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Central Nervous System in Patches Form for the Sustained Release (Diazepam (Valium)

Shivani Bansal
QC Officer
(QC and QA department)

Abstract
Transdermal drug delivery devices are becoming increasingly common in the field of advanced pharmaceuticals. There are many forms of TDDS in contemporary pharmaceuticals, but transdermal patches are the most desirable method of testing. The present research was performed to establish matrix style transdermal patches containing Diazepam with 10 percent Propylene Glycol used as a plasticizer which can serve as a chemical enhancer and 10 percent Ethanol is used as a permeation enhancer. The most popular HPMC or EC adhesive is used. Possible drug(API) and polymer interactions have been investigated in FTIR experiments and solubility of inert solvent ingredients. Crafted transdermal patches for diazepam (Valium). Physicochemical properties were analysed. Formulated patches were carefully studied for in vitro permeation and stability. All data is translated into graphs. All the formulated patches demonstrated strong physical consistency. The continuous release behaviour is calculated by the dissolution analysis. In vitro permeation experiments were conducted using the Franz Diffusion Cell.

Keywords*: Diazepam, Transdermal patches, Permeation enhancer, in-vitro permeation study, dissolution study, plasticizer diazepam (Valium®).*

I. Introduction

Transdermal drug delivery system (TDDS) is a topically delivered drug in the form of patches or semisolids (gels) that distribute drugs for systemic effects at a fixed and regulated pace. Transdermal drug delivery system has many benefits over traditional drug delivery systems, offers controlled drug release, ease of cessation, long time of operation, and prevents hepatic metabolism. The research was performed to include an anxiolytic treatment in transdermal patches. The key goal is to determine the viability of a managed delivery of the therapeutically successful quantity of drugs in the drug delivery mechanism of the matrix type. TDDS is becoming more common nowadays the main mechanism of penetration of drug molecules through the stratum corneum of human skin impact by diffusing through the lipid envelopes of the skin cell. Diazepam has anxiolytic, skeletal muscle relaxant, amnestic anticonvulsant, hypnotic and sedative effects. The pharmacological activity of diazepam increases the influence of the GABA neurotransmitter by binding to the benzodiazepine location of GABA.

Receptor (through the constituent chlorine atom) leading to depression in the central nervous system

Central nervous system (CNS)-related infections and disorders are difficult to treat, since most surgical drugs are unable to cross the blood-brain barrier (BBB) and the blood-spinal cord barrier (BSCB). In the last decade, there has been a growth in bio-based therapeutic agents. Many of these compounds are of a hydrophilic type. It is also important to design an effective distribution mechanism for such goods so that they can cross BBB and meet the target sites within the CNS.

BBB helps to preserve a homeostatic state within the CNS. However this poses a significant hindrance when trying to distribute medications by systemic road. Drugs cannot cross the BBB and must instead be handled immediately through intrusive techniques. Ehrlich was shown for the first time in the early part of the twentieth century that all tissues except the brain are stained when treated intravenously with a dye (Finlay et al., 1996). Later in the 1920s, it was shown that only certain compounds capable of penetrating cerebrospinal fluid (CSF) could affect the activity of the CNS. In 1960, after calling this selective drug permeability as "barriere hematoencephaique," it was shown that only substances with high lipid solubility could reach the CNS (Kroll & Neuwelt, 1998). Tightly packed endothelial cells with various receptors, transporters and efflux pumps aid BBB sustain a homoeostatic state within the brain (Begley & Brightman, 2003; Persidsky et al., 2006).

OBJECTIVES OF THE STUDY

1. To study on Central Nervous System In Patches From For The Sustained Release (Diazepam (Valium)
2. To study on Fabrication of Transdermal Patches

BBB physiology

The BBB is closely comprised of endothelial capillaries with less gaps, less pinocytic activity and more mitochondrial activity compared to the endothelial cell junctions found at other locations in the body. These cells are further surrounded by the mechanism of the astrocytic foot and the basal membrane. These cells, along with pericytes, form tightly knitted junctions that are permeable only to lipid-soluble substances (Selmaj, 1996). The existence of the astrocyte foot mechanism also guarantees high integrity of the BBB. However, solutions such as glucose, amino acids and nucleoside join the CNS continuously. These solutes are capable of joining the luminous and antiluminal portions of the BBB by carrier-mediated phase (Pardridge et al., 1990b; Deeken & Loscher, 2007; Wolburg & Lippoldt, 2002). The permeability of these barriers is further affected by the involvement of astroglial cells, which control the different signals involved in the permeability of BBB (Abbott et al., 2006).

