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Original Article

Formulation and evaluation of Buccal patches of Furosemide

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ABSTRACT: This study is mainly focused on the ability of polymer to increase the bioavailability of Furosemide and to release the drug in controlled predetermined manner. The polymers selected for the study include natural and synthetic polymer like Chitosan and sodium HPMC based on their physicochemical properties. The mucoadhesive buccal patches were prepared by solvent casting method. The prepared patches were subjected to physical evaluations, in vitro diffusion studies and stability study. All the formulations have shown good adhesive property, tensile strength, folding endurance, thickness, pH and moisture content. The diffusion studies have shown that the percentage drug release is from natural polymer (chitosan) based patches is more than the synthetic polymer (sodium HPMC) (89.5% to 97.89%) with chitosan based mucoadhesive patches and 72.97 to 88.75 patches prepared with sodium HPMC in 6 hours. The In vitro drug release, evaluation, stability and accelerated stability studies of the mucoadhesive patches shown that the formulation containing natural polymer 2% has the promising results with 97.89% drug release within 6 hours, folding endurance 211+2, patch thickness 0.7mm, surface pH 6.7, % swelling index 36% moisture content 3.3,tensile strength 2.94+3kg/cm^2.

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INTRODUCTION

Buccal delivery is considered to be a major alternative to the oral and buccal routes of systemic drug delivery. The buccal mucosa provides readily accessible route for Trans- mucosal delivery. Absorption through the buccal mucosa overcomes premature drug degradation due to the enzyme activity and pH of gastro intestinal tract, avoids active drug loss due to presystemic metabolism, acid hydrolysis and therapeutic plasma concentration of the drug can be rapidly achieved. The adhesive properties of such drug delivery platforms can reduce the enzymatic degradation due to the increased intimacy between the delivery vehicle and the absorbing membrane. It has also been used as a pharmaceutical excipient in conventional dosage forms as well as in novel applications involving bio adhesion and trans mucosal drug transport[1].

The average development cost of a new chemical entity (NCE) is approximately $150– 350 million. It often costs substantially less to develop new methods of administration for an existing drug, which results in improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects. Therefore, pharmaceutical companies are under constant pressure to maximize the full potential of a drug candidate. This objective can be accomplished by incorporating the drug into various drug delivery systems. This exercise can lead to convenient dosage forms that overcome previously presented administration problems. For the last two decades, there has been an enhanced demand for more patient-compliant dosage forms[2-3].

1.1 Ideal attributes of a drug delivery system[4]

- Capable in precise control of constant drug delivery rate.
- Capable of controlled delivery rates to accommodate the pharmacokinetics of various drugs.
- Applicable to a wide range and varieties of drug.
- Should not have any effect on drug stability.
- Capable of high order of drug dispersion.
- Since the early 1980s there has been renewed interest in the use of bioadhesive polymers to prolong contact

time in the various mucosal routes of drug administration. The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability. Drug absorption through a mucosal surface is efficient because mucosal surfaces are usually rich in blood supply, providing rapid drug transport to the systemic circulation and avoiding degradation by gastrointestinal enzymes and first pass hepatic metabolism.

Oral Transmucosal Drug Delivery[5]

via mucous membranes of the oral cavity was noted as early as 1847 by Sobvero, the discovery of nitroglycerin, and systemic studies of oral cavity absorption was first reported by Walton in Within the oral cavity delivery of drug is classified into several categories. Absorption of drug 1935. Due to its excellent accessibility and reasonable patient compliance oral mucosal cavity offers attractive route of drug administration. Within the oral mucosal cavity delivery of drug is classified into three categories:

- **Sublingual delivery**, which is a systemic delivery of drug through the mucosal membrane lining the floor of the mouth
- **Buccal delivery**&**Local delivery**, for the treatment of conditions of the oral cavity. The oral cavity is foremost part of digestive system of human body. It is also referred to as "buccal cavity". It is accountable for various primary functions of body. The careful examination of various features of oral cavity can help in development of a suitable Bucco adhesive drug delivery system.

