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Research Article

Evaluation of *Sterculia foetida* Gum as Controlled Release Excipient

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Abstract. The purpose of the research was to evaluate *Sterculia foetida* gum as a hydrophilic matrix polymer for controlled release preparation. For evaluation as a matrix polymer; characterization of *Sterculia foetida* gum was done. Viscosity, pH, scanning electronmicrographs were determined. Different formulation aspects considered were: gum concentration (10–40%), particle size (75–420 μm) and type of fillers and those for dissolution studies; pH, and stirring speed were considered. Tablets prepared with *Sterculia foetida* gum were compared with tablets prepared with Hydroxymethylcellulose K15M. The release rate profiles were evaluated through different kinetic equations: zero-order, first-order, Higuchi, Hixon-Crowell and Korsemeyer and Peppas models. The scanning electronmicrographs showed that the gum particles were somewhat triangular. The viscosity of 1% solution was found to be 950 centipoise and pH was in range of 4–5. Suitable matrix release profile could be obtained at 40% gum concentration. Higher sustained release profiles were obtained for *Sterculia foetida* gum particles in size range of 76–125 μm. Notable influences were obtained for type of fillers. Significant differences were also observed with rotational speed and dissolution media pH. The *in vitro* release profiles indicated that tablets prepared from *Sterculia foetida* gum had higher retarding capacity than tablets prepared with Hydroxymethylcellulose K15M prepared tablets. The differential scanning calorimetry results indicated that there are no interactions of *Sterculia foetida* gum with diltiazem hydrochloride. It was observed that release of the drug followed through surface erosion and anomalous diffusion. Thus, it could be concluded that *Sterculia foetida* gum could be used a controlled release matrix polymer.

KEY WORDS: controlled-release; natural gum; *Sterculia foetida* gum.

INTRODUCTION

The development of controlled release drug delivery system has long been a major area of research in the pharmaceutical industry. Controlled release drug delivery design involves the application of physical and polymer chemistry to dosage form design to produce well characterized and reproducible units that control drug delivery into the body within the specification of the required drug delivery profile (1). The approaches known for modified/controlled drug release, the compressed matrices continue to receive maximum attention, as such devices incur the lowest fabrication cost and there is possibility of incorporating optimum levels of drug in them. Hydrophilic polymers are widely used in the formulation of modified release oral dosage forms. Their convenience and ease of manufacture cut down the cost of the final product. Besides, hydrophilic polymer matrix system offers several additional advantages, well exemplified in the literature (2), over other technologies for controlled release drug delivery. The mechanism of, and the influence of various technological and formulation variables on, the drug release from hydrophilic systems have been well studied and reviewed by many authors (4–7). Until now large number of natural and synthetic polymers, single or in combinations, have been listed as hydrophilic matrix excipients. Natural gums (like xanthan gum, guar gum) have also been examined as matrices for the sustained release of drugs (8,9). Natural gums are often preferred to synthetic materials due to their non-toxicity, low-cost, and easy availability. It is the usual balance of economics and performance that determines the commercial realities. The Pinari tree, *Sterculia foetida,* found in South India, has been well documented for the utility of its various parts (10), gummy exudates of *Sterculia foetida* tree has not been reported or exploited as hydrophilic matrix system. *Sterculia foetida* gum (SFG) gum is obtained from gummy exudates of stem bark of *Sterculia foetida* belonging to the family Sterculiaceae. The SFG is chemically characterized to be containing high acetyl content, a high proportion of D-galactouric acid and the presence of residues of L-rhamnose, D-galactose and ketohexoses (11).

In the present work when SFG in the form of compressed tablets was placed in water, it did not disintegrate, but immediately after hydration developed a highly viscous gelatinous surface barrier layer. Thus, for the same reason, it seemed to be an interesting polymer for the preparation of hydrophilic matrix tablets. According to the current literature survey, until now, no work has been done with SFG polymer as sustained release/controlled release material. The attention was focused on the behavior of the SFG under different

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experimental conditions. Diltiazem HCl was used as a soluble model drug.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride (DIL) was a gift sample from Themis Laboratories, Mumbai, India and *Sterculia foetida* gum (SFG; Medicinal natural products research laboratory, University Institute of Chemical Technology, Mumbai, India) were received as gift samples. Microcrystalline cellulose (MCC; Avicel PH 101, FMC biopolymer), lactose IP, dicalcium phosphate anhydrous (DCP; DMV international), and magnesium stearate (Research lab chemical corporation, India) were used as received. All other chemicals and solvents were of analytical grade and were used without further purification.

