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Original Research Article

FORMULATION AND EVALUATION OF CLOFAZIMINE MUCOADHESIVE SUSTAINED RELEASE TABLETS AND GEL

Sunil Kumar Shah and Megha Agrawal*

Sri Stya Sai College of Pharmacy, Sehore (M.P.) India

Abstract: Difficulty in swallowing (Dysphasia) is a common problem of all age groups, especially the and pediatrics because of physiological changes associated with these groups.
In this view two formulations Mucoadhesive Gel & Mucoadhesive Tablet was prepared to prolong contact time using three different Polymers. Gel formulation was selected as it is a semisolid dosage form. The application of bioadhesive gels provides an extended retention time, adequate drug penetration, as well as high efficacy and patient acceptability.
In this work two Novel formulations Mucoadhesive Gel & tablets was prepared and evaluated using three different polymers (HPMC, Carbopol, Poloxamer) using an antileprotic drug Clofazimine.Gel was prepared by simple mixing method and tablets was prepared by Direct Compression Method using Rotary Tablet Punching Machine. The tablet weight was adjusted to 500mg and 75 tablets for each batch were prepared.

Keywords: Multi-Drug-Resistance, Antituberculosis, Polyethyleneglycol, clofazimine, tablets and gel

Introduction: The term bioadhesion is meant as two materials adhere together in which one material is of biological origin. The term mucoadhesion can be considered to refer to a subgroup of bioadhesion and, more specifically, to the case when the formulation interacts with the mucus layer that covers a mucosal tissue.

For Correspondence:
megipharmagirl124@gmail.com
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The aim was to develop drug delivery systems that would increase the absorption of a drug, for both local and systemic effects, as a result of intimate and prolonged contact at the site of absorption.
The term mucoadhesion appeared in the literature for the first time in 1977 in a medical research paper describing a clinical trial of a locally delivered anaesthetic (Goldstein *et al.*, 1977).
In our present work we are preparing two different types of mucoadhesive formulations-mucoadhesive gel and mucoadhesive tablets.

Mucoadhesive Gel: Gel formulation was selected as it is a semisolid dosage form, has advantage of easy dispersion throughout the mucosa & easy to prepare. However, semisolid dosage forms do not show accurate drug dosing in comparison of tablets, patches, or films. Bioadhesive formulations can be used to overcome the problem of poor retention. Certain bioadhesive polymers, e.g. poloxamer 407, sodium CMC,carbopol, hyaluronic acid, and xanthan gum, shows change of state from a liquid to a semisolid. This type of changes can increases viscosity, that results in sustained & controlled release of drugs.

Mucoadhesive Tablets: Tablets may be defined as solid pharmaceutical dosage forms having drug substances with or without suitable excipients & made by either compression or Molding methods. Various mucoadhesive polymers can be used in tablet manufacturing to overcome problem like poor retention time of a dosage form in the stomach (GIT), thereby improving the oral bioavailability of the drug and also provide more controlled/ sustained release drug profile.

Mechanism Of Mucoadhesion:

Hydration mediated adhesion: Certain hydrophilic polymers have the tendency to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

Bonding mediated adhesion: For adhesion to occur, molecules must bond across the interface. These bond scan arise in the following way (Hassan, 1990).

a) Ionic bonds
b) Covalent bonds
c) Hydrogen bonds
d) Van-der-waals bonds
e) Hydrophobic bonds

Factors Affecting Mucoadhesion:

A. Polymer related factors
1. Molecular weight of polymer
2. Concentration of active polymer
3. Spatial conformation
4. Hydration (swelling)
5. Charge

B. Environment related factors
1. pH:
2. Applied strength
3. Contact time:
4. Swelling:

C. Physiological variables
1. Mucin properties
2. Mucin turnover
3. Disease states

Materials and Method

Ingredients:

Table 1: List of Ingredients Used In Preparation Of Gel And Tablet Formulations.

