RESEARCH PAPER

Received 6 April 1996
Accepted 2 February 1997
Indian J. Pharm. Sci., 1997, 59(2) pp.49-54

Development of Transdermal Patches of Verapamil Hydrochloride using Sodium Carboxymethyl Guar as a Monolithic Polymeric matrix and their invitro release studies

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An attempt has been made to develop Transdermal patches of Verapamil HCl by using Sodium Carboxymethyl Guar as a Polymer matrix, Propylene glycol as the plasticiser and Alupoly foil as the backing membrane. A comparison of various polymers and plasticisers were also made. *In vitro* release studies through mouse skin have shown that Sodium Carboxymethyl Guar as a suitable polymer. The primary skin irritatancy tests have shown that the transdermal patches are non irritant.

VERAPAMIL is a calcium channel blocker used widely in the treatment of supraventicular tachyarrythmias, angina and hypertension and administered as plain and sustain release oral dosage forms.

Although verapamil is almost completely absorbed from the Gastro intestinal tract, it is subjected to considerable firstpass metabolism in the liver. The oral dose required to achieve comparable plasma concentration is about 10 times higher than the intravenous dose. The plasma half life is 2-7 h.

In view of the substantial hepatic first pass effect and the shorter plasma half life, verapamil is chosen as a candidate for exploring its application as Transdermal Drug delivery systems. Permeability studies through mouse skin have shown verapamil to be permeable.

The transdermal route of drug delivery is becoming increasingly popular with the demonstration of the percutaneous absorption of a large number of drugs. Rationale underlying the use of trandermal drug administration has been dealt with detail by Chien[1,2] and physico chemical consideration by Zatz[3]. Various natural and synthetic polymers have been used in the formulation of transdermal matrices. In view of its excellent film forming property, Sodium Carboxymethyl Guar (Sodium CMG) has been chosen and studied for its usefulness as a monolithic polymeric matrix in the development of transdermal patches. The free film and laminated films were studied in detail and found to be suitable for the development of transdermal patches.[4]

EXPERIMENTAL

Materials

Sodium Carboxymethyl Guar has been synthesised in our laboratory. Verapamil Hydrochloride I.P. was obtained from Associated Drug Co., B'lore Alupoly Foil (0.05mm thickness) was purchased from Annapoorna foils, Hyderabad. Propylene.Glycol I.P. was procured from Huls, West Germany.

Preparation of Casting Solutions

The casting solutions were prepared by dissolving appropriate polymers and plasticisers in distilled water. The drug was then added to the solution and dissolved by heating on a water bath and the heating

Table - 1

Formulation details of Transdermal Patches of Verapamil HCl with Sodium Carboxymethyl Guar as the film forming material

Concentration of the Drug Verapamil HCl = 1.0% w/w of solution

Physical appearence of patches were all Uniform

Code	Concentration of the polymer (% w/w of solution	Concentration of the plasticiser Propylene Glycol (% w/w of Polymer)	pH of the Casting solution	Thickness of the patches (microns)	Weight* of the Patches (mg.)	Drug** content $(mg/cm)^2$
A	4.0	2.5	6.5	125 ± 0.8	290	3.9
B	4.0	5.0	6.5	128 ± 0.8	285	4.2
C	4.0	7.5	6.5	126 ± 0.8	278	4.1
D	4.0	10.0	6.4	129 ± 1.5	300	4.1
E	3.0	5.0	6.6	99 ± 0.2	225	3.9
F	2.0	5.0	6.5	35 ± 1.0	95	3.8
G	1.0	5.0	6.0	19 ± 1.2	45	4.1
H	4.0	5.0	6.0	124 ± 1.0	285	4.0
I	4.0	5.0	5.0	123 ± 1.2	275	4.1
J	4.0	5.0	4.0	118 ± 1.3	260	3.9

* = mean of 5 observations.

** = mean of 2 observations.

was continued for 30 min. to effect complete dissolution.

Preparation of Transdermal Patches

Aluminium Foil laminated with low density polyethylene was used as the backing membrane. A foil cup (7.0 cm dia) was prepared by pressing the foil between 2 plastic cups (telescoping one inside the other) developed for this purpose. The foil cup was kept on a table with smooth horizontal surface. About 15 ml of the solution containing the drug and the plasticiser was cast on the foil (38.47 cm^2 area). The cup containing the solution was dried at 50° for 10 h and the patches with 3.6 cm diameter (10 cm^2 area) was cut and taken for **in vitro** release studies. Different patches were prepared by varying the pH of the casting solution and by using different polymers such as gelatin, polyvinyl pyrrolidone, polyvinyl alcohol and combination of PVA and PVP with 1:1 preparation and sodium carboxymethyl cellulose. The formulation details of the casting solutions and the patches are shown in Table No. 1 and 2.

