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Original research article

Transdermal drug delivery system of cardiovascular drug-verapamil

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Abstract

Verapamil is a calcium channel blocker. When administered by orally, undergoes extensive first pass metabolism. When these two drugs are administered via Transdermal rout would reduce deficiencies which associated by oral administration and enhance bioavailability. In the présent study, Transdermal Patches of verapamil hydrochloride were developed by different ratios of Hydroxypropyl Methylcellulose, (HPMC) Eudragit RL-100, Eudragit RS-100 and Ethylcellulose (EC) by solvent evaporation technique. The effect of Dimethyl Sulfoxide (DMSO) on Transdermal Delivery of Verapamil was studied. *Ex vivo* drug release was performed on albino rat abdominal skin by use of Franz diffusion cell. The diffused drug was analysed by Uv-Spectrophotomèter. *In vivo* drug release and important pharmacokinetics were determined on male albino rats, there leased drug in plasma was measured by using HPLC. The drug-polymer interaction was evaluated by FTIR. All formulations were subjected to physicochemical evaluation tests like drug content, weight variation, thickness, moisture absorption and loss, water vapor transmission rate, percentage of flatness, folding endurance, skin irritation and stability. All these test results were showed satisfactory

Keywords: Verapamil, HPLC, Uv-Spectrophotomèter, transdermal patch

1. Introduction

Drugs administered in the traditional forms generally produces bulky range of fluctuations in plasma of drug its leads to unwanted effects like toxicity or poor efficiency of drug. This factor further more repeated dosing and irregular absorption get the approach of the controlled drug delivery (CDDS).

Advantages

- TDDS is to divert the hepatic and pre-systemic metabolism of therapeutic.
- active drug(s) resulting increasing bioavailability.
- To avoid the inconveniences of i.v. therapy and risk.
- Once administer TDDS to decreases dose administration intervals and to provide desirable sustained, extended drug release for fixated period.
- To provide simple end of drug therapy or treatment.
- To ensure better patient conformity due to elimination of multiple dosing.
- To provide better remedial efficiency by avoiding the fluctuations in peaks plasma drug.
- Self-administration is possible.

Disadvantages

- The following characteristics of drugs cannot be suitable for this route.
- The drug(s) need in high dose to produce pharmacological action not suitable.
- Those drugs cause irritation, dermatological disorders.
- Drugs have higher molecular weight.
- Degradation when passing across skin.
- The skin is different in nature from place to place and from person to person and also with age [1].

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Transdermal drug delivery patches preparation

Methods

The TDDS patches are prepared by following methods, which are:

Mercury substrate method

Weighed required quantity of polymers dissolved in solvent mixture, then added plasticizer and drug solution added and vortexed. is then poured within the glass bangles placed on mercury surface in a petriplate the rate drying controlled by covering funnel on surface of petriplate in inversion.

Glass substrate method

According to this method the drug polymeric solution simply poured on a glass petri plate, allowed for dry.

Teflon method

The prepared solutions add plasticizer and drug solution and vortexed for 10min then poured within the Teflon circular plate and this was allowed a side for drying [2-5].

2. Materials and Methods

Analytical method development for verapamil

Preparation of Sorenson Phosphate Buffer pH 7.4

Solution X: 35.61 grams of Na2HPO4.2H2O taken in 1000 ml of (volumetric) flask and up to the mark filled with distilled water, and then mixed until dissolved

Solution Y: 27.6 grams of NaH2PO4.H2O taken in 1000 ml of (volumetric) flask and filled with water up to the mark and then mixed until dissolved.

Taken 40.5 ml of solution X solution and 9.5 ml of Y solution in a 50 ml of flask and mixed together to obtain 50 ml 0.2M buffer and it was checked to confirm the pH is 7.4.

Preparation of verapamil stock solution

100 mg of Verapamil, and placed in 100 ml of volumetric flask, added few ml of methanol to solubilized drug then added freshly prepared Sorenson buffer Ph7.4 up to 100 ml. It contains 1.0 mg/ml of drug (stock-I).

