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Original Research Paper

Evaluation of gum mastic (*Pistacia lentiscus*) as a microencapsulating and matrix forming material for sustained drug release

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ABSTRACT

In this study, a natural gum mastic was evaluated as a microencapsulating and matrix-forming material for sustained drug release. Mastic was characterized for its physicochemical properties. Microparticles were prepared by oil-in-oil solvent evaporation method. Matrix tablets were prepared by wet and melt granulation techniques. Diclofenac sodium (DFS) and diltiazem hydrochloride (DLTZ) were used as model drugs. Mastic produced discrete and spherical microspheres with DLTZ and microcapsules with DFS. Particle size and drug loading of microparticles was in the range of 22–62 μm and 50–87%, respectively. Increase in mastic: drug ratio increased microparticle size, improved drug loading and decreased the drug release rate. Microparticles with gum: drug ratio of 2:1 could sustain DLTZ release up to 12 h and released 57% DFS in 12 h. Mastic produced tablets with acceptable pharmacotechnical properties. A 30% w/w of mastic in tablet could sustain DLTZ release for 5 h from wet granulation, and DFS release for 8 h and 11 h from wet and melt granulation, respectively. Results revealed that a natural gum mastic can be used successfully to formulate matrix tablets and microparticles for sustained drug release.

1. Introduction

The merits of natural gums have been well acknowledged in the past many years; they are readily available, cost effective, eco-friendly, fairly degradable and biocompatible [1,2]. They can be modified and converted into useful semi-synthetic and synthetic materials for pharmaceutical applications [3]. The numerous natural gums such as agar, chitosan, guar gum, xanthan gum, locust been gum and sodium alginate have been

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used successfully for various pharmaceutical applications. Previously, we demonstrated that gum copal and damar can be used to prepare sustained release matrix tablets [2] and microparticles of water soluble and water insoluble therapeutic agents [4]. We have also shown that PEGylation of natural gum rosin yields derivatives having an excellent film forming ability for the drug delivery applications [3,5–7]. In view of this, it is apparent that natural gums and their derivatives are promising candidates to design the sustain drug delivery systems.

Gum mastic is a natural resin obtained from broad-leaved variety of *Pistacia lentiscus* (Family Anacardiaceae), which is a shrub or small tree of the *pistacio* genus growing up to 4 m tall and is cultivated for its aromatic resin [8]. Mastic tree is naturally distributed in areas that enclose the coastal regions of the Mediterranean, Portugal and tropical Africa and grows on all kinds of soil. Gum mastic is produced in the form of small tears that are pale yellow in color. The chief constituent of mastic is resin, which is associated with about 2% of volatile oil. The resin can be separated into the following constituents: α- and β-masticinic acids (together about 4% of the drug), masticolic acid (crystalline, traces), α- and β-masticonic acids (amorphous, about 38%), α-masticoresene (soluble in alcohol, about 30%), β-masticoresene (also called as masticin, insoluble in alcohol, about 20%). The volatile oil of gum mastic contains mostly the d-pinene [9]. Owing to its film-forming propensity, mastic has been used in the preparation of varnishes. Its age-long use in Arab countries was for chewing, where it sweetens the breath and helps preserve the teeth and gums [10]. As a medicinal agent, it has been used in the treatment of gastritis, gastroesophageal reflux diseases and intestinal infections [11]. It has also been evaluated as a crude drug for gastric and duodenal anti-ulcer activity [12]. It was found that mastic has specific antibacterial activity against *Helicobacter pylori* [13].

In the field of drug delivery system, gum mastic has been evaluated for its application in the enteric coating [14], film coating [15], matrix system [16], stability improvement [17,18] and controlled drug release [19–21]. However, all of these studies evaluated gum mastic in combination with either polymers, gums, film formers or matrix forming materials. Recently, Deshpande et al. [22] have shown that gum mastic has potential to produce controlled release spheroid by roller compaction technique. Since gum mastic is safe, well tolerated by humans, hydrophobic and has a film forming ability, it can be used to fabricate the sustained drug delivery devices. This study was thus undertaken with an objective to investigate gum mastic as a microencapsulating and matrix forming material for sustained drug release.

