FORMULATION AND EVALUATION OF MUCCOADHESIVE BUCCAL PATCH CONTAINING DILTIAZEM HYDROCHLORIDE

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Abstract *:* The present study aims to formulate mucoadhesive buccal drug delivery system of Diltiazem Hydrochloride, in view to improve the bioavailability of drug; which undergoes extensive hepatic first-pass metabolism, leading to increased dose and side effects. The concentration of polymers like HPMC-E-5, PVA, and plasticizers like Glycerin, Dibutyl-phthalate, and solvents was optimized through preliminary study. Depending upon the results of Trial Batches, the concentration of polymers and plasticizers was optimized. The results were analyzed. The optimized formulation batch was found to be D4D, containing diltiazem hydrochloride 30mg, PVA 250mg, DBP 5%, and D/W 2ml and Acetone 8ml. The stability study of D4D formulation revealed that formulation was stable.

Key Words: Diltiazem hydrochloride, buccal delivery, buccal patches.

INTRODUCTION

Diltiazem hydrochloride is Diltiazem is a potent vasodilator increasing blood flow and variably decreasing the heart rate via strong depression of A-V node conduction. Its pharmacological activity is somewhat similar to verapamil. Potent vasodilator of coronary vessels.Vasodilator of peripheral vessels. This reduces peripheral resistance and afterload. Negative inotropic effect. Diltiazem causes a modest decrease in muscle ability and reduces heart muscle chemical element consumption. Negative chronotropic effect. Diltiazem causes a modest lowering of heart rate. This effect is due to the slowing of the SA (sinoatrial) node. It results in reduced myocardium oxygen consumption. Negative dromotropic effect. By deceleration conductivity through the Av (atrioventricular) node, diltiazem increases the time needed for each beat. This ends up in reduced heart muscle chemical element consumption by the body.

Systemic bioavailability of diltiazem hydrochloride following oral administration is about 40%, due to extensive presystemic metabolism in the gut wall and wall 75% - 80%.plasma half-life of diltiazem hydrochloride is 3 – 4 hrs.molecular weight is 414.51, and it does not have an objectionable taste. All these factors and problems associated with oral and parenteral routes make diltiazem hydrochloride an appropriate candidate for Bucco-adhesive formulations.

MATERIALS AND METHODS

CHEMICALS: Diltiazem hydrochloride, HPMC – E – 5,Polyvinyl alcohol ,Glycerin , Di- butyl phthalate ,Acetone.

Instruments/Equipments:

I. UV double beam spectrophotometer(Shimadzu Corporation, Japan)
II. FTIR 200 Spectrometer(Spectrum one, PerkinElmer, USA)
III. Hot air oven(spectrumPvt. Ltd)
IV. Franz diffusion cell(Bhanu Scientific Instruments Co. Bangalore)
V. Electronic Balance (CG 153)(Scaltech)
VI. Screw gauge(Dolphin)
VII. Magnetic stirrer(Remi Equipments,Mumbai, India)
VIII. pH-meter(Elico India Pvt. Ltd)
IX. Sonicator(Dolphin)
X. Stability chamber (Thermolab India)

METHODOLOGY

IR spectrum interpretation

The infrared spectrum of the pure Diltiazem Hydrochloride sample was recorded and the spectral analysis was done. The dry sample of the drug was directly placed after mixing and triturating with dry potassium bromide.

UV spectroscopy:

I. Determination of λmax

A 10mg of Diltiazem Hydrochloride was accurately weighed and was first dissolved in 35ml methanol. The solution was then diluted using phosphate buffer (pH- 7.4) to 100 ml. The UV spectrum was recorded in the wavelength range of 200-400 nm.

II. Preparation of calibration curve for Diltiazem hydrochloride

A standard curve was prepared by dissolving 10 mg of diltiazem hydrochloride in 50ml of d/w. It was further diluted with d/w to get solutions in the concentration range of 3 to 15 µg /ml. The absorbances of these solutions were determined spectrophotometrically at 237 nm.

FORMULATION OF BUCCAL PATCHES:

Formulation of Drug Incorporated Buccal Patches:

The reservoir-type buccal patches containing diltiazem HCl were prepared using different ratios of HPMC – E – 5 and polyvinyl alcohol. The polymers in different ratios were dissolved in the respective solvents. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Di-n-butyl phthalate and glycerin were used as plasticizers. Then the solution was poured on the Petri dish having a surface area of 12.99 cm2 and dried at the room temperature. Then the patches were cut into 1cm2 patches.

