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Fabrication of Bucco-matrix tablets of Amoxicillin trihydrate on the basis of release and permeation kinetics

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ABSTRACT

Drug release kinetics from matrix dosage form is governed by polymer swelling and erosion, drug dissolution/diffusion and polymeric combination. For the preparation of controlled release dosage form, hydrophilic, swellable polymers in optimum combination are essential. The major objective of the current study is to prepare Amoxicillin trihydrate-loaded bucco-matrix tablets by direct compression technique and to study the effect of ratio of HPMCK100M and HPMCK15M used in the formulation on the basic properties and on drug-release and permeation kinetics. The tablets offered satisfactory physicochemical results. The buccal strength, detachment force and bond strength of the tablets were good enough to hold the tablets in the buccal region. The drug release data generated during *in vitro* drug release study of bucco-matrix tablets in phosphate buffer pH 6.8 were evaluated by zero-order, first-order, Higuchi, Korsmeyer – Peppas, and Kopcha models. Release exponent (n) of Korsmeyer- Peppas equation of the formulations exhibited diffusion as the principal mechanism of drug release. It was further confirmed by Kopcha model. Evaluation of diffusion and erosion terms in the Kopcha model showed that diffusion dominated swelling or erosion process through out the study. The permeation kinetics of the drug showed linearity when studied across goat buccal mucosa. Permeation coefficient of drug decreased with increase in % swelling index of the formulations.

INTRODUCTION

Drug release kinetics from matrix dosage form is influenced by polymer swelling, polymer erosion, and drug dissolution/diffusion and polymer ratio. For the preparation of controlled release dosage form, hydrophilic, swellable polymers in optimum combination are essential. Successful buccal drug delivery using buccal adhesive systems should have good bioadhesion to hold the formulation in the buccal cavity and maximize the intimacy of contact with buccal membrane. This formulation needs a vehicle that is responsible for releasing the drug at an controlled rate in buccal environment. Hence the use of biocompatible polymers has been the prime focus in the design of bucco-matrix tablets. Hyroxypropyl methylcellulose (HPMC) is a widely used polymer for oral controlled drug delivery systems (Gafourian *et al.*, 2007). HPMCK100M and HPMCK15M along with Carbopol 934p have been selected here. To get controlled release through the use of HPMC like polymers, it generally gets hydrated on the surface to form a gelatinous layer. This gelatinous layer prevents entry of water to the interior area and thus prevent rapid release of drug from the matrices (Choi *et al.*, 2000). This protective gel layer controls the penetration of additional water into the matrix. When the outer gel layer is fully hydrated, it dissolves in the medium and a new inner layer takes the place of the previous one. It again starts reducing the influx of water and controls drug diffusion. Cabopol 934p has been used here as bucccoadhesive agent to retain the tablets in the buccal region (Pathaka *et al.*, 2006).

It has been observed that mechanism of drug release as well as release profiles from matrices is dependent on the type and ratio of the quantity of the polymers used in combination. The hydration rate of the polymer matrix, and thereby the gel formation depends significantly on the ratio of the polymers, viscosity of the polymers (Vazquez *et al.*, 1996). Hence the permeation kinetics of the drug through the buccal membrane is also affected.

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MATERIALS AND METHODS

Amoxicillin trihydrate (Unimerk Remedies, Birganj, Nepal). HPMCK15M, HPMCK100M (Colorcon India Ltd, India) Carbopol 934p (Corel Pharma-Chem, Ahmedabad, India) were gift samples. All the other ingredients were obtained commercially.

Preparation of bucco-matrix tablets

Bucco-matrix tablets of Amoxicillin trihydrate were prepared using HPMC of two grades (K100M and K15M) along with Carbopol 934p using no other varying parameter. The blended mass was transferred to the tablet punching machine 10 stations Mini press -1 single punch tablet machine (Karnavati Engineering Pvt Ltd, Mumbai, India) fitted with a 3 mm punch and die sets adjusted to a compressing weight of 5.5 metric ton. The tablets were compressed with continuous hardness and weight checking. The die and punch surfaces were sufficiently lubricated with magnesium stearate.

Evaluation of bucco-matrix tablets

The bucco-matrix tablets were subjected to various physical tests like weight variation, Friability, Disintegration, Moisture uptake, Moisture content, Drug content as per pharmacopoeial methods.