Sr. no.	Ingredients
1.	Clofazimine
2.	Carbopol 934
3.	Poloxamer 407
4.	HPMC K15
5.	Lactose
6.	Talc

Equipments:

Table 2: List of Equipments Used.

Sr. no.	Equipment
1.	Dissolution apparatus (6 baskets),
2.	Rotary tablet punching machine, minipress-
3.	Monsanto Hardness tester
4.	Friability tester
5.	Hot plate with magnetic stirrer
6.	UV-Vis-Spectrophotometer
7.	Weighing Balance,
8.	Melting Point Apparatus

Preliminary Investigation of Drug (Clofazimine):

Methods of Preparation of Mucoadhesive Gels:

Preparation of Clofazimine Gel by using HPMC K15:

2%, 4%, 6%, 8%, 10% & 12%, plane gel formulation of HPMC K15 were prepared in distilled water by simple mixing method. 12%, formulation was selected on the bases of consistency of gel.

Preparation of Clofazimine Gel by Using Corbopol 934:

0.5, 1% & 2%, plane gel formulation of Carbopol were prepared in distilled water. Out of these, 1% gel formulation was selected on the bases of gel consistency.

Preparation of Clofazimine gel by using poloxamer 407:

The pluronic gels were prepared by modification of the "Cold dispersion" method described by Schmolka.

Formulation of Mucoadhesive Tablets:

Mucoadhesive tablets of Clofazimine were made by direct compression method. Nine formulations (F1-F9) were formulated by using three different mucoadhesive polymers (HPMC K15, Carbopol 934 & Poloxamer 407). Mucoadhesive polymers were used as binder, lactose as diluents and talc as lubricant.

Table 3: Formula for Different Tablet Formulations.

Ingredents (mg)	FORMULATION								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (Clofazimine)	150	150	150	150	150	150	150	150	150
HPMC K 15	100	150	200	-	-	-	-	-	-
Carbopol 934	-	-	-	-	-	-	20	30	40
Poloxamer 407	-	-	-	75	125	175	-	-	-
Lactose	220	170	120	250	200	150	315	305	295
Talc	20	20	20	20	20	20	20	20	20

Evaluation Parameter for Mucoadhesive Gels:

General Appearance: A Visual inspection was done to know the general appearance of gels. There should be no sign of grittiness and formulation must be of uniform texture.

Mucoadhesive force: Mucoadhesive force of all three gel formulation was determined by method and apparatus reported by Choi *et al*., 1998 & koffi et al, 2006. (by using goat stomach mucosa).

Drug Release Profile: Drug release profile of all three gel formulations was carried out in distilled water, by using cellophane membrane. And drug release rate kinetics of the formulations was determined by fitting release result in models of data treatment as follows:

1. Log cumulative percent drug remaining versus time (first order kinetic model).
2. Cumulative percent drug release versus time (zero order kinetic model).
3. Higuchi release kinetic model.
4. Korsmeyer- peppas model.

Evaluation parameter for mucoadhesive tablets:

General Appearance: General appearance was examined by visual inspection. All tablets should be of uniform size, shape, color and surface textures etc.

Weight Variation: Randomly, twenty tablets were selected and individually weighed. The average weight of tablet was calculated. Then individual weight was compared with average weight of tablets.

Thickness: Six tablets were selected randomly from each batch and thickness was measured by using vernical caliper.

Friability: Twenty tablets were weighted and placed in Roche friabilator and equipment was rotated at 25 rpm for 4 minute.

Hardness: Hardness was determined by using Monsanto Hardness tester

Evaluation Methods Of Mucoadhesive Gel

Texture profile analysis of pharmaceutical gels: Texture profile analysis (TPA) of pharmaceutical gels can be performed using a Stable Micro Systems texture analyzer (Model TA-XT 2).