Oral Cavity[6]

Components and structural features of oral cavity:

Oral cavity is that area of mouth which is delineated or surrounded by lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions, **Outer oral vestibule**, which is bounded by cheeks, lips, teeth and gingival (Gums) and **Oral cavity proper**, which extends from teeth and gums back to the feces (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity. A detailed outline of buccal cavity is being given in Fig.1.

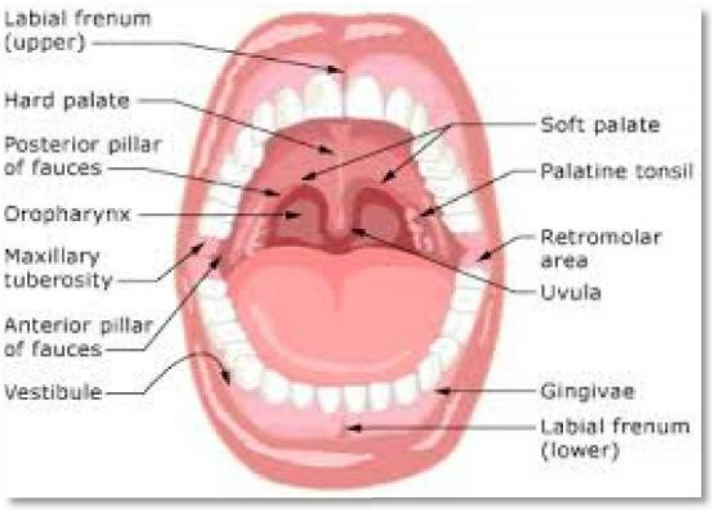

Fig. 1: A detailed outline of buccal cavity

Anatomical Features[7, 8]

The outer surface of the oral cavity is a mucous membrane consisting of an epithelium, basement membrane and lamina propria overlying a submucousa containing blood vessels and nerves. The mucosa can be divided into three types: Masticatory mucosa, found on the gingiva and hard palate. Lining mucosa, found on the lips, cheeks, floor of mouth, undersurface of the tongue and the soft palate. Specialized mucosa found on the upper surface of the tongue and parts of the lips. All consists of a squamous stratified epithelium, many cell layers (40-50 for buccal mucosa) overlying a connective tissue, layer, the lamina propria. The total surface area of oral cavity= 170 cm^2.

Animals

The study was approved by IAEC with approval number: B.U/Pharma/IACE/A/16/01 and the animals were duly kept under standard conditions.

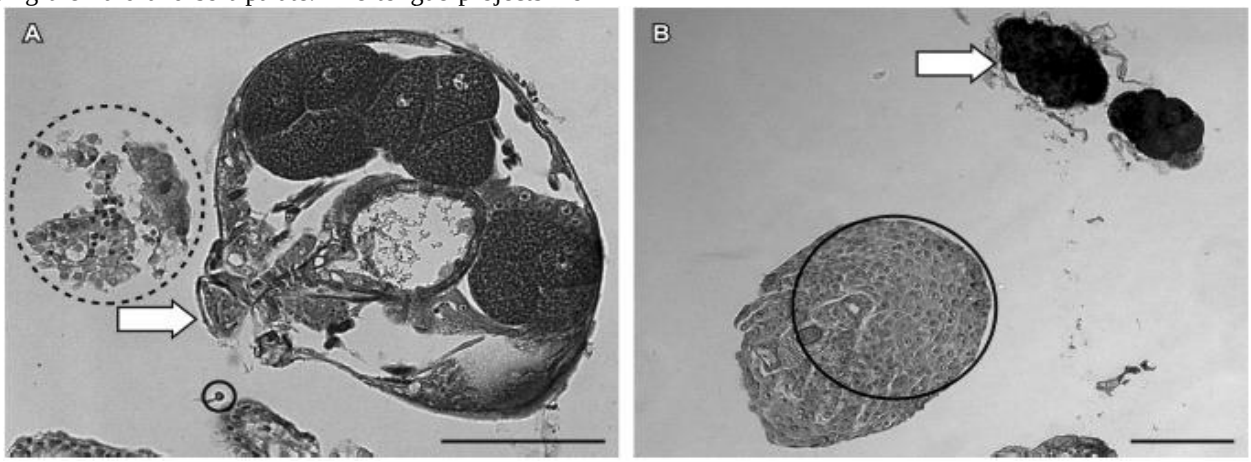

Fig. 2:Cross section of buccal mucosa

Table 1: Thickness and surface area of oral cavity membranes

Oral cavity membrane	Thickness (mm)	Surface area (cm^2)
Buccal mucosa	500-600	05.2
Sublingual mucosa	100-200	26.5
Gingival mucosa	200	--
Palatal	250	20.0

