

Development and *in-vitro* evaluation of mucoadhesive gastroretentive matrix tablets of cephalixin

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Running title: Development of Mucoadhesive Drug Delivery System of Cephalixin

Abstract: Cephalixin is a semi-synthetic cephalosporin β -lactum antibiotic intended for oral administration used to treat urinary tract infections, respiratory tract infections, skin and soft tissue infections. The present investigation concerns the development and evaluation of single unit mucoadhesive drug delivery system of cephalixin. Mucoadhesive drug delivery system (MDDS) prevents degradation and remains the drug release in stomach or upper part of GIT for prolonged period of time, therefore the maximum drug release is maintained at desired site. After oral administration, are designed to prolong the gastric residence time, increase drug bioavailability and target the gastric infections. A mucoadhesive drug delivery system was developed using like mucoadhesive polymers and hydrocolloids, like hydroxypropyl methylcellulose (HPMC K100M), carbopol 934P and Sodium carboxy methyl cellulose (Sodium CMC). The prepared tablets were evaluated in terms of their physical characteristics, *in vitro* release, swelling index, mucoadhesive strength and scanning electron microscopy of optimized formulation. The formulations were optimized for different concentrations of HPMC, carbopol and Sodium CMC. The results of the *in vitro* release studies showed that the optimized formulation could sustain drug release for 12 h. The comparison of drug release profile of all formulations showed that formulations Fa1 which contains more amount of Carbopol 934p and fewer amounts of HPMC K100M and sodium CMC showed maximum drug release.

Keywords: Cephalixin, gastric residence time, hydrocolloids, mucoadhesive, SEM microphotographs.

I. Introduction:

Oral controlled release dosage forms (CRDFs) have been developed for the past three decades due to their considerable therapeutic advantages. However, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal tract, i.e. stomach and small intestine. This is due to the relatively short transit time of the dosage forms in these anatomical segments^[1]. Thus, after only a short period of less than 6 h, the CR-DF has already left the upper gastrointestinal tract and the drug is released in non absorbing distal segments of the gastrointestinal tract. This results in a short absorption phase that is often accompanied by lesser bioavailability^[2].

Interest in controlled and sustained release drug delivery has increased considerably during the past decade. However, for oral administration, all of these systems are limited to some extent because of gastrointestinal (GI) transit. Thus, the duration of most oral sustained release products is approximately 8-12 h due to the relatively short GI transit time, and thus there is drug delivery in selected regions of the gastrointestinal tract (GIT) for the purpose of localized drug delivery is not possible. Because of this region Novel drug delivery system is under investigation^[3, 4].

It was suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage forms with gastro retentive properties would enable an extended absorption phase of these drugs. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence of drug^[5].

In novel drug delivery system several approaches have been suggested to increase GI transit time, addressing the issue of localized drug delivery. The controlled gastric retention of solid dosage forms may be achieved by the floating drug delivery system, swelling or expanding system, modified shape systems, mucoadhesive system, and high-density drug delivery systems or by the simultaneous administration of pharmacological agents that delay gastric emptying^[6].

A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT some drugs are absorbed in a particular portion of the GIT only or are absorbed to a different extent in various segments of the GIT^[7].

The mucoadhesive system is most easy technique and require less time. In this delivery system mucoadhesive polymer used that adheres to mucosa / epithelial surface. Such polymer applied to any mucus membrane. Thus, mucoadhesive polymers would find application in the eye, nose, vagina and GIT including the

buccal cavity and rectum [8,9]. Mucoadhesive gastroretentive system can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility of drugs that are less soluble in a high pH environment [10].

Cephalexin is a semi-synthetic cephalosporin β lactum antibiotic intended for oral administration used to treat urinary tract infections, respiratory tract infections, skin and soft tissue infections [11]. Cephalexin having half-life is 1hour and good absorption in GIT, which remain unionized in stomach but it degraded in alkaline pH. Mucoadhesive drug delivery system prevents degradation and remains the drug release in stomach or upper part of GIT for prolonged period of time, therefore the maximum drug release is maintained at desired site [12].

II. Materials And Methods:

Cephalexin and HPMC K100M were obtained as gifts from Okasa Pharmaceuticals, Satara, India. Sodium CMC was donated by Meditab, Satara, India. Carbopol 934p and all other reagents / chemicals were purchased from Loba Chemicals, Mumbai, India.

