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Effect of Bio-adhesive Polymers like HPMC, Gelatin, Na-CMC and Xanthan Gum on Theophylline Release from Respective Tablets

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Abstract: In order to evaluate the feasible application of bio-adhesive polymers like HPMC-15 cps and 50 cps; gelatin; Na-CMC and xanthan gum in sustained release dosage form (SRDF), tablets containing various amount of bio-adhesive polymers with a model drug like anhydrous Theophylline sodium glycinate were prepared by compression in a hydraulic press (Perkin Elmer) compression machine using 5 ton pressure. The release characteristics of Theophylline (TH) from sustained release tablets were analyzed in triplicate using a thermal shaker (Memmert) with a shaking speed of 50 rpm at $37 \pm 0.5^\circ\text{C}$ in 250 mL of simulated gastric fluid without enzyme for 8 h. At the end of 8 h of dissolution it was found that 61.60% (for 300 mg HPMC-15 cps) and 42.92% (for 500 mg HPMC-15 cps) of TH was released from HPMC-15 cps based tablets, respectively. When HPMC-15cps was increased to 50 cps, 52.12 and 59.66% of TH was released, respectively. Both concentration and viscosity depended sustained release of TH was found. 74.13 and 94.15% of TH was released from Gelatin based SR tablets of the same concentrations, respectively. Gelatin also showed the same concentration effects i.e. release was reduced with an increase in concentration of polymer. 52.40 and 50.95% of TH was released from Na-CMC based SR tablets of the same concentrations, respectively and that of 76.96 and 78.26% of TH from xanthan gum based tablets. It means that there was no remarkable concentration effect of these two polymers on the TH release. In all cases there was almost zero order release fashion. Bio-adhesive polymers like HPMC and gelatin might be successfully applicable in SRDF rather than Na-CMC and xanthan gum studied here.

Key words: Bio-adhesive polymer, sustained release, dissolution, theophylline

INTRODUCTION

The term bio-adhesive describes materials that bind to biological substrate such as, mucosal membrane. Adhesion of bio-adhesive drug delivery devices to mucosal membrane leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systematically delivered drugs (Hannah, 2004). In general terms, adhesion of polymers to tissues may be achieved by (i) physical or mechanical bonds, (ii) primary or covalent chemical bonds and/or (iii) secondary chemical bonds (i.e., ionic). Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus or the folds of the mucosa. Secondary chemical bonds, contributing to bio-adhesive properties, consist of dispersive interactions (i.e., Van der Waals interactions) and stronger specific interactions,

which include hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl ($-\text{OH}$) and the carboxylic groups ($-\text{COOH}$). Adhesive microspheres have been selected on the basis of the physical and chemical bonds formed as a function of chemical composition and physical characteristics, such as surface area.

This invention relates to a bio-adhesive tablet containing at least one bio-adhesive adjuvant and at least one lubricant, with at least one surface of the tablet comprising concentric or parallel, straight and/or curved depressions and to a method for producing the bioadhesive tablets as well as to pharmaceuticals in the form of the bioadhesive tablets. The bioadhesive tablets of the invention nearly completely release the active agent they contain and stimulate its resorption by the tissue while not entering into any undesirable with the biological tissue.

The bioadhesive adjuvant should preferably be a substance that develops adhesion when coming into contact with the mucosa, such as hydroxypropyl methylcellulose (HPMC-15 and 50 cps), Sodium carboxymethyl cellulose (Na-CMC), gelatin, Xanthan gum. It is furthermore considered advantageous that the lubricant facilitates tableting of cohesive mixtures as do talc, Mg-stearate.

The bio-adhesive tablets of the invention can be produced in a known way. Any active agent, especially medicinal substances, can be molded into tablets that adhere to the mucosa by adding a bioadhesive adjuvant, a lubricant and optionally other adjuvant common in tableting using a simple technique. In the organism, the bioadhesive tablet is to adhere to the mucosa immediately upon contacting it, to develop as large a contact area as possible with the mucosa, while containing exclusively toxicologically safe adjuvants.

Xanthan gum, a hydrophilic polymer, was added to the formulation to increase the drug release. Changing the xanthan gum concentration as well as its particle size modified the *in vitro* drug release. Increasing xanthan gum concentrations yielded a faster drug release due to a higher liquid uptake, swelling and erosion rate (Verhoeven *et al.*, 2006).