Characterization of SFG

In all the characterization experiments SFG passed through 120# was used. Solubility of SFG in water and alcohol were determined. For solubility determination 1 g of SFG was dissolved in various amounts of water and for viscosity determination 1% solution was prepared by dissolving 1 g of SFG in 99 g of water and pH of the solution was also noted. In order to understand the morphology of SFG powder was analyzed with the help of scanning electron microscope (Cemeca, Japan). The powder passed through 120# was selected. Powder was mounted on metal holder with silicon adhesive and then sputter coated with gold. Powder was examined with scanning electron microscope at an accelerating voltage of 10 KV.

Compression of Tablets

For preparation of tablets DIL (40#) and SFG (120#) and fillers (40#) like MCC/DCP/lactose were blended in a blender (Karnavati, India) as depicted in Table I. Tablets were prepared by direct compression (DC) through such a compression force that a predetermined hardness (5–6 kg/cm^2) was achieved with a rotary tablet press (Jaguar, India) using 8 mm diameter circular flat punches.

Swelling Studies

Tablets were subjected to swelling studies in 900 ml 0.1 N HCl, Distilled water and pH 7.4 phosphate buffer maintained at 37±0.5 °C. Swelling studies were conducted in triplicate for batch F4. Radial and axial swelling of tablet width was noted, manually from time to time (12,13).

Effect of SFG Particle Size

To demonstrate the effects of particle size tablets were prepared from four different particle sizes viz. no. 40 (176–420 μm), no. 80 mesh (126–175 μm), no. 120 mesh (76–125 μm) and no. 200 mesh (<75 μm) of SFG and 90 mg DIL.

Effect of SFG Concentration

For the purpose of developing formulation with different release rates, matrix tablets containing 10 to 40% of SFG were prepared.

Effect of Filler

The effects of different type of fillers were investigated on the SFG matrix structure. The fillers selected were lactose, MCC and DCP.

In Vitro Release Testing

The release of drug from matrix tablets was measured utilizing USP apparatus 2 (paddle method) at 37±0.5 °C using 900 ml of dissolution medium, at various rotation speeds and buffer compositions. At determined time intervals, 5 ml samples were taken out, filtered through a filter (0.45 μm) and analyzed by using an ultraviolet spectrophotometer (Shimadzu UV-DEC1601) at 237 nm for DIL. Each formulation was tested in triplicate and a mean of three measurements was reported. The effect of dissolution media and rotational speed was studied.

Effect of pH of Dissolution Media

The release profiles of DIL from SFG matrices were determined in two dissolution media, i.e., 0.1 N HCl and phosphate buffer pH 7.4.

Table I. Contents of Matrix Tablet Formulations Prepared According to DC

	Formulations						
Contents (% *w*/*w*)	F1	F2	F3	F4	F5	F6	F7
Diltiazem HCl	89	79	69	59	21	21	21
SFG Powder (no. 120 Sieve)	10	20	30	40	40	40	40
Lactose	–	–	–	–	40	–	–
Microcrystalline Cellulose	–	–	–	–	–	40	–
Dicalcium Phosphate	–	–	–	–	–	–	40
Magnesium Stearate	1	1	1	1	1	1	1
Assay (% Content)	100.25	99.28	102.08	100.14	101.69	98.09	99.87
Friability (%)	0.15	0.21	0.24	0.28	NIL	NIL	NIL

Effect of Rotational Speed

In order to study the influence of hydrodynamic stress on the release rates, dissolution studies were conducted using USP apparatus 2 at 50, 100 and 150 rpm employing the formulation containing the 40% polymer.

Differential Scanning Calorimetry (DSC)

DSC of plain DIL, SFG and tablets from batch F4 were obtained using a Mettler-Toledo DSC 821^e instrument equipped with an intracooler. The samples were sealed in an aluminum pan and heated at a constant rate of 10 °C/min, over a temperature range of 25 to 350 °C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50 ml/min.

Kinetic Treatment

To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi equations (14,15). The above models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Korsemeyer equation), which is often used to describe the drug release behavior from polymeric systems

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where, M_t is the amount of drug release at time t; M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release (16,17). The data was also fitted into Hixon crowell model to study any presence of erosion.