In Vitro Release studies using Mouse Skin

Poly carbobate feeding bottle was modified and used a diffusion cell. The bottle lid was modified to hold the transdermal patches (Backing membrane facing outside and the film facing inside). The bottle was kept horizontally over a magnetic stirrer with heating arrangement to keep the solution under stirring at 32°. A sampling port was provided by drilling a hole at right side top Fig. 1.

Table - 2

Formulation details of Transdermal patches of Verapamil HCl with different polymers as film forming materials

Concentration of the Drug in the casting solution = 1.0% w/w Physical appearence of patches were all Uniform

Code	name of the polymer	Concentration of the polymer (% w/w of solution)	Concentration of the plasticiser Propylene Glycol (% w/w of Polymer)	pH of the Casting solution	Thickness of the patches (microns)	Weight* of the Patches (mg.)	Drug** content (mg/cm)^2
K	Gelatin	10.0	10.0	5.5	150 ± 1.5	275.0	4.0
L	Polyvinyl Alcohol (PVA)	4.0	10.0	6.8	120 ± 1.0	250.0	4.2
M	Polyvinyl Alcohol & Polyvinyl Pyrrolidone (PVA:PVP) {1:1}	4.0	10.0	6.0	118 ± 0.9	240.0	4.3
N	Sodium carboxy Methyl guar	4.0	10.0	6.5	115 ± 0.9	237.0	4.0
O	Sodium carboxy methyl cellulose	4.0	10.0	6.5	125 ± 0.8	290.0	3.9
P	Sodium carboxy Methyl Guar	1.0	5.0	6.4	119 ± 0.9	288.0	4.1

* = mean of 5 observations.

** = mean of 2 observations

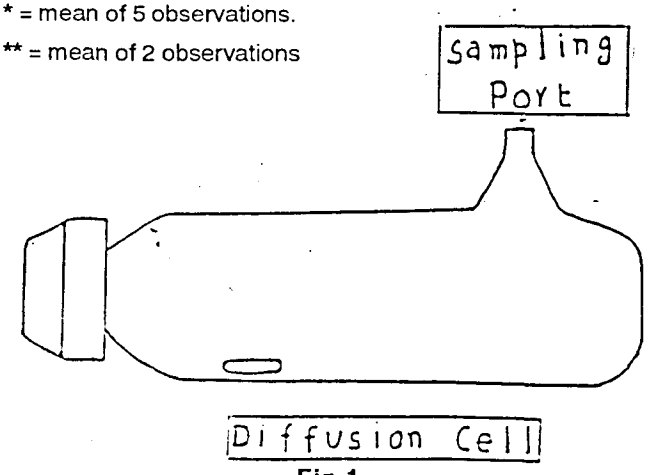

Fig 1

Mouse skin was excised from the abdomen and treated with 0.32 N ammonium hydroxide to facilitate the removal of hair and adhering substances, tissue from the skin surface. The skin was trimmed into circular section of about 4.0 cm diameter and washed well with water. The transdermal patch was then placed over the skin (the polymer matrix facing the stratum corneum side) and mounted with cap of the diffusion cell and clamped securely on to the receptor compartment with dermis side of the skin facing the receptor solution (distilled water 250 ml). The area of the patches exposed for release was 10 cm^2.

The receptor solution was constantly stirred with a star headed magnet and the termperture was main-

Table - 3
Comparative Evaluation of release of Verapamil HCl form various experiments

Patches used	Cumulative release in 9 hours (mg)	Flux $\mu g/cm^2/hr$	Patches used	Cumulative release in 9 hours (mg)	Flux $\mu g/cm^2/hr$
Code A	0.80	8.0	Code I	3.80	42.2
B	1.8	20.0	J	5.10	56.7
C	1.60	17.7	K	0.30	3.3
D	1.95	21.7	L	1.0	11.1
E	2.50	27.8	M	0.90	10.0
F	3.25	36.1	N	0.60	6.7
G	3.60	40.0	O	1.9	21.1
H	2.25	25.0	P	3.75	41.7

Release Profile of Verapamil HCL from Transdermal Patches with different Polymer Matrices

