Design and evaluation of controlled release muco adhesive tablets of diltiazem hydrochloride

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Abstract

In this study, a mucoadhesive dosage form of Diltiazem Hydrochloride was fabricated using a combination of bioadhesive polymers HPMC, MCC and EC in different ratios. The formulations were characterized for physicochemical parameters such as weight variation, friability, hardness, water sorption studies, detachment force measurement and *in vitro* release studies. The best mucoadhesive performance and *in vitro* drug release profile were exhibited by formulation 3.

Key words: Diltiazem Hydrochloride, Mucoadhesive drug delivery, Mucoadhesive polymers, in vitro release, detachment force measurement.

1. Introduction

Development of new drug molecule is expensive and time consuming. Improving safety efficacy ratio of "old" drugs has been attempted using different methods such as individualizing drug therapy, dose titration and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, targeted delivery are other very attractive methods and have been pursued very vigorously (Kshirsagar, 2000)**.** In the recent years, significant interest has been shown in the development of novel bioadhesive dosage forms for mucosal delivery of drugs that attempt to over come these limitations (Rajesh and Joseph, 1994). The concept of muco adhesives was introduced into the controlled drug delivery area, in the early 1980's. Muco adhesive drug delivery system, when utilized the property of bio-adhesion of a certain polymers when become adhesive on hydration and hence can be used for targeting the drug to a particular region of the body for extended period of time (Jain, 2002). High molecular weight polymers are generally used for bioadhesion. Hydrogen bonding due to hydrophilic groups such as –COOH or –OH plays an important role in bioadhesion (Ali, 1999). Muco adhesives are synthetic or natural polymers, which interact with the mucus layer covering the mucosal epithelial surface and mucin molecules consisting a major part of mucus. The concept of muco adhesives has altered many investigators to the possibility that these polymers can be used to overcome physiological barriers in long term drug delivery. They render the treatment more effective and safe, not only for topical disorders but also for systemic problems.

Diltiazem Hydrochloride (Remington's, 1992; Joseph T Dipiro) is a Calcium channel blocker, Anti anginal. It is used in the management of hypertension, cardiac arrhythmias, angina pectoris and migraine. Diltiazem Hydrochloride is rapidly absorbed from the gastro intestinal tract. Only 40% of drug enters systemic circulation because of significant first pass effect in the liver. About 70-85% of circulating drug is bound to plasma proteins. Elimination half life is 3-9 hrs.

The aim of the present work is to develop controlled release formulation of Diltiazem Hydrochloride by mucoadhesive drug delivery system. Diltiazem Hydrochloride was selected in the present work due to short half life requires 3-4 times daily administration, the duration of action is increased by this mucoadhesive drug delivery. Thus due to above said reasons the drug has been selected and it has been formulated into mucoadhesive tablets. In view of various advantages associated with the mucoadhesive drug delivery it is

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proposed to develop the Diltiazem Hydrochloride controlled release tablets.

2. Materials and methods

2.1. Materials

Diltiazem Hydrochloride was obtained as a gift sample from Natco Pharma ltd., Hyderabad. Hydroxy Propyl Methyl Cellulose (HPMC) was obtained from SIRIS Labs, Vijayawada; Magnesium Stearate was obtained from Yarrow Chem. Products, Dom Bivli; Talc, Microcrystalline cellulose(MCC), Agar was obtained from SD fine chemicals, Mumbai; and Ethyl Cellulose (EC) was obtained from CDH, Mumbai.

2.2. Analysis of Diltiazem Hydrochloride

2.2.1. Calibration curve

The drug was analyzed by following the UV Spectrometric analysis procedure. Standard stock solution of Diltiazem Hydrochloride was prepared by dissolving 50mg of drug in distilled water and making up to 50ml with distilled water inorder to get a concentration of 1mg/ml. from this stock solution a series of dilutions ranging from1, 2, 4, 5, 10, 15 & 20 µg/ml were prepared using distilled water. The optical density of the each solutions was measured spectrophotometrically at a ë max of 240 nm (Beer's law is obeyed in the range of 1 to 20 µg/ml). The values are shown in Table 1 and the Calibration curve was plotted and shown in Fig. 1.