DFS is a non-steroidal anti-inflammatory agent that has been widely used to reduce pain and inflammation. Chemically, it is sodium 2-{2-[(2,6 -dichlorophenyl) amino] phenyl} acetate. Owing to its low solubility and high permeability, DFS has been classified as a BCS class 2 compound within the biopharmaceutics classification system. After oral administration, it is completely absorbed, however, due to the first-pass metabolism, only about 50% of the absorbed dose can be available systemically [23]. In addition, the terminal half-life of unchanged DFS is only about 2 h [23]. On the other hand, DLTZ is a calcium channel blocker that has been used in the prevention and long term treatment of angina pectoris and hypertension. It is a low molecular weight (450.99 Dalton) compound, which is soluble in water, methanol and chloroform. Because of the extensive first pass metabolism, oral bioavailability of DLTZ is approximately 40%, and the half-life is reported to be about 3–5 h [24]. The above details in particular suggest that DFS and DLTZ have low oral bioavailability and short biological half life, which make them suitable candidates for the sustained or controlled drug delivery systems.

2. Materials and methods

2.1. *Materials*

Gum mastic was received as a gift sample from M/s Innovative Marketing Services, Mumbai, India. DFS and DLTZ were received as gift samples from M/s Zim Laboratory Ltd., Nagpur, India. Microcrystalline cellulose (Avicel PH 101, FMC, Biopolymer) was received as a gift sample Signet chemical corporation Pvt., Ltd., India. Chloroform (Rankem), petroleum ether 60–80 (Ranbaxy), and heavy liquid paraffin (Rankem) were procured and used. All other chemicals were of analytical grade.

2.2. *Characterization of gum mastic*

Mastic was examined visually for appearance. Acid value was determined as per the method described in literature [25]. The softening and melting temperatures were determined using capillary tube, thermometer and Thiele tube. The solubility in different organic solvents and buffers was determined at 25 ± 1 °C. The MW and polydispersity were determined by the Gel Permeation Chromatography system (Perkin-Elmer) equipped with refractive index detector (La Chrom Detector L-7490). The glass transition temperature (T_g) was determined by the Differential Scanning Calorimetry (DSC, Mettler-Toledo Star System). The viscosity of 20% w/v solution in acetone was measured at 25 ± 1 °C by a Brookfield viscometer using spindle no. 4 (Brookfield Engineering Laboratories, Inc., Stoughton, Massachusetts).

2.3. *Gum mastic microparticles*

2.3.1. *Preparation of microparticles*

Microparticles were prepared by oil-in-oil emulsion solvent evaporation method. Various microparticle compositions are summarized in Table 1. In brief, 1 g mastic was dissolved in 12 ml of dichloromethane. To this, drug powder and magnesium stearate (10% w/w of mastic weight) were added. Resulting dispersion was stirred on a magnetic stirrer for 5 min and emulsified into 150 ml of rotating liquid paraffin in a 250 ml of glass beaker. The above system was stirred (with stirrer blade position in the center of glass beaker) for 4 h at 40 ± 2 °C. As one of the variable, stirrer blade position was changed from center to bottom of the glass beaker. The microparticles were collected by vacuum filtration and washed two times with 25 ml of petroleum ether (60–80). The microparticles were stored in desiccators maintained at 0% relative humidity before further use.

Table 1 – Mastic microparticle formulations.

Batch [a]	Drug	Mastic: drug ratio	Viscosity of paraffin (cP)	Magnesium stearate (%)	Stirrer position
F	DFS	1:1	188	10	Center
V1	DFS	2:1	188	10	Center
V2	DFS	2:1	130	10	Center
V3	DFS	2:1	80	10	Center
M	DFS	2:1	188	20	Center
B	DFS	2:1	188	10	At bottom
D	DLTZ	2:1	188	10	Center

[a] Batch codes were assigned based on formulation variable e.g. the batches in which the viscosity of paraffin was changed were designated as V1, V2 and V3, batch in which concentration of magnesium stearate was changed is designated as M, batch having different drug was designated as D and batch having change in stirrer blade position was designated as B. DFS is diclofenac sodium and DLTZ is diltiazem hydrochloride.

2.3.2. *Evaluation of microparticles*

2.3.2.1. *Mean particle size*. The microparticles were examined by optical microscopy (Leica LaborLux Leitz S bright field microscope, Germany) and the mean particle diameter was determined by measuring about 100 particles using 1 mm stage micrometer.