Gelatin is a thermoreversible or cold-setting polymer. If the gelatin is not refrigerated or reheated, it will slowly convert back to a liquid. Because of this, a gelatin such as Jell-O® should remain refrigerated or it will become tasteless Kool-Aide®. Another popular dessert is Jell-O® instant pudding. It contains a modified food starch instead of gelatin. The instant pudding uses a heat-setting super absorbing thickening polymer (the starch) to create its gelatinous texture (PSLC, 2003). Gelatin and dextran were reported to blended and cross-linked hydrogels to form enzymatically degradable interpenetrating polymeric networks (IPNs) as materials for degradable implants (Kosmala *et al.*, 2000).

It was reported that a study of the erosion rates of matrices containing only indicated that Na-CMC (Belanose) eroded more quickly than HPMC (Dabbagh *et al.*, 1999).

Effect of incorporating pharmaceutical excipients on the *in vitro* release profiles and the release mechanism of monolithic hydroxypropylmethylcellulose (4000 cps) matrix tablets (m-HPMC tablets) in terms of mimicking the dual drug release character of bi-layered Tylenol ER tablets was studied. Release profiles and swelling rates of m-HPMC tablets were found to be highly influenced by the types and amounts of pharmaceutical excipients incorporated. The effect of pharmaceutical excipients on drug release from HPMC-based matrix tablets was found to be mainly due to a change in hydrophilic gel expansion and on physical interactions between the drug and HPMC (Cao *et al.*, 2005).

MATERIALS AND METHODS

Materials: Theophylline Na-Glycinate was a gift sample from Square Pharmaceuticals Bangladesh Limited. Sodium carboxymethylcellulose (Na-CMC), Xanthan gum, Gelatin and hydroxypropyl methylcellulose (HPMC, having a viscosity of 15 cps and 50 cps), were purchased from Loba Chemie Pvt. Ltd., India. Sodium chloride (Loba Chemie Pvt. Ltd., India.) were procured from commercial source. All other reagent used was of analytical grade.

Methodology: For tablet preparation, the amount of active ingredient is 100 mg and the total weight of tablet content was 406 and 609 mg. Theophylline Na-Glycinate, HPMC-15 and 50 cps, gelatin, Na-CMC, xanthan gum as a single bio-adhesive polymer, aerosil and Mg-Stearate were weighed separately (for 20 tablets) according to the formulations in Table 1 using a Mettler balance (AE--50, Switzerland) and mixed thoroughly in a drum blender mounted angularly ensuring thorough mixing. From this mixed mass, amount for individual tablet was weighed out and compressed into tablets in a hydraulic press (Perkin Elmer) compression machine using 5 ton pressure. Before compression, the surface of the die and punch was lubricated with magnesium stearate.

Table 1: The features of matrix tablets

Tablet code	No. of tablets	Drug (mg)	HPMC (15 cps) (mg)	HPMC (50 cps) (mg)	Gelatin (mg)	Na-CMC (mg)	Xanthan Gum (mg)	Aerosil (mg)	Mg. stearate	Total weight (mg)
F-1	20	100	300	-	-	-	-	4	2	406
F-1(a)	20	100	-	300	-	-	-	4	2	406
F-2	20	100	-	-	300	-	-	4	2	406
F-3	20	100	-	-	-	-	-	4	2	406
F-4	20	100	-	-	-	300	-	4	2	406
F-5	20	100	-	-	-	-	300	4	2	406
F-6	20	100	500	-	-	-	-	5	4	609
F-6(a)	20	100	-	500	-	-	-	5	4	609
F-7	20	100	-	-	500	-	-	5	4	609
F-8	20	100	-	-	-	-	-	5	4	609
F-9	20	100	-	-	-	500	-	5	4	609
F-10	20	100	-	-	-	-	500	5	4	609

In vitro dissolution study of tablets: The release characteristics of Theophylline Na-Glycinate from sustained release tablets were supplied in triplicate using a thermal shaker (Mettler) with a shaking speed of 50 rpm at $37 \pm 0.5^\circ\text{C}$ in 250 mL of simulated gastric fluid for 8 h. The dissolution samples were collected at a given interval (30 min), replaced with an equal volume of gastric fluid. The concentration of Theophylline Na-Glycinate release as a function of time was determined using an UV spectrophotometer (Shimadzu, Japan) at λ_{max} 271 nm.

Standard curve preparation: Standard Theophylline Na-Glycinate solution was prepared in the concentration range of $2\text{--}20\ \mu\text{g mL}^{-1}$. Then the absorbance of the standard solution of the different concentration were observed in the UV visible spectrophotometer (UV-1601, SHIMADZU, Japan) at λ_{max} 271 nm. From the observed absorbance, standard calibration curve was made for the assay of Theophylline Na-glycinate.

RESULTS AND DISCUSSION

Various theories have been elaborated in order to describe the process of release of the drug from matrices, by considering either diffusion (Armand *et al.*, 1987), in the case of non-erodible polymers, or erosion with erodible polymers (Bidah and Vergnaud, 1990).