Blood-cerebrospinal fluid barrier that begins at the choroid plexus creates an essential barrier that controls the entrance and exit of multiple substances into the spinal cord. While the endothelial junction of BCFB is not as closely bound as that of BBB, the relative narrower surface area of this barrier compared to BBB, the lower diffusion rate and the rapid clearance rate effectively avoid the entry of larger molecules and proteins and peptides (Bickel et al., 1993).

The involvement of different proteins in the BBB governs the permeability of tight junctions. The proteins at the close junctions of the endothelial BBB vary greatly from those of the epithelial tight junctions. Though epithelial cells are strongly associated with P-face strand, only a low degree of association of endothelial cells with P-face cells is observed. Sealing of close junctions relies on the protein of the transmembrane, occludin. Occludin was the first protein to be identified in the endothelial junction controls. The permeability of close junctions is regulated by occludin phosphorylation. Claudins are another set of proteins present in BBB, the primary purpose of which is to limit permeability. Claudin 1, 3 and 5 are found in endothelial cells among the different forms of claudins discovered. Homophilic and heterophilic associations in BBB are regulated by junctional adhesion molecules and endothelial cell selective adhesion molecules. In addition, tight junctions contain zonula occludens proteins that are part of submembranous tight junction-associated proteins. These proteins are involved in the regulation of the transduction of signals through the membrane (Wolburg & Lippoldt, 2002).

The presence of high amounts of occludin in the brain capillaries raises their electrical resistance to 1000–2000 ohm cm2, which is very high compared to 10 ohm cm2 in the peripheral capillaries. This essentially prohibits the introduction of polar compounds (Butt et al., 1990; Hirase et al., 1997). High vascularization in the brain means that each neuron has its own blood supply. As a consequence, the substrate will obtain direct entry into the target neuron via this blood supply (Pardridge, 2003). However, owing to the powerful efflux pump seen in the CNS, some of the non-polar small molecules are unable to cross BBB. This molecules are easily detected and extracted by these pumps (Golden & Pollack, 2003).

Charge, molecular mass and lipid solubility of a molecule influence their transport through BBB. BBB consists of cells such as microglial cells, pericytes, astrocytes and endothelial cells. The membrane of these cells is negatively charged. BBB does not contain fenestration and pinocytic vesicles. These properties limit the entry of molecules greater than 200 nm in size (Karnovsky, 1967; Reese & Karnovsky, 1967; Kroll & Neuwelt, 1998; Begley, 2004b). CSF also causes a sinking influence in the brain due to constant circulation. This along with the efflux transporters, further decreases the concentration of certain compounds that have managed to resist this safety process (Davson, 1978; Begley, 1996; Pardridge, 1998). However certain chemicals, such as glucose, insulin and amino acids, which are essential for the proper functioning of the brain, can effectively cross BBB even though they are hydrophilic in nature. This is achieved by transporting through unique BBB receptors (Kroll & Neuwelt, 1998). But their concentration still depends on their ability to overcome efflux pumps, particularly P-glycoprotein (Pgp) (Begley, 1996; Pardridge, 1998).

Drugs with higher lipid solubility can reach the brain passively. But with their higher lipid solubility, their amount of dissemination inside the body is also increasing. Owing to the high vascular density found in the CNS, any molecule entering the brain is quickly spread across the brain. Therefore any drug delivery that uses a particular transport mechanism present at the BBB may be of interest to boost bioavailability at the target site. However this involves the recognition of unique characteristics that are exhibited under such pathological conditions (Juillerat-Jeanneret, 2008).

This article lays out a broad outline of the different methods used in the supply of medications to the CNS. The methods are categorised as invasive and non-invasive approaches. The emphasis is on non-invasive methods, which are further sub-categorized into nine different ways commonly used to distribute drugs through BBB. Both methods include a detailed discussion of the nano particulate delivery mechanism and the efflux pump inhibition-based delivery systems. The polymer-based drug delivery mechanism and liposomes are explored in detail under the nanoparticle-based drug delivery system. This delivery mechanisms are more applicable than most drug delivery systems.

Fabrication of Transdermal Patches:

Patches were cast on a glass or an SS mould using a solvent casting process. Five forms of polymer patches have been prepared. The first two formulations were formulated using separate HPMC and EC with a 5 percent blend enhancer. Enhencer was ethanol and propylene was glycol. The combination of the enhancer was 10%. The next one formulations were prepared using HPMC and EC in conjunction with methanol, propylene glycol and methanol. The last two formulations were made using a combination of HPMC and EC and a combination of a chemical enhancer with water..