Material and Instruments

TABLE 2: CHEMICAL USED

S.no.	Names of chemical	Supplier and manufactures
1.	Furosemide	Yarrow chem products Mumbai
2.	H.p.m.c	Himedia Laboratory Pvt Ltd. Mumbai
3.	Chitosan	Yarrow chem products Mumbai
4.	Poly vinyl k30	Centraldrug research house pLtd Bombay
.	Poly vinyl pyrlidone	Centraldrug research house pLtd Bombay
6.	Methanol	Central drug house(p) post Dox New Delhi
7.	Ethanol	Central drug house(p) post Dox New Delhi
8.	Chloroform	Central drug house(p) post Dox New Delhi
9.	Ptassium dihydrogen phosphate	Central drug house(p) post Dox New Delhi
10.	Sodium dihydroxide pellets	Hitech Laboratory New Delhi
11.	N Octenol	SD Fine Chemical Mumbai
12.	Acetone	Yarrow Chem. Products Mumbai
13.	Mercury	Qualikems Eine Chemical Pvt. Ltd New Delhi
14.	Poly ethylene glycol	Central drug house New Delhi
15.	Glycerol	Himedia Laboratory Pvt Ltd. Mumbai

FORMULATION DEVELOPMENT

Table 3: List of used Excipients in the formulation

Ingredients	Purpose
Furosemide	Chemical constituent
sodiumHPMC	Natural Polymer
Chitosan	Synthetic polymer
Methanol	Permeation Enhancer
Glycerine	Plasticer

Table 4: Composition of Buccal Patches of F1- F5code

F.C.	Furosemide (gm)	H.P.M.C. (mg)	PVP (mg)	Glycerol (ml)	Methanol (ml)
F1	2	252	200	0.2	25
F2	2	300	150	0.2	25
F3	2	200	250	0.2	25
F4	2	150	300	0.2	25
F5	2	225	225	0.2	25