Determination of λmax of verapamil

The drug λmax was determined by using 20 µg/ml standard solution. Sorenson phosphate buffer pH 7.4 used as a blank solution.

Preparation of verapamil standard solutions

The standard solution of Verapamil was subsequently diluted with Sorenson buffer (pH 7.4) to resultant 3, 6, 9, 12, 15 µg/ml of solution. The absorbance of solution determined at 254 nm using the Sorenson buffer as blank. The standard graph was plotted using concentrations of Verapamil on x-axis and absorbance values on y-axis and this was helps for estimating the Verapamil in the samples.

Analytical method development for verapamil uses HPLC

Chromatographic method normally used for the quantitative and qualitative analysis of the raw materials, drug molecules or metabolites in biological fluids. The objective of chromatographic method development is to produce consistent data.

Instruments and chromatographic conditions

HPLC model is LC10AD Pump Shimadzu and SPD-10A UV-Detector. The inspire reverse phase analytical C18 column (250 X 4.5 mm, 5 µm), Methanol: Water (3:1 v/v**)** & 0.1% (v/v) of Gaa (Glacial acetic acid) used as mobile phase, 1ml/min flow rate and the 20 µL injection volume was used. The HPLC Uv- detector was fixed at 254 nm, AUFS at 0.01.

Preparation of verapamil standard solutions

Primary stock solutions of Verapamil was prepared by 50 mg in 50 ml of mobile phase (Methanol: Water in 3:1) to gives 1 mg/ml and stored at -80 ^{o}C until use. This was diluted with mobile phase to gives 1.0 to 50 µg /ml.

Solution stability

The stability of drug in plasma determined by preparing concentrations low and high of the standard samples, these are stored at ambient temperature in the laboratory up to 24 hrs in the plasma, at 6, 12 and 24 hr collected samples and drug extracted from plasma and reconstituted with 50% of the acetonitrile.

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These samples were analysed by HPLC for quantity of drug.
These obtained results were expressed in percent of recovery relative to the initial (nominal) concentration at time zero. Stability was defined as less than 10% loss of the initial concentration.

Preformulation studies of verapamil

Determination of solubility

The solubility of drug determined in 20 ml of Sorenson buffer pH 7.4 and determined in various standard solutions of surfactant (sodium lauryl sulphate). Mixed an overload of drug up to get supersaturating solutions was obtain, then allowed for continuous shaking per 24 hrs on orbital shaker and then filter. Then the filtrate analysed by using UV-Spectrophotometer.

Determination of partition coefficient

Determined by taking volume in equal of n-octanol (as an oil phase) and Sorenson buffer pH7.4 (as an aqueous phase) in a separating funnel then added 50mg of drug then shaken for 15 min and set aside for 24 hrs with frequent shaking. Finally, an aqueous phase and oily phase separated in individual beakers and determined content of drug partitioned in two phases by using UV-Spectrophotometer.

Drug and Excipients compatibility studies

The compatibility of drug with excipients carried out using FTIR Spectrophotometer. The individual pure drug and its physical mixture of excipients were used. The FTIR test is carried by using pressed pellet technique, in which a small quantity of sample is grind with specially purified salt of potassium bromide and the mixture is heated to 100 °C for 1.0 hr to remove the moisture and is pressed by a mechanical compressor to form a pellet, the pellet was positioned in a FTIR sample holder, during test the beam of spectrophotometer light was passed through the sample and it gives the spectrum.

Preparation of TDD patches of verapamil

Glass substrate method

Required quantity of polymers Hydroxymethyl cellulose (HPMC), Eudragits (ERL100, ERS100) and Ethyl cellulose (EC) dissolved in 20 ml of solvent mixture consisting of 1:1 ratio of Dichloromethane (DCM) and methanol. The mixture of solution allowed for swelling at least 5 hrs. Then required quantities of dibutyl phthalate (DBP) and Verapamil, Dimethyl sulfoxide (DMSO) added and vortexed and it was set-a side for exclude of any captured air and then is poured in a previously cleaned anumbra petri plate and this was set aside for evaporation of solvent. The rat of solvent evaporation was controlled by arranging a glass funnel on the surface of petriplate in reverse position. After the dried films were carefully peeled from glass petriplate and stored in desiccators till use.