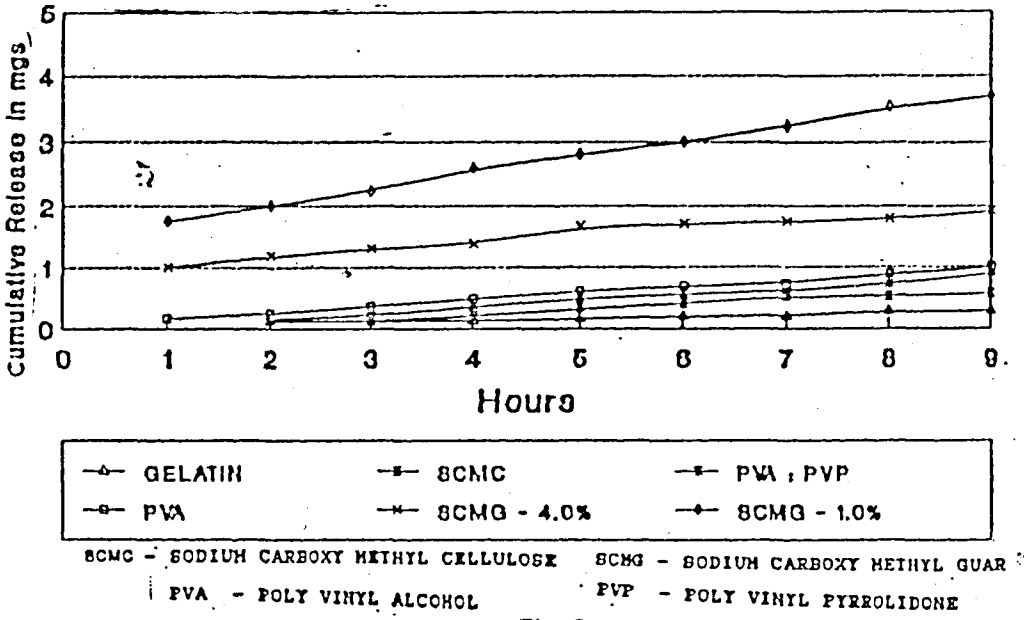

Fig. 2

tained at 32° ± 1°. At specified intervals of every hour for 9 h, 10 ml of the sample was withdrawn and replaced immediately with the same volume of distilled water.

The release of verapamil hydrochloride in to the dissolution medium from various transdermal patches were analysed by UV Spectrophotometry at 229 nm. The releases study of the selected transdermal patches was then carried out for 9 h period

Release Profile of Verapamil HCL from Transdermal Patches influence of Varying Concentrations of Polymer

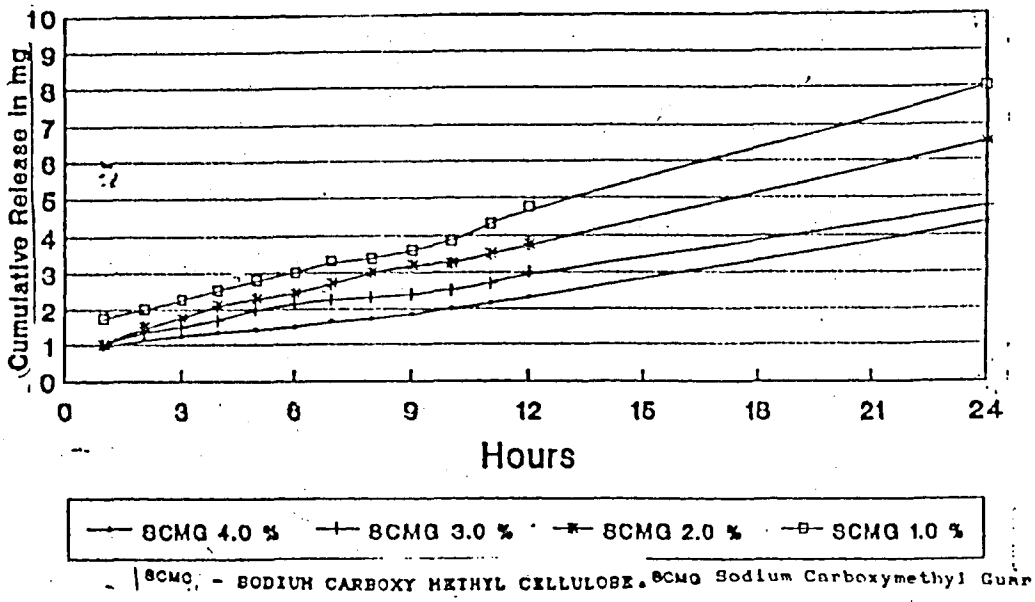

Fig. 3

as usual and the release profile are shown in Figure 2 and 3.

Comparative evaluation of release of Verapamil hydrochloride from various experiments undertaken

The details of the comparison of release of verapamil hydrochloride from various experiments are recorded in Table No. 3. Out of 16 experiments by varying polymer concentration, plasticiser concentration, pH of the casting solution, it has been found that the experiment with Code "J" gave maximum release. The results were confirmed repeating the experiment as follows:

4.0% w/v of sodium carboxymethyl guar was used as the polymer matrix. The plasticiser propylene glycol was used at 5.0% w/w of the polymer sodium carboxymethyl guar. The casting solution was prepared by dissolving the drug, the polymer and the plasticiser in McIlvaine buffer solution at pH 4. The release profiles are shown in Figure 4.

