and 6hrs. and replaced with saliva solution. Samples were then analyzed at 285 nm to analyze the drug released in saliva.

Drug Content

Determination of drug content was one by homogenization of drug balls in 100ml saliva, filtered separately, the resultant solution was diluted suitably with saliva and analyzed by spectrophotometry at 285 nm (UV spectrophotometer, Shimadzu 1700 Japan). All readings were taken in triplicate.

Ex vivo permeation

In vitro penetration investigation of all Acyclovir stacked medication balls was completed utilizing created Franz dissemination cell comprising of contributor and receptor compartment isolated by mucosal film (obtained from nearby slaughter-house and utilized inside 2 hr. of butcher). Definition set in benefactor compartment and receptor compartment was loaded up with counterfeit spit and always mixed utilizing attractive stirrer. Giver and receptor chambers were isolated by mucosal film officially absorbed receptor medium-term before trial.

An equivalent volume of crisp fake spit was included into the receptor compartment after each testing. The experiments were performed in triplicate, and average were calculated.

Ex-vivo mucoadhesion Force

The plan's mucoadhesive strength on the instance of tissue (mucosal film) was dictated by mechanical assembly organized in our college techniques for mucoadhesive power estimation. The tissue pieces were placed away in saliva solidified and defrosted before use to room temperature. A tissue section (holding the mucosal-surface out) on the upper side of a glass-vial using a cyano-acrylate glue was confirmed during testing. Each exposed mucosal film's width was 1.5 cm. The vials were balanced and kept for 10 min at 37 °. The equalization was connected with one vial with a tissue region and another vial was attached to a stature-adjustable skillet.

Accelerated stability testing according to ICH Q1 A (R2) Guidelines

Quickened resistance testing was conducted in accordance with ICH Q1A (R2) regulations by maintaining drug balls at 40 + 2^0C temperature and 75 + 5 percent RH stickiness. The examples were taken back at 0, 30, 60, and 90 days and resolved the physical characteristics (surface, weight loss / gain, muco-adhesive strength, etc.). The zero-time experiments were used as checks.

Selection of optimized Formulation

Selection done on the basis of formulation which shows maximum drug release with optimum mocoadhesive force, maxi-mum drug content and maxi-mum ex - vivo permeation.

RESULT AND DISCUSSION

Melting point of Acyclovir was noted to be 134^{o}C-137 ^{o} C which complies with the literature value of 135^{o}C indicating the identity and purity of drug sample.

Spectrophotometric studies were performed in order to determine Vax of Acyclovir at different physiological pH i.e. Ethanol- Tween80 mixture and saliva.

In order to obtain standard calibration curve different concentrations in range of 1- 6^g/ml of stock solution in saliva was prepared.

Intra-day and inter-day precision value of % RSD between calibration curves with in day at different time point were found to be less than two, Which showed the intraday precision between calibration curves.The data showed that the drug in saliva and ethanol:tween mixture were stable during the study period and analytical method used were reliable.

Table 2- Spectrophotometric determination of Acyclovir

S.NO.	**Media**	**Experimental value(X,max)**
1.	Saliva	285nm
2.	Ethanol Tween80 mixture	285nm

Table 3- Calibration curve data of Acyclovir in Saliva

S.N.	**Concentration (^g/ml)**	**Absorbance+S. D.**
1	1	0.054+0.001
2	2	0.096+0.001
3	3	0.135+0.002
4	4	0.174+0.003
5	5	0.207+0.002
6	6	0.249+0.002

SALIVA

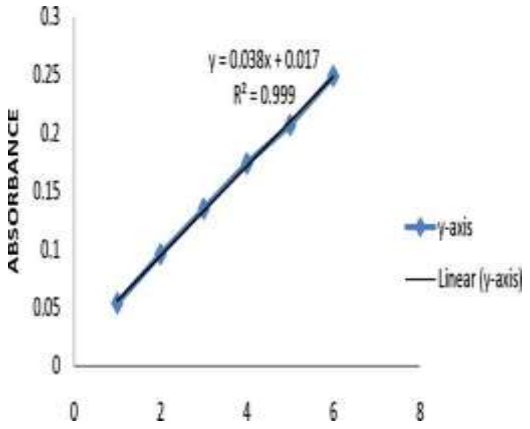

Figure 1- Calibration curve of Acyclovir in Saliva

Table No.-4 Calibration curve data of Acyclovir in Ethanol :Tween mixture(1:1)