2.2.2. Study of drug properties

Drug properties like flowability (angle of repose), bulk density, compressibility index, particle size and its frequency are studied[7]. The results are shown in table 2.

2.2.3. Preparation of mucoadhesive tablets

Four tablet formulations i.e. F1, F2, F3 & F4 were prepared by taking different mucoadhesive polymers at different concentrations and combinations in order to study the effect of polymers on drug release and ultimately to produce controlled release profiles. The formulations were shown in Table 3.

The wet mass of the drug and other excipients was prepared using 50% alcohol as granulating liquid. The wet mass was passed through sieve no. 16 and the resultant wet granules were dried to equilibrium moisture content level at a temperature less than 50ºC in an oven. The dried granules were passed through sieve no. 20 and mixed with the other excipients i.e. lubricant and glidant and they were subjected for compression process using cadmach single pres punch to the optimum hardness. Microcrystalline cellulose was kept in the formula F2 & F3 at inter and intra-granular levels respectively. Then these tablets were stored in a suitable container and subjected to evaluation tests.

2.2.4. Determination of Physicochemical parameters

Average weight of 20 tablets was calculated and then the individual weight of each tablet was found. Percentage deviation was calculated and checked for weight variation. The results were tabulated in table 4. Friability test was carried by taking certain number of tablets as per IP. The results were tabulated in table 5. The hardness of tablet was tested by using Monsanto hardness tester. The hardness was adjusted to 4 kg/ cm^2 during preparation of the tablet itself. However, inorder to know the exact values the test was conducted by taking 10 numbers of tablets. The average volume was calculated from the individuals. The results are tabulated in table 5.

2.2.5. In vitro release studies

The drug release for F2, F3 and F4 were studied by using the I.P Dissolution apparatus-II. In this 900 ml of distilled water at 37 ± 1°C temperature (Dissolution fluid medium) was placed and the paddle was made to make 500 rpm. The 5ml samples were collected at regular intervals of 5, 10, 15, 30, 45, 60, 120, 180 minutes etc. and the test was continued up to 10 hours, with an interval of 1 hr. the optical densities were measured using spectrophotometer at a ë max of 240 nm. From the calibration curve the drug content was calculated and interpreted for the drug release characteristics. The studies were conducted twice and the average values were considered. In order to know the order of drug release, % undissolved Vs time plots were constructed (Dinsheet,1997). The dissolution data for formulations were shown in the table 6. The profiles were shown in fig.2.

2.2.6. Water sorption studies

This was done on 1% Agar gel plates. The tablets were placed with the core facing the gel surface & incubated for 6 hrs. at 37º C. The tablets were weighed before (W1) and after (W2) standing on the agar plate

& examined for any physical change and the amount of percentage swelling and water absorbed is calculated. Percentage swelling is calculated using the formula (W1-W2) / (W1) X 100. The results were tabulated in Table 7 & 8.

2.2.7. Measurement of Mucoadhesive strength

The method described by Y.Madhusudhana Rao followed for mucoadhesive strength measurement by detachment force measurement arrangement is shown in fig 3. It is consist of single organ bath, a stand, glass rod, and a pan for keeping beaker and a reservoir for addition of water on to a beaker. Immediately after slaughter the intestine was removed from the sheep and transported to laboratory and kept at 4º C in Tyrode solution. A fine hole was drilled in the centre of the tablet; a thread was passed through it and tied around the tablet. The other end of the thread is such that in the resting stage the tablet should be at the middle of the intestinal piece. To the other end of the glass rod a pan was tied in which beaker was placed. After inserting the tablet into the GIT segment & lightly pressing the tablet with the forceps, the assembly was kept undisturbed for a period of 30 min. and 1 hr, and then water was added with a burette slowly drop by drop onto the beaker. The amount of water required to pull out the tablet from the intestinal segment represents the force required to pull the tablet against the adhesion. The force in Newton's is calculated by the equation F=0.0098 X w/2, where w is amount of water (Madhusudhana Rao, 1998). The results are tabulated in Table 9.

3. Results and discussion

Mucoadhesive formulations of Diltiazem Hydrochloride were formulated to develop control release formulation. Prior to formulation drug properties like particle size, bulk density, flowability, compressibility index were studied. By observing the values that the drug is not suitable for direct compression technology and it was not passed through the 7mm diameter funnel. The average particle size was found to be 38.54 µm. so we proceed for wet granulation method. By using this method four formulations were formulated with different formulas.