Comparison Of SFG With HPMC K15M

Tablets were prepared with HPMC k15 keeping the formulation similar as described in batch F4 only difference was SFG being replaced with HPMC k15. The punch size, hardness was maintained similar to batch F4 and the tablets were formulated. The *in vitro* release profiles of the tablets were obtained by analyzing the aliquots at the same time interval as described for earlier batches.

RESULTS AND DISCUSSION

Compression of Tablets

DIL tablets exhibited good weight (±2% *w*/*w*) and content uniformity (98–102% *w*/*w*) for all the batches. Friability was less than 0.30% *w*/*w*, which complied with pharmacopoeial limits of USP 2006.

Characterization of SFG

SFG is sparingly soluble in water and it dissolves with hydration. It is practically insoluble in absolute ethanol. The viscosity of 1% SFG was found to be 950 centipoise and pH in range of 4–5. The scanning electron micrographs of SFG at different magnifications are shown in Fig. 1. The figure indicated that SFG particles were near triangular in shape and less than 125 μm in size.

Swelling Studies

Figures 2 and 3 indicate the axial and radial swelling of tablets prepared with SFG (batch F4). Figure 2 indicates the swelling behavior of SFG in acidic, basic and in distilled water. Figure 2 indicated that there is no rapid swelling in the tablets, as the swelling index did not rise rapidly. The pH had no significant ($p>0.05$) difference on the swelling behavior of the SFG. Figure 3 indicates the swelling behavior of tablets (batch F4) in acidic and distilled water. There are no figures indicating the swelling behavior of tablets in basic medium, as swelling behavior was similar to that of distilled water. Figure 3 indicated that the gel structure formed is different in acidic and basic medium. The gel structure is translucent in acidic medium as compared to opaque in distilled water and basic medium.

Effect of SFG Particle Size

The dissolution was performed in distilled water at 100 rpm. Figure 4 indicated that there was complete release of drug in 2 h for 40 and 80# size particles, while in case of 120 and 200# particles complete release was observed in 8 h. The coarser fractions did not hydrate fast enough to form a protective gel layer and the tablet matrix was broken prematurely while the finer (#120 mesh and lower) SFG particles swelled faster to form a protective gel layer, which gave significant ($p<0.05$) sustained release in comparison to 40 and 80# particle size SFG. The interesting observation was that tablet formulations with very fine SFG did not provide

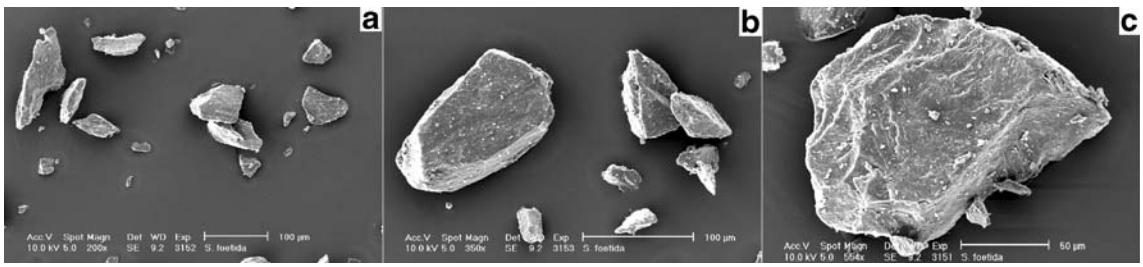

Fig. 1. Scanning Electronmicrogaphs of *Sterculia foetida* gum (*SFG*) passed through 120# at 200× **a**, 350× **b**, and 554× **c** magnifications

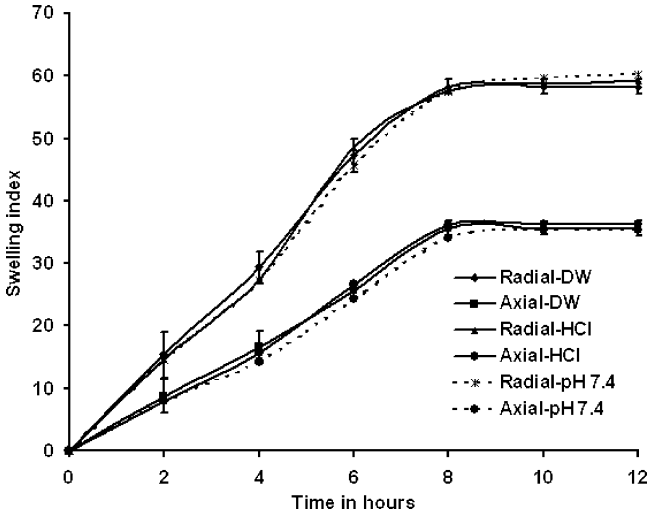

Fig. 2. Swelling index versus time in hours for batch F4 tablets performed in various medias