2.3.2.2. *Scanning electron microscopy*. Morphology and surface topography of mastic microparticles were examined by Scanning Electron Microscopy (JEOL, JXA-840A, Japan).

2.3.2.3. *Drug loading*. 50 mg of the microparticles were grounded in a mortar and were extracted several times with phosphate buffer pH 6.8. The filtered solutions, after making up the volume to 100 ml with phosphate buffer pH 6.8, were assayed spectrophotometrically at 276 nm and 237 nm for DFS and DLTZ content, respectively. The extraction process was applied to at least three sets of microparticles and the drug loading was determined by the following equation,

$$\text{Drug loading (\%)} = (\text{practical drug content}/\text{theoretical drug content}) \times 100$$

2.3.2.4. *In vitro drug release study*. *In vitro* drug release study was carried out in USP 25 paddle type dissolution test apparatus. 100 mg of microparticles were secured in a muslin cloth (mesh # 400) and tied to the paddle rotating at a speed of 75 rpm. A 900 ml of 0.1 N HCl for initial 2 h followed by phosphate buffer pH 6.8 for remaining period of time was used as a dissolution medium. Temperature of medium was maintained at 37 ± 0.5 °C throughout the study. Hourly, 5 ml of the sample was withdrawn and replaced with equivalent quantity of the fresh medium. The samples were analyzed by UV-Spectrophotometer (UV-1601, Shimadzu, Japan) at 276 nm and 237 nm for DFS and DLTZ content, respectively. To study the underlying mechanism of drug release, dissolution data was computed as per kinetic equations [26].

2.4. *Gum mastic matrix tablets*

2.4.1. *Preparation of matrix tablets*

The compositions of matrix tablets are shown in Table 2. Gum mastic as a matrix (15 and 30% w/w), DFS or DLTZ as a model drug and microcrystalline cellulose as a diluent were used in tablet preparations. Mastic was triturated in mortar and all of the ingredients were sifted through ASTM 60 mesh screen before use. The tablets were prepared by wet and melt granulation techniques.

2.4.1.1. *Wet granulation*. The specified quantities of drug and diluent (Table 2) were mixed manually in a polybag for 2 min. The mixture was granulated with solution of mastic in acetone. The granulation end point was achieved using isopropyl alcohol.

Table 2 – Matrix tablet formulations.

Ingredients and method of preparation	Batch[a]					
	G1	G2	D	M	P1	P2
Gum mastic	15%	30%	30%	30%	-	-
DFS	30%	30%	-	30%	30%	-
DLTZ	-	-	30%	-	-	30%
Microcrystalline cellulose (PH 101)	53%	38%	38%	38%	65.5	65.5
PVP K 30	-	-	-	-	2.5%	2.5%
Talc	1%	1%	1%	1%	1%	1%
Magnesium stearate	1%	1%	1%	1%	1%	1%
Wet granulation	✓	✓	✓	×	✓	✓
Melt granulation	×	×	×	✓	×	×

✓ indicates technique used and × represents ‘not used’.

[a] Batch code was based on the formulation variable i.e. the batches in which gum concentration varies are designated as G1 and G2, batch in which drug was changed was designated as D and batch in which method of preparation was changed was M. P1 and P2 indicate tablets of diclofenac sodium and diltiazem hydrochloride, respectively without gum.

As a control, mixture of drug and diluent was granulated with 1% povidone (K-30) solution in isopropyl alcohol. The wet cohesive mass was then sifted through 18-mesh screen and dried in oven at 40 °C for 4 h. The dried granules were allowed to cool to room temperature, sifted through 22-mesh screen and lubricated with 1% talc and 1% magnesium stearate (ASTM 60 mesh passed).

2.4.1.2. Melt granulation. Mastic, drug and diluent (ASTM 60 mesh passed) were mixed manually in polybag for 2 min and placed into a Petri dish. The Petri dish was secured on a heating mentle and the temperature was raised until the mastic softens. The temperature was maintained and the mix was granulated with the help of a spatula. A change in color of the mixture from cream to yellow was granulation end point, which indicates that the drug and excipients particles are covered by mastic layer. Granules were allowed to cool to room temperature, sieved through ASTM 22 mesh screen and were lubricated with 1% talc and 1% magnesium stearate (ASTM 60 mesh passed).

