Chitosan Based Buccoadhesive Tablets of Pentazocine Hydrochloride: *in vitro* and *in situ* Kinetics

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Buccoadhesive tablets of pentazocine hydrochloride were prepared by directly compressing chitosan with sodium alginate or sodium carboxymethylcellulose in weight ratios 5:0, 4:1, 2:3, 3:2, 1:4. The tablets were evaluated for weight variation, hardness, thickness uniformity, drug content uniformity and swelling index. Swelling of sodium carboxymethylcellulose batches was greater than sodium alginate. *In vitro* bioadhesive strength studies showed that formulations containing chitosan and sodium carboxymethylcellulose were more bioadhesive than chitosan and sodium alginate. *In vitro* dissolution studies revealed that all the formulations exhibited non-Fickian release kinetics. Further, *in situ* drug diffusion studies were carried using porcine cheek pouch. The formulation containing a mixture of chitosan and sodium alginate (4:1) showed 100 % release in 8 h in *in vitro* dissolution studies and 52.1 % in drug diffusion studies. Incorporation of sodium glycodeoxycholate (3 %) resulted in 17.9 % enhancement in drug diffusion.

Conventional solid dosage forms like lozenges and sublingual tablets are not able to prolong the systemic delivery of drugs. Also significant fraction of the administered dose may not be available for mucosal absorption due to quick disintegration of dosage forms followed by salivary wash off. Mucoadhesive polymers have the potential to prolong the residence time of the dosage forms in oral cavity and thus are used in the development of oral mucoadhesive devices.

Chitosan is a natural poly cation copolymer consisting of glucosamine and N acetyl glucosamine units. Chitosan has valuable properties as a biomaterial because it is considered to be biocompatible, biodegradable and nontoxic. Chitosan causes a marked enhancement of the permeability of buccal mucosa by interfering with the intercellular lipid lamellae of buccal epithelium that constitutes the permeability barrier. Due to this property it has been used as a buccal penetration enhancer[1,2]. However, its mucoadhesive properties are just satisfactory[3,4]. Therefore, there is a need to combine chitosan with better mucoadhesives in order to increase the mucoadhesion period and drug permeation across buccal mucosa.

Sodium carboxymethylcellulose (SCMC) and sodium alginate are anionic polymers, which have excellent bioadhesive strength. Hence a combination of polymers is expected to combine attributes of different polymers to give superior quality of dosage form.

Pentazocine hydrochloride is a potent agonist and a weak opioid analgesic used postoperatively and in chronic severe pain associated with cancer and trauma. However, its oral bioavailabilty is very low (11-32%) due to extensive first pass metabolism. In addition, its short half- life (2-3 h), low dose (20-100 mg) and high frequency of administration[5] make it suitable for formulation into a bioadhesive tablet.

Therefore this study was designed to develop a pentazocine hydrochloride buccal bioadhesive tablet. Absorption of the drug from oral cavity and attachment of tablet with buccal mucosa without collapse are two prime considerations in the design of these dosage forms. The

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bioadhesive strength of various combinations of chitosan with sodium alginate or SCMC was evaluated. In addition, the formulations were tested for their *in vitro* release and *in situ* diffusion across porcine cheek pouch.

Pentazocine hydrochloride (Ind Swift laboratories Limited, Derra Bassi), chitosan (Fisheries Department, Cochin) were gift samples. Buccoadhesive pentazocine tablet formulations were prepared by direct compression using a concave faced single punch tableting machine (Cadmach, Ahmedabad). Each tablet contained a constant amount of pentazocine hydrochloride (20 mg) and magnesium stearate (1 mg) and a varying composition of buccal bioadhesive polymer mixture of either chitosan and SCMC or chitosan and sodium alginate (Table 1). All the material were passed through a 125 μm sieve and retained on 90 μm sieve. Pentazocine hydrochloride was first mixed with buccal bioadhesive polymer mixture for 10 min. Magnesium stearate was then added and mixing continued for another 10 min. (the angle of repose of the powder determined by funnel method was found to be 20±1.1). The machine was adjusted to produce tablets of approximate weight of 100 mg. The dimensions of the formulated tablets were 7.8±0.1 mm diameters and 1.6±0.05 mm thicknesses.