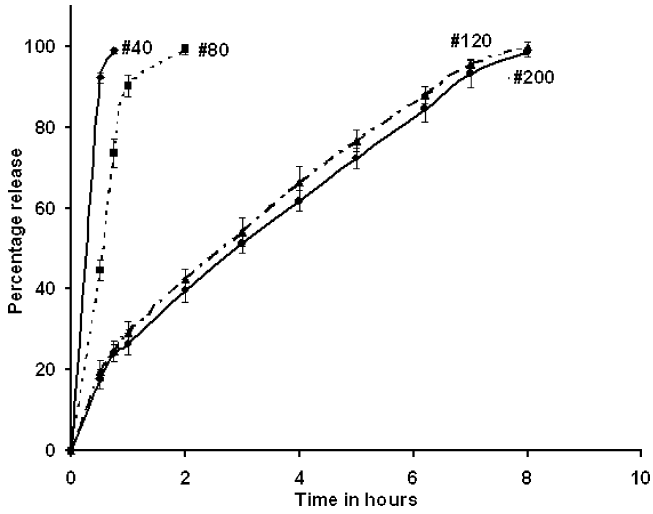

Fig. 4. Effect of SFG particle size on *in vitro* release of DIL

any additional advantages in retarding the DIL release. Based on the above study #120 mesh fraction of SFG was selected as a matrix former in tablets in all subsequent experiments.

Effect of SFG Concentration

For the purpose of developing formulation with different release rates, matrix tablets containing 10 to 40% of SFG were prepared. The dissolution was performed in distilled water at 100 rpm. The release profiles are depicted in Fig. 5, which indicates that the release rate is greatly influenced by the matrix concentration: a direct relationship is noted between the amount of the gum in the formulation and release rate of DIL. With 40% gum, a very slow release of the drug was obtained. By reducing the concentration of SFG, the release rate was enhanced while the tablet properties were maintained. The above findings indicated that as the level of polymer in the formula was increased, the drug released from tablet was decreased. Release retardation with increasing polymer concentration occurred because increasing the polymer percentage in a matrix system generally increases polymer chain entanglement in gels, which in turn results in a stiffer gel and provided more tortuous and resistant barrier to diffusion which resulted in slower release of DIL from SFG matrices (18). At low polymer level, the rate of advancement of the swelling front into glassy polymer and the attrition of the rubbery state polymer may have been nearly equal, resulting in an enhanced diffusion for the drug until the entire drug was released from the tablets (18). The experiments suggested that formulations with reasonably wide spread dissolution profiles may be obtained by varying the polymer level from 10 to 40%.

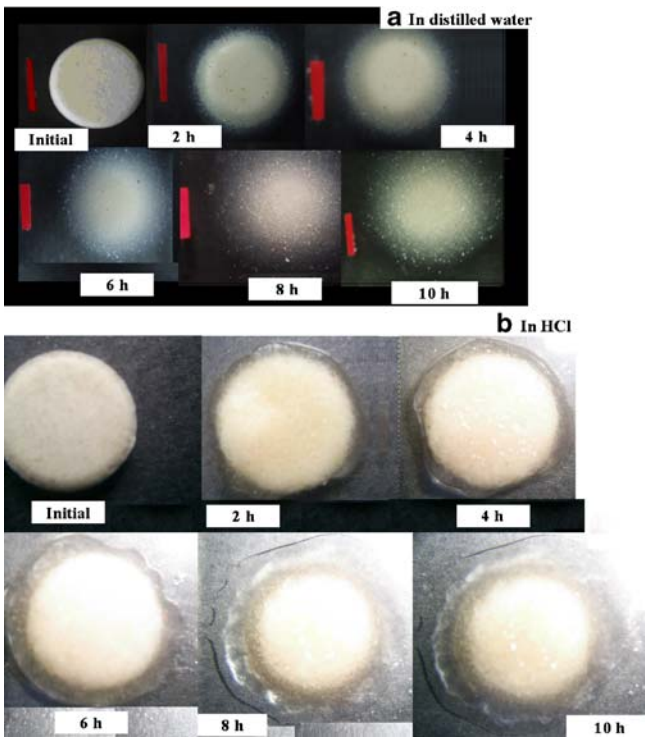

Fig. 3. Photomicrographs of swelling behavior of SFG tablets (batch F4) in distilled water **a** and HCL **b**