RESULTS AND DISCUSSION

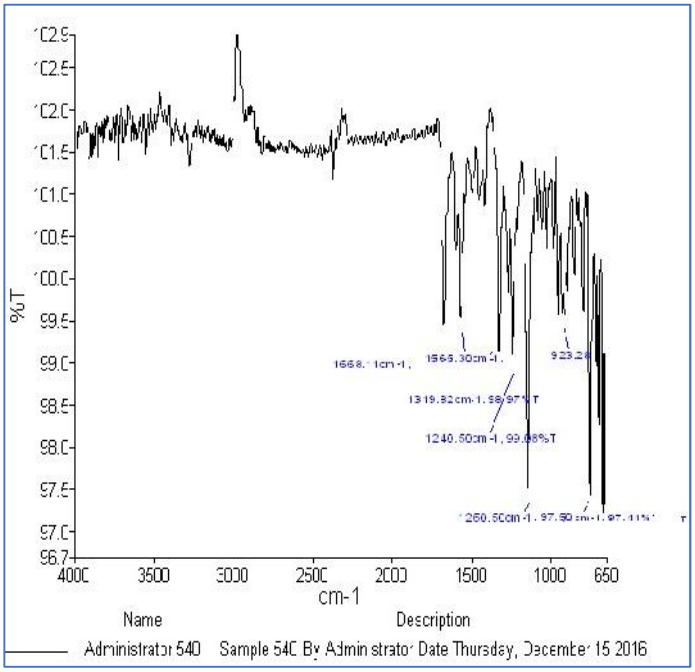

Fig. 3: FTIR of Furosemide

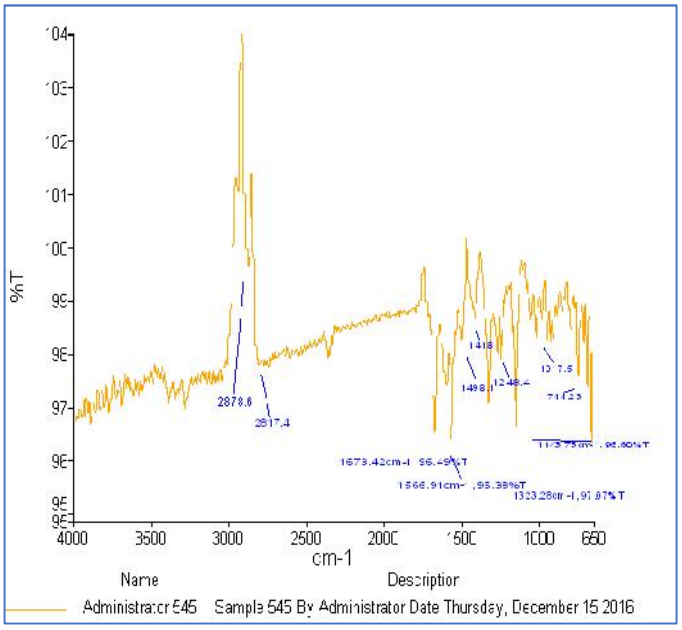

Fig. 4: FTIR of Hydroxy propyl methylcellulose (HPMC)

