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Formulation and *in vitro* Evaluation of Bilayered Buccal Patches of a Proton Pump Inhibitor

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ABSTRACT

Buccal patches of Omeprazole were prepared by solvent evaporation method using HPMC E15, Polyvinyl alcohol and Eudragit which are the hydrophilic polymers in different ratios. The prepared patches were tested for physical parameters like Thickness, Folding endurance, Uniformity of weight, swelling index and Surface pH of patches and *in-vitro* drug release studies. All the physical parameters were fall within the limits. The drug content was uniform in all the formulated buccal patches of Omeprazole. The results indicate uniform distribution of drug within the patches. The release of Omeprazole from the buccal patch was immediate up to 45 mins and sustained up to 24hrs.Among the six formulations, the BM3 shows maximum drug release of 89.11% in 45 mins. The optimized formulation follows zero order kinetics to release the drug from the patches.

Keywords: Omeprazole, buccal patches, HPMC, Eudragit, *in vitro*.

INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However peroral administration of drugs has disadvantage such as hepatic first pass metabolism and enzymatic degradation within the GI tract that prohibits oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal lining of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantage over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better

enzymatic flora for drug absorption[1-2]. The nasal cavity has site for systemic drug delivery has been investigated by many research groups and the route has already reached commercial status with several drugs include LHRH8 and calcitonin. However, the potential irritation and the irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal dosage forms, as well as the large intra- and inter subject variability in mucus secretion in the nasal mucosa, could significantly affect drug absorption from this site. Even though the rectal, vaginal, and ocular mucosal all offer certain advantages, The oral cavity, on the other hand, is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage and the virtual lack of langerhans cells makes the oral mucosa tolerant to potential allergens, further more, oral transmucosal drug delivery bypass first pass effect and avoids presystemic elimination in the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery. Within the oral mucosal cavity, delivery of drugs is classified into three categories; they are Sublingual delivery, buccal delivery, and localdelivery[3-8]. The buccal drug delivery has several advantages which includes bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first metabolism, improved patient compliance due to the elimination of associated pain with injections administration of drugs in unconscious or incapacitated patients, sustained drug delivery, are latively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued and increased ease of drug administration[9-13].

MATERIALS AND METHODS

Materials

Omeprazole, was purchased from Micro labs, Hosur, HPMC E15 was a gift sample from SD fine chemicals, Mumbai, Eudragit was purchased from SD fine chemicals, Mumbai Glycerine was purchased from Spectrum reagents &chemicals private ltd, Chennai and Propylene glycol was purchased from SD fine chemicals, Mumbai. All the excipients and solvents used were of analytical grade.

Methods

Drug Excipient compatibility study Fourier Transform Infrared Spectroscopy

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients which are added to facilitate administration, promote the consistent release and bio availability of the drug and protect it from degradation. Infrared spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug[15-17].

Method

The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quanta of potassium bromide. About 100mg of this mixture was compressed to from a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 400 cm-1 in a Shimadzu FTIR 8400 Spectrophotometer. The IR spectrum of the physical mixture was done to detect any appearance or

disappearance of peaks. The compatibility between the drug and the polymer were evaluated using FTIR matching method[18].

Formulation of Bilayered Buccal patches of Omeprazole

Buccal patches of Omeprazole were prepared by solvent casting technique using film forming polymers such as HPMC E15 and Eudragit.

Primary layer

Buccal mucoadhesive patches were prepared using polymer or polymer blends along with the drug and a suitable solvent mixture. Solvent mixture is the mixture of methanol and dichloromethane. HPMC 15 cps (1750mg for patch 1) was weighed accurately and added in 15 ml of solvent mixture. The contents in the beaker were stirred on magnetic stirrer for 15 min and kept aside for swelling of polymer for about 6hours. Further 10 ml of solvent mixture containing Omeprazole (20mg) was added to the above polymer solution and stirred the dispersion. Then 3 drops (0.0882g) of glycerin was added to the polymer solution. The whole mixture was mixed thoroughly with the help of a magnetic stirrer. The glass mould of size 4.5 cm^2 was placed over a flat surface, which was ensured using spirit level. The drug-polymer mixture was poured into the glass mould. An inverted funnel was placed over the mould overnight for controlled evaporation of the solvent.