Evaluation of Transdermal Patches11- 14

Physical-Chemical Assessment The thickness of the patch:

The thickness of the patch is measured from various points using the Screw Gauge in mm.

Water Vapour Absorption %15:

The 3.15 cm2 films were measured and weighted and then put in the desiccator at 70% RH using saturated potassium bromide solution. The films were taken out and measured for a poor storage every day..

Water Vapour Transmission %16:

The WVT percent was measured using the following formula WVT = WL/S Where W is the water vapour transmitted in g, L is the film thickness in cm and S is the exposed surface area in cm2..

Drug content uniformity:

Patch is split into required pieces and inserted into 100 ml of dissolution or diffusion media used, where all drugs are soluble at a given time and stirred continuously using a mechanical stirrer and the sample is extracted at the end of four hours and the drug content is spectrophotometrically measured at 235 nm..

Skin sensitivity test:

The skin sensitivity test was conducted on a stable rabbit weighing between 2 and 2.5 kilogrammes. Drug intact polymer film of 3.15 sq cm was mounted on the left dorsal surface of the rabbit. After 24 hours, the patch was removed with the aid of an alcohol swab. The skin has been tested for itching.

Stability studies :(Accelerated study)

Both films were exposed to two chosen temperatures of 45°C and 70 per cent of RH in the stability chamber. Transdermal films have been processed in the stabilisation chamber for a period of 4 weeks. The drug content of the films was evaluated at the end of each week. Averages of triplicate readings have been taken.

In-vitro Diffusion Study:

The in vitro diffusion analysis is carried out using Franz Diffusion Cell (Ponmani & Co, Coimbatore). The semi-permeable membrane is used for diffusion. The Franz diffusion cell has two compartments, one is a receptor compartment with an effective volume of approximately 60 ml and an effective permeation area of 3.15 sq.cms. The other compartment is a donor. The semi-permeable membrane is mounted between the donor compartment and the receptor compartment. Weighed volume of Transdermal Diazepam Patch (Valium®). It's positioned on one side of the membrane. The receptor medium is a phosphate buffer pH of 7.4. The receiver compartment is surrounded by a water jacket to hold the temperature at 37 ± 0.5°C. Heat is given by means of a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by a Teflon-coated magnetic bead mounted in the diffusion cell. Samples are removed at each sampling period and replaced by equivalent amounts of fresh receptor fluid at each time. The samples taken are spectrophotometrically analysed at 235 nm. The medicine that is published notes and draws a curve

Table 1: formulation composition for 2000mg mixture

Formulation	Diazepam	HPMC (polymer)	EC	Propylene glycol 3-10% (enhancer)	Ethanol 3-10% (enhancer)	Water
D1	100mg	1600mg		100mg	100mg	
D2	100mg		1600mg	100mg	100mg	
D3	100mg	800mg	800mg	100mg	200ml	
D4	100mg	1000mg	600mg	50mg	50mg	100ml
D5	100mg	1200mg	400mg	100mg	50mg	50ml

Table No: 2 Standard curve of diazepam in phosphate buffer pH 7.4.17

Sr no	mcg/ml	Absorbance
1	0mcg	0.00
2	1mcg	0.122
3	3mcg	0.391
4	5mcg	0.612
5	7mcg	0.865
6	9mcg	1.06

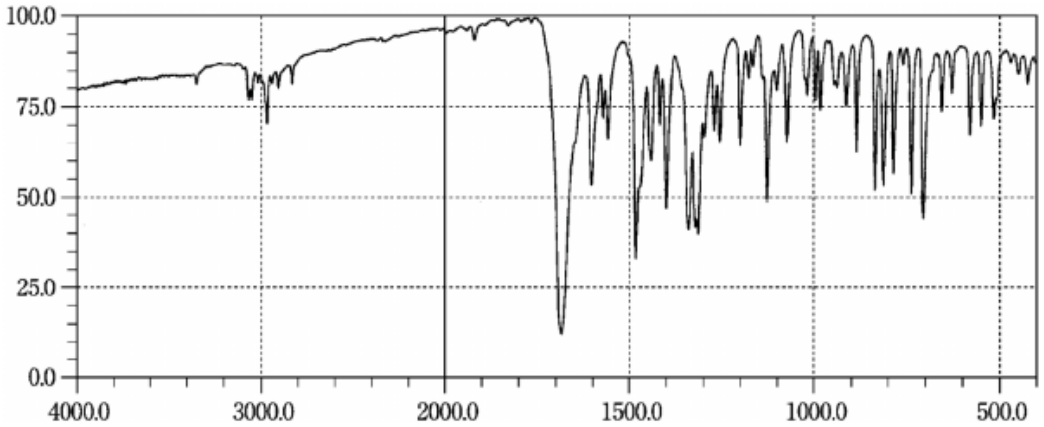

Figure 1 Compatibility Study:
The drug was identified and compatibility was confirmed by FTIR

