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Research Article

FORMULATION AND EVALUATION OF MUCOADHESIVE TABLETS OF DILTIAZEM HCL

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ABSTRACT

The main objective of this study is to develop Mucoadhesive tablets of Diltiazem HCl to prolong the drug release after oral route of administration. Matrix tablets of Diltiazem HCl were prepared using Chitosan, sodium alginate alone and in combination to optimize mucoadhesion properties. The prepared tablets were evaluated for weight variation, thickness, hardness, content uniformity, drug release, swelling index and mucoadhesion force. The formulations prepared in combination with Chitosan and Sodium alginate showed greater swelling index, good in-vitro prolonged drug release upto 12 hours and optimum mucoadhesive properties. Hence the present study concluded that prolonged in-vitro drug release of Diltiazem HCl is possible by formulating into mucoadhesive tablets

INTRODUCTION:

Mucoadhesive drug delivery systems [(1)] are the promising way to attain prolonged release of the drug. The formulation of mucoadhesive drug delivery system is done by using selected mucoadhesive polymers. Mucoadhesive polymers have the property to bind with mucin[(2,3)] of the mucous membrane present throughout the GIT. Thus the formulation shows site specific delivery, prolonged release of the drug avoidance of first pass effect [(4,5)] and enhanced drug bioavailability. Buccal drug delivery [(6)] has gained increased acceptance because the drug is protected in from acidic environment of the stomach and improved drug availability can be seen. Mucoadhesion [(7)] has been utilized in many different dosage forms like tablets, patches, films, semi solids and powders. Diltiazem HCl is the drug of choice for treatment of hypertension. It is having a half-life of 3 to 5 hrs, log p of 2.79[(8)] with high first pass metabolism. This drug is selected in the present study to formulate into mucoadhesive tablets.

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MATERIALS AND METHODS

Materials: Diltiazem HCl was obtained as a gift sample from Ranbaxy Laboratories Pvt Ltd, Gurgaon, Delhi. Chitosan , sodium alginate, avicel, magnesium stearate and talc were purchased from Yarrow chem. Products Pvt Ltd, Mumbai. All other chemicals used were of research analytical grade.

Formulation of Mucoadhesive tablets:

Diltiazem HCl and other excipients mentioned in the formulation Table 1 were blended homogeneously in a mortar. The blended mixture was passed through sieve No.60and 1% magnesium stearate was added and properly mixed. This homogeneous mixture was compressed into tablets using rotary tablet press with 9mm flat punches. A total of 13 formulations were prepared using chitosan, Sodium alginate alone and in combination at various ratios. Lactose was used as diluent and avicel was employed as directly compressible vehicle.

Evaluation of Mucoadhesive tablets:

Tablet thickness and diameter:

To determine the tablet thickness and diameter 20 tablets were selected, thickness and diameter was measured using vernier caliper [9,10]. The average diameter and thickness was calculated.

Weight Variation:

Weight variation test was done by weighing randomly 20 tablets. Average weight was taken from the total weight. Then percentage deviation was calculated [11].

Hardness of tablet:

The hardness was tested using Monsanto hardness tester [12].

Drug content uniformity:

Five tablets from each batch were powdered and a quantity equivalent to 10mg of Diltiazem HCl was accurately weighed and extracted with suitable volume of methanol. Each extract was suitably diluted and analysed Spectrophotometrically at 236nm.the drug content is calculated by using the formula [13].

Friability:

Friability test for prepared tablets was done by using Roche friabilator.10 tablets were weighed and tumbled at 25 rpm for 5 min. The tablets were dedusted and weighed. The percentage friability was calculated by the following formula [14].

$$\%Friability = W0-W/W0*100$$

***In-vitro* dissolution studies**:

In- vitro drug release [15] from the tablets was studied by using USP- type II dissolution apparatus. A 900ml of 6.8 pH phosphate buffer was use as dissolution medium , the temperature is maintained at 37°C at a speed of 50rpm. The dissolution study was carried for about 3 hrs. Aliquots (5ml) was withdrawn and replaced with fresh solution at regular time intervals. Absorbance of the solution was measured at 236nm uing UV-Vis Spectrophotometer. Cumulative percent drug release was calculated from the standard calibration curve.

Mucoadhesive strength:

The mucoadhesive strength [16] of the tablets was measured using the Ultra test (Mecmesin, UK) equipped with a 5 kg load cell. The fresh sheep stomach mucosa was obtained from the slaughter house and kept in krebs buffer and was secured tightly to a circular stainless steel adaptor (diameter 2.2 cm) provided with the necessary equipment. A back up membrane was placed over the Mucoadhesive tablet to be tested and fixed with the help of Cyanoacrylate adhesive to the cylindrical stainless steel adaptor of similar diameter.

