International Journal of Advances in Pharmaceutics
ISSN: 2320–4923; DOI: 10.7439/ijap
Volume 5 Issue 2 [2016]
Journal home page: http://ssjournals.com/index.php/ijap

Research Article

Evaluation of gum sandarac as a novel release controlling polymer for sustained release matrix pellets

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Keywords:
Pellets,
Matrix,
Extrusion,
Ethyl cellulose,
Sandarac

Abstract

Sustained release, prolonged action, extended action are the terms used to identify drug delivery system that are designed to achieve prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. Matrix systems, because of their ease of manufacture, their flexibility to obtain a desirable drug release profile, cost–effectiveness, and broad regulatory acceptance are preferred for formulating these dosage forms. Polymers are the most important part in any type of release modified formulations. Predominantly hydrophobic materials are widely used to fabricate the matrix systems. Various materials are being investigated as polymers as there is scarcity of good polymeric materials to be used in pharmaceutical products. The present study was aimed at evaluating novel natural material gum sandarac, a resin obtained by incision from the stem of *Callitris quadrivalvis*, Ventenat (N.O. Coniferae) Pinaceae as a hydrophobic matrixing material for developing coated pellets for sustained release of drug and comparing it with well known ethyl cellulose as hydrophobic polymeric material.

1. Introduction

The aim of any drug delivery system is to provide therapeutic amount of drug to appropriate site in the body to achieve immediate therapeutic response and to maintain the desired drug concentration. Sustained release, sustained action, prolonged action, extended action are the terms used to identify drug delivery system that are designed to achieve prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose [1]. In the recent years sustained release (SR) dosage forms continue to draw attention in the research for improved patient compliance and decreased incidence of adverse drug reactions. [1,3,4]. Frequently used approaches to achieve adequate control of drug release include matrix systems, because of their ease of manufacture, their flexibility to obtain a desirable drug release profile, cost–effectiveness, and broad regulatory acceptance[1]. The mechanism of drug release from matrix systems is based on diffusion, dissolution and erosion or their combination [5-7].

Polymers are the most important part of release modified formulations. Predominantly hydrophobic materials are widely used to fabricate the matrix systems. Some of these hydrophobic materials include polyvinyl chloride (PVC) [8,], poly-ethylenes [9], ethyl cellulose (EC), acrylic resins and polyamides [4], Cellulose acetate (CA) [10], carrageenan [11], shellac [12], gum copal, gum damar [13] and waxes [14, 15]. While hydrophilic HPMC, CMC, NaCMC [16], have also been studied as matrix formers for sustained drug delivery. Many of these materials have particular advantages and their own limitations. [17], CA was found unable in few cases to surround the drug particles efficiently [10], waxes have major limitation of dimensional instability and heat sensitivity, the rate of drug release through hydrophilic matrices is governed by the rate and extent of swelling of the polymer; consequently ionic strength and pH of surrounding medium affect release

rate from such matrices [18]. In addition, polymers can be toxic, they may not have physical stability towards heat, good compression and flow properties, and high cost also could be a limitation. Although, this scratches the surface of information of some of the various polymeric materials that are investigated as matrix formers, it projects the need to explore the novel polymeric materials for sustained drug delivery. Sandarac gum is a resin obtained by incision from the stem of *Callitris quadrivalvis*, Ventenat (N.O. Coniferae) Pinaceae. It has been used in medicines for various purposes and is a very safe gum resin for internal use [19-21]. Though extensive chemical analysis and research have been carried out with Sandarac [22-24], till date it has not been used as sustained release agent. The objective of this study was to formulate and evaluate matrix pellets of hydrophobic Sandarac gum and Ethyl cellulose and evaluate their matrixing and release retarding ability when used in pellet formulations. Pellets were used as dosage form of choice because though they have inherent advantages as multiple unit dosage form [25-26].