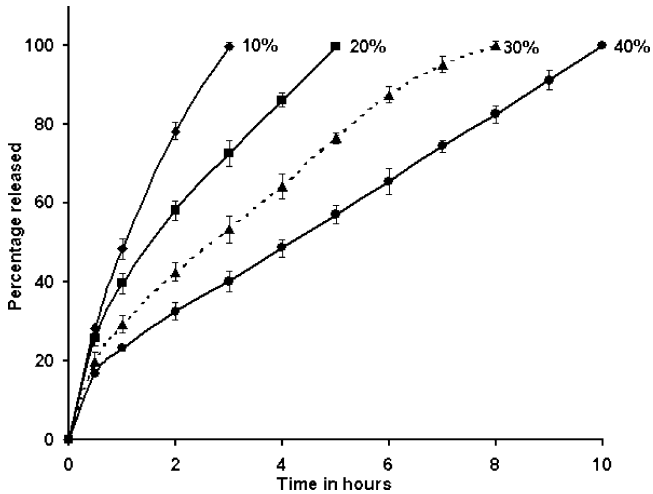

Fig. 5. Effect of concentration on *in vitro* release of DIL from SFG matrix tablets

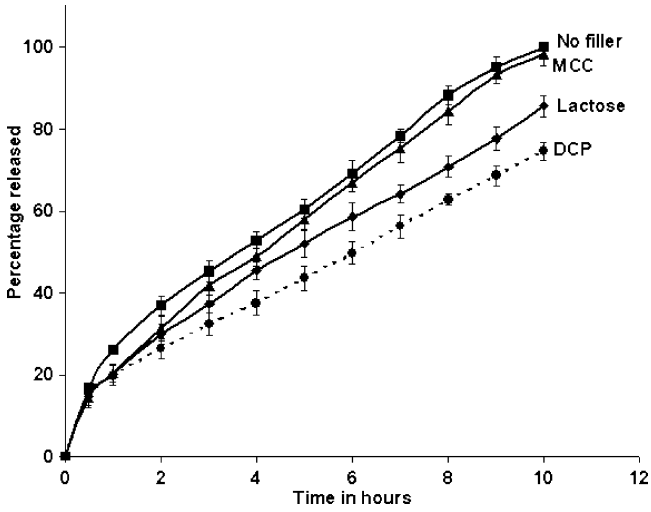

Fig. 6. Effect of fillers on *in vitro* release of DIL from SFG matrix tablets

Effect of Filler

The effect of fillers on SFG matrix tablets is represented in Fig. 6. Since, the diffusional release of a soluble drug such as DIL may primarily be controlled by the gel thickness (diffusion layer), the effect of filler on drug release was studied by holding SFG level at 40%. The dissolution was performed in distilled water at 100 rpm. The release of DIL was significantly different ($p<0.05$) for all the fillers added in the tablets. The presence of swelling, insoluble, water dispersible filler like MCC changed the release profile to a significant ($p<0.05$) extent due to change in the rate of swelling at the tablet surface. When insoluble, non-swelling filler (DCP) was used; DIL did not diffuse out and rather became entrapped in matrix (4). Such types of filler can create "stress cracks" during gelling, resulting in dose dumping or failure of the matrix system because of destruction of integrity of gel layer and/or premature disintegration of the matrix tablet (1). At the same time, soluble fillers will also wet, dissolve and diffuse while insoluble ingredients will be held in place until the polymer erodes or dissolves. In general, the addition of soluble filler (lactose) enhances the dissolution of soluble drugs by decreasing the tortuosity of the diffusion path of the drug, a similar kind of result was observed with lactose (4).

In Vitro Release Testing

For *in vitro* release testing the effect of dissolution media and rotational speed were studied which are discussed below.