2.1. Preparation of Mucoadhesive Tablets of Cephalexin:

Table 1 lists the composition of different mucoadhesive formulations for cephalixin. Mucoadhesive tablet of cephalixin is prepared by direct compression method. All ingredients are accurately weighed and then passed through 60-mesh sieve. Firstly cephalixin and mucoadhesive polymers are mixed by trituration in mortar for 10 min. to form uniform powder. Then talc and MCC were added and mixed for 10 min. Flat 670 mg tablet is prepared in 13 mm flat punch by using multi-station compression machine.

Table 1: Composition of different mucoadhesive tablet formulations of Cephalexin

Ingredients (mg)	Formulation code								
	Fa ₁	Fa ₂	Fa ₃	Fb ₁	Fb ₂	Fb ₃	Fc ₁	Fc ₂	Fc ₃
Cephalexin	500	500	500	500	500	500	500	500	500
Carbopol 934 p	60	60	60	15	30	45	15	30	45
HPMC K100M	15	30	45	60	60	60	45	30	15
Sodium CMC	45	30	15	45	30	15	60	60	60
MCC	35	35	35	35	35	35	35	35	35
Talc	15	15	15	15	15	15	15	15	15

All quantities are in mg; Total weight of individual tablet is: 670.

2.2. Physical Evaluation of mucoadhesive Tablets of Cephalexin:

The prepared tablets were evaluated in terms of their drug content, weight variation, hardness, friability, thickness and diameter uniformity [13].

2.3. Mucoadhesive Strength Measurement:

Mucoadhesive strength of the tablet was measured on the modified physical balance (Fig. 1). The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by Teflon with copper wire and additional weight, to make the right side weight equal with left side pan. Goat or rat stomach mucosa was used as a model membrane and buffer media pH 1.2 was used as moistening fluid [14].



Figure 1: Modified analytical balance for mucoadhesive strength measurement

The addition of weights was stopped when mucoadhesive tablet was detached from the goat or rat stomach mucosa. The weight required to detach mucoadhesive tablet from stomach mucosa was noted as mucoadhesive strength in grams.

2.4. Swelling studies ^[15, 16]:

The Swelling studies were carried out by determining the swelling index using USP Type- I Apparatus (Basket). Tablets were initially weighed (W₀) and then placed in the basket and revolved at 50 rpm for 12 h. At intervals of 1 h, tablets were removed from basket and weighed (W_t). Then swelling index was calculated by using the following formula,

$$\% \text{ Swelling index} = (W_t - W_0 / W_0) \times 100$$

2.5. In-vitro drug release study:

Drug release studies were carried out using a USP type -II Dissolution Test Apparatus (Fig. 2). The tablets from each formulation batch were sticks to the paddles by making one side of tablets moist by using dissolution medium and apparatus was run by maintaining at below stated test conditions. 1 ml aliquots were withdrawn at predetermined time intervals. Every time the equal volume of fresh dissolution medium was added to the bulk. Samples were filtered through Whatman filter paper and analyzed by UV spectrophotometer. Cumulative percentages of the drug dissolved from the preparations were calculated ^[17].



Figure 2: In-vitro drug release study

2.5.1. Parameter for in vitro dissolution study:

1. Dissolution medium= 900 ml acidic buffer pH 1.2
2. Temperature= 37.0±0.5 °c
3. Rotation speed= 50 rpm
4. Sample volume withdrawn= 1 ml
5. Time interval = 1 hour

2.6. Scanning electron microscopy of optimized formulation ^[18]:

Scanning electron microscopy (SEM) has been used to determined particle size distribution and surface morphology. SEM study of tablet was carried out in three states i.e. in dry state by triturating tablet, after swelling of tablet up to 6h and after swelling of tablet up to 12h. Swelling of tablet was done in dissolution test apparatus. The dissolution medium was acidic buffer pH 1.2 and temperature maintained at 37⁰C ± 0.5⁰ C.

III. Results And Discussion:

The average weight of the tablets for all the formulations (Fa₁ to Fc₃) was found to range from 658 to 669 mg with a standard deviation of 1.52 to 4.08. The thickness varied from 3.9 ± 0.01 to 3.9 ± 0.10 mm and hardness from 6.50 to 7.0 kg/cm². The drugs content of various formulations varied between 89.6 to 103.6 %. Tablets of all the batches had acceptable physical characteristics. Result of all physical evaluations is tabulated in Table 2.