2. Materials

Diclofenac sodium (DFS) was received as research sample from Relief Labs, Nagpur, Propranolol hydrochloride (PRP) was generously given by Zydus Cadila Ltd, Ahemadabad. Sandarac gum (GS) was purchased from local market. Ethyl cellulose (EC) was procured from Loba chemicals Mumbai. All other chemicals were of LR grade purchased from SD Fine Chemicals India.

3. Methods

3.1 Compatibility studies:

Compatibility studies were carried out by keeping mixture of drugs and gum sandarac in 1:1, 1:2 and 1:3 ratio in sealed vials at room temperature and at 40^{O}C for one month. Formulation blends were also kept in sealed vial for one month at same conditions and were observed for any physical change. The samples were evaluated by FTIR spectroscopy to find out any incompatibility.

3.2 Preparation of matrix pellets

The composition of matrix pellets is given in Table No. 1. Both the polymers were used at 15% level. PRP or DFS (10%) and MCC (75%) were used to prepare the matrix pellets. The drug (44–mesh) was blended with MCC (44–mesh) in polybag. The blend was wetted with 25% w/v solution of the EC in alcohol and GS in Acetone–isopropyl alcohol (AC: IPA) 1:1mixture. The desired wetting end point was achieved by addition of distilled water. The wet cohesive mass was extruded through the extruder (Umang Pharmatech, Mumbai) with a die roller of 1.5 mm diameter at 15 rpm. The obtained extrudate were spheronized for 10 min in a spheronizer (Umang Pharmatech, Mumbai) using cross–hatch friction plate (groove size: 2mm) with a rotational speed of 900 rpm. The resulting pellets were dried at 40°C for 12 h in oven. The 12/14–mesh fraction of the pellets was selected for the evaluation. Similarly, standard drug–MCC pellets were prepared using povidone (2% w/w) as binder without polymers.

Table No. 1: Formulations for matrix pellets with GS and EC as matrixing agents

Ingredients	Batch % w/w					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
EC	15	15	–	–	–	–
GS	–	–	15	15	–	–
PRP	10	–	10	–	10	
DFS	–	10	–	10	–	10
MCC	73	73	73	73	88	88
PVP	2	2	2	2	2	2

3.3. Evaluation of pellets [27, 28]

The pellets were evaluated for various parameters like bulk density / Tapped density, Compressibility index, Housner ratio Crushing strength and friability of the pellets using standard reported procedures.

The size distribution was carried out using a sieve shaker and set of 4 ASTM sieves (# 10, #14, #20, and #30) for 5 minutes.

The shape and size of the pellets was examined with a screw gauge. Major and minor axes of 12 pellets of each composition were measured. The average of this ratio was expressed as shape factor.

For swelling study 2.0 g of pellets were taken in a 25 ml measuring cylinder and volume of pellets was measured accurately after tapping them to get a constant value. About 10 ml 0f distilled water/ buffer solution was added to it. The cylinder was kept aside and volume was measured after each 30 min.

3.3.1 Drug content

About 100 mg of pellets were grounded carefully in a mortar. The DFS or PRP content was extracted with phosphate buffer pH 6.8 by sonicating for 10–15 min (Sonicator 3.5 L100, PCI Instruments, India). The filtered solutions were diluted and assayed UV spectro-photometrically (UV–1601, Schimadzu, Japan) at 276 nm and 289 nm for DFS and PRP contents respectively.

3.3.2 Drug release studies

The drug release study was carried out in USP XXIV dissolution apparatus Type I (basket; Veego Scientific, India) at 75 rpm and 37 ±0.5°C. Phosphate buffer of pH 6.8 (900) ml was used as a dissolution medium. Hourly 10 ml of the sample was withdrawn and replaced with the equal volume of fresh medium. The withdrawn samples were filtered after suitable dilutions and analyzed by UV–Spectrophotometer (UV–1601, Shimadzu, Japan) at 289 nm or 276 nm for either PRP or DFS contents. All the experiments were carried out in triplicate.