Buccoadhesion test

For the determination of the buccoadhesive strength of the experimental tablets in buccal region, the formulation was attached to goat-buccal mucosa. A small physical balance having two circular pans (diameter, 2 cm) hanged from a rod which was balanced with a fulcrum on a stand, was used as a modified buccoadhesion test assembly (Gupta *et al.*, 1992).

Lower end of a circular pan was attached to the tablet. Immediately after the attachment weights, were placed on the other pan. Placing of weights was continued till the pan got detached. In this project, the buccal strength was determined by measurement of the force of detachment or force of adhesion (Ramana *et al.*, 2007).

Ex -vivo Residence Time

The ex-vivo residence time of the tablets was observed (n= 3) after application of bucco-matrix tablets on freshly cut goat buccal mucosa (Han *et al.*, 1999). The fresh goat buccal mucosa was attached to the inner side of a beaker, about 3 cm from the bottom, with cyanoacrylate glue. One side of each bucco-matrix tablet was wetted with phosphate buffer (pH 6.8) and attached to the goat buccal mucosa by applying a light force.The beaker was filled with 200 mL of phosphate buffer (pH 6.8) and kept at 37^0C ± 1^oC. The beaker was kept on a magnetic stirrer and around 50-rpm stirring rate was applied to mimic the buccal cavity environment. Adhesion of the bucco-matrix tablets was monitored for 12 hours (Chinna, 2011). The time taken for total erosion or dislodgment of the tablet from the goat buccal mucosa was recorded.

Swelling studies (Needleman and Smales, 1995)

The extent of swelling was measured in terms of % of weight gained by the tablet. At the end of specified time intervals tablets kept in 50 ml of pH 6.8 buffer solutions were withdrawn and weighed. The % of weight gained by the tablet was determined by using following formula:

$$\text{Swelling Index \%} = [(Mt-Mo)/Mo)*100$$

Where, Mt-weight of tablets at time‘t’; M_0-Initial weight of tablets

In-vitro drug release

In vitro drug release studies of Amoxicillin trihydrate from bucco-matrix tablets were carried out for a period of 10 h using USP type-II (Paddle) (Lab India Model No DS-8000) dissolution apparatus at 37±0.5ºC at 75 rpm. 900 ml of phosphate buffer pH 6.8 was considered as dissolution medium. At 1h time interval, 5 ml of sample was withdrawn and measured by UV spectrophotometer (Shimazdu, Model No UV-1800) at 272 nm.

Permeation study

To investigate the drug permeation kinetics and permeability coefficient, pieces of goat buccal mucosa were excised, and subsequently separated from the underlying tissues, fats, and muscles. These pieces were then fixed on the Franz diffusion cell, in a way that the mucosa surface faced the donor chamber on which the tablets were fixed with a diffusional area of approximately 0.785 cm^2. The receiver compartment of 65 ml capacity is filled with phosphate buffer pH-6.8. 2 ml of Samples were taken at specific interval for 10 h. and measured spectrophotometrically at 272 nm.

Statistics

All the experimental data were assessed by one-way ANOVA followed by Tukey HSD Test using Vassar Stats software (USA). For assessing statistical significance $P<0.01$ has been considered.

RESULTS AND DISCUSSION

The directly compressible bucco-matrix tablets showed satisfactory physicochemical results. The range of buccal strengths (measured in g) was found to be 20-22 gm for the tablets. Detachment stress was found to be $19.80X10^{-2}$ - $22.34X10^{-2}$ N (Table 1). Though Carbopol 934p has been included as mucoadhesive agent at same quantity (30 mg/tablet) in all the batches, the change in buccal strength as well as detachment stress signifies that HPMCK100M and HPMCK15M have influence on buccoadhesion. The buccal strengths were found to be good enough (Singh and Ahuja., 2002) to hold the formulations attached to the buccal region. Ex-vivo residence time (7 h) was found in the formulation B1. B2 was found to have low ex-residence time of 5 h (Table-1). The combination of Carbopol and HPMC are responsible for rapid swelling which leads to interpenetration of the polymer chains at the interface, and improved attachment of the tablet to the buccal membrane. The batches B1 and B4 showed

1109 % and 990 % weight gain after 10 h respectively. With increase in swelling lead to decrease in viscosity of the polymers present in the tablet thus there was a decrease in weight gain of the bucco-matrix tablets with time. Correlating the buccal strength with swelling index revealed that tablet with higher degree of swelling displayed greater bucucoadhesive strength, i.e. B1 showed higher swelling index (1109%) with higher detachment force $22.34X10^{-2}$ N and bond strength 7905.16 N/m^2. To investigate the drug release mechanism, the data were evaluated by kinetic models representing zero-order (Figure 1), first-order and Higuchi (Bourne., 2002; Higuchi., 1963).