The entire set up was mounted on to the platform of a motorized test stand. During measurement 100 ml of 1 % mucin solution (crude mucin procured from sigma chemical Co, USA) was used to moisten the sheep stomach membrane. The upper support was lowered at a speed of 0.5 mm per second until contact was made with the tissue at the predetermined force of 0.5 N for a contact time of 180 sec. At the end of contact time, the upper support was withdrawn at a speed of 0.5 mm per second to detach the membrane from the tablet. Two parameters mainly the work of adhesion and peak detachment force were used to study the bioadhesiveness of tablets.

Swelling index:

The extent of swelling can be measured in terms of percent weight gain by tablet. From each formulation one tablet was weighed and placed in a beaker containing 200 ml of buffer. After each interval the tablet was removed from the beaker and weighed upto 8 hours. The swelling index [17] was calculated using the following formula.

$$\text{Swelling index} = \frac{W_t - W_0}{W_0} \times 100$$

Where W_t = weight of tablet at time t

W_0 = weight of the tablet before placing in the beaker

X- Ray studies:

The protocol of radiographic studies [18] on healthy rabbits was approved by the animal ethical committee (1047/ac/07/CPCSEA). The study was conducted on the rabbits weighing 2- 2.5 kg. The tablets prepared for radiography were administered orally with water.

After ingestion of Mucoadhesive tablets containing barium sulphate, the rabbits were exposed to X-ray photography in the abdominal region, at the veterinary faculty, which has the authorization to perform this kind of imaging under the law on animal health. The X-ray photographs were taken at 1, 2, 3 and 4 hours after the administration of the tablets. The mean gastric residence time was calculated.

RESULTS AND DISCUSSION:

Thirteen formulations were prepared employing Chitosan, sodium alginate alone and in combination. They were evaluated for weight variation, thickness, hardness, friability and drug content uniformity. All the prepared tablets were found to comply within Pharmacopoeial limits and the results were given in table 2.

***In vitro* dissolution studies:**

The cumulative percentage drug release from the formulations containing Chitosan and sodium alginate was extended upto 12 hrs. It was found that prolonged release of the drug was observed with the formulation containing Chitosan and sodium alginate at 3: 1 ratio than the formulations containing Chitosan and sodium alginate alone. The results are given from table 3 to 5 and in fugure.1.

Swelling index:

The swelling index is the parameter which is used to indicate the swelling ability of the polymer. The swelling index will considerably increase with the increase in polymer concentration. This increase may be due to increased absorption of water in the polymeric matrix. A higher swelling index was observed for the formulation containing Chitosan and sodium alginate in 3:1 ratio (table 6) and figure .2.

Bio adhesion force:

Concentration of Chitosan effects the Bioadhesion force significantly. It was found that the formulation DF 13 showed highest mucoadhesion force due to higher Chitosan concentration. A correlation was found in between percentage swelling and mucoadhesive strength and the results were given in table 7 and figure 3.

X-Ray studies:

In-vivo studies were conducted on healthy rabbits to find the gastric residence time of the tablet. The studies were based on X-ray radiography. Images were taken at different points to find the location of the tablet at 1, 2, 3 and 4hrs. The gastric retention time was increased by the bioadhesive nature of tablets, which was considered desirable for the absorption window drugs.

CONCLUSION:

The study suggest that the Mucoadhesive tablets of Diltiazem hydrochloride was prepared using Chitosan, sodium alginate and in combination with Chitosan and sodium alginate and the drug release was extended upto 12hrs.The tablets demonstrated ample bioadhesive strength .Formulation DF13 was found to be the best formulations to achieve the aim of this study.

Table. No.1: Formulation of Mucoadhesive tablets of Diltiazem HCl

Ingredient(mg)	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8	DF9	DF10	DF11	DF12	DF 13
Diltiazem Hcl	30	30	30	30	30	30	30	30	30	30	30	30	30
Chitosan	15	20	25	30	---	---	---	---	7.5	10	20	10	30
Sodium alginate	---	---	---	---	15	20	25	30	7.5	20	10	30	10
Avicel	30	30	30	30	30	30	30	30	30	30	30	30	30
Lactose	60	55	50	45	60	55	50	45	60	55	55	35	35
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	140	140	140	140	140	140	140	140	140	140	140	140	140