3.3.3 Drug release kinetics

The dissolution data was computed in the light of different kinetic equations [30] which are given below with appropriate numbering.

$$Qt = K_o t \quad (1)$$

$$\text{In } Qt = \text{In } Qo - K_1 . t \quad (2)$$

$$Qt = K_H . \sqrt{t} \quad (3)$$

$$3\sqrt{Qo} - 3\sqrt{Qt} = K_{HC} . t \quad (4)$$

$$3/2\ [1-(1-Qt)^{2/3}] - Qt = K_{BC} . t \quad (5)$$

$$Qt = K_{KP}\ t^n \quad (6)$$

Where, Qt is the amount of drug released in time t. Qo is the initial amount of drug released. K_o, K_1, K_H, K_{HC}, K_{BC} and K_{KP} are the release rate constants for Zero order, First order, Higuchi, Hixson–Crowell, Baker–Lonsdale and Korsmeyer–Peppas kinetic equations.

The equation for zero order rate (1) describes the systems where the drug release rate is independent of its concentration. The first order equation (2) describes the systems where drug release rate depends on its concentration. Higuchi equation (3) describes the drug release by diffusion from an insoluble matrix. The Hixson–Crowell equation (4) describes systems through which drug releases with the changes in surface dimensions and Baker–Lonsdale equation (5) describes drug release from the spherical matrix. The release governed both by diffusion and erosion is best described by Korsmeyer–Peppas equation(6).

4. Results and Discussion

4.1. Compatibility study

There was no change in appearance or compact formation or decolouration in cases of all the samples. FTIR study also showed no change in principle peaks of drug substance indicating no incompatibility.

4.2. Preparation of pellets

Pelletization with extrusion spheronization is a very tricky process. The extrudable blend should have good consistency and extrudable property. Extrudes in turn formed should have sufficient plasticity and cohesiveness to be cut and compacted into uniform pellets. The pellet blend prepared with GS and EC polymers was forming uniform mass but was slightly lacking in cohesiveness due to higher hydrophobic content hence 2% w/w povidone (PVP–K30) was added as additional binder in the formulation. The pellets formed with proper kneading were uniform and more spherical on visual inspection, kneading is very important as sufficient kneading results in proper and uniform wetting of the mass resulting in uniform consistency which can be easily extruded and palletized. Since both EC and GS are hydrophobic, were added in solution form so that they can form uniform matrix in the blend.

4.4.1. Evaluation of pellets

4.4.1.1 Size and shape

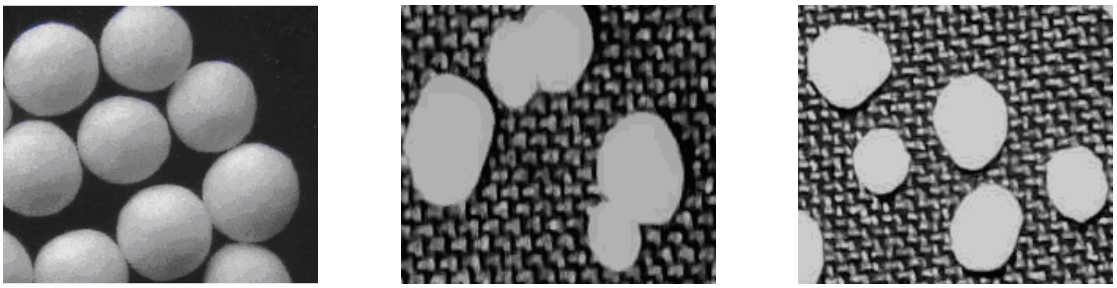
Shape factor is based on a two–dimensional outline analysis and considers both the geometrical shape and the surface texture of the agglomerate [31]. For the shape factor a value of unity considers a perfect spheroid although a value close to 0.6 describes a particle of good sphericity. Shape of pellets was spherical and smooth to visual observation. The plain pellets i.e. without polymers were having very good sphericity. The pellets with GS and EC were having optimum sphericity as all the batches were having index more than 0.6 (See Table No.2.).