Secondary Layer

Buccal mucoadhesive patches were prepared using polymer or polymer blends along with the drug and a suitable solvent mixture. Solvent mixture is the mixture of methanol and dichloro methane. Eudragit RL100D (600mg for all patches) was weighed accurately and added in 15 ml of solvent mixture. The contents in the beaker were stirred on magnetic stirrer for 15 min and kept aside for swelling of polymer for about 6hours. Further 10 ml of solvent mixture containing Omeprazole (20mg) was added to the above polymer solution and stirred the dispersion. Then 3 drops (0.0882g) of glycerin was added to the polymer solution. The whole mixture was mixed thoroughly with the help of a magnetic stirrer. The glass mould of size 4.5 cm^2 was placed over a flat surface, which was ensured using spirit level. The drug-polymer mixture was poured into the glass mould. An inverted funnel was placed over the mould overnight for controlled evaporation of the solvent. The patch was removed from the mould and packed in wax paper and stored in a desiccator. On similar lines all patches were prepared. Similarly, dummy patches were prepared without adding drug.

Physical characterization of buccal patches

Thickness of the patches

The thickness of the patches was evaluated by taking three patches of each formulation and the patch thickness was measured using the Verniercalipers instrument at three different places and the mean value was calculated[19,20].

Folding endurance

Three patches of each formulation of size (2x2 cm) were cut by using sharp blade. Folding endurance was determined by repeatedly folding as mall strip of patch at the same place till it broke. The number of times, the patch could be folded at the same place without breaking gave the value of folding endurance. The mean value was calculated[21-23].

Uniformity of weight of the patches

Uniformity of weight of the patches was measured by taking three patches of each formulation and weighed individually on a

digital balance. The average weight was calculated[24].

Drug content uniformity of the patches

The three patches (2×2 cm) of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 7.4 phosphate buffer was added and continuously stirred for 24hrs. The solutions were filtered, diluted suitably and analysed at 3011 nm in a UV spectrophotometer[25-27].

Swelling index

The degree of swelling of bio adhesive polymer is important factor affecting adhesion. Upon application of the bio adhesive material to at issue a process of swelling may occur. The patches were allowed to swell on the surface of agar plate kept in an incubator maintained at 37±0.20. Increase in the weight of the patch was determined at preset time intervals (1-3 hrs). The percent swelling of the patches was calculated using the formula[28-31]

$$\% S = (Xt - X0/X0) \times 100,$$

Where,
Xt is the weight of swollen patch after time t,
X0 is the initial patch weight at zero time.

Surface pH of patches

The patches were allowed to swell by keeping them in contact with 1 ml of distilled water (pH 6.8±0.1) for 2 hrs at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute. The surface pH of the patches was determined in order to investigate the possibility of any side effects, in the oral cavity. As acidic or alkaline pH is bound to cause irritation to the buccal mucosa, hence attempt was made to keep the surface pH of the patch close to the neutral pH[32-34].

In-vitro drug release studies

In vitro drug release studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 22 ml. Cellulose acetate, acetate ester of cellulose, has been fabricated as semi-permeable membranes for biomedical application. The cellophane membrane (cellulose acetate membrane) was used for the determination of drug from the prepared buccal type patches. The cellulose acetate membrane having a pore size 0.45µ was mounted between the donor and receptor compartment of the diffusion cell. The prepared transdermal film was placed on the cellulose acetate membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads and the temperature was maintained at 32 ± 0.5 °C, because the normal skin temperature of human is 32°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophoto-metrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal[35-39].

Drug release kinetics-model fitting of the diffusion Data

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Nowadays the pharmaceutical industry and the registration authorities focus on drug dissolution studies. Drug dissolution from buccal patches has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some analytical definitions of the Q(t) function are commonly

used such as zero order, first order, Higuchi, Korsmeyers models.

The results of *In-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows.

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchis model)
3. Log cumulative percent drug release versus time (zero order kinetic model)
4. Log cumulative Percent Drug released versus log time (korsmeyers model)

RESULTS AND DISCUSSION

Drug Excipient Compatibility Study

IR spectra of Omeprazole alone and its combination with polymers are evaluated. An IR spectrum of pure Omeprazole shown in the table no 02.

Physical characterization of buccal patches

The physical characterization of the formulated buccal patches were done by various techniques mentioned and the results were tabulated in Table no: 3 for various parameters like thickness of the patches, folding endurance, uniformity of weight of the patches, drug content uniformity of the patches, swelling index, surface pH of patches.