Table 2: Physical Evaluation of mucoadhesive Tablets of Cephalixin

Formulation code	Diameter* (mm)	Thickness* (mm)	Hardness* (Kg/cm ²)	% friability*	Weight variation*
Fa ₁	13±0	3.9 ± 0.05	7.0 ±0.11	0.015	667±4.08
Fa ₂	13±0	3.9 ± 0.06	7.0 ±0.1	0.011	662±3.6
Fa ₃	13±0	3.9 ± 0.06	7.0 ±0.2	0.013	669±1.52
Fb ₁	13±0	3.9 ± 0.05	6.5 ±0.11	0.012	665±2.08
Fb ₂	13±0	3.9 ± 0.04	6.5 ±0.1	0.016	658±3.6
Fb ₃	13±0	3.9 ± 0.05	6.5 ±0.15	0.012	660±3.2
Fc ₁	13±0	3.9 ± 0.06	6.5 ±0.1	0.014	667±2.08
Fc ₂	13±0	3.9 ± 0.06	6.5 ±0.11	0.015	664±1.52
Fc ₃	13±0	3.9 ± 0.04	6.5 ±0.15	0.010	668±1.52

*All values are expressed in Mean \pm S.D

3.1. Mucoadhesive Strength Measurement:

Mucoadhesive strength of all formulations was measured and results are tabulated in Table 3. The mucoadhesive strength of various formulations varied between 20.4 to 24.3 mucoadhesive strength of formulation is depends on different polymers used and concentration of polymers used. Formulation fc_1 to fc_3 which shows maximum mucoadhesive strength containing sodium CMC in maximum quantity than the formulation containing Carbopol 934p and HPMC K100M are constant.

Table 3: % Drug content & Mucoadhesive strength

Formulation code	% Drug content	Mucoadhesive strength*
Fa ₁	99.2	23.2 \pm 1.25
Fa ₂	102.3	22.7 \pm 0.76
Fa ₃	103.6	22 \pm 1.04
Fb ₁	100.5	20.4 \pm 0.5
Fb ₂	96.8	21 \pm 1.5
Fb ₃	94.6	21.5 \pm 1.04
Fc ₁	97.6	23.5 \pm 0.5
Fc ₂	89.6	24 \pm 0.76
Fc ₃	93.9	24.3 \pm 1.5

*All values are expressed in Mean \pm S.D, n= (3)

3.2. Swelling studies:

Swelling index profile of all formulations is shown in Table 4; swelling index of all formulations is varied between 121.77 to 155.28 %. Swelling index profile of all formulations is depending on type of polymers and amount of polymers used in that formulation.

In batch Fa₁ to Fa₃ containing carbopol 934p is constant and remaining two are used in three different concentrations. From these three batches batch Fa₁ containing more amount of carbopol 934p and sodium CMC shows maximum swelling index. In batch Fb₁ to Fb₃ containing HPMC K100M is constant and remaining two are used in three different concentrations. From these three batches batch Fb₂ containing equal amount of carbopol 934p and sodium CMC shows maximum swelling index. In batch Fc₁ to Fc₃ containing sodium CMC is constant and remaining two are used in three different concentrations. From these three batches batch Fc₃ containing more amount of carbopol 934p and sodium CMC shows maximum swelling index.

Table 4: Swelling index study of all formulations

Time (hrs)	% Swelling Index								
	Fa ₁	Fa ₂	Fa ₃	Fb ₁	Fb ₂	Fb ₃	Fc ₁	Fc ₂	Fc ₃
1	60.56	67.62	64.19	54.81	45.86	49.54	56.67	58.63	56.25
2	73.19	68.82	75.98	68.52	58.34	62.31	75.11	68.12	79.48
3	80.80	70.93	85.19	78.01	75.63	69.51	80.50	80.81	92.30
4	98.80	82.22	90.12	82.22	75.78	75.07	81.40	84.13	95.02
5	109.66	89.30	96.70	87.80	81.80	78.82	88.10	91.08	100.20
6	120.24	91.41	107.79	90.21	92.03	83.33	91.90	96.07	102.20
7	127.79	95.48	112.74	91.71	95.78	87.23	98.35	102.41	110.70
8	137.76	105.42	128.33	108.58	109.32	96.84	115.74	121.75	123.30
9	142.29	112.5	138.53	116.71	118.3	108.2	120.38	124.77	127.70
10	146.82	121.23	141.82	122.89	124.91	112.46	125.03	136.25	133.40
11	158.45	123.19	145.42	124.54	127.36	114.86	128.78	134.13	137.10
12	155.28	127.56	150.37	129.36	133.83	121.77	134.33	138.97	140.08

