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Design and evaluation of buccal films of isoxsuprine hydrochloride

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ABSTRACT

An attempt was made to formulate Buccal patches of Isoxsuprine hydrochloride, a potent and long acting vasodilator and uterine suppressant , by using Hydroxyl propyl methyl cellulose(HPMC), Polyvinyl pyrolidone K-30 (PVP K-30) and Hydroxyl ethyl cellulose (HEC). Twelve batches of buccal patches were prepared by solvent casting technique in which the best formulation was found out. The polymers HPMC, HEC, and PVP K-30 were incorporated with Isoxsuprine hydrochloride in various proportions, out of which the best formulation on the ratio (HPMC: HEC: PVPK-30-2:2:1) with the drug was determined. Prepared buccal patches were spherical, uniform in shape and white in colour. The obtained buccal films were evaluated for physico-chemical characteristics, In-vitro release profile, Ex-vivo diffusion study in fresh goat cheek pouch membrane and In-vivo evaluation in rabbits. Higuchis plot studies revealed that the predominant mechanism of drug release was diffusion.

Key words: Isoxsuprine hydrochloride, Polymer, Buccal patches, Goat cheek pouch membrane

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INTRODUCTION

Substantial efforts have been focused on the development of new drug delivery system. Film type dosage forms create a new dimension in the era of controlled drug delivery system. Film type dosage forms can be used for transdermal therapy, ophthalmic therapy and for buccal or sublingual therapy [1, 2]. Remarkable efforts have recently been focused on placing a drug or drug delivery system in a particular region of the body for extended periods of time [3] . This is required not only for the local targeting of the drugs but also for a better control of systemic drug delivery [4,5]. Generally two approaches are theoretically possible to achieve the buccal oriented aims [6-8].

1. The development of mobile drug delivery system that would be physically maintained with the oral cavity in constant with a mucosal surface by a conscious effort of the patient.
2. The design of the immobilized drug delivery that can be retained on the mucosal surface by the adhesive properties of the system itself.

Because of the accessibility of buccal drug delivery, it permits localization of CDDS and allows opportunity to locally modify tissue permeability, inhibit protease activity or decrease immunogenic response [9]. The buccal mucosa is highly perfused with blood vessals and offers a greater permeability than the skin. Moreover the therapeutic serum concentration of the drug can be achieved more rapidly [10, 11] Isoxsuprine hydrochloride(ISH) is a potent and long acting vasodilator and uterine suppressant, which is used in the treatment of peripheral vascular diseases such as arteriosclerosis, thromboangitis, obliterans etc [12]. The total oral daily dose is 10-20mg in three or four divided doses. The short biological half life of the drug tends to think for a sustained release dosage form for ISH [13, 14]. The molecular weight of the drug (337.85), Melting point (205oC with decomposition) and its complete bioavailability (around 90%) were the various important criteria, which should be considered Isoxsuprine hydrochloride for Buccal Drug Delivery [15].

MATERIALS AND METHOD

SOLVENT CASTING TECHNIQUE

Accurately weighed quantity of HPMC, HEC, and PVP K-30 compositions of different formulations (12 BATCHES) got mixed with 10mg of ISH. Out of various formulations the best batch was found out. Buccal films of ISH was prepared by weighing accurately 10.3mg of ISH incorporated with (HPMC: HEC: PVP K-30) (2:2:1) ratio, and then it was transferred to a beaker containing 2.5 ml of distilled water. The solutions were mixed to get a clear solution. Glycerin was added as plasticizer. The whole solution were poured over mercury surface in a Petri dish and allowed to dry at room temperature. The same procedure was repeated with composition of different formulation of drug with polymers.

In- vitro Drug release evaluation.

Commercial semi permeable membrane was employed in this study. The membrane used was transparent and regenerated cellulose type, which was permeable to low molecular weight substances. A film of size 1cm diameter was cut and placed on the semi-permeable membrane. The semi permeable was tied to one end of an open ended cylinder which acted as donor compartment. The entire surface of the membrane was in contact with the receptor compartment containing 300ml of phosphate buffer (PH 6.6). The content of the compartment was agitated by a magnetic stirrer. Samples of 1ml were withdrawn from receptor compartment and replaced by equal volumes of fresh media. The withdrawn samples were analyzed using UV spectrophotometer at 269nm using reagent blank.

Ex- vivo diffusion studies.

Ex- vivo diffusion study of Isoxsuprine hydrochloride was carried out. Fresh Goat cheek pouch membrane was tied to one end of an open cylinder which acts as a donor compartment. The film should be placed in such a way that it should be stuck on the mucous membrane. The receptor compartment was filled

with isotonic phosphate buffer PH 6.6. The assembly was maintained at 37^{o}C and stirred magnetically. Samples were withdrawn at half an hour intervals for 6 hours and analyzed using UV spectrophotometer at 269nm.