The cumulative percent of drug released versus time plot exhibits curvilinear nature, which suggests that drug release is not governed by zero order kinetics. This observation is confirmed by fitting the dissolution data to zero-order model where comparatively low values of correlation coefficients (R^2) are obtained. The results of above mentioned studies show that drug release from the bucco-matrix tablets are much more acquainted with Korsmeyer–Peppas, Kopcha, and Higuchi models. Hence the data were fitted to Korsmeyer-Peppas exponential equation $Mt/M\alpha = Kt^n$, [$Mt/M\alpha$ = the fractional drug release into the dissolution medium, K = a constant , n = diffusional exponent] (Huq *et al.*, 2011). In the present study it was observed (Table 2) that the n varies from 0.1 to 0.7 representing huge change in drug transport mechanism. It is due to the change in polymeric ratio. Among the five batches B2 followed anomalous diffusion (n=0.7) mechanism, whereas drug release from B1, B3 is fully governed by quasi-Fickian and Fickian diffusion (n=0.45 and 0.5 respectively). Further for proper clarification the data were fitted to Kopcha mathematical model. This result is supported by determination of the ratios of the exponents A/B (i.e., diffusional factor A and erosional factor B) (Kopcha., 1991). The ratios (A/B) were greater than 1 in all the batches. In case of B4 and B5 (Table 2) the value of the release exponent, n, were <0.45 indicating that Amoxicillin trihydrate release was controlled not only by diffusion. The diffusion rate of a drug depends on the physical structure of the polymer network and its chemical nature. When the gel gets fully hydrated, drug diffusion occurs through the pores present. In gels where lower hydration occurs, the drug is dissolved in the polymer and is transported between the chains. Cross-linking of the polymers is responsible for increasing the hydrophobicity of the gel formed at the outer surface and reduces the diffusion rate of the drug (Patrick., 2006), .For further confirmation, fitting the data to the Kopcha model showed the evidence of drug release by a combination of diffusion-controlled and chain relaxation–swelling mechanism. In case of B1, due to presence of higher grade of hydroxyl propyl methyl cellulose (HPMCK100M) the gel became more hydrophobic and retarded the diffusion of Amoxicillin trihydrate from the bucco-matrix tablets.

The drug permeation might be described by zero-order kinetics during the time of study (El-Badry and Fathy, 2006). The permeability coefficient was calculated using. P = K. Vr/ S, where, S is the effective surface area of goat buccal mucosa, Vr the volume of receiver chamber, K is the zero order constant, and P is the permeability coefficient. The flux increased considerably with an increase in the ratio of HPMCK15M to HPMCK100M, and was highest in B5.The permeation profiles for each batch was linear with a mean (R^2) value of 0.99. The permeation coefficient found was in a range of $4.43X10^{-2}$ cm/sec to $9.78X10^{-2}$ cm/sec (Table 3). Figure 2 shows a correlation between % swelling index and permeability coefficient of the formulations through goat buccal mucosa. With increase in % swelling index over a period of 10 h the permeability coefficient decreased. Hence it can be concluded that swelling of the formulations forms a sticky, gelatinous mass which inhibits the permeation of Amoxicillin trihydrate through the goat buccal membrane.

Table 1: Physicochemical evaluation of Amoxicillin trihydrate loaded bucco- matrix tablets.