The thickness of formulated patches was ranges from 0.478 to 0.632mm. The buccal patch posses surface pH within the range of salivary pH that is 6.1 to 6.3were found around neutral pH. The content uniformity recovery was possible to the tune of 91.00 to 94.44 %. Films did not show any crack seven after folding for more than 300 for all batches.

In-vitro release profile of Buccal patches containing Omeprazole

The release data of Omeprazole from all the patches is shown in Table 3& fig. 5 at Isotonic Phosphate pH 7.4, the release of Omeprazole from the buccal patch was immediate up to 45 mins and sustained up to 24hrs.Among the six formulations, the BM3 shows maximum drug release of 89.11% in 45 mins, 95.98% in 24 hrs.

Mechanism of release

Data of the *in vitro* release were fitted into different equations and kinetic models to explain the release kinetics of Omeprazole from these buccal patches. The kinetic models used were zero order equation, first order equation, Higuchi release, and Korsmeyer-Peppas models. The interpretation of data was based on the value of the resulting regression coefficients. The dissolution data was best fitted to Higuchis model.

CONCLUSION

The present study clearly demonstrated that Omeprazole can be successfully delivered through buccal route. IR spectroscopic studies indicated that the drug is compatible with the polymer. A buccal patch of Omeprazole was formulated by using a hydrophilic polymer HPMC E15, Eudragit and prepared by Solvent casting method were found to be good in appearance. The formulated buccal patches were evaluated for the Physical parameters like thickness, Folding endurance, Uniformity of weight, swelling Index, Surface pH. The results obtained were within the prescribed limits. The patches were non-irritating with favourable film properties and showed sufficient muco adhesive potential until the drug is absorbed from the formulation. So, it can be concluded that buccal patches of HPMC meets the ideal pre requisites for a buccal device which can be a good way to by-pass hepatic first pass metabolism of Omeprazole.

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Table 1. Composition of different mucoadhesive formulations containing Omeprazole

Composition	BM1	BM2	BM3	BM4	BM5	BM6
HPMC E15	1.75g	2.0g	2.25g	2.5g	2.75g	3g
Glycerine	200µL	200µL	200µL	200µL	200µL	200µL
Eudragit RL 100 D	600mg	600mg	600mg	600mg	600mg	600mg
Glycerine	200µL	200µL	200µL	200µL	200µL	200µL
Drug in primary layer	20mg	20mg	20mg	20mg	20mg	20mg
Drug in secondary layer	20mg	20mg	20mg	20mg	20mg	20mg

Table 2. Vibrational assignments for Omeprazole IR spectrum

Frequency (Cm-1)	Assignment
3431	N-H stretch
3058	Aromatic C-H stretch
2943&2904	C-H stretch
1627	C=C stretch
1587	C=N stretch
1510	CH2 bending
1402&1309	CH bending
1157	C=O stretch
1070	C=S stretch
966, 885 &821	C-H bending

Table 3. Physical Characteristics of buccal patches containing Omeprazole Formulation

Formulation	TN(MEAN ±sd)	UW(MEAN ±sd)	%SI (MEAN ±sd)	Surface pH(MEAN ±sd)	CU(MEAN ±sd)	FE(MEAN ±sd)
BM1	0.478+0.0057	0.252+0	69.90+0.85	6.23+0.0577	92.5+0.901	301
BM2	0.501+0.0015	0.3+0	69.60+0.55	6.23+0.0577	94.44+1.018	308
BM3	0.528+0.0023	0.346+0.0005	78.24+1.37	6.16+0.2309	90.58+1.345	306
BM4	0.561+0.0026	0.391+0	87.96+1.02	6.13+0.1527	91.00+0.370	307
BM5	0.592+0.0005	0.422+0.0005	77.12+0.32	6.26+0.2081	92.85+0.583	302
BM6	0.632+0.0005	0.467+0.0005	63.02+0.02	6.36+0.2081	91.14+2.561	306

TN= thickness, UW= uniformity of weight, SI= percent swelling index, CU = content uniformity, and FE = foldingendurance respectively. *Each value is an average of three determinations.