S.NO.	Concentration (^g/ml)	Absorbance + S.D.
1	1	0.061+0.001
2	2	0.123+0.002
3	3	0.182+0.002
4	4	0.243+0.003
5	5	0.301+0.002
6	6	0.362+0.004

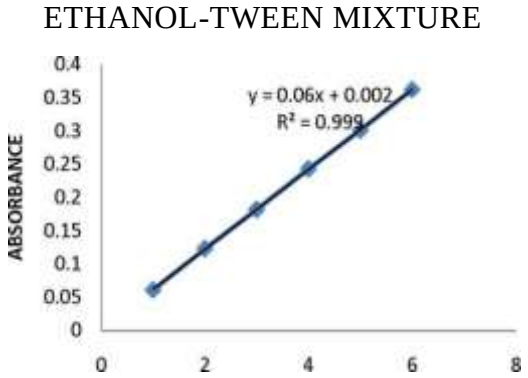

Figure No.2- Calibration curve of Acyclovir in ethanol:tween mixture (1:1)

Table No.5- Validation of analytical method of saliva, ethanol:tween mixture (1:1)

Parameters	Saliva	Ethanol:tween (1:1)
Accuracy (%Recovery)	97-104%	97-103.5%
Regression line equation	Y=0.038x+0.017	Y=0.06x+0.002
(r^2)	0.999	0.999
Intraday precision	>2	>2
Interday precision	>2	>2
LOD(|ig/ml)	1.77	1.379
LOQ(|ig/ml)	5.38	3.44

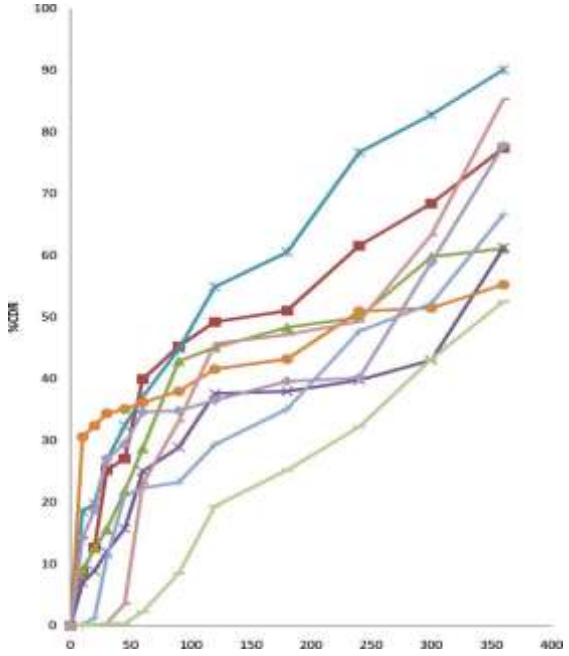

Figure 3- In-vitro drug release profiles of Acyclovir (F1-F9) in saliva

Table No.6- Drug content, ex-vivo permeation and mucoadhesive forc

Formulation	**% Drug Content + S.D.**	**Ex-vivo Permeation (%CDP)^S.D.**	**Mucoadhesive Force + S.D. 2 (dynes/cm)**
F1	84.13+0.23%	77.52+2.12	2744+6.02
F2	77.23+0.21%	61.25+0.98	1960+6.53
F3	81.21+0.17%	61.32+1.82	2548+13.06
F4	94.55+0.14%	90.15+2.10	3136+6.42
F5	78.21+0.09%	55.32+1.12	2094+5.49
F6	84.02+0.13%	66.72+5.72	2678+13.00
F7	89.34+0.18%	85.45+2.11	2874+6.08
F8	79.27+0.24%	52.65+1.52	2029+12.92
F9	86.16+0.31%	78.21+1.21	2613+6.08

Table No.7- In vitro release parameters of Acyclovir loaded drug balls(F4), Marketed Formulations (Althrocin® tablet and Althrocin® liquid suspension.

Formulation Code	%CDR	R^2	Release Kinetics	n value from peppas	Mechanism of release
F4	90.09+2.11	0.9860	Peppas	0.4745	Fickian diffusion
Tablet (Althrocin®)	68.45+0.562	0.9378	Higuchi-matrix	0.8509	Anomalous Transport
Suspension (Althrocin®liquid)	74.25+0.621	0.9843	First Order	0.8724	Anomalous Transport

CONCLUSION

Acyclovir loaded drug balls of F4 can be considered as superior and effective alternative oral dosage form which overcome the drawbacks/Disadvantages associated with commercial suspension (Althrocin® liquid) and tablet (Althrocin®) and also minimize the side-effects due to oral administration of Acyclovir without compromising patient compliance and safety.

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