The lubricated granules obtained by wet and melt granulation were compressed into tablets with a target weight of 250 mg and diameter of 8 mm using 10-station tablet press (Chamunda Pharma Machinery, Ahmedabad, India).

2.4.2. *Evaluation of matrix tablets*

For each batch, 20 randomly drawn tablets were tested for size uniformity (diameter and thickness), weight uniformity (Dhona 200D, Mumbai), friability (Roche friabilator) and hardness (Pfizer hardness tester). The drug content was determined spectrophotometrically.

Drug release study was carried out in USP 25 paddle type dissolution test apparatus. A 900 ml of 0.1 N HCl for initial 2 h and phosphate buffer pH 6.8 for remaining period of time was used as a dissolution medium. Paddle speed was adjusted to 75 rpm and the temperature of medium was maintained at 37 ± 0.5 °C. 5 ml of the sample was withdrawn hourly and analyzed at 276 nm and 237 nm for DFS and DLTZ content, respectively by UV-spectrophotometer.

3. Results and discussion

3.1. *Gum mastic properties*

Physicochemical properties of mastic are summarized in Table 3. Mastic is a low molecular weight (170 g/mol) gum and it melts in the temperature range of 94–96 °C. An acid value of 118 indicates the presence of substantial free carboxyl groups in mastic. T_g of mastic is 46.49 °C, which indicates its film forming propensity even at the lower temperature. It has a polydispersity index of 1.2 suggesting a narrow range of molecular weight distribution in mastic.

Table 3 – Physicochemical properties of mastic.

Physicochemical property	Gum mastic
Color	Yellow
Acid value	118
T_g (°C)	46.49
Melting point (°C)	94–96
Molecular weight (g/mol)	170
Polydispersity index	1.2

T_g is a glass transition temperature.

3.2. *Gum mastic microparticles*

Microparticles were prepared by o/o emulsion solvent evaporation technique. Initially, an attempt was made to produce microparticles in aqueous phase using dichloromethane/0.1 N HCL as an internal phase, but the microparticles were sticky and formed lumps. To avoid lumps, various droplet stabilizers namely magnesium stearate, glyceryl monostearate, talc and span 80 were evaluated and it was found that only magnesium stearate could produce discrete and spherical microparticles of mastic.

The surface morphology of microparticles containing DLTZ and DFS is shown in Fig. 1. As can be seen, mastic formed discrete and spherical microspheres with DLTZ and microcapsules with DFS. The final form i.e. microsphere or microcapsule was dependent on the solubility of drug in mastic solution in dichloromethane (internal phase). DLTZ was soluble, whereas, DFS was in suspended form. The formulation difference was clearly visible in the surface texture of microparticles; rough DLTZ microsphere surface indicates that mastic has formed matrix with drug and the smooth DFS microcapsule indicates that the drug particles have acquired mastic coat to form microcapsules.

In terms of particle size, increase in gum: drug ratio increased the microparticle size (Table 4, F versus V1). It is well known that an increase in gum/polymer concentration in in-

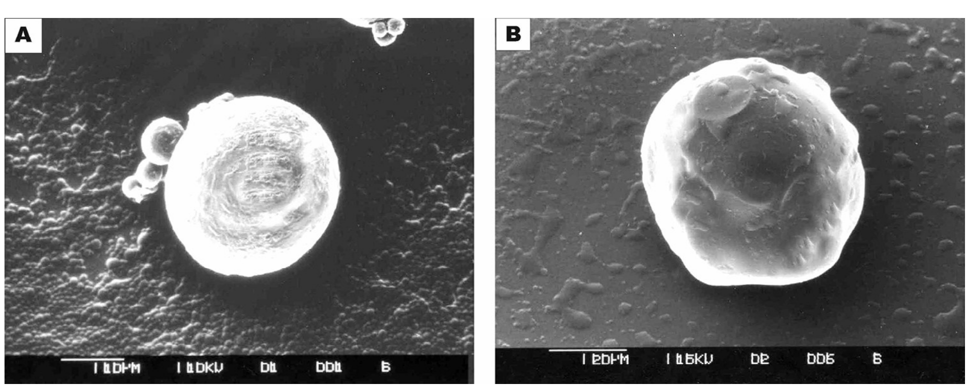

Fig. 1 – Scanning electron microscopy of mastic microparticles containing (A) DLTZ and (B) DFS.

Table 4 – Effect of formulation variables on drug loading and microparticle size.