Effect of pH of Dissolution Media

The dissolution was performed in the two media i.e., 0.1 N HCl and phosphate buffer pH 7.4 at 100 rpm. The release profiles of DIL from SFG matrices are depicted in Fig. 7. Both the initial rate of drug release, and overall shape of release profiles differed significantly ($p<0.05$) in acidic and basic medium. The differences were manifested immediately, with drug release being significantly more rapid in 0.1 N HCl for the first hour of dissolution. The release profile in pH 7.4 was linear with time, where as in pH 1.2, drug release was linear with the square root of time. The above last finding suggests that in acidic pH the release mechanism is predominantly diffusion controlled (19). A change in pH of the dissolution medium can exert an influence on the solubility of the drug or on the hydration of the polymer. Drug solubility data confirmed that DIL remained highly soluble in both the media (determined to be 588 g/l in 0.1 N HCl or 634 g/l in phosphate buffer pH 7.4, 37 °C), meaning drug dissolution was unlikely to be rate limiting in either medium (20). Hence, although above mentioned effects may have been partly due to difference in drug solubility, the findings indicated that the difference observed might be more due to a result of a change in the quality and integrity of the gel barrier formed under acid conditions. In the case of hydration of a SFG tablet in 0.1 N HCl (pH 1.2), on retrieval of the tablet from the dissolution vessel, the outer hydrated surface layer formed around the tablet could be noted visually to possess a very different consistency compared to that formed around tablets which were hydrated in phosphate buffer pH 7.4 as seen in

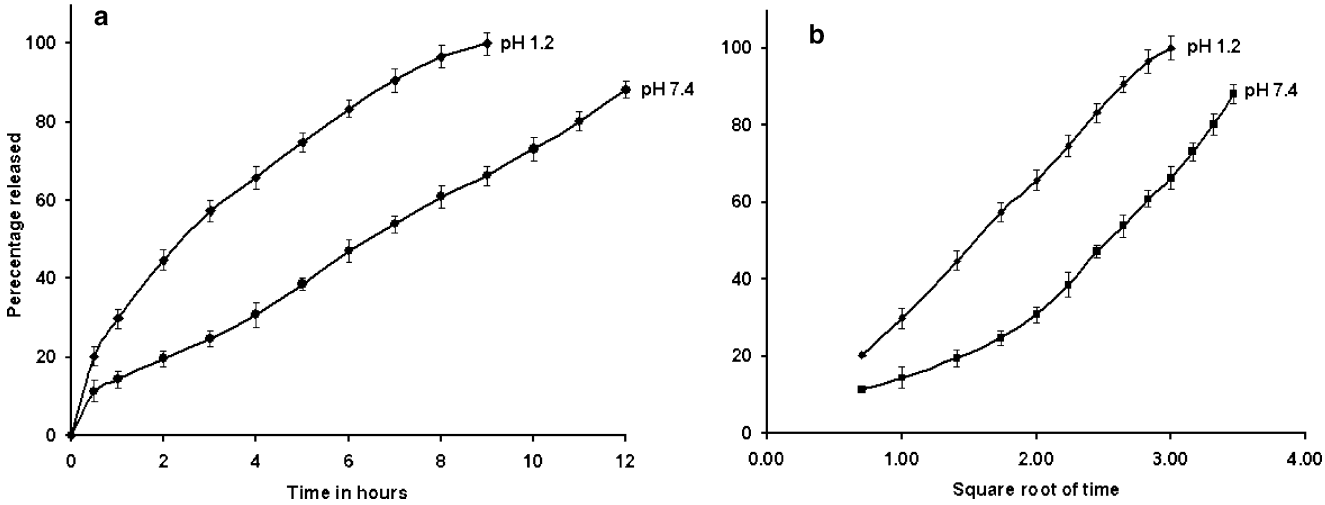

Fig. 7. Effect of dissolution media pH on *in vitro* release of DIL from SFG matrix tablets by **a** zero order treatment and **b** by Higuchi diffusion