Table: 1.Formulation ingredients of DHCL patches

FORMULATION CODE	D R U G (DHCL)	POLYMER	PLASTISCISER	S O L V E N T
D1G	30mg	HPMC-E-5 250gm	Glycerin10%	D/W : ACETONE 2M:8ML
D2G	30mg	HPMC-E-5 250gm	DAB 5%	D/W : ACETONE 2M:8ML
D3G	30mg	HPMC-E-5 250gm	Glycerin10%	D/W : ACETONE 2M:8ML
D4G	30mg	HPMC-E-5 250gm	DAB 5%	D/W : ACETONE 2M:8ML

RESULT& CONCLUSION:

FTIR study :

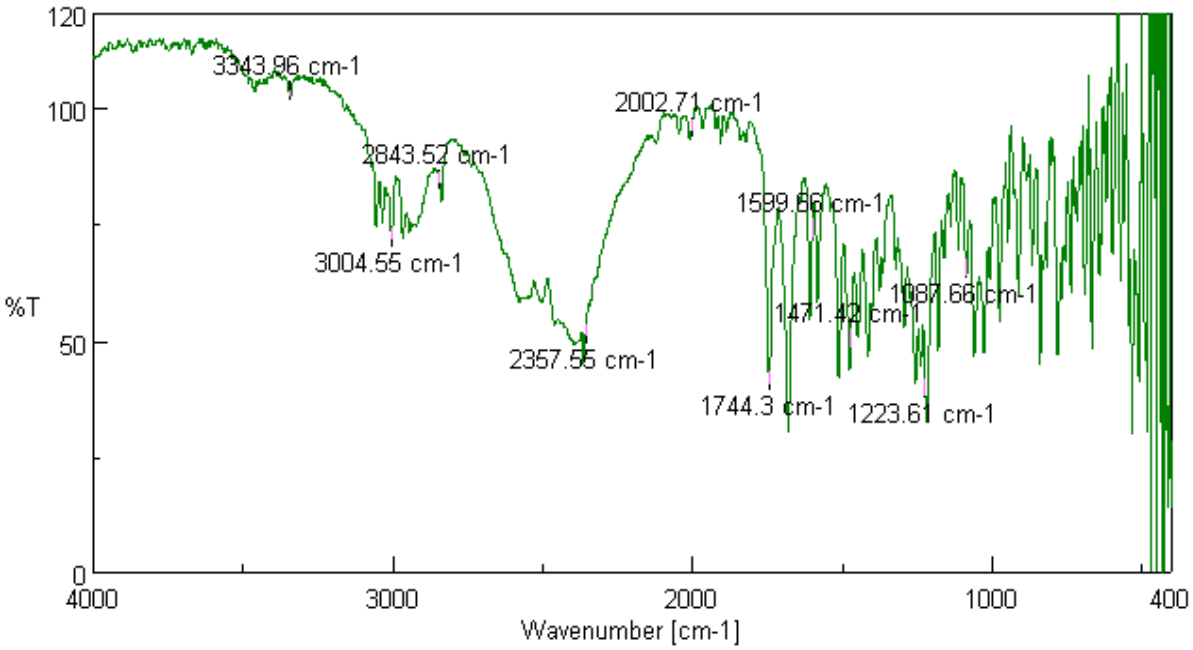

Fig. 01: IR spectra of diltiazem hydrochloride

UV spectroscopy

I. Determination of λmax :

The peak showed in the figure is much similar to the reported peak. The spectrum obtained is shown in the figure i.e. 237nm.