RESULTS AND DISCUSSIONS

Low molecular weight, excellent permeability through the mouse skin, considerable first pass metabolism in the liver and shorter plasma half life of verapamil hydrochloride prompted us to select it as the drug candidate for the development of transdermal patches. Total quantity of verapamil hydrochloride was released within 30 min., when the drug was allowed to release without barrier into the receptor medium. Studies on the effect of varying proportions of the plasticiser propylene glycol as 2.5%, 5.0%, 7.5% and 10.0% w/w of the polymer in the transdermal patches showed an increased amount of cumulative release with increase in the plasticiser concentration. The influence of pH on the release of verapamil hydrochloride was studied by preparing transdermal patches by casting the solution containing the drug plasticiser and the polymer in the McIlvaines' buffer solution with varying pH at 4.0, 5.0, and 6.0. There was increase in the cumulative release with corresponding decrease in pH values. The polymer concentration was kept 4.0% w/v for all the above experiments. The study was performed by varying the thickness of the film, by varying the proportion of the polymer in the casting solution. In

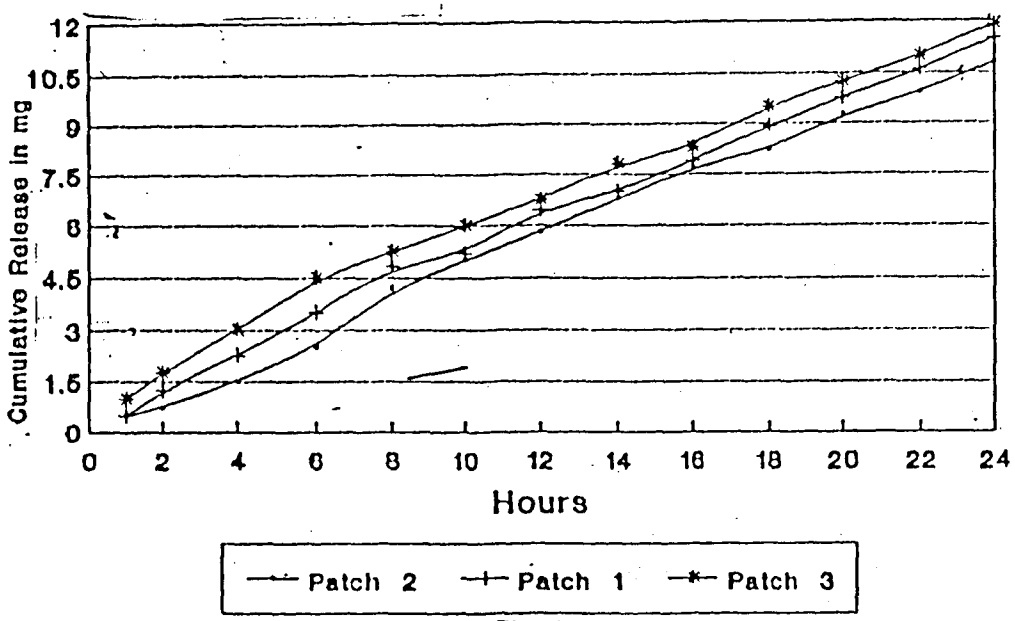

Fig. 4

***In vitro* Release of Verapamil HCl from Transdermal Pathes**

these cases, the percentage of the plasticiser to weight of the polymer was kept constant at their usual concentrations. It has been shown that by decreasing the concentration of the polymer, there was an increase in the drug release.

Subsequently, a study was also performed by preparing and evaluating trandermal patches with different polymers such as gelatin, Hydroxy propyl methyl cellulose, PVA; PVP and sodium carboxymethyl cellulose. It was interesting to observe that the release was better in case of sodium carboxymethyl guar which appeared to be a better polymer for preparing transdermal patches.

Comparative evaluation of release profile of all experiments revealed that experiment with code 'J' gave maximum release. Hence experiments were planned on the guidelines and the release studies were done on three patches having the same composition of experiment with code 'J'. It has been observed that a cumulative release of 11 mg of verapamil hydrochloride could be obtained at 24 h release period.

The primary skin irritancy test studies conducted on albino rabbit skin has shown no signs of erythema or oedema indicating that the transdermal patches are safe for use.

ACKNOWLEDGEMENTS

The authors express their gratitude to the President of Jagdale Scientific Research Foundation Shri R. Nagaraja Rao for his encouragement and providing all the facilities.

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