In first formula (F1) drug and polymer (HPMC) was used at 1:5 ratio. By using hydro-alcoholic (50%v/v) mixture as granulating agent, granules were prepared. The obtained granules are very hard and they are not suitable for compression. This forced us to another formulation. In formulation 2 (F2) drug and polymer (HPMC) was used at 1:1 ratio and MCC was kept at intergranular level. By wet granulation technology granules were prepared and compressed as tablets. The formulated tablets were suitable for evaluation test. The weight variation, hardness, friability were found to be within the official limits. Water sorption studies were conducted by using 1 % agar gel plates. The amount of water absorbed and percentage swelling was showed in table 7 & 8. It was observed from the table that the swelling index was found to be increased slowly i.e. from 15.37% to 32.67% in a period of 1hr to 8hrs respectively. The drug release was also found to depend upon the swellability characteristics of tablet formulation 2. The results of dissolution profiles have indicated that in a period of 8 hrs almost 85% of the drug was released. After 8 hrs period the tablet was completely eroded, and hence in the dissolution studies almost the complete amount of drug release was noticed. The t50% and t90% of drug released were found to be 1.12 hrs and 4.30 hrs respectively. Mucoadhesive strength was measured for 30min and 60min. For 30 min it was found to be 0.30411 N i.e. it was found to be good. In this formulation MCC was kept at intergranular level, because MCC was water insoluble. To study the effect of insoluble MCC in drug release studies, though MCC was kept at intergranular level in F2, the drug release was not influenced by its presence. This was noticed in our dissolution studies i.e. the complete release was noticed though the MCC was present in the medium in insoluble state. Hence, as F2 did not execute control release profiles, Formulation 3 was proposed.

To achieve control release, another formulation (F3) was formulated. In this formula drug and polymer (HPMC) was at 1:1 ratio and MCC was used at intragranular level. By using the wet granulation technique the tablets were formulated and subjected for evaluation tests. The weight variation tests, hardness and friability were with in acceptable limits. Water sorption studies were conducted and water absorption and percentage swelling was calculated and shown in tables 7 & 8. The formulation has absorbed water slowly and it continued for longer period of time. Water sorption studies were conducted for 16hrs. Drug release characteristics were studied. By observing the values the drug release was

found to be 86.63% in 7 hrs. in comparison with F2 the water sorption characteristics were found to be slow i.e. swelling index was increased from 10.85% to 29.10% in a study period of 1 hr to 16 hrs. The drug release profiles were directly dependent on the swelling characteristics. The slower the swellability the more controllable the drugs release. The t50% and t90% values were found to be 1.36hrs and 7.48 hrs respectively, the tmax value was 86.63%.

Between the mucoadhesive strength and water soluble characteristics some comparative observations were noticed. It was observed from the tables 7 & 9 that the mucoadhesive strengths in F2 & F3 were identical, due to the similar concentration of HPMC, the mucoadhesive polymer. But the swellability characteristics were comparatively more in case of F2 and hence high mucoadhesive strengths were observed in F2 and F3 formulations. In case of F3 the slow swellability characteristics have improved the mucoadhesive strength, i.e. it was found to be 0.34N after 1 hour study period. However in case of F4 due to the lesser concentration of HPMC less mucoadhesive strength was noticed after a period of 1 hr study. The swellability characteristics were comparatively higher in comparison with F3. This might be due to the lesser hardness i.e. 3.5 kg/cm^2. Though it was tried to improve its hardness of F4 in our experimentation we could not achieve it.

In formulation F4 drug and polymer mixture was used. In this formula drug: HPMC: EC was used at 1:0.5:1 ratio. The formulated tablets were subjected to evaluation tests. The weight variation, hardness and friability were found to be with in the acceptable limits. Water sorption studies were conducted. Based on the observation initially the water sorption was found to be good. After 1 hr the % drug release was found to be 31.5. After one hour it was increased rapidly i.e. t50% and t90% were found to be 1.6 hrs and 3.6 hrs respectively. By observing the drug release studies this formulation is considered as a conventional dosage form. This is because due to less hardness. Mucoadhesive strength was measured and it was found to be comparatively less than F3.