Batch	Particle size (μm)	Drug loading[a] (%)
F	28 ± 3	58.21 ± 2.06
V1	46 ± 2	72.39 ± 4.31
V2	53 ± 5	81.62 ± 3.28
V3	62 ± 4	87.11 ± 4.11
M	22 ± 6	50.46 ± 3.62
B	39 ± 15	65.16 ± 6.71
D	22 ± 6	65.21 ± 4.23

[a] Each value is a mean ± SD of three determinations. Particle size (mean) was determined by measuring about 100 particles using 1-mm stage micrometer by optical microscopy (Leica LaborLux Leitz S bright field microscope, Germany).

ternal phase increases the viscosity of internal phase and thus increases the emulsion droplet size and eventually the microparticle size [27,28].

An increase in viscosity of paraffin (external phase) decreased the microparticle size (Table 4, V1, V2, V3). The tangential, radial and axial (TRA) flows exist in rotating external phase [29]. In higher viscosity external phase, viscosity dominates TRA flows to prevent droplets coalescence producing smaller microparticles.

Increase in the amounts of magnesium stearate decreased the microparticle size (Table 4, V1 versus M). This was anticipated and can be attributed to droplet stabilizing potential of magnesium stearate.

Interestingly, the change in stirrer blade position from center to bottom of beaker containing external phase resulted into variation in microparticle size. This may be attributed to the imbalance in TRA flows creating different hydrodynamics when the stirrer blade position was at the bottom of the beaker.

Increase in mastic: drug ratio increased the drug loading of microparticles (Table 4, F versus V1). Higher gum concentration produced larger microparticles having less surface area for drug loss. Moreover, it appears that the concentration of mastic at 1:1 ratio with drug was not adequate enough to encapsulate most of the drug material and thus more amount of drug was lost to the external phase. It has been well accepted that the amount of free drug decreases proportionally with the increase in polymer concentration in internal phase [30,31].

Microparticles produced in external phase with viscosity of 188, 130 and 80 cP showed 72.39%, 81.62% and 87.11% drug loadings, respectively (Table 4). Decrease in viscosity of paraffin improved the drug content of microparticles. This was because the low viscous external phase produced larger microparticles offering less surface area for drug loss.

Higher concentration of magnesium stearate decreased microparticle size resulting in lower drug content (Table 4, V1 versus M).

The change in stirrer blade position in beaker from center to bottom lowered the drug content of microparticles. This was because lowering the stirrer's blade position in beaker produced smaller microparticles (Table 4) having greater surface area for the drug loss.

Microparticles containing DFS and DLTZ showed 72.39 and 65.21% drug loadings, respectively. We noticed DLTZ particles in external phase under light microscope, which indicates that the part quantity of DLTZ was lost to the external phase during microparticle preparation. This drug loss might also be ascribed to the higher solubility of DLTZ in external phase.

The increase in mastic: drug ratio produced larger microparticles and thus decreased the drug release rate (Fig. 2A). This was in agreement with the findings by researchers that increase in gum concentration decreases the drug release from microparticles [32–34]. Furthermore, it has been shown that the increase in polymer concentration more often decreases microparticle porosity and thus slows down the drug release rate [35].

Decrease in viscosity of external phase produced larger microparticles (Table 4) and thus decreased the drug release rate (Fig. 2B). In this study, the viscosity of the medium was decreased by adding light liquid paraffin to the heavy liquid paraffin. Light liquid paraffin has greater solvent extraction potential [36] and microparticle porosity decreases with increase in solvent extraction rate until a limiting value [37]. Therefore, addition of light liquid paraffin to decrease viscosity of medium might have produced less porous microparticles resulting in slower drug release.

Increase in concentration of magnesium stearate increased the drug release rate (Fig. 2C). This could be due to the fact that increased amount of magnesium stearate produced smaller microparticles having greater surface area for drug release.

When the stirrer blade position was changed from center to bottom of beaker, the mean microparticle size was decreased (Table 4, V1, V2, V3), which eventually increased the drug release rate (Fig. 2D).

From mastic microparticles, DFS release was slow compared to DLTZ (Fig. 2E), which was due to the low solubility of DFS. All formulations showed slow drug release initially for 2 h, which might be ascribed to the low solubility of DFS and mastic at acidic pH.