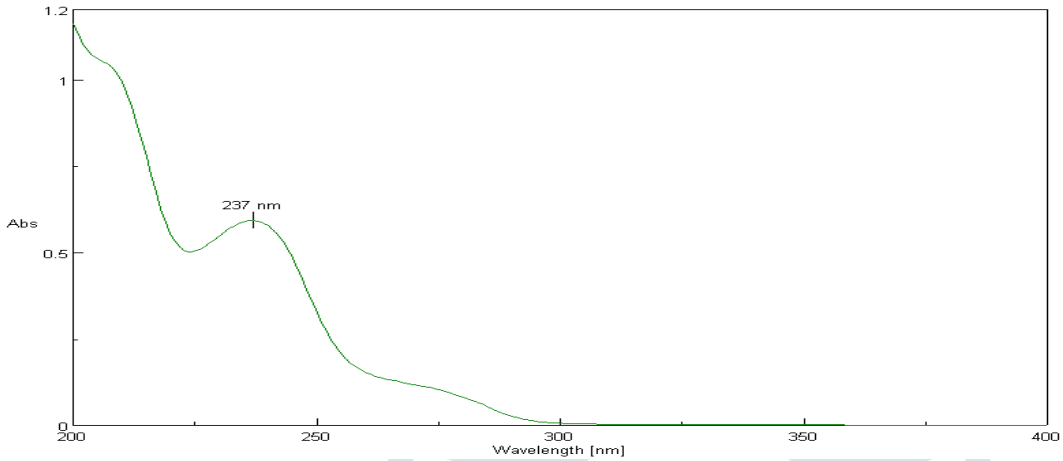

Fig.02: UV spectrum of diltiazem hydrochloride

EVALUATION OF BUCCAL PATCHES:

table 02: physical characterization of buccal patch

SR	CHARECERIZATION	OBSERVATION
1	SHAPE	ROUND
2	COLOUR	TRANSPARENT
3	APPEARANCE	SMOOTH

fig.03buccal patch

table :weight variation, thickness and % moisture absorption and water vapor transmission of buccal patch

FORMULATION code	Waight variation (mg)	**Thickness (mm)**	% MOISTURE UPTAKE	WATER VAPOUR TRANSMISSION, GM CM-2 H-1
D 1 G	329.25±7.365	0.98±0.01	4.5 %	3.930×10-6±0.3841
D 2 D	331±7.958	0.98±0.01	4.8 %	2.216×10-6±0.5804
D 3 G	336.5±2.380	0.98±0.01	5.01 %	1.634×10-6±0.2269
D 4 G	353±8.524	0.98±0.01	5.8 %	1.882×10-6±0.1825

n=3; standard deviations for three determinations

Table03: weight variation, thickness and % moisture absorption and water vapor transmission of buccal patch

Tensile strength and % elongation at break of buccal patch

FORMULATION CODE	TENSILE STRENGTH	% ELONGATION
D1G	2.89 gm/mm2	08.33 %
D2D	3.20 gm/mm2	16.88 %
D3G	3.57 gm/mm2	33.33 %
D4D	3.56 gm/mm2	58.88 %