The formulated tablets were evaluated for weight variation, hardness and friability according to pharmacopeial requirements. Tablets of each formulation were ground in a mortar to powder form. An accurately weighed amount of the powder, equivalent to 20 mg of the drug was transferred into 100 ml volumetric flask. The powder was dissolved in phosphate buffer (pH 6.6) using a magnetic stirrer for 18±2 min. After filtration the solution was assayed spectrophotometrically (UV Visible Spectrophotometer, Beckman, DU-640B, USA) for pentazocine at 278 nm against phosphate buffer blank. The content was calculated from the standard calibration curve of drug in pH 6.6 buffer. The bioadhesive strength of the tablets was measured using a modified physical balance[6]. Porcine cheek pouch was used as a model membrane for measurement of bioadhesive strength and phosphate buffer pH 6.6 as a moistening fluid. The surface of the mucosal membrane was first blotted with a filter paper and then moistened with 25 μl of buffer solution pH 6.6. The weight required to detach the tablet from the mucosal surface was taken as the measure of bioadhesive strength.

The water absorbing capacity of tablets was determined by gravimetry. The swelling rate of the bioadhesive tablets was evaluated by using 1% agar gel plate. The average weight of the tablet was calculated (W_1). The tablets were placed on gel surface in a Petri dish placed

TABLE 1: BUCCOADHESIVE INDICES OF VARIOUS PENTAZOCINE TABLET FORMULATIONS

Formulation Code	Chitosan (mg)	Sodium alginate (mg)	SCMC (mg)	Bioadhesive strength (g)	Swelling index (SI)	Swelling index ratio (SIR)***
A1	80	–	–	4.23±0.29	0.268±0.021	–
A2	64	16	–	10.11±0.29	0.590±0.036	2.201
A3	48	32	–	12.56±0.25	0.998±0.043	3.724
A4*	32	48	–	16.20±0.43	1.610±0.017	6.007
A5*	16	64	–	18.83±0.15	1.710±0.050	6.380
A6**	–	80	–	21.03±0.41	–	–
B1	64	–	16	11.63±0.51	0.689±0.005	2.570
B2	48	–	32	14.03±0.41	1.230±0.029	4.589
B3*	32	–	48	18.96±0.20	1.700±0.101	6.343
B4*	16	–	64	20.63±0.40	2.010±0.140	7.5
B5**	–	–	80	24.30±0.36	–	–

Each value represents mean±SD, (n=3); *Maximum swelling occurred till 4 h, which was followed by erosion; **Swelling could not be measured; ***SIR=SI of the tablets with sodium alginate or SCMC/ SI of tablets with chitosan only. Note: Each tablet contained 20 mg of pentazocine hydrochloride and 1 mg of magnesium stearate.

in an incubator at 37±1°. Tablet was removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 h), wiped with filter paper and reweighed (W_2). The swelling index was calculated by the formula[7], Swelling Index = $(W_2-W_1)/W_1$

The drug release rate was determined using USP dissolution apparatus II. The tablet 100 mg was glued in the center of a 9 cm diameter glass disc. The dissolution media was phosphate buffer pH 6.6 maintained at 37±1° and stirred at 50 rpm. Samples (3 ml) withdrawn at suitable time interval were compensated with fresh dissolution media and assayed spectrophotometrically at 278 nm. Samples were analyzed in triplicate. To examine the release kinetics of pentazocine hydrochloride from the prepared buccoadhesive tablets, the results were analyzed by employing the Peppas and Sahlin equation[8], $M_t/M\alpha=kt^n$, where $M_t/M\alpha$ is fractional drug released at a time t. Value of n was calculated to determine Fickian/ Non- Fickian release characteristics of the drug.

In situ drug release studies were carried out in Franz diffusion cell. The receptor compartment was filled with phosphate buffer pH 7.4 and donor compartment with buffer pH 6.6. The tablets were placed on the membrane sandwiched between receptor and donor compartment with the help of a clamp. The assembly was maintained at 37±1° and medium was stirred at 300 rpm. Samples (1 ml) were withdrawn at suitable intervals and equal volume replaced with fresh phosphate buffer (pH 7.4). Samples were analyzed spectrophotometrically at 278 nm.

The selected formulation was subjected to accelerated storage conditions at 40±2°/75±5% RH for 6 months. The formulation was analyzed for organoleptic characters, hardness, drug content and dissolution studies. F_2 (similarity factor) was applied to compare the *in vitro* dissolution data[9]. To the selected batch of tablet, 3% sodium glycodeoxycholate (GDC) was added as a permeation enhancer and *in situ* drug release studies were carried out in Franz diffusion cell.