Table 4. In vitro release profile of Buccal patches of Omeprazole

Time(mins)	BM1	BM2	BM3	BM4	BM5	BM6
0	0	0	0	0	0	0
5	13.89	13.27	14.73	13.96	10.33	8.66
10	22.34	22.91	33.83	23.93	16.88	11.42
15	32.9	32.49	34.51	33.82	22.13	16.2
30	59.83	69.69	75.03	73.29	25.57	20.52
45	91.44	82.02	89.11	87.47	41.07	23.72
60	93.87	82.99	90.33	88.5	41.65	24.46
120	95.63	83.97	91.39	89.36	42.56	25.03
240	96.9	84.78	92.27	90.57	43.14	25.6
360	97.49	85.75	93.5	91.61	44.06	26.18
480	98.41	86.72	94.38	92.47	44.48	26.42
600	99.68	87.54	95.27	93.51	45.23	26.84
720	77.9	87.53	95.62	93.87	44.47	25.92
1440	90.12	88.5	95.98	94.56	44.71	25.99

BM=Bilayer Buccal Membrane.

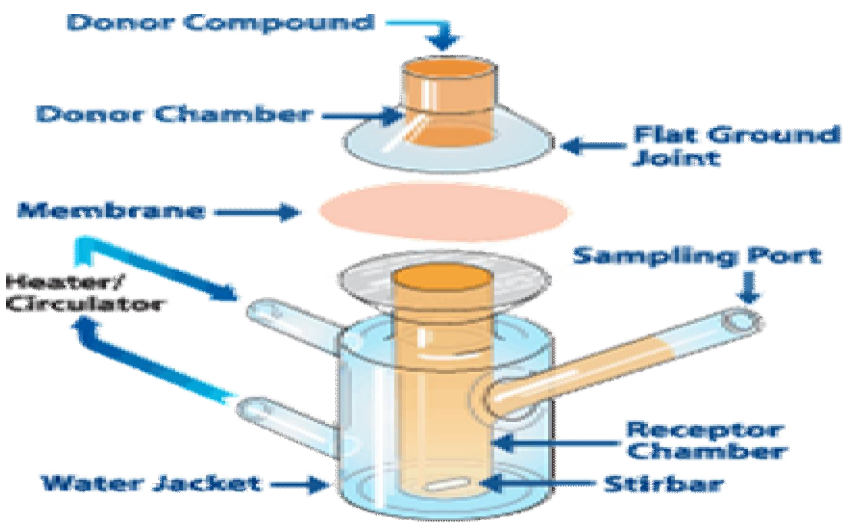

Figure 1. Franz diffusion cell with receptor compartment

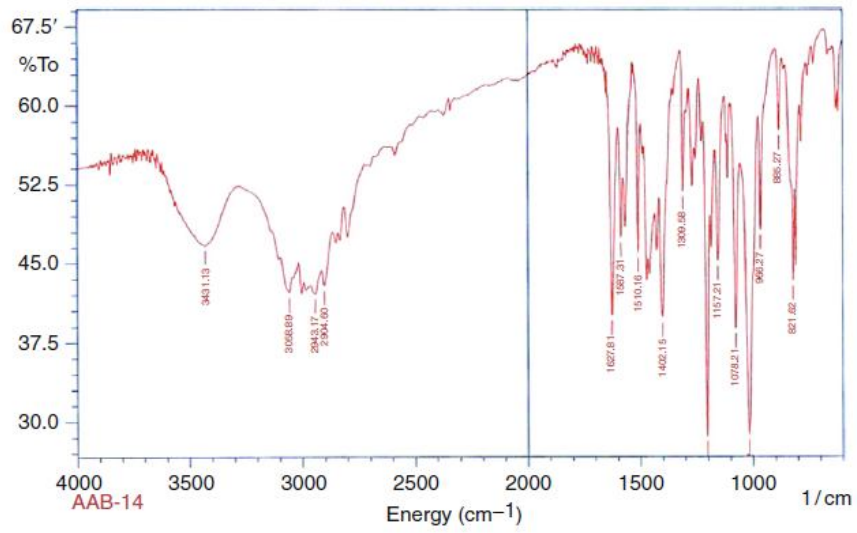

Figure 2. IR Spectrum of Omeprazole

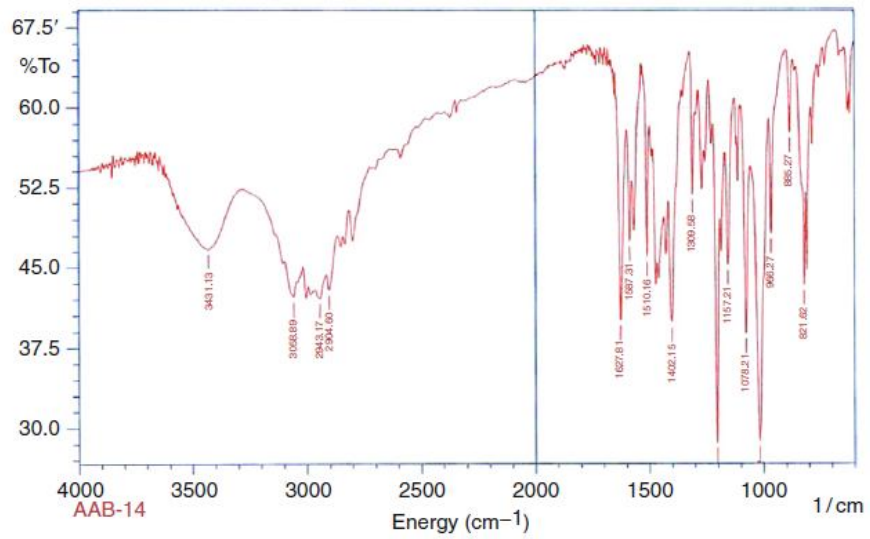

Figure 3. IR Spectrum of Omeprazole + HPMC E15

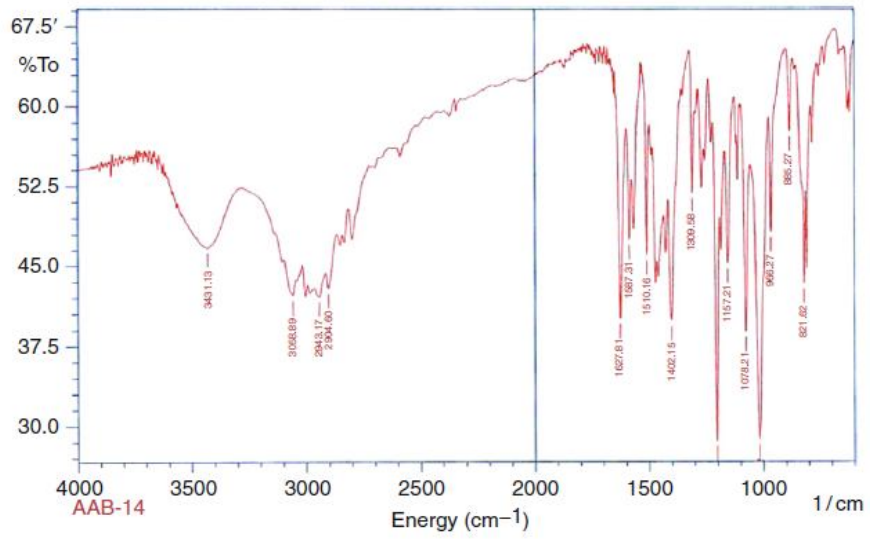

Figure 4. IR Spectrum of Omeprazole + Eudrgit

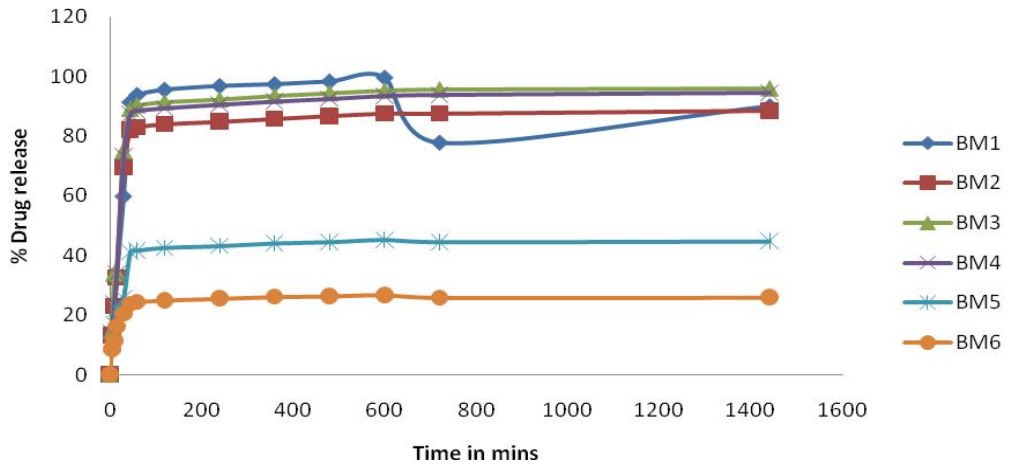

Figure 5. *In vitro* release profile of all formulations containing Omeprazole