Table No. 2: Physical properties of GS and EC matrix pellets

Formulation	Parameters studied							
	% Yield*	Shape factor	Crushing strength kg/cm^2	Friability (%)	Hausner ratio	Carr's Index	Drug content	% Swelling
F1	52. 67	0. 75	1. 4	0. 42	1.10	10. 19	99.89	10.26%
F2	42. 17	0. 64	1. 6	0. 64	1.11	11. 09	98.90	10.06%
F3	55. 24	0. 78	1. 4	0. 44	1.11	11. 21	99.72	11.07%
F4	41. 95	0. 66	1. 5	0. 67	1.12	12. 22	99.44	11.99%
F5	68. 23	0. 89	1. 2	0. 30	1.07	7. 12	99.64	17.21%
F6	74. 17	0. 85	1. 1	0. 37	1.07	6. 98	99.75	15.97%

* % yield of particle of size 850–1400 µm

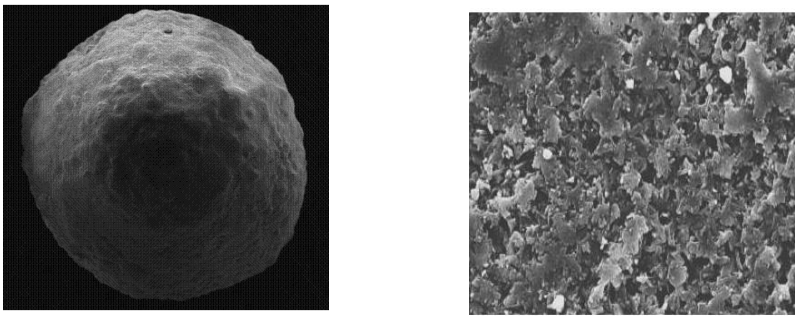
The PRP pellets were having comparatively higher sphericity index than DFS pellets, this can be reasoned to their respective solubilities. PRP being highly soluble than DFS get dissolved in palletizing fluid and thus aid in formation of spherical pellets. The microphotographs of DFS and PRP pellets with GS as matrix former are shown in Fig. 1.



(A) (B) (C)

Fig 1: Microphotographs of (A): Plain pellets (B): DFS: GS matrix pellets (C): PRP GS matrix pellets

The scanning electron micrographs (Fig 2.) indicate comparatively smooth surface of the pellets containing GS.



(A) PRP GS Pellet 25X (C) PRP GS Pellet 500X

Fig. 2: Scanning electron micrographs of matrix pellets

4.4.1.2. Crushing strength and friability of the pellets

According to Aulton et al. [32] the desirable mechanical properties of the pellets are that they are strong, not brittle and have a low elastic resilience. The crushing strength and friability values can be indicative of aforementioned qualities of pellets. The crushing strength and friability values of matrix pellets are summarized in Table No. 2. The PRP pellets showed crushing strength in the range of 1.1–1.7 kg/cm^2, whereas, the crushing strength of DFS pellets ranges in 1.1–1.6 kg/cm^2. This may be due to binding of respective drug and polymers. Friability for all the pellets formulations was less than 0.5, which indicates the good strength for handling of the pellets.

4.4.1.3. Hausner's ratio and compressibility index

Both these properties are derived using bulk density and tapped density. They are basically considered as the indications of flow property of the materials. The Compressibility index is also called as Carr's index or % compressibility. The higher values indicate poor flow and lower values indicate good flow properties. Values in the range of 5–15 are considered indication 0f excellent flow ability. All the pellets formulations show excellent flow properties. Hausner ratio of all formulation batches also indicates good flow properties. These values can be reasoned to nearly spherical shape and smooth surface of the pellets.