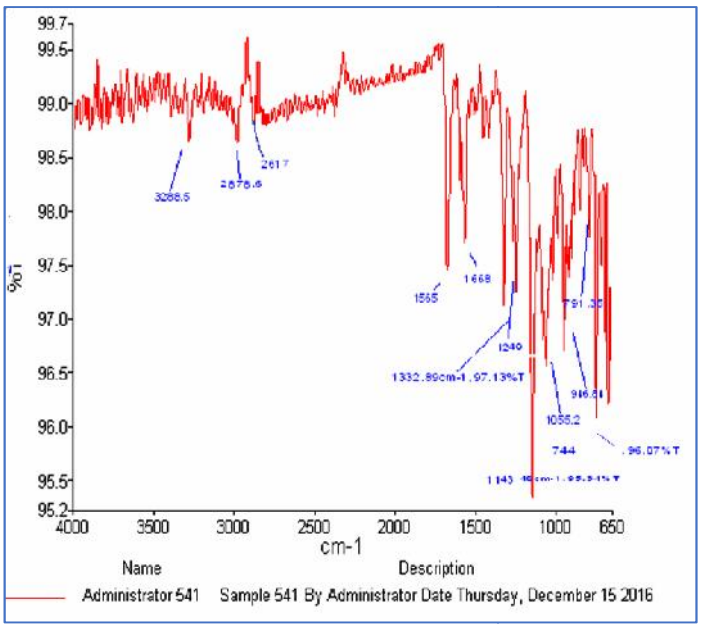

Fig. 5: FTIR of Furosemide with Hydroxy propyl methylcellulose

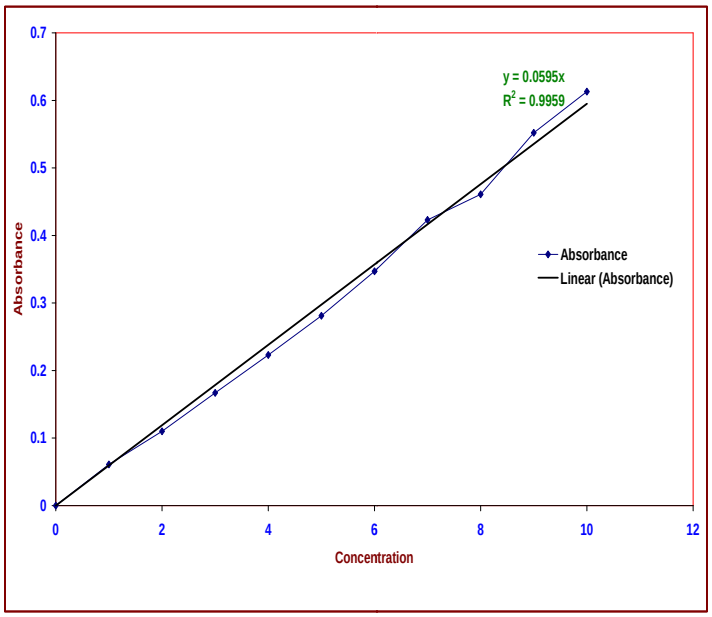

Fig. 6: Calibration curve of furosemide in methanol at max 276 nm

Table 5: Characterization of above Formulations

Formulation code	Thickness (mm)	Weight variation (mg)	Folding endurance	Drug content
F1	0.09 ± .01	35.4 ± 0.24	> 200	29.1 ± .06
F2	0.085 ± .015	34.8 ± 0.32	> 200	29.6 ± .09
F3	0.12 ± .015	36.1 ± 0.29	> 200	28.7 ± .06
F4	0.1 ± .01	34.9 ± 0.38	> 200	29.5 ± .05
F5	0.095 ± .03	35.3 ± 0.19	> 200	28.9 ± .12

Table 6: Comparison of CDR of F1, F2, F3, F4 and F5

Time(hrs)	**F1**	**F2**	**F3**	**F4**	**F5**
------	%CDR	%CDR	%CDR	%CDR	%CDR
0	0	0	0	0	0
1	29.73485	14.20455	17.80303	15.7197	11.74242
2	33.52273	22.53788	27.08333	21.40152	30.49242
3	37.31061	32.00758	35.79545	35.03788	43.93939
4	49.24242	47.53788	46.59091	39.39394	52.27273
5	54.35606	62.68939	53.59848	53.2197	56.62879
6	70.26515	73.10606	62.68939	64.20455	70.64394
7	71.59091	75.56818	73.10606	81.62879	76.51515
8	78.2197	77.65152	92.04545	94.50758	89.58333

Table 7: Kinetic models for *in-vitro* drug release study

MODEL		**F1**	**F2**	**F3**	**F4**	**F5**
ZERO-ORDER	R^2	0.939	0.968	0.986	0.986	0.98
	n	8.816	10.44	10.38	11.32	10.76
FIRST-ORDER	R^2	0.963	0.970	0.814	0.799	0.922
	n	-0.077	-0.090	-0.109	-0.130	-0.108
HIGUCHI	R^2	0.965	0.926	0.924	0.884	0.950
	n	27.25	31.14	30.66	32.68	32.31
KORSEMEYER-PEPPAS	R^2	0.913	0.98	0.984	0.924	0.970
	n	0.505	0.895	0.764	0.645	0.913

Table 8: Drug Concentration Studies Plasma Furosemide Drug in Patches

S.NO.	Time hrs	Plan drug conc. Of emulsion	Market formulation tablet	NF Formulation(mg)
1	0	0±00	0±00	0.94±0.26
2	0.5	0.36+34_0.57	0.67±0.33	2.41±0.25
3	1	1.28±0.34	1.23±0.33	6.34±0.18
4	2	2.76±0.54	4.46±0.07	14.2±0.14
5	4	4.57±0.24	8.59±0.10	11.46±187
6	6	5.98±0.098	7.36±0.53	9.39±0.56
7	8	3.09±0.51	5.73±0.29	5.86±0.88
8	12	0.54±0.78	4.62±0.32	0.56±0.14
9	24	0.00±0.00	0.03±0.01	_

Table 9: Important pharmacokinetic parameter of furosemide formulation

S.No.	Pharmacokinetic parameter	Plan of emulsion	Market tablet	NE Formulation
1	Cmax microgram	5.98±0.78	8.49±0.10	14.25±0.14
2	Tmax (hrs)	6.0	4.0	4.0
3	AUC0-n m.g.hrs/ml	27.18±6.16	34.63±1.14	55.60±1.4
4	AUC tat m.g.h./ml	29.28±2.90	38.20±5.96	57.50±5.3
5	T1/2 (hrs)	5.63±1.76	5.89±1.09	7.63±0.41
6	MRT	2.21±1.03	2.94±2.09	4.19±.64
7	Fr	-		160