In-vivo studies

Method

A healthy rabbit weighing 2.5 to 3kg was taken which was already checked for absence of any diseases. The fore limbs and hind limbs were tied into the iron rod of the Mini operation table; so that rabbit was in dorsal position. The prepared film having the size of 1cm containing 10mg of ISH was placed in buccal membrane with the help of clip. Dextrose solution was transfused continuously throughout the period of study. Periodically 1ml blood samples were taken using a syringe which already contained 1ml of 3.8% sodium citrate solution to prevent blood clotting. These blood samples were subjected for centrifuging at 2,200 Rpm for about 20 minutes. 1ml of supernatant liquid was taken from this and after suitable dilution; these samples were analyzed at 269nm using spectrophotometer.

RESULTS

The buccal patches were subjected to various physico- chemical evaluation tests such as percentage moisture absorption, percentage moisture loss, swelling index and time taken for maximum swelling, water vapour transmission rate, folding endurance, drug content uniformity, thickness and bioadhesive strength. The films were also subjected to In-vitro dissolution studies, Ex-vivo diffusion study using goat check pouch membrane and In-vivo using rabbits. The physico chemical evaluations of the formulations have shown different physical characteristics of the formulation changed according to the nature and composition of the polymers. Invitro dissolution study of drug along with different concentration of polymers i.e. HPMC, HEC and PVP k-30 has been performed. The higher rate and percentage of release of drugs in film containing less concentration of polyvinyl pyrrolidone K-30 i.e. (HPMC: HEC: PVPk-30-2:2:1).is considered as the best batch. As the percentage of polyvinyl pyrollidone K-30 was reduced, the rate of release of drug was increased. Hence the batch (HPMC: HEC: PVPK-30 2:2:1) shows the best nature of films and the graph representing the best sustained drug release. In addition, it shows better stability and suitability. Ex-vivo buccal diffusion studies conducted for buccal films of ISH was carried out by using fresh goat cheek pouch membrane and it shows good release.

In-vivo studies

In-vivo buccal diffusion studies conducted for buccal films of ISH in rabbits also showed zero order release pattern. These in vivo studies of buccal films of ISH in rabbits did not show any inflammation or any other sensitization reactions at the administration site.

CONCLUSION

The Buccal patches prepared by solvent casting technique were spherical, uniform in shape and white color in nature. The formulation containing two parts of HPMC, along with HEC and one part of PVP K-30, has shown best release in concentration independent manner. Good correlation observed between the in-vitro and in- vivo profile revealed the ability of the formulation to reproduce the invitro release pattern through the biological membrane.. Here fair correlations are observed between the invitro and in vivo profiles not only for the justification of best batches, but also for the adaptability of the system to release the drug in a predicted manner. Hence the best formulation HPMC; HEC: PVP K-30(2:2:1) achieved the objective of present study such as reducing the dose, improving the bioavailability by avoiding first pass metabolism and it may have better patient compliance.

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Table- 1: *In-vitro* drug release data (hpmc: hec: pvp k-30 - 2:2:1)

TIME IN MINUTES	DRUG RELEASE IN MG	CUMULATIVE% DRUG RELEASE.
30	0.921	9.21
60	2.132	21.35
90	2.841	28.48
120	3.562	35.71
150	4.384	43.95
180	5.191	52.05
210	5.822	58.39
240	6.561	65.86
270	7.244	72.65
300	8.091	81.15
330	8.721	87.48
360	9.513	95.42

Table-2: Ex-vivo diffusion study using Goat cheek buccal membrane using best formulation. (HPMC: HEC: PVP K-30- 2:2:1)

TIME IN MINUTES	DRUG RELEASE IN mg	CUMULATIVE% DRUG RELEASE.
30	0.67	6.76
60	1.24	12.82
90	1.93	19.49
120	2.51	25.35
150	2.78	28.08
180	3.30	33.33
210	3.78	38.18
240	4.37	44.14
270	4.98	50.30
300	5.53	58.88
330	6.79	68.58
360	7.08	71.51

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Table-3: In-vivo drug release data for best formulation (HPMC: HEC: PVPK-30- 2:2:1)

Time in hours	Amount of Drug remaining.(mg)	Amount of drug release. .(mg)	Percentage drug release.
1	9.1	0.8	8.08
2	7.3	2.6	26.26
3	5.5	4.4	44.44
4	3.8	6.1	61.61
5	3.2	6.7	67.77
6	2.0	7.9	79.79

Table-4: Ex-vivo –In-vitro correlation data.