Rheological characterization: Rheological chararacterization can be performed by using following rheolometers, such as:

Thermostatically controlled Brookfield Programmable Rheometer (Brookfield LVDV III, Brookfield Engineering Laboratories, Middleboro, MA) fitted with CP-52 spindle with cone/ plate geometry (Majithiya *et al.*, 2006).

Measurement of mucoadhesive force: The bioadhesive force, expressed as the detachment stress in dyne/cm2, was determined from the minimal weights that detached the tissues from the surface of each formulation.

Drug release studies: In vitro drug release tests are carried out on the gels by using USP XXIV apparatus 2 with the use of the Enhancer Cell™ 4 cm^2 section.

Results and Discussion

3.1 Preliminary Investigation of Drug (Clofazimine):

Physical Appearance: Clofazimine was a reddish-brown powder.

Melting point: Melting point of Clofazimine was found to be 210°C.

Solubility study: Solubility profile of Clofazimine in various solvents, are given in table .

Table 4 : Solubility Profile of Clofazimine In Various Solvents

S. No.	Solvent	Solubility
1.	Benzene	Very Soluble
2.	Chloroform	Soluble
3.	Methanol	Sparingly soluble
4.	Acetone	Poorly soluble
5.	Ethanol	Sparingly soluble
6.	Ethyl acetate	Poorly soluble
7.	Distilled water	Practically Insoluble
8.	Ether	Insoluble

Evaluation Parameter For Mucoadhesive Gel:

General Appearance: All three gel formulations were good texture profile.

Mucoadhesive Force: Mucoadhesive force of all three gel formulations were determined by using goat stomach mucosa and is given in table . Out of all three polymers, Carbopol showed the maximum mucoadhesive force.

Table 5: Mucoadhesive Force of Polymers Used In Gel Formulations

S. No.	Polymers	Mucoadhesive force (dyne/cm^2)
1.	Poloxamer 407	2.2444
2.	HPMC K15	2.6382
3.	Carbopol 934	3.3739

Drug Release Study: Drug release study data of all three gels are shown in table and figure

Table 6: Data of Release Profile Of Formulated Gels

Time (hr)	Cumulative % drug release		
	HPMC K15 gel	Poloxamer 407 gel	Carbopol 934 gel
0	0	0	0
1	18.45±1.5	12. 83±2.1	4.52±1.7
2	37.46±2.8	27.54 ±2.6	13.74 ±3.5
3	46.45±3.6	36.5±3.3	18.6±2.4
4	64.05±2.3	47.23±2.3	25.03±1.4
5	73.65±4.1	59.74±3.2	34.85±1.6
6	83.82±2.7	66.03±4.3	42.06±2.9
7	87.11±2.1	72.22±2.4	61.73±2.5

Evaluation Parameter for Mucoadhesive Tablets:

General Appearance: General appearance was examined by visual inspection.

Weight variation: All nine tablet batches passed the weight variation test as percentage weight variation was within the pharmacopoeia limits (±5%). Results are shown table.

Table 7 : Weight Variation

BATCH CODE	WEIGHT VARIATION (mg) (N=20)	RESULT
F1	497±1.8	PASSED
F2	495±2.5	PASSED
F3	501±1.67	PASSED
F4	496±1.5	PASSED
F5	503±2.6	PASSED
F6	496±2.8	PASSED
F7	495±3.2	PASSED
F8	501±1.86	PASSED
F9	497±2.2	PASSED

Thickness: The thickness of the tablets was found in the range of 5.6– 6.1 mm.

Friability: Friability of tablets was observed in acceptable range of 0.34-0.84%. It was within the pharmacopeia limit i.e. less than 1%.

Hardness: Hardness of the tablets was found in the range of 6.8-9.4 kg/cm2. That was satisfactory for sustained release formulations.

Mucoadhesive Studies: Mucoadhesive strength of tablets was measured on the modified physical balance. The highest adhesion force and highest strength of the mucoadhesive bond was observed with the carbopol formulations. And it was increasing with increase in concentration of polymer.

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