3.3. In-vitro dissolution studies:

All the nine formulations were subjected to *in-vitro* dissolution studies using a USP type -II Dissolution Test Apparatus. The dissolution medium 1.2 pH buffer was used to study the drug release. The samples were withdrawn at different intervals of time and analyzed at 261.5 nm using UV spectrophotometer. Cumulative percentage drug release was calculated. The data obtained from in vitro release for formulations prepared by direct compression technique are tabulated in the Table 5 (Fig. 3).

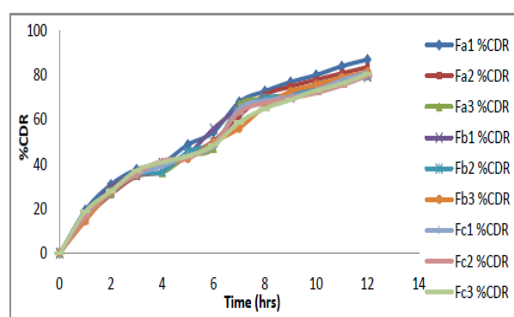
Table 5: In-vitro drug release of all formulations

Time (hrs)	% Cumulative drug Release*								
	Fa ₁	Fa ₂	Fa ₃	Fb ₁	Fb ₂	Fb ₃	Fc ₁	Fc ₂	Fc ₃
0	0	0	0	0	0	0	0	0	0
1	19.1 ±0.82	16.1 ±0.79	17.2 ±1.46	14.8 ±1.79	15.3 ±1.35	15.4 ±0.92	16.5 ±0.55	17.3 ±1.32	19.4 ±0.64
2	30.8 ±0.65	25.7 ±0.62	26.2 ±0.62	28.9 ±1.61	29.0 ±1.43	29.1 ±1.28	27.3 ±0.50	28.7 ±1.27	29.6 ±1.52
3	37.1 ±0.99	34.0 ±0.56	34.1 ±1.31	34.8 ±1.08	36.6 ±1.22	36.9 ±1.76	34.4 ±0.92	34.8 ±1.07	38.8 ±1.61
4	40.3 ±0.55	37.2 ±0.50	38.1 ±1.57	40.4 ±0.72	38.8 ±1.71	40.3 ±0.55	38.5 ±0.78	41.4 ±0.83	40.9 ±1.20
5	49.4 ±0.49	43.9 ±0.80	43.8 ±0.95	43.4 ±1.07	44.3 ±1.20	43.9 ±1.15	45.5 ±0.66	49.1 ±1.25	44.7 ±1.10
6	53.8 ±0.77	51.4 ±0.66	47.6 ±1.80	56.1 ±1.16	51.1 ±1.18	51.2 ±1.22	53.1 ±1.41	51.0 ±1.28	50.0 ±1.55
7	68.6 ±0.47	62.9 ±0.92	61.2 ±1.18	65.8 ±1.81	63.4 ±1.55	58.6 ±1.85	65.5 ±0.90	63.3 ±1.25	60.7 ±1.57
8	72.9 ±0.22	72.4 ±0.93	67.3 ±1.5	68.1 ±1.32	69.7 ±1.15	66.0 ±1.70	68.8 ±0.82	67.4 ±1.53	64.7 ±1.65
9	76.7 ±0.43	75.1 ±0.86	71.7 ±1.38	70.0 ±1.66	71.4 ±0.97	72.7 ±1.43	70.2 ±1.17	69.9 ±1.99	69.1 ±1.91
10	80.9 ±0.48	78.0 ±0.97	75.4 ±1.41	74.9 ±1.64	74.8 ±1.35	75.2 ±1.23	73.0 ±1.35	72.4 ±1.30	73.8 ±1.51
11	84.8 ±0.33	81.9 ±0.45	78.2 ±0.80	77.9 ±1.64	78.7 ±1.70	79.9 ±1.68	77.9 ±0.91	75.6 ±1.88	76.8 ±1.45
12	87.0 ±0.35	83.4 ±0.77	80.7 ±1.14	79.9 ±1.46	80.5 ±1.30	81.2 ±1.17	81.0 ±1.14	79.7 ±1.84	80.1 ±0.61

*All values are expressed in Mean ± S.D, n= (3)

All the tablets of nine formulations showed controlled drug release upto 12 hours. All the nine formulations containing three different polymers which have used in nine different ratio.