Batch	HPMCK 100M: HPMCK15M	Weight variation (mg)	Drug content (%)	Hardness Kg/cm^2	Friability (% loss)	Surface pH	Buccoadhesive strength (gm)	Detachment stress (N)	Ex-vivo residence time (min)
B1	1:0	120 ±0.5	98.22 ± 0.12	4.7±0.1	0.276±0.03	6.7±0.05	22.80 ±0.32	$22.34 X 10^{-2}$	420 ± 0.70
B2	1:1	119 ±0.6	98.16 ± 0.24	4.2±0.1	0.221±0.01	6.8±0.02	20.30 ±0.20	$19.80X 10^{-2}$	310 ± 1.56
B3	0:1	120 ±1.0	98.04 ± 0.22	3.9±0.1	0.171±0.02	6.7±0.02	21.30 ±0.12	$20.80X 10^{-2}$	370 ± 0.80
B4	1:2	119 ±1.0	99.11 ± 0.02	4.8±0.1	0.299±0.02	6.7±0.01	21.0 ±0.2	$20.50X 10^{-2}$	350 ± 1.74
B5	2:1	120 ±0.4	98.54 ± 0.24	4.1±0.1	0.322±0.02	6.8±0.02	22.70 ±0.35	$22.24X 10^{-2}$	390 ± 1.40

Data shows ± SD, N=6 *Tablet weighs 120 mg * 30 mg of Carbopol 934p was included/tablet

Table 2: Kinetics –Data of Drug Release from bucco- matrix tablets.

Formulation	Zero order		First Order		Higuchi Kinetics		Korsmeyer-Peppas		Kopcha model			
	R^2	K_1	R^2	K_2	R^2	K_3	R^2	n	R^2	A	B	A/B
B1	0.786	1.5	0.801	0.003	0.875	6.11	0.885	0.45	0.897	7.49	0.137	54.73
B2	0.926	2.8	0.933	0.006	0.939	10.5	0.927	0.73	0.498	3.47	2.31	1.49
B3	0.793	1.8	0.807	0.003	0.882	7.05	0.892	0.5	0.846	7.22	0.53	13.63
B4	0.974	1.5	0.974	0.005	0.963	5.66	0.926	0.1	0.981	54.55	15.19	3.59
B5	0.876	3.2	0.840	0.009	0.818	11.57	0.728	0.2	0.962	44.72	11.19	3.99

Table 3: Permeation kinetics of the drug from Bucco-matrix tablets through goat buccal mucosa.

Formulation code	Flux (mg/cm^2.h)	Intercept (mg/cm2)	R^2	Permeation coefficient (cm/sec)
B1	1.8804	0.0407	0.9848	4.25X10-2
B2	2.89	0.113	0.9907	4.43 X10-2
B3	2.223	0.9313	0.9909	4.99 X10-2
B4	4.582	3.72	0.991	9.35 X10-2
B5	4.739	4.61	0.994	9.78 X10-2