Table .No. 2: weight variation, thickness, hardness, friability and drug content

Formulation	Weight (mg) (mean ±SD)	Hardness(kg/cm^2)	Friability (%)	Drug content (%)
DF1	139 ± 1.02	4.2±0.12	0.52	92.74
DF2	139± 1.58	4.0±0.14	0.82	99.52
DF3	140± 0.96	4.4±0.28	0.70	94.41
DF4	138± 1.24	4.6±0.31	0.82	92.75
DF5	138±1.62	4.1±0.5	0.90	99.94
DF6	137± 0.84	3.8±0.62	0.72	98.41
DF7	140± 0.78	4.5±0.31	0.81	101.32
DF8	139± 1.08	5.2±0.21	0.89	100.47
DF9	139±1.23	5.0±0.22	0.84	99.70
DF10	138±1.22	5.3±0.15	0.56	98.66
DF11	139±1.23	5.2±0.62	0.68	95.65
DF12	140±1.78	5.4±0.71	0.72	97.05
DF13	140±0.96	5.3±0.82	0.52	98.11

Table. No. 3: Cumulative percentage of drug released from formulations with Chitosan

Cumulative percent drug released				
Time (hrs)	DF1	DF2	DF3	DF4
1	29.66±0.44	24.68±0.34	22.62±0.39	20.82±0.33
2	38.9±0.37	30.25±0.40	30.82±0.44	26.71±0.39
3	57.66±0.41	46.63±0.44	38.7±0.48	34.25±0.39
4	69.74±0.52	57.64±0.54	46.72±0.58	42.76±0.47
5	82.73±0.45	69.71±0.51	57.64±0.30	47.60±0.36
6	98.93±0.08	81.65±0.46	67.62±0.53	56.72±0.38
7	-	96.64±0.57	81.12±0.46	73.85±0.45
8	-	-	98.42±0.52	96.62±0.47

Table. No. 4: Cumulative percentage of drug released from formulations with Sodium alginate

Cumulative percent drug released				
Time (hrs)	DF5	DF6	DF7	DF8
1	23.74±0.57	23.66±0.49	20.26±0.71	19.87±0.47
2	38.14±0.52	36.78±0.5	26.34±0.61	23.24±0.56
3	45.63±0.58	45.81±0.28	34.66±0.49	30.32±0.64
4	68.30±0.55	56.73±0.52	45.28±0.54	40.24±0.55
5	81.92±0.34	62.66±0.42	60.24±0.47	53.22±0.82
6	97.94±0.82	75.75±0.57	71.13±0.63	66.28±0.44
7	-	94.70±0.54	81.76±0.32	79.92±52
8	-	-	94.24±0.33	97.32±0.78

Table. No. 5: Cumulative percentage of drug released from formulations with Chitosan& Sodium alginate

Cumulative percent drug released					
Time (hrs)	**DF9**	**DF10**	**DF11**	**DF12**	**DF13**
1	27.91±0.50	24.41±0.51	23.76±0.56	23.13±0.56	16.73±0.55
2	33.83±0.75	31.78±0.31	33.9±0.64	36.81±0.35	24.14±0.78
3	40.70±0.71	44.58±0.46	45.66±0.57	42.70±0.83	33.37±0.46
4	55.98±0.83	59.75±0.43	50.71±0.53	50.26±0.12	44.44±043
5	62.81±0.62	62.72±0.35	54.97±0.83	55.09±0.42	50.69±0.53
6	69.82±0.48	68.46±0.22	62.15±0.36	62.81±0.76	57.14±0.36
7	74.23±0.33	71.6±0.15	69.46±0.32	69.82±0.11	63.81±0.74
8	95.74±0.39	84.69±0.46	74.47±0.22	74.03±0.36	71.96±0.97
9	-	98.09±0.44	82.58±0.51	83.43±0.44	76.16±0.57
10	-	-	95.74±0.39	94.66±0.18	82.58±0.51
11	-	-	-	-	90.02±0.42
12	-	-	-	-	98.76±0.56

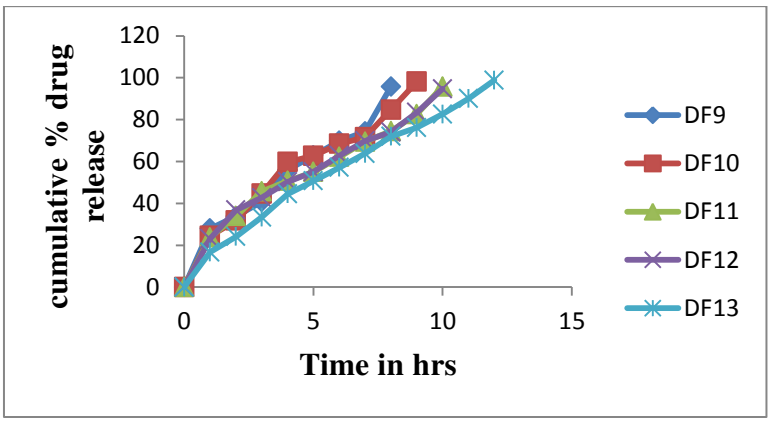

Figure .No. 1: cumulative % drug release for formulations DF9 to DF 13

Table . No. 6: Swelling index of formulations DF1 TO DF13

Formulation	Percent swelling index
DF1	56.06
DF2	64.90
DF3	66.25
DF4	63.33
DF5	65.34
DF6	68.76
DF7	69.24
DF8	74.83
DF9	82.12
DF10	84.36
DF11	86.96
DF12	88.76
DF13	90.78