n=3; standard deviations for three determinations

Table 04: Tensile strength and % elongation at break of buccal patch

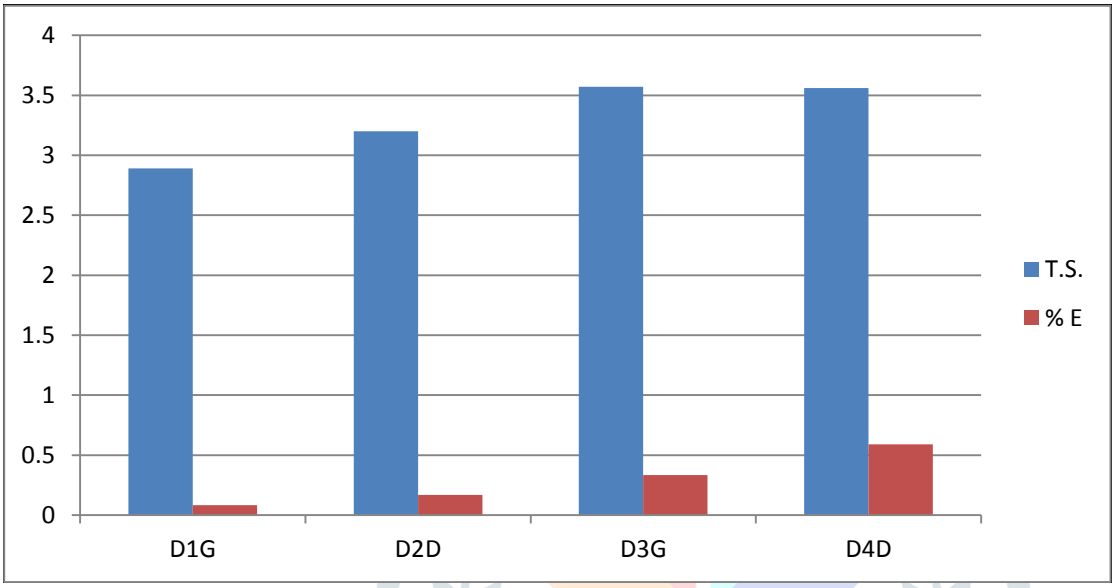

Fig.04: Tensile strength and % elongation at break of buccal patch

surface pH and folding endurance of buccal patch

FORMULATION	SURFACE pH	FOLDING ENDURANCE
D1G	6.16	208 ± 4
D2D	5.8	216 ± 2
D3G	6.9	221 ± 5
D4D	7.2	284 ± 3

n=3; standard deviations for three determinations

Table 05:.surface pH and folding endurance of buccal patch

Drug content of the buccal patch

SR. NO.	FORMULATION CODE	DRUG CONTENT
1	D1G	98.89 ± 0.64
2	D2D	98.62 ± 0.72
3	D3G	99.31 ± 0.37
4	D4D	99.34 ± 0.95

n=3; SD for three determinations

Table 06: drug content of the buccal patch

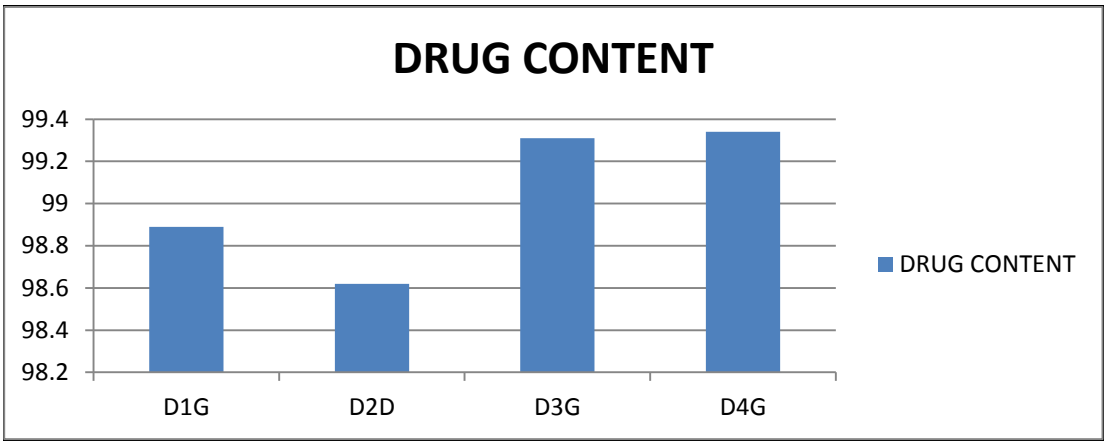

Fig.05: drug content of the buccal patch

SWELLINGINDEX :

The comparative percentage swelling of various formulation shown in table and fig.also.

Table 07: swelling index of buccal patch

SR. NO.	FORMULATION CODE	SWELLING INDEX
1	D1G	31.62±0.889
2	D2D	37.64±0.996
3	D3G	40.02±1.416
4	D4D	41.16±1.242

n=3; standard deviations for three determinations

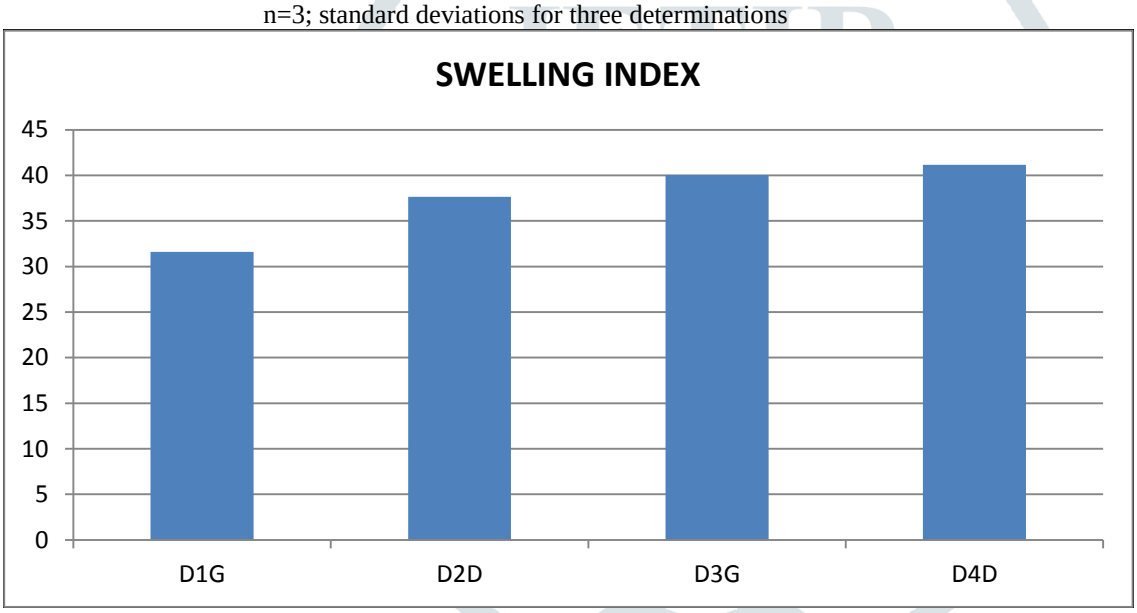

Fig.06: Swelling index of buccal patch

DIFFUSION STUDY:

Among all four formulations shows that formulation D4D has better drug release compared to other formulations.