The drug release characteristics are to be altered due to the presence of EC in formulation 4. However it was observed in our present study, obtained granules have exhibited lesser hardness to the resultant tablets. The future scope for these studies is the alteration of the binders and production of tablets with ideal hardness of 5 kg/cm^2.

By observing the above results it was noticed that formulation 3 was found to be control release formulation. In this formulation MCC was kept at intragranular level due to its aqueous insolubility it controls the drug release rather than its intergranular level.

4. Conclusion

From these studies it was concluded that a rational selection of the type and amount of the mucoadhesive polymers and other excipients are necessary in designing the control release mucoadhesive tablets, as they directly influence the ultimate release characteristics.

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Table 1: Concentration Vs Absorbance of Diltiazem Hydrochloride at 240 nm

S.No	Concentration (µg/ml)	Absorbance
1	1	0.060
2	2	0.121
3	4	0.231
4	5	0.284
5	10	0.574
6	15	0.806
7	20	1.026

Table 2: Drug properties of Diltiazem Hydrochloride

S.No	Property	Results
1	Angle of repose	Drug molecule did not pass through the 7 mm diameter funnel tube
2	Bulk Density(gm/cc)	0.55
3	Compressibility index (%)	16.66
4	Average Particle size(µm)	35.548

Table 3: Composition of various mucoadhesive tablets

S.No	Ingredients	Quantity (mg) per 1 Tablet			
		F1	F2	F3	F4
1	Diltiazem hydrochloride	60	60	60	60
2	Hydroxy Propyl Methyl Cellulose	300	60	60	30
3	Micro Crystalline Cellulose	--	100	100	70
4	Ethyl Cellulose	--	--	--	60
5	Magnesium Stearate	0.3	0.3	0.3	0.3
6	Talc	0.3	0.3	0.3	0.3
	Total weight	**360.6**	**220.6**	**220.6**	**220.6**

Table 4: Weight variation data of tablet formulations

S.No	Formulation	Weight variation		Passed/ Failed
		Max. Deviation	Min. Deviation	
1	F2	+2.55	-2.08	Passed
2	F3	+3.20	-2.90	Passed
3	F4	+4.55	-3.08	passed

Table 5: Percentage friability & Hardness of tablet formulations

S.No	Formulation	%Friability	Hardness(kg/cm²)
1	F2	0.78	4.5
2	F3	0.85	4.0
3	F4	0.90	3.5

Table 6: Rate of drug release of formulations F2, F3, and F4

s.no	Time	F2		F3		F4	
		Concentration (µg/ml)	% Drug release	Concentration (µg/ml)	% Drug release	Concentration (µg/ml	% Drug release
1	5 min	3.96	6.02	6.30	9.62	12.60	19.25
2	10 min	6.03	9.16	9.00	13.75	13.50	20.62
3	15 min	8.82	13.14	10.80	16.50	17.10	26.12
4	30 min	14.58	22.17	15.30	23.37	21.60	33.00
5	45 min	17.64	26.82	17.10	26.12	27.90	46.62
6	60 min	21.15	32.16	25.20	38.50	31.50	48.12
7	2 hrs	30.15	45.84	37.80	57.75	45.90	70.12
8	3 hrs	37.80	57.48	46.80	71.50	58.50	89.38
9	4 hrs	44.10	67.06	52.20	79.75	66.60	101.75
10	5 hrs	47.25	71.85	54.00	82.50	71.10	108.63
11	6 hrs	54.00	82.11	54.90	83.88	72.00	110.00
12	7 hrs	56.25	85.53	56.70	86.63	72.90	111.38

Table 7: Percentage swelling for formulations F2, F3, and F4

Time in Hours	F2	F3	F4
1	15.37%	10.85%	10.40%
2	18.25%	14.50%	17.09%
4	26.69%	18.15%	29.65%
8	32.67%	23.94%	36.10%
16	Tablet eroded	29.10%	39.5%