SUMMARY AND CONCLUSION

The study presents a good approach to increase the bioavailability of the poorly bio available drug and its release in a controlled manner. Some drugs have wide therapeutics use for the treatment of various diseases but sometimes, their oral does not produce therapeutic effects because of their poor bioavailability. Oral dosage forms are most widely used because of the advantages over parental dosage form like patient compliance, cheap, having less side effects etc. The drug selected for incorporation in the mucoadhesive buccal patch. Though oral route is considered as safest route of drug administration, but pre-systemic metabolism of the drug is the main disadvantage, which results in the incomplete availability of drug in systemic circulation. An alternative approach is buccal drug delivery which provides prolonged and sustained drug release through buccal mucosa.

In the present investigation matrix type buccal patches Furosemide, Polymer hydroxypropylemethylcellulose, (Chitosan) & glycerol as both plasticizer and penetration enhancer were developed and evaluated for the precise delivery of drug penetration across the buccal mucosa.

Wide range of approaches in the design and implementation of buccal drug delivery system including prolonged release patch preparation, mucoadhesion, *in-vitro* penetration and release profile, *in-vivo* studies, biocompatibility, toxicity studies etc have been critically examined.

Matrix system based Buccal patches of Furosemide were prepared of Glycerol as both plasticizer and penetration enhancer.

The result of present investigation stated that HPMC and chitosan have good matrix/film forming characteristics which was confirmed by the visual and physiological characterization of the patches. The *in-vitro* and *ex-vivo* studies indicated that successful buccal patches of Furosemide could be prepared using hydrophilic polymers viz. Chitosan employing solvent casting technique. It was found during investigation that as the concentration of chitosan was increased the release rate also inclined and the patches showed lesser mucoadhesion time while on the other hand as the concentration of Chitosan was increased the drug release was found to be controlled and the patch also reflected sufficient mucoadhesion time period.

Buccal delivery is a major alternative to the oral and parenteral routes of systemic drug delivery. The buccal mucosa provides readily accessible route for Buccalmucosal delivery. Absorption through the buccal mucosa overcomes premature drug degradation due to the enzyme activity and pH of gastro intestinal tract, avoids active drug loss due to pre-systemic metabolism, acid hydrolysis and therapeutic plasma concentration of the drug can be rapidly achieved. The adhesive properties of such drug delivery platforms can reduce the enzymatic degradation due to the increased intimacy between the delivery vehicle and the absorbing membrane. It has also been used as a pharmaceutical excipient in conventional dosage forms as well as in novel applications involving bioadhesion and buccalmucosal drug transport.

It has been found that oral controlled release dosage forms are not suitable for variety of important drugs characterized by the incomplete availability of drug in systemic circulation.

However, the success of a drug to be used for systemic delivery via buccal route depends mainly on the ability of the drug to permeate through buccal mucosa in sufficient quantities which

can be achieved with the help of penetration enhancers. Thus, the role of penetration enhancers comes into play. They act on polar and non- polar molecules by altering the multi lamellate pathway for penetration and even increase drug diffusivity through mucous membrane proteins. Hence, penetration enhancers have a very significant impact on the design and development of an effective product. Furosemide is the preferred drug because it has plasma half-life of 3-4 hrs and has low bioavailability which is an essential condition for formulation of buccal patches. Moreover, sustained release of drug in certain situations may be desirable to improve the bioavailability and the therapeutic efficacy of the drugs.In this study, hydrophilic polymers like Chitosan were used in different concentrations.

In conclusion, the present data indicate a confirm reproducibility of developing Furosemide Buccal Patches that could be used for treating several predicaments. The drug release was found to be sustained and prolonged and thus, multiple dose regimens could be best replaced by single buccal formulation. Further study in respect to *in-vivo* performance after application of buccal patch is required to substantiate the therapeutic efficiency of these systems.

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