DIFFUSION STUDY OF D4D:

Table 08: diffusion study of D4D

TIME	PURE DRUG	ABS	CONC.	AVG %	% CDR (D4D)	% LOG CDR
5	0.0623	0.0124	0.03	0.106	0.106	0.7958
10	0.087	0.0488	0.03	0.106	0.212	0.6736
15	0.245	0.0882	0.11	0.353	0.565	0.2471
30	0.363	0.189	0.3	0.992	1.557	0.1922
45	0.454	1.128	0.4	1.335	2.898	0.4620
60	6.736	1.32	2.06	6.892	9.744	0.9887
90	14.95	2.122	2.56	8.546	18.29	1.2622
120	24.92	2.462	4.21	14.02	32.31	3.5093
150	36.41	2.652	5.06	16.87	49.18	1.6917
180	49.92	5.344	5.48	18.25	67.43	1.8288
240	66.24	5.963	11.06	36.87	89.3	2.1417
300	84.82	7	12.96	43.2	98.3	2.1682
360	103.4	7.001	15.71	103.04	123.89	2.1786

COMPARATIVE STUDY OF PURE DRUG Vs D4D

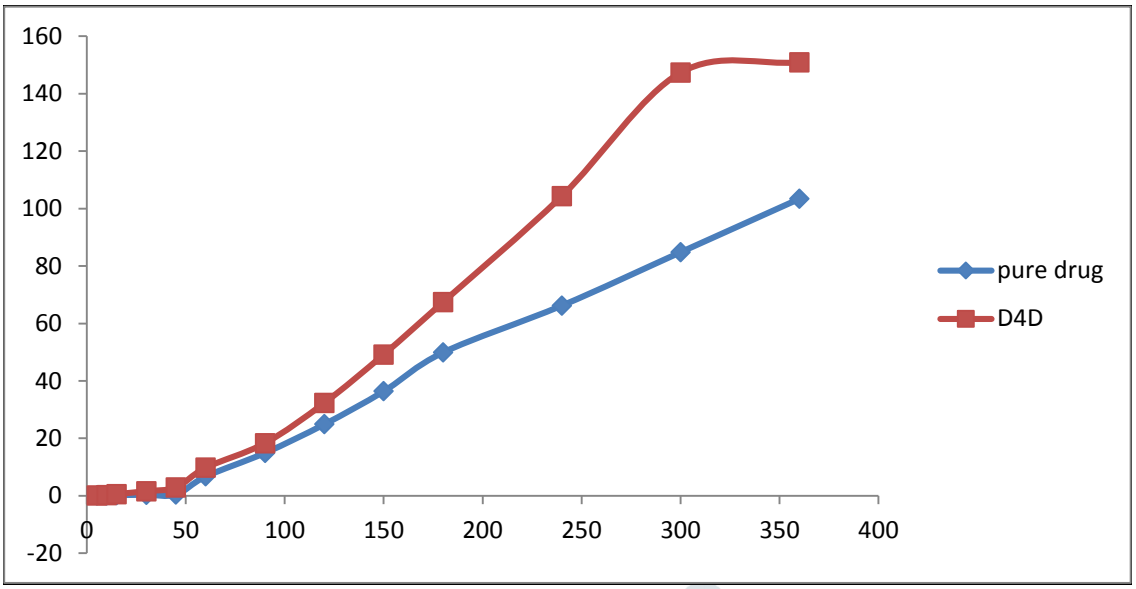

Fig.07: a comparative study of pure drug Vs D4D

STABILITY STUDY:

Table 09: stability study

FORMULATION CODE	TIME	APPEARANCE	THICKNESS(mm)	DRUG CONTENT
D 1 G	1month	Smooth	0.98	80.80±0.98
D 2 D	1month	Rough	0.98	89.62±0.67
D 3 G	1month	Smooth	0.98	90.00±0.12
D 4 D	1month	Smooth	0.98	99.34±0.11

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