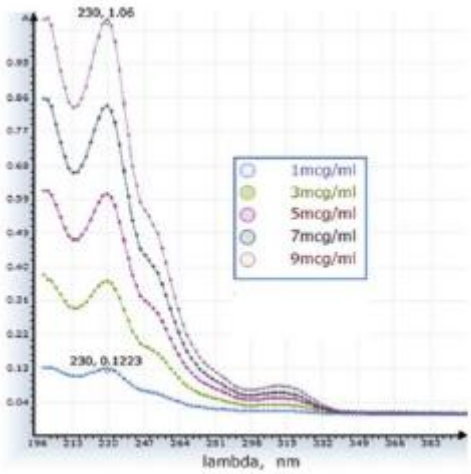

Figure 2

Skin sensitivity Test:
The skin discomfort test on rabbits shows no signs of skin reactions or sensitivities and erythema, making the fabricated Transdermal patch appropriate for further tests.

Table No 3 In-Vitro diffusion studies of various formulations

Sr no	Time hr	D1 %	D2 %	D3 %	D4 %	D5 %
1	0	0	0	0	0	0
2	2	12.23	10.13	12.23	7.23	9.31
3	4	18.78	27.34	23.13	12.12	18.67
4	6	23.45	32.77	30.34	19.45	26.34
5	8	29.34	45.98	50.56	34.34	36.56
6	10	34.45	50.56	58.34	50.13	45.35
7	12	39.87	65.45	69.12	55.34	52.89
8	14	41.49	78.56	75.34	63.23	57.45
9	16	43.75	88.98	80.66	67.12	62.12
10	18	46.31			69.56	67.34
11	20	49.45			72.34	72.32
12	22	57.23			74.13	78.23
13	24	66.97			79.23	82.12

Table No: 4 Cumulative % and Kinetic Values obtained from different formulations

Formulation	Drug % in 24 h	Zero order plot Regression	1st order plot Regression	Higuchi order plot Regression
D4	82.12%	0.997	0.907	0.989
D5	79.23%	0.879	0.786	0.986

The calibration curve of pure diazepam (Fig. 1) was plotted with a phosphate buffer pH of 7.4. Compatibility between the substance and the polymer was studied by using FTIR absorption spectra and by testing the solubility of the substance used in the inert solvent patch and by checking the crystallisation and precipitation. A preliminary research on the safety of diazepam with HPMC and EC showed that there was no association between the substance and polymer as a result of FTIR spectra and that there was no physical interaction between diazepam and HPMC, EC, ethanol and propylene glycol solution. The polymers form an essential part of the Transdermal distribution mechanism. The commonly used polymers for the manufacture of transdermal atches are cross-linked polyethylene glycol (PEG) networks, hydroxy propyl methyl cellulose (HPMC), acrylic acid matrices, ethyl cellulose (EC), organogels, polyvinyl pyrrolidine (PVP), ethyl vinyl acetate (EVA) copolymers, and chitosan, etc. Among these polymers, the mixture of HPMC and EC was chosen for the preparation of diazepam patches. Since HPMC is an efficient polymer as a continuous release control rate, HPMC also acts as a stabilising agent. It is therefore widely used in the formulation of the patch diazepam (Valium®). Physico-chemical characteristics such as patch length, patch weight, percentage of moisture absorbed, percentage of moisture loss, and drug quality analysis were found to be within reasonable limits. Patches also contain ethanol, which also serves as a preservative

II. CONCLUSION

The Fake Transdermal Diazepam Patch (Valium®). Seen strong controlled release properties. The findings of this analysis indicate that diazepam can be used as a permeation enhancer and propylene glycol plasticizer for a transdermal patch comprising HPMC & EC, as well as a chemical enhancer for managed opioid release over a span of 24 hours for anxiolytic treatment. The Transdermal drug delivery system has a bright future in a successful ransdermal delivery system. The combination of the chemical enhancer indicates a successful permeation of diazepam in the blood.

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