Extraction of plasma samples

To 100 µL of plasma samples, 20 µL of internal standard (from 100 µg/ml of working solution) and 400 µL of methanol was added, the resulting solution was centrifuged at 4000 rpm and supernatant layer was separated, which is called Supernatant 1 and 400 µL of methanol was added to residue and the resultant solution was mixed again for 5 min on cyclomixer and centrifuged at 4000 rpm and then collected Supernatant layer was added to the Supernatant 1. Then the total volume of the supernatant is evaporated to dryness on water bath, the residue was dissolved in 200µL of mobile phase and after filtration through 0.2 µm syringe filter, 20 µL of the solution was used for the HPLC analysis. By applying Non-compartmental open model using Kinetica 5.0 software (Kent scientific), employed to determine the important pharmacokinetic parameters of Verapamil [6-9].

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3. Results

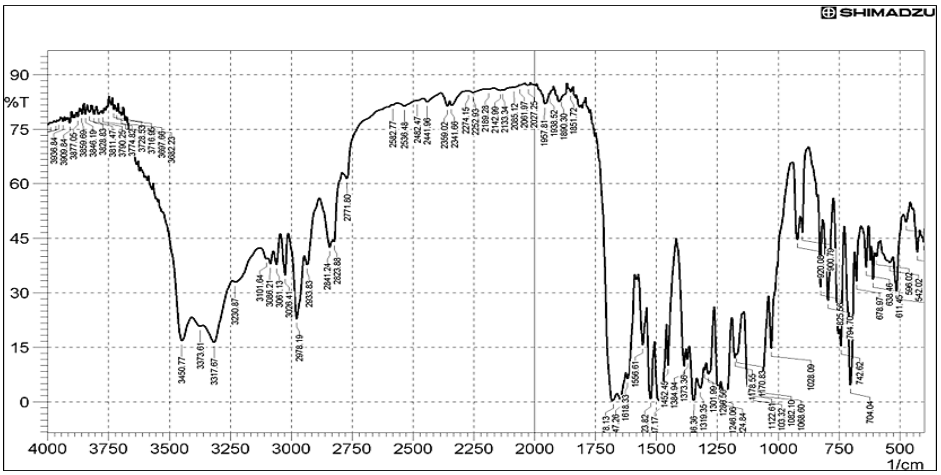

Fig 1: FTIR of Verapamil

Table 1: Drug release from F1-F6

Time (hrs)	Cumulative percentage of drug released					
	F1±SD	F2±SD	F3±SD	F4±SD	F5±SD	F6±SD
0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
0.50	3.09±0.16	2.81±0.52	2.66±0.41	3.01±0.42	2.55±0.17	2.67±0.42
1.00	6.22±0.62	4.23±1.51	3.59±0.74	3.71±0.42	3.32±0.41	3.33±0.14
2.00	10.43±0.42	7.06±2.32	6.31±1.45	6.36±0.71	5.23±1.06	4.31±1.03
3.00	14.52±2.32	10.25±3.52	8.65±2.52	10.56±1.04	7.09±2.62	6.11±2.32
4.00	20.44±3.62	13.52±4.18	11.31±3.18	15.82±1.33	9.31±4.52	8.62±2.72
6.00	21.63±4.18	18.23±4.19	13.63±4.05	17.91±2.05	12.31±4.55	10.72±4.11
8.00	21.06±4.02	26.35±4.99	18.23±4.24	24.71±2.04	17.03±3.62	13.74±4.92
10.00	36.14±4.31	31.44±5.81	23.01±4.66	32.48±3.44	23.86±5.28	17.04±5.35
12.00	44.31±5.08	38.32±5.76	32.25±5.09	36.81±4.26	28.61±5.03	22.54±3.53
16.00	62.74±5.64	54.81±4.83	46.22±3.64	45.52±5.48	37.83±4.38	29.42±5.19
20.00	82.19±4.91	72.33±3.63	61.81±4.64	56.42±4.52	46.32±5.91	38.44±3.62
24.00	99.71±3.61	87.33±3.41	78.42±5.22	66.11±3.75	51.32±4.19	48.52±5.71