The correlation coefficient values for linearity according to different kinetic equations are shown in Table 5. Mastic microparticles exhibited zero order drug release, and the release kinetics did not change by the variables of this study.

Table 5 – Correlation coefficients (*r*) according to different kinetic equations to describe drug release from mastic microparticles.

Formulation	Correlation coefficient (*r*) for kinetic model				
	First order	B-L[a]	H-C[b]	Zero order	Higuchi
F	0.977	0.962	0.990	0.996	0.991
V1	0.980	0.944	0.986	0.994	0.969
V2	0.951	0.869	0.960	0.973	0.933
V3	0.966	0.892	0.970	0.980	0.944
M	0.973	0.930	0.983	0.996	0.974
B	0.973	0.939	0.984	0.996	0.980
D	0.826	0.880	0.895	0.976	0.944

[a] Baker-Lonsdale.
[b] Hixson-Crowell.

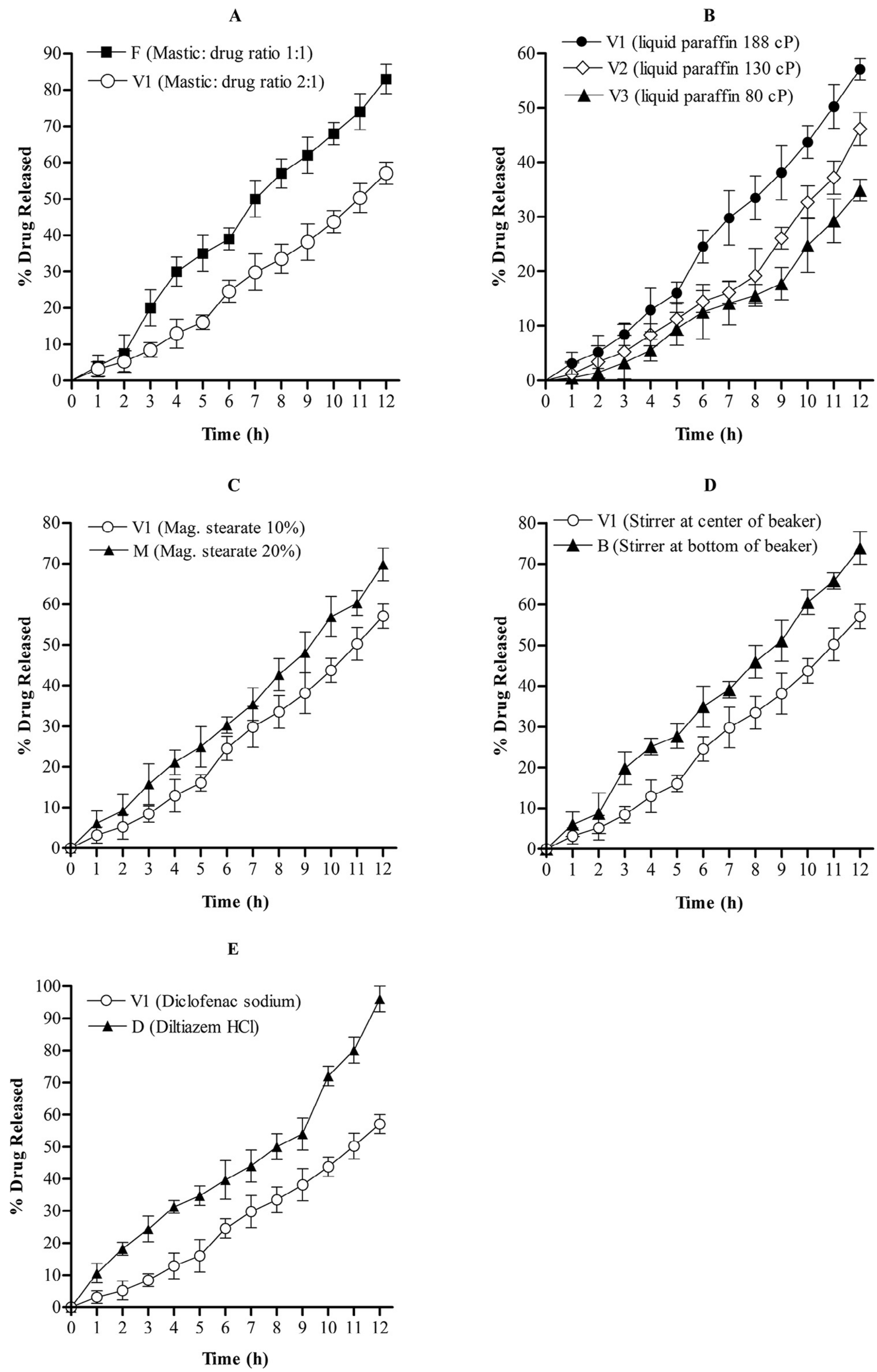

Fig. 2 – Effect of (A) gum concentration, (B) viscosity of paraffin, (C) amount of magnesium stearate, (D) stirrer blade position and (E) type of drug on drug release from microparticles.

3.3. *Matrix tablets*

Gum mastic produced tablets with acceptable pharmacotechnical properties (Table 6). The hardness of matrix tablets was about 5.0 kg/cm^2. The tablet weight and diameter was kept constant at 250 mg and 8 mm, respectively. The hardness was slightly decreased when mastic was added as a matrix forming material in the tablets. This may be attributed to the lower T_g (Table 3) and less compressibility of mastic. All tablets were about 5 mm thick. The surface of tablets produced by wet

Table 6 – Pharmacotechnical properties of matrix tablets.

Batch	Hardness (kPa)	Friability (%)	Drug content (%)	Weight (mg)	Thickness (mm)	Diameter (mm)
G1	5.39 ± 1.13	0.26 ± 0.08	98.72 ± 0.92	249.3 ± 1.26	4.08 ± 0.012	8.03 ± 0.009
G2	5.17 ± 1.70	0.22 ± 0.05	100.41 ± 0.17	250.2 ± 1.53	4.12 ± 0.014	8.00 ± 0.010
D	5.28 ± 1.26	0.24 ± 0.06	99.87 ± 0.88	250.3 ± 1.39	4.03 ± 0.017	8.02 ± 0.007
M	5.66 ± 1.18	0.25 ± 0.03	100.25 ± 0.76	248.7 ± 1.71	4.10 ± 0.011	8.07 ± 0.008
P1	5.23 ± 1.52	0.23 ± 0.07	101.06 ± 0.51	249.4 ± 1.02	4.11 ± 0.016	8.05 ± 0.011
P2	5.18 ± 1.83	0.28 ± 0.08	99.76 ± 0.63	250.1 ± 1.44	4.08 ± 0.013	8.01 ± 0.015

Friability is a mean of three values, all other values are mean of 10 determination ± SD.