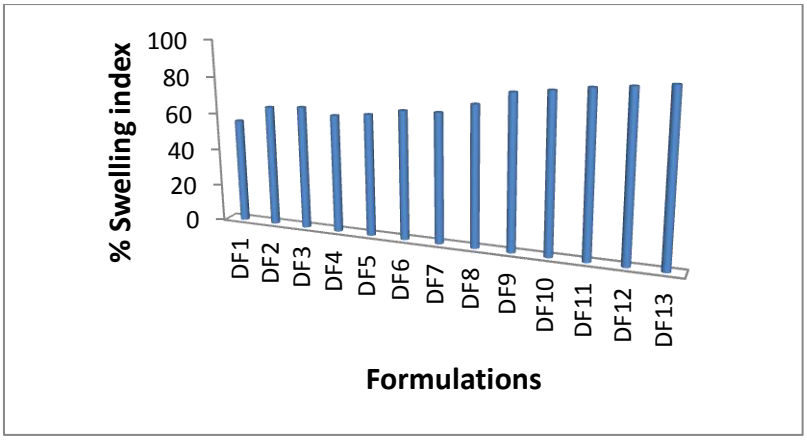

Figure .No. 2: Swelling index of formulations DF 1 to DF13

Table. No. 7: Bioadhesion study - Detachment force method

Formulation code	Detachment force (N)[a]	Work of adhesion (mj)[a]
DF1	0.33 ± 0.03	0.04 ± 0.07
DF2	0.37 ± 0.15	0.05 ± 0.13
DF3	0.40 ± 0.09	0.06 ± 0.15
DF4	0.42 ± 0.18	0.07 ± 0.32
DF5	0.45 ± 0.10	0.05 ± 0.24
DF6	0.49 ± 0.20--	0.05 ± 0.35
DF7	0.52 ± 0.42	0.06 ± 0.22
DF8	0.54 ± 0.35	0.07± 0.17
DF9	0.42 ± 0.27	0.06 ± 0.09
DF10	0.48 ± 0.35	0.07 ± 0.11
DF11	0.28 ± 0.14	0.06 ± 0.51
DF12	0.30 ± 0.19	0.08 ± 0.44
DF13	0.32 ± 0.23	0.09 ± 0.37

Mean ± SD; [a]n=3; N=Newtons; mj:milli jouls

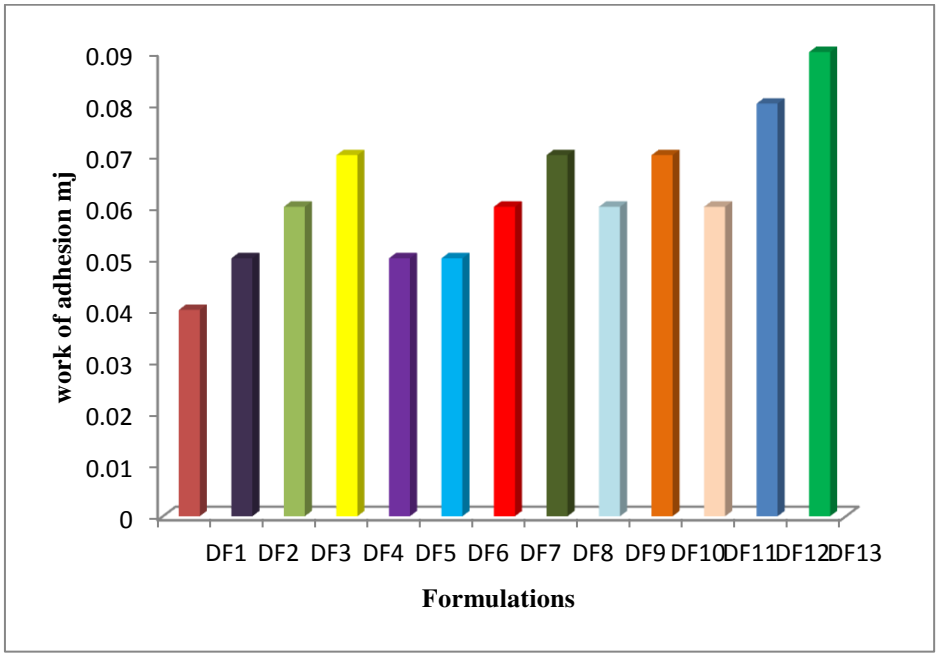

Figure .No. 3: Bioadhesion strength of formulations DF1 to DF 13

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