The average drug content of the tablet was found to lie between 99.5-100.5%, which lies within pharmacopeial limits. The bioadhesive strength of formulations was linearly correlated with the concentration of SCMC ($y=8.328+0.1758x$; $r=0.9912$) or sodium alginate ($y=7.313+0.1758x$; $r=0.9966$). The tablet formulations containing SCMC (B1-B5) were found to possess marginally superior bioadhesive strength than those containing sodium alginate (A2-A6). Table 1 summarizes the buccoadhesive strength and swelling index of various tablet formulations. The tablets containing SCMC exhibited greater water uptake as compared to those containing an equivalent quantity of sodium alginate. The ratio of swelling index of tablets containing 16 mg, 32 mg, 48 mg and 64 mg SCMC to that containing only chitosan was found to be 2.6, 4.6, 6.3 and 7.5, respectively whereas, these ratios for tablets containing an equivalent amount of sodium alginate were 2.2, 3.7, 6.0 and 6.4, respectively. These results indicate better bioadhesion and water uptake properties of tablets prepared using a combination of chitosan and SCMC. Greater swelling of the formulation containing SCMC can be attributed to its more hydrophilic nature than that of sodium alginate. Formulations A4, A5 and B3, B4 showed maximum swelling at 4 h after which the polymer started eroding slowly in the medium while for the formulations A6 and B5 that contained highest amounts of sodium alginate and SCMC, respectively, swelling index could not be measured. Swelling of the polymer has been reported to help in interpenetration of mucus and polymer and makes bioadhesion possible[10]. Hence, enhanced swelling of formulations containing SCMC can be expected to exhibit better bioadhesive character.

No interference was occurring due to tablet excipients or due to α-cyanoacrylate glue at this wavelength. Combination of chitosan with SCMC or sodium alginate in different ratios showed different *in vitro* drug release rates. A comparison between the formulations containing sodium alginate (fig. 1) and SCMC (fig. 2) shows an extended drug release from the tablet formulated with SCMC. Hence, the slow release of pentazocine seems to be due to an increased diffusional thickness because of greater relaxation of the cellulosic chains. This finding is in consonance with the earlier reports[11].

However, a critical examination of the formulations showed that the time required for 100% release of the drug decreases with an increase in the concentration of either sodium alginate or SCMC. Chitosan-sodium alginate matrixes have been reported to increase the dissolution rate of ketoprofen due to hydrophilic nature of sodium alginate[12].

Formulations A2 containing chitosan and sodium alginate (4: 1) and B2 containing chitosan and SCMC (3: 2) took 8 h to release 100% of the drug. These formulations exhibited comparatively lower bioadhesive strengths of 10.11 g and 11.63 g, respectively. Other formulations

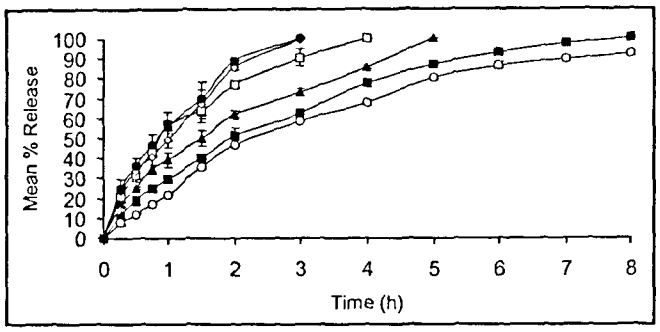

Fig. 1: *In vitro* release profile of pentazocine hydrochloride

Release of pentazocine hydrochloride from various tablet formulations prepared with chitosan and sodium alginate in phosphate buffer pH 6.6. (-○-) A1, (-■-) A2, (-▲-)A3, (-□-) A4-, (-◇-) A5, (-•-)A6

showing greater bioadhesive strength required significantly less time to release 100% of the drug. The value of 'n' for batch A2 was 0.6244 and batch B2 was 0.8001 indicating a combination of both diffusion and chain relaxation mechanisms.

In situ release studies showed ≅52 % and ≅43 % drug release from formulation A2 and B2, respectively. (Fig. 3) As the concentration of chitosan increased, permeation through the buccal mucosa increased. This could be attributed to its interaction with the negative charge on mucosal surface and by interfering with the lipid organization of buccal epithelium[1].

Incorporation of GDC (3% w/w) to formulation A2 increased drug diffusion to 70%. GDC is reported to interfere

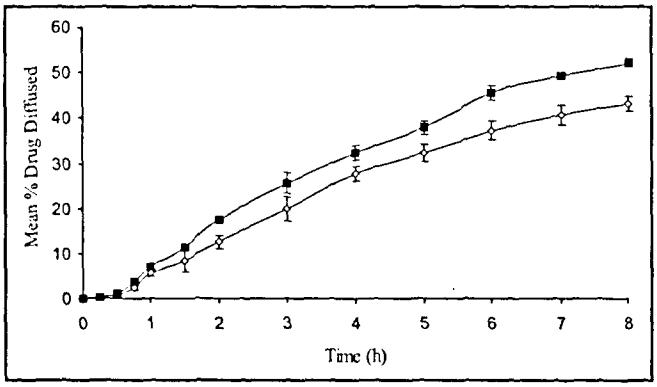

Fig. 3: *In situ* diffusion of pentazocine hydrochloride from formulation A2 and B2