granulation was smooth and shiny, which suggests that the solvent has facilitated mastic layer formation on drug-diluent particles via wet granulation.

All the mastic tablets showed good strength for handling; the friability values did not exceed 0.3% in any case. The weight variation and drug content uniformity values were well within the limits. As the variables, effect of mastic concentration, method of preparation and type of drug on release profiles of matrix tablets was principally investigated.

The drug release profiles of tablets are shown in Fig. 3. Increase in gum mastic concentration decreased the drug release rate. In wet granulation method, when a mixture of drug and diluent is granulated by the solution of gum, gum forms a film around drug particles. Increase in gum concentration increases the number of drug particles that are covered by the gum coat. In addition, the thickness of gum coat can be expected to increase proportionally with the amount of gum in tablets, which also slows down the drug release.

The release of DLTZ was faster compared to DFS from mastic matrix tablets. This can be attributed to the solubility of native drugs; DFS is sparingly soluble, whereas DLTZ is a freely water soluble drug. Also, it seems that the acidic pH decreased DFS release for initial 2 h from the tablets. Contrary, the release profile of DLTZ was unaffected by the pH of media.

The method of preparation (wet versus melt granulation) showed impact on the drug release from matrix tablets. A 30% w/w mastic could sustain DFS release for 8 h and 11 h when the tablets were prepared by wet and melt granulation, respectively. As can be seen from Table 7, the amount of free DFS in granules prepared by wet and melt granulation was 9.89% and 20.59%, respectively. This suggests that more amount of free drug was present in tablets prepared by the melt granulation technique than by the wet granulation technique. As more drug was free, the remaining drug embedded in the mastic-matrix had relatively higher mastic: drug ratio. Therefore, these tablets showed initial fast release followed by subsequent slower drug release. A 15% w/w mastic in tablets could not sustain the drug release beyond 4 h.