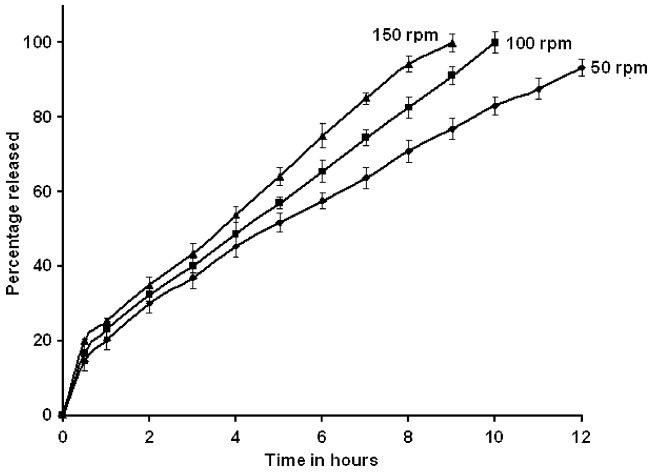

Fig. 8. Effect of rotational speed on *in vitro* release of DIL from SFG matrix tablets

Fig. 3. The 0.1 N HCl (pH 1.2) hydrated layer was not viscous and adhesive in nature, but possessed different mechanical properties to those produced at neutral pH. The spongy voluminous hydrated structure was produced at pH 1.2 in contrast to the viscous, gelatinous layer formed around the tablet at pH 7.4. The above data indicated that faster release of highly water-soluble model drug into acid medium (pH 1.2) is therefore almost a reflection of the inferior barrier properties of the composite layer, relative to those of the continuous gel layer at pH 7.4.

Effect of Rotational Speed

In order to study the influence of hydrodynamic stress on the release rates, dissolution studies were conducted in distilled water using apparatus 2 at 50, 100 and 150 rpm employing the formulation containing the 40% polymer. As shown in Fig. 8, there was a high initial release of the DIL i.e. ranging from 14% to over 20% by 30 min and then there was no significant ($p>0.05$) effect of rpm till around 240 min. After 240 min, the drug release rate was increased as the rotational speed was increased. The initial independency of release on agitation rate/stirring speed may suggest that the drug release, which proceeded via diffusion process, is internalized and occurs within the tablets. If diffusion occurs in a static layer of fluid surrounding to tablet, changes in agitation rate should have altered the drug release profile. Thus, the possible reason for high initial release of DIL is due to presence the drug on the edge of matrix will be comparatively free from the gel structure and thus tend to dissolve rapidly (21). The possible explanation for the rapid release of the drug after 240 min is that as the rotation speed is increased, surface erosion and gel disruption can occur faster and consequently drug release is increased. Thus, the results indicated that in the present system both the matrix diffusion and the erosion play an important role on release rate of DIL.

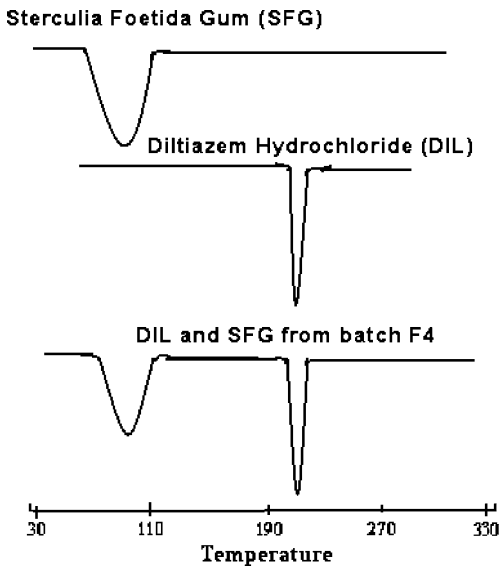

Fig. 9. DSC scans of *Sterculia foetida* Gum (*SFG*), diltiazem hydrochloride (*DIL*) and mixture SFG and DIL (batch F4)

Table II. Kinetic Treatment for Release Data for Batch F4 in Distilled Water

Model	r^2	k	n
First order	0.9250	-0.0933	–
Zero order	0.9717	9.0931	–
Higuchi	0.9718	31.236	–
Hixon crowell	0.9856	−0.2522	–
Peppas–Korsmeyer	0.9868	-0.1948	0.5854

r^2 Correlation coefficient, n diffusional release exponent, k release rate constant

Differential Scanning Calorimetry

The DSC scan of DIL, SFG and the tablet from batch F4 is represented in Fig. 9. The figure indicated no presence of interaction or complexation. Thus, a conclusion could be inferred that the release extension is not caused by any interaction between DIL and SFG but due to the swelling behavior of the gum, which prevented the dumping of the entire contents into the medium.