4.4.1.4. Swelling study

The plain pellets of both the drug showed maximum up to 15-17% swelling in the medium i.e. 6.8 pH phosphate buffer. The DFS pellets show slower initial swelling due to lower solubility of the drug which delays the penetration of the medium into pellets and thus shows lower initial values. The PRP is very soluble in medium and thus the medium radically penetrates the pellets and thus show maximum initial swelling. In the pellets with hydrophobic polymers whatever swelling was observed might be mainly because of MCC, the polymers being having no or negligible swelling because of nature does not assisting the swelling of pellets. The swelling behaviour of pellets is given in Table No. 2.

4.4.15. Drug content

The drug content was determined to analyse content uniformity of all the batches. All the pellets formulations show very good content uniformity ranging from 98.90 to 99.89% of drug of labelled drug amount (Table No.2). This shows that the adequate and uniform mixing and kneading of the blend was achieved.

4.4.1.6. *In vitro* Drug release studies

Plots of the fraction of drug released versus time for the pellets formulations is shown in Fig. 3. When the dissolution was carried out in pH 1.2 HCl solution for first 2 hours, the drug release was very low for PRP and negligible for DFS, the EC and GS being insoluble polymers and DFS being insoluble in acidic pH. Though PRP was released upto small extent, to maintain uniformity, the dissolution was carried out only in pH 6.8 pH phosphate buffer and only data of drug release in this pH is given in results.

The DFS pellets show relatively prolonged release in all the formulations as compared to the PRP pellets. The initial release of PRP pellets was quite higher than DFS pellets showing burst release. This can be attributed to the relative solubility of the drugs, PRP being very soluble and DFS being sparingly soluble. The soluble content in the formulation migrates towards the periphery of the formulation during the process of drying. This phenomenon results in the concentration of the soluble materials on the formulation surface. Also pellets present an extremely large surface area and a high release rate potential compared to the corresponding tablet formulation. Due to the large surface area pellets will normally give a considerable burst effect, i.e. an immediate initial release of a significant proportion of the drug substance because of the rapid dissolution of the solid drug particles, positioned on the surface of the pellets. Due to this all the formulations of PRP showed faster initial release.

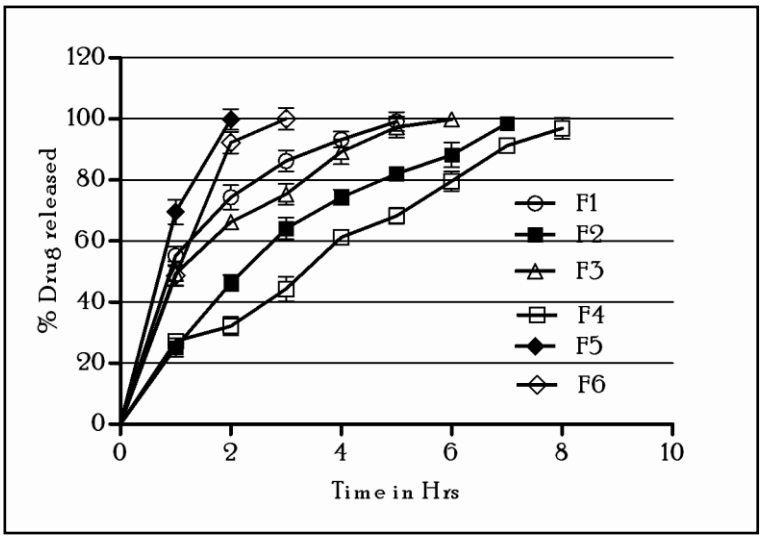
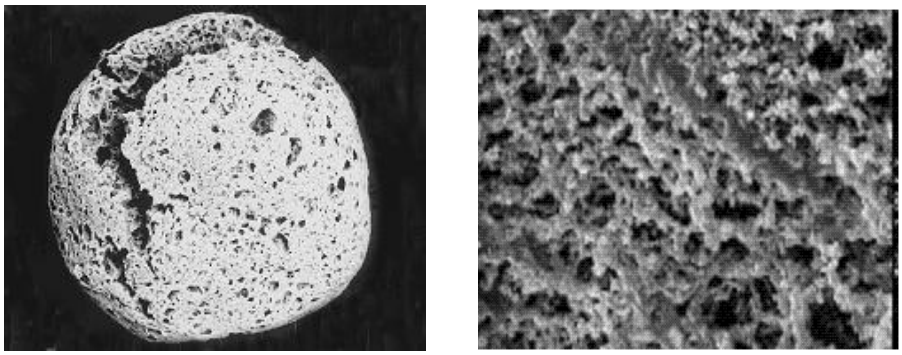