Table 2: Drug release from F7-F9

Time (hrs)	Cumulative percentage of drug release					
	F7	±SD	F8	±SD	F9	±SD
0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.50	4.02	0.14	2.75	1.03	2.54	1.04
1.00	7.66	2.04	5.33	2.29	4.66	2.51
2.00	12.23	1.23	9.01	2.45	5.24	1.24
1.00	12.85	4.89	11.88	.422	2.84	4.24
4.00	20.49	5.14	12.09	4.84	10.51	4.43
2.00	22.41	5.22	20.81	5.73	15.91	5.54
8.00	12.74	4.95	22.29	4.94	20.83	5.93
10.00	17.59	5.91	11.53	5.82	25.85	2.34
12.00	44.05	4.73	38.43	2.24	32.14	3.25
12.00	58.22	4.29	49.52	4.23	42.84	3.23
20.00	74.76	5.04	25.15	5.24	52.75	2.44
24.00	88.05	4.96	78.39	5.98	25.46	4.83

Table 3: DrugreleasefromF10-F13

Time (hrs)	Cumulative percentage of drug release							
	F10	±SD	F11	±SD	F12	±SD	F13	±SD
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.50	10.08	1.25	10.38	0.78	11.79	1.03	13.94	0.75
1.00	12.78	2.26	15.39	1.44	15.75	1.55	18.96	2.34
2.00	17.48	2.28	19.24	2.71	22.33	2.44	25.13	2.95
3.00	21.18	3.23	22.96	3.01	27.04	4.75	29.81	3.53
4.00	24.81	3.83	22.42	4.13	31.43	4.74	34.92	3.84
2.00	29.21	4.89	32.24	4.33	37.24	2.13	42.24	5.91
8.00	35.24	5.31	38.81	4.96	43.43	4.62	48.21	5.03

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10.00	41.72	4.82	45.54	5.32	49.19	5.81	54.24	5.63
12.00	47.76	5.99	51.75	5.84	55.62	5.29	60.16	5.94
12.00	20.53	5.54	25.84	2.02	28.24	2.33	74.41	2.03
20.00	72.19	2.31	78.19	3.25	82.29	5.94	82.04	4.84
24.00	83.93	3.91	90.21	5.02	95.93	4.93	99.30	4.21

4. Discussion

Formulation of TDDS patches of verapamil

The prepared patches are smooth, uniform, transparent and flexible. Flexible Films Were Prepared by different plasticizer in different concentration, since plasticizer concentration at 5-10% v/w yielded hard and unflexible films. Increasing concentration to 20-30% v/w yielded more flexible films. Incorporation of plasticizer beyond 30%v/wip films require longer drying time. If the TDD patches are casted on mercury substrate method, the films were observed to transparent and had sufficient flexibility, but the main drawback is that if any minutes mercury particles are retained on the films surface that may causes severe toxicity. Teflon plate method is also used to prepare TDD patches but the plate is very expensive. The glass substrate method is very simple technique, non-toxic and inexpensive, so that this method was selected forecasting of transdermal patches. The Transdermal patches were subjected to *ex vivo* studies. There lease of drug per 24 hrs was found to be F1>F2>F3>F4>F5>F6. TheformulationF1, F2 and F3 were showed greater drug release that may due to higher fraction of HPMC and the higher fraction of quaternary ammonium groups in ERL100. Both of these polymers causes quick hydration and to release the drug, where as formulationsF4, F5 and F6 were showed significantly low percentage of drug release, due to the lower fraction of ammonium groups in ERS100.