Standard or working curve: A straight line was found when absorbance was plotted against concentration (Fig. 1). The slope value was found out from this straight line and used to calculate the drug concentration with proper volume corrections.

Effect of polymer (HPMC-15 cps) on the release of Theophylline from F-1 and F-6: The release profiles of Theophylline from F-1 and F-6 were shown in Fig. 2. F-1 contains 300 mg of HPMC-15 cps and F-6 contains 500 mg of HPMC-15 cps. About 5.81 and 1.52% of Theophylline released from F-1 and F-6, respectively after 30 min of dissolution period. After 4 h of dissolution period F-1 and F-6 released 38.32 and 20.08% of Theophylline respectively. At the end of 8 h of dissolution it was found that 61.60 and 42.92% of Theophylline have been released from F-1(a) and F-6(a) respectively. HPMC-15 cps is a hydrophilic gel forming agents. It is preferred the formulators to modulate drug release mainly due to its claim to form strong viscous gel in contact with water. It has been observed that the release of Theophylline decreased when the amount of polymer increased.

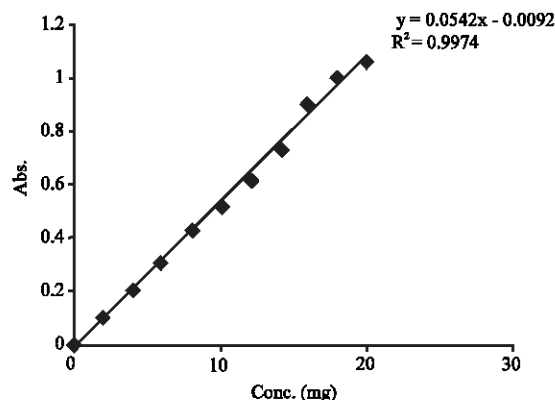


Fig. 1: Standard curve of theophylline Na-glycinate

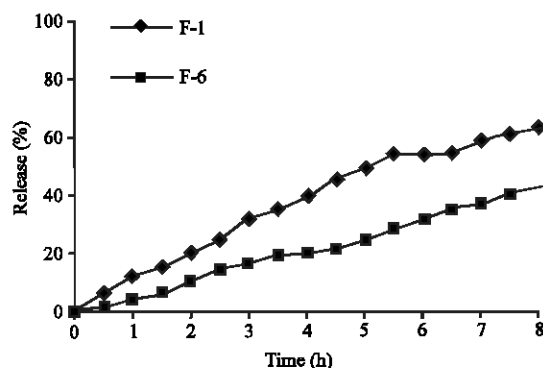


Fig. 2: Theophylline release profiles from HPMC-15 cps based tablets

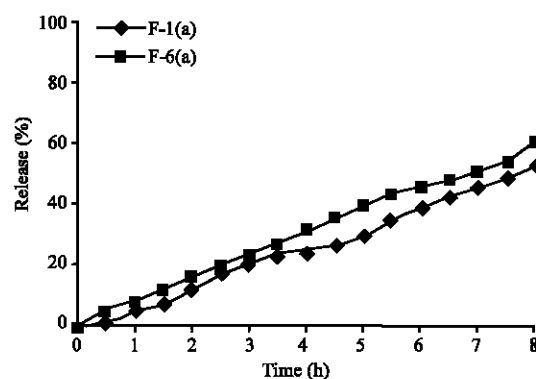


Fig. 3: Theophylline release profiles from HPMC-50 cps based tablets

Effect of polymer (HPMC-50 cps) on the release of Theophylline from F-1(a) and F-6(a): Tablets of F-1(a) and F-6(a) were prepared by the same process as described earlier. The release profiles of Theophylline from F-1(a) and F-6(a) were shown in Fig. 3. F-1(a) contains 300 mg of HPMC-50 cps and F-6(a) contains 500 mg of HPMC-50 cps. About 1.19 and 5.46% of Theophylline released from F-1(a) and F-6(a), respectively after 30 min of dissolution

period. After 4 h of dissolution period, F-1(a) and F-6(a) released 23.84 and 31.81% of Theophylline, respectively. At the end of 8 h of dissolution it was found that 52.12 and 59.66% of Theophylline have been released from F-1(a) and F-6(a), respectively.

Effect of polymer (Gelatin) on the release of Theophylline from F-2 and F-7: Tablets of F-2 and F-7 were prepared by the same process as described earlier. The release profiles of Theophylline from F-2 and F-7 were shown in Fig. 4. F-2 contains 300 mg of Gelatin and F-7 contains 500 mg of Gelatin. About 1.43 and 3.33% of Theophylline released from F-2 and F-7, respectively after 30 min of dissolution period. After 4 h of dissolution period F-2 and F-7 released 57.87 and 69.14% of theophylline, respectively. At the end of 8 h of dissolution, it was found that 74.13 and 94.15% of theophylline have been released from F-2 and F-7, respectively.