Fig 3: Drug release from GS and EC matrix pellets.

The plain pellets gave faster drug release releasing complete drug content within 2–3 hours. PRP pellets released 100% drug in 5 hours with EC and in 6 hours with GS at 15% level. DFS was released completely in 7 hours with EC and 96 % in 8 hours with GS. As the pelletization was completed with water the properties of drug were important for they affected the initial as well as prolonged drug release. As polymer in the form of solution was added in the pellet blends it formed complete matrix with drug exciepient blend and thus enabling a good sustain action. The faster release was observed due to subsequent addition of water in the blend. To check this, a smaller batch size of pellets was prepared without adding water and completing pelletization entirely with organic solvent, it gave only upto 35% drug release in 8 hours (data not shown). The problem with these pellets was that the batch yield of optimum size was very low with very low % yield (<25%) of desired pellets size and the pellets formed were of very poor quality with very low spherisity index

and rough and non–uniform surface, they were like granules. The SEM of DFS: GS matrix pellet after dissolution is shown in Fig. 4. The micrograph indicates extensive pore formation in the pellet due to diffusion of drug from the core.



30X **500X**

Fig 4: SEM of DFS: GS matrix pellet after dissolution

4.4.1.1.7. Release kinetics

The values for correlation coefficient according to the different kinetic equations are given in Table No. 2.4. The matrix pellets containing hydrophobic polymer and PRP showed drug release by zero order kinetics which indicated drug load independent release of drug from these formulations. On the other hand, the pellets containing hydrophobic polymer and DFS released drug by Higuchi square root kinetic indicating that diffusion was the main factor controlling the drug release rate.

Table No. 3: Correlation coefficients (r) for PRP and DFS matrix pellets

Formulation	Correlation coefficient (r) for Kinetic model					
	Zero Order	Ist Order	Higuchi	H–C[a]	B–L*	K–P[$]
F1	0.993	0.974	0.992	0.983	0.952	0.969
F2	0.968	0.905	0.987	0.932	0.968	0.938
F3	0.996	0.974	0.995	0.985	0.938	0.979
F4	0.984	0.928	0.991	0.954	0.950	0.962

*Baker–Lonsdale; [a] Hixson–Crowell; [$] Korsmeyer–Peppas kinetic models

The drug transport inside pharmaceutical systems and its release sometimes involves multiple steps provoked by different physical or chemical phenomenon, making it difficult, or even impossible, to get a mathematical model describing it in the correct way. These models better describes the drug release from the systems when it results from a simple phenomenon [30].

5. Conclusion

GS was found to be very efficient matrix forming agent for pellets formulations and was able to sustain drug release comparable with well known EC. PRP pellets were superior to DFS pellets in sphericity and surface smoothness. GS and EC were capable of sustaining drug release for considerable time, upto7-8 hours, in case of DFS and 5 to 6 hours in case of PRP at 15% w/w level. PRP was released with faster rate than DFS in all the formulations. The DFS was released by Higuchi diffusion kinetics while PRP in same matrices showed Zero order release kinetics.

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