In batch Fa1 to Fa3 containing Carbopol 934p is constant and remaining two are used in three different concentrations. In batch Fb1 to Fb3 and batch Fc1 to Fc3 containing HPMC K100M and sodium CMC are constant respectively and remaining two are used in three different concentrations. The comparison of drug release profile of all formulations showed that formulations Fa1 which contains more amount of Carbopol 934p and fewer amounts of HPMC K100M and sodium CMC showed maximum drug release.

**Figure 3: Drug release of tablets of all batches**

3.4. Scanning Electron Microscopy:

The swelling behavior of the mucoadhesive gastroretentive tablet of cephalixin was studied by Scanning Electron Microscopy (SEM). SEM study is done for only optimized formulation i.e. Fa₁. SEM microphotographs of mucoadhesive gastroretentive tablet of cephalixin are reported below in three states (Fig. 4) i.e. in dry state, after 6 h and after 12 h. In dry state the polymer size is small but in 6 h and 12 h state the polymer size is increased. After 6 hrs the polymer size is increased as compared to dry state but less increased as compared to 12 h. After 12 h polymer size is maximum that indicate the release is depend on swelling of polymers. Due to this formulation Fa₁ shows maximum release up to 12 h.

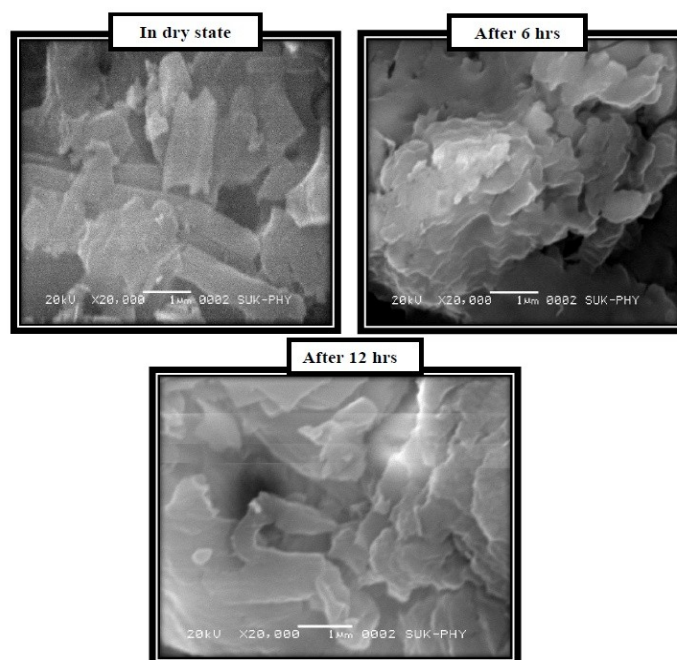


Figure 4: Scanning electron microscopy of optimized formulation Fa₁

IV. Conclusion:

In the present work, formulations of cephalexin gastroretentive mucoadhesive tablets were prepared by direct compression method.

In-vitro release of mucoadhesive gastroretentive tablet of cephalexin shows that the formulation Fa₁ was found to be the best formulation as it releases 87% cephalexin in a controlled manner with constant fashion over extended period of time (up to 12 h).

From present work it can be concluded that, *In-vitro* release and mucoadhesive strength was achieved by use of Carbopol 934p and sodium CMC in combination, instead of HPMC K100M.

Carbopol 934p and Sodium CMC have given extra adhesion property and helped to maintain the integrity of the tablets, gastroretentive mucoadhesive tablet give good mucoadhesion and a controlled release.

SEM microphotographs of mucoadhesive gastroretentive tablet of cephalexin (formulation Fa₁) shows controlled release pattern.

Overall study shown that the novel drug delivery system combining gastroretentive properties could increases drug retention time in stomach.

Hence, finally it was concluded that the prepared mucoadhesive tablet of cephalexin may prove to be potential candidate for safe and effective controlled drug delivery over an extended period of time for gastroretentive drug delivery system.

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