Effect of polymer (Na-CMC) on the release of Theophylline from F-4 and F-9: Tablets of F-4 and F-9 were prepared by the same process as described earlier. The release profiles of Theophylline from F-4 and F-9 were shown in Fig. 5. F-4 contains 300 mg of Na-CMC and F-9 contains 500 mg of Na-CMC. About 0.59 and 2.73% of Theophylline released from F-4 and F-9, respectively after 30 min of dissolution period. After 4 h of dissolution period F-4 and F-9 released 27.12 and 27.72% of Theophylline, respectively. At the end of 8 h of dissolution, it was found that 52.40 and 50.95% of Theophylline have been released from F-4 and F-9, respectively.

Effect of polymer (xanthan gum) on the release of Theophylline from F-5 and F-10: Tablets of F-5 and F-10 were prepared by the same process as described earlier. The release profiles of Theophylline from F-5 and F-10 were shown in Fig. 6. F-5 contains 300 mg of xanthan gum and F-6 contains 500 mg of Xanthan gum. About 1.19 and 3.99% of theophylline released from F-5 and F-10, respectively after 30 min of dissolution period. After 4 h of dissolution period F-5 and F-10 released 46.27 and 40.67% of theophylline, respectively. In case of F-10 after 6 h of dissolution period there is a vast release of active ingredient. At the end of 8 h of dissolution, it was found that 76.96 and 78.26% of Theophylline have been released from F-5 and F-10, respectively. It has been observed that there was no significant effect of drug release for the increase of polymer.

Release fashion: In almost all cases the release fashion i.e., % release vs. time curves were approximately straight lines, which approximates to the zero order release fashion.

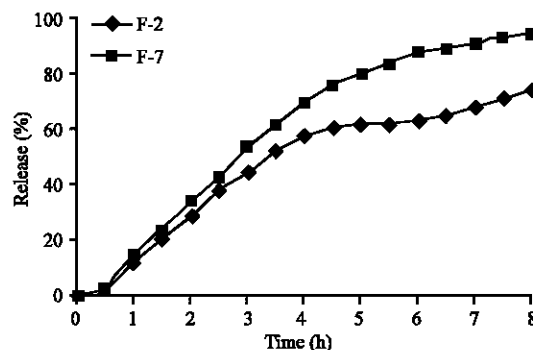


Fig. 4: Theophylline release profiles from gelatin based tablets

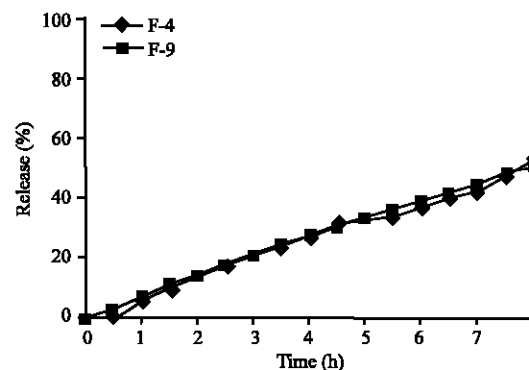


Fig. 5: Theophylline release profiles from Na-CMC based tablets

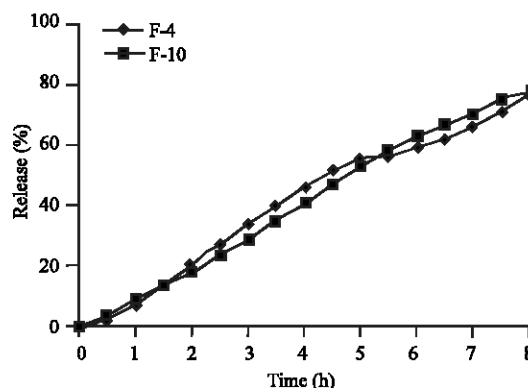


Fig. 6: Theophylline release profiles from xanthan gum based tablets

CONCLUSIONS

Bio-adhesive polymers like HPMC, Gelatin, Na-CMC and Xanthan gum were evaluated in sustaining the drug release from their respective tablets. Both the HPMC showed the concentration as well as grade-dependent sustained release of TH. Gelatin also showed

concentration dependent TH release whereas Na-CMC and Xanthan gum showed a very little dependency with sustaining the TH release. In all cases the release fashion was approximately zero order process. The potential application of HPMC with their different grades and Gelatin might be feasible in SRDF.

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