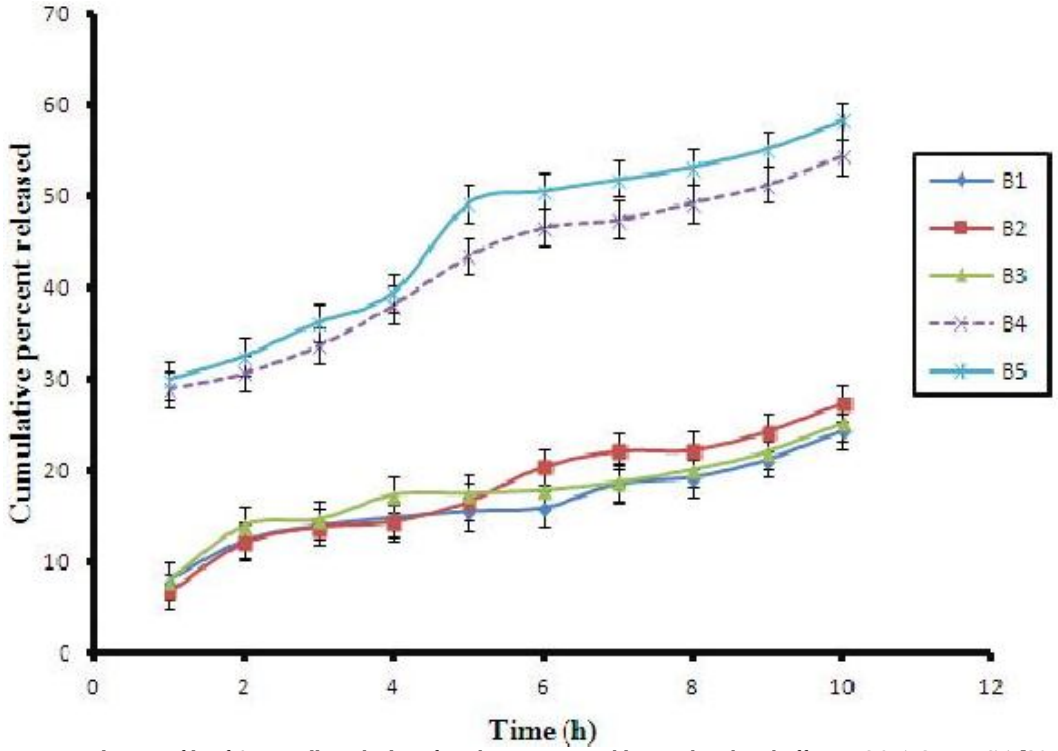

Fig. 1: Drug release profile of Amoxicillin trihydrate from bucco-matrix tablets in phosphate buffer pH-6.8, (±SD, N=6)) [30 KB]

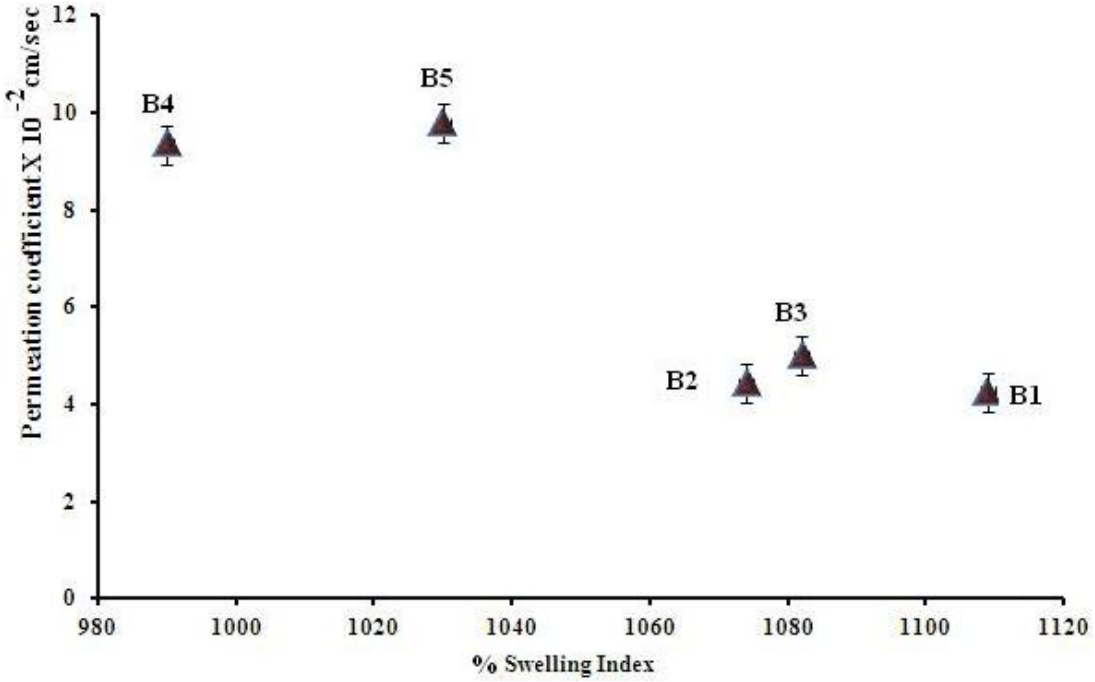

Fig. 2: Correlation between swelling index and permeation coefficient of the bucco-matrix tablets in phosphate buffer pH-6.8 (±SD, N=6).

CONCLUSIONS

The work included development of Amoxicillin trihydrate loaded bucco-matrix tablets as extended release formulations. HPMCK100M, HPMCK15M have been employed as release rate controlling polymers and Carbopol 934p as mucoadhesive polymer. From the results obtained, it can be concluded that a significant variation is observed in the *In vitro* release pattern of Amoxicillin trihydrate from the bucco-matrix tablet in relation to change the ratio of two grades of HPMC. There was variation in transport mechanism from quasi diffusion to anomalous by changing the ratio of HPMCK100M and HPMCK15M. Drug permeation through the membrane clearly indicates a skin-dependent permeation and is strongly controlled by the stratum corneum diffusion process. After getting successful results in in-vitro drug release as well as permeation study, ex-vivo drug release studies has to be done. In vivo studies are another future prospect to get a clear picture of IVIVC.

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