Kinetic Treatment

Table II indicates the correlation coefficient and kinetic rate constant for various models tested. The data indicates

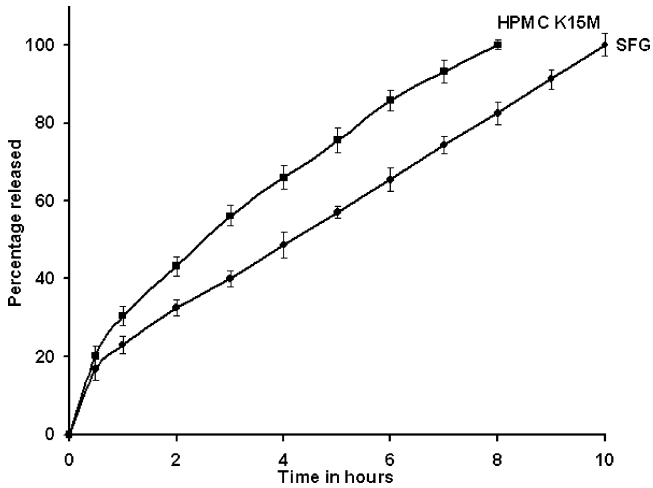

Fig. 10. Comparison of *in vitro* release of DIL from SFG and HPMC k15 prepared matrix tablets

that the release of DIL did not follow first and zero order kinetics. The release of the DIL by a matrix system was generally produced by two simultaneous mechanisms: (a) erosion or attrition of the outermost, least consistent gel layer, (b) dissolution of the active principle in the liquid medium and diffusion through the gel barrier when formed (1,22,23). The values of kinetic date confirmed that the release from SFG is through surface erosion and anomalous diffusion, when DIL is used as model drug and dissolution is performed in distilled water.

Comparison of SFG With HPMC K15M

HPMC K4M and K15M are widely used as hydrophilic/swellable matrix forming polymer (24–26). SFG is also a hydrophilic and swellable gum, which can be used as matrix former in preparation of controlled release tablets. When the release of HPMC K4M was compared with that of SFG; release from HPMC K4M was faster. Thus, it was decided to use HPMC K15M for comparison with SFG. Figure 10 represents typical release profiles of DIL, in distilled water at 100 rpm, from SFG and HPMC K15M matrices, each containing 40% polymer, expressed in % released *vs*. time. The release of DIL was slower in SFG prepared tablets as compared to HPMC k15M ones. Figure 10 indicated that release behavior of DIL from SFG and HPMC matrices differ significantly ($p<0.05$) with respect to the following important considerations. Firstly, an initial burst release of the drug is observed with HPMC matrix, which is less with SFG matrix. Such a burst effect with HPMC was also observed by other investigations (3). The two release patterns were compared statistically using paired Student's *t* test. Even though 1% solution of HPMC had a viscosity of around 15,000 centipoise (27) as compared to 950 centiposie for SFG; the release rate was lower for SFG prepared tablets when dissolution were performed in distilled water using DIL as a model drug. The phenomenon can be explained by the rate of swelling, which was slower for SFG tablets. Here the important thing to note that hydrophilic matrix systems are often therapeutically undesirable because the total amount of the drug release is remarkably influenced by the initial controlled release from the dosage form. Secondly, the overall rate of release of DIL from HPMC matrix is higher than that from SFG matrix. The $t_{50\%}$ for HPMC and SFG were 4.1 and 2.3 h respectively. The result is clear indication that SFG had higher drug retarding ability than HPMC. The drug release from SFG matrices is linear with time (percent release *vs* time) until the end of the experiment while the release of DIL from HPMC matrices decrease with increase in time, which is characterized by the Higuchi equation (percent release *vs* square root of time). To get constant drug level in the blood plasma zero order kinetics (linear with time) is a pre requisite and such the profile could be better achieved from SFG matrices.

CONCLUSIONS

The presence of higher concentration of gum and rotational speed during dissolution has great influence on release rate of drug from SFG matrix. Matrix erosion plays an important role in release mechanism. SFG is suitable for drugs having different solubility and it does not show any interactions with DIL; it was also proved to be better than HPMC K15 polymer in controlling the drug release. Thus, it could be concluded that SFG is promising controlled release polymeric material.

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