Cumulative % drug release(Exvivo)	Cumulative % drug release(In-vitro)
6.76	9.21
12.82	21.35
19.49	28.48
25.35	35.71
28.08	43.95
33.33	52.05
38.18	58.39
44.14	65.86
50.30	72.65
58.88	81.15
68.58	87.48
71.51	95.42

Table-5: Invivo- Invitro correlation data.

Cumulative % drug release(Invivo)	Cumulative % drug release(Invitro)
8.08	9.21
26.26	21.35
44.44	28.48
61.61	35.71
67.77	43.95
79.79	52.05

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Figure-1: HPMC:HEC:PVP K-30-2:2:1

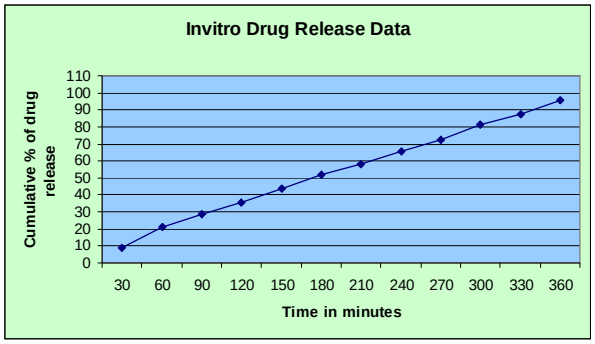

Figure-2: HPMC: HEC: PVPK-30-2:2:1

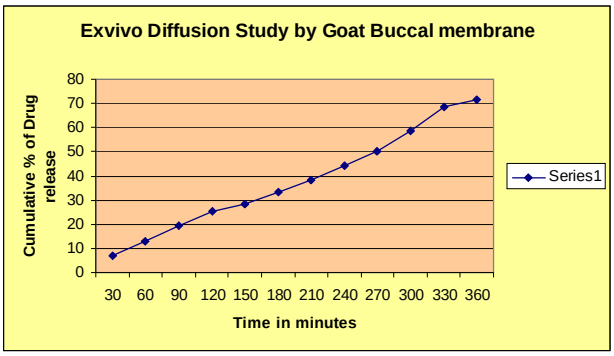

Figure-3: HPMC: HEC: PVPK-30-2:2:1.

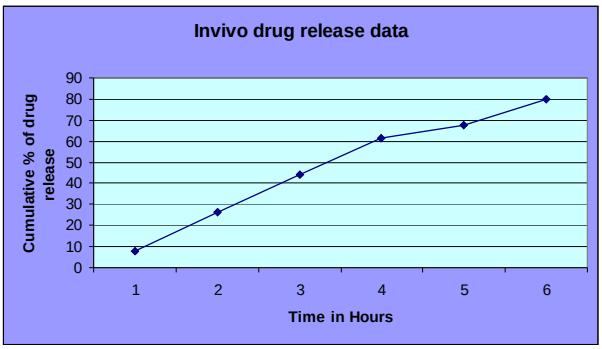

Figure-4

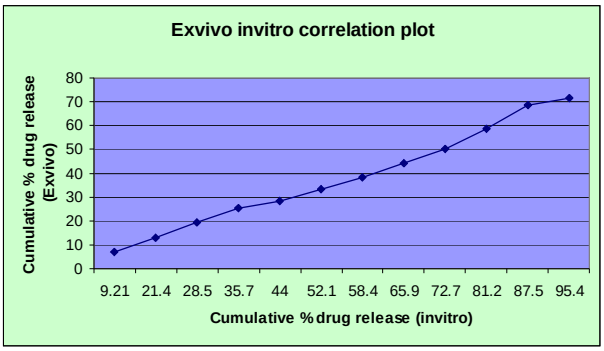

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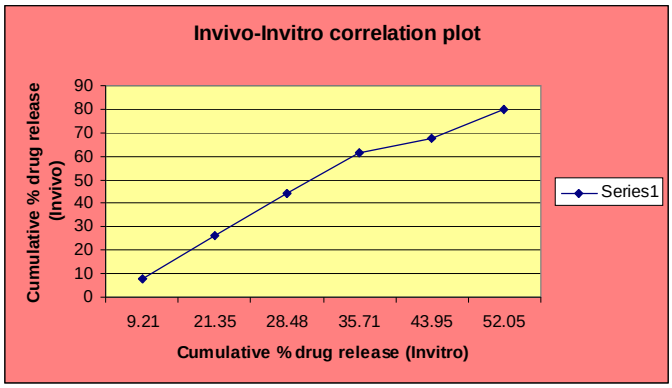
Figure-5



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