DFS release from matrix tablets was slow for initial 2 h, which can be attributed to the low solubility of drug and mastic at acidic pH. For the initial 2 h, tablets prepared by wet and melt granulation showed comparable drug release. However, at the third and fourth hours, drug release from the tablets prepared by melt granulation was faster (due to the presence of more free drug; see Table 7). After 4 h, tablets produced by melt granulation technique showed relatively slower drug release due to the higher mastic: drug ratio in tablets as explained earlier.

The DLTZ and DFS tablets without mastic showed complete drug release in 1 and 3 h, respectively (Fig. 3).

The drug release from matrix tablets (G2 in Table 8) prepared by wet granulation (mastic 30%) followed Higuchi square root kinetics indicating that the drug was released principally by diffusion mechanism. Decrease in mastic concentration sifted the drug release kinetics to Hixon–Crowell, which suggests that the drug release was governed by matrix erosion at the lower mastic concentrations. Type of drug also affected the drug release kinetics; sparingly soluble drug (DFS) followed Higuchi square root kinetics, whereas, highly soluble drug (DLTZ) followed a zero order drug release from mastic matrix tablets. Granulation technique had no substantial impact on the drug release kinetics from matrix tablets.

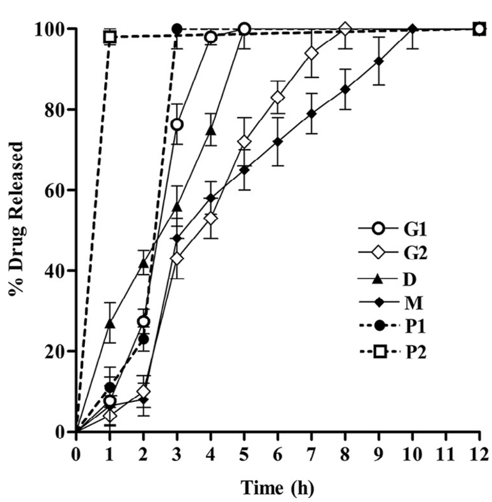

Fig. 3 – Drug release from mastic matrix tablets.

Table 7 – Amount of free drug in granules prepared by different techniques.

Drug[a]	Granules prepared by	% Free drug in granules
DFS	Wet granulation	9.89 ± 4.67
DFS	Melt granulation	20.59 ± 3.43
DLTZ	Wet granulation	17.28 ± 3.22
DLTZ	Melt granulation	16.07 ± 3.09

[a] DFS – diclofenac sodium, DLTZ – diltiazem hydrochloride.

Table 8 – Correlation coefficients (*r*) according to different kinetic equations to describe drug release from matrix tablets.

Formulation	Correlation coefficient (*r*) for kinetic model				
	First order	B-L[a]	H-C[b]	Zero order	Higuchi
G1	0.963	0.966	0.973	0.956	0.969
G2	0.929	0.938	0.984	0.981	0.988
D	0.845	0.863	0.914	0.993	0.976
M	0.907	0.932	0.975	0.951	0.976

[a] Baker–Lonsdale.
[b] Hixson–Crowell.

4. Conclusion

A natural gum mastic, obtained from broad-leaved variety of *Pistacia lentiscus*, is a low molecular weight gum having a narrow range of molecular weight distribution. It has a low T_g (46.49 °C) and could be used successfully to formulate microparticles and matrix tablets for sustained drug release. Microparticles prepared with DFS and DLTZ were discrete, uniform and spherical, with particle size of less than 70 µm and drug loading more than 50%. Magnesium stearate was a suitable droplet stabilizer to produce discrete and spherical microparticles of mastic by oil in oil solvent evaporation technique. Increase in mastic: drug ratio increased microparticle size, improved drug loading and decreased the drug release rate. Interestingly, the change in stirrer blade position from center to the bottom of beaker during microparticles preparation caused variation in microparticle size. The drug release from mastic microparticles followed a zero order release kinetics. Mastic matrix tablets showed acceptable pharmacotechnical properties and sustained drug release. Melt granulation improved efficacy of mastic as a sustained release matrix former in tablets. The drug release from matrix tablets followed different release kinetics depending on the variables of the study. Results revealed that gum mastic has potential to produce the microparticles and matrix tablets for sustained drug release.

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Conflicts of interest

The authors declare that there is no conflicts of interest.

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