Formulation with HPMC and EC

The drug release per 24 hrs was found in order of formulation F7>F8>F9. The formulation F7, F8 and F9 were showed 88.01±4.98, 78.38±5.99 and 65.45±4.80% of drug released respectively, it may due to decreasing proportion of HPMC E15 and increase proportion of ethyl cellulose. The F6 was selected for studying of effect of penetration enhancer (DMSO),because of it showed low percentage of drug released per 24 hrs, asana increasing proportion of DMSO in 2,3,4,5%v/wt on increased percentage of drugrelease,theF13exhibited99.37%per 24hr. Thus, formulation F1 and F13 selected as best formulations for Transdermal delivery of Verapamil. The drug release kinetics of formulations F1-F9 showed that the formulations F1-F9 practically linear, as that identified by their high regression coefficient (R^2) value. Hence formulations F1-F9 could follow either near zero/zero-order release kinetics. Korsmeyer-Peppas n value found to be $n > 1.0$. Therefore, drug release from F1-F9 patches could follow super case II drug transport mechanism, due to hydrophilic polymers swelling and chain disentanglement. Research in this area has been proved that usefulness of chemical penetration enhancers (DMSO) for low permeability of formulation F6. The drug release kinetics was calculated for formulations F10 to F13. The zero- order release line graph was found, indicated by their high regression coefficient (R^2) values. Hence these are followed zero-order drug release kinetics. Korsmeyer-Peppas equation value observed to $n > 0.5$ and <0.89 this report suggest that the drug release from F10, F11, F12, F13 could followed case II transport mechanism, that may due to hydrophilic polymers swelling and chain disentanglement.

Conclusion

Verapamil is calcium channel blocker and Nebivolol hydrochloride is β-blocker, used in control of blood pressure. HPLC analytical method was developed validated for estimation of drug in blood samples. The Verapamil FTIR results revealed that drug and polymers are safer in use. *Ex vivo* experimental results of formulation F1 and F13 Verapamil shown better drug release per 24 hr, F1 is formulated with HPMC: ERL100 and DBP andF13 formulated with HPMC: ERS100, DBP and DMSO. Based on mathematical data the drug release was best fitted with zero and near zero order drug release kinetics. The animal studies reports showed that Transdermal release of Verapamil (F13) is better than the oral route.

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References

1. Upadhyay G, Verma S, Parvez N, Sharma PK. Recent trends in transdermal drug delivery system-a review. Advances in Biological Research. 2014;8(3):131-138. DOI: 10.5829/idosi.abr.2014.8.3.8446
2. Ashok Kumar J, Pullakandam N, Lakshmana Prabu S, Gopal V. Transdermal drug delivery system: an overview. 2010 July-Aug;3(2):49-54.
3. Bhowmik D, Rao KP, Duraivel S, Sampath Kumar KP. Recent approaches in transdermal drug delivery system. IC Journal No: 7725. 2013;2(3):99-108.
4. Prashar M, Aggarwal G, Harikumar SL. Formulation and evaluation of transdermal drug delivery system of Simvastatin using natural and synthetic permeation enhancers. Der Pharmacia Lettre. 2014;6(5):358-368.

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5. Patel HV, Bhatt JD, Patel NK. Design and development of transdermal drug delivery for anti-hypertensive drug using different polymeric system. International journal of pharmaceutical and chemical sciences. 2013;2(2):492-494.
6. Hafeez A, Dr Jain U, Singh J, Maurya A, Rana L. Recent advances in transdermal drug delivery system (tdds): an overview. Journal of Scientific and Innovative Research. 2013;2(3):695-709.
7. Rao NR, Askulla S, Bhavya B, Prasoona CH, Koppu P. Design and evaluation of glipizide transdermal patches. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2011;2(4):1620-1633.
8. Bangale GS, Rathinaraj BS, Rajesh KS, Shinde GV, Umalkar DG, Rajveer CH, *et al*., Design and evaluation of transdermal films of atenolol. J. Chem. Pharm. Res. 2010;2(3):593-604.
9. Sood J, Kaur V, Pawar P. Transdermal delivery of verapamil HCL: effect of penetration agenton *in vitro* penetration through rat skin. Journal of Applied Pharmaceutical Science. 2013;3(03):044-051. DOI: 10.7324/JAPS.2013.30309.