Effect of polymers chitosan and sodium alginate or SCMC on the *in situ* diffusion of pentazocine hydrochloride. (-■-)A2, (-◇-) B2

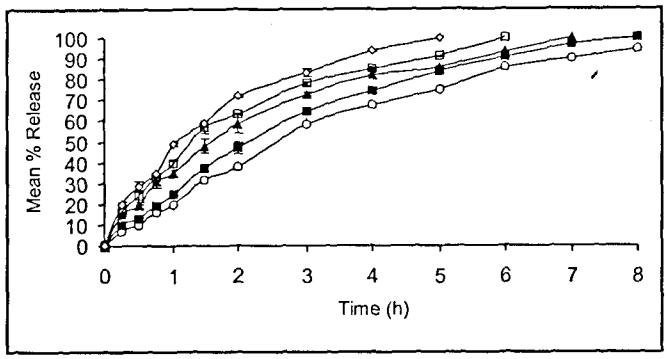

Fig. 2: *In vitro* release profile of pentazocine hydrochloride

Release of pentazocine hydrochloride from various tablet formulations prepared with chitosan and SCMC in phosphate buffer pH 6.6. (-○-) B1, (-■-) B2, (-▲-)B3, (-□-)B4-, (-◇-) B5

with the epithelial lipids and hence, decrease the diffusional path length[13]. It also causes the extraction of membrane lipids or modifies cell membrane integrity in such a way that the intracellular domain is opened up and transepithelial pathway is significantly shortened leading to an increase in percent drug diffused.

Formulation A2 showed no change in physical characteristics and drug release profile when subjected to accelerated stability studies. SUPAC IR states that an f_2 value between 50 and 100 suggests that the dissolution profiles are similar. In our study f_2 value was found to be 63.98 thus suggesting a similar dissolution profile of the fresh sample and aged.

This study investigated that sodium alginate and SCMC can be used to formulate pentazocine hydrochloride buccoadhesive tablets. An increase in the bioadhesive strength was observed with SCMC but SCMC is not able to sustain the release of the drug for longer period of time because of hydrophilic nature of SCMC. Thus, these observations presented show that the tablets prepared from chitosan and sodium alginate have the potential for use in buccal delivery. This delivery system provides good bioadhesion and can give a prolonged release of pentazocine for 8 h.

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Spectrophotometric Assay of Cefpirome sulfate

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A simple and sensitive spectrophotometric method for the determination of cefpirome sulfate in pure and dosage forms is proposed. The drug forms a stable green complex with ferric chloride and 3-methyl-2-benzathiazolinone hydrazone, exhibiting maximum absorption at 635 nm. The complex obeys Beer's law in the concentration range of 2.5-20 μg/ml.

Cefpirome sulfate[1,2] ((6R, 7R)-7-[(2)-2-(2-aminothiazol-4-yl) 2-methoxy imino acetylamino]-3-(6,7–dihydro-5H-cyclopenta [b] pyridinium-1-yl-methyl)-8-oxo-5-thia-1-azabicyclo [4.2.0]- oct-2-ene-2-carboxylate monosulfate) is a broad-spectrum antibiotic belonging to the fourth generation cephalorosporins. It is recommended in the treatment of complicated respiratory tract infections, skin and soft tissue infections and bacteraemia. A literature survey revealed that only HPLC methods have been reported for the determination of the drug in biological fluids[3-8]. In the present investigation a new spectrophotometric method has been developed for the estimation of the drug using ferric chloride and 3-methyl-2-benzathiazolinone hydrazone (MBTH). In this method, ferric chloride oxidizes MBTH, which in turn complexes with the drug forming a green chromophore which exhibites an absorption maximum at 635 nm.

A stock solution of cefpirome sulfate (1 mg/ml) was prepared in distilled water and is suitably diluted to get a working standard solution of 100 μg/ml strength. Ferric chloride solution (0.5 % w/v) and MBTH (0.2 % w/v) were prepared in distilled water. Spectral measurements were made on a Systronics UV/Vis spectrophotometer (model 117) with 10-mm matched quartz cells.

To a series of 10 ml volumetric flasks, aliquots of standard drug solution, ranging from 0.25-2.0 ml were added. This was followed by the addition of 2.0 ml of ferric chloride and 2.0 ml of MBTH, after which the flasks were kept aside for 30 min. Appropriate quantity of distilled water was added to each flask to bring the total volume to 10 ml. The absorbance of the green colored complex formed was measured at 635 nm against a reagent blank. A calibration curve for the absorbances of different concentrations of the drug was plotted. The optical characteristics and the precision data of the proposed method have been calculated and presented in Table 1.

This method was also applied for assaying cefpirome sulfate in a parenteral preparation. For this, a sample of

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