Table 8: Water sorption studies of formulations F2, F3, and F4

S.No	Time	Formulation	Initial weight(gm)	Final weight(gm)	Water absorbed
1	1hr	F2	0.2400	0.2836	0.436
		F3	0.2299	0.2579	0.280
		F4	0.2299	0.2566	0.267
2	2hrs	F2	0.2400	0.2936	0.536
		F3	0.2299	0.2689	0.390
		F4	0.2299	0.2773	0.474
3	4hrs	F2	0.2400	0.3263	0.863
		F3	0.2299	0.2809	0.510
		F4	0.2299	0.3268	0.969
4	8hrs	F2	0.2400	0.3565	0.1165
		F3	0.2299	0.3023	0.724
		F4	0.2299	0.3598	0.1299
5	16hrs	F2	0.2400	Tablet eroded	--
		F3	0.2299	0.3243	0.944
		F4	0.2299	0.3800	0.1501

Table 9: Detachment force measurement data for formulations

S.No	Formulations	Volume of water requires(ml)		Force (Newton's)	
		30 min	60 min	30 min	60 min
1	F2	62	24	0.304	0.117
2	F3	62	71	0.304	0.3482
3	F4	60	34	0.294	0.1667

Fig 1: Calibration curve of Diltiazem Hydrochloride

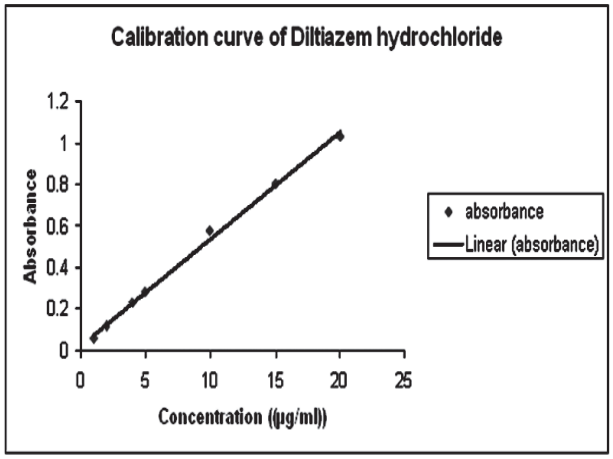


Fig 2: Dissolution profiles of F2, F3 and F4

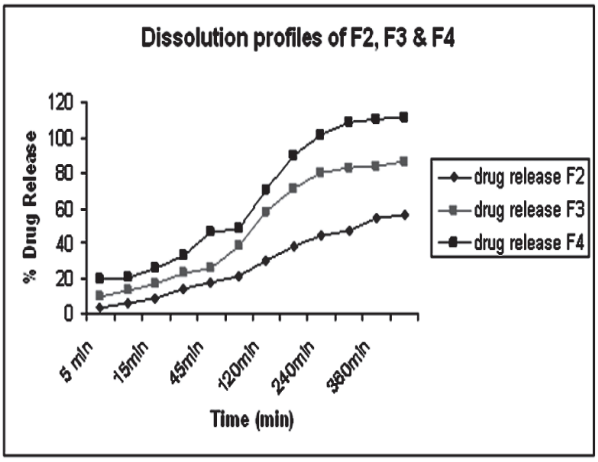
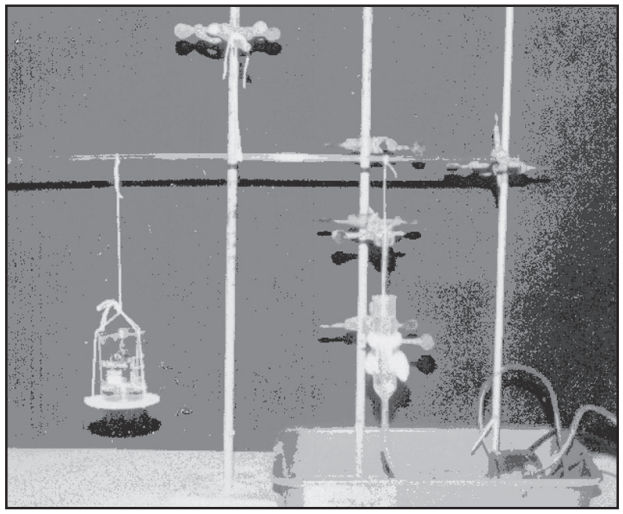


Fig 3: Detachment force measurement apparatus arrangement



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